NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

Implantable cardiac monitors (BioMonitor 2-AF, Confirm Rx insertable cardiac monitor and Reveal LINQ Insertable Cardiac Monitoring System) to detect atrial fibrillation after cryptogenic stroke

Final scope

September 2018

1 Introduction

The Reveal LINQ insertable cardiac monitor (ICM) is manufactured by Medtronic Limited. The medical technologies topic oversight group identified the Reveal LINQ ICM as potentially suitable for evaluation by the Diagnostics Assessment Programme on the basis of a briefing which was published as a NICE medtech innovation briefing. Clinical experts contacted during scoping have also provided input and advice on the topic area for this scope.

The final scope was informed by discussions at the scoping workshop on 26 July 2018 and the assessment subgroup on 8 August 2018.

A glossary of terms and a list of abbreviations are provided in appendices A and B.

2 Description of the technologies

This section describes the properties of the diagnostic technologies based on the company's notification to NICE. NICE has not carried out an independent evaluation of these descriptions.

2.1 Purpose of the medical technology

Implantable cardiac monitors (also known as implantable loop recorders or insertable cardiac monitors) are used to monitor heart rhythm over a longer period of time than heart rhythm monitors which are worn externally. They can be used to identify atrial fibrillation which is not present all the time (intermittent or paroxysmal atrial fibrillation). The devices may improve detection of intermittent atrial fibrillation in people who have had a cryptogenic

stroke, that is, an ischaemic stoke with no identified cause. If atrial fibrillation is diagnosed, anticoagulant therapy can be offered with the aim of reducing the risk of having another stroke.

The monitors are implanted under the skin of a person's chest using a small incision under local anaesthetic. They continuously monitor subcutaneous ECG for several years and automatically record information if the device detects an arrhythmia, or if a person activates their device because they are experiencing symptoms that are associated with arrhythmia; however clinical experts commented that the activation feature is of limited use in this population, because most episodes are asymptomatic. These recorded ECGs are remotely transmitted to clinicians for review to determine if atrial fibrillation has occurred, and allow clinical decisions about continued monitoring or treatment to be made. The implantable monitors are for single use only.

The devices contain algorithms that automatically detect atrial fibrillation. The algorithm parameters can be varied to adjust what ECG features are identified as potential atrial fibrillation. Clinical experts have commented that manufacturer's recommended, or standard, settings for detecting atrial fibrillation after cryptogenic stroke would generally be used. Other uses of the monitors, for example cardiac monitoring after transient loss of consciousness, are beyond the scope of this assessment.

2.2 Product properties

2.2.1. BioMonitor 2-AF (Biotronik SE & Co KG)

The BioMonitor 2-AF system consists of:

- a BioMonitor 2-AF insertable cardiac monitor (dimensions 88 x 15 x 6 mm),
- an optional Remote Assistant for patient-activated recordings,
- a remote monitoring system (a CardioMessenger Smart transmitter) which sends data to the Biotronik Home Monitoring Service Centre (HMSC) through a cellular phone network,
- a Renamic programmer for the insertable cardiac monitor.

<u>Device implantation</u>

The BioMonitor 2-AF is implanted using a Fast Insertion Tool (FIT) accessory kit. An incision of at least 1.5cm is first cut. The FIT 1 tool is used to form a pocket for the device under the skin and the FIT 2 allows implantation and positioning of the device. The company state that the implantation procedure

is usually done in a catheterisation lab or sterile room by a cardiologist, electrophysiologist, cardiac physiologist or nurse. Most implantations are done by cardiologists; but nurse- or physiologist-led procedures are becoming more common. The company provides training in the use of the device, done by Biotronik's Education and Technical team. The company state that this takes between 1 and 3 hours (depending on the level of experience). The battery life of the device is estimated as 4 years, assuming data being sent from the device once per day. The company state that a decision about whether to remove the device once it is no longer in use should be made by clinicians.

During implantation, the device is activated using a portable device that can remotely communicate with the BioMonitor 2-AF. This allows the device to be activated, and its parameters to be varied from standard settings if required.

The company state that follow-ups are needed at regular, agreed upon intervals. The first follow-up should be done about 3 months after implantation, with subsequent follow-up checks done once a year. These follow-up appointments involve checking the detection function of the device and updating the parameters programmed into the device when necessary.

Atrial fibrillation detection

Heart rhythm is continuously monitored by the BioMonitor 2-AF and ECGs are automatically recorded when atrial fibrillation is detected. Atrial fibrillation is detected based on irregular RR intervals, absence of P waves and atrial rate greater than 300 beats per minute. Parameters for sensing settings can be adjusted to vary the sensitivity of atrial fibrillation detection. There are also standard settings for parameters, such as AF sensitivity (described in the product manual).

In addition to atrial fibrillation, the BioMonitor 2-AF can also detect other cardiac arrhythmias; such as high ventricular rate, asystole, bradycardia, and sudden ventricular rate drop.

The Remote Assistant device can also be used to record an ECG while, or immediately after, a patient experiences symptoms that may indicate atrial fibrillation is happening. When the implanted monitor is triggered in this way, a 7.5 minute ECG is stored; 7 minutes pre-episode and 0.5 minutes post-episode. Up to 55 individual episodes can be stored automatically, in addition to 4 patient-activated recordings.

Remote monitoring

Recordings made by the BioMonitor 2-AF are automatically and wirelessly sent to a transmitter unit as a daily device message. Data are encrypted and sent as anonymous data to the Biotronik Home Monitoring Service Centre over mobile phone networks. Data is stored in Germany and can be accessed by clinicians through an online platform. Automatic alerts are sent to clinicians when a reading is received which meets pre-defined criteria. Clinicians should always review readings to make a final diagnosis.

A previous version of the device, the BioMonitor, is no longer available. The company state that the differences between the current and previous device relate to hardware; the BioMonitor 2 is approximately two thirds the size and has improved transmission and recording capacity. The same atrial fibrillation detection algorithm is used.

2.2.2 Confirm Rx Insertable Cardiac Monitor (Abbott Medical UK / St. Jude Medical)

The Confirm Rx system consists of:

- a Confirm Rx Insertable Cardiac Monitor (ICM; dimensions 49 x 9.4 x 3.1 mm),
- a remote monitoring system (the myMerlin application installed on a smartphone or tablet) and the Merlin.net Patient Care Network (PCN)
- a Merlin Patient Care System (PCS) and a magnet (to interrogate and programme the insertable cardiac monitor).

If a patient or their carer does not have a smartphone, the company may provide a mobile device with the remote monitoring app installed. The battery life of the device is estimated as 2 years, assuming an average of 1 automatically detected episode a day and 1 patient-activated episode per month.

Device implantation

The Confirm Rx ICM is implanted using proprietary insertion and incision tools. The device is implanted using a small cut made using the incision tool done under local anaesthetic. The insertion tool is then used to implant the device under the skin. The company state that in the UK the procedure is commonly performed by cardiologists, cardiac physiologists and nursing staff.

Atrial fibrillation detection

Heart rhythm is continuously monitored by the Confirm Rx, and ECGs are automatically recorded when atrial fibrillation is detected. The Confirm Rx ICM assess 3 aspects of ECG trace to identify potential atrial fibrillation: regularity of rhythm pattern, variance of R-R intervals and how sudden the onset of arrhythmia is. All 3 tests must indicate atrial fibrillation to trigger episode recording. The settings used by the device to detect atrial fibrillation can be varied; for example, to set the length of episode needed to trigger a recording. In addition to atrial fibrillation, the device will also detect bradyarrhythmias, tachyarrhythmias and pauses.

People can also trigger the device to record an ECG using the myMerlin app.

Remote monitoring

Recordings made by the Confirm Rx ICM are transmitted using Bluetooth to a smartphone or tablet with the myMerlin app. The app can be downloaded from the company's website. The company state that the app automatically reads data from the implanted device and sends it to a database using a cellular or Wi-fi network during the night, and recommend that a smartphone or tablet with the app installed is kept by a person's bedside at night to allow data transmission. The ICM encrypts its wireless communications and will only transmit to a single authenticated and paired myMerlin app at any given time. Emails or SMS notifications can be sent to alert that a recording has been sent. Clinicians can then access transmitted ECG recordings on the Merlin.net PCN by logging on with a User ID and password. Access to the Merlin.net PCN is restricted to authorised users set by the clinic administrator.

2.2.3 Reveal LINQ Insertable Cardiac Monitoring System (Medtronic Limited)

The Reveal LINQ Insertable Cardiac Monitoring System consists of:

- a Reveal LINQ Insertable Cardiac Monitor (ICM) device (dimensions 45 x 7 x 4 mm),
- an optional Reveal Patient Assistant handheld device which is held over the ICM by the user to start an ECG recording or mark an event on the ECG record,
- a remote monitoring system (a bedside MyCareLink Patient Monitor) which sends data to the MyCareLink network cloud storage facility and
- a MyCareLink Programmer which is a portable computer system that is used to program the ICM devices by a healthcare professional.

Device implantation

The Reveal LINQ ICM is implanted using proprietary insertion and incision tools. The incision tool makes a small opening in the skin (less than 1 cm) and the insertion tool is used to make a small pocket for the ICM and implant the device under the skin. In most cases the procedure is done using local anaesthetic. It has been reported that the implantation does not need to be done by a cardiologist (for example, it could be done by cardiac physiologists, nurses, neurologists or stroke physicians) and does not need to be done in a cardiac catheterisation lab (Mittal et al. 2015; Roebuck et al. 2015; Kanters et al. 2015; Di Odoardo et al. 2017). Training in implanting the device is provided by the Medtronic field team and is also available on-line. The battery life of the device is estimated as 3 years (assuming an average of 1 auto-detected episode per day and 1 patient-activated episode per month). While the device does not need to be removed, the company suggests removal when it is no longer required.

The Medtronic CareLink Programmer is used to programme the device settings by placing the programming head over the device. This includes adding patient details, the reason for monitoring (including cryptogenic stroke) and the time that data recorded by the device should be transmitted to the Patient Monitor (see below). There are also programmable parameters that determine when an episode of arrhythmia is recorded by the device; for example, 'AF detection sensitivity' and recording threshold (the length of episode required before it is recorded by the device). There are also company recommended settings that are applied as a default (including AF detection sensitivity) when cryptogenic stroke is selected as the reason for monitoring.

Atrial fibrillation detection

The Reveal LINQ ICM continuously monitors heart rhythm and identifies potential atrial fibrillation episodes from a person's ECG trace using an algorithm. An ECG trace is assessed in 2 minute 'windows' which are considered as positive if atrial fibrillation is present for longer than a programmable threshold. If the algorithm detects a potential episode of atrial fibrillation, the ECG trace is stored. The device can also be programmed to only store episodes that persist for a set period of time (6, 10, 20, 30 or 60 minutes). A total atrial fibrillation burden is also calculated, consisting of all 2 minute windows in which atrial fibrillation was present for longer than threshold value. In addition to atrial fibrillation, the Reveal LINQ ICM can also detect tachyarrhythmia, bradyarrhythmia or pause episodes. The device contains an accelerometer to allow changes in patient activity over time to be monitored.

The Patient Assistant device (a battery operated hand held device) can also be used to record an ECG while, or immediately after, a patient experiences symptoms that may indicate atrial fibrillation is happening (for example, loss of consciousness or palpitations). This involves pressing a button on the Patient Assistant and holding it over the implanted device.

The ICM can store up to 27 minutes of ECG from arrhythmias detected automatically and up to 30 minutes from patient-activated episodes.

Remote monitoring

Rhythm abnormalities recorded by the Reveal LINQ ICM are wirelessly transmitted to the MyCareLink Patient Monitor and then sent to a CareLink server in the Netherlands. Transmitted and stored data are encrypted. A care alert is sent to clinicians when the device detects a rhythm abnormality, who can access the data through the CareLink website using a password protected log-in. Alternatively, daily notifications of cardiac activity can be sent. The device will also send alerts if the battery is low. If the device is unable to communicate with CareLink it will register as 'disconnected'.

The company also offers a triage and monitoring service (FOCUSON) to review ECG recordings made by the Reveal LINQ ICM. ECGs are reviewed by cardiologists and ECG technicians at a Monitoring and Triaging Service Centre. Any clinically-relevant cases requiring clinical action or escalation are notified to the NHS clinician by phone or email. Detected episodes are categorised by colour (red, amber or green). The company state that red events are notified on the same working day and within 1 hour from when the transmission reaches the CareLink Network service. Amber events are notified by email on the next working day, and green events are aggregated and notified in a weekly email.

The Reveal LINQ ICM was released in the UK in February 2014. The previous version of this device, the Reveal XT, also had an AF detection algorithm; however, earlier ICMs from the company (Reveal DX, Reveal Plus, Reveal and Cardiac Monitor) did not. The Reveal LINQ ICM is smaller and has more data memory than the Reveal XT.

3 Target condition

Atrial fibrillation in people with a cryptogenic stroke or transient ischaemic attack

3.1 Atrial fibrillation

Atrial fibrillation is a type of arrhythmia which causes an irregular or abnormally fast heart rate. It is the most common arrhythmia. When a person experiences atrial fibrillation, it causes the upper chambers of the heart (the atria) to beat irregularly which makes the heart less effective at moving blood into the ventricles. This can cause clots to form in the blood which may subsequently cause a stroke. About 20 to 30% of people with an ischaemic stroke are diagnosed with atrial fibrillation (before, during or after the event) and untreated atrial fibrillation is associated with a 5-fold increased risk of stroke and a 3-fold increased risk of heart failure (Camm et al. 2012; Kirchhof et al. 2016). Early detection of atrial fibrillation allows adoption of preventative treatment; for example oral anticoagulants to reduce the risk of stroke.

The abnormal electrical impulses in the heart muscle which cause atrial fibrillation can be persistent, permanent or intermittent. This causes the 3 types of atrial fibrillation:

- Permanent atrial fibrillation: atrial fibrillation present all the time.
- Persistent atrial fibrillation: episodes last longer than 7 days (if left untreated)
- Paroxysmal (intermittent) atrial fibrillation: intermittent episodes which usually last less than 2 days and stop without treatment.

Symptoms which suggest that someone may have atrial fibrillation include feeling dizzy, being short of breath, feeling tired and having heart palpitations. Atrial fibrillation can also be asymptomatic.

3.2 Cryptogenic stroke

Ischaemic strokes occur when arteries to the brain are blocked (usually by blood clots), and consequently, blood flow is reduced. Such blood clots can form in the large or small arteries in the brain (a thrombotic stroke), often when arteries narrow because of atherosclerosis (the build-up of fatty material inside an artery). Alternatively, blood clots can form elsewhere and travel to the brain (embolisms). For example, blood clots forming in the heart (cardioembolisms) can cause strokes (cardioembolic stroke). Sources of cardioembolisms include myocardial infarction, mechanical prosthetic valve, dilated myocardiopathy, and mitral rheumatic stenosis, infective endocarditis,

marantic endocarditis, atrial myxoma, patent foramen ovale, atrial septal aneurysm, atrial or ventricular septal defects, calcific aortic stenosis, and mitral annular calcification (Arboix and Alio, 2010). Atrial fibrillation is a common cause of cardioembolisms.

Cryptogenic strokes are defined as those with no identified probable cause after diagnostic assessment, and account for around 15 to 40% of ischaemic strokes (Zhang and Kasner, 2016). Several classification systems have been used to define cryptogenic stroke (reviewed in Zhang and Kasner, 2016); however, they do not provide detail on the extent of diagnostic testing required before the definition applies. An alternative term has been proposed to provide detail on what tests should be carried out before a stroke is considered to have an unknown cause: embolic stroke of undetermined source (ESUS). These include brain imaging (CT or MRI), electrocardiograms, transthoracic echocardiogram, rhythm monitoring for at least 24 hours and imaging of extra- and intra-cranial arteries (Zhang and Kasner, 2016; Bridge and Thijs, 2016). An international survey reported that 16% of people with ischaemic stroke met ESUS criteria (the true value may be higher as additional patients had an incomplete assessment required to diagnose an ESUS; Perera et al. 2016).

Clinical experts commented that an initial assessment to characterise and identify potential causes of stroke or transient ischaemic attack (TIA) would typically include taking patient history and a physical examination, blood tests and assessing blood pressure, a brain scan, carotid ultrasound and echocardiography. Tests for atrial fibrillation are done when people are treated for stroke (see section 3.4.1). However, if the atrial fibrillation is paroxysmal it may not have been present at the time of the stroke, or during subsequent diagnostic tests. Further longer term testing can potentially detect paroxysmal atrial fibrillation.

3.2.1 Prevalence of atrial fibrillation

About 57,000 people in England experienced a stroke for the first time in 2016 (First stroke estimates in England: 2007 to 2016, Public Health England), with ischaemic stroke accounting for about 85% of cases. About 20 to 30% of people with an ischaemic stroke are diagnosed with atrial fibrillation (before, during or after the event). The proportion of people with cryptogenic stroke for whom atrial fibrillation is detected after the acute event by an implantable cardiac monitoring device varies between studies (potentially due to differences in reported length of monitoring), but is up to around 30% (Sanna et al. 2018; Nouh et al. 2016). The detected episodes of paroxysmal atrial fibrillation are usually asymptomatic; for example 100% of episodes

(Christensen et al. 2014), 92% of episodes (Poli et al. 2016) and 81% episodes (Brachmann et al. 2016).

3.2.2 *Risk factors for paroxysmal atrial fibrillation with cryptogenic stroke*

Several studies have looked to identify risk factors that predict the likelihood of paroxysmal atrial fibrillation for people with cryptogenic stroke (for example, Favilla et al. 2015; Poli et al. 2016; reviewed in Bridge and Thijs, 2016). However, clinical expert opinion was that in current practice no single, or subset, of factors are generally used to determine if paroxysmal atrial fibrillation is likely. The decision to do further monitoring for atrial fibrillation is made by stroke physicians and cardiologist based on the characteristics of the stroke, and potentially the presence of atrial ectopic beats.

3.3 Cryptogenic transient ischaemic attack (TIA)

A TIA is caused when there is a temporary disruption of blood flow to part of the brain. Cardiac embolisms, which are often caused by atrial fibrillation, can also result in TIAs. TIAs are considered as part of the spectrum of ischaemic stroke (Geraghty et al., 2016; Korompoki et al. 2017). Studies have suggested a lower incidence of atrial fibrillation in people with TIA, compared to stroke (Pedersen et al. 2018). Clinical experts commented that, because they are on a continuum of the same disease pathway, the diagnostic-work up for people with stroke and TIA is similar.

3.4 Diagnostic and care pathway

The NICE guideline on atrial fibrillation provides recommendations on diagnosis and management of the condition, and is currently being updated.

3.4.1 Diagnostic pathway

The NICE guideline on stroke and transient ischaemic attack in over 16s: diagnosis and initial management provides recommendations on recognising and diagnosing stroke and TIA, the use of brain and carotid imaging, potential surgical treatment and pharmacological treatment for people with acute stroke. An update of this guideline is planned.

Diagnostic assessment for a person who has had a stroke or TIA includes physical examination, testing for hyperlipidaemia, haematology tests, brain and carotid imaging and further testing as clinically indicated. Tests for atrial fibrillation are done, particularly if the stroke is thought likely to have been caused by a cardioembolism.

Initial assessment for atrial fibrillation

The NICE guideline on atrial fibrillation recommends using manual pulse palpation to assess for an irregular pulse that may indicate atrial fibrillation in people presenting with stroke or TIA. An ECG is recommended for people in whom atrial fibrillation is suspected because an irregular pulse has been detected. Clinical experts commented that 12 lead ECGs are used on admission to assess for atrial fibrillation in people who have had a stroke. They also commented that in-patient Holter ECG monitoring and in-patient cardiac telemetry are also used in the NHS, although noted that use varies across England.

The 2016 European Society of Cardiology (ESC) Guidelines for the management of atrial fibrillation recommends that for people with TIA or ischemic stroke "…screening for AF is recommended by short-term ECG recording followed by continuous ECG monitoring for at least 72 hours" (Kirchhof et al. 2016).

The 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association states that "Cardiac monitoring is recommended to screen for atrial fibrillation and other potentially serious cardiac arrhythmias that would necessitate emergency cardiac interventions. Cardiac monitoring should be performed for at least the first 24 hours" (Powers et al. 2018).

Outpatient ECG monitoring

If there is a clinical suspicion of paroxysmal atrial fibrillation, but no arrhythmia detected during initial diagnostic investigations, further outpatient ECG monitoring is used. For people with suspected paroxysmal atrial fibrillation (undetected by standard ECG recording), the NICE guideline on atrial fibrillation recommends using:

- a 24‑hour ambulatory ECG monitor in those with suspected asymptomatic episodes or symptomatic episodes less than 24 hours apart
- an event recorder ECG in those with symptomatic episodes more than 24 hours apart.

Event-ECG recorders were defined in the full guideline as any electrocardiographic recording device which recorded only particular events, identified either automatically by a software program to detect arrhythmic episodes or by the onset of symptoms (when the patient manually switches on the device for the duration of the symptomatic episode), or a combination of

the two. Ambulatory ECG monitors were defined as any electrocardiographic recording device that continuously recorded cardiac electrical activity while the patient was able to move around relatively freely without hindrance.

Further guidance is available on longer term ECG monitoring:

- The Royal College of Physicians' national clinical guideline for stroke recommends that "People with ischaemic stroke or TIA who would be eligible for secondary prevention treatment for atrial fibrillation and in whom no other cause of stroke has been found should be considered for more prolonged ECG monitoring (24 hours or longer), particularly if they have a pattern of cerebral ischaemia on brain imaging suggestive of cardioembolism."

- Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack (a guideline for healthcare professionals from the American Heart Association/American Stroke Association) recommends that for "…patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (≈30 days) for AF is reasonable within 6 months of the index event (Class IIa; Level of Evidence C)" (Kernan et al. 2014).

- The 2016 European Society of Cardiology (ESC) Guidelines for the management of atrial fibrillation recommends that for people who have had a stroke "…additional ECG monitoring by long-term noninvasive ECG monitors or implanted loop recorders should be considered to document silent atrial fibrillation" (Kirchhof et al. 2016).

- The 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association states that:

    - The clinical benefit of prolonged cardiac monitoring to detect atrial fibrillation after acute ischaemic stroke is uncertain.

    - In some patients with acute ischaemic stroke, prolonged cardiac monitoring to provide additional information to plan subsequent secondary preventive treatment may be reasonable, although the effect on outcomes is uncertain (Powers et al. 2018).

- The Canadian Stroke Best Practice Recommendations: Acute Inpatient Stroke Care Guidelines, Update 2015 recommends that in "…cases where the electrocardiogram or initial cardiac rhythm monitoring (e.g. 24 or 48 h ECG monitoring) does not show atrial fibrillation but a

cardioembolic mechanism is suspected, prolonged ECG monitoring, up to 30 days duration, is recommended in selected patients for detection of paroxysmal atrial fibrillation (Evidence Level B)" (Casaubon et al. 2016).

- The Health Technology Expert Review Panel at the Canadian Agency for Drugs and Technologies in Health (CADTH) state that for people who have been discharged from hospital after a stroke or TIA and who did not undergo continuous cardiac monitoring while in hospital, 7 days of continuous outpatient cardiac monitoring with an ambulatory Holter monitor or external loop recorder is recommended.

Current NHS practice

Clinical experts commented that there is considerable variation in practice for outpatient ECG monitoring after a stroke or TIA across the NHS. Studies report no clear consensus on the optimal duration or modality of rhythm monitoring post-stroke or TIA (Merinopoulos et al. 2017). Most commonly people have outpatient ECG monitoring with a Holter monitor for 24 to 48 hours. Some centres offer longer Holter monitoring for 7 or 14 days. Clinical experts also noted that newer external ECG 'patch' monitors are now available which can be used for 14 days (or up to 1 month with the use of consecutive patches); however, these devices are currently not widely used in the NHS and require external assessment of measured ECG traces. Clinical experts and the literature states that external (that is, not implanted) ambulatory ECG monitor devices can typically only be used for 30 days at most, and patient compliance decreases with monitoring over time (Azfal et al. 2015; Galli et al. 2016; Gladstone et al. 2014; Kamel et al. 2013).

Clinical experts also highlighted that further testing for atrial fibrillation would only be considered if a person would be able to have anticoagulants if the condition was detected, potentially based on the HAS-BLED score for bleeding risk.

Implantable cardiac monitors

Clinical experts commented that implantable cardiac monitors for ECG would be used if any initial external ambulatory ECG monitoring did not identify atrial fibrillation, but there was still a suspicion of the condition. Literature also suggests that the more expensive implantable monitors should only be used as part of a 'step-wise' approach to longer term monitoring if atrial fibrillation is still suspected despite a negative result from external ambulatory monitoring (Galli et al. 2016).

3.4.2 Care pathway

Treatment for atrial fibrillation

The NICE guideline on stroke and transient ischaemic attack and Clinical Knowledge Summary on Stroke and TIA recommend initiating antiplatelet therapy on diagnosis of ischaemic stroke or TIA. Anticoagulation treatment should not be used routinely for the treatment of acute stroke.

If atrial fibrillation is diagnosed after a stroke, the NICE guideline on atrial fibrillation has recommendations for care:

- **Treatment to lower risk of stroke**
  Including assessing stroke and bleeding risk using the CHA2DS2VASc and HAS-BLED scores, and treatments to lower the risk of stroke (apixaban, dabigatran etexilate, rivaroxaban or a vitamin K antagonist). NICE technology appraisal guidance has been produced on apixaban (TA275), dabigatran etexilate (TA249) and rivaroxaban (TA256). In addition, a further anticoagulant is now available and has been assessed by NICE in TA guidance 355 (edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation).

- **Treatment to control heart rate and rhythm**
  Includes different interventions that are offered as part of a rate control strategy (beta-blockers, calcium channel blocker, digoxin) or rhythm control strategy (pharmacological and/or electrical rhythm control), where appropriate.

The guideline also covers the use of left atrial ablation if drug treatment has failed to control symptoms of atrial fibrillation or is unsuitable.

3.5 Patient issues and preferences

A reduction in subsequent strokes or TIAs caused by the earlier diagnosis of atrial fibrillation and use of anticoagulants will have substantial patient benefits.

Clinical experts commented that if devices do not function correctly, for example if they don't transmit data or if the battery runs out too quickly, the devices will need to be removed, and another device potentially fitted which will be associated with an additional implantation procedure and its associated risks and side effects. In addition, clinical experts commented that skin erosion can occur which causes the implanted monitors to become exposed.

The size of the devices may also be an issue for patients in terms of how cosmetically acceptable they are, and the extent of any scarring. The extent of any adverse events related to fitting the devices (for example, infection) will also be an issue for patients, as will the length of time needed to fit the device. Reductions in the number of visits to hospital needed as part of post-stroke or TIA follow-up care (to obtain data from monitors) would benefit patients.

Clinical experts commented that people who become pregnant after having a device implanted often prefer to have it removed.

4 Comparator

No further testing after outpatient external ambulatory ECG monitoring.

Clinical experts commented that if no atrial fibrillation is detected following use of an external ambulatory ECG monitor, no further monitoring for atrial fibrillation is likely to be done, unless an implantable cardiac monitor is available. Undetected atrial fibrillation may be later identified if it causes symptoms (for example, palpitations), incidentally when a person's pulse is checked (for example, when blood pressure is taken), or on investigation after a recurrent stroke or TIA.

5 Scope of the assessment

Table 1 Scope of the assessment

Decision question	Does the use of implantable cardiac monitors to assess for suspected paroxysmal atrial fibrillation in people who have had a cryptogenic stroke represent a cost effective use of NHS resources?
Populations	People with a cryptogenic stroke (which includes cryptogenic transient ischaemic attack [TIA]) for whom there is a suspicion of paroxysmal atrial fibrillation, and who have had at least 24 hours of outpatient external ambulatory ECG monitoring that has not detected atrial fibrillation. <u>Potential subgroups</u> • People with varying lengths of previous outpatient external ambulatory ECG monitoring that has not detected atrial fibrillation (for example 1, 2, 7, 14 or 30 days) • People with a cryptogenic TIA • People with a cryptogenic stroke (excluding TIA)
Interventions	• BioMonitor 2-AF

	• Confirm RX • Reveal LINQ
Comparator	No further monitoring for atrial fibrillation (after at least 24 hours of outpatient external ambulatory ECG monitoring that has not detected atrial fibrillation).
Healthcare setting	Secondary and tertiary care
Outcomes	Intermediate measures for consideration may include: • Diagnostic accuracy • Diagnostic yield (number of atrial fibrillation diagnoses) • Detection of other cardiac pathologies or incidental findings (non-atrial fibrillation) • Time to diagnosis of atrial fibrillation • Time to initiation of anticoagulants • Uptake of anticoagulants • Incidences of device failure (such as inability to transmit data or unexpectedly short battery life) and device removal because of failure or adverse events • Hospitalisations caused by atrial fibrillation • Number of outpatient visits related to monitoring for atrial fibrillation • Ease of use of devices for clinicians (including insertion)
	Clinical outcomes for consideration may include: • Mortality • Morbidity (including further strokes or TIAs, other thromboembolisms and heart failure, any complications arising from preventative treatment, such as adverse effects of anticoagulation treatment, and any adverse events related to implanting or removing the devices, such as infection or inflammation)
	Patient-reported outcomes for consideration may include: • Health-related quality of life • Acceptability of the devices to patients
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Costs related to implanting and removing the devices including staff and infrastructure costs • Costs related to the implantable cardiac monitor technologies (including training and consumable costs)

	• Costs related to maintenance of devices and ongoing monitoring (such as staff time to review and interpret ECGs recorded by the devices) • Costs related to preventative treatments, such as anticoagulants or antiplatelet therapies, and appointments required for changes of medication • Costs related to treatment for conditions related to atrial fibrillation (such as stroke and heart failure) • Costs related to adverse events caused by anticoagulation therapies or implanting/removing the devices
	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes, including the risk of a further stroke, between the technologies being compared.

6 Other issues for consideration

Previous versions of devices

Any updates made to devices, in terms of hardware or analytical software, can affect diagnostic accuracy for atrial fibrillation. Studies reporting data obtained using earlier versions of the devices may therefore not give an accurate indication of the current version's effectiveness. Companies have highlighted that the algorithms used by the devices have changed over time, with the aim of reducing the number of false positive diagnoses.

Length of monitoring

Clinical experts using implantable cardiac monitors have commented that the length of time the device is implanted for and monitored varies considerably; from 3 months to several years (or until the battery runs out). Economic modelling should investigate the effect of varying the length of monitoring on cost effectiveness.

Definition of 'cryptogenic stroke'

As noted in section 3.2, the extent of testing done before a stroke is considered 'cryptogenic' can vary in practice, and may also vary between studies.

Clinically significant atrial fibrillation

There is considerable variation in practice regarding how long an episode of arrhythmia should last before a person is diagnosed as having atrial fibrillation; that is, what is considered as 'clinically significant' atrial fibrillation. Consequently, studies vary in the length of an episode that they consider as atrial fibrillation (Dilaveris and Kennedy (2017). Notably, the length of atrial fibrillation that has to happen before a device records an episode can be varied by clinicians. This variation may affect estimates of device performance between studies.

Clinical experts commented that there was uncertainty about what length of atrial fibrillation episode would, in practice, be used to determine if anticoagulants should be offered. It was acknowledged that 30 seconds or longer is an often used definition, but some clinical experts noted that in the cryptogenic stroke setting an episode shorter than this may result in anticoagulants being offered.

Reference standard for atrial fibrillation

Several studies have compared the accuracy of implantable cardiac devices to detect atrial fibrillation against external ECG monitors (Lee and Mittal, 2018). However these studies typically only compare implantable cardiac monitors with other ECG monitors for a short period of time, because the comparator ECG monitors can't be used for longer term monitoring.

There appears to be no widely used 'gold standard' for assessing the accuracy of devices to detect atrial fibrillation, particularly over longer periods of time. Implantable cardiac monitors have been suggested as the most reliable method to detect atrial fibrillation over long time periods. Alternatively, continuous ECG monitoring using cardiac implantable electronic devices (CIEDs; such as pacemakers and defibrillators) has been suggested as a gold standard, although use is restricted to people who need these interventions (Andrade et al. 2016; Podd et al. 2016).

Patient activated recordings

Clinical experts have commented that the patient activated feature of the devices may be of less use after cryptogenic stroke, because the majority of atrial fibrillations are asymptomatic. If the implantable cardiac monitor systems are available from manufacturers without the patient activator device, the impact of not providing this device on cost effectiveness should be assessed.

Location and staff involved in device implantation

Clinical experts have commented that the implantable cardiac monitors do not need to be inserted in a catheterisation lab, and typically most implantation procedures would be done in a clinical treatment room with a sink, lockable door and appropriate sterile conditions. In addition, the device is usually not implanted by cardiologists, but is done by health professionals with appropriate training; including nurses, cardiac physiologists, members of the stroke service team.

The British Heart Rhythm Society has produced draft guidance to facilitate the safe implantation and management of implantable loop recorders by nurses or physiologists (Standards for insertion, follow up and explant of implantable loop recorders [ILRs] by non-medical staff). This draft document was available for consultation at the time of writing.

Clinical experts commented that a review would be done about 4 weeks after the procedure to check the wound. Subsequent checks of the implantation site would only be done if patients reported concerns.

Frequency of assessing potential arrhythmia alerts

Clinical experts commented that to realise the benefits of the technology, remote monitoring would need to be done because requiring patients to attend frequent appointments to download data from the device would not be practicable. Ideally, any alerts sent by devices would be checked every day; however, this would not be possible for all services. Clinical experts suggested that daily checking between Monday and Friday with some variability in the level of checking over the weekend would be reasonable. Checking at longer frequencies, such as over weeks or months, would reduce the effectiveness of monitoring.

Triaging services

Companies may offer services to triage ECG recordings made by their devices (with the aim of reducing the number of false positive results NHS staff need to review). Clinical experts commented that this service may be useful to reduce the impact on NHS staff of implementing longer term monitoring. If available, the impact of these services on the cost effectiveness of devices should be considered.

7 Potential equality issues

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

Men have a higher risk of developing atrial fibrillation than women. In addition, the incidence of atrial fibrillation increases with age. It has also been reported that women with atrial fibrillation experience worse symptoms than men, and have a higher risk of stroke and death (Ko et al. 2017). The incidence of atrial fibrillation has been reported as lower for people of south Asian or Caribbean family origin (Amponsah, et al. 2013). These potential equalities issues are related to the condition and are unlikely to be impacted on by the use of the technology.

People who have had a stroke may have a cognitive or physical disability and may require their carer to use a patient activation recorder and ensure data is transmitted.

People who live in rural areas may have less access to internet or cellular networks (such as 4G) and could have problems accessing, or have less reliable access to, the remote monitoring functions of the devices. If so, there may be a need for more hospital visits for monitoring. Alternatively, clinical experts commented that people living in remote areas may benefit from use of these devices because after initial implantation and check-up the remote monitoring feature means there is limited need to visit hospital.

8 Potential implementation issues

Key considerations for adoption highlighted during discussions with expert contributors are:

Care pathways and cross-departmental working

An agreed care pathway would be needed to adopt this technology, and such pathways are not common in the NHS. Joint working between cardiology, stroke and care of the elderly services will be needed to develop such pathways. Experts commented that communication between teams was facilitated by the use of internal computerised referral forms and regular multidisciplinary team meetings where eligible patients were discussed. Arrangements also need to be put in place to check for alerts sent by the device, assess if the alert is a true or false positive and then decide on further monitoring or changes to treatment.

Clinician perceptions

Some experts highlighted that barriers to adoption relate to clinician perceptions of the incidence and clinical importance of atrial fibrillation in people with cryptogenic stroke, misconceptions about what is involved in

implanting the device and a perceived lack of awareness of the technology among stroke physicians.

Device implantation

A lack of capacity in cardiology and stroke services to implant the devices was highlighted as a barrier to wide scale adoption. Experts highlighted that the devices are being implanted by nurse specialists, cardiac physiologists and cardiologists. Experts also commented that the Reveal LINQ device is being implanted in outpatient settings, but highlighted that the preferred location would be a clinical environment where cleanliness and a local sterile field could be guaranteed.

Adoption levers

Identified adoption levers that could help uptake of these devices are a recognition of the benefits of reducing recurrent strokes, the relative ease of implanting the devices (compared to previous versions) and that data is automatically uploaded for review which would reduce hospital appointments. In addition, the devices are already routinely used in the NHS; for example for monitoring for arrhythmias in people with syncope.

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Appendix A Glossary of terms

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

Cryptogenic stroke
An ischaemic stroke with no identified probable cause after diagnostic assessment.

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

External ambulatory ECG monitor
An ECG monitor that allows people to move around relatively freely and which is attached without the need for surgical implantation, such as Holter monitors.

Implantable cardiac monitor
Devices that monitor heart rhythm over long periods of time and which are implanted under the skin of a person's chest using a small incision under local anaesthetic.

In-patient cardiac telemetry
Continuous monitoring of a person's heart, including ECG, with data transmitted from a monitor to a separate monitoring station.

Paroxysmal atrial fibrillation
Intermittent episodes of atrial fibrillation which usually last less than 2 days and stop without treatment.

Transient ischaemic attack (TIA)
A 'mini stroke' cause by a temporary disruption of blood flow to the brain (see NHS choices for more detail).

Appendix B Abbreviations

CADTH
Canadian Agency for Drugs & Technologies in Health

CIED
Cardiac implantable electronic device

ECG
Electrocardiogram

ICM
Insertable cardiac monitor

TIA
Transient ischaemic attack

Appendix C References

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