
Medical Policy



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Title: Ambulatory Event Monitors and Mobile Cardiac Outpatient Telemetry

Description/Background

CARDIAC ARRHYTHMIAS

Cardiac monitoring is routinely used in the inpatient setting to detect acute changes in heart rate or rhythm that may need urgent response. For some conditions, a more prolonged period of monitoring in the ambulatory setting is needed to detect heart rate or rhythm abnormalities that may occur infrequently. These cases may include the diagnosis of arrhythmias in patients with signs and symptoms suggestive of arrhythmias as well as the evaluation of paroxysmal atrial fibrillation (AF).

Cardiac arrhythmias may be suspected because of symptoms suggestive of arrhythmias, including palpitations, dizziness, or syncope or presyncope, or because of abnormal heart rate or rhythm noted on exam. A full discussion of the differential diagnosis and evaluation of each of these symptoms is beyond the scope of this review, but some general principles on the use of ambulatory monitoring is discussed.

Arrhythmias are an important potential cause of syncope or near-syncope, which may in some cases be described as dizziness. An ECG is generally indicated whenever there is suspicion of a cardiac cause of syncope. Some arrhythmic causes will be apparent on ECG. However, in patients in whom an ECG is not diagnostic, longer monitoring may be indicated. 2009 guidelines from the Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC) suggest that in individuals with clinical or ECG features suggesting a arrhythmic syncope, ECG monitoring is indicated and state that the "duration (and technology) of monitoring should be selected according to the risk and the predicted recurrence rate of syncope."¹ Similarly, guidelines from the National Institute for Health and Care Excellence (NICE) on the evaluation of transient loss of consciousness (TLoC), published in 2010 and updated in 2014, recommends the use of an ambulatory ECG in individuals with a suspected arrhythmic cause of syncope. The type and duration of monitoring recommended is

based on the individual's history particularly the frequency of transient loss of consciousness.² The Holter monitor is recommended if transient loss of consciousness occurs several times a week. If the frequency of transient loss of consciousness is every one to two weeks, an external event recorder is recommended; and if the frequency is less than once every two weeks, an implantable event recorder is recommended.

Similar to syncope, the evaluation and management of palpitations is patient-specific. In cases where the initial history, examination, and ECG findings are suggestive of an arrhythmia, some form of ambulatory ECG monitoring is indicated. A position paper from the European Heart Rhythm Association (2011) indicated that, for individuals with palpitations of unknown origin who have clinical features suggestive of arrhythmia, referral for specialized evaluation with consideration for ambulatory ECG monitoring is indicated.³

Atrial Fibrillation Detection

Atrial fibrillation (AF) is the most common arrhythmia in adults. It may be asymptomatic, or be associated with a broad range of symptoms, including lightheadedness, palpitations, dyspnea, and a variety of more nonspecific symptoms (e.g., fatigue, malaise). It is classified as paroxysmal, persistent, or permanent based on symptom duration. Diagnosed AF may be treated with antiarrhythmic medications with the goal of rate or rhythm control. Other treatments include direct cardioversion, catheter-based radiofrequency- or cryoenergy-based ablation, or one of several surgical techniques, depending on the patient's comorbidities and associated symptoms.

AF is associated with the development of thrombi in the atria, often the left atrial appendage. Patients with AF are at risk for ischemic stroke due to the risk of embolism of the thrombus. Multiple clinical trials have demonstrated that anticoagulation reduces the ischemic stroke risk in patients at moderate or high risk of thromboembolic events. Oral anticoagulation in patients with AF reduces the risk of subsequent stroke and was recommended by American Heart Association, American College of Cardiology, and Heart Rhythm Society in 2014 joint guidelines on patients with a history of stroke or transient ischemic attack (TIA).⁴

Ambulatory ECG monitoring may play a role in several situations in the detection of AF. In patients who have undergone ablative treatment for AF, if ongoing AF can be excluded with reasonable certainty, including paroxysmal AF which may not be apparent on ECG during an office visit, anticoagulation therapy could potentially be stopped. In some cases where identifying paroxysmal AF is associated with potential changes in management, longer term monitoring may be considered. There are well-defined management changes that occur in patients with AF. However, until relatively recently the specific role of long-term (i.e., >48 hours) monitoring in AF was not well-described.

Patients with cryptogenic stroke are often monitored for the presence of AF, because AF is estimated to be the cause of cryptogenic stroke in more than 10% of patients, and AF increases the risk of stroke.^{5,6} Paroxysmal AF confers an elevated risk of stroke, just as persistent and permanent AF do. In individuals with a high risk of stroke, particularly those with a history of ischemic stroke that is unexplained by other causes, prolonged monitoring to identify paroxysmal AF has been investigated.

Cardiac Rhythm Ambulatory Monitoring Devices

Ambulatory cardiac monitoring with a variety of devices permits the evaluation of cardiac electrical activity over time, in contrast to static ECG, which only permits the detection of abnormalities in cardiac electrical activity at a single point in time.

A Holter monitor is worn continuously and records cardiac electrical output continuously throughout the recording period. Holter monitors are capable of recording activity for up to about 24 to 72 hours. Traditionally, most Holter monitors had three channels based on three ECG leads. However, some currently available Holter monitors have up to 12 channels. Holter monitors are an accepted intervention in a variety of settings where a short period (24-48 hours) of comprehensive cardiac rhythm assessment is needed (e.g., suspected arrhythmias when symptoms [syncope, palpitations] are occurring daily). These devices are not the focus of this review.

Various classes of devices are available for situations where longer monitoring than can be obtained with a traditional Holter monitor is needed. Because there may be many devices within each category, a comprehensive description of each is beyond our scope. Specific devices may vary in how data are transmitted to the location where the ECG output is interpreted. Data may be transmitted via cellular phone or landline, or by direct download from the device after its return to the monitoring center. The device classes are described in Table 1.

Table 1: Ambulatory Cardiac Rhythm Monitoring Devices

Device Class	Description	Example Devices
Noncontinuous devices with memory (event recorder)	Devices that are not worn continuously but rather activated by the patient and applied to the skin in the precordial area when he/she develops symptoms	<ul style="list-style-type: none"> Zio® Event Card (iRhythm Technologies) REKA E100™ (REKA Health)
Continuous recording devices with longer recording periods	Devices that are continuously worn and continuously recording via 1 or more cardiac leads and able to store data for a longer period than a traditional Holter (14 days)	<ul style="list-style-type: none"> Zio®XT Patch and ZIO ECG Utilization Service (ZEUS) Event Card (iRhythm Technologies)
External memory loop devices (patient or autotriggered)	Devices that are continuously worn and continuously store a single channel of ECG data in a refreshed memory. If the device is activated, the ECG is then recorded from the memory loop for the preceding 30 to 90 seconds and for the next minute or so. These devices may be activated by a patient when symptoms occur (patient triggered) or by an automated algorithm when changes suggestive of an arrhythmia are detected (autotriggered)	<ul style="list-style-type: none"> Patient-triggered: Explorer™ Looping Monitor (LifeWatch Services) Autotriggered: LifeStar AF Express™ Auto-Detect Looping Monitor (LifeWatch Services) Autotriggered or patient-triggered: King of Hearts Express® AF (Card Guard Scientific Survival)
Implantable memory loop devices (patient or autotriggered)	Devices that are similar in design to external memory loop devices but implanted under the skin in the precordial region.	<ul style="list-style-type: none"> Autotriggered: Reveal® XT ICM (Medtronic) and Confirm Rx Insertable™ Cardiac Monitor (Abbott) Autotriggered: BioMonitor, Biotronik)
Mobile cardiac outpatient telemetry	Continuously recording or autotriggered memory loop devices that transmit data to a	<ul style="list-style-type: none"> CardioNet MCOT (Bio Telemetry)

central recording station with real-time monitoring and analysis.

- LifeStar Mobile Cardiac Telemetry (LifeWatch Services)
-
- Zio AT (iRhythm)

ECG: electrocardiogram

There are also devices that combine features of multiple classes. For example, the LifeStar ACT ExHolter (LifeWatch Services) is a 3-channel Holter monitor but is converted to a mobile cardiac telemetry system if a diagnosis is inconclusive after 24-48 hours of monitoring. The BodyGuardian® Heart Remote Monitoring System (Preventice Services) is an external autotriggered memory loop device that can be converted to a real-time monitoring system. The eCardio Verité™ system (eCardio) can be changed between a patient-activated event monitor and a continuous telemetry monitor. The Spiderflash-T (LivaNova) is an example of an external auto-triggered or patient-triggered loop recorder, but, like the ZioPatch, can record two channels for 14 to 40 days.

Regulatory Status:

Some of the newer devices are described in the Background section for informational purposes. Because there may be many devices within each category, a comprehensive description of individual devices is beyond the scope of this review. U. S. FDA product codes include: DSH, DXH, DQK, DSI, MXD and MHX.

Medical Policy Statement

The following ambulatory cardiac monitors are considered established for patients meeting patient selection guidelines:

- Patient-activated or auto-activated external ambulatory event monitors
- Implantable ambulatory event monitors, either patient-activated or auto-activated
- Continuous ECG rhythm recording and storage devices for longer than 48 hours up to 21 days (e.g., ZioPatch®).

They are considered useful diagnostic options when indicated.

The use of real time outpatient cardiac telemetry (also known as mobile cardiac outpatient telemetry MCOT) as a diagnostic tool entails recording of cardiac arrhythmia, according to pre-set parameters AND its **real time** transmission to a central service center for immediate action, if needed. The transmission of recorded arrhythmias in real time is experimental /investigational as its clinical utility has not been established. Additionally, although MCOT IS useful in the recording of cardiac arrhythmias, its incremental benefit over other approved methods of detecting cardiac arrhythmias via prolonged cardiac monitoring has not been proven, and is therefore considered not medically necessary.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

INCLUSIONS:

- Patient-activated or auto-activated *external* ambulatory event monitors OR the use of *long-term (greater than 48 hours)* external ECG monitoring by continuous rhythm recording and storage (e.g., **Zio Patch®**) are established as diagnostic alternatives to Holter monitoring in patients
 - Who experience symptoms suggestive of cardiac arrhythmias (i.e., palpitations, dizziness, presyncope or syncope) OR
 - With atrial fibrillation who have been treated with catheter ablation, and in whom discontinuation of systemic anticoagulation is being considered, OR
 - Patients with cryptogenic stroke.
- *Implantable* ambulatory event monitors, either patient-activated or auto-activated, are established for:
 - A small subset of patients who experience recurrent symptoms so infrequently that a prior trial of Holter monitor or other external ambulatory event monitors has been unsuccessful.
 - Patients who require long term monitoring for atrial fibrillation.

EXCLUSIONS:

- Real-time outpatient cardiac telemetry (also known as mobile cardiac outpatient telemetry or MCOT) as a diagnostic approach in patients who experience infrequent symptoms (less frequently than every 48 hours) suggestive of cardiac arrhythmias (i.e., palpitations, dizziness, presyncope or syncope). This technology is considered not medically necessary as direct evidence for improved health outcomes with the use of continuous, real-time monitoring for suspected arrhythmias is lacking, and evidence for a significant incremental improvement in outcomes with the continuous, real-time monitoring, compared with standard monitoring, is lacking.
- Other uses of ambulatory event monitors, including outpatient cardiac telemetry and mobile applications, are considered experimental/investigational, including but not limited to:
 - Monitoring asymptomatic patients with risk factors for arrhythmia
 - Detection of myocardial ischemia by detecting ST segment changes (intracardiac ischemia monitoring systems)
 - Monitoring effectiveness of antiarrhythmic medications who have not met other inclusionary criteria.

CPT/HCPCS Level II Codes (*Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) in this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.*)

Established codes:

33285	33286	93241	93242	93243	93244
93245	93246	93247	93248	93268	93270
93271	93272				

[*Surgical codes include reimbursement for the monitor](#)

[Other codes \(investigational, not medically necessary, etc.\):](#)

93228

93229

0497T

0498T

0650T

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

This review is structured around 3 questions: First, in what clinical situations, and with what classes, do ambulatory event monitors (AEMs) improve health outcomes? Second, under what circumstances are implantable AEMs associated with improved outcomes? Third, under what circumstances is real-time monitoring associated with improved outcomes?

For some of AEMs discussed herein, including those that include real-time monitoring and analysis, the technologies represent an enhancement to existing technology and are intended to improve outcomes compared with event monitors. As such, to demonstrate an improvement in health outcomes, there must be a clinically significant incremental benefit when the additional technology, such as real-time monitoring, is added.

Ambulatory Event Monitors (AEMs) in the Detection of Arrhythmias

The first four sections of the policy focus on clinical situations for which the use of long-term AEMs may be associated with improved health outcomes.

- The use of long-term AEMs in the diagnosis of cardiac rhythm abnormalities in individuals with signs and/or symptoms of arrhythmias, such as dizziness, syncope or near syncope, or palpitations, is discussed. Specific arrhythmias may be relatively nonspecific in terms of the symptoms they cause. However, the diagnosis of some arrhythmias has well-defined management implications that are known to improve outcomes, such as the use of an implantable cardioverter defibrillator (ICD) in individuals with potentially lethal arrhythmias, or antiarrhythmic drugs or pulmonary vein isolation for the treatment of atrial fibrillation

(AF). Therefore, the identification of an arrhythmia is considered a reasonable endpoint in this case.

- The use of long-term AEMs for the detection of AF in patients following catheter ablation, for which management (use of anticoagulation therapy) may be changed based on AF detection.
- The use of long-term AEMs for the detection of AF in patients following cryptogenic stroke, for which management (use of anticoagulation therapy) may be changed based on AF detection.
- The use of long-term AEMs for the detection of AF in asymptomatic patients.

The last two sections of the policy focus on types of long-term AEMs: implantable AEMs and outpatient cardiac telemetry.

AUTOACTIVATED EXTERNAL OR CONTINUOUS AMBULATORY EVENT MONITORING FOR PATIENTS WITH ARRHYTHMIA SYMPTOMS

CLINICAL CONTEXT AND TEST PURPOSE

The purpose of patient- or autoactivated external ambulatory event monitoring or continuous ambulatory event monitoring in patients who have signs and/or symptoms of arrhythmia is to provide an alternative detection method for AF.

The question addressed in this evidence review is: does the use of patient- or autoactivated or continuous ambulatory event monitoring for patients with symptoms of arrhythmia improve net health outcome compared with electrocardiogram (ECG) only or 24 to 48 hour Holter monitoring?

The following **PICO** was used to select literature to inform this review.

Patients

The relevant population of interest are individuals with signs or symptoms suggestive of arrhythmia.

Interventions

The intervention being considered is patient- or autoactivated external event monitoring or continuous ambulatory event monitoring. Patient-activated devices are applied to the skin in the precordial area by the patient when symptoms are developing. Continuous event monitoring devices are worn continuously and are recording activity continuously and can store data longer than the Holter monitor.

Alternative AF detection methods that are used include an ECG or 24- to 48-hour Holter monitoring. An ECG provides information on cardiac electrical activity at one point in time. A Holter monitor is worn continuously and records cardiac electrical output continuously throughout the recording period. Holter monitors are capable of recording activity for 24 to 72 hours.

Comparators

Alternative AF detection methods that are used include an ECG or 24- to 48-hour Holter monitoring. An ECG provides information on cardiac electrical activity at one point in time. A Holter monitor is worn continuously and records cardiac electrical output continuously

throughout the recording period. Holter monitors are capable of recording activity for 24 to 72 hours.

Outcomes

The general outcome of interest is diagnostic yield of the monitors in detecting arrhythmias. To measure incremental benefits of the patient-activated or continuous monitors, direct comparisons with the Holter monitor, or indirect comparisons of the number of detections in the first 48 hours with the number of detections during longer monitoring periods can be made.

Study Selection Criteria

For the evaluation of clinical validity of autoactivated or patient-activated external ambulatory event monitoring for patients with arrhythmia symptoms, studies that met the following criteria were considered:

- To assess the clinical validity, studies should report sensitivity, specificity, positive and negative predictive values. Alternatively, studies reporting on diagnostic yield are informative.
- To assess the clinical utility, studies should demonstrate how results of the tests impacted treatment decisions and overall management of the patient.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). Below are studies providing evidence on the diagnostic yield of long-term AEMs in symptomatic patients.

Long-Term Ambulatory Event Monitoring in Symptomatic Patients

Newer devices are available that record cardiac rhythms continuously for longer periods of time than traditional Holter monitors. Several studies have evaluated the diagnostic yield of continuous monitoring for more than 48 hours, either directly through comparison with Holter monitoring or indirectly by calculating the proportion of arrhythmias detected in the first 48 hours of monitoring. The diagnostic yield of monitoring with external event monitors depends on the underlying population, the inherent sensitivity of the device, and the duration of monitoring.

Systematic Review

Hoefman et al (2010) published a systematic review on diagnostic tools for detecting cardiac arrhythmias.⁷ The literature search, conducted through March 2007, identified 28 studies for inclusion; 12 were single-arm studies and 16 were comparative studies. A meta-analysis was not possible due to the heterogeneity of the study populations and the devices tested. This review included studies of patients presenting with palpitations and compared the yield of remote monitoring for several classes of devices: Holter monitors; patient-activated event recorders; autotriggered event recorders; and implantable loop recorders (ILRs). The yield varied among devices, with the auto-trigger devices providing the highest range of detection (72-80%), followed by patient-activated devices (17-75%), and Holter monitors (33-35%).

Randomized Controlled Trial

Steinhubl et al (2018) conducted an RCT comparing active home-based cardiac monitoring with the iRhythm Zio initiated immediately after study recruitment (n=1364) vs active monitoring after 4 months (n=1291).⁸ A cohort of patients (n=3476) without monitoring, matched by age, sex, and CHA₂DS₂VASc were part of a concurrent observational study. The

primary endpoint was newly diagnosed AF at four months among those actively monitored at initiation vs. those just beginning the monitoring. The secondary endpoint was newly diagnosed AF at one year among the actively monitored groups combined vs. the matched observational controls. For the primary endpoint, at 4 months follow-up, 3.9% of the immediate group and 0.9% of the delayed group had newly diagnosed AF (absolute difference, 3.0%; 95% confidence interval [CI]: 1.8% to 4.1%). For the secondary endpoint, at 1 year follow-up, 6.7 per 100 person-years in the monitored group and 2.6 per 100 person-years in the control group had newly diagnosed AF. At one year, patients who were actively monitored were more likely to initiate anticoagulants, and have more cardiology visits and more primary care visits. There were no differences in emergency room visits or hospitalizations between the monitored and unmonitored groups after one year.

Observational Studies

Farris et al (2019) reviewed the records of patients who had undergone 30-day rhythm monitoring with the LifeWatch device at a single institution.⁹ A total of 3.4% of the patients had a new diagnosis of AF (402 per 1000 patient-years). The most common management response to the new diagnoses was to initiate anticoagulation therapy.

Tuakhia et al (2013) evaluated the diagnostic yield of the Zio Patch.¹⁰ Data from the manufacturer was used to identify 26,751 first-time users of the device. The most common clinical indications were palpitations (40.3%), atrial fibrillation (AF) (24.3%), and syncope (15.1%). Mean duration of use was 7.6 days, and 95.9% of patients wore the device for more than 48 hours. At least one episode of arrhythmia was detected in 16,142 (60.3%) patients. The authors compared the detection rate in the first 48 hours with the detection rate over the entire time the device was worn, with 70.1% of patients having their arrhythmia detected within the first 48 hours and 29.9% having their first arrhythmia detected after the first 48 hours. These data confirmed previous studies that had shown a substantial proportion of arrhythmias in symptomatic patients can be detected with a 48-hour period of monitoring and that longer monitoring periods increase the detection rate.

Barrett et al (2014) compared arrhythmia detection rates in 146 patients who underwent simultaneous monitoring with a 24-hour Holter monitor and a 14-day Zio Patch monitor.¹¹ Included were patients referred for evaluation of a suspected cardiac arrhythmia at single institution. For the detection of atrioventricular block, sinus pause, polymorphic ventricular tachycardia, supraventricular tachycardia, or AF, Holter monitoring detected 61 arrhythmias, while the Zio Patch detected 96 ($p < 0.001$). Over the monitoring period, the same 60 arrhythmia events were detected by both devices, with 36 only detected by the Zio Patch and one only detected by the Holter. The investigators conducted within-subject comparisons of arrhythmia detection for the 24-hour period during which both devices were worn. Holter monitoring detected 61 arrhythmia events, compared with 52 detected by the Zio Patch ($p = 0.013$). This study also suggested that extended monitoring may increase the diagnostic yield of cardiac monitoring. However, a relatively large number of missed events occurred with the Zio Patch during the period of simultaneous monitoring, which may have clinical significance if its performance is similar in non-research settings.

Solomon et al (2016) evaluated the diagnostic yield for potentially high-risk arrhythmias during 14 days of continuous recording with the Zio Patch among 122,454 patients (122,815 recordings) included in a manufacturer registry.¹² Patients included in the series all underwent monitoring with the device from November 2011 to December 2013. Mean wear time was 9.6 days. Overall, there were 22,443 (18%) patients with sustained ventricular tachycardia, 1,766

(1.4%) patients with sinus pauses of 3 seconds or more, 521 (0.4%) patients with AF pauses of 3 seconds or more, 249 (0.2%) patients with symptomatic pauses, and 1,468 (0.4%) with high-grade heart block, which were considered potentially high-risk arrhythmias. After 24 and 48 hours of monitoring, 52.5% and 65.5%, respectively, of potentially high-risk arrhythmias were detected. Seven days of monitoring identified 92.9% of potentially high-risk arrhythmias.

Wineinger et al (2018) reported on 13,293 individuals with paroxysmal AF who were referred for extended cardiac rhythm evaluation based on a clinical indication and wore the Zio Patch as part of standard clinical care.¹³ The median time to the first detected paroxysmal AF event was 24.9 hours (IQR 2.7 to 83.9 hours). After 24 hours of monitoring, 49.4% of individuals had experienced a paroxysmal AF event, increasing to 63.1% after 48 hours of monitoring and to 89.7% after 7 days of monitoring.

In a retrospective cohort study using data from two integrated health care delivery systems in California, Go et al (2018) examined the association of AF burden with the risk of stroke in patients with paroxysmal AF who were not receiving anticoagulants.¹⁴ The analysis included data from 1965 patients who were receiving monitoring with the Zio Patch. The highest tertile of AF burden (11.4% or higher), as measured by up to 14 days of continuous monitoring, was associated with a more than 3-fold higher risk of ischemic stroke compared to the lower 2 tertiles, even after controlling for known stroke risk factors.

Bolourchi et al (2015) evaluated the diagnostic yield of 14 days of monitoring with the Zio Patch in a series of 3,209 children included in a manufacturer registry.¹⁵ Patient age ranged from one month to 17 years. Indications for monitoring included palpitations (n=1,138 [35.5%]), syncope (n=450 [14.0%]), unspecified tachycardia (n=291 [9.1%]), paroxysmal supraventricular tachycardia (SVT) (n=264 [8.2%]) and chest pain (n=261 [8.1%]). The overall prevalence of any arrhythmia was 12.1%, with 44.1% of arrhythmias occurring after the first 48 hours of monitoring. Arrhythmias were detected in 10.0% of patients who were referred for palpitations, 6.7% of patients referred for syncope, 14.8% of patients referred for tachycardia, 22.7% of patients referred for paroxysmal SVT, and 6.5% of patients referred for chest pain.

Single-center studies, summarized in Table 2, have reported on the diagnostic yield and timing of detection of arrhythmias in patients monitored with the Zio Patch for a variety of arrhythmias. These studies generally reported high rates of arrhythmia detection.

Table 2: Single-Center Studies Reporting on Zio Patch Yield

Study	Patient Population	Monitoring Indication	Main Findings
Eisenberg et al (2014) ¹⁶	524 Consecutive patients evaluated in an academic EP practice	<p style="text-align: center;">Indication</p> <ul style="list-style-type: none"> • Surveillance for unspecified arrhythmia or palpitations: 47% • Known/suspected AF: 30% • Syncope: 8% • Bradycardia surveillance: 4% • Tachycardia surveillance: 5% • Chest pain: 2% 	<ul style="list-style-type: none"> • Significant arrhythmias detected in 297 (57%) • 66% had 1st arrhythmia detected within 2 days of monitoring • 25% of patient triggered events were associated with clinically-significant arrhythmias

Schreiber et al (2014) ¹⁷	174 patients with symptoms suggestive of arrhythmia seen in an ED	<ul style="list-style-type: none"> • Palpitations: 44.8% • Syncope: 24.1% • Unspecified arrhythmias detected in the ED: 11.5% 	<ul style="list-style-type: none"> • >1 significant arrhythmia other than chronic AF (≥ 4 beats VT, paroxysmal AF, ≥ 4 beats SVT, ≥ 3 second pause, 2nd degree Mobitz II or 3rd degree AV block, or symptomatic bradycardia) detected in 83 (47.7%) • Median time to arrhythmia detection: <ul style="list-style-type: none"> ○ Any arrhythmia: 1.0 days (IQR 0.2 to 2.8 days) ○ VT: 3.1 days ○ Sinus pause: 4.2 days ○ Significant Heart block: 5.8 days
Mulls et al (2019) ¹⁸	59 consecutive patients seen in an outpatient electrophysiology clinic	Premature ventricular contractions (PVCs)	<ul style="list-style-type: none"> • Median of minimum 24-hour PVC burden: 4.5% (IQR 2.6% to 11.2%) • Median of maximum 24-hour PVC burden: 16.2% (IQR 11.7% to 26.2%) • Mean 24-hour PVC burden: 9.0% (IQR 6.4% to 17.9%) • Median difference between maximum 24-hour PVC burden and minimum 24-hour burden: 2.45-fold (IQR 1.68- to 5.55-fold)
Reed et al (2018) ¹⁹	86 patients evaluated in an ED	Syncope	<ul style="list-style-type: none"> • 9/86 (10.5%) had a symptomatic significant arrhythmia endpoint (95% CI 4.0 to 16.9)

AF: atrial fibrillation; AV: atrioventricular; ED: emergency department; EP: electrophysiology; IQR: interquartile range; SVT: supraventricular tachycardia; VT: ventricular tachycardia

Comparison of Devices

Eysenck et al (2019) compared 4 external cardiac monitors (Zio XT Monitor, NUUBO vest, Carnation Ambulatory Monitor, and Novacor R Test) with the gold standard of permanent pacemakers in the ability to detect AF.²⁰ Patients who had permanent pacemakers (n=21) wore each of the external monitors for 2 weeks, in randomized order. A total of 1108 AF episodes were identified by the pacemakers during the study period. Results showed that the Zio, NUUBO, and Carnation monitors were more accurate in AF diagnosis compared with the Novacor R Test, when using the pacemaker detection episodes as the reference standard.

Health Quality Ontario (2017) published an assessment comparing long-term continuous AEMs with external cardiac loop recorders for detecting arrhythmias.²¹ The assessment included a systematic review of the literature on the effectiveness of both devices for detecting arrhythmias. No studies directly comparing long-term continuous AEMs with external loop

recorders (ELRs) were found, so indirect comparisons were constructed using 24-hour Holter monitors as the common comparator. Twelve cohort studies were included; seven addressed long-term AEMs and five addressed ELRs. Using a meta-regression model to control for variation in device-wearing time and baseline syncope rate, the estimated difference between the long-term continuous AEMs and ELRs in their ability to detect arrhythmias was small (risk difference, 0.01; 95%CI, -0.18 to 0.20). Both devices were more effective than a 24-hour Holter. However, the quality of evidence was evaluated as poor using GRADE criteria.

Some evidence suggests that auto-triggered event monitors have an inherently higher yield than patient-activated AEMs. Several studies, including an analysis of a database of 100000 patients, have compared the diagnostic yield of automatic and patient-activated arrhythmia recordings and reported an improved yield with auto-triggering devices.²²⁻²⁴

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. No RCTs supporting clinical utility were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. Clinical validity of long-term ambulatory monitoring in patients with arrhythmia symptoms was demonstrated in one RCT and in several large observational studies showing additional AF detection beyond the time frame of when a Holter monitor would be used (24 to 48 hours). When arrhythmia events are detected, management of patients typically involve antiarrhythmic or anticoagulant therapies, which are proven effective in stroke prevention. Therefore, longer term monitoring may improve health outcomes.

Section Summary: Continuously Worn Cardiac Monitors with Longer Recording Periods

The available evidence on continuously worn cardiac monitors that can store data for longer periods of time than standard Holter monitoring indicates that such devices typically detect greater numbers of arrhythmias during extended follow-up than 24- or 48-hour Holter monitoring. The evidence to suggest that long-term continuous monitors are superior to external loop recorders in detecting arrhythmias is not strong.

LONG-TERM AMBULATORY CARDIAC MONITORING FOR PATIENTS WITH ATRIAL FIBRILLATION FOLLOWING ABLATION

Clinical Context and Test Purpose

All patients treated with ablation are given anticoagulation for up to three months post-procedure, with many patients remaining on long-term anticoagulation. In patients with an apparently successful ablation who do not show signs or symptoms of recurrent AF at time periods longer than three months post-ablation, a decision whether to continue treatment with anticoagulants needs to be made. Studies have demonstrated that late recurrences are not

uncommon after ablation and that these recurrent episodes are often asymptomatic.^{25,26} However, the presence of recurrent episodes of AF is a predictor of future thromboembolic events. In a large observational study of 565 patients post-ablation, Chao et al (2011) found the 2 major predictors of thromboembolism were the CHADS2 score and the presence of recurrent episodes of AF.²⁷

The purpose of AEMs (either patient-activated or continuous) in patients with AF following ablation is to provide an alternative detection method for recurrent AF in order to accurately assess the need for anticoagulation therapy.

The question addressed in this evidence review is: Does the use of AEMs (either patient-activated or continuous) improve the net health outcome of patients with AF following ablation compared with ECG only or 24- to 48-hour Holter monitoring?

The following **PICO** was used to select literature to inform this review.

Patients

The relevant population of interest are individuals with AF following ablation.

Interventions

The intervention being considered is patient- or autoactivated external event monitoring or continuous ambulatory event monitoring. Patient-activated devices are applied to the skin in the precordial area by the patient when symptoms are developing. Continuous event monitoring devices are recording activity continuously and can store data longer than the Holter monitor.

Comparators

Alternative surveillance methods that are used include an ECG or 24- to 48-hour Holter monitoring. An ECG provides information on cardiac electrical activity in one point in time. A Holter monitor is worn continuously and records cardiac electrical output continuously throughout the recording period. Holter monitors are capable of recording activity for 24 to 72 hours.

Outcomes

The general outcome of interest is diagnostic yield of the monitors in detecting arrhythmias. If arrhythmias do not recur following ablation, patients may consider discontinuing anticoagulation therapy.

Study Selection Criteria

For the evaluation of clinical validity of autoactivated or patient-activated external ambulatory event monitoring for patients with arrhythmia symptoms, studies that met the following criteria were considered:

- To assess the clinical validity, studies should report sensitivity, specificity, positive and negative predictive values. Alternatively, studies reporting on diagnostic yield are informative.
- To assess the clinical utility, studies should demonstrate how results of the tests impacted treatment decisions and overall management of the patient.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Randomized Controlled Trials

In a prospective, randomized study, Kapa et al (2013) compared implantable loop monitors with conventional transtelephonic recorders in the assessment of arrhythmia burden after catheter ablation.²⁸ Forty-four patients were enrolled and randomized; all patients received the implantable loop recorder post-ablation. Six patients were excluded due to requests for device removal or loss to follow-up. During the first six months after ablation, all subjects underwent conventional monitoring that consisted of twice-daily one-minute pulse rate assessments by the patient and three 30-day transtelephonic monitoring periods. At six months post-ablation, patients were allocated to the randomization arm (on a 1:1 basis at initial enrollment) of either the implantable loop recorder (transmission of data every 31 days) or conventional monitoring (twice daily 1-minute pulse-rate assessment, and 1 trans-telephonic recording for 30 days at month 11). At 6 months post-ablation, conventional monitoring detected AF in 7 (18%) of 38 patients and the implantable loop recorder confirmed AF in all of these patients. ILR monitoring also detected AF in an additional 11 (29%) patients. During the subsequent six-month period, five of 18 patients in the conventional monitoring arm refused ongoing monitoring due to discomfort and lifestyle restrictions; of the remaining 13, five (38%) had a recurrence of AF. In the implantable loop recorder group, five (25%) of 20 patients had recurrence of AF. During the randomization period, 71% of patients in the ILR group discontinued their antiarrhythmic drugs compared with 44% in the conventional monitoring group over the randomization period ($p=0.04$).

Observational Studies

Reporting on the prospective DISCERN-AF (Discerning Symptomatic and Asymptomatic Episodes Pre and Post-Radiofrequency Ablation of AF) study, Verma et al (2013) evaluated the incidence of asymptomatic AF episodes for three months before and 18 months after ablation in 50 patients implanted with a cardiac monitor.²⁹ Patients were instructed to keep a standardized diary record of arrhythmia symptoms. Based on diary reporting of symptoms, 29 (58%) of 50 patients were arrhythmia-free after ablations were completed; based on occurrence of symptoms or the detection of AF on intermittent (every 3 month) ECG or Holter monitor, 28 patients (56%) were arrhythmia free after ablation. Six (12%) patients had arrhythmias detected on implantable monitoring alone.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. No RCTs were identified. Below is an observational study providing indirect evidence.

Several other observational studies have followed patients who stopped anticoagulation after an evaluation, which included ambulatory monitoring, was negative for recurrent episodes. These patients appear to have a low subsequent rate of thromboembolic events. In one study (Themistoclakis et al, 2010) evaluated 3,355 patients from five clinical centers, 2,692 discontinued anticoagulation at 3-6 months post-ablation and 663 continued anticoagulation medication.³⁰ During a mean follow-up of 28 months, two (0.07%) patients who discontinued anticoagulation experienced an ischemic stroke. This rate did not differ significantly from the stroke rate in patients who continued anticoagulation (0.45%). The rate of major hemorrhage was lower for patients who discontinued anticoagulation (2%) compared to those who continued (0.04%; $p < 0.001$).

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. An RCT and observational studies have shown that ambulatory monitoring was able to detect AF recurrences that were not detectable based on symptoms alone. No RCTs were identified that compared health outcomes for patients managed with and without ambulatory monitoring. However, there is a large observational study demonstrating that following ablation and a comprehensive evaluation including ambulatory monitoring that indicates a patient is low-risk, patients may consider discontinuing anticoagulation therapy. Patients who discontinued anticoagulation therapy following ablation experienced comparably low rates of stroke compared with patients remaining on anticoagulation therapy, and had statistically lower occurrences of major hemorrhage.

Section Summary: Long-term AEMs for Patients with AF Following Ablation

Evidence includes an RCT and several observational studies that make a strong indirect argument that long-term monitoring for asymptomatic episodes of atrial fibrillation with ambulatory event monitors will lead to changes in management of long-term anticoagulation. One study reported that patients who discontinued anticoagulation therapy after ambulatory monitoring was negative for recurrent episodes, experienced a low rate of stroke similar to patients who remained on anticoagulation therapy. These changes in management based on ambulatory monitoring are likely to improve outcomes.

LONG-TERM AMBULATORY CARDIAC MONITORING FOR PATIENTS WITH CRYPTOGENIC STROKE

Clinical Context and Test Purpose

Approximately 5% of patients with cryptogenic stroke will have atrial fibrillation diagnosed on ECG and/or telemetry monitoring in the hospital. The use of continuous telemetry monitoring has been compared with Holter monitoring for patients hospitalized for stroke or transient ischemic attack (TIA); these results are inconclusive as to which is the preferred method.^{31,32} Longer-term ambulatory event monitoring will identify additional patients with asymptomatic episodes, with rates of detection estimated at 6% to 26% of patients.^{5,33,34}

The purpose of long-term ambulatory cardiac monitoring in patients who have a history of cryptogenic stroke is to provide an alternative detection method for AF in order to accurately inform the decision to receive anticoagulation therapy.

The question addressed in this evidence review is: Does the use of long-term ambulatory cardiac event monitoring improve the net health outcome in patients with cryptogenic stroke compared with standard evaluation for stroke, including ECG and 24-hour Holter monitoring?

The following **PICO** was used to select literature to inform this review.

Patients

The relevant population of interest are individuals with a history of cryptogenic stroke with negative standard workup for AF.

Interventions

The intervention being considered is patient- or auto-activated external event monitoring or continuous ambulatory event monitoring. Patient-activated devices are applied to the skin in the precordial area by the patient when symptoms are developing. Continuous event monitoring devices are worn continuously and are recording activity continuously and can store data longer than the Holter monitor.

Comparators

The comparator is standard evaluation for stroke, including ECG or 24- to 48-hour Holter monitoring. An ECG provides information on cardiac electrical activity in one point in time. A Holter monitor is worn continuously and records cardiac electrical output continuously throughout the recording period. Holter monitors are capable of recording activity for 24 to 72 hours.

Outcomes

The general outcome of interest is diagnostic yield of the monitors in detecting arrhythmias. Accurate detection of arrhythmias may be used to inform management decisions concerning anticoagulation therapy.

Study Selection Criteria

For the evaluation of clinical validity of autoactivated or patient-activated external ambulatory event monitoring for patients with arrhythmia symptoms, studies that met the following criteria were considered:

- To assess the clinical validity, studies should report sensitivity, specificity, positive and negative predictive values. Alternatively, studies reporting on diagnostic yield are informative.
- To assess the clinical utility, studies should demonstrate how results of the tests impacted treatment decisions and overall management of the patient.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). Below are systematic reviews and RCTs providing evidence for the clinical validity of long-term ambulatory monitoring of patients with cryptogenic stroke.

Systematic Reviews

Sposato et al (2015) conducted a systematic review and meta-analysis of studies assessing rates of newly diagnosed AF after cryptogenic stroke or TIA based on cardiac monitoring, stratified into four sequential screening phases: phase 1 (emergency department) consisted of

admission ECG; phase 2 (in hospital) comprised serial ECG, continuous inpatient ECG monitoring, continuous inpatient cardiac telemetry, and in-hospital Holter monitoring; phase 3 (first ambulatory period) consisted of ambulatory Holter monitoring; and phase 4 (second ambulatory period) consisted of mobile cardiac outpatient telemetry (MCOT), external loop recording, and implantable loop recording.³⁵ In total, 50 studies with 11,658 patients met the inclusion criteria. Studies were mixed in their patient composition: 22 (28%) included only cryptogenic stroke cases, four (5%) stratified events into cryptogenic and non-cryptogenic, and 53 (67%) included unselected patient populations. The proportion of patients diagnosed with post-stroke AF during the ambulatory phases 10.7% (95% CI, 5.6% to 17.2%) in phase 3, and 16.9% (95% CI, 13.0% to 21.2%) in phase 4. The overall AF detection yield after all phases of sequential cardiac monitoring was 23.7% (95% CI, 17.2% to 31.0%). In phase 4, there were no differences between the proportion of patients diagnosed with poststroke AF by MCOT (15.3%; 95% CI, 5.3% to 29.3%), external loop recording (16.2%; 95% CI, 0.3% to 24.6%), or implantable loop recording (16.9%; 95% CI, 10.3% to 24.9%; $p=0.97$).

Kishore et al (2014) conducted a systematic review and meta-analysis of prospective observational studies and RCTs that have reported detection rates of newly diagnosed AF in patients with ischemic stroke or TIA who had had any cardiac monitoring for at least 12 hours.³⁶ Thirty-two studies were included: 18 studies included patients with ischemic stroke only, one study that included TIA only, and 13 studies included both ischemic stroke and TIA. Reviewers reported significant study heterogeneity. Among unselected patients (i.e., selected on the basis of stroke pathogenesis, age, or prescreening for AF), the detection rate of any new AF was 6.2% (95% CI, 4.4% to 8.3%) and among selected patients was 13.4% (95% CI, 9.0% to 18.4%). In cryptogenic strokes, new AF was detected in 15.9% (95% CI, 10.9% to 21.6%). Among selected patients, the AF detection rate during 24-hour Holter monitoring was 10.7% (95% CI, 3.4% to 21.5%), while the detection rate during monitoring beyond 24 hours (including more prolonged Holter monitoring, implantable and non-implantable loop recording, and MCOT) was 14.7% (95% CI, 10.7% to 19.3%).

The Kishore study and others suggest that longer periods of cardiac monitoring increase the likelihood of AF detection. However, many of these asymptomatic episodes of AF are brief and the relationship to the preceding stroke uncertain, as there are other potential causes of asymptomatic stroke. The ideal study to evaluate the role of cardiac monitoring in the management of patients with cryptogenic stroke would be trials that randomize patients to a strategy involving event monitoring or routine care with evaluation of rates of detection of AF and stroke-related outcomes.

Randomized Controlled Trials

Four RCTs were identified that evaluated ambulatory monitoring in patients with cryptogenic stroke. One small pilot RCT published by Kamel et al (2013) randomized 40 patients with cryptogenic ischemic stroke or high-risk TIA to usual care or to 21 days of MCOT (see Table 3).³⁷ There were no cases of atrial fibrillation detected in either group (see Table 4).

A second small pilot trial published by Higgins et al (2013) randomized 100 patients with ischemic stroke and no history of AF presenting within seven days of a cryptogenic ischemic stroke to either standard care, which included 12-lead ECG, 24-hour Holter monitoring, and/or echocardiography, at the discretion of the treating practitioner, or to standard care plus cardiac event monitoring with Novacor R-test Evolution 3, and ELR device (see Table 3).³⁸ Sustained AF (recorded for the complete 20-second rhythm strip after event triggering) was detected

significantly more often with the ELR than with standard care at 14-day follow-up. The difference did not differ statistically at 90-day follow-up (see Table 4).

Sanna et al (2014) reported on results from the CRYSTAL-AF trial, an RCT that evaluated whether long-term with implantable cardiac monitors in patients who had cryptogenic stroke would lead to changes in anticoagulant management and/or improved outcomes (see Table 3).^{39,40} The trial randomized 441 patients to continuous monitoring with the Reveal XT ICM or routine care. Eligibility criteria included no known history of AF, cryptogenic stroke, or TIA with infarct, and no mechanism determined after a workup that included 12-lead ECG, 24-hour Holter monitoring, transesophageal echocardiography, CT or magnetic resonance angiography of the head and neck, and hypercoagulability screening (for patients <55 years old). Analysis was intention-to-treat. Of the 441 patients randomized, 416 (94.3%) completed six-month follow-up, two were lost to follow-up, five died, and 18 exited the trial before six months. Crossover occurred in 12 patients in the ICM group and six in the control group. AF was detected in 8.9% of the ICM group compared with 1.4% of the control group (hazard ratio [HR], 6.43; 95% CI, 1.90 to 21.74). The median time from randomization to detection of AF was 41 days (interquartile range [IQR], 14-84) in the ICM group and 32 days (IQR, 2-73) in the control group. Most AF episodes in the ICM group were asymptomatic (74%), compared with 33% of those in the control group. The rate of AF detection was similarly greater in the ICM group at the 12-month follow-up (Table 4). A majority of patients who had AF detected were prescribed anticoagulation therapy. Five (2.4%) of the 208 ICM inserted were removed due to infection or erosion of the device pocket. Brachmann et al (2016) reported 3-year follow-up results from the CRYSTAL AF trial.⁴¹ At trial closure, 48 subjects had completed 3 years of follow-up (n=24 in each treatment group). By 3 years, the HR for detecting AF for ICM-monitored vs control patients was 8.8 (95% CI, 3.5 to 22.2; p<0.001).v

Gladstone et al (2014) reported results from the EMBRACE study, an RCT that compared 30-day auto-triggered external loop cardiac event monitors with conventional 24-hour monitors for the detection of AF in patients with cryptogenic stroke (see Table 3).⁴² Included patients were aged 55 years or older, with no known history of AF, and an ischemic stroke or TIA of undetermined cause within the prior six months. All patients underwent standard screening for AF with one or more ECGs and one or more 24-hour Holter monitors. In total, 572 patients were randomized to an external loop event recorder (ER910AF Cardiac Event Monitor, Braemar) or to a 24-hour Holter monitor. Among intervention group subjects, 82% completed at least three weeks of monitoring. AF was detected in 45 (16.1%) of 280 patients in the intervention group, compared with 9 (3.2%) of 277 in the control group (risk difference, 12.9 percentage points; 95% CI, 8.0 to 17.6; p<0.001). At 90-day of follow-up, patients in the intervention group (18.6%) were more likely to be treated with anticoagulants than the control group (11.1%; absolute treatment difference, 7.5 percentage points; 95% CI, 1.6 to 13.3; p=0.01).

Kaura et al (2018) compared monitoring with the Zio Patch to short-term Holter monitoring in 120 patients following TIA or ischemic stroke.⁴³ Patch-based monitoring was superior to standard monitoring for the detection of paroxysmal AF over the 90-day follow-up period (16.3% vs. 2.1%; odds ratio 8.0; 95% CI 1.1 to 76.0; P =.026).

Table 3. Summary of RCT Characteristics for AEM for Cryptogenic Stroke

Study	Country	Sites	Dates	Participants	Interventions (n)	
					Active	Comparator
Kamel et al (2013) ³⁷	U.S.	1	2009-2011	Cryptogenic ischemic stroke or high-risk TIA	MCOT (20)	Standard (20)
Higgins et al (2013) ³⁸	U.K.	2	2010-2011	Transient or persistent symptoms of acute TIA	ELR (50)	Standard (50)
Sanna et al (2014) ⁴⁰ & Brachmann et al (2016) ⁴¹	Canada, Europe, U.S.	55	2009-2012	Cryptogenic ischemic stroke or TIA	ILR (221)	Standard (220)
Gladstone et al (2014) ⁴²	Canada	16	NR	Cryptogenic ischemic stroke or TIA	ELR (280)	Standard (277)
Kaura et al (2019) ⁴³	United Kingdom	2	NR	Cryptogenic ischemic stroke or TIA	Zio Patch (60)	Standard (60)

AEMs: ambulatory event monitors; ELR: external loop recorder; ILR: implantable loop recorder; MCOT: mobile cardiac outpatient telemetry; NR: not reported RCT: randomized controlled trial; TIA: transient ischemic attack.

Table 4. Summary of RCT Results for AEMs for Cryptogenic Stroke

Study	FU	AF Detection			p	Additional Findings
		AEM, %	Standard, %			
Kamel et al (2013) ³⁷	90 d	0	0	NS	<ul style="list-style-type: none"> MCOT identified atrial tachycardia in 2 patients (1 incorrectly labeled as AF by telemetry software) MCOT identified 2 nonsustained ventricular tachycardia 	
Higgins et al (2013) ³⁸	14 d 90 d	18 22	2 8	<0.05 0.09	<ul style="list-style-type: none"> No difference between groups for recurrent stroke, TIA, or mortality Percent patients on oral anticoagulation therapy significantly higher in ILR group vs. standard group At 3-y FU, recurrent stroke or TIA occurred in 30 patients in ILR group and in 24 in standard group 	
Sanna et al (2014) ⁴⁰ ; Brachmann et al (2016) ⁴¹	6 mo 12 mo 3 y	8.9 12.4 30	1.4 2.0 3.0	<0.001 <0.001 <0.001	<ul style="list-style-type: none"> At 3-y FU, recurrent stroke or TIA occurred in 30 patients in ILR group and in 24 in standard group 	
Gladstone et al (2014) ⁴²	90 d	16.1	3.2	<0.001	<ul style="list-style-type: none"> Atrial premature beats were identified in a regression model as a potential predictor of AF detection 	
Kaura et al (2019) ⁴³	90 d	16.3	2.1	.026	<ul style="list-style-type: none"> AF detection at 28 days was 14.0% (6 patients) in the Zio Patch group vs. 2.1% (1 patient) in the standard group (P = .05) 	

AEM: ambulatory event monitor; AF: atrial fibrillation; FU: follow-up; ILR: implantable loop recorder; MCOT: mobile cardiac outpatient telemetry; RCT: randomized controlled trial; TIA: transient ischemic attack.

Nonrandomized Studies

Nonrandomized and noncomparative studies published before the RCTs described above have reported on AF detection rates after cryptogenic stroke and long-term monitoring with various types of monitors, including implantable loop recorders,^{6,44,45} and continuous monitors with longer recording periods,⁴⁶ along with a pilot study evaluating the Zio Patch for AF detection post-stroke.⁴⁷

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. No RCTs were identified demonstrating clinical utility.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. Clinical validity of long-term ambulatory monitoring in patients with cryptogenic stroke has been demonstrated in systematic reviews and RCTs that showed higher rates of AF detection with long-term monitoring. Because most patients with a history of stroke who have AF detected will be treated with anticoagulation, and because anticoagulation is an effective treatment for stroke prevention, it can be concluded that longer term monitoring of patients with cryptogenic stroke will improve outcomes.

Section Summary: Long-term AEM for Patients with Cryptogenic Stroke

Randomized studies, including 2 large RCTs, have demonstrated that long-term monitoring is associated with higher rates of AF detection than Holter monitors among patients with cryptogenic stroke. Because most patients with a history of stroke who have AF detected will be treated with anticoagulation, and because anticoagulation is an effective treatment for stroke prevention, it can be concluded that longer-term monitoring of patients with cryptogenic stroke will improve outcomes.

LONG-TERM AEMS AND AF DETECTION IN ASYMPTOMATIC PATIENTS

Clinical Context and Test Purpose

Screening for AF in asymptomatic patients has been proposed to reduce burden of stroke. Evaluating the net benefit of screening for AF in asymptomatic patients requires considering: risk of stroke in absence of screening; incremental benefit of earlier vs. later treatment for stroke when AF is detected; and potential harms of overdiagnosis.

Assessing the prevalence of asymptomatic AF is difficult because of the lack of symptoms. Approximately a third of all patients with AF are estimated to be asymptomatic.⁴⁸ Studies have suggested that most paroxysmal episodes of AF are asymptomatic.^{49,50} It is uncertain whether patients with paroxysmal AF have a stroke risk comparable to those with persistent or permanent AF; some studies have suggested the risk of stroke is similar^{51,52} while in a systematic review of 12 studies (total n=99996 patients), Ganesan et al (2016) found that the

risks of thromboembolism and all-cause mortality were higher with nonparoxysmal than with paroxysmal AF.⁵³ The clinical management of symptomatic and asymptomatic AF is the same. Anticoagulation should be initiated if reduction in risk of embolization exceeds complications due to increased bleeding risk.

Screening for AF in asymptomatic patients could be either systematic or targeted to high-risk populations. European guidelines for screening for AF are based on a large-cluster RCT (Fitzmaurice et al [2007]; N=14,802) of opportunistic pulse taking versus systematic screening with 12-lead ECG or standard care in general practice.⁵⁴ This RCT showed that systematic and opportunistic screening detected similar rates of AF, and both were superior to standard care. The mechanisms of how and when to screen for AF in unselected populations have not been well-studied.

The purpose of long-term ambulatory cardiac monitoring in patients who are asymptomatic with risk factors for AF is to provide an alternative method of detecting AF.

The question addressed in this evidence review is: Does the use of long-term ambulatory cardiac monitoring in patients who are asymptomatic with risk factors for AF improve net health outcome compared with no additional evaluation or standard of care?

The following **PICO** was used to select literature to inform this review.

Patients

The relevant population of interest are asymptomatic individuals with risk factors for AF.

Interventions

The intervention being considered is patient- or autoactivated external event monitoring or continuous ambulatory event monitoring. Patient-activated devices are applied to the skin in the precordial area by the patient when symptoms are developing. Continuous event monitoring devices are worn continuously and are recording activity continuously and can store data longer than the Holter monitor.

Comparators

The comparators are no additional evaluation or standard care. Standard care may include an ECG and/or pulse palpation.

Outcomes

The general outcome of interest is diagnostic yield of the monitors in detecting arrhythmias. Accurate detection of arrhythmias may be used to inform management decisions of the asymptomatic patients.

Study Selection Criteria

For the evaluation of clinical validity of autoactivated or patient-activated external ambulatory event monitoring for patients with arrhythmia symptoms, studies that met the following criteria were considered:

- To assess the clinical validity, studies should report sensitivity, specificity, positive and negative predictive values. Alternatively, studies reporting on diagnostic yield are informative.

- To assess the clinical utility, studies should demonstrate how results of the tests impacted treatment decisions and overall management of the patient.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Observational Studies

Turakhia et al (2015) reported on results for a single-center noncomparative study evaluating the feasibility and diagnostic yield of a continuous recording device with longer recording period (the Zio® Patch) for patients with risk factors for AF.⁵⁶ The study included 75 patients older than age 55 with at least two risk factors for AF (coronary disease, heart failure, hypertension, diabetes, or sleep apnea), without a history of prior AF, stroke, TIA, implantable pacemaker or defibrillator, or palpitations or syncope in the prior year. Of the 75 subjects, 32% had a history of significant valvular disease, and 9.3% had prior valve replacement. Most subjects (97%) were considered to be at moderate to high risk of stroke (CHA₂DS₂ - VASc ≥2). After a mean follow-up of 7.6 days, AF was detected in four (5.3%) subjects, all of whom had CHA₂DS₂ -VASc scores of 2 or greater. All patients with AF detected had an initial episode within the first 48 hours of monitoring. Five patients had detected episodes of atrial tachyarrhythmias lasting at least 60 seconds.

Heckbert et al (2018) reported results of an ancillary study of the Multi-Ethnic Study of Atherosclerosis (MESA), designed to determine the prevalence of AF, atrial flutter, and other arrhythmias in participants 45–84 years of age and free of clinically-recognized cardiovascular disease.⁵⁷ A total of 1122 participants completed one or two monitoring episodes using the Zio Patch. The mean age of participants at the time of monitoring was 75 (SD 8) years. Among the 804 participants with no prior history of clinically-recognized AF/flutter, 32 (4.0%) had AF/flutter detected during the monitoring period, representing a new diagnosis. Among the 32 individuals with AF/flutter detected, the arrhythmia was detected at device activation or during the initial 24 hours in 15 (47%), during the second 24 hours in 5 (16%), and during days 3 to 12 of monitoring in 12 (38%).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Randomized Controlled Trials

Halcox et al (2017) conducted an RCT (REmote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation) which screened patients for AF using the AliveCor Kardia monitor (n=500) or routine care (n=501).⁵⁵ Patients were 65 years and older, asymptomatic, with CHA₂DS₂-VASc scores of 2 or higher. Patients randomized to the Kardia monitor arm undertook twice-weekly, 30-second single-lead ECG recordings and uploaded the information to a secure server. Analysis was performed using an automated software system and forwarded to a physiologist reading service. Abnormal ECG readings were sent to cardiologists. Appropriate care was arranged when arrhythmias were detected. Patients in the routine care arm were followed by their general practitioners. All patients were contacted at 12, 32, and 52 weeks. At 52-week follow-up, 19 patients in the Kardia monitor arm and 5 patients in the routine care arm were diagnosed with AF (HR, 3.9; 95% CI, 1.4 to 10.4; p=0.007). There

were no significant differences in the rates of mortality; stroke, TIA, or spontaneous embolism; deep vein thromboembolism or pulmonary embolism; or other cardiovascular events between groups.

An RCT reported by Gladstone et al (2021) evaluated screening for AF with continuous ambulatory monitoring (the Zio XT patch worn for up to 4 weeks) compared to standard care (routine clinical follow-up plus a pulse check and heart auscultation at baseline and 6 months) in 876 asymptomatic adults over age 75 with hypertension and without known AF.⁵⁸ The primary outcome was AF detected by continuous monitoring or clinically within 6 months. At 6-month follow-up, AF was detected in 23 of 434 participants (5.3%) in the screening group, compared to 2 of 422 (0.5%) in the control group (relative risk, 11.2; 95% CI, 2.7 to 47.1; $p=0.001$; absolute difference, 4.8%; 95% CI, 2.6% to 7.0%; $p<0.001$; number needed to screen, 21). Anticoagulant treatment was initiated in 4.1% of the screening group compared to 0.9% of the control group (relative risk, 4.4; 95% CI, 1.5 to 12.8; $p=0.007$; absolute difference, 3.2%; 95% CI, 1.1% to 5.3%; $p=0.003$). During the 6-month study period, 1 participant died (control group; cardiovascular death) and 2 participants had an ischemic stroke (both in the screening group). One patient had a TIA (screening group). The trial was not powered to detect clinical outcomes and was of insufficient duration to draw conclusions on health outcomes.

Section Summary: Long-term AEM for Asymptomatic Patients

For the use of ambulatory monitoring in the diagnosis of AF in asymptomatic but higher risk patients, noncomparative studies demonstrated that monitoring with the Zio Patch resulted in a small percentage (4% to 5%) of AF detection. The studies showed use of the ambulatory monitors would result in higher AF detection compared with routine care. One RCT followed patients for 1 year and did not detect a difference in stroke occurrence between a monitored group and a standard of care group. In a second RCT conducted in older adults with hypertension, continuous monitoring led to detection of AF in 5.3% of the screening group compared to 0.5% of the control group, and initiation of anticoagulant treatment in 4.1% of the screening group compared to 0.9% of the control group at 6 months. The trial was not powered to detect clinical outcomes and was of insufficient duration to draw conclusions on health outcomes. The other studies did not discuss changes in patient management or health outcomes based on monitoring. Studies reporting on improved outcomes with longer follow-up are needed.

IMPLANTABLE LOOP RECORDERS (ILRs) FOR PATIENTS WITH SYMPTOMS OF ARRHYTHMIA

Clinical Context and Test Purpose

This section discusses the use of implantable loop recorders (ILRs), with a focus on clinical situations when use of an ILR at the beginning of a diagnostic pathway is indicated. It is expected that a longer period of monitoring with any device category is associated with a higher diagnostic yield. A progression in diagnostics from an external event monitor to ILR in cases where longer monitoring is needed, is considered appropriate. However, there may be situations where it is sufficiently likely that long-term monitoring will be needed and that an ILR as an initial strategy may be reasonable.

The purpose of ILRs in patients with signs or symptoms suggestive of arrhythmia with infrequent symptoms is to provide an alternative method of arrhythmia detection.

The question addressed in this evidence review is: Does the use of ILRs in individuals with signs or symptoms suggestive of arrhythmia with infrequent symptoms improve net health benefits compared with no additional evaluation, standard care, or external AEMs?

The following **PICO** was used to select literature to inform this review.

Patients

The relevant population of interest are individuals with signs or symptoms suggestive of arrhythmia with infrequent symptoms.

Interventions

The intervention of interest is an ILR. ILRs store electrical cardiac activity data. When activated (by patient or automatically), the cardiac activity is recorded from the memory loop. ILRs are implanted under the skin in the precordial area.

Comparators

Comparators of interest include no additional evaluation, standard care, or external AEMs. External AEMs may be patient- or autoactivated. Patient-activated devices are applied to the skin in the precordial area by the patient when symptoms are developing. Continuous event monitoring devices are worn continuously and are recording activity continuously, storing data longer than the Holter monitor.

Outcomes

The general outcome of interest is diagnostic yield of the ILRs in detecting arrhythmias. Accurate detection of arrhythmias may be used to inform management decisions of the individuals with infrequent symptoms.

Study Selection Criteria

For the evaluation of clinical validity of autoactivated or patient-activated external ambulatory event monitoring for patients with arrhythmia symptoms, studies that met the following criteria were considered:

- To assess the clinical validity, studies should report sensitivity, specificity, positive and negative predictive values. Alternatively, studies reporting on diagnostic yield are informative.
- To assess the clinical utility, studies should demonstrate how results of the tests impacted treatment decisions and overall management of the patient.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews

Solbiati et al (2017) conducted a systematic review and meta-analysis on the diagnostic yield of ILRs in patients with unexplained syncope.⁵⁹ The literature search, conducted through November 2015, identified 49 studies, published between 1998 and 2015, enrolling a total of 4381 patients. The methodologic quality of the studies was assessed using QUADAS and QUADAS-2. The diagnostic yield of ILR, defined as the proportion of patients in which ILR was useful in determining a syncope diagnosis was 44% (95% CI, 40% to 48%; I²=80%).

Diagnoses included arrhythmic syncope, ventricular arrhythmia, supraventricular arrhythmia, and bradyarrhythmia. Reviewers noted that an important analytic limitation was the considerable heterogeneity among studies, partly because definitions of syncope and methods to assess unexplained syncope were inconsistent.

Burkowicz et al (2016) conducted a systematic review and meta-analysis of ILRs in the diagnosis of syncope and the detection of AF.⁶⁰ For syncope diagnosis, the review identified three RCTs comparing ILRs with a conventional diagnosis strategy (Holter monitoring). In pooled analysis, an ILR diagnosis strategy was associated with a higher likelihood of the endpoint of diagnostic yield (relative risk [RR] 4.17, 95% CI 2.57 to 6.77, $I^2=14\%$). The RCTs (Da Costa et al [2013],⁶¹ Farwell et al [2004],⁶² and Krahn et al [2001]⁶³) are described below.

Afzal et al (2015) reported on a systematic review and meta-analysis of studies comparing ILRs with wearable AEMs for prolonged outpatient rhythm monitoring after cryptogenic stroke.⁶⁴ Reviewers included 16 studies (total n=1770 patients)-3 RCTs and 13 observational studies. For ILR-monitored patients, the median monitoring duration was 365 days (range, 50-569 days), while for wearable device-monitored patients, the median monitoring duration was 14 days (range, 4-30 days). Compared with wearable AEMs, ILRs were associated with significantly higher rates of AF detection (23.3% vs. 13.6%; odds ratio, 4.54; 95% CI, 2.92 to 7.06; $p<0.05$).

Randomized Controlled Trials

Podoleanu et al (2014) reported on results of an open-label RCT comparing two strategies for evaluating syncope; an experimental strategy involving the early use of an ILR and a conventional evaluation strategy excluding an ILR (see Table 5).⁶⁵ The trial included patients who had a single syncope (if severe and recent), or at least two syncopes in the past 12 months. The syncope had to be unexplained at the end of clinical examination that included a workup with 12-lead ECG, echocardiography, and head-up tilt-test. Patients randomized to ILR received the Reveal or Reveal Plus device. After 14 months of follow-up, a definitive cause of syncope was established more frequently in the ILR group than in the standard care group (see Table 6). Arrhythmic causes of syncope in the ILR group included two (5%) cases of atrioventricular (AV) block, four (10%) cases of sinus node disease, one (2.5%) case of AF, one (2.5%) case of ventricular fibrillation, and three (8%) other tachycardias. In the conventionally managed group, eight patients had a diagnosis of presumed reflex syncope.

A small RCT by Da Costa et al (2013) compared use of an ILR with a conventional follow-up strategy in 78 patients with a first episode of syncope (see Table 5).⁶⁶ A significant number of patients had cardiomyopathy (23%), AF (15.4%), and/or bundle branch block (58%) on ECG. Twenty-one (27%) patients had at least one arrhythmia detected, with a significant difference in detection rate for the ILR group compared with the conventional follow-up group (see Table 6).

Giada et al (2007) conducted an RCT assessing two diagnostic strategies in 50 patients with infrequent (≤ 1 episode per month) unexplained palpitations: an ILR strategy (n=26) and a conventional strategy (n=24) including 24 hour Holter, four weeks of ambulatory ECG monitoring with an external recorder, and an electrophysiologic study if the two prior evaluations were negative) (see Table 5).⁶⁷ Prior cardiac evaluation in eligible patients included standard ECG and echocardiography. Rhythm monitoring was considered diagnostic when a symptom-rhythm correlation was demonstrated during spontaneous palpitations that

resembled pre-enrollment symptoms. In the conventional strategy group, a diagnosis was made in five (21%) subjects, after a mean time to diagnosis of 36 days, based on external ECG monitoring in two subjects and electrophysiologic studies in three subjects. In the ILR group, a diagnosis was made in 19 subjects after a mean time to diagnosis of 279 days (see Table 6).

Farwell et al (2004) reported on an RCT comparing the diagnostic yield of an ILR (Reveal Plus) with a conventional diagnostic strategy in 201 patients with unexplained syncope (see Table 5).⁶² Eligible patients were evaluated at a single institution for recurrent syncope and had no definitive diagnosis after a basic initial workup (including 12-lead ECG, Holter monitoring in patients with suspected cardiac syncope, upright cardiac sinus massage, and tilt-table testing). At last follow up, more loop recorder patients had an ECG diagnosis than control patients (HR for ECG diagnosis 8.93, 95% CI 3.17 to 25.19, P<0.0001) (see Table 6). Seven of the loop recorder patients were diagnosed with the device's auto-trigger feature. In the loop recorder group, 34 patients had an ECG-directed therapy initiated (vs.4 in the control group; HR=7.9, 95% CI 2.8 to 22.3). No device-related adverse events were reported.

An earlier RCT by Krahn et al (2001) compared a conventional monitoring strategy (ELR monitoring for 2-4 weeks, followed by tilt-table and electrophysiologic testing) with at least one year of monitoring using an ILR in 60 subjects with unexplained syncope (n=30 per group) (see Table 5).⁶³ Eligible patients had previous clinical assessment, at least 24 hours of continuous ambulatory monitoring or inpatient telemetry, and a transthoracic echocardiogram. A diagnosis was made in 20% of those in the conventional monitoring arm and in 52% of those in the ILR arm (see Table 6).

Table 5. Summary of RCT Characteristics for ILRs for Arrhythmia

Study	Country	Sites	Dates	Participants	Interventions (n)	
					Active	Comparator
Podoleanu et al (2014)	France	13	2004-2008	Single recent syncope or 2 in past 12 mo	ILR (39)	Standard (39)
Da Costa et al (2013)	France	Multiple, NS	2005-2010	Single syncope	ILR (41)	Standard (37)
Giada et al (2007)	Italy	Multiple, NS	NR	Unexplained palpitations	ILR (26)	Standard (24)
Farwell et al (2004)	England	1	2000-2001	≥2 unexplained syncope in past 12 mo	ILR (103)	Standard (98)
Krahn et al (2001)	England	1	NR	Single or recurrent unexplained syncope	ILR (27)	ELR (30)

ELR: external loop recorder; ILR: implantable loop recorder; NR: not reported; NS: not specified; RCT: randomized controlled trials

Table 6. Summary of RCT Results for ILRs for Arrhythmia

Study	FU	Diagnosis Made, n (%)			Additional Findings
		ILR	Standard	p	
Podoleanu et al (2014)	14 mo	18 (46)	2 (5)	<0.001	<ul style="list-style-type: none"> Advanced cardiology tests performed less frequently in ILR group vs. standard (p=0.05) No difference in QOL

Da Costa et al (2013)	27 mo ^a	15 (37)	4 (11)	0.02	Earlier diagnosis in ILR group permitted earlier pacemaker implantation. However, earlier implantation did not improve survival (potentially due to small sample)
Giada et al (2007)	≥12 mo	19 (73)	5 (21)	<0.001	9 of 19 patients with negative results with standard care crossed over to ILR and 6 of them received a diagnosis
Farwell et al (20004)	≥6 mo	34 (33)	4 (4)	<0.001	<ul style="list-style-type: none"> • ECG-directed therapy was initiated quicker in the ILR group • No difference in syncopal episodes, mortality, or QOL
Krahn et al (2001)	12 mo	14 (52)	6 (20)	0.012	<ul style="list-style-type: none"> • Crossover offered to patients with negative results • 1 of 6 switching to ELR was diagnosed and 8 of 13 switching to ILR was diagnosed (p=0.07)

ECG: electrocardiogram; FU: follow-up; HR: hazard ratio; ILR: implantable loop recorder; QOL: quality of life; RCT: randomized controlled trial
^a Mean

Observational Studies

Several observational studies compared the diagnostic yield of ICMs to the Holster monitor. Other observational studies reported management outcomes following diagnoses, such as anticoagulation initiation or cardiac procedures.

Magnusson et al (2018) presented outcomes in a cohort of patients who received ILRs (n=173).⁶⁷ Among the patients evaluated for syncope, 39 (27%) were diagnosed with an arrhythmia necessitating a pacemaker and 2 (1%) were diagnosed with an arrhythmia necessitating an implantable cardioverter defibrillator.

Maines et al (2017) described outcomes in 154 consecutive patients receiving the Reveal LINQ ILR.⁶⁸ After a mean follow-up of 12 months, a diagnosis was made in 99 (64%) patients. In response to the diagnoses, 20 patients initiated anticoagulation therapy, 18 patients had pacemakers implanted, 22 patients underwent electrophysiological study and ablation, and 14 changed antiarrhythmic medications.

Ciconte et al (2017) published results from 66 patients with documented AF or symptoms attributable to AF, who were given an implantable monitoring device (BioMonitor).⁶⁹ Recordings from the monitoring device were compared with 48-hour Holter monitoring results performed 4 weeks after implantation. Sensitivity and positive predictive value for AF detection of the implantable monitoring device were 95% and 76%, respectively.

Bhangu et al (2016) reported on the diagnostic yield of ILRs in a series of 70 elderly patients with unexplained falls.⁷⁰ Cardiac arrhythmias were detected in 49 (70%) of the patients within a mean time of 47 days. A fall in 14 (20%) patients were attributed to the arrhythmia. Ten patients received a cardiac pacemaker.

Nolker et al (2016) published results of the Performance of an Implantable Cardiac Monitor to Detect Atrial Fibrillation study, in which readings from an ICM (Confirm ICM, St. Jude Medical) were compared with readings from a Holter monitor used for 4 days at least 2 weeks post implant.⁷¹ Patients had either been diagnosed with or had a clinical suspicion of paroxysmal

AF (n=90). Due to difficulties with synchronizing the Holter monitor and the implanted device, data from only 79 patients were used in calculations. Patient-level sensitivity, positive predictive value, specificity, and negative predictive value were 100%, 64%, 86%, and 84%, respectively. Episode-level sensitivity, positive predictive value, specificity, and negative predictive value were 95%, 64%, 87%, and 76%, respectively.

Sanders et al (2016) reported on the diagnostic yield for AF with the Reveal LINQ device, a miniaturized ILR with a detection algorithm designed to detect AF.⁷² This nonrandomized, prospective trial included 151 patients, most of whom (81.5%) were undergoing monitoring for AF ablation or AF management. Compared with Holter-detected AF, the ILR had a diagnostic sensitivity and specificity for AF of 97.4% and 97.0%, respectively.

Ziegler et al (2015) reported on a large (n=1247) set of patients identified from the manufacturer's registry undergoing ILR monitoring for AF detection after a cryptogenic stroke.⁷³ Over a median follow-up of 182 days, 1521 episodes of AF were detected in 147 patients. Overall, 42 (29%) patients had a single episode of AF and 105 (71%) patients had multiple episodes. The overall detection rate (12.2% at 182 days) was somewhat higher than that reported in the CRYSTAL AF trial.

In a report from a registry of patients who received or were about to receive an ILR (the Reveal Plus, DX, or XT device) because of unexplained syncope, Edvardsson et al (2014) described the monitoring yield in 570 patients implanted and followed for at least a year or until diagnosis.⁷⁴ Most (97.5%) patients had a standard ECG before implantation of the ILR, 11.8% had prior ELR, and 54.6% had in-hospital ECG monitoring. During the monitoring period, 218 (38%) patients had recurrent syncope. The proportion of specific diagnoses based on the ILR is not reported, but of subjects who had a recurrence, 42.2% had a pacemaker implanted, 4.6% had an implantable cardioverter defibrillator placed, 4.1% received antiarrhythmic drug therapy, and 3.7% underwent catheter ablation.

Hindricks et al (2010) evaluated the accuracy of an auto-triggered ILR in 247 patients at high-risk for paroxysmal AF.⁷⁵ All patients underwent simultaneous 46-hour continuous Holter monitoring, and the authors calculated the performance characteristics of the loop recorder using physician-interpreted Holter monitoring as the criterion standard. The sensitivity of the loop recorder for detecting AF episodes of 2 or more minutes was 88.2%, increasing to 92.1% for episodes of 6 or more minutes. AF was falsely identified by the loop recorder in 19 of 130 patients who did not have AF while on a Holter monitor, for a false-positive rate of 15%. AF burden was accurately measured by the loop recorder, with the mean absolute difference between the loop recorder and Holter monitor of 1.4%.

Hanke et al (2009) compared an auto-trigger ILR with 24-hour Holter monitoring done at 3-month intervals in 45 patients who had undergone surgical ablation for AF.⁷⁶ After a mean follow-up of 8.3 months, the ILR identified AF in 19 (42%) patients in whom Holter monitoring recorded sinus rhythm.

Safety of ILRs

Mittal et al (2015) reported on safety outcomes related to the use of an ILR, based on data from two studies, the Reveal LINQ Usability study and the Reveal LINQ Registry.⁷⁷ The Usability study enrolled 151 patients at 16 European and Australian centers; adverse events were reported for the first month of follow up. The Registry is a multicenter post-marketing

surveillance registry, with a planned enrollment of at least 1,200. At the time of analysis, 161 patients had been enrolled. For Registry patients, all adverse events were recorded when they occurred. The device is inserted with a preloaded insertion tool via a small skin incision. In the Usability study, one serious adverse event was recorded (insertion site pain); in the Registry study, two serious adverse events were recorded (one case each of insertion site pain and insertion site infection). The rates of infection and procedure-related serious adverse events in the Usability study were 1.3% and 0.7%, respectively, and were 1.6% and 1.6%, respectively, in the Registry study.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. No RCTs providing evidence for clinical utility were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. Evidence for clinical validity was provided by several RCTs, which showed that significantly more diagnoses were made with ILRs compared with Holter monitors or other standard care. Many observational studies reported the initiation of treatment (for example, anticoagulation therapy or pacemaker implantation) following the confirmation of diagnoses with the ILR. Because these treatments are known to be effective, it can be concluded that long-term monitoring with ILRs will improve health outcomes.

Section Summary: ILRs for Patients with Symptoms of Arrhythmia

Studies of prolonged use of ILRs in patients have reported high rates of arrhythmia detection compared with external event monitoring or Holter monitoring. These studies support the use of a progression in diagnostics from an external event monitor to ILR when longer monitoring is needed. Some available trials evaluating the detection of AF after ablation procedures or in patients with cryptogenic stroke used ILRs as an initial ambulatory monitoring strategy, after a negative Holter monitor. Many observational studies reported the initiation of treatment (for example, anticoagulation therapy or pacemaker implantation) following the confirmation of diagnoses with the ILR. Because these treatments are known to be effective, it can be concluded that long-term monitoring with ILRs will improve health outcomes.

MOBILE CARDIAC OUTPATIENT TELEMETRY FOR PATIENTS WITH SYMPTOMS OF ARRHYTHMIA

Clinical Context and Test Purpose

This section addresses whether the addition of real-time monitoring to ambulatory cardiac monitoring (MCOT) is associated with improved outcomes. Two factors must be addressed in evaluating MCOT: (1) the inherent detection capability of the monitoring devices and (2) whether the real-time transmission and interpretation of data confers an incremental health

benefit. The proposed addition of real-time monitoring suggests that there may be a subset of individuals who require immediate intervention when an arrhythmia is detected. Because it is not clear which patients comprise that subset, or whether identification of those patients in the outpatient setting leads to improved outcomes (e.g., reduced risks of sudden cardiac death), the evaluation of the second factor requires studies that directly assess outcomes, not just arrhythmia detection rates.

The purpose of outpatient cardiac telemetry in patients with signs or symptoms suggestive of arrhythmia is to provide an alternative method of transmitting electrical cardiac activity data to healthcare providers.

The question addressed in this evidence review is: Does the use of outpatient cardiac telemetry added to ambulatory cardiac monitoring improve net health outcome in patients with signs or symptoms suggestive of arrhythmia compared with ambulatory cardiac event monitoring alone?

The following **PICO** was used to select literature to inform this review.

Patients

The relevant population of interest are patients with signs or symptoms suggestive of arrhythmia.

Interventions

The therapy being considered is MCOT system which transmits ambulatory cardiac monitoring data in real-time to healthcare providers.

Comparators

The comparator of interest is ambulatory cardiac monitoring alone.

Outcomes

The general outcome of interest is the incremental benefit of transmitting the ambulatory cardiac monitoring data in real-time.

Study Selection Criteria

For the evaluation of clinical validity of autoactivated or patient-activated external ambulatory event monitoring for patients with arrhythmia symptoms, studies that met the following criteria were considered:

- To assess the clinical validity, studies should report sensitivity, specificity, positive and negative predictive values. Alternatively, studies reporting on diagnostic yield are informative.
- To assess the clinical utility, studies should demonstrate how results of the tests impacted treatment decisions and overall management of the patient.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Randomized Controlled Trials

An RCT by Rothman et al (2007), compared MCOT with standard event monitors (Table 7).⁷⁸ This trial involved 305 patients randomized to the LOOP recorder or to MCOT (CardioNet) and monitored for up to 30 days. The unblinded study at 17 centers enrolled patients with symptoms of syncope, presyncope, or severe palpitations occurring less frequently than once per 24 hours and a nondiagnostic 24-hour Holter or telemetry monitor within the prior 45 days. Test results were read by an electrophysiologist blinded to the monitoring device assignment. Most patients in the control group had a patient-triggered event monitor. Only a subset of patients (n=50) had auto-trigger devices, thus precluding a comparison between MCOT and auto-trigger devices. Of the 305 patients, 266 completed at least 25 days of monitoring. A diagnostic end point (confirmation or exclusion of arrhythmic cause of symptoms) was found in 88% of MCOT patients and in 75% of LOOP patients (p=0.008). The difference in rates was primarily due to detection of asymptomatic (not associated with simultaneous symptoms) arrhythmias in the MCOT group, symptoms consisting of rapid AF and/or flutter (15 patients vs. one patient), and ventricular tachycardia defined as more than three beats and rate greater than 100 (14 patients vs. two patients). These differences were thought to be clinically significant rhythm disturbances and the likely causes of the patients' symptoms. The trialists did not comment on the clinical impact (changes in management) of these findings in patients for whom the rhythm disturbance did not occur simultaneously with symptoms. In this trial, median time to diagnosis in the total study population was seven days in the MCOT group and nine days in the LOOP group (Table 8). The trialists did not comment on the clinical impact (changes in management) of these findings in patients for whom the rhythm disturbance did not occur simultaneously with symptoms.

Table 7. Summary of RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions		Duration
					Active	Comparator	
Rothman (2007) ⁷⁷	US	17	NR	Patients with a high clinical suspicion of a malignant arrhythmia, with syncope, presyncope, or severe palpitations, and a nondiagnostic 24-hr Holter test	Mobile automated cardiac outpatient telemetry (CardioNet)	Patient-activated external looping event monitor	Confirmation of a diagnosis, up to 30 days
					N=134	N=132	

NR: not reported; RCT: randomized controlled trial

Table 8. Summary of RCT Results

Study	Confirmation or Exclusion of Arrhythmic Cause of Symptoms, n(%)	Confirmation or Exclusion of Arrhythmic Cause of Symptoms in Subgroup with Syncope, n(%)	Confirmation or Exclusion of Arrhythmic Cause of Symptoms in Subgroup Auto-triggered Recorder, n(%)	Time to Diagnosis Median (95% CI)
Rothman (2007) ⁷⁷	263	113	50	263
MCOT	117 (88.0)	55 (88.7)	21 (87.5)	7 (4 to 11)
LOOP	98 (75.4)	35 (68.6)	12 (46.2)	9 (7 to 15)
p-value	0.008	0.008	0.002	NR

Observational Studies

Arrhythmia Detection

Derkac et al (2017) retrospectively reviewed the BioTelemetry database of patients receiving ambulatory ECG monitoring, selecting patients prescribed MCOT (n=69,977) and patients prescribed AT-LER, an auto-trigger looping event recorder (n=8513).⁷⁹ Patients were diagnosed with palpitations, syncope and collapse, AF, tachycardia, and/or TIA. Patients given the MCOT were monitored for an average of 20 days and patients given the AT-LER were monitored an average of 27 days. The diagnostic yield using MCOT was significantly higher than that using AT-LER for several events: 128% higher for AF, 54% higher for bradycardia, 17% higher for ventricular pause, 80% higher for SVT, and 222% higher for ventricular tachycardia. Mean time to diagnosis for each asymptomatic arrhythmia was shorter for patients monitored by MCOT than by AT-LER. There was no discussion of management changes or health outcomes based on monitoring results.

Kadish et al (2010) evaluated the frequency with which events transmitted by MCOT represented emergent arrhythmias, thereby indirectly assessing the clinical utility of real-time outpatient monitoring.⁸⁰ Medical records from 26,438 patients who had undergone MCOT during a 9-month period from a single service provider were retrospectively examined. During a mean monitoring period of 21 days, 21% (5,459) had an arrhythmic event requiring physician notification. Of these, 1% (260) had an event that could be considered potentially emergent. These potentially emergent events included 120 patients with wide-complex tachycardia, 100 patients with sinus pauses six seconds or longer, and 42 with sustained bradycardia at less than 30 beats per minute.

A number of uncontrolled case series have reported on arrhythmia detection rates of MCOT.⁸¹⁻⁸⁴ One study (Joshi et al [2005]) described the outcomes of a consecutive case series of 100 patients.⁸⁰ Included patients had the following symptoms: palpitations (47%), dizziness (24%), or syncope (19%). Patients being evaluated for the efficacy of drug treatment (25%) were also included. Clinically significant arrhythmias were detected in 51% of patients, but half of these patients were asymptomatic. The authors commented that the automatic detection results in an increased diagnostic yield, but there was no discussion of its unique feature (i.e., the real-time analysis, transmission and notification of arrhythmia).

AF Detection

In the largest study evaluating the diagnostic yield of MCOT for AF, Favila et al (2015) evaluated a retrospective cohort of 227 patients with cryptogenic stroke or TIA who underwent 28 days of monitoring with MCOT.⁸⁵ AF was detected in 14% (31/227) of patients, of whom three reported symptoms at the time of AF. Oral anticoagulation was initiated in 26 (84%) patients diagnosed with AF. Of the remaining five (16%) not on anticoagulation therapy, one had a prior history of gastrointestinal bleeding, three were unwilling to accept the risk of bleeding, and one failed to follow-up.

Miller et al (2013) retrospectively analyzed paroxysmal AF detection rates among 156 patients evaluated with MCOT within six months of a cryptogenic stroke or TIA.³⁴ Over a median 21-

day period of MCOT monitoring (range, 1 to 30 days), AF was detected in 17.3% of patients. Mean time to first occurrence of AF was 9 days (range, 1 to 21 days).

In another uncontrolled case series, Tayal et al (2008) retrospectively analyzed patients with cryptogenic stroke who had not been diagnosed with atrial fibrillation by standard monitoring.⁸⁴ In this study, 13 (23%) of 56 patients with cryptogenic stroke had AF detected by MCOT. Twenty-seven asymptomatic atrial fibrillation episodes were detected in the 13 patients; 23 of them were less than 30 seconds in duration. In contrast, Kalani et al (2015) reported a diagnostic yield for AF of 4.7% (95% CI, 1.5% to 11.9%) in a series of 85 patients with cryptogenic stroke.⁸⁶ In this series, 82.4% of patients had completed transesophageal echocardiography, cardiac magnetic resonance imaging, or both, with negative results. Three devices were used and described as MCOT devices: 34% received LifeStar ACT ambulatory cardiac telemetry, 41% received the LifeStar AF Express autodetect looping monitor, and 25% received the Cardiomedix cardiac event monitor. While the authors reported that there was a system in place to transmit the data for review, it is unclear whether data were sent in “real-time.”

Narasimha et al (2018) published results of a study in which 33 patients wore both an ELR and a Kardia monitor to screen for AF during a period of 14 to 30 days.⁸⁷ Patients were 18 years or older, had palpitations less often than daily but more frequently than several times per month, and prior nondiagnostic ECGs. Exclusion criteria included myocardial infarction within the last three months, history of ventricular tachycardia/fibrillation, unstable angina, and syncope. Study personnel viewed the Kardia monitor recordings once daily and a physician was contacted if a serious or sustained arrhythmia was detected. Patients were also monitored by the ELR company, which notified a physician on call when necessary. All 33 patients had a diagnosis using the Kardia monitor and 24 patients received a diagnosis using the ELR ($p=0.001$).

Dorr et al (2019) compared the diagnostic accuracy of a smartwatch system with cardiologists' interpretation of an ECG in the diagnostic accuracy to detect AF.⁸⁸ The smartwatch system uses an algorithm to enable rhythm analysis of the photoplethysmographic signals. The population consisted of 508 hospitalized patients who had interpretable ECG and photoplethysmographic recordings. The photoplethysmographic algorithm compared with the cardiologists' diagnoses had a sensitivity of 94% and a specificity of 98%. A limitation of the study was that many of the recordings were excluded due to insufficient signal quality (148 of 672). The investigators concluded that detection of AF is feasible with a smartwatch, though signal quality issues need to be resolved and a broader population needs to be tested.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. No RCTs were identified that evaluated the management of patients with and without mobile cardiac monitoring.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. Evidence for clinical validity consists of one RCT and several observational studies. The RCT reported a larger proportion of patients receiving a diagnosis in the MCOT group compared with the LOOP group, though time to diagnosis was not significantly different. In addition, no studies demonstrated an incremental benefit of the real-time transmission and interpretation of data compared with the usual monitoring timeline.

Section Summary: MCOT for Patients with Symptoms of Arrhythmia

The available evidence has suggested that MCOT is likely to be at least as good at detecting arrhythmias as ambulatory event monitoring. Compared with ambulatory event monitoring, MCOT is associated with the theoretical advantage of real-time monitoring, permitting for emergent intervention for potentially life-threatening arrhythmias. One study reported that 1% of arrhythmic events detected on MCOT during a mean monitoring period of 21 days per patient, could be considered potentially emergent. However, no studies were identified that addressed whether the use of MCOT is associated with differences in the management of or outcomes after these potentially emergent events. The addition of real-time monitoring to outpatient ambulatory monitoring is considered an enhancement to existing technology. Currently, the evidence does not demonstrate a clinically significant incremental benefit for MCOT.

SUMMARY OF EVIDENCE

Ambulatory Event Monitoring

For individuals who have signs and/or symptoms suggestive of arrhythmia(s) who receive patient- or autoactivated external ambulatory event monitoring or continuous ambulatory monitoring storing information for more than 48 hours, the evidence includes prospective and retrospective studies reporting on the diagnostic yield. Relevant outcomes are overall survival and morbid events. Studies have shown that continuous monitoring with longer recording periods clearly detects more arrhythmias than 24- or 48-hour Holter monitoring. Particularly for patients who, without the more prolonged monitoring, would only undergo shorter term monitoring, the diagnostic yield is likely to identify arrhythmias that may have therapeutic implications. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have AF following ablation who receive long-term ambulatory cardiac monitoring, the evidence includes an RCT comparing ambulatory event monitoring with standard care and several observational studies. Relevant outcomes are overall survival, morbid events, medication use, and treatment-related morbidity. The RCT evaluating a long-term monitoring strategy after catheter ablation for AF reported significantly higher rates of AF detection. The available evidence has suggested that long-term monitoring for AF post-ablation is associated with improved outcomes. However, the specific type of monitoring associated with the best outcomes is not established, because different long-term monitoring devices were used across the studies. Trials demonstrating improved outcomes have used event monitors or implantable monitors. In addition, there are individual patient considerations that may make 1 type of monitor preferable over another. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have cryptogenic stroke with a negative standard workup for AF who receive long-term ambulatory cardiac monitoring, the evidence includes systematic reviews of RCTs comparing ambulatory event monitoring with standard care. Relevant outcomes are overall survival, morbid events, medication use, and treatment-related morbidity. RCTs evaluating a long-term AF monitoring strategy post-stroke have reported significantly higher rates of AF detection with longer term ambulatory monitoring. The available evidence has suggested that long-term monitoring for AF after cryptogenic stroke is associated with improved outcomes, but the specific type of monitoring associated with the best outcomes is not established, because different long-term monitoring devices were used across the studies. Trials demonstrating improved outcomes have used event monitors or implantable monitors. In addition, there are individual patient considerations that may make 1 type of monitor preferable over another. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic with risk factors for AF who receive long-term ambulatory cardiac monitoring, the evidence includes an RCT and 2 nonrandomized studies. Relevant outcomes are overall survival, morbid events, medication use, and treatment-related morbidity. The studies showed use of the ambulatory monitors would result in higher AF detection compared with routine care. However, the RCT followed patients for 1 year and did not detect a difference in stroke occurrence between the monitored group and the standard of care group. The other studies did not discuss changes in patient management or health outcomes based on monitoring. Studies reporting on improved outcomes with longer follow-up are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Implantable Loop Recording

For individuals who have signs and/or symptoms suggestive of arrhythmia with infrequent symptoms who receive patient- or autoactivated implantable ambulatory event monitoring, the evidence includes RCTs comparing implantable loop recorders with shorter term monitoring, usually 24- to 48-hour Holter monitoring. Relevant outcomes are overall survival, morbid events, medication use, and treatment-related morbidity. Studies assessing prolonged implantable loop recorders in patients have reported high rates of arrhythmia detection compared with shorter external event or Holter monitoring. These studies have supported use of a progression in diagnostics from an external event monitor to implantable loop recorder when longer monitoring is needed. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Outpatient Cardiac Telemetry

For individuals who have signs and/or symptoms suggestive of arrhythmia who receive outpatient cardiac telemetry, the evidence includes an RCT and nonrandomized studies evaluating rates of arrhythmia detection using outpatient cardiac telemetry. Relevant outcomes are overall survival and morbid events. The available evidence has suggested that outpatient cardiac telemetry is at least as good at detecting arrhythmias as ambulatory event monitoring. However, studies have not evaluated whether the real-time monitoring feature of outpatient cardiac telemetry leads to reduced cardiac events and mortality. The evidence is insufficient to determine the effects of the technology on health outcomes.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 9.

Table 9. Summary of Key Trials

NCT No	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02392754	Home-Based Screening for Early Detection of Atrial Fibrillation in Primary Care Patients Aged 75 Years and Older (SCREEN-AF)	822	Jan 2020
NCT03001765	Impact of an Intensive Monitoring Strategy in Symptomatic Patients with Suspected Arrhythmia (IMPACT)	150	Jul 2019
NCT03221777	Atrial Fibrillation Occurring Transiently With Stress (AFOTS): Understanding the Risks of Recurrent AF. Study in Non-cardiac Surgery and in Medical Illness Patients	276	Oct 2021
NCT04126486	GUARD-AF: reducInG Stroke by Screening for UndiAgnosed atRial Fibrillation in Elderly inDividuals	52,000	Jul 2021
NCT02684825	Detection of Silent Atrial Fibrillation aFter Ischemic StrOke (SAFFO)	424	Jun 2021
NCT02786940	Remote Cardiac Monitoring of Higher-Risk Emergency Department Syncope Patients after Discharge (REMOSYNC)	99	Mar 2023
NCT03541616	Prevalence of Subclinical Atrial Fibrillation in High Risk Heart Failure Patients and Its Temporal Relationship With Hospital Readmission for Heart Failure	240	Apr 2022
NCT03072693	Daily ambulatory remote monitoring system vs. conventional therapy for the post-discharge management of acute decompensated heart failure	879	Jul 202022
Unpublished			
NCT02428140a	Post-Embolic Rhythm Detection with Implantable Versus External Monitoring (PERDIEM)	300	Dec 2019
NCT02793895	Detection of Atrial Fibrillation After Cardiac Surgery (SEARCH-AF)	396	Dec 2020

^a Denotes industry involvement; NCT: national clinical trial

SUPPLEMENTAL INFORMATION

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

2014 Input

In response to requests, input was received from three physician specialty societies and four academic medical centers (three reviews) while this policy was under review in 2014. Input was obtained to provide information related to MCOT and new devices. There was no consensus whether MCOT is medically necessary. While reviewers agreed that MCOT is comparable to event monitors for arrhythmia detection, they did not agree on whether the real-time monitoring provides incremental benefit over external event monitors or is associated with improved health outcomes compared with external event monitors. There was consensus on the medical necessity of externally worn event monitors with longer continuous recording periods as an alternative to Holter monitors or event monitors. For implantable memory loop

devices that are smaller than older-generation devices, there was consensus that these devices improve the likelihood of obtaining clinically useful information due to improved ease of use, but there was no consensus that such devices improve clinical outcomes and are medically necessary.

2009 Input

In response to requests, input was received from one physician specialty society and four academic medical centers (five reviews) while this policy was under review in 2009. There were differences among reviewers on outpatient cardiac telemetry, with some reviewers concluding it had a role in certain subsets of patients (e.g., in those with sporadic atrial fibrillation). Other reviewers commented that the value of this technology should be considered in both providing a diagnosis and in making treatment decisions. At times, excluding arrhythmia as a cause of a patient’s symptoms is an important finding.

PRACTICE GUIDELINES AND POSITION STATEMENTS

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

International Society for Holter and Noninvasive Electrocardiology et al

In 2017, the International Society for Holter and Noninvasive Electrocardiology and the Heart Rhythm Society (HRS) issued a consensus statement on ambulatory electrocardiogram and external monitoring and telemetry.⁸⁹ Below are 2 summary tables from the consensus statement, detailing advantages and limitations of ambulatory electrocardiogram techniques (see Table 10) and recommendations for the devices that are relevant to this evidence review (see Table 11).

Table 10. Advantages and Limitations of Ambulatory ECG Techniques

ECG Monitoring Technique	Advantages	Limitations
Holter monitoring	<ul style="list-style-type: none"> Records and documents continuous 3- to 32-lead ECG signal simultaneously with biologic signals during normal daily activities Physicians familiar with analysis software and scanning services 	<ul style="list-style-type: none"> Frequent noncompliance with symptom logs and event markers Frequent electrode detachments Signal quality issues due to skin adherence, tangled wires, dermatitis Absence of real-time data analysis Poor patient acceptance of electrodes
Patch ECG monitors	<ul style="list-style-type: none"> Long-term recording of ≥14 d Excellent patient acceptance 	<ul style="list-style-type: none"> Limited ECG from closely spaced electrodes, lacking localization of arrhythmia origin Inconsistent ECG quality due to body type variations

External loop recorders	<ul style="list-style-type: none"> Records only selected ECG segments marked as events either automatically or manually by patient Immediate alarm generation on event detection 	<ul style="list-style-type: none"> Single-lead ECG, lacking localization of arrhythmia origin Cannot continuously document cardiac rhythm Requires patient to wear electrodes continuously
Event recorders	<ul style="list-style-type: none"> Records only selected ECG segments after an event is detected by patient Immediate alarm generation at event detected by patient Well-tolerated by patient 	<ul style="list-style-type: none"> Single-lead ECG, lacking localization of arrhythmia origin Cannot continuously document cardiac rhythm Diagnostic yield dependent on patient ability to recognize correct symptom
Mobile cardiac telemetry	<ul style="list-style-type: none"> Multilead, so higher sensitivity and specificity of arrhythmia detection Streams data continuously; can be programmed to autodetect and autoseed events at prescribed time intervals Immediate alarm generation on event without patient interaction 	<ul style="list-style-type: none"> □ Long-term patient acceptance is reduced due to requirement of daily electrode changes

ECG: electrocardiogram

Table 11. Select Recommendations for Ambulatory ECG and External Monitoring or Telemetry, International Society for Holter and Noninvasive Electrocardiology/HRS

Recommendation	COR ^a	LOE ^b
Selection of ambulatory ECT		
Holter monitoring when symptomatic events anticipated within 48 h	I	B-NR
Extended ambulatory ECG (15-30 d) when symptomatic events are not daily or are uncertain	I	B-R
Continuous monitoring (1-14 d) to quantify arrhythmia burden and patterns	I	B-NR
Specific conditions for use of ambulatory ECG		
Unexplained syncope, when tachycardia suspected	I	B-R
Unexplained palpitation	I	B-R
Detection of atrial fibrillation, triggering arrhythmias, and post-conversion pauses	IIa	B-NR
Cryptogenic stroke, to detect undiagnosed atrial fibrillation	I	B-R

ECG: electrocardiogram; COR: class of recommendation; LOE: level of evidence

a COR definitions: I: strong recommendation; IIa: benefit probably exceeds risk;

b LOE definitions: B-NR: moderate level based on well-executed nonrandomized studies; B-R: moderate level based on randomized trials.

American College of Cardiology et al

The American College of Cardiology, the American Heart Association, and HRS (2019) updated guidelines initially issued in 2014, on the management of patients with atrial fibrillation (AF).⁹⁰ These guidelines recommended the use of Holter or event monitoring if the diagnosis of the type of arrhythmia is in question, or as a means of evaluating rate control.

The same associations collaborated on guidelines in 2017 on the evaluation and management of patients with syncope⁹¹ and patients with ventricular arrhythmias⁹². Cardiac monitoring recommendations are summarized below in Tables 12 and 13.

Table 12. Cardiac Monitoring Recommendations AHA/ACC/HRS

Recommendation	COR ^a	LOE ^b
Choice of a specific cardiac monitor should be determined on the basis of frequency and nature of syncope events	I	C-EO
To evaluate selected ambulatory patients with syncope of suspected arrhythmic etiology, the following external cardiac monitoring approaches can be useful: Holter monitor, transtelephonic monitor, external loop recorder, patch recorder, and mobile cardiac outpatient telemetry.	Ila	B-NR
To evaluate selected ambulatory patients with syncope of suspected arrhythmic etiology, an implantable cardiac monitor can be useful.	Ila	B-R

COR: class of recommendation; LOE: level of evidence

^a COR definitions: I: strong recommendation; Ila: benefit probably exceeds risk

^b LOE definitions: B-NR: moderate level based on well-executed nonrandomized studies; B-R: moderate level based on randomized trials; C-EO: consensus of expert opinion based on clinical experience.

Table 13. Patient Selection Recommendations by Cardiac Rhythm Monitor AHA/ACC/HRS

Type of Monitor	Patient Selection
Holter monitor	Symptoms frequent enough to be detected within 24 to 72 h
Patient-activated event monitor	<ul style="list-style-type: none"> Frequent spontaneous symptoms likely within 2 to 6 wk Limited use when syncope associated with sudden incapacitation
External loop recorder (patient or auto-triggered)	Frequent spontaneous symptoms likely to occur within 2 to 6 wk
External patch recorder	<ul style="list-style-type: none"> Alternative to external loop recorder Leadless, so more comfortable, resulting in improved compliance Offers only 1-lead recording
Mobile cardiac outpatient telemetry	<ul style="list-style-type: none"> Spontaneous symptoms related to syncope and rhythm correlation High-risk patients needing real-time monitoring
Implantable cardiac monitor	Recurrent, infrequent, unexplained syncope

ACC: American College of Cardiology; AHA: American Heart Association; HRS: Heart Rhythm Society.

Heart Rhythm Society, European Heart Rhythm Association, et al

A consensus document on catheter and surgical ablation for AF was published in 2012 by the Heart Rhythm Society (HRS) the European Heart Rhythm Association (EHRA), and the European Cardiac Arrhythmia Society (ECAS)⁹³ and updated in 2017.⁹⁴ This document did not contain formal practice guidelines, but provided general recommendations based on literature review and expert consensus. Use of AEMs post-ablation was addressed in two sections of the document. First, in the section discussing the use of anticoagulation following ablation, the following statement was made:

“Patients in whom discontinuation of systemic anticoagulation is being considered based on patient values and preferences should consider undergoing continuous or frequent ECG monitoring to screen for AF recurrence.”

In the section on postoperative rhythm monitoring of patients who are post-ablation the following statements were made:

“The success of AF ablation is based in large part on freedom from AF recurrence based on ECG monitoring. Arrhythmia monitoring can be performed with the use of noncontinuous or continuous ECG monitoring tools.”

The statement referenced a table of ambulatory cardiac monitoring devices (Holter, patch, external loop, implantable loop, wearable multi-sensors, Smartphone monitors), describing unique features of each. The table did not evaluate the safety or efficacy of these devices, nor recommend one over another.

European Heart Rhythm Association (EHRA)

In 2009, the EHRA published guidelines on the use of diagnostic implantable and external loop recorders.⁹⁵ For the indications that the EHRA considered established at the time of publication, the guidelines made the following statements about indications for implantable and external recorders (see Table 14).

Table 14. Guidelines on Use of Diagnostic Implantable and External Loop Recorders

Recommendation	COR	LOE
<p>“ILR is indicated:</p> <ul style="list-style-type: none"> • “In an early phase of evaluation of patients with recurrent syncope of uncertain origin who have: • “absence of high-risk criteria that require immediate hospitalization or intensive evaluation...”; and • “a likely recurrence within battery longevity of the device.” 	I	A
<p>“ELRs are indicated in patients with recurrent palpitations, undocumented by conventional ECG techniques, who have: inter-symptom interval <4 weeks and absence of high-risk criteria...which require immediate hospitalization or intensive evaluation.”</p>	I	B
<p>“ILR may be indicated to assess the contribution of bradycardia before embarking on cardiac pacing in patients with suspected or certain neutrally mediated syncope presenting with frequent or traumatic syncopal episodes.”</p>	Ila	B
<p>“ILRs may be indicated in selected cases with severe infrequent symptoms when ELRs and other ECG monitoring systems fail to document the underlying cause.”</p>	Ila	B
<p>“ELRs may be indicated in patients with recurrent (pre) syncopes who have:</p> <ul style="list-style-type: none"> • “inter-symptom interval of ≤4 weeks, and • “suspicion of arrhythmic origin and • “absence of high-risk criteria that require immediate hospitalization or intensive evaluation...” 	Ila	B

COR: class of recommendations; ECG: electrocardiogram; ELR: external loop recorder; ILR: implantable loop recorder; LOE: level of evidence

American Academy of Neurology

In 2014, the American Academy of Neurology updated its guidelines on the prevention of stroke in patients with nonvalvular atrial fibrillation (NVAF).⁹⁶ These guidelines made the following recommendations on the identification of patients with occult NVAF:

- A1. “Clinicians might obtain outpatient cardiac rhythm studies in patients with cryptogenic stroke without known NFAF, to identify patients with occult NVAF (Level of evidence: C)
- A2. Clinicians might obtain cardiac rhythm studies for prolonged periods (e.g., for one or more weeks) instead of shorter periods (e.g., 24 hours) in patients with cryptogenic stroke without known NVAF, to increase the yield of identification of patients with occult NVAF (Level of evidence: C).”

U.S. Preventive Services Task Force Recommendations

Not Applicable

Government Regulations

National:

National Coverage Determination (NCD) for Electrocardiographic Services (20.15), effective date 8/26/04:⁹⁷

Nationally Covered Indications

The following indications are covered nationally unless otherwise indicated:

1. Computer analysis of EKGs when furnished in a setting and under the circumstances required for coverage of other EKG services.
2. EKG services rendered by an independent diagnostic testing facility (IDTF), including physician review and interpretation. Separate physician services are not covered unless he/she is the patient's attending or consulting physician.
3. Emergency EKGs (i.e., when the patient is or may be experiencing a life-threatening event) performed as a laboratory or diagnostic service by a portable x-ray supplier only when a physician is in attendance at the time the service is performed or immediately thereafter.
4. Home EKG services with documentation of medical necessity.
5. Trans-telephonic EKG transmissions (effective March 1, 1980) as a diagnostic service for the indications described below, when performed with equipment meeting the standards described below, subject to the limitations and conditions specified below. Coverage is further limited to the amounts payable with respect to the physician's service in interpreting the results of such transmissions, including charges for rental of the equipment. The device used by the beneficiary is part of a total diagnostic system and is not considered DME separately. Covered uses are to:
 - a. Detect, characterize, and document symptomatic transient arrhythmias;
 - b. Initiate, revise, or discontinue arrhythmic drug therapy; or,
 - c. Carry out early post-hospital monitoring of patients discharged after myocardial infarction (MI); (only if 24-hour coverage is provided, see C.5. below).

Certain uses other than those specified above may be covered if, in the judgment of the local contractor, such use is medically necessary.

Additionally, the transmitting devices must meet at least the following criteria:

- d. They must be capable of transmitting EKG Leads, I, II, or III; and,
- e. The tracing must be sufficiently comparable to a conventional EKG.

24-hour attended coverage used as early post-hospital monitoring of patients discharged after MI is only covered if provision is made for such 24-hour attended coverage in the manner described below:

24-hour attended coverage means there must be, at a monitoring site or central data center, an EKG technician or other non-physician, receiving calls and/or EKG data; tape recording devices do not meet this requirement. Further, such technicians should have immediate, 24-hour access to a physician to review transmitted data and make clinical decisions regarding the patient. The technician should also be instructed as to when and how to contact available facilities to assist the patient in case of emergencies.

Local:

WPS Local Coverage Determination (LCD) for Electrocardiographic (EKG or ECG) Monitoring (Holter or Real-Time Monitoring) (L34636); For services performed on or after 01/01/2021: Real time outpatient cardiac telemetry is covered for patients meeting selection criteria.

Long-Term ECG Monitoring is defined as a diagnostic procedure, which can provide continuous recording capabilities of ECG activities of the patient's heart while the patient is engaged in daily activities. These can include continuous, patient-demand or *auto-detection devices. The purpose of these tests is to provide information about rhythm disturbances and waveform abnormalities and to note the frequency of their occurrence.

Cardiac Event Detection (CED) is a 30-day service for the purpose of documentation and diagnosis of paroxysmal or suspected arrhythmias.

Holter Monitoring (24-hour ECG monitoring) is a study used to evaluate the patient's ambient heart rhythm during a full day's (24 Hours) cycle. A wearable EKG monitor records the overall rhythm and significant arrhythmias.

A. Medical Necessity:

The medical necessity indications listed in this policy must be present in order for these tests to be covered.

B. Indications for external 48-hour ECG recording (CPT/HCPCS codes 93224-93227) include one or more of the following

1. Symptoms such as:

- Arrhythmias
- Chest pain
- Syncope (lightheadedness) or near syncope
- Vertigo (dizziness)
- Palpitations
- Transient ischemic episodes
- Dyspnea (shortness of breath)

2. Evaluation of the response to antiarrhythmic drug therapy.

3. Evaluation of myocardial infarction (MI) survivors with an ejection fraction of 40% or less.

4. Assessment of patients with coronary artery disease with active symptoms, to correlate chest pain with ST-segment changes.

5. Other acute and subacute forms of ischemic heart disease.

6. To detect arrhythmias post ablation procedures.

C. The use of external electrocardiographic recording for more than 48 hours up to 21 days by continuous rhythm recording and storage, may be considered medically necessary in patients treated for reasons listed in the ICD-10-CM list to monitor for asymptomatic episodes in order to evaluate treatment response, The use of external electrocardiographic event monitors for more than 48 hours up to 21 days that are either patient-activated or auto-activated may be considered medically necessary as a diagnostic alternative to Holter monitoring in patients who experience infrequent symptoms (less frequently than every 48 hours) suggestive of cardiac arrhythmias (i.e., palpitations, dizziness, presyncope, or syncope).

D. Long term 30-day monitoring; Telephonic Transmission of ECG (CPT codes 93228*, 93229,

and 93268-93272) involve 24 hour attended monitoring per 30 day period of time; no other EKG monitoring codes can be billed simultaneously with these codes.

Indications for performing a Telephonic Transmission:

- a. Arrhythmias ;
- b. Chest pain ;
- c. Syncope (lightheadedness) or near syncope ;
- d. Vertigo (dizziness) ;
- e. Palpitations (ICD-9 code 785.1);
- f. Transient ischemic episodes ;
- g. Dyspnea (shortness of breath) .
- h. To initiate, revise or discontinue arrhythmia drug therapy.
- i. Evaluation of myocardial infarction (MI) survivors.
- j. Evaluation of acute and subacute forms of ischemic heart disease.
- k. Assessment of patients with coronary artery disease with active symptoms, to correlate chest pain with ST-segment changes.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Electrocardiogram (ECG) Body Surface Imaging
- Acoustic Cardiography

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through July 2021, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
8/26/05	8/26/05	9/8/05	Joint policy established
3/8/06	3/8/06	3/13/06	HCPCS codes updated
7/1/07	5/10/07	6/28/07	Routine maintenance
11/1/08	8/19/08	9/21/08	Routine maintenance, S codes added
7/1/09	4/21/09	6/25/09	Routine maintenance, no change in policy determination
11/1/10	8/28/10	8/17/10	Routine maintenance. Deleted codes S0345, S0346 and S0347 removed from policy
5/1/12	2/21/12	2/21/12	Policy title changed from "Real Time Outpatient Cardiac Telemetry" to "Ambulatory Event Monitors and Mobile Cardiac Telemetry. Added other monitoring devices. Added new CPT codes 0195T-0198T to policy. Description and rationale updated to mirror BCBSA policy. Additional references added.
7/1/13	4/16/13	5/7/13	Medically necessary indication for use of event monitors in patients with atrial fibrillation treated with catheter ablation revised for clarity and for wording to be consistent with recent guidelines. Not medically necessary indication for MCOT changed to reflect revised language for not medically necessary technologies. Additional investigational indications added for use of continuous monitors that record for periods longer than 72 hours, and for monitoring patients with cryptogenic stroke.
5/1/14	2/18/14	3/6/14	Changed status of CPT code 0295T-0298T (e.g., ZioPatch) to established if patient selection criteria are met. Changed status of real time cardiac outpatient telemetry (MCOT) from experimental/investigational to not medically necessary.
11/1/15	8/18/15	9/28/15	Routine maintenance Added inclusion for "patients with cryptogenic stroke who have a negative standard work-up for atrial fibrillation including a 24-hour Holter monitor." Changed MCOT from not medically necessary to not medically necessary AND experimental/investigational.
11/1/16	9/23/16	8/26/16	Routine policy maintenance <ul style="list-style-type: none"> • Updated rationale & references

			<ul style="list-style-type: none"> Removed ICD-9 codes from Gov. section Added language to inclusions and exclusions
3/1/17	12/13/16	12/13/16	Brought back for discussion, Aetna/Anthem change in coverage
3/1/18	12/12/17	12/12/17	Routine policy maintenance, added references 15, 17, 45, 48 and 55. No change in policy status. Deleted codes 0302T-0307T, added 0497T and 0498T as E/I.
3/1/19	12/11/18		<p>The following was added to exclusions, “and mobile applications, are considered experimental/investigational, including but not limited to:</p> <ul style="list-style-type: none"> Monitoring asymptomatic patients with risk factors for arrhythmia <p>Added references 47, 49-50, 60-61, 68, 75, and 77. No change in policy status. Deleted codes 33282 and 33284, added code 33285 and 33286 effective 1/1/19.</p>
3/1/20	12/17/19		Rationale updated and reformatted. Added references 8, 9, 16, 60, 61, 81 and 83. No change in policy status.
3/1/21	12/15/20		Routine policy maintenance, added references 13, 14, 18 and 43. No change in policy status. Codes 0295T-0298T deleted, codes 93241-93248 added as established.
11/1/21	8/17/21		Added code 0650T as E/I effective 7/1/21. Updated rationale added reference #58. No change in policy status.

Next Review Date:

4th Qtr. 2022

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: AMBULATORY EVENT MONITORS AND MOBILE CARDIAC OUTPATIENT
TELEMETRY

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered per policy criteria
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.