NICE National Institute for Health and Care Excellence

NICE guidance

Implantable cardiac monitors to detect atrial fibrillation after cryptogenic stroke

HealthTech guidance

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces MIB141 and DG41.

1 Recommendations

1.1 Reveal LINQ is recommended as an option to help to detect atrial fibrillation after cryptogenic stroke, including transient ischaemic attacks (TIA), only if:

- non-invasive electrocardiogram (ECG) monitoring has been done and
- a cardiac arrhythmic cause of stroke is still suspected.

1.2 Clinicians should consider if disabled people may need support from a carer to help set up the MyCareLink Patient Monitor, to ensure data from Reveal LINQ are transmitted for review.

More research is needed

1.3 There is not enough evidence to recommend the routine adoption of BioMonitor 2-AF (or its successor device BIOMONITOR III) or Confirm Rx to help to detect atrial fibrillation after cryptogenic stroke. Further research is recommended to assess the diagnostic yield (a measure of how many people with atrial fibrillation are diagnosed) of these devices for atrial fibrillation when used in people who have had a cryptogenic stroke (see section 5.1).

Why the committee made these recommendations

After a cryptogenic stroke (a stroke with no identified cause), implantable cardiac monitors can be used for long-term monitoring to identify people with atrial fibrillation if this is thought to have been a cause of the stroke. Clinical trial evidence shows that using Reveal devices increases the detection of atrial fibrillation in people who have had a cryptogenic stroke (including TIA). If people then have an oral anticoagulant medicine, it is also likely to reduce the number of further strokes or TIAs compared with not using implantable cardiac monitors. How much this reduces strokes or TIAs is not known. There are other uncertainties about the impact of using the device in the NHS, such as how many times it produces a false positive alert (that is, incorrectly identifies atrial fibrillation).

However, even after considering these uncertainties, the committee concluded that Reveal LINQ is still likely to be a cost-effective use of NHS resources, if it's used after non-invasive ECG and no other cause for the stroke has been found. There is an unmet need for people who have had a cryptogenic stroke because there is no other option for long-term monitoring for suspected atrial fibrillation. Therefore, Reveal LINQ is recommended for use in the NHS.

There's not enough evidence to show if using Confirm Rx or BioMonitor 2-AF (or any previous versions of the technologies) increases atrial fibrillation detection compared with not using implantable cardiac monitors in people who have had a cryptogenic stroke. The evidence from Reveal devices cannot be used to make decisions about Confirm Rx or BioMonitor 2-AF. This is because the devices use different algorithms to identify potential atrial fibrillation episodes and it's not certain that they will show similar performance in detecting atrial fibrillation when used in people who have had a cryptogenic stroke. Further research is needed to find out if these devices are clinically and cost effective. Therefore, they are not recommended for routine adoption in the NHS.

2 The diagnostic tests

Clinical need and practice

Atrial fibrillation

2.1 Atrial fibrillation is a type of arrhythmia that causes an irregular or abnormally fast heart rate. It is the most common arrhythmia. When someone has atrial fibrillation, the upper chambers of their heart (the atria) 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 cause a stroke. The abnormal electrical impulses in the heart muscle that cause atrial fibrillation can be persistent, permanent or intermittent. Paroxysmal atrial fibrillation involves intermittent episodes that usually last less than 2 days and stop without treatment.

Cryptogenic stroke

2.2 Cryptogenic strokes (including transient ischaemic attack [TIA]) have no identified probable cause after diagnostic assessment, and account for around 15% to 40% of ischaemic strokes. When people have treatment for stroke, they are tested for atrial fibrillation. However, if they have paroxysmal atrial fibrillation, it may not happen during the initial assessment, or during subsequent diagnostic tests. Further longer-term testing can potentially detect it, for example by using heart rhythm monitors that can be worn, or implanted. These continuously monitor the heart's electrical activity while a person goes about their daily routine.

The interventions

2.3 Implantable cardiac monitors are also known as implantable loop recorders or insertable cardiac monitors. They monitor heart rhythm for longer than heart rhythm monitors that are worn externally (for example, Holter monitors) and can

therefore be used for long-term monitoring (potentially over years, rather than days) for suspected atrial fibrillation. Implantable cardiac monitors can identify atrial fibrillation and could be particularly helpful for identifying paroxysmal atrial fibrillation in people who have had a cryptogenic stroke. If people are diagnosed with atrial fibrillation, they can then be offered anticoagulant therapy to reduce the risk of having another stroke or TIA.

2.4 The monitors are implanted under the skin of the person's chest using a small incision under local anaesthetic. They can continuously monitor heart rhythm for several years, and they record information if the device detects an arrhythmia. The devices use algorithms based on electrocardiogram (ECG) features to detect potential atrial fibrillation. The algorithm parameters can be varied to adjust the ECG features identified and flagged as potential atrial fibrillation. Recorded ECGs are remotely transmitted to clinicians, who determine if the person has had atrial fibrillation. They then decide to either continue to monitor or to treat.

BioMonitor 2-AF (Biotronik SE & Co KG)

2.5 The BioMonitor 2-AF system consists of:

- a BioMonitor 2-AF insertable cardiac monitor (dimensions 88 mm × 15 mm × 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 through a cellular phone network
- a Renamic programmer for the insertable cardiac monitor.

2.6 BioMonitor 2-AF is implanted using a Fast Insertion Tool (FIT) accessory kit. First an incision of at least 1.5 cm is made. Then the FIT 1 tool is used to form a pocket for the device under the skin, and the FIT 2 is used to implant and position the device. The battery life of the device is estimated as 4 years, assuming data are sent from the device once a day. The company says that clinicians should decide whether to remove the device once it is no longer in use.

2.7 The BioMonitor 2-AF continuously monitors heart rhythm and ECGs are automatically recorded when atrial fibrillation is detected. Atrial fibrillation is detected based on irregular RR intervals (the interval between heartbeats), 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 atrial fibrillation sensitivity (described in the product manual). BioMonitor 2-AF can also detect other cardiac arrhythmias such as high ventricular rate, asystole, bradycardia, and sudden ventricular rate drop.

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

BIOMONITOR III (Biotronik SE & Co KG)

2.9 During the assessment phase for this guidance, the manufacturer of BioMonitor 2-AF launched BIOMONITOR III, a new implantable cardiac monitor device, which supersedes the existing version. The new device uses the same algorithm to detect atrial fibrillation as the BioMonitor 2-AF. The predicted battery life and cost are also the same. The device is smaller and lighter than the BioMonitor 2-AF and can be used with a patient app.

Confirm Rx Insertable Cardiac Monitor (Abbott Medical UK)

2.10 The Confirm Rx system consists of:

- a Confirm Rx Insertable Cardiac Monitor (dimensions 49.0 mm × 9.4 mm × 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 and a magnet (to interrogate and program the insertable cardiac monitor).

2.11 Confirm Rx is implanted using proprietary insertion and incision tools. The device is implanted under local anaesthetic through a small cut made using the incision tool. The insertion tool is then used to implant the device under the skin. 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 a month.

2.12 Heart rhythm is continuously monitored by Confirm Rx, and ECGs are automatically recorded when atrial fibrillation is detected. Confirm Rx assesses 3 aspects of ECG trace to identify potential atrial fibrillation: regularity of rhythm pattern, variance of RR 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. Confirm Rx also detects bradyarrhythmias, tachyarrhythmias and pauses.

2.13 Recordings made by Confirm Rx 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 says that the app automatically reads data from the implanted device and sends the data to a database using a cellular or Wi-Fi network during the night. It recommends that a smartphone or tablet with the app installed is kept by the person's bedside at night to allow data transmission. Confirm Rx encrypts its wireless communications and only transmits 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.

Reveal LINQ Insertable Cardiac Monitoring System (Medtronic Limited)

2.14 The Reveal LINQ Insertable Cardiac Monitoring System consists of:

- a Reveal LINQ Insertable Cardiac Monitor device (dimensions 45 mm × 7 mm × 4 mm)
- an optional Reveal Patient Assistant handheld device, which is held over the implanted Reveal LINQ monitor 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
- a MyCareLink Programmer, which is a portable computer system used by a healthcare professional to program the devices.

2.15 Reveal LINQ is implanted using proprietary incision and insertion 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 device and to implant it under the skin.

2.16 Reveal LINQ continuously monitors heart rhythm and identifies potential atrial fibrillation episodes from the person's ECG trace using an algorithm. An ECG trace is assessed in 2-minute windows which are considered 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). Total atrial fibrillation is also calculated, consisting of all 2-minute windows in which atrial fibrillation was present for longer than the threshold value. Reveal LINQ can also detect tachyarrhythmia, bradyarrhythmia or pause episodes. The device contains an accelerometer to allow changes in patient activity over time to be monitored.

2.17 Rhythm abnormalities recorded by Reveal LINQ 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. They 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 also sends alerts if the battery is low. If the device is unable to communicate with CareLink it registers as disconnected.

2.18 The company also offers a triage and monitoring service (FOCUSON) to review ECG recordings made by Reveal LINQ. 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 says that red events are notified on the same working day from when the transmission reaches the CareLink Network service. Amber events are notified by email by the next working day, and green events are aggregated and notified in a weekly email.

The comparator

No further testing after outpatient external ambulatory ECG monitoring

2.19 The clinical experts said that if no atrial fibrillation is detected by an external ambulatory ECG monitor, the person is unlikely to have any further monitoring for atrial fibrillation, unless an implantable cardiac monitor is available. Undetected atrial fibrillation may be later identified if it causes symptoms (for example, palpitations), incidentally when someone's pulse is checked (for example, when blood pressure is taken), or on investigation after a recurrent stroke or TIA. Therefore, the comparator is no further monitoring.

3 Evidence

The diagnostics advisory committee considered evidence from several sources on implantable cardiac monitors (BioMonitor 2-AF, Confirm Rx and Reveal LINQ) to assess for suspected paroxysmal atrial fibrillation in people who have had a cryptogenic stroke. Full details of all the evidence are in the committee papers.

Clinical effectiveness

3.1 The external assessment group (EAG) did a systematic review to identify evidence on the clinical effectiveness and diagnostic accuracy of implantable cardiac monitors to detect suspected atrial fibrillation after cryptogenic stroke. The devices reviewed were:

- BioMonitor 2-AF
- Confirm Rx
- Reveal LINQ.

3.2 Studies were included if they assessed the devices in people who had had a cryptogenic stroke or cryptogenic transient ischaemic attack (TIA), and paroxysmal atrial fibrillation was suspected. Because of the small number of studies identified, the requirement for at least 24 hours of outpatient external ambulatory electrocardiogram (ECG) monitoring without atrial fibrillation detection before the devices were implanted (as per current practice) was not applied. Also, data from earlier versions of the devices were considered.

3.3 Because only 1 study (the CRYSTAL-AF randomised controlled trial) met the EAG's initial eligibility criteria, the EAG relaxed the study inclusion criteria to consider single-arm observational studies. The EAG did not change the population inclusion criteria because it considered that data from non-cryptogenic stroke populations would not represent the device's performance in people with cryptogenic stroke or TIA. This is because non-cryptogenic stroke populations have different incidence rates of atrial fibrillation. However, the EAG provided a summary of studies highlighted by the device manufacturers that

were not done in a cryptogenic stroke population. The EAG further highlighted that the patient population, duration of monitoring and the type of atrial fibrillation would affect estimates of device performance.

Comparative studies

3.4 One study (reported in 6 publications) compared the effectiveness of using 1 of the devices with conventional follow up: the CRYSTAL-AF study. This was an open-label, parallel group randomised controlled trial that used Reveal XT (an earlier version of Reveal LINQ). The XT model is larger. The EAG said that evidence from diagnostic accuracy studies (see sections 3.48 and 3.49) suggests that Reveal LINQ has better specificity and sensitivity than the XT, is easier to implant and causes fewer complications.

3.5 People aged 40 or older who had a recent episode of cryptogenic symptomatic TIA or recent episode of cryptogenic ischaemic stroke had Reveal XT (n=221) or conventional follow-up care (n=220). People with TIA were only enrolled if they had a visible lesion on MRI or CT that fitted the symptoms of the TIA, and at least 1 of the following symptoms: speech problems, limb weakness or hemianopsia. Follow up in the control group was ECG monitoring at the discretion of the site investigator. The study was done in 55 centres across 14 countries in Europe (none in the UK), Canada and the US. The EAG said that there were similar numbers of withdrawals between the 2 arms (except for crossovers, see section 3.12). Data were collected for up to 36 months of follow up, but relatively few people reached this point (24 in each arm). Mean duration of follow up was 20.3 months for Reveal XT and 19.2 months for conventional follow-up care.

3.6 The EAG noted that, although there were no significant differences in baseline characteristics between study arms, there were differences in the numbers of people with patent foramen ovale and history of prior stroke. However, these were small and unlikely to be because of systematic issues with randomisation. The clinical experts said that the population was slightly younger than people expected to be eligible for an implantable cardiac monitor in the UK. Also, a higher proportion of TIA (rather than stroke) would be expected in clinical practice (closer to 20%, instead of about 9% seen in each of the study arms). All patients would be expected to be taking an antiplatelet agent (about 96% in each

arm were using an antiplatelet agent at baseline).

3.7 The EAG's clinical experts said that the tests used in the trial to define a stroke as cryptogenic were broadly the same as what would be done in the NHS. Pre-enrolment screening for atrial fibrillation was Holter monitoring for 71.2% of people (median duration of 23 hours, interquartile range 21 hours to 24 hours), and the remaining people had inpatient telemetry monitoring only. The EAG said that this meant almost 30% of people did not have any outpatient ECG monitoring (as specified in the scope) and that not all patients who did have outpatient ECG monitoring had it for at least 24 hours.

3.8 This trial was sponsored by Medtronic, manufacturers of the device used in the study. The EAG said that the authors of publications for this study reported employment, grants and personal fees from this company. The EAG considered that this was the most robust clinical evidence for Reveal LINQ, even though it relates to an earlier version of the device.

Non-comparative studies

3.9 Comparative data were not identified for BioMonitor 2-AF, Confirm Rx or the current Reveal LINQ version. Therefore, the EAG reviewed single-arm observational studies in cryptogenic stroke (including TIA) populations to identify available data on these devices. Biotronik submitted a technical validation report comparing the accuracy of BioMonitor 2-AF with Reveal LINQ during consultation (see section 3.21).

3.10 Twenty six observational studies (reported in 60 publications) were found. All but 1 study assessed either Reveal LINQ or Reveal XT. In 1 study (Israel et al. 2017), 13% of people used the BioMonitor (an earlier version of BioMonitor 2-AF), but results were not reported by device. The EAG said that these studies therefore do not provide any data for BioMonitor 2-AF or Confirm Rx, but that they did supplement data from the CRYSTAL-AF study.

3.11 Sample sizes in the studies ranged from 14 to 1,247. Only 1 study (Cotter et al. 2013) was done in the UK. Most studies (17) were prospective single-arm observational studies. There were 5 retrospective studies (Asaithambi et al. 2018,

Chalfoun et al. 2016, Heckle et al. 2018, Li et al. 2018 and Salahuddin et al. 2015). One did not report a clear methodology (Cotter et al. 2013). Ritter et al. (2013) did a within-patient comparison of Reveal XT and 7-day Holter ECG monitoring. Choe et al. (2015) used the CRYSTAL-AF dataset to predict how many cases of atrial fibrillation detected by Reveal XT would have been detected by shorter length intermittent ECG monitoring strategies using simulations. Ziegler et al. (2017) presented data from a registry of people who had Reveal LINQ and used simulations to predict how many people with atrial fibrillation detected by the device would have been identified by shorter (non-continuous) ECG monitoring.

Quality assessment of studies

Randomised controlled trials

3.12 The CRYSTAL-AF study was assessed using the Cochrane risk of bias 2.0 tool. The full quality assessment is in the diagnostics assessment report starting from page 28. There was some concern about risk of bias because the trial was open-label and not all people had the randomised intervention required by the study protocol (5.4% of people assigned to Reveal XT got conventional follow up; 2.7% of people assigned conventional follow up got Reveal XT). Also, device implantation was delayed for 11.5% of people who had Reveal XT (median length of delay was 6 days, interquartile range 1 day to 32 days). The EAG noted that results were analysed by intention-to-treat population, which included patients who did not have Reveal XT, received it late, or crossed over to conventional follow up. This means the estimated benefit of having the device may be underestimated. Delays in implanting Reveal XT were mostly short and unlikely to affect outcomes. The EAG said that the lack of blinding was unlikely to affect relative atrial fibrillation detection rates between groups. It noted that only a small number of people were followed up after 12 months, so the 24-month and 36-month results are likely to be less reliable than results from 6 months and 12 months, but the direction of this bias is unclear.

Observational studies

3.13 The EAG said that it was not able to formally quality assess the 26 additional

studies identified that were not randomised controlled trials. However, it considered them all to be at high risk of bias because of their single-arm designs. Because of heterogeneity between the studies, the EAG did not consider it appropriate to pool results from these studies. This included the model of device used, detection settings, patient characteristics, rigour of stroke assessment, severity of index stroke, definition and adjudication of atrial fibrillation, and length of follow up.

Evidence on ability to detect atrial fibrillation

Diagnostic yield (atrial fibrillation detection rate)

3.14 Atrial fibrillation detection rate at 6 months was the CRYSTAL-AF study's primary outcome (episodes had to last more than 30 seconds). At 6 months, 19 people were diagnosed with atrial fibrillation in the Reveal XT arm and 3 people in the conventional follow-up arm. More atrial fibrillation was detected with Reveal XT at all time points (see table 1). Reveal XT increased atrial fibrillation detection across all pre-specified subgroups (age, sex, race or ethnic group, index event, presence or absence of patent foramen ovale, and CHADS2 score), with no significant interactions. Most people who had atrial fibrillation detected by Reveal XT were asymptomatic (34 out of the 42 detected by 36 months). Estimated detection rates are higher in the 36-month Kaplan–Meier analysis because of the non-informative censoring (that is, people who dropped out for reasons unrelated to the study) of patients lost to follow up (atrial fibrillation detection rate estimated as 30% with Reveal XT and 3% with conventional follow up).

Table 1 Atrial fibrillation detection in CRYSTAL-AF

Months	Reveal XT: cumulative number of patients with AF detected	Conventional follow up: cumulative number of patients with AF detected
1	8 (3.6)	1 (0.5)
6	19 (8.6)	3 (1.4)
12	29 (13.1)	4 (1.8)
24	38 (17.2)	5 (2.3)
36	42 (19.0)	5 (2.3)

Abbreviations: AF, atrial fibrillation; ITT, intention to treat.

3.15 All 26 observational studies reported atrial fibrillation detection rate. Detection rates varied widely, ranging from 6.7% to 40.9% (length of monitoring varied between studies). Several studies reported atrial fibrillation detection rates over multiple time points. The EAG said that the studies generally show that a minority of patients are diagnosed in the first month (about 10% of those detected by 1 year). Around 70% to 80% (of the total number of people with atrial fibrillation detected in a study) are diagnosed by 6 months, and a small number after a year of monitoring. All or most of the detected atrial fibrillation in the observational studies (when stated) were asymptomatic, as in CRYSTAL-AF.

3.16 Two observational studies estimated how many atrial fibrillation episodes would have been detected by intermittent ECG monitoring. These used datasets generated by Reveal XT (in CRYSTAL-AF; Choe et al. 2015) or Reveal LINQ (from a large registry of patients with the device [n=1,247]; Ziegler et al. 2017). The studies assumed Reveal devices had 100% sensitivity. The studies estimated that even the best intermittent ECG monitoring strategies would detect less than a third of atrial fibrillation detected by Reveal devices.

Diagnostic yield: other (non-atrial fibrillation) cardiac pathologies

3.17 CRYSTAL-AF did not report any results for the detection of other cardiac pathologies.

3.18 Five non-comparative observational studies reported incidental detection of other arrhythmias. The EAG said that the proportion of patients detected with other arrhythmias is about 10% of the total number of people in a study. This mainly consists of bigeminy, pause and bradycardia. Two studies reported the breakdown of arrhythmias and gave rates of 1% (atrial flutter, cardiac arrest, sick sinus node, bigeminy, ventricular tachycardia) to 7% to 8% (atrioventricular block and ventricular extra systole). Full details are on page 51 of the diagnostics assessment report. The studies did not say if the other detected arrhythmias were treated, or if outcomes were improved because these arrhythmias were identified. Also, because these were non-comparative studies, the extent of any increase in detection compared with conventional follow up could not be

determined.

Diagnostic accuracy

3.19 No data relevant to this outcome were reported in CRYSTAL-AF.

3.20 Two non-comparative observational studies reported the proportion of episodes detected by the devices that were not verified as atrial fibrillation by a clinician. Li et al. (2018) reported 79.7% for Reveal LINQ and Israel et al. (2017) reported that over 90% of detected episodes were not confirmed by review (Reveal XT and BioMonitor). The EAG noted that Medtronic had said that the number of false positive alerts varies depending on the device model used, and the configuration for detection (including episode duration) that is programmed by the operator. Data on device accuracy (for all devices) in non-cryptogenic stroke populations from studies identified by manufacturers are presented later (see section 3.41).

3.21 During the first consultation on this guidance, the manufacturer of the BioMonitor 2-AF submitted an unpublished technical validation report comparing the accuracy of the Reveal LINQ and BioMonitor devices. This was done by replaying ECG data recorded by a Holter monitor in a previous trial into the sensing electrodes of the Reveal LINQ and BioMonitor devices. The report stated that because the atrial fibrillation detection algorithm of the BioMonitor 2-AF and BIOMONITOR III are the same, the results are applicable to both devices. People enrolled in the original trial had documented atrial fibrillation episodes or symptoms attributable to atrial fibrillation, were scheduled for catheter ablation or had had it, but were still experiencing atrial fibrillation-related symptoms. Of the participants, 70% had a history of paroxysmal atrial fibrillation. The rest had a history of persistent atrial fibrillation. However, the EAG highlighted that the report also stated that people with long-standing persistent or permanent atrial fibrillation were excluded. The EAG pointed out that this was contradictory and meant that the characteristics of the population in the study were not clear. At consultation on the draft guidance, BioMonitor's manufacturer commented that all ECG data fed into the devices as part of the study were for less than 48 hours. It said that therefore they represented paroxysmal atrial fibrillation episodes only. In the study, atrial fibrillation episodes detected, or not, by clinician assessment of the Holter monitor ECG trace was used to classify true and false positives and

false negative atrial fibrillation episodes detected by the Reveal LINQ and BioMonitor. Atrial fibrillation episode sensitivity for BioMonitor and Reveal LINQ were 78.0% and 79.0% respectively. Patient-averaged positive predictive values were 98.7% for BioMonitor and 99.7% for Reveal LINQ.

Evidence on clinical outcomes

Time to diagnosis of atrial fibrillation

3.22 The EAG said that atrial fibrillation was detected in only 5 people in the conventional follow-up arm of CRYSTAL-AF (and none after 24 months; see table 1). This means it is difficult to make any conclusions about the effect of using Reveal XT from the median time to atrial fibrillation detection data. Atrial fibrillation was detected in more people with longer follow up, and therefore the median time to detection also increased. There was a greater increase in the median time to atrial fibrillation detection with Reveal XT compared with conventional follow up across all time points. The EAG said that the low detection rate of atrial fibrillation in the conventional follow-up arm was the likely cause of this difference.

3.23 There were 18 observational studies that reported time from device insertion to atrial fibrillation detection. Average follow up ranged from 7 months to 20 months, and median time to first atrial fibrillation detection had a wide range, from 21 days to 217 days. When reported, interquartile ranges also showed high variability within studies.

Atrial fibrillation-related hospitalisation

3.24 No data were reported in CRYSTAL-AF or the observational studies.

Incidence of outpatient monitoring

3.25 No data were reported in CRYSTAL-AF or the observational studies.

Uptake of anticoagulants

3.26 Most people diagnosed with atrial fibrillation using Reveal XT started having an oral anticoagulant (more than 90%) in the CRYSTAL-AF study. The reasons people did not start on anticoagulants after being diagnosed with atrial fibrillation were not clear. The EAG noted that some people who were not diagnosed with atrial fibrillation in the trial were also started on anticoagulants. Reasons for this were not provided.

3.27 Seven observational studies (Asaithambi et al. 2018, Carrazco et al. 2018, Christensen et al. 2014, Etgen et al. 2013, Li et al. 2018, Merce et al. 2013 and Seow et al. 2018) reported that uptake of anticoagulants for people with atrial fibrillation detected by Reveal XT or LINQ was high: between 83.3% and 100%.

Time to start of anticoagulants

3.28 No data were reported in CRYSTAL-AF or the observational studies.

Incidences of device failure and removal

3.29 No incidence of Reveal XT failure was reported in CRYSTAL-AF. The device had to be removed early because of infection or pocket erosion from 5 out of 208 (2.4%) people by 36 months.

3.30 Three non-comparative observational studies reported how many devices were removed during follow up. In Christensen et al. (2014), Reveal XT was removed prematurely in 5.7% people because of skin reactions and discomfort. A further 3.4% of people chose to have the device removed after more than 1 year without atrial fibrillation being detected. In Asaithambi et al. (2018), 2.6% of people chose to have Reveal LINQ removed, and for 0.9% of people the devices migrated or fell out. In Ritter et al. (2013), study participants were offered removal of Reveal XT once atrial fibrillation was detected. But they did not report how many of the 30% of removals were because of this, or for other reasons such as discomfort.

Ease of use of devices for clinicians

3.31 No data were reported in CRYSTAL-AF or the observational studies.

Mortality

3.32 No data were reported in CRYSTAL-AF or the observational studies.

Further strokes or TIAs

3.33 In CRYSTAL-AF, a non-significant trend of fewer recurrent events (stroke or TIA) in the Reveal XT arm was reported (see table 2). The study was not powered for this outcome. It is not clear if the recurrent stroke or TIA events occurred in people who were diagnosed with atrial fibrillation or not.

Table 2 Cumulative incidence of further strokes or TIAs in CRYSTAL-AF

Month	Reveal XT (n=221): people having another stroke or TIA(n [%])	Conventional follow up (n=220): people having another stroke or TIA(n [%])	Hazard ratio(95% CI)
6	11 (5.0)	18 (8.2)	Not reported
12	15 (6.8)	19 (8.6)	0.63 (0.22 to 1.80)
36	20 (9.1)	24 (10.9)	0.77 (0.30 to 1.97)

Abbreviations: CI, confidence interval; TIA, transient ischaemic attack.

3.34 Of the studies, 6 non-comparative observational studies reported variable incidences of secondary stroke or TIA in people with an implantable cardiac monitor: from 0% to 14.6%.

Other thromboembolisms

3.35 No data were reported in CRYSTAL-AF or the observational studies.

Device-related adverse events

3.36 The EAG said that the incidence of device-related adverse effects (such as pain and infection) was relatively low for people who had Reveal XT implanted in CRYSTAL-AF. However, adverse events did lead to the device being removed in 2.4% of patients. The proportion of people with serious adverse events was slightly higher for Reveal XT (30.8%) than conventional follow up (27.9%). More people had non-serious adverse events in the Reveal XT arm (18.6%) than in the conventional follow-up arm (4.1%). No details of these events were reported, and the EAG said that it was unclear why there was a difference between the study arms. Reveal XT is larger than Reveal LINQ.

3.37 For 5 non-comparative observational studies, there were no complications from the procedure or insertion site reported at follow up (length of follow up was not specified). These were Merce et al. (2013), Reinke et al. (2018) and Ritter et al. (2013) for Reveal XT; Poli et al. (2016) for Reveal LINQ and XT; and Israel et al. (2017) for Reveal XT and BioMonitor.

Anticoagulant-related adverse events

3.38 No data were reported in CRYSTAL-AF or the observational studies.

Evidence on patient-reported outcomes

Health-related quality of life

3.39 Health-related quality-of-life data were collected in CRYSTAL-AF using the EuroQol 5-Dimensions (EQ-5D) tool. Unpublished data were provided by the company as academic in confidence so they cannot be reported here.

Acceptability of the devices to patients

3.40 No data were reported in CRYSTAL-AF or the observational studies.

Evidence from non-cryptogenic stroke populations

3.41 The EAG provided a narrative summary of studies in non-cryptogenic stroke populations identified by manufacturers of the devices. These studies were not done in populations who had exclusively had a cryptogenic stroke or TIA although some were in a 'mixed population' (less than 50% of the study population had a cryptogenic stroke or TIA and subgroup analysis was not provided). All studies were either single-arm observational studies or assessed the diagnostic accuracy of the devices compared with Holter monitoring. The EAG highlighted that the performance of the devices depends on the patient population, atrial fibrillation incidence rate, and the type of atrial fibrillation. Therefore, the results from these studies do not necessarily represent the devices' performance in people with cryptogenic stroke.

3.42 The EAG did not do a full systematic literature search to validate the inclusion of the studies. This was because of time constraints and concerns about the applicability of results to the cryptogenic stroke population. The EAG said that the data may have study selection bias as well as clinical heterogeneity caused by the variation in the patient populations of each of the studies.

Abbott Medical

3.43 The company said the Detect AF study (Nölker et al. 2016) was potentially relevant for assessing Confirm Rx. The EAG noted that the device used in Detect AF was the Confirm model DM2102. This is an older and larger model of Confirm Rx. The EAG was unsure how the software in this earlier version compared with the current Confirm Rx.

3.44 Detect AF was a prospective observational study. It assessed the diagnostic accuracy of the Confirm system in detecting atrial fibrillation compared with Holter monitoring (reference standard) with simultaneous use of the devices. In

per-patient analysis, sensitivity of the Confirm system was 100%, positive predictive value was 64.0%, specificity was 85.7% and negative predictive value was 100%. Most of the episodes of atrial fibrillation detected by the Confirm system but not confirmed by the Holter monitor were because of irregular sinus rhythms. No adverse events associated with the device were reported.

Biotronik SE & Co

3.45 The EAG discussed 5 single-arm prospective observational studies (in 8 publications) provided by Biotronik. Three of these studies (which included data on diagnostic accuracy) were unpublished and were provided as academic or commercial in confidence so details cannot be reported here.

3.46 Reinsch et al. (2018) reported that BioMonitor 2 was successfully implanted in a catheterisation laboratory with a median time from first cut to final suture of 8 minutes (interquartile range 7 minutes to 10 minutes). Ooi et al. (2017) reported that all insertions of the device were made on first attempt in a catheterisation laboratory with a median time of 9 minutes (interquartile range 5 minutes to 14 minutes). Ooi et al. reported that 1 pocket infection occurred when using the device. Reinsch et al. reported that no devices implanted in the study migrated, and 1 person needed the device removing because of device-related pocket infection. Another patient complained of slight discomfort.

3.47 Reinsch et al. reported results from patient satisfaction surveys. Of the respondents, 7% reported moderate to severe pain and 20% reported mild pain within 24 hours of device insertion. One person reported a moderate impairment in daily life. Of the respondents, 63% said that the cosmetic result was 'very satisfying' and 30% said 'satisfying'.

Medtronic Limited

3.48 The EAG discussed 5 studies highlighted by the company. Two compared the diagnostic accuracy of Reveal devices (per-patient analysis) with Holter monitoring for detecting atrial fibrillation (Hindricks et al. 2010 and Sanders et al. 2016). In Hindricks et al. (2010), Reveal XT was used (the XPECT trial). Another

study (Puerefellner et al. 2014) used data from this trial and recalculated accuracy estimates when changes were made to the atrial fibrillation detection algorithm. This incorporated data on P waves when classifying patients, and this algorithm change was applied in Reveal LINQ. Sanders et al. (2016) used Reveal LINQ. A subsequent study (Puerefellner et al. 2018) was published using this dataset (and the XPECT data) to calculate the accuracy of a modified algorithm for detecting atrial fibrillation (using the TruRhythm algorithm that has now been incorporated in the device). Data on the diagnostic accuracy reported in these studies are shown in table 3.

Table 3 Diagnostic accuracy estimates for Reveal XT and Reveal LINQ

Measure	XPECT study	XPECT dataset	LINQ usability study	LINQ usability dataset
Sensitivity (%)	96.1	96.1	97.4	100
Specificity (%)	85.4	90.0	97.0	99.0
Positive predictive value (%)	79.3	84.9	92.5	97.4
Negative predictive value (%)	97.4	97.5	99.0	100
Accuracy (%)	89.3	92.2	97.1	99.3

Positive predictive value, negative predictive value and accuracy for the XPECT dataset calculated by the EAG using data in Puerefellner et al. (2014).

3.49 The EAG said that the studies showed improved detection of atrial fibrillation by Reveal LINQ compared with Reveal XT. Changes made to the algorithm also improved detection. But the results should be interpreted with caution because these studies were not done in people who had had a cryptogenic stroke. However, the EAG said that these data suggest that Reveal LINQ is likely to be as effective as Reveal XT, if not better, at detecting atrial fibrillation. Therefore, the clinical data from CRYSTAL-AF (which uses the Reveal XT) could be a conservative estimate of the clinical effectiveness of the device.

3.50 Mittal et al. (2015) reported adverse event data from 2 observational studies that used Reveal LINQ. An infection occurred in 1.5% of people, an adverse event in 4.0% and a serious adverse event in 1.1%.

Ongoing studies

3.51 The EAG identified 8 potentially relevant ongoing studies from searches of trial registries and electronic databases, in addition to company submissions. There are 3 ongoing randomised controlled trials assessing Reveal LINQ. Of these, 1 is in people with cryptogenic stroke. This is a Canadian randomised trial comparing the clinical and cost effectiveness of Reveal LINQ with external loop recording in 300 people who have had cryptogenic stroke. It was estimated to complete in December 2019 (PERDIEM; NCT02428140). One ongoing study identified is assessing Confirm Rx: the SMART registry (NCT03505801). This is a post-approval study planned for at least 2,000 patients with Confirm Rx across multiple indications, with a planned subgroup analysis for cryptogenic stroke. Completion was expected during 2019. At consultation on the draft guidance, a stakeholder submitted a recent conference abstract (Yokokawa et al. 2019). The abstract gave only limited methodological detail. In this study, people were randomised to have either Confirm Rx or Reveal LINQ implanted (n=80; 52 had cryptogenic stroke but no subgroup analysis was provided). The abstract reported that 28 of 51 atrial fibrillation events (55%) were detected accurately by Reveal LINQ and 131 of 301 atrial fibrillation events (44%) were accurately detected by Confirm Rx (p=0.13).

Cost effectiveness

Systematic review of cost-effectiveness evidence

3.52 The EAG did a systematic review to identify any published economic evaluations of implantable cardiac monitors to detect atrial fibrillation in people with cryptogenic stroke. There were 5 studies that met the EAG inclusion criteria. Of these, 2 assessed the cost effectiveness of Reveal XT compared with standard care monitoring (DeAngelis et al. 2016 and Diamantopoulos et al. 2016). Another study assessed BioMonitor 2-AF (Maervoet et al. 2017; further details provided as unpublished report and model by the device manufacturer as commercial in confidence), and 2 studies did not indicate which implantable cardiac monitor was being assessed (Quiroz et al. 2017 and Thijs et al. 2018). Only 1 study (Diamantopoulos et al. 2016) was based on an NHS payer perspective and was discussed in the diagnostics assessment report.

Diamantopoulos et al. (2016)

3.53 This study was a cost–utility analysis. It compared use of Reveal XT in people who have had a cryptogenic stroke or TIA with conventional follow up, as assessed in the CRYSTAL-AF study. A Markov model structure was used with 3 main health states for atrial fibrillation status: free, detected and undetected. The deterministic base case produced an incremental cost-effectiveness ratio (ICER) of £17,175 per quality-adjusted life year (QALY) gained for Reveal XT compared with standard care (£2,587 higher costs, 0.151 additional QALYs). The probabilistic ICER was lower.

3.54 The EAG considered that results from this model were potentially unreliable because there was uncertainty about how parameters in the model had been estimated. The estimation of treatment effects by indirect comparison, atrial fibrillation incidence and detection rates used in the analysis were particularly unclear. The study authors used indirect comparisons to estimate hazard ratios for the benefit of anticoagulants on the occurrence of ischaemic stroke, bleeding events, intracranial haemorrhages, extracranial haemorrhages and mortality. The EAG tried to verify these figures but was unable to because there were insufficient details in the publication about how the indirect comparisons were done and how publications that informed the analysis were identified. The EAG also considered that estimation of some of the hazard ratios could be flawed. For example, the authors estimated a hazard ratio to adjust mortality in the model, but the source data used are based on standardised mortality ratios. Furthermore, people without atrial fibrillation detected were assumed to be offered aspirin, but the EAG's clinical experts said that clopidogrel would be used as an antiplatelet treatment.

Modelling approach

3.55 The EAG developed a de novo economic model to assess the cost effectiveness of using implantable cardiac monitors (BioMonitor 2-AF, Confirm Rx or Reveal LINQ) to assess for suspected paroxysmal atrial fibrillation in people who have had a cryptogenic stroke (including TIA).

Model structure

3.56 The EAG developed a 2-stage economic model. The first stage (an Excel model developed by the EAG) modelled people having either monitoring for suspected paroxysmal atrial fibrillation after a cryptogenic stroke (including TIA) with the implantable cardiac monitors or conventional follow up. Everyone starts the model having antiplatelet therapy (clopidogrel) for stroke prevention. At every 3-month cycle in the model, a proportion of people have atrial fibrillation. For people with an implantable cardiac monitor, all cases of atrial fibrillation are detected, and treatment is switched to anticoagulants (atrial fibrillation detected). For people with conventional follow up, a proportion of people with atrial fibrillation are detected (and switch to anticoagulants) but most are not (atrial fibrillation undetected) and remain on antiplatelet therapy.

3.57 For the subsequent long-term anticoagulation model, the EAG adapted a published economic model to model the long-term effect of people with detected atrial fibrillation (anticoagulant treatment) or undetected atrial fibrillation (remain on antiplatelet therapy with clopidogrel). This is the 'adapted direct oral anticoagulant (DOAC) model' (Sterne et al. 2017 and Welton et al. 2017). People enter the model after having atrial fibrillation in an 'atrial fibrillation well' state. After this, clinical events can occur. These are TIA, ischaemic stroke, intracranial haemorrhage, myocardial infarction, clinically relevant (extracranial) bleed or systemic embolism (multiple events can happen to one person over the course of the model). The risks of these events happening in the model were based on a population with a history of ischaemic stroke and paroxysmal atrial fibrillation. The model structure is the same for people with detected and undetected atrial fibrillation. However, the probability of the events happening depends on the treatment used (anticoagulants or antiplatelet therapy).

Model population

3.58 The population in the model was people who had had a cryptogenic stroke (including TIA), when there was suspected paroxysmal atrial fibrillation. These people had had at least 24 hours of outpatient external ambulatory ECG monitoring that had not detected atrial fibrillation. Characteristics were based on the population in the CRYSTAL-AF study, with a mean age of 61 years and about 65% people assumed to be men.

Comparator

3.59 In the model, the EAG used data from the control arm of CRYSTAL-AF for the comparator. People in the study were assessed at scheduled visits (every 3 months) and unscheduled visits if they were having symptoms of atrial fibrillation. Tests included ECGs and Holter monitoring (for 24 hours, 48 hours or 7 days).

Model inputs

3.60 Diagnostic yield data from CRYSTAL-AF were used for the number of people with atrial fibrillation detected by an implantable cardiac monitor or by conventional follow up. No equivalent data were identified for BioMonitor 2-AF or Confirm Rx (or the current Reveal LINQ version). Therefore, the EAG assumed equal efficacy for all devices. A published model (Sterne et al. 2017 and Welton et al. 2017; the 'adapted DOAC' model) was used to model longer-term clinical outcomes for people with atrial fibrillation that is detected (treatment with an anticoagulant) or not detected (treatment with an antiplatelet drug). Outcomes included were ischaemic stroke, myocardial infarction, TIA, systemic embolism, clinically relevant extracranial bleed, intracranial haemorrhage and all-cause mortality.

Costs

3.61 All costs in the model were valued in 2018, in UK pounds sterling. Device costs are shown in table 4.

Table 4 Cost of the implantable cardiac monitors

Device	Unit cost (£ excluding VAT)
BioMonitor 2-AF	1,030
Confirm Rx	1,600
Reveal LINQ	1,800

3.62 Medtronic also offers an optional triage service for use with Reveal LINQ

(FOCUSON) that was included in scenario analyses. There were 2 cost options included: £187 per patient per year or £374 per patient per device. The EAG did not include the cost of reviewing alerts generated by the devices in the base case.

Implantation and device removal costs

3.63 In the base case, the EAG estimated the cost of implanting the devices as £24.17. This was based on advice from the clinical experts about the staff involved (cardiologist and nurse) and time taken for the procedure (10 minutes). The cost of removing the devices was assumed to be £238, based on NHS reference costs schedule 2017/18 (EY13Z – removal of electrocardiography loop recorder, outpatient setting, treatment function code 320). Costs associated with adverse events from implanting the devices were not included in the EAG's analysis.

Comparator arm and follow-up costs

3.64 The EAG based costs for the comparator on the conventional follow-up arm of CRYSTAL-AF. Costs per cycle in the model were calculated based on the proportion of people having testing every 3 months or no testing in the study. The unit cost of monitoring was £141, based on the NHS reference costs schedule 2017/18 (HRG code EY51Z – ECG monitoring or stress testing [outpatient procedures, service code 320]). The EAG assumed that people with an implantable cardiac monitor will have 1 face-to-face follow up a month after the procedure and then will be remotely monitored. For people in the conventional follow-up arm who do not have atrial fibrillation detected, follow-up appointments are assumed to happen after 1, 3, 6 and 12 months, based on clinical expert advice. If atrial fibrillation is detected, a follow-up appointment is assumed to discuss treatment. The cost of an initial follow up (£163.36) and subsequent follow up (£128.05) were taken from NHS reference costs.

Treatment and clinical event costs

3.65 The costs of DOACs and clopidogrel were taken from the BNF September 2018 to

March 2019 edition. Costs of acute and chronic health events were taken from NHS reference costs or Luengo-Fernandez et al. (2013).

Health-related quality of life and QALY decrements

3.66 The EAG did a systematic review to identify relevant utility values to update the adapted DOAC model. There were 2 papers (Berg et al. 2010 and Luengo-Fernandez et al. 2013) with relevant utility values for ischaemic stroke, intracranial haemorrhage, myocardial infarction and TIA events. These were included in the model and were used to update the adapted DOAC model. The utility value used for people with atrial fibrillation in a 'well' health state (that is, when no clinical events such as stroke have occurred) was 0.78 (Berg et al. 2010). The duration of disutility for an acute event was assumed to be 3 months (1 model cycle).

Base-case assumptions

3.67 The following assumptions (in addition to those described in previous sections) were applied in the base-case analysis:

- The prevalence of atrial fibrillation in this population was equal to the detection rate in CRYSTAL-AF.
- Reveal LINQ was as good as Reveal XT (the device used in CRYSTAL-AF) for detecting atrial fibrillation.
- BioMonitor 2-AF and Confirm Rx were equivalent to Reveal XT or Reveal LINQ for detecting atrial fibrillation.
- The detection of atrial fibrillation was capped at 3 years for BioMonitor 2-AF even though the manufacturer said the battery life is expected to be 4 years. This was because atrial fibrillation detection data were only available for 3 years of follow up.
- Atrial fibrillation detection was capped at 2 years for Confirm Rx because this is the expected battery life of the device, and the clinical experts advised that devices are unlikely to be replaced once a battery expires.

- After 3 years, detection rates of atrial fibrillation are the same in both the implantable cardiac monitors and conventional follow-up arms.
- Once atrial fibrillation was detected, all patients accepted anticoagulation.
- DOACs were the only anticoagulation therapies offered (use of warfarin was investigated in a scenario analysis).

Base-case results

3.68 During the first consultation on this guidance, errors were identified in the economic model. NICE commissioned a review of the model by the NICE Decision Support Unit (DSU) who validated the coding and corrected a further minor error. The updated cost-effectiveness results produced by the DSU were provided for the third committee meeting (see table 5 for deterministic results). Probabilistic results (shown in section 3.72) and deterministic results were similar.

Table 5 Base-case deterministic pairwise cost-effectiveness analysis (compared with conventional follow up) – from DSU report (November 2019 committee meeting)

Type of monitoring	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Conventional follow up	7,600	1.74	–	–	–
Reveal LINQ	9,092	1.88	1,492	0.14	10,342
BioMonitor 2-AF	8,322	1.88	722	0.14	5,006
Confirm Rx	8,866	1.84	1,267	0.10	12,879

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

3.69 The ICERs in table 5 were produced by separate comparisons of each of the 3 implantable cardiac monitors with conventional follow up. The lower number of QALYs generated by Confirm Rx is because the battery is assumed to last 2 years, rather than 3 years. The EAG noted that if BioMonitor 2-AF battery life was 4 years, rather than 3 years, as assumed in the model, the device might detect more cases of atrial fibrillation than are captured in the analyses.

3.70 The fully incremental analysis is shown in table 6. The EAG advised that the BioMonitor 2-AF and Confirm Rx results should be viewed with caution because they are based on a strong assumption of equivalence with Reveal LINQ. The difference in costs between BioMonitor 2-AF and Reveal LINQ is because of the difference in costs of the devices alone.

Table 6 Base-case deterministic incremental cost-effectiveness analysis – from DSU report (November 2019 committee meeting)

Type of monitoring	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Conventional follow up	7,600	1.74	–	–	–
Reveal LINQ	9,092	1.88	226	0.00	Dominated
BioMonitor 2-AF	8,322	1.88	722	0.14	5,006
Confirm Rx	8,866	1.84	544	-0.05	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year. Dominated means that using the device costs more but produced fewer, or the same number of, QALYs than the comparator.

Scenario analyses

3.71 The EAG did some scenario analysis to assess the effect of some of the assumptions made in the model. Selected results are shown in table 7.

Table 7 Selected scenario analyses – from DSU updated model (November 2019 committee meeting)

Scenario	Reveal LINQ ICER	BioMonitor 2-AF ICER	Confirm Rx ICER
Base case	10,342	5,006	12,879
Addition of FOCUSON triage service provided by Medtronic for Reveal LINQ Option 1: £187 per patient per year	14,100	NA	NA
Addition of FOCUSON triage service provided by Medtronic for Reveal LINQ Option 2: one-off fee of £374 per patient per device	12,934	NA	NA

Scenario	Reveal LINQ ICER	BioMonitor 2-AF ICER	Confirm Rx ICER
No monitoring in conventional follow-up arm (monitoring costs and cases of AF detected in the conventional follow-up arm removed)	11,617	6,823	14,304

Abbreviations: AF, atrial fibrillation; DOAC, direct oral anticoagulant; ICER, incremental cost-effectiveness ratio; NA, not applicable.

Probabilistic sensitivity analysis

3.72 The DSU provided updated probabilistic sensitivity analysis for the third committee meeting. The ICERs in table 8 were produced by separate comparisons of each of the 3 implantable cardiac monitors with conventional follow up.

Table 8 Probabilistic pairwise cost-effectiveness analysis (compared with conventional follow up)

Type of monitoring	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Conventional follow up	7,600	1.74	–	–	–
Reveal LINQ	9,093	1.88	1,493	0.14	10,350
BioMonitor 2-AF	8,323	1.88	723	0.14	5,014
Confirm Rx	8,867	1.84	1,268	0.10	12,888

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

3.73 From the cost-effectiveness acceptability curves (each device was compared independently with conventional follow up), at a maximum acceptable ICER of £20,000 per QALY, all 3 devices had an almost 100% probability of being cost effective.

4 Committee discussion

Clinical need

Technologies that improve paroxysmal atrial fibrillation detection after cryptogenic stroke or TIA could have substantial benefits for people

4.1 The patient expert told the committee how, when someone has a stroke or transient ischaemic attack (TIA) with no identifiable cause, they can live in fear of having another stroke. This is because they know that the cause of the stroke is not being treated. This can make them anxious and want to visit the GP often for reassurance. Paroxysmal atrial fibrillation is often a cause of cryptogenic stroke. But it's often not detected because it's not present when someone has their initial assessment. If atrial fibrillation is detected, the clinical experts highlighted the importance of offering anticoagulants, rather than antiplatelet therapy, to reduce the risk of a further stroke or TIA. The patient expert explained that people who have had a cryptogenic stroke tend to be younger than people who have had a stroke with a known cause. Therefore, they're more likely to be working and have dependants, such as elderly parents or children. They pointed out the benefits of preventing further strokes, including reducing post-stroke dementia and the psychological impact of sudden illness. The clinical experts said that current practice is to monitor for suspected atrial fibrillation for up to about 14 days at most using Holter monitors if implantable cardiac monitors are not available. A patient expert said that at the moment, monitoring often misses atrial fibrillation in people who have had a stroke, who could benefit from treatment. The committee concluded that identifying the cause of a cryptogenic stroke is important to reduce risk of a further stroke or TIA. Technologies that can identify paroxysmal atrial fibrillation missed by current post-stroke follow-up testing could have substantial benefits for people who have had a cryptogenic stroke.

Implantable cardiac monitors can reassure people who have had a cryptogenic stroke or TIA, and their carers

4.2 The patient expert said that, if atrial fibrillation is suspected after a stroke or TIA, people can often be anxious that new symptoms may be related to the condition, and that they should report them to their doctor. A continuous electrocardiogram (ECG) monitor can reassure people that if they have symptoms, the monitor will detect any atrial fibrillation that caused them, and can be used to confirm or rule out the condition. Because the devices can remotely monitor people, they may need fewer follow-up appointments after a cryptogenic stroke. This could particularly benefit people living in remote areas far from a hospital. The patient expert said that after a stroke people are fatigued for a long time. Travelling to follow-up appointments can be tiring, costly and time-consuming. People may also need to go with a carer to help them and describe symptoms. The committee concluded that implantable cardiac monitors could have quality-of-life benefits beyond preventing another stroke.

Clinical effectiveness

The CRYSTAL-AF study population broadly represents people with cryptogenic stroke in the NHS

4.3 The only study identified by the external assessment group (EAG) that compared the effectiveness of using an implantable cardiac monitor with conventional follow up after a cryptogenic stroke was the CRYSTAL-AF study. The clinical experts said that it's important that non-invasive ECG monitoring is done before an implantable cardiac monitor is considered. They also said that the length of monitoring in the NHS can vary. Holter monitors are typically used for 24 hours to 7 days. Not everyone in CRYSTAL-AF had outpatient ECG monitoring before having an implantable cardiac monitor fitted. Those who did were monitored for a median of 23 hours. The committee also considered that participants in CRYSTAL-AF were younger than would be expected for people who have had a stroke (mean age about 61.5 years). However, the clinical experts explained that people with cryptogenic stroke are usually younger than the overall stroke population. The committee concluded that the population in the CRYSTAL-AF

study broadly represented people with cryptogenic stroke who would have an implantable cardiac monitor fitted in the NHS.

People in the control arm of CRYSTAL-AF may have been tested more for atrial fibrillation than is usual in the NHS

4.4 Some people in the control arm of the CRYSTAL-AF study, who did not have a cardiac monitor implanted, were tested for atrial fibrillation every 3 months using ECG, including Holter monitoring. The clinical experts said that in current practice, the amount of testing for atrial fibrillation varies if an implantable cardiac monitor is not used, but it is likely to be less than in CRYSTAL-AF. They also said that people may only be tested again for atrial fibrillation if they have another stroke. The committee concluded that testing for atrial fibrillation in the control arm of CRYSTAL-AF may be more than is done in the NHS, which may underestimate the increased yield of people with atrial fibrillation reported for the intervention arm.

Reveal XT increases atrial fibrillation detection, but the effect on further stroke or TIA reduction is uncertain

4.5 In the CRYSTAL-AF study, Reveal XT detected more people with atrial fibrillation than conventional follow up (see table 1). There were also fewer strokes or TIAs in the Reveal XT arm of the study (see table 2). However, because of the length of follow up and sample size, the true effect of the device on reducing stroke or TIA incidence is uncertain; the 95% confidence interval for the hazard ratio at 12 months was 0.22 to 1.80. The committee concluded that there was good evidence that Reveal XT detected more people with atrial fibrillation than conventional follow up, and that this was likely to be seen in clinical practice. However, the extent of a subsequent reduction in stroke or TIA occurrence is uncertain.

CRYSTAL-AF data can be used to assess how well Reveal LINQ detects atrial fibrillation in people who have had a cryptogenic stroke, but not BioMonitor 2-AF or Confirm Rx

4.6 The CRYSTAL-AF study used Reveal XT, a predecessor model of Reveal LINQ. Changes have been made to the atrial fibrillation detection algorithm that is now used in Reveal LINQ. There was some evidence that suggested this had improved its ability to detect atrial fibrillation. The clinical experts said that the atrial fibrillation detection algorithms in other manufacturers' devices may use the same features of an ECG to detect potential atrial fibrillation. But how these features are used to determine if atrial fibrillation is likely to be present, or to classify an arrythmia as atrial fibrillation or another type of arrythmia, is likely to differ between devices. At consultation, the manufacturer of the BioMonitor submitted an unpublished technical validation report that compared the ability of the BioMonitor 2-AF and Reveal LINQ to detect atrial fibrillation from a Holter monitor recording (see section 3.21). The EAG commented that this was not a clinical comparison of the devices, which might perform differently when implanted. The study was also not done in a cryptogenic stroke population, where the device may perform differently because of different patient characteristics. The committee noted that the study had a small population size and had not been published and so was not peer reviewed. Clinical experts commented that electrode positioning is different for Holter monitors and implantable cardiac monitors. So the ECG output from a Holter monitor is not the same as the signal that an implantable cardiac monitor receives. The results could therefore be considered to be artificial and not reflect clinical reality. The committee considered that this study did not show that the Reveal LINQ and BioMonitor devices were comparable in detecting atrial fibrillation in a cryptogenic stroke population. The committee concluded that it is feasible that data from Reveal XT are likely to apply to the updated version from the same manufacturer, Reveal LINQ. But there is too much uncertainty over whether the data can be used to show the performance of the BioMonitor 2-AF or Confirm Rx to detect atrial fibrillation in people who have had a cryptogenic stroke. Therefore, the committee did not accept that evidence from the CRYSTAL-AF study could be applied to these devices.

Cost effectiveness

It is not appropriate to use data from CRYSTAL-AF to model the performance of BioMonitor 2-AF or Confirm Rx

4.7 The EAG used diagnostic yield data (a measure of how many people with atrial fibrillation were diagnosed) from the CRYSTAL-AF study in the economic model for all 3 devices. The committee considered data from this study to be appropriate to assess how well Reveal LINQ detected atrial fibrillation in people who have had a cryptogenic stroke. But it did not think it was appropriate to use it for BioMonitor 2-AF or Confirm Rx (see section 4.6). In the absence of clinical or comparative data for these devices in people who have had a cryptogenic stroke, the committee concluded that it was not appropriate to consider the cost-effectiveness estimates for BioMonitor 2-AF or Confirm Rx.

It is appropriate to use a linked evidence approach to estimate the impact of implantable cardiac monitors on stroke or TIA incidence

4.8 Based on data from the CRYSTAL-AF study, the extent of any reduction in further stroke or TIA as a result of using an implantable cardiac monitor is uncertain (see section 4.5). The EAG used diagnostic yield data from CRYSTAL-AF to estimate the increase in cases of atrial fibrillation detected by implantable cardiac monitors (compared with conventional follow up). It then used an existing model (Sterne et al. 2017 and Welton et al. 2017) to estimate the effect of subsequent anticoagulant or antiplatelet treatment on the incidence of clinical events such as stroke. The committee considered that the absolute risk of stroke may differ between people with permanent or persistent atrial fibrillation and people with paroxysmal atrial fibrillation. The clinical experts said that people with paroxysmal atrial fibrillation do benefit from anticoagulant treatment. The EAG ran the model with the risks of events adjusted to reflect a secondary stroke population with paroxysmal atrial fibrillation. The committee concluded that there is uncertainty about the impact of using implantable cardiac monitors on the reduction of further strokes or TIAs. But it agreed that, in the absence of long-term data on this, the EAG's approach of linking evidence on the extent of atrial fibrillation

detection, the impact of diagnosis on treatment choice, and the effect of treatment on the incidence of subsequent clinical events such as stroke and TIA in the economic model, was suitable for decision making.

Not including adverse events caused by implanting Reveal LINQ is unlikely to have a large impact on cost-effectiveness estimates

4.9 The EAG's economic model did not include the effect of any adverse events caused by implanting the devices. The EAG explained that the proportions of people who had non-serious adverse events was reported in CRYSTAL-AF, but there were no details on what these events were. Therefore, the EAG could not include any costs or disutilities caused by these events in the model. The clinical and patient experts said that there are some minor issues caused by the devices, such as irritation and pain when they are fitted or removed, or if someone unintentionally exposes the device through the skin, but that these are not common and do not have severe consequences. The committee concluded that not including any adverse events caused by implanting the devices was unlikely to have had a large effect on cost-effectiveness estimates.

There may be uncaptured benefit in detecting non-atrial fibrillation arrythmia, but the impact of this on patient outcomes is uncertain

4.10 The model did not include detection of non-atrial fibrillation arrythmias. There was not much evidence on the number of these arrhythmias detected by the devices, and what evidence there was, came from non-comparative observational studies. The clinical experts explained that most asymptomatic non-atrial fibrillation arrythmia detected by the implantable cardiac monitors would not lead to any change in care. The committee concluded that using the devices may increase detection of non-atrial fibrillation arrythmias, but that the extent of this increase, and the clinical significance of these arrythmias and consequent impact on patient outcomes, is highly uncertain.

The base case may overestimate how much monitoring for atrial

fibrillation is done in current practice, which lowers the ICER

4.11 The EAG used the control arm of the CRYSTAL-AF study to model current practice ('conventional follow up'). The committee had earlier concluded that this may include more monitoring for suspected atrial fibrillation than would be done in the NHS (see section 4.4). This may make the increased diagnostic yield of atrial fibrillation for Reveal LINQ in the model a conservative estimate. But it may also mean that the model overestimates the cost of monitoring for atrial fibrillation in current practice. The EAG did a scenario analysis in which no further monitoring for atrial fibrillation was done in current practice (that is, no people with atrial fibrillation were detected or cost of monitoring included). This increased the incremental cost-effectiveness ratio (ICER) for Reveal LINQ by about £1,300 per quality-adjusted life year (QALY) gained. The committee concluded that the EAG's scenario may be too extreme, in that some monitoring is likely to be done in the NHS for people with no implantable cardiac monitor fitted. However, the amount of assessment for atrial fibrillation in current practice is likely to have been overestimated in the base-case model, which lowered the base-case ICER by up to about £1,300 per QALY gained.

The number of false positive alerts from Reveal LINQ is uncertain, and including this in the economic model increases the base-case ICER

4.12 The base-case model did not include the cost of interpreting alerts produced by Reveal LINQ. The EAG explained that this was because of a lack of data on the number of alerts produced by the device. The clinical experts said that the device would produce false positive alerts. Anecdotal evidence differed on the impact of false positive alerts on workload. One clinical expert said that alerts from the devices can generate several hours of work per day for electrophysiologists to review, although this was based largely on alerts from people with syncope. However, another clinical expert said that it takes minimal time to review alerts generated for possible atrial fibrillation (less than 10 seconds), and that the increase in workload for technicians would be minimal. The clinical experts highlighted that the number of alerts can vary widely between people and noted that cardiac physiologists need to triage the alerts. The EAG did 2 scenario analyses that included the costs of an optional triage service for alerts offered by

Medtronic for Reveal LINQ. This increased the ICER by about £2,600 to £3,800 per QALY gained, depending on the cost option used. The clinical experts said that the costs used (£187 per patient per year or £374 per patient) are likely to be a realistic estimate and could be considered a reasonable proxy for the costs of triaging alerts in the NHS. The committee concluded that there is uncertainty about the likely number of false alerts that Reveal LINQ generates in people who have had a cryptogenic stroke if used in routine clinical practice, and the impact on services. Including costs for reviewing alerts in the economic model would increase the ICER for Reveal LINQ, although it is uncertain by how much.

The EAG's model, following DSU review and amendment, is suitable for decision making

4.13 At the first committee meeting, the committee was concerned by the difference between the deterministic and probabilistic base-case results provided by the EAG. There was a large difference in the incremental costs and QALYs generated for the devices (compared with conventional follow up) between these analyses. For the second committee meeting, the EAG provided updated analyses in which an error in the model code used to run the probabilistic sensitivity analysis was corrected. The updated base-case probabilistic sensitivity analysis results were now very similar to the deterministic results. At the first committee meeting, the committee was concerned that the model results may not be realistic (lacking face validity) because of the small number of total QALYs generated in the model. At the second committee meeting, the EAG explained that this was because QALYs in the model were only generated by people who had episodes of atrial fibrillation, which was 30% of the total population. No QALYs were considered for the remaining 70% because there would be no difference in the number of QALYs generated between people with implantable cardiac monitors fitted and conventional follow up (and therefore no impact on ICERs). The EAG further explained that the cohort modelled had a starting age of 62, had all had a stroke or TIA, and all had atrial fibrillation. Therefore, they did not consider that the number of QALYs generated was unrealistic. During the first consultation on this guidance, an error was identified in the model. On reviewing the model, the EAG identified another error. NICE commissioned a review of the model by NICE's Decision Support Unit (DSU). The DSU checked the model and corrected another small error. Updated model results were presented at the third committee

meeting. The committee concluded that, considering the DSU's review of the model, the corrections made to the model and the explanations provided, the revised model was suitable for decision making.

The different parameters used in the EAG's and Diamantopoulos et al. models are unlikely to affect decision making

4.14 The updated cost-effectiveness estimate for the Reveal LINQ provided for the third meeting was now lower than the results of a previous economic model that also used data from CRYSTAL-AF (Diamantopoulos et al. 2016; see sections 3.53 and 3.54). The EAG's updated base-case ICER was £10,342 compared with £17,175 per QALY gained for Diamantopoulos et al. and the incremental QALYs were similar (0.14 and 0.15). The EAG explained that the difference between the results of the models was driven by differences in how the impact of anticoagulant treatment was modelled. Because of differences in model structure, the outcomes included, and the mechanisms used to estimate outcomes, the EAG considered a direct comparison of the parameters used in each model to be difficult and potentially not very informative. The DSU's amended version of the EAG's model estimated that the number of strokes that would be avoided by using an implantable cardiac monitor was 52 per 1,000 people with cryptogenic stroke, compared with 40 per 1,000 people estimated by the Diamantopoulos et al. model. The committee recalled that the size of any reduction in further stroke or TIA caused by using the devices was uncertain (see section 4.5). The committee concluded that there was uncertainty about which was the most appropriate approach to modelling the impact of anticoagulant treatment. The acute and post-stroke utilities were lower in the Diamantopoulos et al. model, which would also have contributed to the difference in incremental QALYs between models. At consultation, several stakeholders commented that the underlying model used (reported in Sterne et al.) was developed for a primary stroke population. The EAG explained that they had adjusted parameters in the model (for example, risk of further stroke, TIA, systemic embolism, intracranial haemorrhage and bleeds) for a secondary stroke population. Stakeholders also highlighted that the impact of a secondary, rather than primary, stroke may have been underestimated in the model. For example, the costs of ongoing treatment and impact on someone's health-related quality of life. The committee concluded that there is uncertainty about the most appropriate parameters to use to model

the longer-term effects of anticoagulant and antiplatelet treatment in this population, but that the different parameters used in the EAG's and Diamantopoulos et al. models are unlikely to affect decision making.

The most plausible ICER for Reveal LINQ is likely to be less than £20,000 per QALY gained

4.15 The committee only considered cost-effectiveness estimates for Reveal LINQ (see section 4.7). The probabilistic ICER for Reveal LINQ in the EAG's model was almost identical to the deterministic value. The deterministic base case for Reveal LINQ compared with conventional follow up was £10,342 per QALY gained. If assessment for atrial fibrillation in the conventional follow-up arm is removed from the EAG's base-case model, the ICER increases by about £1,300 per QALY gained. However, the assumption that no longer-term monitoring for atrial fibrillation is done in standard monitoring is unlikely (see section 4.11). In addition, costs of reviewing alerts produced by Reveal LINQ were not included in the base-case model. If the cost of a triage service was included, the EAG's base-case ICER increased by about £2,600 to £3,800 per QALY gained (see section 4.12). The committee concluded that there was uncertainty about the most plausible ICER for Reveal LINQ. Including its preferences in the EAG's model would increase the base-case ICER, but this was unlikely to increase to over £20,000 per QALY gained. The committee concluded that the most plausible ICER for Reveal LINQ is likely to be less than £20,000 per QALY gained.

Reveal LINQ is likely to be a cost-effective use of NHS resources

4.16 The committee agreed that Reveal LINQ was likely to be clinically effective because it identifies more people who have atrial fibrillation after a cryptogenic stroke or TIA than current practice. The committee recalled its conclusion that technologies that improve the detection of paroxysmal atrial fibrillation after cryptogenic stroke or TIA could have substantial benefits for patients. In addition, there is an unmet need for longer-term monitoring for atrial fibrillation after a cryptogenic stroke or TIA (see sections 4.1 and 4.2). The committee considered that the most plausible ICER for Reveal LINQ is likely to be less than £20,000 per QALY gained (see section 4.15). Therefore, the committee concluded that

Reveal LINQ is likely to be a cost-effective use of NHS resources.

Reveal LINQ should only be used after non-invasive ECG monitoring has been done

4.17 The inclusion criteria for CRYSTAL-AF included a requirement for a 12-lead ECG and 24-hour ECG monitoring for atrial fibrillation detection to establish the diagnosis of cryptogenic stroke (before use of an implantable cardiac monitor). The amount of atrial fibrillation detected in this study population was used for the cost-effectiveness estimates for Reveal LINQ in this assessment. During consultation, stakeholders highlighted that longer duration non-invasive monitors (that is, monitors that are not implanted) are increasingly available and questioned if this would impact the cost effectiveness of Reveal LINQ. The committee recalled that clinical experts had emphasised that Reveal LINQ would only be used after all available non-invasive monitoring had been done. Therefore, these non-invasive monitors were not comparators to implantable cardiac devices. However, longer duration non-invasive monitoring is likely to detect some cases of atrial fibrillation that shorter duration non-invasive monitoring would miss, and therefore there may be a lower yield of people with atrial fibrillation subsequently detected by implantable cardiac monitors. The EAG commented that longer duration non-invasive monitoring of up to a month was unlikely to have a large impact on the cost effectiveness of Reveal LINQ. They based their comment on exploratory model analysis that assumed that anyone with atrial fibrillation in the first month of CRYSTAL-AF would not have had an implantable cardiac monitor (reducing the diagnostic yield for Reveal LINQ in the model). Clinical experts highlighted that it is important that non-invasive ECG monitoring is done first before Reveal LINQ is considered, and that the type and duration of non-invasive monitoring will vary by local availability across the NHS. The committee concluded that it's important that Reveal LINQ is only used if paroxysmal atrial fibrillation is still suspected after non-invasive ECG monitoring has been done.

Reveal LINQ should only be used if the device is discussed with patients and they, or a carer, are able to set up the MyCareLink Patient Monitor

4.18 The committee noted that clinicians should discuss implanting the device with patients and give advice about the MyCareLink Patient Monitor, which needs to be set up to transmit rhythm abnormalities recorded by Reveal LINQ. The committee noted that disabled people may need a carer to help set up the MyCareLink Patient Monitor to ensure data are transmitted.

Research considerations

Further evidence is needed to show the effectiveness of BioMonitor 2-AF and Confirm Rx to detect atrial fibrillation in people with cryptogenic stroke

4.19 The committee considered that there was no evidence plausibly showing that BioMonitor 2-AF and Confirm Rx (or previous versions) were as effective as Reveal devices at detecting atrial fibrillation in people with cryptogenic stroke. And the committee noted that it was difficult to get good comparative data on this. Only diagnostic yield data from a Reveal device were available to model cost effectiveness. A randomised controlled trial comparing Reveal LINQ with Confirm Rx was highlighted during consultation (Yokokawa et al. 2019; see section 3.51). Most of the people in the trial had had a cryptogenic stroke. But the study was only available as a conference abstract. Details of the methodology were limited, and it was not clear why the number of events detected in the Reveal LINQ and Confirm Rx arms were so different. Abbott Medical UK, which makes Confirm Rx, said it was not involved in the study and could not give any more information. The committee considered that it did not have enough information to be able to use the study to assess if Reveal LINQ and Confirm Rx had similar effectiveness. However, it concluded that the study did show that it was feasible to do a trial comparing the effectiveness of different implantable cardiac monitors to detect atrial fibrillation in a cryptogenic stroke population.

5 Recommendations for further research

What research is needed

5.1 Further research is recommended to assess the diagnostic yield of the BioMonitor 2-AF and Confirm Rx (or later devices) for atrial fibrillation when used in people who have had a cryptogenic stroke. The committee noted that existing ongoing research may provide further data for these devices (see section 3.51 and section 4.19).

6 Implementation

NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

In addition, NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for the developing specific research study protocols as appropriate. NICE will also incorporate the research recommendations in section 5 into its guidance research recommendations database and highlight these recommendations to public research bodies.

7 Diagnostics advisory committee members and NICE project team

Committee members

This topic was considered by the diagnostics advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the test to be assessed. If it is considered there is a conflict of interest, the member is excluded from participating further in that assessment.

The minutes of each committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Additional specialist committee members took part in the discussions for this topic:

Specialist committee members

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Mrs Joanne Denman
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Mrs Jo Jerrome
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Dr Justin Lee
Consultant cardiac electrophysiologist, Sheffield Teaching Hospitals NHS Trust

Miss Cara Mercer
Chief cardiac physiologist, United Lincolnshire Hospitals NHS Trust

NICE project team

Each diagnostics assessment is assigned to a team consisting of a technical analyst (who acts as the topic lead), a technical adviser and a project manager.

Thomas Walker
Topic lead

Rebecca Albrow
Technical adviser

Donna Barnes
Project manager

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