National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

Lead-I electrocardiogram (ECG) devices for detecting atrial fibrillation using single time point testing in primary care

This overview summarises the key issues for the diagnostics advisory committee's consideration. This document is intended to be read with NICE's final scope for the assessment and the diagnostics assessment report. A glossary of terms is in appendix B.

1 Background

1.1 Introduction

The purpose of this assessment is to evaluate the clinical and cost effectiveness of using the following lead-I ECG devices: imPulse, Kardia Mobile, MyDiagnostick, RhythmPad GP and Zenicor-ECG. The specific clinical scenario assessed is their use for single time point testing to detect atrial fibrillation in people presenting to primary care with signs or symptoms of the condition and who have an irregular pulse. Other similar devices may be available and the devices may be used in other scenarios, such as screening, but these are outside the scope of this assessment.

The devices allow an ECG to be taken soon after an irregular pulse is detected by manual pulse palpation to determine if atrial fibrillation is present. This may mean that people who are at risk of having a stroke and who will benefit from preventative anticoagulation treatment are identified earlier. Being able to quickly record ECGs when atrial fibrillation is suspected could

also help to identify people with intermittent (paroxysmal) atrial fibrillation that may have stopped before a 12-lead ECG can be done.

Lead-I ECG devices can also be used by people at home for self-testing and longer-term monitoring when paroxysmal atrial fibrillation is suspected, but this is outside of the scope for this assessment which focuses on single-time point testing done in primary care.

The lead-I ECG devices included in this assessment have built-in software, or software that can be loaded onto a computer, which can analyse ECG traces and help clinicians assess whether atrial fibrillation is potentially present.

Provisional recommendations on the use of lead-I ECGs will be made by the diagnostics advisory committee at the committee meeting on 20 November 2018.

1.2 Scope of the assessment

Table 1 Scope of the assessment

Decision question	Does the use of lead-I ECG devices to detect atrial fibrillation in people presenting to primary care with signs or symptoms of the condition and who have an irregular pulse represent a cost-effective use of NHS resources?
Populations	People with signs or symptoms that may indicate underlying atrial fibrillation and when manual pulse palpation suggests atrial fibrillation. Signs and symptoms of atrial fibrillation include: • breathlessness (dyspnoea) • palpitations • dizziness (syncope) • chest discomfort. If data allow, the following subgroup may be considered: • People who are unable to use the device electrodes as recommended by the companies (for example, people with movement disorders).
Interventions	A single lead-I ECG carried out by a healthcare professional using 1 of the following technologies, with anticoagulation

	therapy for people with a positive result: • imPulse • Kardia Mobile • MyDiagnostick • RhythmPad GP • Zenicor-ECG. The analysis should explore the effect of using a device's algorithm, or interpretation of the lead-I ECG trace by a suitably qualified healthcare professional, on the diagnostic accuracy of the lead-I ECG devices.
Comparator	Manual pulse palpation followed by a 12-lead ECG in primary or secondary care before starting anticoagulation therapy. 12-lead ECG, carried out and interpreted by a trained healthcare professional, will be the reference standard for assessing diagnostic accuracy.
Healthcare setting	Primary care
Outcomes	Intermediate measures for consideration may include: • diagnostic accuracy • time to ECG diagnosis of atrial fibrillation • 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 atrial fibrillation diagnoses).
	Clinical outcomes for consideration may include: • mortality • morbidity (including stroke, other thromboembolisms and heart failure, and any complications arising from preventative treatment, such as adverse effects of anti-arrhythmic, rate control or anticoagulation treatment).

	Patient-reported outcomes for consideration may include: • health-related quality of life • acceptability of the devices.
	Costs will be considered from an NHS and personal social services perspective. Costs for consideration may include: • Costs related to assessing people with signs or symptoms of atrial fibrillation (including staff time to carry out tests and interpret results). • Costs related to using the lead-I ECG devices (including maintenance, software installation, training and consumable costs). • Treatment for conditions related to atrial fibrillation (such as stroke and heart failure), including emergency presentations as a result of delayed diagnoses, and preventative treatment costs (including medication for preventing stroke and rate or rhythm control strategies). • 12-lead ECG measurement and interpretation costs. • Costs related to assessing people who are diagnosed with atrial fibrillation (such as echocardiography). • Costs related to further assessment for people with suspected paroxysmal atrial fibrillation (such as ambulatory ECG monitors or event recorders).
	The cost effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

Further details including descriptions of the interventions, comparator, care pathway and outcomes are in the final scope.

2 The evidence

This section summarises data from the diagnostics assessment report compiled by the external assessment group (EAG).

2.1 Clinical effectiveness

The EAG did a systematic review to identify evidence on the diagnostic accuracy and clinical effect of using lead-I ECG devices (imPulse, Kardia Mobile, MyDiagnostick, RhythmPad GP and Zenicor-ECG) to detect atrial fibrillation. Details of the systematic review start on page 30 of the diagnostics assessment report. Included studies were those that used the devices at a single time point to detect atrial fibrillation (rather than repeated use over a period of time). Because no studies were identified in the population of interest (people with signs and symptoms of atrial fibrillation and an irregular pulse on manual palpation), the EAG included studies done in a population who were asymptomatic. The EAG included in this definition people who did not present with signs and symptoms of atrial fibrillation (for example, breathlessness or palpitations) with or without a previous diagnosis of atrial fibrillation. It included people with other cardiovascular comorbidities and people who were attending a cardiovascular clinic.

The EAG divided their review into 2 parts; studies reporting diagnostic accuracy of the devices and studies reporting the clinical effect of the devices.

Evidence on diagnostic accuracy

Nine studies were included in the diagnostic test accuracy review. An overview of the included studies is shown in table 2 (further details are in table 3 on page 38 of the diagnostics assessment report). All the studies either enrolled people with a known atrial fibrillation status (that is, people known to have atrial fibrillation and people with no history of the condition), or who were recruited from cardiology services. Only Desteghe et al. 2017 provided the reasons people were admitted to a cardiology service; 3.4% were admitted because of symptomatic atrial fibrillation.

Only 1 study was done in primary care (Vaes et al. 2014), with the rest in secondary or tertiary care. Two studies were done in the UK (Crockford et al. 2013 and Williams et al. 2015). No studies assessed the imPulse device.

In all studies the reference standard was a 12-lead ECG interpreted by a trained healthcare professional (a cardiologist, electrophysiologist or GP with a special interest in cardiology). The index test (lead-I ECG) and reference standard (12-lead ECG) were both done within 6 hours of each other in all but 2 studies (Crockford et al. 2013; Vaes et al. 2014). In these 2 studies the interval between tests was not reported. This may have affected the results because paroxysmal atrial fibrillation (that is, intermittent episodes that resolve without treatment) may have stopped between tests being done.

Table 2 Overview of studies included in the EAG's diagnostic accuracy review

Device	Study	Population in study	Interpreter of device output
Kardia Mobile	Desteghe et al. 2017[a] (Belgium)	Inpatients in a cardiology ward (35.6% had a history of atrial fibrillation)	• Electrophysiologists • Algorithm Results presented separately
	Haberman et al. 2015 (USA)	Cardiology clinic patients[b]	Electrophysiologist
	Koltowski et al. 2017[c] (Poland)	People in tertiary care	Cardiologist
	Lau et al. 2013 (Australia)	People at a cardiology department (24% had a history of atrial fibrillation)	Algorithm
	Williams et al. 2015 (UK)	People attending an atrial fibrillation clinic who were known to have atrial fibrillation and people with unknown atrial fibrillation status (who were attending the clinic for reasons unrelated to atrial fibrillation)	• Cardiologist • GP with special interest in cardiology Results presented separately
MyDiagnostick	Desteghe et al. 2017[a] (Belgium)	Inpatients in a cardiology ward (35.6% had a history of atrial fibrillation)	• Electrophysiologists • Algorithm Results presented separately
	Tieleman et al. 2014 (Netherlands)	People attending an outpatient cardiology clinic or a specialised	Algorithm

		atrial fibrillation outpatient clinic	
	Vaes et al. 2014 (Belgium)	People known to have atrial fibrillation (83.4%) and people with no history of the condition invited to participate by GPs	Algorithm
RhythmPad GP	Crockford et al. 2013[d] (UK)	People referred to an electrophysiology department	Algorithm
Zenicor-ECG	Doliwa et al. 2009 (Sweden)	People with atrial fibrillation, atrial flutter or sinus rhythm attending a cardiology outpatient clinic	Cardiologist

[a] Desteghe et al. assessed both the Kardia Mobile and MyDiagnostick.

[b] Results from additional participants in this study (healthy young adults and elite athletes) were not included in the EAG's analyses.

[c] Koltowski et al. was only available as a conference proceeding.

[d] A poster based on conference proceedings was used for data extraction and quality assessment.

Quality assessment of diagnostic accuracy studies

The QUADAS-2 tool was used to assess study quality. Full results are in the diagnostic assessment report from page 40. For patient selection, the EAG judged that all 9 studies had an unclear risk of bias and a high level of concern for applicability (because none were done in a population who had symptoms).

For 2 studies there was limited information available in the publication; Crockford et al. was a conference poster (an abstract of this work was also published) and Koltowski et al. was only available as a conference proceeding.

The included studies varied in how the devices gave a positive result for atrial fibrillation. This was either based on the lead-I ECG device's diagnostic algorithm or on clinician interpretation of an ECG trace generated by the devices. The EAG judged that studies in which the device output was interpreted by a trained healthcare practitioner were more applicable (low

concern) than those in which a lead-I ECG device algorithm alone was used (high concern; Lau et al. 2013, Tieleman et al. 2014 and Vaes et al. 2014). The EAG presented results in 2 sections depending on how atrial fibrillation was identified (by clinicians or by the device's algorithm alone).

Diagnostic accuracy results: Lead-I ECG interpreted by a trained healthcare professional

Data were included from 4 studies, which assessed Kardia Mobile alone (Haberman et al. 2014; Williams et al. 2015), Kardia Mobile and MyDiagnostick (Desteghe et al. 2017) and Zenicor-ECG alone (Doliwa et al. 2009).

Desteghe et al. reported separate accuracy estimates from lead-I ECGs interpreted by 2 electrophysiologists; only pooled estimates using data from electrophysiologist 1 are shown in table 2 (values are similar when data from electrophysiologist 2 is used). Williams et al. reported separate accuracy estimates from lead-I ECGs interpreted by a cardiologist or by a GP with a special interest in cardiology. Pooled accuracy estimates shown in table 3 used data from Williams et al. when the lead-I ECG interpreter was a cardiologist (interpreters in other studies were cardiologists or electrophysiologists). Pooled accuracy estimates using data from Williams et al. when the interpreter was a GP with a special interest in cardiology (not shown) were similar. However, the study showed a decrease in specificity when a GP interpreted the lead-I ECG; 76% (95% confidence interval [CI] 64% to 85%) compared with 86% (95% CI 76% to 94%) when a cardiologist interpreted them.

Meta-analyses used data from the Desteghe study for either MyDiagnostick or Kardia Mobile separately (that is, data on the accuracy of the 2 devices from this study were not included in the same pooled estimate).

Table 3 Pooled diagnostic accuracy estimates for lead-I ECGs interpreted by a trained healthcare professional

Meta-analysis	Lead-I devices in included studies (number of studies)	Pooled sensitivity % (95% CI)	Pooled specificity % (95% CI)
All devices[a,c]	Kardia Mobile (3[b,d]), Zenicor-ECG (1[e])	93.9 (86.2 to 97.4)	96.5 (90.4 to 98.8)
All devices[a,c]	Kardia Mobile (2), MyDiagnostick (1[b,f]), Zenicor-ECG (1[e])	90.8 (83.8 to 95.0)	95.6 (89.4 to 98.3)
Kardia Mobile[a,c]	Kardia Mobile (3[d])	94.0 (85.1 to 97.7)	96.8 (88.0 to 99.2)

[a] Data from electrophysiologist 1 from Desteghe et al. 2017
[b] Data from Desteghe et al. 2017 from either Kardia Mobile or MyDiagnostick
[c] Data from Williams et al. 2015 from cardiologist interpreting lead-I ECG
[d] Desteghe et al. 2017; Haberman et al. 2015; Williams et al. 2015
[e] Doliwa et al. 2009
[f] Desteghe et al. 2017

Forest plots and summary receiver operating characteristic (SROC) plots are in the diagnostic assessment report from page 42. Across all the meta-analyses done by the EAG, when the interpreter of the lead-I ECG trace was a trained healthcare professional, sensitivity ranged from 89.8% to 94.3% and specificity ranged from 95.6% to 97.4%.

Only Kardia Mobile had sufficient studies to produce a device-specific pooled estimate (shown in table 3). Accuracy estimates from individual studies for other devices are presented in table 4. The EAG commented that there are insufficient data to formally assess differences between the lead-I ECG devices.

Table 4 Individual study diagnostic accuracy estimates for lead-I ECGs interpreted by a trained healthcare professional

Lead-I ECG device	Study	Sensitivity % (95% CI)	Specificity % (95% CI)
MyDiagnostick[a]	Desteghe et al. 2017	85.0 (62.0 to 97.0)	95.0 (92.0 to 98.0)
Zenicor-ECG	Doliwa et al. 2009	92.0 (81.0 to 98.0)	96.0 (86.0 to 100.0)
[a] Data from electrophysiologist 1 from Desteghe et al.			

The EAG identified an additional study that reported accuracy data for Kardia Mobile (Koltowski et al. 2017), but was not included in the pooled analysis because it did not report the number of true and false positives or negatives. The sensitivity reported in this study was 92.8% and specificity was 100%.

Diagnostic accuracy results: ECG trace interpreted by the device's algorithm

Four studies that reported sensitivity and specificity of the lead-I ECG device when the trace was interpreted by the device's algorithm alone were included in meta-analyses. Two studies reported data for MyDiagnostick alone (Tieleman et al. 2014; Vaes et al. 2014), 1 study for Kardia Mobile alone (Lau et al. 2013) and 1 study for both MyDiagnostick and Kardia Mobile (Desteghe et al. 2017). Pooled sensitivity and specificity estimates from meta-analyses are presented in table 5. One identified study (Crockford et al. 2013) reported sensitivity (67%) and specificity (97%) for RhythmPad GP. However the EAG did not include this in the meta-analyses because the device's algorithm has since been modified, which may affect the sensitivity and specificity of the device.

Table 5 Pooled diagnostic accuracy estimates for lead-I ECG traces interpreted by device algorithm alone

Meta-analysis	Lead-I devices in included studies (number of studies)	Pooled sensitivity % (95% CI)	Pooled specificity % (95% CI)
All devices[a]	Kardia Mobile (1[b]), MyDiagnostick (3[c])	96.2 (86.0 to 99.0)	95.2 (92.9 to 96.8)
All devices[a]	Kardia Mobile (2[d]), MyDiagnostick (2[e])	95.3 (70.4 to 99.4)	96.2 (94.2 to 97.6)

MyDiagnostick	MyDiagnostick (3[c])	95.2 (79.0 to 99.1)	94.4 (91.9 to 96.2)
Kardia Mobile	Kardia Mobile (2[d])	88.0 (32.3 to 99.1)	97.2 (95.1 to 98.5)

[a] Data from Desteghe et al. 2017 from either Kardia Mobile or MyDiagnostick
[b] Lau et al. 2013
[c] Desteghe et al. 2017; Tieleman et al. 2014; Vaes et al. 2014
[d] Desteghe et al. 2017; Lau et al. 2013
[e] Tieleman et al. 2014; Vaes et al. 2014

Forest plots and summary receiver operating characteristic (SROC) plots are in the diagnostic assessment report from page 51. The EAG commented that the available data were not sufficient to formally assess differences between the different lead-I ECG devices.

The EAG further noted that the lead-I ECG device manufacturers stated that atrial fibrillation should not be diagnosed using the algorithm alone; ECG traces produced by the devices should be reviewed by a qualified healthcare professional.

Comparisons between lead-I ECG devices

The EAG commented that the available data were not sufficient to formally assess differences between the different lead-I ECG devices. Desteghe et al. (2017) assessed the concordance between Kardia Mobile and MyDiagnostick. There was no statistically significant difference in agreement between the devices (based on kappa values) when assessing all patients (p=0.677) or after excluding those with an implanted device (for example, pacemaker or implantable cardiac defibrillator; p=0.411).

The EAG commented that the pooled sensitivity and specificity values were similar across all the meta-analyses done, irrespective of how the lead-I ECG trace was interpreted (algorithm or healthcare professional) or which lead-I ECG devices were used (pooled estimates produced by the EAG used the Kardia Mobile, MyDiagnostick and Zenicor-ECG).

Diagnostic accuracy results: further studies excluded from the EAG's main report

The EAG identified further studies that reported sensitivity and specificity estimates of the lead-I ECG devices, but did not include them in its main report because they did not meet 1 of the eligibility criteria for inclusion; that is, that the reference standard in the studies was not a 12-lead ECG interpreted by a trained healthcare professional. However, these studies provide some additional diagnostic accuracy data (including on 1 device for which no other accuracy data was identified; the imPulse) and have been included to aid committee discussion. In 4 of the studies, the performance of the device's algorithms was assessed by a healthcare professional reviewing the generated lead-I ECG trace (Chan et al. 2016; Lowres et al. 2014; Orchard et al. 2016; Tieleman et al. 2014). In a further study (Reeves; an unpublished report submitted by the manufacturer of the imPulse device), the lead-I ECG trace was interpreted by healthcare professionals, but additional clinical information and consensus among assessors of a 12-lead ECG was used as a reference standard.

Three of the studies were done in primary care (Chan et al. 2016; Orchard et al. 2016; Tieleman et al. 2014), although not in the UK. None of the studies were done in people with signs or symptoms of atrial fibrillation.

Results from these studies are presented in table 6. Further details are in appendix 6 of the diagnostics assessment report. The EAG did not critically appraise these studies.

Table 6 Diagnostic accuracy results of additional studies (excluded from main report) identified by the EAG

Study	Population in study	Reference standard	Sensitivity % (95% CI)	Specificity % (95% CI)
imPulse: Interpreted by cardiology registrars, cardiac physiologists or specialist cardiac nurses				
Reeves (unpublished)	People admitted to a cardiology service after cardiac surgery, or	'Clinical ECG diagnosis' based on interpretation	Range: 67 to 96	Range: 58 to 83

	after a cardiac-related event	of lead-I ECG trace		
		A combination of interpretation of the lead-I ECG and a consensus review of a 12-lead ECG	Range: 67 to 100	Range: 83 to 100
Kardia Mobile: Interpreted by algorithm				
Chan et al. 2016	People attending a general outpatient clinic, and who had a history of hypertension and/or diabetes mellitus or were aged 65 years or older	Lead-I ECG interpreted by cardiologist	71.4 (51.3 to 86.8)	99.4 (98.7 to 99.8)
Lowres et al. 2014	People using a pharmacy (aged 65 years or older and without a severe coexisting medical condition)	Lead-I ECG interpreted by cardiologist	98.5 (92.0 to 100.0)	91.4 (89.0 to 93.0)
Orchard et al. 2016	People (aged 65 years or older) attending GP practices for flu vaccination (included people known to have a history of atrial fibrillation)	Lead-I ECG interpreted by cardiologist	95.0 (83.0 to 99.0)	99.0 (98.0 to 100.0)
MyDiagnostick: Interpreted by algorithm				
Tieleman et al. 2014[a]	People attending GP practices for flu vaccination	Lead-I ECG interpreted by cardiologist	100.0	99.0
[a] Data from a different population in this study were included in the EAG's main report, however the reference standard was not a 12-lead ECG interpreted by a trained healthcare professional for all populations reported.				

Evidence on clinical effect of the lead-I ECG devices

The EAG included 19 studies in its clinical impact review. Seven were done in primary care (Orchard et al. 2014; Chan et al. 2016; Chan et al. 2017; Gibson et al. 2017; Hussain and Thakrar, 2016; Kaasenbrood et al. 2016; Orchard et al. 2016). Two of these studies were done in the UK (Gibson et al. 2017; Hussain and Thakrar, 2016).

A quality assessment of these studies is in the diagnostics assessment report from page 64. Five studies were available as conference abstracts only, so were not assessed.

No studies were identified that assessed the clinical effect of lead-I ECG devices when used for people with signs and symptoms of atrial fibrillation.

Diagnostic yield

Thirteen studies reported diagnostic yield of atrial fibrillation detection by lead-I ECG devices (various devices), which ranged from 0.38% to 5.84%. However, the location of testing varied between studies; primary care (6 studies), secondary care (2 studies), tertiary care (1 study) and in the community (4 studies). In primary care studies, the range was 0.49% to 5.84%. None of the studies assessed people with signs and symptoms of atrial fibrillation. The enrolled populations varied from the general population or people who were attending primary care for a reason unrelated to atrial fibrillation (for example, for flu vaccination) to people admitted to a cardiology ward and people with known atrial fibrillation. The prevalence of atrial fibrillation in the populations is therefore likely to vary and may not be applicable to the population that is the focus of this assessment.

Forest plots showing the diagnostic yields reported in the studies are in the diagnostics assessment report starting from page 71.

Test failure rate

Test failure rate (which included both the device failing to produce a result and producing a poor quality ECG trace) varied between 0.1% and 9% (various

devices). Reasons suggested for uninterpretable lead-I ECGs were the presence of sinus tachycardia or bradycardia, that patients had a tremor or that hospitalised patients were unable to hold the devices firmly enough.

Time to diagnosis of atrial fibrillation

A study done in Australia (Lowres et al. 2014) reported a time to diagnosis of atrial fibrillation of 16.6 days (standard deviation of 14.3 days), from detection by an initial lead-I ECG diagnostic test at a pharmacy to confirmed diagnosis with a 12-lead ECG.

Ease of use of devices

Tieleman et al. (2014) reported that people were able to use MyDiagnostick with minimal instructions. Chan et al. (2017) reported that Kardia Mobile was easy to use. Orchard et al. (2016) commented that it may be difficult for elderly people to hold the device still enough to take a reading. In Desteghe et al. (2017), 7% people were excluded from the study because they could hold not the devices as intended (the study used both MyDiagnostick and Kardia Mobile).

Effect on clinical decision-making

In Hussain and Thakrar (2016) 5 out of 6 people had a change in the clinical management of their condition after atrial fibrillation was detected by Kardia Mobile (1 person died as an inpatient after referral to hospital). In Lowres et al. (2014), oral anticoagulants were prescribed for 6 out of 10 new patients with atrial fibrillation detected by a lead-I ECG followed by a 12-lead ECG interpreted by a cardiologist.

Evidence on patient- and healthcare professional reported outcomes

In Orchard et al. (2016), which used Kardia Mobile, patients and GPs commented that they liked using the device. Chan et al. (2017) reported that all patients asked were willing to have further testing with Kardia Mobile at future GP visits, and 86% of GPs surveyed considered that the device was useful for atrial fibrillation screening and they would use it in their daily

practice. Gibson et al. (2017) reported generally positive responses to using MyDiagnostick; although some issues with implementing use of the device were raised. A further study reported that Kardia Mobile was easily administered and that no one declined testing with the device (Hussain and Thakrar, 2016). In Chan et al. (2017), interviewed patients commented that having access to the lead-I ECG device in the surgery was more convenient than having to attend another healthcare facility for a 12-lead ECG.

Several studies identified drivers and barriers to implementing use of the devices. Further details are in section 3.3.3 of the diagnostics assessment report (from page 68).

'Real world' data

Unpublished evidence on the use of Kardia Mobile across Eastbourne, Hailsham and Seaford clinical commissioning group and Hastings and Rother clinical commissioning group was provided by a specialist committee member. Over a 2-year period the device was used in primary care or home visits if people had an irregular pulse or signs of atrial fibrillation. There were 183 ECG traces reported, identifying 128 new patients with atrial fibrillation. Notably the proportion of people newly diagnosed with atrial fibrillation (69.9%) was considerably higher than the diagnostic yield in studies identified by the EAG (0.38% to 5.84%).

2.2 Costs and cost effectiveness

The EAG did a search to identify existing studies investigating the cost effectiveness of lead-I ECGs in detecting atrial fibrillation using single time point testing in primary care. It also constructed a de novo economic model to assess this.

Systematic review of cost-effectiveness evidence

The EAG did a systematic review to identify published full economic evaluations of lead-I ECG devices for detecting atrial fibrillation. Studies were excluded if they assessed the devices for repeated ECG measurements

(rather than at a single time point) or if they assessed the devices for use in a screening population or an asymptomatic ('silent atrial fibrillation') population. The EAG did not identify any published studies that met their inclusion criteria. However, the EAG highlighted 2 recently published economic evaluations (Welton et al. 2017 and Jacobs et al. 2018) that 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.

Economic analysis

The EAG developed a de novo economic model designed to evaluate the cost effectiveness of using lead-I ECG devices for single time point testing of people presenting to primary care with signs and symptoms of atrial fibrillation and who have an irregular pulse.

Model structure

The model compares the effect of using a lead-I ECG device in primary care for people with signs and symptoms of atrial fibrillation who have an irregular pulse (detected by manual pulse palpation) with standard diagnostic testing (that is, without the use of a lead-I ECG device). There was considerable uncertainty about how patients would move through the care pathway depending on the results of lead-I ECGs and any subsequent testing (12-lead ECG or Holter monitoring). The EAG used advice from clinical experts to structure the model and derive estimates of the proportions of people having subsequent testing. The model is in 2 phases: a diagnostic phase followed by a post-diagnostic phase.

Diagnostic phase

This phase covers the initial assessment of people presenting to primary care with signs and symptoms of atrial fibrillation, and who have had manual pulse palpation that shows an irregular pulse. The model compares 2 strategies: referral for a subsequent 12-lead ECG to check for atrial fibrillation ('standard

diagnostic pathway') or use of a lead-I ECG in primary care at the same primary care appointment to check for atrial fibrillation ('lead-I ECG pathway').

Atrial fibrillation can be permanent, persistent or intermittent. In intermittent atrial fibrillation, episodes resolve (typically within 7 days) without treatment; it is also known as paroxysmal atrial fibrillation. ECGs done at a single point in time can miss these intermittent episodes if they finish before the test is done. In the model, the EAG has included testing for suspected paroxysmal atrial fibrillation by using a type of ECG device that can be carried around to continuously monitor a person's heart rhythm (a Holter monitor) and has assumed that this will be done for 7 days.

Standard diagnostic pathway

In the standard diagnostic pathway, all people are referred for a 12-lead ECG to test for atrial fibrillation (that is, without a lead-I ECG being done). In the base-case analyses the EAG have assumed a 12-lead ECG is not immediately available in primary care, and that, based on clinical advice, people will have to wait either 2 or 14 days for this. During this time, people have no treatment for atrial fibrillation, and people with atrial fibrillation remain at higher risk of having a cerebrovascular event than people without the condition. If the 12-lead ECG is negative, people proceed to either have no further testing for atrial fibrillation (50%), or Holter monitoring to test for suspected paroxysmal atrial fibrillation (50%). Holter monitoring detects a proportion of people with paroxysmal atrial fibrillation (70%), and is assumed not to incorrectly detect atrial fibrillation in people without the condition. If the 12-lead ECG is positive, atrial fibrillation is diagnosed and treatment can begin. A proportion of people in the model have paroxysmal atrial fibrillation (50% in the base case), and in a proportion of these people atrial fibrillation stops before a 12-lead ECG can be done (48%), so the 12-lead ECG is negative (although the atrial fibrillation may be detected in some cases by subsequent Holter testing, as described above).

Lead-I ECG pathway

A separate arm of the model assessed the effect of including lead-I ECG testing in primary care when an irregular pulse is detected. The model structure is described below, depending on whether the lead-I ECG was positive or negative for atrial fibrillation:

- **Lead-I ECG positive**: Everyone with a positive lead-I ECG result (which can be true or false positive) has a subsequent 12-lead ECG. Clinical experts have said that 12-lead ECGs are needed here, not to confirm atrial fibrillation detected by a lead-I ECG, but to check for additional structural cardiac abnormalities and inform further management decisions. In the base case, everyone with a positive lead-I ECG is assumed to have atrial fibrillation (correctly or incorrectly), even if a subsequent 12-lead ECG is negative.
- **Lead-I ECG negative**: 80% of people are still sent for a 12-lead ECG despite a negative lead-I ECG result (to assess for potential non-atrial fibrillation arrhythmias), but have no treatment for atrial fibrillation while waiting for this test. The 12-lead ECG identifies some false negative results from the lead-I ECG. If the 12-lead ECG results are negative, people either have no further testing for atrial fibrillation or have Holter testing for potential paroxysmal atrial fibrillation. People with a negative lead-I ECG who do not have a subsequent 12-lead ECG either have no further testing for atrial fibrillation (50%), or have Holter monitoring for paroxysmal atrial fibrillation (50%). People with positive results from either 12-lead ECG or Holter monitoring start treatment for atrial fibrillation.

The diagnostic phase model covers the first 3 months after the initial primary care appointment in which an irregular pulse is detected (standard diagnostic pathway) or an irregular pulse is detected and a lead-I ECG is done (lead-I ECG pathway). By the end of the diagnostic phase, people have either been diagnosed as having atrial fibrillation or no atrial fibrillation has been detected (described as ‘ruled out’ in the EAG’s report); either correctly or incorrectly.

People diagnosed with atrial fibrillation can have anticoagulants and rate control treatment (beta blockers).

People can have up to 2 cerebrovascular events (transient ischaemic attack, ischaemic stroke or haemorrhagic stroke), a non-major bleeding event or die; modelled using a Markov model. The probability of having a cerebrovascular event for people with atrial fibrillation is reduced if they are taking anticoagulants. However, anyone taking anticoagulants has an associated higher risk of having a bleeding event.

Post-diagnostic phase

Following the 3-month diagnostic phase model, people enter a second Markov model. This has the same structure as the Markov model in the diagnostic phase after a diagnosis has been made, but runs over a 30-year timespan (with 3-month cycles). People enter based on their history of cerebrovascular events (none, 1 or 2) and can have further cerebrovascular events, non-major bleeding events or die (shown in figure 1).

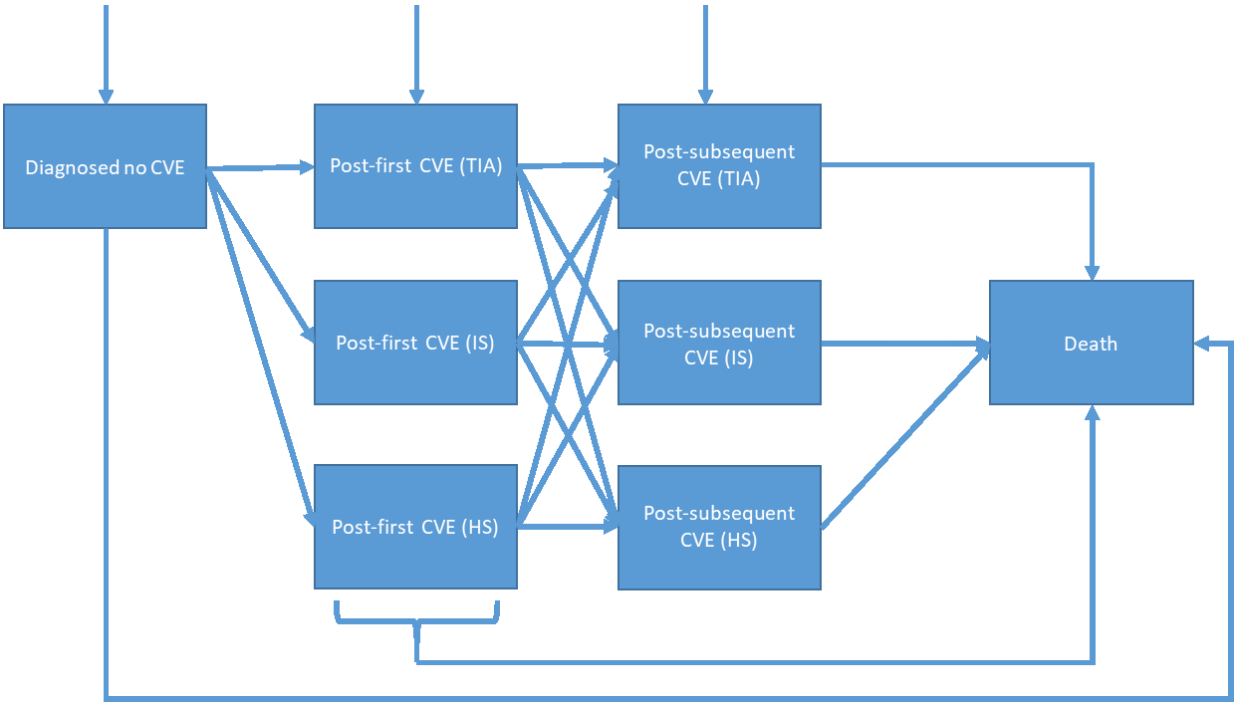

Figure 1 Diagram of post-diagnostic phase Markov model (diagnostics assessment report, figure 25)

Abbreviations: CVE, cerebrovascular event; TIA, transient ischaemic attack; IS, ischaemic stroke; HS, haemorrhagic stroke

Benefits of lead-I ECG testing in the model

The benefits of testing using a lead-I ECG in the model come from:

- Earlier detection of atrial fibrillation. People start anticoagulation treatment earlier, reducing the risk of cerebrovascular events (which is higher for people with untreated atrial fibrillation). Rate control treatment (beta blockers) is also started earlier, which improves quality of life by reducing symptoms.

- More detection of paroxysmal atrial fibrillation, because an ECG can be done when an irregular pulse is detected. If no lead-I ECG is available, it is assumed that the first ECG done is a 12-lead ECG either 2 or 14 days later. The model assumes that for 48% people with paroxysmal atrial fibrillation the episode will stop before the 12-lead ECG is done. This is true in the model whether the 12-lead ECG is carried out 2 or 14 days later. Many of these people have undiagnosed atrial fibrillation and so have higher risk of cerebrovascular events for the rest of their lives (in base-case analysis; scenario analysis D assumes that all paroxysmal atrial fibrillation is detected after 5 years regardless of whether a lead-I ECG is used or not).

The EAG commented that most patient benefits come from more detection of paroxysmal atrial fibrillation.

Conversely, using lead-I ECGs can also result in false positive diagnoses of atrial fibrillation. This results in unnecessary treatment, including anticoagulation, which increases a person's risk of bleeding.

Model inputs

The starting age of the modelled cohort was 70 years old, and the model was run over 30 years. The cohort consisted of people with signs and symptoms of

atrial fibrillation and an irregular pulse; including people with atrial fibrillation (assumed to be 20% based on clinical advice) and people without the condition (assumed to have either atrial or ventricular ectopy). The EAG modelled a cohort of 53.88 people; based on the estimated number of people with signs and symptoms of atrial fibrillation and an irregular pulse who would visit an individual GP each year.

Diagnostic accuracy of lead-I ECG devices

Estimates of the diagnostic accuracy of the 5 lead-I ECG devices were obtained from the EAG's systematic review and meta-analyses (described in section 2.1). The EAG used estimates of accuracy based on healthcare practitioners interpreting the ECG traces, because it assumed that a device's algorithm would not be used in isolation when deciding if a person has atrial fibrillation. An exception was for RhythmPad GP which had accuracy data based only on the device's algorithm. The EAG also used estimates for a generic lead-I ECG device, based on pooled estimates from studies using different lead-I ECG devices (see table 3).

Table 7 Sensitivity and specificity values of lead-I ECG devices used in the economic model

Lead-I ECG	Interpreter of ECG	Data source	Sensitivity %	Specificity %
imPulse	Healthcare professional	Reeves (unpublished)	83.5[a]	91.5[a]
Kardia Mobile[d]	Healthcare professional	Pooled analysis[b]	94.0	96.8
MyDiagnostick	Healthcare professional	Desteghe et al. (2017)[c]	85.0	95.0
RhythmPad GP	Algorithm	Crockford et al. (2013)	67.0	97.0
Zenicor-ECG	Healthcare professional	Doliwa et al. (2009)	92.0	96.0
Generic lead-I device	Healthcare professional	Pooled analysis	93.9	96.5

[a] EAG used the midpoint from the range reported in the Reeves report

[b] Pooled estimate from 3 studies; see table 3

[c] Desteghe et al. reported accuracy estimates from 2 electrophysiologists. Estimates used in the base case were from electrophysiologist 1 (see table 4); values from electrophysiologist 2 were used in a scenario analysis (sensitivity of 80.0%, specificity of 98.0%)

[d] Alternative accuracy estimates based on a pooled estimate where data from electrophysiologist 2 from Desteghe were used in a scenario analysis; sensitivity 91.3%, specificity 97.4%

Treatment effects: Mortality and cerebrovascular events

For people with atrial fibrillation, the rate of mortality and cerebrovascular events (transient ischaemic attack, ischaemic or haemorrhagic stroke) in people untreated with anticoagulants was taken from Sterne et al. (2017). The effect of anticoagulants on the incidence of these events in people with atrial fibrillation was also taken from this study. For people without atrial fibrillation the rate of mortality and cerebrovascular events was taken from various sources (for example, Public Health England report, Office for National Statistics report, Rothwell et al. 2005).

The risk of cerebrovascular events and mortality for people with untreated atrial fibrillation does not vary by type of atrial fibrillation; that is, risk is the same for paroxysmal, permanent and persistent atrial fibrillation.

After people have a cerebrovascular event, their risk of mortality increases. The EAG assumed that this risk was 2.6 times greater based on a study of stroke survivors in Norway (Mathisen et al. 2016). The risk of having a further cerebrovascular event was based on a meta-analysis of stroke survivors (Mohan et al. 2011) with increased risk in the first year, then a lower risk from year 2 onwards.

Treatment effect: Clinically relevant bleeding

The risk of clinically relevant bleeding is increased for people who have anticoagulants, based on Sterne et al. (2017). This is the case for people both with and without atrial fibrillation.

Costs

Lead-I ECG device costs

Annual costs of the devices used in the base-case model are shown in table 8. Because the lead-I ECG could be used outside the scope of this assessment, the EAG also did a scenario analysis that excluded the cost of the devices.

Table 8 Estimated annual cost of lead-I ECG devices

Lead-I ECG	Item	Unit cost (£)[d]	Expected lifespan (years)	Annual cost (£)	Unit cost per test[c] (£)
imPulse	Device	175	2	87.50	1.62
Kardia Mobile	Device	82.50	5	16.50[a]	0.31
MyDiagnostick	Device	450	3	90	1.67
RhythmPad GP	Device	1,100	1[b]	1,100	20.42
Zenicor-ECG	Device and 36 month licence	1,980	10	6,13.27	11.40
	Extra 36 month licence	1,780	3		

[a] Cost of any additional tablet or device needed not included (the effect of additional cost for a tablet or smartphone is assessed in scenario analysis F)

[b] EAG assumed 1-year lifespan based on product manual stating that service life of the product is 1 year (the effect of extending lifespan to 3 years is assessed in scenario analysis G)

[c] Assumes 54 people tested per year

[d] Excluding VAT

No extra cost was included for administering and interpreting the lead-I ECG because it was assumed that this could be done during a standard GP consultation.

Cost of 12-lead ECGs and Holter monitoring

The EAG devised base cases which differed depending on where 12-lead ECGs were done. If a 12-lead ECG was done in primary care, the cost of administering it was assumed to be £12.34. This was based on the costs of the device, disposables and staff time to do and interpret the ECG. The cost of administering a 12-lead ECG in secondary care was assumed to be £52

(from NHS reference costs). The cost of Holter monitoring was assumed to be £120.23.

Treatment and event costs

Costs for anticoagulant (apixaban) and rate control (beta blockers) treatment were obtained from the British national formulary and NHS drug tariff. Costs of bleeding events and transient ischaemic attack were taken from NHS reference costs. Age and sex-adjusted 1- and 5-year costs for strokes were from the Sentinel Stroke National Audit Programme's cost and cost-effectiveness report (2016). Further details on costs are in the diagnostics assessment report, starting on page 100.

Health-related quality of life and QALY decrements

Berg et al. (2010) was used to provide utility values for people with atrial fibrillation. Utility values from people who had atrial fibrillation and were symptomatic were used in the model for people with atrial fibrillation who did not have treatment. Utility values from people with atrial fibrillation who were asymptomatic were used in the model for people with atrial fibrillation who had treatment. Beta blockers were assumed to improve symptoms for people with atrial fibrillation. People without atrial fibrillation were assumed to be having a short symptomatic episode caused by atrial or ventricular ectopy that resolves itself quickly. Regression equations from Berg et al. were used in the model for calculating utility values adjusted for age, sex and symptom type. Example utilities for people aged 70 are shown in table 9. The EAG assumed that people who had signs and symptoms of atrial fibrillation but did not have the condition would have the same utility value as people who had the condition and had treatment.

Table 9 Utility values used in base case economic model (at age 70; age- and sex-adjusted)

	Atrial fibrillation status (95% CI)	
	Atrial fibrillation	**No atrial fibrillation**
Untreated	0.665 (0.537 to 0.881)	0.744 (0.480 to 0.942)
Treated	0.744 (0.480 to 0.942)	0.744 (0.480 to 0.942)

Utility decrements for cerebrovascular and adverse events

For people who had an ischaemic or haemorrhagic stroke, a lifetime utility decrement was applied at the time of the first stroke (no further decrements were applied for subsequent strokes). The size of the decrement was −0.272 (95% CI −0.345 to −0.198) for both types of stroke, from Berg et al. (2010).

Transient ischaemic attacks and bleeding events were assumed to have no long-term effect on health-related quality of life, and no utility decrement was applied for these events.

Base-case results

For decision-making, the incremental cost-effectiveness ratios (ICERs) per quality-adjusted life year (QALY) gained or lost will be considered. The following assumptions (in addition to those described above) were applied in the base-case analysis:

- 20% of people presenting to primary care with signs and symptoms of atrial fibrillation, and who have an irregular pulse, have atrial fibrillation.
- 50% of people with atrial fibrillation have paroxysmal atrial fibrillation. The EAG commented that there is a lack of evidence on the prevalence of paroxysmal atrial fibrillation in people with symptoms, and noted that a recent study (Welton et al. 2017) had reported wide variation in prevalence (although not necessarily in a symptomatic population). The effect of varying this prevalence was investigated in sensitivity analysis.
- 10% of lead-I ECG tests need additional interpretation by a cardiologist.
- 12-lead ECGs have 100% sensitivity and specificity for atrial fibrillation (if a person is in atrial fibrillation at the time of the test).
- For 48% of people with paroxysmal atrial fibrillation the episode will have stopped by the time a subsequent 12-lead ECG is done (2 or 14 days after the initial primary care consultation at which an irregular pulse is detected); based on data from Israel et al. (2004).
- Holter testing for paroxysmal atrial fibrillation is assumed to have 100% sensitivity and specificity (if atrial fibrillation occurs during testing). Holter

testing is assumed to be for 7 days and 70% people with atrial fibrillation are assumed to have an episode in that time (based on data from Kirchoff et al. 2006).

- Only people who are diagnosed with atrial fibrillation and who have a CHA_2DS_2-VASc score of 2 or more have anticoagulation treatment; 82.4% of people with atrial fibrillation are assumed to have a CHA_2DS_2-VASc score of 2 or more, and 81.2% of these are assumed to take anticoagulants (based on NHS Quality and Outcomes Framework 2016/2017 indicator AF007).
- People having anticoagulation treatment have apixaban (simplifying assumption).
- Treatment with anticoagulants starts immediately after a positive lead-I ECG result (simplifying assumption).
- People whose atrial fibrillation is undetected and who have a cerebrovascular event are assumed to have their atrial fibrillation diagnosed as part of treatment.

The EAG produced 4 base cases, depending on when and where 12-lead ECGs were done:

- 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.

In pairwise analyses, all the lead-I ECG devices were compared independently with the standard pathway (that is, no use of a lead-I ECG device). Results from base-case 1 are shown in table 10.

Table 10 Base case 1: Pairwise cost-effectiveness analysis (compared with standard pathway)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Standard pathway	514,187	447.963	-	-	-

Kardia Mobile	515,551	449.249	1,364	1.286	1,060
imPulse	530,745	448.987	16,557	1.024	16,165
MyDiagnostick	521,233	449.024	7,046	1.061	6,638
Zenicor-ECG	518,468	449.199	4,281	1.236	3,462
RhythmPad GP	518,436	448.573	4,249	0.610	6,962
Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio					

The ICERs produced in pairwise comparisons from the other 3 base cases were similar (table 11).

Table 11 Pairwise cost-effectiveness analysis (compared with standard pathway) for base cases 2, 3 and 4

	ICER[a] (£)		
	Base-case 2	**Base-case 3**	**Base-case 4**
Standard pathway	–	–	–
Kardia Mobile	749	783	481
imPulse	15,246	15,826	14,921
MyDiagnostick	6,068	6,301	5,743
Zenicor-ECG	3,066	3,175	2,788
RhythmPad GP	5,966	6,337	5,376
Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio [a] all ICERs shown are per QALY gained			

In fully incremental analyses across all the base cases, all lead-I ECG devices were dominated by Kardia Mobile (that is, it cost less but produced more QALYs). The ICERs for Kardia Mobile compared to the standard pathway were the same as for the pairwise comparison.

Analysis of alternative scenarios

The EAG investigated the effect of varying some of the base-case assumptions in scenario analyses. Analyses were done using base-case 1, which the EAG commented was the least cost-effective base-case scenario. Results of scenarios A to J are described in table 12.

Table 12 Scenario analyses A to J in base-case 1

Scenario	Results
Scenario A Cost of lead-I ECG devices removed (because the devices may be used outside the scope of this assessment).	In incremental analysis, Kardia Mobile still dominates all other devices. The ICER compared to the standard pathway is £1,047 per QALY gained.
Scenario B Alternative sensitivity and specificity for MyDiagnostick used in analysis (from Desteghe et al.; see table 6).	MyDiagnostick is no longer dominated by Kardia Mobile. The Kardia Mobile has an ICER of £5,503 per QALY gained compared to the MyDiagnostick.
Scenario C Only lead-I ECG testing (that is, 12-lead ECG and Holter testing removed).	In incremental analysis, Kardia Mobile still dominates all other devices. The ICER compared to the standard pathway is £1,252 per QALY gained.
Scenario D The model timespan is limited to 5 years (instead of 30 years). This is used as a proxy for all people with undiagnosed atrial fibrillation being identified within 5 years.	In incremental analysis, Kardia Mobile still dominates all other devices. The ICER compared to the standard pathway is £1,534 per QALY gained.
Scenario E 40 scenarios in which the proportions of people referred for Holter monitoring (for paroxysmal atrial fibrillation) in the model after lead-I or 12-lead ECG testing are varied (between 0 and 100%).	Pairwise analysis was done to compare Kardia Mobile only with the standard pathway. Kardia Mobile either still dominated or had an ICER below £7,600 per QALY gained.
Scenario F Assessing the impact of including the costs of a smartphone or tablet with the Kardia Mobile	In a threshold analysis, a smartphone or tablet would need to cost more than £2,850 for the Kardia Mobile to no longer dominate the other lead-I ECG devices. The ICER for Kardia Mobile compared to the standard pathway remains less than £20,000 per QALY gained if a smartphone or tablet costs less than £24,362.
Scenario G Increasing the lifespan of the RhythmPad GP to 3 years (from 1 year)	In incremental analysis, Kardia Mobile still dominates all other devices. The ICER compared to the standard pathway is £1,060 per QALY gained.
Scenario H Including a QALY decrement for bleeds	In incremental analysis, Kardia Mobile still dominates all other devices. The ICER compared to the standard pathway is £1,060 per QALY gained.
Scenario I Alternative sensitivity and specificity values for Kardia Mobile (based on	All lead-I ECG devices were dominated by Kardia Mobile or Zenicor-ECG. The Zenicor-ECG had an ICER of £242,994

data from electrophysiologist 2 from Desteghe used in pooled analysis)	per QALY gained when compared to the Kardia Mobile.
Scenario J Assuming that rates of haemorrhagic stroke are the same for people treated with NOACs who do not have atrial fibrillation as for people treated with NOACs who have atrial fibrillation	In incremental analysis, Kardia Mobile still dominates all other devices. The ICER compared to the standard pathway is £2,618 per QALY gained.
Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio	

Sensitivity analyses

Deterministic sensitivity analysis

The model was most sensitive to the prevalence of paroxysmal atrial fibrillation (assumed to be 50% in the base case) in one-way analyses for all of the lead-I ECG devices except RhythmPad GP (for which it had the third largest effect). Cost effectiveness improved as the prevalence of paroxysmal atrial fibrillation increased. If the prevalence of paroxysmal atrial fibrillation was assumed to be 100%, all devices except the imPulse and MyDiagnostick became dominant over the standard pathway. Alternatively, lower prevalence estimates of paroxysmal atrial fibrillation made the devices less cost effective (increased incremental costs and decreased incremental QALYs).

Tornado diagrams are in the diagnostics assessment report from page 119.

Probabilistic sensitivity analysis

In a probabilistic sensitivity analysis (done in base case 1) all other lead-I ECG devices were dominated by the Kardia Mobile in a fully incremental analysis. In pairwise comparisons with the standard pathway, ICERs were similar to the deterministic results, and all were less than £17,000 per QALY gained.

Cost-effectiveness acceptability curves for all devices are in the diagnostics assessment report from page 189 and an addendum to the report. Analysis was done using base-case 1. In pairwise comparisons, all lead-I ECGs had a higher probability of cost effectiveness than the standard pathway at

maximum acceptable ICER values over £10,000, except imPulse which had a higher probability from about £16,000. When comparing all devices together (rather than pairwise with standard care), Kardia Mobile has the highest probability of cost effectiveness across all ICER values (figure 2).

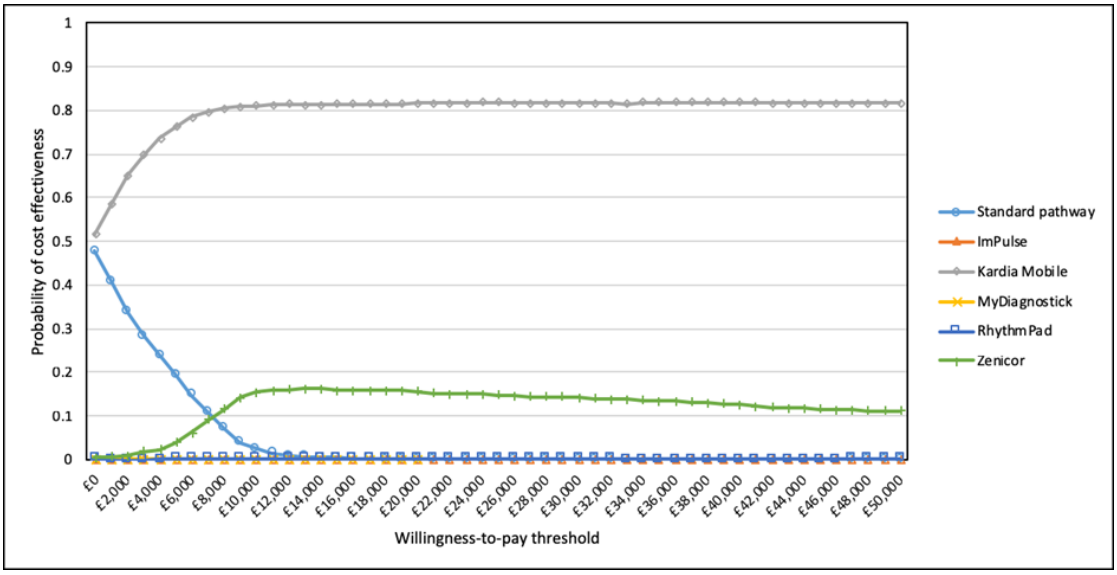

Figure 2 CEAC Base case 1 (diagnostics assessment report addendum, figure 1)

3 Summary

Clinical effectiveness

The EAG commented that pooled sensitivity and specificity values were similar across the different meta-analyses irrespective of who interpreted the lead-I ECG trace (healthcare professional or device algorithm) or lead-I ECG device used. Accuracy estimates were high; pooled sensitivity values were 88% or higher, pooled specificity values were all in excess of 94%. Multiple studies assessed Kardia Mobile and MyDiagnostick, although only Kardia Mobile had a device-specific pooled sensitivity and specific value based on the trace being interpreted by a trained healthcare professional. Single studies were identified for imPulse (an unpublished study), RhythmPad GP and Zenicor-ECG.

The EAG compared the estimates of lead-I ECG accuracy with those of manual pulse palpation from a systematic review (Welton et al. 2017). Pooled sensitivity estimates for lead-I ECGs were similar to manual pulse palpation (91.6%; 95% CI 75% to 98.6%), but pooled estimates of specificity were higher than for manual pulse palpation (78.8%; 95% CI 51% to 94.5%).

There were little data on the clinical effect of the lead-I ECG devices. In general healthcare professionals and patients liked the devices. In the few studies identified, atrial fibrillation detected by the devices tended to influence subsequent treatment decisions. The failure rate of the devices varied between 0.1% and 9%.

Cost effectiveness

In all pairwise comparisons with the standard pathway (that is, with no use of a lead-I ECG) across the 4 base cases, the Kardia Mobile had an ICER of less than £1,100 per QALY gained. The pairwise ICERs were below £6,500 per QALY gained for the MyDiagnostick, RhythmPad GP and Zenicor-ECG, and were below £16,000 per QALY gained for the imPulse.

In fully incremental analyses, Kardia Mobile dominated the other lead-I ECGs.

Model results were largely qualitatively unchanged in the EAG's scenario analyses. One-way sensitivity analysis showed that results were sensitive to the prevalence of paroxysmal atrial fibrillation. At 100% prevalence, all lead-I ECG devices except the imPulse and MyDiagnostick dominated the standard pathway.

In probabilistic sensitivity analysis, when comparing all the lead-I ECG devices, the Kardia Mobile had the highest probability of cost-effectiveness across all maximum acceptable ICER values. In pairwise comparisons with the standard pathway, all lead-I ECGs had a higher probability of cost effectiveness than the standard pathway at maximum acceptable ICER values over £10,000, except imPulse which had a higher probability from about £16,000.

4 Issues for consideration

Clinical effectiveness

The studies providing data on device accuracy were not done in populations matching the scope (that is, people presenting to primary care with signs and symptoms of atrial fibrillation and an irregular pulse). Instead, the study populations were people who were asymptomatic for atrial fibrillation (although many did have a history of the condition). If the severity of atrial fibrillation differs between the scope and study populations, this would affect estimates of device accuracy to detect atrial fibrillation.

No studies were identified that compared the ability of the lead-I ECG devices to detect atrial fibrillation with a 12-lead ECG done at a later time (by which time paroxysmal atrial fibrillation may have resolved). Instead, in the identified accuracy studies a 12-lead ECG was done at approximately the same time as the lead-I ECG. To assess the potential benefit of lead-I ECGs to detect cases of paroxysmal atrial fibrillation (compared with 12-lead ECGs done at a later point) in the economic model, the EAG had to make assumptions about the prevalence of paroxysmal atrial fibrillation and the proportion of people with paroxysmal atrial fibrillation that would have resolved by the time a 12-lead ECG could be done.

In studies in which lead-I ECGs were interpreted by a healthcare professional, this was a cardiologist, electrophysiologist or a GP with a special interest in cardiology. The lowest specificity value came from a study in which the interpreter was a GP with a special interest in cardiology. GPs in primary care in the NHS are likely to have less experience in interpreting ECGs than the healthcare professionals in the studies, which may affect device accuracy.

Different levels of data were identified for the lead-I ECG devices for single time point testing for atrial fibrillation; with Kardia Mobile and MyDiagnostick having the most data. A study that assessed both these devices (Desteghe et al. 2017) reported no statistically significant difference in agreement between

them. One study per device was identified for imPulse (an unpublished study), RhythmPad GP (based on the results of an algorithm that has since been changed) and Zenicor-ECG; and only the Zenicor-ECG study was included in meta-analyses.

No data were identified on the effect of lead-I ECG results on clinical decision-making in primary care; for example, how GPs would deal with positive or negative results.

Cost effectiveness

The diagnostic accuracy estimates used in the model were from the systematic review and meta-analysis (discussed above) so did not exactly match the scope population. The devices may have different accuracies in the scope population, which could affect their cost effectiveness.

Pooled sensitivity and specificity estimates for Kardia Mobile were used in the model (see table 7). Estimates used in the model for the other devices were from individual studies. The imPulse estimates came from an unpublished study and the RhythmPad GP values were based on the performance of the device's algorithm. The EAG selected 1 of the 3 studies to provide accuracy estimates for MyDiagnostick because the data were based on a healthcare practitioner interpreting the trace (rather than the device's algorithm).

The cost of a smartphone or tablet needed to operate Kardia Mobile was not included in base-case cost estimates for this device in the model. However, based on a threshold analysis, the EAG commented that unless the additional cost of smartphone or tablet was at least £2,885 the Kardia Mobile would still dominate the other lead-I ECG devices. The ICER of Kardia Mobile compared to the standard pathway would remain below £20,000 per QALY gained as long as the price of a smartphone or tablet is not more than £24,362. The lifespan of RhythmPad GP was assumed to be 1 year based on the product manual stating that service life of the product is 1 year; a longer lifespan would have reduced the cost per use. In a scenario analysis in which this was

extended to 3 years, the RhythmPad GP was still dominated by the Kardia Mobile.

The EAG assessed the lead-I ECG devices against a standard care pathway in which there is a delay until a 12-lead ECG can be done after an irregular pulse suggesting atrial fibrillation is detected. The EAG commented that there was unlikely to be any diagnostic benefit if a 12-lead ECG can be done on the same day as the irregular pulse is detected. However, the EAG's analysis did show that lead-I ECGs are potentially cost effective even if there is a relatively short delay (2 days) until a 12-lead ECG can be done.

No utility decrement was applied for bleeding events in the base case. A scenario analyses was done to include a QALY decrement for bleeds (scenario H; report addendum) which assumed that the impact of bleeds would only be for 14 days.

The model results are sensitive to the prevalence of paroxysmal atrial fibrillation. The EAG noted that the model results should be viewed with caution if it is clinically plausible that the prevalence of paroxysmal atrial fibrillation is likely to be substantially less than 50% (the value used in the base case). However, the devices will be more cost effective if the prevalence is higher than this. The EAG were unable to find a value for this prevalence in the literature. It noted that a published fixed effects meta-analysis (Welton et al. 2017) reported that the prevalence of paroxysmal atrial fibrillation (in a population not explicitly defined as being symptomatic for the condition) varied widely, between 5.9% and 83.5%.

5 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

The devices may not be suitable for use in people with upper limb amputations or missing fingers. In addition, some people may need help holding the devices in the required way to obtain a reading; for example, people who have had a stroke or who have arthritis in their hands may not be able to grip a device unaided. The accuracy of readings taken using the devices may be adversely affected if a person has a tremor or a skin condition. Some of the devices are not for use in people with a pacemaker or implantable defibrillator.

6 Implementation

The EAG identified several studies that highlighted potential implementation issues. A barrier to using the devices related to the difficulty for some patients to hold the device still enough to take a reading. Orchard et al. (2014) reported barriers to adoption identified by 3 GPs: not having the required software available and practice IT issues, needing to charge devices and problems with the technology not working.

Further potential implementation issues identified by the NICE adoption and impact team are:

Lead-I ECG interpretation and training

Skills in interpreting lead-I ECG traces to identify potential atrial fibrillation will vary across primary care and concerns about the ability of healthcare practitioners to interpret results may be a barrier to adoption. Devices included in this assessment have software that analyses the generated ECG traces and indicates whether atrial fibrillation is potentially present. This may help to overcome this adoption barrier.

Procurement and commissioning

Any cost savings generated by using the devices is likely to occur in secondary care (for example, reduced hospitalisation for strokes prevented by earlier detection of atrial fibrillation) rather than in primary care where the devices are purchased. Clinical experts have suggested that there would be

greater success in securing funding if the device was supporting a local initiative; for example, to reduce strokes or reduce low-risk referrals to secondary care cardiology.

Clinical experts have also suggested that healthcare professionals will need immediate access to the devices. When buying the devices it will therefore be necessary to consider how many healthcare professionals will need access to them.

Device usability

Any difficulties in converting generated ECG traces into a format suitable for a person's records (for example, a PDF file) and transferring this to the necessary system for storage may deter healthcare professionals from routinely using the devices. The availability of additional technology to use the devices, such as a Wi-Fi signal and devices with Bluetooth connectivity, could also act as barriers to adoption of the devices.

Information governance and IT

The ability to save and send information could be a risk to data protection and information governance if not done correctly. If clinicians and managers have a concern that using the devices could pose a risk to data protection and information governance, this could act as a barrier to adoption. Companies have stated that they have appropriate systems in place to ensure the devices and software comply with the relevant policies and law; however organisations seeking to adopt these technologies will need appropriate governance in place, with the flexibility to update as regulations and legislation change.

7 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A. The diagnostics assessment report for this assessment was prepared by Liverpool Reviews and Implementation Group (LRiG):

Duarte R, Stainthorpe A, Greenhalgh J 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. Liverpool Reviews and Implementation Group (LRiG), University of Liverpool, 2018

B. The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Manufacturers of technologies included in the final scope:

- AliveCor
- Zenicor Medical Systems
- Mydiagnostick Medical
- Cardiocity
- Plessey Semiconductors

Other commercial organisations:

- iRhythm Technologies

Professional groups and patient/carer groups:

- British Cardiovascular Society
- Royal College of Physicians
- Anticoagulation UK
- Arrhythmia Alliance
- Atrial Fibrillation Association
- Syncope Trust And Reflex anoxic Seizures

Research groups:

- None

Associated guideline groups:

- None

Others:

- Department of Health and Social Care
- Healthcare Improvement Scotland
- Medicines and Healthcare Products Regulatory Agency
- NHS England
- Welsh Government

Appendix B: Glossary of terms

Cardiac arrhythmia
An abnormality of the heart's rhythm; which can beat too slowly, too quickly or irregularly.

Electrocardiogram (ECG)
A test to monitor the heart's rhythm and electrical activity using sensors applied to the skin (see the NHS website).

Heart palpitations
Heart beats that are suddenly more noticeable, and which can feel like the heart is pounding, fluttering or beating irregularly (see the NHS website).

Lead-I ECG
The term 'lead' in electrocardiography refers to the 12 different vectors along which the heart's depolarisation is measured. Each of these leads represents the electrical potential difference between 2 points. Lead-I is the voltage between the (positive) left arm electrode and right arm (negative) electrode. Handheld lead-I ECG devices use thumb and finger contacts with simple touch electrodes, rather than the adhesive electrodes attached to the skin for 12-lead ECGs.

Paroxysmal atrial fibrillation
Intermittent episodes of atrial fibrillation (which can be asymptomatic) that usually stop within 48 hours without treatment (see the NHS website).