Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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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). Itis 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.

Stroke in AF occurs primarily as a result of thromboembolism from the left atrium. The lack of atrial contractions in AF leads to blood stasis in the left atrium, and this low flow state increases the risk of thrombosis. The area of the left atrium with the lowest blood flow in AF, and therefore the highest risk of thrombosis, is the left atrial appendage. 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 is recommended by American Heart Association, American College of Cardiology, and Heart Rhythm Society (2014) joint guidelines on patients with a history of stroke or transient ischemic attack.(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 does. 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 3 channels based on 3 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	Device Examples
Noncontinuous devices with memory (event recorder)	Devices not worn continuously but rather activated by patient and applied to the skin in the precordial area when symptoms develop	• Zio® Event Card (iRhythm Technologies) • REKA E100™ (REKA Health)
Continuous recording devices with longer recording periods	Devices continuously worn and continuously record via ≥1 cardiac leads and store data longer than traditional Holter (14 days)	• Zio®XT Patch and ZIO ECG Utilization Service (ZEUS) System (iRhythm Technologies)
External memory loop devices (patient- or autotriggered)	Devices continuously worn and store a single channel of ECG data in a refreshed memory. When the device is activated, the ECG is then recorded from the memory loop for the *preceding* 30-90 seconds and for next 60 seconds or so. 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 (auto-triggered).	• Patient-triggered: Explorer™ Looping Monitor (LifeWatch Services) • Auto-triggered: LifeStar AF Express™ Auto-Detect Looping Monitor (LifeWatch Services) • Auto-triggered or patient-triggered: King of Hearts Express® AF (Card Guard Scientific Survival)
Implantable memory loop devices (patient- or auto-triggered)	Devices similar in design to external memory loop devices but implanted under the skin in the precordial region	• Auto-triggered or patient-triggered: Reveal® XT ICM (Medtronic) and Confirm Rx Insertable™ Cardiac Monitor (Abbott) • Auto-triggered: BioMonitor, Biotronik)
Mobile cardiac outpatient telemetry	Continuously recording or auto-triggered memory loop devices that transmit data to a central recording station with real-time monitoring and analysis	• CardioNet MCOT™ (BioTelemetry) • 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 2 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 safety and efficacy of ambulatory cardiac monitors have been established. They may be considered a useful diagnostic option when specified criteria are met.

Inclusionary and Exclusionary Guidelines

INCLUSIONS:
Patient-activated or auto-activated *external* ambulatory event monitors (AEMs) **OR** continuous ambulatory monitors that record and store information for periods longer than 48 hours up to 21 days (e.g., Zio Patch®) used as a diagnostic alternative to Holter monitoring when **one** of the following are met:

- Symptoms are suggestive of cardiac arrhythmias (i.e., palpitations, dizziness, presyncope or syncope)
- Atrial fibrillation has been treated with catheter ablation and the discontinuation of systemic anticoagulation is being considered
- Diagnosis of cryptogenic stroke.

Implantable ambulatory event monitors (patient-activated or auto-activated) when **one** of the following have been met:

- Recurrent symptoms are so infrequent that a prior trial using an external ambulatory event monitor (e.g., Holter or other monitor) has been unsuccessful
- Long term monitoring for atrial fibrillation is required.

Mobile Cardiac Outpatient Telemetry (MCOT) when **both** of the following are met

- **One** of the following conditions are present:
  - Symptoms suggestive of cardiac arrhythmias which occur less than once every 48 hours
  - Unconfirmed suspicion of paroxysmal atrial fib following cryptogenic stroke when the monitoring is intended to guide medical management with anticoagulants
- A non-diagnostic external ambulatory cardiac event monitoring trial of not less than 14 continuous days has been completed

EXCLUSIONS:

- Other uses of ambulatory event monitors, including but not limited to:
  - Monitoring asymptomatic individuals with risk factors for arrhythmia
  - Detection of myocardial ischemia by detecting ST segment changes (intracardiac ischemia monitoring systems)
  - Monitoring effectiveness of antiarrhythmic medications in the absence of 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	93228	93229	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.):

93799 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 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 2 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 following PICO was used to select literature to inform this review.

Populations

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 1 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%).

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.(8) 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.(9) 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.(10) 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.(11) 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.(12) 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.(13) 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.(14) 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 reported high rates of arrhythmia detection.

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

Study	Population	Monitoring Indication	Main Findings
		Indication (%)	
Eisenberg et al (2014)[15,]	524 consecutive patients evaluated in an academic EP practice	• Surveillance for unspecified arrhythmia or palpitations (47) • Known/suspected AF (30) • Syncope (8) • Bradycardia surveillance (4) • Tachycardia surveillance (5) • Chest pain (2)	• Significant arrhythmias detected in 297 (57%) • 66% had 1st arrhythmia detected within 2 days of monitoring • 25% of patient-triggered events associated with clinically significant arrhythmias
Schreiber et al (2014)[16,]	174 patients with symptoms	• Palpitations 44.8)	• >1 significant arrhythmia other than chronic AF (≥4 beats VT, paroxysmal AF, ≥4 beats SVT,

	suggestive of arrhythmia seen in an ED	• Syncope (24.1) • Unspecified arrhythmias detected in the ED (11.5)	≥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: ○ Any arrhythmia: 1.0 day (IQR, 0.2 to 2.8) ○ VT: 3.1 days ○ Sinus pause: 4.2 days ○ Significant heart block: 5.8 days
Mullis et al (2019) [17,]	59 consecutive patients seen in an outpatient EP clinic	PVCs	• 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)[18,]	86 patients evaluated in an ED	Syncope	• 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.(19) 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.(20) 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.(21-23)

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 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: Auto-Activated or Continuous Ambulatory Monitoring for Patients with Arrhythmia Symptoms
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. Several observational studies indicated that patients who had arrhythmias detected were more likely to receive anticoagulant therapy, antiarrhythmic therapy, and ablation or other cardiac procedures. Because these treatments have been proven effective for stroke prevention, it can be concluded that longer term monitoring of patients with arrhythmia symptoms will improve outcomes.

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.(26)

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

Populations
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 1 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.(27) 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 3 months before and 18 months after ablation in 50 patients implanted with a cardiac monitor.(28) 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 post-ablation. Patient detection of symptoms underestimates the AF occurrence rate following ablation, with 12% of patients having arrhythmias that were only detected through monitoring.

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.(29) 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 monitory 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.(30,31) Longer-term ambulatory event monitoring will identify additional patients with asymptomatic episodes, with rates of detection estimated at 6% to 26% of patients.(5,32,33)

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

Populations
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 1 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.(34) 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.(35) 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

Five 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.(36) 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).(37) 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).(38,39) 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.(40) 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).

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).(41) Patients were ages 55 years or older, with no known history of AF, and an ischemic stroke or TIA of undetermined cause within the prior 6 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.(42) 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	Active	Comparator
					Interventions (n)	
Kamel et al (2013)[36]	United States	1	2009-2011	Cryptogenic ischemic stroke or high-risk TIA	MCOT (20)	Standard (20)
Higgins et al (2013)[37]	United Kingdom	2	2010-2011	Transient or persistent symptoms of acute TIA	ELR (50)	Standard (50)
Sanna et al (2014)[39] & Brachmann et al (2016)[40]	Canada, Europe, United States	55	2009-2012	Cryptogenic ischemic stroke or TIA	ILR (221)	Standard (220)
Gladstone et al (2014)[41]	Canada	16	NR	Cryptogenic ischemic stroke or TIA	ELR (280)	Standard (277)
Kaura et al (2019)[42]	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			Additional Findings
		AEM, %	Standard%	p-value	
Kamel et al (2013)[36]	90 days	0	0	NS	• 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)[37]	14 days 90 days	18 22	28	<.05 .09	• No difference between groups for recurrent stroke, TIA, or mortality
Sanna et al (2014)[39]; Brachmann	6 months 12	8.9 12.4 30	1.4 2.0 3.0	<.001 <.001 <.001	• Percent patients on oral anticoagulation therapy significantly higher in ILR group vs. standard group

et al (2016)[40],	months 3 years				• At 3-year follow-up, recurrent stroke or TIA occurred in 20 patients in ILR group and in 24 in standard group
Gladstone et al (2014)[41],	90 days	16.1	3.2	<.001	• Atrial premature beats was identified in a regression model as a potential predictor of AF detection
Kaura et al (2019)[42],	90 days	16.3	2.1	.026	• 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; NS: not significant; 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,(6,43,44) and continuous monitors with longer recording periods,(45) along with a pilot study evaluating the Zio Patch for AF detection post-stroke.(46)

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 Ambulatory Cardiac Monitoring 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 AMBULATORY CARDIAC MONITORING FOR 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.(47) Studies have suggested that most paroxysmal episodes of AF are asymptomatic.(48,49) 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 (50,51) while in a systematic review of 12 studies (total n=99,996), 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.(53) 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 following PICO was used to select literature to inform this review.

Populations
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
To assess the clinical validity, 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).

Randomized Controlled Trials

Three RCTs reported the diagnostic yield of ambulatory event monitoring compared to usual care.(54-56) Characteristics of the trials are shown in Table 5 and diagnostic yield in Table 6. All 3 studies found that ambulatory event monitoring resulted in a greater diagnostic yield than usual care. These studies are discussed in detail in the Clinically Useful section, below. A fourth RCT, mSTOPS, included a concurrent observational study with 3-year outcomes, and is discussed in the Observational Studies section.(57)

Observational Studies

Observational studies have shown that the use of ambulatory monitors would result in higher AF detection compared with routine care.

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.(58) The study included 75 patients older than age 55 with at least 2 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 (CHA_2DS_2 – VASc ≥2). After a mean follow-up of 7.6 days, AF was detected in four (5.3%) subjects, all of whom had CHA_2DS_2 -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.(59) 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%).

Steinhubl et al (2018) conducted a RCT with a concurrent observational study (mSToPS) to evaluate home-based cardiac monitoring with the iRhythm Zio.(57) Individuals from a US health plan were randomized to monitoring initiated immediately after study recruitment (n=1364) vs active monitoring after 4 months (n=1291). A cohort of patients (n=3476) without monitoring, matched by age, sex, and CHA2DS2VASc score were part of a concurrent observational study. The primary endpoint was newly diagnosed AF at 4 months among those actively monitored at initiation versus those just beginning the monitoring. The secondary endpoint was newly diagnosed AF at 1 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 1 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 1 year.

Steinhubl et al (2021) reported 3-year outcomes for the observational cohort.(60) At the end of 3 years, AF was newly diagnosed in 11.4% (n = 196) of those actively monitored versus 7.7% (n = 261) in observational controls (P <.01). The rate of the combined endpoint of death, stroke, systemic emboli and myocardial infarction was 3.6 per 100 person-years (95% CI 3.1 to 5.1) in actively monitored individuals and 4.5 (95% CI 4.0 to 5.0) in the observational cohort (adjusted Hazard Ratio 0.79, P =.02). Rates of hospitalizations for bleeding were 0.32 per 100 person-years in the actively monitored cohort versus 0.71 per 100 person-years in the control cohort with an (adjusted Incidence Rate Ratio 0.47; P <.01). Among the screened cohort with incident AF, one-third were diagnosed through screening. Clinical events were common in the 4 weeks surrounding a diagnosis, and the study authors noted that although the clinical event rate was lower in the actively monitored cohort, the difference in detection rates at 3 years indicated that screening did not diagnose AF prior to the development of complications, and so the influence of screening on health outcomes is unclear. In addition to its potential for bias in unmeasured confounders, this study was limited by its use of claims data for outcome measurement.

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
Three RCTs have compared long-term ambulatory event monitoring to usual care in asymptomatic individuals at higher risk.(54-56)

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).(54) Patients were 65 years and older, asymptomatic, with CHA_2DS_2-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. The trial was not powered to detect clinical outcomes and was of insufficient duration to draw conclusions on health outcomes.

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.(55) 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.

Svendsen et al (2021) reported results of the LOOP trial.(56) This was the only RCT that was powered to detect clinical outcomes; results are shown in Table 7. Screening resulted in an increase in AF detection and anticoagulation initiation but no significant reduction in the risk of stroke or systemic arterial embolism (Table 7). A higher-than-anticipated proportion of participants in the control group were diagnosed with atrial fibrillation (12.2% compared with anticipated 3.0%), indicating that control group participants could have been more likely to consult their physician. Additionally, atrial fibrillation episodes detected in the control group are likely to have lasted longer than atrial fibrillation detected by monitors, increasing the probability of detection and potentially decreasing the protective effect of anticoagulant treatment. In a post hoc analysis of the LOOP trial focused on stroke severity and prior stroke history, Diederichsen et al (2023) found that screening did not result in a significant decrease in ischemic (HR 0.76; 95% CI, 0.57-1.03; p=.07) or severe (HR 0.69; 95% CI, 0.44-1.09; p=.11) strokes compared with usual care.(61) In an exploratory subgroup analysis of participants without prior stroke, the HRs were 0.68 (95% CI, 0.48-0.97; p=.04) and 0.54 (95% CI, 0.30-0.97; p=.04), respectively, indicating a possible reduction in these outcomes among individuals without prior stroke. In another subgroup analysis of the LOOP trial also reported by Diederichsen et al (2023), screening led to an increase in bradyarrhythmia diagnoses and pacemaker implantations compared with usual care but no change in the risk of syncope (HR, 0.83; 95% CI, 0.56-1.22; p=.34) or sudden death (HR, 1.11; 95% CI, 0.64-1.90; p=.71).(62)

Study limitations are summarized in Tables 8 and 9. Two of the 3 trials were of insufficient duration and power to draw conclusions on health outcomes. In the LOOP trial, no participants were lost to follow-up and the median follow-up duration was 64.5 months (interquartile range

59.3 to 69.8 months), however only 16.4% of participants were still followed up for the primary outcome at the 6th year follow-up, and the study authors note that results at this timepoint should be interpreted with caution. No study included blinded outcome assessment, and their relevance is limited due to a lack of racial diversity in the study populations.

Table 5. Randomized Controlled Trials of Ambulatory Event Monitoring Versus Usual Care-Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Ambulatory Event Monitoring	**Usual Care**
Halcox et al (2017)[54,] REHEARSE-AF ISRCTN10709813	UK	1	2015-2017	65 years and older, asymptomatic, with CHA2DS2-VASc scores of 2 or higher.	N = 500 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	N = 501 Followed by general practitioners
Gladstone et al (2021)[55,] NCT02392754	Canada and Germany	Multiple	2015-2019	Asymptomatic adults over age 75 with hypertension and without known AF	Zio XT patch worn for up to 4 weeks	Standard care (routine clinical follow-up plus a pulse check and heart auscultation at baseline and 6 months)
Svendsen et al (2021)[56,] LOOP Trial NCT02036450	Denmark	4	2014-2016	Eligibility criteria: Ages 70 to 90 years, with at least 1 of 4 conditions: hypertension, diabetes, previous stroke, or heart failure Exclusions: atrial fibrillation, a	N = 1501 Continuous ECG monitoring via automated remote transmissions with daily physician review of all transmissions. If	N = 4503 Annual interview with a study nurse and standard contact with the participant's general practitioner)

		history of atrial fibrillation, a pacemaker, anticoagulation medicine, or contraindication to anticoagulation.	atrial fibrillation lasting at least 6 min was detected, the participant was contacted and initiation of oral anticoagulation was recommended Median duration of monitoring was 39.3 months (IQR 36.8 to 41.5).	

NR: not reported; IQR: interquartile range

Table 6. Diagnostic Yield of Atrial Fibrillation in Randomized Controlled Trials

Study	Intervention	Control	Relative Risk (95% CI)	P-Value
Halcox et al (2017)[54,]	19/500 (3.8%)	5/501 (1.0%)	HR 3.9 (1.4 to 10.4)	.007
Gladstone et al (2021)[55,]	23/434 (5.3%)	2/422 (0.5%)	RR 11.2 (2.7 to 47.1)	.001
Svendsen et al (2021)[56,] LOOP Trial NCT02036450	477/1501 (31.8%)	550/4503 (12.2%)	HR 3.17 (2.81 to 3.59)	<.0001

AF: atrial fibrillation; ECG: electrocardiogram; IQR: interquartile range; NR: not reported.

Table 7. Management Changes and Health Outcomes in the LOOP Trial

Study	Oral anti-coagulation	Primary Endpoint (Combined stroke or systemic arterial embolism)	Combined secondary endpoint ischemic stroke, transient ischemic attack, or systemic arterial embolism	Combined secondary endpoint stroke, systemic arterial embolism, or cardiovascular death	Cardiovascular Death	All-Cause Death
Svendsen et al (2021)[56,] LOOP Trial NCT02036450						
Implantable loop recorder	445/1501 (29.7%)	67/1501 (4.5%)	96/1501 (6.4%)	104/1501 (6.9%)	43/1501 (2.9%)	168/1501 (11.2%)
Usual Care	591/4503 (13.1%)	251/4503 (5.6%)	316/4503 (7.0%)	376/4503 (8.3%)	157/4503 (3.5%)	507/4503 (11.3%)
HR (95% CI)	2.72 (2.41 to 3.08	0.80 (0.61 to 1.05)	0.92 (0.73 to 1.15)	0.83 (0.67 to 1.04)	0.83 (0.59 to 1.16)	1.00 (0.84 to 1.19)
P value	<.0001	.11	.47	.10	.27	1.00

CI: confidence interval; HR: hazard ratio.

Table 8. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]

Halcox et al (2017)	4. Race not reported; majority of participants were of White European ethnicity		1 year insufficient duration to draw conclusions on health outcomes.
Gladstone et al (2021)	4. 94% White, 1.5% Black		6 months was insufficient duration to draw conclusions on health outcomes.
Svendsen et al (2021) LOOP Trial NCT02036450	4. Race not reported; Danish population might not be relevant to US population	Study participation could have biased control group participants and/or their physicians to screen for AF.	Only 16.4% of participants were still followed up for the primary outcome at year 6

AF: Atrial fibrillation
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 9. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Halcox et al (2017)		1. Not blinded			4. Not powered to detect differences in health outcomes	
Gladstone et al (2021)		1. Not blinded			4. Not powered to detect differences in health outcomes	
Svendsen et al (2021) LOOP Trial NCT02036450		1. Not blinded				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Long-term Ambulatory Cardiac Monitoring for Asymptomatic Patients

Multiple observational studies showed that use of ambulatory monitors would result in higher AF detection compared with routine care. Randomized controlled trials found higher AF detection and initiation of anticoagulants with monitoring, but no impact on health outcomes. The only RCT (LOOP Trial) with sufficient statistical power and duration to evaluate health outcomes found no difference between monitoring and standard care on the primary endpoint of combined stroke or systemic arterial embolism (HR 0.80; 95% CI 0.61 to 1.05; P =.11) or any secondary endpoints after 6 years of follow-up.

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

Populations

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.(63) 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.(64) 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],(65) Farwell et al [2004],(66) and Krahn et al [2001;67]) 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.(68) 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).(69) 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.

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 10).(65) 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 2 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 10).(70) 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).(66) 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 1 year of monitoring using an ILR in 60 subjects with unexplained syncope (n=30 per group) (see Table 10).(67) 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 10. Summary of RCT Characteristics for ILRs for Arrhythmia

					Interventions (n)	
Study	**Country**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
Podoleanu et al (2014)	France	13	2004-2008	Single recent syncope or 2 in past 12 months	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 months	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 11. Summary of RCT Results for ILRs for Arrhythmia

Study	FU	Diagnosis Made, n (%)			Additional Findings
		ILR	Standard	p-value	
Podoleanu et al (2014)	14 months	18 (46)	2 (5)	<0.001	• Advanced cardiology tests performed less frequently in ILR group vs. standard (p=0.05) • No difference in quality of life
Da Costa et al (2013)	27 months[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 months	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 (2004)	≥6 months	34 (33)	4 (4)	<0.001	• ECG-directed therapy was initiated quicker in the ILR group • No difference in syncopal episodes, mortality, or quality of life
Krahn et al (2001)	12 months	14 (52)	6 (20)	0.012	• 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

Multiple observational studies compared the diagnostic yield of ICMs to the Holster monitor and reported high rates of arrhythmia detection.(71-76) Several observational studies reported management outcomes following diagnoses, such as anticoagulation initiation or cardiac procedures.(77-80)

Safety of Implantable Loop Recorders

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.(81) 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.

Populations
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.(82) 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 7 days in the MCOT group and 9 days in the LOOP group. 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 12. Summary of RCT Characteristics

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

NR: not reported; RCT: randomized controlled trial

Table 13. 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 Autotriggered Recorder, n (%)	Time to Diagnosis, median (95% CI)
Rothman (2007)	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

CI: confidence interval; LOOP: looping event monitor; MCOT: mobile cardiac outpatient telemetry; NR: not reported; RCT: randomized controlled trial.

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).(83) 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.

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.(84) 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 6 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.(85-88) One study (Joshi et al [2005]) described the outcomes of a consecutive case series of 100 patients.(85) 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).

Atrial Fibrillation 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.(89) 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.(33) 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).

Tayal et al (2008) retrospectively analyzed patients with cryptogenic stroke who had not been diagnosed with atrial fibrillation by standard monitoring.(88) 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.(90) 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.(91) 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.(92) 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.

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. Mobile cardiac outpatient telemetry (MCOT)

is used when there are spontaneous symptoms related to syncope and rhythm correlation. High-risk patients whose rhythm requires real-time monitoring may benefit from 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 RCTs and observational studies. Relevant outcomes are OS, morbid events, medication use, and treatment-related morbidity. Multiple observational studies showed that use of ambulatory monitors would result in higher AF detection compared with routine care. Randomized controlled trials found higher AF

detection and initiation of anticoagulants with monitoring, but no impact on health outcomes. The only RCT (LOOP Trial) with sufficient statistical power and duration to evaluate health outcomes found no difference between monitoring and standard care on the primary endpoint of combined stroke or systemic arterial embolism (HR 0.80; 95% CI 0.61 to 1.05; P =.11) or any secondary endpoints after 6 years of follow-up. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 the 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. These extended monitoring strategies can be useful in the evaluation of suspected bradycardia or conduction disorders. The evidence is sufficient 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 14.

Table 14. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03072693	Daily Ambulatory Remote Monitoring System vs Conventional Therapy for the Post-Discharge Management of Acute Decompensated Heart Failure	876	Apr 2023
NCT04126486[a]	GUARD-AF: reducinG Stroke by Screening for UndiAgnosed atRial Fibrillation in Elderly inDividuals	11,931	Jun 2023
NCT02786940	Remote Cardiac Monitoring of Higher-Risk Emergency Department Syncope Patients after Discharge (REMOSYNC)	99	March 2023
NCT03541616	Prevalence of Subclinical Atrial Fibrillation in High Risk Heart Failure Patients and Its Temporal Relationship With Hospital Readmission for Heart Failure	242	Mar 2023
NCT04306978	Impact of the CareLink Express Remote Monitoring System on Early Detection of Atrial Fibrillation and Cardiovascular Risk Reduction in Patients With Implantable Cardiac Pacemakers	200	Jan 2023
NCT04371055	Intensive Heart Rhythm Monitoring to Decrease Ischemic Stroke and Systemic Embolism - the Find-AF 2 Study	5200	Dec 2026
NCT03940066	Evaluation of Ambulatory Monitoring of Patients After High-risk Acute Coronary Syndrome Using Two Different Systems: Biomonitor-2 and Kardia Mobile	169	Jun 2023
Unpublished			

NCT03221777	Atrial Fibrillation Occurring Transiently With Stress (AFOTS): Understanding the Risks of Recurrent AF. Study in Non-cardiac Surgery and in Medical Illness Patients	281	Nov 2022 (Completed; last update Jan 2023)

NCT: national clinical trial.
[a] Denotes industry involvement

Supplemental Information

CLINICAL INPUT RECEIVED THROUGH PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

2014 Input

In response to requests, input was received from 3 physician specialty societies and 4 academic medical centers (3 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.

American Academy of Neurology

In 2014, the American Academy of Neurology updated its guidelines on the prevention of stroke in patients with nonvalvular AF (NVAF).(93) These guidelines made the following recommendations on the identification of patients with occult NVAF:

- "Clinicians might obtain outpatient cardiac rhythm studies in patients with cryptogenic stroke without known NVAF, to identify patients with occult NVAF (Level C).

- Clinicians might obtain cardiac rhythm studies for prolonged periods (e.g., for 1 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 C)."

American Heart Association, American College of Cardiology, and Heart Rhythm Society

The American College of Cardiology, the American Heart Association, and HRS (2019) updated guidelines initially issued in 2014,(4) on the management of patients with atrial fibrillation (AF).(94) 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 (2017) collaborated on guidelines for the evaluation and management of patients with syncope (95) and patients with ventricular arrhythmias.(96) Cardiac monitoring recommendations are summarized below.

Table 15. 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.[95,]	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.[95,]	IIa	B-NR
To evaluate selected ambulatory patients with syncope of suspected arrhythmic etiology, an implantable cardiac monitor can be useful.[95,]	IIa	B-R
Ambulatory electrocardiographic monitoring is useful to evaluate whether symptoms including palpitations, presyncope, or syncope, are caused by ventricular arrhythmia[96,]	I	B-NR
In patients with cryptogenic stroke (i.e., stroke of unknown cause), in whom external ambulatory monitoring is inconclusive, implantation of a cardiac monitor (loop recorder) is reasonable to optimize detection of silent AF.[94,]	IIa	B-R

ACC: American College of Cardiology; AF: atrial fibrillation; AHA: American Heart Association; COR: class of recommendation; HRS: Heart Rhythm Society; 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; C-EO: consensus of expert opinion based on clinical experience.

Table 16. 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 hours
Patient-activated event monitor	• Frequent spontaneous symptoms likely within 2 to 6 weeks • 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 weeks
External patch recorder	• Alternative to external loop recorder • Leadless, so more comfortable, resulting in improved compliance • Offers only 1-lead recording
Mobile cardiac outpatient telemetry	• 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.

International Society for Holter and Noninvasive Electrocardiology/Heart Rhythm Society

The International Society for Holter and Noninvasive Electrocardiology and the Heart Rhythm Society (HRS; 2017) issued a consensus statement on ambulatory electrocardiogram and external monitoring and telemetry.(97) Below are 2 summary tables from the consensus

statement, detailing advantages and limitations of ambulatory electrocardiogram techniques and recommendations for the devices that are relevant to this evidence review .

Table 17. Advantages and Limitations of Ambulatory ECG Techniques, International Society for Holter and Noninvasive Electrocardiology/HRS

ECG Monitoring Technique	Advantages	Limitations
Holter monitoring	• 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	• 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	• Long-term recording of ≥14 days • Excellent patient acceptance	• Limited ECG from closely spaced electrodes, lacking localization of arrhythmia origin • Inconsistent ECG quality due to body type variations
External loop recorders	• Records only selected ECG segments marked as events either automatically or manually by patient • Immediate alarm generation on event detection	• Single-lead ECG, lacking localization of arrhythmia origin • Cannot continuously document cardiac rhythm • Requires patient to wear electrodes continuously
Event recorders	• Records only selected ECG segments after an event is detected by patient • Immediate alarm generation at event detected by patient • Well-tolerated by patient	• 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	• Multilead, so higher sensitivity and specificity of arrhythmia detection • Streams data continuously; can be programmed to autodetect and autosend events at prescribed time intervals • Immediate alarm generation on event without patient interaction	• Long-term patient acceptance is reduced due to requirement of daily electrode changes

ECG: electrocardiogram; HRS: Heart Rhythm Society

Table 18. 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 ECG		
Holter monitoring when symptomatic events anticipated within 48 hours	I	B-NR
Extended ambulatory ECG (15 to 30 days) when symptomatic events are not daily or are uncertain	I	B-R
Continuous monitoring (1 to 14 days) 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 postconversion 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.

U.S. Preventive Services Task Force Recommendations

In 2022, the U.S. Preventive Services Task Force updated its recommendation on Screening for Atrial Fibrillation and concluded, "For adults 50 years or older who do not have signs or symptoms of atrial fibrillation: The current evidence is insufficient to assess the balance of benefits and harms of screening for AF (Grade: I statement).(98)

Government Regulations

National:

National Coverage Determination (NCD) for Electrocardiographic Services (20.15). Effective Date 8/26/04; Implementation Date: 12/10/04

Ambulatory electrocardiography (AECG) refers to services rendered in an outpatient setting over a specified period of time, generally while a patient is engaged in daily activities, including sleep. AECG devices are intended to provide the physician with documented episodes of arrhythmia, which may not be detected using a standard 12-lead EKG. AECG is most typically used to evaluate symptoms that may correlate with intermittent cardiac arrhythmias and/or myocardial ischemia. Such symptoms include syncope, dizziness, chest pain, palpitations, or shortness of breath. Additionally, AECG is used to evaluate patient response to initiation, revision, or discontinuation of arrhythmic drug therapy.

Descriptions of Ambulatory EKG Monitoring Technologies

1. Dynamic electrocardiography devices that continuously record a real-time EKG, commonly known as Holter™ monitors, typically record over a 24-hour period…
2. An event monitor, or event recorder, is a patient-activated or event-activated EKG device that intermittently records cardiac arrhythmic events as they occur… Cardiac event monitor technology varies among different devices. For patient-activated event monitors, the patient initiates recording when symptoms appear or when instructed to do so by a physician (e.g., following exercise). For self-sensing, automatically triggered monitors, an EKG is automatically recorded when the device detects an arrhythmia, without patient intervention. Some devices permit a patient to transmit EKG data transtelephonically (i.e., via telephone) to a receiving center where the data is reviewed…

   They include:
   - Pre-symptom memory loop recorder (external or implantable)…
   - Post-symptoms recorder (external)…

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:

Electrocardiographic (EKG or ECG) Monitoring (Holter or Real-Time Monitoring) (L34636); Effective date: 10/1/15; Revision date: 10/28/21.

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 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 greater than 48 hours and up to 7 days or for greater than 7 days up to 15 days by continuous rhythm recording and storage, may be considered medically necessary in patients treated for reasons listed in the diagnosis list to monitor for asymptomatic episodes in order to evaluate treatment response. The use of external electrocardiographic event monitors for greater than 48 hours and up to 7 days or for greater than 7 days up to 15 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 involves 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
   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 October 14, 2023, 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 • Updated rationale & references • 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		• The following was added to exclusions, "and mobile applications, are considered experimental/investigational, including but not limited to: ○ Monitoring asymptomatic patients with risk factors for arrhythmia • 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.
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.

5/1/22	2/15/22		• MCOT now established with criteria. Rationale section updated.
5/1/23	2/21/23		• Routine policy maintenance • No change in policy status. • Codes 0497T and 0498T deleted 1/1/23 replaced by code 93799. (ds)
3/1/24	12/19/23		• Routine maintenance (slp) • Vendor managed: N/A

Next Review Date: 4th Qtr. 2024

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; criteria apply
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.