Healthcare Improvement Scotland | SHTG Advice on health technologies

SHTG Assessment
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Detection of paroxysmal atrial fibrillation in patients with newly diagnosed ischaemic stroke

What were we asked to look at?

The National Planning atrial fibrillation subgroup asked us to review the published evidence on the clinical and cost-effectiveness of various strategies to detect paroxysmal atrial fibrillation (PAF) in patients with newly diagnosed ischaemic stroke who are selected to have prolonged electrocardiogram (ECG) monitoring.

Why is this important?

There is variation across NHSScotland in provision of prolonged ECG monitoring for patients with ischaemic stroke. Some NHS boards refer all patients with ischaemic stroke/transient ischaemic attack (TIA) for prolonged monitoring, whilst other boards refer very few patients. The decision to refer patients is partly dependent on access to monitoring, and there is variation across boards in the criteria for selecting patients. There is also variation across boards in the technologies used to monitor patients, and how the technologies are used (for example, how long patients are monitored for). In addition, access to analyst time – with shortages in some NHS boards – can also lead to variation in monitoring practice.

What was our approach?

We conducted a literature review to identify evidence of the clinical and cost-effectiveness of various monitoring strategies to detect PAF. We also reviewed evidence relating to safety and patient issues, and explored the possibility of using existing economic models to inform decision-making in Scotland.

What next?

This SHTG Assessment will be considered by the National Planning atrial fibrillation subgroup to inform more consistent practice across boards.

Key findings

- There is insufficient evidence to draw robust conclusions about the comparative clinical and cost-effectiveness of different types of ambulatory electrocardiogram to detect PAF. Our review compared Holter devices, event recorder technologies, and patch technologies.
- NICE medical technologies guidance published in 2020 recommends the patch technology, Zio XT, as an option for people with suspected cardiac arrhythmias who would benefit from ambulatory ECG monitoring for longer than 24 hours. The guidance states that data should be collected on factors such as long-term clinical outcomes and resource use.
- A health technology assessment published in 2016 by the Canadian Agency for Drugs and Technologies in Health (CADTH) recommends 7 days of continuous outpatient cardiac monitoring with either an ambulatory Holter monitor or external loop recorder for patients who have been discharged from hospital after a stroke or TIA and who did not undergo continuous cardiac monitoring while in hospital.
- Two systematic reviews reported that the detection rate for any new atrial fibrillation (AF) was greater in selected (defined as 'prescreened') patients following stroke or TIA, compared with unselected patients, and greater again in patients with cryptogenic strokes. The definition of 'selected' patients varied and included older age, more extensive testing for arrhythmias before enrolment, or presumed cardioembolic/cryptogenic cause. One review reported lower AF detection rates in TIA cohorts compared with cohorts including both stroke and TIA patients.
- There is insufficient evidence to define the optimal duration of long-term monitoring.
- The length of AF that warrants treatment with anticoagulants is not clear from the published evidence.
- In patients with cryptogenic stroke, extended ECG monitoring for AF detection may be economically worthwhile when traditional willingness-to-pay thresholds are adopted. However, there was substantial variation in the reported incremental cost effectiveness ratios (ICERs). The feasibility of direct comparison of cost-effectiveness across technologies is also limited by heterogeneity in modelling assumptions.

Contents

Definitions

Atrial fibrillation (AF): A type of cardiac arrhythmia, which causes pooling of blood that leads to thrombosis formation and is associated with an increased risk of a stroke or TIA.[1]

Ischaemic Stroke: An ischaemic stroke is caused by thrombosis of the cerebral vessels or by emboli from a proximal arterial source or the heart.[1]

Transient Ischaemic Attack (TIA): A neurological deficit lasting less than 24 hours, caused by cerebral ischaemia.[1]

Literature search

A systematic search of the primary and secondary literature was carried out between 26 August and 8 September 2020 to identify systematic reviews, health technology assessments and other evidence based reports. The Medline and Embase databases were searched for systematic reviews, meta-analyses and economic studies. Results were limited to English language studies.

Key websites were searched for guidelines, policy documents, clinical summaries and ongoing trials.

Concepts used in all searches included:stroke, transient ischaemic attack, ambulatory electrocardiography, Philips DigiTrak XT, Lifecard CF, Sorin Spiderview, Zenicor-ECG, Zio patch, BodyGuardian® MINI. A full list of resources searched and terms used is available on request.

Research questions

Main question

What is the most clinically and cost-effective strategy to detect paroxysmal atrial fibrillation (PAF) in patients with newly diagnosed ischaemic stroke who are selected to have prolonged electrocardiogram (ECG) monitoring?

Additional questions

What is the clinical and cost-effectiveness of Holter versus event recorder versus patch technologies in the detection of PAF in patients with newly diagnosed ischaemic stroke selected to have prolonged ECG monitoring?

In patients with newly diagnosed ischaemic stroke, which patients should have prolonged ECG monitoring to detect PAF?

What is the optimum duration of prolonged ECG monitoring to detect PAF?

What length of atrial fibrillation (AF) warrants treatment with anticoagulants?

Introduction

One third of ischaemic strokes or transient ischaemic attacks (TIA) are cryptogenic (of obscure or unknown origin).[2] Some people with cryptogenic stroke/TIA will have undiagnosed AF, which increases their risk of a subsequent stroke. People with cryptogenic stroke are routinely assessed for undiagnosed AF. When AF is diagnosed, patients are normally offered anticoagulants to reduce the risk of another stroke. It is estimated that treatment with anticoagulants reduces the risk of subsequent stroke by up to 60%.[3] There is no gold-standard monitoring method, and so the true prevalence of AF in patients with a history of stroke or TIA is uncertain.

Assessment for AF in this patient group typically involves using a standard ECG device to monitor heart rhythm over a short period (typically a few seconds). This can be effective for detecting permanent AF, but may miss intermittent, or paroxysmal, AF.[4] In patients with cryptogenic stroke suspected of having PAF, prolonged ECG monitoring may be offered using ambulatory ECG technology. There is variation across NHSScotland in the ambulatory ECG technologies used, and how long they are used for. There is also variation with regards to how long an episode of AF should last for the person to be diagnosed as having AF. The most common threshold used in the NHS care pathway is 2 minutes.[4]

In 2017, three relevant national standards for stroke services in Scotland were introduced:[5]

- Stroke services should have written, locally agreed criteria to select those patients with stroke or TIA who should be offered prolonged ECG monitoring to detect PAF.
- Patients meeting those criteria should have prompt access to at least 72 hours of ECG monitoring to detect paroxysmal AF.
- The results of the prolonged monitoring should be available within 2 weeks of referral for monitoring to facilitate early secondary prevention.

Health technology description

Our assessment included the following categories of ambulatory electrocardiograms to detect PAF: Holter technologies, event recorder technologies and patch technologies. It should be noted that as the technologies evolve, the distinction between these categories is beginning to blur. For example, some of the latest Holter devices use patch-type electrodes.

Holter technologies

A Holter monitor is a battery-operated portable device that measures and records heart activity (ECG) continuously for 24 to 48 hours or longer depending on the type of monitoring required. Longer periods of monitoring can be achieved by reducing the number of leads (from three to two to single), but this reduces the diagnostic accuracy. The device is the size of a small camera, connected to wires with silver disc-shaped electrodes that attach to the skin.[6] The most recent versions of the technology use single patch-type electrodes attached to the sternum.

Patients carry the standard Holter monitor in a pouch or pocket, and are unable to bathe or shower with the electrodes attached. The device is fitted by a cardiac physiologist, and patients are required to attend at least two hospital visits (to have the device fitted and to return it). Data from the monitor is analysed by the cardiac physiologist. In NHS Lothian, clinical experts advise that 5 days monitoring requires about 30-45 minutes of analyst time, and costs approximately £32. The latest versions of some software incorporate semi-automated AF detection algorithms which may reduce this time (Prof. M Dennis, Professor of Stroke Medicine, University of Edinburgh. Personal communication, 19 February 2021).

A variety of Holter technologies are currently in use in NHSScotland for prolonged monitoring for PAF in people who have had a stroke. However, the most common is the Lifecard® CF, by Spacelabs Healthcare.

Event recorder technologies

There are two types of event recorder technologies: a loop memory monitor and a symptom event monitor.

A loop memory monitor is a small device which can be programmed to record patients' ECG for a set period of time. The electrodes remain attached and the monitor constantly records the ECG, but does not save it, unless activated to do so. When patients feel symptoms, they push a button to activate the monitor, and it stores the ECG for the period before and during symptoms. Some loop memory monitors are activated to record when they detect abnormal heart rhythms. Like the Holter monitors, the electrodes on loop memory monitors are constantly attached, and patients must remove the device to have a bath or shower.[7, 8]

A symptom event monitor can be either a hand-held device or worn on a patient's wrist. The monitors only record patients' ECG when symptoms occur, not before or after. When the patient feels a symptom or irregular heartbeat, they place the monitor on their chest and activate a recording button.[7, 8] The symptom event monitors are of little value in detection of PAF, since PAF is not usually associated with symptoms.

The loop memory recorder most commonly used in NHSScotland is the R.Test Evolution 4® by Novacor UK Limited. The device is normally fitted by a cardiac physiologist, and patients are typically required to attend at least two hospital visits. The loop memory recorder produces fewer data than a Holter monitor, and therefore takes less time for a cardiac physiologist to analyse (Prof. M Dennis, Professor of Stroke Medicine, University of Edinburgh. Personal communication, 19 February 2021).

Patch technologies

Patch technologies do not use wires or electrodes, but use an adhesive patch that sticks to the chest. They monitor ECG activity for several days, and are water-resistant so do not need to be removed for washing. They are single-use (though the electronic components may be reusable), and can be fitted by a non-specialist. They can be posted to patients, and returned via post. Analysis can be done locally or outsourced.

Patch technologies are not currently used in NHSScotland. One patch allows for up to 7 days of continuous monitoring in the home setting, and the company also offer reporting as an alternative to NHS clinicians providing report reading and analysis.[3]

The technology in this area is rapidly evolving, for example:

- Some recent Holter devices use patch-type electrodes
- The latest versions of some software incorporate semi-automated AF detection algorithms which may reduce the time taken to analyse data
- Some newer patch technologies incorporate event recording with real-time reporting of suspected AF via mobile phone links.

Other technologies for ambulatory cardiac monitoring, such as implantable devices, are beyond the scope of this assessment.

Use of the technologies in NHSScotland

There is variation in the use of the technologies across NHSScotland. The Planning for Government group carried out a review of ambulatory ECG availability for the monitoring for stroke/TIA patients (Table 1) (Prof. M Dennis, Professor of Stroke Medicine, University of Edinburgh. Personal communication, October 2020).

Table 1: Ambulatory ECG technologies in use in NHSScotland (2020)

NHS Board	Number of sites (Acute)	Technologies for inpatient use	Technologies for outpatient use
Ayrshire & Arran	1	Philips DigiTrak XT (Holter) 3 days	Philips DigiTrak XT (Holter) 3 days
Borders	1	Lifecard CF (Holter) 3 days	Lifecard CF (Holter) 2 days
Dumfries and Galloway	2	Telemetry 1 day	Introducing Novacor R Test (Event Recorder)
Fife	1	Novacor R Test (Event Recorder) 3 days	Lifecard CF 3 days
Forth Valley	1	Novacor R Test (Event Recorder) 2 days	Lifecard CF 2 days
Grampian	1 2	Novacor R Test (Event Recorder) 3 days Sorin (Holter) 3 days	Sorin Spiderview™ (Holter) 3 days
Greater Glasgow and Clyde	5	Lifecard CF (Holter) 3 days	Lifecard CF (Holter) 3 days
Highland	1	Novacor R Test (Event Recorder) 7 days	Novacor R Test (Event Recorder) (7 days)
Lanarkshire	3	Lifecard CF (Holter) 3 days	Lifecard CF (Holter) 3 days
Lothian	3	Lifecard CF (Holter) 5 days	Lifecard CF (Holter) 5 days
Orkney	1	72 hr Holter Spiderview Sorin to link with Aberdeen	72 hr Holter Spiderview Sorin to link with Aberdeen
Shetland	1	Lifecard CF (Holter) 3 days	Lifecard CF (Holter) 3 days

Tayside	2	Novacor R Test (Event Recorder) 3 days	Novacor R Test (Event Recorder) 3 days
Western Isles	1	Novacor R Test (Event Recorder) 7 days	Novacor R Test (Event Recorder) 7 days

Epidemiology

The Scottish Stroke Improvement Plan (2017) included the following criteria for selecting patients for prolonged monitoring:[5]

Ischaemic stroke or TIA and

a. No known history of atrial fibrillation and

b. No contraindication or definite indication for lifelong oral anticoagulation

- with any one of the following:

a. History of frequent palpitations

b. Syncope or pre-syncope

c. Recent myocardial infarction

d. Recent cardiac surgery

e. Cardiac failure

f. Ischaemic stroke/TIA affecting more than one vascular territory

g. An ischaemic stroke/TIA with no other explanation (for example known carotid disease, patent foramen ovale or lacunar infarction associated with small vessel disease).

Following the introduction of national standards[5] , a retrospective audit of stroke/TIA patients carried out by stroke services across Scotland, estimated that 3,000-3,500 patients (including inpatients and outpatients) per year would meet the criteria for monitoring. If monitoring were to be carried out following all ischaemic events, this would increase to over 10,000 patients each year (Prof. M Dennis, Professor of Stroke Medicine, University of Edinburgh. Personal communication, October 2020).

Clinical effectiveness

Health Technology Assessments

Canadian Agency for Drugs and Technologies in Health (2016)

In 2016, the Canadian Agency for Drugs and Technologies in Health (CADTH) published a high-quality health technology assessment (HTA) *Monitoring for Atrial Fibrillation in Discharged Stroke and Transient Ischaemic Attack Patients*.[1] The technologies included in the evaluation were ambulatory Holter monitors, electronic loop recorders (ELRs), implantable loop recorders, and mobile cardiac outpatient telemetry. Based on the HTA, CADTH recommended:

> For patients who have been discharged from hospital after a stroke or TIA and who did not undergo continuous cardiac monitoring while in hospital, the Health Technology Expert Review Panel recommends seven days of continuous outpatient cardiac monitoring with an ambulatory Holter monitor or external loop recorder.[9]

The HTA included an assessment of clinical effectiveness, cost effectiveness and patient issues. The results of the clinical effectiveness review have been summarised below. The results relating to cost effectiveness and patient issues are summarised under the 'Patient and social aspects' and 'Cost effectiveness' sections.

The clinical effectiveness review included 36 studies (four randomised controlled trials (RCTs), 22 single-arm prospective cohort studies, and ten retrospective cohort studies). All studies included patients with ischaemic stroke, but four included only patients with 'embolic stroke of undetermined source' (ESUS), which is another term for cryptogenic stroke. Fifteen studies also included patients with TIA. The duration of AF that was accepted as a positive result varied substantially by study and included: any duration, less than 30 seconds, and greater than 10 seconds/30 seconds/1 minute/2 minutes and 6 minutes. The included studies were too heterogeneous to undertake meta-analyses, and so the results were presented as a narrative synthesis. With regards to the specific technologies of relevance to this SHTG Assessment, CADTH reported the following:

- **Ambulatory Holters**: In 13 studies using ambulatory Holters (including two RCTs: Gladstone et al 2014 and Higgins et al 2013), the proportion of patients diagnosed with AF post-stroke or TIA ranged between 1.7% and 27.3%. With the exception of one study, diagnostic yield generally increased when monitoring for more than one day. There was no pattern observed between diagnostic yield and the mean age or sex of study participants.
- **External Loop Recorders:** In nine studies evaluating ELRs (including the two RCTs by Gladstone et al 2014 and Higgins et al 2013), the proportion of patients diagnosed with AF post-stroke or TIA ranged between 1.8% and 20.0%. Diagnostic yield

generally increased in studies with a greater mean age. There was no pattern observed between diagnostic yield and duration of monitoring or gender of study participants.

- **Comparison between devices:** Two RCTs (Gladstone et al 2014 and Higgins et al 2013) performed a head-to-head comparison between ELRs and ambulatory Holters among ESUS patients. Both studies were two-armed trials, in which all patients underwent initial in-hospital ECG monitoring. In Gladstone et al the diagnostic yield with ELRs was superior, and the absolute mean difference (95% confidence interval - CI) in the proportion of patients diagnosed with AF post-stroke or TIA between devices was 13.0% (95% CI, 8.2% to 17.8%). Higgins et al also reported higher diagnostic yield with ELR, but the absolute difference was not statistically significant at 8% (95% CI, –4.7% to 20.7%). In both studies, the mean duration of monitoring was longer with ELR than ambulatory Holter (7 and 30 days versus one day). Between studies, there were differences in how AF was defined, mean time to monitoring, and mean duration of monitoring. The authors of the HTA note that the Higgins et al study was underpowered.

Results for implantable loop recorders and mobile cardiac outpatient telemetry have not been included here as they are not relevant to the research question.

With regards to the SHTG Assessment research questions about which patients should be monitored, the optimum duration of monitoring, and the clinical significance of short-duration paroxysms, the CADTH review reported the following:

- There is a substantial increase in diagnostic yield when monitoring for longer than 24 hours.
- While monitoring patients beyond 30 days demonstrated greater diagnostic yield compared with less than 30 days, improvements were modest.
- The longer someone is monitored, the greater the likelihood of detecting AF, for any definition of AF (paroxysms of any duration versus at least one paroxysm longer than 30 seconds). The clinical and prognostic significance of short-duration paroxysms is unknown. With few comparative studies, there was insufficient evidence to distinguish the clinical effectiveness between devices or the optimal duration of long-term monitoring.

ECRI Institute (2018)

The CADTH HTA did not include any information on patch technologies. These are relatively new devices with limited available published evidence. A product brief on the Bardy Carnation Ambulatory Monitor (CAM™) published by ECRI in 2018[10] included only a small number of studies which did not exclusively recruit people who had ischaemic strokes. The briefing noted that the evidence was inconclusive, at a high-risk of bias, and required validation in large, diagnostic cohort studies.

Guidelines

European Society of Cardiology Guidelines (2020)

The European Society of Cardiology (ESC) guidelines for the diagnosis and management of atrial fibrillation, published in 2020, recommended:[11]

- In patients with acute ischaemic stroke or TIA and without previously known AF, monitoring for AF is recommended using a short-term ECG recording for at least the first 24 hours, followed by continuous ECG monitoring for at least 72 hours whenever possible.
- In selected stroke patients without previously known AF, additional ECG monitoring using long-term non-invasive ECG monitors or insertable cardiac monitors should be considered, to detect AF.

The first recommendation was based on evidence from three RCTs and a prospective multicentre cohort study. The second recommendation was based on large non-randomised study.

NICE Medical Technologies Guidance (2020)

In 2020, NICE published medical technologies guidance on Zio XT, a patch technology, for detecting cardiac arrhythmias:[12]

- Zio XT is recommended as an option for people with suspected cardiac arrhythmias who would benefit from ambulatory electrocardiogram (ECG) monitoring for longer than 24 hours only if NHS organisations collect information on:
  - resource use associated with use of Zio XT
  - longer-term clinical consequences for people who have monitoring with Zio XT (such as incidences of further stroke, transient ischaemic attack and other thromboembolisms, arrhythmia-related hospitalisations, mortality, uptake of anticoagulants or other changes in medication related to the monitoring result)
- Evidence shows that Zio XT is convenient and easy to wear, with an improved diagnostic yield (a measure of how many people with cardiac arrhythmia are diagnosed) compared with standard 24-hour Holter monitoring. The technology is likely to be cost neutral or cost saving compared with 24-hour Holter monitoring, but more evidence is needed
- NHS organisations using Zio XT should make sure that the service complies with general data protection regulations (GDPR), and that informed consent covers how a person's data will be used.

Systematic Reviews

Five additional systematic reviews were identified. Three did not add to the evidence presented above, as they included largely the same studies and drew the same conclusions.[13-15] The remaining two systematic reviews are described below. One included a subgroup analysis of detection rates using prolonged monitoring of new AF in selected versus unselected patients.[16] The second focused solely on TIA patients.[17]

Kishore et al (2014)

A well-conducted systematic review, with meta-analysis, aimed to determine the frequency of newly detected AF using noninvasive or invasive cardiac monitoring after ischaemic stroke or transient ischaemic attack.[16] It included subgroup analyses of selected (prescreened or cryptogenic) versus unselected patients and according to duration of monitoring. A total of 32 studies were analysed (although ten of these were only available as abstracts), encompassing 5,038 study participants.

- The overall detection rate of any new AF was 11.5% (95% CI 8.9% to 14.3%), with high heterogeneity between studies (I^2=88.2%). The authors noted that because the criteria for PAF were frequently not reported, they were unable to undertake further analyses of detection rates based on differing diagnostic criteria
- Detection rate of any new AF among unselected patients was 6.2% (95% CI, 4.4% to 8.3%; I^2=86.3%) and among selected patients was 13.4% (95% CI, 9.0% to 18.4%; I^2=88.8%). In cryptogenic strokes, new AF was detected in 15.9% (95% CI, 10.9% to 21.6%). Again, heterogeneity was high between studies.

Based on the limited evidence available, the authors concluded that selecting a high-risk population (for example, people who have had cryptogenic stroke) and using multiple interventions and periodic follow up is likely to improve detection rates. The optimum duration and method of monitoring remains unclear.

Korompoki et al (2017)

A systematic review and meta-analysis aimed to determine the rate of newly diagnosed AF using different methods of ECG monitoring in TIA.[17] The primary outcome was the frequency of detection of AF lasting at least 30 seconds. Seventeen studies enrolling 1,163 patients were included. The results are summarised as follows:

- The overall pooled proportion of TIA patients with newly detected AF was 4% (95% CI 2% to7%), although significant heterogeneity was observed among studies meaning the result needs to be interpreted with caution (I^2=60.61%, p=0.00)
- AF was more likely to be detected in selected (7%, 95% CI 2% to 14%) compared with unselected patients (3%, 95% CI 2% to 5%), although the authors reported significant heterogeneity between groups (p=0.041). The definition of 'selected' patients varied,

and included higher age, more extensive testing for arrhythmias before enrolment, or presumed cardioembolic/cryptogenic cause

- Pooled mean AF detection rates rose with duration of monitoring: 4% (≤24 hours), 5% (>24 hours to 7 days) and 6% (>7 days), respectively. No significant heterogeneity was observed between the studies (p=0.558). The authors suggest that further research is needed to establish the value of monitoring beyond 7 days in this patient group
- The yield of non-invasive monitoring was significantly lower than that of invasive monitoring (4% v. 11%). Significant heterogeneity was observed among studies (p=0.05). The authors note that this finding should be interpreted with caution due to the small numbers of people in the studies receiving invasive monitoring (n=44), the fact that they were likely selected, and the wide variety of monitoring times in the non-invasive group (ranging from 24 hours to 30 days).

The authors conclude that AF detection is lower in TIA patients than reported for combined ischaemic stroke and TIA cohorts in previous meta-analyses. This is a well-conducted review, but the heterogeneity between the studies means that the authors were unable to draw robust conclusions. The authors state the need for further prospective studies to determine the optimal diagnostic procedure for AF detection in TIA patients.

Randomised Controlled Trials

Only one RCT was identified that was not already picked up in the HTAs and systematic reviews.

Wachter et al (2017) – Find-AF$_{\text{RANDOMISED}}$

An open-label RCT from Germany (n=398) evaluated whether enhanced and prolonged rhythm monitoring (EPM) was better for the detection of AF than standard care procedures in patients with acute ischaemic stroke.[18] Patients had acute ischaemic stroke (symptoms for 7 days or less), were aged 60 years or older, and presented with sinus rhythm and without history of AF. EPM consisted of 10-day Holter-electrocardiogram-monitoring at baseline, and at 3 months and 6 months of follow-up. Standard care consisted of at least 24 hours of rhythm monitoring. After 6 months, AF was detected in 14% of patients in the EPM group (27 out of 200 patients) versus 5% in the control group (nine of 198 patients, absolute difference 9%, 95% CI 3·4 to 14·5, p=0·002; number needed to screen 11). The mean time and standard deviation (SD) from randomisation to AF detection were similar in both groups (33 days [SD 51] *v* 36 days [SD 56]; p=0·88). The authors concluded that these findings support the consideration of all patients aged 60 years or older with stroke for prolonged monitoring if the detection of AF would result in a change in medical management. Whilst the open-label nature of this RCT could potentially introduce bias, it was well-conducted and described.

The authors highlighted that it is still unknown whether short AF episodes detected by means of extensive heart rhythm monitoring should be treated similarly to conventionally-detected AF.

A sub-analysis of this trial was published in 2020.[19] The analysis aimed to evaluate whether brain natriuretic peptide (BNP) helps to identify patients with stroke at high risk for PAF, and whether it can be used to select patients for EPM more effectively. The authors reported that median BNP was higher in patients with PAF compared with patients without AF in both study arms at baseline (57.8 *v* 28.3 pg/mL in the EPM arm, p=0.0003; 46.2 *v* 27.7 pg/mL, p=0.28 in the control arm) and after 3 months (74.9 *v* 31.3 pg/mL, p=0.012 in the EPM arm, 99.3 *v* 26.3 pg/mL, p=0.02 in the control arm). They concluded that: 'BNP measured early after ischaemic stroke identifies a subgroup of patients with stroke at increased risk for AF, in whom EPM is particularly efficacious.'

Observational studies and other study types

A search was carried out for observational studies (and 'other' study types) published since the CADTH HTA (2016), but none were identified that alter the conclusions of the evidence presented above. For completeness, they are decribed briefly below.

*With regards to the clinical effectiveness of the technologies, two observational studies and a qualitative evaluation were identified***.**

Two prospective observational studies comparing external loop recording with continuous ECG recording were identified, [20, 21] along with a qualitative evaluation of a patch technology.[3]

A prospective observational study (n=1,412) compared external loop recording (Novacor R Test Evolution 4) with simultaneous continuous ECG recording (Lifecard CF, a Holter technology) for AF detection in patients who had acute ischaemic stroke or TIA.[20] Patients were monitored for 48 hours. The authors reported a high false positive rate with external loop recording. Similar results were reported in an earlier observational study (with the same lead author) comparing the diagnostic value of seven-day external loop recording with two-day Holter recording for detecting AF after ischaemic stroke or TIA (n=191).[21] Seven-day external loop recording did not detect significantly more patients with AF than two-day Holter recording, and external loop recording was associated with a high rate of false positives.

A qualitative evaluation of the patient, clinical, and organisational experiences of adopting a new patch technology (Carnation ambulatory monitor by Bardy Diagnostics, Inc.) was published by the Digital Health and Wellness Group (University of Strathclyde) in March 2020.[3] This described a 'test of change' in a hospital in NHS Lanarkshire using the patch technology for 14 day continuous monitoring in the AF screening pathway in secondary

care. The technology was used in 64 patients, and the manufacturer conducted the report reading and analysis, rather than NHS staff.

The report concluded that:

> Findings revealed that patients found the new monitoring device acceptable. Stroke clinicians and nurses invested additional time in training (4 half days) to use the software, apply the devices and in home-visits to apply devices but also highly valued the availability of 14 days of continuous data. For further adoption of this type of service, it is critical to explore whether clinicians would adopt a system or service that produces the reports for them or whether they would prefer to have the reports generated by NHS staff (trust and control versus cost and capacity for reporting).

For the research question on which patients should have prolonged ECG monitoring, four observational studies evaluated the use of scores for predicting PAF, and two explored patient characteristics that increased the chance of AF being detected.

Four studies were identified that evaluated the use of scores for predicting PAF.

- One prospective observational study from Portugal (n=67) evaluated the STAF (Score for the Targeting of Atrial Fibrillation) score, but concluded that it did not prove useful in predicting PAF in elderly people who have had a stroke with acute ischaemic stroke receiving prolonged Holter monitoring.[22] Similarly, a retrospective cohort study from Turkey (n=133) concluded that the STAF score has a limited utility for predicting PAF in patients with cryptogenic embolic strokes.[23]
- One study aimed to develop and validate a risk score for the detection of PAF in patients after ischaemic stroke with 72 hours of Holter-ECG monitoring.[24] The analysis included the individual patient data of three prospective studies (IDEAS, Find-AF and FIND-$AF_{randomised}$), encompassing 1,556 patients. All patients were from central Europe. A clinical score was developed from one cohort and externally validated on two other study cohorts. The score was called AS5F (Age, Stroke Severity NIHSS[1]>5 to Find AF). The authors reported an area under the curve (AUC) of 0.752 for AS5F when used for prediction of new-onset PAF within a monitoring interval of 72 hours.
- The C_2HEST score (coronary artery disease or chronic obstructive pulmonary disease [1 point each]; hypertension [1 point]; elderly [age ≥75 years, 2 points]; systolic heart failure [2 points]; thyroid disease [hyperthyroidism, 1 point]) was initially proposed for predicting incident AF in the general population. One study aimed to evaluate this risk score in a post–ischaemic stroke population.[25] Validation was based on a hospital-based nationwide cohort with 240,459 French people with post–ischaemic stroke. The authors reported that the C_2HEST score had good discrimination with a C index of 0.734 (95% CI 0.732 to 0.736).

[1] National Institutes of Health Stroke Scale

Two observational studies explored patient characteristics that increased the chance of AF being detected, namely age, greater levels of obesity, hypertension, heart failure and chronic obstructive pulmonary disorder.[26, 27] Another prospective observational study showed a low rate of PAF among younger patients (less than 60 years old) presenting with stroke, on the basis of 21-day cardiac monitoring with an external loop recorder.[28] Finally, a prospective observational study from Japan (n=206) concluded that brain natriuretic peptide, atrial premature contraction (APC) count, and APC short runs in the standard clinical workup seemed to be predictors of covert AF.[29] These studies do not confidently identify which patients should be selected for prolonged ambulatory ECG monitoring.

*Regarding the optimum duration of prolonged ECG monitoring to detect PAF***,** The observational studies identified were in agreement with the evidence already discussed, in that longer durations of ambulatory ECG monitoring were associated with greater AF detection rates, but they did not help define the optimum length of monitoring.[22, 30]

No additional observational studies were identified to help answer the question of the length of AF warrants treatment with anticoagulants.

Ongoing studies

The following trials are due to complete in the next couple of years:

https://www.clinicaltrials.gov/ct2/show/NCT03441022 Continuous Data Collection and Analysis for Stroke Prevention Using a Wearable Sensor (estimated study completion: August 2021)

https://clinicaltrials.gov/ct2/show/NCT01938248 Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA) (estimated study completion: December 2022)

https://clinicaltrials.gov/ct2/show/NCT02618577 Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes (NOAH) (estimated study completion: March 2022)

Safety

The CADTH review concluded that there was insufficient evidence in the clinical review to suggest any differences in safety (that is, stroke recurrence and stroke and/or all-cause mortality) between the outpatient monitoring devices.[1]

Patient and social aspects

The CADTH HTA included a systematic review and thematic synthesis of the literature on patient preferences and experience.[1] The review included people with any indication for outpatient cardiac monitoring devices, not just those who had experienced a stroke or TIA. People who have had a stroke or TIA may experience a unique set of challenges, compared with other people using outpatient cardiac monitoring devices. Nine studies (one qualitative descriptive study, two RCTs and six single-arm clinical trials) were identified that met the inclusion criteria. Seven studies were from Europe, one was from India and one from America.

The authors concluded that most patients found outpatient cardiac monitoring devices to be comfortable and easy to use. Side effects included skin irritation, pressure and problems around washing/showering. Patient preferences appeared to be based on overall comfort and ease of use, and these factors had an influence on patient adherence. It was not clear from the studies identified whether outpatient monitoring had any impact on patients' quality of life or levels of anxiety. The authors reported that due to limited data, it was unclear whether there were meaningful differences between the experiences of men and women, although some women reported discomfort from the device when wearing a bra. The authors also note that older people may experience more difficulty with these technologies, compared with younger people, but again the data is too limited to draw robust conclusions.

Cost effectiveness

Two reviews of economic evaluations were identified.[1, 31] The CADTH review conducted a bespoke economic evaluation (which was then included in the more recent review by Chew et al[31]). One other study that was not included in either review was also identified.[32]

The objective of the Chew et al review was to identify and synthesise the existing literature on the cost-effectiveness of prolonged rhythm monitoring devices for AF detection in cryptogenic stroke, compared with standard care.[31] Eight studies were included. Each study evaluated an extended ECG monitoring strategy compared with conventional Holter monitoring (one study compared conventional Holter to three alternate strategies): (1) 'extended' or 7- to 10-day ECG monitoring (three studies), (2) 'prolonged' or 30-day ECG monitoring (three studies) or (3) 2 to 3 years of 'very prolonged' monitoring with an implantable loop recorder (four studies).

The majority of cost-utility analyses reported incremental cost-effectiveness ratios that 'may be economically attractive compared with conventional monitoring when traditional

willingness-to-pay thresholds are adopted'; and two studies reported cost savings. The authors concluded that:

> In patients with cryptogenic stroke, extended ECG monitoring for AF detection may be economically attractive when traditional willingness-to-pay thresholds are adopted. However, there was substantial variation in the reported ICERs. The direct comparison of cost-effectiveness across technologies is limited by heterogeneity in modeling assumptions.[31]

The CADTH study identified six papers based on five published evaluations.[1] It is not clear whether or not these studies had been identified through a process of systematic review. One study by Kamel et al[33] extended an existing model by O'Brien and Gage[34], which was not included in the CADTH review of economic evaluations because the interventions were medicines to treat AF in patients diagnosed with the disease, whereas the Kamal et al study looked at what proportion of patients with AF would be diagnosed and then receive medicines to treat AF. Aside from this study, and the studies looking at implantable loop recorders, the included economic evaluations in the Chew et al and CADTH reviews are relevant to the assessment question here and are shown in Table 2 below.

The bespoke CADTH model that was created alongside the review is based on data from three RCTs (FIND-AF, CRYSTAL-AF and EMBRACE) and found that 7-day cardiac monitoring in patients with a very recent history of stroke or TIA, who did not receive in-hospital continuous monitoring (that is, patients who received ECG only) is likely to identify a substantial number of patients with AF at an acceptable incremental cost, which varied between CAD$50,000 and CAD$80,000 per QALY gained (2015 price year) depending on the rate of oral anticoagulant (OAC) uptake and the OAC prescribed. This translates to £32,132 to £51,411 per QALY gained for GBP at 2021 prices, not accounting for differences in the context between the Canadian health service in 2015 and the NHS in 2021.[35] Optimal duration of cardiac monitoring remained unclear (in the model 60% of patients received 24 hour monitoring in the comparator group compared with 7-day cardiac monitoring). Given the base case population were healthy patients following a stroke or TIA who would have not otherwise been evaluated using continuous monitoring techniques, the results were acknowledged to be at least in part due to the increase in diagnostic yield in this population who may not otherwise have had their AF picked up, whereas longer-term monitoring strategies (including 30-day ELR or ILR) were unlikely to be cost-effective because patients in the trials that evaluated these strategieswere already at higher risk and had already undergone 24 hours or more of continuous in-hospital monitoring as a result. [36, 37]

The inclusion criteria of studies in the reviews varied and this creates difficulty in understanding how the individual study populations, and varied comparisons of interest, influence the conclusions. Both reviews concluded there was a considerable amount of heterogeneity in the evidence identified. The same is true of the study by Kaura et al (2019) which compared 14-day ECG monitoring patch (Zio® Patch, iRhythm Technologies) with

short-duration Holter monitoring for the detection of episodes of PAF lasting at least 30 seconds within 90 days after an ischaemic non-lacunar stroke or TIA within the past 72 hours, and found it to be cost-effective in terms of the number of strokes that could be avoided.[32]

It should be noted that there was overlap between the reviews in that four studies were common to both the Chew et al and CADTH reviews[33, 38-40], and one of these (Diamantopoulos et al, 2016)[38] had looked at implantable devices not relevant to this assessment. A further four studies in the Chew 2020 review had also only included types of device that are outwith the scope of this assessment. The CADTH model also appears in the Chew et al review. A summary of the overlap between reviews is provided in Table 2 below.

Table 2: Economic evaluation studies identified via review or elsewhere

Identified from review(s)	Study	Setting; price year	Included patients	Intervention	Intervention Duration	Comparator	Comparator Duration	Outcome measure of effectiveness used
CADTH and Chew	Kamel et al 2010[33]	US (literature based); 2010	Hypothetical cohort of patients aged 70 following an ischaemic stroke. Patients had non-valvular AF.	7 days outpatient cardiac monitoring	7-10 days	standard care (aspirin is prescribed after ischaemic stroke and no outpatient cardiac monitoring is performed)	unclear how long aspirin is prescribed for	QALYs gained
CADTH and Chew	CADTH[1] (subgroup)	Canada; 2015	Patients aged 70 years or older with a recent stroke or TIA and no history of AF diagnosis	7 day cardiac event monitoring (ELR)	7 - 10 days	Standard practice (60% of patients received a 24-hour Holter)	24 hours; 0 hours (Reported as 60% of patients received 24 hours)	QALYs gained

CADTH	Mayer et al 2013[41] (primary analysis)	Germany; 2011	Patients (mean age 68) after first ischaemic stroke or TIA, presenting in sinus rhythm. AF not previously diagnosed. No contraindication of OAC therapy.	7 days Holter monitoring	7-10 days	24 hour Holter ECG	24 hour	QALYs gained
CADTH	Mayer et al 2013[41] (secondary analysis)	Germany; 2011	Patients (mean age 68) after first ischaemic stroke or TIA, presenting in sinus rhythm. AF not previously diagnosed. No contraindication of OAC therapy.	7 days Holter monitoring in a subgroup only, preselected by TTE (TTE/7-d-Holter).	7-10 days	24 hour Holter ECG	24 hour	QALYs gained
CADTH and Chew	Yong et al 2016[40] (secondary analyses)	Canada; 2014 (converted to US dollars)	Patients aged ≥55 years after a recent cryptogenic stroke or TIA and negative 24-hour Holter ECG	7-day and 14-day ECG monitoring (using an external auto-triggered event loop recorder)	7-14 days	repeat 24-hour ECG (Holter)	24+ hours (already filtered by initial 24 hour screen)	QALYs gained

Chew	Diekmann et al 2019[42]	Germany; not reported	Patients aged 60+ following recent ischaemic stroke lasting >24 h (additional symptom/diagnostic criteria)	10 days extended and prolonged Holter monitoring was performed after stroke and at 3 and 6 months	7-10 days; repeated after 3 and 6 months	Continuous ECG monitoring once, directly after the initial stroke.	24 hour	QALYs gained
CADTH and Chew	Yong et al 2016[40] (primary analysis)	Canada; 2014 (converted to US dollars)	Patients aged ≥55 years after a recent cryptogenic stroke or TIA and negative 24-hour Holter ECG	30-day ECG monitoring (using an external auto-triggered event loop recorder)	30 days	repeat 24-hour ECG (Holter)	24+ hours (already filtered by initial 24 hour screen)	QALYs gained.
CADTH and Chew	CADTH[1] (subgroup)	Canada; 2015	Patients aged 70 years or older with a recent stroke or TIA and no history of AF diagnosis	30-day event triggered recorder (ELR)	30 days	24-hour Holter	24+ hours (already filtered by initial 24 hour screen)	QALYs gained
CADTH and Chew	Levin et al 2015[39]	Sweden; 2013 (converted to Euros)	Patients aged 75-years or older with a recent ischaemic stroke/TIA (within 14 days) and no previously known AF.	30 days intermittent electrocardiogram (ECG) recordings using a handheld recording device,	30 days	24 h continuous Holter ECG; no screening	24 hours; 0 hours	Strokes avoided, life-years gained, QALYs gained.

				at regular time intervals				
-	Kaura et al 2019[32]	UK NHS; 2017	Patients aged 18 years of age or older having had ischaemic non-lacunar stroke or TIA within the past 72 hours	14-day patch-based monitor	14 days	Short-duration Holter ECG	24 hours; 0 hours (reported as "usually" 24 hours)	Strokes avoided.

The extent to which these data influence conclusions is unclear. While models of the diagnostic process for PAF are possible, the available evidence base on the most cost-effective strategy for doing so is heterogeneous in terms of the populations studied, the monitoring intervention(s) and comparator strategies used, the duration of follow up and the outcome of interest in terms of health benefit (e.g. strokes avoided and/or QALYs gained).

Conclusion

What is the clinical and cost-effectiveness of Holter versus event recorder versus patch technologies in the detection of PAF in patients with newly diagnosed ischaemic stroke selected to have prolonged ECG monitoring?

There is insufficient evidence to draw robust conclusions on the comparative clinical and cost-effectiveness of patch versus Holter versus event recorder technologies. Drawing conclusions is made even more challenging by the fact that the technology in this area is rapidly evolving.

For patch technologies, the evidence base is still at a relatively early stage of development. The existing evidence is inconclusive, and requires validation in larger diagnostic studies. NICE medical technologies guidance published in 2020 states that patch technology Zio XT is recommended (with caveats) as an option for people with suspected cardiac arrhythmias who would benefit from ambulatory ECG monitoring for longer than 24 hours.

Evidence from RCTs comparing ELRs and ambulatory Holters among people with cryptogenic stroke is insufficient to distinguish the relative clinical effectiveness of the different devices.

An HTA by CADTH (2016) recommended 7 days of continuous outpatient cardiac monitoring with either an ambulatory Holter monitor or external loop recorder for patients who have been discharged from hospital after a stroke or TIA and who did not undergo continuous cardiac monitoring while in hospital.

In patients with newly diagnosed ischaemic stroke, which patients should have prolonged ECG monitoring to detect paroxysmal atrial fibrillation?

One systematic review reported that the detection rate of any new AF was greater in selected people with stroke, compared with unselected patients, and greater again in patients with cryptogenic strokes.[16] Similar findings were reported in another systematic review, which focused on selected and unselected TIA patients. This review reported lower AF detection rates in TIA cohorts compared with cohorts including both stroke and TIA patients.[17] Both reviews reported high heterogeneity between the included studies, meaning that the results need to be treated with caution.

What is the optimum duration of prolonged ECG monitoring to detect PAF?

There is insufficient evidence to define the optimal duration of long-term monitoring.

The CADTH HTA reported that there is a substantial increase in diagnostic yield when monitoring for longer than 24 hours, with greatest diagnostic yields in patients who are monitored for the greatest duration. However, they also note that any improvements in diagnostic yield were modest after 30 days.[1]

Guidelines from the European Society of Cardiology (2020) recommend that in all patients with acute ischaemic stroke or TIA without previously known AF, monitoring for AF is recommended using a short-term ECG recording for at least the first 24 hours, followed by continuous ECG monitoring for at least 72 hours whenever possible. The guidelines also note that in selected people with stroke, additional ECG monitoring using long-term non-invasive ECG monitors or insertable cardiac monitors should be considered. However, the guidelines do not specify the length of time the devices should be used in this selected patient group.[11]

What length of AF warrants treatment with anticoagulants?

The identified studies did not help to answer this question, and there remains considerable variation with regards to the length of AF that is deemed to warrant treatment. The CADTH HTA reported that in the included studies the duration of AF that was accepted as a positive result varied greatly and included any duration, less than 30 seconds, and greater than 10 seconds/30 seconds/1 minute/2 minutes and 6 minutes. The authors conclude that the clinical and prognostic significance of short-duration paroxysms is unknown.[1]

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Appendix 1: Further economic modelling considerations

The cost-effectiveness component of this work identified several economic evaluations in atrial fibrillation which did not meet our inclusion criteria. Given the prevalence of AF and the existence of so many models of the care pathway, initially it seemed possible/plausible to develop a bespoke model for Scotland that compares strategies of relevance.

We explored this by first matching the NHS Board use of Holter and Event Loop Recorders (ELRs) to one or more of the study arms included in the cost-effectiveness section of this SHTG Assessment. Table A1 draws on Table 1 from the assessment to show which interventions are used in inpatient and outpatient settings across Scotland.

Table A1: Types of recorder in use by each NHS Board

Type of Recorder	Number of sites using this technology	Boards using this technology (inpatients)	Boards using this technology (outpatients)
Holter 2 days	2		NHS Borders (Lifecard CF), NHS Forth Valley (Lifecard CF)
Holter 3 days	14 (15 outpatients)	NHS Ayrshire and Arran (Philips DigiTrak XT); NHS Grampian (Sorin); NHS Greater Glasgow & Clyde (Lifecard CF); NHS Lanarkshire (Lifecard CF)	NHS Ayrshire and Arran (Philips DigiTrak XT); NHS Dumfries & Galloway (unspecified); NHS Fife (Lifecard CF); NHS Grampian (Sorin); NHS Greater Glasgow & Clyde (Lifecard CF); NHS Lanarkshire (Lifecard CF)
Holter 5 days	3	NHS Lothian (Lifecard CF)	NHS Lothian (Lifecard CF)
Event Loop recorder 2 days	1	NHS Forth Valley (Novacor R Test)	
Event Loop recorder 3 days	4 (1 outpatients)	NHS Fife (Novacor R Test); NHS Grampian (Novacor R Test); NHS Tayside (Novacor R Test)	NHS Tayside (Novacor R Test)

Type of Recorder	Number of sites using this technology	Boards using this technology (inpatients)	Boards using this technology (outpatients)
Event Loop recorder 7 days	2	NHS Highland (Novacor R Test); NHS Western Isles (Novacor R Test)	NHS Highland (Novacor R Test); NHS Western Isles (Novacor R Test)
Telemetry 1 day	2	NHS Dumfries & Galloway	
Unknown	2	NHS Orkney; NHS Shetland	NHS Orkney; NHS Shetland

As shown, 3 days of Holter monitoring is by far the most commonly used technology in Scotland. For creating a model to compare the different strategies in use, we would need to compare 2, 3 and 5 days of Holter monitoring against 2, 3 and 7 days of Event Loop recording or 1 day of telemetry.

Table A2 has grouped the individual arms from studies to consider how much available evidence exists for each of the comparisons that would need to be made to identify the optimal strategy for Scotland. Table A2 does not exclude on the basis of demographics of the study population, so some populations may not reflect the included assessment population (e.g. some studies related to screening for AF in the community). Nor does it distinguish between inpatient and outpatient based monitoring studies (although we have noted the particular setting in which it is used by any NHS Board in Scotland). The Table provides the available published evidence containing at least one study arm that is relevant (same or – if on a nearby row in the table - has the potential to approximate) to the devices and duration of monitoring as used in clinical practice in Scotland.

As can be seen, most of the interventions and durations found in the literature are not used currently in Scottish clinical practice. Of those that are, the main studies of relevance found in the assessment report were the review by Kishore et al, as well as the studies by Sejr et al 2019, Sejr et al 2017, Uphaus et al 2019 and Pagola et al 2018. Aside from the Kishore et al review, most of these studies are observational. The conclusions regarding Kishore et al in our assessment report describe too much heterogeneity for the authors to draw robust conclusions.

Although it may be feasible to use the comparative studies included in the list below to create an indirect comparison model from which to parameterise an economic model, it is not advisable to do so given the heterogeneity in the specifics of these individual studies. If clinicians in Scotland wish to explore priorities for further research in this area, discussions

about the relevance of each of the included papers in the Kishore et al review (selective population subgroup) to Scottish clinical practice, may be a useful starting point.

Table A2: Types of recorder in use by each NHS Board

Study	Intervention of interest	Duration of monitoring (days)	Use by NHS Board in Scotland
Diekmann 2019	Continuous ECG monitoring	1	NHS Dumfries and Galloway (inpatient)
Oguz 2020	Continuous ECG monitoring	1	
Wachter 2017 (RCT)	Continuous ECG monitoring	1	
Wasser 2020	Continuous ECG monitoring	1	
Sejr 2019	Continuous ECG monitoring	2	
Alves 2019	Continuous ECG monitoring	2	
Korompoki (review)	Continuous ECG monitoring	2	
European Society of Cardiology guidelines	Continuous ECG monitoring	3	
Oguz 2020	Continuous ECG monitoring	14	
Lumikari 2019	Continuous ECG monitoring	28	
Levin 2015	Continuous ECG monitoring	30	
McIntyre 2020	Continuous ECG monitoring	30	
Korompoki (review)	ELR	1	
Sejr 2019	ELR	2	NHS Forth Valley (inpatients)

Study	Intervention of interest	Duration of monitoring (days)	Use by NHS Board in Scotland
Kishore (review)	ELR	3	NHS Fife (inpatients); NHS Grampian (inpatients); NHS Tayside (both).
CADTH (subgroup)	ELR	7	NHS Highland (both); NHS Western Isles (both).
Yong 2016 (secondary analyses)	ELR	7	
Higgins (in CADTH)	ELR	7	
Kishore (review)	ELR	7	
Sejr 2017	ELR	7	
Yong 2016 (secondary analyses)	ELR	14	
Yayehd 2015	ELR	21	
Yong 2016 (primary analysis)	ELR	30	
CADTH (subgroup)	ELR	30	
Gladstone (in CADTH)	ELR	30	
Kishore (review)	ELR	30	

Study	Intervention of interest	Duration of monitoring (days)	Use by NHS Board in Scotland
Mayer 2013 (primary analysis)	Holter	1	
Yong 2016 (secondary analyses)	Holter	1	
CADTH (subgroup)	Holter	1	
Levin 2015	Holter	1	
Kaura 2019	Holter	1	
MSAC	Holter	1	
NICE Xio XT	Holter	1	
Barrett 2014	Holter	1	
Rosenberg 2013	Holter	1	
Eysenck 2019	Holter	1	
Steinhubl 2018	Holter	1	
Gladstone (in CADTH)	Holter	1	
Higgins (in CADTH)	Holter	1	
Korompoki (review)	Holter	1	

Study	Intervention of interest	Duration of monitoring (days)	Use by NHS Board in Scotland
Kishore (review)	Holter	1	
Kishore (review)	Holter	2	NHS Borders (outpatients); NHS Forth Valley (outpatients)
Sejr 2017	Holter	2	
Kishore (review)	Holter	3	NHS Ayrshire and Arran (both); NHS Dumfries and Galloway (outpatients); NHS Fife (outpatients); NHS Grampian (inpatients); NHS Greater Glasgow and Clyde (both); NHS Lanarkshire (both).
Uphaus 2019	Holter	3	
Pagola 2018	Holter	3	
N/A†	Holter	5	NHS Lothian (both)
Alves 2019	Holter	7	
Mayer 2013 (primary analysis)	Holter	7	
Miyazaki 2020	Holter	7	
Diekmann 2019	Holter	10	
Wachter 2017 (RCT)	Holter	10	
Wasser 2020	Holter	10	
Pagola 2018	Holter	15	
Pagola 2018	Holter	28	

Study	Intervention of interest	Duration of monitoring (days)	Use by NHS Board in Scotland
Kaura 2019	Patch	14	
NICE Xio XT	Patch	14	
Barrett 2014	Patch	14	
Rosenberg 2013	Patch	14	
Eysenck 2019	Patch	14	
Steinhubl 2018	Patch	14	
Yenikomshian (review)	Patch	14	
CADTH (subgroup)	"Standard practice"*	0.6	
Diamantopoulis 2016	"Standard practice"*	0.69	
NICE Reveal (LINQ)	"Standard practice"*	0.69	
NICE BioMonitor	"Standard practice"*	0.69	
NICE Confirm Rx	"Standard practice"*	0.69	
Marvoet 2019	"Standard practice"*	0.69	

† - although no study specifically explored 5 day duration Holter monitoring, it is likely that the durations specified in the study write up do not necessarily reflect average monitoring durations and so it is likely that the evidence in surrounding rows for 3-7 days may be relevant to NHS Lothian.
*described as standard practice in the literature. For the Duration of monitoring column the estimate for days for these studies was averaged depending on the proportion of the study sample who received no further monitoring and those who received e.g. 24 hours monitoring, etc.