National Institute for Health and Care Excellence

Final

Atrial fibrillation: diagnosis and management

Evidence review A: Effectiveness of tests for detection

NICE guideline NG196

Intervention evidence review

April 2021

Final

Developed by the National Guideline Centre, Royal College of Physicians

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1 Detection of AF - effectiveness of tests

1.1 Review question: What is the most clinically and cost-effective method for detecting atrial fibrillation in people with cardiovascular risk factors for AF and/or symptoms suggestive of AF?

1.2 Introduction

Understanding how best to detect AF in clinical practice has important implications for patients, healthcare professionals and the National Health Service. Knowing the optimal methods for AF detection would enable healthcare providers to organize and implement patient services more effectively. Conventional approaches for detecting AF involve identifying patients with an irregular pulse and then performing a 12-lead ECG in those with suspected AF, or using longer-term investigations such as 24 hour tape in those who have had an unexplained stroke. Since the last guideline review, different approaches to how AF can be detected have been investigated and, importantly, greater evidence for long-term clinical outcomes from these approaches have been reported. The evidence was therefore reviewed to assess both effectiveness and cost-effectiveness of different approaches to detect AF and compared to the currently accepted methods for AF detection.

1.3 PICO table

For full details see the review protocol in Appendix A:.

Table 1: PICO characteristics of review question

Population	People aged over 18 with symptoms suggestive of AF (including breathlessness, palpitations, syncope/dizziness, chest discomfort) and/or with cardiovascular risk factors for AF (including TIA, stroke, Heart Failure, hypertension, valve disease).
Intervention(s)	Any point of care tests used to detect AF For example (non-exhaustive list): • Manual pulse checking • Pulse oximeters • US devices • Blood pressure monitors • Non-portable (but non-12 lead) ECG devices • Portable ECG devices • Smart portable devices eg phones, watches • 12 lead ECG (when gold standard is long-term loop recording – see section below) Where the same test is used with a differing number of recordings across studies, these should be regarded as separate test strategies, and should thus be dealt with separately. Tests using differing periods of recording will also be dealt with separately.
Comparison(s)	Each other No test applied / usual care
Outcomes	• Quality of life • Mortality • Stroke and thromboembolism • Major bleeding

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	• All cause hospitalisation • Confirmed diagnosis of AF • Initiated anticoagulants for AF All outcomes deemed critical
Study design	RCTs

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[50] Methods specific to this review question are described in the review protocol in Appendix A:.

1.5 Clinical evidence

1.5.1 Included studies

A search was conducted for randomised trials comparing the effectiveness of different point of care diagnostic tests for atrial fibrillation. This did not include invasive tests such as implanted cardiac monitors as these are not point of care tests.

Twelve studies (14 RCTs) were included in the review.[3, 8, 20-22, 27, 31-33, 37-39, 57, 62]

These covered 9 different comparisons, as follows:

1. 2 year early detection programme using ECG, physical examination and medical history vs usual care[3]
2. 1 lead ECG vs usual care[8, 22, 27]
3. 48 hours Holter vs handheld event monitor[39]
4. Pulse palpation and ECG vs usual care[20, 32]
5. Skin-patch ECG vs usual care[38, 57]
6. Holter from 21-28 days vs usual care[33, 37]
7. Holter 3x10 days in 6 months vs usual care, including 24 hour or longer ECG[62]
8. Ambulatory ECG with 30 day event triggered event recorder vs 24 hour ECG[21]
9. Standard monitoring + 7 days non-invasive cardiac monitoring vs standard monitoring[31]

Comparisons 1-4 were in an out-patient setting, predominantly involving patients with symptoms suggestive of AF. Comparisons 7-9 involved in-patients with an acute stroke/TIA. Comparisons 5 and 6 both involved 2 studies, with one study from each category.

These are summarised in Table 2, and evidence from these studies is summarised in the clinical evidence summary (Table 3).

See also the study selection flow chart in Appendix C:, study evidence tables in Appendix D:, forest plots in Appendix E: and GRADE tables in Appendix F:.

1.5.2 Excluded studies

See the excluded studies list in Appendix I:.

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1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Expertise of intervention interpreter	comments
EARLY, 2015 trial: Benito 2015[3]	Intervention: A 2-year programme for early detection of AF was carried out in the intervention group, with an office visit every 6 months that involved an electrocardiogram (ECG), physical examination, and a complete medical history Comparator: Usual care. No other details given, except that 'no specific action was taken in the control group'.	Inclusion: From the electronic health records for this population, all patients without a diagnosis of AF but with one or more of the main risk factors for AF: age ≥ 65 years, arterial hypertension, ischaemic heart disease, valvular heart disease, diabetes, and/or congestive heart failure. The identification of all risk factors was based on the medical history recorded by each patient's physician, with some added conditions required for inclusion: (i) patients with a diagnosis of arterial hypertension or diabetes were included only if they received the corresponding treatment, (ii) valvular heart disease diagnosis had to be confirmed by an echocardiogram, (iii) ischaemic heart disease diagnosis had to be confirmed by an electrocardiogram, stress test, catheterization, or computed tomography angiogram, and (iv) heart failure diagnosis had to be confirmed by chronic treatment, an echocardiogram or an acute episode that required emergency care and/or hospital admission. Exclusion: Patients unable to come to the healthcare centre to participate in the study were excluded. Patients who	Not stated/unclear	Confirmation of AF diagnosis: *Intervention group* 10 = early detection programme, 1 = during hospital ER visit for UTI *Control group* 1 = private cardiologist diagnosis, 4 = incidental diagnosis 'in the hospital', 1= diagnosed during ER visit for HF

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Study	Intervention and comparison	Population	Expertise of intervention interpreter	comments
		had a pacemaker, could not be contacted by telephone, or declined to participate in the study were also excluded		
mSToPS, 2018 trial: Steinhubl 2018[57]	Intervention: ECG screening was carried out using the iRhythm ZioXT, a Food and Drug Administration–approved, single-use, water-resistant, 14-day, ambulatory ECG monitoring skin adhesive patch that monitors and retains in memory the wearer's continuous ECG for up to 2weeks Comparator: usual care. No additional treatment for the 4 month duration of the follow up	Inclusion: male age>55; female age >65; prior stroke/TIA or HF or DM and hypertension or mitral valve disease or LVH or COPD requiring home O2 or sleep apnea or PE or MI or obesity Exclusion: Current or prior AF, flutter or tachycardia; receiving OADs; hospice care; end stage renal disease; moderate or worse dementia; implantable pacemaker/defibrillator; skin allergy to adhesive patches; metastases; Aetna Compassionate Care Program participants	unclear	Confirmation of AF diagnosis: 30s or greater AF detected by device or new clinical diagnosis recorded in claims data For ethical reasons, the control group were given the skin patch treatment after the end of the study
REHEARSE AF trial: Halcox 2017[27]	Intervention: ECG devices - 1 lead handheld (AliveCor Heart Monitor). Participants in the intervention iECG arm were instructed to undertake twice-weekly recording and transmission of a 30-second single-lead iECG trace to a secure server (Monday and Wednesday recommended, plus additional submissions if symptomatic) over a 12-month period	Individuals >65 years of age with a CHADS-VASc score ≥2 not in receipt of OAC therapy without a known diagnosis of AF currently, a known contraindication to anticoagulation, or permanent cardiac pacing implantation were recruited. Participants were required to have access to the internet via WiFi and to be able to operate the AliveCor Kardia system (AliveCor Inc, Mountain View, CA) attached to an iPod (Apple Inc, Cupertino, CA) after simple instruction.	Cardiologist/electrophysiologist	Confirmation of AF diagnosis: 1 lead ECG – abnormal iECGs over-read by a cardiologist; control – diagnosed by local clinicians, with all AF diagnoses validated by study cardiologist

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Study	Intervention and comparison	Population	Expertise of intervention interpreter	comments
	Comparator: usual care. Patients in the RC arm were followed up as normal by their general practitioner. No other details given.			
Kinlay, 1996 trial: Kinlay 1996[39]	Intervention: Holter. 48 hours of Holter monitoring (Marquette Electronics) Comparator: Handheld event monitor (Aerotel; Medtronic). This is a transtelephonic post-event recorder. These handheld devices are given to patients and are applied to the chest when symptoms occur. The patient presses a button to record about 30 seconds of the cardiac rhythm, which is stored in the memory of the de- vice. The recording is later transmitted over the telephone for printing and interpretation. The patient kept the event monitor until two recordings were obtained during symptoms or until 3 months had passed	Inclusion: Patients referred to cardiovascular unit at Teaching Hospital with palpitations Exclusion: Researchers excluded patients being monitored for silent ischemia, assessment of therapy, syncope, or other research studies or inpatient monitoring; patients considered too old, too feeble, or too young to use the event monitor; and patients who had previously had Holter monitoring for their symptoms.	Cardiologist/electrophysiologist	Confirmation of AF diagnosis: tracings of Holter and event recorder read by blinded cardiologist

Study	Intervention and comparison	Population	Expertise of intervention interpreter	comments
SAFE, 2005 trial: Hobbs 2005[32] Fitzmaurice, 2007 trial: Fitzmaurice 2007[20]	Intervention: Pulse palpation + ECG. Pulse palpation given and if positive, 12 lead ECG performed. Comparator: usual care. No details given, but the usual strategies at the GP practices would have applied.	Inclusion: Study researchers recruited 50 general practices from the Midlands Research Practices Consortium (MidReC). All patients aged 65 or over from these practices were eligible for participation in the study, though patients could be excluded if their own general practitioner thought participation inadvisable. Exclusion: None	Unclear	Confirmation of AF diagnosis: identified in case notes at follow up The groups being evaluated in the paper were: opportunistic screening vs systematic screening vs usual care, but the paper contained useful information on tests (pulse palpation followed by ECG if pulse palpation was positive). This was used for both screening groups but only the results for the opportunistic arm were used as the intervention group. This is because the systematic arm involved all patients being invited for screening, whereas the opportunistic arm only involved palpation (and ECG if appropriate) during routine consultation. Only the latter bears relevance to this review.
Hoefman, 2005 trial: Hoefman 2005[33]	Intervention: Holter. A Card Guard CG-6106 loop recorder was used for up to 4 weeks. This recorder continuously registers and updates a two lead ECG. When a patient chooses to activate the recorder it stores information 30 seconds before and 2 minutes after the moment of activation. A maximum of three registrations could be stored in the memory,	Inclusion: Consecutive patients who consulted their GP for a new episode of palpitations and/or light-headedness were recruited from October 1999 until June 2002. Palpitations were defined as any feeling of an abnormal heartbeat or rhythm. Light headedness was defined as feelings of faintness or going to faint. Exclusion: Patients younger than 18 years, fitted with a pacemaker, being currently treated by a cardiologist, or needing immediate intervention and/or referral were excluded.	Cardiologist/electrophysiologist	Confirmation of AF diagnosis: GP diagnosis, based on all available information

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Study	Intervention and comparison	Population	Expertise of intervention interpreter	comments
	hereafter an acoustic signal indicated that the memory was fully stored. Comparator: usual care. Standard care. GP maintained responsibility for patient care and could use all regular health care interventions (including referral to cardiologists).			
Kamel, 2013 trial: Kamel 2013[37]	Intervention: Holter. Cardionet Mobile Cardiac Outpatient Telemetry for 21 days, after initial minimum of 24 hours hospital telemetry. Comparator: usual care – routine follow up, after initial minimum of 24 hours hospital telemetry.	Inclusion: Adult patients with ischemic stroke or high-risk transient ischemic attack (ABCD2 score ≥4). Exclusion: Patients with lacunar infarcts, ≥50% stenosis of relevant arteries, likely cardioembolism, or other apparent cause; patients ineligible to receive anticoagulation or with onset >60 days previously; patients with detected AF during 24 hours cardiac monitoring as inpatients with onset of symptoms >60 days previously	Unclear	Confirmation of AF diagnosis: 'new diagnosis of AF'. No information on how confirmed.
Find-AF, 2017 trial: Wachter 2017[62]	Intervention: Holter. 3 x 10 days Holter monitoring (with ECG analysis in a central core laboratory) within 6 months. Comparator: usual care. Standard care workup,	Inclusion: Eligible patients were 60 years or older with acute (clinical symptom onset ≤7 days) ischaemic strokes (documentation of an acute lesion on brain imaging or duration of symptoms ≥24 h). We included patients for whom the detection of atrial fibrillation has therapeutic consequences and for whom no evidence-based therapy is available	Cardiologist/electrophysiologist	Confirmation of AF diagnosis: assessed by expert adjudication committee'

Study	Intervention and comparison	Population	Expertise of intervention interpreter	comments
	including 24 hr or longer ECG (Holter or telemetry)	after minimal diagnostic work-up (admission ECG and ultrasonography of the brain supplying arteries). Exclusion: patients with known or documented atrial fibrillation, those with an indication or contraindication for oral anticoagulation, and those with a relevant symptomatic ipsilateral carotid stenosis		
Gladstone, 2014 trial: Gladstone 2014[21]	Intervention: Ambulatory ECG monitoring with a 30 day event-triggered loop recorder, after standard 24 hour ECG. Comparator: 24 hour ECG monitoring after standard 24 hour ECG	Inclusion: Patients were eligible for enrolment if they were 55 years of age or older, did not have known atrial fibrillation, and had had an ischemic stroke or TIA of undetermined cause (according to TOAST [Trial of Org 10172 in Acute Stroke Treatment] criteria) within the previous 6 months, diagnosed by a stroke neurologist after a standard workup, including 12-lead ECG, ambulatory ECG monitoring with the use of a Holter monitor for a minimum of 24 hours, brain and neurovascular imaging, and echocardiography Exclusion: Patients were excluded if the most likely etiologic diagnosis had already been determined (large-vessel or small-vessel disease or other known cause).	Cardiologist/electrophysiologist	
Higgins, 2013 trial: Higgins 2013[31]	Intervention: Patients randomized to the intervention group underwent usual standard practice investigation (see	Inclusion: Patients within 7 days of TIA or acute ischaemic stroke Exclusion: History of AF or atrial flutter; any irreversible condition for long term anticoagulation	Cardiologist/electrophysiologist	Confirmation of AF diagnosis: ECG confirmed

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Study	Intervention and comparison	Population	Expertise of intervention interpreter	comments
	comparator description) plus additional monitoring (AM) for the detection of AF (SP-AM). AM comprised 7 days of noninvasive cardiac-event monitoring, performed with the Novacor R-test Evolution 3 device. Comparator: Standard practice monitoring. Investigations that afforded the opportunity for AF detection comprised additional 12-lead ECGs (subsequent to the admission 12-lead ECG), 24-hour Holter monitoring, and echocardiography (which, as coupled with cardiac rhythm monitoring, afforded the opportunity for AF detection). 24-hour Holter recordings were reported centrally at the recruiting hospital cardiology laboratory and reviewed thereafter by treating clinicians.			
Kaura, 2019[38]	Intervention: 14 day ECG skin patch: ZioPatch® (iRhthym Technologies, USA). This is an adhesive cardiac monitoring patch which provides an	Inclusion: Eligible patients were 18 years of age or older and were diagnosed with having had an ischaemic non-lacunar stroke or TIA within the past 72 h by a stroke physician or neurologist. Patients with a TIA were	Unclear	Confirmation of diagnosis: ECG confirmed

Study	Intervention and comparison	Population	Expertise of intervention interpreter	comments
	alternative method for prolonged ECG monitoring for the detection of PAF. The waterproof patch is applied non-invasively to the anterior chest wall for continuous monitoring for up to 14 days without requiring any complex setup. The ECG trace uses the Zio XT algorithmic support to highlight areas for human interpretation. Comparator: Usual care, including short duration Holter	enrolled only if there were cortical symptoms of hemianopia or dysphasia at presentation or if their diffusion-weighted cerebral MRI scan was positive in a non-lacunar distribution. Exclusion: The main exclusion criteria were a history of AF or atrial flutter, carotid stenosis > 50%, a pre-existing indication or contraindication for permanent anticoagulation therapy		
Goldenthal, 2019[22] Caceres, 2020[8]	Intervention: Alive Cor. AliveCor Kardia Mobile for 6 months. Patients randomized to the iHEART intervention received an iPhone and cellular service plan with unlimited data/text messaging, and the Alive Cor Kardia Mobile ECG monitor for 6 months. If they already owned a smartphone compatible with the Kardia Mobile device, they had the option to use the KardiaMobile device with their own phone.	Been treated for AF (see comments) with ablation or cardioversion leading to normal sinus rhythm immediately after the procedure; age 18 and older; a history of documented AF and at least one AF risk factor (sedentary lifestyle, obesity, hypertension, smoking, and diabetes). Exclusion: Patients with a history of cognitive impairment and those unwilling to have their clinical data collected or receive text messages were excluded from the study.	Unclear	This population had pre-existing AF, and thus appears to be from a different population to the protocol population (people for whom there is a suspicion of AF), but the study has been included because the participants had been successfully treated with ablation/cardioversion within 30 days previously, and therefore there would be a need to test for AF recurrence. In this way, the paper is in line with other papers, where the primary aim is to detect AF. However to reflect the different population the GRADE rating has been downgraded for 'indirectness'.

Study	Intervention and comparison	Population	Expertise of intervention interpreter	comments
	Comparator: standard care			Confirmation of diagnosis: Recurrence was defined as one of the following: a KardiaMobile rhythm strip showing AF/AFL as determined by a physician, an ECG in the EHR displaying an AF/AFL confirmed by a physician, or a note in the EHR from a physician stating that the patient had a recurrent AF/AFL.

See Appendix D:for full evidence table.

1.5.4 Quality assessment of clinical studies included in the evidence review. Follow ups are the longest available.

Table 3: Clinical evidence summary: Holter 21-30 days versus usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Holter 21-30 days versus usual care (95% CI)
Health related quality of life	0 (0)		Not estimable		
Mortality	0 (0)		Not estimable		
Stroke and systemic thromboembolism	0 (0)		Not estimable		
Major bleeding	0 (0)		Not estimable		
All-cause hospitalisation	0 (0)		Not estimable		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Holter 21-30 days versus usual care (95% CI)
Confirmed diagnosis of AF	284 (2 studies) 21-28 days	⊕⊕⊕⊖ MODERATE[a] due to risk of bias	RD 0.05 (-0.03 to 0.12)	Moderate	
				9 per 1000	50 more per 1000 (from 30 fewer to 120more)
Initiated anticoagulation for AF	0 (0)		Not estimable		

[a] serious risk of bias due to lack of reporting of allocation concealment

Table 4: Clinical evidence summary: Holter 3x10d over 6m versus usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Holter 3x10d over 6m versus usual care (95% CI)
Health-related quality of life	0 (0)		Not estimable		
Mortality	398 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	RR 0.66 (0.24 to 1.82)	Moderate	
				46 per 1000	16 fewer per 1000 (from 35 fewer to 38 more)
Stroke and thromboembolic complications	398 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW[b c] due to risk of bias, imprecision	RR 0.57 (0.24 to 1.32)	Moderate	
				71 per 1000	31 fewer per 1000 (from 54 fewer to 23 more)
major bleeding	398 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW[b],c due to risk of bias, imprecision	RR 2.97 (0.31 to 28.31)	Moderate	
				5 per 1000	10 more per 1000 (from 3 fewer to 137 more)
All cause hospitalisation	0				

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Holter 3x10d over 6m versus usual care (95% CI)
	(0)		Not estimable		
Confirmed diagnosis of AF	398 (1 study) 6 months	⨁⨁⨁⨀ MODERATE[a] due to imprecision	RR 2.23 (1.16 to 4.27)	Moderate	
				61 per 1000	75 more per 1000 (from 10 more to 199 more)
Initiating OACs	398 (1 study) 6 months	⨁⨁⨁⨀ MODERATE[a] due to imprecision	RR 2.23 (1.16 to 4.27)	Moderate	
				61 per 1000	75 more per 1000 (from 10 more to 199 more)

[a] 95% CIs crossed one MID
[b] No HCP or patient blinding (can affect objective outcomes through differences in care or belief about care)
[c] 95% CIs crossed both MIDs

Table 5: Clinical evidence summary: Ambulatory ECG with 30 day event monitor compared to 24 hr ECG

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 24 hr ECG	Risk difference with Ambulatory ECG with 30 day event monitor (95% CI)
Health-related quality of life	0 (0)		Not estimable		
Mortality	572 (1 study) 90 days	⨁⨀⨀⨀ VERY LOW[b,c] due to risk of bias, imprecision	RR 0.99 (0.06 to 15.8)	Moderate	
				4 per 1000	0 fewer per 1000 (from 4 fewer to 59 more)
Stroke and thromboembolic complications	572 (1 study) 90 days	⨁⨀⨀⨀ VERY LOW[b,c] due to risk of bias, imprecision	RR 0.99 (0.06 to 15.8)	Moderate	
				4 per 1000	60 fewer per 1000 (from 4 fewer to 59 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 24 hr ECG	Risk difference with Ambulatory ECG with 30 day event monitor (95% CI)
Major bleeding	0 (0)		Not estimable		
All cause hospitalisation	0 (0)		Not estimable		
Confirmed diagnosis of AF	561 (1 study) 90 days	⨁⨁⨁⨀ MODERATE[a] due to risk of bias	RR 6.13 (2.81 to 13.38)	Moderate	
				25 per 1000	128 more per 1000 (from 45 more to 310 more)
initiated OACs for AF	559 (1 study) 90 days	⨁⨁⨀⨀ LOW[a,d] due to risk of bias, imprecision	RR 1.67 (1.11 to 2.53)	Moderate	
				111 per 1000	74 more per 1000 (from 12 more to 170 more)

[a] serious risk of bias due to unclear reporting of allocation concealment
[b] Very serious risk of bias due to lack of allocation concealment; also no patient or HCP blinding, which could influence even objective outcomes due to differences in care or belief about care.
[c] 95% CIs crossed both MIDs
[d] 95% CIs crossed 1 MID

Table 6: Clinical evidence summary: Holter 48hrs versus handheld event monitor

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Holter 48hrs versus handheld event monitor (95% CI)
Health related quality of life	0 (0)		Not estimable		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Holter 48hrs versus handheld event monitor (95% CI)
Mortality	0 (0)		Not estimable		
Stroke and systemic thromboembolism	0 (0)		Not estimable		
Major bleeding	0 (0)		Not estimable		
All-cause hospitalisation	0 (0)		Not estimable		
Confirmed diagnosis of AF	86 (1 study) 3 months	⨁⨁⨀⨀ LOW[a] due to imprecision	Peto OR 0.13 (0.01 to 1.27)	Moderate	
				70 per 1000	60 fewer per 1000 (from 69 fewer to 17 more)
Initiated anticoagulation for AF	0 (0)		Not estimable		

[a] 95% CIs crossed both MIDs

Table 7: Clinical evidence summary: Skin patch ECG compared to usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Skin patch ECG (95% CI)
Health related quality of life	0 (0)		Not estimable		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Skin patch ECG (95% CI)
Mortality	91 (1 study) 90 days	⨁⨀⨀⨀ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 7.91 (0.16 to 399.51)	Moderate	
				0 per 1000	20 more per 1000 (from 40 fewer to 80 more)
Stroke and systemic thromboembolism	90 (1 study) 90 days	⨁⨀⨀⨀ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.09 (0.07 to 16.94)	Moderate	
				21 per 1000	2 more per 1000 (from 20 fewer to 335 more)
Major bleeding	0 (0)		Not estimable		
All cause hospitalisation	0 (0)		Not estimable		
confirmed diagnosis of AF	2749 (2 studies) 90 days – 4 months	⨁⨁⨁⨀ MODERATE[a] due to risk of bias	RR 4.43 (2.45 to 8.02)	Moderate	
				15 per 1000	51 more per 1000 (from 22 more to 105 more)
OAC initiation	90 (1 study) 90 days	⨁⨁⨀⨀ LOW[a,b] due to risk of bias, imprecision	RR 7.65 (0.98 to 59.68)	Moderate	
				21 per 1000	140 more per 1000 (from 0 fewer to 1000 more)

[a] Serious risk of bias for attrition bias, and very serious risk of bias for attrition and performance bias
[b] Imprecision serious if the 95% Cis crossed one MID and very serious if they crossed both MIDs

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Table 8: Clinical evidence summary: 2 year early detection program inc. ECG compared to usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with 2 year early detection program inc. ECG (95% CI)
Health related quality of life	0 (0)		Not estimable		
mortality	928 (1 study) 2 years	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.88 (0.32 to 2.4)	Moderate	
				17 per 1000	2 fewer per 1000 (from 12 fewer to 24 more)
Stroke and thromboembolic complications	0 (0)		Not estimable		
Major bleeding	0 (0)		Not estimable		
All cause hospitalisation	0 (0)		Not estimable		
Confirmed diagnosis of AF	902 (1 study) 2 years	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.92 (0.72 to 5.16)	Moderate	
				13 per 1000	12 more per 1000 (from 4 fewer to 54 more)
Initiation of OACS	902 (1 study) 2 years	⊕⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 5.25 (1.16 to 23.83)	Moderate	
				4 per 1000	17 more per 1000 (from 1 more to 91 more)

[a]Very serious risk of bias due to unclear allocation concealment and possible attrition bias
[b] 95% CIs crossed both MIDs
[c] 95% CIs crossed 1 MID

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Table 9: Clinical evidence summary: 1 lead handheld ECG compared to usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with 1 lead handheld ECG (95% CI)
Health-related quality of life – Atrial Fibrillation Effect on Quality of Life (higher score better)	262(1 study) 6 months	⊕⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness	MD: 7.3(-1.13 to 15.73)	NA	The 1 lead ECG group were 7.3 points better than the usual care group (95% CIs: 1.13 points worse to 15.73 points better)
Health-related quality of life – SF-36 physical (higher score better)	262(1 study) 6 months	⊕⊖⊖⊖ VERY LOW[a,c] due to risk of bias, indirectness	1.2 (-1.35 to 3.75)	NA	The 1 lead ECG group were 1.2 points better than the usual care group (95% CIs: 1.35 points worse to 3.75 points better)
Health-related quality of life – SF-36 mental (higher score better)	262(1 study) 6 months	⊕⊖⊖⊖ VERY LOW[a,c] due to risk of bias, indirectness	MD: -0.5 (-3.24 to 2.24)	NA	The 1 lead ECG group were 0.5 points worse than the usual care group (95% CIs: 3.24 points worse to 2.24 points better)
EuroQol index (higher score better)	262(1 study) 6 months	⊕⊖⊖⊖ VERY LOW[a,c] due to risk of bias, indirectness	MD: 0 (-0.059 to 0.059)	NA	The 1 lead ECG group were 0 points better than the usual care group (95% CIs: 0.059 points worse to 0.059 points better)
EuroQol VAS (higher score better)	262(1 study) 6 months	⊕⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness	MD: 4.3 (-1.38 to 9.98)	NA	The 1 lead ECG group were 4.3 points better than the usual care group (95% CIs: 1.38 points worse to 9.98 points better)
Health-related quality of life – University of Toronto Atrial Fibrillation Severity Scale (higher score worse)	262(1 study) 6 months	⊕⊖⊖⊖ VERY LOW[a,c] due to risk of bias, indirectness	MD: -0.8 (-3.74 to 2.14)	NA	The 1 lead ECG group were 0.8 points better than the usual care group (95% CIs: 2.14 points worse to 3.74 points better)
mortality	999 (1 study) 1 year	⊕⊖⊖⊖ VERY LOW[a,d]	RR 0.6 (0.15 to 2.51)	Moderate	
				10 per 1000	4 fewer per 1000 (from 8 fewer to 15 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with 1 lead handheld ECG (95% CI)
		due to risk of bias, imprecision			
Stroke and thromboembolism	998 (1 study) 1 year	⨁⊖⊖⊖ VERY LOW[a,d] due to risk of bias, imprecision	RR 0.6 (0.22 to 1.64)	Moderate	
				20 per 1000	8 fewer per 1000 (from 16 fewer to 13 more)
major bleeding	999 (1 study) 1 year	⨁⊖⊖⊖ VERY LOW[a,d] due to risk of bias, imprecision	RR 2.01 (0.18 to 22.12)	Moderate	
				2 per 1000	2 more per 1000 (from 2 fewer to 42 more)
Hospitalisation	233 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness	RR 0.82 (0.61 to 1.11)	Moderate	
				475 per 1000	86 fewer per 1000 (from 185 fewer to 52 more)
confirmed diagnosis of AF	1232 (2 studies) 6 months – 1 year	⨁⊖⊖⊖ VERY LOW[a,d] due to risk of bias, imprecision	RR 1.97 (0.62 to 6.30)	Moderate	
				87 per 1000	207 more per 1000 (from 81 fewer to 1000 more)
initiation of OACs	999 (1 study) 1 year	⨁⨁⨁⨁ HIGH	RR 4.78 (1.64 to 13.95)	Moderate	
				8 per 1000	30 more per 1000 (from 5 more to 104 more)

[a] Serious risk of bias because of a lack of patient or HCP blinding, which can affect even objective outcomes because of differences in care or belief about care

[b] 95% CIs crossed 1 MID. For quality of life outcomes, the MIDs were defined by 0.5 x sd in the control group at baseline. Accordingly, MIDS were 12.6 for Atrial Fibrillation Effect on Quality of Life, 4.75 for SF-36 physical, 4.8 for SF-36 mental, 0.105 for EQ5D index, 7.35 for EQ-5D VAS, and 4.95 for University of Toronto Atrial Fibrillation Severity Scale

[c] Downgraded for indirectness as population had received ablation, and therefore slightly different to protocol population

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with 1 lead handheld ECG (95% CI)
[d] 95% Cis crossed both MIDs. For quality of life outcomes, the MIDs were defined by 0.5 x sd in the control group at baseline. Accordingly, MIDS were 12.6 for Atrial Fibrillation Effect on Quality of Life, 4.75 for SF-36 physical, 4.8 for SF-36 mental, 0.105 for EQ5D index, 7.35 for EQ-5D VAS, and 4.95 for University of Toronto Atrial Fibrillation Severity Scale					

Table 10: Clinical evidence summary: 7 days cardiac monitoring + standard monitoring compared to standard monitoring alone

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard monitoring alone	Risk difference with 7 days cardiac monitoring + standard monitoring (95% CI)
Health-related quality of life	0 (0)		Not estimable		
mortality	0 (0)		Not estimable		
Stroke and thromboembolic complications	0 (0)		Not estimable		
Major bleeding	0 (0)		Not estimable		
All cause hospitalisation	0 (0)		Not estimable		
				Moderate	

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard monitoring alone	Risk difference with 7 days cardiac monitoring + standard monitoring (95% CI)
confirmed diagnosis of AF	100 (1 study) 90 days	⨁⨁⨁⊖ MODERATE[a] due to imprecision	RR 2.75 (0.94 to 8.06)	80 per 1000	140 more per 1000 (from 5 fewer to 565 more)
Initiation of OACs	100 (1 study) 90 days	⨁⨁⨁⊖ MODERATE[a] due to imprecision	RR 2.6 (1 to 6.75)	Moderate	
				100 per 1000	160 more per 1000 (from 0 more to 575 more)

[a] 95% CIs crossed 1 MID

Table 11: Clinical evidence summary: Pulse palpation and ECG versus usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Pulse palpation and ECG versus usual care (95% CI)
Health related quality of life	0 (0)		Not estimable		
Mortality	0 (0)		Not estimable		
Stroke and systemic thromboembolism	0 (0)		Not estimable		
Major bleeding	0 (0)		Not estimable		
All-cause hospitalisation	0 (0)		Not estimable		
Confirmed diagnosis of AF				Moderate	

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Pulse palpation and ECG versus usual care (95% CI)
	9088 (1 study) 1 year	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 1.57 (1.10 to 2.26)	10 per 1000	6 more per 1000 (from 1 more to 13 more)
Initiated anticoagulation for AF	0 (0)		Not estimable		

[a] serious risk of bias due to unclear allocation concealment
[b] Population included people outside review population
[c] 95% CIs crossed 1 MID

See Appendix F: for full GRADE tables.

1.6 Economic evidence

1.6.1 Included studies

One health economic study with the relevant comparison was included in this review.[17, 51] This is summarised in the health economic evidence profile below (Table 12) and the health economic evidence table in Appendix H:.

1.6.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G:.

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1.6.3 Summary of studies included in the economic evidence review

Table 12: Health economic evidence profile: Standard diagnostic pathway vs lead-I devices

Study	Applicability	Limitations	Other comments	Mean cost (d) (e)	Mean effects (QALYs) (e)	Cost effectiveness (e)	Uncertainty
Duarte 2019[17] [51](UK)	Partially applicable [(a)]	Potentially serious limitations[(b)]	• Probabilistic model based on meta-analysis of RCTs (systematic review conducted in same paper) • Cost-utility analysis (QALYs) • Population: Adults with signs or symptoms indicative of AF plus irregular pulse assessed by manual pulse palpations presenting at primary care. • Comparators:[(c)] **Intervention 1:** Standard diagnostic pathway (all sent for 12-lead ECG, no treatment of AF whilst waiting for 12-lead ECG test. Further testing for paroxysmal AF using holter monitor undertaken for those with negative 12 lead ECG.) **Intervention 2:** Kardia Mobile (interpreted by trained healthcare professional) **Intervention 3:** imPulse (interpreted by trained healthcare professional) **Intervention 4:** MyDiagnostick (interpreted by trained healthcare professional) **Intervention 5:**	<u>Base Case 1:</u> 1: £9,543 2: £9,569 3: £9,851 4: £9,674 5: £9,590 6: £9,623 7: £9,622 <u>Base Case 2:</u> 1: £9,547 2: £9,566 3: £9,848 4: £9,671 5: £9,588 6: £9,620 7: £9,619 <u>Base Case 3:</u> 1: £9,585 2: £9,604 3: £9,886 4: £9,709 5: £9,626 6: £9,658 7: £9,657	<u>Base Case 1:</u> 1: 8.314 2: 8.338 3: 8.333 4: 8.334 5: 8.338 6: 8.337 7: 8.325 <u>Base Case 2:</u> 1: 8.313 2: 8.337 3: 8.333 4: 8.333 5: 8.337 6: 8.336 7: 8.325 <u>Base Case 3:</u> 1: 8.314 2: 8.338 3: 8.333 4: 8.334 5: 8.338 6: 8.337 7: 8.325	**ICER (2 vs. 1):** <u>Base Case 1:</u> £1,060 per QALY gained (pa) <u>Base Case 2:</u> £749 per QALY gained (pa) <u>Base Case 3:</u> £783 per QALY gained (pa) <u>Base Case 4:</u> £481 per QALY gained (pa) <u>In all Base Cases:</u> **Intervention 2 dominates** (less costly and more effective**) the other interventions** (3,4,5,6 and 7)	Probability Kardia mobile cost effective (£20K threshold): just over 80% **Analysis of uncertainty:** Number of scenario analyses conducted. Results were sensitive to using alternative sensitivity and specificity values for MyDiagnostick. However, Kardia Mobile remained the most cost effective option. The one-way sensitivity

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Study	Applicability	Limitations	Other comments	Mean cost (d) (e)	Mean effects (QALYs) (e)	Cost effectiveness (e)	Uncertainty
			any lead-I ECG device (interpreted by trained healthcare professional) **Intervention 6:** Zenicor-ECG (interpreted by trained healthcare professional) **Intervention 7:** RhythmPad-GP (interpreted by algorithm) Time horizon: 30 years	<u>Base Case 4:</u> 1: £9,589 2: £9,601 3: £9,883 4: £9,706 5: £9,623 6: £9,655 7: £9,654	<u>Base Case 4:</u> 1: 8.313 2: 8.337 3: 8.333 4: 8.333 5: 8.337 6: 8.336 7: 8.325	95% CI: NR	analysis showed that the results were sensitive to the assumed prevalence of paroxysmal AF versus persistent and permanent AF. (f)

Abbreviations: ECG: echocardiogram; ICER= incremental cost-effectiveness ratio; pa= probabilistic analysis; QALY= quality-adjusted life years; RCT= randomised controlled trial

(a) Does not include all comparators in protocol

(b) Economic evaluation is limited by the lack of diagnostic test accuracy data in the population of interest; therefore the results are based on data from asymptomatic population. The resource use data and outcomes data were not based on a systematic review and may not reflect full body of evidence. The economic evaluation is only relevant to primary care practices where patients have to wait at least 48 hours between an initial consultation with the GP and a 12-lead ECG.

(c) Interventions 2-7: all positives are diagnosed with AF and sent for 12-lead ECG. They will commence treatment for AF prior to 12-lead ECG (rate control and anticoagulation). If12-lead negative, a proportion will have paroxysmal testing with a holter monitor and a proportion will have AF ruled out. For negative lead-I, a proportion would have 12-lead, a proportion would have holter and a proportion would have AF ruled out. None would commence any treatment for AF until further tests undertaken.

(d) 2018 costs UK pounds. Cost components incorporated: Device costs, cost of tests, treatment, prescriptions, monitoring, and cardiovascular and adverse event costs.

(e) Base Case 1: 12-lead ECG in primary care, 2 days to 12-lead ECG; Base Case 2: 12-lead ECG in primary care, 14 days to 12-lead ECG; Base Case 3: 12-lead ECG in secondary care, 2 days to 12-lead ECG; Base Case 4: 12-lead ECG in secondary care, 14 days to 12-lead ECG

(f) Decreased prevalence of paroxysmal AF increased incremental costs and decreased incremental QALYs for lead-I ECG devices versus the standard pathway. In an extreme scenario, where the prevalence of paroxysmal AF was assumed to be zero, incremental QALYs decreased sufficiently to become negative and resulted in some lead-I ECG devices (ImPulse, MyDiagnostick and RhythmPad) being dominated by the standard pathway. Increasing the prevalence of paroxysmal AF to 1 resulted in all lead-I ECG devices except ImPulse and MyDiagnostick dominating the standard pathway.

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1.6.4 Unit costs

Current practice in primary care is manual pulse checking in people with symptoms suggestive of AF and in people with cardiovascular risk factors. This is followed by a 12 lead ECG in those who are found to have an irregular pulse.

The manual pulse checking is not considered to incur significant additional time and therefore could be done during a standard GP consultation.

The 12 lead ECG however would be an additional cost. This is either done within the GP practice where a 12-lead ECG is available or they are referred to hospital for the test. The results of the tests would need to be interpreted whether they are conducted in the practice or in hospital. The committee noted this would likely be done by the GP, and in some cases they may seek advice and guidance from a cardiologist.

The cost of having a 12-lead ECG within a GP practice was micro-costed in the Lead-1 DG35,[17, 51] using resource use data from a screening study for AF in the NHS (Hobbs et al 2005[32]). This is summarised in Table 13.The unit cost of having the ECG test conducted in hospital is also provided by DG35 but has been updated using the current 2017/2018 NHS reference cost[15] (Table 13).

In addition to the unit costs provided from DG35, the unit costs of a GP (per standard consultation), practice nurse, advice and guidance from a cardiologist are provided in Table 14 for consideration.

Table 13: Healthcare costs per 12-lead ECG test (primary and secondary care) NICE DG35

	Unit cost	Source	Activity	Time taken	Cost per test
Primary care[32]					
Device	£2.25 per use	Estimate			£2.25
Disposables	£1.13 per use	Hobbs 2005			£1.13
Nurse	£42 per hour	PSSRU	Administration	7 min*	£4.90
GP	£137 per hour	PSSRU	Interpretation	1min*	£2.28
Cardiologist	£107 per hour	PSSRU	Interpretation	1min*	£1.78
Total cost per 12-lead ECG test in primary care					£12.34
Secondary care					
Electrocardiogram monitoring or stress testing	£38 per test	NHS reference costs 2017/18[15] (HRG: EY51Z DADS)			£38

** Based on Hobbs 2005[32]*

Table 14: Unit costs associated with ECG

Item	Unit cost
General practitioner (per 9.22 min consultation)	£37[(a)]
General practice nurse (per hour)	£42[(a)]
Advice and guidance from cardiologist	£30[(b)]

Source: (a) PSSRU Unit costs 2018[9]; (b) non-mandatory benchmark price for advice and guidance, tariff with two working day quality standard met, source: 2019/2020 National Tariff Payment System: non-mandatory currencies and prices.[52]

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A number of alternatives to manual pulse checking and ECGs were reported in the two reviews for this question.

Some of the comparators are a 12 lead ECG interpreted by someone other than a cardiologist (in some cases a more junior member of staff) or even a computer algorithm. The difference in cost will be staff time and/or the acquisition of the algorithm.

Unit costs for some of the alternative technologies that are mentioned in the clinical review are provided in Table 15. This is not a comprehensive list but rather illustrative of the cost. Of note the equipment that remains within a GP practice would be used multiple times and so the cost per patient would be the cost of the machine divided by the total usage over the machine lifetime. Please note mobile phone apps or the cost of a mobile phone were not included in this illustration, these are used in PPG comparators.

Table 15: Unit costs of alternative technologies

Item	Unit cost
Home based / mobile monitors	
AliveCor Kardia Mobile: Electrocardiograph Handheld Cordless includes Arrhythmia Screening Device Screen Display a Min of 200 Readings Storage English Manual uses a free app with Auto AF Detection	£102.11
Omron HCG-801-E: Electrocardiograph handheld Cordless includes Arrhythmia screening Device on Screen Display and has a Minimum of 200 Readings Storage and English Manual Heartscan Basic Unit no Software Optional Extra Indicates Potential ECG A	£246.31
Microlife WATCHBPHOME(A): Automatic with AFIB detection complete with carry case and standard adult cuff 5 years warranty	£103.23
Holter monitor	
Novacor: R.Test Evolution 4 - automatic arrythmia detection device	£2185.02
Clinic based monitors	
Microlife WATCHBP03-AFIB: Automatic with AFIB detection complete with pouch & straps with standard adult cuff 5 years warranty	£1,670.97
Mircolife WATCHBP-O3AFIB: WatchBP Two Cuffs includes Software and AFIB Detection 5 Year Warranty	£851.62

Source: NHS Supply Chain Catalogue 2018[53]

Of note, the NICE DG35[17, 51] included the unit costs of Lead-1 devices, reported in Table 16 and Table 17 for consideration:

Table 16: Cost per lead-I ECG test from NICE DG35

Device	Annual device cost (exc. VAT)	Number of patients tested per year	Peripherals cost per test	Unit cost per test*
imPulse	£87.50	54	0.00	£1.62
Kardia Mobile	£16.50	54	0.00	£0.31
MyDiagnostick	£90.00	54	0.00	£1.67
RhythmPadGP	£1,100.00	54	0.00	£20.42
Zenicor ECG	£613.27	54	0.02	£11.40
Generic lead-I device	£381.45	54	0.02	£7.10

**some costs may not calculate precisely due to rounding*
Source: NICE DG35[17, 51]

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Table 17: Cost of administration and interpretation of lead-1 ECG test NICE DG35

	Unit cost	Source	Time taken	Cost per test
Algorithm	£0		0	£0
GP(a)	£0		0	£0
Cardiologist	£107 per hour	PSSRU	1 minute(b)	£1.78

Source: NICE DG35[17, 51]
(a) Assumes done in consultation
(b) Based on Hobbs 2005[32]

1.6.5 Health economic evidence statement

- One cost-utility analysis found that in adults with signs or symptoms indicative of AF plus irregular pulse assessed by manual pulse palpations presenting at primary care, Kardia Mobile (interpreted by trained healthcare professional) was cost effective compared to a standard diagnostic pathway (ICER range depending on base case scenario: £1,060-£481 per QALY gained). It also found that Kardia Mobile was dominant (less costly and more effective) compared to imPulse (interpreted by trained healthcare professional), MyDiagnostick (interpreted by trained healthcare professional), any lead-I ECG device (interpreted by trained healthcare professional), Zenicor-ECG (interpreted by trained healthcare professional) and RhythmPad-GP (interpreted by algorithm). This analysis was assessed as partially applicable with potentially serious limitations.

1.7 The committee's discussion of the evidence

Please see evidence review B.

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References

1. Amara W, Montagnier C, Cheggour S, Boursier M, Gully C, Barnay C et al. Early detection and treatment of atrial arrhythmias alleviates the arrhythmic burden in paced patients: the SETAM study. Pacing and Clinical Electrophysiology. 2017; 40(5):527-536

2. Anonymous. Diagnosis of atrial fibrillation: which role for 24-hour holter monitoring? Zeitschrift für Allgemeinmedizin. 2015; 91(6):249-250

3. Benito L, Coll-Vinent B, Gomez E, Marti D, Mitjavila J, Torres F et al. EARLY: A pilot study on early diagnosis of atrial fibrillation in a primary healthcare centre. Europace: European Pacing, Arrhythmias, and Cardiac Electrophysiology. 2015; 17(11):1688-1693

4. Berg J, Lindgren P, Nieuwlaat R, Bouin O, Crijns H. Factors determining utility measured with the EQ-5D in patients with atrial fibrillation. Quality of Life Research. 2010; 3:381-390

5. Brachmann J, Morillo CA, Sanna T, Di Lazzaro V, Diener HC, Bernstein RA et al. Uncovering atrial fibrillation beyond short-term monitoring in cryptogenic stroke patients: Three-year results from the Cryptogenic Stroke and Underlying Atrial Fibrillation Trial. Circulation: Arrhythmia and Electrophysiology. 2016; 9(1):e003333

6. Brachmann J, Sanna T, Diener HC, Morillo C. Study of continuous cardiac monitoring to assess atrial fibrillation after cryptogenic stroke (CRYSTAL-AF). 2009. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00784265/full Last accessed: 04/02/2020.

7. Burkowitz J, Merzenich C, Grassme K, Bruggenjurgen B. Insertable cardiac monitors in the diagnosis of syncope and the detection of atrial fibrillation: a systematic review and meta-analysis. European Journal of Preventive Cardiology. 2016; 23(12):1261-1272

8. Caceres BA, Hickey KT, Bakken SB, Biviano AB, Garan H, Goldenthal IL et al. Mobile electrocardiogram monitoring and health-related quality of life in patients with atrial fibrillation: findings from the iPhone Helping Evaluate Atrial Fibrillation Rhythm Through Technology (iHEART) study. Journal of Cardiovascular Nursing. 2020; 35(4):327-336

9. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ. 2005; 331(7521):897-900

10. Chan PH, Wong CK, Pun L, Wong YF, Wong MMY, Chu DWS et al. Head-to-head comparison of the AliveCor heart monitor and Microlife WatchBP Office AFIB for atrial fibrillation screening in a primary care setting. Circulation. 2017; 135(1):110-112

11. Chua SK, Chen LC, Lien LM, Lo HM, Liao ZY, Chao SP et al. Comparison of arrhythmia detection by 24-hour holter and 14-day continuous electrocardiography patch monitoring. Acta Cardiologica Sinica. 2020; 36(3):251-259

12. Coutts SB, Choi PMC. Seven days of non-invasive cardiac monitoring early postischaemic stroke or TIA increases atrial fibrillation detection rate compared with current guideline-based practice. Evidence-Based Medicine. 2014; 19(4):152

13. Da Costa A, Defaye P, Romeyer-Bouchard C, Roche F, Dauphinot V, Deharo JC et al. Clinical impact of the implantable loop recorder in patients with isolated syncope, bundle branch block and negative workup: a randomized multicentre prospective study. Archives of Cardiovascular Diseases. 2013; 106(3):146-154

ISBN: 978-1-4731-4043-1

14. Dahal K, Chapagain B, Maharjan R, Farah HW, Nazeer A, Lootens RJ et al. Prolonged cardiac monitoring to detect atrial fibrillation after cryptogenic stroke or transient ischemic attack: a meta-analysis of randomized controlled trials. Annals of Noninvasive Electrocardiology. 2016; 21(4):382-388

15. Department of Health. NHS reference costs 2017-18. 2018. Available from: https://improvement.nhs.uk/resources/reference-costs/#rc1718 Last accessed: 21/01/20.

16. Diamantopoulos A, Sawyer LM, Lip GY, Witte KK, Reynolds MR, Fauchier L et al. Cost-effectiveness of an insertable cardiac monitor to detect atrial fibrillation in patients with cryptogenic stroke. International Journal of Stroke. 2016; 11(3):302-312

17. Duarte R, Stainthorpe A, Mahon J, Greenhalgh J, Richardson M, Nevitt S et al. Lead-I ECG for detecting atrial fibrillation in patients attending primary care with an irregular pulse using single-time point testing: a systematic review and economic evaluation. PloS One. 2019; 14(12):e0226671

18. Dussault C, Toeg H, Nathan M, Wang ZJ, Roux JF, Secemsky E. Electrocardiographic monitoring for detecting atrial fibrillation after ischemic stroke or transient ischemic attack. Circulation: Arrhythmia and Electrophysiology. 2015; 8(2):263-269

19. Eysenck W, Freemantle N, Sulke N. A randomized trial evaluating the accuracy of AF detection by four external ambulatory ECG monitors compared to permanent pacemaker AF detection. Journal of Interventional Cardiac Electrophysiology. 2020; 57(3): 361-369

20. Fitzmaurice DA, Hobbs FD, Jowett S, Mant J, Murray ET, Holder R et al. Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomised controlled trial. BMJ. 2007; 335(7616):383

21. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J et al. Atrial fibrillation in patients with cryptogenic stroke. New England Journal of Medicine. 2014; 370(26):2467-2477

22. Goldenthal IL, Sciacca RR, Riga T, Bakken S, Baumeister M, Biviano AB et al. Recurrent atrial fibrillation/flutter detection after ablation or cardioversion using the AliveCor KardiaMobile device: iHEART results. Journal of Cardiovascular Electrophysiology. 2019; 30:2220-2228

23. Gonzalez Blanco V, Perula de Torres LA, Martin Rioboo E, Martinez Adell MA, Parras Rejano JM, Gonzalez Lama J et al. Opportunistic screening for atrial fibrillation versus detecting symptomatic patients aged 65 years and older: A cluster-controlled clinical trial. Medicina Clínica. 2017; 148(1):8-15

24. Guhl E, Althouse AD, Pusateri AM, Kimani E, Paasche-Orlow MK, Bickmore TW et al. The atrial fibrillation health literacy information technology trial: pilot trial of a mobile health app for atrial fibrillation. JMIR Cardio. 2020; 4(1):e17162

25. Guo Y, Lane DA, Wang L, Zhang H, Wang H, Zhang W et al. Mobile health technology to improve care for patients with atrial fibrillation. Journal of the American College of Cardiology. 2020; 75(13):1523-1534

26. Guo Y, Lip GY. Mobile health for cardiovascular disease: the new frontier for af management: observations from the Huawei Heart Study and mAFA-II randomised trial. Arrhythmia & Electrophysiology Review. 2020; 9(1):5-7

27. Halcox JPJ, Wareham K, Cardew A, Gilmore M, Barry JP, Phillips C et al. Assessment of remote heart rhythm sampling using the AliveCor heart monitor to

ISBN: 978-1-4731-4043-1

screen for atrial fibrillation: The REHEARSE-AF Study. Circulation. 2017; 136(19):1784-1794

28. Harris K, Edwards D, Mant J. How can we best detect atrial fibrillation? The journal of the Royal College of Physicians of Edinburgh. 2012; 42(Suppl 18):5-22

29. Hickey KT, Biviano AB, Garan H, Sciacca RR, Riga T, Warren K et al. Evaluating the utility of mHealth ECG heart monitoring for the detection and management of atrial fibrillation in clinical practice. Journal of Atrial Fibrillation. 2017; 9(5):1546

30. Higgins P, MacFarlane PW, Dawson J, McInnes GT, Langhorne P, Lees K. ECG monitoring strategy to identify AF after stroke. ISRCTN Registry. Springer Nature, 2010. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00983010/full

31. Higgins P, MacFarlane PW, Dawson J, McInnes GT, Langhorne P, Lees KR. Noninvasive cardiac event monitoring to detect atrial fibrillation after ischemic stroke: a randomized, controlled trial. Stroke. 2013; 44(9):2525-2531

32. Hobbs FD, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S et al. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. Health Technology Assessment. 2005; 9(40)

33. Hoefman E, van Weert HC, Reitsma JB, Koster RW, Bindels PJ. Diagnostic yield of patient-activated loop recorders for detecting heart rhythm abnormalities in general practice: a randomised clinical trial. Family Practice. 2005; 22(5):478-484

34. ISRCTN Registry. ECG monitoring to detect atrial fibrillation after stroke. 2013. Available from: http://www.isrctn.com/ISRCTN97412358 Last accessed: 04/02/2020.

35. Kaasenbrood F, Hollander M, de Bruijn SH, Dolmans CP, Tieleman RG, Hoes AW et al. Opportunistic screening versus usual care for diagnosing atrial fibrillation in general practice: a cluster randomised controlled trial. British Journal of General Practice. 2020; 70(695):e427-e433

36. Kamalvand K, Tan K, Kotsakis A, Bucknall C, Sulke N. Ambulatory patient-activated arrhythmia monitoring: comparison of a new wrist-applied monitor with a conventional precordial device. Journal of Electrocardiology. 1997; 30(2):127-131

37. Kamel H, Navi BB, Elijovich L, Josephson SA, Yee AH, Fung G et al. Pilot randomized trial of outpatient cardiac monitoring after cryptogenic stroke. Stroke. 2013; 44(2):528-530

38. Kaura A, Sztriha L, Chan FK, Aeron-Thomas J, Gall N, Piechowski-Jozwiak B et al. Early prolonged ambulatory cardiac monitoring in stroke (EPACS): an open-label randomised controlled trial. European Journal of Medical Research. 2019; 24(1):25

39. Kinlay S, Leitch JW, Neil A, Chapman BL, Hardy DB, Fletcher PJ. Cardiac event recorders yield more diagnoses and are more cost-effective than 48-hour Holter monitoring in patients with palpitations. A controlled clinical trial. Annals of Internal Medicine. 1996; 124(1 Pt 1):16-20

40. Kishore A, Vail A, Majid A, Dawson J, Lees KR, Tyrrell PJ et al. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. Stroke. 2014; 45(2):520-526

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41. Lees KR. ECG monitoring to detect atrial fibrillation after stroke. 2010. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00982884/full Last accessed: 04/02/2020.

42. Levin LA, Husberg M, Sobocinski PD, Kull VF, Friberg L, Rosenqvist M et al. A cost-effectiveness analysis of screening for silent atrial fibrillation after ischaemic stroke. Europace: European Pacing, Arrhythmias, and Cardiac Electrophysiology. 2014; 17(2):207-214

43. Liao J, Khalid Z, Scallan C, Morillo C, O'Donnell M. Noninvasive cardiac monitoring for detecting paroxysmal atrial fibrillation or flutter after acute ischemic stroke: a systematic review. Stroke. 2007; 38(11):2935-2940

44. Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J et al. Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies: The SEARCH-AF study. Thrombosis and Haemostasis. 2014; 111(6):1167-1176

45. Makowska E, Szymot J, Soszyriska M, Kulakowski P. Evaluation of patients with palpitations: cardiac event recorder versus 48-hour Holter monitoring. Annals of Noninvasive Electrocardiology. 2000; 5(4):315-321

46. Miller DJ. Randomised controlled trial: Prolonged cardiac monitoring after cryptogenic stroke superior to 24 h ECG in detection of occult paroxysmal atrial fibrillation. Evidence-Based Medicine. 2014; 19(6):235

47. Moran P, Teljeur C, Ryan M, Smith S. Systematic screening for the detection of atrial fibrillation. Cochrane Database of Systematic Reviews 2016, Issue 6. Art. No.: CD009586. DOI: 10.1002/14651858.CD009586.pub3.

48. Morgan S, Mant D. Randomised trial of two approaches to screening for atrial fibrillation in UK general practice. British Journal of General Practice. 2002; 52(478):373-374, 377-380

49. Musat DL, Milstein N, Mittal S. Implantable loop recorders for cryptogenic stroke (plus real-world atrial fibrillation detection rate with implantable loop recorders). Cardiac Electrophysiology Clinics. 2018; 10(1):111-118

50. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [Updated October 2018]. London. National Institute for Health and Care Excellence, 2014. Available from: https://www.nice.org.uk/process/pmg20/chapter/introduction-and-overview

51. National Institute for Health and Clinical Excellence. Lead-I ECG devices for detecting symptomatic atrial fibrillation using single time point testing in primary care. Diagnostics guidance [DG35]. London. National Institute for Health and Clinical Excellence (NICE), 2019. Available from: https://www.nice.org.uk/guidance/dg35#

52. NHS Improvement. National Tariff Payment System: non-mandatory prices 2019-2020. 2019. Available from: https://improvement.nhs.uk/resources/national-tariff/ Last accessed: 21/01/2020.

53. NHS Supply Chain Catalogue. 2018. Available from: http://www.supplychain.nhs.uk/ Last accessed: 21/01/2020.

54. Orchard J, Li J, Freedman B, Webster R, Salkeld G, Hespe C et al. Atrial fibrillation screen, management, and guideline-recommended therapy in the rural primary care setting: a cross-sectional study and cost-effectiveness analysis of ehealth tools to support all stages of screening. Journal of the American Heart Association. 2020:e017080

ISBN: 978-1-4731-4043-1

55. Podd SJ, Sugihara C, Furniss SS, Sulke N. Are implantable cardiac monitors the 'gold standard' for atrial fibrillation detection? A prospective randomized trial comparing atrial fibrillation monitoring using implantable cardiac monitors and DDDRP permanent pacemakers in post atrial fibrillation ablation patients. Europace: European Pacing, Arrhythmias, and Cardiac Electrophysiology. 2016; 18(7):1000-1005

56. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA et al. Cryptogenic stroke and underlying atrial fibrillation. New England Journal of Medicine. 2014; 370(26):2478-2486

57. Steinhubl SR, Waalen J, Edwards AM, Ariniello LM, Mehta RR, Ebner GS et al. Effect of a home-based wearable continuous ECG monitoring patch on detection of undiagnosed atrial fibrillation: the mSToPS randomized clinical trial. JAMA. 2018; 320(2):146-155

58. Sticherling C, Zabel M, Spencker S, Meyerfeldt U, Eckardt L, Behrens S et al. Comparison of a novel, single-lead atrial sensing system with a dual-chamber implantable cardioverter-defibrillator system in patients without antibradycardia pacing indications: results of a randomized study. Circulation: Arrhythmia and Electrophysiology. 2011; 4(1):56-63

59. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass screening for untreated atrial fibrillation: the STROKESTOP study. Circulation. 2015; 131(25):2176-2184

60. Swancutt D, Hobbs R, Fitzmaurice D, Mant J, Murray E, Jowett S et al. A randomised controlled trial and cost effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in the over 65s: (SAFE). BMC Cardiovascular Disorders. 2004; 4:12

61. Wachter R. Finding atrial fibrillation in stroke - evaluation of enhanced and prolonged holter monitoring. 2013. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00985610/full Last accessed: 04/02/2020.

62. Wachter R, Groschel K, Gelbrich G, Hamann GF, Kermer P, Liman J et al. Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AF-RANDOMISED): an open-label randomised controlled trial. Lancet Neurology. 2017; 16(4):282-290

63. Wasser K, Weber-Kruger M, Jurries F, Liman J, Hamann GF, Kermer P et al. The cardiac diagnostic work-up in stroke patients-A subanalysis of the Find-AF randomised trial. PloS One. 2019; 14(5):e0216530

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Appendices

Appendix A: Review protocols

Table 18: Review protocol: Diagnosis of AF

ID	Field	Content
0.	PROSPERO registration number	[Complete this section with the PROSPERO registration number once allocated]
1.	Review title	Clinical and cost-effectiveness of tools for detecting atrial fibrillation in people with cardiovascular risk factors for AF and/or symptoms suggestive of AF
2.	Review question	What is the most clinically and cost-effective method for detecting atrial fibrillation in people with cardiovascular risk factors for AF and/or symptoms suggestive of AF?
3.	Objective	To identify the most clinically and cost-effective methods of detecting AF in this population in the primary care clinic.
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Searches will be restricted by: English language Human studies Letters and comments are excluded. Other searches: Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Atrial Fibrillation
6.	Population	Inclusion: People aged over 18 with symptoms suggestive of AF (including breathlessness, palpitations, syncope/dizziness, chest discomfort) and/or with cardiovascular risk factors for AF (including TIA, stroke, Heart Failure, hypertension, valve disease). Exclusion: Severe valve disease
7.	Intervention/Exposure/Test	Any point of care tests used to detect AF For example (non-exhaustive list): • Manual pulse checking

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ID	Field	Content
		• Pulse oximeters • US devices • Blood pressure monitors o Microlife BPM o Watch BP Home A • Non-portable (but non-12 lead) ECG devices • Portable ECG devices o My Diagnostick o AliveCor Kardia • Smart portable devices eg phones, watches • 12 lead ECG (when gold standard is long-term loop recording – see section below) Where the same test is used with a differing number of recordings across studies, these should be regarded as separate test strategies, and should thus be dealt with separately. Tests using differing periods of recording will also be dealt with separately. For example, pulse oximeters for 2 minutes will be in a separate category of index test to pulse oximeters used for 1 hour, and they could be compared to each other as separate index tests.
8.	Comparator/Reference standard/Confounding factors	Each other No test applied / usual care
9.	Types of study to be included	Systematic reviews RCTs (including those with a cross-over design). Non-randomised studies will be excluded.
10.	Other exclusion criteria	Non-English language studies. Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	Quality of life Mortality Stroke and thromboembolism Major bleeding All cause hospitalisation Confirmed diagnosis of AF Initiated anticoagulants for AF Longest follow up point always used
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above.

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ID	Field	Content
		10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent.

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ID	Field	Content
		Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.
17.	Analysis of sub-groups	Stratification None Sub-grouping If serious or very serious heterogeneity (I2>50%) is present within any stratum, sub-grouping will occur according to the following strategies: Expertise of index test interpreter (studies where the clinician is trained in the use of the index test, such as cardiologist/electrophysiologist versus studies with a non-electrophysiologically trained clinician (e.g. GP) versus studies where the test is performed by patient/carer versus studies where tests is fully automated)
18.	Type and method of review	☐ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☒ Other (please specify): RCT review of diagnostic tools
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	
22.	Anticipated completion date	
23.	Stage of review at time of this submission	Review stage: Started / Completed Preliminary searches: ☐ / ☑ Piloting of the study selection process: ☐ / ☑ Formal screening of search results against eligibility criteria: ☐ / ☑ Data extraction: ☐ / ☑

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ID	Field	Content		
		Risk of bias (quality) assessment	☐	☑
		Data analysis	☐	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Sharon Swain Mark Perry Nicole Downes Sophia Kemmis Betty Elizabeth Pearton		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].		
29.	Other registration details			
30.	Reference/URL for published protocol			
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts		

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ID	Field	Content	
		issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Atrial Fibrillation, AF detection tools	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

Table 19: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and health economic study filters – see appendix B below. For questions being updated from NICE guideline CG180, the search will be run from October 2013, which was the cut-off date for the searches. For questions being updated from the NICE guideline CG36 and for new questions, the search will be run from 2003.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2003 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual.[50] **Inclusion and exclusion criteria**

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- If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.
- If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.
- If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2003 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'.
- Studies published before 2003 (including any such studies included in the previous guideline(s))will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B: Literature search strategies

This literature search strategy was used for the following review:

- **Clinical and cost-effectiveness of tools for detecting atrial fibrillation in people with cardiovascular risk factors for AF and/or symptoms suggestive of AF**

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[50]

For more information, please see the Methods Report published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 20: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 10 September 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies
Embase (OVID)	1974 – 10 September 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 9 of 12 CENTRAL to 2020 Issue 9 of 12	None

Medline (Ovid) search terms

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12

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14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to English language
25.	exp "sensitivity and specificity"/
26.	(sensitivity or specificity).ti,ab.
27.	((pre test or pretest or post test) adj probability).ti,ab.
28.	(predictive value* or PPV or NPV).ti,ab.
29.	likelihood ratio*.ti,ab.
30.	likelihood function/
31.	((area under adj4 curve) or AUC).ti,ab.
32.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
33.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
34.	gold standard.ab.
35.	or/25-34
36.	randomized controlled trial.pt.
37.	controlled clinical trial.pt.
38.	randomi#ed.ab.
39.	placebo.ab.
40.	randomly.ab.
41.	clinical trials as topic.sh.
42.	trial.ti.
43.	or/36-42
44.	Meta-Analysis/
45.	exp Meta-Analysis as Topic/
46.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
47.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
48.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
49.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
50.	(search* adj4 literature).ab.
51.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
52.	cochrane.jw.
53.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
54.	or/44-53
55.	Epidemiologic studies/
56.	Observational study/
57.	exp Cohort studies/

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58.	(cohort adj (study or studies or analys* or data)).ti,ab.
59.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
60.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
61.	Controlled Before-After Studies/
62.	Historically Controlled Study/
63.	Interrupted Time Series Analysis/
64.	(before adj2 after adj2 (study or studies or data)).ti,ab.
65.	exp case control study/
66.	case control*.ti,ab.
67.	Cross-sectional studies/
68.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
69.	or/55-68
70.	24 and (35 or 43 or 54 or 69)
71.	((portable or ambulatory or monitor* or lead* or handheld or hand held or daily or long-term or short-term or strap* or device*) adj3 (ECG* or EKG* or electrocardio*)).ti,ab.
72.	((ECG* or EKG* or electrocardio*) adj2 (assess* or check* or monitor* or detect* or screen* or diagnos* or measure*)).ti,ab.
73.	(iECG* or Holter*).ti,ab.
74.	((ambulatory or event) adj monitor*).ti,ab.
75.	*electrocardiography/ or electrocardiography, ambulatory/
76.	(ILR* or loop record*).ti,ab.
77.	((heart or cardiac) adj monitor*).ti,ab.
78.	(pulse adj2 (assess* or check* or monitor* or detect* or screen* or diagnos* or measure* or palpation*)).ti,ab.
79.	(pulse oximetr* adj device*).ti,ab.
80.	oximetry/
81.	Pulse/
82.	((blood pressure or BP) adj2 (assess* or check* or monitor* or detect* or screen* or diagnos* or measure*)).ti,ab.
83.	Blood Pressure Monitors/ or Blood Pressure Monitoring, Ambulatory/
84.	(AliveCor or MyDiagnostic*).ti,ab.
85.	(Microlife or WatchBP or "watch BP").ti,ab.
86.	(Heartscan or Zenicor or AliveECG or Kardia*).ti,ab.
87.	(photoplethysmograph* or PPG).ti,ab.
88.	(smartwatch* or smart watch* or Applewatch* or Apple watch* or wrist watch* or wristwatch* or fitness band* or fitness tracker* or smartphone* or smart phone* or mobile phone*).ti,ab.
89.	(wearable adj2 (technology or device* or sensor* or ECG or EKG or electrocardio*)).ti,ab.
90.	(mhealth or m-health or "mobile health").ti,ab.
91.	telemedicine/
92.	point of care.ti,ab.
93.	((targeted or oppotunistic) adj2 (detect* or screen*)).ti,ab.
94.	or/71-93
95.	70 and 94

Embase (Ovid) search terms

1.	exp atrial fibrillation/

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2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to English language
23.	exp "sensitivity and specificity"/
24.	(sensitivity or specificity).ti,ab.
25.	((pre test or pretest or post test) adj probability).ti,ab.
26.	(predictive value* or PPV or NPV).ti,ab.
27.	likelihood ratio*.ti,ab.
28.	((area under adj4 curve) or AUC).ti,ab.
29.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
30.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
31.	diagnostic accuracy/
32.	diagnostic test accuracy study/
33.	gold standard.ab.
34.	or/23-33
35.	random*.ti,ab.
36.	factorial*.ti,ab.
37.	(crossover* or cross over*).ti,ab.
38.	((doubl* or singl*) adj blind*).ti,ab.
39.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
40.	crossover procedure/
41.	single blind procedure/
42.	randomized controlled trial/
43.	double blind procedure/
44.	or/35-43
45.	systematic review/
46.	Meta-Analysis/
47.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.

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48.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
49.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
50.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
51.	(search* adj4 literature).ab.
52.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
53.	cochrane.jw.
54.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
55.	or/45-54
56.	Clinical study/
57.	Observational study/
58.	family study/
59.	longitudinal study/
60.	retrospective study/
61.	prospective study/
62.	cohort analysis/
63.	follow-up/
64.	cohort*.ti,ab.
65.	63 and 64
66.	(cohort adj (study or studies or analys* or data)).ti,ab.
67.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
68.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
69.	(before adj2 after adj2 (study or studies or data)).ti,ab.
70.	exp case control study/
71.	case control*.ti,ab.
72.	cross-sectional study/
73.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
74.	or/56-73
75.	34 or 44 or 55 or 74
76.	22 and (34 or 44 or 55 or 74)
77.	((portable or ambulatory or monitor* or lead* or handheld or hand held or daily or long-term or short-term or strap* or device*) adj3 (ECG* or EKG* or electrocardio*)).ti,ab.
78.	((ECG* or EKG* or electrocardio*) adj2 (assess* or check* or monitor* or detect* or screen* or diagnos* or measure*)).ti,ab.
79.	(iECG* or Holter*).ti,ab.
80.	((ambulatory or event) adj monitor*).ti,ab.
81.	*electrocardiography/
82.	*ambulatory electrocardiography/
83.	(ILR* or loop record*).ti,ab.
84.	((heart or cardiac) adj monitor*).ti,ab.
85.	(pulse adj2 (assess* or check* or monitor* or detect* or screen* or diagnos* or measure* or palpation*)).ti,ab.
86.	(pulse oximetr* adj device*).ti,ab.
87.	*oximetry/
88.	*pulse rate/

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89.	((blood pressure or BP) adj2 (assess* or check* or monitor* or detect* or screen* or diagnos* or measure*)).ti,ab.
90.	*blood pressure monitor/
91.	(AliveCor or MyDiagnostic*).ti,ab.
92.	(Microlife or WatchBP or "watch BP").ti,ab.
93.	(Heartscan or Zenicor or AliveECG or Kardia*).ti,ab.
94.	(photoplethysmograph* or PPG).ti,ab.
95.	(smartwatch* or smart watch* or Applewatch* or Apple watch* or wrist watch* or wristwatch* or fitness band* or fitness tracker* or smartphone* or smart phone* or mobile phone*).ti,ab.
96.	(wearable adj2 (technology or device* or sensor* or ECG or EKG or electrocardio*)).ti,ab.
97.	(mhealth or m-health or "mobile health").ti,ab.
98.	*telemedicine/
99.	point of care.ti,ab.
100.	((targeted or oppotunistic) adj2 (detect* or screen*)).ti,ab.
101.	or/77-100
102.	76 and 101

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Atrial Fibrillation] explode all trees
#2.	((atrial or atria or atrium or auricular) near/3 fibrillat*):ti,ab
#3.	AF:ti,ab
#4.	#1 or #2 or #3
#5.	((portable or ambulatory or monitor* or lead* or handheld or hand held or daily or long-term or short-term or strap* or device*) near/3 (ECG* or EKG* or electrocardio*)):ti,ab
#6.	((ECG* or EKG* or electrocardio*) near/2 (assess* or check* or monitor* or detect* or screen* or diagnos* or measure*)):ti,ab
#7.	(iECG* or Holter*):ti,ab
#8.	((ambulatory or event) next monitor*).ti,ab
#9.	MeSH descriptor: [Electrocardiography] this term only
#10.	MeSH descriptor: [Electrocardiography, Ambulatory] this term only
#11.	(ILR* or loop record*):ti,ab
#12.	((heart or cardiac) next monitor*):ti,ab
#13.	(pulse near/2 (assess* or check* or monitor* or detect* or screen* or diagnos* or measure* or palpation*)):ti,ab
#14.	(pulse oximetr* next device*).ti,ab
#15.	MeSH descriptor: [Oximetry] this term only
#16.	MeSH descriptor: [Pulse] this term only
#17.	((blood pressure or BP) near/2 (assess* or check* or monitor* or detect* or screen* or diagnos* or measure*)).ti,ab
#18.	MeSH descriptor: [Blood Pressure Monitors] this term only
#19.	MeSH descriptor: [Blood Pressure Monitoring, Ambulatory] this term only
#20.	(AliveCor or MyDiagnostic*):ti,ab
#21.	(Microlife or WatchBP or "watch BP"):ti,ab
#22.	(Heartscan or Zenicor or AliveECG or Kardia*):ti,ab
#23.	(photoplethysmograph* or PPG):ti,ab
#24.	(smartwatch* or smart watch* or Applewatch* or Apple watch* or wrist watch* or wristwatch* or fitness band* or fitness tracker* or smartphone* or smart phone* or mobile phone*):ti,ab

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#25.	(wearable near/2 (technology or device* or sensor* or ECG or EKG or electrocardio*)):ti,ab
#26.	(mhealth or m-health or "mobile health"):ti,ab
#27.	MeSH descriptor: [Telemedicine] this term only
#28.	point of care:ti,ab
#29.	((targeted or oppotunistic) near/2 (detect* or screen*)):ti,ab
#30.	(or #5-#29)
#31.	#4 and #30

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the Atrial Fibrillation population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA - this ceased to be updated after March 2018). NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional health economics searches were run on Medline and Embase.

Table 21: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2003– 10 September 2020	Exclusions Health economics studies
Embase	2003– 10 September 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	NHSEED - 2003 to March 2015 HTA - 2003 –2003 to 31 March 2018	None

Medline (Ovid) search terms

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/

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20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to English language
25.	economics/
26.	value of life/
27.	exp "costs and cost analysis"/
28.	exp Economics, Hospital/
29.	exp Economics, medical/
30.	Economics, nursing/
31.	economics, pharmaceutical/
32.	exp "Fees and Charges"/
33.	exp budgets/
34.	budget*.ti,ab.
35.	cost*.ti.
36.	(economic* or pharmaco?economic*).ti.
37.	(price* or pricing*).ti,ab.
38.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
39.	(financ* or fee or fees).ti,ab.
40.	(value adj2 (money or monetary)).ti,ab.
41.	or/25-40
42.	24 and 41

Embase (Ovid) search terms

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.

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20.	or/12-19
21.	4 not 20
22.	limit 21 to English language
23.	health economics/
24.	exp economic evaluation/
25.	exp health care cost/
26.	exp fee/
27.	budget/
28.	funding/
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic* or pharmaco?economic*).ti.
32.	(price* or pricing*).ti,ab.
33.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
34.	(financ* or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/23-35
37.	22 and 36

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Atrial Fibrillation EXPLODE ALL TREES
#2.	(((atrial or atria or atrium or auricular) adj3 fibrillat*))
#3.	(AF)
#4.	(#1 or #2 or #3)

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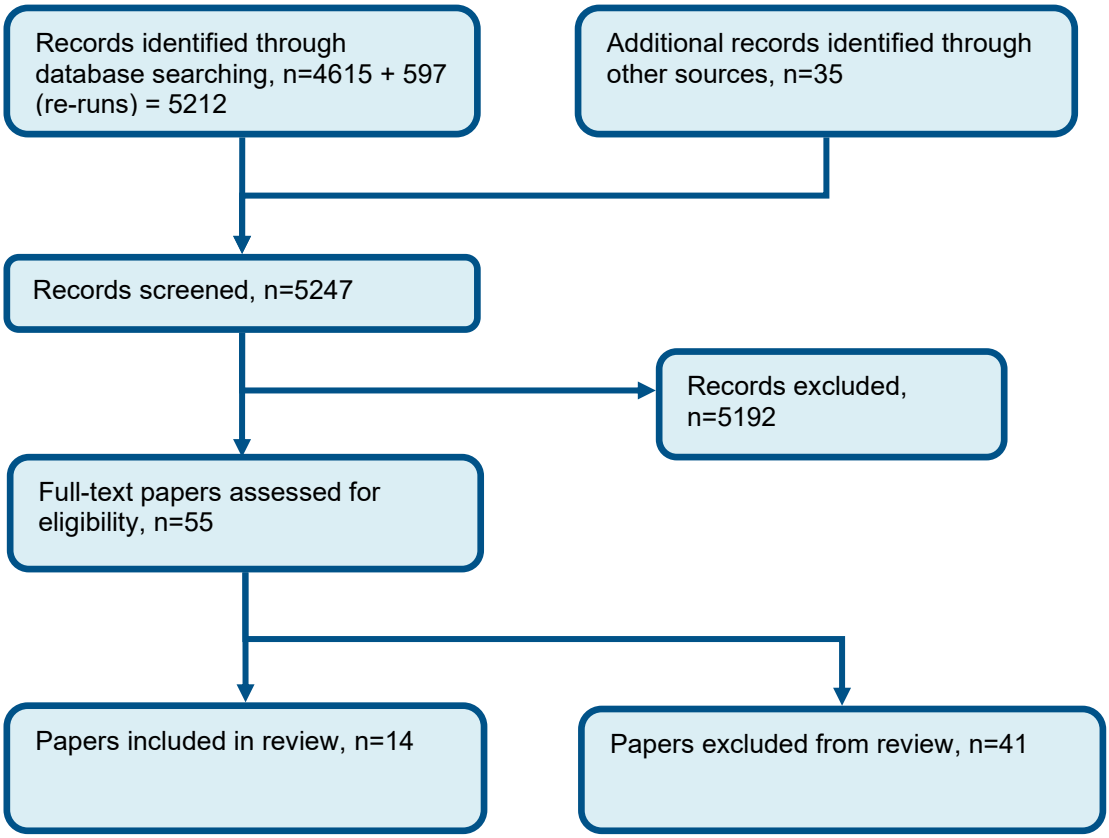
Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of diagnosis of AF



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Appendix D: Clinical evidence tables

Study	**EARLY, 2015 trial: Benito 2015[3]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=4000)
Countries and setting	Conducted in Spain; Setting: Primary healthcare centre in Spain
Line of therapy	1st line
Duration of study	Follow up (post intervention): 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ECG, clinical examination and full medical history
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	From the electronic health records for this population, all patients without a diagnosis of AF but with one or more of the main risk factors for AF: age ≥ 65 years, arterial hypertension, ischaemic heart disease, valvular heart disease, diabetes, and/or congestive heart failure. The identification of all risk factors was based on the medical history recorded by each patient's physician, with some added conditions required for inclusion: (i) patients with a diagnosis of arterial hypertension or diabetes were included only if they received the corresponding treatment, (ii) valvular heart disease diagnosis had to be confirmed by an echocardiogram, (iii) ischaemic heart disease diagnosis had to be confirmed by an electrocardiogram, stress test, catheterization, or computed tomog- raphy angiogram, and (iv) heart failure diagnosis had to be confirmed by chronic treatment, an echocardiogram or an acute episode that required emergency care and/or hospital admission.
Exclusion criteria	Patients unable to come to the healthcare centre to participate in the study were excluded. Patients who had a pacemaker, could not be contacted by telephone, or declined to participate in the study were also excluded

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Recruitment/selection of patients	Pre-selected from a reference population of 30,451 members of a GP practice in Spain.
Age, gender and ethnicity	Age - Mean (SD): 69 (10). Gender (M:F): 49:51. Ethnicity: Unclear
Further population details	
Extra comments	Intervention/control: female 51%/51%; age >65 71%/66%; hypertension 72%/71%; DM2 18%/23%; IHD 11%/11%; Valvular HD 5%/3.6%; HF 1.5%/1.5%; >2 risk factors 16.9%/17.3% . This study randomised patients before assessment of the exclusion criteria. Although this should not be a problem in such a large study (there should be a very similar array of people excluded from both groups because exclusion criteria are independent of the group allocation) there were a large number of people who refused to participate, which is a problem as this is definitely related to group allocation.
Indirectness of population	No indirectness
Interventions	(n=2000) Intervention 1: Other. A 2-year programme for early detection of AF was carried out in the intervention group, with an office visit every 6 months that involved an electrocardiogram (ECG), physical examination, and a complete medical history including anamnesis related to symptoms indicating the possible presence of AF (palpitations, chest pain, dyspnoea, fatigue, and dizziness). Chronic medication (≥3 months) was also recorded. On the first visit, a nurse instructed the participants on warning signs, taught them to take their own pulse in a resting position, and requested they do so once a month. If the patient observed an arrhythmic pulse or other warning signs, the instruction was to visit the healthcare centre as soon as possible. If outside of working hours, the patient was instructed to go to the nearest medical centre or, if the symptoms were incapacitating, to call the emergency medical services. In a pilot proof, the median time invested by the nurse was 11 min for the first visit and 6 min for each subsequent visit.. Duration 2 years. Concurrent medication/care: None. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: Not stated / Unclear (n=2000) Intervention 2: usual care. No specific action was taken in the CG. The clinical history was reviewed using the electronic medical records system at the end of the study period (2 years after inclusion); patients were contacted by telephone as needed to obtain complete information.. Duration 2 years. Concurrent medication/care: None. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: Not stated / Unclear

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Funding	Academic or government funding (FIS (Fondo de Investigacio Sanitaria).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OTHER versus USUAL CARE

Protocol outcome 1: Mortality
- Actual outcome: Death at 2 years; Group 1: 7/463, Group 2: 8/465
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1537, Reason: 262 not contacted, 153 exclusion criteria, 3 already dead, 78 not attached to health centre, 425 declined to take part, 616 not found. The problem was that the study randomised before recruitment - thus randomisation was completely upset by the inevitable exclusions.; Group 2 Number missing: 1535, Reason: 1449 not contacted, 38 exclusion criteria, 6 already dead, 42 no longer assigned to health centre. The problem was that the study randomised before recruitment - thus randomisation was completely upset by the inevitable exclusions.

Protocol outcome 2: Confirmed diagnosis of AF
- Actual outcome: Newly diagnosed AF at 2 years; Group 1: 11/440, Group 2: 6/462
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1560, Reason: 262 not contacted, 153 exclusion criteria, 3 already dead, 78 not attached to health centre, 425 declined to take part, 616 not found. 23 further lost without explanation. The problem was that the study randomised before recruitment - thus randomisation was completely upset by the inevitable exclusions; Group 2 Number missing: 1538, Reason: 1449 not contacted, 38 exclusion criteria, 6 already dead, 42 no longer assigned to health centre. 3 further lost without explanation. The problem was that the study randomised before recruitment - thus randomisation was completely upset by the inevitable exclusions.

Protocol outcome 3: Initiated anticoagulants for AF
- Actual outcome: Started on OACS at 2 years; Group 1: 10/440, Group 2: 2/462
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1560, Reason: 262 not contacted, 153 exclusion criteria, 3 already dead, 78 not attached to health centre, 425 declined to take part, 616 not found. 23 further lost without explanation. The problem was that the study randomised before recruitment - thus randomisation was completely upset by the inevitable exclusions; Group 2 Number missing: 1538, Reason: 1449 not contacted, 38 exclusion criteria, 6 already dead, 42 no longer assigned to health centre. 3 further lost without explanation. The problem was that the study randomised before recruitment - thus randomisation was completely upset by the inevitable exclusions.

Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Stroke/thromboembolism ; Major bleeding

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Study	Find-AF, 2017 trial: Wachter 2017[62]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=398)
Countries and setting	Conducted in Germany; Setting: 4 stroke units
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Arrhythmia as showing absolutely irregular RR-intervals (without any repetitive ECG pattern), lacking a distinct P-wave on surface ECG , and showing an atrial cycle length of less than 200 milliseconds (or >300 beats per min), if visible. Included only episodes that lasted long enough to record a 12-lead ECG or at least 30 s on a rhythm strip.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible patients were 60 years or older with acute (clinical symptom onset ≤7 days) ischaemic strokes (documentation of an acute lesion on brain imaging or duration of symptoms ≥24 h). Patients for whom the detection of atrial fibrillation has therapeutic consequences and for whom no evidence-based therapy is available after minimal diagnostic work-up (admission ECG and ultrasonography of the brain supplying arteries) also included.
Exclusion criteria	Excluded patients with known or documented atrial fibrillation, those with an indication or contraindication for oral anticoagulation, and those with a relevant symptomatic ipsilateral carotid stenosis (>50% according to the North American Symptomatic Carotid Endarterectomy Trial [NASCET] classification), as this is a cause of stroke with evidenced-based therapeutic recommendations. In a protocol amendment this criterion was extended to patients with clinically significant vertebral artery stenosis of more than 50%, intracranial stenosis suspicious of atherosclerotic origin, and those with acute arterial dissections, because many of these patients require dual antiplatelet therapy.

ISBN: 978-1-4731-4043-1

Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 73(7). Gender (M:F): Define. Ethnicity: unclear
Further population details	
Extra comments	Intervention/control: hypertension 78.5%/80.7%; DM 28%/26.4%; hyperlipidaemia 38.5%/44.2%; current smoker17%/18.2%; previous ischaemic stroke 17%/18.2%; previous TIA 6.5%/9.1%; HF 5.5%/4.6%; MI 10%/9.1%; CAD 13.5%/17.3%; mean ejection fraction 60%/60%; symptoms >24 hrs 6%/4.5%; lacunar lesion 37.1%/44.1%; medium or high risk scores of cardioembolism 30%/28.3%; score on NIH stroke scale 3/2;lacunar syndrome 19.1%/29.8%; mean CHADSVASC 4.8/4.8; mean CHADS 3.5/3.5
Indirectness of population	No indirectness
Interventions	(n=200) Intervention 1: Holter. 3 x 10 days Holter monitoring (with ECG analysis in a central core laboratory) within 6 months. Holter was two channel (5 lead) and used at baseline, 3 months and 6 months. Duration 6 months. Concurrent medication/care: Once AF detected no further Holters were performed. Patients who refused to repeat the Holter-ECGs at the follow-up visits were offered to use a thumb-sensor ECG-device (Zenicor-EKG;Zenicor, Stockholm, Sweden) and were encouraged to record at least two 30 s ECG-episodes per day on 10 consecutive days to provide a compensatory form of prolonged ECG-monitoring.. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: cardiologist/electrophysiologist (n=198) Intervention 2: usual care. Standard care workup, including 24 hr or longer ECG (Holter or telemetry). Duration 6 months. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: cardiologist/electrophysiologist
Funding	Study funded by industry (Boehringer Ingelheim)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HOLTER versus USUAL CARE

Protocol outcome 1: Mortality
- Actual outcome: deaths at 12 months; Group 1: 6/200, Group 2: 9/198

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Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Stroke/thromboembolism - Actual outcome: Recurrent strokes/TIAs at 12 months; Group 1: 8/200, Group 2: 14/198; Comments: Intervention: 5 strokes and 3 TIAS Control: 9 strokes and 5 TIAs Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Major bleeding - Actual outcome: GI bleeding, secondary haemorrhagic transformation and epistaxis at 12 months; Group 1: 3/200, Group 2: 1/198; Comments: epistaxis case in intervention group (is this major bleeding?). 2 GI bleeds in intervention group. SHT in control group Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Confirmed diagnosis of AF - Actual outcome: Detection of AF or flutter on ECG (assessed by centralised expert committee) at 12 months; Group 1: 27/200, Group 2: 12/198 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Initiated anticoagulants for AF - Actual outcome: Started OACs at 12 months; Group 1: 27/200, Group 2: 12/198 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation

ISBN: 978-1-4731-4043-1

Study	Fitzmaurice, 2007 trial: Fitzmaurice 2007[20] SAFE, 2005 trial: Hobbs 2005[32]
Study type	RCT (cluster randomised; Parallel)
Number of studies (number of participants)	1 (n=14802 (23 intervention and 25 control practices))
Countries and setting	Conducted in United Kingdom; Setting: Computerized general practices in England
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Study researchers recruited 50 general practices from the Midlands Research Practices Consortium (MidReC). All patients aged 65 or over from these practices were eligible for participation in the study, though patients could be excluded if their own general practitioner thought participation inadvisable.
Exclusion criteria	None
Recruitment/selection of patients	All those within the 50 general practices. Reasons for the specific selection of the 50 general practices not given (except that they were in the Midlands Research Practices Consortium, but presumably there are >50 in that consortium).
Age, gender and ethnicity	Age - Mean (SD): 75.3(7.2). Gender (M:F): 42.6:57.4. Ethnicity: Not reported
Further population details	
Extra comments	No details other than age and gender. From the 50 practices, the intention was to recruit a random sample of 400 from each intervention (screening) and 200 from each control practice, though this varied depending on practice size. From

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	the intervention clusters there was additional individual randomization to form the 2 screening groups - systematic and opportunistic.
Indirectness of population	No indirectness
Interventions	(n=4933) Intervention 1: Other . Opportunistic screening. Pulses recorded. ECG performed if pulse detection was positive. The notes of patients in the opportunistic arm (including those with known atrial fibrillation) were flagged with either a manual paper flag or computer flag to encourage pulse recording during routine consultation. Patients with an irregular pulse asked to attend a further ECG screening clinic.. Duration 12 months of screening for each practice, but individual screening done in one session. Concurrent medication/care: Primary care physicians and other members of the primary healthcare team in the intervention practices attended investigator days at which they were given educational materials informing them of the importance of detecting atrial fibrillation and the available treatment options.. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: unclear (n=4933) Intervention 2: Other . Systematic screening. All patients allocated to systematic screening (including those with known atrial fibrillation) were invited by post to attend an ECG screening clinic. . Duration 12 months of screening for each practice, but individual screening done in one session. Concurrent medication/care: Practice nurses attended an electrocardiography training day before they started screening clinics. Training included how to perform electrocardiography (with an electronic machine to ensure standardized high quality tracings) and basic interpretation of the electrocardiogram (specifically how to identify atrial fibrillation).. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: unclear (n=4936) Intervention 3: usual care. No screening - usual GP care. Duration NA. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: unclear
Funding	Academic or government funding (NHS research and development health technology assessment programme (No 96/22/11).)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OTHER versus OTHER Protocol outcome 1: Confirmed diagnosis of AF	

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- Actual outcome: New incidence of AF. The cases with known pre-existing AF at baseline were not included in the analysis. at 12 months; Group 1: 75/4575, Group 2: 74/4562; Comments: The cases with known pre-existing AF at baseline were not included in the analysis. Opportunistic 75/4575 and systematic 74/4562 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 358, Reason: 18 notes missing, 340 excluded as had baseline AF. ; Group 2 Number missing: 351, Reason: 32 notes missing, 339 excluded as had baseline AF. RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OTHER versus USUAL CARE Protocol outcome 1: Confirmed diagnosis of AF - Actual outcome: New incidence of AF. The cases with known pre-existing AF at baseline were not included in the analysis. at 12 months; Group 1: 75/4575, Group 2: 47/4513; Comments: The cases with known pre-existing AF at baseline were not included in the analysis. Other = opportunistic screening Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 358, Reason: 18 notes missing, 340 excluded as had baseline AF. ; Group 2 Number missing: 423, Reason: 34 notes missing, 389 excluded as had baseline AF.	
Protocol outcomes not reported by the study	Quality of life; Hospitalisation; Mortality; Stroke/thromboembolism; Major bleeding; Initiated anticoagulants for AF

ISBN: 978-1-4731-4043-1

Study	Gladstone, 2014 trial: Gladstone 2014[21]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=572)
Countries and setting	Conducted in Canada; Setting: Recruited from 16 stroke centres within Canadian Stroke Consortium.
Line of therapy	1st line
Duration of study	Intervention + follow up: 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ECG documented AF, lasting >30s
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were eligible for enrolment if they were 55 years of age or older, did not have known atrial fibrillation, and had had an ischemic stroke or TIA of undetermined cause (according to TOAST [Trial of Org 10172 in Acute Stroke Treatment] criteria) within the previous 6 months, diagnosed by a stroke neurologist after a standard workup, including 12-lead ECG, ambulatory ECG monitoring with the use of a Holter monitor for a minimum of 24 hours, brain and neurovascular imaging, and echocardiography
Exclusion criteria	Patients were excluded if the most likely etiologic diagnosis had already been determined (large-vessel or small-vessel disease or other known cause).
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): 72.5 (8.5). Gender (M:F): 314:257. Ethnicity: Intervention/control: white 89.9%/91.2%; Asian 5.2%/4.9%; Black 2.1%/0.7%; Other 2.8%/3.2%
Further population details	

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Extra comments	Intervention/control: age 72.5/73.2;Modified Rankin score <=2 95.8%/92.3%; hypertension 71.3%/67%; DM 19.2%/19.3%; hyperlipidaemia 66.8%/62.1%; current smoker 6.6%/8.4%; previous ischeamic stroke 15.7%/12.6%; >1 previous stroke 4.2%/4.2%; previous TIA 14.7%/16.1%; CHF 1.7%/2.5%; MI 16.8%/14.7%; angioplasty or stenting 8.4%/8.1%; CABG 10.1%/6.7%; valve surgery 2.1%/0.4%; Index event stroke 65.7%/60.4%; Index event TIA 34.3%; 39.6%; Days from index to randomisation 76.6/73.7
Indirectness of population	No indirectness
Interventions	(n=287) Intervention 1: Other . Ambulatory ECG monitoring with a 30 day event-triggered loop recorder, after standard 24 hour ECG. Duration 30 days. Concurrent medication/care: The event recorder (ER910AF Cardiac Event Monitor, Braemar) automatically recorded atrial fibrillation on the basis of irregularity in the R-R interval, an established method for the detection of atrial fibrillation,16 over a period of 30 beats at any rate. The devices had a 30-minute memory capacity and were programmed to record up to 2.5 minutes per episode. Recorders were attached to a dry-electrode (nonadhesive) belt worn around the chest (Cardiac Bio-Systems) to enable better compliance by the patients with prolonged monitoring than has been typically observed with conventional adhesive skin-contact electrodes. The intervention group was instructed to wear the monitor as much as possible for 30 days. If atrial fibrillation was detected before 30 days, patients could stop wearing the monitor. Recorded ECG data were transmitted transtelephonically for central interpretation. All the episodes of atrial fibrillation were adjudicated by a cardiologist and an internist who were unaware of the patient's demographic and clinical characteristics, and any disagreements were resolved by discussion with an independent cardiologist. Results were sent to the study sites, and decisions regarding anticoagulant therapy were made at the discretion of the treating physicians. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: cardiologist/electrophysiologist (n=285) Intervention 2: Other . 24 hour ECG monitoring after standard 24 hour ECG. Duration 24 hours. Concurrent medication/care: The event recorder (ER910AF Cardiac Event Monitor, Braemar) automatically recorded atrial fibrillation on the basis of irregularity in the R-R interval, an established method for the detection of atrial fibrillation,16 over a period of 30 beats at any rate. The devices had a 30-minute memory capacity and were programmed to record up to 2.5 minutes per episode. Recorders were attached to a dry-electrode (nonadhesive) belt worn around the chest (Cardiac Bio-Systems) to enable better compliance by the patients with prolonged monitoring than has been typically observed with conventional adhesive skin-contact electrodes. The intervention group was instructed to wear the monitor as much as possible for 24 hours. Recorded ECG data were transmitted transtelephonically for central interpretation. All the episodes of atrial fibrillation were adjudicated by a cardiologist and an internist who were unaware of the patient's demographic and clinical characteristics, and any disagreements were resolved by discussion with an independent cardiologist. Results were sent to the study sites, and decisions regarding anticoagulant therapy were made at the discretion of the treating physicians. Indirectness: No indirectness

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	Further details: 1. Expertise of test interpreter: cardiologist/electrophysiologist
Funding	Academic or government funding (Supported by peer-reviewed operating grants from the Canadian Stroke Network, one of the Networks of Centres of Excellence of Canada.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OTHER versus OTHER Protocol outcome 1: Mortality - Actual outcome: death at 90 days; Group 1: 1/287, Group 2: 1/285 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Stroke - Actual outcome: stroke at 90 days; Group 1: 1/287, Group 2: 1/285; Comments: Both were fatal strokes Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Confirmed diagnosis of AF - Actual outcome: Detection of one or more episodes of ECG-documented AF or flutter lasting 30 or more seconds documented by the study monitors at 90 days; Group 1: 44/284, Group 2: 7/277; Comments: The primary outcome was slightly different in that diagnosis of AF was made with the monitor and / or clinically. However in the context of this question, it makes more sense to stick to this secondary outcome which was AF detection made only with the ambulatory ECG Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7, Reason: 1 died from stroke, 1 adverse skin reaction, 5 withdrew; Group 2 Number missing: 6, Reason: 1 died from stroke, 5 withdrew Protocol outcome 4: Initiated anticoagulants for AF - Actual outcome: Oral anticoagulant use at 90 days; Group 1: 52/280, Group 2: 31/279 Risk of bias: All domain - HIgh, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7, Reason: 1 died from stroke, 1 adverse skin reaction, 5 withdrew; Group 2 Number missing: 6, Reason: 1 died from stroke, 5 withdrew	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Stroke/thromboembolism ; Major bleeding

ISBN: 978-1-4731-4043-1

Study	Higgins, 2013 trial: Higgins 2013[31]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in United Kingdom; Setting: 2 acute stroke services in Glasgow
Line of therapy	1st line
Duration of study	Follow up (post intervention): 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: sustained paroxysmal AF: PAF recorded for a minimum of 20s on a rhythm strip
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients within 7 days of TIA or acute ischaemic stroke
Exclusion criteria	History of AF or atrial flutter; any irreversible condition for long term anticoagulation
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): 65.8(12.3). Gender (M:F): 56:44. Ethnicity: unclear
Further population details	
Extra comments	Qualifying event stroke 68%; qualifying event TIA 32%; hypertension 58%; DM 15%; IHD 16%;
Indirectness of population	No indirectness

ISBN: 978-1-4731-4043-1

Interventions	(n=50) Intervention 1: ECG devices – 7 days monitoring plus standard practice monitoring. Patients randomized to the intervention group underwent usual standard practice investigation plus additional monitoring (AM) for the detection of AF (SP-AM). AM comprised 7 days of noninvasive cardiac-event monitoring, performed with the Novacor R-test Evolution 3 device. The device weighs <50 g and garners cardiac rhythm data through 2 electrodes, placed respectively at the sternum and apex. This approximates to a CM5 lead configuration. The R-test device used a loop recording system to capture cardiac rhythm episodes of 30 seconds duration (the maximum period of dysrhythmia recordable with the R-test device settings used in the study), triggered automatically by possible AF recognition. Ten seconds of rhythm preceding and 20 seconds subsequent to the trigger point were captured.. Duration 7 days. Concurrent medication/care: Monitoring commenced immediately after randomization, with interim downloads at 24, 72, and 168 hours to permit interim analysis of any captured events and to avoid losing any detected AF episodes (with a 20-minute memory, the device automatically stores the most prolonged rhythm disturbances preferentially over briefer ones). The SP-AM group also had digital 12-lead ECGs recorded at 24 and 72 hours with a Lexor Cardiolex ECG. The cardiac-event monitoring and digital ECG data were transferred to a central cardiac electrocardiology laboratory (Glasgow Royal Infirmary) led by 1 of the authors, for storage and analysis. This is an accredited specialist core laboratory, with extensive experience in ECG reporting and cardiac monitoring data for many international trials. A trained technician established whether the recordings were normal or showed possible evidence of AF, based on absence of discernible organized atrial activity and irregular ventricular response. Recordings with suspected AF were reviewed by an experienced electrocardiologist. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: cardiologist/electrophysiologist (n=50) Intervention 2: usual care. Standard practice monitoring. Investigations that afforded the opportunity for AF detection comprised additional 12-lead ECGs (subsequent to the admission 12-lead ECG), 24-hour Holter monitoring, and echocardiography (which, as coupled with cardiac rhythm monitoring, afforded the opportunity for AF detection). 24-hour Holter recordings were reported centrally at the recruiting hospital cardiology laboratory and reviewed thereafter by treating clinicians. Duration unclear. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: cardiologist/electrophysiologist
Funding	This study was competitively funded by a grant from the Chief Scientist Office (CSO), Scotland (CZG/2/745) and supported by the Scottish Stroke Research Network. The funder did not contribute to study design, study conduct, report preparation, or submission. Six R-test Evolution 3 cardiac-event monitors and accompanying software for rhythm analysis, required for conduct of the study, were donated by Novacor, who also provided free on-site training in use of the equipment. Novacor did not contribute to study design, study conduct, report preparation, or submission.

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OTHER NON-12 LEAD versus USUAL CARE Protocol outcome 1: Confirmed diagnosis of AF - Actual outcome: detection of sustained (>20s) PAF at 90 days; Group 1: 11/50, Group 2: 4/50; Comments: paper also gave results for non-sustained (any duration) AF. These were intervention 24/50 and control 5/50. Risk of bias: All domain - Low, Selection - Low, Blinding - low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Initiated anticoagulants for AF - Actual outcome: anticoagulation for any indication at 90 days; Group 1: 13/50, Group 2: 5/50 Risk of bias: All domain - Low, Selection - Low, Blinding - low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Mortality; Hospitalisation ; Stroke/thromboembolism ; Major bleeding

ISBN: 978-1-4731-4043-1

Study	Hoefman, 2005 trial: Hoefman 2005[33]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=244)
Countries and setting	Conducted in Netherlands; Setting: GP practices
Line of therapy	1st line
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cardiologist interpretation of ECG traces plus GP decision based on that and on other data
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Consecutive patients who consulted their GP for a new episode of palpitations and/or light-headedness were recruited from October 1999 until June 2002. Palpitations were defined as any feeling of an abnormal heartbeat or rhythm. Light headedness was defined as feelings of faintness or going to faint.
Exclusion criteria	Patients younger than 18 years, fitted with a pacemaker, being currently treated by a cardiologist, or needing immediate intervention and/or referral were excluded.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (range): event recorder 50; usual care 49. Gender (M:F): 26:74. Ethnicity: unclear
Further population details	
Extra comments	events recorder/usual care: DM 6%/5%; IHD 9%/8%; hypertension 24%/12%; time since first episode >1 year: 38%/38%;

ISBN: 978-1-4731-4042-1

Indirectness of population	No indirectness
Interventions	(n=127) Intervention 1: Holter. A Card Guard CG-6106 loop recorder was used. This recorder continuously registers and updates a two lead ECG. When a patient chooses to activate the recorder it stores information 30 seconds before and 2 minutes after the moment of activation. A maximum of three registrations could be stored in the memory, hereafter an acoustic signal indicated that the memory was fully stored. . Duration 6 weeks. Concurrent medication/care: The intervention group received a recorder and training on how to use the device. Patients were asked to wear the recorder continuously. For quality assurance patients made a training ECG at home and sent it by telephone to the research centre. If necessary, this procedure was repeated until a good quality ECG was obtained. Each week all patients had to send in a test ECG to ensure the event recorder was working well. The patients were instructed to make a recording and send it to the research centre every time they experienced symptoms similar to the ones for which they consulted the GP. They could use the CER for a maximum period of four weeks. The procedure was stopped earlier if an ECG was diagnostic or three good-quality recordings without abnormalities were obtained during symptomatic periods. All ECGs were immediately assessed by trained health professionals who could take action if necessary. In addition all the ECGs were reviewed and classified by an experienced cardiologist, who was informed about the symptoms of the patient. These reviewed results were sent to the GP.. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: cardiologist/electrophysiologist (n=117) Intervention 2: usual care. Standard care. Gp maintained responsibility for patient care and could use all regular health care interventions (including referral to cardiologists). Duration 6 weeks. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: cardiologist/electrophysiologist
Funding	Academic or government funding (Funding: this research was funded by the Dutch College for Health Insurance(CVZ) and by AGIS health insurances.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HOLTER versus USUAL CARE

Protocol outcome 1: Confirmed diagnosis of AF
- Actual outcome: Diagnosis of AF by GP at 6 months; Group 1: 12/127, Group 2: 2/117
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: no reason given; Group 2 Number missing: 0

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Quality of life ; Hospitalisation ; Mortality ; Stroke/thromboembolism ; Major bleeding ; Initiated anticoagulants for AF	Protocol outcomes not reported by the study

ISBN: 978-1-4731-4043-1

Study	Kamel, 2013 trial: Kamel 2013[37]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in USA; Setting: Patients discharged and being seen as outpatients after stroke
Line of therapy	1st line
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Use of Cardionet mobile cardiac outpatient telemetry which has >99% sensitivity of AF. To ensure specificity all device-labelled AF episodes were manually reviewed by a cardiologist
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients with ischemic stroke or high-risk transient ischemic attack (ABCD2 score ≥4).
Exclusion criteria	Patients with lacunar infarcts, ≥50% stenosis of relevant arteries, likely cardioembolism, or other apparent cause; patients ineligible to receive anticoagulation or with onset >60 days previously; patients with detected AF during 24 hours cardiac monitoring as inpatients with onset of symptoms >60 days previously
Recruitment/selection of patients	unclear
Age, gender and ethnicity	Age - Mean (SD): 67(12). Gender (M:F): 57:43. Ethnicity: Not reported
Further population details	

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Extra comments	previous stroke or TIA 35%; hypertension 73%; antihypertensive medication on admission 53%; DM 25%; hyperlipidaemia 45%; statin on admission 35%; CAD 5%; HF 3%; current or former smoker 25%; TIA as index event 33%; median NIH stroke score on admission 3. This study was designed to evaluate OUTPATIENT cardiac monitoring, not inpatient monitoring - hence the exclusion of those identified by 24 hour telemetry as having AF as inpatients
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Holter. Cardionet Mobile Cardiac Outpatient Telemetry for 21 days. Began a mean 22 days after stroke (no more details provided). Duration 1 year (21 days of monitoring) . Concurrent medication/care: Patients discharged with antiplatelet therapy, with a plan to begin anticoagulation if AF had been diagnosed. All patients scheduled to see primary care physician within 1 months and the stroke clinic within 3 months and patients were educated to report symptoms of AF at these visits.. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: unclear (n=20) Intervention 2: usual care. Usual care (see below) - no monitoring. Duration 1 year. Concurrent medication/care: Patients discharged with antiplatelet therapy, with a plan to begin anticoagulation if AF had been diagnosed. All patients scheduled to see primary care physician within 1 months and the stroke clinic within 3 months and patients were educated to report symptoms of AF at these visits.. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: unclear
Funding	Other (Cahill Family Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HOLTER versus USUAL CARE

Protocol outcome 1: Confirmed diagnosis of AF
- Actual outcome: Diagnosis of AF at 1 year; Group 1: 0/20, Group 2: 0/20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Mortality ; Stroke/thromboembolism ; Major bleeding ; Initiated anticoagulants for AF

ISBN: 978-1-4731-4043-1

Study	Kinlay, 1996 trial: Kinlay 1996[39]
Study type	RCT (order of diagnostic test randomised; Crossover: unclear)
Number of studies (number of participants)	1 (n=45)
Countries and setting	Conducted in Australia; Setting: Cardiovascular department in teaching hospital
Line of therapy	1st line
Duration of study	Follow up (post intervention): 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Electrogram rhythm strip obtained while symptoms occurred
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients referred to cardiovascular unit at Teaching Hospital with palpitations
Exclusion criteria	Researchers excluded patients being monitored for silent ischemia, assessment of therapy, syncope, or other research studies or inpatient monitoring; patients considered too old, too feeble, or too young to use the event monitor; and patients who had previously had Holter monitoring for their symptoms.
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): 45 (19). Gender (M:F): 5:38. Ethnicity: consecutive
Further population details	
Extra comments	palpitations occurred at least every 2 weeks 81%; perception of regular palpitations 56%; estimate of longest attack 74 mins; mean pulse 76; sbp 131; dbp 77; IHD 9.3%; hypertension 33%; smoker 16%

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Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Holter. 48 hours of Holter monitoring (Marquette Electronics).. Duration 48 hours. Concurrent medication/care: During Holter monitoring, patients were asked to record in a diary when their index palpitation symptoms occurred during the 48-hour recording period. Patients also recorded the symptoms associated with their palpitations, including dizziness, nausea, shortness of breath, chest discomfort or pain, and arm pain. We defined these criteria before the study. To check the correctness of the interpretation of arrhythmias, we used a full-disclosure method that allowed review of all 48 hours of electrogram recording. A cardiologist blinded to the results from the event recorder read the reports and electrocardiogram printouts of arrhythmias during symptomatic and asymptomatic periods. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: cardiologist/electrophysiologist (n=45) Intervention 2: Other . Event monitor (Aerotel; Medtronic). This is a transtelephonic post-event recorder. These handheld devices are given to patients and are applied to the chest when symptoms occur. The patient presses a button to record about 30 seconds of the cardiac rhythm, which is stored in the memory of the de- vice. The recording is later transmitted over the telephone for printing and interpretation. The patient kept the event monitor until two recordings were obtained during symptoms or until 3 months had passed.. Duration 3 months. Concurrent medication/care: Tracings for the event recorder were read by another cardiologist who was also blinded to patient data and results of 48 hour Holter monitoring. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: cardiologist/electrophysiologist
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HOLTER versus OTHER Protocol outcome 1: Confirmed diagnosis of AF - Actual outcome: Atrial fibrillation or flutter recorded at 3 months; Group 1: 0/43, Group 2: 3/43 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: left after Holter arm as found leads to uncomfortable; Group 2 Number missing: 2	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Mortality ; Stroke/thromboembolism ; Major bleeding ; Initiated anticoagulants for AF

ISBN: 978-1-4731-4043-1

Study	mSToPS, 2018 trial: Steinhubl 2018[57]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2659)
Countries and setting	Conducted in USA; Setting: Health insurance plan members; siteless clinical trial
Line of therapy	1st line
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Rhythm assessed by algorithm
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	male age>55; female age >65; prior stroke/TIA or HF or DM and hypertension or mitral valve disease or LVH or COPD requiring home O2 or sleep apnea or PE or MI or obesity
Exclusion criteria	Current or prior AF, flutter or tachycardia; receiving OADs; hospice care; end stage renal disease; moderate or worse dementia; implantable pacemaker/defibrillator; skin allergy to adhesive patches; metastases; Aetna Compassionate Care Program participants
Recruitment/selection of patients	Eligible patients invited by email and then led through an online consent and information process
Age, gender and ethnicity	Age - Range of means: immediate/delayed: 73.5/73.1. Gender (M:F): 1633:1026. Ethnicity: unclear
Further population details	

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Extra comments	Immediate/delayed: CHADSVASC median 3/3; stroke 13.7%/14.1%; HF 5.1%/4.6%; hypertension 77.1%/76.8%; DM 38.7%/36.5%; sleep apnea 25%/28.9%; prior MI 5.5%/5.6%; COPD 9.4%/8.7%; obesity (BMI>30 or obesity diagnosis such as Bariatric Surgery) 17.3%/18.4%; CRF 10.8%/9.6%
Indirectness of population	No indirectness
Interventions	(n=1366) Intervention 1: ECG devices - other non-12 lead. ECG screening was carried out using the iRhythm ZioXT, a Food and Drug Administration–approved, single-use, water-resistant, 14-day, ambulatory ECG monitoring skin adhesive patch that monitors and retains in memory the wearer's continuous ECG for up to 2weeks. Participants received their patch within 2 weeks (immediate group) along with instructions for self-application. Participants were asked to wear the patch and to return it to patch developer via prepaid mail package. All participants were asked to wear 2 different patches for a period of up to 2 weeks for each patch, each 3months apart to evaluate the additional potential benefit of more than 2weeks of monitoring.. Duration 4 weeks. Concurrent medication/care: After participants returned the patch, the rhythm data stored in the device were analyzed using a Food and Drug Administration–approved algorithm. The results then underwent technical review for report generation and quality assurance after which the report was uploaded to a secure website for independent review by the study's principal investigator. All possible ECG diagnoses of AF were adjudicated, blinded to any diagnosis, by the Clinical Events Adjudication Committee. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: treatments differ in categorisation (n=1293) Intervention 2: usual care. No additional treatment for the 4 month duration of the follow up. . Duration 4 months. Concurrent medication/care: After cessation of 4 month study this group given the patch.. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: treatments differ in categorisation
Funding	Study funded by industry (Dr Steinhubl reported receiving grants from Janssen, Qualcomm Foundation, and the National Institutes of Health (NIH)/National Center for Advancing Translational Sciences (grant UL1TR001114) and other funding fromDynoSense, EasyG, Spry Health, and Striiv. DrWaalen reported receiving grants from Janssen Pharmaceuticals. Ms Edwards and Mr Mehta are employees of Healthagen Outcomes. Ms Ebner reported receiving grants and other funding from Qualcomm and Janssen Pharmaceuticals. Dr Carter reported being an employee of Janssen Scientific Affairs and a stockholder in Johnson&Johnson. Ms Felicione and Dr Sarich are employees of Janssen Research&Development and stockholders in Johnson&Johnson. Dr Topol reported receiving grants from the NIH (Clinical and Translational Science Award) and the Qualcomm Foundation. No other disclosures were reported.)

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OTHER NON-12 LEAD versus USUAL CARE Protocol outcome 1: Confirmed diagnosis of AF - Actual outcome: Incidence of new AF cases at 4 months; Group 1: 53/1366, Group 2: 12/1293 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Mortality ; Stroke/thromboembolism ; Major bleeding ; Initiated anticoagulants for AF

ISBN: 978-1-4731-4043-1

Study	REHEARSE AF trial: Halcox 2017[27]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1004)
Countries and setting	Conducted in United Kingdom; Setting: Local GP practices
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Individuals >65 years of age with a CHADS-VASc score ≥2. Participants were required to have access to the internet via WiFi and to be able to operate the AliveCor Kardia system (AliveCor Inc, Mountain View, CA) attached to an iPod (Apple Inc, Cupertino, CA) after simple instruction.
Exclusion criteria	In receipt of OAC therapy; known diagnosis of AF currently; a known contraindication to anticoagulation; or permanent cardiac pacing implantation
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): 72.6(5.4). Gender (M:F): Define. Ethnicity: Unclear
Further population details	
Extra comments	iECG/usual care: HF 1%/2%; hypertension 54%/55%; DM 26%/28%; Stroke or TIA 7%/6%; vascular disease 14%/16%; CHADSVASC 1%/1%

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Indirectness of population	No indirectness
Interventions	(n=500) Intervention 1: ECG devices - 1 lead handheld. Participants in the intervention iECG arm were instructed to undertake twice-weekly recording and transmission of a 30-second single-lead iECG trace to a secure server (Monday and Wednesday recommended, plus additional submissions if symptomatic) over a 12-month period. iECG traces were analyzed by an automated analysis software algorithm (AliveCor version 2.2.0 [build 21]) and sent for offline analysis by a physiologist-led electrocardiographic reading service (Technomed Ltd UK). Abnormal ECGs were overread by a cardiologist. Clinical review and appropriate care was arranged for those clinically significant arrhythmia.. Duration 12 months. Concurrent medication/care: AF was defined as a 30-second iECG recording with irregular rhythm without p waves. All new AF diagnoses were confirmed and reviewed by a senior study cardiologist who made arrangements for OAC initiation and clinical management according to current UK (National Institute for Health and Care Guidelines) guidance.. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: cardiologist/electrophysiologist (n=501) Intervention 2: usual care. Patients in the RC arm were followed up as normal by their general practitioner.. Duration 12 months. Concurrent medication/care: RC participants with AF were diagnosed and managed by local clinicians, with all AF diagnoses validated by a study cardiologist. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: cardiologist/electrophysiologist
Funding	Study funded by industry (The study was funded predominantly by the Welsh Government but in part by a project grant from AliveCor. The study data were analyzed and reported independently without involvement of the company. None of the authors has received personal financial support for speaking or consulting on behalf of AliveCor Inc. There are no other disclosures to report.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: 1 LEAD HANDHELD versus USUAL CARE

Protocol outcome 1: Mortality
- Actual outcome: Death at 12 months; Group 1: 3/498, Group 2: 5/501
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: lost to follow up (no other reasons given); Group 2 Number missing: 0

Protocol outcome 2: Stroke/thromboembolism
- Actual outcome: Stroke/TIA/SE at 12 months; Group 1: 6/498, Group 2: 10/500

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Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: lost to follow up (no other reasons given); Group 2 Number missing: 0 Protocol outcome 3: Major bleeding - Actual outcome: Clinically significant bleeds at 12 months; Group 1: 2/498, Group 2: 1/501 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: lost to follow up (no other reasons given); Group 2 Number missing: 0 Protocol outcome 4: Confirmed diagnosis of AF - Actual outcome: Diagnosis of AF (using iECG) at 12 months; Group 1: 19/498, Group 2: 5/501 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: lost to follow up (no other reasons given); Group 2 Number missing: 0 Protocol outcome 5: Initiated anticoagulants for AF - Actual outcome: Treatment with anticoagulation at 12 months; Group 1: 19/498, Group 2: 4/501; Comments: iECG arm : 9 warfarin, 10 DOAC; control arm: 3 warfarin, 1 DOAC (also 1 with clopidogrel but not counted as an anticoagulant as antiplatelet agent) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: lost to follow up (no other reasons given); Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation

Study	**EPACS, 2019 trial: Kaura, 2019[38]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=116)
Countries and setting	Conducted in UK; Setting: Secondary care
Line of therapy	1st line

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Duration of study	Follow up (post intervention): 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ECG evidence of PAF lasting at least 30s within 90 days, clinical examination such as echocardiography
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible patients were 18 years of age or older and were diagnosed with having had an ischaemic non-lacunar stroke or TIA within the past 72 h by a stroke physician or neurologist. Patients with a TIA were enrolled only if there were cortical symptoms of hemianopia or dysphasia at presentation or if their diffusion-weighted cerebral MRI scan was positive in a non-lacunar distribution.
Exclusion criteria	The main exclusion criteria were a history of AF or atrial flutter, carotid stenosis > 50%, a pre-existing indication or contraindication for permanent anticoagulation therapy
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age – Range of means: 70 -70.7. Gender (M:F): 55:35. Ethnicity: Asian 3/90; Black 21/90; White 66/90
Further population details	
Extra comments	Intervention/control: index event stroke 81.4%/91.5%; prior stroke?TIA: 27.9%/14.9%; hypertension 60.5%/63.8%; DM 23.3%/21.3%; IHD 18.6%/10.6%; hypercholesterolaemia 39.5%/36.2%
Indirectness of population	No indirectness
Interventions	(n=56) Intervention 1: Patch based monitoring using the ZioPatch® (iRhthym Technologies, USA). This is an adhesive cardiac monitoring patch which provides an alternative method for prolonged ECG monitoring for the detection of PAF. The waterproof patch is applied non-invasively to the anterior chest wall for continuous monitoring for up to 14 days without requiring any complex setup. The ECG trace uses the Zio XT algorithmic support to highlight areas for human interpretation. Duration 14 days. Concurrent medication/care: Also had the standard practice of short term Holter monitoring, using the Lifecard CF Holter. Indirectness: No indirectness

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	Further details: 1. Expertise of test interpreter: Not stated / Unclear (n=60) Intervention 2: usual care. Patients assigned to the conventional medical therapy arm received current medical therapy of ambulatory Holter monitoring only (duration determined by treating physician, which was usually 24 h), either arranged as an inpatient or outpatient depending on the anticipated duration of inpatient stay as per hospital protocol. Duration 14 days. Concurrent medication/care: None. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: Not stated/ unclear
Funding	This work was supported by an investigator-initiated research Grant from Bristol-Myers Squibb-Pfizer alliance (Grant Number CV185-475).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PATCH versus USUAL CARE

Protocol outcome 1: Mortality
- Actual outcome: Death at 90 days; Group 1: 1/44, Group 2: 0/47
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12, Reason: 10 Holter monitors not applied, 1 declined Holter as patch detected PAF already, 1 inadequate Zio patch signal.; Group 2 Number missing: 13, Reason: 13 Holter monitors not applied

Protocol outcome 2: Stroke/thromboembolism
- Actual outcome: Further stroke or TIA at 90 days; Group 1: 1/43, Group 2: 1/47
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13, Reason: 1 death, 10 Holter monitors not applied, 1 declined Holter as patch detected PAF already, 1 inadequate Zio patch signal.; Group 2 Number missing: 13, Reason: 13 Holter monitors not applied

Protocol outcome 3: Confirmed diagnosis of AF
- Actual outcome: Detection of PAF >30s at 90 days; Group 1: 7/43, Group 2: 1/47
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13, Reason: 1 death, 10 Holter monitors not applied, 1 declined Holter as patch detected PAF already, 1 inadequate Zio patch signal.; Group 2 Number missing: 13, Reason: 13 Holter monitors not applied

Protocol outcome 4: Initiated anticoagulants for AF
- Actual outcome: Started on OACS at 2 years; Group 1: 7/43, Group 2: 1/47
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;

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Indirectness of outcome: No indirectness ; Group 1 Number missing: 13, Reason: 1 death, 10 Holter monitors not applied, 1 declined Holter as patch detected PAF already, 1 inadequate Zio patch signal.; Group 2 Number missing: 13, Reason: 13 Holter monitors not applied	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Major bleeding

Study	**iHEART, 2019 trial: Goldenthal, 2019[22] Caceres, 2020[8]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=238)
Countries and setting	Conducted in USA; Setting: Secondary care
Line of therapy	1st line
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Recurrence was defined as one of the following: a KardiaMobile rhythm strip showing AF/AFL as determined by a physician, an ECG in the EHR displaying an AF/AFL confirmed by a physician, or a note in the EHR from a physician stating that the patient had a recurrent AF/AFL.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Inclusion criteria were ablation/cardioversion in past 30 days leading to normal sinus rhythm; age 18 and older; a history of documented AF and at least one AF risk factor (sedentary lifestyle, obesity, hypertension, smoking, and diabetes). Patients also needed to express willingness to participate for the full 6-monthduration of the trial and demonstrate an ability to use a smartphone, send and receive text messages, and successfully use the AliveCor KardiaMobile ECG monitor (AliveCor).

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Exclusion criteria	Patients with a history of cognitive impairment and those unwilling to have their clinical data collected or receive text messages were excluded from the study.
Recruitment/selection of patients	Subjects were recruited for the iHEART study from the cardiac electrophysiology clinics within the Division of Cardiology at Columbia University Medical Center in New York, NY, United States of America. These individuals were identified as potential study subjects by their health-care providers who obtained verbal approvals before the study team approached them.
Age, gender and ethnicity	Age – mean (sd):61(12). Gender (M:F): 184:54. Ethnicity: white (intervention/control) 77%/76%, Black or African American 3%/7%, Asian 1%/4%, unclear 20%/14%
Further population details	Intervention/control: procedure at enrolment DCCV 48%/65%, RFA 52%/35%; PAF 68%/61%, Persistent AF 32%/39%; previous stroke/TIA 10%/8%; CHF 19%/26%; DM 12%/14%; hypertension 57%/63%; OACs 87%/91%; enlarged LA diameter 54%/59%
Extra comments	
Indirectness of population	Seriously indirect: the population were in sinus rhythm post ablation/ electrical cardioversion treatment but deemed at risk of recurrence. Although this makes the population relevant for AF detection, the population is slightly different to the protocol population.
Interventions	(n=131) Intervention 1: AliveCor Kardia Mobile for 6 months. Patients randomized to the iHEART intervention received an iPhone and cellular service plan with unlimited data/text messaging, and the Alive Cor Kardia Mobile ECG monitor for 6 months. If they already owned a smartphone compatible with the Kardia Mobile device, they had the option to use the KardiaMobile device with their own phone. Patients also received motivational text messages three times per week relating to management of AF and risk factors (eg, obesity, sedentary lifestyle), for example, “Limit sugary d rinks to no more than 36 oz a week.” Patients were trained on how to use the phone; how to use the Kardia application which connects to the KardiaMobile device to record ECGs; and how to record ECGs and symptoms using the KardiaMobile device. Patients were instructed to record a daily ECG and additional ECGs whenever they experienced symptoms perceived to be associated with an atrial arrhythmia. Upon discovery of any arrhythmia, patients contacted their health-care provider, and all treatment, management, and follow-up for the arrhythmia were determined by the

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	patient's provider. Duration 6 months. Concurrent medication/care: Nil. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: Not stated / Unclear (n=131) Intervention 2: usual care. No details provided. Duration 6 months. Concurrent medication/care: None. Indirectness: No indirectness Further details: 1. Expertise of test interpreter: Not stated/ unclear
Funding	This study was funded by R01 from the National Institute of Nursing Research (R01NR014853).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AliveCor versus USUAL CARE

Protocol outcome 2: Quality of life
- Actual outcome: Atrial Fibrillation Effect on Quality of Life – global score; MD: 7.3 (95% CI: -1.13 to 15.73)
Risk of bias: All domain – Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 75, Reason: unclear.; Group 2 Number missing: 76, Reason: unclear
- Actual outcome: SF-36 physical; MD: 1.2 (95% CI: -1.35 to 3.75)
Risk of bias: All domain – Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 74, Reason: unclear.; Group 2 Number missing: 75, Reason: unclear
- Actual outcome: SF-36 mental; MD: -0.5 (95% CI: -3.24 to 2.24)
Risk of bias: All domain – Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 74, Reason: unclear.; Group 2 Number missing: 75, Reason: unclear
- Actual outcome: EuroQol Index; MD: 0 (95% CI: -0.059 to 0.059)
Risk of bias: All domain – Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 73, Reason: unclear.; Group 2 Number missing: 75, Reason: unclear
- Actual outcome: EuroQol VAS; MD: 4.3 (95% CI: -1.38 to 9.98)
Risk of bias: All domain – Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 71, Reason: unclear.; Group 2 Number missing: 74, Reason: unclear
- Actual outcome: University of Toronto Atrial Fibrillation Severity Scale; MD: -0.8 (95% CI: -3.74 to 2.14)
Risk of bias: All domain – Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 74, Reason: unclear.; Group 2 Number missing: 77, Reason: unclear

Protocol outcome 2: Confirmed diagnosis of AF
- Actual outcome: Detection of recurrence at 6 months; Group 1: 58/115, Group 2: 49/118
Risk of bias: All domain – Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;

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Indirectness of outcome: No indirectness ; Group 1 Number missing: 16, Reason: 4 other, 1 double, 1 no procedure, 10 no device.; Group 2 Number missing: 13, Reason: other 1, double 1, no procedure 6, lost to follow up 5 Protocol outcome 3: Hospitalisation - Actual outcome: all cause hospitalisations; Group 1: 45/115, Group 2: 56/118 Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 16, Reason: 4 other, 1 double, 1 no procedure, 10 no device.; Group 2 Number missing: 13, Reason: other 1, double 1, no procedure 6, lost to follow up 5	
Protocol outcomes not reported by the study	Mortality; Stroke or thromboembolism; Major bleeding; Initiated OACs for AF

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Appendix E: Forest plots

E.1 Holter 21-30 days vs usual care

Figure 2: Health related quality of life

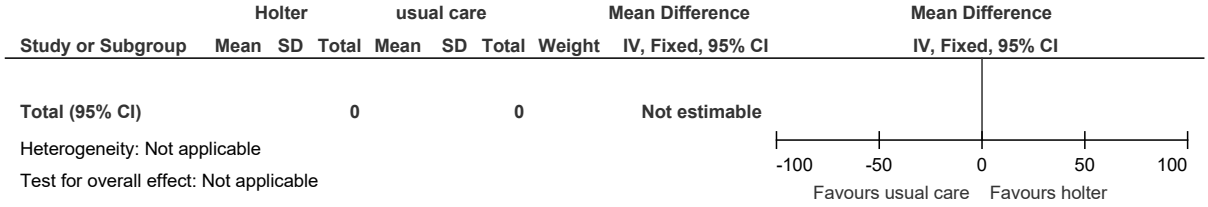

Figure 3: Mortality

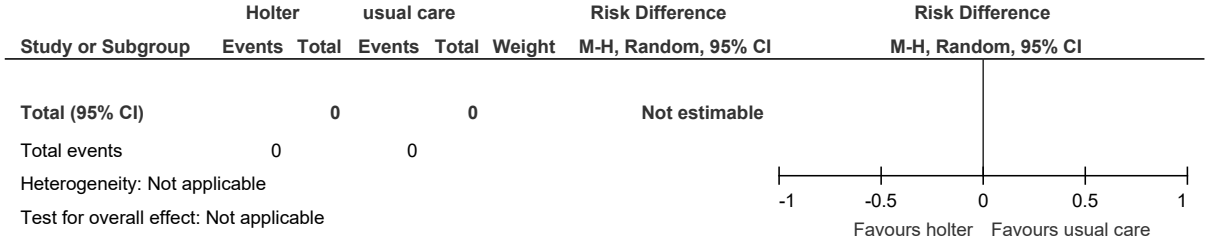

Figure 4: Stroke and thromboembolic complications

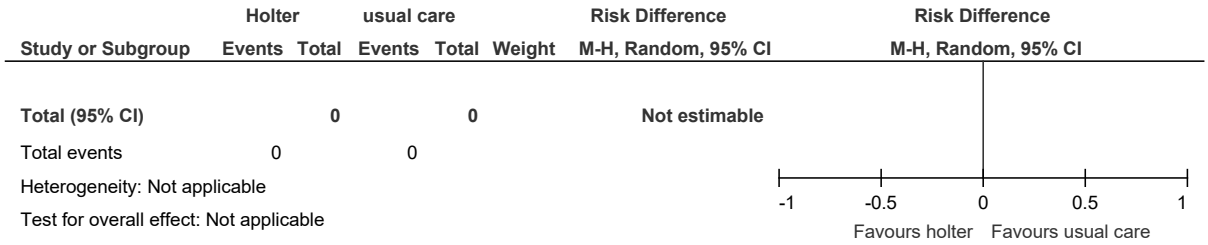

Figure 5: Major bleeding

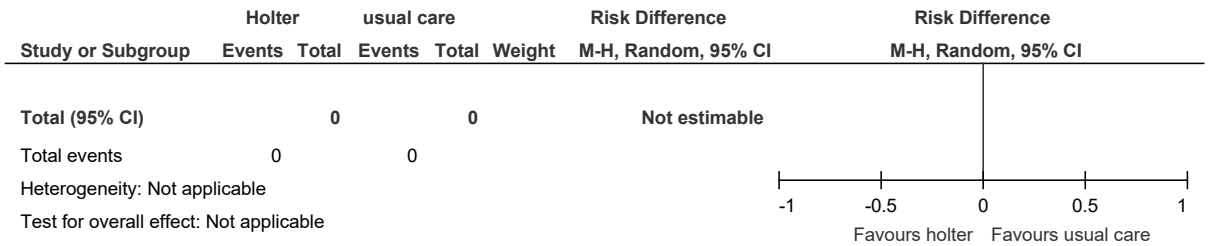

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Figure 6: All cause hospitalisation

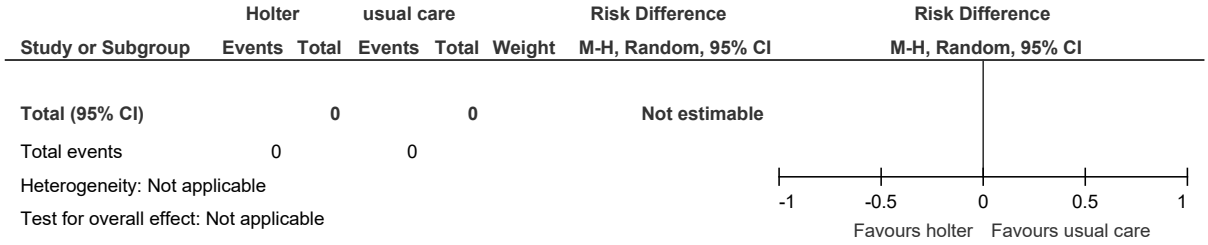


Figure 7: confirmed diagnosis of AF

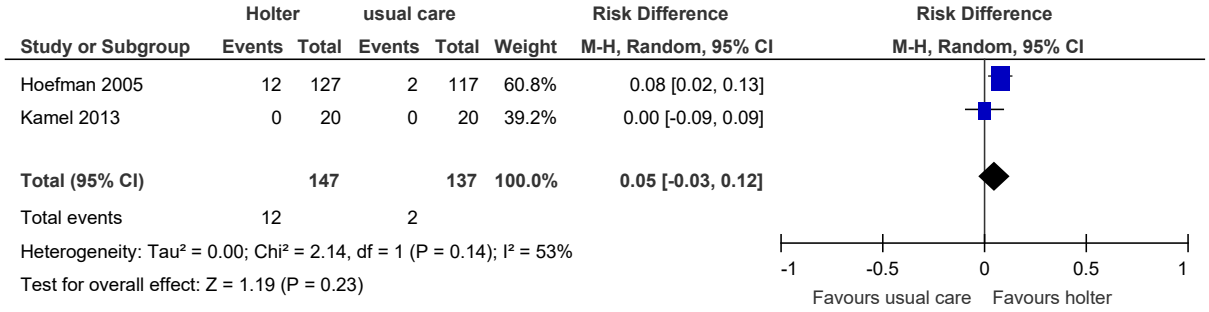
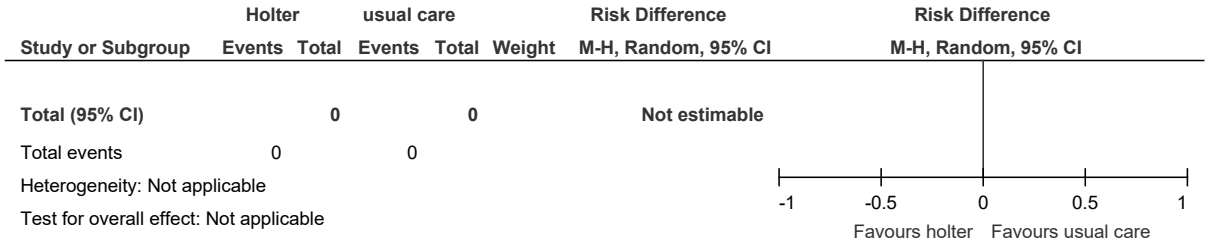


Figure 8: Initiated anticoagulants for AF



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E.2 Holter 3 x 10 days over 6m vs usual care

Figure 9: Health-related quality of life

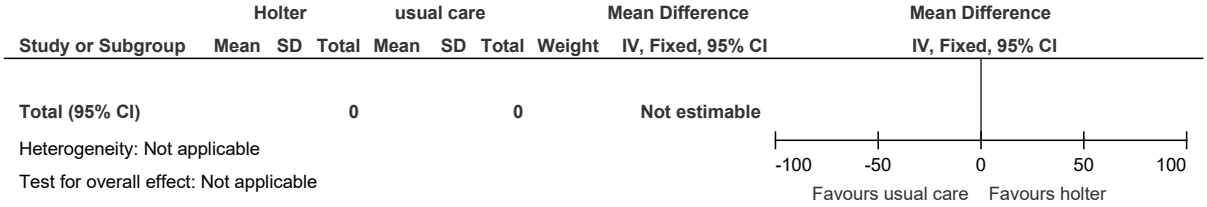

Figure 10: mortality

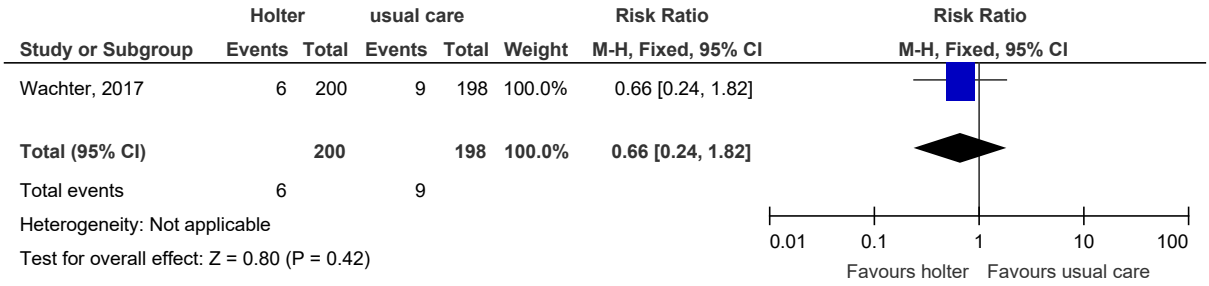

Figure 11: Stroke and thromboembolic complications

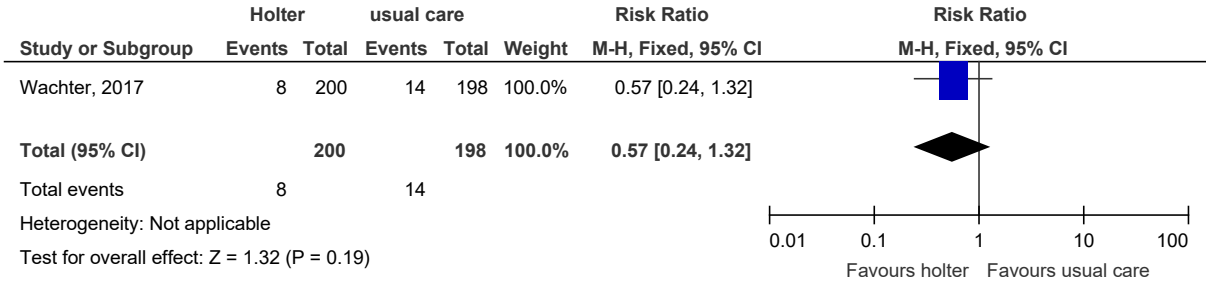

Figure 12: Major bleeding

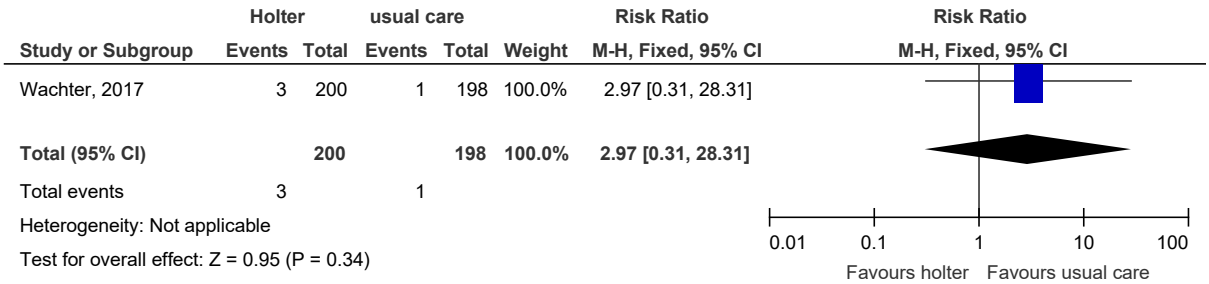

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Figure 13: All cause hospitalisation

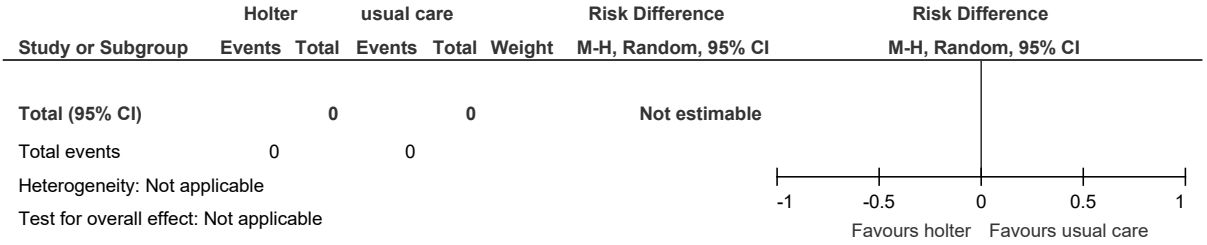


Figure 14:confirmed diagnosis of AF

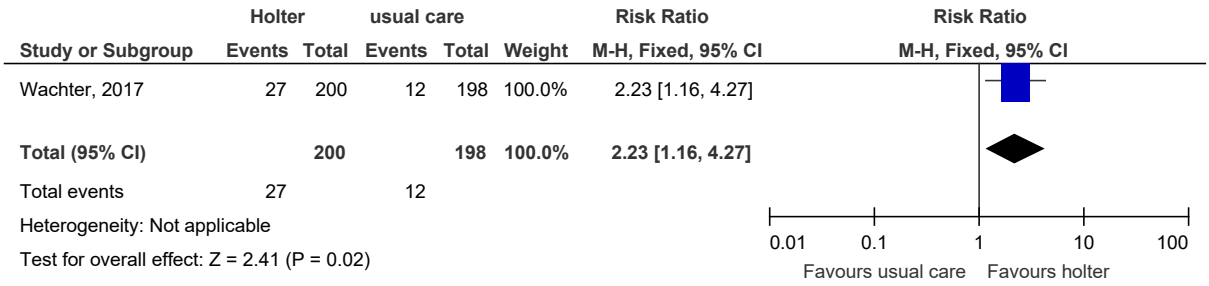
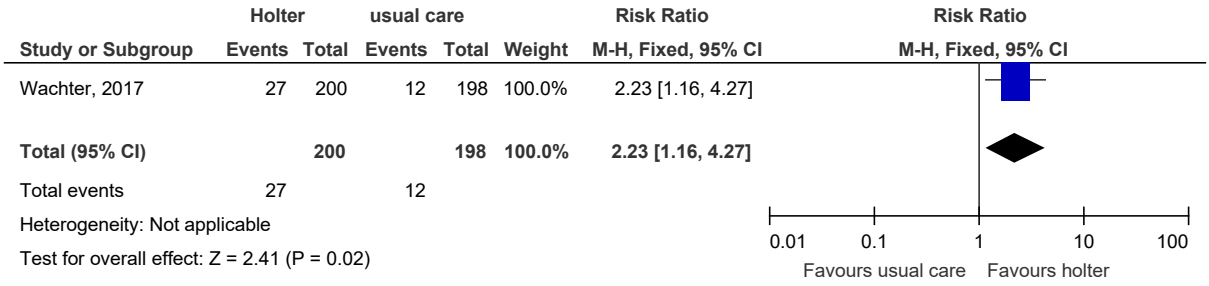


Figure 15: Initiating OACs



E.3 Ambulatory ECG with 30 day event monitor vs 24 hr ECG

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Figure 16: Health-related quality of life

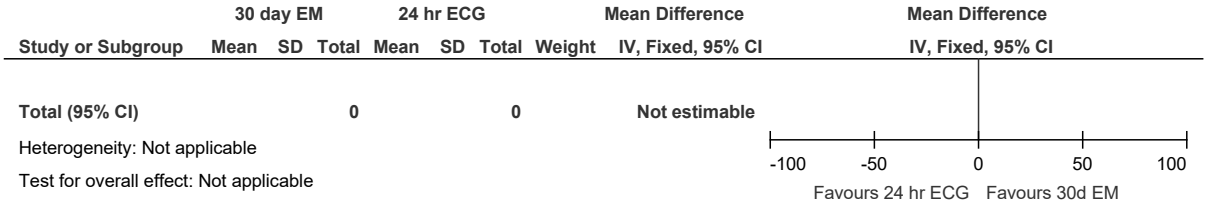

Figure 17: Mortality

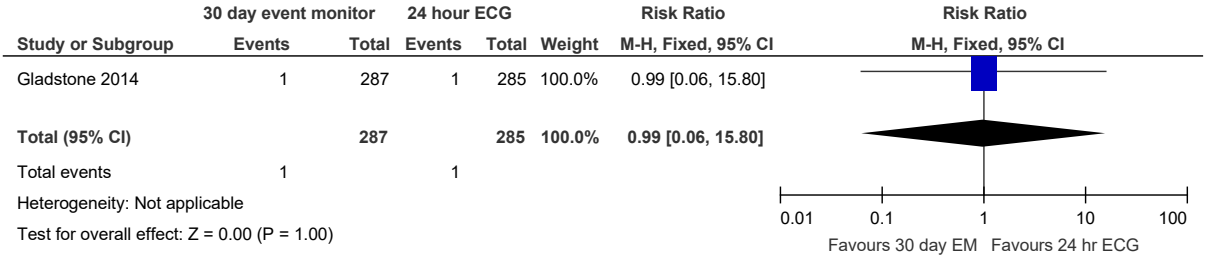

Figure 18: Stroke

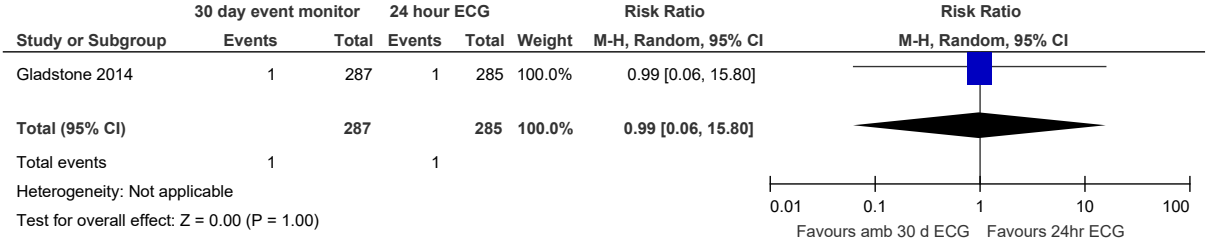

Figure 19: Major bleeding

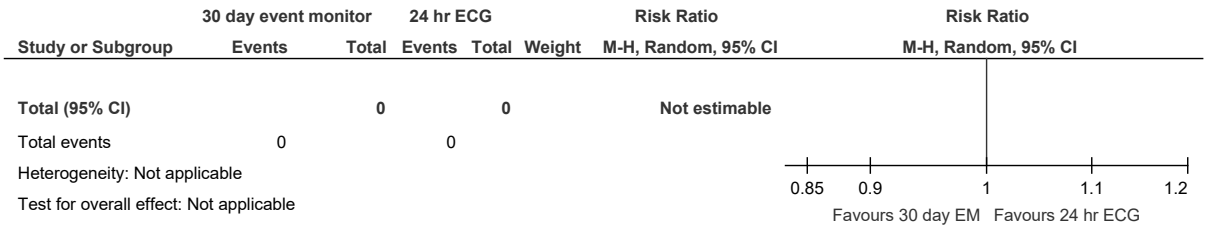

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Figure 20: All cause hospitalisation

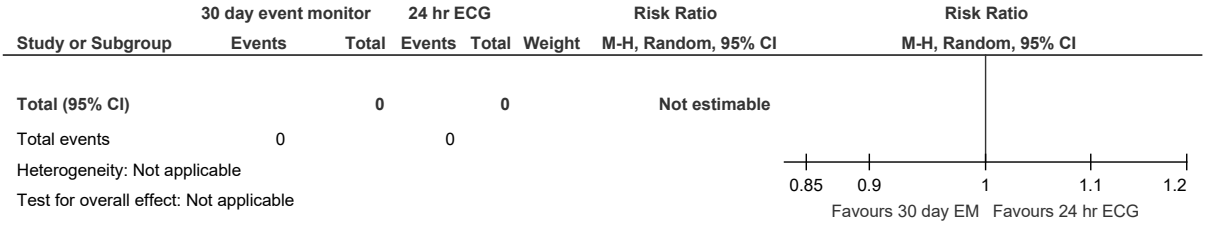


Figure 21: Confirmed diagnosis of AF

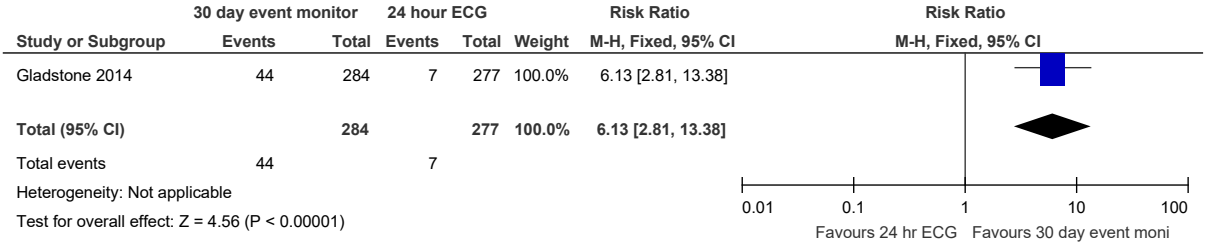
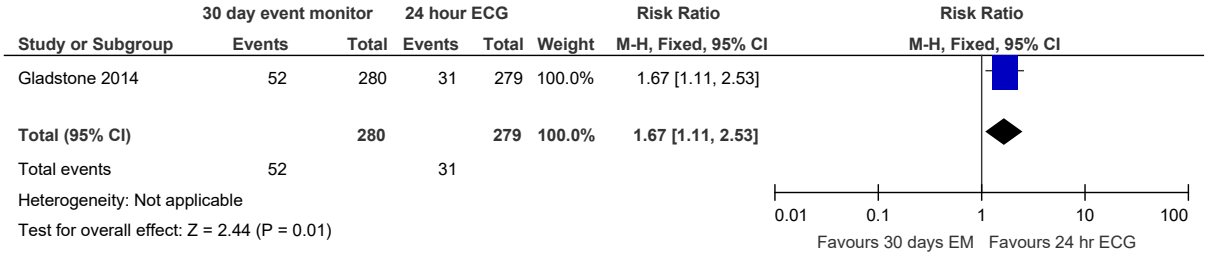


Figure 22:Initiation of OACs



E.4 Holter 48 hrs vs handheld event monitor

Figure 23: Health-related quality of life

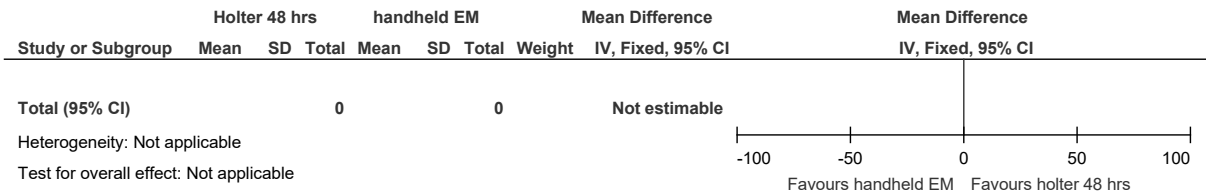


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Figure 24: Mortality

Study or Subgroup	Holter Events	Holter Total	handheld EM Events	handheld EM Total	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

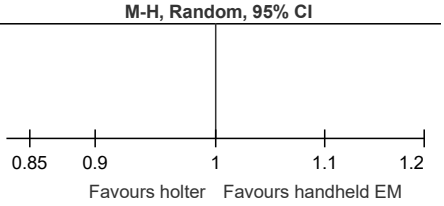

Figure 25: stroke and thromboembolic complications

Study or Subgroup	Holter Events	Holter Total	handheld EM Events	handheld EM Total	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

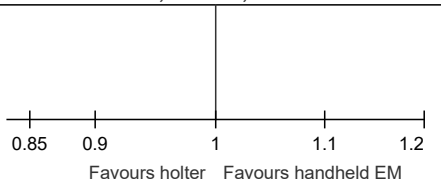

Figure 26: Major bleeding

Study or Subgroup	Holter Events	Holter Total	handheld EM Events	handheld EM Total	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

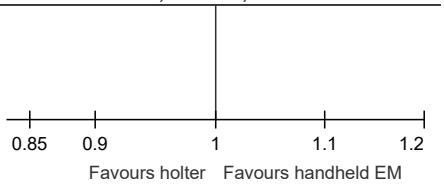

Figure 27: All cause hospitalisation

Study or Subgroup	Holter Events	Holter Total	handheld EM Events	handheld EM Total	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

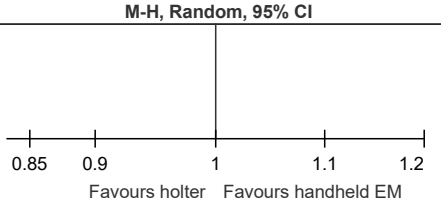

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Figure 28: Confirmed diagnosis of AF

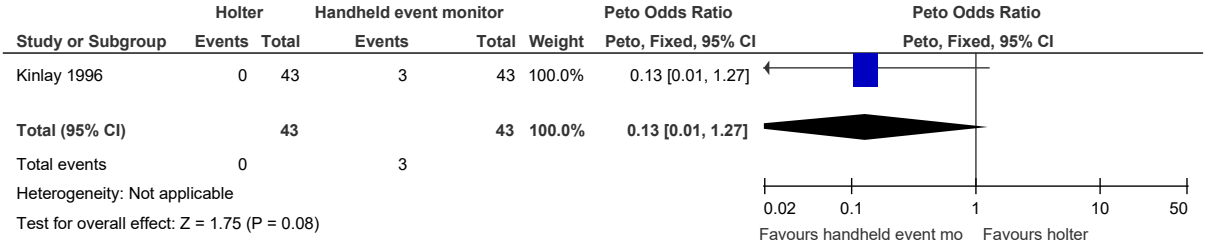
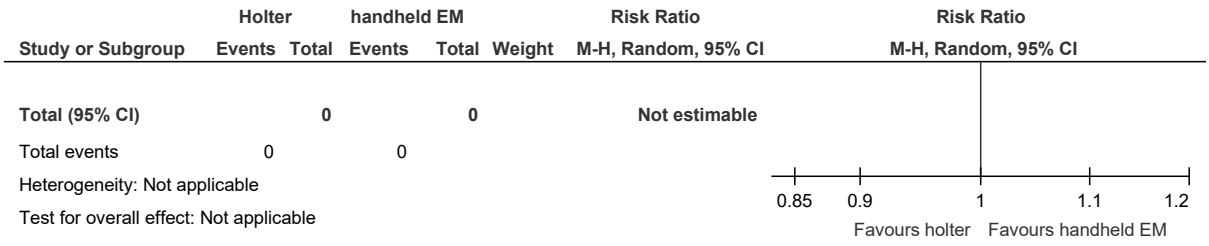


Figure 29: Initiated anticoagulants for AF



E.5 Skin patch ECG vs usual care

Figure 30: Health-related quality of life

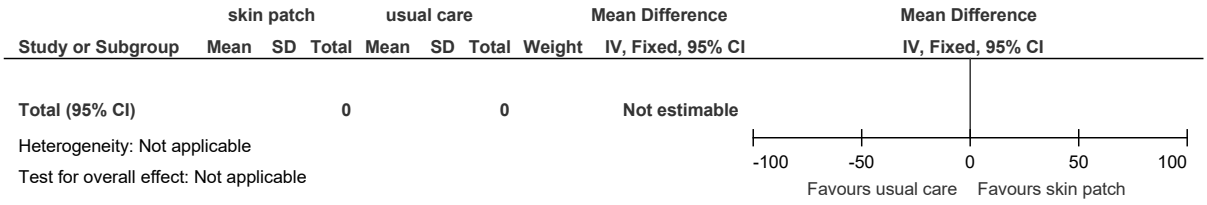


Figure 31: Mortality

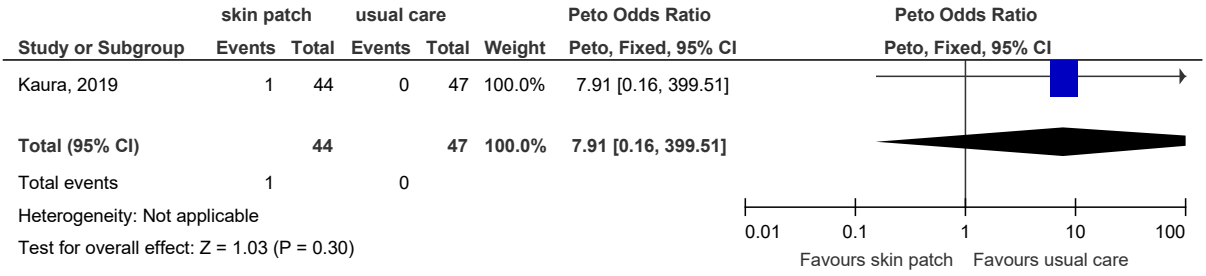


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Figure 32: Stroke and thromboembolic complications

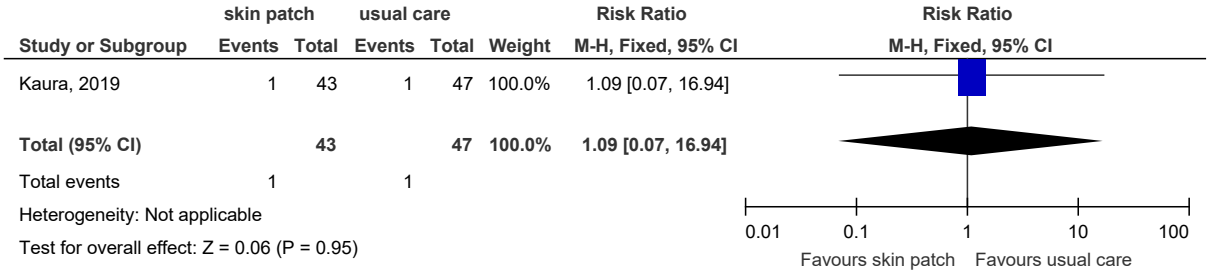

Figure 33: Major bleeding

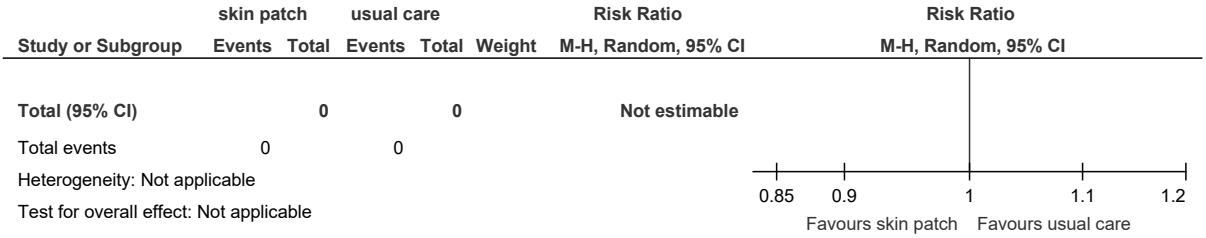

Figure 34: All cause hospitalisation

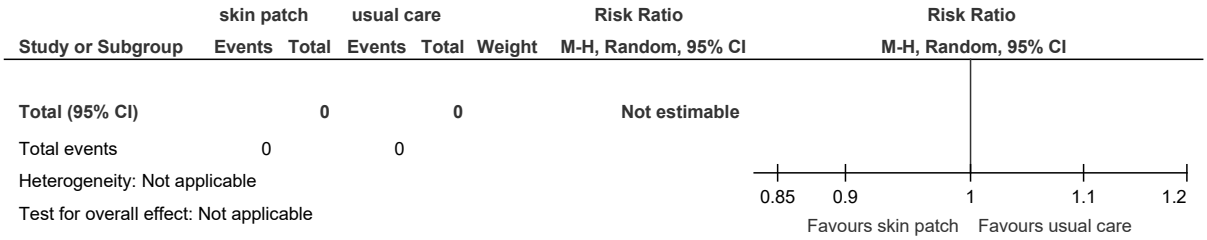

Figure 35: confirmed diagnosis of AF

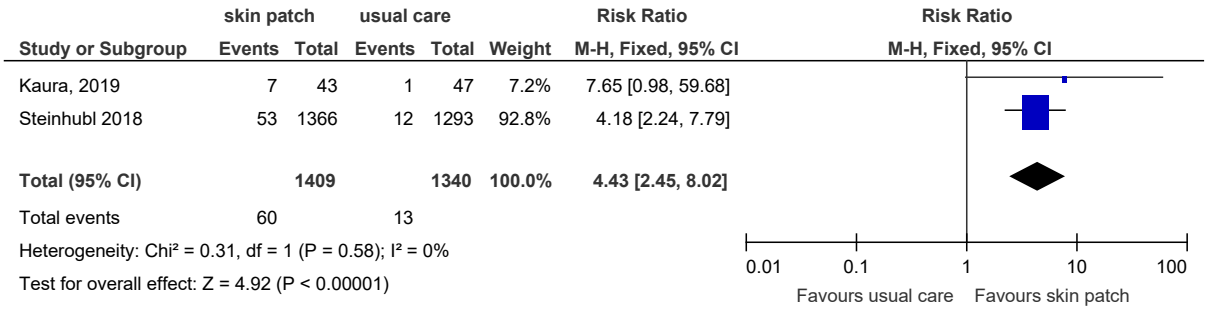

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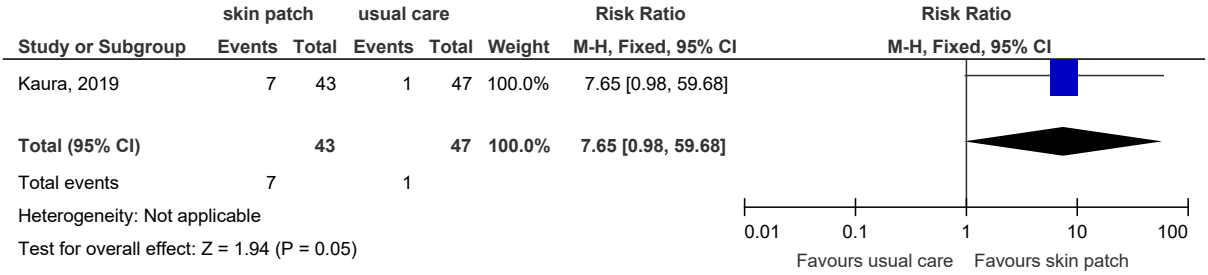
Figure 36: Initiation of OACs



E.6 2 year early detection inc. ECG vs usual care

Figure 37: Health-related quality of life

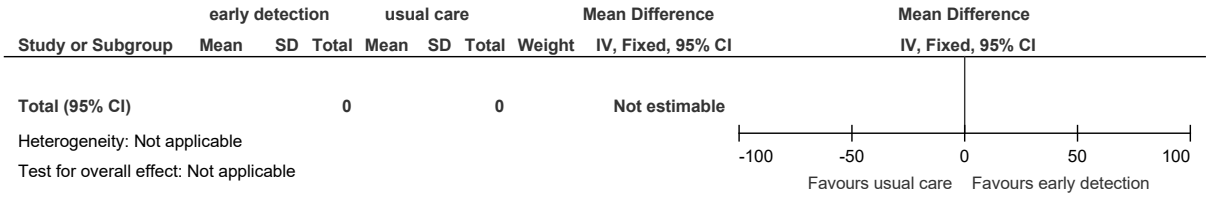


Figure 38: Mortality

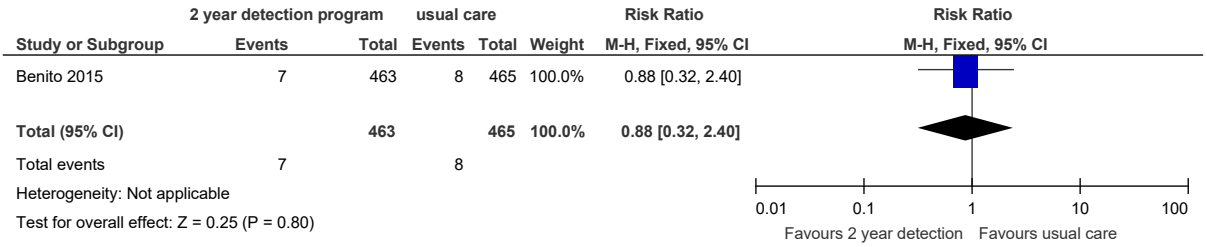


Figure 39: Stroke and thromboembolic complications

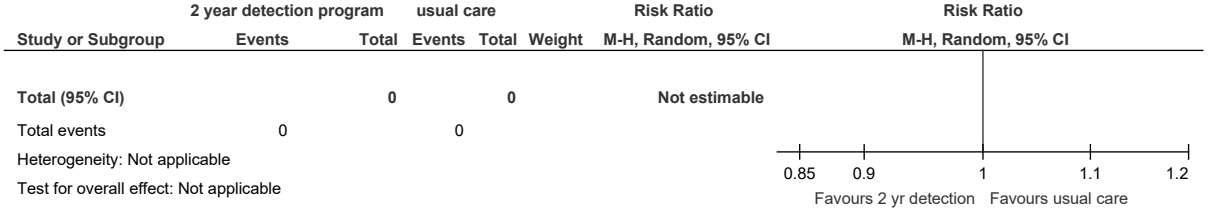


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Figure 40: Major bleeding

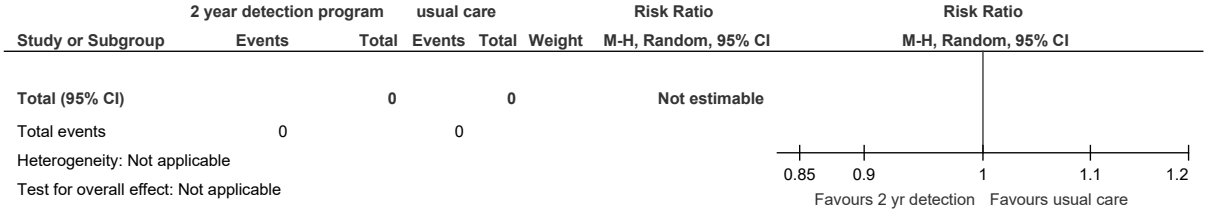


Figure 41: All cause hospitalisation

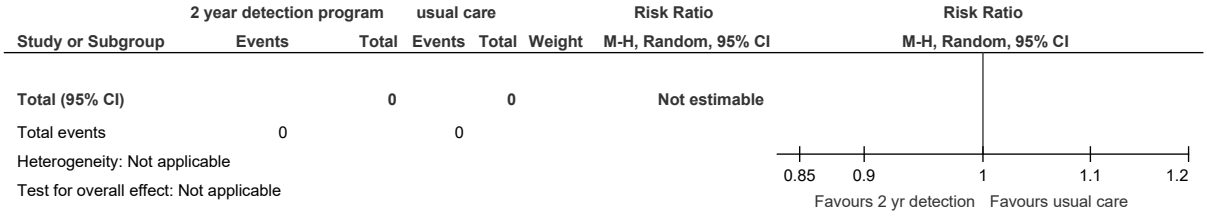


Figure 42: confirmed diagnosis of AF

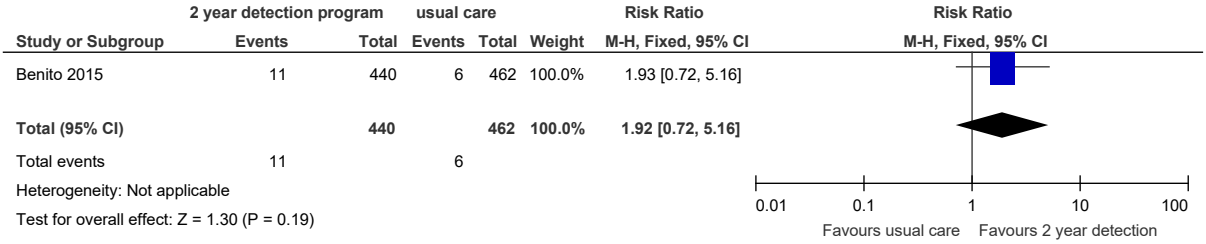
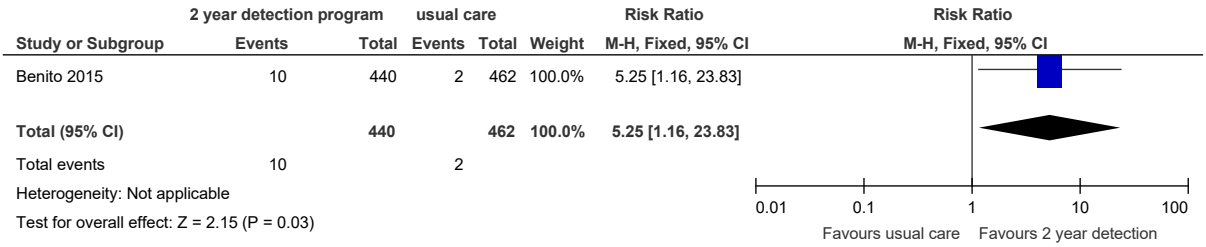


Figure 43:Initiation of OACs



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E.7 1 lead handheld ECG vs usual care

Figure 44: Health-related quality of life - Atrial Fibrillation Effect on Quality of Life – global score

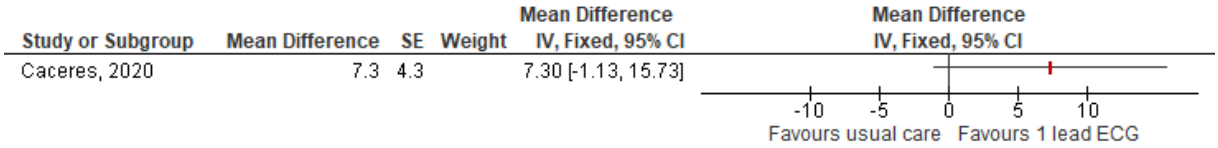

Figure 45: Health-related quality of life – SF36 Physical

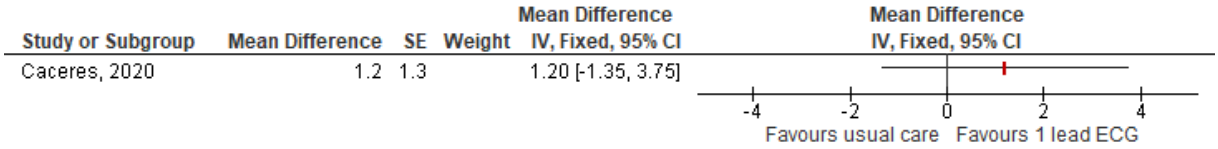

Figure 46: Health-related quality of life – SF-36 mental

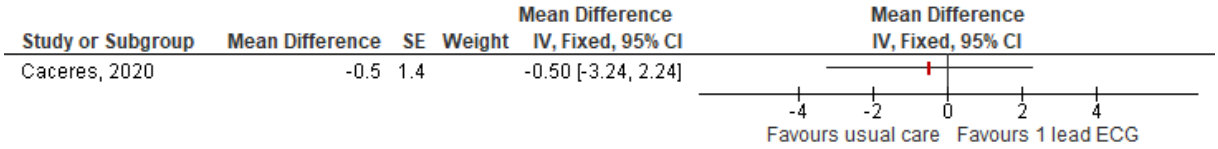

Figure 47: Health-related quality of life – EuroQol index

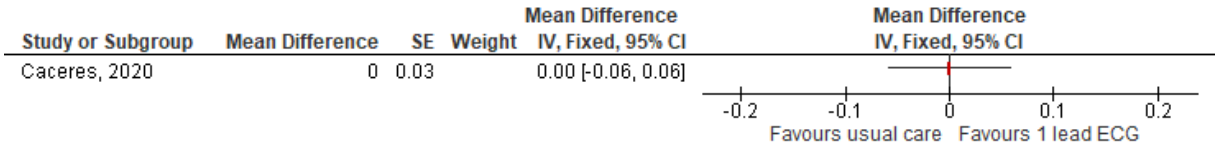

Figure 48: Health-related quality of life – EuroQol VAS

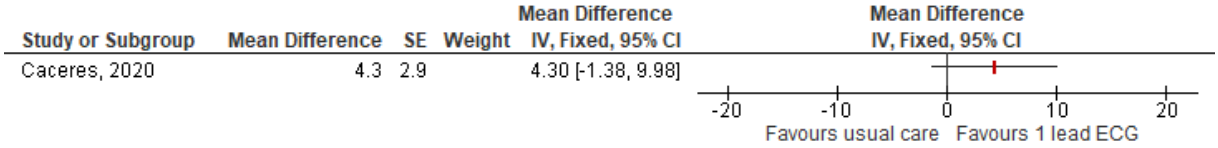

Figure 49: University of Toronto Atrial Fibrillation Severity Scale

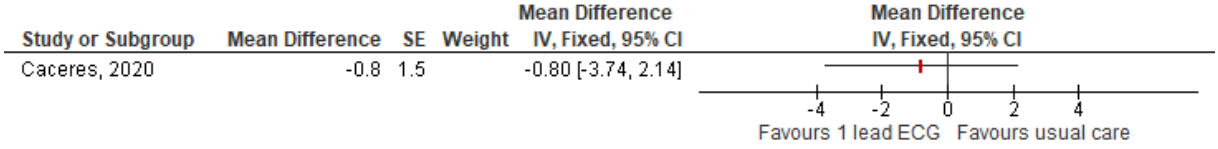

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Figure 50: mortality

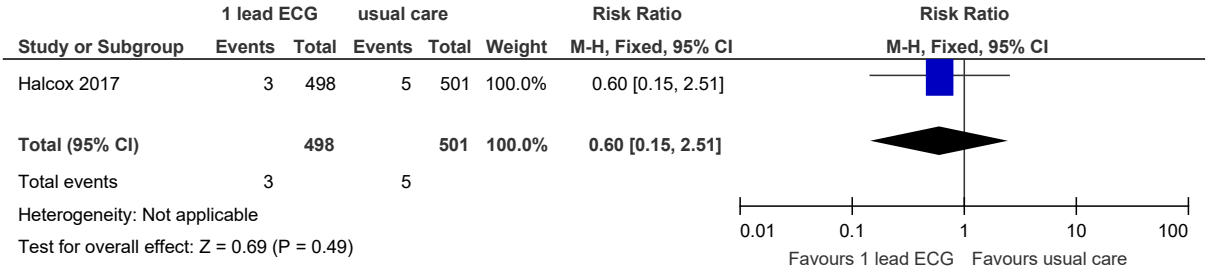

Figure 51: Stroke or thromboembolic complications

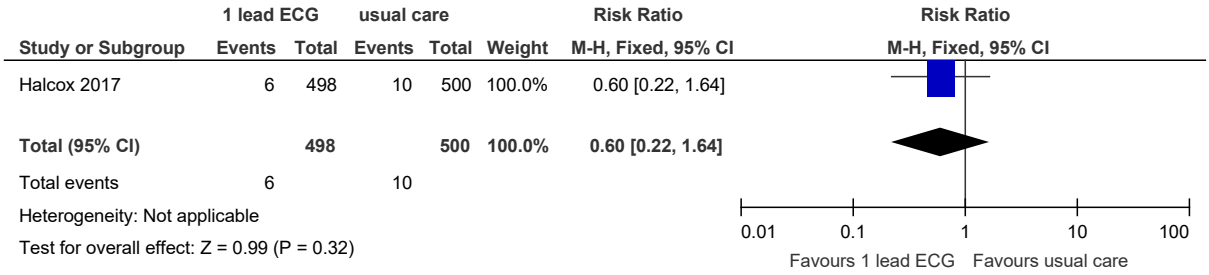

Figure 52: Major bleeding

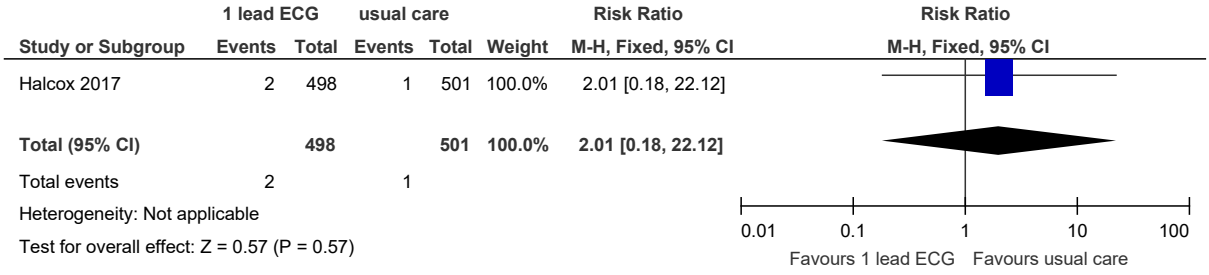

Figure 53: All cause hospitalisation

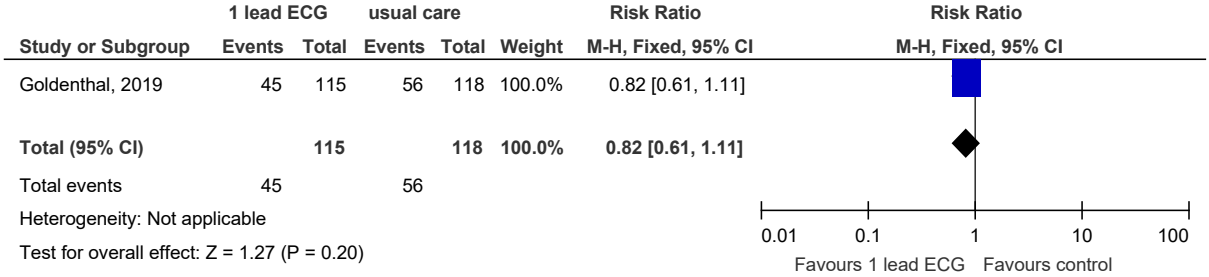

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Figure 54: confirmed diagnosis of AF

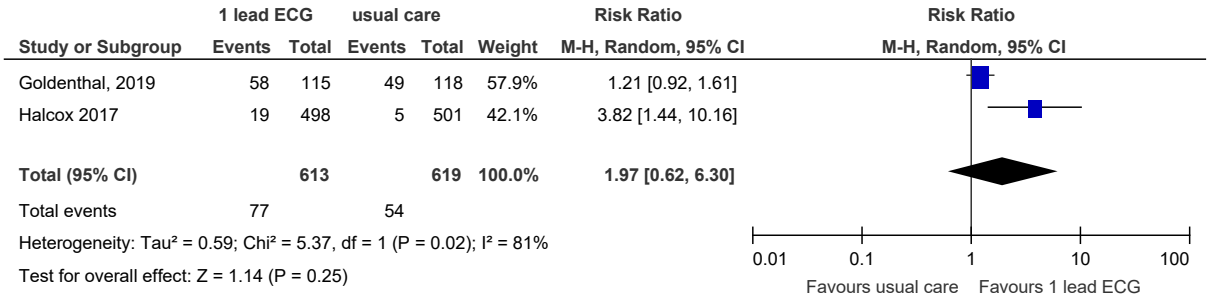
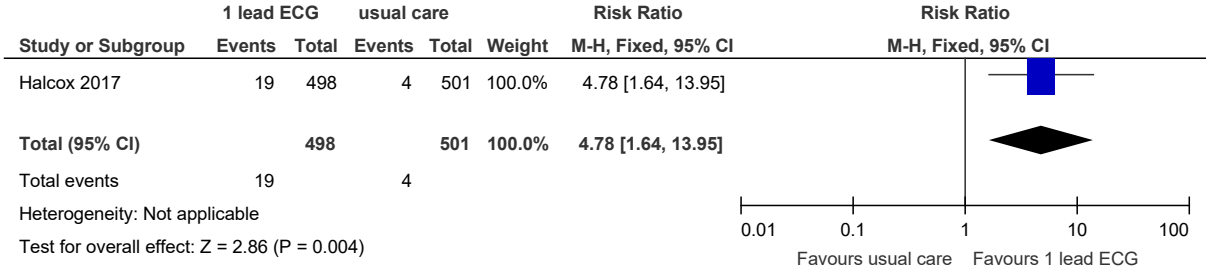


Figure 55: Initiation of OACS for AF



E.8 7 days cardiac monitoring + standard care vs standard care

Figure 56: Health-related quality of life

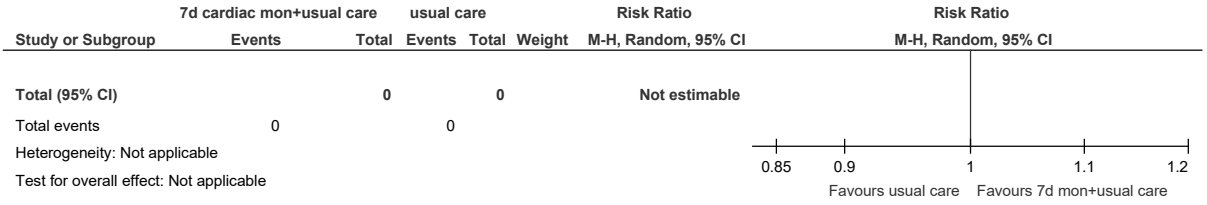


Figure 57: mortality

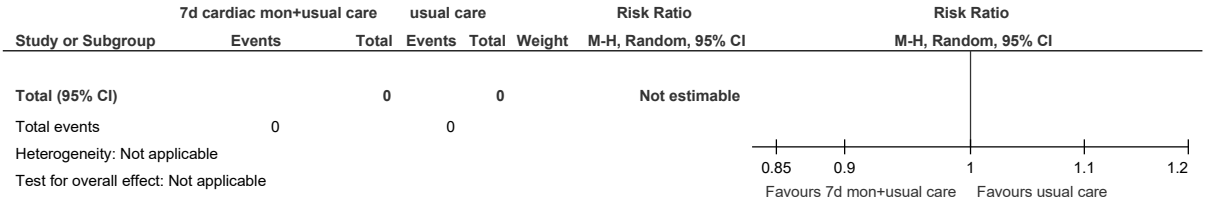


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Figure 58: Stroke and thromboembolic complications

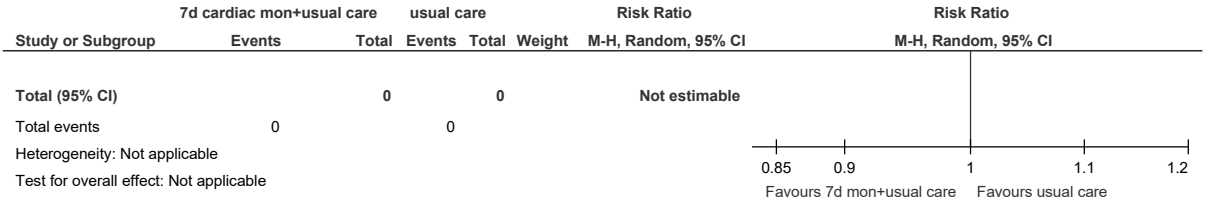


Figure 59: Major bleeding

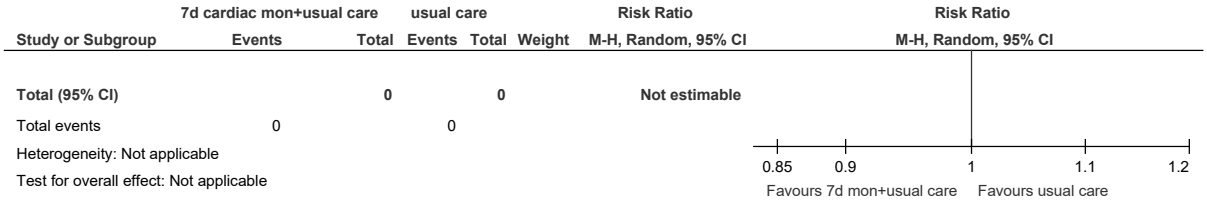


Figure 60: All-cause hopsitalisation

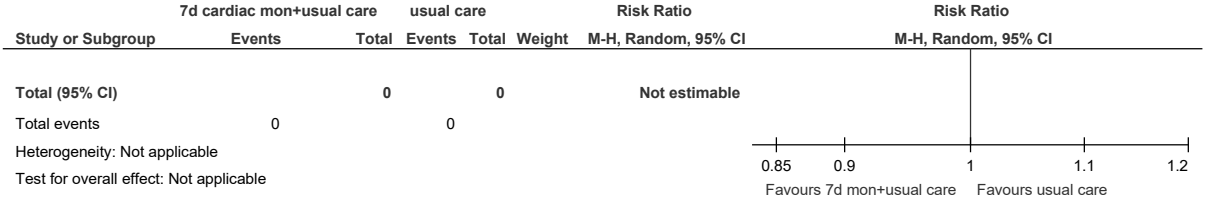


Figure 61: confirmed diagnosis of AF (sustained (>20s) PAF at 90 days)

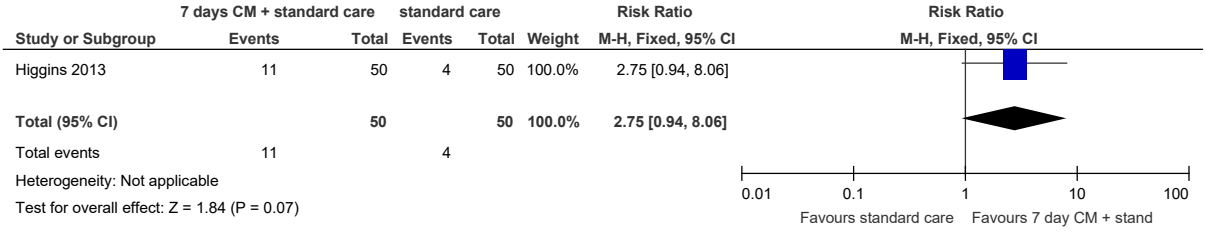
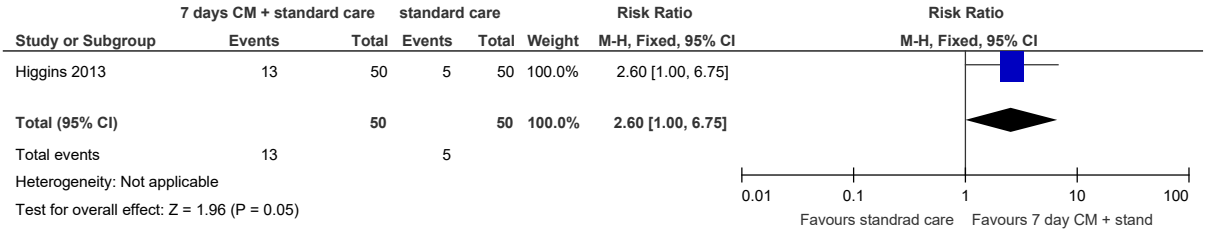


Figure 62: Initiation of OACs



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E.9 Pulse palpation and ECG versus usual care

Figure 63: Health-related quality of life

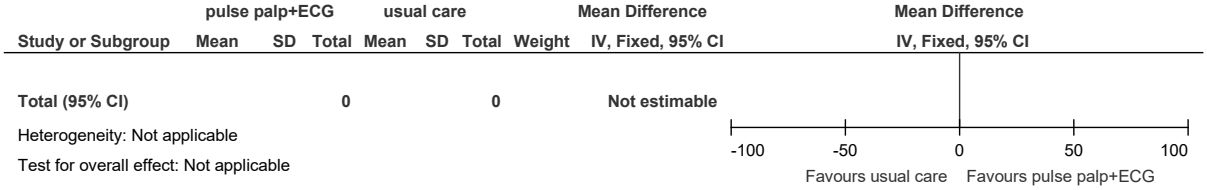

Figure 64: Mortality

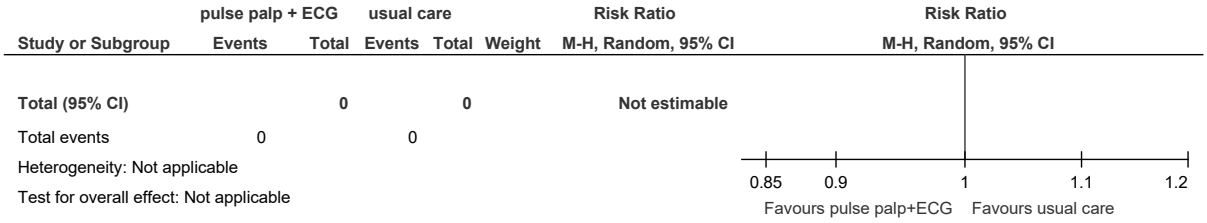

Figure 65: Stroke and thromboembolic complications

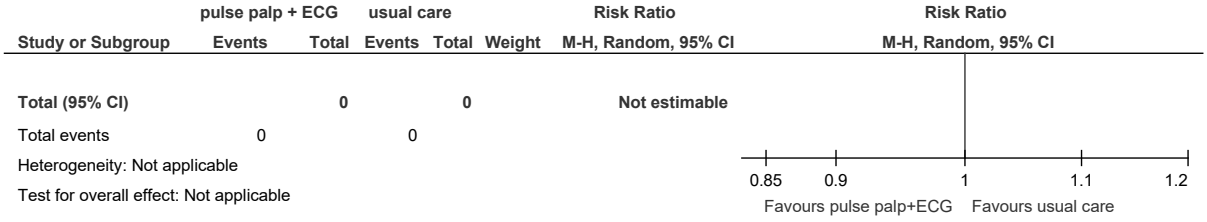

Figure 66: Major bleeding

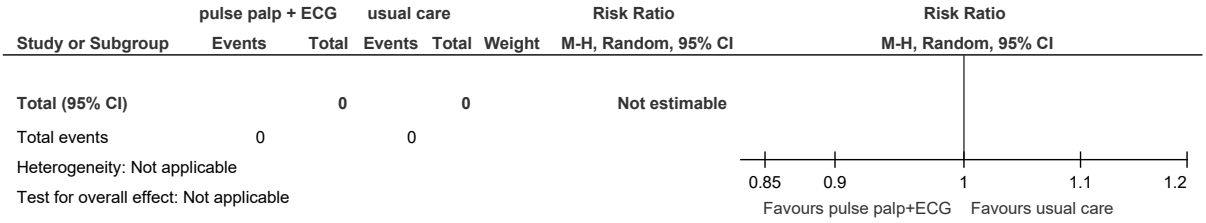

Figure 67: All cause hospitalisation

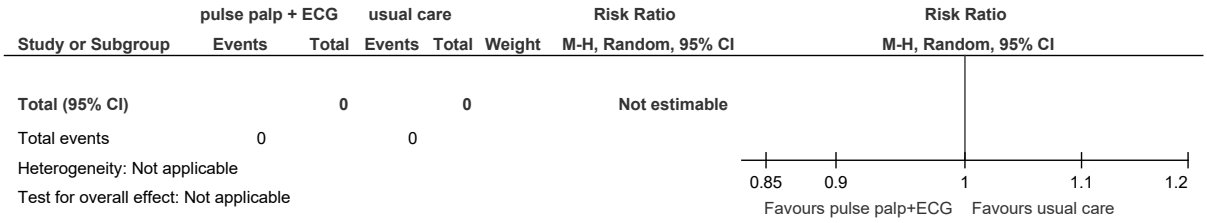

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Figure 68: Confirmed diagnosis of AF

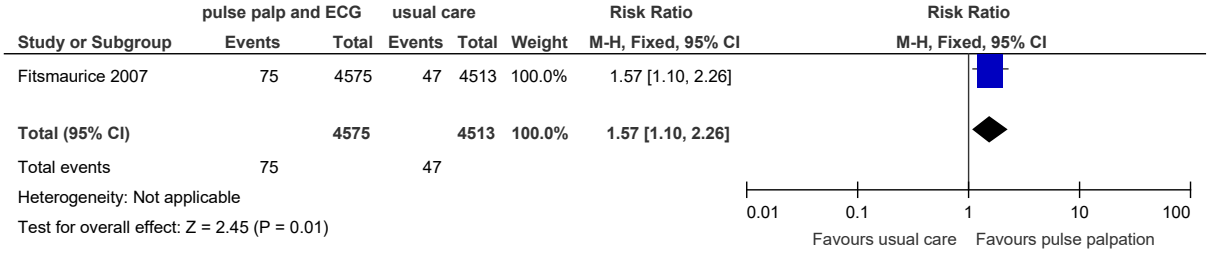
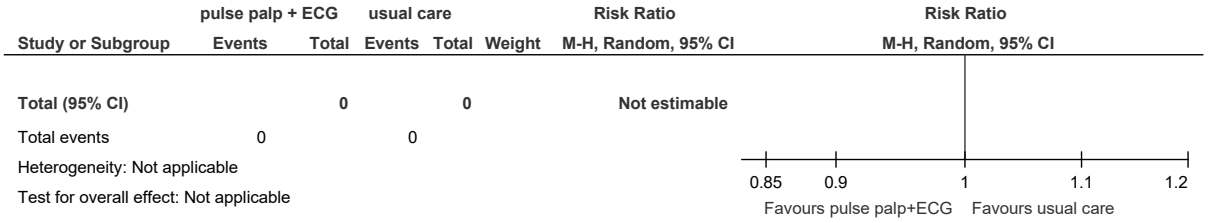


Figure 69: Initiated anticoagulants for AF



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Appendix F: GRADE tables

Table 22: Clinical evidence profile: Holter 21-30 days versus usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Holter 21-30 days versus usual care	Control	Relative (95% CI)	Absolute		
Health-related quality of life												
0	No evidence available					none	0	-	-	not pooled		
Mortality												
0	No evidence available					none	0	-	-	not pooled		
Stroke and thromboembolic complications												
0	No evidence available					none	0	-	-	not pooled		
Major bleeding												
0	No evidence available					none	0	-	-	not pooled		
All cause hospitalisation												

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0	No evidence available					none	0	-	-	not pooled		
Confirmed diagnosis of AF (follow-up 21-28 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/147 (8.2%)	0.9%	RD 0.05 (-0.03 to 0.12)	50 more per 1000 (from 30 fewer to 120 more)	⊕⊕⊕O MODERATE	CRITICAL
Initiated OACs for AF												
0	No evidence available					none	0	-	-	not pooled		

[1] serious risk of bias due to lack of reporting of allocation concealment

Table 23: Clinical evidence profile: Holter 3x10d over 6m versus usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Holter 3x10d over 6m versus usual care**	**Control**	**Relative (95% CI)**	**Absolute**		
Health-related quality of life												
0	No evidence available					none	0	-	-	not pooled		
Mortality (follow-up mean 6 months)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/200 (3%)	4.6%	RR 0.66 (0.24 to 1.82)	16 fewer per 1000 (from 35 fewer to 38 more)	⊕OOO VERY LOW	CRITICAL

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Stroke and thromboembolic complications (follow-up mean 6 months)											
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	8/200 (4%)	7.1%	RR 0.57 (0.24 to 1.32)	31 fewer per 1000 (from 54 fewer to 23 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up mean 6 months)											
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/200 (1.5%)	0.5%	RR 2.97 (0.31 to 28.31)	10 more per 1000 (from 3 fewer to 137 more)	⊕OOO VERY LOW	CRITICAL
All cause hospitalisation											
0	No evidence available					none	0	-	-	not pooled		
Confirmed diagnosis of AF (follow-up mean 6 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	27/200 (13.5%)	6.1%	RR 2.23 (1.16 to 4.27)	75 more per 1000 (from 10 more to 199 more)	⊕⊕⊕O MODERATE	CRITICAL
Initiated OACs for AF (follow-up mean 6 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	27/200 (13.5%)	6.1%	RR 2.23 (1.16 to 4.27)	75 more per 1000 (from 10 more to 199 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] 95% CIs crossed one MID
[2] No HCP or patient blinding (can affect objective outcomes through differences in care or belief about care)
[3] 95% CIs crossed both MIDs

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Table 24: Clinical evidence profile: Ambulatory ECG with 30 day event monitor vs 24 hr ECG

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ambulatory ECG with 30 day event monitor	Control	Relative (95% CI)	Absolute		
Health-related quality of life												
0	No evidence available					none	0	-	-	not pooled		
Mortality												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/287 (0.35%)	0.4%	RR 0.99 (0.06 to 15.8)	0 fewer per 1000 (from 4 fewer to 59 more)	⊕OOO VERY LOW	CRITICAL
Stroke and thromboembolic complications												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/287 (0.35%)	0.4%	RR 0.99 (0.06 to 15.80)	0 fewer per 1000 (from 4 fewer to 59 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding												
0	No evidence available					none	0	-	-	not pooled		
All cause hospitalisation												
0	No evidence available					none	0	-	-	not pooled		

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Confirmed diagnosis of AF												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	44/284 (15.5%)	2.5%	RR 6.13 (2.81 to 13.38)	128 more per 1000 (from 45 more to 310 more)	⊕⊕⊕O MODERATE	CRITICAL
Initiated OACs for AF												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	52/280 (18.6%)	11.1%	RR 1.67 (1.11 to 2.53)	74 more per 1000 (from 12 more to 170 more)	⊕⊕OO LOW	CRITICAL

[1] serious risk of bias due to unclear reporting of allocation concealment
[2] Very srious risk of bias due to lack of allocation concealment; also no patient or HCP blinding, which could influence even objective outcomes due to differences in care or belief about care.
[3] 95% CIs crossed both MIDs
[4] 95% CIs crossed 1 MID

Table 25: Clinical evidence profile: Holter 48hrs versus handheld event monitor

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Holter 48hrs versus handheld event monitor**	**Control**	**Relative (95% CI)**	**Absolute**		
Health-related quality of life												
0	No evidence available					none	0	-	-	not pooled		
Mortality												
0	No evidence available					none	0	-	-	not pooled		

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Stroke and thromboembolic complications												
0	No evidence available					none	0	-	-	not pooled		
Major bleeding												
0	No evidence available					none	0	-	-	not pooled		
All cause hospitalisation												
0	No evidence available					none	0	-	-	not pooled		
Confirmed diagnosis of AF												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/43 (0%)	7%	Peto OR 0.13 (0.01 to 1.27)	60 fewer per 1000 (from 69 fewer to 17 more)	⊕⊕OO LOW	CRITICAL
Initiated OACs for AF												
0	No evidence available					none	0	-	-	not pooled		

[1] 95% CIs crossed both MIDs

Table 26: Clinical evidence profile: Skin patch ECG vs usual care

Quality assessment						No of patients	Effect			Quality	Importance

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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Skin patch ECG	Usual care	Relative (95% CI)	Absolute		
Health-related quality of life												
0	No evidence available					none	0	-	-	not pooled		
Mortality												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/44 (2.3%)	0%	Peto OR 7.91 (0.16 to 399.51)	20 more per 1000 (from 40 fewer to 80 more)	⊕OOO VERY LOW	CRITICAL
Stroke and thromboembolic complications												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/43 (2.3%)	2.1%	RR 1.09 (0.07 to 16.94)	2 more per 1000 (from 20 fewer to 335 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding												
0	No evidence available					none	0	-	-	not pooled		
All cause hospitalisation												
0	No evidence available					none	0	-	-	not pooled		
Confirmed diagnosis of AF												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	60/1409 (4.3%)	1.5%	RR 4.43 (2.45 to 8.02)	51 more per 1000 (from 22 more to 105 more)	⊕⊕⊕O MODERATE	CRITICAL

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Initiated OACs for AF												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/43 (16.3%)	2.1%	RR 7.65 (0.98 to 59.68)	140 more per 1000 (from 0 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL

[1] Serious risk of bias for attrition bias, and very serious risk of bias for attrition and performance bias
[2] Imprecision serious if the 95% Cis crossed one MID and very serious if they crossed both MIDs

Table 27: Clinical evidence profile: 2 year early detection program inc. ECG vs usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**2 year early detection program inc. ECG**	**Usual care**	**Relative (95% CI)**	**Absolute**		
Health-related quality of life												
0	No evidence available					none	0	-	-	not pooled		
Mortality												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/463 (1.5%)	1.7%	RR 0.88 (0.32 to 2.4)	2 fewer per 1000 (from 12 fewer to 24 more)	⊕OOO VERY LOW	CRITICAL
Stroke and thromboembolic complications												
0	No evidence available					none	0	-	-	not pooled		
Major bleeding												

0	No evidence available					none	0	-	-	not pooled		
All cause hospitalisation												
0	No evidence available					none	0	-	-	not pooled		
Confirmed diagnosis of AF												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/440 (2.5%)	1.3%	RR 1.92 (0.72 to 5.16)	12 more per 1000 (from 4 fewer to 54 more)	⊕OOO VERY LOW	CRITICAL
Initiated OACs for AF												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	10/440 (2.3%)	0.4%	RR 5.25 (1.16 to 23.83)	17 more per 1000 (from 1 more to 91 more)	⊕OOO VERY LOW	CRITICAL

[1] Very serious risk of bias due to unclear allocation concealment and possible attrition bias
[2] 95% CIs crossed both MIDs
[3] 95% CIs crossed 1 MID

Table 28: Clinical evidence profile: 1 lead handheld ECG vs usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**1 lead handheld ECG**	**Usual care**	**Relative (95% CI)**	**Absolute**		
Health-related quality of life – Atrial Fibrillation Effect on Quality of Life (higher score better)												

1	randomised trials	Very serious[1]	no serious inconsistency	Serious indirectness[3]	Serious[2]	none	131	131	-	MD: 7.3(-1.13 to 15.73)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Health-related quality of life – SF-36 physical (higher score better)												
1	randomised trials	Very serious[1]	no serious inconsistency	Serious indirectness[3]	No serious imprecision	none	131	131	-	MD: 1.2 (-1.35 to 3.75)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Health-related quality of life – SF-36 mental (higher score better)												
1	randomised trials	Very serious[1]	no serious inconsistency	Serious indirectness[3]	No serious imprecision	none	131	131	-	MD: -0.5 (-3.24 to 2.24)	⊕⊖⊖⊖ VERY LOW	CRITICAL
EuroQol index (higher score better)												
1	randomised trials	Very serious[1]	no serious inconsistency	Serious indirectness[3]	No serious imprecision	none	131	131	-	MD: 0 (-0.059 to 0.059)	⊕⊖⊖⊖ VERY LOW	CRITICAL
EuroQol VAS (higher score better)												
1	**randomised trials**	**Very serious[1]**	no serious inconsistency	Serious indirectness[3]	Serious[2]	none	131	131	-	MD: 4.3 (-1.38 to 9.98)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Health-related quality of life – University of Toronto Atrial Fibrillation Severity Scale (higher score worse)												
1	randomised trials	Very serious[1]	no serious inconsistency	Serious indirectness[3]	No serious imprecision	none	131	131	-	MD: -0.8 (-3.74 to 2.14)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Mortality												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	3/498 (0.6%)	1%	RR 0.6 (0.15 to 2.51)	4 fewer per 1000 (from 8 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL

Stroke and thromboembolic complications												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	6/498 (1.2%)	2%	RR 0.6 (0.22 to 1.64)	8 fewer per 1000 (from 16 fewer to 13 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/498 (0.4%)	0.2%	RR 2.01 (0.18 to 22.12)	2 more per 1000 (from 2 fewer to 42 more)	⊕OOO VERY LOW	CRITICAL
All cause hospitalisation												
1	randomised trials	serious[1]	no serious inconsistency	Serious indirectness[3]	Serious[2]	none	45/115 (39.1%)	47.5%	RR 0.82 (0.61 to 1.11)	86 fewer per 1000 (from 185 fewer to 52 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Confirmed diagnosis of AF												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	77/613 (12.6%)	8.7%	RR 1.97 (0.62 to 6.3)	207 more per 1000 (from 81 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Initiated OACs for AF												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/498 (3.8%)	0.8%	RR 4.78 (1.64 to 13.95)	30 more per 1000 (from 5 more to 104 more)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] Serious risk of bias because of a lack of patient or HCP blinding, which can affect even objective outcomes because of differences in care or belief about care; Very serious bias because of high levels of selection bias and very high attrition bias.

[2] 95% CIs crossed 1 MID. For quality of life outcomes, the MIDs were defined by 0.5 x sd in the control group at baseline. Accordingly, MIDS were 12.6 for Atrial Fibrillation Effect on Quality of Life, 4.75 for SF-36 physical, 4.8 for SF-36 mental, 0.105 for EQ5D index, 7.35 for EQ-5D VAS, and 4.95 for University of Toronto Atrial Fibrillation Severity Scale

[3] Downgraded for indirectness as population had received ablation, and therefore slightly different to protocol population

[4] 95% Cis crossed both MIDs. For quality of life outcomes, the MIDs were defined by 0.5 x sd in the control group at baseline. Accordingly, MIDS were 12.6 for Atrial Fibrillation Effect on Quality of Life, 4.75 for SF-36 physical, 4.8 for SF-36 mental, 0.105 for EQ5D index, 7.35 for EQ-5D VAS, and 4.95 for University of Toronto Atrial Fibrillation Severity Scale

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Table 29: Clinical evidence profile: 7 days cardiac monitoring + standard monitoring vs standard monitoring alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	7 days cardiac monitoring + standard monitoring	Standard monitoring alone	Relative (95% CI)	Absolute		
Health-related quality of life												
0	No evidence available					none	0	-	-	not pooled		
Mortality												
0	No evidence available					none	0	-	-	not pooled		
Stroke and thromboembolic complications												
0	No evidence available					none	0	-	-	not pooled		
Major bleeding												
0	No evidence available					none	0	-	-	not pooled		
All cause hospitalisation												
0	No evidence available					none	0	-	-	not pooled		
Confirmed diagnosis of AF												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	11/50 (22%)	8%	RR 2.75 (0.94 to 8.06)	140 more per 1000 (from 5 fewer to 565 more)	⊕⊕⊕O MODERATE	CRITICAL
Initiated OACs for AF												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	13/50 (26%)	10%	RR 2.6 (1 to 6.75)	160 more per 1000 (from 0 more to 575 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] Serious risk of bias due to lack of HCP or patient blinding that can create spurious differences in even objective outcomes through differences in care or belief about care
[2] 95% CIs crossed both MIDs
[3] 95% CIs crossed 1 MID

Table 30: Clinical evidence profile: Pulse palpation and ECG versus usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pulse palpation and ECG versus usual care**	**Control**	**Relative (95% CI)**	**Absolute**		
Health-related quality of life												
0	No evidence available					none	0	-	-	not pooled		
Mortality												
0	No evidence available					none	0	-	-	not pooled		

Stroke and thromboembolic complications												
0	No evidence available					none	0	-	-	not pooled		
Major bleeding												
0	No evidence available					none	0	-	-	not pooled		
All cause hospitalisation												
0	No evidence available					none	0	-	-	not pooled		
Confirmed diagnosis of AF												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	75/4575 (1.6%)	1%	RR 1.57 (1.10 to 2.26)	6 more per 1000 (from 1 more to 13 more)	⊕OOO VERY LOW	CRITICAL
Initiated OACs for AF												
0	No evidence available					none	0	-	-	not pooled		

[1] serious risk of bias due to unclear allocation concealment
[2] Population included people outside review population
[3] 95% CIs crossed 1 MID

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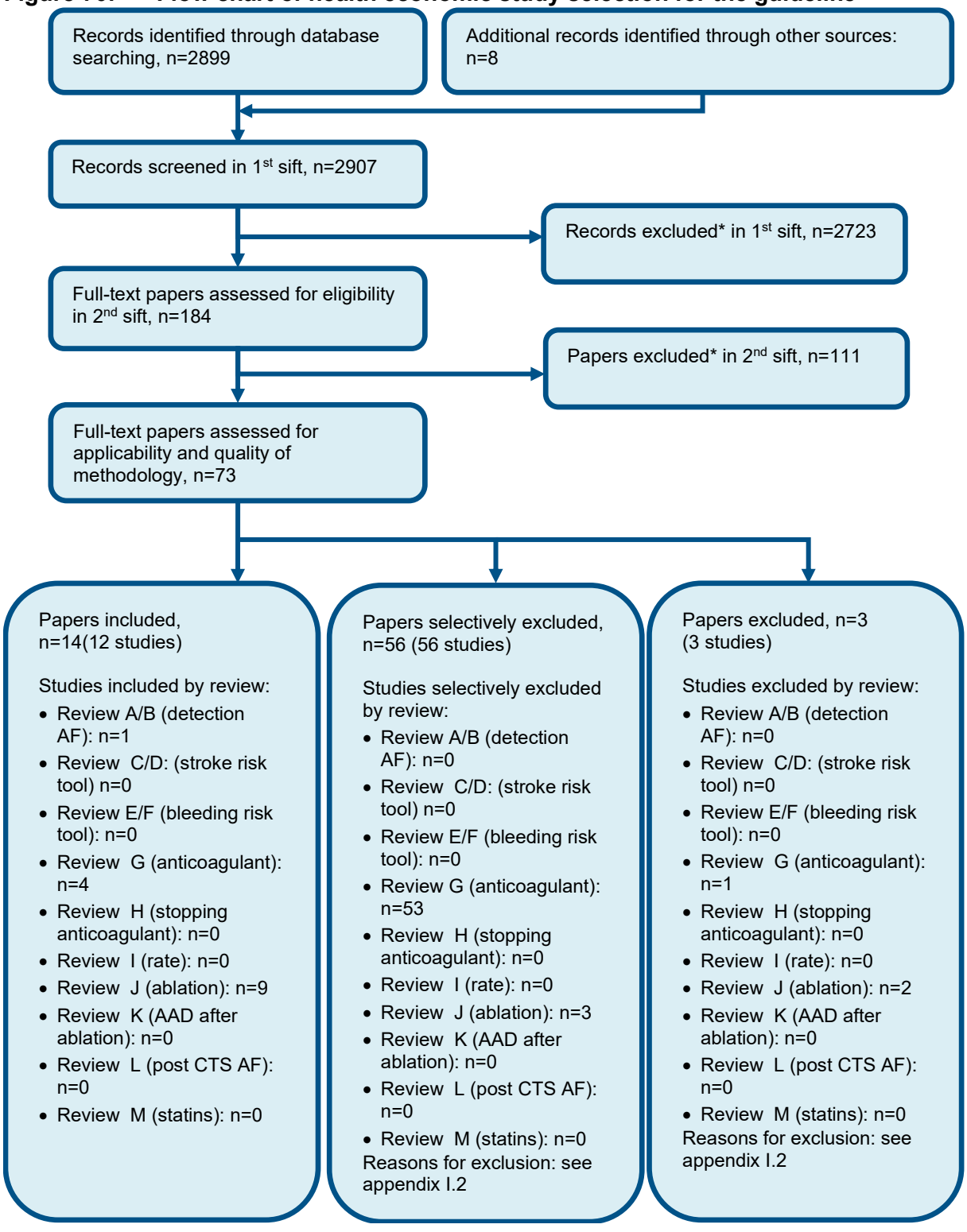
Appendix G: Health economic evidence selection

Figure 70: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

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Appendix H: Health economic evidence tables

Study	NICE DG35 2019[17, 51]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** A decision tree and two cohort Markov models. The decision tree describes the pathway that a patient presenting to primary care with signs and symptoms of AF and an irregular pulse follows in the initial GP consultation. The first Markov model captures the differences in the costs and benefits of treatment (standard diagnostic pathway versus lead-I ECG pathway) during the first 3 months after the initial appointment (daily cycles). During this period, some patients will have a diagnosis of AF and start treatment	**Population:** Adults with signs or symptoms indicative of AF plus irregular pulse assessed by manual pulse palpations presenting at primary care. **Cohort settings:** Mean age: 70 years Male: 48.4% **Intervention 1:** Standard diagnostic pathway (all sent for 12-lead ECG, no treatment of AF whilst waiting for 12-lead ECG test. Further testing for paroxysmal AF using holter monitor undertaken for those with negative 12 lead ECG.) **Intervention 2:** [(b)] Kardia Mobile (interpreted by trained healthcare professional)	**Total costs (mean per patient):** Base Case 1: 12-lead ECG in primary care, 2 days to 12-lead ECG Intervention 1: £9,543 Intervention 2: £9,569 Intervention 3: £9,851 Intervention 4: £9,674 Intervention 5: £9,590 Intervention 6: £9,623 Intervention 7: £9,622 Base Case 2: 12-lead ECG in primary care, 14 days to 12-lead ECG Intervention 1: £9,547 Intervention 2: £9,566 Intervention 3: £9,848 Intervention 4: £9,671 Intervention 5: £9,588 Intervention 6: £9,620 Intervention 7: £9,619 Base Case 3: 12-lead ECG in secondary care, 2 days to 12-lead ECG Intervention 1: £9,585	**QALYs (mean per patient):** Base Case 1: 12-lead ECG in primary care, 2 days to 12-lead ECG Intervention 1: 8.314 Intervention 2: 8.338 Intervention 3: 8.333 Intervention 4: 8.334 Intervention 5: 8.338 Intervention 6: 8.337 Intervention 7: 8.325 Base Case 2: 12-lead ECG in primary care, 14 days to 12-lead ECG Intervention 1: 8.313 Intervention 2: 8.337 Intervention 3: 8.333 Intervention 4: 8.333 Intervention 5: 8.337 Intervention 6: 8.336 Intervention 7: 8.325 Base Case 3: 12-lead ECG in secondary care, 2 days to 12-lead ECG	**Incremental cost effectiveness analysis:** Base Case 1: 12-lead ECG in primary care, 2 days to 12-lead ECG **ICER (Intervention 2 versus Intervention 1):** £1,060 per QALY gained (pa) 95% CI: NR **Intervention 2 dominates (less costly and more effective)** the other interventions (3,4,5,6 and 7) Base Case 2: 12-lead ECG in primary care, 14 days to 12-lead ECG **ICER (Intervention 2 versus Intervention 1):** £749 per QALY gained (pa) 95% CI: NR **Intervention 2 dominates** the other interventions (3,4,5,6 and 7) Base Case 3: 12-lead ECG in secondary care, 2 days to 12-lead ECG **ICER (Intervention 2 versus Intervention 1):** £783 per QALY gained (pa)

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for AF whilst other patients will have further tests to diagnose or to rule out AF (where 'rule out' means no diagnosis of AF is recorded in the patient's notes and no treatment for AF is started). These further tests are a 12-lead ECG followed by a holter monitor for suspected paroxysmal AF. Cardiovascular events are captured in this first model as well as death. The second Markov model captures the differences in lifetime costs and benefits after diagnosis of AF or the time when AF is ruled out. Patients remain in the second Markov model until death. The Markov model health states include cardiovascular event, haemorrhagic stroke, ischaemic stroke, transient ischaemic attack and death. **Perspective:** UK NHS **Time horizon**: 30 years [(a)] **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Intervention 3:** imPulse (interpreted by trained healthcare professional) **Intervention 4:** MyDiagnostick (interpreted by trained healthcare professional) **Intervention 5:** any lead-I ECG device (interpreted by trained healthcare professional) **Intervention 6:** Zenicor-ECG (interpreted by trained healthcare professional) **Intervention 7:** RhythmPad-GP (interpreted by algorithm) Interventions 2-7: all positives are diagnosed with AF and sent for 12-lead ECG. They will commence treatment for AF prior to 12-lead ECG (rate control and anticoagulation). If 12-lead negative, a proportion will have paroxysmal testing with a holter monitor and a proportion will have AF	Intervention 2: £9,604 Intervention 3: £9,886 Intervention 4: £9,709 Intervention 5: £9,626 Intervention 6: £9,658 Intervention 7: £9,657 <u>Base Case 4: 12-lead ECG in secondary care, 14 days to 12-lead ECG</u> Intervention 1: £9,589 Intervention 2: £9,601 Intervention 3: £9,883 Intervention 4: £9,706 Intervention 5: £9,623 Intervention 6: £9,655 Intervention 7: £9,654 **Currency & cost year:** 2018 UK pounds **Cost components incorporated:** Device costs, cost of tests, treatment, prescriptions, monitoring, and cardiovascular and adverse event costs	Intervention 1: 8.314 Intervention 2: 8.338 Intervention 3: 8.333 Intervention 4: 8.334 Intervention 5: 8.338 Intervention 6: 8.337 Intervention 7: 8.325 <u>Base Case 4: 12-lead ECG in secondary care, 14 days to 12-lead ECG</u> Intervention 1: 8.313 Intervention 2: 8.337 Intervention 3: 8.333 Intervention 4: 8.333 Intervention 5: 8.337 Intervention 6: 8.336 Intervention 7: 8.325	95% CI: NR **Intervention 2 dominates** the other interventions (3,4,5,6 and 7) <u>Base Case 4: 12-lead ECG in secondary care, 14 days to 12-lead ECG</u> **ICER (Intervention 2 versus Intervention 1):** £481 per QALY gained (pa) 95% CI: NR **Intervention 2 dominates** the other interventions (3,4,5,6 and 7) **Analysis of uncertainty:** Different scenario analyses were conducted such as varying the unit cost associated with lead-I ECG, alternative sensitivity and specificity for MyDiagnostick, diagnosis and decisions made to refer for paroxysmal testing based only on the lead-I ECG results, time horizon was limited to 5 years. The scenario analysis showed that although results were sensitive to using alternative sensitivity and specificity values for MyDiagnostick, Kardia Mobile remained the most cost effective option. The scenario analysis showed that results were invariant to the following assumptions: • Whether the cost of the lead-I ECG device is included in the analysis

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	ruled out. For negative lead-I, a proportion would have 12-lead, a proportion would have holter and a proportion would have AF ruled out. None would commence any treatment for AF until further tests undertaken.			• Patients with AF incorrectly ruled out are not diagnosed with AF prior to a CVE • Removal of 12-lead ECG and holter monitoring from the lead-I ECG pathway • Shortening the time horizon to 5 years The one-way sensitivity analysis showed that the results were sensitive to the assumed prevalence of paroxysmal AF versus persistent and permanent AF. Decreased prevalence of paroxysmal AF increased incremental costs and decreased incremental QALYs for lead-I ECG devices versus the standard pathway. In an extreme scenario, where the prevalence of paroxysmal AF was assumed to be zero, incremental QALYs decreased sufficiently to become negative and resulted in some lead-I ECG devices (ImPulse, MyDiagnostick and RhythmPad) being dominated by the standard pathway. Increasing the prevalence of paroxysmal AF to 1 resulted in all lead-I ECG devices except ImPulse and MyDiagnostick dominating the standard pathway. The results of the probabilistic sensitivity analysis indicate that at a threshold of £20,000 per QALY just over 80% of iterations showed Kardia Mobile would be the most cost effective option, followed by Zenicor-ECG with around 15% of iterations. In no iterations at a WTP threshold of £20,000 per QALY was the standard pathway found to be the most cost effective option.

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Data sources
Health outcomes: The de novo economic analysis was undertaken that follows the diagnostic pathway for patients presenting to primary care with signs and symptoms indicative of AF and an irregular pulse. Diagnostic test accuracy data were not available for the population of interest (symptomatic patients with suspected AF and an irregular pulse presenting to primary care), therefore diagnostic test accuracy data in an asymptomatic population was used as a proxy for the population of interest (systematic review and meta-analysis conducted as part of same paper). Model population parameters such as prevalence of AF taken from published literature (e.g. UK and US registry data) and expert assumption. The mortality and Cardiovascular event rates in the AF-positive population were estimated based on published risk (or hazard) ratios or incidence rates (primarily from NMA conducted by Sterne 2017). **Quality-of-life weights:** Utility values for the symptomatic and asymptomatic AF-positive population calculated using the baseline coefficients from the study by Berg[4] and adjusted for model age, sex ratio and symptom proportions. Age- and sex-specific general population EQ-5D-3L index values using the UK time trade-off value set were taken from reference data published by the EuroQol Group and weighted by the proportions in the model. Utility decrements for acute adverse events were taken from various published sources. **Cost sources:** The annual cost of each lead-I ECG device was calculated as the unit cost per device (excluding 20% VAT) divided across the expected life of the device in years plus annual licence fee. An average cost for a generic lead-I ECG device was calculated using the simple mean of the annual cost of individual devices. The costs per administration and interpretation of lead-I ECG tests were from the PSSRU. The unit cost of a 12-lead ECG device is estimated in line with the estimate used in NICE Guideline 45 (NG45). Electrocardiogram monitoring or stress testing was from the NHS reference costs 2016/17. Drug costs were obtained from the British National Formulary and prices from the NHS Drug Tariff (July 2018). The cost of each acute bleed and TIA event was calculated as the weighted average of the appropriate Healthcare Resource Group (HRG) codes included in the NHS Reference Costs 2016/17. **Other**: The economic evaluation is only relevant to primary care practices where patients have to wait at least 48 hours between an initial consultation with the GP and a 12-lead ECG.
Comments
Source of funding: This Diagnostics Assessment Report was commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence as project number 16/30/05. **Limitations:** Does not include all comparators in protocol. The economic evaluation is limited by the lack of diagnostic test accuracy data in the population of interest; therefore the results are based on data from asymptomatic population. The resource use data and outcomes data were not based on a systematic review and may not reflect full body of evidence.
Overall applicability:(c) Partially applicable **Overall quality:**(d) *Potentially serious limitations*

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years

(a) Results are presented over a time horizon of 30 years with patients entering the model at age 70.

(b) Lead-I ECG devices are handheld instruments for detecting atrial fibrillation using single-time point testing in primary care.

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

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Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 31: Studies excluded from the clinical review

Study	Exclusion reason
Amara 2017[1]	Inappropriate comparison. Incorrect interventions. Not a point of care device - implanted remote monitor
Anon 2015[2]	citation only
Brachmann 2009[6]	Not a point of care device – ICM (intra-cardiac monitor)
Brachmann 2016[5]	citation only
Burkowitz 2016[7]	SR of ICMs – references checked
Chan 2017[10]	Non randomised
Chua, 2020[11]	non-randomised
Coutts 2014[12]	Commentary on Higgins
Da costa 2013[13]	Not a point of care device – Intra-cardiac monitor
Dahal 2016[14]	SR - REFERENCES CHECKED
Diamantopoulos 2016[16]	cost effectiveness simulation
Dussault 2015[18]	SR - REFERENCES CHECKED
Eysenck 2020[19]	Did not address protocol outcomes; patients with pacemakers
Gonzalez Blanco 2017[23]	Comparing screening strategies rather than diagnostic tests. In both groups the same tests are used (pulse palpation and ECG), the only difference between groups being the screening strategy in terms of who is screened. The review question compares tests not populations screened.
Guhl, 2020[24]	Patients already diagnosed with AF - not the review population
Guo, 2020[26]	editorial
Guo, 2020[25]	Patients already diagnosed with AF - not the review population
Harris 2012[28]	Review
Hickey 2017[29]	Non-randomised

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Higgins 2010[30]	citation only
Isrctn 2013[34]	Citation only
Kaasenbrood, 2020[35]	Full version not available; only abstract version available.
Kamalvand 1997[36]	Did not address protocol outcomes
Kishore 2014[40]	SR - REFERENCES CHECKED
Lees 2010[41]	Citation only
Levin 2014[42]	cost-effectiveness analysis and non-randomised study
Liao 2007[43]	SR - REFERENCES CHECKED
Lowres 2014[44]	Not an RCT
Makowska 2000[45]	Did not cover protocol outcomes
Miller 2014[46]	Commentary on Gladstone
Moran 2016[47]	SR - REFERENCES CHECKED
Morgan 2002[48]	Comparing screening strategies rather than diagnostic tests. In both groups the same tests are used (pulse palpation and ECG), the only difference between groups being the screening strategy in terms of who is screened. The review question compares tests not populations screened
Musat 2018[49]	Not point of care devices
Orchard, 2020[54]	non-randomised
Podd 2016[55]	Not point of care devices
Sanna 2014[56]	Not point of care devices
Sticherling 2011[58]	Not point of care devices
Svennberg 2015[59]	Non-comparative; although there was randomisation to two groups only results for one arm are provided.
Swancutt 2004[60]	Protocol
Wachter 2013[61]	Citation only
Wasser 2019[63]	subanalysis of Wachter 2017

I.2 Excluded health economic studies

None

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