FINAL REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

The clinical and cost effectiveness of lead-I electrocardiogram (ECG) devices for detecting atrial fibrillation using single-time point testing in primary care [DAP39]

This Diagnostics Assessment Report was commissioned by the NIHR HTA Programme as project number 16/30/05

Completed 19th October 2018

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: The clinical and cost effectiveness of lead-I electrocardiogram (ECG) devices for detecting atrial fibrillation using single-time point testing in primary care

Produced by: Liverpool Reviews and Implementation Group (LR*i*G)

Authors: Rui Duarte, Senior Research Fellow, LR*i*G, University of Liverpool

Angela Stainthorpe, Research Associate, LR*i*G, University of Liverpool

Janette Greenhalgh, Senior Research Fellow, LR*i*G, University of Liverpool

Marty Richardson, Research Associate, LR*i*G, University of Liverpool

Sarah Nevitt, Research Associate, LR*i*G, University of Liverpool

James Mahon, Director, Coldingham Analytical Services

Eleanor Kotas, Information Specialist, LR*i*G, University of Liverpool

Angela Boland, Associate Director, LR*i*G, University of Liverpool

Howard Thom, Research Fellow, School of Social and Community Medicine, University of Bristol

Tom Marshall, Professor of Public Health and Primary Care, Institute of Applied Health Research, University of Birmingham

Mark Hall, Consultant Cardiologist and Electrophysiologist, Liverpool Heart and Chest Hospital

Yemisi Takwoingi, Senior Research Fellow, Test Evaluation Research Group, University of Birmingham

Correspondence to: Rui Duarte, Liverpool Reviews and Implementation Group, University of Liverpool, [redacted]

Date completed: 19th October 2018

PROSPERO registration: CRD42018090375

Source of funding: This Diagnostics Assessment Report was commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence as project number 16/30/05.

Declared competing interests of the authors: None.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Duarte R, Stainthorpe A, Greenhalgh J, Richardson M, Nevitt S, Mahon J, Kotas E, Boland A, Thom H, Marshall T, Hall M, Takwoingi Y. The clinical and cost effectiveness of lead-I electrocardiogram (ECG) devices for detecting atrial fibrillation using single-time point testing in primary care. Liverpool Reviews and Implementation Group (LR*i*G), University of Liverpool, 2018.

ABSTRACT

Background

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia and is associated with increases in the risk of stroke and in the risk of congestive heart failure. Lead-I electrocardiogram (ECG) devices are handheld instruments that can be used to detect AF at a single-time point in people who present with relevant signs and symptoms.

Objectives

To assess the diagnostic test accuracy, the clinical impact and the cost effectiveness of single-time point lead-I ECG devices for the detection of AF in people presenting to primary care with signs or symptoms of AF and who have an irregular pulse compared with manual pulse palpation (MPP) followed by a 12-lead ECG in primary or secondary care.

Methods

The systematic review methods followed published guidance. Electronic databases were searched until March 2018. Two reviewers screened the search results, extracted data and assessed the quality of the included studies. Summary estimates of diagnostic accuracy were calculated using bivariate models. Clinical impact outcomes were synthesised narratively.

We developed an economic model consisting of a decision tree and two cohort Markov models. The decision tree describes the pathway that a patient presenting to primary care with signs and symptoms of AF and an irregular pulse follows in the initial GP consultation. The first Markov model captures the differences in the costs and benefits of treatment (standard diagnostic pathway versus lead-I ECG pathway) during the first 3 months after the initial appointment. During this period, some patients will have a diagnosis of AF and start treatment for AF whilst other patients will have further tests to diagnose or to rule out AF (where 'rule out' means no diagnosis of AF is recorded in the patient's notes and no treatment for AF is started). The second Markov model captures the differences in lifetime costs and benefits after diagnosis of AF or the time when AF is ruled out.

Results

No studies were identified that evaluated the use of lead-I ECG devices for patients with signs and symptoms of AF. Due to the absence of data, studies with a focus on asymptomatic populations were considered for inclusion and these data were used as a proxy for people with signs and symptoms of AF. Therefore, the diagnostic accuracy and clinical impact results presented are derived from on an asymptomatic population. Thirteen publications reporting on nine studies were included in the diagnostic test accuracy review, of which four studies

were included in a meta-analysis (involving 118 AF cases out of 580 participants). The summary sensitivity of lead-I ECG devices was 93.9% (95% confidence interval [CI]: 86.2% to 97.4%) and summary specificity was 96.5% (95% CI: 90.4% to 98.8%).

Twenty-four publications of 19 studies were included in the clinical impact review. In these studies, the percentage of new patients diagnosed with AF ranged from 0.38% to 5.84%. One study reported limited clinical outcome data. Acceptability of lead-I ECG devices was reported in four studies, with generally positive views.

The de novo economic model yielded incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALY). The results of the pairwise analysis show that all lead-I ECG tests lie on the efficiency frontier in each of the four base case analyses with ICERs below the £20,000-£30,000 threshold usually considered to be cost effective by NICE. Kardia Mobile is the most cost effective option in a full incremental analysis and dominates the standard pathway and other lead-I ECG devices (costing less and generating more QALYs) with the exception of the generic lead-I ECG device which generates a very small QALY gain but at a cost that produces an ICER well above £30,000 per QALY gained.

Conclusions

The use of single-time point lead-I ECG devices for the detection of AF in people with signs and symptoms of AF and an irregular pulse appears to be a cost effective use of NHS resources compared with MPP followed by a 12-lead ECG in primary or secondary care, given the assumptions used in the base case model. The current standard diagnostic pathway for the diagnosis of AF shows that every patient with signs and symptoms of AF are advised to have a 12-lead ECG test. The benefits accumulated during the time interval between the lead-I ECG and confirmatory12-lead ECG tests are sufficiently large for lead-I ECG devices to be cost effective in this specific population.

Study registration

The protocol for this review is registered on PROSPERO as CRD42018090375.

Funding

This Diagnostics Assessment Report was commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence as project number 16/30/05.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	adverse event
AF	atrial fibrillation
AHSN	Academic Health Science Health Network
AUC	area under the curve
BNF	British National Formulary
CASP	Critical Appraisal Skills Programme
CCG	Clinical Commissioning Group
CDSR	Cochrane Database of Systematic Reviews
CEAC	cost-effectiveness acceptability curves
CENTRAL	Cochrane Central Database of Controlled Trials
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPI	Consumer Price Index
CRD	Centre for Reviews and Dissemination
CVE	cardiovascular events
DADS	directly accessed diagnostic services
DARE	Database of Abstracts of Reviews of Effects
DTA	diagnostic test accuracy
EAG	External Assessment Group
ECG	electrocardiogram
ESC	European Society for Cardiology
GP	general practitioner
HR	hazard ratio
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost effectiveness ratio
ICH	intracerebral haemorrhage
IQR	interquartile region
IT	information technology
MI	myocardial infarction
MPP	manual pulse palpation
NA	not applicable
NG	NICE guideline
NICE	National Institute for Health and Care Excellence
NOAC	non-vitamin K antagonist oral anticoagulant
NR	not reported
OAC	oral anticoagulant
ONS	Office of National Statistics
PHE	Public Health England
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality adjusted life year
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	randomised controlled trial
ROC	receiver operating characteristic

SD	standard deviation
SE	standard error
SR	systematic review
SROC	summary receiver operating characteristic
SSNAP	Sentinel Stroke National Audit Programme
TIA	transient ischemic attack

GLOSSARY

Cost effectiveness analysis	An economic analysis that converts effects into health terms and describes the costs per additional health gain
Decision modelling	A theoretical construct that allows the comparison of the relationship between costs and outcomes of alternative healthcare interventions
Decision tree	A model of a series of related choices and their possible outcomes
False negative	Incorrect negative test result – an affected individual with a negative test result
False positive	Incorrect positive test result – an unaffected individual with a positive test result
Incremental cost effectiveness ratio	The difference in the mean costs of two interventions in the population of interest divided by the difference in the mean outcomes in the population of interest
Index test	The test whose performance is being evaluated
Markov model	An analytical method particularly suited to modelling repeated events or the progression of a chronic disease over time
Meta-analysis	Statistical techniques used to combine the results of two or more studies and obtain a combined estimate of effect
Negative predictive value	Probability that people with a negative test result truly do not have the disease
Opportunity costs	The cost of forgone outcomes that could have been achieved through alternative investments
Positive predictive value	Probability that people with a positive test result truly have the disease
Probabilistic sensitivity analysis	A method of quantifying uncertainty in a mathematical model, such as a cost-effectiveness model
Receiver operating characteristic curve	A graph which illustrates the trade-offs between sensitivity and specificity that result from varying the diagnostic threshold
Reference standard	The best currently available diagnostic test against which the index test is compared
Sensitivity	Proportion of people with the target disorder who have a positive test result
Specificity	Proportion of people without the target disorder who have a negative test result
True negative	Correct negative test result – an unaffected individual with a negative test result
True positive	Correct positive test result – an affected individual with a positive test result

PLAIN ENGLISH SUMMARY

Atrial fibrillation (AF) is the most common type of abnormal heart rhythm. People with AF are more likely to have a serious stroke or die compared with people without the condition. Many people go to their general practitioner (GP) with the signs and symptoms commonly linked to AF such as feeling dizzy, being short of breath, feeling tired and having heart palpitations. GPs check for AF by taking the patient's pulse by hand. If the GP thinks the patient might have AF, a 12-lead electrocardiogram (ECG) test is arranged. Lead-I (i.e. one lead) ECGs are handheld electronic devices that could more accurately detect AF than a manual pulse check. If GPs were to routinely use lead-I ECG devices, people with suspected AF could receive treatment while waiting for the AF diagnosis to be confirmed by a 12-lead ECG. This study aimed to assess whether the use of lead-I ECGs in GP surgeries would benefit these patients and offer good value for money. We reviewed all studies examining how well lead-I ECGs identify people with AF, and we assessed the economic value of using these devices. We found no evidence examining the use of lead-I ECGs for people with signs and symptoms of AF. As an alternative, we searched for evidence on the use of lead-I ECGs for people with no symptoms of AF and used these data to assess cost effectiveness. We found that using lead-I ECGs offers value for money when compared to a manual pulse check followed by a 12-lead ECG. For people with signs and symptoms of AF and an irregular pulse, where there is a long delay between first use of the manual pulse check or lead-I ECG and confirmation by a 12-lead ECG test result, the use of lead-I ECGs is most cost effective.

SCIENTIFIC SUMMARY

Background

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia and is associated with conditions such as hypertension, heart failure, coronary artery disease, valvular heart disease, obesity, diabetes mellitus and chronic kidney disease. The National Institute for Health and Care Excellence (NICE) clinical guideline CG180 recommends that, after positive manual pulse palpation (MPP), the diagnosis of AF should be confirmed based on the results of an electrocardiogram (ECG). People that present to primary care with signs or symptoms of the condition (i.e. palpitations, dizziness, shortness of breath and tiredness) and who have an irregular pulse should receive a referral for a 12-lead ECG in the days following their initial primary care appointment, if a 12-lead ECG is not available in the practice. Lead-I ECG devices are handheld instruments that can be used in primary care to detect AF at a single-time point in people who present with relevant signs and symptoms and who have an irregular pulse.

Objectives

The aim of this study was to assess the diagnostic test accuracy, the clinical impact and the cost effectiveness of single-time point lead-I ECG devices for the detection of AF in people presenting to primary care with signs or symptoms of the condition and who have an irregular pulse compared with MPP followed by a 12-lead ECG in primary or secondary care (prior to initiation of anticoagulation therapy). To achieve this aim we:

1. conducted systematic reviews of the diagnostic accuracy and clinical impact of lead-I ECG for (1) detecting AF in people presenting to primary care with signs or symptoms of the condition, or, if evidence was not available for this population/setting, for (2) detecting AF in an asymptomatic population defined as people presenting to any setting without symptoms of AF, with or without a previous diagnosis of AF
2. developed an economic model to assess the cost effectiveness of single-time point lead-I ECG devices compared with MPP followed by a 12-lead ECG in primary or secondary care (prior to initiation of anticoagulation therapy) in people presenting to primary care with signs and symptoms of AF who have an irregular pulse.

Methods: Assessment of clinical impact and diagnostic test accuracy

Electronic databases (MEDLINE, MEDLINE Epub Ahead of Print and MEDLINE In-Process, EMBASE, PubMed and Cochrane Databases of Systematic Reviews, Cochrane Central Database of Controlled Trials, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) were searched up to March 2018. Eligible studies assessed the

diagnostic accuracy or clinical impact of specified lead-I ECG devices (i.e. imPulse, Kardia Mobile, MyDiagnostick, RhythmPad GP and Zenicor ECG) in people presenting with signs or symptoms of AF and who have an irregular pulse. Studies that assessed the diagnostic accuracy of lead-I ECG devices used at a single-time point to detect AF in an asymptomatic population were considered for inclusion due to the non-existence of studies in symptomatic populations. We considered an asymptomatic population to comprise people not presenting with symptoms of AF, with or without a previous diagnosis of AF.

Two reviewers independently screened the search results, extracted data and assessed the methodological quality of the included diagnostic accuracy studies using the QUality Assessment of Diagnostic Accuracy Studies - 2 (QUADAS-2) tool. The methodological quality of cross-sectional and case-control studies evaluating the clinical impact of lead-I ECG devices was assessed using the Newcastle-Ottawa quality assessment scale.

The sensitivity and specificity of each index test were summarised in forest plots and plotted in receiver operating characteristic (ROC) space. Pooled estimates of sensitivity and specificity with 95% confidence intervals (CIs) were obtained using bivariate models. When there were few studies, the bivariate model was reduced to two univariate random effects logistic regression models by assuming no correlation between sensitivity and specificity across studies. Judgement of heterogeneity, and hence the choice of simpler hierarchical models were informed by the visual appearance of forest plots and summary receiver operating characteristic (SROC) plots, in addition to clinical judgement regarding potential sources of heterogeneity. The analyses were stratified by whether diagnosis of AF was made by a trained healthcare professional interpreting the lead-I ECG trace, or by the lead-I ECG algorithm. For both sets of analyses, the reference standard was interpretation of the 12-lead ECG trace by a trained healthcare professional. When studies reported data for two types of lead-I ECG device and two different interpreters, one dataset was chosen and sensitivity analyses were performed using the alternative datasets. Clinical impact outcomes were synthesised narratively.

Methods: Assessment of cost effectiveness

We reviewed the literature to identify published economic evaluations of lead-I ECG devices for the detection of AF in people presenting to primary care with signs or symptoms of the condition and who have an irregular pulse. Electronic databases (MEDLINE, MEDLINE Epub Ahead of Print and MEDLINE In-Process, EMBASE, PubMed, EconLit and NHS Economic Evaluation Database) were searched up to April 2018. Additional searches were carried out to identify supporting information on costs and health state utility data.

A de novo economic analysis was undertaken that follows the diagnostic pathway for patients presenting to primary care with signs and symptoms indicative of AF and an irregular pulse. The sensitivity and specificity of the different lead-I ECG devices were taken from the results of the diagnostic test accuracy review. A probabilistic sensitivity analysis (PSA) is presented to reflect uncertainty in the model inputs as well as extensive deterministic sensitivity analysis and scenario analysis to assess the impact of uncertainty in model assumptions. We report the total costs of the annual number of symptomatic patients with positive MPP seen by a single GP, total quality adjusted life years (QALYs) for these patients, incremental costs and QALYs, and incremental cost effectiveness ratios (ICERs). Several scenario analyses were undertaken to investigate the impact on the size of the ICER per QALY gained of varying some of the base case assumptions. Costs and outcomes in future years over a lifetime time horizon were discounted at an annual rate of 3.5%.

Results

The electronic database searches resulted in the identification of 1151 citations (915 unique records). No studies were identified for the population of interest (i.e. people with signs or symptoms that may indicate underlying AF and who have an irregular pulse). Therefore, all the studies included in the systematic reviews assessed the diagnostic accuracy and clinical impact of lead-I ECG devices used at a single-time point to detect AF in an asymptomatic population.

Diagnostic test accuracy

We identified 13 publications reporting on nine studies. In these studies, the index test was interpreted by the device algorithm or by a trained healthcare professional; trained healthcare professionals included cardiologists, electrophysiologists and general practitioners. All studies used a 12-lead ECG device interpreted by a trained healthcare professional as the reference standard.

Interpreter of lead-I ECG: trained healthcare professional

Data from four studies contributed to the meta-analyses (two studies of Kardia Mobile alone, one study of Zenicor-ECG and one study of MyDiagnostick and Kardia Mobile). The main meta-analysis (number of AF cases=118, total N=580), indicated that the pooled sensitivity of lead-I ECG devices was 93.9% (95% CI: 86.2% to 97.4%) and pooled specificity was 96.5% (95% CI: 90.4% to 98.8%). Across the sensitivity analyses, numerical results were similar; pooled sensitivity values ranged from 88.0% to 96.2% and pooled specificity values ranged from 94.4% to 97.4%.

Interpreter of lead-I ECG: algorithm

Data from four studies were included in the meta-analyses (two studies of MyDiagnostick alone, one study of Kardia Mobile alone and one study MyDiagnostick and Kardia Mobile). Meta-analysis (number of AF cases=219, total N=842) showed a pooled sensitivity of 96.2% (95% CI: 86.0% to 99.0%) and pooled specificity was 95.2% (95% CI: 92.9% to 96.8%). Numerical results were similar across the sensitivity analyses; pooled sensitivity values ranged from 88.0% to 95.2% and pooled specificity values ranged from 94.4% to 97.2%.

Clinical impact

We identified 24 publications reporting on 19 studies with a total of 33,993 participants. The index tests evaluated included ImPulse (one study), Kardia Mobile alone (11 studies), MyDiagnostick alone (four studies), Zenicor ECG (one study) and MyDiagnostick and Kardia Mobile (one study). Test failure rate was reported in nine studies and ranged from 0.1% to 9%. Results for test failure rate included both failure of the lead-I ECG algorithm to produce a result and poor quality of the lead-I ECG trace. Diagnostic yield was reported in 13 studies. The percentage of new patients diagnosed with AF ranged from 0.38% to 5.84%. Data for this outcome were considered too heterogeneous for a pooled estimate to be clinically meaningful. Only one study reported the concordance between lead-I ECG devices (Kardia Mobile and MyDiagnostick) observing no difference in agreement between the devices. Two studies reported a change in treatment management following the use of the Kardia Mobile lead-I ECG in new patients diagnosed with AF. Acceptability of lead-I ECG devices was reported in four studies, with generally positive views.

Cost effectiveness

We did not identify any studies that assessed the cost effectiveness of single-time point lead-I ECG devices compared with MPP followed by a 12-lead ECG in primary or secondary care in people presenting to primary care with signs and symptoms of AF who have an irregular pulse.

A decision tree and two cohort Markov models were built in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA). The decision tree describes the pathway that a patient presenting to primary care with signs and symptoms of AF and an irregular pulse follows in the initial GP consultation. The first Markov model captures the differences in the costs and benefits of treatment (standard diagnostic pathway versus lead-I ECG pathway) during the first 3 months after the initial appointment. During this period, some patients will have a diagnosis of AF and start treatment for AF whilst other patients will have further tests to diagnose or to rule out AF (where ‘rule out’ means no diagnosis of AF is recorded in the patient’s notes and no treatment for AF is started). The second Markov model captures the

differences in lifetime costs and benefits after diagnosis of AF or the time when AF is ruled out.

The de novo economic model yielded ICERs per QALY gained. The results of the pairwise analysis show that all lead-I ECG tests lie on the efficiency frontier in each of the four base case analyses with ICERs below the £20,000-£30,000 threshold usually considered to be cost effective by NICE. Kardia Mobile is the most cost effective option in a full incremental analysis and dominates the standard pathway and other lead-I ECG devices (costing less and generating more QALYs) with the exception of the generic lead-I ECG device which generates a very small QALY gain but at a cost that produces an ICER well above £30,000 per QALY gained.

Conclusions

There is no evidence available for the use of single-time point lead-I ECG devices for the detection of AF in people with signs and symptoms of AF and an irregular pulse. The results of this assessment suggest that lead-I ECG devices represent a cost effective use of NHS resources compared with MPP followed by a 12-lead ECG in primary or secondary care. The current standard pathway for the diagnosis of AF shows that patients with the signs and symptoms of AF and an irregular pulse are advised to have a 12-lead ECG test. The benefits accumulated during the time interval between the lead-I ECG tests and the confirmatory 12-lead ECG tests are sufficiently large for lead-I ECG devices to be cost effective in this specific population.

Study registration

The protocol for this review is registered on PROSPERO as CRD42018090375.

Funding

This Diagnostics Assessment Report was commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence as project number 16/30/05.

1 BACKGROUND

1.1 Description of the target condition

Atrial fibrillation (AF) refers to a disturbance in heart rhythm (arrhythmia) that is caused by abnormal electrical activity in the upper chambers of the heart (atria).[1] The arrhythmia reduces the efficiency of the heart to move blood into the ventricles, increasing the risk of blood clots and consequent stroke.[1] AF is associated with conditions such as hypertension, heart failure, coronary artery disease, valvular heart disease, obesity, diabetes mellitus and chronic kidney disease.[2]

1.1.1 Types of atrial fibrillation

Three types of AF (based on presentation and duration of the arrhythmia) are described in Table 1.

Table 1 Types of atrial fibrillation

Type of AF	Description
Paroxysmal (intermittent)	Intermittent episodes that usually last less than 7 days and stop without treatment
Persistent	Episodes that last longer than 7 days and do not terminate without treatment
Permanent	Present all the time

Source: NICE CG180[3]

AF can be categorised as valvular or non-valvular for the purposes of choosing the most suitable treatment. Categorisation as valvular or non-valvular refers to the underlying condition causing AF (i.e. whether there is valve disease present or not) rather than the duration of AF episodes. Both valvular and non-valvular AF can be paroxysmal, persistent or permanent. Patients diagnosed with paroxysmal AF may develop persistent or permanent AF.[2] It is also possible, but most unusual, for some people with persistent AF to revert to normal sinus rhythm.[2]

1.1.2 Symptoms of atrial fibrillation

Patients with AF may experience palpitations, dizziness, shortness of breath and tiredness. However, AF can be asymptomatic and may only be identified when people attend medical appointments for conditions other than AF. Due to the intermittent nature of the symptoms, many cases of paroxysmal AF remain undiagnosed.[2] Cases of paroxysmal AF may only be detected as a consequence of a prolonged monitoring period, rather than through a single examination.[2]

1.1.3 Epidemiology

AF is the most common type of cardiac arrhythmia. Estimates from 2010 suggested that worldwide, 20.9 million men and 12.6 million women were living with AF.[2] Higher rates of AF

are recorded in developed compared with undeveloped countries, however this may be due to reporting differences.[2] Higher rates of AF are recorded in people Western countries (estimated incidence rate of 9.03 per 1000 patients years)[4] compared with people in Asian countries (estimated incidence rate of 5.38 per 1000 patients years).[5] Despite a higher exposure to AF potential risk factors such as hypertension or obesity, African Americans were found to have a lower age and sex-adjusted risk of being diagnosed with AF compared with white Americans.[6]

In the 2016 European Society of Cardiology (ESC) guidelines, the prevalence of AF in the European Union is reported to be 3%.[2] The ESC also notes that one in four middle-aged people in Europe and the US will develop AF.[2] The prevalence of AF in Europe is projected to increase over time due to the ageing population, increases in incidences of conditions associated with AF and improvements in the detection of AF.[2]

The overall age-adjusted incidence of AF per 1000 person years in UK primary care setting has increased from 1.11 (95% confidence interval [CI]: 1.09 to 1.13) in 1998–2001 to 1.33 (95% CI: 1.31 to 1.35) in 2007–2010, with ongoing increases in incidence in people aged 75 years and older.[7]

In the NHS Quality and Outcomes Framework for 2015 to 2016, the prevalence of AF in England is estimated to be 1.7%, which equates to 985,000 people.[8] However, as noted, AF can be asymptomatic and 1.7% may be an underestimate of the true prevalence.[9] Based on a reference population in a region of Sweden, Public Health England has estimated that the true prevalence of AF in England is likely to be 2.5% and that 1.4 million people in England are living with AF.[10] The most recent data from the NHS Quality and Outcomes Framework for 2016 to 2017 indicate that the prevalence of AF in England is 1.8%, equating to 1,066,000 people.[8] An assessment of electronic primary care records identified an increase in the prevalence of AF in the UK from 2.14% in 2000 to 3.29% in 2016 in those aged 35 years and older.[11]

The prevalence of AF increases with age and a higher proportion of men than women live with the condition (2.9% and 2.0%, respectively).[10] The median age at which people are diagnosed with AF is 75 years.[10] The highest number of cases of AF in males occurs between the ages of 75 to 79 years and, in females, the highest number of AF diagnoses occurs between the ages of 80 to 84 years.[10] Although fewer women than men have AF, women have greater mortality than men due to AF-related strokes.[10]

Cases of paroxysmal AF are estimated to comprise between 25% and 62% of cases of AF treated in hospitals and GP practices.[12] Patients with paroxysmal AF tend to be younger and

have fewer co-morbidities (for example, hypertension or congestive heart failure) than patients with persistent or permanent AF.[12,13]

1.1.4 Impact of atrial fibrillation

Untreated AF is a major risk factor for stroke. AF is associated with a five-fold increase in the risk of stroke and a three-fold increase in the risk of congestive heart failure.[14] Strokes with AF as the underlying cause may be more severe than strokes unrelated to AF.[15] Each year in the UK, 100,000 people in the UK have a stroke and one in five of those strokes has AF as the underlying cause.[16]

There is evidence to suggest that there are differences in the risk of stroke between patients with paroxysmal, persistent and permanent AF, with paroxysmal AF carrying a lower risk of stroke than persistent or permanent AF.[17,18] The risk of stroke is similar for patients with symptomatic and asymptomatic AF.[19]

The ESC reports that, annually, between 10% and 40% of patients with AF are hospitalised and that patients with AF have impaired health-related quality of life (HRQoL), regardless of co-existing cardiovascular conditions.[2] Cognitive decline and vascular dementia are common conditions arising from the onset of AF.[2]

1.1.5 Current diagnostic and treatment pathways

The National Institute for Health and Care Excellence (NICE) clinical guideline CG180[3] provides recommendations for the diagnosis and management of AF. An update of CG180[3] is in progress.

Diagnosis of atrial fibrillation

In CG180,[3] NICE recommends the use of manual pulse palpation to detect the presence of an irregular pulse that may indicate underlying AF in people who have symptoms such as breathlessness/dyspnoea, palpitations, syncope/dizziness, chest discomfort, previous stroke or suspected transient ischaemic attack.

Clinical experts commented during the scoping stage for this assessment that people presenting with a stroke or transient ischaemic attack would have electrocardiogram (ECG) testing for AF in secondary care and are, therefore, outside of the scope of an assessment focussing on diagnosis in primary care.

If AF is suspected because of an irregular pulse, NICE recommends[3] that the diagnosis should be confirmed based on the results of an ECG. People who have suspected paroxysmal AF that is not detected by the ECG should be monitored with either a 24-hour ambulatory monitor, or an event recorder ECG. People with confirmed AF may also undergo echocardiography to

further inform the management of their condition. The current diagnostic pathway for people presenting to primary care with signs or symptoms of the condition and who have an irregular pulse is depicted in Figure 1.

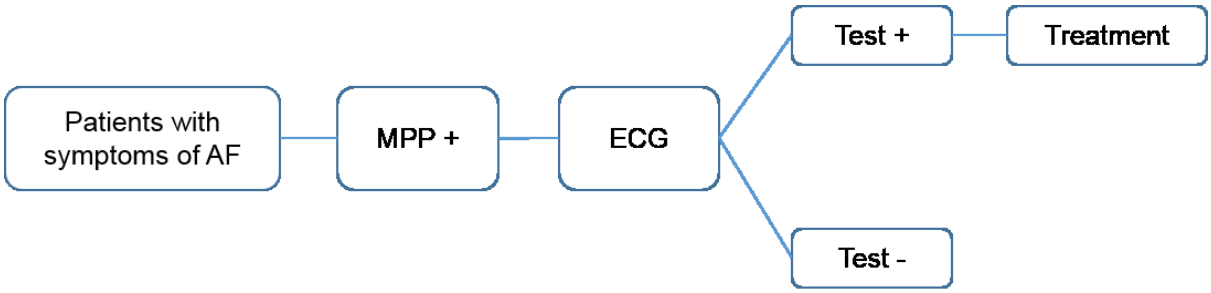

Figure 1 Current clinical pathway

AF=atrial fibrillation; ECG=electrocardiogram, MPP=manual pulse palpation

Management of atrial fibrillation

An overview of the treatment pathway described in CG180[3] is provided in Figure 2. As shown in Figure 2, the management of AF is subdivided into four algorithms.

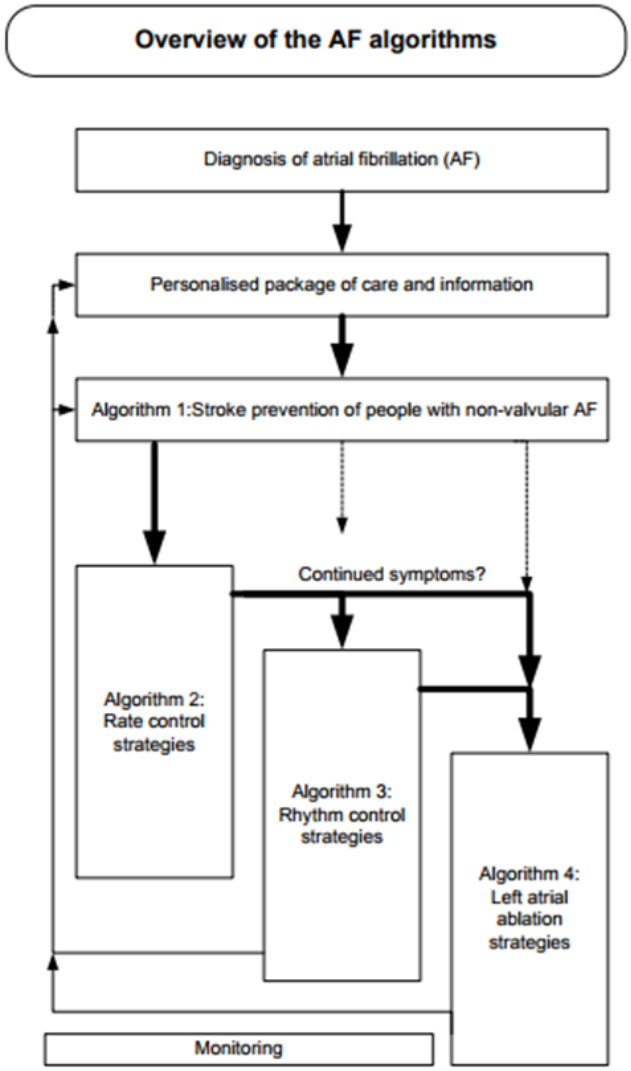

Figure 2 Overview of atrial fibrillation algorithms

Source: NICE CG180[3]

The aim of treatment is to reduce the symptoms of AF and prevent the potential consequences of undiagnosed AF, such as stroke.[3]

Reducing stroke risk

In CG180,[3] NICE recommends that patients with AF should be assessed for their risk of stroke and their risk of bleeding. The risk of stroke should be assessed using the CHA_2DS_2VASc[20] algorithm (history of congestive heart failure, hypertension, age ≥75 [doubled], diabetes mellitus, prior stroke or transient ischemic attack [doubled], vascular disease, age 65–74, female) and the risk of bleeding should be assessed using the HAS-BLED[21] algorithm (hypertension, abnormal liver/renal function, stroke history, bleeding predisposition, labile international normalised ratio, age, drug/alcohol use).

Depending on the age of the patient, the results of the CHA_2DS_2VASc[20] assessment, and the results of the HAS-BLED[21] assessment, patients with non-valvular AF may be offered stroke prevention treatment with either a vitamin K antagonist (usually warfarin) or a non-vitamin K antagonist oral anticoagulant (NOAC), i.e. either apixaban, dabigatran etexilate, rivaroxaban or edoxaban.

Rate and rhythm control

In CG180,[3] NICE recommends (with some exceptions) that people with AF who need drug treatment as part of their rate control strategy should be offered either a standard beta-blocker or a rate-limiting calcium-channel blocker. Digoxin may be offered to sedentary people who have non-paroxysmal AF. If monotherapy does not control the AF symptoms, and the symptoms are due to poor ventricular rate control, dual therapy with any two of a beta-blocker, diltiazem or digoxin is recommended.[3] For rhythm control, NICE[3] recommends pharmacological treatment with or without electrical rhythm control (cardioversion).

In CG180,[3] NICE also recommends strategies for left atrial ablation to control AF.

1.2 Description of technologies under assessment

The technologies assessed (i.e. index tests) were lead-I ECG devices. Lead-I ECG devices are handheld instruments that can be used in primary care to detect AF at a single-time point in people who present with relevant signs and symptoms (i.e. palpitations, dizziness, shortness of breath and tiredness). Although lead-I ECG devices may also be used for ongoing or repeated testing for AF, and the diagnosis of non-AF conditions, this use is outside of the scope of this assessment.

Lead-I ECG devices feature touch electrodes, internal storage for ECG recordings, as well as software with an algorithm to interpret the ECG trace and indicate the presence of AF. Data from the lead-I ECG device can be uploaded to a computer to allow further analysis if necessary (e.g. in cases of paroxysmal AF).

The manufacturers of lead-I ECG devices all state that the diagnosis of AF should not be made using the algorithm alone, and that the ECG traces measured by the devices should be reviewed by a qualified healthcare professional. The use of lead-I ECG devices following detection of an irregular pulse by manual pulse palpation may allow people with AF to initiate and benefit from earlier treatment with anticoagulants instead of waiting for the results of a confirmatory 12-lead ECG as per current practice.

Five different lead-I ECG devices are included in the final scope issued by NICE: imPulse,[22] Kardia Mobile,[23] MyDiagnostick,[24] RhythmPad GP[25] and Zenicor ECG.[26] The features of each device are described in sections 1.2.1 to 1.2.5 respectively. All devices are CE marked.

1.2.1 imPulse (Plessey Semiconductors Ltd)

The imPulse (™) lead-I ECG device is provided with downloadable software for data analysis (imPulse Viewer) and a cable for charging the device. The ECG readings are taken by holding the device in both hands and placing each thumb on a separate sensor on the device for a pre-set length of time (from 30 seconds to 10 minutes). To operate, the device requires the associated software to be installed on a nearby PC or tablet. Data are transferred to hardware hosting the analytical software using Bluetooth, with the recorded ECG trace being displayed in real-time.

Once the recording has finished, the generated ECG trace can be saved in the imPulse viewer. Previously recorded readings can also be loaded into this viewer and ECG traces can be saved as a PDF. The software has an AF algorithm which analyses the reading and states whether AF is unlikely, possible or probable. In the event of a 'possible' or 'probable' result, the company recommends that the person should undergo further investigation, and that the algorithm should not be used for a definitive clinical diagnosis of AF.

1.2.2 Kardia Mobile (AliveCor Ltd)

The Kardia Mobile lead-I ECG device works with the Kardia Mobile app to record and interpret ECGs. In addition to the Kardia Mobile device and app (which is free to download), a compatible Android or Apple smartphone or tablet is required.

Two fingers from each hand are placed on the Kardia Mobile device to record an ECG that is sent wirelessly to the device hosting the Kardia Mobile app. The default length of recording is 30 seconds; however, this can be extended up to 5 minutes. The measured ECG trace is then automatically transmitted as an anonymous file to a European server for storage as an encrypted file.

The app uses an algorithm to classify measured ECG traces as either (i) normal, (ii) possible AF detected, or (iii) unclassified. The instructions for use state that the Kardia Mobile app assesses the patient for AF only, and the device will not detect other cardiac arrhythmias. Any detected non-AF arrhythmias, including sinus tachycardia, are labelled as unclassified. The company states that any ECG labelled as 'possible AF' or 'unclassified' should be reviewed by a cardiologist or trained healthcare professional. ECG traces measured by the device can be sent from a smartphone or tablet by email as a PDF attachment and stored in the patient's records. The first version of the Kardia app did not have automatic diagnostic functionality. The AF algorithm was added to the app in January 2015. The Kardia Mobile has previously been available as the AliveCor Heart Monitor.

1.2.3 MyDiagnostick (Mydiagnostick Medical B.V.)

The MyDiagnostick lead-I ECG recording is generated after a patient holds the metal handles at each end of the device for 1 minute. A light on the device will turn green if no AF is detected, or turn red if AF is detected. If an error occurs during the reading the device produces both an audible warning and a visible warning from the light on the device. Up to 140 ECG recordings can be recorded on the device before it starts to overwrite previous recordings. The MyDiagnostick device can be connected to a computer via a USB connection to download the generated ECG trace for review and storage using free software that can be downloaded from the MyDiagnostick website.

1.2.4 RhythmPad GP (Cardiocity)

The RhythmPad GP lead-I ECG readings are taken by placing the palms of both hands on the surface of the device for 30 seconds. Alternative configurations can be used if a person is unable to place their hands flat on the device, for example, if they have arthritis. The software needs to be installed on a device running Windows XP or a later version and which has a USB port. Data are transferred directly to a computer using the USB connection for storage on the device's hard drive in PDF format.

The software includes an algorithm that can determine if a person is in AF, or has bradycardia, tachycardia, sinus arrhythmia, premature ventricular contractions or right bundle branch block. The recorded ECG trace is also available for further analysis by a healthcare professional. The company recommends that a 12-lead ECG device is used to confirm a case of AF detected by the RhythmPad GP device.

1.2.5 Zenicor-ECG (Zenicor Medical Systems AB)

The Zenicor-ECG is a system with two components: a lead-I ECG device (Zenicor-EKG 2) and an online system for analysis and storage (Zenicor-EKG Backend System version 3.2). The online system is not locally installed, the device transmits data to a remote server which can be accessed using a web browser without prior installation of software and requires a user licence. ECG readings are taken by placing both thumbs on the device for 30 seconds. The instructions for use state that the electrodes in the Zenicor EKG-2 should be replaced after every 500 measurements. The device is powered by three alkaline batteries which, the company states, are expected to last for at least 200 measurements and transmissions.

Once a measurement is made using the Zenicor-EKG 2 device, the ECG measurement can be transferred from the device (using a built-in mobile network modem) to a Zenicor server in Sweden. Here, the ECG trace is analysed using the Zenicor-EKG Backend System, which includes an automated algorithm. The algorithm categorises an ECG into one of 12 groups

corresponding to potential arrhythmias, one of which includes AF. The algorithm will also report if the recorded ECG trace cannot be analysed. The company states that a clinician needs to manually interpret the ECG trace generated by the Zenicor-ECG to make a final diagnosis of AF.

The measured ECG trace can be downloaded or printed as a PDF report. The company states that the ECG is available via the web-interface about 4 to 5 seconds after the ECG has been transmitted from the device.

The company states that the Zenicor EKG-2 does not store, contain, or transmit any patient identifiable information. ECGs are sent via the built-in mobile network modem to the Zenicor server labelled with the device's identity number. Communication between the Zenicor server and a web browser accessing it are encrypted.

1.3 Comparator

To evaluate the diagnostic accuracy of lead-I ECG devices, the comparator of interest is other lead-I ECG devices as described above or no comparator (please see Table 2 for further details). To evaluate the clinical impact of lead-I ECG devices, the comparator of interest is manual pulse palpation followed by a 12-lead ECG in primary or secondary care prior to initiation of anticoagulation therapy.

1.4 Reference standard

Index test results are compared to the results of a reference standard for the purposes of assessment of diagnostic test accuracy. The reference standard is used to verify the presence or absence of the target condition. The reference standard for this assessment is 12-lead ECG performed and interpreted by a trained healthcare professional.

1.5 Aim of the assessment

The aim of this assessment is to evaluate whether the use of lead-I ECG devices to detect AF in people presenting to primary care with signs or symptoms of the condition and who have an irregular pulse represents a cost effective use of NHS resources compared with manual pulse palpation followed by a 12-lead ECG in primary or secondary care prior to initiation of anticoagulation therapy.

2 METHODS FOR ASSESSING DIAGNOSTIC TEST ACCURACY AND CLINICAL IMPACT

Two systematic literature reviews were conducted to evaluate (1) the diagnostic test accuracy of single-time point lead-I ECG for the diagnosis of AF using 12-lead ECG as the reference standard in people with signs or symptoms that may indicate underlying AF and who have an irregular pulse, and (2) the clinical impact of single-time point lead-I ECG devices compared with manual pulse palpation (MPP) followed by a 12-lead ECG (in primary or secondary care). The systematic review methods followed the general principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for conducting reviews in health care,[27] NICE's Diagnostics Assessment Programme manual[28] and the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.[29] The systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for diagnostic test accuracy (DTA) studies.[30] The PRISMA-DTA checklist and PRISMA-DTA for abstracts checklist are presented in Appendix 1 and Appendix 2 of this report respectively.

2.1 Search strategy

The search strategies were designed to focus on the specified devices (i.e. imPulse, Kardia Mobile, MyDiagnostick, RhythmPad GP and Zenicor ECG) and target condition (i.e. AF). No study design filters were applied and all electronic databases were searched from inception until 9th March 2018. The search strategy used for the MEDLINE database is presented in Appendix 3 of this report. The MEDLINE search strategy was adapted to enable similar searches of the other relevant electronic databases. The following databases were searched for relevant studies:

- MEDLINE (Ovid)
- MEDLINE Epub Ahead of Print and MEDLINE In-Process (Ovid)
- EMBASE (Ovid)
- PubMed
- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Central Database of Controlled Trials (CENTRAL)
- Database of Abstracts of Reviews of Effects (DARE) (Cochrane)
- Health Technology Assessment Database (HTA) (Cochrane)

The results of the searches were uploaded to, and managed, using EndNote X8 software. The reference lists of relevant systematic reviews and eligible studies were hand-searched to identify further potentially relevant studies. Data submitted by the manufacturers of the five lead-I ECG devices that are the focus of this assessment were considered for inclusion in the review.

2.2 Eligibility criteria

The eligibility criteria for the inclusion of studies assessing the clinical impact or diagnostic test accuracy of lead-I ECG devices are presented in Table 2.

Although the index test (i.e. test being evaluated) must have been performed in a primary care setting, studies in which the index tests were performed and interpreted by a cardiologist in a secondary or tertiary setting were eligible for inclusion as it is plausible that, in clinical practice, the test results could be sent for remote interpretation by a cardiologist.

Studies that assessed the diagnostic test accuracy or the clinical impact of lead-I ECG devices used at a single-time point to detect AF in an asymptomatic population were considered for inclusion if no studies were identified in symptomatic populations. We considered as an asymptomatic population, people not presenting with symptoms of AF, with or without a previous diagnosis of AF. These patients could have other cardiovascular comorbidities or could be attending a clinic for cardiovascular related reasons but not presenting with signs or symptoms of AF. The use of lead-I ECG devices for ongoing or repeated testing for AF is outside of the scope of this assessment.

Studies that did not present original data (i.e. reviews, editorials and opinion papers), case reports and non-English language studies were excluded from the review. Conference proceedings published from 2013 onwards were considered for inclusion.

Table 2 Eligibility criteria

Population	(1) People with signs or symptoms that may indicate underlying AF and who have an irregular pulse; (2) Asymptomatic population* if no evidence for (1) is available	
Setting	Primary care (ideal), secondary or tertiary care	
Index tests	Lead-I ECG using one of the following technologies: • imPulse • Kardia Mobile • MyDiagnostick • RhythmPad GP • Zenicor-ECG	
	Clinical impact	**Diagnostic test accuracy**
Comparator	Manual pulse palpation followed by a 12-lead ECG in primary or secondary care prior to initiation of anticoagulation therapy or other lead-I ECG devices as specified above	Other lead-I ECG devices as specified above, or no comparator
Reference standard	Not applicable	12-lead ECG performed and interpreted by a trained healthcare professional
Outcomes (at least one)	Intermediate outcomes • Time to diagnosis of AF • Time to initiation of preventative treatment (such as interventions to prevent stroke) • Concordance between lead-I ECG devices • Test failure rate • Time to complete testing and store produced ECG trace • Ease of use of devices (for patients and healthcare professionals), including training requirements • Impact of test results on clinical decision making • Number of 12-lead ECGs carried out • Diagnostic yield (number of AF diagnoses)	Diagnostic test accuracy • Numbers of true positive, false negative, false positive and true negative test results
	Clinical outcomes • Mortality • Morbidity (including stroke, other thromboembolisms and heart failure, and any complications arising from preventative treatments, such as adverse effects of anti-arrhythmic, rate control or anticoagulation treatment)	
	Patient-reported outcomes • Health-related quality of life • Acceptability of the devices	
Study design	RCTs, cross-sectional, case-control, cohort studies and uncontrolled single arm studies. Qualitative studies were considered to evaluate the ease of use of the devices	Diagnostic cross-sectional and case-control studies

AF=atrial fibrillation; ECG=electrocardiogram; RCT=randomised controlled trial
* Asymptomatic population defined as people presenting with no symptoms of AF, with or without previously diagnosed AF

2.3 Study selection

The citations identified were assessed for inclusion in the review using a two stage process. First, two reviewers independently screened all the titles and abstracts identified by the electronic searches to identify the potentially relevant articles to be retrieved. Second, full-text copies of these studies were obtained and assessed independently by two reviewers for inclusion using the eligibility criteria outlined in Table 2. Any disagreements were resolved through discussion at each stage, and, if necessary, in consultation with a third reviewer.

2.4 Data extraction

A data extraction form was designed, piloted and finalised to enable data extraction relating to study authors and year of publication, study design, characteristics of study participants, prevalence of comorbidities, prevalence of AF by type, characteristics of the index, comparator and reference standard test (including length of monitoring, who performed and interpreted the test), the order in which the index and comparator / reference standard test were performed, whether the person who interpreted the reference standard test was blind to the results of the index test, and the outcome measures as described in Table 2.

Data extraction was performed by one reviewer and checked for accuracy by a second reviewer. Any disagreements were resolved through discussion, and, if necessary, in consultation with a third reviewer. The manufacturers of the index tests and the corresponding authors of the studies selected for assessment of diagnostic test accuracy were contacted for missing data or clarification of the data presented.

2.5 Quality assessment

The methodological quality of diagnostic test accuracy studies was assessed using the QUality Assessment of Diagnostic Accuracy Studies - 2 (QUADAS-2) tool tailored to the review question.[31] The QUADAS-2 tool considers four domains: patient selection, index test(s), reference standard and flow of patients through the study and the timing of the tests.

The methodological quality of cross-sectional and case-control studies evaluating the clinical impact of lead-I ECGs was assessed using the Newcastle-Ottawa quality assessment scale.[32,33] We had planned to use the Cochrane Risk of Bias tool[34] to assess the methodological quality of randomised controlled trials (RCTs) of clinical impact but no RCTs were identified.[34]

Qualitative studies were assessed using the Critical Appraisal Skills Programme (CASP) tool.[35]

Quality assessment of the included studies was undertaken by one reviewer and checked by a second reviewer. Any disagreements were resolved by discussion, and, if necessary, in consultation with a third reviewer.

2.6 Methods of analysis/synthesis of diagnostic test accuracy studies

2.6.1 Statistical analysis and data synthesis

Individual study results

The sensitivity and specificity of each index test from studies of diagnostic accuracy were summarised in forest plots and plotted in receiver operating characteristic (ROC) space.

Meta-analysis

The bivariate model was used to obtain pooled estimates of sensitivity and specificity for lead-I ECG devices.[36] The pooled estimates for sensitivity and specificity were plotted in ROC space with a 95% confidence region around this summary estimate. The 95% confidence region depicts a range of sensitivity and specificity values within which the analyst can be 95% confident that the true sensitivity and specificity values for the index test lie.

The analyses were stratified by whether diagnosis of AF was made by a trained healthcare professional interpreting the lead-I ECG trace, or by the lead-I ECG algorithm. Within these stratified analyses, it was not possible to compare the diagnostic accuracy of different types of lead-I ECG device by adding a covariate for device type, due to the sparsity of the data. We were also unable to perform subgroup analyses to assess the impact of potential sources of heterogeneity on the diagnostic accuracy of lead-I ECG devices due to sparsity of the data.

For one study[37] that reported data for two types of lead-I device (MyDiagnostick and Kardia Mobile) and for two different interpreters of lead-I and 12-lead ECG traces for the same patient cohort, we performed multiple analyses so that we could investigate the impact of varying the type of lead-I ECG device and interpreter on the results of the overall pooled analysis. Therefore, no set of patients was double-counted in any of the meta-analyses performed. The data for lead-I ECG device (MyDiagnostick defined as device 1 and Kardia Mobile defined to be device 2) and electrophysiologist (1 or 2) that were included in the main analysis were randomly selected using the command r(uniform) in Stata version 14 to randomly generate the number 1 or 2 first for device, followed by electrophysiologist. Additional analyses are presented as sensitivity analyses.

One study[38] reported data for one lead-I device (Kardia Mobile) and two different interpreters (cardiologist and a GP with an interest in cardiology) of lead-I and 12-lead ECG traces. The data interpreted by the cardiologist was used in the main analysis as the interpreters in the

other included studies were either cardiologists or electrophysiologists. The analysis with data interpreted by the GP is presented as a sensitivity analysis.

The bivariate model was fitted using the metandi and xtmelogit commands in Stata version 14. Summary receiver operating characteristic (SROC) plots were produced using RevMan 5.3. When there were few studies, the bivariate model was reduced to two univariate random effect logistic regression models by assuming no correlation between sensitivity and specificity across studies.[39] When little or no heterogeneity was observed on forest plots and SROC plots, the models were further simplified into fixed effect models by eliminating the random effects parameters for sensitivity and/or specificity.[39] Judgement of heterogeneity was based on the visual appearance of forest plots and SROC plots in addition to clinical judgement regarding potential sources of heterogeneity.

2.6.2 Sensitivity analyses

We had planned to conduct sensitivity analyses by excluding studies judged to have a high risk of bias, or if we were uncertain about the appropriateness of including some studies in the primary meta-analyses. Sensitivity analyses stratified by risk of bias of the studies was not performed due to the small number of studies included in the meta-analysis and similar risk of bias judgements across the studies.

2.7 Methods of analysis/synthesis of clinical impact studies

We had planned to perform meta-analysis of the clinical and intermediate outcomes stated in Table 2 if possible. After data extraction, we considered pooling data for the outcome of diagnostic yield. However, on examination of forest plots displaying diagnostic yield data for the included studies, we judged the data were to be too heterogeneous for pooling to give clinically meaningful results. Therefore, we produced forest plots displaying individual study results from all included studies and additional forest plots displaying individual study results stratified by device type, and by setting. These plots were produced in Stata 14, using the metaprop command.

2.8 Other considerations

'Real world' data describing the clinical impact of lead-I ECG devices were received from the Kent Surrey Sussex Academic Health Science Health Network (AHSN) and the data are included in Section 3.3.3.

3 RESULTS OF THE ASSESSMENT OF DIAGNOSTIC TEST ACCURACY AND CLINICAL IMPACT

3.1 Study selection

The searches of the electronic databases resulted in the identification of 1151 citations. After the removal of duplicate records, we identified 915 potential citations. Following initial screening of titles and abstracts, 54 publications were considered to be potentially relevant and were retrieved to allow assessment of the full-text publication.

No studies were identified for the population of interest (i.e. people with signs or symptoms that may indicate underlying AF and who have an irregular pulse). Therefore, all the included studies assessed the diagnostic test accuracy and clinical impact of lead-I ECG devices used at a single-time point to detect AF in an asymptomatic population (see Section 2.2). We considered an asymptomatic population to comprise people not presenting with symptoms of AF, with or without a previous diagnosis of AF. These patients could have co-existing cardiovascular conditions or could be attending a clinic for cardiovascular related reasons but not presenting with signs or symptoms of AF.

After review of the full-text publication, 13 publications[37,38,40-50] reporting on nine studies were included in the diagnostic test accuracy review and 24 publications[37,40-47,50-64] reporting on 19 studies were included in the clinical impact review. Where there were overlaps in data and reporting due to studies being reported in several papers and abstracts, we selected the publication with the most complete data and treated it as the main publication. The PRISMA[65] flow chart detailing the screening process for the review is shown in Figure 3. Studies excluded at the full-text paper screening stage with reasons for exclusion are presented in Appendix 4.

We contacted the authors of three studies[46,49,50] to obtain additional data on diagnostic test accuracy or clarify the data on diagnostic test accuracy reported in the publication, one set of authors provided additional information that allowed their study[46] to be included in the diagnostic test accuracy meta-analysis. One set of authors also provided additional information on their study,[49] but stated the algorithm had been modified since the study was reported. For this reason, the sensitivity and specificity of the lead-I ECG device used are presented but not included in the meta-analysis.

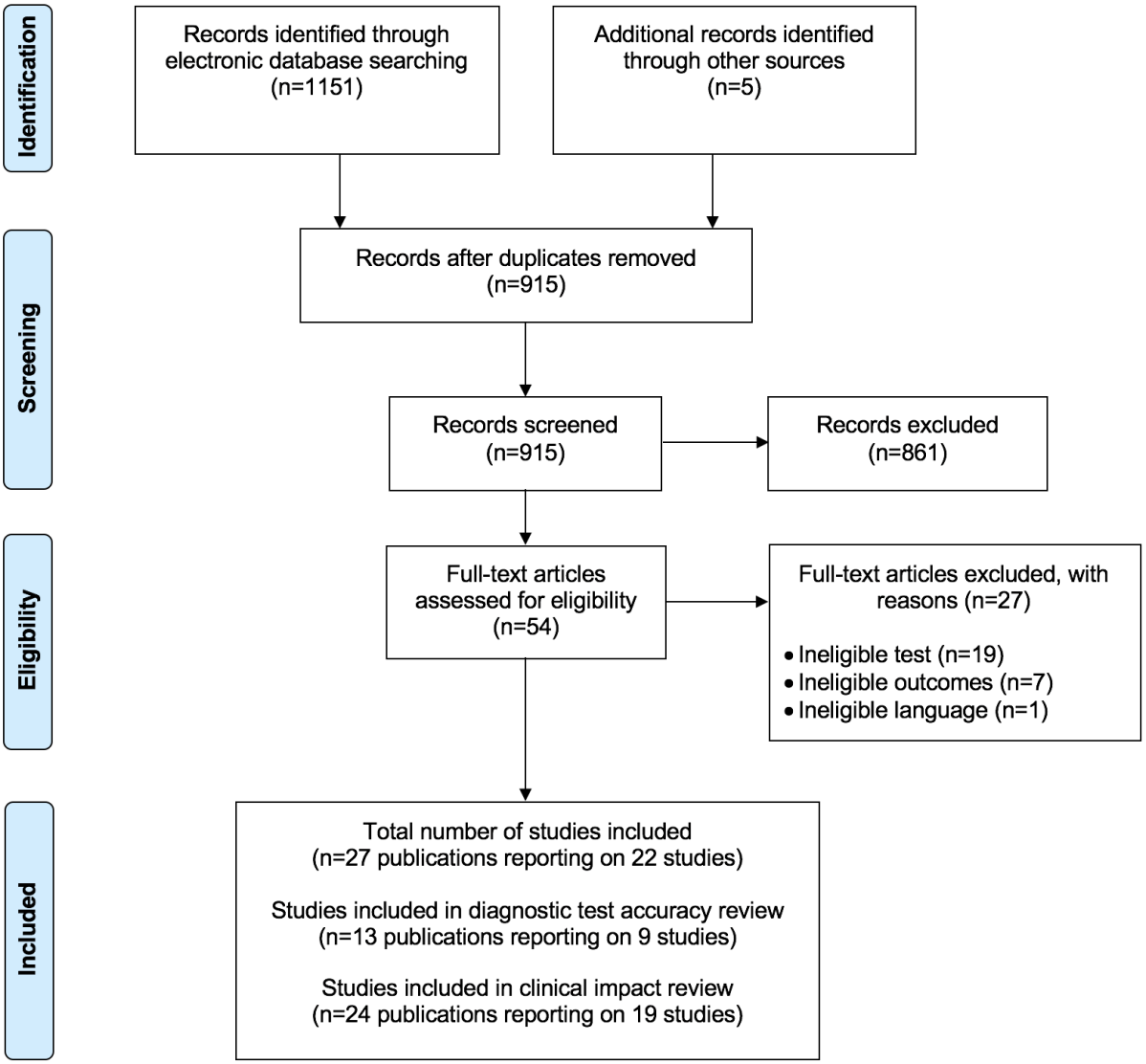

Figure 3 PRISMA flow chart

3.2 Assessment of diagnostic test accuracy

3.2.1 Characteristics of the included studies

The characteristics of the nine included diagnostic test accuracy studies are summarised in Table 3.

Table 3 Characteristics of studies included in the diagnostic test accuracy review

Study	Study design; country and setting	Population; number in analysis and recruitment details	Age; sex and risk factors for AF	Lead-I ECG device	Interpreter of lead-I ECG	Test sequence
Crockford 2013[49]	Cross-sectional; UK; secondary care	Patients referred to an electrophysiology department; N=176; NR	Age; sex and risk factors: NR	RhythmPad GP	Algorithm	12-lead ECG followed by lead-I ECG
Desteghe 2017[37]	Case-control; Belgium; tertiary care	Inpatients at cardiology ward; N=265; NR	Mean age ± SD (years): 67.9 ± 14.6 Sex: 138 (43.1%) female Pacemaker: 4/55 (7.3%) were intermittently paced, and 18/55 (32.7%) were not being paced during the recordings Known AF: 114/320 (35.6%) AF at time of study: 11.9% on 12-lead ECG; 3.4% of all patients admitted because of symptomatic AF Paroxysmal AF: 54.4%	MyDiagnostick and Kardia Mobile	Algorithm and two electrophysiologists (results presented separately for algorithm and two electrophysiologists)	12-lead ECG followed by lead-I ECG (order for the use of the different lead-I ECG tests not specified)
Doliwa 2009[42]	Case-control; Sweden; secondary care	People with AF, atrial flutter or sinus rhythm; N=100; patients were recruited from a cardiology outpatient clinic	Age; sex and risk factors: NR	Zenicor-ECG	Cardiologist	12-lead ECG followed by lead-I ECG
Haberman 2015[44]	Case-control; USA; community and secondary care	Healthy young adults, elite athletes and cardiology clinic patients; N=130; NR*	Mean age ± SD (years): 59 ± 15 Sex: 73 (56%) male Risk factors: NR	Kardia Mobile	Electrophysiologist	Lead-I ECG followed by 12-lead ECG
Koltowski 2017[50]	Cross-sectional; Poland; tertiary care	Patients in a tertiary care centre; N=100; NR	Age; sex and risk factors: NR	Kardia Mobile	Cardiologist	Lead-I ECG followed by 12-lead ECG
Lau 2013[46]	Case-control; Australia; secondary care	Patients at cardiology department; N=204; NR	Age and sex: NR Known AF: 48 (24%)	Kardia Mobile	Algorithm	Lead-I ECG followed by 12-lead ECG

Tieleman 2014[47]	Case-control; Netherlands; secondary care	Patients with known AF and patients without a history of AF attending an outpatient cardiology clinic or a specialised AF outpatient clinic; N=192; random selection of patients due to have a 12-lead ECG	Mean age ± SD (years): 69.4 ± 12.6 Sex: 48.4% male Risk factors: NR	MyDiagnostick	Algorithm	Lead-I ECG followed by 12-lead ECG
Vaes 2014[48]	Case-control; Belgium; primary care	Patients with known AF and patients without a history of AF; N=181; GP invitation	Mean age ± SD (years): 74.6 ± 9.7 Sex: 91 (48%) female Known AF: 151 (83.4%)	MyDiagnostick	Algorithm	Lead-I ECG followed by 12-lead ECG
Williams 2015[38]	Case-control; UK; secondary care	Patients with known AF attending an AF clinic and patients with AF status unknown who were attending the clinic for non-AF related reasons; N=95; patients attending clinic appointments who were due to have a 12-lead ECG	Age; sex and risk factors: NR	Kardia Mobile	Cardiologist and general practitioner with an interest in cardiology	12-lead and lead-I ECG carried out simultaneously

AF=atrial fibrillation; ECG=electrocardiogram; GP=general practice; NR=not reported; SD=standard deviation

* Community population not included in the analysis as these comprised healthy young adults and elite athletes; only secondary care patients were included in the analysis

The studies included in the diagnostic test accuracy review were either case-control studies[37,38,42,44,46-48] or cross-sectional studies.[49,50] Two of the studies were based in the UK.[38,49] Only one study was performed in primary care,[48] with the remaining studies being conducted in either secondary[38,42,44,46,47,49] or tertiary care.[37,50] All the studies either included patients with a known history of AF or recruited the patients from cardiology clinics. Only one study[37] presented the reasons for patient's admission to a cardiology department. There were 11 patients (3.4% of all patients) admitted because of symptomatic AF, all with a known history of AF. The study by Haberman[44] also included a community based population comprising of healthy young adults and elite athletes. Results of the healthy young adults and elite athletes were excluded from the analysis as they did not meet the population inclusion criteria for this review and do not represent the usual population with AF (i.e. age of 75 years or over).[10] The study by Lau[46] included a 'learning set' and data from this group were used to optimise the algorithm. The 'learning set' data were excluded from our analysis as, according to the author of the study [Ben Freedman, University of Sydney, 15th June 2018, personal communication], two separate cardiologists interpreted the rhythm strips, and interpretation by cardiologist A seemed to have a bias towards sensitivity, with a resultant lower specificity, while interpretation by cardiologist B had a slightly lower sensitivity, with a resulting higher specificity.

Only one study included results based on lead-I ECG interpretation by the device algorithm and a trained healthcare professional presenting the results separately for each interpreter.[37] One study[38] presented data for lead-I ECG trace interpreted by a cardiologist and a GP with an interest in cardiology, with the results separately for each interpreter. In four studies,[46-49] the lead-I ECG was interpreted by the device algorithm alone.

The lead-I ECG devices used in the included studies were Kardia Mobile,[38,44,46,50] MyDiagnostick,[47,48] RhythmPad GP[49] and Zenicor-ECG.[42] The study by Desteghe[37] used both Kardia Mobile and MyDiagnostick and presented the results separately for each device.

The trained healthcare professional interpreting the 12-lead ECG (i.e. reference standard) in all the studies included in the diagnostic test accuracy review were either a cardiologist[38,42,46-48,50], electrophysiologist[37,44,49] or a GP with an interest in cardiology.[38]

3.2.2 Quality assessment of diagnostic accuracy studies

All included studies were assessed for risk of bias and applicability using the QUADAS-2 tool. A summary of the results of the assessment of risk of bias and applicability concern across all studies is presented in Table 4. The full assessment for each included study is presented in Appendix 5.

Table 4 QUADAS-2 assessment of diagnostic test accuracy studies

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
* Crockford 2013[49]	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Desteghe 2017[37]	Unclear	Low	Low	Low	High	Low	Low
Doliwa 2009[42]	Unclear	Low	Low	Low	High	Low	Low
Haberman 2015[44]	Unclear	Unclear	Unclear	Low	High	Low	Low
** Koltowski 2017[50]	Unclear	Unclear	Unclear	Low	High	Unclear	Low
Lau 2013[46]	Unclear	Low	Low	Low	High	High	Low
Tieleman 2014[47]	Unclear	Low	Low	Low	High	High	Low
Vaes 2014[48]	Unclear	Low	Low	Unclear	High	High	Low
Williams 2015[38]	Unclear	Low	Low	Unclear	High	Low	Low

* The poster based on the conference proceeding by Crockford[49] was provided and used for the purposes of data extraction and quality assessment
** The study by Koltowski[50] was available only as a conference proceeding

All included studies were judged as having an unclear risk of bias for the patient selection domain. Only one study[47] reported the method for patient inclusion and there was an overall lack of information regarding patient eligibility for participation in the studies, and whether any patients were excluded at the stage of study selection. All of the included studies were judged to have a high applicability concern for patient selection as none of these studies were performed in the population of interest (i.e. people with signs or symptoms that may indicate underlying AF and who have an irregular pulse). One study[37] included a proportion (3.4%) of patients admitted to a cardiology department because of symptomatic AF, however all of these patients had a known history of AF.

Three studies[44,49,50] were judged to be at unclear risk of bias in the index test domain as there was lack of information as to whether the index tests were interpreted without knowledge of the reference standard test result. The remaining six studies[37,38,42,46-48] were judged to be at low risk of bias on the index test domain. Studies in which the index test was interpreted by a trained healthcare professional were judged to be more applicable (low concern)[37,38,42,44] than those interpreted by the lead-I ECG device algorithm alone.[46-48] Two studies[49,50] were judged to be of unclear applicability concern because of lack of information in the publication.

Three studies[44,49,50] were judged to be at unclear risk of bias for the reference standard domain because they did not explicitly report whether the interpreters of the reference standard were blinded to the results of the index test. The reference standard for all of the included studies

was a 12-lead ECG interpreted by a trained healthcare professional; therefore, all the studies were judged to have low concern regarding applicability of the reference standard.

Risk of bias was judged as unclear for three studies[38,48,49] for the flow and timing domain as, not all patients were included in the study analyses.

3.2.3 Diagnostic test accuracy results

Interpreter of lead-I ECG: trained healthcare professional

All lead-I ECG devices – main analysis

We investigated the sensitivity and specificity of a lead-I ECG device when the trace was interpreted by a trained healthcare professional and the reference standard was a 12-lead ECG interpreted by a trained healthcare professional. Data from four studies[37,38,42,44] were included in a meta-analysis. Two studies had data for Kardia Mobile alone,[38,44] one study had data for Zenicor-ECG[42] and one study had data for MyDiagnostick and Kardia Mobile.[37] One additional study[50] had data for Kardia Mobile but was not included in the pooled analysis as the numbers of true positive, false negative, false positive and true negative test results were not reported. The sensitivity and specificity values reported in this study[50] were 92.8% and 100% respectively. Four meta-analyses were conducted to investigate the impact of using data for each combination of type of lead-I ECG device (MyDiagnostick or Kardia Mobile) and interpreter (electrophysiologist 1 or electrophysiologist 2) from the Desteghe study[37] on the results of the meta-analysis. Both electrophysiologists interpreted the lead-I ECG trace and the 12-lead ECG trace. The data based on the use of Kardia Mobile lead-I ECG device and interpretation by electrophysiologist 1 were randomly selected to be included in the main analysis. Additional meta-analyses are presented as sensitivity analyses (Figure 6). One study[38] reported data for one lead-I device (Kardia Mobile) and two different interpreters (cardiologist and a GP with an interest in cardiology) of lead-I and 12-lead ECG traces. The data interpreted by the cardiologist was used in the main analysis as the interpreters in the other included studies were either cardiologists or electrophysiologists. The analysis with data interpreted by the GP is presented as a sensitivity analysis (Figure 10).

The forest plot displaying the results of the individual studies included in the meta-analysis are presented in Figure 4.

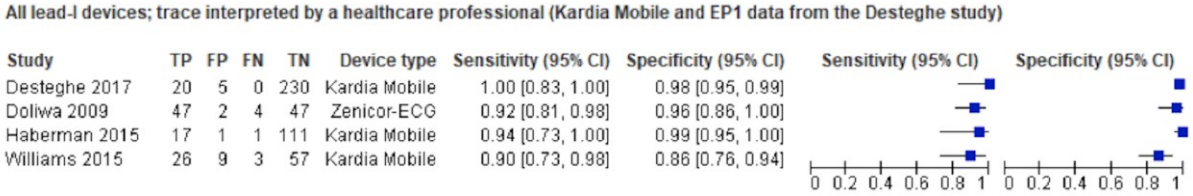

Figure 4 Forest plot of individual studies included in the meta-analysis of all lead-I ECG devices (trace interpreted by a trained healthcare professional)

CI=confidence interval; EP1=electrophysiologist 1; FN=false negative; FP=false positive; TN=true negative; TP=true positive

The SROC plot which shows the individual study results as well as the meta-analysis result is presented in Figure 5. Visual inspection of Figure 4 and the individual study results presented in Figure 5 show that the results were relatively homogenous between the included studies in this meta-analysis. However, due to some potential heterogeneity between studies, we adopted a conservative approach and used a bivariate model with random-effects in the meta-analysis.

This meta-analysis included 580 participants, of whom 118 had AF. The pooled sensitivity was 93.9% (95% CI: 86.2% to 97.4%) and pooled specificity was 96.5% (95% CI: 90.4% to 98.8%).

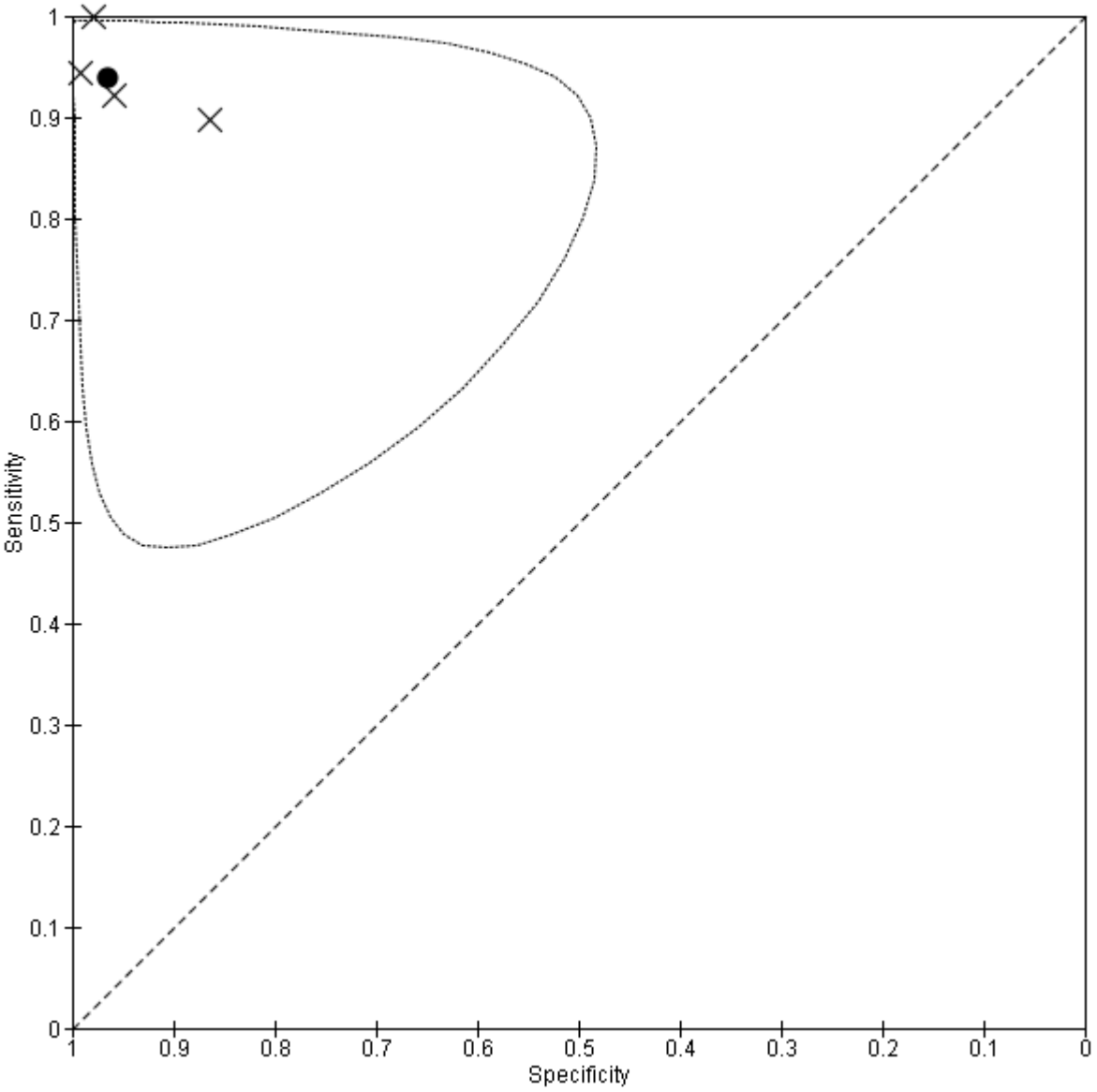

Figure 5 Summary receiver operating characteristic plot for lead-I ECG device as index test with trace interpreted by a trained healthcare professional and 12-lead ECG interpreted by a trained healthcare professional as reference standard (using Kardia Mobile lead-I ECG device and electrophysiologist 1 data from the Desteghe study)

X individual study result
● meta-analysis result
····· confidence region

All lead-I ECG devices – sensitivity analyses

Forest plots displaying the results of the individual studies included in the meta-analyses are presented in Figure 6.

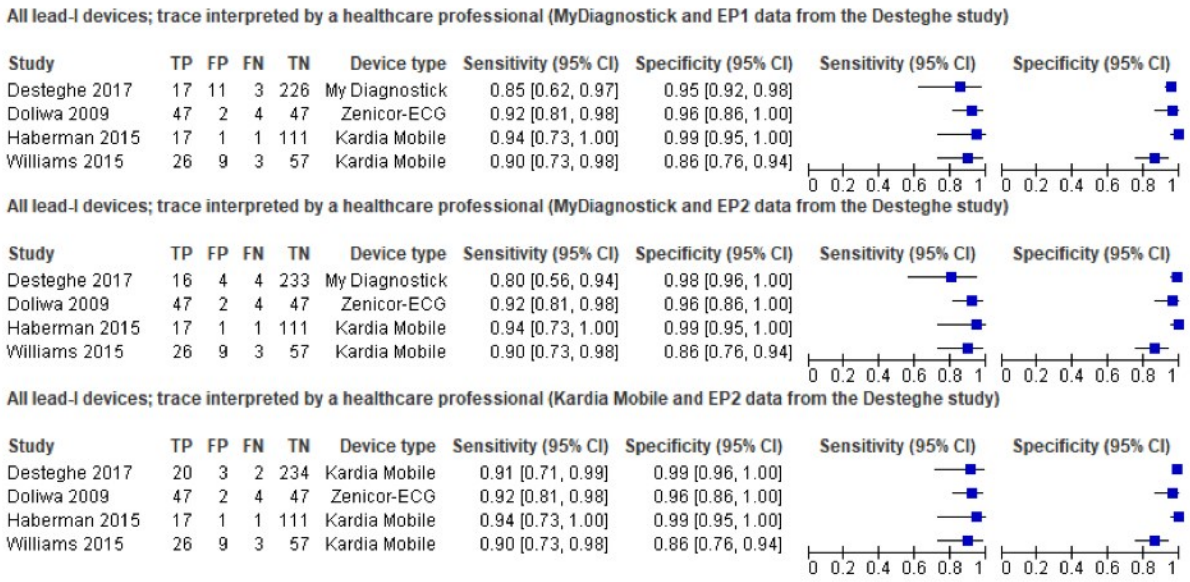

Figure 6 Forest plots of individual studies included in each meta-analysis of all lead-I ECG devices (trace interpreted by a trained healthcare professional)

CI=confidence interval; EP1=electrophysiologist 1; EP2=electrophysiologist 2; FN=false negative; FP=false positive; TN=true negative; TP=true positive

SROC plots are presented in Figures 7-9. Visual inspection of Figure 6 and the individual study results presented in Figure 7-9 show that the results were relatively homogenous across the included studies in these meta-analyses. However, due to some potential heterogeneity between studies, we adopted a conservative approach and used a bivariate model with random-effects in the meta-analysis.

Pooled sensitivity values from these additional meta-analyses ranged from 89.8% to 91.8%, while pooled specificity values ranged from 95.6% to 97.1% (Table 5). Overall, the use of Kardia Mobile or MyDiagnostick lead-I ECG and interpretation by the different electrophysiologists does not seem to make a difference to the pooled results. Considering only the Desteghe study,[37] specificity is similar across all combinations whereas the sensitivity of Kardia Mobile seems higher than the sensitivity of MyDiagnostick and EP1 seems to show slightly higher sensitivity than EP2.

Table 5 Results from the meta-analyses of all lead-I ECG devices (trace interpreted by a trained healthcare professional)

Data input from the Desteghe study[37]	# AF cases	N	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)
MyDiagnostick device and EP1 data	118	582	90.8% (83.8% to 95.0%)	95.6% (89.4% to 98.3%)
MyDiagnostick device and EP2 data	118	582	89.8% (82.7% to 94.1%)	96.8% (90.6% to 99.0%)
Kardia Mobile device and EP2 data	120	584	91.8% (85.1% to 95.7%)	97.1% (90.8% to 99.1%)

#=number of; AF=atrial fibrillation; CI=confidence interval; EP1=electrophysiologist 1; EP2=electrophysiologist 2

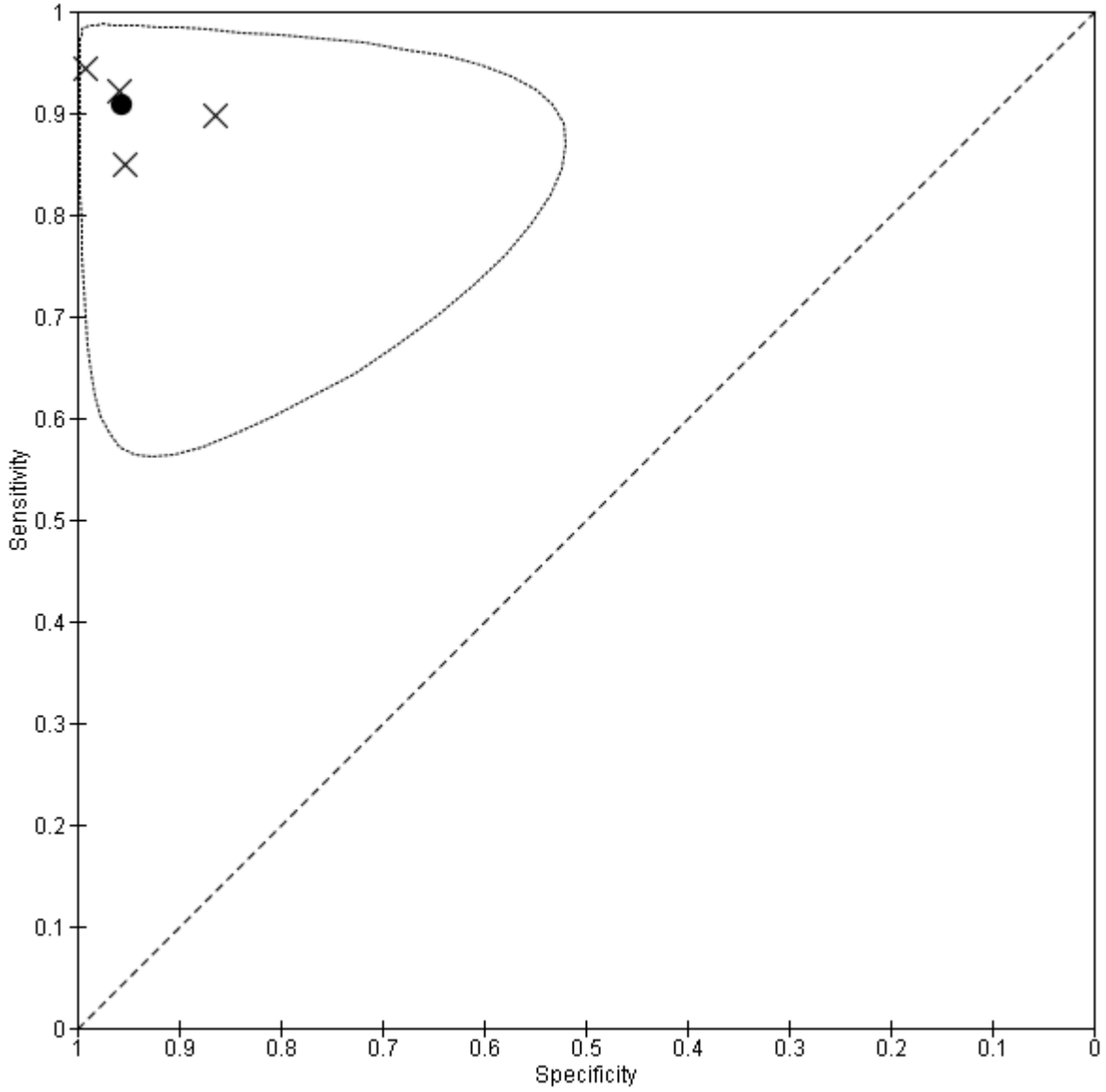

Figure 7 Summary receiver operating characteristic plot for lead-I ECG device as index test with trace interpreted by a trained healthcare professional and 12-lead ECG interpreted by a trained healthcare professional as reference standard (using MyDiagnostick lead-I ECG device and electrophysiologist 1 data from the Desteghe study)

X individual study result
● meta-analysis result
····· confidence region

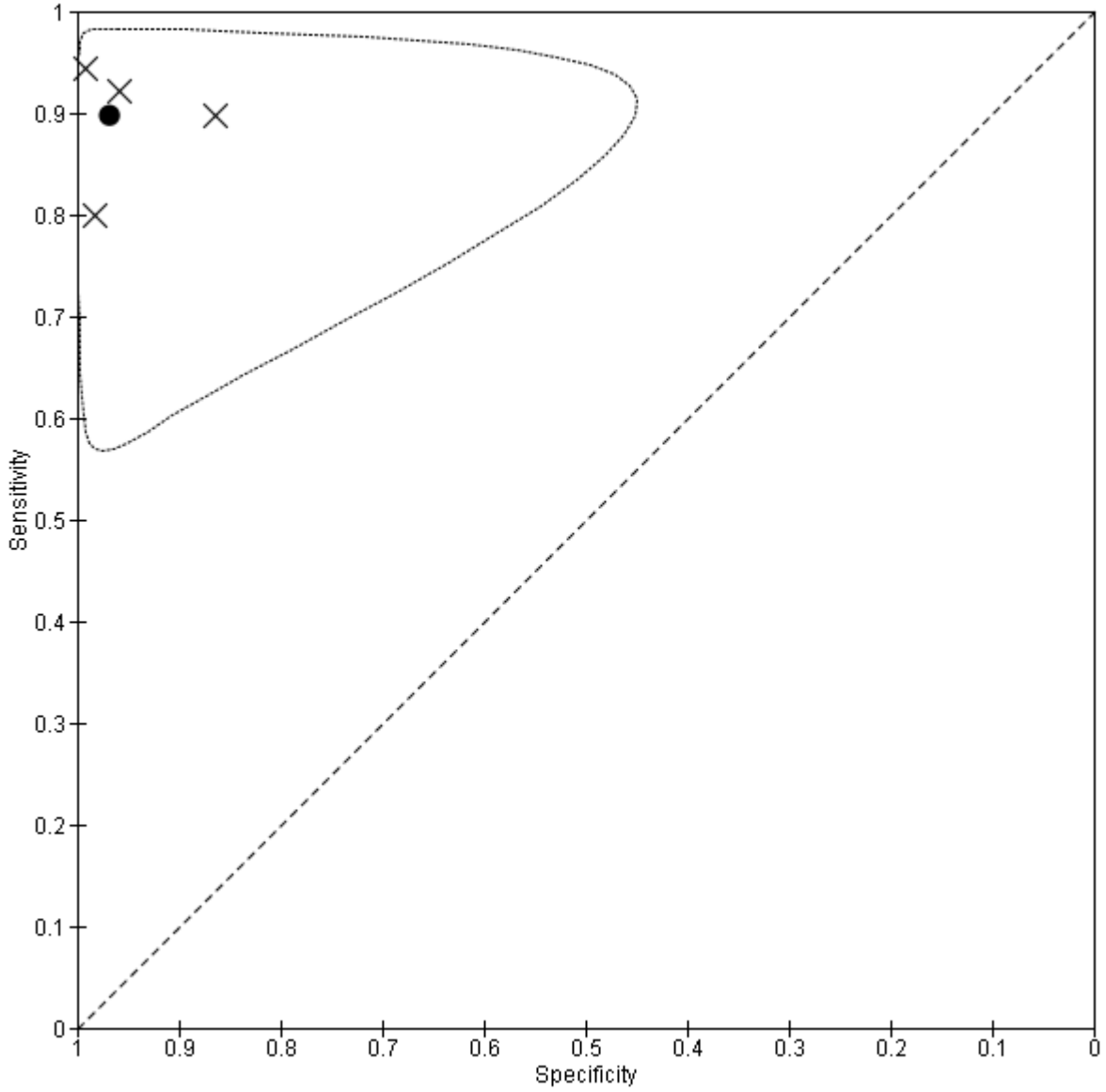

Figure 8 Summary receiver operating characteristic plot for lead-I ECG device as index test with trace interpreted by a trained healthcare professional and 12-lead ECG interpreted by a trained healthcare professional as reference standard (using MyDiagnostick lead-I ECG device and electrophysiologist 2 data from the Desteghe study)

X individual study result
● meta-analysis result
····· confidence region

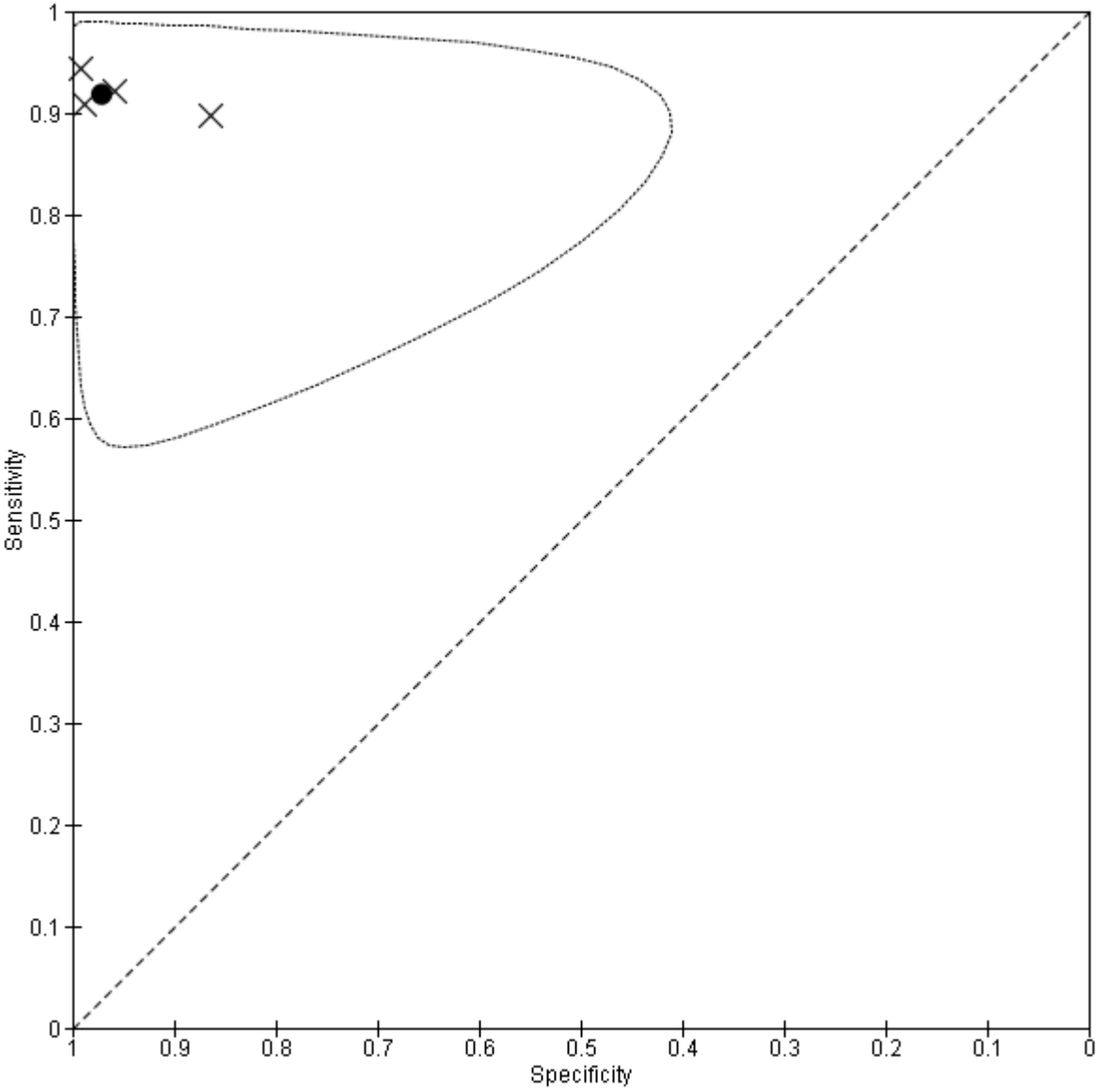

Figure 9 Summary receiver operating characteristic plot for lead-I ECG device as index test with trace interpreted by a trained healthcare professional and 12-lead ECG interpreted by a trained healthcare professional as reference standard (using Kardia Mobile lead-I ECG device and electrophysiologist 2 data from the Desteghe study)

X individual study result
● meta-analysis result
····· confidence region

One study[38] also presented data interpreted by a GP with an interest in cardiology for one lead-I device (Kardia Mobile) and these data were included in a sensitivity analysis. The forest plot displaying the results of the individual studies included in the meta-analysis is presented in Figure 10.

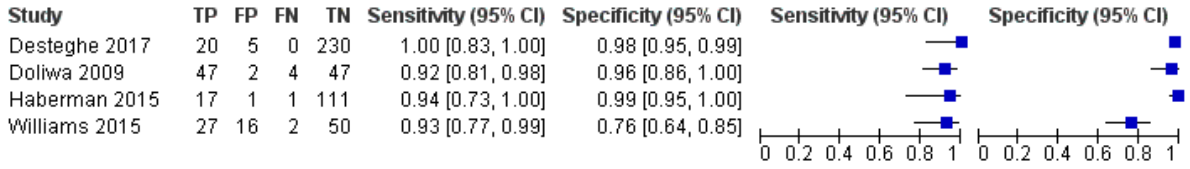

Figure 10 Forest plots of individual studies included in the meta-analysis with trace interpreted by a trained healthcare professional (using Kardia Mobile lead-I ECG device, EP1 data from the Desteghe study and trace interpreted by a GP in the Williams study)

CI=confidence interval; EP1=electrophysiologist 1; FN=false negative; FP=false positive; TN=true negative; TP=true positive

The SROC plot which shows the individual study results as well as the meta-analysis result is presented in Figure 11. Visual inspection of Figure 10 and the individual study results presented in Figure 11 show that the results were relatively homogenous across the included studies in this meta-analysis but specificity is lower (76%) when the lead-I ECG trace is interpreted by the GP in the Williams study[38] compared to the interpretation by a cardiologist (86%) (see Figure 4). Due to some potential heterogeneity between studies, we adopted a conservative approach and used a bivariate model with random-effects in the meta-analysis.

For this meta-analysis (number of AF cases=118, total N=580), the sensitivity was 94.3% (95% CI: 87.9% to 97.4%) and specificity was 96.0% (95% CI: 85.4% to 99.0%).

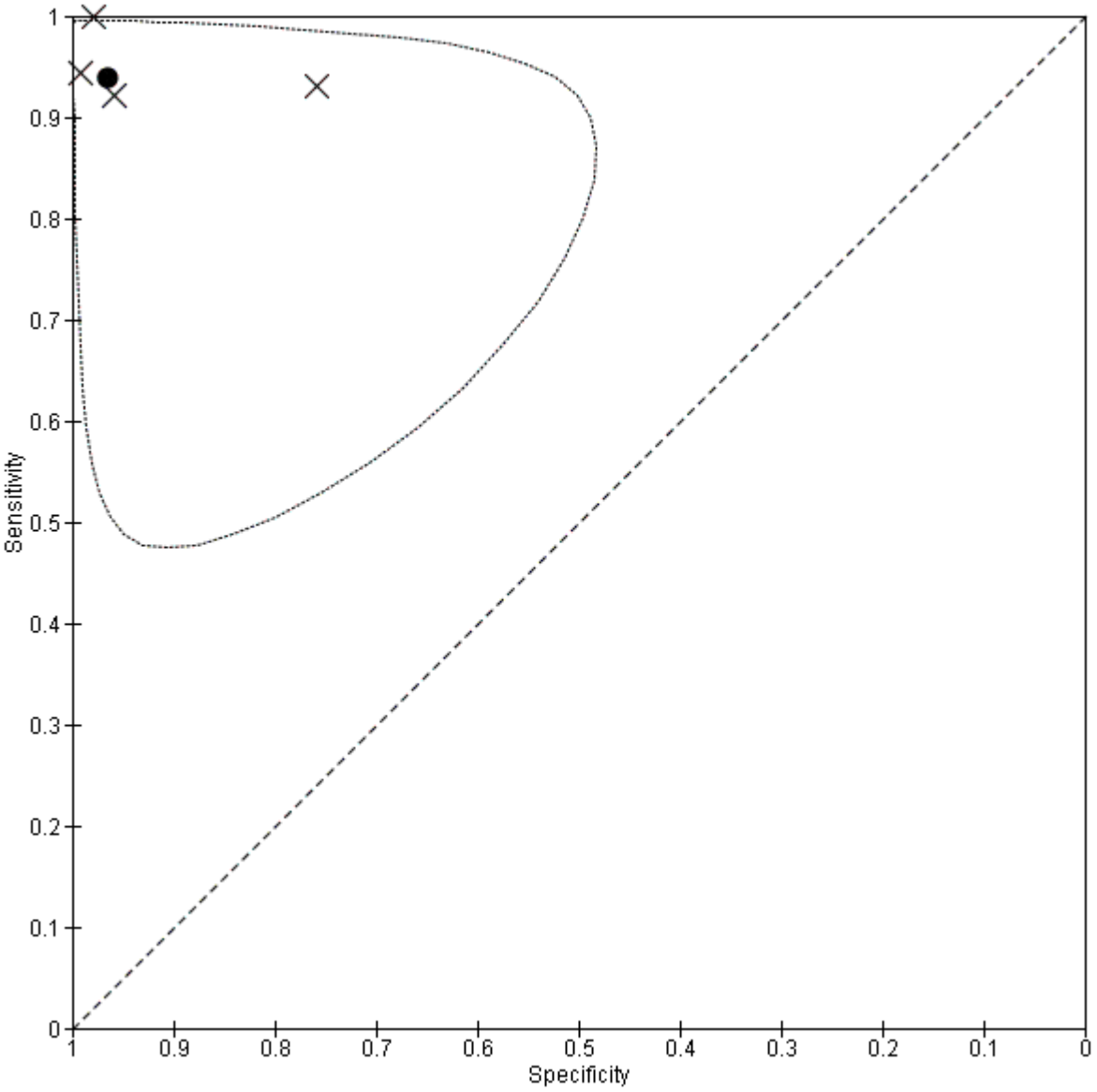

Figure 11 Summary receiver operating characteristic plot for lead-I ECG device as index test with trace interpreted by a trained healthcare professional (using Kardia Mobile lead-I ECG device, EP 1 data from the Desteghe study and trace interpreted by a GP in the Williams study)

X individual study result
● meta-analysis result
····· confidence region

Kardia Mobile lead-I ECG device

Data for the Kardia Mobile device only were derived from three studies.[37,38,44] We conducted two meta-analyses to investigate the impact of using data for each interpreter (electrophysiologist 1 or electrophysiologist 2) from the Desteghe study[37] on the results of the meta-analysis. Forest plots displaying the results of the individual studies included in each meta-analysis are presented in Figure 12.

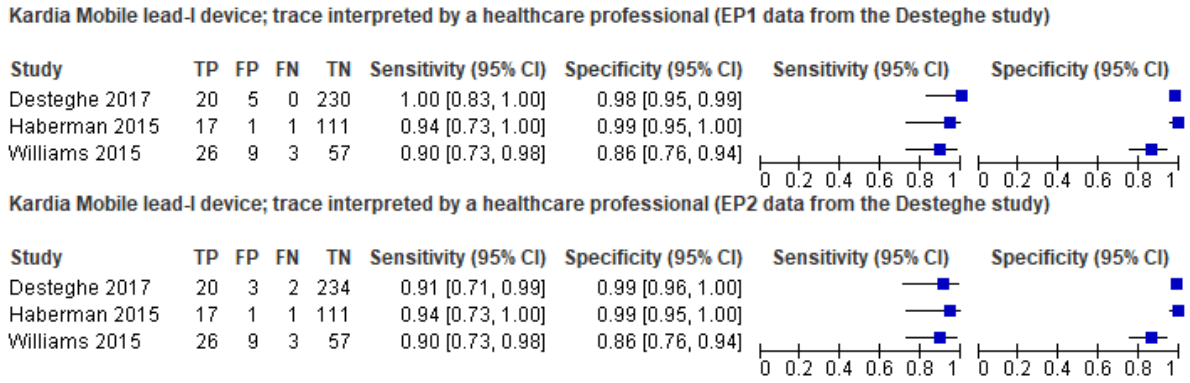

Figure 12 Forest plots of individual studies included in each meta-analysis of Kardia Mobile lead-I ECG device (trace interpreted by a trained healthcare professional)

For both meta-analyses, we fitted a univariate random effects logistic regression model for specificity and a univariate fixed effects logistic regression model for sensitivity as minimal variability in sensitivity was observed across the studies.

For the meta-analysis that included electrophysiologist 1 data from the Desteghe study[37] (number of AF cases=67, total N=480), sensitivity was 94.0% (95% CI: 85.1% to 97.7%) and specificity was 96.8% (95% CI: 88.0% to 99.2%). For the meta-analysis that included electrophysiologist 2 results from the Desteghe study[37] (number of AF cases=69, total N=484), sensitivity was lower (91.3% [95% CI: 82.0% to 96.0%]), while specificity was slightly higher (97.4% [95% CI: 88.3% to 99.5%]). As only three studies[37,38,44] were included in this analysis, it was not possible to produce confidence regions.

There were insufficient data to generate pooled estimates of sensitivity and specificity for other types of lead-I ECG device based on the interpreter of lead-I ECG being a trained healthcare professional, or to formally assess differences between different types of devices. The sensitivity and specificity estimates for Zenicor-ECG and MyDiagnostick lead-I ECG devices are presented in Figure 6.

Interpreter of lead-I ECG: algorithm

All lead-I ECG devices

We investigated the sensitivity and specificity of the lead-I ECG device when the trace was interpreted by the device algorithm alone. The reference standard was interpretation of the 12-lead ECG trace by a trained healthcare professional. Data from four studies[37,46-48] were included in a meta-analysis. Two studies had data for MyDiagnostick alone,[47,48] one study had data for Kardia Mobile alone[46] and one study had data for MyDiagnostick and Kardia Mobile.[37] One study[49] reported sensitivity (67%) and specificity (97%) for RhythmPad GP. Although the authors of this study[49] provided the numbers of true positive, false negative, false positive and

true negative test results, these were not included in the pooled analysis as the authors reported that the algorithm had since been modified [Chris Crockford, CardioCity, 3rd August 2018, personal communication via NICE]. We conducted two meta-analyses in order to investigate the impact of using data for each type of lead-I ECG device (MyDiagnostick or Kardia Mobile) from the Desteghe study[37] on the results of the initial meta-analysis. In the Desteghe study[37] the same patient cohort was tested using both lead-I ECG devices. We performed multiple analyses so that we could investigate the impact of varying the type of lead-I ECG device on the results of the overall pooled analysis and no set of patients was double-counted. Forest plots displaying the results of the individual studies included in each meta-analysis are presented in Figure 13.

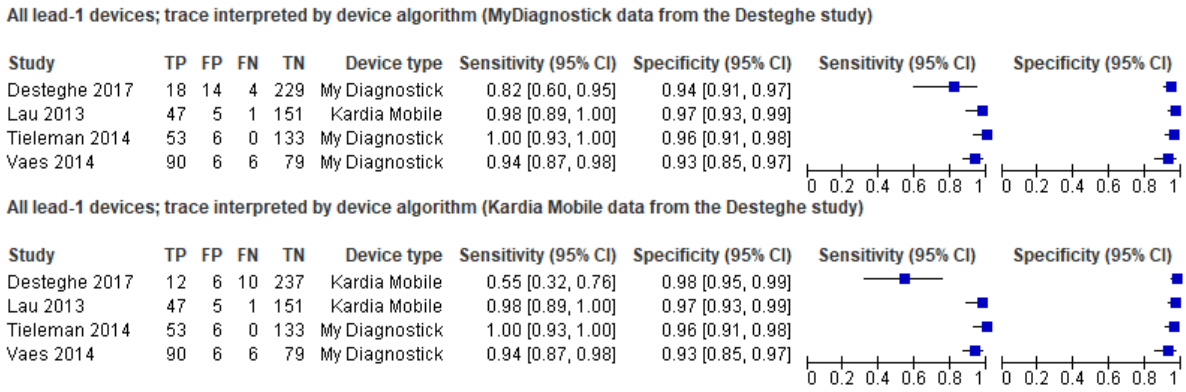

Figure 13 Forest plots of individual studies included in each meta-analysis of all lead-I ECG devices (trace interpreted by the device algorithm)

SROC plots are presented in Figure 14 and Figure 15. Results were relatively homogenous across the included studies in both meta-analyses. However, due to some potential heterogeneity between studies, we adopted a conservative approach and used a bivariate model with random-effects in the meta-analysis.

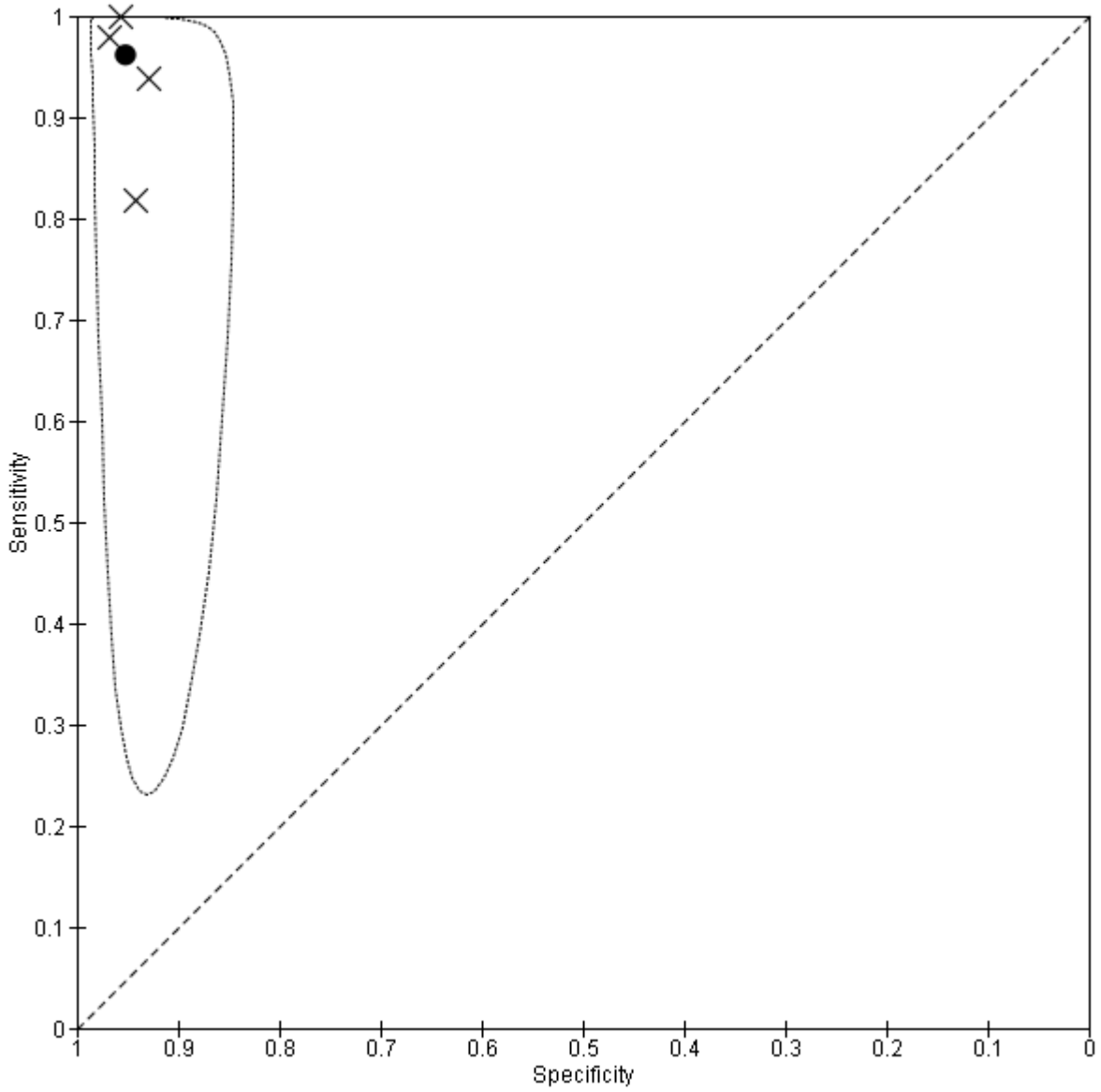

Figure 14 Summary receiver operating characteristic plot for lead-I ECG device as index test with trace interpreted by device algorithm and 12-lead ECG interpreted by a trained healthcare professional as reference standard (using MyDiagnostick lead-I ECG device data from the Desteghe study)

X individual study result
● meta-analysis result
····· confidence region

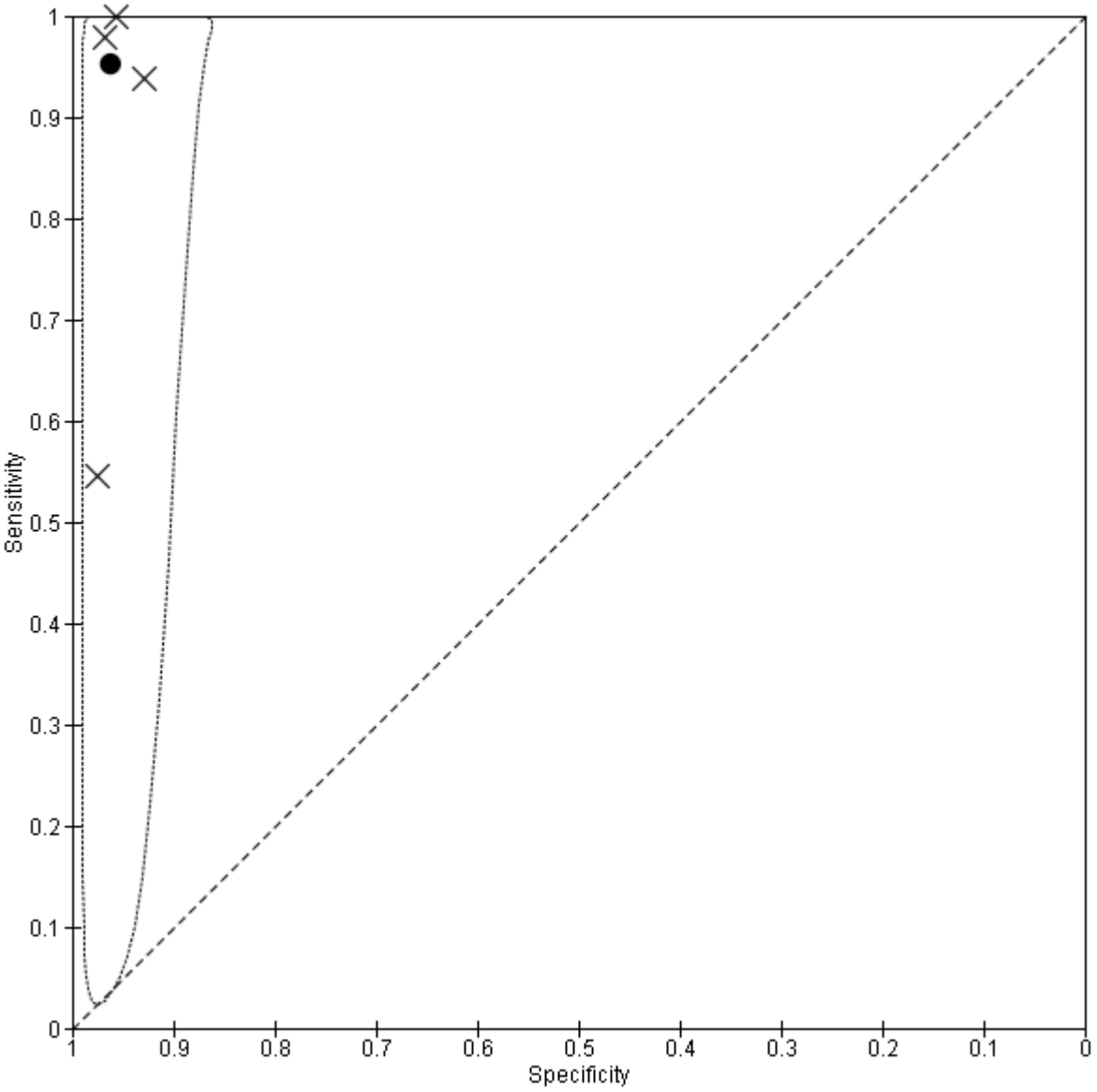

Figure 15 Summary receiver operating characteristic plot for lead-I ECG device as index test with trace interpreted by device algorithm and 12-lead ECG interpreted by a trained healthcare professional as reference standard (using Kardia Mobile lead-I ECG device data from the Desteghe study)

X individual study result
● meta-analysis result
····· confidence region

For the meta-analysis that included MyDiagnostick data from the Desteghe study[37] (number of AF cases=219, total N=842), sensitivity was 96.2% (95% CI: 86.0% to 99.0%) and specificity was 95.2% (95% CI: 92.9% to 96.8%). For the meta-analysis that included Kardia Mobile data from the Desteghe study[37] (number of AF cases=219, total N=842), pooled estimates for sensitivity (95.3% [95% CI: 70.4% to 99.4%]) and specificity (96.2% [95% CI: 94.2% to 97.6%]) were similar to those obtained from the meta-analysis including MyDiagnostick data from the Desteghe study.[37]

MyDiagnostick lead-I ECG device

A forest plot displaying the results of the individual studies included in this meta-analysis is presented in Figure 16.

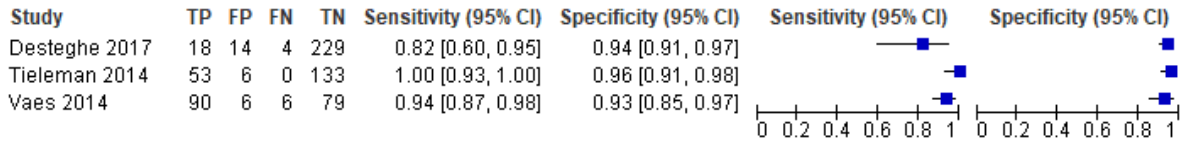

Figure 16 Forest plot displaying the results of individual studies included in the meta-analysis for MyDiagnostick lead-I ECG device with trace interpreted by device algorithm

As only three studies[37,47,48] were included in this analysis, it was not possible to produce an SROC plot with a confidence region.

For MyDiagnostick, data from three studies[37,47,48] (number of AF cases=171, total N=638) were included in the meta-analysis; sensitivity was 95.2% (95% CI: 79.0% to 99.1%) and specificity was 94.4% (95% CI: 91.9% to 96.2%). For this meta-analysis, we fitted a univariate random effects logistic regression model for sensitivity and a univariate fixed effect logistic regression model for specificity, as minimal variability in specificity was observed across studies. Results were relatively homogenous across the three included studies.

Kardia Mobile lead-I ECG device

We estimated sensitivity and specificity for the Kardia Mobile device, and for the MyDiagnostick device separately. A forest plot displaying the results of the individual studies included in this meta-analysis is presented in Figure 17. In the Desteghe study,[37] sensitivity (55% [95% CI: 32% to 76%]) was much lower than in the Lau study[46] (98% [95% CI: 89% to 100%]).

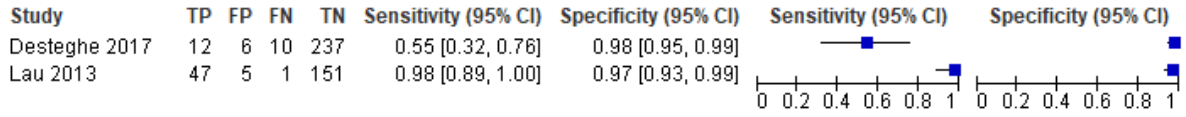

Figure 17 Forest plot displaying the results of individual studies included in the meta-analysis for Kardia Mobile lead-I ECG device with trace interpreted by device algorithm

As only two studies[37,46] were included in this analysis, it was not possible to produce an SROC plot with a confidence region.

For Kardia Mobile, data from two studies (number of AF cases=70, total N=469) were included in the meta-analysis; sensitivity was 88.0% (95% CI: 32.3% to 99.1%), and specificity was 97.2% (95% CI: 95.1% to 98.5%). For this meta-analysis, we fitted a univariate random effects

logistic regression model for sensitivity and a univariate fixed effect logistic regression model for specificity, as minimal variability in specificity was observed across studies.

Data were not sufficient to pool estimates of sensitivity and specificity for other types of lead-1 device based on the interpreter of lead-I ECG being a trained healthcare professional, or to formally assess differences between different types of devices.

3.2.4 Summary of findings: diagnostic test accuracy

No studies were identified that evaluated the diagnostic test accuracy of lead-I ECG devices in people presenting to primary care with signs and symptoms of AF and an irregular pulse.

Of the nine included studies, only one study[48] was conducted in primary care. The remaining eight studies were conducted in secondary, tertiary or community settings.

Of the nine included studies, only one study,[37] explicitly stated that some patients (n-11, 3.4%) had signs and symptoms of AF on admission to a cardiology ward. Another study,[48] included a large proportion of people with known AF (83.4%); however, it is not clear if the patients had signs and symptoms of AF at the time of the assessment and/or if the patients had been previously diagnosed with AF.

As pre-specified in the protocol,[66] due to a lack of evidence, we then focused the reviews on an asymptomatic population in any setting. We considered an asymptomatic population to comprise people not presenting with symptoms of AF, with or without a previous diagnosis of AF. These patients could have had co-existing cardiovascular conditions or could have been attending a cardiovascular clinic but did not present with signs or symptoms of AF. We identified 13 publications[37,38,40-50] reporting on nine studies assessing the diagnostic test accuracy of lead-I ECG devices in an asymptomatic population. However, all of these studies were judged to have a high applicability concern for patient selection as none were performed in the population and setting of interest.

We included studies where the interpreter of the lead-I ECG trace was a trained healthcare professional[37,38,42,44,50] and also studies that included interpretations of the lead-I ECG trace by the lead-I ECG device algorithm only.[37,46-49] The lead-I ECG devices used in the studies were Kardia Mobile,[38,44,46] MyDiagnostick[47,48] and Zenicor-ECG.[42] The study by Desteghe[37] used both Kardia Mobile and MyDiagnostick.

Results from the meta-analyses conducted are summarised in Table 6. Across all meta-analyses where the interpreter of the lead-I ECG trace was a trained healthcare professional, the sensitivity ranged from 89.8% to 94.3% and the specificity ranged from 95.6% to 97.4%. Across all meta-analyses where the interpreter of the lead-I ECG trace was the device algorithm, the sensitivity ranged from 88% to 96.2% and the specificity ranged from 94.4% to

97.2%. Pooled sensitivity and specificity values were similar across the different meta-analyses irrespective of interpreter of the lead-I ECG trace or lead-I ECG device used. However, it should be noted that studies in which the index test was interpreted by the lead-I ECG device algorithm alone were judged to have a high applicability concern for the index test domain. This judgment was based on the consideration made by all the manufacturers of lead-I ECG devices that the diagnosis of AF should not be made using the algorithm alone, and that the ECG traces measured by the devices should be reviewed by a qualified healthcare professional.

Details of the excluded studies and reasons for exclusion from the diagnostic test accuracy review, but which report sensitivity and specificity values for the lead-I ECG devices investigated in this assessment, are presented in Appendix 6. The diagnostic accuracy estimates that were used in the cost effectiveness assessment are presented in Table 16.

Table 6 Results from meta-analyses of lead-I ECG devices

Data input from the Desteghe* and Williams** studies	Lead-I ECG device (# studies) in the meta-analyses	# AF cases	N	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)
Lead-I ECG trace interpreted by a trained healthcare professional (main analysis)					
Kardia Mobile device and EP1* and cardiologist** data	Kardia Mobile (3), Zenicor-ECG (1)	118	580	93.9% (86.2% to 97.4%)	96.5% (90.4% to 98.8%)
Lead-I ECG trace interpreted by a trained healthcare professional (sensitivity analyses, cardiologist data)**					
MyDiagnostick device and EP1* data	Kardia Mobile (2), Zenicor-ECG (1), MyDiagnostick (1)	118	582	90.8% (83.8% to 95.0%)	95.6% (89.4% to 98.3%)
MyDiagnostick device and EP2 data	Kardia Mobile (2), Zenicor-ECG (1), MyDiagnostick (1)	118	582	89.8% (82.7% to 94.1%)	96.8% (90.6% to 99.0%)
Kardia Mobile device and EP2* data	Kardia Mobile (3), Zenicor-ECG (1)	120	584	91.8% (85.1% to 95.7%)	97.1% (90.8% to 99.1%)
Lead-I ECG trace interpreted by a trained healthcare professional (sensitivity analyses, GP data)**					
Kardia Mobile device and EP1* and GP** data	Kardia Mobile (3), Zenicor-ECG (1)	118	580	94.3% (87.9% to 97.4%)	96.0% (85.4% to 99.0%)
Lead-I ECG trace interpreted by a trained healthcare professional (sensitivity analyses, Kardia Mobile)					
Kardia Mobile device and EP1* data	Kardia Mobile (3)	67	480	94.0% (85.1% to 97.7%)	96.8% (88.0% to 99.2%)
Kardia Mobile device and EP2* data	Kardia Mobile (3)	69	484	91.3% (82.0% to 96.0%)	97.4% (88.3% to 99.5%)
Lead-I ECG trace interpreted by lead-I ECG device algorithm alone					
MyDiagnostick device* data	Kardia Mobile (1), MyDiagnostick (3)	219	842	96.2% (86.0% to 99.0%)	95.2% (92.9% to 96.8%)
Kardia Mobile device* data	Kardia Mobile (2), MyDiagnostick (2)	219	842	95.3% (70.4% to 99.4%)	96.2% (94.2% to 97.6%)
MyDiagnostick device only	MyDiagnostick (3)	171	638	95.2% (79.0% to 99.1%)	94.4% (91.9% to 96.2%)
Kardia Mobile device only	Kardia Mobile (2)	70	469	88.0% (32.3% to 99.1%)	97.2% (95.1% to 98.5%)

#=number of; AF=atrial fibrillation; CI=confidence interval; EP1=electrophysiologist 1; EP2=electrophysiologist 2; GP=general practitioner
* From the Desteghe study[37]
**From the Williams study[38]

3.3 Assessment of clinical impact

3.3.1 Characteristics of the included studies

The characteristics of the 18 quantitative studies included in the clinical impact review are summarised in Table 7. One qualitative study[52] included in the clinical impact review conducted semi-structured interviews with patients, receptionists, practice nurses and GPs.

Eleven of the studies included in the clinical impact review were cross-sectional studies,[50,51,53,55-58,60,62-64] while seven were case-control studies[37,42,44,46,47,59,61] and one study was qualitative.[52] Seven studies were conducted in primary care,[52,53,56-59,61] five in secondary care,[42,46,47,62,64] two in tertiary care[37,50] and the remaining four were conducted in a community setting.[51,55,60,63] One study[44] included participants recruited from secondary care, but also included (as separate groups) elite athletes and healthy young adults. As discussed in Section 3.2.1, the results for these populations[44] were excluded from the analysis as they did not meet our inclusion criteria for population and do not represent the usual population with AF (i.e. those aged 75 years or over).

Four studies included only people without known AF.[51,57,60,64] Three studies[53,58,63] may have included only people without known AF as participants were either attending a primary care clinic or the study was conducted in a community setting. However, these studies were only available as conference abstracts and did not provide sufficient information to enable us to determine whether the population did, or did not, have a history of AF. The remaining 11 studies recruited people with known AF, cardiovascular comorbidities or people who were attending a clinic for cardiovascular related reasons.[37,42,44,46,47,50,55,56,59,61,62]

Table 7 Characteristics of the quantitative studies included in the clinical impact review

Study	Study design; country and setting	Population; number in analysis and recruitment details	Age; sex and risk factors for AF	Lead-I ECG device	Interpreter of lead-I ECG	Test sequence
Battipaglia 2016[51]	Cross-sectional; UK; community	General population without known AF or implanted pacemaker; N=855; campaign for rhythm awareness in a shopping centre	Age; sex and risk factors: NR	MyDiagnostick	Cardiologist	NA
Chan 2016a[55]	Cross-sectional; China; community	People aged 18 or older; N=13,122; screening programme publicised via channels including media promotion and placement of posters in community centres by non-governmental organisations	Mean age ± SD (years): 64.7 ± 13.4 Sex: 9384 (71.5%) female Hypertension - 5012 (38.2%) Diabetes - 1944 (14.8%) Hyperlipidaemia - 2613 (19.9%) Heart failure - 97 (0.7%) Stroke - 367 (2.8%) Coronary artery disease - 295 (2.2%) Valvular heart disease - 114 (0.9%) Peripheral vascular disease - 66 (0.5%) Obstructive sleep apnoea - 146 (1.1%) Thyroid disease - 517 (3.9%) COPD - 56 (0.4%) Cardiothoracic surgery - 354 (2.7%)	Kardia Mobile	Cardiologist	NA
Chan 2016b[56]	Cross-sectional; China; primary care	People with history of hypertension and/or diabetes mellitus or ≥65 years of age; N=1013; patients recruited from a general outpatient clinic	Mean age ± SD (years): 68.4 ± 12.2 Sex: 539 (53.2%) female Hypertension - 916 (90.4%) Diabetes - 371 (36.6%) Coronary artery disease - 164 (16.2%) Previous stroke - 106 (10.5%) Mean CHA_2DS_2VASc ± SD - 3.0 ± 1.5	Kardia Mobile	Algorithm and cardiologist	12-lead ECG performed only when a diagnosis of AF was made by the algorithm (results not presented)
Chan 2017[53]	Cross-sectional; Hong Kong; primary care	Patients ≥65 years attending primary care clinics; N=1041; NR	Age ≥65 years Sex and risk factors: NR	Kardia Mobile	Cardiologist	NA

Desteghe 2017[37]	Case-control; Belgium; tertiary care	Inpatients at cardiology ward; N=265; NR	Mean age ± SD (years): 67.9 ± 14.6 Sex: 138 (43.1%) female Pacemaker: 4/55 (7.3%) were intermittently paced, and 18/55 (32.7%) were not being paced during the recordings Known AF: 114/320 (35.6%) AF at time of study: 11.9% (on 12-lead ECG) Paroxysmal AF: 54.4%	MyDiagnostick and Kardia Mobile	Algorithm and electrophysiologist	12-lead ECG followed by lead-I ECG (order for the use of the different lead-I ECG tests not specified)
Doliwa 2009[42]	Case-control; Sweden; secondary care	People with atrial fibrillation, atrial flutter or sinus rhythm; N=100; patients were recruited from a cardiology outpatient clinic	Age; sex and risk factors: NR	Zenicor-ECG	Cardiologist	12-lead ECG followed by lead-I ECG
Gibson 2017[57]	Cross-sectional; UK; primary care	Patients ≥65 years without a diagnosis of AF, attending a practice nurse or health care assistant clinic; N=445; NR	Age; sex and risk factors: NR	MyDiagnostick	Algorithm	NA
Haberman 2015[44]	Case-control; USA; community and secondary care	Healthy young adults, elite athletes and cardiology clinic patients; N=130; NR*	Mean age ± SD (years): 59 ± 15 Sex: 73 (56%) male Risk factors: NR	Kardia Mobile	Electrophysiologist	Lead-I ECG followed by 12-lead ECG
Hussain 2016[58]	Cross-sectional; UK; primary care	Patients attending a flu clinic; N=357; lead-I ECG used while patients waited for flu vaccination	Age >65 years: N=257 Sex and risk factors: NR	Kardia Mobile	GP	NA
Kaasenbrood 2016[59]	Case-control; Netherlands; primary care	Patients aged over 60 years with and without known AF attending for flu vaccination; N=3269; asked by nurses	Mean age ± SD (years): 69.4 ± 8.9 Sex: 1602 (49%) male Risk factors: NR	MyDiagnostick	Algorithm and cardiologist	NA
Koltowski 2017[50]	Cross-sectional; Poland; tertiary care	Patients in a tertiary care centre; N=100; NR	Age; sex and risk factors: NR	Kardia Mobile	Cardiologist	Lead-I ECG followed by 12-lead ECG

Lau 2013[46]	Case-control; Australia; secondary care	Patients at cardiology department; N=204; NR	Age and sex: NR Known AF: 48 (24%)	Kardia Mobile	Algorithm	Lead-I ECG followed by 12-lead ECG
Lowres 2014[60]	Cross-sectional; Australia; community	People aged ≥65 years entering the pharmacy without a severe coexisting medical condition; N=1000; availability of screening in participating pharmacies was advertised through flyers displayed within each pharmacy, and pharmacists and staff also directly approached potentially eligible clients	Mean age ± SD (years): 76 ± 7 Sex: 436 (44%) male Risk factors: NR	Kardia Mobile	Algorithm and cardiologist	Pulse palpation followed by lead-I ECG (12-lead ECG used for participants with suspected unknown AF indicated by lead-I device)
Orchard 2016[61]	Case-control; Australia; primary care	Patients with known AF and patients without a history of AF attending for flu vaccination; N=972	New AF (N=7) Mean age ± SD (years): 80 ± 3 Sex: 3/7 male Known AF (N=29) Mean age ± SD (years): 77.1 ± 1 Sex: 15 (52%) male All AF (N=36) Mean age ± SD (years): 78 years ± 1 Sex: 18 (50%) male Risk factors: NR	Kardia Mobile	Algorithm and cardiologist	Lead-I ECG followed by 12-lead ECG in cases where AF was detected by lead-I (and was a new diagnosis)
Reeves (NR)[62]	Cross-sectional; UK; secondary care	Patients aged 18 years or older recovering in the Cardiac Intensive Care Unit or a cardiac surgery ward, following cardiac surgery, or who had been admitted to the Coronary Care Unit or a cardiology ward after a cardiac related event; N=53; research nurses working in one or other of the clinical settings identified and approached eligible patients	Age: 23 to 90 years (range) Sex: 37 (70%) male Risk factors: NR	imPulse	2 cardiology registrars, 2 cardiac physiologists and 2 specialist cardiac nurses	Lead-I ECG and 12-lead ECG recorded simultaneously

Tieleman 2014[47]	Case-control; Netherlands; secondary care	Patients with known AF and patients without a history of AF visiting an outpatient cardiology clinic or a specialised AF outpatient clinic; N=192; random selection of patients due to have a 12-lead ECG	Mean age ± SD (years): 69.4 ± 12.6 Sex: 48.4% male Risk factors: NR	MyDiagnostick	Algorithm	Lead-I ECG followed by 12-lead ECG
	Primary care	People with unknown AF status; N=676; people attending GP for flu vaccination	Mean age ± SD (years): 74 ± 7.1 Sex and risk factors: NR	MyDiagnostick	Algorithm and cardiologist	NA
Waring 2016[63]	Cross-sectional; UK; community	People aged 65 years and older; N=1153; NR	Age; sex and risk factors: NR	Kardia Mobile	Cardiologist	NA
Yan 2016[64]	Cross-sectional; Hong Kong; secondary care	People aged 65 years and older without a history of AF; N=9046; consecutive patients attending clinics	Mean age ± SD (years): 79 ± 12.1 Sex: 49.4% male Risk factors: NR	Kardia Mobile	Cardiologist	NA

AF=atrial fibrillation; COPD=chronic obstructive pulmonary disease; ECG=electrocardiogram; GP=general practitioner; NA=not applicable; NR=not reported; SD=standard deviation
* Only secondary care patients were included in the analysis. Community population not included in the analysis as these comprised healthy young adults and elite athletes.

3.3.2 Quality assessment

The methodological quality of the four cross-sectional[51,55,56,60] and the two case-control studies[59,61] included in the clinical impact review of lead-I ECG devices were assessed using the Newcastle-Ottawa quality assessment scale.[32,33] The results of the quality assessment of cross-sectional and case-control studies are presented in Table 8.

The methodological quality of the diagnostic accuracy studies included in the clinical impact review were assessed using the QUADAS-2 tool.[31] A summary of the results for the risk of bias in studies[37,42,44,46,47] included in the clinical impact review but which have already been assessed as part of the diagnostic test accuracy review is presented in Table 4 and Appendix 5 (full assessment). A summary of the risk of bias for one diagnostic accuracy study,[62] not eligible for inclusion in the diagnostic test accuracy review is presented in Table 9

Study	Selection				Comparability	Outcome	
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of exposure	Based on design and analysis	Assessment of outcome	Statistical test
Battipaglia 2016[51]	-	-	+	+	-	++	+
Chan 2016a[55]	-	-	+	+	-	++	+
Chan 2016b[56]	-	-	+	+	-	++	+
Kaasenbrood 2016[59]	-	-	+	+	-	+	+
Lowres 2014[60]	-	+	+	+	-	++	+
Orchard 2016[61]	-	-	+	+	-	++	+

(-) does not meet the criteria for the domain; (+) meets one of the criteria for the domain; (++) meets two of the criteria for the domain

Table 9; the full assessment for this study[62] is presented in Appendix 5.

Five studies[53,57,58,63,64] that were only available as conference abstracts and that were assessed to meet the study eligibility criteria for inclusion in the clinical impact review were subjected to data extraction only and not to quality assessment because of a lack of information to enable judgement on some of the quality assessment criteria.

Overall, the quality of the six studies[51,55,56,59-61] was similar across the different domains. All included studies were considered not to be representative of the target population. Only one study[60] included a sample size calculation. In all studies, the test failure rate was low, therefore, it was considered that the response rate was satisfactory. All of the included studies described the intervention. None of the studies accounted for confounding factors in the analyses presented. The assessment of the outcome was described in all the studies;

however, those studies with an independent blind assessment or where there was record linkage, were judged to be of better quality than studies where the assessment was not blind or with record linkage. The statistical tests used to analyse the data were clearly described and appropriate in all included studies.

The diagnostic accuracy study[62] was judged to have an unclear risk of bias for the domain of patient selection and a high applicability concern for patient selection. This study[62] was judged to be at low risk of bias on the index test domain as the test results were interpreted without knowledge of the reference standard test result and therefore there was low applicability concern for this domain. All the interpreters of the reference standard test results were blind to the results of the index test; therefore, the study[62] was judged to be at low risk of bias for the reference standard domain. However, there were two reference standards; (1) a clinical ECG diagnosis based on additional information not available to the assessors, and (2) consensus (three of the four assessors) which matched this clinical ECG diagnosis. Therefore, this study[62] was judged to have a high concern regarding applicability of the reference standard test.

The methodological quality of the qualitative study[52] included in the clinical impact review was assessed using the CASP tool[35] and the results are presented in Table 10. In the qualitative study,[52] semi-structured interviews were conducted with two receptionists, one nurse, three GPs and eight patients across three GP practices. The aim of the study was to investigate the feasibility of using practice nurses and receptionists to systematically screen patients for AF aged 65 years or over using a lead-I ECG device (Kardia Mobile) prior to the GP consultation. No details were available regarding the selection of the interviewees; although the study aim was to investigate the feasibility for practice nurses and receptionists to use the lead-I ECG device, these were the least represented groups in the interviews. The researchers do not discuss their own potential biases, relationships with participants or choice of locations for the study to be conducted. Although the methods are not described in-depth, the publication clearly states how the interviews were analysed, how themes were derived from the data and that interviews ceased once information saturation was reached. The duration of the interviews ranged from 5 to 40 minutes. Considering there were four different groups of participants (i.e. receptionists, nurses, GPs and patients), it is unclear how information saturation was reached, especially for nurse's views since only one nurse was interviewed.

Table 8 Quality assessment of the case-control and cross-sectional studies included in the clinical impact review

Study	Selection				Comparability	Outcome	
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of exposure	Based on design and analysis	Assessment of outcome	Statistical test
Battipaglia 2016[51]	-	-	+	+	-	++	+
Chan 2016a[55]	-	-	+	+	-	++	+
Chan 2016b[56]	-	-	+	+	-	++	+
Kaasenbrood 2016[59]	-	-	+	+	-	+	+
Lowres 2014[60]	-	+	+	+	-	++	+
Orchard 2016[61]	-	-	+	+	-	++	+

(-) does not meet the criteria for the domain; (+) meets one of the criteria for the domain; (++) meets two of the criteria for the domain

Table 9 QUADAS-2 assessment of diagnostic test accuracy studies

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Reeves (NR)[62]	Unclear	Low	Low	Low	High	Low	High

NR=not reported

Table 10 CASP assessment of qualitative studies

Section A: Are the results valid?		
1. Was there a clear statement of the aims of the research?	Yes	X
	Can't tell	
	No	
2. Is a qualitative methodology appropriate?	Yes	X
	Can't tell	
	No	
3. Was the research design appropriate to address the aims of the research?	Yes	X
	Can't tell	
	No	
4. Was the recruitment strategy appropriate to the aims of the research?	Yes	
	Can't tell	X
	No	
5. Was the data collected in a way that addressed the research issue?	Yes	X
	Can't tell	
	No	
6. Has the relationship between researcher and participants been adequately considered?	Yes	
	Can't tell	X
	No	
Section B: What are the results?		
7. Have ethical issues been taken into consideration?	Yes	X
	Can't tell	
	No	
8. Was the data analysis sufficiently rigorous?	Yes	X
	Can't tell	
	No	
9. Is there a clear statement of findings?	Yes	X
	Can't tell	
	No	
Section C: Will the results help locally?		
10. How valuable is the research?		
The authors discuss the implications of the study for a GP setting. However, the points raised do not necessarily follow from the results of their study.		

3.3.3 Clinical impact results

Intermediate outcomes

The results for the most commonly reported intermediate outcomes (test failure rate, time to complete test and store the ECG trace, number of 12 lead ECGs carried out and diagnostic yield) are provided in Table 11.

Table 11 Results for intermediate outcomes

Study	Lead-I ECG device	Test failure rate	Time to complete testing and storage	Number of 12-lead ECGs carried out	Diagnostic yield (% new AF cases)
Battipaglia 2016[51]	MyDiagnostick	60/855 (7%)	15 seconds rhythm strips	NA	7/855 (0.82%)
Chan 2016a (45)[55]	Kardia Mobile	56/13122 (0.4%)	30 seconds rhythm strips	NA	101/13122 (0.77%)
Chan 2016b (46)[56]	Kardia Mobile	13/1026 (1.3%)	30 seconds rhythm strips	Unclear	5/1013 (0.49%)
Chan 2017[53]	Kardia Mobile	NR	NR	NA	15/1041 (1.44%)
Desteghe 2017[37]	MyDiagnostick and Kardia Mobile	MyDiagnostick 8/265 (3%) for both electrophysiologist 1 and 2 Kardia Mobile 10/265 (3.8%) for electrophysiologist 1 and 6/265 (2.3%) for electrophysiologist 2	MyDiagnostick - 1 minute recording Kardia Mobile - 30 seconds recording	265	1/265 (0.38%)
Doliwa 2009[42]	Zenicor-ECG	NR	10 seconds rhythm trace. Registration, transfer and evaluation of the information take less than 5 minutes	100	NR
Gibson 2017[57]	MyDiagnostick	NR	NR	NA	26/445 (5.84%)
Haberman 2015[44]	Kardia Mobile	1/381 (0.3%) based on overall study population	NR	130	NR

Hussain 2016[58]	Kardia Mobile	NR	30 to 45 seconds to apply	NA	6/357 (1.68%)
Kaasenbrood 2016[59]	MyDiagnostick	3/3269 (0.1%) uninterpretable results	1 minute recording	NA	37/3269 (1.13%)
Koltowski 2017[50]	Kardia Mobile	NR	NR	100	NR
Lau 2013[46]	Kardia Mobile	NR	1 minute	204	NR
Lowres 2014[60]	Kardia Mobile	4/1000 (0.4%) excluded due to excessive movement artefact	Less than 5 minutes	35	15/1000 (1.50%)
Orchard 2016[61]	Kardia Mobile	82/1044 (7.9%) recorded ECGs unclassified of which 20 were due to unreadable trace	5 minutes (range 1.5 to 10)	30	8/973 (0.82%)
Reeves (NR)[62]	imPulse	5/53 (9%)	2 minutes recording	53	NR
Tieleman 2014[47]	MyDiagnostick	NR	1 minute recording	192 (secondary care population)	11/676 (1.63%) (primary care population)
Waring 2016[63]	Kardia Mobile	NR	NR	NA	5/1153 (0.43%)
Yan 2016[64]	Kardia Mobile	NR	NR	NA	121/9046 (1.34%)

ECG=electrocardiogram; NA=not applicable; NR=not reported

Results for failure rate included both failure of the lead-I ECG algorithm to produce a result and poor quality of the lead-I ECG trace (i.e. uninterpretable or illegible trace).

Time to diagnosis of AF was reported by only one study[60] (16.6±14.3 days (mean ± SD). This was measured as the mean time between initial diagnostic test with lead-I ECG at a pharmacy and confirmation of result with a 12-lead ECG.

One study[47] reported that the participants were able to use the device with minimal instructions (i.e. MyDiagnostick) and another study considered that the lead-I ECG device (i.e. Kardia Mobile) was easy to operate.[53] A key barrier was identified related to the ease of use of the lead-I ECG devices. Specifically, the difficulty for elderly patients to hold the device very still to take a reading.[61] One study[37] reported that 24/344 (7%) patients were excluded because they were not able to hold the devices properly (MyDiagnostick and Kardia Mobile lead-I ECG

devices were used in study and lead-I ECG device on which this proportion is based was not provided).

Only the Desteghe study[37] reported the concordance between lead-I ECG devices (i.e. Kardia Mobile and MyDiagnostick) and there were no differences in agreement (based on kappa values) between both devices when including all patients (P=0.677) and after the exclusion of patients with an implanted device (i.e. pacemaker or implantable cardioverter defibrillator) (P=0.411).

Two studies[58,60] reported the impact of test results on clinical decision making. In the Hussain study,[58] there was a change in treatment management as a consequence of screening using the Kardia Mobile lead-I ECG for five of six new cases of AF in 357 people tested (one patient was clinically unwell and died as an inpatient following referral to the hospital). Oral anticoagulants (OACs) were prescribed in 6/10 new cases of AF as a consequence of using the lead-I ECG device followed by a 12-lead ECG interpreted by a cardiologist.[60] Of five participants with unknown recurrence of AF three years or more after cardioversion, three participants were prescribed OACs following review by a cardiologist.[60]

Diagnostic yield was reported in 13 studies.[37,47,51,53,55-61,63,64] The percentage of new patients diagnosed with AF ranged from 0.38% to 5.84%. The percentages of new patients diagnosed with AF in each of the included studies are presented in Figure 18 (all included studies), in Figure 19 (studies grouped by type of lead-I ECG device) and in Figure 20 (studies grouped by setting).

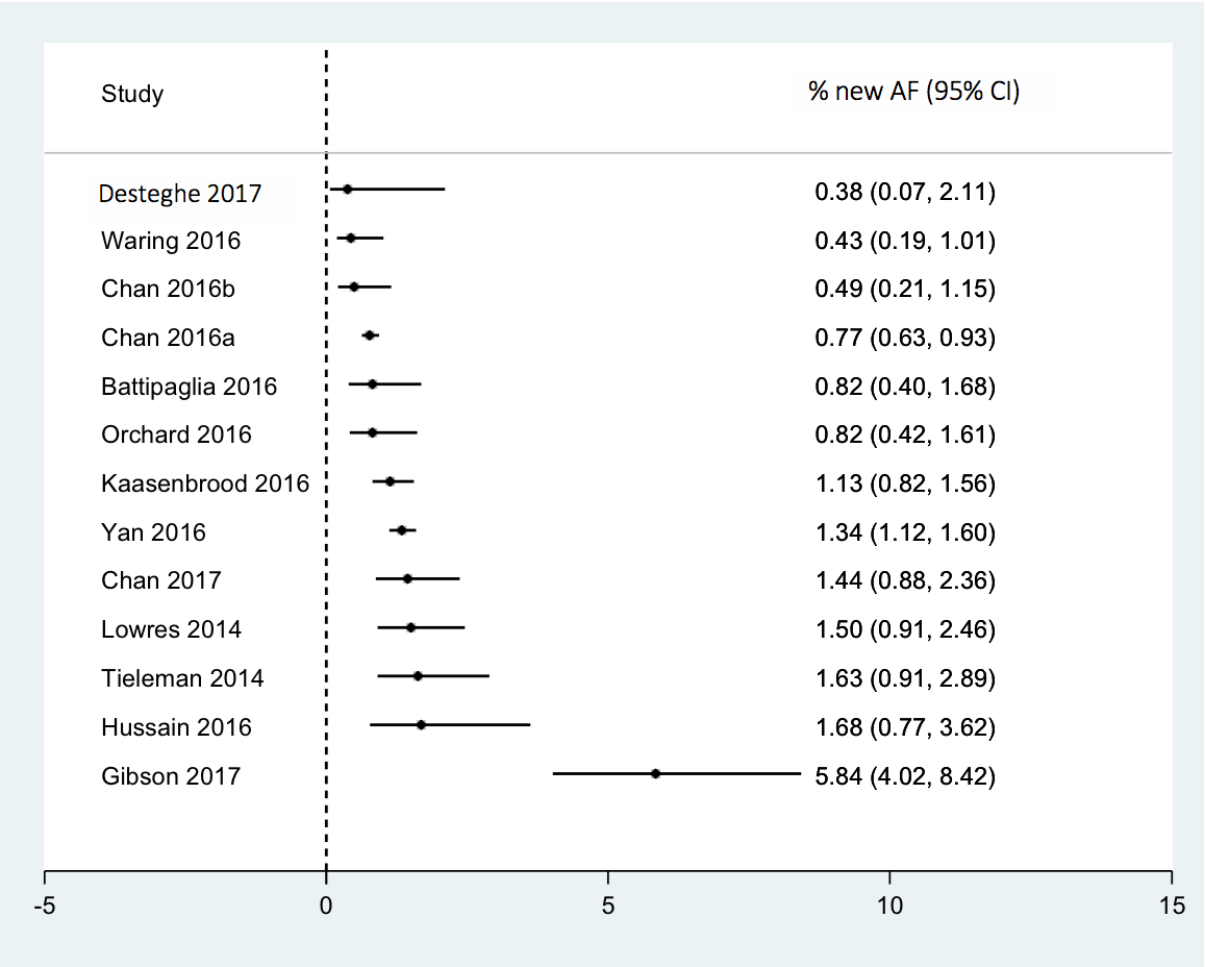

Figure 18 Forest plot displaying the diagnostic yield (percentage of new AF diagnoses) in each study

AF=atrial fibrillation; CI=confidence interval

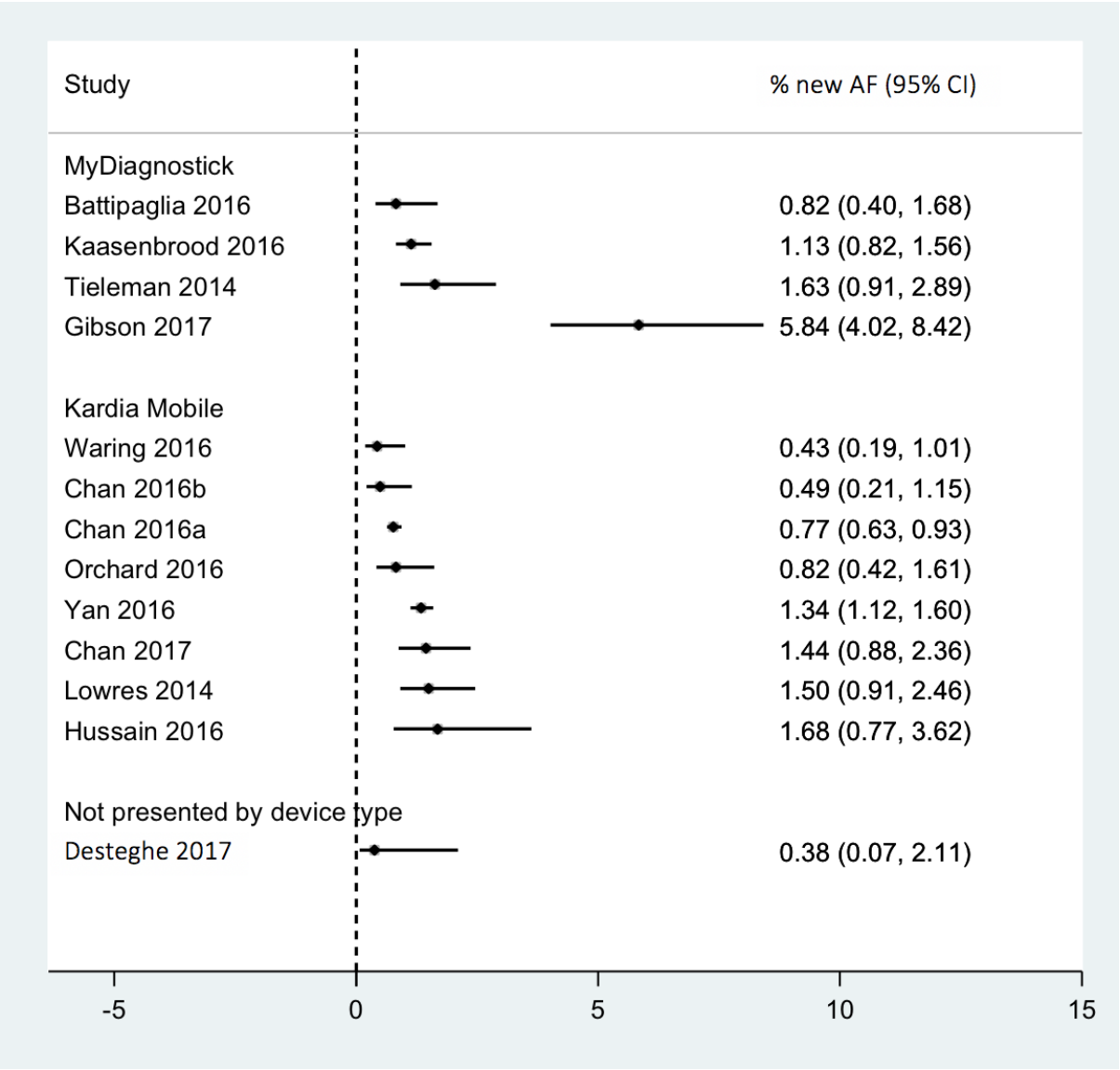

Figure 19 Forest plot displaying the diagnostic yield (percentage of new AF diagnoses) in each study (studies grouped by type of lead-1 device)

AF=atrial fibrillation; CI=confidence interval

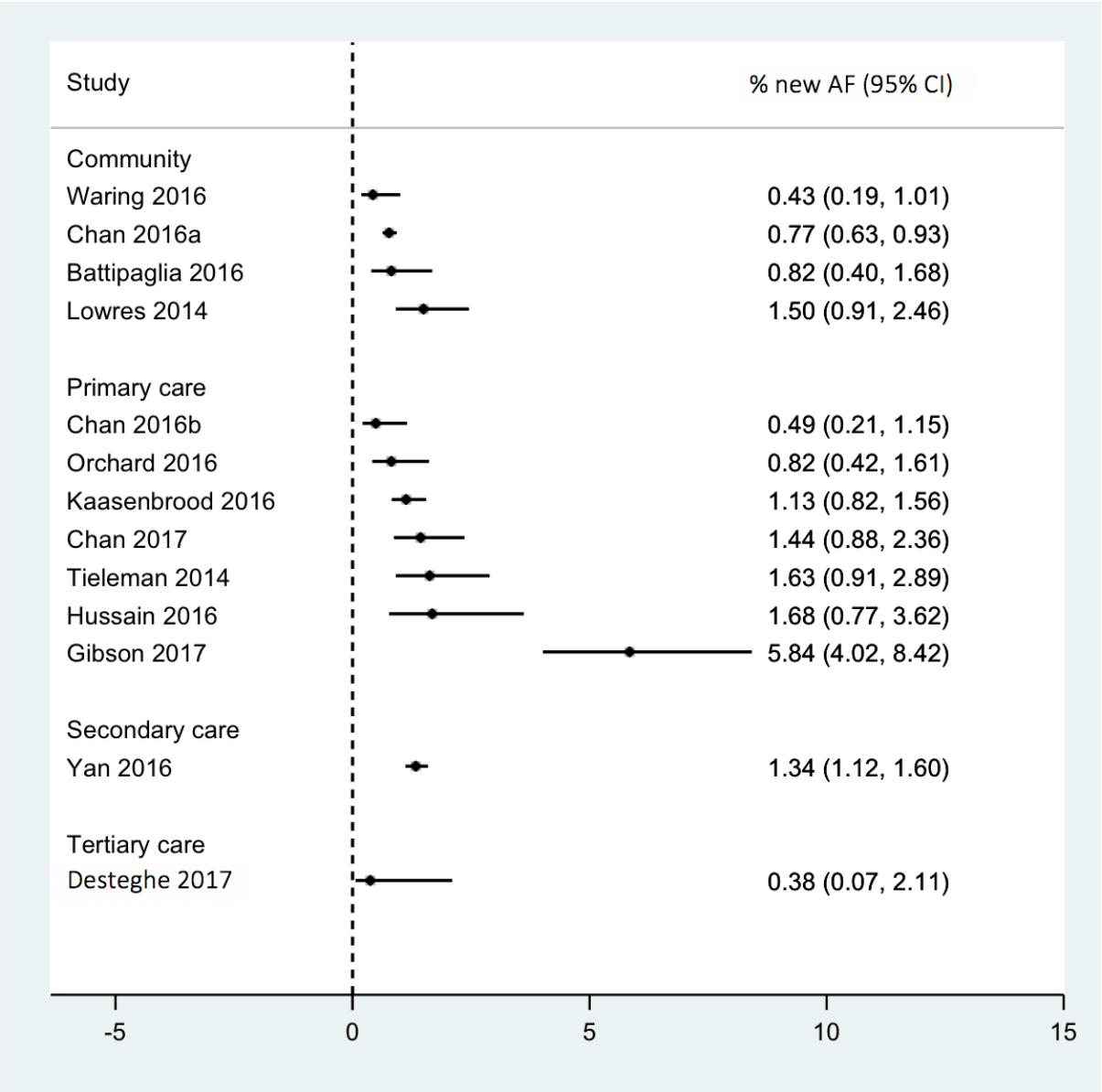

Figure 20 Forest plot displaying the diagnostic yield (percentage of new AF diagnoses) in each study (studies grouped by setting)

AF=atrial fibrillation; CI=confidence interval

Time to initiation of preventative treatment was not reported in any of the identified studies.

Clinical outcomes

Only one study[58] reported clinical outcomes. The 12-lead ECG trace was normal and the patient did not receive anticoagulant therapy, but later had a stroke. The authors reported that the Kardia Mobile lead-I ECG trace was difficult to interpret for this patient who likely had AF.

Patient-reported outcomes

Acceptability of the lead-I ECG devices was reported in four studies.[53,57,58,61] In one of the studies using the Kardia Mobile lead-I ECG device, the staff indicated that the patients

generally liked the device and the screening process; while the GPs liked the lead-I ECG device, the fact that it raised awareness of AF and also liked nurses performing the screening.[61] One study reported that all patients were willing to undergo repeated screening with the Kardia Mobile lead-I ECG in future GP visits and 86% of the GPs considered that the lead-I ECG device was useful for AF screening and they would use it in their daily practice.[53] Although the views were generally positive, one study reported that patients' suggestions for improvements on the use of the MyDiagnostick lead-I ECG device included more time to decide about the test and a clearer explanation of results (unclear if this is in the context of patient self-use of the device or the clinician's explanation of the results).[57] In the same study, interviews with seven staff members suggested that although the opportunity to detect and treat AF was valued, challenges such as technical problems, documentation and referral, and management of workload, needed to be overcome.[57] In one study,[58] the process was found to be acceptable and it was considered that the Kardia Mobile lead-I ECG test was easily administered and no patients refused to be tested.

Barriers and enablers to the use of lead-I ECG devices in primary care for AF screening were explored in a qualitative study.[52] The study investigated the feasibility of using practice nurses and receptionists to systematically screen patients for AF aged 65 years or over using a lead-I ECG device (Kardia Mobile) prior to the GP consultation. Barriers that were identified by three GPs were: having to rely on others to carry out the screening, not having the required software, practice information technology (IT) being blocked, remembering to charge the phone and the technology not working. GPs liked the lead-I ECG device and its portability, considered that use of the lead-I ECG can add value, provide reassurance and act as a prompt to look for other health conditions. The eight patients who were interviewed did not understand the reasons for screening and were not interested if the result was negative. However, they considered that having access to the lead-I ECG device in the surgery was more convenient than having to attend another health care facility for a 12-lead ECG and they stated that they were impressed with the technology. One practice nurse mentioned two barriers: (i) the possible lack of availability of the lead-I ECG device when required and (ii) that the results have to be reviewed by a GP. The practice nurse was able to confidently screen patients and explain the process, considered that the use of the lead-I ECG device raised practice awareness of AF and believed that the lead-I ECG device algorithm was an enabler to the screening of AF. Both receptionists, although they expressed their ease with using the device, only explicitly identified barriers as they were reluctant to ask patients to use the lead-I ECG device, were uncertain about how to explain the purpose of the AF screening and were unsure how to respond to patients' questions.

None of the studies identified reported on HRQoL.

'Real world' data

Evidence was submitted on the use of Kardia Mobile lead-I ECG across Eastbourne, Hailsham & Seaford Clinical Commissioning Group (CCG) and Hastings & Rother CCG [Kent Surrey Sussex AHSN and Richard Blakey, AliveCor in East Sussex, unpublished evidence submitted via NICE]. Over a two-year period, Kardia Mobile lead-I ECG was used in primary care or during home visits if people were found to have an irregular pulse or symptoms indicative of AF. During the two years of the project, 183 lead-I ECG traces were reported, identifying 128 new cases of AF. There was also a higher increase in the prevalence of AF in the participating CCGs (2.73% to 2.96% for Hastings & Rother CCG and 3.01% to 3.22% for Eastbourne, Hailsham & Seaford CCG) compared to other CCGs in the Kent Surrey Sussex area.[8]

3.3.4 Summary of findings: clinical impact

As per the diagnostic test accuracy review, no studies were identified that evaluated the clinical impact of lead-I ECG devices in people presenting to primary care with signs and symptoms of AF and an irregular pulse, which limits the applicability of the results presented. Therefore, the 23 publications[37,40-47,50,51,53-64] reporting on the 18 studies that were included in the clinical impact review were also focused on an asymptomatic population. Four studies included only people without known AF.[51,57,60,64] Three studies[53,58,63] may have included only people without known AF as participants were either attending a primary care clinic or the study was conducted in a community setting. However, information describing these studies was limited and the data were only available as conference abstracts.

Test failure rate was reported in nine studies[37,44,51,55,56,59-62] and ranged from 0.1% to 9%. Results for test failure rate included both failure of the lead-I ECG algorithm to produce a result and poor quality of the lead-I ECG trace. Diagnostic yield was reported in 13 studies.[37,47,51,53,55-61,63,64] The percentage of new patients diagnosed with AF ranged from 0.38% to 5.84%. Two studies[58,60] reported a change in treatment management following the use of the Kardia Mobile lead-I ECG for new patients diagnosed with AF. Acceptability of lead-I ECG devices was reported in four studies.[53,57,58,61] with generally positive views. Time to initiation of preventative treatment and HRQoL were not reported in any of the identified studies.

The 'real world' data submitted by Kent Surrey Sussex AHSN reports on the use of Kardia Mobile lead-I ECG device for people with symptoms of AF and an irregular pulse during a two-year project. Although the information available was limited (Microsoft PowerPoint presentation and a one-page summary), we considered that it was relevant to the population of interest. Data from this two-year project showed that the percentage of new patients diagnosed with AF during the project was 69.9%, which is considerably higher than the diagnostic yield reported in our included studies (0.38% to 5.84%).

4 METHODS FOR ASSESSING COST EFFECTIVENESS

The EAG's economic evaluation assesses the cost effectiveness of single-time point lead-I ECG devices compared with MPP for people presenting to primary care with signs and symptoms of AF who have an irregular pulse followed by a 12-lead ECG in primary or secondary care (prior to initiation of anticoagulation therapy). The economic evaluation includes a systematic review of existing economic evaluations of lead-I ECG devices and the creation of a de novo economic model.

The economic evaluation is applicable to the use of lead-I ECG devices in primary care practices where there is a wait of at least 48 hours between initial presentation and follow up with a 12-lead ECG.

4.1 Systematic review of cost-effectiveness evidence

4.1.1 Search strategy

The EAG undertook a systematic review to identify published full economic evaluations of lead-I ECG devices for detecting AF. A search filter to identify economic evaluations was applied to the search strategies and the electronic databases were searched from inception until the 24th April 2018. The search strategy used in MEDLINE is presented in Appendix 7 of this report. The MEDLINE search was adapted to enable similar searching of the other relevant electronic databases. The following databases were searched for relevant studies:

- MEDLINE (Ovid)
- MEDLINE Epub Ahead of Print and MEDLINE In-Process (Ovid)
- EMBASE (Ovid)
- PubMed
- EconLit (EBSCO)
- NHS Economic Evaluation Database (NHS EED)

The results of the searches were uploaded to, and managed using, EndNote X8 software. The reference lists of relevant systematic reviews and eligible studies were hand-searched to identify further potentially relevant studies.

Broader searches were carried out to identify existing economic models of ECG devices when used for the detection of AF. Separate searches were carried out to identify supporting information on costs and health state utility data.

4.1.2 Eligibility criteria

In stage 1, all titles and abstracts identified via searches of the electronic databases were screened for relevance according to pre-specified eligibility criteria (Table 12). Any studies that did not meet the criteria were excluded. The EAG planned to obtain full-text manuscripts

for all economic evaluations identified at stage 1 to assess relevance against the pre-specified eligibility criteria (stage 2).

Table 12 Eligibility criteria for economic literature search

	Inclusion criteria	Exclusion criteria
Intervention or comparator	Single-time point lead-I or single lead ECG, manual pulse palpation	Ambulatory, inserted, multiple assessments
Indication	Atrial fibrillation	Not atrial fibrillation
Study design*	Full economic evaluation	Partial economic evaluation, methodological paper
Perspective	UK or European perspective	Non-European perspective
Population	Adults with signs or symptoms indicative of AF plus irregular pulse assessed by manual pulse palpations presenting at primary care	Screening population, adults with asymptomatic or silent AF

* studies published only as letters or abstracts/conference proceedings were considered for inclusion if sufficient information was available

4.1.3 Data extraction and quality assessment strategy

The EAG planned to extract data relating to bibliographic information (author[s] and year of publication); general information (country, condition, intervention and comparator[s]); methodological characteristics (type of economic evaluation, perspective, time horizon, discount rate, key cost categories, year of valuation and key outcomes) and main findings. The EAG planned to assess the quality of all economic evaluations identified for inclusion in the review using the Drummond[67] 10-point checklist.

4.1.4 Results of the systematic review of existing cost-effectiveness evidence

The searches of electronic databases resulted in the identification of 40 unique citations after de-duplication. Following screening of titles and abstracts, all 40 records were excluded as they did not include the relevant interventions or comparator, did not consider an eligible study population or were not full economic evaluations.

4.1.5 Conclusions of the systematic review of cost-effectiveness evidence

The EAG did not identify any published papers that met the inclusion criteria for the systematic review.

4.2 Development of a de novo economic model

4.2.1 Approach to modelling

The EAG did not identify any studies in a systematic review of the economic literature that evaluated the cost effectiveness of single-time point lead-I ECG devices compared with MPP followed by a 12-lead ECG in primary or secondary care (prior to initiation of anticoagulation

therapy) in people presenting to primary care with signs and symptoms of AF who have an irregular pulse. The EAG therefore undertook a de novo economic analysis.

The economic analysis follows the diagnostic pathway for patients presenting to primary care with signs and symptoms indicative of AF plus an irregular pulse. Results are presented over a time horizon of 30 years with patients entering the model at age 70.

The economic evaluation is only relevant to primary care practices where patients have to wait at least 48 hours between an initial consultation with the GP and a 12-lead ECG; this allows the benefit of early anticoagulation and rate control treatment for those patients who receive a positive lead-I ECG to be considered.

A decision tree and two cohort Markov models were built in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA). The decision tree describes the pathway that a patient presenting to primary care with signs and symptoms of AF and an irregular pulse follows in the initial GP consultation. The first Markov model captures the differences in the costs and benefits of treatment (standard diagnostic pathway versus lead-I ECG pathway) during the first 3 months after the initial appointment. During this period, some patients will have a diagnosis of AF and start treatment for AF whilst other patients will have further tests to diagnose or to rule out AF (where 'rule out' means no diagnosis of AF is recorded in the patient's notes and no treatment for AF is started). The second Markov model captures the differences in lifetime costs and benefits after diagnosis of AF or the time when AF is ruled out.

4.2.2 Population

The modelled patient population is adults presenting to primary care with signs and symptoms of AF who have an irregular pulse. The diagnostic test accuracy data included in the model are based on the results of a systematic review (Section 3.1). However, no studies included in the systematic review were available for the population of interest. All studies were in asymptomatic patients and had either a known history of AF or were recruited from cardiology clinics. Only one study[48] was carried out in primary care. It has been recognised that diagnostic accuracy test specificity and sensitivity may be affected by prevalence, with the use of a test in a more severely diseased population associated with the better performance of the test.[68] It is therefore possible that the sensitivity and specificity data from the systematic review do not represent the diagnostic test accuracy of lead-I ECG in the population of interest. It is not possible to know how the sensitivity and specificity of lead-I ECG devices would be affected by different populations. The economic evaluation is therefore limited by the lack of diagnostic test accuracy data in the population of interest.

The symptomatic population with an irregular pulse is assumed to consist of people with AF and people with atrial or ventricular ectopy. Clinical advice to the EAG is that the only other condition that would produce an irregular pulse similar to that found with AF is atrial or ventricular ectopy. It is assumed that the symptoms of patients with AF, or atrial or ventricular ectopy, are not severe enough to require urgent referral to cardiology. Advice from the NICE Clinical Knowledge Summary[69] on managing atrial and ventricular ectopy for patients without underlying heart disease is to reassure patients.

The mean age of patients in the model base case is 70 years. The proportions of males and females are based on the age-adjusted ratio in the general population.[70]

4.2.3 Comparators

Diagnostic test accuracy data were not available for the population of interest (symptomatic patients with suspected AF and an irregular pulse presenting to primary care) for any devices listed in the final scope issued by NICE[9] (Section 3.2.1). The EAG therefore searched for diagnostic test accuracy data in an asymptomatic population as pre-specified in the protocol to use as a proxy for the population of interest. The economic model includes only the diagnostic strategies for which proxy diagnostic test accuracy data were available. The diagnostic strategies (following MPP and before 12-lead ECG) included in the economic model are:

- standard diagnostic pathway (no further testing)
- any lead-I ECG device (interpreted by trained healthcare professional)
- imPulse (interpreted by trained healthcare professional)
- Kardia Mobile (interpreted by trained healthcare professional)
- MyDiagnostick (interpreted by trained healthcare professional)
- RhythmPad-GP (interpreted by algorithm)
- Zenicor-ECG (interpreted by trained healthcare professional)

4.2.4 Model structure

The model comprises decision trees and two cohort Markov models that describe the patient pathway over a lifetime horizon of 30 years. A decision tree covers the patient pathway in the initial consultation. Patients then feed into a cohort Markov structure with daily cycles for 3 months. This first Markov model includes all testing for AF after the initial GP consultation (12-lead ECG and Holter monitoring for paroxysmal AF). By the end of the first 3-month Markov model, all patients have an AF diagnosis or have had AF ruled out. Patients then move into

the second Markov model. All patients in the second Markov model have had AF diagnosed or ruled out (either correctly or incorrectly). Patients remain in the second Markov model until death. The cycle length is 3 months in the second Markov model. Costs and benefits are discounted at 3.5% per year.

Diagnostic phase

The diagnostic phase of the model encompasses the initial consultation and the first 3 months following the initial consultation. At the end of the first 3-month period in the model, all patients who remain alive have had AF either diagnosed or ruled out (whether correctly or incorrectly; here 'ruled out' means that no diagnosis of AF is recorded in the patient's notes and no treatment for AF has started).

A decision tree structure describes the pathway that a patient presenting to primary care with signs and symptoms of AF and an irregular pulse follows in the initial GP consultation. Patients then enter a cohort Markov model in either a testing state (whilst waiting for the results of a 12-lead ECG or paroxysmal test) or in a diagnosed state (AF diagnosed or ruled out). Patients may stay in the testing period for a maximum number of days, depending on the test. Clinical advice to the ERG is that patients who cannot have a 12-lead ECG in the GP practice immediately would have to wait between 2 and 14 days for the test. Patients receiving testing for paroxysmal AF using a Holter monitor will stay in the paroxysmal testing state for 7 days.

After the end of the testing period, patients who received a 12-lead ECG may move to another testing state (paroxysmal test), to a diagnosed state (AF diagnosed or ruled out) or to the death state. At the end of the testing period, patients receiving a paroxysmal test may move to a diagnosed state (AF diagnosed or ruled out) or to the death state.

Patients may move out of a testing state before the end of the testing period by experiencing a cardiovascular event (CVE) or death. Patients who experience a CVE and who have not had AF diagnosed or ruled out are assumed to receive a diagnosis as part of treatment for the CVE. CVEs included in the model are transient ischaemic attack (TIA), ischaemic stroke (IS) and haemorrhagic stroke (HS). Patients can experience up to two CVEs. Adverse events (AEs) are included in the model as clinically relevant (e.g., non-major bleeds). An AE can be experienced in any state and does not affect the risk of transition to another state.

The schematics for the decision tree element of the diagnostic phase of the model are shown in Figure 21, Figure 22 and Figure 23. The schematic for the Markov element of the diagnostic phase of the model is shown in Figure 24.

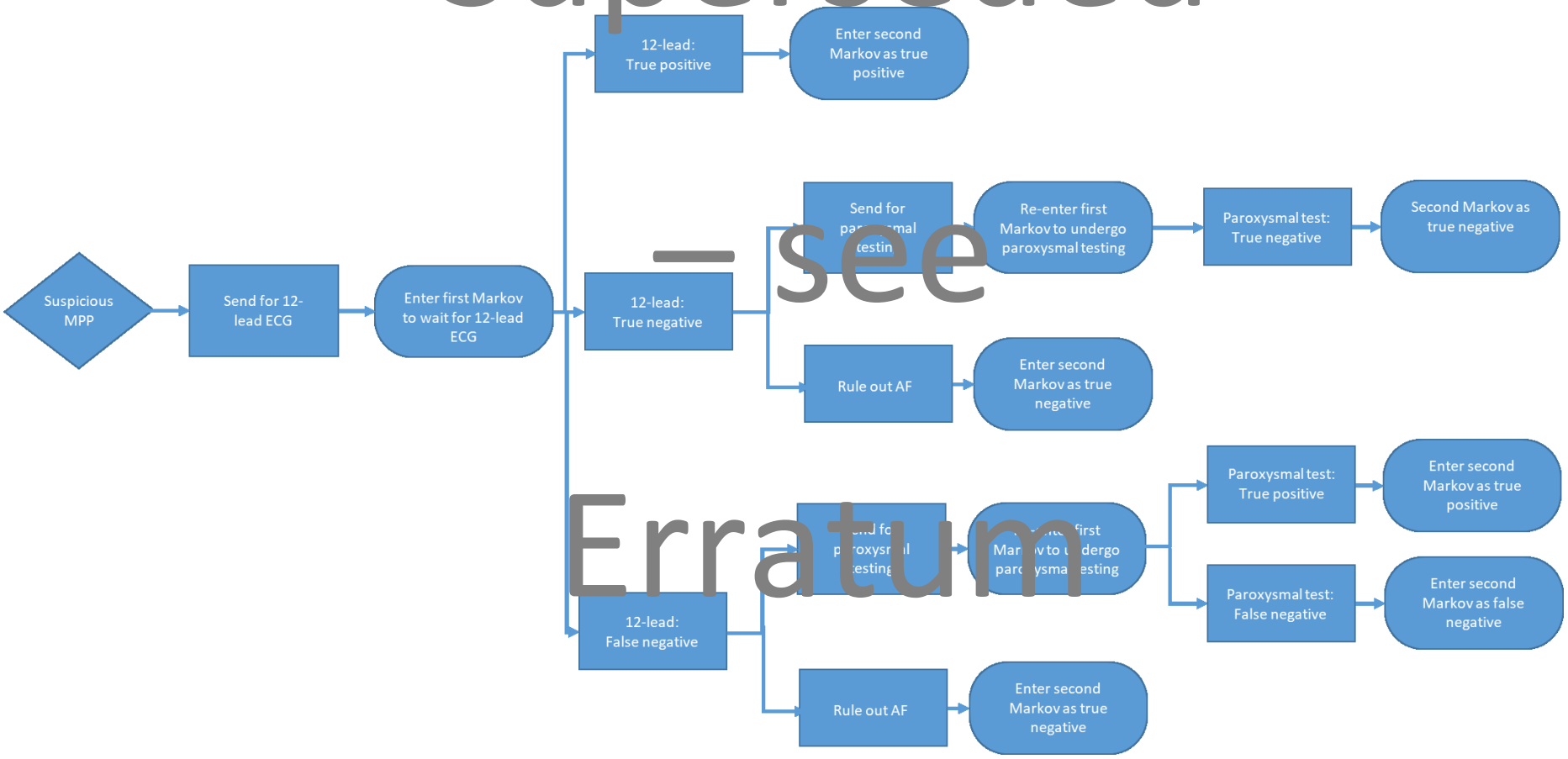

Figure 21 Diagnostic phase - decision tree: standard diagnostic pathway

AF=atrial fibrillation, ECG=electrocardiogram; MPP=manual pulse palpation

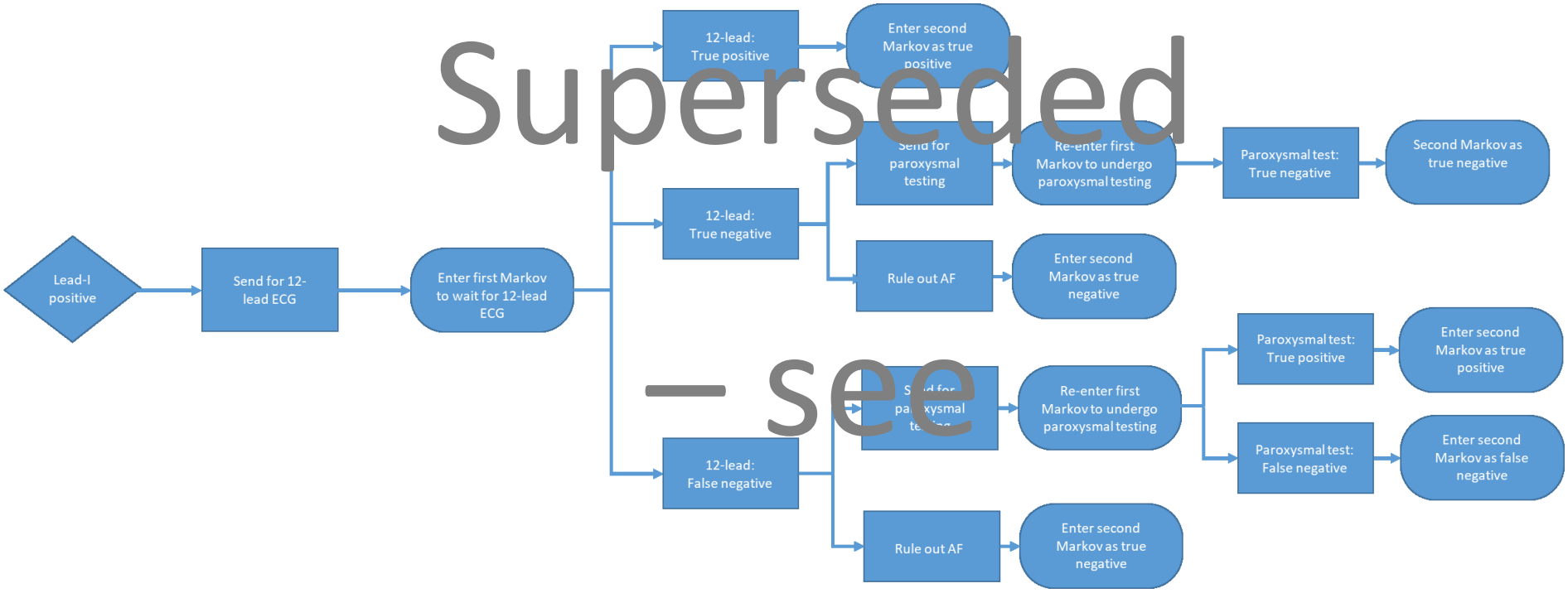

Figure 22 Diagnostic phase - decision tree: lead-I ECG diagnostic pathway (positive result)

AF=atrial fibrillation, ECG=electrocardiogram; MPP=manual pulse palpation

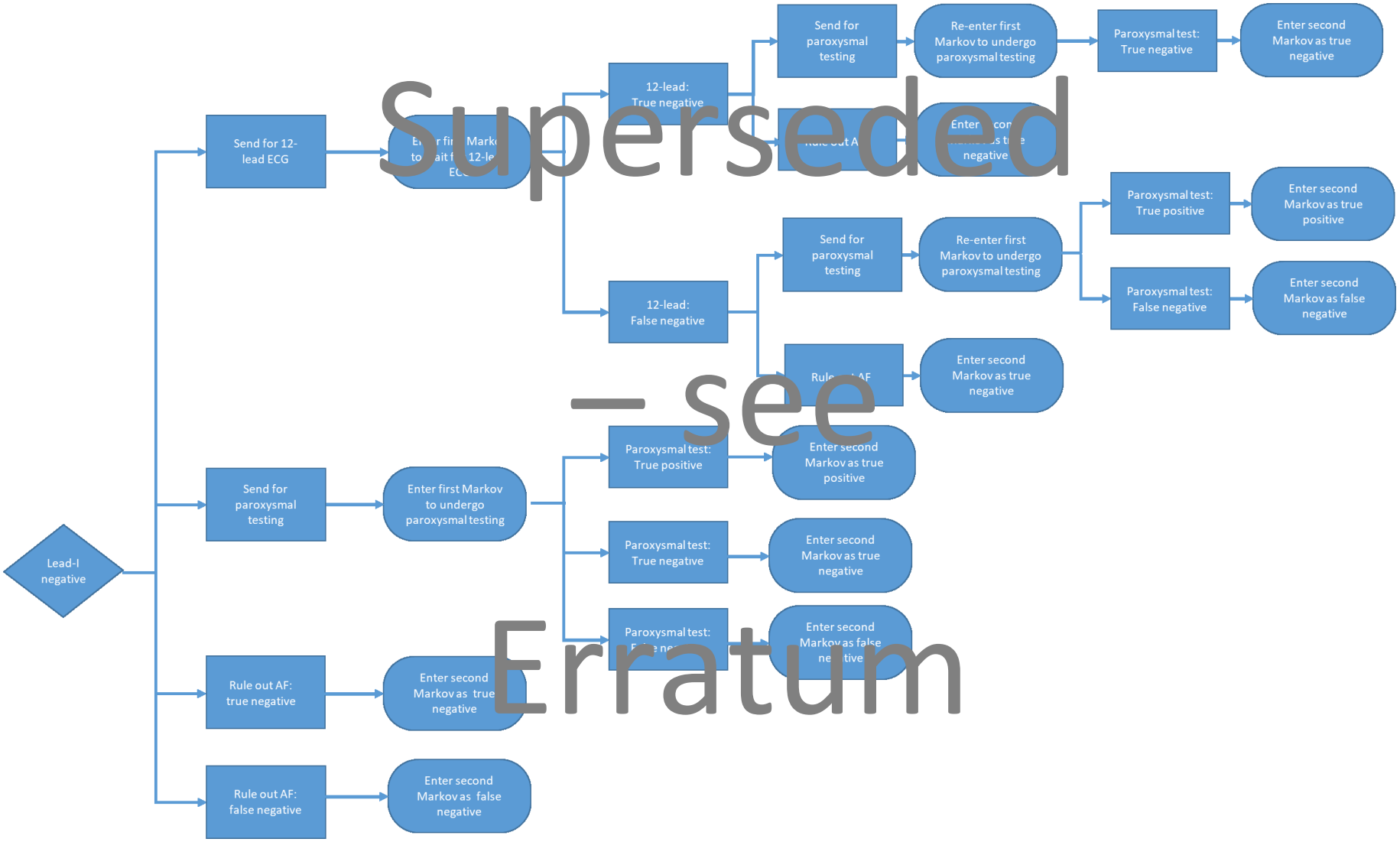

Figure 23 Diagnostic phase - decision tree: lead-I ECG diagnostic pathway (negative result)
AF=atrial fibrillation, ECG=electrocardiogram; MPP=manual pulse palpation

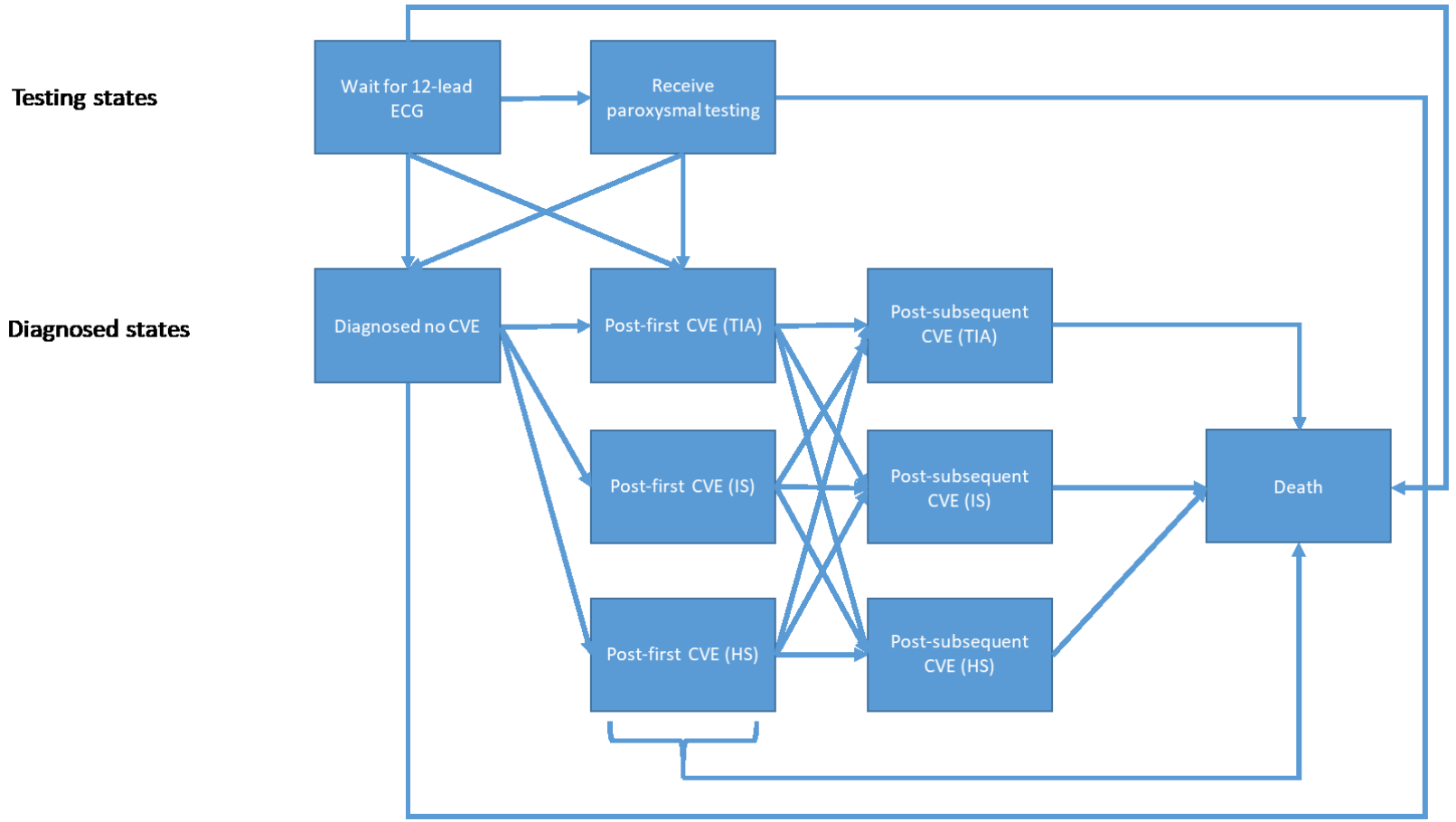

Figure 24 Diagnostic phase - Markov model

Note: transition to the death state is possible from all health states
CVE=cardiovascular event; ECG=electrocardiogram; HS=haemorrhagic stroke; IS=ischaemic stroke; TIA=transient ischaemic attack

Standard pathway

All patients in the standard pathway are sent for a 12-lead ECG. No patients receive treatment for AF whilst waiting for the 12-lead ECG test.

All patients with a positive result from a 12-lead ECG are assumed to be correctly diagnosed with AF and begin treatment. A proportion of patients with a negative result from the 12-lead ECG are sent for further testing for paroxysmal AF and a proportion of patients have AF ruled out at this point in the pathway. All patients with a positive result from further testing for paroxysmal AF with a Holter montior are correctly diagnosed with AF and begin treatment. All patients with a negative result from a paroxysmal test have AF ruled out. A proportion of patients who have AF ruled out after either a 12-lead ECG or paroxysmal test will have false negative results due to patients with paroxysmal AF not being in AF at the time of the 12-lead ECG or paroxysmal test.

Lead-I ECG pathway: positive result

All patients in the lead-I ECG pathway with a positive result from a lead-I ECG (who are either true positives or false positives for AF) are diagnosed with AF and sent for a 12-lead ECG following the initial consultation. Clinical advice to NICE, as reported in the final scope,[9] is that a 12-lead ECG is important for people diagnosed with AF to identify any additional abnormalities, such as left ventricular hypertrophy. All patients in the lead-I ECG pathway with a positive result from a lead-I ECG begin rate control treatment for AF before the 12-lead ECG and no patients receive Holter monitoring to test for paroxysmal AF before the 12-lead ECG. Patients with positive lead-I ECG test results begin treatment with NOACs and rate control after the initial GP consultation unless contraindicated, as per the final scope issued by NICE.[9]

Patients with a positive 12-lead ECG result retain the (correct) diagnosis of AF and continue treatment. Patients with a negative 12-lead ECG result are either assumed to have paroxysmal AF and continue treatment, have AF ruled out and discontinue treatment for AF or are sent for further testing for paroxysmal AF. The latter group of patients remains on treatment during further testing.

All patients with a positive result from a paroxysmal test are correctly diagnosed with AF and stay on treatment. Patients with a negative result from a paroxysmal test either have AF ruled out and discontinue treatment or are assumed to have paroxysmal AF based upon the original lead-I ECG diagnosis and continue treatment despite the negative 12-lead ECG and paroxysmal test result. A proportion of patients who have AF ruled out after either a 12-lead ECG or paroxysmal test will have false negative results due to patients with paroxysmal AF not being in AF at the time of the 12-lead ECG or paroxysmal test.

Lead-I ECG pathway: negative result

No patients begin treatment following a negative result from a lead-I ECG test. Clinical advice to the EAG about whether or not patients who receive a negative result from a lead-I ECG would be sent for a 12-lead ECG or for further testing for paroxysmal AF (Appendix 9) indicated substantial variation in clinical practice. The EAG has assumed in the base case that 80% of patients who receive a negative result from a lead-I ECG would be sent for a 12-lead ECG, 10% would be sent for ambulatory Holter monitoring and the remaining 10% of patients would have AF ruled out. The EAG acknowledges that this base case may not represent clinical practice anywhere in the UK; however, it considers that these assumptions may represent 'average' clinical practice, given the variation in clinical advice received. These assumptions are tested in scenario analyses.

All patients with a positive result from a 12-lead ECG are correctly diagnosed with AF and begin treatment. A proportion of patients with a negative result from the 12-lead ECG are sent for further testing for paroxysmal AF and a proportion of patients have AF ruled out at this point in the pathway. All patients with a positive result from a paroxysmal test are correctly diagnosed with AF and begin treatment. All patients with a negative result from a paroxysmal test have AF ruled out. A proportion of patients who have AF ruled out after either a 12-lead ECG or paroxysmal test will have false negative results due to patients with paroxysmal AF not being in AF at the time of testing.

Post-diagnostic phase

Once AF has been either diagnosed or ruled out, patients move into a second cohort Markov model that tracks the costs and benefits of these decisions over their lifetime (Figure 25). The second Markov model follows the same structure as the first Markov model after AF has been diagnosed or ruled out. Patients enter the second Markov model in a diagnosed state (AF diagnosed or ruled out) having experienced zero, one or two CVEs. In each cycle, patients with zero or one previous CVEs can remain in their current state, move to a worse state following a CVE or move to the death state. Patients with two previous CVEs remain in that state until death. Patients who have incorrectly had AF ruled out and experience a CVE are assumed to have their AF diagnosed as part of the treatment for the CVE. These patients then move onto treatment for AF.

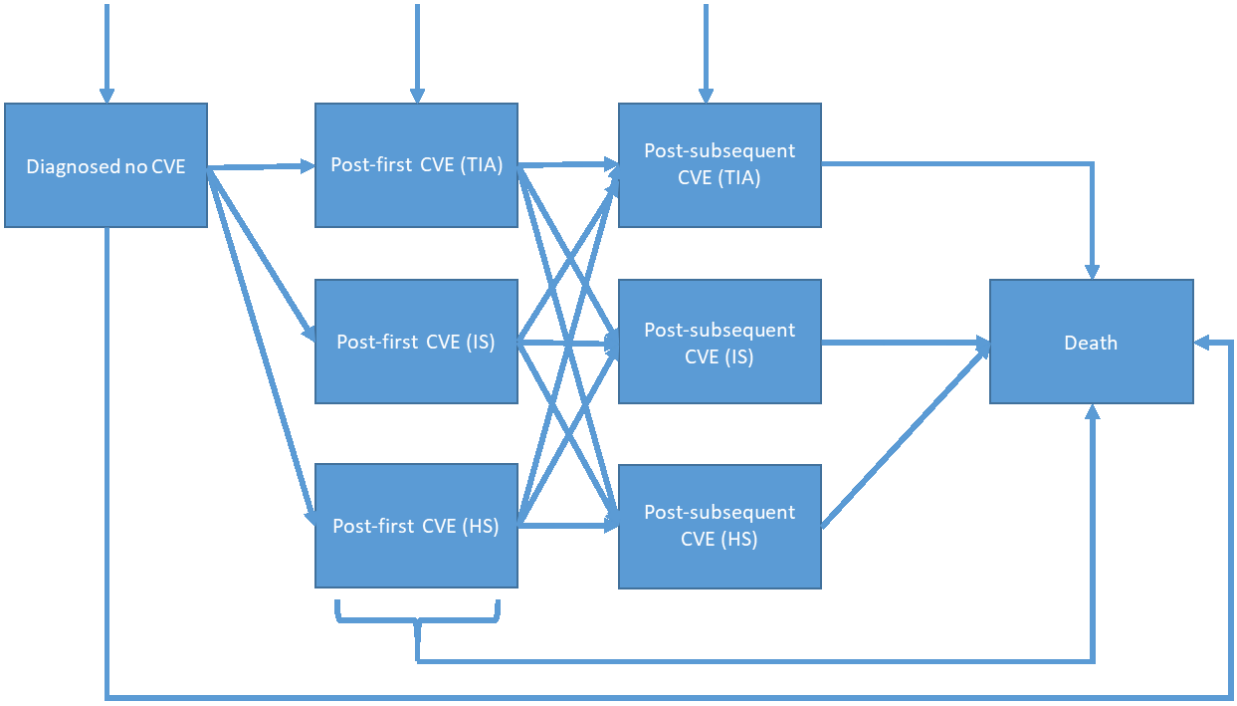

Figure 25 Post-diagnostic phase - Markov model

Note: death is possible from all states
CVE=cardiovascular event; HS=haemorrhagic stroke; IS=ischaemic stroke; TIA=transient ischaemic attack

4.2.5 Model parameters

Patient population

Signs and symptoms of AF

The modelled patient population is people with signs and symptoms of AF plus an irregular pulse. This population includes patients with AF and patients without AF who are similarly symptomatic. Clinical advice to the EAG is that the symptomatic population with an irregular pulse but without AF will consist of people with atrial or ventricular ectopy. Estimates of the proportion of patients with signs and symptoms of AF plus an irregular pulse who have AF versus those who have atrial or ventricular ectopy were not available in the literature. Clinical advice to the EAG is that around 20% of patients with signs and symptoms of AF plus an irregular pulse would have AF.

Prevalence of AF

Estimates of the prevalence of AF by age and sex were taken from a paper by Adderley.[11] The age-sex specific prevalence estimates reported by Adderley[11] are based on the results of a study carried out using primary care records from UK general practice in 2016. The prevalence estimates in this paper[11] were identified by the EAG as being the most up-to-date estimates available for the UK primary care population. Age-sex standardised prevalence rates used in the model are shown in Table 13.

Table 13 Prevalence of AF by age and sex

Age group (years)	Prevalence per 1000 population	
	Men (95% CI)*	Women (95% CI)*
45.54	7.6 (5.9 to 9.3)	2.55 (2.26 to 2.88)
55–64	24.01 (23.18 to 24.86)	9.28 (8.79 to 9.86)
65–74	66.78 (65.85 to 67.70)	34.25 (33.33 to 35.19)
75–84	147.38 (145.20 to 149.60)	97.56 (95.70 to 99.40)
≥ 85	220.94 (218.40 to 223.50)	165.33 (163.00 to 167.60)

Source: Adderley[11]
* Confidence interval estimated by EAG

Proportion of AF population who are symptomatic

The proportion of patients with AF who are symptomatic is taken from an observational cohort study of data from the US Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF registry) by Piccini.[71] The study reports that women with AF were more likely to be symptomatic than men (67.9% versus 57.5%). The proportions of women and men with AF who are symptomatic used in the model are 0.679 (95% CI 0.665 to 0.693) and 0.575 (95% CI 0.562 to 0.588) respectively.

Proportion of patients with undiagnosed symptomatic AF who have paroxysmal AF

The proportion of patients with symptomatic undiagnosed AF who have paroxysmal AF is could not be found in the literature. A fixed-effects meta-analysis published by Welton[72] found that the proportion of patients with paroxysmal AF (not explicitly symptomatic) varied substantially between studies[73-75] included in the meta-analysis (from 0.059 to 0.835). Given the wide range reported by Welton[72] and the lack of evidence specifically on incidence rates for symptomatic paroxysmal AF, in the base case it was assumed that 50% of patients in the model with AF would have paroxysmal AF with sensitivity analysis exploring the impact if the proportion changes between all patients with AF having paroxysmal AF and no patients having paroxysmal AF.

Proportion of symptoms reported by symptomatic patients

The prevalence of AF symptoms in men and women was taken from a study of gender differences in clinical presentation in AF by Schnabel.[76] The prevalence of symptoms was used in the EAG's model to estimate the disutility associated with having symptoms indicative of AF. The Schnabel[76] paper does not give associated EQ-5D measures for the symptoms noted in the study, so symptoms were mapped to a set of symptoms given in a HRQoL study by Berg.[77] The paper by Berg[77] gives utility decrement estimates for various AF symptoms, but does not list the baseline frequency of those symptoms. The prevalence of symptoms from the Schnabel[76] paper is shown in Table 14. The prevalence of symptoms used in the model after mapping to symptoms reported by Berg[77] is shown inTable 15.

Table 14 Prevalence of reported AF symptoms reported in Schnabel

Symptom	Occasional, intermediate or frequent symptoms at baseline by gender in patients with new-onset AF (<90 days), N=847	
	Men	Women
Palpitations	291 (61%)	267 (73%)
Fatigue	321 (67%)	270 (75%)
Dizziness	156 (33%)	159 (44%)
Dyspnoea	282 (58%)	240 (66%)
Chest pain	142 (30%)	99 (27%)
Anxiety	208 (44%)	218 (61%)

Source: Schnabel[76]

Table 15 Prevalence of reported AF symptoms used in the model

Symptoms reported by Berg[77]	Modelled prevalence
Shortness of breath	62%
Fatigue	70%
Other AF symptoms	52%
Congestive heart failure symptoms	29%
Angina pectoris symptoms	29%

Eligible population

The modelled cohort (eligible population) is the estimated mean number of people with signs and symptoms of AF plus an irregular pulse that would present to a single GP over the course of a year. The eligible population is calculated using the equation:

$$n_{AF} + n_{noAF} = \frac{n_{AF}(1 - p_{AF})}{p_{AF}}$$

where n_{AF} is the number of symptomatic patients with AF estimated to visit a GP in one year, n_{noAF} is the number of symptomatic patients without AF estimated to visit a GP in one year and p_{AF} is the estimated proportion of patients with signs and symptoms of AF who have AF and are estimated to visit a GP in one year.

The cost of a lead-I ECG device is estimated on a per patient basis depending on whether a GP practice has one lead-I ECG device per GP or whether a single lead-I ECG device is shared amongst all GPs in the same practice. Real-world evidence from a report [Kent Surrey Sussex AHSN and Richard Blakey, AliveCor in East Sussex, unpublished evidence submitted via NICE] indicates that each GP in a practice will have use of their own device. It is assumed, in the EAG base case, that each GP in a practice will have access to their own device.

Number of GPs per practice

The mean number of GPs per practice in England was taken from the Practice List Size and GP Count report (January 2018) published by NHS Business Services.[78] The mean number of GPs per practice used in the model is 5.90 (95% CI 5.81 to 5.99).

Practice list size

The mean practice list size in England was taken from the Practice List Size and GP Count report (January 2018) published by NHS Business Services.[78] The mean practice list size used in the model is 8187 (95% CI 8068 to 8306). The corresponding average list size per GP is 8187 / 5.90 = 1388 patients.

Proportion of patients for whom use of the lead-I ECG device will be unsuitable

There will be a proportion of patients for whom use of the lead-I ECG device will be unsuitable and this number is likely to vary depending on the device given the different methods of operation. The manufacturer of the RhythmPad GP device estimates that around 6% of patients would not be able to get a usable reading from the lead-I ECG test due to low-voltage emitted from the patient's hands or because the patient is deemed to be isoelectric. A value of 6% is applied in the model to all index tests to estimate the proportion of people unable to use the lead-I ECG device.

Proportion of lead-I ECG tests interpreted by algorithm, GP or cardiologist

It is assumed in the EAG base case analysis that the algorithm will not be used in isolation for making a judgement on whether patients have AF. Diagnostic accuracy data according to interpretation by a trained healthcare professional were applied for each index test with the exception of the RhythmPad GP device. Sensitivity and specificity estimates were only available for algorithm interpretation for the RhythmPad GP device and these have been used in the model as a proxy for interpretation by a trained healthcare professional. The proportion of lead-I ECG test results that require interpretation by a cardiologist is assumed to be 10%, following assumptions in a previous economic evaluation of screening tests for AF.[72]

Diagnostic test accuracy

Lead-I ECG devices

The diagnostic test accuracy estimates for each lead-I ECG index test have been taken from the available published evidence (Section 3.1). Sensitivity and specificity values included in the model base case for each index test are presented in Table 16. It is assumed that all patients presenting to a GP whilst experiencing symptoms of AF will be in AF at the time of

the lead-I ECG test and so the sensitivity and specificity of the lead-I ECG devices are equal for paroxysmal and permanent or persistent AF.

Table 16 Sensitivity and specificity values used in the economic model

Index test	Interpreter	Source	Sensitivity	Specificity
imPulse	Healthcare professional	Reeves (NR)	83.5%*	91.5%*
Kardia Mobile	Healthcare professional	Pooled analysis	94.0%	96.8%
MyDiagnostick	Healthcare professional	Desteghe 2017 (EP1)	85.0%	95.0%
RhythmPad GP	Algorithm	Crockford 2013	67.0%	97.0%
Zenicor-ECG	Healthcare professional	Doliwa 2009	92.0%	96.0%
Generic lead-I device	Healthcare professional	Pooled analysis from EAG SR	93.9%	96.5%

SR=systematic review
*Estimated as midpoint of range

Sensitivity and specificity estimates for the MyDiagnostick device varied depending on the interpreter (EP1 and EP2) of the results. Interpreter EP1 produced results with higher sensitivity and lower specificity than interpreter EP2. The EAG has used the diagnostic accuracy estimates for the MyDiagnostick device from EP1 in the base case, as these had the highest sensitivity and might be expected to produce the most benefits from patients receiving early NOAC treatment. Diagnostic accuracy results based on interpretation of MyDiagnostick lead-I ECG trace by EP2 are presented as a scenario analysis. Sensitivity and specificity values used in the scenario analysis are presented in Table 17.

Table 17 Sensitivity and specificity values used in an economic model scenario analysis

Index test	Interpreter	Source	Sensitivity	Specificity
MyDiagnostick	Healthcare professional	Desteghe 2017 (EP2)	80.0%	98.0%

12-lead ECG

The EAG has assumed that 12-lead ECG tests have 100% specificity and sensitivity when patients are in AF at the time of the test, as a 12-lead ECG is the gold standard reference test for lead-I ECG devices.

A proportion of patients with paroxysmal AF will not be in AF at the time of the 12-lead ECG. The estimate of the proportion of patients with paroxysmal AF who are not in AF at the time of the 12-lead ECG is taken from a study by Israel[79] to investigate the long-term risk of recurrence of AF. This trial was conducted in patients with an existing diagnosis of paroxysmal or persistent AF who were receiving antiarrhythmic therapy. Patients were given an implantable device to record episodes of AF and were also followed up with standard resting ECGs. The EAG acknowledges that the trial population is different to that in the model and notes this as

a limitation. In the Israel study,[79] 47.5% (46 out of 97) of patients had an episode of AF picked up by the implanted device that was not picked up by resting ECG. The EAG has used this estimate in the model to represent the proportion of patients with paroxysmal AF who are not in AF at the time of a 12-lead ECG.

Holter monitoring

The EAG has assumed that Holter monitor tests have 100% specificity and sensitivity when patients are in AF at the time of the test.

The estimate of the proportion of patients with paroxysmal AF who are not in AF at the time of a 7-day Holter monitor test was taken from a paper reporting the consensus of members of the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association on outcome parameters for atrial fibrillation trials.[80] This report suggests that 7-day Holter monitoring will detect around 70% of AF recurrences.

Treatment after diagnosis

According to NICE CG180,[3] patients with a positive diagnosis of AF and a CHA_2DS_2-VASc score of 2 or more should be offered anticoagulation treatment (once bleeding risk has been taken into account). It is assumed in the model that a proportion of patients who are AF-positive and have a CHA_2DS_2-VASc score of 2 or more will receive both anticoagulation (NOACs) and rate control (beta blockers). No patients are modelled to receive anticoagulation without rate control treatment. The remaining patients will not receive anticoagulation, either due to contraindications or patient choice, but a proportion will still receive rate control treatment. The proportion of patients who have a positive lead-I ECG test who do not receive anticoagulation but do receive rate control is assumed to be 100% in the base case.

Proportion of AF-positive patients with CHA_2DS_2-VASc score ≥2

The proportion of AF-positive patients with a CHA_2DS_2-VASc score of 2 or more used in the base case analysis is 82.4%. This value is calculated as the ratio of the number of patients with AF in England with a CHA_2DS_2-VASc score of 2 or more and the registered number of patients diagnosed with AF in England reported in the NHS Quality and Outcomes Framework 2016/2017 indicator AF007.[8]

Proportion of AF-positive patients with CHA_2DS_2-VASc score ≥2 treated with anticoagulants

The proportion of AF-positive patients with a CHA_2DS_2-VASc score of 2 or more who are treated with anticoagulants used in the base case analysis is 81.2%. This value is taken from the NHS Quality and Outcomes Framework 2016/2017 indicator AF007.[8]

Proportion of patients who receive anticoagulation who receive NOACs

The proportion of patients who receive anticoagulation who receive NOACs used in the base case model is calculated from May 2018 data from the openprescribing.net database published by the University of Oxford.[81] The openprescribing.net database brings together raw, GP-level prescribing data published by NHS Digital.[82] Analysis of the data from the openprescribing.net database indicates that NOAC prescriptions (apixaban, rivaroxaban, dabigatran and edoxaban) have increased steadily in England compared to warfarin prescriptions and overtook warfarin prescriptions in March 2018. The EAG notes that these figures are for anticoagulants prescribed for any condition and are not restricted to prescriptions for AF but the EAG considers the rapid increase in use of NOACs over warfarin suggests that NOACs are becoming the treatment of choice for patients and physicians. To produce a tractable model without unnecessary complexity, the EAG assumed all patients would be prescribed a NOAC rather than warfarin. This assumption also allows the maximum potential benefit from earlier diagnosis with lead-I ECG to be achieved; clinical advice to the EAG is that NOAC prescribing could happen immediately but warfarin prescribing would always first require an appointment with the anticoagulation clinic.

The overall proportion of patients diagnosed with AF (false or true positives following testing) who receive NOACs is estimated to be 66.9%. This proportion is based on estimates of the proportion of patients with a CHA_2DS_2-VASc score ≥2 and the proportion of those patients treated with anticoagulants (assumed to be 100% NOACs) (Table 18).

Table 18 Calculation of the proportion of AF patients treated with NOACs

	Value used in model	Cumulative proportion of AF population
Proportion of AF-positive patients with CHA2DS2-VASc score ≥2	82.4%	82.4%
Proportion of AF-positive patients with CHA2DS2-VASc score ≥2 treated with anticoagulants (assumed to be NOACs)	81.2%	66.9%

NOACs=new oral anticoagulants

The EAG used a single NOAC - apixaban - as the basis for modelling costs and outcomes for patients receiving NOAC therapy. Apixaban has been shown to be the most cost effective NOAC for patients with AF in England and Wales, but other NOACs have been found to have similar costs and benefits.[83] Apixaban is also the most commonly prescribed NOAC in England and accounted for almost 50% of all NOAC prescriptions in May 2018 (Figure 26). This approach has been taken in previous economic evaluations for AF.[72]

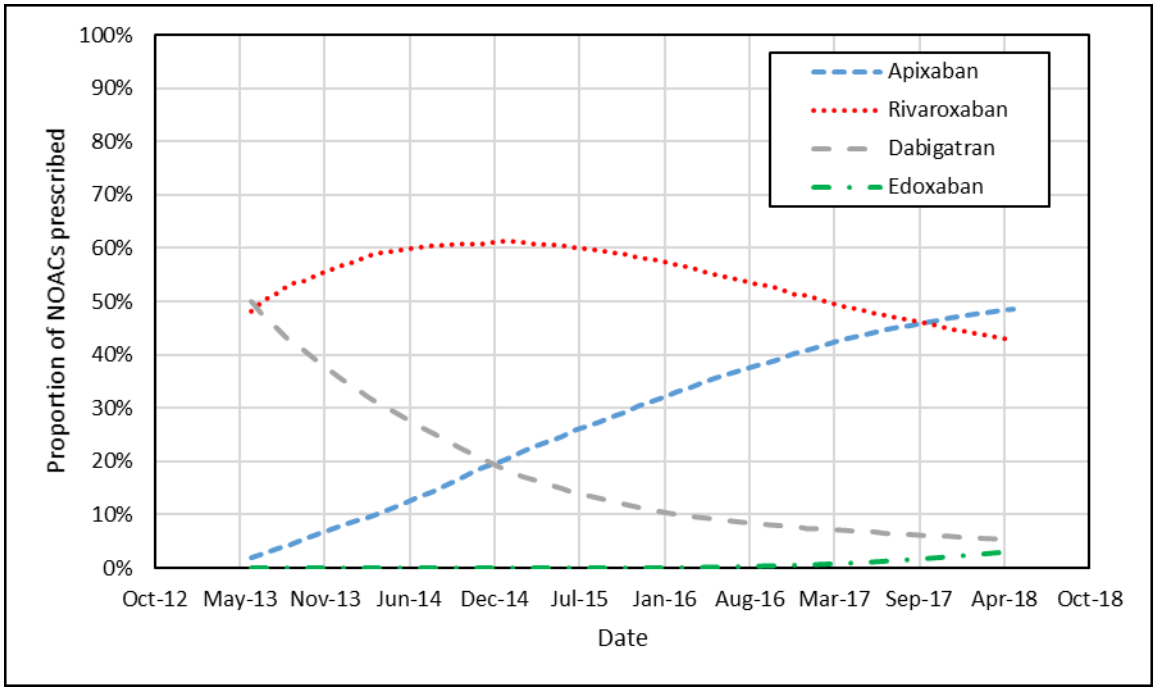

Figure 26 Proportions of apixaban, rivaroxaban, dabigatran and edoxaban prescribed in England

Source: openprescribing.net, University of Oxford[81]

Time to initiation of anticoagulation treatment after lead-I ECG test

Clinical advice to the EAG on how long it would take for a patient to be prescribed NOACs (if indicated) after a positive lead-I ECG test varied substantially depending on local Clinical Commissioning Group guidelines. In some cases, patients would be prescribed NOACs immediately after taking the lead-I ECG test during the initial consultation. In others, patients would need to wait 2 or more weeks for an appointment at an anticoagulation clinic. It is assumed in the base case analysis that treatment with NOACs will be offered immediately to those patients who do not have contraindications. This approach was used to capture the full potential benefit of beginning NOAC treatment earlier than would be the case in the standard diagnostic pathway (when anticoagulation treatment is assumed to begin immediately after the 12-lead ECG test).

Time to 12-lead ECG

Clinical advice to the EAG on how long it would take for a patient to receive a 12-lead ECG varied substantially. In some cases, the patient would be expected to have a 12-lead ECG within 48 hours. In others, the wait might be up to 2 weeks. The EAG has produced base case cost effectiveness estimates for two scenarios (2 days and 14 days) to account for the variation in time to 12-lead ECG in clinical practice.

Mortality rates (no previous CVEs)

Age- and sex-adjusted general mortality rates for England[84] were used to estimate deaths in the AF-negative population. Annual mortality rates are interpolated linearly between published annual mortality rates and then converted to daily probabilities using the equation $p = 1 - e^{-(1+\lambda)^{\frac{1}{365.25}}-1}$.

Age- and sex-adjusted mortality rates in the AF-positive population were estimated based on either published risk (or hazard) ratios or incidence rates. Single incidence rates were adjusted for age according to the proportionate mortality risk for the given age in the general population. Risk ratios were applied to mortality rates in the appropriate comparative population. It was assumed that proportionate risk remains stable over time. Mortality rates and mortality risk ratios for patients with no history of CVEs are given in Table 19.

Table 19 Mortality rates and risk ratios (no previous CVEs) used in the economic model

State	Source	Value type	Value	Use
AF: treated: NOAC	Sterne 2017[83]	HR versus warfarin (under 80 years)	0.89	
AF: untreated	Sterne 2017[83]	HR versus warfarin	1.178	
AF: treated: Warfarin	Sterne 2017[83]	Annual rate (70 years)	0.038	Reference value
No AF: treated: NOAC No AF: untreated	ONS[84]	Annual rate	Various	

ONS=Office of National Statistics; HR=hazard ratio; AF=atrial fibrillation; HR=hazard ratio; NOAC=new oral anticoagulant

Mortality rates (previous CVEs)

The risk of death for people who have had a subsequent IS, HS or TIA was increased versus the mortality risk of people who have not had a previous CVE by applying a hazard ratio to mortality rates for people with no previous CVEs. The hazard ratio was taken from a study of stroke survivors in Norway[85] which reported mortality hazard ratios for stroke survivors (IS, HS or TIA) with a mean age of 67 compared to people without these events over 16 years. This study did not report results according to AF status, which is a limitation of the data. The HR after repeated stroke or TIA versus mortality in the general population reported in the Mathisen study[85] was 2.6. The EAG considered it appropriate to apply the HR to all ages in the model, since analysis of the Kaplan-Meier data from the Mathisen study[85] suggested that HR was proportional over time. As the HR reported in the Mathisen study[85] was pooled for patients with IS, HS and TIA, the EAG assumed that the risk of death after any CVE was 2.6 times greater than the risk of death with no history of CVEs. This increased mortality rate is applied for life once a patient experiences a CVE.

Cardiovascular and adverse event rates (no previous CVEs)

The CVEs included in the model are: ischaemic stroke, TIA and haemorrhagic stroke. Clinically relevant bleeds are considered to be AEs. Rates for AEs are assumed to be independent and do not take account of the history of previous events.

Age- and sex-adjusted CVE rates in the AF-positive population for patients with no history of previous CVEs are estimated based on either published risk (or hazard) ratios, incidence rates or probabilities. Incidence rates are adjusted for age according to the proportionate mortality risk for the given age in the general population. Probabilities are adjusted for age by translating the probability into a rate before adjusting by the proportionate mortality risk for the given age in the general population Risk ratios are applied to CVE in the appropriate comparative population. It is assumed that proportionate risk remains stable over time.

CVE rates in the untreated AF-negative population with no history of previous CVEs are estimated based on published incidence rates. CVE rates in the NOAC- and warfarin-treated AF-negative population (that is, the false positive population) are estimated based on the following rule: if the risk ratio for a particular event between the treated and untreated AF-positive populations is greater than one, increase the risk for that event in the treated AF-negative population. If the risk ratio for a particular event between the treated and untreated AF-positive populations is one or less, the model uses general population rates[84] for that event.

Base case CVE and AE rates used in the economic model are given in Table 20, Table 21, Table 22 and Table 23. Rates for warfarin treatment are given where rates for NOAC and no treatment are calculated using a hazard ratio versus warfarin.

Table 20 Cardiovascular and adverse event rates: ischaemic stroke

State	Source	Value type	Value
AF: treated: NOAC	Sterne 2017[83]	HR versus warfarin	0.9
AF: treated: warfarin	Sterne 2017[83]	Annual rate (70 years)	0.012
AF: untreated	Sterne 2017[83]	HR versus warfarin	1.178
No AF: treated: NOAC			General population
No AF: untreated	PHE 2018[86]	Annual rate (female, 50 years)	0.0007
		Annual rate (female, 60 years)	0.0013
		Annual rate (female, 70 years)	0.0030
		Annual rate (female, 80 years)	0.0060
		Annual rate (female, 90 years)	0.0108
		Annual rate (male, 50 years)	0.0012
		Annual rate (male, 60 years)	0.0023
		Annual rate (male, 70 years)	0.0044
		Annual rate (male, 80 years)	0.0064
		Annual rate (male, 90 years)	0.0099

PHE=Public Health England; HR=hazard ratio; AF=atrial fibrillation; NOAC=new oral anticoagulants

Table 21 Cardiovascular and adverse event rates: bleed

State	Source	Value type	Value
AF: treated: NOAC	Sterne 2017[83]	HR versus warfarin	0.82
AF: treated: warfarin	Sterne 2017[83]	Annual rate (70 years)	0.066
AF: untreated	Sterne 2017[83]	HR versus warfarin	0.543
No AF: treated: NOAC	Calculated	HR versus untreated	1.511
No AF: untreated	NHS Reference Costs 2016/17[87] Includes: gastrointestinal bleed (FD03A:FD03H), unspecified haematuria (LB38C:LB38H), non-malignant GI tract disorders (FD10A: FD10M)	Annual rate (assume 70 years)	0.011*

HR=hazard ratio; AF=atrial fibrillation; NOAC=new oral anticoagulants
*Estimated as incidence of activity reported in NHS Reference Costs[87] per population in England (19 or over) reported by the Office for National Statistics[84]

Table 22 Cardiovascular and adverse event rates: transient ischaemic attack

State	Source	Value type	Value
AF: treated: NOAC	Sterne 2017[83]	HR versus warfarin	0.740
AF: treated: Warfarin	Sterne 2017[83]	Annual rate (70 years)	0.025
AF: untreated	Sterne 2017[83]	HR versus warfarin	1.617
No AF: treated: NOAC			General population
No AF: untreated	Rothwell 2005[88]*	Annual rate (female, 50 years)	0.0003
		Annual rate (female, 60 years)	0.0011
		Annual rate (female, 70 years)	0.0022
		Annual rate (female, 80 years)	0.0057
		Annual rate (female, 90 years)	0.0093
		Annual rate (male, 50 years)	0.0002
		Annual rate (male, 60 years)	0.0005
		Annual rate (male, 70 years)	0.0014
		Annual rate (male, 80 years)	0.0034
		Annual rate (male, 90 years)	0.0080

HR=hazard ratio; AF=atrial fibrillation; NOAC=new oral anticoagulants
*Incidence rates estimated from published figures

Table 23 Cardiovascular and adverse event rates: haemorrhagic stroke

State	Source	Value type	Value
AF: treated: NOAC	Sterne 2017[83]	HR versus warfarin	0.46
AF: treated: warfarin	Sterne 2017[83]	Annual rate (70 years)	0.009
AF: untreated	Sterne 2017[83]	HR versus warfarin	0.543
No AF: treated: NOAC			General population
No AF: untreated	Rothwell 2005[88]*	Annual rate (female, 50 years)	0.00002
		Annual rate (female, 60 years)	0.00019
		Annual rate (female, 70 years)	0.00034
		Annual rate (female, 80 years)	0.00100
		Annual rate (female, 90 years)	0.00104
		Annual rate (male, 50 years)	0.00002
		Annual rate (male, 60 years)	0.00019
		Annual rate (male, 70 years)	0.00026
		Annual rate (male, 80 years)	0.00171
		Annual rate (male, 90 years)	0.00078

HR=hazard ratio; AF=atrial fibrillation; NOAC=new oral anticoagulants
*Incidence rates estimated from published figures

Cardiovascular and adverse event rates (previous CVEs)

A meta-analysis of stroke recurrence was conducted in 2010 that reported recurrence rates of 6.5% at one year and 14.3% at five years.[89] These subsequent stroke rates were applied to people in the model after their first TIA, IS or HS. The proportion of subsequent strokes that were TIA, IS or HS was calculated using proportionate incidence rates reported in a study by Rothwell.[88] The annual recurrent stroke rate between year two and year five was calculated by assuming the rate was constant between years two and five. The subsequent stroke rate from year five onwards was assumed to be the same as in years two to five. Having a subsequent stroke after first IS or HS post-discharge did not alter any transition probabilities in the model as the increase in mortality risk was assumed to have been captured after the initial IS or HS. The probability of subsequent stroke and the proportion of subsequent strokes that are TIA, IS or HS are shown in Table 24.

Table 24 Probability of subsequent stroke and the proportion of subsequent strokes that are TIA, IS or HS

Event		Base case	Source
Probability of subsequent CVE (annual)	Year 1	0.065	Mohan 2011[89]
	Year 2 onwards	0.038	
Probability that subsequent CVE is:	TIA	0.640	Rothwell 2005[88]
	IS	0.057	
	HS	0.303	

CVE=cardiovascular event; HS=haemorrhagic stroke; IS=ischaemic stroke; TIA=transient ischaemic attack

Utilities

State-specific utilities

Utility values have been estimated for symptomatic and asymptomatic populations with and without AF. Utility values for the symptomatic AF-positive population have been applied to those patients who are not treated. Utility values for the asymptomatic AF-positive population have been applied to those patients who are treated. Symptomatic patients without AF are assumed to have the same health-related quality of life as treated (symptomatic) patients with AF, regardless of whether they are treated inappropriately due to a false positive result from a lead-I ECG test.

Utility values for the symptomatic and asymptomatic AF-positive population are based on a study by Berg.[77] Berg provides the coefficients of two regression models fitted to the results of the EQ-5D-3L[90] questionnaire completed at baseline and follow-up as part of a large European survey of patients with AF. Mean age-specific utility values for symptomatic patients with AF were calculated using the baseline coefficients from the study by Berg[77] and adjusted for model age, sex ratio and symptom proportions. Mean age-specific utility values for asymptomatic patients with AF were calculated similarly using the coefficients at follow-up.

In the base case, it is assumed that utility values for the symptomatic AF-negative population are equal to utility values for the symptomatic AF-positive population. Utility values for the asymptomatic AF-negative population were assumed to follow population norms.[91] Age- and sex-specific general population EQ-5D-3L index values using the UK time trade-off value set were taken from reference data published by the EuroQol Group[91] and weighted by the proportions in the model.

Table 25 Age- and sex-adjusted utility values (age 70) used in the base case model

	AF (95% CI)	No AF (95% CI)
Untreated (symptomatic)	0.665 (0.537 to 0.881)	0.665 (0.537 to 0.881)
Treated (asymptomatic)	0.744 (0.480 to 0.942)	0.665 (0.537 to 0.881)

AF=atrial fibrillation
Source: Adapted from Berg[77] and Janssen[91]

Cardiovascular and adverse event utility decrements

Lifetime utility decrements were assumed to apply to all ischaemic and haemorrhagic stroke events (Table 26). Utility decrements for stroke were taken from the study by Berg.[77] Utility decrements were applied at the time of the first IS or HS and no further decrements were applied for any subsequent IS or HS. Bleed and TIA events were assumed to be acute events that fully resolve and have no long-term impact on HRQoL.

Table 26 Utility decrements for acute adverse events

AE	Base case		Sensitivity analysis	
	Decrement	Source	Decrement or value	Source
Ischaemic stroke	-0.272 (95% CI: -0.345 to -0.198)	Berg 2010[77]	-0.59	Robinson 2001[92]
Haemorrhagic stroke	Assumed equal to ischaemic stroke		Value for ICH: -0.108 (95% CI: -0.135 to -0.082)	Berg 2010[77]

AE=adverse event; ICH=intracerebral haemorrhage; MI=myocardial infarction; SE=standard error; TIA=transient ischemic attack

Test costs

Annual lead-I ECG device unit costs

The annual cost of each lead-I ECG device was calculated as the unit cost per device (including 20% VAT) divided across the expected life of the device in years plus annual licence fee. No companies reported any maintenance costs associated with their devices, so these have not been included in the model. An average cost for a generic lead-I ECG device was calculated using the simple mean of the annual cost of individual devices. The annual cost of each index test included in the model is given in Table 27. Lead-I ECG devices are also likely to be used in populations other than the population with signs and symptoms of AF, which would decrease the unit cost per use of each device. The impact on cost effectiveness of not including the cost of the lead-I ECG device has been investigated in a sensitivity analysis.

Table 27 Annual costs of lead-I ECG devices

Device	Item	Unit cost	Life	Annual cost
imPulse	Device	£210	2 years	£105
Kardia Mobile	Device	£99	5 years	£19.80
MyDiagnostick	Device	£540	3 years	£180
RhythmPadGP	Device	£1320	1 year	£1320
Zenicor ECG	Device	£2374	10 years	£949.60
	User licence	£2136	3 years	
Generic lead-I ECG device				£514.88

Cost per lead-I ECG test

The cost per lead-I ECG test in the standard diagnostic pathway was zero, as it was assumed the only resource use in this context was the cost of the GP consultation. The cost of the initial GP consultation is assumed to be equal in both diagnostic pathways and is not included in the model. An extra 5 minutes of GP consultation time is included in the model for the lead-I ECG diagnostic pathway. The results of a study by Hobbs[93] showed that administration of a 12-lead ECG took 7 minutes of nurse time on average. It is assumed that the lead-I ECG test will take less time than a 12-lead ECG to administer, but will still take more time than the MPP in the standard diagnostic pathway to allow the GP to explain what they are doing and to interpret the results.

The cost per lead-I ECG test was calculated as the annual cost per device divided by the number of patients in the eligible population per year plus any extra costs associated with each use of the device; the Zenicor-ECG device was the only index test included in the model to incur extra costs with each use, as the manufacturer recommends that the electrodes are replaced after 500 uses.

It is assumed that review of the results of a lead-I ECG test by a cardiologist would take 1 minute, in accordance with results from the study by Hobbs.[93] The costs per index test and cost of interpreting the lead-I ECG test included in the model are given in Table 28 and Table 29.

Table 28 Cost per lead-I ECG test

Device	Annual cost	Number of patients tested per year	Peripherals cost per test	Unit cost per test
imPulse	£105.00	54	0.00	£1.95
Kardia Mobile	£19.80	54	0.00	£0.37
MyDiagnostick	£180.00	54	0.00	£3.34
RhythmPadGP	£1,320.00	54	0.00	£24.50
Zenicor ECG	£949.60	54	0.02	£17.65
Generic lead-I device	£514.88	54	0.02	£9.58

Table 29 Cost per administration and interpretation of lead-I ECG test

	Unit cost	Source	Time taken	Cost per test
Algorithm	£0		0	£0
GP	£37.00 per 9.22 minute consultation	PSSRU[94]	5 minutes	£20.07
Cardiologist	£107 per hour	PSSRU[94]	1 minute*	£1.78

*Based on data from Hobbs[93]

Cost per 12-lead ECG test

The cost per 12-lead ECG test varies depending on whether the test is carried out in primary or secondary care.

For 12-lead ECG tests carried out in primary care, the unit cost of a 12-lead ECG device is estimated to be £2,251 in line with the estimate used in NICE Guideline 45 (NG45)[95] inflated to 2017 prices using the Office for National Statistics Consumer Price Index (ONS CPI) for Medical Services [DKC3].[96] It is assumed in the model that a 12-lead ECG device may be used 1000 times before being replaced, in line with the assumption in NICE NG45,[95] which equates to £2.25 per use. The cost of disposables such as electrodes and gels is estimated to be £1.13 per use, uplifted to 2017 prices from the estimate used in NICE NG45.[95]

The cost of administering a 12-lead ECG test in secondary care is estimated using the NHS Reference Cost[97] for Electrocardiogram Monitoring or Stress Testing (directly accessed diagnostic services HRG: EY51Z).

The costs of administering the 12-lead ECG test in primary and secondary care are summarised in Table 30.

Table 30 Healthcare practitioner costs per 12-lead ECG test (primary and secondary care)

	Unit cost	Source	Activity	Time taken	Cost per test
Primary care					
Device	£2.25 per use	Estimate			£2.25
Disposables	£1.13 per use	Hobbs[93]			£1.13
Nurse	£42 per hour	PSSRU[94]	Administration	7 minutes*	£4.90
GP	£137 per hour	PSSRU[94]	Interpretation	1 minute*	£2.28
Cardiologist	£107 per hour	PSSRU[94]	Interpretation	1 minute*	£1.78
Total cost per 12-lead ECG test in primary care					£12.34
Secondary care					
Electrocardiogram Monitoring or Stress Testing	£52 per test	NHS Reference costs 2016/17 (HRG: EY51Z DADS)[97]		N/A	£52

HRG=Healthcare Resource Group; DADS=directly accessed diagnostic services
*Based on data from Hobbs[93]

Cost per paroxysmal test

Further testing for paroxysmal AF is represented by the use of a Holter monitor. The cost of a Holter monitor test is taken from an estimate in a NICE Medtech innovation briefing [MIB101][98] published in March 2017. The list price of a Holter monitor device in the NHS Supply Chain catalogue is given as £1632.14 in NICE MIB101.[98] It assumed that the device will be used 1000 times before needing to be replaced, giving a marginal cost per use of £1.63. The cost of administering and interpreting a Holter monitor test is estimated in NICE MIB101[98] to be £118.60 including overheads. The total cost per each Holter monitor test in the model is £120.23.

Treatment costs

NOAC drug costs

The cost of treatment with NOACs was assumed to equal the cost of treatment with apixaban. The cost of 1 month's (28 days) treatment with apixaban was calculated using dosing information from the British National Formulary[99] and prices from the NHS Drug Tariff (July 2018)[100] and adjusted to apply to the number of days of treatment before receiving a 12-lead ECG. It was assumed that dosages would be prescribed in equal proportions. The number of

packs used per month for each dosage was calculated based on the least costly combination of pack sizes. The base case drug cost of apixaban used in the model was £165.30 per 28 days (Table 31).

Table 31 Drug costs: apixaban

Dose (mg) (BNF)[99]	Frequency (per day) (BNF)[99]	Tablet size (mg) (NHS)[100]	Pack size (tablets) (NHS)[100]	Packs per 28 days	Pack cost (NHS)[100]	Monthly cost per dose
5	2	5	56	1	£53.20	£53.20
2.5	2	2.5	60	1	£57.00	£57.00
					Average cost per 28 days	£55.10

Source: BNF;[99] NHS Drug Tariff[100]

Rate control drug costs

The cost of treatment with beta blockers was used as a proxy for the cost of all rate control treatments. The cost of 1 month's (28 days) treatment with each of three beta blockers (atenolol, metoprolol and propranolol) was calculated using dosing information from the British National Formulary[99] and prices from the NHS Drug Tariff (July 2018)[100] and adjusted to apply to the number of days of treatment before receiving a 12-lead ECG. It was assumed that dosages would be prescribed in equal proportions. The number of packs used per month for each dosage was calculated based on the least costly combination of pack sizes. The base case drug cost of rate control drugs used in the model was £2.59 per 28 days (Table 32).

Table 32 Drug costs: rate control

Dose (mg) (BNF)[99]	Frequency (per day) (BNF)[99]	Tablet size (mg) (NHS)[100]	Pack size (tablets) (NHS)[100]	Packs per 28 days	Pack cost (NHS)[100]	Monthly cost per dose
Atenolol						
50	1	50	28	1	£0.47	£0.47
100	1	100	28	1	£0.51	£0.51
					Average cost per 28 days	£0.49
Metoprolol						
50	2	50	28	2	£0.78	£1.56
50	3	50	28	3	£0.78	£2.34
					Average cost per 28 days	£1.95
Propranolol						
10	2.61	2.61	2.61	2.61	2.61	2.61
10	3.48	3.48	3.48	3.48	3.48	3.48
20	5.22	5.22	5.22	5.22	5.22	5.22
20	6.96	6.96	6.96	6.96	6.96	6.96
30	7.83	7.83	7.83	7.83	7.83	7.83
30	10.44	10.44	10.44	10.44	10.44	10.44
40	2.64	2.64	2.64	2.64	2.64	2.64
40	3.52	3.52	3.52	3.52	3.52	3.52

	Average cost per 28 days	5.34
All drugs		
	Average cost per 28 days	£2.59

Source: BNF;[99] NHS Drug Tariff[100]

Prescription costs

The EAG model base case includes a prescription cost for each treated patient. The same prescription cost was applied regardless of the number of treatments a patient receives (anticoagulation plus rate control or rate control alone). The prescription fee included in the model was £1.29 per prescription and was taken from the NHS Drug Tariff (July 2018).[100]

NOAC monitoring costs

No costs were included in the model for monitoring patients taking NOAC or rate control treatment.

Cardiovascular and adverse event costs

Acute event costs

The cost of each acute bleed and TIA event was calculated as the weighted average of the appropriate Healthcare Resource Group (HRG) codes included in the NHS Reference Costs 2016/17.[97] The full cost of each event was applied. Costs used in the model base case for each event are shown inTable 33.

Table 33 Acute costs per adverse event

AE	HRG codes	Mean cost per event (£) (IQR)
Bleed	Gastrointestinal Bleed without Interventions (FD03F:FD03H) Unspecified Haematuria with Interventions (LB38C:LB38E)	704.05(592.24 to 782.48)
TIA	Transient Ischaemic Attack (AA29C:AA29F)	729.62 (570.08 to 837.65)

AE=adverse event; HRG=Healthcare Resource Group; IQR=interquartile range; TIA= transient ischaemic attack
Source: NHS Reference Costs 2016/17[87]

Long-term cardiovascular event costs

Age- and sex-adjusted 1- and 5-year costs for ischaemic and haemorrhagic stroke were taken from the Sentinel Stroke National Audit Programme (SSNAP) Cost and Cost-effectiveness report 2016 (Table 34 andTable 35).[101] One-year costs were applied in the first year after the stroke event. The annual costs between year two and year five were calculated by assuming that the difference in cost between year one and year five accrued linearly between years two and five. The cost from year five onwards was assumed to be the same as in years two to five. Costs restart at year one for patients who experience a subsequent CVE.

Table 34 Mean cost of ischaemic stroke, by age and sex

Sex	Age	1 Year		5 Year	
		NHS	Social care	NHS	Social care
Male	40-64	£9,779	£2,241	£16,017	£8,835
Male	65-74	£11,495	£3,684	£16,843	£14,110
Male	75-84	£13,217	£7,620	£17,816	£25,148
Male	85-100	£14,906	£13,070	£18,613	£38,623
Female	40-64	£9,627	£2,312	£15,954	£9,308
Female	65-74	£11,705	£3,878	£16,987	£14,668
Female	75-84	£13,441	£7,923	£17,995	£26,370
Female	85-100	£15,803	£13,500	£18,947	£38,585

Source: SSNAP[101]

Table 35 Mean cost of haemorrhagic stroke, by age and sex

Sex	Age	1 Year		5 Year	
		NHS	Social care	NHS	Social care
Male	40-64	£11,465	£3,661	£17,857	£15,063
Male	65-74	£12,773	£4,862	£18,188	£18,960
Male	75-84	£14,605	£10,545	£19,389	£36,994
Male	85-100	£16,291	£15,551	£19,896	£49,256
Female	40-64	£11,260	£3,256	£17,538	£13,508
Female	65-74	£12,734	£5,285	£18,143	£20,476
Female	75-84	£14,747	£11,379	£19,103	£37,630
Female	85-100	£16,481	£15,425	£19,750	£46,730

Source: SSNAP[101]

Summary of base case assumptions

Parameter assumptions and sources used in the base case model are summarised in Table 36.

Table 36 Base case model assumptions

Parameter	Assumption or source	Justification
AF status at initial consultation	All patients with AF are in AF at the time of the initial consultation	Population is patients presenting to primary with signs and symptoms of AF and an irregular pulse. These symptoms are assumed to be caused by AF if the patient has AF.
Mean age	70 years	Mean age observed in RCTs used by Sterne[83] and to estimate CVE rate parameters
% female	51.6%	Age-adjusted proportion in the general population, assumed to match proportion in GP lists
AF prevalence	Adderley 2018	Recent data from UK primary care
Proportion of AF undiagnosed	Turakhia 2018	Recent data
Proportion of AF with signs and symptoms	Mapped from Schnabel[76] to Berg[77]	Real world data [Kent Surrey Sussex AHSN]

Proportion of patients with undiagnosed symptomatic AF who have paroxysmal AF	50%	Assumption due to wide range reported by Welton and the lack of evidence specifically on incidence rates for symptomatic paroxysmal AF
Number of lead-I ECG devices per practice	One per GP	Previous economic evaluation[72]
Proportion of lead-I ECG tests interpreted by GP and cardiologist	10%	Data from Hobbs[93] estimates 7 minutes for a nurse to administer a 12-lead ECG. Assume less than 7 minutes for a lead-I ECG, but some extra time still required to explain and carry out procedure
Extra time taken to administer lead-I ECG test	0 minutes	Test is assumed to be administered during standard GP appointment
Proportion of patients receiving anticoagulation	Only CHA2DS2-VASc ≥2 receive anticoagulation (if not contraindicated)	Scope
Proportion of patients receiving anticoagulation who receive NOACs	100%	Simplifying assumption based on evidence that prescriptions for NOACs overtook prescriptions for warfarin in 2018
Time from diagnosis to anticoagulation	Immediate	Simplifying assumption allowing the maximum potential benefit from earlier diagnosis with lead-I ECG
Proportion of patients receiving 12-lead ECG	100% for standard pathway and lead-I positive 80% for lead-I negative	Standard pathway: NICE CG180[3] Lead-I positive (AF diagnosed): NICE CG180[3] Lead-I negative: assumption based on clinical advice (Appendix 9) and varied in sensitivity analyses
Diagnostic accuracy of 12-lead ECG	100% sensitivity and specificity for those patients in AF at time of test	12-lead ECG is reference test for lead-I devices, hence must be assumed to be 100% accurate
Proportion of patients with paroxysmal AF not in AF at time of 12-lead ECG	47.5%	Data from Israel 2004
Diagnostic accuracy of Holter monitor	100% sensitivity and specificity for those patients in AF at time of test	Simplifying assumption
Proportion of patients with paroxysmal AF not in AF at time of Holter monitor	30%	Data from Kirchoff 2006

4.2.6 Uncertainty

Uncertainty in parameter values and the impact this could have on results has been explored both through the scenario and sensitivity analyses. Parameters have been varied through probability sensitivity analysis parameters where probability distributions could be derived from, or were provided in, the literature. Probabilistic sensitivity analysis results have been presented as cost-effectiveness acceptability curves (CEACs) where different willingness to pay thresholds for a QALY are used to show which strategy is likely to have the largest net benefit for that threshold.

4.2.7 Interpreting results

Incremental cost-effectiveness ratios

The results of cost-effectiveness analysis are presented as ICERs per QALY gained. These are calculated by dividing the difference in costs associated with two alternative strategies by the difference in QALYs:

$$ICER = \frac{Cost\ of\ B - Cost\ of\ A}{QALY\ of\ B - QALY\ of\ A}$$

Where more than two strategies are compared, the ICER is calculated according to the following process:

1. the strategies are ranked in terms of cost, from least to most expensive
2. if a strategy is more expensive and less effective than the preceding strategy it is said to be 'dominated' and is excluded from further analysis
3. ICERs are then calculated for each strategy compared with the next most expensive non-dominated option. If the ICER for a strategy is higher than that of the next most effective strategy, then it is ruled out by 'extended dominance'
4. ICERs are recalculated excluding any strategy subject to dominance or extended dominance
5. the non-dominated strategies form an ‘efficiency frontier’ of strategies that are cost-effective and can then be judged against the value of an ICER that is generally considered cost-effective by NICE, i.e. £20,000 - £30,000 per QALY gained.

4.3 Base case results

The model included a hypothetical cohort of 53.88 patients. This figure equates to the estimated number of patients with signs and symptoms indicative of AF and with an irregular pulse who would visit a single GP annually and be eligible for testing with a lead-I ECG device. Of the total eligible population in the model, 10.78 had AF and 43.11 did not have AF.

Four base case scenarios were investigated to estimate cost effectiveness depending on the waiting times for a 12-lead ECG test and the location of the 12-lead ECG test. The base case scenarios are:

- Base Case 1: 12-lead ECG in primary care, 2 days to 12-lead ECG
- Base Case 2: 12-lead ECG in primary care, 14 days to 12-lead ECG
- Base Case 3: 12-lead ECG in secondary care, 2 days to 12-lead ECG

- Base Case 4: 12-lead ECG in secondary care, 14 days to 12-lead ECG

4.3.1 Base Case 1: 12-lead ECG in primary care, 2 days to 12-lead ECG

Costs and QALYs generated in Base Case 1 are shown in Table 37 and Table 38 respectively.

Table 37 Base Case 1: Total costs of annual number of symptomatic patients with positive MPP seen by a single GP'

Strategy	Lead-I ECG device	Treatment (NOACs & rate control)	CVEs and AEs	12-lead ECG	Paroxysmal testing (holter monitor)	Total costs
Standard pathway	£0	£113,996	£528,101	£566	£2,742	£645,405
Kardia Mobile	£29	£125,315	£514,693	£477	£2,740	£643,255
imPulse	£115	£138,606	£516,927	£480	£2,737	£658,864
MyDiagnostick	£190	£129,484	£516,584	£477	£2,737	£649,471
Generic lead-I device	£526	£126,099	£514,716	£477	£2,740	£644,558
Zenicor-ECG	£961	£127,295	£515,117	£477	£2,740	£646,589
RhythmPad*	£1,330	£123,071	£520,106	£471	£2,732	£647,909

AE=adverse events; CVE=cardiovascular events
*Algorithm interpretation

Table 38 Base Case 1: QALYs and patient outcomes

Strategy	IS	HS	TIA	False negatives	False positives	Bleeds	Total QALYs
Standard pathway	10.091	1.988	7.676	1.607	0.000	35.650	464.978
Kardia Mobile	9.925	1.861	7.632	0.144	1.879	35.115	465.767
imPulse	9.952	1.883	7.637	0.197	3.662	35.200	465.643
MyDiagnostick	9.943	1.880	7.637	0.161	2.194	35.175	465.638
Generic lead-I device	9.925	1.861	7.632	0.147	1.508	35.117	465.768
Zenicor-ECG	9.930	1.865	7.633	0.193	1.723	35.130	465.742
RhythmPad*	9.993	1.919	7.646	0.795	1.292	35.266	465.332

AE=adverse events; CVE=cardiovascular events; QALY=quality adjusted life year; IS=ischaemic stroke; HS=haemhorragic stroke; TIA=transient ischaemic accident
*Algorithm interpretation

Pairwise cost effectiveness results from the Base Case 1 analysis for each index test versus the standard diagnostic pathway are presented in Table 39 and incremental analysis are shown in Table 40**Error! Reference source not found.**.

Table 39 Base Case 1: Pairwise cost effectiveness analysis

Strategy	Costs	QALYs	Incremental costs	Incremental QALYs	ICER/ QALY gained
Standard pathway	£645,405	464.978			
Kardia Mobile	£643,255	465.767	-£2,150	0.789	Dominates
imPulse	£658,864	465.643	£13,459	0.665	£20,228
MyDiagnostick	£649,471	465.638	£4,066	0.660	£6,161

Generic lead-I device	£644,558	465.768	-£847	0.790	Dominates
Zenicor-ECG	£646,589	465.742	£1,184	0.764	£1,551
RhythmPad*	£647,909	465.332	£2,504	0.354	£7,069

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
*Algorithm interpretation

Table 40 Base Case 1: Incremental cost effectiveness analysis

Strategy	Costs	QALYs	Incremental costs	Incremental QALYs	ICER/ QALY gained
Kardia Mobile	£643,255	465.767			
Generic lead-I device	£644,558	465.768	£1,304	0.001	£1,411,448
Standard pathway	£645,405	464.978	£847	-0.790	Dominated
Zenicor-ECG	£64[illegible]	[illegible]	[illegible]	[illegible]	Dominated
RhythmPad*	£64[illegible]	465.332	£3,3[illegible]	-0.436	Dominated
MyDiagnostick	£649,471	465.638	£4,913	-0.130	Dominated
imPulse	£658,864	465.643	£14,305	-0.124	Dominated

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
*Algorithm interpretation

4.3.2 Base Case 2: 12-lead ECG in primary care, 14 days to 12-lead ECG

Costs and QALYs generated in Base Case 2 are shown in Table 41 and Table 42 respectively.

Table 41 Base Case 2: Total costs of annual number of symptomatic patients with positive MPP seen by a single GP

Strategy	Lead-I ECG device	Treatment (NOACs & rate control)	CVEs and AEs	12-lead ECG	Paroxysmal testing (holter monitor)	Total costs
Standard pathway	£0	£113,822	£528,648	£565	£2,737	£645,772
Kardia Mobile	£29	£124,991	£514,623	£476	£2,737	£642,857
imPulse	£[illegible]	£[illegible]38,260	£516,855	£479	£2,734	£658,443
MyDiagnostick	£190	£129,[illegible]61	£516,512	£476	£2,734	£649,063
Generic lead-I device	£526	£125,773	£514,647	£476	£2,737	£644,159
Zenicor-ECG	£961	£126,967	£515,047	£477	£2,736	£646,188
RhythmPad*	£1,330	£122,740	£520,230	£470	£2,728	£647,498

AE=adverse events; CVE=cardiovascular events
*Algorithm interpretation

Table 42 Base Case 2: QALYs and patient outcomes

Strategy	IS	HS	TIA	False negatives	False positives	Bleeds	Total QALYs
Standard pathway	10.090	1.987	7.678	1.607	0.000	35.660	464.951
Kardia Mobile	9.922	1.860	7.630	0.144	1.377	35.101	465.845
imPulse	9.949	1.883	7.636	0.397	3.657	35.183	465.714
MyDiagnostick	9.945	1.880	7.635	0.360	2.151	35.159	465.713
Generic lead-I device	9.923	1.861	7.630	0.147	1.506	35.103	465.846
Zenicor-ECG	9.927	1.865	7.631	0.192	1.721	35.116	465.819

RhythmPad*	9.990	1.919	7.644	0.793	1.291	35.245	465.405

AE=adverse events; CVE=cardiovascular events; QALY=quality adjusted life year; IS=ischaemic stroke; HS=haemhorragic stroke; TIA=transient ischaemic accident
*Algorithm interpretation

Pairwise cost effectiveness results from the Base Case 2 analysis for each index test versus the standard diagnostic pathway are presented in Table 43 and incremental analysis are shown in Table 44.

Table 43 Base Case 2: Pairwise cost effectiveness analysis

Strategy	Costs	QALYs	Incremental costs	Incremental QALYs	ICER/ QALY gained
Standard pathway	£645,772	464.951			
Kardia Mobile	£642,857	465.845	-£2,916	0.894	Dominates
imPulse	£658,443	465.714	£12,670	0.763	£16,611
MyDiagnostick	£64[illegible]	[illegible]	[illegible]	[illegible]	£4,321
Generic lead-I device	£64[illegible]	[illegible]	-£1,6[illegible]	0.895	Dominates
Zenicor-ECG	£646,188	465.819	£415	0.868	£479
RhythmPad*	£647,498	465.405	£1,725	0.454	£3,801

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
*Algorithm interpretation

Table 44 Base Case 2: Incremental cost effectiveness analysis

Strategy	Costs	QALYs	Incremental costs	Incremental QALYs	ICER/ QALY gained
Kardia Mobile	£642,857	[illegible]			
Generic lead-I device	£644,159	465.846	£1,303	0.001	£2,237,664
Standard pathway	£645,772	464.951	£1,613	-0.895	Dominated
Zenicor-ECG	£646,188	465.819	£2,028	-0.027	Dominated
RhythmPad*	£647,498	465.405	£3,338	-0.441	Dominated
MyDiagnostick	£649,063	465.713	£4,903	-0.133	Dominated
imPulse	£658,443	465.714	£14,283	-0.132	Dominated

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
*Algorithm interpretation

4.3.3 Base Case 3: 12-lead ECG in secondary care, 2 days to 12-lead ECG

Costs and QALYs generated in Base Case 3 are shown in Table 45 and Table 46 respectively.

Table 45 Base Case 3: Total costs of annual number of symptomatic patients with positive MPP seen by a single GP

Strategy	Lead-I ECG device	Treatment (NOACs & rate control)	CVEs and AEs	12-lead ECG	Paroxysmal testing (holter monitor)	Total costs
Standard pathway	£0	£113,996	£528,101	£2,801	£2,742	£647,640
Kardia Mobile	£29	£125,315	£514,693	£2,360	£2,740	£645,138
imPulse	£115	£138,606	£516,927	£2,372	£2,737	£660,757
MyDiagnostick	£190	£129,484	£516,584	£2,358	£2,737	£651,353
Generic lead-I device	£526	£126,099	£514,716	£2,362	£2,740	£646,443
Zenicor-ECG	£961	£127,295	£515,117	£2,362	£2,740	£648,474
RhythmPad*	£1,330	£123,071	£520,306	£2,329	£2,732	£649,767

AE=adverse events; CVE=cardiovascular events
*Algorithm interpretation

Table 46 Base Case 3: QALYs and patient outcomes

Strategy	IS	HS	TIA	False negatives	False positives	Bleeds	Total QALYs
Standard pathway	10.091	1.988	7.676	1.607	0.000	35.650	464.978
Kardia Mobile	9.925	1.860	7.632	0.144	1.379	35.115	465.767
imPulse	9.952	1.883	7.638	0.397	3.662	35.200	465.643
MyDiagnostick	9.948	1.880	7.637	0.361	2.154	35.175	465.638
Generic lead-I device	9.925	1.861	7.632	0.147	1.508	35.117	465.768
Zenicor-ECG	9.930	1.865	7.633	0.193	1.723	35.130	465.742
RhythmPad*	9.993	1.919	7.646	0.795	1.292	35.266	465.332

AE=adverse events; CVE=cardiovascular events; QALY=quality adjusted life year; IS=ischaemic stroke; HS=haemhorragic stroke; TIA=transient ischaemic accident
*Algorithm interpretation

Pairwise cost effectiveness results from the Base Case 3 analysis for each index test versus the standard diagnostic pathway are presented in Table 47 and incremental analysis are shown in Table 48.

Table 47 Base Case 3: Pairwise cost effectiveness analysis

Strategy	Costs	QALYs	Incremental costs	Incremental QALYs	ICER/ QALY gained
Standard pathway	£647,640	464.978			
Kardia Mobile	£645,138	465.767	-£2,502	0.789	Dominates
imPulse	£660,757	465.643	£13,117	0.665	£19,714
MyDiagnostick	£651,353	465.638	£3,713	0.660	£5,626
Generic lead-I device	£646,443	465.768	-£1,197	0.790	Dominates
Zenicor-ECG	£648,474	465.742	£834	0.764	£1,092
RhythmPad*	£649,767	465.332	£2,128	0.354	£6,007

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
*Algorithm interpretation

Table 48 Base Case 3: Incremental cost effectiveness analysis

Strategy	Costs	QALYs	Incremental costs	Incremental QALYs	ICER/ QALY gained
Kardia Mobile	£670,910	463.215			
Generic lead-I device	£672,214	463.216	£1,305	0.001	£1,437,285
Standard pathway	£673,722	462.423	£1,507	-0.792	Dominated
Zenicor-ECG	£674,255	463.189	£2,040	-0.026	Dominated
RhythmPad*	£675,685	462.779	£3,471	-0.436	Dominated
MyDiagnostick	£677,170	463.086	£4,955	-0.130	Dominated
imPulse	£686,575	463.091	£14,361	-0.125	Dominated

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
*Algorithm interpretation

4.3.4 Base Case 4: 12-lead ECG in secondary care, 14 days to 12-lead ECG

Costs and QALYs generated in Base Case 4 are shown in Table 49 and Table 50 respectively.

Table 49 Base Case 4: Total costs of annual number of symptomatic patients with positive MPP seen by a single GP

Strategy	Lead-I ECG device	Treatment (NOACs & rate control)	CVE and AEs	12 lead ECG	Paroxysmal testing (holter monitor)	Total costs
Standard pathway	£0	£113,822	£528,648	£2,795	£2,737	£648,002
Kardia Mobile	£29	£124,991	£514,623	£2,356	£2,737	£644,737
imPulse	£115	£138,260	£516,855	£2,368	£2,734	£660,332
MyDiagnostick	£190	£129,151	£516,512	£2,354	£2,734	£650,941
Generic lead-I device	£526	£125,773	£514,647	£2,357	£2,737	£646,040
Zenicor-ECG	£961	£126,967	£515,04	£2,358	£2,736	£648,069
RhythmPad*	£1,330	£122,746	£520,230	£2,325	£2,728	£649,353

AE=adverse events; CVE=cardiovascular events
*Algorithm interpretation

Table 50 Base Case 4: QALYs and patient outcomes

Strategy	IS	HS	TIA	False negatives	False positives	Bleeds	Total QALYs
Standard pathway	9.990	1.937	7.67	1.107	0.000	35.660	464.951
Kardia Mobile	9.922	1.860	7.63	0.444	1.317	35.101	465.845
imPulse	9.949	1.883	7.636	0.397	3.657	35.183	465.714
MyDiagnostick	9.945	1.880	7.635	0.360	2.151	35.159	465.713
Generic lead-I device	9.923	1.861	7.630	0.147	1.506	35.103	465.846
Zenicor-ECG	9.927	1.865	7.631	0.192	1.721	35.116	465.819
RhythmPad*	9.990	1.919	7.644	0.793	1.291	35.245	465.405

AE=adverse events; CVE=cardiovascular events; QALY=quality adjusted life year; IS=ischaemic stroke; HS=haemhorragic stroke; TIA=transient ischaemic accident
*Algorithm interpretation

Pairwise cost effectiveness results from the Base Case 4 analysis for each index test versus the standard diagnostic pathway are presented in Table 51 and incremental analysis are shown in Table 52.

Table 51 Base Case 4: Pairwise cost effectiveness analysis

Strategy	Costs	QALYs	Incremental Costs	Incremental QALYs	ICER/ QALY gained
Standard pathway	£648,002	464.951			
Kardia Mobile	£644,737	465.845	-£3,265	0.894	Dominates
imPulse	£660,332	465.714	£12,330	0.763	£16,166
MyDiagnostick	£650,941	465.713	£2,939	0.761	£3,860
Generic lead-I device	£646,040	465.846	-£1,962	0.895	Dominates
Zenicor-ECG	£648,069	465.819	£67	0.868	£77
RhythmPad*	£649,353	465.405	£1,351	0.454	£2,976

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
*Algorithm interpretation

Table 52 Base Case 4: Incremental cost effectiveness analysis

Strategy	Costs	QALYs	Incremental Costs	Incremental QALYs	ICER/ QALY gained
Kardia Mobile	£644,737	465.845			
Generic lead-I device	£646,040	465.846	£1,304	0.001	£2,239,352
Zenicor-ECG	£648,002	464.951	£1,962	-0.895	Dominated
Standard pathway	£648,069	465.819	£2,028	-0.027	Dominated
RhythmPad*	£649,353	465.405	£2,613	-0.441	Dominated
MyDiagnostick	£650,941	465.713	£1,961	-0.133	Dominated
imPulse	£660,332	465.714	£11,292	-0.132	Dominated

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
*Algorithm interpretation

4.3.5 Summary of base case cost effectiveness results

The results of the pairwise analysis show that all lead-I ECG tests lie on the efficiency frontier in each of the four base case analyses with ICERs below the £20,000-£30,000 threshold usually considered to be cost effective by NICE. Kardia Mobile is the most cost effective option in a full incremental analysis and dominates the standard pathway and other lead-I ECG devices (costing less and generating more QALYs) with the exception of the generic lead-I ECG device which generates a very small QALY gain but at a cost that produces an ICER well above £30,000 per QALY gained.

Lead-I ECG devices are more cost effective when there is a longer wait to 12-Lead ECG (as treatment for AF with a lead-I ECG device is assumed in the model to start earler than in the standard pathway) and if the 12-lead ECG is perfomed in hospital. The majority of the patient benefit, however, comes after diagnosis due to a greater proportion of patients who are

correctly diagnosed with AF and treated for AF even if this benefit is slightly offset by an increase in patients incorrectly diagnosed with AF with a lead-I ECG device.

4.4 Scenario analyses

Scenario analyses were undertaken to investigate the impact on the ICER per QALY gained of varying some of the base case assumptions. Results for scenario analyses using the least cost effective base case (Base Case 1 [12-lead ECG in primary care, 2 days to 12-lead ECG]) are presented; if the conclusions drawn from results remain unchanged from the least cost effective scenario for lead-I ECG testing, they should also remain unchanged for the more cost effective scenarios.

The scenario analyses were:

- Scenario A: The unit cost associated with the lead-I ECG device changed from full cost of the device to no cost. This assumption was varied to take into account other populations that might use a lead-I ECG device in primary care that would share the cost of the device
- Scenario B: Sensitivity and specificity estimates from interpretation of the MyDiagnostick lead-I ECG trace by GP
- Scenario C: Diagnosis and decisions made to refer for paroxysmal testing based only on the lead-I ECG results ie. no referral for 12-lead ECG or holter monitor.
- Scenario D: The time horizon is limited to 5 years to reflect clinical feedback to the EAG that it is plausible that all patients with paroxysmal AF not correctly diagnosed with AF after lead-I, 12-lead ECG or holter monitoring will be picked up within 5 years if they do not have a CVE.
- Scenarios E1 to E40: The proportions of patients sent for further testing for paroxysmal AF depending on the outcomes of the combined lead-I ECG and 12-lead ECG tests are varied. Clinical advice provided to the EAG highlighted the significant difference in clinical practice around how patients with positive or negative lead-I ECG and 12-lead ECG results would continue on the diagnostic pathway so each scenario may represent the true 'base case' scenario for a specific GP or practice depending on the diagnostic pathway they follow.

4.4.1 Scenario A: Unit cost associated with the lead-I ECG device

Incremental cost effectiveness results from Scenario A, which investigates the impact of removing the unit cost of the lead-I ECG device from the analysis (using 12-lead ECG in primary care, 2 days to 12-lead ECG) are presented in Table 53.

Table 53 Scenario A: Impact of removing the unit cost of the lead-I ECG device from the analysis, pairwise cost effectiveness analysis

Strategy	Costs	QALYs	Incremental Costs	Incremental QALYs	ICER/ QALY gained
Kardia Mobile	£643,235	465.767			
Generic lead-I device	£644,042	465.768	£807	0.001	£874,104
Standard pathway	£645,405	464.978	£1,363	-0.790	Dominated
Zenicor-ECG	£645,638	465.742	£1,596	-0.026	Dominated
RhythmPad*	£646,589	465.332	£2,547	-0.436	Dominated
MyDiagnostick	£649,291	465.638	£5,249	-0.130	Dominated
imPulse	£658,759	465.643	£14,717	-0.124	Dominated

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
*Algorithm interpretation

4.4.2 Scenario B: Alternative sensitivity and specificity estimates for MyDiagnostick

Pairwise cost effectiveness results from Scenario B, which investigates the impact of using the sensitivity and specificity estimates based on interpretation of the MyDiagnostick lead-I ECG trace by EP2 (using 12-lead ECG in primary care, 2 days to 12-lead ECG), are presented in Table 54.

Table 54 Scenario B: Impact of using the sensitivity and specificity estimates based on interpretation of the MyDiagnostick lead-I ECG trace by EP2, pairwise cost effectiveness analysis

Strategy	Costs	QALYs	Incremental Costs	Incremental QALYs	ICER/ QALY gained
Standard pathway	£645,405	464.978			
MyDiagnostick	£642,261	465.533	-£3,144	0.555	Dominates

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

4.4.3 Scenario C: Diagnosis without 12-Lead ECG/holter monitor

Incremental cost effectiveness results from scenario C which investigates the impact of removing 12-lead ECG and holter monitoring from the lead-I ECG diagnostic pathway (compared to using 12-lead ECG in primary care, 2 days to 12-lead ECG) are presented in Table 55.

Table 55 Scenario C: Impact of removing 12-lead ECG from the lead-I ECG diagnostic pathway, incremental analysis

Strategy	Costs	QALYs	Incremental Costs	Incremental QALYs	ICER/ QALY gained
Kardia Mobile	£644,572	465.631			
Standard pathway	£645,405	464.978	£833	-0.652	Dominated
Generic lead-I device	£645,958	465.631	£1,386	0.000	£7,606,119
Zenicor-ECG	£649,390	465.590	£3,432	-0.041	Dominated

MyDiagnostick	£657,391	465.431	£11,433	-0.200	Dominated
imPulse	£667,976	465.424	£22,019	-0.206	Dominated
RhythmPad*	£668,772	464.976	£22,814	-0.655	Dominated

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
*Algorithm interpretation

4.4.4 Scenario D: 5-year time horizon

Incremental cost effectiveness results from scenario D investigating a 5-year time horizon as a proxy for all undiagnosed patients being identified within 5 years (12-lead ECG in primary care, 2 days to 12-lead ECG) are presented in Table 56.

Table 56 Scenario D: Impact of 5-year time horizon, incremental analysis

Strategy	Costs	QALYs	Incremental Costs	Incremental QALYs	ICER/ QALY gained
Standard pathway	£101,492	173.166			
Kardia Mobile	£102,572	173.736	£1,079	0.570	£1,892
Generic lead-I device	£103,382	173.736	£811	0.000	Dominated
Zenicor-ECG	£104,390	173.719	£1,819	-0.018	Dominated
RhythmPad	£104,439	173.466	£1,867	-0.270	Dominated
MyDiagnostick	£104,858	173.652	£2,286	-0.084	Dominated
imPulse	£108,458	173.647	£5,886	-0.089	Dominated

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

4.4.5 Scenario E1 to E40: Varying proportion of patients sent for holter testing after lead-I ECG and 12-lead ECG results

Incremental cost effectiveness results from scenarios E1 to E40 exploring the uncertainty in the proportion of people sent for paroxysmal testing following lead-I ECG and 12-lead ECG results (12-lead ECG in primary care, 2 days to 12-lead ECG) are presented in Table 57. Given the complexity of the results, each scenario is only shown for the standard pathway compared to Kardia Mobile, the lead-I ECG test that was found to be the most cost effective option in the base case analyses.

Table 57 Scenario E Varying percentage of patients sent for holter monitoring for paroxysmal AF depending on the lead-I ECG and 12-lead ECG results, incremental analysis

Scenario	Lead-I pathway (% of patients being referred for holter monitoring)		Standard pathway (% of patients being referred for holter monitoring)	Standard pathway		Lead-I ECG pathway (Kardia Mobile)		Incremental		ICER
	Lead-I ECG negative, 12- lead negative	Lead-I ECG positive, 12-lead negative	MPP positive, 12-lead negative	Costs	QALYs	Costs	QALYs	Costs	QALYs	
E1	0%	0%	0%	£648,812	464.544	£649,748	464.603	£937	0.059	£15,895
E2	0%	100%	0%	£648,812	464.544	£64[illegible],608	465.722	-£7,204	1.178	Dominates
E3	0%	75%	0%	£648,812	464.544	£64[illegible],673	465.444	-£5,139	0.901	Dominates
E4	0%	50%	0%	£648,812	464.544	£64[illegible],713	465.165	-£3,098	0.621	Dominates
E5	0%	25%	0%	£648,812	464.544	£647,737	464.884	-£1,075	0.341	Dominates
E6	25%	100%	0%	£648,812	464.544	£642,463	465.748	-£6,348	1.204	Dominates
E7	25%	75%	0%	£648,812	464.544	£644,529	465.471	-£4,282	0.927	Dominates
E8	25%	50%	0%	£648,812	464.544	£646,571	465.191	-£2,241	0.648	Dominates
E9	25%	25%	0%	£648,812	464.544	£648,595	464.911	-£217	0.367	Dominates
E10	50%	100%	0%	£648,812	464.544	£643,319	465.774	-£5,493	1.231	Dominates
E11	50%	75%	0%	£648,812	464.544	£645,386	465.497	-£3,425	0.954	Dominates
E12	50%	50%	0%	£648,812	464.544	£647,428	465.218	-£1,383	0.674	Dominates
E13	75%	100%	0%	£648,812	464.544	£644,175	465.801	-£4,637	1.257	Dominates
E14	75%	75%	0%	£648,812	464.544	£646,243	465.524	-£2,569	0.980	Dominates
E15	100%	100%	0%	£648,812	464.544	£645,030	465.827	-£3,781	1.283	Dominates
E16	0%	100%	25%	£647,111	464.761	£641,608	465.722	-£5,504	0.961	Dominates
E17	0%	75%	25%	£647,111	464.761	£643,673	465.444	-£3,439	0.683	Dominates
E18	0%	50%	25%	£647,111	464.761	£645,713	465.165	-£1,398	0.404	Dominates
E19	0%	25%	25%	£647,111	464.761	£647,737	464.884	£625	0.123	£5,081
E20	0%	100%	50%	£645,40[illegible]	464.978	£641,608	465.722	-£3,797	0.744	Dominates
E21	0%	75%	50%	£64[illegible],40[illegible]	464.9[illegible]8	£64[illegible],673	465.444	-£1,732	0.466	Dominates

E22	0%	50%	50%	£645,405	464.978	£645,713	465.165	£308	0.187	£1,649
E23	0%	100%	75%	£643,691	465.195	£641,608	465.722	-£2,083	0.527	Dominates
E24	0%	75%	75%	£643,691	465.195	£643,673	465.444	-£18	0.250	Dominates
E25	0%	100%	100%	£641,966	465.410	£641,608	465.722	-£359	0.312	Dominates
E26	25%	25%	25%	£647,111	464.761	£648,594	466.911	£1,483	0.150	£9,915
E27	50%	50%	50%	£645,405	464.978	£647,428	465.218	£2,023	0.240	£8,438
E28	50%	50%	25%	£647,111	464.761	£647,428	465.218	£317	0.457	£693
E29	75%	75%	25%	£647,111	464.761	£646,243	465.524	-£869	0.763	Dominates
E30	75%	75%	50%	£645,405	464.978	£646,243	465.524	£838	0.545	£1,536
E31	75%	75%	75%	£643,691	465.195	£646,243	465.524	£2,552	0.329	£7,757
E32	100%	100%	25%	£647,111	464.761	£645,030	465.827	-£2,081	1.066	Dominates
E33	100%	100%	50%	£645,405	464.978	£645,030	465.827	-£375	0.849	Dominates
E34	100%	100%	75%	£643,691	465.195	£645,030	465.827	£1,339	0.632	£2,118
E35	25%	50%	50%	£645,405	464.978	£646,571	465.191	£1,166	0.213	£5,465
E36	50%	50%	75%	£643,691	465.195	£647,428	465.218	£3,737	0.023	£160,187
E37	25%	75%	75%	£643,691	465.195	£644,529	465.471	£839	0.276	£3,036
E38	25%	75%	75%	£643,691	465.195	£644,529	465.471	£839	0.276	£3,036
E39	50%	75%	75%	£643,691	465.195	£645,386	465.497	£1,695	0.303	£5,602
E40	100%	100%	100%	£641,966	465.410	£645,030	465.827	£3,064	0.417	£7,352

ICER=incremental cost effectiveness ratio; MPP=manual pulse palpation; QALY=quality adjusted life year

4.5 Deterministic sensitivity analysis

One-way sensitivity analyses were run to identify the individual parameters with the biggest impact on the model results. Tornado diagrams are presented in Figure 27 to Figure 32 for each index test using Base Case 1 (12-lead ECG in primary care, 2 days to 12-lead ECG).

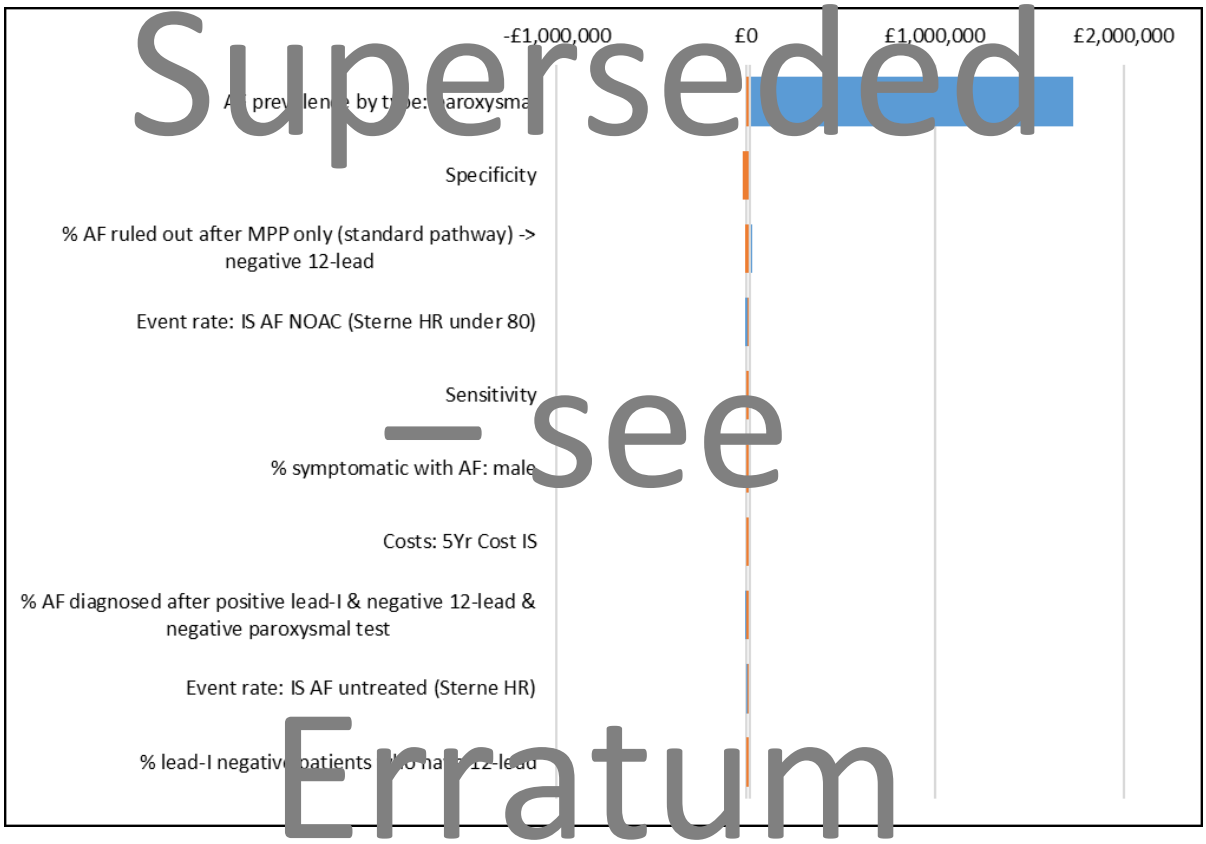

Figure 27 Tornado diagram: Base Case 1: ImPulse

Figure 28 Tornado diagram: Base Case 1: Kardia Mobile

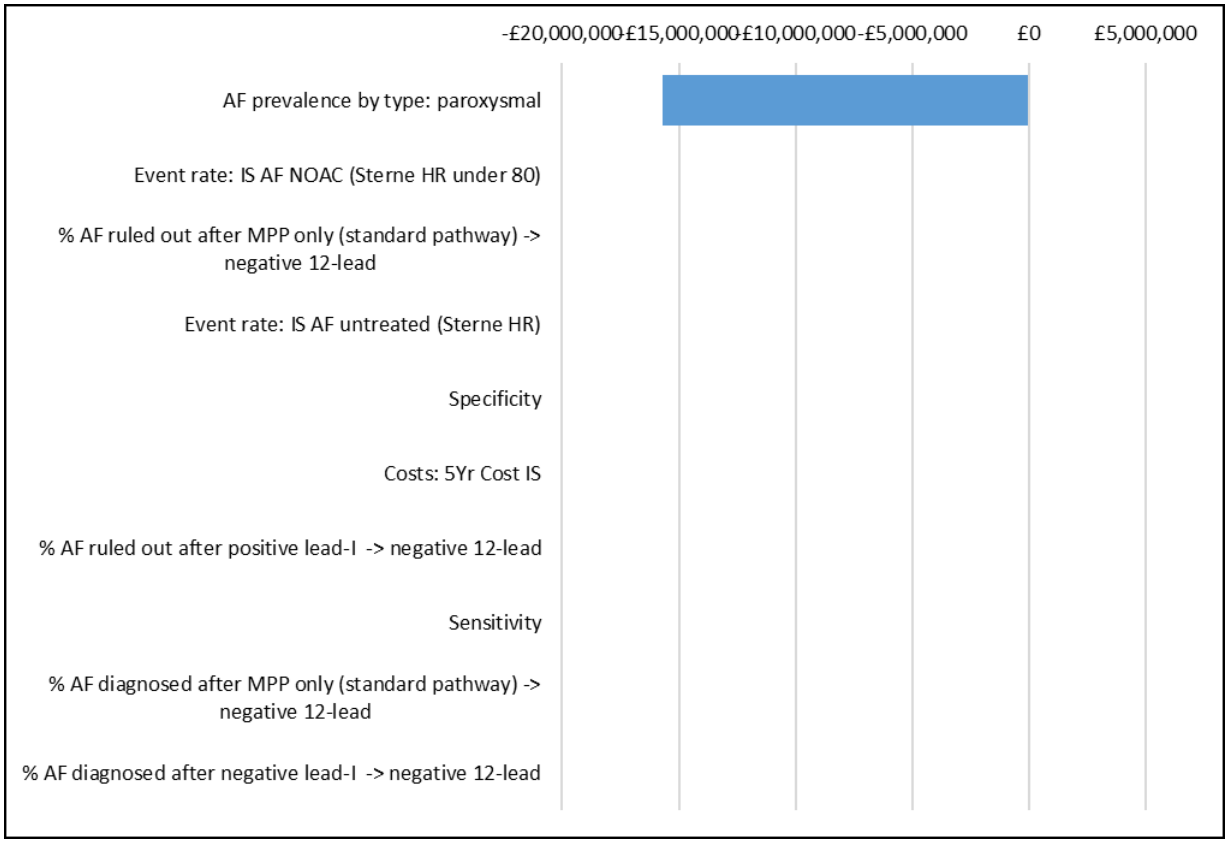

Figure 29 Tornado diagram: Base Case 1: MyDiagnostick

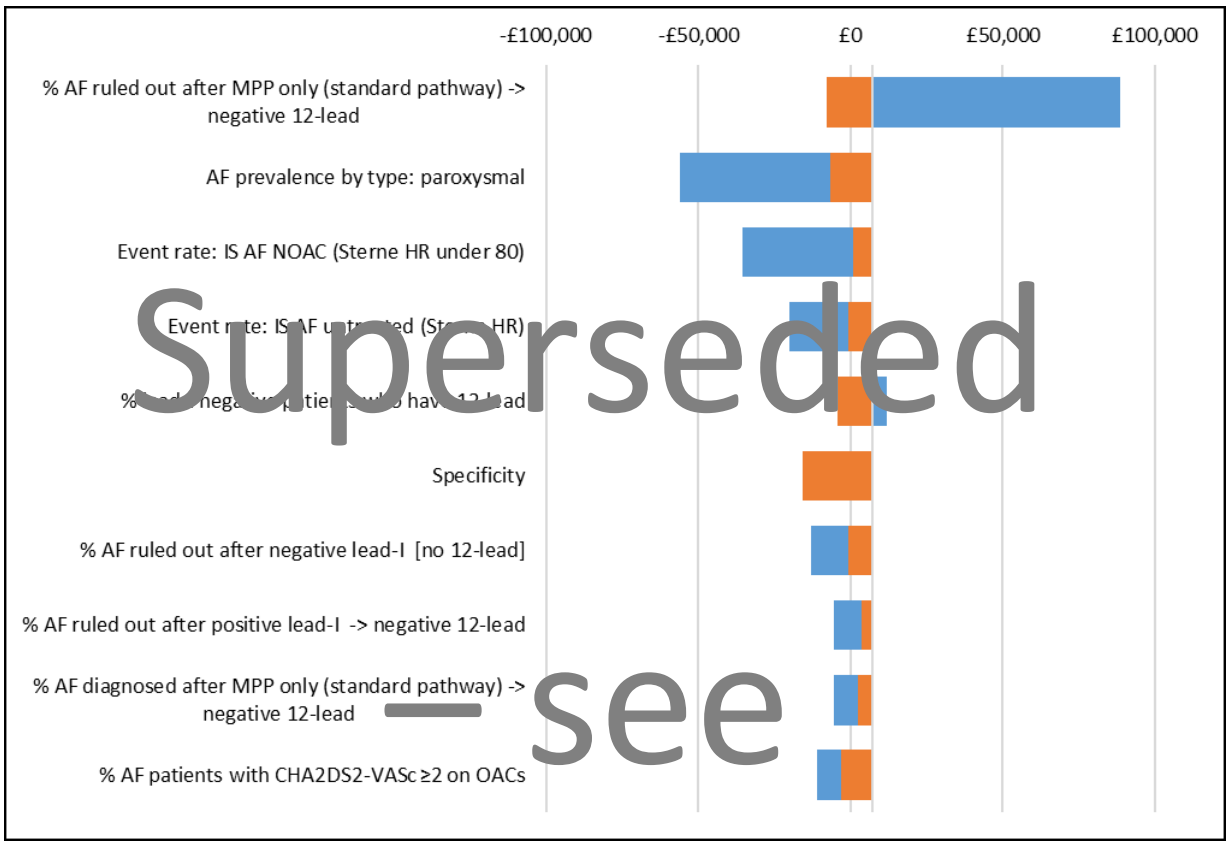

Figure 30 Tornado diagram: Base Case 1: RhythmPad GP

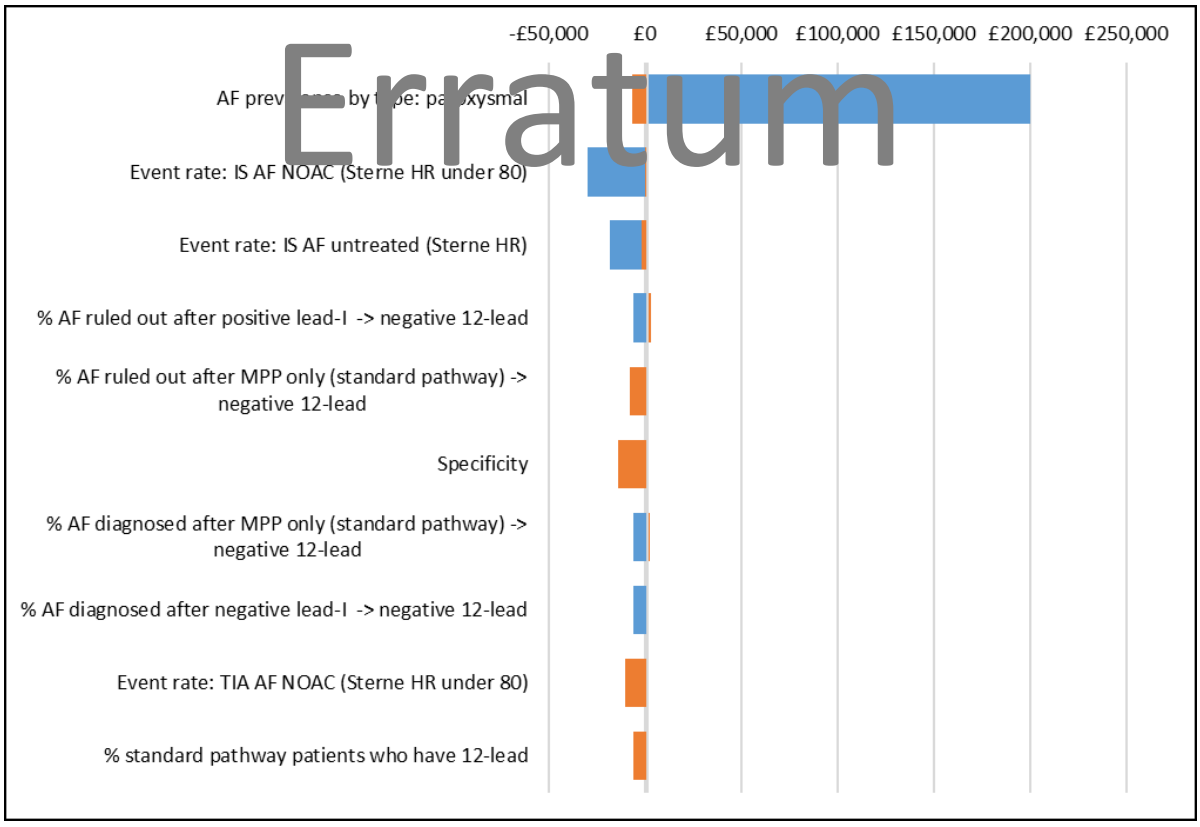

Figure 31 Tornado diagram: Base Case 1: Zenicor ECG

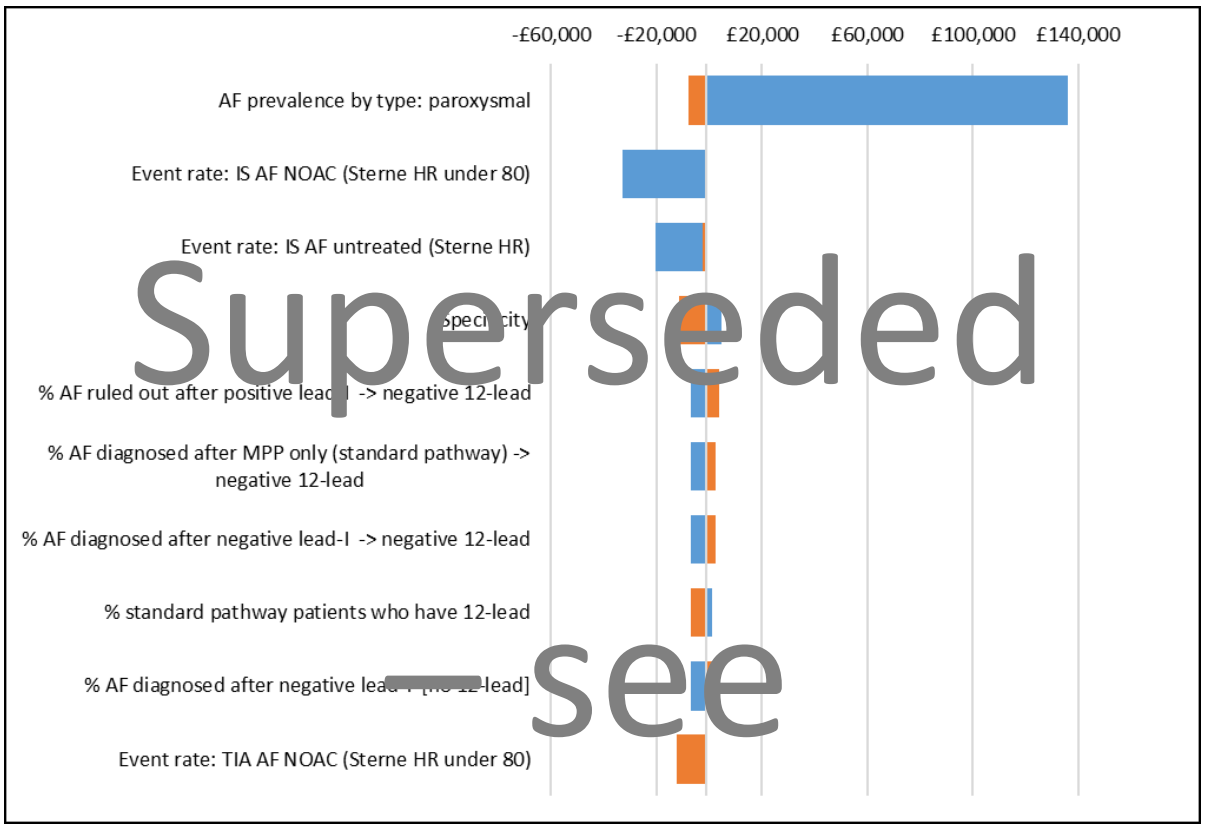

Figure 32 Tornado diagram: Base Case 1: Generic lead-I device

4.6 Probabilistic sensitivity analysis

Probability sensitivity analyses were undertaken for the lead-I ECG pathway with each index test compared with the standard diagnostic pathway. The cost effectiveness acceptability curves (CEACs) in Base Case 1 for each device are presented in Figure 33 to Figure 38. The CEAC for all devices is shown in Figure 39. The parameters for the probability sensitivity analysis are presented in Appendix 8.

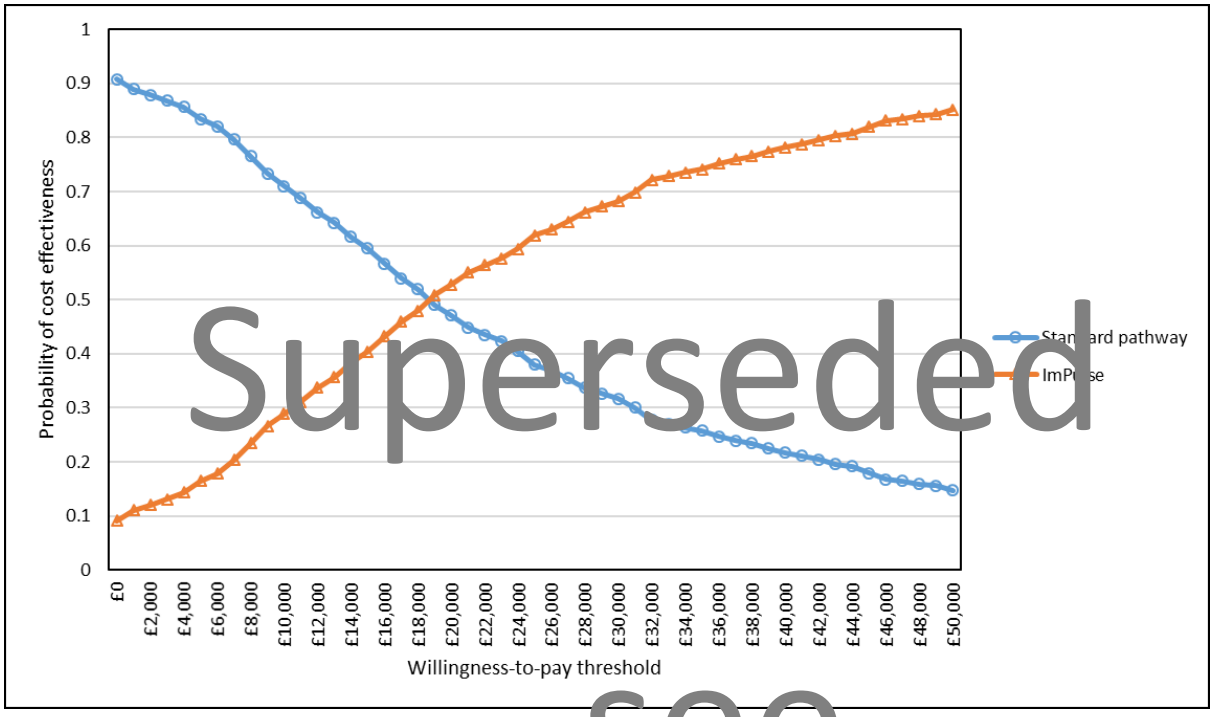

Figure 33 CEAC Base Case 1: imPulse

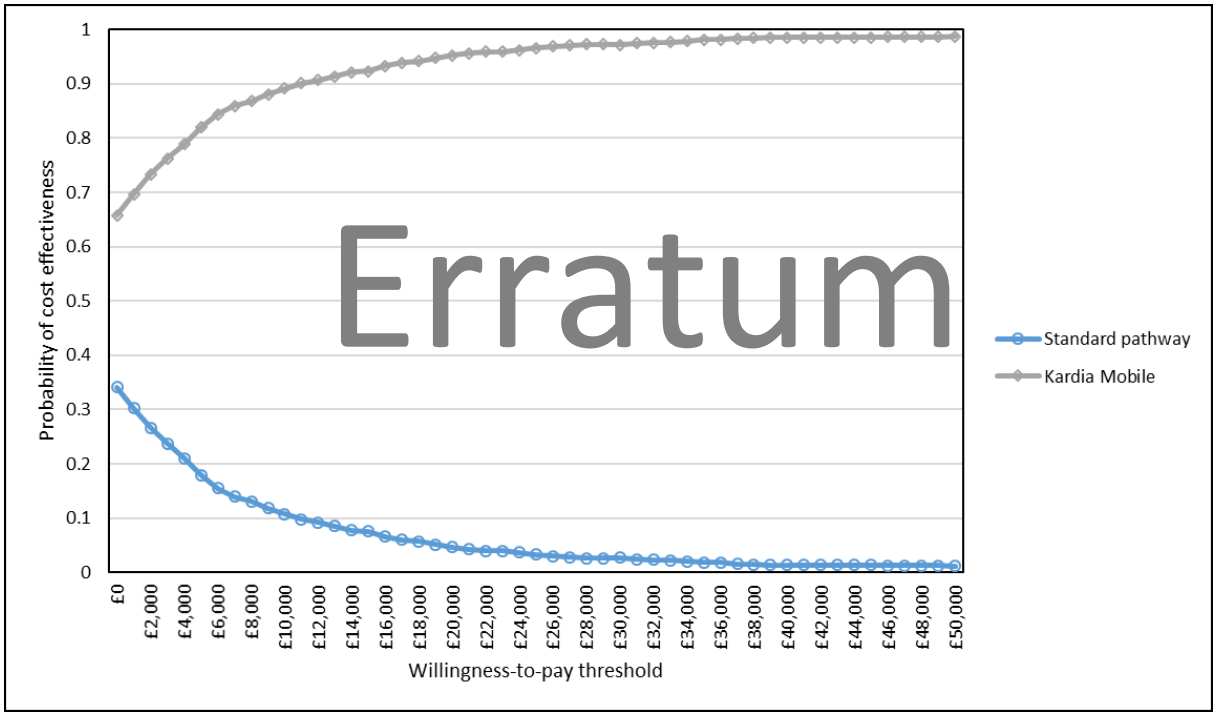

Figure 34 CEAC Base Case 1: Kardia Mobile

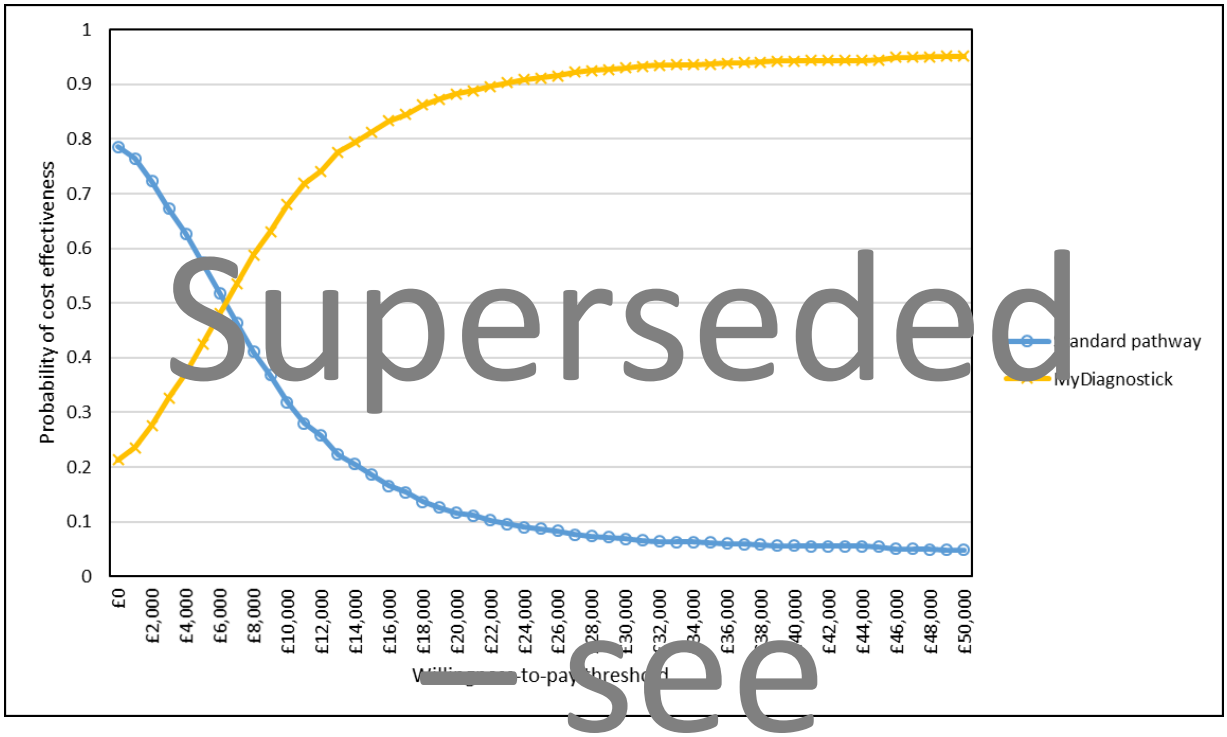

Figure 35 CEAC Base Case 1: MyDiagnostick

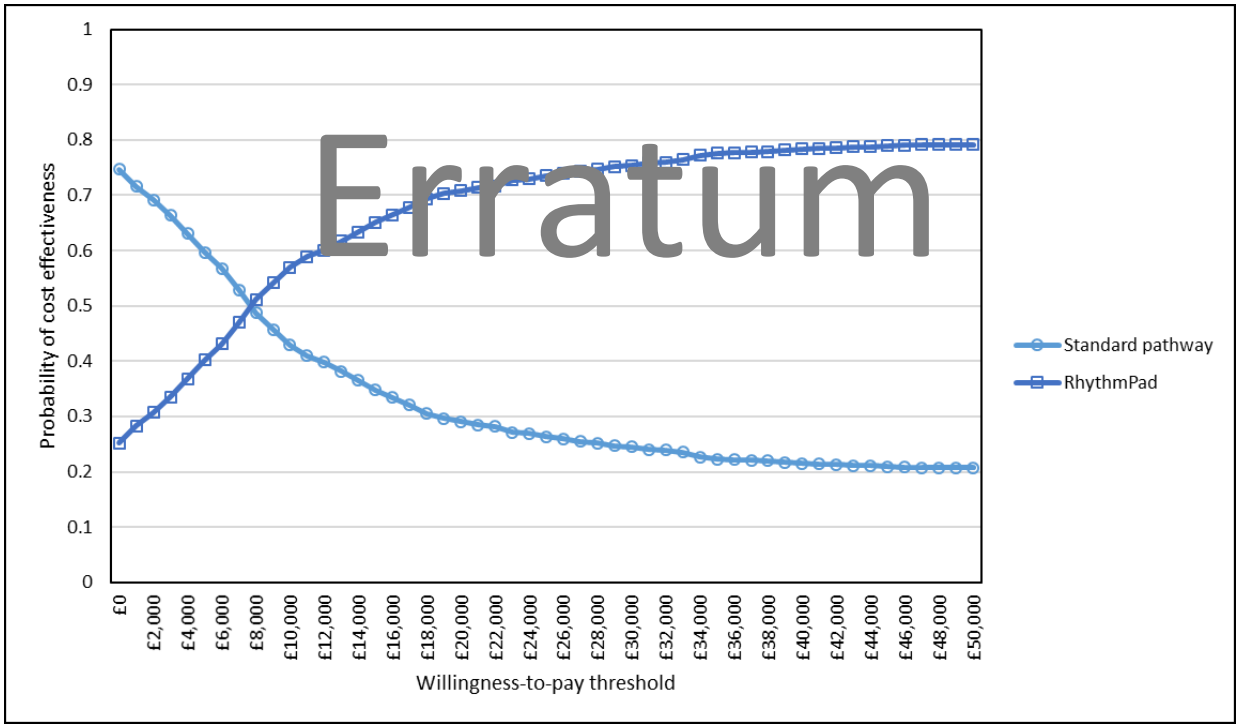

Figure 36 CEAC Base Case 1: RhythmPad GP

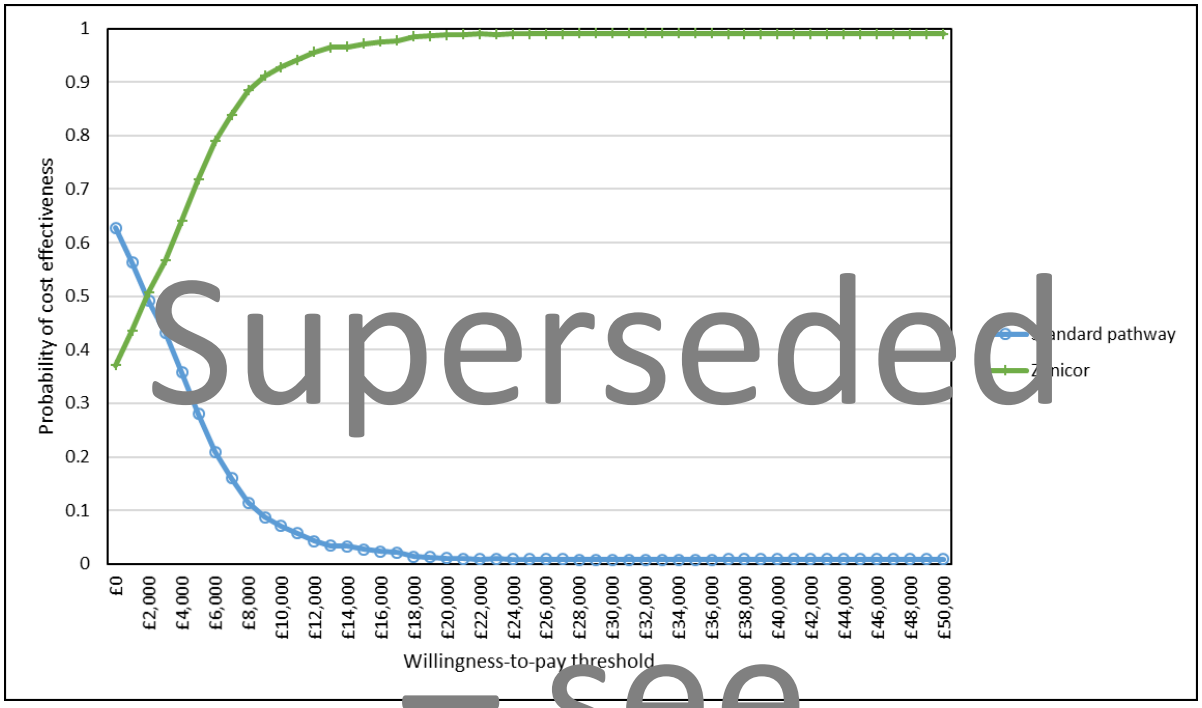

Figure 37 CEAC Base Case 1: Zenicor ECG

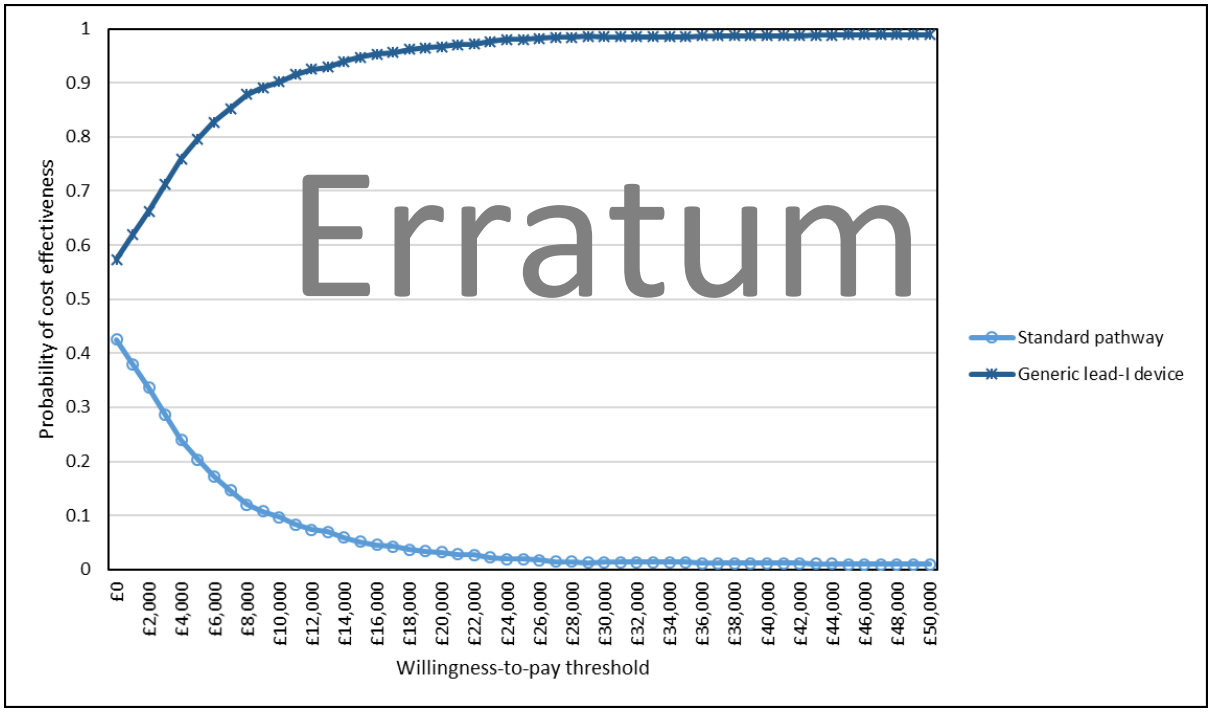

Figure 38 CEAC Base Case 1: Generic lead-I ECG device

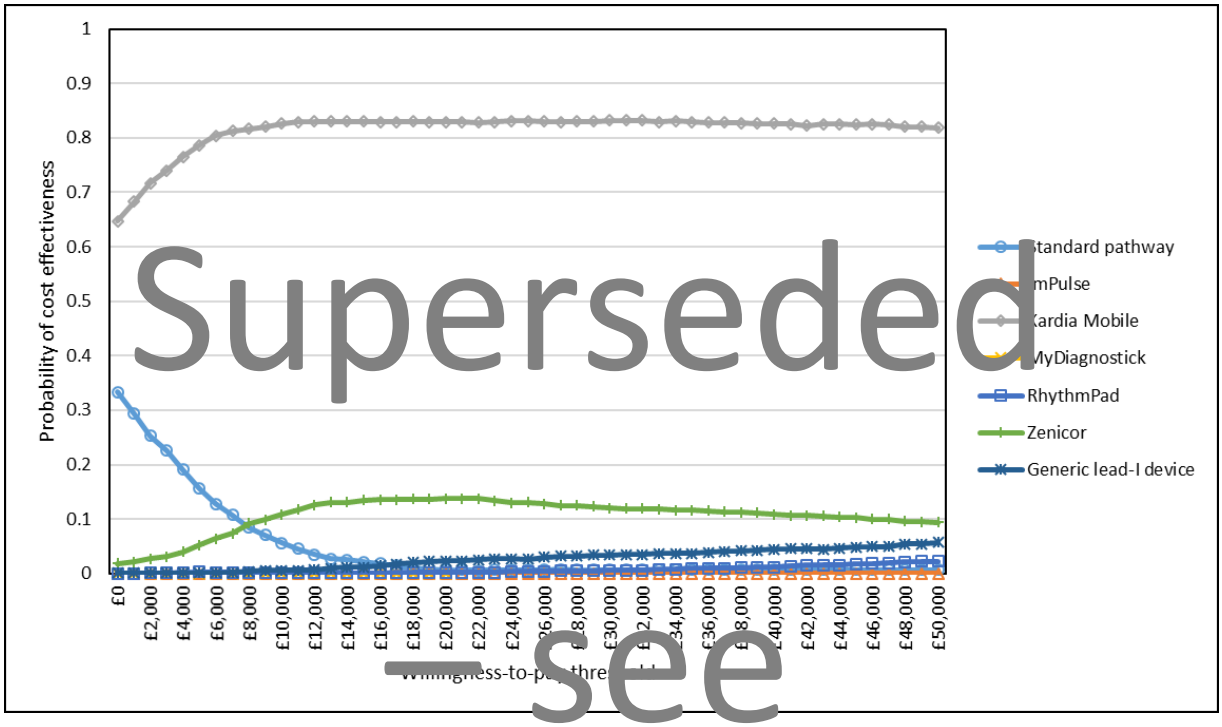

Figure 39 CEAC Base Case 2: all lead-I ECG devices

4.6.1 Summary of scenario and sensitivity analyses cost effectiveness results

The one-way sensitivity analysis showed that the results were sensitive to the assumed prevalence of paroxysmal AF versus persistent and permanent AF. Decreased prevalence of paroxysmal AF increased incremental costs and decreased incremental QALYs for lead-I ECG devices versus the standard pathway. At the extreme, where the prevalence of paroxysmal AF was assumed to be zero, incremental QALYs decreased sufficiently to become negative and resulted in some lead-I ECG devices (MyDiagnostick and RhythmPad) being dominated by the standard pathway. The ICERs per QALY gained yielded for other lead-I ECG devices when the prevalence of paroxysmal AF was zero were very large due to very small incremental QALYs. When the prevalence of paroxysmal AF was assumed to be 1, incremental costs decreased and incremental QALYs decreased. Increasing the prevalence of paroxysmal AF to 1 resulted in all lead-I ECG devices except one (ImPulse) dominating the standard pathway.

The result for each lead-I ECG device were also sensitive to variations in the rate of strokes for patients with AF. The results for one device (RhythmPad GP) were sensitive to the proportion of patients who had AF ruled out following a negative 12-lead ECG.

The results of the probability sensitivity analysis indicate that all lead-I ECG devices included in this assessment would be cost effective in at least 50% of cases with a willingness to pay threshold of around £20,000.

The scenario analysis showed that results were invariant to the following assumptions:

- Whether the cost of the lead-I ECG device is included in the analysis
- Alternative sensitivity and specificity values for MyDiagnostick
- Patients with AF incorrectly ruled out are not diagnosed with AF prior to a CVE
- Removal of 12-lead ECG and holter monitoring from the lead-I ECG pathway

The finding that removal of 12-lead ECG and holter monitoring from the lead-I ECG pathway did not affect cost effectiveness results is unsurprising given that if a patient had paroxysmal AF they were assumed to be in AF at the time of lead-I ECG monitoring and as such the majority of paroxysmal AF will be detected with lead-I ECG without the need for 12-lead ECG or holter monitoring. However, this result should be interpreted with caution as the potential further benefits of a specific diagnosis of paroxysmal AF or of the more detailed diagnosis from 12-lead ECG testing was not considered in the model. Similarly, the extensive scenario analysis on the use of holter monitoring following 12-lead ECG tests, with or without lead-I ECG testing, showed that only in one scenario – when 50% of patients with negative 12-lead ECG following lead-I ECG and 75% of patients with negative 12-lead ECG in the standard pathway were sent for holter monitoring – was the ICER for Kardia Mobile over £30,000 per QALY compared to the standard pathway. However, the ICER was substantially above £30,000 per QALY at £160,187 which suggests that the actual cost effectiveness of lead-I ECG devices may depend on the current level of use of holter monitoring in an area and how this would change with the introduction of lead-I ECG devices.

5 DISCUSSION

5.1 Assessment of diagnostic test accuracy

No studies were identified that evaluated the diagnostic accuracy of lead-I ECG devices in people presenting to primary care with signs and symptoms of AF and an irregular pulse. Since no studies were identified for the population and setting of interest, the review focused on an asymptomatic population as pre-specified in the protocol.[66] We considered an asymptomatic population to comprise people not presenting with symptoms of AF, with or without a previous diagnosis of AF. These patients could have had co-existing cardiovascular conditions or could have been attending a cardiovascular clinic but did not present with signs or symptoms of AF.

We identified 13 publications[37,38,40-50] reporting on nine studies assessing the diagnostic test accuracy of lead-I ECG devices. In three studies,[42,44,50] the lead-I ECG trace was interpreted by one trained healthcare professional (i.e. cardiologist or electrophysiologist). In one study,[38] the lead-I ECG trace was interpreted independently by a cardiologist and by a GP with an interest in cardiology. In one study,[37] the trace was interpreted independently by two electrophysiologists and by the device algorithm. In four studies[46-49] the lead-I ECG trace was interpreted by the device algorithm alone. The reference standard in all of the included studies was a 12-lead ECG interpreted by a trained healthcare professional. The trained healthcare professional was either a cardiologist, an electrophysiologist or a GP with an interest in cardiology. The analyses were stratified by interpreter of the lead-I ECG trace.

In the included studies, the sensitivity of lead-I ECG devices ranged from 80% to 100% and specificity ranged from 76% to 99% when the lead-I ECG trace was interpreted by a trained healthcare professional. The lowest specificity value (76%) was observed when interpretation of the lead-I ECG trace was performed by a GP with an interest in cardiology; sensitivity was similar to that observed in the other included studies.[38]

In the main meta-analysis, where the lead-I ECG trace was interpreted by a trained healthcare professional, the pooled sensitivity and specificity values were 93.9% and 96.5% respectively. In the sensitivity analyses, pooled sensitivity values ranged from 88.0% to 96.2% and pooled specificity values ranged from 94.4% to 97.4%.

Across the meta-analyses where the lead-I ECG trace was interpreted by the device algorithm, the sensitivity ranged from 88% to 96.2% and the specificity ranged from 94.4% to 97.2%. Pooled sensitivity and specificity values were similar across the different meta-analyses irrespective of interpreter of the lead-I ECG trace or lead-I ECG device used.

In one study,[37] inter-rater variability between the two electrophysiologist interpreters was observed. When the lead-I ECG trace was interpreted by EP1, sensitivity values were consistently higher than when interpreted by EP2 irrespective of the lead-I ECG device being used (i.e. MyDiagnostick or Kardia Mobile). Specificity values were similar irrespective of interpreter of the lead-I ECG trace (i.e. EP1 or EP2) and lead-I ECG device being used (i.e. MyDiagnostick or Kardia Mobile). The authors suggested that the reason for discordance between interpretation of lead-I ECG trace and 12-lead ECG was the presence of repetitive atrial or ventricular premature beats, which may have misguided the electrophysiologists to classify those lead-I ECG traces incorrectly as AF.[37] The same reasons were suggested for the low sensitivity value reported when the lead-I ECG trace was interpreted by the lead-I ECG device algorithm. The sensitivity values reported were lower than those observed in other studies irrespective of lead-I ECG device algorithm interpretation (i.e. MyDiagnostick or Kardia Mobile).

The sensitivity results from the meta-analyses of lead-I ECG traces interpreted by a trained healthcare professional or lead-I ECG device algorithm (92%; 95% CI: 85% to 96%)[102] were similar to the sensitivity results reported for MPP in systematic reviews (91.6%; 95% CI: 75% to 98.6%)[72]. The specificity values for lead-I ECG traces interpreted by a trained healthcare professional or lead-I ECG device algorithm were relatively higher (82%; 95% CI: 76% to 88%)[102] than those reported for MPP (78.8%; 95% CI: 51% to 94.5%).[72]

The included studies did not evaluate the presence of paroxysmal AF using prolonged monitoring following a negative 12-lead ECG. It is likely that, in clinical practice, prolonged monitoring will be considered for people presenting with signs and symptoms of AF who have an irregular pulse and a positive lead-I ECG followed by a negative 12-lead ECG. In the included studies, the index test and reference standard were both performed within a 6 hour time interval, with the exception of two studies[48,49] where the time interval between use of the index test and reference standard was not specified. A patient correctly identified as having AF could have this diagnosis ruled out if the AF episode had stopped at the time of assessment with a 12-lead ECG. It is not clear if there was an appropriate interval between assessments in the Crockford study,[49] therefore, it is possible that paroxysmal AF may have contributed to a lower sensitivity than that reported in the other studies; the specificity reported in the Crockford study[49] was similar to the values reported in other studies. In the Vaes study,[48] the sensitivity and specificity values observed were similar to the values reported in other studies.

In the systematic review of diagnostic test accuracy, none of the studies of lead-I ECG devices included people presenting to primary care with signs and symptoms of AF and an irregular pulse. This means that all of the results presented in this systematic review are derived from an asymptomatic population and most for a setting other than primary care. It is plausible that,

if the population in the review had been people with signs and symptoms of AF and an irregular pulse, the sensitivity of lead-I ECG devices where the trace was interpreted by a trained healthcare professional would have been higher. However, it is also plausible that, in such a population, the specificity of lead-I ECG devices where the trace was interpreted by a trained healthcare professional would have been lower.

5.2 Assessment of clinical impact

No studies were identified that evaluated the clinical impact of lead-I ECG devices in people presenting to primary care with signs and symptoms of AF and an irregular pulse. Since no studies were identified for the population and setting of interest, the review focused on an asymptomatic population as pre-specified in the protocol.[66]

We identified 23 publications reporting on 18 studies with a total of 33,993 participants and one study that conducted semi-structured interviews with two receptionists, one nurse, three GPs and eight patients across three GP practices. The index tests evaluated included ImPulse (one study),[62] Kardia Mobile alone (11 studies),[44,46,50,53,55,56,58,60,61,63,64] MyDiagnostick alone (four studies),[47,51,57,59] Zenicor ECG (one study)[42] and MyDiagnostick and Kardia Mobile (one study).[37] In nine studies,[42,44,50,51,53,55,58,63,64] the lead-I ECG trace was interpreted by one trained healthcare professional (i.e. cardiologist, electrophysiologist or GP). In four studies,[56,59-61] the lead-I ECG trace was interpreted independently by one trained healthcare professional and by the device algorithm. In three studies[46,47,57] the lead-I ECG trace was interpreted by the device algorithm alone. In one study,[37] the trace was interpreted independently by two electrophysiologists and by the device algorithm. In one study,[62] the lead-I ECG trace was interpreted independently by two cardiology registrars, two cardiac physiologists and two specialist cardiac nurses.

Diagnostic yield was the most commonly reported outcome in 13 studies.[37,47,51,53,55-61,63,64] The diagnostic yield reported in these studies ranged from 0.38% to 5.84% and was similar across the studies taking into account the type of lead-I ECG device used and setting in which the study was conducted. One study[57] conducted in UK primary care reported the greatest diagnostic yield. However, this study[57] was only available as a conference abstract and the reason for the high diagnostic yield is unclear because of the limited information available. Data submitted by Kent Surrey Sussex AHSN [Kent Surrey Sussex AHSN and Richard Blakey, AliveCor in East Sussex, unpublished evidence submitted via NICE] on the use of Kardia Mobile lead-I ECG device for people with symptoms of AF and an irregular pulse during a 2-year project reported a diagnostic yield of 69.9%. It is plausible that the diagnostic yield in people presenting to primary care with signs and symptoms of AF and an irregular pulse would be more comparable to the values reported by the Kent Surrey Sussex AHSN than those

reported in the published evidence available and included in the systematic review of clinical impact of lead-I ECG devices.

Test failure rate was reported in nine studies[37,44,51,55,56,59-62] and ranged from 0.1% to 9%. Test failure rate considered both failure of the lead-I ECG algorithm to produce a result and poor quality of the lead-I ECG trace. Possible reasons suggested for uninterpretable lead-I ECGs were sinus tachycardia or bradycardia (Kardia Mobile),[61] that patients suffered from tremor, or hospitalised patients were too weak to hold the devices firmly enough (not specified if Kardia Mobile or MyDiagnostick).[37]

Two studies[58,60] reported a change in treatment management following the use of the Kardia Mobile lead-I ECG with OACs being prescribed for most new patients diagnosed with AF. Acceptability of lead-I ECG devices was reported in four studies.[53,57,58,61] with generally positive views. A key barrier that was identified related to the ease of use of the lead-I ECG was the difficulty for elderly patients to hold the device very still to take a reading.[61] Furthermore, one study[37] reported that 7% of patients were excluded because they were not able to hold the devices properly. A qualitative study[52] suggested that nurses in GP practices could confidently use a lead-I ECG device (Kardia Mobile) and were well placed to explain the process and conduct AF screening in people aged 65 years or over before their GP appointment. However, only one nurse was interviewed as part of this study, so there are concerns about the generalisability of this finding. Moreover, the study was conducted to evaluate the feasibility of screening in an asymptomatic population and so it is unclear if the results would be applicable to the population of interest in this apraisal. Time to initiation of preventative treatment and HRQoL were not reported in any of the identified studies.

Only one study[58] reported on clinical outcomes. One patient who did not receive anticoagulant therapy after a lead-I ECG trace that was difficult to interpret followed by a normal 12-lead ECG result, later had a stroke. The importance of prolonged monitoring in cases of suspected AF which may be paroxysmal is evident. It has been reported that a period of 2-week monitoring using a hand-held device identified 7.4% (30/403) cases of paroxysmal AF who had screened negative on a 12-lead ECG but who had two or more risk factors based on the $CHADS_2$ risk classification.[73]

5.3 Assessment of cost effectiveness

No published studies were identified that evaluated the cost effectiveness of lead-I ECG devices compared with MPP for people presenting to primary care with signs and symptoms of AF and an irregular pulse. As no published data evaluating the diagnostic test accuracy and the clinical impact of lead-I ECG devices were identified for people presenting to primary care

with signs and symptoms of AF and an irregular pulse, diagnostic test accuracy data in an asymptomatic population were used as a proxy for the population of interest.

The de novo economic model yielded ICERs per QALY gained. The results of the pairwise analysis show that all lead-I ECG tests lie on the efficiency frontier in each of the four base case analyses with ICERs below the £20,000-£30,000 threshold usually considered to be cost effective by NICE. Kardia Mobile is the most cost effective option in a full incremental analysis and dominates the standard pathway and other lead-I ECG devices (costing less and generating more QALYs) with the exception of the generic lead-I ECG device which generates a very small QALY gain but at a cost that produces an ICER well above £30,000 per QALY gained.

Lead-I ECG devices are more cost effective when there is a longer wait to 12-Lead ECG (as treatment for AF with a lead-I ECG device is assumed in the model to start earlier than in the standard pathway) and if the 12-lead ECG is performed in hospital. The majority of the patient benefit, however, comes after diagnosis due to a greater proportion of patients who are correctly diagnosed with AF and treated for AF even if this benefit is slightly offset by an increase in patients incorrectly diagnosed with AF with a lead-I ECG device.

The one-way sensitivity analysis showed that the results were particularly sensitive to the assumed prevalence of paroxysmal AF versus persistent and permanent AF. Decreasing the prevalence of paroxysmal AF increased incremental costs and decreased incremental QALYs for lead-I ECG devices versus the standard pathway. In the extreme, decreasing the prevalence of paroxysmal AF to zero yielded either very large, positive ICERs per QALY gained or resulted in lead-I devices being dominated by the standard pathway. The model results were also shown to be sensitive to the rate of ischaemic strokes in patients with AF. Results should therefore be interpreted with caution if it is considered clinically plausible that the prevalence of paroxysmal AF in the symptomatic population may be substantially lower than 50%.

In line with the conclusions of the EAG concerning the use of lead-I ECG devices for people presenting to primary care with signs and symptoms of AF and an irregular pulse, the results of recently published economic evaluations[72,103] have suggested that lead-I ECG devices may represent a cost effective use of resources for systematic, opportunistic screening of people aged 65 years and over during a routine GP appointment. Lead-I ECG devices may be cost effective for an asymptomatic population because only people that have a positive lead-I ECG test will have a subsequent 12-lead ECG test carried out. If a lead-I ECG test or an alternative screening test were not used, people with asymptomatic AF would remain undiagnosed until the time of an event (e.g., stroke). People with asymptomatic AF who are diagnosed early and

receive appropriate treatment gain health benefits in comparison to people whose AF remains undiagnosed and who do not receive treatment for AF.

In the current NICE CG180[3] it is recommended that an ECG is performed in all people, whether symptomatic or not, in whom AF is suspected because an irregular pulse has been detected. There is an emergence of novel technologies to assist in the diagnosis of AF such as lead-I ECG devices. These technologies need to be clearly distinguished from the 12-lead ECG devices that are described in the updated NICE CG180.[3]

5.4 Strengths and limitations

No published data evaluating the diagnostic accuracy, the clinical impact or the cost effectiveness of lead-I ECG devices were identified for people presenting to primary care with signs and symptoms of AF and an irregular pulse. Therefore, all the results presented within this assessment need to be interpreted with caution as the results are based on data from an asymptomatic population, used as a proxy for the population of interest. However, we present the first economic evaluation of lead-I ECG devices for people presenting to primary care with signs and symptoms of AF and an irregular pulse.

Diagnostic test accuracy results are reported for all lead-I ECG devices (i.e. imPulse, Kardia Mobile, MyDiagnostick, RhythmPad GP and Zenicor ECG) within the scope of this assessment. However, for RhythmPad GP, results were based on interpretation by the lead-I ECG algorithm only and, according to the manufacturer [Chris Crockford, CardioCity, 3rd August 2018, personal communication via NICE], the device algorithm has been modified since publication of the identified study,[49] and therefore the sensitivity and specificity estimates observed may have been affected. One study[62] reporting on the diagnostic test accuracy of the imPulse lead-I ECG device was excluded from the diagnostic test accuracy review because the reference standard was ineligible. The sensitivity and specificity values from this study[62] were, however, considered in the economic evaluation.

Since January 2018, Kardia Mobile lead-I ECG devices started to be rolled out to primary care practices as part of the NHS England-funded NHS Innovation Accelerator (NIA), delivered in partnership with England's 15 AHSNs.[104] The aim of the initiative is to improve the detection of people with AF in order to reduce the number of strokes.[104,105] It has been suggested that with this initiative, the lead-I ECG device can be used at any time, regardless of whether the patients have signs and symptoms of AF.[106]

5.5 Conclusions

The results of the systematic reviews of diagnostic test accuracy and clinical impact of lead-I ECG devices suggest that these devices are an important addition to the armamentarium of a

GP when diagnosing AF. However, only evidence supporting their use in an asymptomatic population was identified from the published literature. In people with signs and symptoms of AF and an irregular pulse, it is recommended that a 12-lead-ECG is performed. If a 12-lead ECG is carried out on the day of the initial appointment, there is unlikely to be any diagnostic benefit to using a lead-I ECG over a 12-lead ECG in the symptomatic population since patients with AF are in AF at the time of the initial appointment (and therefore at the time of the lead-I ECG test and any 12-lead ECG that takes place soon after the initial appointment). Only if there is a time interval between the use of a lead-I ECG and a 12-lead ECG, would any health benefits from early treatment initiation be obtained by patients. To allow for these benefits to be considered, the economic evaluation considered primary care practices where patients have to wait at least 48 hours between their initial consultation with the GP and a confirmatory 12-lead ECG.

Future research investigating the diagnostic test accuracy of lead-I ECG devices in people presenting to primary care with signs and symptoms of AF and an irregular pulse should take into consideration the added value that such studies would provide. Kardia Mobile lead-I ECG devices are being rolled out for use in a primary care setting for routine screening in people aged 65 years or over. If a lead-I ECG device is available in a primary care practice, the GP will already have had the choice to use the lead-I ECG device for people with signs and symptoms of AF and an irregular pulse.

6 ACKNOWLEDGMENTS

The authors would like to thank Sophie Beale (Research Associate, LR*i*G, University of Liverpool) for feedback on a draft version of the report.

6.1 Contributions of authors

All authors contributed to the conception and design of the study or the analysis and interpretation of the data, drafting or revising the report, and final approval of the version to be published.

Rui Duarte (Senior Research Fellow, Health Technology Assessment Lead), managed the project, contributed to the development of the methods for the systematic review, conducted the review of diagnostic test accuracy and clinical impact and supervised the statistical analysis and economic modelling work.

Angela Stainthorpe (Research Associate, Health Economics and Modelling), conducted the review of cost effectiveness evidence, developed the health economic model, identified inputs to the economic model, and conducted the economic evaluation.

Janette Greenhalgh (Senior Research Fellow, Systematic Reviewer), contributed to the systematic review of diagnostic test accuracy and clinical impact and acted as the second reviewer in the systematic review.

Marty Richardson (Research Associate, Statistician), contributed to the statistical analysis methods, performed the statistical analysis for the diagnostic test accuracy review, acted as the third reviewer in the systematic review to resolve conflicts.

Sarah Nevitt (Research Associate, Statistician), contributed to the statistical analysis for the diagnostic test accuracy review.

James Mahon, (Director, Health Economics and Modelling), contributed to the development of the health economic model and to the economic evaluation.

Eleanor Kotas (Research Associate, Information Specialist), devised and performed the literature searches.

Angela Boland (Associate Director, Health Economics), provided senior advice to the project.

Howard Thom (Research Fellow, Health Economics and Modelling), provided input to the health economic model.

Tom Marshall (Professor of Public Health and Primary Care), provided input to the report from a primary care perspective.

Mark Hall (Consultant Cardiologist and Electrophysiologist), provided input to the report from a secondary care perspective.

Yemisi Takwoingi (Senior Research Fellow, Statistician), provided input on the systematic review and statistical analysis methods for assessment of diagnostic test accuracy and clinical impact.

7 REFERENCES

1. National Institute for Health and Care Excellence (NICE). Clinical knowledge summaries: atrial fibrillation. 2015.; Available from: https://cks.nice.org.uk/atrial-fibrillation#!topicsummary [accessed January 2018]. Accessed.
2. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, *et al.* 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016; 37:2893-62.
3. National Institute for Health and Care Excellence (NICE). Atrial fibrillation: management. clinical guideline CG180. 2014.; Available from: https://www.nice.org.uk/guidance/cg180/chapter/Introduction [accessed January 2018]. Accessed.
4. Dewland TA, Olgin JE, Vittinghoff E, Marcus GM. Incident atrial fibrillation among Asians, Hispanics, blacks, and whites. Circulation. 2013; 128:2470-7.
5. Bai Y, Wang YL, Shantsila A, Lip GYH. The Global Burden of Atrial Fibrillation and Stroke: A Systematic Review of the Clinical Epidemiology of Atrial Fibrillation in Asia. Chest. 2017; 152:810-20.
6. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, *et al.* Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J. 2009; 158:111-7.
7. Lane DA, Skjoth F, Lip GYH, Larsen TB, Kotecha D. Temporal trends in incidence, prevalence, and mortality of atrial fibrillation in primary care. J Am Heart Assoc. 2017; 6.
8. NHS Digital. Quality and outcomes framework (QOF) - 2016-2017. 2017.; Available from: https://digital.nhs.uk/catalogue/PUB30124 [accessed January 2018]. Accessed.
9. National Institute for Health and Care Excellence (NICE). Lead-I electrocardiogram (ECG) devices for detecting atrial fibrillation using single-time point testing in primary care: final scope. 2018.; Available from: https://www.nice.org.uk/guidance/gid-dg10018/documents/final-scope. Accessed.
10. Public Health England. Atrial fibrillation prevalence estimates in England: application of recent population estimates of AF in Sweden. 2017.; Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/644869/atrial_fibrillation_AF_briefing.pdf [accessed January 2018]. Accessed.
11. Adderley NJ, Ryan R, Nirantharakumar K, Marshall T. Prevalence and treatment of atrial fibrillation in UK general practice from 2000 to 2016. Heart. 2018.
12. Lip GYH, Hee FLLS. Paroxysmal atrial fibrillation. QJM: An International Journal of Medicine. 2001; 94:665-78.
13. Lown M, Yue A, Lewith G, Little P, Moore M. Screening for atrial fibrillation using economical and accurate technology (SAFETY)—a pilot study. BMJ Open. 2017; 7.
14. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, *et al.* 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Eur Heart J. 2012; 33:2719-47.
15. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, *et al.* Stroke severity in atrial fibrillation. the framingham study. Stroke. 1996; 27:1760-4.
16. Stroke Association. State of the nation: stroke statistics. 2017.; Available from: https://www.stroke.org.uk/sites/default/files/state_of_the_nation_2017_final_1.pdf [accessed June 2018]. Accessed.
17. Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, Alings M, *et al.* Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. Eur Heart J. 2015; 36:281-7a.
18. Senoo K, Lip GY, Lane DA, Buller HR, Kotecha D'Agostino RB. Residual risk of stroke and death in anticoagulated patients according to the type of atrial fibrillation: AMADEUS trial. Stroke. 2015; 46:2523-8.
19. Flaker GC, Belew K, Beckman K, Vidaillet H, Kron J, Safford R, *et al.* Asymptomatic atrial fibrillation: demographic features and prognostic information from the atrrial fibrillation follow-up investigation of rhythm management (AFFIRM) study. Am Heart J. 2005; 149:657-63.
20. MDCalc. CHA_2DS_2-VASc score for atrial fibrillation stroke risk. 2015.; Available from: http://www.mdcalc.com/cha2ds2-vasc-score-for-atrial-fibrillation-stroke-risk/ [Accessed June 2018]. Accessed.
21. MDCalc. HAS-BLED score for major bleeding risk.: MD-Calc; 2018.; Available from: https://www.mdcalc.com/has-bled-score-major-bleeding-risk [Accessed January 2018]. Accessed.
22. Plessey. imPULSE. 2018.; Available from: http://www.plesseysemiconductors.com/products/impulse/ [accessed January 2018]. Accessed.
23. Alive Technologies. Kardia Mobile. 2018; Available from: https://www.alivetec.com/pages/alivecor-heart-monitor [accessed January 2018]. Accessed.
24. Applied Biomedical Systems BV. Mydiagnostick. 2018; Available from: https://www.mydiagnostick.com/ [accessed January 2018]. Accessed.
25. Cardiocity Ltd. RhythmPadGP. 2017.; Available from: http://www.cardiocity.com/?portfolio=rhythm-pad-gp [accessed January 2018]. Accessed.
26. Zenicor Medical Systems AB. Zenicor-ECG. 2018.; Available from: https://zenicor.com/zenicor-ekg/ [accessed January 2018]. Accessed.
27. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking systematic reviews in health care. 2009.; Available from: http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm [accessed January 2018]. Accessed.
28. National Institute for Health and Care Excellence (NICE). Diagnostic assessment programme manual [Internet]. 2011; Available from: http://www.nice.org.uk/media/A0B/97/DAPManualFINAL.pdf [accessed January 2018]. Accessed.
29. Cochrane Diagnostic Test Accuracy Working Group. Handbook for DTA reviews. 2009.; Available from: http://srdta.cochrane.org/handbook-dta-reviews [accessed January 2018]. Accessed.
30. McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, Clifford T, *et al.* Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. Jama. 2018; 319:388-96.
31. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, *et al.* QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of Internal Medicine. 2011; 155:529-36.

32. Herzog R, Alvarez-Pasquin MJ, Diaz C, Del Barrio JL, Estrada JM, Gil A. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. BMC public health. 2013; 13:154.
33. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute 2012.
34. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, *et al.* The cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343:d5928.
35. CASP. Qualitative research: appraisal tool. 10 questions to help you make sense of qualitative research. 2006.; Available from: www.phru.nhs.uk/Doc_Links/Qualitative_Appraisal_Tool.pdf [accessed February 2018]. Accessed.
36. Chu H, Cole SR. Bivariate meta-analysis of sensitivity and specificity with sparse data: a generalized linear mixed model approach. J Clin Epidemiol. 2006; 59:1331-2; author reply 2-3.
37. Desteghe L, Raymaekers Z, Lutin M, Vijgen J, Dilling-Boer D, Koopman P, *et al.* Performance of handheld electrocardiogram devices to detect atrial fibrillation in a cardiology and geriatric ward setting. Europace. 2017; 19:29-39.
38. Williams J, Pearce K, Benett I. The effectiveness of a mobile ECG device in identifying AF: sensitivity, specificity and predictive value. Br J Cardiol. 2015; 22:70-2.
39. Takwoingi Y, Guo B, Riley RD, Deeks JJ. Performance of methods for meta-analysis of diagnostic test accuracy with few studies or sparse data. Stat Methods Med Res. 2017; 26:1896-911.
40. Desteghe L, Raymaekers Z, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, *et al.* Accuracy and cost-effectiveness of two handheld electrocardiogram recorders to screen for atrial fibrillation in a hospital setting. Eur Heart J. 2016; 37 (Supplement 1):1265.
41. Desteghe L, Raymaekers Z, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, *et al.* Accuracy and usability of handheld electrocardiogram recorders to detectatrial fibrillation in hospitalised patients. Europace. 2016; 18 (Supplement 1):i177.
42. Doliwa PS, Frykman V, Rosenqvist M. Short-term ECG for out of hospital detection of silent atrial fibrillation episodes. Scand Cardiovasc J. 2009; 43:163-8.
43. Haberman ZC, Jahn RT, Bose R, Tun H, Shinbane JS, Doshi RN, *et al.* Wireless smart phone equipped ECG enables large scale screening in diverse populations. Heart Rhythm. 2014; 1):S312.
44. Haberman ZC, Jahn RT, Bose R, Tun H, Shinbane JS, Doshi RN, *et al.* Wireless smartphone ECG enables large-scale screening in diverse populations. J Cardiovasc Electrophysiol. 2015; 26:520-6.
45. Lau J, Lowres N, Neubeck L, Brieger DB, Sy RW, Galloway C, *et al.* Validation of an iphone ECG application suitable for community screening for silent atrial fibrillation: a novel way to prevent stroke. Circulation Conference: American Heart Association. 2012; 126.
46. Lau JK, Lowres N, Neubeck L, Brieger DB, Sy RW, Galloway CD, *et al.* iPhone ECG application for community screening to detect silent atrial fibrillation: a novel technology to prevent stroke. Int J Cardiol. 2013; 165:193-4.
47. Tieleman RG, Plantinga Y, Rinkes D, Bartels GL, Posma JL, Cator R, *et al.* Validation and clinical use of a novel diagnostic device for screening of atrial fibrillation. Europace. 2014; 16:1291-5.
48. Vaes B, Stalpaert S, Tavernier K, Thaels B, Lapeire D, Mullens W, *et al.* The diagnostic accuracy of the MyDiagnostick to detect atrial fibrillation in primary care. BMC family practice. 2014; 15:113.
49. Crockford CJ, Ahmed O, Kaba R, Berry R. An analysis of the applicability of lead1 screening for cardiac arrhythmia in primary care settings using novel sensing technology & multiple commercial algorithms for automating detection to increase PPV of referrals for further investigation. Europace. 2013; 4):iv20.
50. Koltowski L, Balsam P, Glowczynska R, Peller M, Maksym J, Blicharz L, *et al.* Comparison of kardia mobile (one lead ECGs records) with 12-lead ECGs in 100 consecutive patients with various cardiovascular disorders. Europace. 2017; 19 (Supplement 3):iii353.
51. Battipaglia I, Gilbert K, Hogarth AJ, Tayebjee MH. Screening for atrial fibrillation in the community using a novel ECG recorder. J Atr Fibrillation. 2016; 9:1433.
52. Orchard J, Freedman SB, Lowres N, Peiris D, Neubeck L. iPhone ECG screening by practice nurses and receptionists for atrial fibrillation in general practice: the GP-SEARCH qualitative pilot study. Australian family physician. 2014; 43:315-9.
53. Chan LL, Chan SC, Yan BP. Feasibility and acceptability of atrial fibrillation screening using a hand-held ECG device in general practice setting in Hong Kong. Value in Health. 2017; 20 (9):A599.
54. Chan NY, Choy CC. Community screening for atrial fibrillation in a Chinese population using a smartphone-based wireless single-lead ECG. J Am Coll Cardiol. 2015; 1:A467.
55. Chan NY, Choy CC. Screening for atrial fibrillation in 13 122 Hong Kong citizens with smartphone electrocardiogram. Heart. 2016a; 12.
56. Chan PH, Wong CK, Poh YC, Pun L, Leung WW, Wong YF, *et al.* Diagnostic performance of a smartphone-based photoplethysmographic application for atrial fibrillation screening in a primary care setting. J Am Heart Assoc. 2016b; 5.
57. Gibson J, Hanjari M, Watkins C, Chauhan U. Opportunistic detection of atrial fibrillation in primary care: a mixed methods evaluation of the introduction of new healthcare technology. Eur Stroke J. 2017; 2 (1 Supplement 1):112.
58. Hussain W, Thakrar D. The use of a handheld device in identifying atrial fibrillation patients during flu vaccination clinics. Europace. 2016; 18 (Supplement 2):ii19.
59. Kaasenbrood F, Hollander M, Rutten FH, Gerhards LJ, Hoes AW, Tieleman RG. Yield of screening for atrial fibrillation in primary care with a hand-held, single-lead electrocardiogram device during influenza vaccination. Europace. 2016; 18:1514-20.
60. Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J, *et al.* Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. the SEARCH-AF study. Thromb Haemost. 2014; 111:1167-76.
61. Orchard J, Lowres N, Freedman SB, Ladak L, Lee W, Zwar N, *et al.* Screening for atrial fibrillation during influenza vaccinations by primary care nurses using a smartphone electrocardiograph (iECG): a feasibility study. Eur J Prev Cardiol. 2016; 23:13-20.
62. Reeves B. Preliminary evaluation of the viewing function of the imPulse ECG monitor.NR.

63. Waring O, Davidson N, Stout M, Pearce K. Detection of atrial fibrillation in community locations using novel technology's as a method of stroke prevention in the over 65's asymptomatic population - should it become standard practise? Europace Conference: heart rhythm congress 2016 United kingdom. 2016; 18.Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/744/CN-01406744/frame.html [Accessed June 2018].18.
64. Yan BPY, Chan LLY, Lee VWY, Freedman B. Medical outpatient clinics an ideal setting for atrial fibrillation screening using a handheld single-lead ECG with automated diagnosis. Eur Heart J. 2016; 37 (Supplement 1):888.
65. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009; 339.
66. Duarte R, Stainthorpe A, Greenhalgh J, Richardson M, Marshall T, Hall M*, et al.* The clinical and cost effectiveness of lead-I electrocardiogram (ECG) devices for detecting atrial fibrillation using single-time point testing in primary care. PROSPERO CRD42018090375 2018; Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018090375. Accessed.
67. Drummond M, T. J. Guidelines for authors and peer reviewers of economic submissions to the BMJ. the BMJ economic evaluation working party. BMJ. 1996; 313:275-83.
68. Leeflang MM, Rutjes AW, Reitsma JB, Hooft L, Bossuyt PM. Variation of a test's sensitivity and specificity with disease prevalence. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2013; 185:E537-44.
69. National Institute for Health and Care Excellence (NICE). NICE Clinical Knowledge Summary on managing atrial and ventricular ectopy. 2015.; Available from: https://cks.nice.org.uk/palpitations#!scenario [Accessed June 2018]. Accessed.
70. Office for National Statistics. National life tables: United Kingdom. 2017; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables [Accessed June 2018]. Accessed 06 July 2018.
71. Piccini JP, Simon DN, Steinberg BA, et al. Differences in clinical and functional outcomes of atrial fibrillation in women and men: two-year results from the orbit-af registry. JAMA Cardiology. 2016; 1:282-91.
72. Welton NJ, McAleenan A, Thom HH, Davies P, Hollingworth W, Higgins JP*, et al.* Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2017; 21:1-236.
73. Engdahl J, Andersson L, Mirskaya M, Rosenqvist M. Stepwise screening of atrial fibrillation in a 75-year-old population: implications for stroke prevention. Circulation. 2013; 127:930-7.
74. Aronsson M, Svennberg E, Rosenqvist M, Engdahl J, Al-Khalili F, Friberg L*, et al.* Cost-effectiveness of mass screening for untreated atrial fibrillation using intermittent ECG recording. Europace. 2015; 17:1023-9.
75. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass Screening for Untreated Atrial Fibrillation: The STROKESTOP Study. Circulation. 2015; 131:2176-84.
76. Schnabel RB, Pecen L, Ojeda FM, Lucerna M, Rzayeva N, Blankenberg S*, et al.* Gender differences in clinical presentation and 1-year outcomes in atrial fibrillation. Heart. 2017; 103:1024-30.
77. Berg J, Lindgren P, Nieuwlaat R, Bouin O, Crijns H. Factors determining utility measured with the EQ-5D in patients with atrial fibrillation. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2010; 19:381-90.
78. NHS Business Services. Practice list size and GP count for each practice | NHSBSA. 2018.; Available from: https://www.nhsbsa.nhs.uk/prescription-data/organisation-data/practice-list-size-and-gp-count-each-practice [Accessed June 2018]. Accessed 04 July 2018.
79. Israel CW, Grönefeld G, Ehrlich JR, Li Y-G, Hohnloser SH. Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: implications for optimal patient care. Journal of the American College of Cardiology. 2004; 43:47-52.
80. Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener H-C*, et al.* Outcome parameters for trials in atrial fibrillationRecommendations from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association. EP Europace. 2007; 9:1006-23.
81. EBM DataLab UoO. OpenPrescribing.net. 2018; Available from: https://openprescribing.net/ [Accessed 06 July 2018]. Accessed.
82. NHS Digital. Practice level prescribing in England: a summary. 2018.; Available from: https://digital.nhs.uk/data-and-information/areas-of-interest/prescribing/practice-level-prescribing-in-england-a-summary [Accessed 12 August 2018]. Accessed.
83. Sterne JA, Bodalia PN, Bryden PA, Davies PA, Lopez-Lopez JA, Okoli GN*, et al.* Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis and cost-effectiveness analysis. Health Technology Assessment Volume. 2017; 21.
84. Office for National Statistics. Estimates of the population for the UK, England and Wales, Scotland and Northern Ireland - office for national statistics. 2018.; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland [Accessed June 2018]. Accessed 06 July 2018.
85. Mathisen SM, Dalen I, Larsen JP, Kurz M. Long-Term Mortality and Its Risk Factors in Stroke Survivors. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2016; 25:635-41.
86. Public Health England. First stroke estimates in England: 2007 to 2016. 2018.; Available from: https://www.gov.uk/government/publications/first-stroke-estimates-in-england-2007-to-2016 [Accessed 12 August 2018]. Accessed 12 August 2018.
87. NHS Improvement. National schedule of reference costs 2016/17. 2017.; Available from: https://improvement.nhs.uk/resources/reference-costs/ [Accessed 12 August 2018]. Accessed.
88. Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE*, et al.* Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (oxford vascular study). The Lancet Oncol. 2005; 366:1773-83.
89. Mohan KM, Wolfe CD, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. Stroke. 2011; 42:1489-94.
90. The EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. Health Policy. 1990; 16:199-208.

91. Janssen B, Szende A. Population norms for the EQ-5D. In: Szende A, Janssen B, Cabases J, editors. Self-Reported Population Health: An International Perspective based on EQ-5D. Dordrecht: Springer Netherlands; 2014. p. 19-30.

92. Robinson A, Thomson R, Parkin D, Sudlow M, Eccles M. How patients with atrial fibrillation value different health outcomes: a standard gamble study. Journal of Health Services Research and Policy. 2001; 6:92-8.
93. Hobbs F, Fitzmaurice D, Mant J, Murray E, Jowett S, Bryan S*, et al*. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. the SAFE study. Health technology assessment (winchester, england). 2005; 9(40).Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/854/CN-00530854/frame.html.9 40.
94. Curtis L BA. Unit costs of health and social care 2017. 2017; Available from: https://www.pssru.ac.uk/project-pages/unit-costs/[Accessed June 2018]. Accessed.
95. National Institute for Health and Care Excellence (NICE). Routine preoperative tests for elective surgery (NG45). 2016; Available from: https://www.nice.org.uk/guidance/ng45 [Accessed June 2018]. Accessed.
96. Office for National Statistics. Inflation and price indices. 2017; Available from: https://www.ons.gov.uk/economy/inflationandpriceindices. Accessed 2018.
97. Department of Health. NHS reference costs 2016/17. 2017; Available from: https://improvement.nhs.uk/resources/reference-costs/ Accessed 19/03/18. Accessed.
98. NICE. Zio Service for detecting cardiac arrhythmias: Medtech innovation briefing [MIB101]. 2017; Available from: https://www.nice.org.uk/advice/mib101. Accessed 19.10.2018.
99. British National Formulary. BNF online. 2018; Available from: http://www.bnf.org/products/bnf-online/ [Accessed June 2018]. Accessed.
100. NHS Business Services. NHS electronic drug tariff. 2018.; Available from: http://www.drugtariff.nhsbsa.nhs.uk/#/00553921-DA/DA00553911/Part%20VIIIA%20-%20Basic%20Prices%20of%20Drugs [Accessed June 2018]. Accessed 20 July 2018.
101. Sentinel Stroke National Audit Programme. Cost and Cost-effectiveness analysis. 2016.; Available from: https://www.strokeaudit.org/SupportFiles/Documents/Health-Economics/Health-economic-report-2016.aspx [Accessed 12 August 2018]. Accessed 12 August 2018.
102. Taggar JS, Coleman T, Lewis S, Heneghan C, Jones M. Accuracy of methods for detecting an irregular pulse and suspected atrial fibrillation: A systematic review and meta-analysis. Eur J Prev Cardiol. 2016; 23:1330-8.
103. Jacobs MS, Kaasenbrood F, Postma MJ, Van Hulst M, Tieleman RG. Cost-effectiveness of screening for atrial fibrillation in primary care with a handheld, single-lead electrocardiogram device in the Netherlands. Europace. 2018; 20:12-8.
104. West of England Academic Heath Science Networks. AliveCor Kardia Mobile: NHS England mobile ECG device project. 2018; Available from: https://www.weahsn.net/wp-content/uploads/KardiaAlivecore-Guidance-Document-v-12-BC-DE-UK-15.02.2018.pdf. Accessed.
105. NHS England Midlands and East. Atrial fibrillation. 2018; Available from: https://www.england.nhs.uk/mids-east/clinical-networks/east-midlands-clinical-network/our-networks/cardiovascular/atrial-fibrillation/. Accessed.
106. McKee S. NHS rolls out KardiaMobile to accelerate detection of arrhythmia. 2018; Available from: http://www.pharmatimes.com/news/nhs_rolls_out_kardiamobile_to_accelerate_detection_of_arrhythmia_1222263. Accessed.

8 APPENDICES

Appendix 1 PRISMA-DTA checklist

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
TITLE / ABSTRACT			
Title	1	Identify the report as a systematic review (+/- meta-analysis) of diagnostic test accuracy (DTA) studies.	NA
Abstract	2	Abstract: See PRISMA-DTA for abstracts.	Appendix 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	pp 21-6
Clinical role of index test	D1	State the scientific and clinical background, including the intended use and clinical role of the index test, and if applicable, the rationale for minimally acceptable test accuracy (or minimum difference in accuracy for comparative design).	pp 26-9
Objectives	4	Provide an explicit statement of question(s) being addressed in terms of participants, index test(s), and target condition(s).	p 29
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	p 20
Eligibility criteria	6	Specify study characteristics (participants, setting, index test(s), reference standard(s), target condition(s), and study design) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	p 32-3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	p 30
Search	8	Present full search strategies for all electronic databases and other sources searched, including any limits used, such that they could be repeated.	Appendix 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	p 33
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p 33

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
Definitions for data extraction	11	Provide definitions used in data extraction and classifications of target condition(s), index test(s), reference standard(s) and other characteristics (e.g. study design, clinical setting).	p 32
Risk of bias and applicability	12	Describe methods used for assessing risk of bias in individual studies and concerns regarding the applicability to the review question.	p 33-4
Diagnostic accuracy measures	13	State the principal diagnostic accuracy measure(s) reported (e.g. sensitivity, specificity) and state the unit of assessment (e.g. per-patient, per-lesion).	p 34
Synthesis of results	14	Describe methods of handling data, combining results of studies and describing variability between studies. This could include, but is not limited to: a) handling of multiple definitions of target condition. b) handling of multiple thresholds of test positivity, c) handling multiple index test readers, d) handling of indeterminate test results, e) grouping and comparing tests, f) handling of different reference standards	p 34-5
Meta-analysis	D2	Report the statistical methods used for meta-analyses, if performed.	p 34-5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	p 35
RESULTS			
Study selection	17	Provide numbers of studies screened, assessed for eligibility, included in the review (and included in meta-analysis, if applicable) with reasons for exclusions at each stage, ideally with a flow diagram.	p 36-7
Study characteristics	18	For each included study provide citations and present key characteristics including: a) participant characteristics (presentation, prior testing), b) clinical setting, c) study design, d) target condition definition, e) index test, f) reference standard, g) sample size, h) funding sources	p 38-9
Risk of bias and applicability	19	Present evaluation of risk of bias and concerns regarding applicability for each study.	p 40-2
Results of individual studies	20	For each analysis in each study (e.g. unique combination of index test, reference standard, and positivity threshold) report 2x2 data (TP, FP, FN, TN) with estimates of diagnostic accuracy and confidence intervals, ideally with a forest or receiver operator characteristic (ROC) plot.	p 43-55
Synthesis of results	21	Describe test accuracy, including variability; if meta-analysis was done, include results and confidence intervals.	p 43-55
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression; analysis of index test: failure rates, proportion of inconclusive results, adverse events).	p 44-55

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence.	p 56-8
Limitations	25	Discuss limitations from included studies (e.g. risk of bias and concerns regarding applicability) and from the review process (e.g. incomplete retrieval of identified research).	p 115
Conclusions	26	Provide a general interpretation of the results in the context of other evidence. Discuss implications for future research and clinical practice (e.g. the intended use and clinical role of the index test).	p 116
FUNDING			
Funding	27	For the systematic review, describe the sources of funding and other support and the role of the funders.	p 20

Appendix 2 PRISMA-DTA for Abstracts checklist

Section/topic	#	PRISMA-DTA for Abstracts Checklist item	Reported on page #
TITLE and PURPOSE			
Title	1	Identify the report as a systematic review (+/- meta-analysis) of diagnostic test accuracy (DTA) studies.	NA
Objectives	2	Indicate the research question, including components such as participants, index test, and target conditions.	p 16
METHODS			
Eligibility criteria	3	Include study characteristics used as criteria for eligibility.	p 16-7
Information sources	4	List the key databases searched and the search dates.	p 16
Risk of bias & applicability	5	Indicate the methods of assessing risk of bias and applicability.	p 17
Synthesis of results	A1	Indicate the methods for the data synthesis.	p 17
RESULTS			
Included studies	6	Indicate the number and type of included studies and the participants and relevant characteristics of the studies (including the reference standard).	p 18
Synthesis of results	7	Include the results for the analysis of diagnostic accuracy, preferably indicating the number of studies and participants. Describe test accuracy including variability; if meta-analysis was done, include summary results and confidence intervals.	p 18-9
DISCUSSION			
Strengths and limitations	9	Provide a brief summary of the strengths and limitations of the evidence	p 20
Interpretation	10	Provide a general interpretation of the results and the important implications.	p 20
OTHER			
Funding	11	Indicate the primary source of funding for the review.	p 20
Registration	12	Provide the registration number and the registry name	p 20

Appendix 3 Draft search strategy (MEDLINE)

1	Lead-I ECG.tw.
2	single lead ECG.tw.
3	(lead I or single lead or automated algorithm).tw.
4	Electrocardiography/
5	(electrocardiog* or ECG).tw.
6	4 or 5
7	3 and 6
8	lead I electrocardiog*.tw.
9	single lead electrocardiog*.tw.
10	1 or 2 or 7 or 8 or 9
11	Atrial Fibrillation/
12	AF.tw.
13	(Atr* adj3 Fibrill*).tw.
14	11 or 12 or 13
15	10 and 14
16	Kardia Mobile.tw.
17	MyDiagnostick.tw.
18	RhythmPad.tw.
19	Zenicor-ECG.tw.
20	imPulse.tw.
21	10 and 20
22	15 or 16 or 17 or 18 or 19 or 21
23	Animals/ not Humans/
24	22 not 23

Appendix 4 Excluded studies

Ineligible intervention (19 studies)

Boyle KO, Morra D, Dorian P, McCrorie A, Haddad P, Taylor L, et al. Atrial fibrillation screening using a handheld ecg device: Results from the heart and stroke foundation (hsf) "be pulse aware" campaign. Stroke. 2013; 44 (12):e184.

Chellappan K, Ab Malek SNH, Jaafar R, Aminuddin A. Self-monitoring technique for stroke prevention among atrial fibrillation patients. International Journal of Stroke. 2016; 11 (Supplement 3):248.

Chen YH, Hung CS, Huang CC, Hung YC, Hwang JJ, Ho YL. Atrial fibrillation screening in nonmetropolitan areas using a telehealth surveillance system with an embedded cloud-computing algorithm: Prospective pilot study. JMIR Mhealth Uhealth. 2017; 5:e135.

Claes N, Van Laethem C, Goethals M, Goethals P, Mairesse G, Schwagten B, et al. Prevalence of atrial fibrillation in adults participating in a large-scale voluntary screening programme in belgium. Acta Cardiol. 2012; 67:273-8.

Gilani M, Eklund JM, Makrehchi M. Automated detection of atrial fibrillation episode using novel heart rate variability features. Conf Proc IEEE Eng Med Biol Soc. 2016; 2016:3461-4.

Hobbs F, Fitzmaurice D, Mant J, Murray E, Jowett S, Bryan S, et al. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The safe study. Health technology assessment (Winchester, England). 2005; 9(40): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/854/CN-00530854/frame.html.

Kaleschke G, Hoffmann B, Drewitz I, Steinbeck G, Naebauer M, Goette A, et al. Prospective, multicentre validation of a simple, patient-operated electrocardiographic system for the detection of arrhythmias and electrocardiographic changes. Europace. 2009; 11:1362-8.

Kearley K, Selwood M, Van den Bruel A, Thompson M, Mant D, Hobbs FR, et al. Triage tests for identifying atrial fibrillation in primary care: A diagnostic accuracy study comparing single-lead ecg and modified bp monitors. BMJ Open. 2014; 4:e004565.

Mant J, Fitzmaurice DA, Hobbs FDR, Jowett S, Murray ET, Holder R, et al. Accuracy of diagnosing atrial fibrillation on electrocardiogram by primary care practitioners and interpretative diagnostic software: Analysis of data from screening for atrial fibrillation in the elderly (safe) trial. British Medical Journal. 2007; 335:380-2.

McManus DD, Lee J, Maitas O, Esa N, Pidikiti R, Carlucci A, et al. A novel application for the detection of an irregular pulse using an iphone 4s in patients with atrial fibrillation. Heart Rhythm. 2013; 10:315-9.

McManus D, Chong JW, Soni A, Saczynski JS, Esa N, Napolitano C, et al. Pulse-smart: Pulse-based arrhythmia discrimination using a novel smartphone application. J Cardiovasc Electrophysiol. 2016; 27:51-7.

Mortelmans C, Van Haelst R, Van Der Auwera J, Grieten L, Vandervoort P, Vaes B. Validation of a new smartphone application for the diagnosis of atrial fibrillation in primary care. Europace. 2017; 19 (Supplement 3):iii16.

Newham WG, Tayebjee MH. Excellent symptom rhythm correlation in patients with palpitations using a novel smartphone based event recorder. J Atr Fibrillation. 2017; 10:1514.

Proietti M, Mairesse GH, Goethals P, Scavee C, Vijgen J, Blankoff I, et al. A population screening programme for atrial fibrillation: A report from the belgian heart rhythm week screening programme. Europace. 2016; 18:1779-86.

Rajendram R, Patel S, Kale S, Nangalia V. Ability of clinicians trained in intensive care to interpret rhythm strips. Journal of the Intensive Care Society. 2014; 1):S70-S1.

Sandhu RK, Deif B, Barake W, Agarwal G, Connolly SJ, Dolovich L, et al. Identification of actionable atrial fibrillation using an integrated cardiovascular screening approach in community pharmacies. Heart Rhythm. 2016; 1):S415-S6.

Somerville S, Somerville J, Croft P, Lewis M. Atrial fibrillation: A comparison of methods to identify cases in general practice. The British Journal of General Practice. 2000; 50:727-9.

Vyas V, Duran J, Ansaripour A, Niedzielko M, Steel A, Bakhai A. Does a 12-lead ecg more reliably detect atrial fibrilation than a rhythm strip only ecg? Value in Health. 2014; 17 (7):A485-A6.

Winkler S, Axmann C, Schannor B, Kim S, Leuthold T, Scherf M, et al. Diagnostic accuracy of a new detection algorithm for atrial fibrillation in cardiac telemonitoring with portable electrocardiogram devices. J Electrocardiol. 2011; 44:460-4.

Ineligible outcomes (7 studies)

Ara F, Crockford C, John I, Kaba RA. Novel galvanised titanium-based ecg technology can reliably detectarrhythmias. Europace. 2015; 3):iii53.

Chan PH, Wong CK, Pun L, Wong YF, Wong MM, Chu DW*, et al.* Diagnostic performance of an automatic blood pressure measurement device, microlife watchbp home a, for atrial fibrillation screening in a real-world primary care setting. BMJ Open. 2017; 7:e013685.

Chung EH, Guise KD. Qtc intervals can be assessed with the alivecor heart monitor in patients on dofetilide for atrial fibrillation. Journal of Electrocardiology. 2015; 48:8-9.

Grieten L, Van Der Auwera J, Vandervoort P, Rivero-Ayerza M, Van Herendael H, De Vusser P*, et al.* Evaluating smartphone based photoplesythmography as a screening solution for atrial fibrillation: A digital tool to detect afib? Journal of the American College of Cardiology. 2017; 69 (11 Supplement 1):2499.

Jacobs MS, Kaasenbrood F, Postma MJ, Van Hulst M, Tieleman RG. Cost-effectiveness of screening for atrial fibrillation in primary care with a handheld, single-lead electrocardiogram device in the netherlands. Europace. 2018; 20:12-8.

Khanbhai ZM, Manning SE, Hussain W. Community pharmacist led atrial fibrillation screening program has the potential to improve atrial fibrillation detection rates and reduce stroke risk. Circulation Conference: American Heart Association's. 2016; 134.

Mehta DD, Nazir NT, Trohman RG, Volgman AS. Single-lead portable ecg devices: Perceptions and clinical accuracy compared to conventional cardiac monitoring. Journal of Electrocardiology. 2015; 48:710-6.

Ineligible language (1 study)

Reimert M, Verhoeven A. Screening for atrial fibrillation with single-lead hand-held ecg. Huisarts en Wetenschap. 2017; 60:474.

Appendix 5 QUADAS-2 quality assessment

Ideal study

Population	People with signs or symptoms that may indicate underlying AF and who have an irregular pulse
Presentation	Presenting to primary care on account of signs and symptoms associated with AF (i.e. palpitations, dizziness, shortness of breath and tiredness)
Prior tests	No prior testing for AF
Index test	Lead-I ECG using one of the following technologies: • imPulse • Kardia Mobile • MyDiagnostick • RhythmPad GP • Zenicor ECG
Purpose	To detect AF at a single-time point in people who present with relevant signs and symptoms to primary care without previously diagnosed AF
Target disorder	AF
Reference standard	12-lead ECG performed and interpreted by a trained healthcare professional

QUADAS-2 assessment of studies included in the diagnostic test accuracy review

Crockford 2013[49]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Method used in the study for patient selection not described.		
Was a consecutive or random sample of patients enrolled?		Unclear
Was a case-control design avoided?		Unclear
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Patients who had been referred to an electrophysiology department. Reason for referral not provided.		
Is there concern that the included patients do not match the review question?	**Concerns**	**HIGH**

DOMAIN 2: INDEX TEST

A. Risk of Bias

RhythmPad GP. No details provided regarding who performed the tests. Sequence of tests and blinding of interpreters not clear.		
Were the index test results interpreted without knowledge of the results of the reference standard?		Unclear
If a threshold was used, was it pre-specified?		Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**UNCLEAR**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

12-lead ECG interpreted by a cardiologist. No details provided regarding who performed the tests.		
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

All patients received the index test and reference standard. Data from 24 patients were excluded due to data integrity, or to copies of traces of lead-I ECG or 12-lead ECG not being available at the end of the study. The reference standard was performed before the index test but the interval between assessments is not clear.

Was there an appropriate interval between index test and reference standard?		Unclear
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Yes
For comparative accuracy studies, did all patients receive all index tests		NA
Were all patients included in the analysis?		No
Could the patient flow have introduced bias?	**Risk**	**UNCLEAR**

Desteghe 2017[37]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Method used in the study for patient selection not described.		
Was a consecutive or random sample of patients enrolled?		Unclear
Was a case-control design avoided?		Unclear
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Hospitalised patients screened for AF at a cardiology ward. A proportion of the screened population (35.6%) had known AF based on chart review. Reasons for admission were coronary angiography/elective revascularisation (n=100, 31.2%), electrophysiological examination/ablation (n=64, 20%), heart failure (n=37, 11.6%), acute coronary syndrome (n=36, 11.3%), device implantation or replacement (n=32, 10%), symptomatic AF (n=11, 3.4%) or other (n=40, 12.5%).		
Is there concern that the included patients do not match the review question?	**Concerns**	**HIGH**

DOMAIN 2: INDEX TESTS

A1. Risk of Bias

MyDiagnostick lead-I ECG device. No details provided regarding who performed the tests. Lead-I ECG performed immediately after the use of the reference standard and interpreted by device algorithm and two electrophysiologists blind to the diagnosis based on both the algorithm and reference standard.		
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**LOW**

B1. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**LOW**

A2. Risk of Bias

Kardia Mobile lead-I ECG. No details provided regarding who performed the tests. Lead-I ECG performed immediately after the use of the reference standard and interpreted by device algorithm and two electrophysiologists blind to the diagnosis based on both the algorithm and reference standard.		
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**LOW**

B2. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

Full 10 seconds 12-lead ECG performed by a trained nurse immediately before use of lead-I ECG devices. 12-lead ECG interpreted by two electrophysiologists blind to the results of the lead-I ECG algorithm.

Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Twenty-four patients excluded from the 2x2 table because they were not able to hold the devices properly. The reference standard was performed immediately before the index tests.

Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Yes
For comparative accuracy studies, did all patients receive all index tests		Yes
Were all patients included in the analysis?		No
Could the patient flow have introduced bias?	**Risk**	**LOW**

Doliwa 2009[42]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Method used in the study for patient selection not described.		
Was a consecutive or random sample of patients enrolled?		Unclear
Was a case-control design avoided?		Unclear
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Patients with atrial fibrillation, atrial flutter or sinus rhythm were recruited from a cardiology outpatient clinic to evaluate the sensitivity and specificity with lead-I ECG for sinus rhythm and atrial fibrillation detection. Reason for cardiology outpatient appointment not provided.		
Is there concern that the included patients do not match the review question?	**Concerns**	**HIGH**

DOMAIN 2: INDEX TEST

A. Risk of Bias

Zenicor-ECG. No details provided regarding who performed the tests. Lead-I ECG performed immediately after the use of the reference standard and interpreted by a cardiologist blind to the 12-lead ECG registration.		
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

12-lead ECG performed immediately before the use of lead-I ECG device and interpreted by a cardiologist. No details provided regarding who performed the tests.		
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

All patients received the index test and reference standard. All patients were included in the 2x2 table. The reference standard was performed immediately before the index test.		
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Yes
For comparative accuracy studies, did all patients receive all index tests		NA
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?	**Risk**	**LOW**

Haberman 2015[44]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Method used in the study for patient selection not described.		
Was a consecutive or random sample of patients enrolled?		Unclear
Was a case-control design avoided?		Unclear
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Patients were recruited from a cardiology outpatient clinic to evaluate the sensitivity and specificity with lead-I ECG device for sinus rhythm and atrial fibrillation detection. Unclear if any patients had been previously diagnosed with AF. Reason for cardiology outpatient appointment not provided.		
Is there concern that the included patients do not match the review question?	**Concerns**	**HIGH**

DOMAIN 2: INDEX TEST

A. Risk of Bias

Kardia Mobile lead-I ECG. Test acquisitions performed and supervised by study investigators. Lead-I ECG performed immediately before the use of the reference standard and interpreted by two electrophysiologists. Unclear if interpreters of the test were blind to the results of the reference standard.		
Were the index test results interpreted without knowledge of the results of the reference standard?		Unclear
If a threshold was used, was it pre-specified?		Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

12-lead ECG performed immediately after the use of lead-I ECG device and interpreted by two electrophysiologists. Test acquisitions performed and supervised by study investigators.		
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

All patients received the index test and reference standard. All patients were included in the 2x2 table. The reference standard was performed immediately after the index test.		
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Yes
For comparative accuracy studies, did all patients receive all index tests		NA
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?	**Risk**	**LOW**

Koltowski 2017[50]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Method used in the study for patient selection not described.		
Was a consecutive or random sample of patients enrolled?		Unclear
Was a case-control design avoided?		Unclear
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Patients in a tertiary care centre were recruited to evaluate the diagnostic accuracy of the Kardia Mobile lead-I ECG device. Reasons for patients attending the tertiary care centre not provided.		
Is there concern that the included patients do not match the review question?	**Concerns**	**HIGH**

DOMAIN 2: INDEX TEST

A. Risk of Bias

Kardia Mobile lead-I ECG. Test acquisitions performed by one physician. Lead-I ECG performed before the use of the reference standard and interpreted by three teams comprised of two cardiologists and one internal medicine specialist.		
Were the index test results interpreted without knowledge of the results of the reference standard?		Unclear
If a threshold was used, was it pre-specified?		Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**UNCLEAR**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

12-lead ECG performed after the use of lead-I ECG device and interpreted by three teams comprised of two cardiologists and one internal medicine specialist. Test acquisitions performed by one physician.		
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

All patients received the reference standard. One patient did not receive the index test. The reference standard was performed after the index test.		
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Yes
For comparative accuracy studies, did all patients receive all index tests		NA
Were all patients included in the analysis?		No
Could the patient flow have introduced bias?	**Risk**	**LOW**

Lau 2013[46]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Method used in the study for patient selection not described.		
Was a consecutive or random sample of patients enrolled?		Unclear
Was a case-control design avoided?		Unclear
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Patients screened for AF at a cardiology department. A proportion of the screened population (24%) had known AF. Reason for patient attendance at cardiology department not provided.		
Is there concern that the included patients do not match the review question?	**Concerns**	**HIGH**

DOMAIN 2: INDEX TEST

A. Risk of Bias

Kardia Mobile lead-I ECG. No details provided regarding who performed the tests. Lead-I ECG performed within six hours after the use of the reference standard and interpreted by device algorithm alone.		
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**HIGH**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

12-lead ECG performed within six hours before the use of lead-I ECG device and interpreted by a cardiologist. No details provided regarding who performed the tests.		
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

All patients received the index test and reference standard. All patients were included in the 2x2 table. The index test was performed within six hours after the reference standard.		
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Yes
For comparative accuracy studies, did all patients receive all index tests		NA
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?	**Risk**	**LOW**

Reeves (NR)[62]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Research nurses identified and approached eligible patients.		
Was a consecutive or random sample of patients enrolled?		Unclear
Was a case-control design avoided?		Unclear
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Patients hospitalised after cardiac surgery or a cardiac-related event were recruited from cardiac intensive care unit, coronary care unit and cardiac surgery and cardiology wards in a regional specialist cardiac centre. The aim of the study was to obtain proof-of-principle data that the imPulse lead-I ECG device can capture and display an ECG trace with sufficient detail and viewing quality to allow experienced practitioners to detect AF.		
Is there concern that the included patients do not match the review question?	**Concerns**	**HIGH**

DOMAIN 2: INDEX TEST

A. Risk of Bias

imPulse lead-I ECG. It is not clear who performed the tests. Lead-I ECG performed at the same time as the 12-lead ECG. The index test was interpreted by two cardiology doctors, two specialist cardiac nurses and two cardiac physiologists, all with expertise in assessing ECGs blind to the 12-lead ECG registration.		
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

12-lead ECG performed at the same time as the lead-I ECG device and interpreted by two cardiology doctors, two specialist cardiac nurses and two cardiac physiologists. There were two reference standards; the first was the clinical ECG diagnosis and the second was the ECG diagnosis for a subgroup of patients for whom there was consensus among the assessors' 12-lead diagnoses (at least 3 of 4 in agreement) that the diagnosis was SR or AF and this consensus diagnosis matched the clinical ECG diagnosis. No details provided regarding who performed the tests.

Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**HIGH**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

All patients received the index test and 12-lead ECG. All patients were included in the 2x2 table, however, interpretations by all of the six assessors were not presented. The 12-lead ECG was performed at the same time as the index test.

Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Unclear
For comparative accuracy studies, did all patients receive all index tests		NA
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?	**Risk**	**LOW**

Tieleman 2014[47]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Random selection of patients visiting an outpatient cardiology clinic or a specialised AF outpatient clinic.		
Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Unclear
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Patients with known AF and patients without a history of AF visiting an outpatient cardiology clinic or a specialised AF outpatient clinic. Reasons for patients attending the clinics not presented.		
Is there concern that the included patients do not match the review question?	**Concerns**	**HIGH**

DOMAIN 2: INDEX TEST

A. Risk of Bias

MyDiagnostick lead-I ECG. No details provided regarding who performed the tests. Lead-I ECG performed immediately before the use of the reference standard and trace interpreted by device algorithm alone.		
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**HIGH**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

12-lead ECG performed immediately after the use of lead-I ECG device and interpreted by a cardiologist blind to the results of the index test. No details provided regarding who performed the tests.		
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

All patients received the index test and reference standard. All patients were included in the 2x2 table. The reference standard was performed immediately after the index test.		
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive a reference standard?		Yes
Did patients receive the same reference standard?		Yes
For comparative accuracy studies, did all patients receive all index tests		NA
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?	**Risk**	**LOW**

Vaes 2014[48]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

General practitioners invited patients with known, paroxysmal or chronic AF to participate in the study to achieve a prevalence of AF of at least 50%. Subjects without a history of AF were also invited to participate in the study.		
Was a consecutive or random sample of patients enrolled?		Unclear
Was a case-control design avoided?		No
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Patients with known AF (N=161) and patients without a history of AF (N=30) presenting to primary care. Reasons for patients attending a primary care appointment not presented.		
Is there concern that the included patients do not match the review question?	**Concerns**	**HIGH**

DOMAIN 2: INDEX TEST

A. Risk of Bias

MyDiagnostick lead-I ECG device. A researcher who was not blinded to the medical history of the patient performed the tests. Lead-I ECG performed before the use of the reference standard and trace interpreted by device algorithm alone.		
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**HIGH**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

12-lead ECG performed after the use of the lead-I ECG device and interpreted by a cardiologist blind to the results of the index test. A researcher who was not blinded to the medical history of the patient performed the tests.		
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Ten patients were excluded from the 2x2 table as the pacemaker was active at the moment of the ECG recording. The reference standard was performed after the index test but timing not specified.		
Was there an appropriate interval between index test and reference standard?		Unclear
Did all patients receive a reference standard?		No
Did patients receive the same reference standard?		Yes
For comparative accuracy studies, did all patients receive all index tests		NA
Were all patients included in the analysis?		No
Could the patient flow have introduced bias?	**Risk**	**UNCLEAR**

Williams 2015[38]

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Method used in the study for patient selection not described.		
Was a consecutive or random sample of patients enrolled?		Unclear
Was a case-control design avoided?		Unclear
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?	**Risk**	**UNCLEAR**

B. Concerns regarding applicability

Patients with known AF attending an AF clinic and patients with AF status unknown who were attending the clinic for non-AF related reasons.		
Is there concern that the included patients do not match the review question?	**Concerns**	**HIGH**

DOMAIN 2: INDEX TEST

A. Risk of Bias

Kardia Mobile lead-I ECG. No details provided regarding who performed the tests. Lead-I ECG performed at the same time as the reference standard and interpreted by a cardiologist and a GP with an interest in cardiology. Interpreters of the test were blind to the results of the reference standard.		
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
If a threshold was used, was it pre-specified?		Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?	**Concerns**	**LOW**

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

12-lead ECG performed at the same time as the index test and interpreted by a cardiologist and a GP with an interest in cardiology blind to the results of the index test. No details provided regarding who performed the tests.		
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index test?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk**	**LOW**

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns**	**LOW**

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Four patients excluded due to artefacts in ECG recordings (not clear whether these artefacts were in the lead-I or 12-lead ECG traces). The reference standard was performed at the same time as the index test.		
Was there an appropriate interval between index test and reference standard?		No
Did all patients receive a reference standard?		No
Did patients receive the same reference standard?		Yes
For comparative accuracy studies, did all patients receive all index tests		NA
Were all patients included in the analysis?		No
Could the patient flow have introduced bias?	**Risk**	**UNCLEAR**

Appendix 6 Studies reporting on lead-I ECG diagnostic test accuracy that were excluded from the diagnostic test accuracy review

For the purposes of presenting all available diagnostic accuracy data for lead-I ECG devices, this section reports on studies that were excluded from the diagnostic test accuracy review but that provide sensitivity and specificity for the lead-I ECG devices investigated in this assessment. The characteristics of the studies that did not meet all of the eligibility criteria but that presented sensitivity and specificity data of lead-I ECG devices is presented in Table 58.

Some studies were excluded from the diagnostic test accuracy review as although reporting sensitivity and specificity, they did not present data for the true positive, false negative, false positive and true negative test results[49,50] or because the reference standard in the study was not a 12-lead ECG interpreted by a trained healthcare professional.[56,60-62] The reference standard used in these studies is presented in Table 59. None of the excluded studies was conducted in people with signs or symptoms of AF. One of the studies was included in the diagnostic test accuracy review, but one of its populations was excluded as the reference standard used was not a 12-lead ECG interpreted by a trained healthcare professional.[47]

Two studies were available only as conference abstracts[49,50] while one study was available only as a report submitted by the manufacturer of the lead-I device.[62] Five of the studies[49,50,56,60,61] were cross-sectional in design and two were cohort studies.[47,62] Three studies were performed in primary care,[47,56,61] two studies in secondary care,[49,62] one study in tertiary care[50] and one study was performed in a community setting.[60] Only two studies[47,60] did not recruit at least a proportion of people with known AF, with known cardiovascular comorbidities[56] or attending a clinic for a cardiovascular related condition.[49,50,61,62]

Table 58 Characteristics of studies not eligible for inclusion in the diagnostic test accuracy review but presenting sensitivity and specificity results of lead-I ECG devices

Study	Study design; country and setting	Population; number in analysis and recruitment details	Age; sex and risk factors for AF	Reason for exclusion from the diagnostic test accuracy review
Chan 2016b (46)[56]	Cross-sectional; China; primary care	People with history of hypertension and/or diabetes mellitus or ≥65 years of age; N=1013; patients recruited from a general outpatient clinic	Mean age ± SD (years): 68.4 ± 12.2 Sex: 539 (53.2%) female Hypertension - 916 (90.4%) Diabetes - 371 (36.6%) Coronary artery disease - 164 (16.2%) Previous stroke - 106 (10.5%) Mean CHA_2DS_2VASc ± SD - 3.0 ± 1.5	Ineligible reference standard

Lowres 2014[60]	Cross-sectional; Australia; community	People aged ≥65 years entering the pharmacy without a severe coexisting medical condition; N=1000; availability of screening in participating pharmacies was advertised through flyers displayed within each pharmacy, and pharmacists and staff also directly approached potentially eligible clients	Mean age ± SD (years): 76 ± 7 Sex: 436 (44%) male Risk factors: NR	Ineligible reference standard
Orchard 2016[61]	Cross-sectional; Australia; primary care	Patients with known AF and patients without a history of AF attending for flu vaccination; N=972	New AF (N=7) Mean age ± SD (years): 80 ± 3 Sex: 3/7 male Known AF (N=29) Mean age ± SD (years): 77.1 ± 1 Sex: 15 (52%) male All AF (N=36) Mean age ± SD (years): 78 years ± 1 Sex: 18 (50%) male Risk factors: NR	Ineligible reference standard
Reeves[62]	Cohort; UK; secondary care	Patients aged 18 years or older recovering in the Cardiac Intensive Care Unit or a cardiac surgery ward, following cardiac surgery, or who had been admitted to the Coronary Care Unit or a cardiology ward after a cardiac related event; N=53; research nurses working in one or other of the clinical settings identified and approached eligible patients	Age: 23 to 90 years (range) Sex: 37 (70%) male Risk factors: NR	Ineligible reference standard
Tieleman 2014[47]	Cohort; Netherlands; primary care	People with unknown AF status; N=676; people attending GP for flu vaccination	Mean age ± SD (years): 74 ± 7.1	Ineligible reference standard

AF=atrial fibrillation; NR=not reported; SD=standard deviation

The reference standard used in the studies to assess the diagnostic test accuracy of lead-I ECG devices was interpretation of the lead-I ECG trace by a trained healthcare professional.[47,56,60,61] One study[62] used a clinical ECG diagnosis where additional information was available to the assessors and also a consensus among the assessors of 12-lead ECG (at least 3 of 4 in agreement) that matched the clinical ECG diagnosis.

Information on index test used, reference standard and diagnostic accuracy results for the studies that did not meet all of the eligibility criteria but that presented sensitivity and specificity data of lead-I ECG devices are presented in Table 59.

One study,[62] although ineligible for inclusion in the diagnostic test accuracy review, presented sensitivity and specificity results for the imPulse lead-I ECG device. The sensitivity reported for imPulse lead-I ECG ranged from 67% to 100% and the specificity from 58% to 100%.[62]

We did not assess the methodological quality of these studies as they did not meet the eligibility criteria for inclusion in the diagnostic accuracy review.

Table 59 Sensitivity and specificity results presented in studies not eligible for inclusion in the diagnostic test accuracy review

Study	Lead-I ECG device	Interpreter of lead-I ECG	Reference standard	Sensitivity	Specificity
Chan 2016b (46)[56]	Kardia Mobile	Algorithm and cardiologist	Lead-I ECG trace interpreted by cardiologist	71.4% (95% CI: 51.3% to 86.8%)	99.4% (95% CI: 98.7 to 99.8%)
Lowres 2014[60]	Kardia Mobile	Algorithm and cardiologist	Lead-I ECG trace interpreted by cardiologist	98.5% (95% CI: 92% to 100%)	91.4% (95% CI: 89% to 93%)
Orchard 2016[61]	Kardia Mobile	Algorithm and cardiologist	Lead-I ECG trace interpreted by cardiologist	95% (95% CI: 83% to 99%)	99% (95% CI: 98% to 100%)
Reeves[62]	imPulse	2 cardiology registrars, 2 cardiac physiologists and 2 specialist cardiac nurses	Clinical ECG diagnosis (may have been made on the basis of additional information available to the assessors)	Range=67% to 96%	Range=58% to 83%
			Consensus among the assessors of 12-lead ECG diagnoses (at least 3 of 4 in agreement) and consensus diagnosis matched the clinical ECG diagnosis	Range=67% to 100%	Range=83% to 100%

Tieleman 2014[47]	MyDiagnostick	Algorithm and cardiologist	Lead-I ECG trace interpreted by cardiologist	100%	99%

CI=confidence interval; ECG=electrocardiogram

Appendix 7 Draft search strategy economic evaluations (MEDLINE)

1 Lead-I ECG.tw.

2 single lead ECG.tw.

3 (lead I or single lead or automated algorithm).tw.

4 Electrocardiography/

5 (electrocardiog* or ECG).tw.

6 4 or 5

7 3 and 6

8 lead I electrocardiog*.tw.

9 single lead electrocardiog*.tw.

10 1 or 2 or 7 or 8 or 9

11 Kardia Mobile.tw.

12 MyDiagnostick.tw.

13 RhythmPad.tw.

14 Zenicor-ECG.tw.

15 imPulse.tw.

16 10 or 11 or 12 or 13 or 14

17 10 and 15

18 16 or 17

19 Economics/

20 "costs and cost analysis"/

21 Cost allocation/

22 Cost-benefit analysis/

23 Cost control/

24 Cost savings/

25 Cost of illness/

26 Cost sharing/

27 "deductibles and coinsurance"/

28 Medical savings accounts/

29 Health care costs/

30 Direct service costs/

31 Drug costs/

32 Employer health costs/

33 Hospital costs/

34 Health expenditures/

35 Capital expenditures/

36 Value of life/

37 exp economics, hospital/

38 exp economics, medical/

39 Economics, nursing/

40 Economics, pharmaceutical/

41 exp "fees and charges"/

42 exp budgets/

43 (low adj cost).mp.

44 (high adj cost).mp.

45 (health?care adj cost$).mp.

46 (fiscal or funding or financial or finance).tw.

47 (cost adj estimate$).mp.

48 (cost adj variable).mp.

49 (unit adj cost$).mp.

50 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.

51 or/19-50

52 18 and 51

Appendix 8 Parameters for probability sensitivity analysis

Description	Mean value	LB	UB	SD	Alpha	Beta	Distribution
Event rate: ae_AFNOAC_bleed_SterneHRo80	0.630	0.473	0.788	0.155			Lognormal
Event rate: ae_AFNOAC_bleed_SterneHRu80	0.820	0.615	1.025	0.155			Lognormal
Event rate: ae_AFNOAC_ICH_SterneHRo80	2.780	2.085	3.475	0.155			Lognormal
Event rate: ae_AFNOAC_ICH_SterneHRu80	0.460	0.345	0.575	0.155			Lognormal
Event rate: ae_AFNOAC_stroke_SterneHRo80	0.740	0.555	0.925	0.155			Lognormal
Event rate: ae_AFNOAC_stroke_SterneHRu80	0.900	0.675	1.125	0.155			Lognormal
Event rate: ae_AFNOAC_TIA_SterneHRo80	0.760	0.570	0.950	0.155			Lognormal
Event rate: ae_AFNOAC_TIA_SterneHRu80	0.740	0.555	0.925	0.155			Lognormal
Event rate: ae_AFuntrt_bleed_Sterne	0.543	0.511	0.575	0.036			Lognormal
Event rate: ae_AFuntrt_ICH_Sterne	2.777	3.113	2.509	0.066			Lognormal
Event rate: ae_AFuntrt_stroke_f65_Lowres	0.026	0.019	0.032	0.003	62.317	2343.726	Beta
Event rate: ae_AFuntrt_stroke_f75_Lowres	0.050	0.038	0.063	0.006	60.737	1149.163	Beta
Event rate: ae_AFuntrt_stroke_m65_Lowres	0.019	0.014	0.024	0.002	62.746	3188.317	Beta
Event rate: ae_AFuntrt_stroke_m75_Lowres	0.050	0.038	0.063	0.006	60.737	1149.163	Beta
Event rate: ae_AFuntrt_stroke_Sterne	2.777	3.113	2.509	0.066			Lognormal
Event rate: ae_AFuntrt_TIA_Sterne	1.617	1.935	1.434	0.091			Lognormal
Event rate: ae_AFWarf_bleed_SterneHaz	0.066	0.050	0.083	0.008	59.710	844.987	Beta
Event rate: ae_AFWarf_ICH_SterneHaz	0.009	0.007	0.012	0.001	63.389	6680.122	Beta
Event rate: ae_AFWarf_stroke_SterneHaz	0.012	0.009	0.015	0.002	63.220	5205.113	Beta
Event rate: ae_noAFuntrt_bleed_f50_Button	60.000	45.000	75.000				Binomial
Event rate: ae_noAFuntrt_bleed_f60_Button	75.000	56.250	93.750				Binomial
Event rate: ae_noAFuntrt_bleed_f70_Button	159.000	119.250	198.750				Binomial
Event rate: ae_noAFuntrt_bleed_f80_Button	344.000	258.000	430.000				Binomial
Event rate: ae_noAFuntrt_bleed_f90_Button	739.000	554.250	923.750				Binomial
Event rate: ae_noAFuntrt_bleed_m50_Button	101.000	75.750	126.250				Binomial
Event rate: ae_noAFuntrt_bleed_m60_Button	131.000	98.250	163.750				Binomial
Event rate: ae_noAFuntrt_bleed_m70_Button	247.000	185.250	308.750				Binomial
Event rate: ae_noAFuntrt_bleed_m80_Button	488.000	366.000	610.000				Binomial
Event rate: ae_noAFuntrt_bleed_m90_Button	864.000	648.000	1080.000				Binomial

Event rate: ae_noAFuntrt_bleed_NHS	0.011	0.008	0.014	0.001	63.270	5573.516	Beta
Event rate: ae_noAFuntrt_ICH_NHS	0.000	0.000	0.000	0.000	63.979	195185.287	Beta
Event rate: ae_noAFuntrt_ICHintra_f50_Rothwell	0.022	0.017	0.028				Binomial
Event rate: ae_noAFuntrt_ICHintra_f60_Rothwell	0.189	0.142	0.236				Binomial
Event rate: ae_noAFuntrt_ICHintra_f70_Rothwell	0.343	0.257	0.428				Binomial
Event rate: ae_noAFuntrt_ICHintra_f80_Rothwell	1.003	0.752	1.254				Binomial
Event rate: ae_noAFuntrt_ICHintra_f90_Rothwell	1.041	0.781	1.302				Binomial
Event rate: ae_noAFuntrt_ICHintra_m50_Rothwell	0.022	0.017	0.028				Binomial
Event rate: ae_noAFuntrt_ICHintra_m60_Rothwell	0.189	0.142	0.236				Binomial
Event rate: ae_noAFuntrt_ICHintra_m70_Rothwell	0.261	0.196	0.327				Binomial
Event rate: ae_noAFuntrt_ICHintra_m80_Rothwell	1.706	1.279	2.132				Binomial
Event rate: ae_noAFuntrt_ICHintra_m90_Rothwell	0.778	0.583	0.972				Binomial
Event rate: ae_noAFuntrt_stroke_f65_Lowres	0.005	0.004	0.006	0.001	63.682	12932.543	Beta
Event rate: ae_noAFuntrt_stroke_f75_Lowres	0.012	0.009	0.015	0.002	63.220	5205.113	Beta
Event rate: ae_noAFuntrt_stroke_m65_Lowres	0.007	0.005	0.009	0.001	63.539	8885.546	Beta
Event rate: ae_noAFuntrt_stroke_m75_Lowres	0.015	0.011	0.018	0.002	63.051	4255.511	Beta
Event rate: ae_noAFuntrt_stroke_f50_PHE	0.729	0.546	0.911				Binomial
Event rate: ae_noAFuntrt_stroke_f60_PHE	1.347	1.010	1.683				Binomial
Event rate: ae_noAFuntrt_stroke_f70_PHE	2.968	2.226	3.710				Binomial
Event rate: ae_noAFuntrt_stroke_f80_PHE	6.044	4.533	7.555				Binomial
Event rate: ae_noAFuntrt_stroke_f90_PHE	10.770	8.077	13.462				Binomial
Event rate: ae_noAFuntrt_stroke_m50_PHE	1.246	0.935	1.558				Binomial
Event rate: ae_noAFuntrt_stroke_m60_PHE	2.285	1.714	2.856				Binomial
Event rate: ae_noAFuntrt_stroke_m70_PHE	4.423	3.317	5.529				Binomial
Event rate: ae_noAFuntrt_stroke_m80_PHE	6.400	4.800	8.000				Binomial
Event rate: ae_noAFuntrt_stroke_m90_PHE	9.897	7.422	12.371				Binomial
Event rate: ae_noAFuntrt_stroke_f50_Rothwell	0.082	0.061	0.102				Binomial
Event rate: ae_noAFuntrt_stroke_f60_Rothwell	1.060	0.795	1.325				Binomial
Event rate: ae_noAFuntrt_stroke_f70_Rothwell	4.076	3.057	5.095				Binomial
Event rate: ae_noAFuntrt_stroke_f80_Rothwell	9.538	7.154	11.923				Binomial

Event rate: ae_noAFuntrt_stroke_f90_Rothwell	17.283	12.962	21.603				Binomial
Event rate: ae_noAFuntrt_stroke_m50_Rothwell	0.489	0.367	0.611				Binomial
Event rate: ae_noAFuntrt_stroke_m60_Rothwell	1.793	1.345	2.242				Binomial
Event rate: ae_noAFuntrt_stroke_m70_Rothwell	6.685	5.014	8.356				Binomial
Event rate: ae_noAFuntrt_stroke_m80_Rothwell	9.293	6.970	11.617				Binomial
Event rate: ae_noAFuntrt_stroke_m90_Rothwell	19.810	14.857	24.762				Binomial
Event rate: ae_noAFuntrt_stroke_NHS	0.004	0.003	0.005	0.000	63.764	17526.576	Beta
Event rate: ae_noAFuntrt_TIA_f50_Rothwell	0.287	0.215	0.359				Binomial
Event rate: ae_noAFuntrt_TIA_f60_Rothwell	1.098	0.824	1.373				Binomial
Event rate: ae_noAFuntrt_TIA_f70_Rothwell	2.213	1.660	2.766				Binomial
Event rate: ae_noAFuntrt_TIA_f80_Rothwell	5.706	4.279	7.132				Binomial
Event rate: ae_noAFuntrt_TIA_f90_Rothwell	9.321	6.991	11.651				Binomial
Event rate: ae_noAFuntrt_TIA_m50_Rothwell	0.165	0.124	0.207				Binomial
Event rate: ae_noAFuntrt_TIA_m60_Rothwell	0.549	0.412	0.687				Binomial
Event rate: ae_noAFuntrt_TIA_m70_Rothwell	1.359	1.019	1.699				Binomial
Event rate: ae_noAFuntrt_TIA_m80_Rothwell	3.389	2.542	4.236				Binomial
Event rate: ae_noAFuntrt_TIA_m90_Rothwell	8.041	6.031	10.051				Binomial
Event rate: ae_noAFuntrt_TIA_NHS	0.001	0.001	0.001	0.000	63.955	92182.602	Beta
% patients contraindicated for lead-I device use	0.060	0.045	0.075	0.008	60.100	941.567	Beta
Cycle length	3.000	3.000	3.000				Fixed
Discount costs	0.035	0.000	0.060				Fixed
Discount benefits	0.035	0.000	0.060				Fixed
Include cost of extra anticoagulation discussion?	No	Yes	Yes				Fixed
Include cost of 12-lead device?	Yes	No	Yes				Fixed
Include cost of 12-lead test?	Yes	Yes	Yes				Fixed
Include cost of lead-I device	Yes	No	Yes				Fixed
Include dispensing cost?	Yes	No	Yes				Fixed
Use different NOAC dose and event rate for >80 years?	No	No	Yes				Fixed
Number of lead-I ECG devices per practice	1.000	0.170	1.000				Fixed
Proportion of 12-lead ECGs interpreted by: Cardiologist	0.100	0.000	0.200	0.050	3.500	31.500	Beta
Proportion of symptoms: Angina pectoris symptoms	0.287	0.215	0.359	0.036	45.351	112.719	Beta
Proportion of symptoms: Shortness of breath	0.618	0.463	0.772	0.077	23.846	14.755	Beta

Proportion of symptoms: Congestive heart failure	0.287	0.215	0.359	0.036	45.351	112.719	Beta
Proportion of symptoms: Fatigue	0.704	0.528	0.881	0.088	18.213	7.643	Beta
Proportion of lead-I tests interpreted by: Cardiologist	0.100	0.000	0.200	0.050	3.500	31.500	Beta
AF prevalence by type: paroxysmal	1.000	0.000	1.000				Fixed
% of lead-I negative or standard pathway patients given rate control	0.000	0.000	0.000				Uniform
Cost per use: 12-lead	3.377	2.533	4.221	0.138			Lognormal
Sensitivity: algorithm	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	Beta
Sensitivity	0.939	0.862	0.974	0.028	67.664	4.396	Beta
Specificity: algorithm	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	Beta
Specificity	0.965	0.904	0.988	0.021	72.942	2.646	Beta
% female	0.516	0.258	0.775	0.129	7.221	6.761	Beta
Utility: Symptom decrements: Bleed	0.000	0.000	0.000				Lognormal
Utility: Symptom decrements: HS	0.272	0.345	0.198	0.169			Lognormal
Utility: Symptom decrements: IS	0.272	0.345	0.198	0.169			Lognormal
Utility: Symptom decrements: TIA	0.000	0.000	0.000				Lognormal
Proportion of symptoms: Other symptoms	0.517	0.388	0.647	0.065	30.374	28.340	Beta
Utility: general population female 50	0.849	0.800	1.000	0.014	3677.556	0.000	Gamma
Utility: general population female 55	0.815	0.730	1.000	0.015	2952.111	0.000	Gamma
Utility: general population female 60	0.815	0.730	1.000	0.015	2952.111	0.000	Gamma
Utility: general population female 65	0.777	0.690	1.000	0.016	2358.316	0.000	Gamma
Utility: general population female 70	0.777	0.690	1.000	0.016	2358.316	0.000	Gamma
Utility: general population female 75	0.712	0.630	0.890	0.019	1404.277	0.001	Gamma
Utility: general population female 80	0.712	0.630	0.890	0.019	1404.277	0.001	Gamma
Utility: general population female 85	0.712	0.630	0.890	0.019	1404.277	0.001	Gamma
Utility: general population male 50	0.845	0.800	1.000	0.018	2203.781	0.000	Gamma
Utility: general population male 55	0.777	0.690	1.000	0.020	1509.323	0.001	Gamma
Utility: general population male 60	0.777	0.690	1.000	0.020	1509.323	0.001	Gamma
Utility: general population male 65	0.781	0.690	1.000	0.018	1882.596	0.000	Gamma
Utility: general population male 70	0.781	0.690	1.000	0.018	1882.596	0.000	Gamma
Utility: general population male 75	0.753	0.690	1.000	0.026	838.771	0.001	Gamma
Utility: general population male 80	0.753	0.690	1.000	0.026	838.771	0.001	Gamma
Utility: general population male 85	0.753	0.690	1.000	0.026	838.771	0.001	Gamma
Mean GPs per practice	5.898	5.805	5.991				Fixed
Mean GP list size	8187.121	1591.795	1630.954				Fixed

% of untreated lead-I positive patients given rate control	1.000	1.000	1.000				Fixed
Costs: bleed	704.049	592.435	782.475	0.085			Lognormal
Costs: TIA	729.616	570.081	837.648	0.117			Lognormal
Costs: 1YrCostIS	15387.635	11540.727	17695.781	0.130			Lognormal
Costs: 5Yr Cost IS	31315.530	23486.647	36012.859	0.130			Lognormal
Costs: 1YrCostHS	17833.307	13374.980	20508.303	0.130			Lognormal
Costs: 5YrCostHS	37907.660	28430.745	43593.809	0.130			Lognormal
AF prevalence: female	0.034	0.026	0.043	0.004	61.774	1741.839	Beta
AF prevalence: male	0.067	0.050	0.083	0.008	59.659	833.711	Beta
% AF undiagnosed: female	0.157	0.118	0.196	0.020	53.795	288.848	Beta
% AF undiagnosed: male	0.120	0.090	0.150	0.015	56.200	412.133	Beta
% AF symptomatic: female	0.679	0.509	0.849	0.085	19.865	9.391	Beta
% AF symptomatic: male	0.575	0.431	0.719	0.072	26.625	19.679	Beta
% symptomatic with AF: female	0.200	0.150	0.250	0.025	51.000	204.000	Beta
% symptomatic with AF: male	0.200	0.150	0.250	0.025	51.000	204.000	Beta
% AF patients with CHA2DS2-VASc ≥2	0.824	0.618	1.000	0.096	12.278	2.624	Beta
% AF patients with CHA2DS2-VASc ≥2 on OACs	0.812	0.609	1.000	0.098	12.157	2.821	Beta
% OACs that are NOACs	1.000	1.000	1.000				Fixed
Time taken to administer lead-I test	0.000	0.000	7.000				Fixed
% standard pathway patients who have 12-lead	1.000	0.500	1.000				Fixed
% patients with paroxysmal AF NOT in AF at 12-lead	0.475	0.356	0.594	0.059	33.125	36.612	Beta
% lead-I positive patients who have 12-lead	1.000	0.000	1.000				Fixed
% lead-I negative patients who have 12-lead	0.800	0.000	1.000				Fixed
% AF diagnosed after MPP only (standard pathway) -> negative 12-lead	0.000	0.000	1.000				Fixed
% AF ruled out after MPP only (standard pathway) -> negative 12-lead	0.500	0.000	1.000				Fixed
% sent for paroxysmal testing after MPP only (standard pathway) -> negative 12-lead	0.500	0.000	1.000				Fixed
% AF diagnosed after MPP only (standard pathway) [no 12-lead]	0.000	0.000	1.000				Fixed
% AF ruled out after MPP only (standard pathway) [no 12-lead]	0.500	0.000	1.000				Fixed
% sent for paroxysmal testing after MPP only (standard pathway) [no 12-lead]	0.500	0.000	1.000				Fixed
% AF diagnosed after negative lead-I -> negative 12-lead	0.000	0.000	1.000				Fixed
% AF ruled out after negative lead-I -> negative 12-lead	0.500	0.000	1.000				Fixed
% sent for paroxysmal testing after negative lead-I -> negative 12-lead	0.500	0.000	1.000				Fixed

% AF diagnosed after negative lead-I [no 12-lead]	0.000	0.000	1.000				Fixed
% AF ruled out after negative lead-I [no 12-lead]	0.500	0.000	1.000				Fixed
% sent for paroxysmal testing after negative lead-I [no 12-lead]	0.500	0.000	1.000				Fixed
% AF diagnosed after positive lead-I -> negative 12-lead	0.500	0.000	1.000				Fixed
% AF ruled out after positive lead-I -> negative 12-lead	0.000	0.000	1.000				Fixed
% sent for paroxysmal testing after positive lead-I -> negative 12-lead	0.500	0.000	1.000				Fixed
% AF diagnosed after positive lead-I [no 12-lead]	0.000	0.000	1.000				Fixed
% AF ruled out after positive lead-I [no 12-lead]	0.500	0.000	0.000				Fixed
% sent for paroxysmal testing after positive lead-I [no 12-lead]	0.500	0.000	1.000				Fixed
% patients with paroxysmal AF NOT in AF at paroxysmal test	0.300	0.225	0.375	0.038	44.500	103.833	Beta
RR for mortality: previous CVE: AF NOAC	2.600	2.600	2.600				Fixed
RR for mortality: previous CVE: AF Warfarin	2.600	2.600	2.600				Fixed
RR for mortality: previous CVE: AF untreated	2.600	2.600	2.600				Fixed
RR for mortality: previous CVE: no AF	2.600	2.600	2.600				Fixed
% subsequent strokes that are HS	0.057	0.042	0.071	0.007	60.324	1006.196	Dirichlet
% subsequent strokes that are IS	0.640	0.626	0.654	0.007	2949.534	1657.159	Dirichlet
% subsequent strokes that are TIA	0.303	0.289	0.317	0.007	1280.959	2944.294	Dirichlet
% AF diagnosed after MPP & negative 12-lead & negative paroxysmal test	0.000	0.000	1.000				Fixed
% AF ruled out after MPP & negative 12-lead & negative paroxysmal test	1.000						Fixed
% AF diagnosed after negative lead-I & negative 12-lead & negative paroxysmal test	0.000	0.000	1.000				Fixed
% AF ruled out after negative lead-I & negative 12-lead & negative paroxysmal test	1.000						Fixed
% AF diagnosed after positive lead-I & negative 12-lead & negative paroxysmal test	1.000	0.000	1.000				Fixed
% AF ruled out after positive lead-I & negative 12-lead & negative paroxysmal test	0.000						Fixed

Appendix 9 Questions For Clinicians

1. **For patients who present at a GP practice with signs and symptoms of AF and in whom manual pulse palpation (MPP) suggests AF and who DO NOT HAVE a lead-I ECG before being sent for a 12-lead ECG in either a GP practice or acute setting:**

   In what proportion of patients who then receive a negative 12-lead ECG would you undertake testing for paroxysmal AF?

Expert 1	This largely depends on whether they were having symptoms when they had the 12 lead ECG; if symptomatic and NO AF on the 12 lead ECG then no further AF screening necessary. If asymptomatic during the 12 lead ECG but risk factors for AF (T2DM, HTN, IHD, Valvular heart disease, Obesity, Alcohol, Age, past history of cryptogenic stroke) then degree of suspicion is higher and a period of prolonged ambulatoiry monitoring should be considered.
Expert 2	50%
Expert 3	All
Expert 4	There is no fixed answer to this question. How far I go will depend on patient demographics (age group etc), my own clinical suspicion, and the consequences to the patient if AF is missed. In someone with CHADS-VASc 0 and a wishy-washy history, I won't go any further.
Expert 5	Depends, if negative for AF but shows few ectopics may not need testing, but otherwise 100%.
Expert 6	This is a very difficult question as it will depend very much on the individual clinician. If they are aware of the SAFE study then they will expect at least 8 in 10 people with an irregular pulse not to have AF and they may stop at this point. My advice when teaching GP colleagues is that they should undertake a CHADSVASc score (even though they are in sinus rhythm) and if the score is high then this is actually a reasonable determinant as to those where you would expect to find AF and maybe further investigation would be worth while. This is my practice. The problem is the next recording which is often something as unhelpful as a 24hr ECG.

2. Please note – This section refers to making decisions based on interpreting the trace produced by a lead-I ECG and not on the results of the lead-I ECG algorithm.

   For patients who present at a GP practice with signs and symptoms of AF and in whom MPP suggests AF and who DO HAVE a lead-I ECG before being sent for a 12-lead ECG in either a GP practice or acute setting:

   a) Patients with a negative lead-I ECG in a GP practice:

      Would you expect all patients with a negative lead-I ECG to be sent for a 12-lead ECG?

Expert 1	No, see earlier answer, if they were symptomatic at the time of the lead-I ECG and NO AF detected then further 12 lead testing may not be necessary in the context of low clinical suspicion and or the lead-I ECG has detected ectopics; unless there were other reasons to do so, such as risk factors for AF or CVD as listed above, or heart murmur detected on auscultation.
Expert 2	No
Expert 3	Yes, unless alternative diagnosis made.
Expert 4	Yes
Expert 5	Would ask for a 12 lead ECG if not had one recently. No protocol but probably 6 months.
Expert 6	I would not suggest that those who have symptoms and signs of AF at the time of review and then have a negative lead-I ECG should be referred for a 12-lead ECG. This is a sinus rhythm trace correlating to symptoms which excludes AF. Clearly this is dependant on the clarity of the trace. I personally do not rely on the automated interpretation. In the younger cohort who still have physiological sinus arrhythmia the algorithm could easily suggest AF.

If not, what proportion of patients with a negative lead-I ECG would you expect to be sent for a 12-lead ECG?

Expert 1	I would expect the majority of patients to have a 12 lead ECG in this instance.
Expert 2	70%
Expert 3	Not applicable (see response to the previous question).
Expert 4	Not applicable (see response to the previous question).
Expert 5	Probably 75%
Expert 6	Personally none, we have symptom trace correlation and no further ECG is warranted if the lead-I trace is of sufficient quality.

In what proportion of patients with a negative lead-I ECG who are not sent for a 12-lead ECG would you undertake testing for paroxysmal AF using a Holter ECG monitor or event recorder?

Expert 1	Every patient being referred for ambulatory ECG monitoring should have a 12 lead ECG as part of their diagnostic assessment. In this instance if you suspect an underlying arrhythmia a lead-I ECG does not provide enough information to look for other important causes of structural heart disease. i.e. a 12 lead ECG should be a prerequisite for ambulatory holter recording.
Expert 2	10-20%
Expert 3	All, unless alternative diagnosis made (e.g. you might diagnose ectopic beats on lead I-ECG)
Expert 4	Hypothetical question. I expect everyone to be sent for a 12 lead ECG.
Expert 5	Our protocol is if sent for testing for paroxysmal AF, all need a 12-lead ECG.
Expert 6	See above. If symptomatic at the time of the trace and this shows sinus rhythm then we have the wrong diagnosis.

b) Patients with a positive lead-I ECG in a GP practice followed by a negative 12-lead ECG (done at a later timepoint, i.e. between 48 hours and 14 days after the positive lead-I ECG):

In what proportion of these patients would you diagnose AF with no further tests?

Expert 1	A diagnosis of AF can be made securely on a lead-I ECG but further testing is still usually required with a 12 lead ECG, blood testing and usually an echocardiogram" The majority will require further testing.
Expert 2	80-90% (assuming some will be false positives - if however we take a positive ECG to be completely accurate then 100% would be diagnosed).
Expert 3	Majority.
Expert 4	If I have seen the tracing myself, and concur with the interpretation, then 100%.
Expert 5	If lead-I ECG positive, then negative 12-lead ECG is not relevant. Diagnosis is paroxysmal AF.
Expert 6	If I have an ECG trace showing AF (reviewed not algorithm driven) then this would be sufficient.

In what proportion of these patients would you undertake testing for paroxysmal AF?

Expert 1	This depends on the quality and confidence of the clinical decision maker with their lead-I ECG device recording.
Expert 2	By testing do you mean further ECG evidence or is there an assumption that the diagnosis of AF is confirmed and 'testing' means extra tests linked to AF such as an echocardiogram?
Expert 3	Depends on ongoing symptom burden and/or concerns regarding co-existing bradycardia.
Expert 4	Depends on the need for symptom correlation.
Expert 5	100% would get an ambulatory ECG.
Expert 6	I have the diagnosis and do not need to work further. They now need working up as AF as per local protocol.

c) Patients with a negative lead-I ECG in a GP practice followed by negative 12-lead ECG (done at a later timepoint, i.e. between 48 hours and 14 days after the positive lead-I ECG):

In what proportion of these patients would you rule out a diagnosis of AF?

Expert 1	See earlier, this depends if they were symptomatic at the the time of the recordings.
Expert 2	70-80%
Expert 3	100% if symptoms/signs present at time of lead I-ECG.
Expert 4	0%
Expert 5	Probably 90 - 95% rule out.
Expert 6	I would accept the patient does not have AF at this time, they may have an atrialopathy but that is a slightly different topic.

In what proportion of these patients would you undertake testing for paroxysmal AF?

Expert 1	In those with a high degree of suspicion of AF and risk factors as outlined earlier.
Expert 2	20-30%
Expert 3	Only if subsequent clinical suspicion.
Expert 4	See answer to question 1.
Expert 5	Difficult to answer because either ECG may have given an alternative diagnosis. Possibly 10% have frequent atrial ectopics and therefore I go on to investigate for paroxysmal AF, a further 5% to 10% I feel it was paroxysmal AF but resolves before I can get lead-I ECG trace.
Expert 6	Only if symptomatic.

3. For patients who present at a GP practice with signs and symptoms of AF and in whom MPP suggests AF, who DO HAVE AF but who have had their AF RULED OUT

after testing (with lead-I ECG and/or 12 lead ECG and/or Holter and event monitoring):

What proportion of patients would you expect to have their AF diagnosed - before having a cardiovascular event - within 12 months of initially presenting at a GP practice?

Expert 1	Unknown – 20-30% of patients presenting with first stroke will either be known AF and not anticoagulated or will be first presentation of AF (Southport DGH stroke admission data 2012-13).
Expert 2	20%
Expert 3	Difficult to answer but <50 %.
Expert 4	I don't understand how anyone can rule out AF just because the tests are negative. Absence of proof is not the same as proof of absence.
Expert 5	Really difficult to tell because even with current array of testing we may still be missing paroxysmal AF. Only better way is review of trials of patients with pacemakers or Implantable loop recorders.
Expert 6	This is very difficult, you are suggesting the false negatives and I am unaware in a general population if this has been examined. If you look in a high risk population (post ESUS) then we can reference STOPSTROKE, EMBRACE and CRYSTAL. But this is a very high risk population.

What proportion of patients would you expect to have their AF diagnosed - before having a cardiovascular event - within 5 years of initially presenting at a GP practice?

Expert 1	Unknown – see above.
Expert 2	50%
Expert 3	>50%
Expert 4	100%
Expert 5	See response to the previous question.
Expert 6	Would be interested to see if anyone has this data.

4. Testing for paroxysmal AF:

In the diagnosis of paroxysmal AF, would all patients use both a Holter ECG monitor and event recorder? If not, what proportion of patients would use (i) Holter ECG monitor or (ii) event recorder and what proportion would use both?

Expert 1	This will dpend on frequency of symptoms – with daily or near daily symptoms a 24-hr Holter has a greater chance of arrhythmia capture. In patients with less frequent symptoms an event recorder or prolonged period of ambulatory monitoring will have a higher chance of arrhythmia capture.
Expert 2	50/50 split – depending on access to which is available, only 20% we go on to use both.
Expert 3	Either/or but not both.
Expert 4	Depends on symptoms. I can't put a number on this.
Expert 5	For paroxysmal AF we always use an event recorder for 7 days (R test) unless patient getting symptoms consistent with frequent AF more than once daily.
Expert 6	Is this high risk or low risk cohorts? I feel it would be very different in different cohorts.

How long would you routinely use (i) Holter ECG monitor (ii) event recorder or (iii) both to test for paroxysmal AF?

Expert 1	See above.
Expert 2	Depends on duration/frequency of symptoms. Holters are generally 24-48 hrs. Event recorders 5 days to 3 week (eg hand held cardio memo recorder).
Expert 3	7 – 14 days.
Expert 4	Depends on symptoms. There is no fixed answer.
Expert 5	Usually 7 days. Can be up to 30 days with battery change on day 15 but rarely tolerated. We do also loan AliveCor ECGs if patients happy to use them. Loan is up to 2 months.
Expert 6	If post stroke the evidence would suggest 2-4 weeks (EMBRACE) but in CRYSTAL 30% were found to develop AF at 3 years.

What is the diagnostic and treatment pathway for patients who have paroxysmal AF ruled out by the results of a Holter ECG monitor and/or event recording?

Expert 1	To seek medical advice as soon as possible when symptomatic if no diagnosis yet made.
Expert 2	If there is no diagnosis of AF after a search then no further routine testing would take place unless the patient re-presents or there is a change in their symptoms to warrant further investigation.
Expert 3	Nil else unless ongoing clinical concern.
Expert 4	I do not think you can rule out paroxysmal AF just because your Holter or event recorder is negative.
Expert 5	Usually discharge back to GP. We are now loaning lead-I ECG devices to patients for up to 2 months. Very high risk e.g. transient ischemic attack / stroke with high probability due to AF may be considered for implantable loop recorders.
Expert 6	Never seen one.

5. Diagnostic pathway for patients with signs and symptoms of AF and an irregular pulse who <u>DO NOT HAVE AF</u>:

Do you think the introduction of lead-I ECGs into the diagnostic pathway for patients, with signs and symptoms of AF and in whom MPP suggests AF but who <u>do not have AF,</u> will

affect the diagnosis and treatment of the other conditions causing symptoms in these patients?

If yes, how?

Expert 1	Possibly, if the process stops after the Lead-I ECG recording. The clinical context and AF, CVD risk status must be taken into consideration, as other carfiac conditions migh be missed.
Expert 2	Yes, an irregular pulse may feel like AF but be simple ectopic heart beats. This can mean that these patients are not sent for further routine testing and could be treated with lifestyle advice (reduced caffeine/alcohol) or offered drugs such as beta blockers.
Expert 3	Alternative diagnoses might be made e.g. ectopic beats which will allow inform treatment / management decisions.
Expert 4	Yes. It may correlate symptoms to another non-AF arrhythmia, which will require treatment in its own right.
Expert 5	Yes. Lead-I ECG devices will pick up ectopics and pauses.
Expert 6	This is probably ectopy (atrial or ventricular) as these are the commonest non-sustained dysrhythmias. Questions around how much ectopy would make the diagnosis and what is the significance is hotly debated but unknown. This would be investigated as a palpitation and would have a varied pathway depending on local opinion and protocol.