Technoleg Iechyd Cymru
Health Technology Wales

Appraisal Summary

Handheld single lead electrocardiogram devices to detect atrial fibrillation in older adults and those with intermittent episodes

Why did HTW appraise this topic?

Atrial fibrillation (AF) is an abnormal heart rhythm and is characterised by rapid and irregular beating of the atrial chambers of the heart resulting from structural and electrical causes. It is the most common cardiac arrhythmia and can be either persistent, with sustained abnormal rhythm for more than seven days, or intermittent, with varying frequency and length of episodes.

Handheld single-lead (lead-I) electrocardiogram (ECG) devices have been developed to rapidly assess heart rhythm using portable devices and they present an alternative to existing approaches. These devices function by allowing a person to grip a piece of hardware that can detect heart rhythm and this rhythm can be assessed by linked software or provide a reading to a clinician. Despite the innovative nature of the technology, it is unclear whether use of lead-I ECG can detect a greater number of cases of AF and improve outcomes in a cost-effective way compared to existing approaches.

Health Technology Wales (HTW) was asked to consider use of this technology in screening by partners working in a Local Health Board in Wales. In response, an evidence review was completed to address the three following questions: 1) What is the diagnostic accuracy of handheld lead-I ECG for the detection of atrial fibrillation?; 2) What is the effectiveness of handheld lead-I ECG devices in single point of time screening for unknown AF in people aged over 65 in primary care and the community; 3) What is the effectiveness of handheld lead-I ECG devices to detect intermittent atrial fibrillation after an inconclusive clinical examination?

What evidence did HTW find?

HTW identified and included two systematic reviews on the diagnostic accuracy of lead-I ECG, nine primary studies and four economic evaluations examining effectiveness or cost-effectiveness of lead-I ECG in screening for unknown AF, and two primary studies examining effectiveness in detection of intermittent AF. Several further studies relating to organisational and patient issues also informed the report.

For screening for unknown AF, three distinct approaches to screening were found in the included (during usual contacts or influenza vaccination clinics in primary care, or in community-based pharmacies). The evidence suggests that screening with lead-I ECG is able to identify limited number of unknown cases of AF and small numbers of patients had treatment initiated as a result. When studies compared screening with lead-I ECG to pulse palpitation, the results suggested that the approaches were equivalent and lead-I ECG was not shown to be more

beneficial. Few studies examined outcomes beyond identification of AF and there was limited evidence on longer-term benefits and harms associated with lead-I ECG screening. Available economic evidence suggested there was a potential for lead-I ECG to deliver value when compared to no screening but value was less clear when compared to screening with pulse palpitation.

For detection of intermittent AF in people with inconclusive clinical examinations, a randomised controlled trial suggested that use of lead-I ECG can identify additional cases and reduce time to diagnosis. These results were replicated even when all participants received both lead-I ECG and 24-hour Holter monitoring. However, studies were limited by short-term follow-up and were not able to provide evidence on whether increased and quicker diagnosis reduces serious health outcomes and mortality for this population. No economic evidence was identified in this setting.

There are a number of organisational and patient issues around use of lead-I ECG that should be considered regarding implementation. The uptake of screening for unknown AF was limited in several studies and clinicians raised concerns about receiving appropriate equipment and being able to embed screening in workflows. Patients generally appeared amenable to screening for AF and found lead-I ECG devices straightforward to use. However, there is some concern that patients may try to attempt to interpret heart rhythm readings themselves rather than relying on device software or assessment by clinicians.

What was the outcome of HTW's Appraisal?

Health Technology Wales is a national body working to improve quality of care in Wales. We collaborate with partners across health, social care, and industry to issue independent Guidance that informs commissioning within NHS Wales. We are supported by an Assessment Group, who ensure our work adheres to high standards of methodological and scientific rigour, and an Appraisal Panel, who consider evidence within the Welsh context and produce HTW Guidance. More details on our appraisal process, the assessment group, and the appraisal panel can be found on the HTW website.

In this case, the HTW Assessment Group considered the evidence presented in Evidence Appraisal Report 028. They concluded that there was not sufficient evidence to support the development of Guidance by the HTW Appraisal Panel and they did not see merit in HTW providing additional economic modelling. Due to this, they recommended publication of the appraisal as an Evidence Summary.

Evidence Appraisal Report 028 follows below and provides full details for this topic.

Technoleg Iechyd Cymru
Health Technology Wales

Evidence Appraisal Report

Handheld single lead electrocardiogram devices to detect atrial fibrillation in older adults and those with intermittent episodes

1. Purpose of the evidence appraisal report

This report aims to identify and summarise evidence that addresses the three following questions: 1) What is the diagnostic accuracy of handheld single lead electrocardiograms for the detection of atrial fibrillation?; 2) What is the effectiveness of handheld lead-I ECG devices in single point of time screening for unknown AF in people aged over 65 in primary care and the community; 3) What is the effectiveness of handheld single lead electrocardiogram devices to detect intermittent atrial fibrillation after an inconclusive clinical examination?

Evidence Appraisal Reports are based on rapid systematic literature searches, with the aim of identifying the best clinical and economic evidence on health technologies. Researchers critically evaluate this evidence. The draft Evidence Appraisal Report is reviewed by experts and by Health Technology Wales (HTW) multidisciplinary advisory groups before publication.

2. Health problem

Atrial fibrillation (AF) is an abnormal heart rhythm and is characterised by rapid and irregular beating of the atrial chambers of the heart resulting from structural and electrical causes (Staerk et al. 2017). It is the most common cardiac arrhythmia and can be either persistent, with sustained abnormal rhythm for more than seven days, or intermittent, with varying frequency and length of episodes. Arrhythmias can be self-limiting in their early stages and resolve without treatment but can also be progressive, meaning that intermittent AF can become persistent over time and abnormal rhythms can eventually become permanent and less amenable to treatment. Both persistent and intermittent AF can be symptomatic, with people experiencing shortness of breath, or sensing that their heart rate is too fast, irregular, or is skipping beats. They may also experience chest pain and fatigue. However, AF often does not cause symptoms and can go undetected for long periods of time (Heidt et al. 2016).

AF can be major risk factor for stroke and strokes in AF patients are associated with higher morbidity and mortality than strokes from other causes. Furthermore, AF is implicated in heart failure and other cardiovascular diseases and there is some evidence that AF is associated with increased rates of dementia. Ultimately, AF is associated with a substantial risk of death across all age groups (Staerk et al. 2017) and identification and treatment is important in reducing these risks.

There are a range of options for managing and treating AF. Drug treatments can be targeted at restoring normal heart rhythm (e.g. antiarrhythmics) or rate (e.g. beta-blockers) or on reducing

risk of stroke (e.g. anticoagulants). Non-drug treatments are also available and in more acute cases, electrical cardioversion can be used to restore normal rhythm, or ablation can be used to prevent abnormal electrical impulses (Xu et al. 2016). These interventions have the possibility of harm to patients (i.e. increased risk of bleeding with anticoagulants) and these must be balanced with potential benefits when clinicians are making treatment decisions in response to identification of asymptomatic AF (Lown & Moran 2019). Alongside these medical interventions, there is growing evidence that lifestyle interventions targeting modifiable risk factors for AF (e.g. hypertension, dyslipidaemia, smoking, obesity) can also play a role in reducing persistence and complications of AF (Gallagher et al. 2016)

Recent work has suggested that the overall age-standardised prevalence of diagnosed AF is around 3.3% in the United Kingdom (UK). Rates increase substantially after age 65 with rates of 66.78 and 34.25 per 1000 for men and women aged 65 to 74, rising to 220.94 and 165.33 per 1000 at over age 85 (Adderley et al. 2019). Men are also at higher risk than women. Modelling studies in the UK and United States (US) have estimated that AF could be undetected in 1 to 2% of adults over 65 and a substantial number of these people would be at moderate or high risk of stroke (British Heart Foundation 2019, Turakhia et al. 2018). In the UK, the British Heart Foundation suggests this number could be higher with up to 300,000 people having undiagnosed AF (British Heart Foundation 2019). Due to changing population characteristics, the prevalence of AF is increasing over time and will continue to present a growing burden of illness (Adderley et al. 2019).

3. Health technology

Handheld single-lead (lead-I) electrocardiogram (ECG) devices have been developed to rapidly assess heart rhythm using portable devices. The exact details of handheld lead-I ECGs vary by product but each requires a hardware component that allows a person to place fingers or thumbs from both hands on two sets of electrodes. The hardware then takes a reading of heart rhythm that can be used to assess AF. In some devices, the hardware is able to provide interpretation. In others, data is transmitted to a nearby computer, smartphone, or tablet where it is interpreted by software or is further transferred to a centralised server for assessment. Algorithms are often used to provide an initial assessment and can indicate absence or potential presence of AF. The devices also highlight if the recording was uninterpretable. Clinicians are able to view recorded ECG traces or rhythm strips to make their own judgement.

There are a range of handheld lead-I ECGs that are CE-marked and available commercially in the UK:

- imPulse (Plessey Semiconductors Ltd)
- Kardia Mobile (AliveCor Ltd)
- MyDiagnostick (MyDiagnostick Medical BV)
- Zenicor-ECG (Zenicor Medical Systems AB)
- HeartCheck (CardioComm Solutions Inc)
- HeartScan ECG Monitor (Omron Healthcare UK Ltd)

Another previously available lead-I ECG, RhythmPad GP (Cardiocity Ltd), is no longer on the market. Alongside handheld devices, there are also a range of other lead-I ECG devices including chest straps, smartwatches, and patches. However, these were considered outside the scope of the appraisal.

Handheld lead-I ECGs can be used for a range of purposes and in this appraisal will be considered for screening for undetected atrial fibrillation in primary care or community settings, or for at-home use by people with suspected intermittent AF who have experienced symptoms but have

inconclusive results during clinical assessment. For the purposes of screening in primary care or the community, the most relevant comparator would be manual pulse palpitation by a trained healthcare professional. If AF was suspected, both manual pulse palpitation and lead-I ECG may need to be followed by a full 12-lead ECG to confirm diagnosis and provide a full assessment of other cardiac abnormalities (NICE 2014). For people with suspected intermittent AF and inconclusive clinical assessment, the relevant comparator would be standard care. This can include use of 24-hour or longer-term ECG monitoring using electrodes attached to the chest and abdomen, or repeat visits when symptoms are present (NICE 2014). These methods of detection can be impracticable to use over longer periods due to the need to wear electrodes, and this presents problems for identifying intermittent arrhythmias that may resolve for a period after a patient presents and then begin again after. Lead-I ECGs may provide a more practical approach that can be used for longer periods.

In England, the National Institute of Health and Clinical Excellence (NICE) published diagnostics guidance on the use of lead-I ECGs for symptomatic atrial fibrillation using single point testing in primary care concluded that there was not enough evidence to recommend routine adoption (NICE 2019). Nonetheless, use of lead-I ECG devices for screening and monitoring of AF in England has been encouraged by the NHS Innovation Accelerator and purchase of required technology is supported by central funding through Academic Health Science Networks (NHS Innovation Accelerator 2017). A medtech innovation briefing (MIB232) on Kardia Mobile devices is also available (NICE 2020). In Wales, lead-I ECG use has been supported by the Bevan Commission in limited settings with funding from their exemplar programme (Bevan Commission 2020). Lead-I ECG is also mentioned in the Wales Cardiac Network clinical pathway for AF and considering use of commercially available lead-I ECG devices is recommended to capture intermittent episodes (Wales Cardiac Network 2018). However, it is unclear how widespread adoption has been beyond pilot evaluations.

4. Evidence search methods

We searched for evidence that could be used to answer the three following review questions: 1) What is the diagnostic accuracy of handheld lead-I ECG devices in the identification of AF?; 2) What is the effectiveness of handheld lead-I ECG devices in single point of time screening for unknown AF in people aged over 65 in primary care and the community; 3) What is the effectiveness of handheld single lead electrocardiogram devices to detect intermittent AF after an inconclusive clinical examination?

The criteria used to select evidence for the appraisal are outlined in Appendix 1. These criteria were developed following comments from the HTW Assessment Group and UK experts. A systematic literature search for evidence was undertaken and was last updated on 21 January 2021. The search strategy used in the report was adapted from a review completed to support NICE diagnostic guidance on single lead ECG devices for detection of symptomatic atrial fibrillation assessment on the effectiveness (NICE 2019). The databases searched included: Medline, Embase, Cochrane Library, ClinicalTrials.gov, CPD York. The web pages of relevant health technology assessment groups were also searched. Appendix 2 summarises the selection of articles for inclusion in the review.

5. Clinical effectiveness

Our approach to the selection of studies for clinical effectiveness was as follows. For research question 1, two systematic reviews on the diagnostic accuracy of lead-I ECG devices were available. These were considered the highest level of evidence and observational studies were

considered to be superseded by this evidence. For research question 2 (on effectiveness of handheld lead-I ECG for single point of time screening for AF in primary care and community settings), three distinct approaches to screening were identified: screening during usual care in primary care clinics (by receptionist/nurses or by doctors), screening during influenza vaccination clinics in primary care, and screening in community-based pharmacies. For each of these three approaches, no relevant systematic reviews were found and randomised controlled trials (RCT) were considered the highest priority evidence. If an RCT was available then it was included along with observational studies on similar interventions conducted in the UK setting. If an RCT was not available, then relevant observational studies in high-income settings were included. Studies in low and middle-income countries were considered to be in a sufficiently different setting to warrant exclusion. For research question 3 (on effectiveness of handheld lead-I ECG to detect intermittent atrial fibrillation after an inconclusive clinical examination), no relevant systematic reviews were found and as above, RCTs were considered the highest priority evidence. Due to the limited number of studies found, evidence from observational studies was also included. Across both research questions, all eligible economic evaluations were included.

Leading from this approach to selection, for research question 1, we included one systematic review conducted as part of an earlier health technology assessment (HTA) conducted by NICE (Duarte et al. 2019) and one further systematic review which reported results by community and hospital subgroups (Wong et al. 2020). For research question 2, we included two RCTs (Kaasenbrood et al. 2020, Uittenbogaart et al. 2020) and one UK-based observational study (Grubb et al. 2019) on screening during routine contacts in primary care clinics, two observational studies on screening at influenza clinics in primary care (Savickas et al. 2020, Orchard et al. 2016), four observational studies on screening in community-based pharmacies (Lowres et al. 2014, Sandhu et al. 2016, Zaprutko et al. 2020, Zink et al. 2020), and four economic evaluations (Tassie et al. 2016, Tarride et al. 2017, Jacobs et al. 2018, Lowres et al. 2014). For research question 3, we included one RCT (Reed et al. 2019) and one observational study (Hendrikx et al. 2014) on detecting intermittent AF after inconclusive clinical examination.

The findings of studies are presented in narrative form: pooling of outcome data was considered inappropriate due to heterogeneity of study interventions and designs. Throughout, percentages are reported as a proportion of the total number of participants in a study arm for RCTs or the total participants for observational studies. For diagnostic accuracy, positive and negative predictive values and overall accuracy were calculated if the required data was reported.

5.1 Diagnostic accuracy of handheld lead-I ECG

Two systematic reviews compared the diagnostic accuracy of handheld lead-I ECG devices to the reference standard of 12-lead ECG interpreted by a trained healthcare professional. Details of the systematic reviews and their findings are reported below and summarised in Table 1 and 2.

Duarte et al. (2019) completed their systematic review as part of the NICE Diagnostic Assessment Programme and aimed to examine diagnostic accuracy for people with signs or symptoms of AF. They were not able to identify studies in this population so according to their pre-specified approach, they included studies of diagnostic accuracy in asymptomatic populations across all ages and populations. All studies used 12-lead ECG interpreted by a professional as their reference standard and results for healthcare professional and algorithm interpretation of lead-I ECG are reported separately. Information on false and true positives and negatives were reported for pooled analyses allowing calculation of positive and negative predictive value and overall accuracy.

Wong et al. (2020) concluded their search more recently and were able to include additional studies to the NICE review. The review included studies comparing handheld lead-I ECG interpreted by algorithm to 12-lead ECG interpreted by a trained health professional. The

definition of handheld lead-I ECG used in the study included wrist and chest strap devices, as well as those with patches. This conflicts with the definition of handheld lead-I ECG used in this appraisal and only outcomes that related to the products listed above were included. As a result, the outcomes from this review relate to a subgroup analysis of community and hospital settings with the Kardia Mobile device only. The review notes that one study on accuracy used a now redundant algorithm and may reduce the reported accuracy in the hospital setting.

The included systematic reviews have a wider population profile than the specific criteria for the research questions addressed in the appraisal. This may cause some issues regarding generalisability of evidence. However, due to the nature of detecting AF using traces from an ECG recording, the accuracy is not anticipated to vary widely across differing levels of incidence. Of the two reviews, this issue is most present in Duarte et al. (2019) and the inclusion of Wong et al. (2020) provides information on subgroups that may relate more closely to diagnostic accuracy of the devices for populations in this appraisal.

5.1.1 Sensitivity and specificity

Across four studies, Duarte et al. (2019) gave a pooled sensitivity and specificity of 93.9% (95%CI 86.2% to 97.4%) and 96.5% (95%CI 90.4% to 98.8%) when trained health professionals interpreted lead-I ECG recordings. When an algorithm was used, sensitivity and specificity were 96.2% (95%CI 86.0% to 99.0%) and 95.2% (95%CI 92.9% to 96.8%).

When reported according to setting, Wong et al. (2020) found differing levels of sensitivity and specificity across community and hospital settings for lead-I interpreted by algorithm. In the community, sensitivity was 82% (95%CI 65% to 91%) compared to 91% (95%CI 66% to 98%) in hospital, and specificity was 99% (95%CI 99% to 100%) and 97% (95%CI 94% to 98%) in community and hospital respectively.

5.1.2 Positive and negative predictive value

From data reported by Duarte et al. (2019), the positive predictive value of handheld lead-I ECG devices was calculated to be 86.6% when interpreted by a trained healthcare professional and 82.8% when interpreted by algorithm. The negative predictive value of handheld lead-I ECG devices was calculated to be 98.2% when interpreted by a trained healthcare professional and 97.2% when interpreted by algorithm

5.1.3 Overall accuracy

From data reported by Duarte et al. (2019), the overall accuracy of handheld lead-I ECG devices was calculated to be 95.7% when interpreted by a trained healthcare professional and 94.6% when interpreted by algorithm

5.1.4 Comparative diagnostic accuracy

Duarte et al. (2019) included one study that compared Kardia Mobile with MyDiagnostick. No difference in agreement was found between devices suggesting their accuracy is comparable.

5.1.5 Receiver operating characteristic (ROC)

The impact of altering discrimination thresholds on diagnostic ability were not in the scope of the systematic reviews and no data on these is included.

Table 1. Systematic review: Duarte et al. (2019)

Included studies	Inclusion criteria	Quality	Observation/notes
Number of studies: 13 publications reporting on 9 studies* **Total number of patients:** 1422 **Publication year:** 2020 **Mean participant age:** Not reported	**Review period:** up to March 2018 **Review purpose:** To assess the diagnostic test accuracy of single point in time lead-I ECG devices using algorithms or healthcare professional interpretation **Included study designs:** Diagnostic accuracy studies with lead-I ECG devices compared to 12-lead ECG interpreted by a trained healthcare professional as the reference test **Included outcome measures:** sensitivity, specificity, true positive, true negatives, false positives, false negatives, comparative accuracy, test failure	**Tool:** Quality Assessment of Diagnostic Accuracy Studies—2 (QUADAS-2) **Risk of Bias:** 9 studies had unclear risk of bias for at least one domain. No studies were rated as high risk of bias for any domain **Applicability:** 9 studies had high level of concern for applicability for symptomatic populations	The review was completed as part of the NICE Diagnostics Assessment Programme. Its initial intent was to examine the accuracy of lead-I ECG for symptomatic populations but no studies in this population were identified and asymptomatic populations were included. The review includes a wide range of populations, including older adults without symptoms, people in specialist care, and young people. These populations diverge from those included in later parts of the appraisal, which may have an impact on generalisability but due to the nature of determining arrhythmia from ECG recordings this risk may be limited,

Results

Lead-I ECG interpreted by trained healthcare professional

Number of studies	Technology	Diagnostic accuracy
4^	Kardia Mobile (n=3) Zenicor-ECG (n=1)	Sensitivity: 93.9% (95%CI 86.2% to 97.4%) Specificity: 96.5% (95%CI 90.4% to 98.8%) Positive predictive value: 86.6% Negative predictive value: 98.2% Overall accuracy: 95.7%

Lead-I ECG interpreted by algorithm

Number of studies	Technology	Diagnostic accuracy
4^	Kardia Mobile (n=3) Zenicor-ECG (n=1)	Sensitivity: 96.2% (95%CI 86.0% to 99.0%) Specificity: 95.2% (95%CI 92.9% to 96.8%) Positive predictive value: 82.8% Negative predictive value: 97.2% Overall accuracy: 94.6%

Comparative diagnostic accuracy of lead-I ECG devices		
Number of studies	**Technology**	**Results**
1	Kardia Mobile MyDiagnostick	No difference was reported; there was no difference in agreement between the devices

* Only studies relating to diagnostic accuracy are included here. The review also include studies on clinical impact but includes studies that are not relevant here.
^ One study used both Kardia Mobile and MyDiagnostick and interpretation was completed by two EPs. In the review, results are reported multiple times according to device and EP to avoid double counting. The results reported here relate to Kardia Mobile and EP1 and comparison of all analysis suggests there was minimal impact on findings

CI = confidence interval, ECG = electrocardiogram, EP = electrophysiologist lead-I = single lead, NR = not reported

Table 2. Systematic review: Wong et al. (2020)

Included studies	Inclusion criteria	Quality	Observation/notes
Number of studies: 8 publications reporting on 8 studies* **Total number of patients:** Not reported **Publication year:** 2020 **Mean participant age:** Not reported	**Review period:** up to March 2019 **Review purpose:** To assess the diagnostic test accuracy of single point in time lead-I ECG devices using algorithms **Included study designs:** Diagnostic accuracy studies with lead-I ECG devices interpreted by algorithm compared to 12-lead ECG interpreted by a trained healthcare professional as the reference test **Included outcome measures:** sensitivity, specificity	**Tool:** QUality Assessment of Diagnostic Accuracy Studies—2 (QUADAS-2) **Risk of Bias:** 1 study was at high risk of bias, 4 studies at low risk, and 3 studies had unclear risk of bias due to incomplete reporting **Applicability:** The review did not provide details of applicability	The reporting of the subgroup using lead-I ECG in the community may have higher generalisability to screening in primary care and community settings whereas the reporting for hospital may be more reflective of populations with intermittent AF. As only results from Alivecor/Kardia Mobile were reported separately, the results do not provide information on other devices A now redundant algorithm was used for interpretation of Kardia Mobile in one study and this study was an outlier and had lower sensitivity than seen in other studies.

Results

Lead-I ECG interpreted by algorithm in the community

Number of studies	Technology	Diagnostic accuracy
4	Kardia Mobile (n=4)	Sensitivity: 82% (95%CI 65% to 91%) Specificity: 99% (95%CI 0.99% to 100%)

Lead-ECG interpreted by algorithm in hospital

Number of studies	Technology	Diagnostic accuracy
4	Kardia Mobile (n=4)	Sensitivity: 91% (95%CI 66% to 98%) Specificity: 97% (95%CI 94% to 98%)

* Only studies reporting on Alivecor/Kardia Mobile are included here. The review included results that pooled handheld lead-I ECG with other wrist or chest strap-based devices that are not relevant here.

CI = confidence interval, ECG = electrocardiogram, lead-I = single lead, QUADAS-2 = quality assessment of diagnostic accuracy studies - 2

5.2 Detection of unknown atrial fibrillation in older adults in primary care and the community

The review identified three discrete approaches to screening for unknown atrial fibrillation in older adults in primary care and the community. In primary care, screening can be completed during routine appointments or can be completed in conjunction with influenza vaccination clinics. In addition, community pharmacists can complete opportunistic screening in the course of their work. The results for each of these three approaches are reported separately below.

Across the approaches, only two RCTs were identified (Kaasenbrood et al. 2020, Uittenbogaart et al. 2020). Other studies were observational and did not include a control group. No evidence was found on the effectiveness of asking GPs to screen all eligible patients with handheld lead-I ECG devices compared to asking all GPs to screen eligible patients with manual pulse palpitation. Due to this, it appears that a key comparator is missing from available evidence.

5.2.1 Screening during routine contacts in primary care

We identified two RCTs (Kaasenbrood et al. 2020, Uittenbogaart et al. 2020) and one UK-based observational study (Grubb et al. 2019) that examined the effectiveness of screening for unknown AF in older adults during usual care in primary care. The details of these studies are shown in Table 3 and summarised below.

Kaasenbrood et al. (2020) conducted a pragmatic multi-centre cluster RCT across 31 general practices in the Netherlands. Practices were randomised to be in the intervention cluster, where they were provided between two and eight MyDiagnostick ECG handheld lead-I ECG devices and asked to screen all eligible participants, or the control cluster, where they were informed of the study and its aims. The authors state that the diagnosis of AF was not emphasised in information to control practices, and so details of the exact nature of the control group ae unclear. In the intervention cluster, eligible participants were asked to highlight possible symptoms of AF and then had a lead-I ECG reading taken. If the MyDiagnostick ECG device signalled possible AF then a GP reviewed the trace and obtained a 12-lead ECG. The lead-I ECG or 12-lead ECG reading was then sent to a study cardiologist. If the lead-I ECG did not signal possible AF then no action was taken. The calculated sample size was for 5000 participants from each arm and recruitment took place for one year in each practice.

In total, 17107 participants were considered eligible for the trial (intervention, n=8581; control, n=8526) but only 919 (10.7%) participants in the intervention cluster were screened using a lead-I ECG device. For the eligible population, the mean age for participants in the intervention cluster was 74.3 years (SD, 7.3) and 74.5 years (SD, 7.3) in the control cluster. The majority of participants were female (intervention, 54.5%; control, 54.1%), and had a range of pre-existing comorbidities, most notably high rates of hypertension (intervention, 50.9%; control, 50.4%).

The study was limited by the low rates of use of lead-I ECG screening and the authors present several serious limitations that may limit the validity of this study and its findings. All participants were required to complete consent forms and research questionnaires prior to screening and although the trial attempted to be pragmatic, it is possible that this reduced the screening rate. Of greater concern, the authors suggest that some GPs used the lead-I ECGs without recording consent and therefore these numbers were included in routine detection.

Another RCT was conducted in 96 general practices in the Netherlands (Uittenbogaart et al. 2020). Practices were randomised to an intention to screen arm or a usual care arm. Intention to screen practices were directed to screen all patients aged 65 or over, with no known history of atrial fibrillation with three approaches, including a MyDiagnostick handheld lead-I ECG device, in a randomised order. Staff were trained in the use of these approaches and an automatic reminder to screen was embedded in patient records. If AF was indicated by any of the screening

approaches, a 12-lead ECG was conducted or requested. In the usual care practices, staff were aware of the aims of the study but did not receive any equipment or training. They were expected to follow the Dutch College of Practitioners guidelines for AF that recommend assessing heart rhythm for people presenting with relevant symptoms (e.g. shortness of breath, dizziness, chest pain). The guidelines do not recommend systematic screening for people without symptoms. Two hundred patients were selected at random from each study practice and their electronic records were reviewed to establish adherence to study protocols and identification of previously unknown AF.

The study reviewed records for 19189 of the planned 19200 participants as one small practice had fewer than anticipated eligible patients. After excluding those that were not eligible on review and attrition, there were 8874 participants in the intervention arm at follow up, and 9102 in the control arm. At baseline, the mean age of participants in the intervention and control group was 75.0 years (SD 6.9) and 75.2 years (SD 6.8) respectively. The majority were female (intervention, 54.3%; control, 55.0%) and pre-existing comorbidities were common with hypertension most prevalent (intervention, 48.7%; control, 49.6%).

Another UK-based observational study conducted an evaluation of screening during routine contacts in primary care (Grubb et al. 2019) and placed Kardia Mobile handheld lead-I ECG devices in 23 general practices across Scotland. Each practice had a designated member of staff responsible for screening. Patients aged 65 and older, with no history of AF, who were attending an annual chronic disease assessment were eligible. Participants also needed to have one or more risk factors for stroke in addition to age. Handheld lead-I ECG recordings were taken and transmitted to a cardiologist who made a provisional diagnosis of AF. These cases were referred for 12-lead ECG according to local systems. The study completed screening in 1805 (85.0%) of 2124 eligible patients over 13 months of recruitment. The mean age of the sample was 74.9 years (SD, 71) and most were men (1102, 61.1%).

Table 3. Study characteristics: Screening during routine contacts in primary care

Reference	Study design	Intervention and Comparator	Screening Procedure	Relevant outcomes	Additional notes/Comments on applicability
Grubb et al. (2019)	Prospective observational Multicentre (n = 26, Scotland, United Kingdom) Participants (n = 1805) Enrolment period: August 2014 to October 2015 Follow-up: Not reported	Intervention: Screening with Kardia Mobile handheld lead-I ECG device	GPs asked to recruit all eligible people during regular appointments Lead-I ECG device recordings were transmitted to a cardiologist for confirmation of diagnosis Newly diagnosed cases managed according to usual care processes	• Number of participants with unknown AF • Number of participants initiated on anticoagulants due to screening • Quality of lead-I ECG recordings	Three additional practices were recruited partway through the study due to low uptake of screening The eligible population required one or more risk factors for stroke apart from age. This may represent a higher risk group for AF leading to higher rates of detection.
Kaasenbrood et al. (2020)	Randomised controlled trial Multicentre (n = 31, Netherlands) Participants (n = 604) Enrolment period: October 2014 to March 2016 Follow-up: Not reported	Intervention: Screening with MyDiagnostick handheld lead-I ECG device Comparator: General practices were briefly informed of the study and not provided any further intervention	GPs asked to recruit all eligible people during regular appointments If MyDiagnostick device was positive, then recordings were sent to a cardiologist for review Management was left to GP discretion and usual care processes were followed in the control cluster	• Number of participants with unknown AF • Number of participants initiated on anticoagulants due to screening	The authors state that control practices were informed of the aims of the study without emphasising the diagnosis of AF. However, there is limited information on the details provided.
Uittenbogaart et al. (2020)	Randomised controlled trial Multicentre (n = 96, Netherlands) Participants (n = 17976) Enrolment period: September 2015 to August 2018 Follow-up: Up to 12 months	Intervention: Screening with MyDiagnostick handheld lead-I ECG device Comparator: Usual care as recommended by Dutch College of General Practitioner atrial fibrillation guidelines	Practice staff were trained in the use of lead-I ECG equipment and instructed to recruit all eligible people when attending the practice. GPs had reminders embedded in electronic medical records that prompted screening for eligible patients.	• Number of participants with unknown AF	The study reports both an intention to screen and per protocol analysis. The primary outcome data used in this report is the intention to screen analysis but per protocol analyses are also described in text.

AF= atrial fibrillation, ECG=electrocardiogram; hr= hour, lead-I= single lead

5.2.1.1 Atrial fibrillation detection

Kaasenbrood et al. (2020) reported that detection rates across the intervention and control clusters were comparable (123, 1.43% vs. 117, 1.37%, OR, 1.05, 95%CI, 0.81 to 1.35, p=0.73). In the intervention group, 28 of the cases of unknown AF were identified from the pool of 919 participants who received lead-I ECG screening and 95 were identified through usual methods of care. The lead-I ECG gave a false positive result in 47 of 919 participants (5.1%). No further action was taken after a negative result so false negatives could not be reported.

Uittenbogaart et al. (2020) reported on newly identified cases of atrial fibrillation for a group who were eligible to each be screened using multiple approaches (including lead-I ECG) compared to those who were received usual care. In an intention to screen analysis, the proportion of cases of new atrial fibrillation detected was comparable between arms (144, 1.62% vs. 139, 1.52%, OR, 1.06, 95%CI, 0.84 to 1.35, p = 0.60). A per protocol analysis for a subgroup of the population who received screening as was indicated by the study protocol is also presented. From this analysis, it is possible to ascertain that only 48 of 4085 (1.18%) new cases of AF were identified by lead-I ECG.

In the observational study, 92 (5.1%) of the 1805 participants were diagnosed with unknown AF (Grubb et al. 2019). Ectopic beats that were not classified as AF after review were found to be present in 175 patients (9.7%).

5.2.1.2 Detection of other cardiac arrhythmias

Detection of cardiac arrhythmias other than atrial fibrillation were not reported in any study.

5.2.1.3 Treatment planning and change in treatment management

The Kaasenbrood et al. (2020) cluster RCT reported that there was initiation of anticoagulants for 110 (1.28%) participants in the intervention arm and 106 (1.24%) in the control arm. In the intervention arm, 23 of those with initiation of anticoagulants were detected through lead-I ECG and 87 through routine methods.

In the UK-based observational study, of the 92 participants to have confirmed AF, 74 (4.10%) were prescribed anticoagulants (Grubb et al. 2019). Ten participants were not recommended anticoagulation due to bleeding risk and six declined medication.

5.2.1.4 Health service utilisation

Outcomes related to health service utilisation, such as number of contacts with services or hospitalisations, were not reported in any of the studies.

5.2.1.5 Serious outcomes

Kaasenbrood et al. (2020) planned to present the number of cardiovascular events as secondary outcomes but do not report these outcomes due to the lack of difference between intervention and control arms on detection of AF. The other studies did not report these outcomes either. This means outcome data was available for all-cause mortality, stroke, heart failure, thromboembolisms, or other serious events, and adverse events after treatment initiation were not reported.

5.2.1.6 Health-related quality of life

Generic or condition-specific health-related quality of life measures were not reported in the included studies.

5.2.1.7 Patient satisfaction

Patient satisfaction was not reported in the included studies.

5.2.1.8 Usability and barriers to uptake

Kaasenbrood et al. (2020) do not provide quantitative information on usability or professional satisfaction but state that low rates of screening uptake were likely due to several factors including lack of incentive to screen, inertia regarding screening, time constraints, need for written consent from participants.

Table 4. Effectiveness outcomes for screening during routine contacts in primary care

Outcome	Study	Intervention	Comparator	Relative effect
Detection of cardiac arrhythmia				
Number of cases of unknown AF detected	Grubb et al. (2019)	92/1805 5.1%	NA	NA
	Kaasenbrood et al. (2020)	123/8581 1.43%	117/8526 1.37%	OR: 1.05 (95%CI: 0.81 to 1.35) p = 0.73
	Uittenbogaart et al. (2020)	144/8874 1.62%	139/9102 1.52%	OR: 1.06 (95%CI: 0.84 to 1.35) p = 0.60
Number of cases of other symptomatic rhythms detected	NR			
Treatment planning and change in treatment management				
Number of participants with initiation of anticoagulants	Grubb et al. (2019)	74/1805 4.10%	NA	NA
	Kaasenbrood et al. (2020)	110/8581 1.28%	106/8526 1.24%	NR
Health service utilisation				
No studies reported on health-service utilisation				
Serious outcomes				
Number of cardiovascular events	Kaasenbrood et al. (2020)	Study reported that reporting of cardiovascular events was planned but was not done due to lack of difference between intervention and control arms on detection of unknown AF		
Health-related quality of life				
No studies reported on health-related quality of life				
Patient satisfaction				
No studies reported on patient satisfaction				
Usability and barriers to uptake				
Reasons for low uptake of screening	Kaasenbrood et al. (2020)	Study reported that low uptake of screening was likely due to: lack of incentive, inertia regarding screening, time constraints, need for written consent from participants.		

CI= Confidence interval, NA=Not applicable, NR= not reported, OR= Odds ratio

5.2.2 Screening during influenza vaccination in primary care

Two observational studies that examined the effectiveness of screening for unknown AF in older adults during influenza vaccinations programmes in primary care were identified (Savickas et al. 2020, Orchard et al. 2016). The details of these studies are shown in Table 5 and summarised below.

Orchard et al. (2016) conducted an evaluation of screening at influenza vaccination clinics over a single influenza season in general practices in Sydney, Australia. Practice nurses that were delivering vaccinations in the study practices received the Kardia Mobile handheld lead-I ECG devices and all people attending the clinics aged 65 years and over were eligible. Potential participants were notified of the screening in a letter that was sent to them alongside an invitation for vaccination and then on attending a clinic, they consented to take part if they wished. A lead-I ECG reading was then taken and an algorithm indicated whether AF was suspected. If AF was suspected then a 12-lead ECG was obtained and management was then left to a participants usual GP. As part of the study, all lead-I ECGs were over read by a cardiologist. Of the eligible 2476 people attending clinic, 972 (39.3%) completed screening. The study team did not have access to data on baseline characteristics on all participants but those with newly identified AF are reported as having a mean age of 80 years (SD, 3) and three of seven were male (42.9%). The mean CHA2DS2-VASc score was 4 (SD, 0.8). This measure is used to assess risk of stroke and a mean score of 4 would indicate a high risk.

Savickas et al. (2020) conducted an evaluation of screening at influenza vaccination clinics over two vaccination seasons across four general practices in the NHS Canterbury and Coastal Clinical Commissioning Group area. Clinical pharmacists were provided with a Kardia Mobile handheld lead-I ECG and those aged 65 years or over attending the clinic were eligible. The study assumed that those with known AF would self-exclude from screening and results are reported for those with newly identified AF. Participants first had a manual pulse palpitation and this was followed by a lead-I ECG recording. Multiple ECGs were recorded if the quality was poor initially. A provisional diagnosis was provided by the device algorithm and was sent to a cardiologist for over reading. Management then followed usual practice processes for all participants. In total, 604 participants were screened and they had a mean age of 73 years (range, 69 to 78), and were mostly women (396, 57.3%). The total population eligible for screening was not reported.

Table 5. Study characteristics: Screening during influenza vaccination in primary care

Reference	Study design	Intervention and Comparator	Screening Procedure	Relevant outcomes	Additional notes/Comments on applicability
Orchard et al. (2016)	Prospective observational Multicentre (n = 5, Australia) Participants (n = 973) Enrolment period: April to June 2015 Follow-up: Not reported	Intervention: Screening with Kardia Mobile handheld lead-I ECG device	All people aged 65 and over and attending an influenza vaccination clinic were eligible and were notified of the study in a letter that accompanied invitation to the clinic. Participants provided verbal consent at the clinic if they wished to take part. The lead-ECG reading was interpreted by algorithm and all readings were also reviewed by two research cardiologists. Further management was at the discretion of participants GP.	• Number of cases of unknown AF • Number of participants initiated on anticoagulants due to screening	One of the eight identified cases came from a participant where the algorithm suggested they had normal rhythm. This case was identified by cardiologist over reading all ECGs, which would be unlikely in usual practice.
Savickas et al. (2020)	Prospective observational Multicentre (n = 4, United Kingdom) Participants (n = 604) Enrolment period: October 2017 to February 2018 and October to December 2018 Follow-up: Not reported	Intervention: Screening with Kardia Mobile handheld lead-I ECG device	Consecutive sampling was used to approach all eligible participants for screening The lead-I ECG reading was interpreted by algorithm, and a pharmacist who was not blinded to algorithm interpretation. Pharmacists also completed pulse palpitation. The cardiologist was responsible for diagnosis and provided recommendation on intervention. The study team then followed up with participants to ensure appropriate treatment was offered.	• Number of cases of unknown AF • Number of participants initiated on anticoagulants due to screening • Patient satisfaction	All eligible participants were approached for screening but the number of participants who declined screening is not reported. The screening procedure may have divergences from normal care and lack of blinding may have influenced findings.

AF= atrial fibrillation, ECG=electrocardiogram; hr= hour, lead-I= single lead

5.2.2.1 Atrial fibrillation detection

Orchard et al. (2016) found that 44 of 972 screened participants were flagged as possible AF by the lead-I ECG algorithm. Of these, no history of AF was recorded in 15 participants, and seven participants were confirmed as having newly identified AF. In one further case, the algorithm did not suggest AF was present but on review by a cardiologist, the recording was determined to show AF. In total therefore, eight (0.84%) newly identified cases of AF were found by screening. Savickas et al. (2020) report that 26 of 604 participants were reported as having possible AF. Of these, 18 had known AF and only three cases were diagnosed as new AF after 12-lead ECG. In addition, 75 lead-I ECG recordings were unclassified or unreadable and one further case of new AF was identified with 12-lead ECG from this group. A total of four (0.66%) unknown cases of AF were therefore detected from the screened population.

5.2.2.2 Detection of other cardiac arrhythmias

Detection of cardiac arrhythmias other than AF was not reported in either study.

5.2.2.3 Treatment planning and change in treatment management

Orchard et al. (2016) found that of the eight participants with newly identified AF, three were initiated on anticoagulants. Savickas et al. (2020) reported that of the four participants with newly identified AF, three (0.50%) were initiated on anticoagulants after screening.

5.2.2.4 Health service utilisation

Outcomes related to health service utilisation, such as number of contacts with services or hospitalisations, were not reported in included studies.

5.2.2.5 Serious outcomes

None of the included studies reported outcome data for all-cause mortality, stroke, heart failure, thromboembolisms, or other serious events, and did not report adverse events after treatment initiation. The short term-follow-up times used in the studies would be unlikely to provide useful information on these outcomes.

5.2.2.6 Health-related quality of life

Generic or condition-specific health-related quality of life measures were not reported in the included studies.

5.2.2.7 Patient satisfaction

In Savickas et al. (2020), participants were asked to complete a feedback questionnaire on their experiences and satisfaction. All respondents were reported to have rated the screening experience as ‘very good’ or ‘good’ and 99% indicated that they would be willing to have annual repeat screening. In addition, 96% of respondents were reported to think that routine screening was ‘very important’ or ‘important’. In open-ended questions, some respondents were said to have highlighted that the service could improve access to healthcare and they were pleased with the information that was provided with it.

5.2.2.8 Usability and issues related to uptake

No studies reported information on the usability of the device or issues related to uptake. Orchard et al. (2016) report qualitative findings, which are presented in Section 8.

Table 6. Effectiveness outcomes for screening during influenza vaccination in primary care

Outcome	Study	Intervention	Comparator	Relative effect
Detection of cardiac arrhythmia				
Number of cases of unknown AF detected	Orchard et al. (2016)	8/942 0.84%	NA	NA
	Savickas et al. (2020)	4/604 0.66%	NA	NA
Number of cases of other cardiac arrhythmias detected	NR			
Treatment planning and change in treatment management				
Number of participants with initiation of anticoagulants	Orchard et al. (2016)	3/942 0.32%	NA	NA
	Savickas et al. (2020)	3/604 0.50%	NA	NA
Health service utilisation				
No studies reported on health-service utilisation				
Serious outcomes				
No studies reported on serious outcomes				
Health-related quality of life				
No studies reported on health-related quality of life				
Patient satisfaction				
Satisfaction of screening experience, willingness for repeat screening, and perceptions of importance	Savickas et al. (2020)	All respondents were reported to have rated the screening experience as 'very good' or 'good'; 99% indicated that they would be willing to have annual repeat screening; 96% of respondents were reported to think that routine screening was 'very important' or 'important'.		
Usability and issues related to uptake				
No studies reported quantitative information on usability or issues related to uptake. Qualitative findings from Orchard et al. (2016) are reported later.				

AF= Atrial fibrillation, NA=Not applicable

5.2.3 Screening in community-based pharmacies

Four observational studies that examined the effectiveness of screening for unknown AF in older adults in community pharmacies were identified (Lowres et al. 2014, Sandhu et al. 2016, Zaprutko et al. 2020, Zink et al. 2020). The details of these studies are shown in Table 7 and summarised below.

Sandhu et al. (2016) conducted an evaluation of an AF screening in 30 pharmacies across Alberta and Ontario, Canada (Program for the Identification of Actionable Atrial Fibrillation: In the Pharmacy Setting; PIAAF). Screening was advertised in the pharmacy, in local newspapers, and at information sessions in conjunction with senior's activities, and those entering the pharmacy who were aged 65 or older and did not self-report a history of AF or use of anticoagulant medication were eligible to be approached. A recording was taken using the HeartCheck lead-I ECG device and downloaded to CardioComm software. It was then read by a technician and two study cardiologists. A 12-lead ECG and family practitioner follow-up was recommended for people with suspected AF. Across the pharmacies, 1145 participants were recruited over a seven month time period. Due to the opportunistic nature of the study, the total population eligible for screening could not be captured. Characteristics for the sample as a whole were not reported.

Lowres et al. (2014) conducted an evaluation of an AF screening programme in 10 community pharmacies across areas of Sydney, Australia with differing demographic characteristics. All people aged 65 years or older were eligible to take part and an opportunistic screening approach was used to recruit 1000 participants. The Kardia Mobile device was used to take a recording; this was interpreted by the pharmacists and then sent to a cardiologist for confirmation. A trained pharmacist also completed pulse palpitation and recorded their interpretation of rhythm. If AF was suspected then the participant's GP was contacted and was asked to confirm any history of known AF. A total of 1000 participants completed screening but due to the nature of the screening the total eligible population was unknown. Across the whole sample, the mean age of the sample was 76 years (SD, 7), most were women (n=564, 56%), and the mean CHA2DS2-VASc score was 1.5 (SD, 1). Results for those with no history of AF are reported as a subgroup with 891 participants.

Zaprutko et al. (2020) conducted a prospective observational evaluation of an AF screening programme in 10 community pharmacies across urban and rural areas of Poland. Each pharmacy had a Kardia Mobile device with dedicated computer application available and all those attending the pharmacy who looked to be 65 years or older were invited to take part in the study. Recordings were taken if there was no known history of AF and the application provided a diagnosis, which was then sent to a cardiologist for confirmation. Follow-up by a clinician was used to further determine whether AF had been previously identified. Across the year of the study, a total of 525 ECGs were performed. The total eligible population was not reported but 1064 people were asked to take part. A number of these were under 65 years old and not eligible and 290 did not wish to take part. The mean age was 73.72 years (SD, 6.49), most were women (n=358, 68.19%) and the vast majority were at high risk of stroke with a CHA2DS2-VASc of two or over (n=503. 95.81%).

Zink et al. (2020) conducted a prospective observational evaluation based in community pharmacies in Aachen, Germany. Ninety pharmacies were provided with MyDiagnostick handheld lead-I ECG devices and were asked to screen all customers aged 65 or older. Cases of potential AF detected by screening were validated in a four-level recorded ECG analysis. A follow up was conducted by phone-call, paper questionnaire, or research visit and details on hospitalisation and mortality were recorded. During a four week enrolment period, 7295 people attending pharmacy for screened for eligibility and 7107 participants were recruited and had complete data. The mean age was 74 years (SD 5.9), most were women (58%), and the group had significant comorbidities with high risk of stroke (CHA2D2-VASc, mean 3.3).

Table 7. Study characteristics: Screening in community-based pharmacies

Reference	Study design	Intervention and Comparator	Screening Procedure	Relevant outcomes	Additional notes/Comments on applicability
Lowres et al. (2014)	Prospective observational Multicentre (n = 10, Sydney, Australia) Participants (n = 604) Enrolment period: June 2012 to January 2013 Follow-up: Not reported	Intervention: Screening with Kardia Mobile handheld lead-I ECG device	Screening was opportunistic with pharmacists approaching those who looked over 65 and flyers displayed in the pharmacy offering the screening. Participants were screened with the handheld device and the reading was read and interpreted by the pharmacist and forwarded to a cardiologist. Cases with confirmed AF were referred to their GP for usual review and management	• Number of participants with unknown AF • Number of participants initiated on anticoagulants due to screening • Number of GP appointments after detection of unknown AF	The algorithm for the lead-I ECG device was not available at the time of the study meaning a cardiologist reviewed all cases
Sandhu et al. (2016)	Prospective observational Multicentre (n = 30, Alberta and Ontario, Canada) Participants (n = 604) Enrolment period: October 2014 to April 2015 Follow-up: 3 months	Intervention: Screening with HeartCheck handheld lead-I ECG device	An awareness campaign was initiated in recruitment areas and those aged over 65 were eligible for screening while visiting a study pharmacy. A handheld lead-I ECG was taken along with an automated blood pressure reading and the ECG readings were read by a trained technician with over reading from two study cardiologists. Participants with suspected AF were recommended to receive a 12-lead ECG and results were sent to the participant and their clinicians. Those who were positive were recommended to have family practitioner review within 6 weeks.	• Number of participants with unknown AF • Number of participants initiated on anticoagulants due to screening • Number of GP appointments after detection of unknown AF • Satisfaction with screening	The screening programme was accompanied by an awareness campaign with support from Heart and Stroke Canada, newspaper advertising and outreach. It is not clear the added effect of this approach and may not be generalisable to screening only programmes.

Reference	Study design	Intervention and Comparator	Screening Procedure	Relevant outcomes	Additional notes/Comments on applicability
Zaprutko et al. (2020)	Prospective observational Multicentre (n = 10, Poland) Participants (n = 604) Enrolment period: December 2017 to November 2018 Follow-up: Not reported	Intervention: Screening with Kardia Mobile handheld lead-I ECG device	Every person entering the pharmacy who looked 65 years or older were asked to join the study and people with a history of AF were excluded. ECG readings were taken with the Kardia Mobile device and transmitted to a cardiologist for interpretation. If AF was confirmed by a cardiologist then participants were asked to collect the readings from the pharmacist and contact their GP for review.	• Number of participants with unknown AF • Number of cases of other cardiac arrhythmias detected	Participants needing to collect results and arrange for GPs to review themselves may present a barrier to acting on diagnosis.
Zink et al. (2020)	Prospective observational Multicentre (n = 90, Germany) Participants (n = 7107) Enrolment period: January and February 2017 Follow-up: 12 months	Intervention: Screening with MyDiagnostick handheld lead-I ECG	All individuals aged 65 or over attending a study pharmacy were invited to receive screening. Limited details on the procedure are reported.	• Number of participants with unknown AF • Mortality at 12 month follow up • Hospitalisation for cardiovascular causes	The study includes an analysis of outcomes relative to those with no AF and those without previously detected AF.

AF= atrial fibrillation, ECG=electrocardiogram; hr= hour, lead-I= single lead

5.2.3.1 Atrial fibrillation detection

The PIAAF-Pharmacy study reported that new AF was suspected in 27 cases (2.4%; 95% CI 1.6 to 3.4) with another 2 having suspected AF which was not reported as newly diagnosed (Sandhu et al. 2016). Eighteen of these 29 cases underwent a 12-lead ECG within 72 hours and AF was confirmed in four cases, with the remaining cases having normal sinus rhythm. At a 3-month study follow-up, AF was confirmed by 12-lead ECG in five cases. It is unclear where the five cases identified at 3-months overlap with the four cases found at 72-hour follow up. Nor are the results according to unknown and previously known AF. The number and proportion of previously unknown cases is therefore unclear.

Lowres et al. (2014) report that when lead-I ECG traces were reviewed by a cardiologist, new AF was identified in 15 participants and AF was not previously known in 10 of these cases (1.1%). In the other five cases, AF was determined to have been previously known but recurrence of unstable rhythm had not yet been identified during routine care. The study reports that using manual pulse palpitation, pharmacists were able to identify 11 of 15 cases of unknown AF confirmed by a cardiologist. When interpreting lead-I ECG results themselves, pharmacists identified 9 out of 15 cases. At the time of the study the Kardia Mobile algorithm was not available but when retrospectively applied it was found to identify all cases of new AF. Detection of cases with no previous episode of AF was not reported separately for pulse palpitation, pharmacist interpretation of lead-I ECG, or the lead-I ECG algorithm and the number of false positive for AF were not reported.

In Zaprutko et al. (2020), the lead-I ECG algorithm detected a possible AF finding in 17 participants (3.5%). On review, a cardiologist confirmed AF in 11 cases (2.1%). Two recordings were reclassified as other symptomatic rhythms and three were judged as not interpretable due to artefacts and poor quality. In one further case, the cardiologist identified AF from the recording where the lead-I ECG algorithm indicated it could not provide diagnosis. After telephone follow-up by a clinician, it was established that five of these participants had previously diagnosed AF. This means that in total, seven (1.3%) previously unknown cases of AF were detected during screening. The authors do not report whether the case identified only by the cardiologist was previously known or unknown.

Zink et al. (2020) report that 256 (3.6%) cases of previously unidentified AF were discovered as a result of screening.

5.2.3.2 Detection of other cardiac arrhythmias

Zaprutko et al. (2020) identified three participants with possible cardiac arrhythmias other than AF. Each of these had rhythm with supraventricular complexes or temporary atrial stimulation.

5.2.3.3 Treatment planning and change in treatment management

The PIAAF-Pharmacy study reported that five participants were prescribed anticoagulant medication at six week follow-up and a further eight participants were prescribed anticoagulants at three month follow-up (Sandhu et al. 2016). In total, this means 13 of the 1145 participants (1.2%) were started on anticoagulants as a result of screening.

Lowres et al. (2014) reported that of the 10 cases with new AF and no previous history, six were prescribed oral anticoagulant medication. Two were judged to have intermittent AF and medication was not started, one chose not to receive follow-up outside of the study, and one did not receive medication for unknown reasons. In total, this means six of the 891 participants (0.7%) were started on anticoagulants as a result of screening. Those with a recurrence of AF were treated with oral anticoagulants in three cases.

5.2.3.4 Health service utilisation

The PIAAF-Pharmacy study reported that only seven of 29 cases with AF suspected from the lead-I ECG were seen by their family practitioners or in an AF clinic within six weeks of screening (Sandhu et al. 2016). One participant had two ED attendances due AF and no participants were hospitalised.

Lowres et al. (2014) reported that GP review was completed in 14 of 15 of the cases of AF which were previously unknown or had recurred. These results were not reported separately for those with unknown only and other outcomes on ED attendance and hospitalisation were not reported.

Zink et al. (2020) reported on hospitalisations for cardiovascular reasons. Raw data is not presented but for those with newly identified AF, the rate of hospitalisation was 0.246 per 1000 person days.

5.2.3.5 Serious outcomes

Zink et al. (2020) reported on all-cause mortality after one year follow up for their cohort. Raw data is not presented but they report a rate of 0.052 deaths per 1000 person days for participants with newly identified AF.

5.2.3.6 Health-related quality of life

Generic or condition-specific health-related quality of life measures were not reported in the included studies.

5.2.3.7 Patient satisfaction

In the PIAAF-Pharmacy study, participants that attended a 3-month follow-up AF clinic were asked about their satisfaction with screening (Sandhu et al. 2016). All reported they were very satisfied (18, 78.3%) or somewhat satisfied (5, 21.7%) with the screening session at the community pharmacy.

5.2.3.8 Usability or issues related to uptake

None of the included studies reported on how usable the lead-I ECG devices were during screening and none reported on issues related to uptake of screening.

Table 8. Effectiveness outcomes for screening in community-based pharmacies

Outcome	Study	Intervention	Comparator	Relative effect
Detection of cardiac arrhythmia				
Number of cases of unknown AF detected	Lowres et al. (2014)	10/891 1.12%	NA	NA
	Zaprutko et al. (2020)	7/520 1.35%	NA	NA
	Zink et al. (2020)	256/7107 3.6%	NA	NA
Number of cases of other cardiac arrhythmias detected	Zaprutko et al. (2020)	3/520 0.58%	NA	NA
Treatment planning and change in treatment management				
Number of participants with initiation of anticoagulants	Sandhu et al. (2016)	13/1145 1.14%	NA	NA
	Lowres et al. (2014)	6/891 0.67%	NA	NA
Health service utilisation				
Number of participants with GP contact within 6-weeks of new diagnosis	Sandhu et al. (2016)	7 (from 27 participants with suspected AF)^	NA	NA
Number of ED visits related to AF	Sandhu et al. (2016)	2 (from 27 participants with suspected AF)^	NA	NA
Number of hospitalisations	Sandhu et al. (2016)	0 (from 27 participants with suspected AF)^	NA	NA
Rate of hospitalisation for cardiovascular cause	Zink et al. (2020)	0.246 per 1000 person days	NA	NA
Serious outcomes				
All-cause mortality	Zink et al. (2020)	0.052 per 1000 person days	NA	NA
Health-related quality of life				
No studies reported on health-related quality of life				

Patient satisfaction		
Satisfaction with screening	Sandhu et al. (2016)	All respondents reported they were very satisfied (n=18, 78.3%) or somewhat satisfied (n=5, 21.7%) with the screening.
Usability and issues related to uptake		
No studies reported on usability or issues related to uptake		

AF= atrial fibrillation, NA=Not applicable, NR= not reported
^ the study does not report these outcomes separately for those with new AF only

5.3 Detection of intermittent atrial fibrillation after inconclusive clinical examination

Two studies were identified that examined detection of intermittent atrial fibrillation after inconclusive clinical examination (Hendrikx et al. 2014, Reed et al. 2019). The details of these studies are shown in Table 9 and summarised below

One open-label RCT on the detection of intermittent AF after inconclusive clinical examination was identified by our literature search (Reed et al. 2019). In this Investigations of Palpitations in the ED (IPED) trial, participants presenting with an episode of palpitations or pre-syncope but unclear diagnosis after assessment were recruited from emergency departments and acute medical units in 10 general hospitals across the UK. They were randomised to a control group where they received standard care with usual methods of diagnosis at the discretion of clinicians (e.g. Holter monitoring, subsequent ED or GP visit) or an intervention group where they received standard care with usual methods of diagnosis plus lead-I ECG. Both groups were then followed up at 90 days and hospital and GP records were reviewed to obtain data on outcomes. Participants were also contacted by telephone as an additional follow up. The study did not report the overall use of different diagnosis methods across the two groups.

In the IPED trial (Reed et al. 2019), the average age of participants was 39.6 years (SD, 13.8) and most were women (n=137, 56.6%). The most common frequency of symptoms was monthly (n=52, 21.6%) with the most recent episode reported as lasting more than an hour (n=82, 33.9%). Concomitant use of medication at baseline was low with 15 participants (6.2%) receiving beta-agonists, and 3 (1.2%) already prescribed antiarrhythmics. Risk of stroke or significant risk factors were not reported.

A further observational study was included (Hendrikx et al. 2014). In this prospective, cross-sectional study, participants with ambiguous palpitations or dizziness and no clear diagnosis after clinical examination were recruited from a hospital clinic in Northern Sweden. All participants received continuous 24-hour Holter monitoring with a Breamer DL700 device and they also received a Zenicor handheld lead-I ECG for intermittent monitoring. Participants were instructed to take two 30-second recordings with the lead-I ECG each day for 28 days, as well as recording if they felt symptoms. Holter recordings were automatically analysed by a PC-based system and both the lead-I ECG and Holter recordings were evaluated by two blinded investigators.

The average age of participants was 54.1 years (SD 16.4, range 21-79) and most were women (n=53, 55.8%). The median number of palpitations in the last year was 110 (IQR 27.3-176.3) with median duration of 10 minutes (IQR 3.5-30). At baseline, 19 (20%) of participants had a low risk of stroke (CHA2DS2-VASc = 0), 45 (47.4%) had a moderate risk of stroke (CHA2DS2-VASc = 1), and 31 (32.6%) had a high risk of stroke (CHA2DS2-VASc $\geqslant$ 2).

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Table 9. Study characteristics: Detection of intermittent AF after inconclusive clinical examination

Reference	Study design	Intervention and Comparator	Procedure	Relevant outcomes	Additional notes/Comments on applicability
Reed et al. (2019)	Randomised controlled trial Multicentre (n = 10, United Kingdom) Participants (n = 243) Enrolment period: Not reported Follow-up: 90 days	Intervention: Standard care with Kardia Mobile handheld lead-I ECG Comparator: Standard care	Participants recruited from emergency department or acute medical units after experiencing palpitations or pre-syncope but clinical examination not showing atrial fibrillation Standard methods of diagnosis used for both groups with intervention participants also receiving lead-ICG and were asked to record during symptomatic episodes	• Number of participants with symptomatic rhythm detected • Mean time to symptomatic rhythm detection • Number of participants with cardiac arrhythmia detected • Mean time to cardiac arrhythmia detection • Serious outcomes (i.e. all-cause mortality, major cardiac adverse events) • Change in treatment management • Health service utilisation (i.e. inpatient, outpatient, GP, ED, ECGs) • Patient satisfaction • Monitor adherence • Intervention and healthcare utilisation cost	Conducted with pragmatic methods in a UK setting Overall rates of use of methods of diagnosis used in standard care were not reported limiting inferences on generalisability
Hendrikx et al. (2014)	Prospective observational Single centre (n = 1, Västerbotten, Sweden) Participants (n = 95) Enrolment period: Not reported Follow-up: 28 days	Intervention: 28-day Zenicor-EKG handheld lead-I ECG Comparator: 24-hr Holter monitoring	Participants recruited from a hospital clinic after experiencing palpitations or dizziness but a clear diagnosis not available All participants received 24-hour Holter monitoring and all were asked to make twice daily recordings with lead-I ECG	• Number of cases of cardiac arrhythmia detected • Mean time to cardiac arrhythmia detection • Usability • Monitor adherence	Inclusion of 24-hour Holter monitoring for all participants helps demonstrate additional benefits of longer term lead-I ECG monitoring

AF= atrial fibrillation, ECG=electrocardiogram; hr= hour, lead-I= single lead

5.3.1 Symptomatic cardiac arrhythmia detection

In the IPED trial (Reed et al. 2019), a symptomatic cardiac arrhythmia was detected at 90 days in 11 (8.9%; 95%CI 3.9 to 13.9%) participants in the intervention group and one (0.9%; 95%CI 0.0 to 2.5%) participant in the standard care group (RR 10.3, 95%CI 1.3 to 78.5; p = 0.006). Of the identified symptomatic cardiac arrhythmias, there were eight (6.41%) cases of AF identified in the intervention group and none (0.0%) in the standard care group. There were also three cases of supraventricular tachycardia (SVT) and one case of atrial flutter in the intervention group with none in the control group, and one case of sinus bradycardia in the control group and none in the intervention group. The authors did not report which method of diagnosis detected cardiac arrhythmias or the significance of the comparison.

In the observational study, two (2.1%) cases of AF were identified by 24-hour Holter monitoring (Hendrikx et al. 2014). These two cases and a further seven cases were identified by intermittent monitoring with lead-I ECG for a total of 9 (9.5%) cases. Other cardiac arrhythmias were present with SVT identified in no participants by 24-hour Holter monitoring versus three (3.2%) participants with lead-I ECG, and atrioventricular-block II (AV-block II) identified in 1 (1.1%) participant with 24-hour Holter monitoring and one (1.1%) different participant with lead-I ECG. An analysis of identification of all cardiac arrhythmias was conducted and demonstrated that intermittent handheld lead-I ECG was superior to Holter monitoring (p=0.0094).

5.3.2 Mean time to cardiac arrhythmia detection

In the IPED trial (Reed et al. 2019), the mean time to symptomatic cardiac arrhythmia was 9.9 days (SD 15.6, range 1-55) and 48.0 days (single participant) in the standard care (p<0.0004). The mean time to identification of AF was not reported separately from other types of cardiac arrhythmia.

The observational study reported that one case of AF was identified by lead-I ECG on day one of follow-up, five cases were identified between days two and 14, and three cases were identified between days 15 and 28 (Hendrikx et al. 2014). The timing of identification of other cardiac arrhythmias were not reported.

5.3.3 Symptomatic rhythm detection

In the IPED trial (Reed et al. 2019), symptomatic rhythm was detected at 90 days in 69 (55.6%; 95%CI 46.9 to 64.4%) participants in the intervention group versus 11 (9.5%; 95%CI 4.2 to 14.8) participants in the standard care group (RR 5.9, 95%CI 3.3 to 10.5; p<0.0001). In the intervention arm, symptomatic rhythms were detected by AliveCor in 65 cases and other methods in 5 cases. In the control group, AliveCor was not used and 11 cases were identified by other methods. The overall use of other monitoring methods was not reported and nor was significance for method of diagnosis.

5.3.4 Mean time to symptomatic rhythm detection

In the IPED trial (Reed et al. 2019), the mean time to symptomatic rhythm detection was 9.5 days (SD 16.1, range 0-83) versus 42.9 days (SD 16.0, range 12-66) in the standard care (p<0.0001).

5.3.5 Serious outcomes

In the IPED trial (Reed et al. 2019), a serious outcome occurred in 11 (8.9%) participants in the intervention group and two (1.7%) participants in the standard care group. Of the serious outcomes, there were no all-cause deaths in the intervention group and one (0.9%) in the standard care group. The authors state that this death was thought unrelated to the participant's initial presentation to the emergency department for palpitations or pre-syncope. There were no major adverse cardiac events (myocardial infarction, life-threatening arrhythmia, insertion of a

pacemaker or internal cardiac defibrillator, or insertion of a pacing wire) in the intervention group and one (0.9%) in the standard care group. Anti-arrhythmia medical therapy was initiated for one (0.8%) participant in the intervention group and no participants in the intervention group. Significant structural heart disease was identified in no participants in the intervention group and one (0.9%) in the standard care group. The identification of cardiac arrhythmia was included under serious outcomes and is separately reported above.

The studies did not report outcome data for stroke, heart failure, or thromboembolisms, and did not report adverse events after treatment initiation. The short term-follow-up times used in the studies would be unlikely to provide useful information on these outcomes.

5.3.6 Treatment planning and change in treatment management

In the IPED trial (Reed et al. 2019), 12 (9.6%) participants in the intervention group were being treated or were planning to be treated for symptomatic cardiac arrhythmia versus six (5.2%) in the control group. This difference was not statistically significant (p=0.192). As reported in serious outcomes, one participant in the intervention group (0.8%) underwent anti-arrhythmia medical therapy.

5.3.7 Health service utilisation

In the IPED trial (Reed et al. 2019), there were more participants with one or more ED presentations after index visit in the intervention group (12; 9.7%; 95%CI 4.5 to 14.9%) than in the standard care group (3; 2.6%; 95%CI 0.0 to 5.5%; p=0.031). There were no significant differences in the number of inpatient days (p>0.999), the number of outpatient presentations (p=0.058), number of GP presentations (p=0.312), or ECGs performed (p=0.143) due to palpitations or pre-syncope across the intervention and standard care groups.

5.3.8 Health-related quality of life

Generic or condition-specific health-related quality of life measures were not reported in the included studies.

5.3.9 Patient satisfaction

The IPED trial included a questionnaire to assess patient satisfaction with using the AliveCor lead-I ECG (Reed et al. 2019). Eighty (64%) of participants strongly agreed or agreed that the device was easy to use, 67 (53.6%) participants strongly agreed or agreed that they had no problem recording a heart tracing, 59 (47.2%) participants strongly agreed or agreed that they had no problem sending a heart tracing to the study team, and 51 (40.8%) strongly agreed or agreed that the device would be useful in diagnosing the cause of symptoms.

5.3.10 Usability and adherence

In the observational study, the authors reported that all participants were able to complete recording of a heart tracing using the lead-I ECG (Hendrikx et al. 2014). The IPED trial did not report whether participants were observed being able to complete recording prior to monitoring.

The IPED trial included a questionnaire to assess monitor adherence while using the AliveCor lead-I ECG (Reed et al. 2019). Sixty-six (52.8%) participants strongly agreed or agreed that the device was always available when they had symptoms and needed to record a heart tracing, 54 (43.5%) participants strongly agreed or agreed that during the study period they were able to record a heart tracing when they had similar symptoms to their initial visit to the ED.

In the observational study, participants were asked to record two registrations per day for 28 days, as well as any time they felt symptoms (Hendrikx et al. 2014). The median number of registrations was 59 (IQR 48.5 to 65) suggesting high monitoring adherence.

Table 10. Effectiveness outcomes for detection of intermittent AF after inconclusive clinical examination

Outcome	Study	Intervention	Comparator	Relative effect
Detection of cardiac arrhythmia				
Number of cases of unknown AF detected	Hendrikx et al. (2014)	9/95 9.47%	2/95 2.11%	NR
	Reed et al. (2019)	8/124 6.41%	0/117 0%	NR
Number of cases of other cardiac arrhythmia detected	Hendrikx et al. (2014)	4/95 3.20%	1/95 1.06%	NR
	Reed et al. (2019)	11/124 8.87%	1/116 0.86%	RR: 10.3 (95%CI: 1.3 to 78.5) p = 0.006
Mean time to detection of cardiac arrhythmia	Reed et al. (2019)	9.9 days	48.0 days	NR (p = 0.0004)
Treatment planning and change in treatment management				
Number of participants with initiation of anticoagulants for all arrhythmias	Reed et al. (2019)	12/124 9.68%	6/117 5.13%	NR (p = 0.192)
Health service utilisation				
Number of GP contacts	Reed et al. (2019)	NR	NR	No significant difference between groups (p = 0.312). Number of events not reported.
Participants with ⩾1 ED visits related to arrhythmias	Reed et al. (2019)	12/124 9.68%	3/117 2.56%	p = 0.031
Number of outpatient contacts	Reed et al. (2019)	NR	NR	No significant difference between groups (p < 0.999). Number of events not reported.
Number of inpatient days	Reed et al. (2019)	NR	NR	No significant difference between groups (p = 0.058). Number of events not reported.
Number of ECGs performed	Reed et al. (2019)	NR	NR	No significant difference between groups (p = 0.143). Number of events not reported.
Serious outcomes				
All-cause mortality	Reed et al. (2019)	0/124 0%	1/116 0.86%	Significance level not reported

Major adverse cardiac events	Reed et al. (2019)	0/124 0%	1/116 0.86%	Significance level not reported
Health-related quality of life				
No studies reported on health-related quality of life				
Patient satisfaction				
Satisfaction with device and screening	Reed et al. (2019)	Eighty (64%) of participants strongly agreed or agreed that the device was easy to use, 67 (53.6%) participants strongly agreed or agreed that they had no problem recording a heart tracing, 59 (47.2%) participants strongly agreed or agreed that they had no problem sending a heart tracing to the study team, and 51 (40.8%) strongly agreed or agreed that the device would be useful in diagnosing the cause of symptoms.		
Usability and adherence				
Usability	Hendrikx et al. (2014)	All participants were observed completing a heart tracing with the lead-I ECG device		
Monitor adherence	Hendrikx et al. (2014)	Participants recorded a median of 59 (IQR 48.5 to 65) tracings. This was more than the instructed twice a day reading.		
	Reed et al. (2019)	Sixty-six (52.8%) participants strongly agreed or agreed that the device was always available when they had symptoms and needed to record a heart tracing, 54 (43.5%) participants strongly agreed or agreed that during the study period they were able to record a heart tracing when they had similar symptoms to their initial visit to the ED.		
CI= Confidence interval, NA=Not applicable, NR= not reported, RR= Risk ratio				

6. Ongoing trials

Three ongoing RCTs that are of relevance to this appraisal were identified in literature search (see Table 11) and one further RCT was noted by expert reviewers.

One of these trials is designed to examine the effectiveness of screening for unknown AF with handheld lead-I ECG in primary care for adults aged 65 and older (Ashburner et al. 2019) and has completed enrolment with a total of 35308 participants across sites in the Massachusetts General Hospital primary care network. The primary outcome is incident AF over 12 months and has secondary outcomes related to initiation and maintenance of anticoagulants, stroke, and major haemorrhage. The study is reported as completed but results are not yet available. In addition, experts noted that an RCT will be conducted as part of the SAFER study. At present, feasibility studies RCT are ongoing (ISRCTN16939438) and the design of the RCT is not yet confirmed.

Two of these ongoing trials are examining the effectiveness of lead-I ECG monitoring compared to Holter monitoring for the detection of AF in symptomatic patients with inconclusive clinical examinations. The WAHOO trial is currently recruiting in Australia with the aim of including 80 participants (ACTRN12619000793112). Participants would then be randomised to continuous handheld lead-I ECG monitoring or up to 15 days of multi-day Holter monitoring over six months. The primary outcome will be definite diagnosis of arrhythmia at six months shown by symptom-rhythm correlation and secondary outcomes will include number of identified problematic rhythms, quality of readings, monitor adherence, initiation of medical therapy, adverse events, and quality of life. The study is anticipated to complete in July 2021. The CATCH-AF trial is currently recruiting in British Columbia, Canada and aims to include 220 participants (NCT04302311). Participants would be randomised to handheld lead-I ECG monitoring with 24-hour Holter monitoring available as needed or Holter monitoring alone. The primary outcome will be time to detection of AF according to Kaplan-Meier (K-M) survival curves. The study is anticipated to complete in July 2022.

Table 11. Summary of ongoing randomised controlled trials

Study information	Status	Research question & outcome measures
Detection of unknown AF in older adults during routine contacts primary care		
Registration: NCT03515057 **Sponsor:** Massachusetts General Hospital **Acronym:** VITAL-AF **Country:** United States **Target recruitment:** 35308 participants **Follow-up:** 24 months	**Recruitment status**: Active, not recruiting **Estimated completion date:** January 2021 **Last updated:** 31/01/2020	To assess the effectiveness of screening for undiagnosed AF in primary care for higher risk patients **Population**: Adults 65 years or older attending regularly scheduled office visits **Intervention**: Screening with Kardia Mobile handheld lead-I ECG **Comparator**: Usual care **Primary Outcome Measure**: Incident AF during study period [12 months]

Study information	Status	Research question & outcome measures
Detection of intermittent AF after inconclusive clinical examination		
Registration: ACTRN12619000793112 **Sponsor:** Western Sydney Local Health District **Acronym:** WAHOO **Country:** Australia **Target recruitment:** 80 participants **Follow-up:** 6 months	**Recruitment status:** Recruiting **Estimated completion date:** July 2021 **Last updated:** 22/01/2020	To study effectiveness of lead-I ECG versus traditional Holter monitoring to aid diagnosis of cardiac arrhythmias in patients with rapid heart rhythms **Population**: Adults 18 years and older with symptoms of AF but no documentation of AF with a 12-lead ECG **Intervention**: Kardia Mobile handheld lead-I ECG **Comparator**: Multi-day Holter monitoring **Primary Outcome Measure**: Definite diagnosis of arrhythmia with symptom-rhythm correlation [6 months]
Registration: NCT04302311 **Sponsor:** Victoria Cardiac Arrhythmia Trials **Acronym:** CATCH-AF **Country**: Canada **Target recruitment:** 220 participants **Follow-up:** 6 months	**Recruitment status:** Recruiting **Estimated completion date:** July 2022 **Last updated:** 10/03/2020	To investigate whether continuous use of the Kardia Mobile lead-I ECG device is superior in diagnosing AF compared to normal 24-hr Holter monitoring **Population**: Adults 18 years and older with symptoms of AF but no documentation of AF with a 12-lead ECG **Intervention**: Kardia Mobile lead-I ECG with Holter monitoring as needed **Comparator**: 24-hour Holter monitoring **Primary Outcome Measure**: Time to atrial fibrillation diagnosis according to K-M survival curves [6 months]
AF= atrial fibrillation, K-M= Kaplan-Meier, ECG=electrocardiogram; hr= hour, lead-I= single lead		

7. Economic evaluation

7.1 Health economic evidence review

The titles and abstracts of records identified in the search for this review were screened and five health economic studies were deemed potentially relevant. The full texts of these studies were reviewed against the inclusion/exclusion criteria. Following consideration of the full texts, one study was excluded because it included people with a history of atrial fibrillation (Lowres et al. 2014). The remaining four studies were included in the review. One of the studies was deemed to be directly applicable to our decision context as it considered a UK perspective (Tassie et al. 2016). The remaining three studies were only partially applicable as they considered healthcare systems in other countries (Tarride et al. 2017, Jacobs et al. 2018, Tarride et al. 2018). All of the included studies considered the use of a handheld lead-I ECG for screening for atrial fibrillation in patients deemed to be at high risk.

The cost-utility analysis considering the UK context (Tassie et al. 2016) is summarised in Table 12 below. The analysis assessed the cost-effectiveness of opportunistic screening for atrial fibrillation with a single-lead ECG (AliveCor) in people aged 65 years or older deemed to be at high risk. The analysis found screening to be more effective and less costly than standard care (no screening) and therefore dominant. The result was somewhat sensitive to changes in population age, risk of stroke and assumptions around what constitutes current practice (assuming pulse palpitation would be used to screen patients). Changes in these parameters and assumptions

led to screening with AliveCor being more costly overall so it was no longer dominant. However, the resulting ICERs in these scenarios were below £20,000 per QALY indicating that screening with AliveCor was still cost-effective.

The cost-utility analyses conducted in other settings present similar results (summarised in appendix 3). Tarride et al. (2017) assessed the cost-effectiveness of screening people aged 65 years or older for atrial fibrillation in Canadian pharmacies using a hand-held single-lead ECG (HeartCheck, CardioComm Solutions). The results indicated that screening for atrial fibrillation in pharmacies was cost-effective with an ICER of CAD$7,480. Tarride et al. (2018) assessed the cost-effectiveness of screening people aged 65 years or older for atrial fibrillation in Canadian family practices using a hand-held single-lead ECG. The results indicated that screening for atrial fibrillation in pharmacies was cost-effective with an ICER of CAD$4,788. Jacobs et al. (2018) assessed the cost-effectiveness of screening for atrial fibrillation using a single-lead ECG (MyDiagnostick) in people aged 65 years or older attending the seasonal influenza vaccination in the Netherlands. The results indicated that screening with MyDiagnostick was less costly and more effective than no screening and therefore dominant.

While the results demonstrate the potential for screening to be cost-effective, there are some limitations that should be considered. Most notably, there is uncertainty around what constitutes standard practice for this patient group and therefore uncertainty around the likelihood of atrial fibrillation being detected using approaches adopted in standard practice. Some of the analyses assumed that 'pulse palpitation' may be used. Notably, pulse palpitation was found to the most cost-effective strategy in the analyses that considered it (Tarride et al. 2017, Tarride et al. 2018).

Table 12. Summary of included health economic study: Tassie et al. (2016)

Study details	Study population and design	Data sources	Results	Quality assessment
Author and year: Tassie et al. (2016) **Country:** Scotland **Type of economic analysis:** Cost-utility analysis **Perspective:** UK NHS and Personal Social Services (PSS) **Currency:** UK pound sterling (£) **Price year:** 2014/15 **Time horizon:** 30 years **Discounting:** Costs and benefits were discounted at 3.5% per year **Potential conflict of interest:** None reported	**Population** Modelled cohort of 'high risk' patients with a chronic disease presenting for their annual Quality and Outcomes Framework (QOF) check-up. Chronic diseases included cerebrovascular disease, diabetes, hypertension, vascular disease and chronic kidney disease All patients had a CHA2DS2-VASc (congestive heart failure, prior hypertension, age, diabetes, stroke/TIA, vascular disease and gender) score of 2 or above. Patients were 65 years old or greater and 60% male. **Interventions** Screening with single lead ECG (AliveCor) **Comparator** No screening Authors state that no screening is likely to reflect current practice. A questionnaire was sent to participating GPs in the	**Source of baseline and effectiveness data:** The sensitivity and specificity of ECG recordings using a smart phone were estimated from a published study (Lau et al [2013]). Average sensitivity (97.5%) and specificity (92.0%) were estimated from the values reported by two independent cardiologists in the study. Transition probabilities were estimated from a published HTA of anticoagulants for the prevention of venous thromboembolic disease and stroke in atrial fibrillation. The HTA included a systematic review and network meta-analysis of RCTs. Three-monthly transition probabilities were estimated from the reported mean hazard of events for warfarin. These values were combined with the reported hazard ratios of NOACs and no treatment relative to warfarin to calculate transition probabilities for patients receiving NOACs, no treatment and undiagnosed. **Source of resource use and cost data:** The cost of the AliveCor device was based upon the costs of an Alive AliveCor portable ECG monitor smartphone adapter and an apple iphone smartphone with data only sim and installed AliveCor application. The cost was annuitized over the expected serviceable working life of these devices (assumed to be 5 years). The estimated annual cost was then divided by the target number of patients per	**Costs** AliveCor: £1,923 No screening: £2,006 Incremental: AliveCor saves £83 **QALYs** AliveCor: 9.55 No screening: 9.53 Incremental: 0.02 **ICER (cost per QALY)** Screening with AliveCor is found to be dominant (more effective and less costly) **Sensitivity analysis** Several deterministic sensitivity analyses were conducted. Screening was found to be dominant in the majority of modelled scenarios. Screening was not found to be dominant when the time horizon was shorter (10 years), the starting age was older (75,8), risk of stroke with no treatment was lower or where it was assumed that pulse palpation was used in 100% of patients as part of usual care. However, even in these cases, the ICER for AliveCor was	**Applicability** The analysis was deemed to be directly applicable because it considered a UK NHS and PSS perspective. **Limitations** The analysis was generally considered to be of high quality but some potentially serious limitations were identified: • Study has not been formally published and peer reviewed • Uncertainty around the detection of atrial fibrillation in this patient group using standard practice

Study details	Study population and design	Data sources	Results	Quality assessment
	main pilot study and the majority of respondents reported that they do not routinely test for atrial fibrillation. **Study design** Cost-utility analysis using a Markov model.	practice (250) to give an estimated cost per use. The cost of using the AliveCor device was estimated using data collected from a resource use and costing questionnaire sent to GP practices. The information collected allowed for the incremental cost of conducting the screen as part of a standard GP appointment to be estimated as well as the cost of training for each practice. A training and screening cost per patient was estimated by dividing by the target number of patients per practice (250). The cost of consultant time to interpret and report the results was estimated by collecting time durations from participating consultants and combining it with unit cost data. Average drug costs for the NOACs were estimated from the BNF while warfarin costs were estimated from a NICE costing report as part of a clinical guideline on atrial fibrillation (CG180). The proportions of patients receiving warfarin, NOACs and no treatment were also derived from the NICE report. The costs of managing a clinically relevant bleed or a systemic embolism were estimated from NHS reference costs. Management costs for stoke or intracranial haemorrhage were based on a population study of acute and long-term care costs after stroke in patients with atrial fibrillation. **Source of quality of life data:** Quality of life values for each health state were sourced from studies used in a previous NICE	below a threshold of £20,000 per QALY indicating that it would be cost-effective. Probabilistic sensitivity analysis was conducted. AliveCor was reported to be the dominant strategy in 79.5% of simulations at a threshold of £30,000 per QALY. At a threshold of £20,000 per QALY, AliveCor had an 82% probability of being cost-effective (value approximated from graph presented in report).	

Study details	Study population and design	Data sources	Results	Quality assessment
		technology appraisal submission on Rivaroxaban. One of the studies used data from a UK population while the other used data from a Norwegian population. Quality of life decrements for adverse events were assumed to apply for one model cycle (three months). In the case of a clinically relevant bleed or a systemic embolism, after this three-month period, quality of life was assumed to return to the value of stable atrial fibrillation. In the case of a stroke or intracranial haemorrhage, a lower long-term quality of life value was applied in addition to the three-month decrement. Where patients experienced more than one adverse event, quality of life values were assumed to be multiplicative. All quality of life values were adjusted to account for decreasing quality of life as people age.		

Abbreviations
QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; EQ-5D: EuroQol five-dimensions questionnaire; HTA: Health Technology Assessment; NICE: National Institute for Health and Care Excellence; NOACs: novel oral anticoagulants; BNF: British National Formulary; CHA2DS2-VASc: congestive heart failure, prior hypertension, age, diabetes, stroke/TIA, vascular disease and gender score; QOF: Quality and Outcomes Framework; TIA: transient ischaemic attack; RCT: randomised controlled trial; ECG: echocardiogram

8. Organisational Issues

Several studies reported organisational issues that are relevant and there may be other issues to consider in the use of lead-I ECG for screening or detection of intermittent AF.

In one study examining screening using lead-I ECG, staff completed qualitative interviews about their experiences of implementing and delivering screening (Orchard et al. 2014). GPs liked the portability and instant nature of the results from the lead-I ECG device and they also reported it was helpful to be prompted about people's general cardiovascular health. Despite presence of the algorithm, GPs reported that they relied on their own interpretation but felt it was helpful to have reassurance of the algorithm as corroboration. Practice nurses felt confident delivering screening and reported people were keen to take part. Receptionists were involved in carry out screening in the study and they reported that they felt they had competing tasks that prevented them completing screens, were hesitant to ask people to take part, and were not able to communicate full information to people. One GP reported that nurses completed screening and then a GP interpreted the reading. This was not the reported method in any studies and it is worth considering the organisational realities of screening when different professional groups are involved.

One study interviewed staff in relation to AF screening with lead-I devices during influenza clinics and reported findings with their quantitative results (Orchard et al. 2016). GPs were reported to have liked the device and found the approach of screening during influenza vaccination clinics positive. They did however note that this season is already busy and adding appointments to discuss screening results would add to the need for resources. In addition, some other barriers were present and unreliable IT systems and internet were raised as concerns. Practice nurses who led the screening were confident in completing the process and they felt it allowed them additional interactions with patients on reasons other than vaccination. They also noted how busy they were in this period and noted that time needed to deal with a positive result could have knock on effects on the timing of the clinic. A high level of variation in recruitment rates were seen across the study and practice managers were seen as key to championing the service. One practice manager noted that they had been proactive in assessing how testing would fit into the vaccination clinic and that this led to success. Managers were also able to highlight barriers regarding time restraints and the need to consider IT support. They suggested that funding may need to be tied to screening to make it feasible.

In another study related to screening in pharmacies, community pharmacists were interviewed about their experiences as part of an implementation evaluation (Lowres et al. 2015). Most pharmacists were reported to have received positive feedback about the screening with people finding it useful and feeling comfortable with pharmacists being involved. However, it was also reported that some people did not see the role of pharmacists in screening and for others time was needed to explain pharmacists expanding role in health along with the screening itself. In terms of barriers, some reported that they were not often able to fit screening into workflow and it was often bundled with wider screening services like blood pressure and cholesterol monitoring. Technical issues were also reported with pharmacies without Wi-Fi finding the device slow to use and a familiarization period was needed before competent use. Pharmacists reported that for long-term sustainability, reimbursement for time would need to be considered along with ensuring stronger links to GPs to report findings.

Alongside the issues identified in qualitative studies, there may be other organisational issues to consider. First, there was divergence between expert reviewers on how lead-I ECG could be used in usual practice for both screening in primary care and the community and use in intermittent populations. For screening, some indicated that a lead-I ECG reading would be sufficient for a GP to action a change in treatment whereas others felt review from a GP with special interest in cardiology or a full 12-lead ECG would always be needed. A survey-based study that asked

members of the European Heart Rhythm Association Young Electrophysiology Working Group how they would respond to handheld lead-I ECG detection of AF reinforced that there is limited agreement on appropriate management in response to handheld lead-I ECG findings (Manninger et al. 2020). For asymptomatic patients with AF indicated on handheld lead-I ECG, 87% of respondents indicated that they would be likely or very likely to request further diagnostic tests, such as a full 12-lead ECG. Despite the consensus on the need for further diagnosis, there were conflicting responses on whether anticoagulant treatment would be appropriate on the basis of handheld lead-I ECG findings.

For intermittent AF, it was suggested that a dedicated pathway would be needed to manage identification and outsourced over reading services may need to be used. Second, previous reports on adoption of lead-I ECG and comments from expert reviewers highlighted that at present, clinicians would need to link some lead-I ECG devices to their own personal devices (e.g. smartphone, tablet) and this was seen as problematic (Wessex Academic Health Science Network 2019). Finally, for intermittent AF, lead-I ECG devices would need to be taken home for continuous monitoring. No studies reported on whether there could be loss of ECG devices or whether there may be an impact of transport and at home use on calibration and length of life of the devices. This may need to be considered in routine practice and on review, experts commented that this issue has not been considered and could lead to reluctance in using devices in this way.

There may also be other benefits not identified in the literature. In Wales, people who live in rural areas may have difficulties in attending hospital for assessment of intermittent AF and lead-I ECGs may offer a method that reduces the need for multiple visits. Similarly, there may be other groups who face difficulties in attending hospitals due to mobility or other issues and lead-I ECG devices may also be beneficial for these groups. These issues were not examined in any identified studies but may provide benefit alongside other measures of clinical and economic effectiveness.

9. Patient issues

9.1 Patient perspectives and attitudes to screening and detection of unknown or intermittent AF

Two studies that looked at patients' experiences and perceptions of detection of AF were identified in the systematic review. Both studies interviewed patients in conjunction with a screening programme conducted by either receptionists or primary care nurses (Lown et al. 2020, Orchard et al. 2014).

In Lown et al. (2020), people who had taken part in a screening programme for AF in primary care were invited to take part in qualitative interviews to ask about the experiences and attitudes to screening. In the study, people over 65 who did not have AF were invited to the general practice for a specific nurse-led screening appointment where four technologies were used in random order (handheld lead-I ECG, blood pressure cuff, chest strap monitor, and patch based sensor). It is noteworthy that the study chose not to include those diagnosed with new AF as they may have different perspectives and attitudes. There was also over representation of women in the sample. The study was not included in the clinical effectiveness review because results for detection of previously unknown AF were not reported separately for the relevant technology. However, the results of this qualitative study provide useful insights in patient issues related to screening and are included here.

Participants' understanding of atrial fibrillation was unclear after taking part in the screening programme. The majority knew that AF related to the heart and but less than half recognised that

AF was related to regularity of heart beats (6/15) and few participants made the link between AF and cardiovascular events like stroke and heart attack (2/15). In terms of attitudes to screening, most participants were reported to have given positive opinions as they felt that knowing if you had a problem and identifying it early could be beneficial. One participant was quoted as highlighting that stroke was debilitating and treatment could prevent this. Potential negatives that were raised were that screening might increase anxiety about health and that the financial costs of screening might outweigh the benefits. There was a possibility that in some cases the intent of screening had been misunderstood with one participant feeling reassured that they had a healthy heart when screening related only to heart rhythm and AF.

When asked about the devices used in the screening, some participants had no preference for the devices. Some participants stated that handheld lead-I ECG devices were the simplest as they only involved holding an object with your thumbs in position, and others expressed a preference for methods other than the blood pressure cuff due to discomfort. More potential issues with the devices were raised when asked if participants would be content to take them home and use them over a longer term and this may be relevant to detection of intermittent ECG. However, the population had recently been confirmed as not having AF and this may alter their perspectives compared to someone with intermittent symptoms. Participants indicated that wearable devices could be left on and you would be free to do other things whereas using the handheld lead-I ECG requires you to fully engage. Most participants seemed to indicate that over short periods daily monitoring may be acceptable as long as there was a valid reason but might cause anxiety or take too much time over longer periods.

In Orchard et al. (2014), people who took part in a nurse and receptionist-led handheld lead-I ECG screening programme were invited to complete qualitative interviews as part of a process evaluation. In the study, people aged 65 and older attending a general practice for routine care were approached by a nurse or receptionist and if they agreed to participate they completed a lead-I ECG reading. The methods for recruitment and the characteristics of the population are not fully reported but eight participants completed qualitative interviews. In the study, no cases of unknown AF were identified but it is not reported whether the group in this study had previously known or no history of AF.

In the study, participants were interested in being able to see their heart rhythm with the technology but after screening there appeared to be a lack of understanding of the purpose of it or what AF was. Some other reported more pressing concerns related to the purpose of their GP visit over the need for screening.

Expert reviewers suggested that these findings were in line with their experiences but also noted that the older patient populations were, the more likely difficulties in using the devices or possessing smart phones or tablets would become.

9.2 Patient surveys

HTW has collaborated with the British Heart Foundation (BHF) to survey their patient network regarding their experience using handheld lead-I ECG for detection of AF.

The British Heart Foundation is a UK national charity supporting research into heart conditions with patient communities linking people across the UK and Wales. Questionnaires for this appraisal were collaboratively designed with BHF and HTW to ask questions regarding dally life living with AF, using hand-held ECG devices, and screening for AF and other conditions. BHF distributed the questionnaires to the Welsh patient network and then their UK patient network. Six completed questionnaires were returned during the time-frame.

9.2.1 Living with AF

Respondents advised that they had been living with AF and/or AF symptoms from five to 20 plus years and experience symptoms such as fatigue, palpitations/fluttering, dizziness/light headedness, tiredness, breathlessness, nausea, chest pain, adrenaline surges and sudden onset feelings of dread/despair. The majority of respondents advised that, as well as AF/AF symptoms, they also live with other heart conditions, such as heart failure, aneurisms, atrial arrhythmia and cardiomyopathy. The most common methods for successfully controlling AF reported include medication, such as beta-blockers, diet and exercise, and maintaining a healthy lifestyle, including abstaining from caffeine and alcohol. One respondent was fitted with a pacemaker and another reported unsuccessful attempts to manage their AF:

"I've had 3 ablations, and have worked through a range of rate and rhythm control medications which have been unable to provide lasting relief, so for the last year I just live with it without interventions. Flecanide and Bisoprol worked for several years but now have no effect".

Respondents placed significant importance on maintaining a healthy lifestyle to effectively manage their AF and other heart related conditions:

"In my case I am relatively symptom free, my heart rate is well-controlled and I can exercise without much difficulty having learnt the importance of exercise for heart health at my first Cardiac rehab programme some 20 years ago. I am now 73 and do Pilates and aerobic exercise currently online."

"As a non-medic, I put my relatively good health down to maintaining a consistent exercise routine, following doctors' orders"

The majority of respondents advised that gaining a diagnosis of AF was a long and difficult process, with one report of experiencing symptoms for over 10 years and needing to undergo several echocardiograms and additional tests before arriving at a diagnosis. This was particularly the case where symptoms were intermittent. One described their experience as:

"Difficult. Testing at hospital failed to identify any problem, as it never happens at rest or anywhere near medical staff. A second series of tests a year later to try and identify cause of spells of sudden breathlessness also showed nothing until it kicked in during a stress echo test using a treadmill".

In one case, a respondent did report a quick and easy diagnosis with existing diagnostic approaches.

Living with AF was described as "totally debilitating" with "no obvious explanation" by one respondent:.

"The difficulty of living day to day with light headedness and the fear of passing out. This can limit driving and socialising and have a detrimental effect on concentration and work .The unpredictability, not knowing if tomorrow will be a good day and being unable to make plans."

Respondents acknowledged that the experience of living with AF varies greatly depending on the individual, but collectively reported that AF is often misdiagnosed, particularly if a person has been diagnosed with another heart condition before their AF developed:

"On many occasions my AF was interpreted by my ICD (Implanted cardioverter device) as ventricular tachycardia or fibrillation and proceeded to deliver therapy (shocks). Cardiologists and Electrophysiologists should ask if the patient suffers with AF, so that different thresholds and settings can be programmed in the ICD"

Respondents also advised that not all symptoms are physical and reported on the impact of hormonal changes:

"When first diagnosed, I classified my main symptoms for the purpose of tracking as "fluttering", "pain" and "the feeling". It was a way of describing this terrible wave of doom. My GP explained the relationship between the autonomic nervous system, adrenalin and the heart which helped me to cope with what I found the worst symptom"

"I was (surprisingly) completely asymptomatic during pregnancy with my first child, but symptoms returned with my cycle a couple of months after his birth. My cardiologist noted that there was very little information available about this. A lot of birth control is not compatible with my symptoms".

9.2.2 Using handheld lead-I ECG devices

Respondents who had experience with using hand-held lead-I-ECG devices indicated they had purchased them themselves for home use as part of care plans devised with their cardiologist. Devices used by respondents were AliveCor Kardia mobile devices. All respondents reported that the devices were easy to use and user friendly. No difficulties regarding use of the devices were reported. The majority of respondents advised that they were confident in their ability to use these devices when bringing them home. Respondents were less confident in their ability to interpret and fully understand the ECG readings but reported that the devices gave them some general reassurance about their condition. The responses raised some concern that people may try to interpret the actual trace rather than relying on the devices algorithm to highlight potential AF:

"I can't interpret the ECG wave pattern, but it gives a simple Normal/AF output. I can see the varied time intervals in the wave when in AF".

"To me, some would look like AF so I would send the reading to be analysed (and it was only extra heartbeats or taccychardia). Some looked very innocuous to me and turned out to be AF."

In general, the devices were reported to be useful and reassuring to users and some indicated that they felt wider useful could be beneficial:

"A useful monitor for patients to gain confidence in their condition"

"If effective and 'value for money' such hand-held devices available via GP surgeries, pharmacies, health centres, etc. could save much time and resources in hospitals and speed up diagnosis/triage."

9.2.3 Screening for AF

All respondents confirmed that they would be happy and confident to answer screening questions for AF and other medical conditions in a range of healthcare settings by various healthcare professionals, including pharmacists, chemists and GPs and for conditions unrelated to their visit to the healthcare setting.

9.2.4 Summary

The majority of respondents confirmed that arriving at a diagnosis of AF was difficult and lengthy with significant impacts on their lives:

"I found it very upsetting that the GP and cardiologists were unable to diagnose my AF which led to me having a heart attack. I consider myself lucky that it wasn't a stroke and that I am still alive but I have been left with a reduced quality of life and had to take early retirement as I was left unable to work"

According to respondents, handheld lead-I ECG devices have been successfully used in the diagnosing of AF:

"They are very easy to use and can be carried around in wallet or pocket and can be used to check at any time when symptoms seem to be occurring. I've used the output as evidence during consultations with the cardiologist."

The devices are easy to use and provide users with reassurance about their condition. There remains some concern around understanding the readings of devices but this depends on the individual user:

"Perhaps do not show the actual ECG reading to the user. We are not (most often) medical professionals capable of interpreting the reading. It can create confusion and worry. A simple result (e.g. "normal sinus rhythm" or "AF") without seeing the ECG reading may be better. The ECG reading could be stored in case it needs to be sent off or read by a GP or cardiologist?"

For people with AF and AF related symptoms, confirming a diagnosis can be difficult, time consuming and can have negative impacts on quality of life. This remains a primary concern for the patient community.

"Many people living with AF (paroxysmal or persistent) don't always recognise it and tend to just cope with feeling unwell. As you know, this cohort of people are at high risk of stroke and if identified early, could benefit from treatment. There are many devices and apps available for patients to monitor their AF and learn to control it through various relaxation methods. The national stroke prevention programme should help to identify people with AF"

10. Conclusions

There is a developing body of evidence on the effectiveness and cost-effectiveness of handheld lead-I ECG for detection of AF in different settings. Previous systematic reviews have examined the diagnostic accuracy of handheld lead-I ECG for detecting AF and results generally suggest levels of sensitivity and specificity of above 90%. This may be lower in community settings and this could be important as a consideration for screening programmes in the general population.

Several approaches to screening adults over 65 for previously unknown AF were identified. When used in routine contacts in primary care, identified RCTs did not demonstrate that screening with lead-I ECG was more beneficial than standard care and they suggest that opportunistic approaches using pulse palpitation are equivalent to more systematic device-based approaches to screening. Across screening in influenza vaccination clinics and community pharmacy, low rates of unknown AF were generally found and few patients received initiation of treatment as a result. In the single study that did compare lead-I ECG with pulse palpitation, pharmacists were able to identify the majority of unknown cases of AF manually suggesting lead-I ECG does not provide additional benefit. Few studies examined outcomes beyond identification of AF and where this was reported, both mortality and hospitalisation were not common. On these outcomes, there was no evidence on the longer-term benefits and harms associated with screening and resulting changes in treatment. Available economic evidence suggested that screening with lead-I ECG may have value compared to no screening but that equivalent screening with pulse palpitation may be most cost-effective.

For the detection of intermittent AF for people who have had inconclusive clinical examinations, we identified two studies. The available RCT demonstrated that lead-I ECGs are beneficial in identifying cases and reducing time to identification. These results are replicated even when all participants receive 24-hour Holter monitoring which provides additional support to the use of lead-I ECG in this setting. Across both studies, participants were reported to have limited issues

using the devices, adherence to monitoring was very high, and satisfaction with the approach appeared to be high.

There are a number of organisational issues that should be considered regarding implementation. Uptake of screening was low in a number of studies and it was suggested that screening for unknown AF may not fit into workflows and that incentives may be needed, No literature was found on organisational issues for detection of intermittent AF and a consideration of how the technology could fit into existing pathways would be needed. Concerning patients' perspectives, identified literature and responses to a survey for this report suggested that people are amenable to using lead-I ECG devices in general screening and found the devices easy to use. The responses raised some questions around whether people felt they needed to be able to interpret heart rhythm readings themselves rather than relying on built in algorithms and clinicians should be aware of this when discussing usage.

11. Contributors

This topic was proposed by Robert Salter, Specialist Healthcare Scientist, Clinical Engineering, Cwm Taf Morgannwg University Health Board.

The HTW staff and contract researchers involved in writing this report were:

- A Cleves, Assistant Library Manager & Assistant Information Specialist – literature searches
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- G Hopkin, Health Services Researcher - clinical author
- M Prettyjohns, Principal Researcher – health economics author
- A Evans, PPI Officer – PPI author
- D Jarrom, Health Services Researcher – quality assurance check
- S Hughes, Health Economist – quality assurance check
- S McAllister, Project Manager – project management
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The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

A range of clinical experts from the UK provided material and commented on a draft of this report. Their views were documented and have been actioned accordingly. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control, and the views expressed are those of Health Technology Wales.

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Appendix 1. PICO frameworks

Research Question 1	What is the diagnostic accuracy of handheld lead-I ECG devices for the detection of atrial fibrillation?

	Inclusion criteria	Exclusion criteria
Population	General population	
Intervention	Handheld single lead electrocardiogram interpreted by trained healthcare professional or algorithm Known devices are as follows: • imPulse • Kardia Mobile • MyDiagnostick • Zenicor-ECG • HeartCheck	Patch- or strap-based (e.g. chest, wrist) single lead echocardiogram devices
Reference standard	12-lead ECG performed and interpreted by a trained healthcare professional	
Outcome measures	Diagnostic accuracy outcomes • Sensitivity • Specificity • PPV • NPV • ROC curve We will include studies that report any of these outcomes, or that report sufficient information to allow them to be calculated independently (Number of true positive, true negative, false positive and false negative test results)	
Study design	We will prioritise the following study types, in the order listed: Systematic reviews of interventions or diagnostic accuracy Randomised trials or studies of interventions or diagnostic accuracy that employ a suitable reference standard Non-randomised comparative trials Single-arm trials that report any relevant outcome	

	We will only include evidence for lower priority evidence where outcomes for each condition/symptom of interest are not reported by a higher priority source. We will also search for economic evaluations or original research that can form the basis of an assessment of costs/cost comparison.
Search limits	No date limits
Other factors	n/a

Research Question 2	What is the effectiveness of handheld lead-I ECG devices in single point of time screening for unknown AF in people aged over 65 in primary care and the community?

	Inclusion criteria	Exclusion criteria
Population	People aged 65 years or older who may have previously unknown asymptomatic atrial fibrillation	
Intervention	Handheld single lead electrocardiogram interpreted by trained healthcare professional or algorithm Used at a single point of time in primary health care or community settings Known devices are as follows: • imPulse • Kardia Mobile • MyDiagnostick • Zenicor-ECG • HeartCheck	Patch- or strap-based (e.g. chest, wrist) single lead echocardiogram devices Used in hospital or secondary care settings Used for long term at-home monitoring
Comparison/ Comparators	Usual or routine screening (e.g. no screening, asymptomatic detection of atrial fibrillation based on manual pulse palpation followed by a 12-lead ECG)	
Reference standard	12-lead ECG performed and interpreted by a trained healthcare professional	
Outcome measures	Clinical effectiveness and patient outcomes • Detection of atrial fibrillation and other cardiac arrhythmias • Changes in patient management (such as initiation of treatment) • 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) • Health-related quality of life • Patient satisfaction	

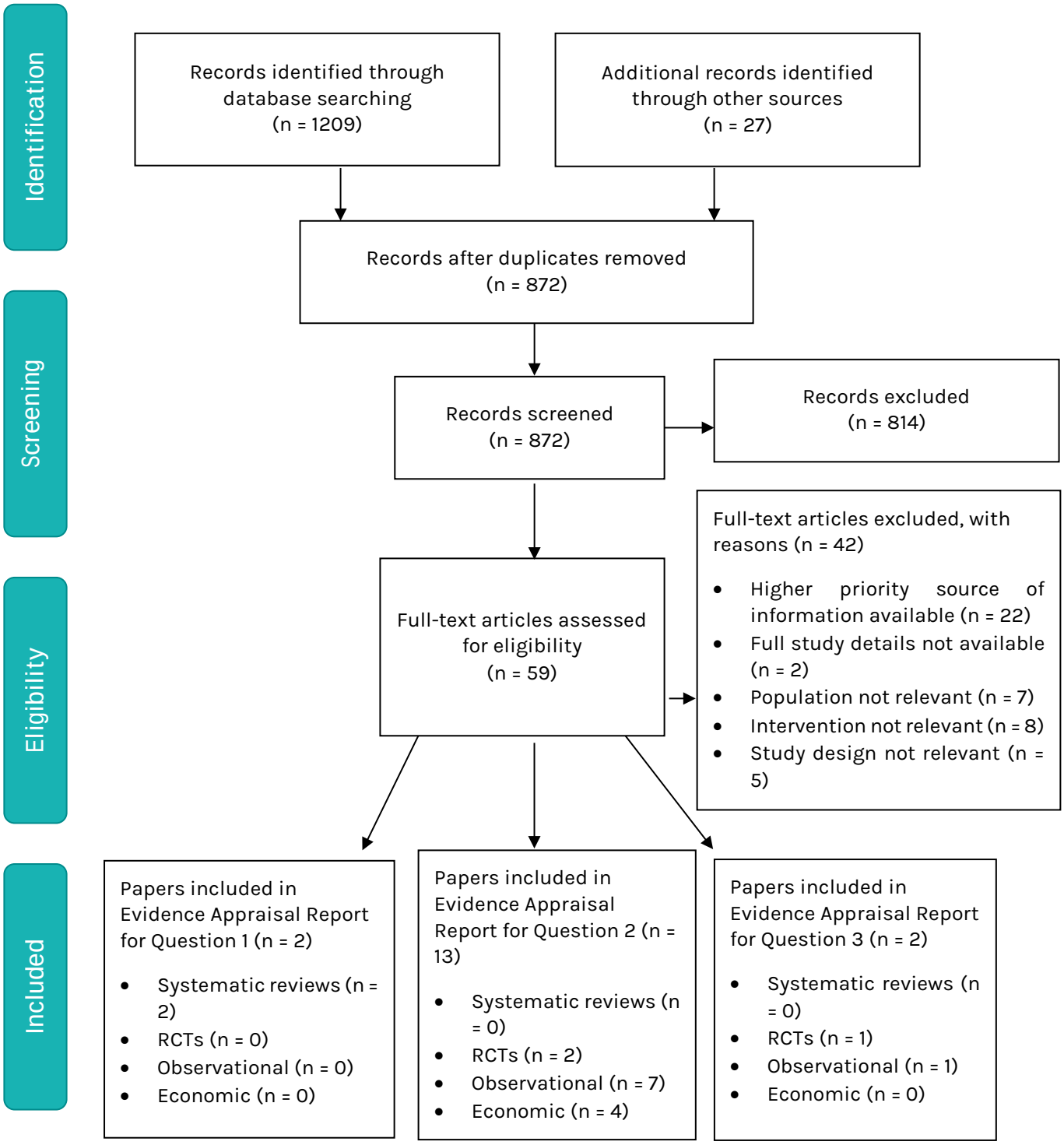
Study design	We will prioritise the following study types, in the order listed: Systematic reviews of interventions or diagnostic accuracy Randomised trials or studies of interventions or diagnostic accuracy that employ a suitable reference standard Non-randomised comparative trials Single-arm trials that report any relevant outcome We will only include evidence for lower priority evidence where outcomes for each condition/symptom of interest are not reported by a higher priority source. We will also search for economic evaluations or original research that can form the basis of an assessment of costs/cost comparison.
Search limits	No date limits
Other factors	n/a

Research Question 3	What is the effectiveness of handheld lead-I ECG devices to detect intermittent atrial fibrillation after an inconclusive clinical examination?

	Inclusion criteria	Exclusion criteria
Population	People with suspected paroxysmal atrial fibrillation after an inconclusive clinical examination	
Intervention	Handheld single lead electrocardiogram interpreted by trained healthcare professional or algorithm Used in any healthcare setting Known devices are as follows: • imPulse • Kardia Mobile • MyDiagnostick • Zenicor-ECG • HeartCheck	Patch- or strap-based (e.g. chest, wrist) single lead electrocardiogram devices
Comparison/ Comparators	Usual or routine care (e.g. 12-lead ECG alone, 24-hour ambulatory ECG monitoring, event-based external loop recorders)	
Reference Standard	24-hour ambulatory ECG monitoring and/or event-based external loop recorders interpreted by a trained healthcare professional	
Outcome measures	Clinical effectiveness and patient outcomes • Detection of atrial fibrillation and other cardiac arrhythmias • Time to detection • Changes in patient management (such as earlier initiation of preventative treatment for strokes) • 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) • Health-related quality of life • Patient satisfaction	

Study design	We will prioritise the following study types, in the order listed: Systematic reviews of interventions or diagnostic accuracy Randomised trials or studies of diagnostic accuracy that employ a suitable reference standard Non-randomised comparative trials Single-arm trials that report any relevant outcome We will only include evidence for "lower priority" evidence where outcomes for each condition/symptom of interest are not reported by a "higher priority" source. We will also search for economic evaluations or original research that can form the basis of an assessment of costs/cost comparison.
Search limits	No date limits
Other factors	n/a

Appendix 2. PRISMA flow diagram outlining selection of papers for clinical and cost effectiveness



Appendix 3. Summary of included health economic studies from non-UK settings

Study details	Study population and design	Data sources	Results	Quality assessment
Author and year: Tarride et al. (2018) **Country:** Canada **Type of economic analysis:** Cost-utility analysis **Perspective:** Canadian public payer perspective **Currency:** Canadian dollars (CAD$) **Price year:** 2017 **Time horizon:** Lifetime **Discounting:** Costs and benefits discounted at 1.5% per year **Potential conflict of interest:** One of the authors reported consulting fees from Boehringer Ingelheim, Servier, and Bayer, and has research grants from Boehringer Ingelheim and Bayer. Another author reports	**Population** Modelled population was based on the characteristics of the cohort in the Program for the Identification of "Actionable" Atrial Fibrillation in the Family Practice Setting (PIAAF-FP) study. PIAAF-FP was a cohort study involving 2,054 seniors opportunistically screened for atrial fibrillation in 22 Canadian family practices. The mean age of the cohort was 73.7 years old and 47% were male. Approximately 60% had hypertension, 28% had diabetes, 7% had prior stroke, transient ischemic attack or systemic, 7% had a myocardial infarction and 3% had heart failure. 64% of the cohort had a CHA2DS2-VASc score ≥3. The findings from the PIAAF-FP study indicated that 0.7% of participants had undiagnosed or undertreated atrial fibrillation. **Strategies considered** The analysis considered screening strategies for the detection of atrial fibrillation. Four strategies were considered: 1. No screening	**Source of baseline and effectiveness data:** Evidence from the PIAAFFP clinical study were used to determine atrial fibrillation detection rates with each screening strategy. Based on the PIAAFFP study, it was assumed that 77% of patients diagnosed with actionable atrial fibrillation would initiate oral anticoagulant therapy. The long-term consequences of each screening strategy were estimated using data from published sources and following the approach adopted in a previous economic evaluation (Tarride et al. 2017). The annual risk of stroke in the absence of oral anticoagulant therapy was based on findings from a cohort study of patients with atrial fibrilation. The relative risk of ischemic stroke and major bleeding for patients receiving warfarin was based on a published meta-analysis (Lip et al 2006). Relative risks of events for direct oral anti-coagulants compared to warfarin were derived using	**Costs** No screening: $214 Pulse check: $202 BP-AF: $211 SL-ECG: $222 **QALYs** No screening: 8.7420 Pulse check: 8.7436 BP-AF: 8.7430 SL-ECG: 8.7436 **ICER (cost per QALY) when compared against no screening** Pulse check: Dominant (more effective and less costly than no screening) BP-AF: Dominant (more effective and less costly than no screening) SL-ECG: $4,788 per QALY **ICER (cost per QALY) when comparing all strategies** Pulse check found to be the dominant strategy (more effective and less costly than all other strategies)	**Applicability** The analysis was deemed to be only partially applicable to the UK NHS because it considered the Canadian healthcare system. **Limitations** Some potentially serious limitations were identified: • The methodology and sources used to estimate cost and quality of life values were reported in insufficient detail. • The analysis is based upon modelled predictions of atrial fibrillation-related events rather than observed data. Therefore there will be some inherent uncertainty around the number of events (such as strokes) and the impact that earlier detection and treatment may have. • Swedish registry data of atrial fibrillation diagnosed in the hospital were used for estimates of stroke and major bleeding. This may not be representative of the cohort considered in this analysis. • Study on which detection rates were based used screening at a single point in

Study details	Study population and design	Data sources	Results	Quality assessment
research funding from Eli Lilly, Shire Pharmaceuticals, Merck and Pfizer. Another author reports consulting fees from Bayer, Boehringer Ingelheim, Pfizer, Bristol-Myers Squib, and has research grants from Boehringer Ingelheim, Bayer, Pfizer, and Bristol-Myers Squibb. Cohort study on which the economic analysis was based was supported by the Canadian Stroke Prevention Intervention Network, Boehringer Ingelheim, and in-kind support from CardioComm and ManthaMed.	2. Screening with 30-second radial pulse check (pulse check) 3. Screening with a blood pressure machine with AF detection algorithm (BP-AF) 4. Screening with single lead ECG (SL-ECG) **Study design** Economic evaluation to accompany the PIAAF-FP cohort study. A cost-utility analysis was conducted based on a Markov decision model.	evidence from a systematic review (Ruff et al. 2014). **Source of resource use and cost data:** The cost of each screening strategy was estimated using resource utilisation data from PIAAF-FP. The cost estimate included the cost of the device as well as the cost of nurse time to conduct and relay information for each screen. To confirm results, it was assumed that patients with a positive screen would receive a 12-lead ECG. All patients testing negative with a 12-lead ECG were assumed to be tested with a 24 hour Holter monitor. Costs for a 12-lead ECG and 24 hour Holter Monitor were sourced from Canadian reference costs (Schedule of Benefits for Physician Services from the Ontario Ministry of Health and Long Term Care). Medication costs for oral anticoagulants were based on reimbursement prices from the Ontario Drug Benefit formulary. It was assumed that 52% would be prescribed direct oral anticoagulants and 48% would be prescribed warfarin. It was further assumed that 10% would discontinue treatment per year.	**Sensitivity analysis** A series of deterministic sensitivity analyses were conducted. Pulse check remained the dominant strategy in the majority of modelled scenarios. Notable exceptions were when it was assumed that the proportion of diagnosed patients that receive anticoagulants was lowered or when the atrial fibrillation detection rate was increased in the 'no screening' arm. In these scenarios, pulse check was no longer dominant but it was still cost-effective as the ICER result was always well below a threshold of $50,000 per QALY. At a threshold of $50,000 per QALY, screening with pulse check had the highest probability of being cost-effective (63%). Screening with SL-ECG had a 25% probability of being cost-effective while screening with BP-AF and no screening had probabilities of 9% and 3%, respectively (values	time. Therefore, cases of paroxysmal atrial fibrillation were probably missed, which could have led to an underestimate of overall cases.

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		Various sources were used for the cost of managing events. The cost of managing an ischemic stroke in the first year was based on a published study investigating ischemic stroke costs in Canada in the first year. The cost of managing an intracranial hemorrhage in the first year was based on a prospective study investigating the cost of stroke in the first year in Canada. The cost of managing an ischemic stroke or intracranial haemorrhage in subsequent years was based on values reported in a published cost-effectiveness analysis of catheter ablation for rhythm control of atrial fibrillation. The cost of managing major bleeds was based on a published patient cost estimator from the Canadian Institute for Health Information (CIHI). **Source of quality of life data:** Baseline quality of life values for the general population were sourced from a study of UK population norms for EQ-5D. Separate values were sourced for men and women aged 75 years and older. Decreased quality of life following a stroke was estimated using quality of life values reported for different modified Rankin Scale	estimated from graph presented in report).	

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		(mRS) values. The values were sourced from a study that mapped mRS measurements to EQ-5D. Methodology was not fully reported but it appears that the impact of a stroke on quality of life was estimated using the difference in quality of life between people with a mRS score of 0-2 and 3-5.		
Author and year: Tarride et al. (2017) **Country:** Canada **Type of economic analysis:** Cost-utility analysis **Perspective:** Canadian public payer perspective **Currency:** Canadian dollars (CAD$) **Price year:** 2016 **Time horizon:** Lifetime **Discounting:** Costs and benefits discounted at 1.5% per year	**Population** Modelled population was based on the characteristics of the cohort in the Program for the Identification of 'Actionable' Atrial Fibrillation in the Pharmacy setting (PIAAF–Pharmacy) study The program involved screening people aged 65 years and older, attending community pharmacies in Canada, who were not receiving oral anticoagulation. **Strategies considered** The analysis considered screening strategies for the detection of atrial fibrillation. Two strategies were considered: 1. No screening 2. Screening with a hand-held, single lead ECG device (HeartCheck, CardioComm Solutions)	**Source of baseline and effectiveness data:** The proportion of patients testing positive for atrial fibrillation with a single-lead ECG was based on data from the PIAAF–Pharmacy study. The probability of this positive result being correct i.e. the positive predictive value (PPV) was based on unpublished data from a similar atrial fibrillation screening study conducted in physicians' offices. Based on the PIAAF-Pharmacy study, it was assumed that 71% of people diagnosed with actionable atrial fibrillation would initiate oral anticoagulant therapy. The long-term consequences of each screening strategy were estimated using data from published sources. The annual risk of stroke in the absence of oral anticoagulant therapy was	**Costs** No screening: $418 Screening: $444 Incremental: $26 **QALYs** No screening: 6.876 Screening: 6.880 Incremental: 0.004 **ICER (cost per QALY)** $7,480 per QALY **Sensitivity analysis** A series of deterministic sensitivity analyses were conducted. Screening for atrial fibrillation was found to be cost-effective at a threshold of $50,000 per QALY in most deterministic sensitivity analyses. Notable exceptions were where the proportion of	**Applicability** The analysis was deemed to be only partially applicable to the UK NHS because it considered the Canadian healthcare system. **Limitations** Some potentially serious limitations were identified: • The methodology and sources used to estimate cost and quality of life values were reported in insufficient detail. • The analysis is based upon modelled predictions of atrial fibrillation-related events rather than observed data. Therefore there will be some inherent uncertainty around the number of events (such as strokes) and the impact that earlier detection and treatment may have.

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Potential conflict of interest: One of the authors received a Pfizer Canada Postdoctoral Mentoree Award. Another author received research grants from Boehringer Ingelheim, Bristol-Myers Squibb and Pfizer. Cohort study on which the economic analysis was based was supported by the Canadian Stroke Prevention Intervention Network, Boehringer Ingelheim and inkind support from CardioComm.	**Study design** Economic evaluation to accompany the PIAAF–Pharmacy cohort study. A cost-utility analysis was conducted based on a Markov decision model.	based on findings from a cohort study of patients with atrial fibrillation. The relative risk of ischemic stroke and major bleeding for patients receiving warfarin was based on a published meta-analysis (Lip et al 2006). Relative risks of events for direct oral anti-coagulants compared to warfarin were derived using evidence from a systematic review (Ruff et al. 2014). **Source of resource use and cost data:** Cost data from the PIAAF–Pharmacy study was used to calculate the cost per screen. Total screening cost was estimated including the cost of the single lead ECG, confirmatory 12-lead ECG and Holter monitor test, training to use screening devices, time spent in-pharmacy for screening sessions and time spent transmitting results to family physicians. Total screening cost was divided by the number of participants screened in the study to give a cost per screen. To confirm results, it was assumed that patients with a positive screen would receive a 12-lead ECG. All patients testing negative with a 12-lead ECG were assumed to be tested with a 24 hour Holter monitor. Costs for a	diagnosed patients that receive anticoagulants was lowered, the PPV of single-lead ECG was lowered or when the atrial fibrillation detection rate was increased in the 'no screening' arm. In these scenarios, pulse check was no longer dominant but it was still cost-effective as the ICER result was always well below a threshold of $50,000 per QALY. In probabilistic sensitivity analysis, atrial fibrillation screening was found to have a 91% probability of being cost-effective at a threshold of $50,000 per QALY.	• Swedish registry data of atrial fibrillation diagnosed in the hospital were used for estimates of stroke and major bleeding. This may not be representative of the community-based cohort considered in this analysis. • Study on which detection rates were based used screening at a single point in time. Therefore, cases of paroxysmal atrial fibrillation were probably missed, which could have led to an underestimate of overall cases.

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		12-lead ECG and 24 hour Holter Monitor were sourced from Canadian reference costs (Schedule of Benefits for Physician Services from the Ontario Ministry of Health and Long Term Care). Medication costs for oral anticoagulants were based on reimbursement prices from the Ontario Drug Benefit formulary. Based on Canadian registry data, it was assumed that 52% would be prescribed direct oral anticoagulants and 48% would be prescribed warfarin. Based on the ARISTOTLE trial, it was assumed that 10% would discontinue oral anticoagulant treatment per year. Monitoring costs for people receiving warfarin were included based on estimates used in a Canadian economic evaluation of atrial fibrillation treatments. Various sources were used for the cost of managing events. The cost of managing an ischemic stroke in the first year was based on a published study investigating ischemic stroke costs in Canada in the first year. The cost of managing an intracranial haemorrhage in the first year was based on a prospective study investigating the cost of stroke in the first year in Canada. The cost		

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		of managing an ischaemic stroke or intracranial haemorrhage in subsequent years was based on values reported in a published cost-effectiveness analysis of catheter ablation for rhythm control of atrial fibrillation. The cost of managing major bleeds was based on a published patient cost estimator from the Canadian Institute for Health Information (CIHI). **Source of quality of life data:** Baseline quality of life values for the general population were sourced from a study of UK population norms for EQ-5D. Separate values were sourced for men and women aged 75 years and older. Decreased quality of life following a stroke was estimated using quality of life values reported for different modified Rankin Scale (mRS) values. The values were sourced from a study that mapped mRS measurements to EQ-5D. The impact of a stroke on quality of life was estimated using the difference in quality of life between people with a mRS score of 0-2 and 3-5.		
Author and year: Jacobs et al. (2018) **Country:**	**Population** People aged 65 years and over attending the seasonal influenza vaccination in the Netherlands.	**Source of baseline and effectiveness data:** The risks of clinical events for NOACs and warfarin were based	**Costs** No screening: €12,554 Screening: €11,790 Incremental: -€763.75	**Applicability** The analysis was deemed to be only partially applicable to the UK NHS because it considered

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Netherlands **Type of economic analysis:** Cost-utility analysis **Perspective:** Societal perspective (although productivity was not considered due to age of population). **Currency:** Euros (€) **Price year:** 2014 **Time horizon:** Lifetime **Discounting:** Health gains were discounted by 1.5% per year and costs were discounted by 4% per year. **Potential conflict of interest:** One of the authors is co-inventor of MyDiagnostick and receives royalties from Applied Biomedical Systems (ABS). One of the authors reported grants and personal fees from Boehringer Ingelheim and personal fees from Bayer, Pfizer and Bristol Meyer Squibb.	**Strategies considered** The analysis considered screening strategies for the detection of atrial fibrillation. Two strategies were considered: 1. No screening 2. Screening with a hand-held, single lead ECG device (MyDiagnostick). **Study design** Cost-utility analysis based on a decision tree and Markov model.	on data from clinical trials (ARISTOTLE RE-LY and ROCKET AF). Combined event rates were estimated by calculating weighted means from the trials. Event rates for patients with atrial fibrillation without stroke prevention were based on relative risks compared with warfarin. Age-specific mortality rates were used to estimate mortality over a patient's lifetime, (starting at 75 years). The mortality rate was assumed to be 3.7 times higher following an ischaemic event or ICH. After a myocardial infarction, the age-related mortality was assumed to be 1.05 times higher. **Source of resource use and cost data:** The cost of the ECG device was based on an assumption of one device for every general practitioner (GP) practice in the Netherlands. The cost amortized over a 3-year period. Personnel costs were estimated based on a tariff cost per hour and an estimate of total number of hours needed for the screening programme. It was assumed that nurses would perform the screening in primary care. The cost of cardiologist time was	**QALYs** No screening: 7.75 Screening: 8.02 Incremental: 0.27 **ICER (cost per QALY)** Screening was found to be dominant (more effective and less costly). **Sensitivity analysis** A series of deterministic sensitivity analyses were conducted. Changes in the cost of IS, the probability of IS and the cost of NOACs were found to have the biggest influence on the results. Changes in these parameters led to scenarios where screening was more costly overall than no screening. Sensitivity analyses were presented with a focus on incremental costs rather than the ICER. However, it appears that screening remained cost-effective in all modelled scenarios (assuming a threshold of €20,000 per QALY). In probabilistic	the healthcare system in the Netherlands. **Limitations** Some potentially serious limitations were identified: • The methodology and sources used to estimate cost and quality of life values were reported in insufficient detail. • Event rates were based on studies with a relatively short follow-up period. These data were extrapolated to cover the patient's expected lifetime, assuming the effect would remain constant over time. • The results of sensitivity analyses were not fully reported • Some key aspects do not appear to have been considered in sensitivity analysis (such as variation in quality of life estimates)

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Another authors received grants and honoraria from various pharmaceutical companies, including those developing, producing, and marketing new oral anticoagulants. Another author reported grants from Bayer and personal fees from Boehringer Ingelheim.		incorporated for evaluating positive MyDiagnostick readings for suspected atrial fibrillation. Drug costs (NOACs and warfarin) were estimated based on total costs as presented by the Dutch Care Institute Monitoring costs were based on average costs per patient per year. For patients receiving NOACs, the cost of an annual GP visit to measure renal function was included. The costs for IS and ICH were estimated, based upon the severity of the event. A higher cost was applied for the acute IS or ICH event. After this, all patients moved to the post-event phase with matching costs. Costs for fatal IS and fatal ICH were applied separately and derived from a study evaluating cost-effectiveness of treatment with statins in the prevention of coronary heart disease. Costs for managing systemic emobolims were estimated on the assumption that 50% of patients do not need intensive treatment. The cost was estimated using an average of the lowest and highest costs as defined by the Dutch Health Authority (NZA). The costs for acute MI were based on mean treatment costs, non-	sensitivity analysis, screening had a 99.8% probability of being cost-effective at a threshold of €20,000 per QALY.	

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		differentiating for type of MI and type of intervention applied. Costs for minor ECH were based on an assumption of one emergency room (ER) visit. Costs for major ECH were based on treatment costs for a GI haemorrhage. It was assumed that patients would make a full recovery from ECH within three months. **Source of quality of life data:** Baseline quality of live values were estimated on the basis of EQ-5D scores matching ICD codes for each event. A quality of life reduction for patients receiving anticoagulant therapy was applied (for patients receiving NOACs or warfarin). The quality of life impact of an IS or ICH event was estimated based on a non-randomized controlled cluster trial and a previous economic evaluation of rivaroxaban. In the trial, quality of life was measured at hospital discharge and six months after the event occurred. This was then subdivided based on modified Rankin Scales (mRS) of 0–1, 2–3, 4, and 5. The utilities from this trial were recalculated as part of the economic evaluation of rivaroxaban. For IS, the utilities		

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		were based on two categories: mRS 1–2 (minor) and 3–5 (major). For ICH, a weighted average was calculated between the mRS scores based on frequency. A higher disutility was applied in the model cycle where the event occurred. After this, patients moved to the post-event phase with matching utility. The quality of life impact of a major GI haemorrhage was estimated based on an assumption of a temporary utility of 0.8 for one week. Minor haemorrhage was assumed to have no disutility.		

Abbreviations
QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; EQ-5D: EuroQol five-dimensions questionnaire; CHA2DS2-VASc; modified Rankin Scale (mRS); ECG; BP-AF: blood pressure machine with AF detection algorithm; SL-ECG: Screening with single lead ECG; PPV: positive predictive value; NOAC: novel oral anticoagulants; ICH: intracranial haemorrhage; IS: ischaemic stroke; MI: myocardial infarction; ECH: extracranial haemorrhage; ER: emergency room; GI: gastrointestinal