

**2.02.08 Ambulatory Event Monitors and Mobile Cardiac Outpatient Telemetry**

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<b>Section:</b>	2.0 Medicine	<b>Page:</b>	Page 1 of 52

**Policy Statement**

- I. 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 (see Policy Guidelines section) may be considered **medically necessary** in **any** of the following situations:
  - A. Infrequent symptoms (less frequently than every 48 hours) suggestive of cardiac arrhythmias (i.e., palpitations, dizziness, presyncope, or syncope)
  - B. History of atrial fibrillation (AF) and prior catheter ablation, and in whom discontinuation of systemic anticoagulation is being considered
  - C. History of cryptogenic stroke with a negative standard workup for AF including a 24-hour Holter monitor (see Policy Guidelines section)
  
- II. The use of implantable ambulatory event monitors, either patient-activated or auto-activated, may be considered **medically necessary** in **any** of the following situations:
  - A. Recurrent symptoms (i.e., palpitations, dizziness, presyncope, or syncope) and a negative prior evaluation with external ambulatory event monitors
  - B. Prior history of cryptogenic stroke and concern for AF
  - C. Prior atrial fibrillation (AF) with ablation, and concern for possible recurrent AF (see Policy Guidelines section)
  
- III. The following are considered **investigational**:
  - A. Outpatient cardiac telemetry (also known as mobile cardiac outpatient telemetry) for evaluating infrequent symptoms (less frequently than every 48 hours) suggestive of cardiac arrhythmias (i.e., palpitations, dizziness, presyncope, syncope)
  - B. Outpatient cardiac telemetry (also known as mobile cardiac outpatient telemetry) for any other condition, disease or symptoms
  - C. Ambulatory event monitors, including outpatient cardiac telemetry and mobile applications for monitoring asymptomatic individuals with risk factors for arrhythmia
  - D. Ambulatory event monitors, including outpatient cardiac telemetry and mobile applications for monitoring the effectiveness of antiarrhythmic medications
  - E. Ambulatory event monitors, including outpatient cardiac telemetry and mobile applications for detection of myocardial ischemia by detecting ST-segment changes

**NOTE:** Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

**Policy Guidelines**

The available evidence has suggested that long-term monitoring for atrial fibrillation post-ablation or after cryptogenic stroke is associated with improved outcomes, but the specific type of monitoring associated with the best outcomes is not well-defined. Trials demonstrating improved outcomes have used either event monitors or implantable monitors. In addition, there are individual considerations that may make 1 type of monitor preferable over another.

Therefore, for the evaluation of individuals with cryptogenic stroke who have had a negative standard workup for atrial fibrillation including 24-hour Holter monitoring, or for the evaluation of atrial fibrillation after an ablation procedure, the use of long-term monitoring with an external event monitor, OR a continuous ambulatory monitor that records and stores information for periods longer

than 48 hours, OR an implantable ambulatory monitor may be considered medically necessary for individuals who meet the criteria outlined above.

### Types of Devices

There are many devices on the market (see table below). A traditional Holter monitor has several leads (attached with sticky pads) and a device that can be worn with a cord around the neck or on the waist. They are usually used for 24 to 48 hours only, but can be used for longer time periods (1 to 2 weeks). They cannot transmit data remotely.

Patch type devices are small, self-contained, and attach with a single patch (about 2x5 inches) to the chest wall. They are usually water resistant and can be disposable. Once removed, they can be connected to a computer for analysis. They are usually unable to be marked for review when a patient has symptoms, and rely on computer algorithms for analysis.

Loop recorders are small devices that continuously record and when activated due to symptoms can retrieve the 5 minutes prior to that. They are attached to leads or a belt around the chest. Activation can be automatic (based on algorithms) or manual (by the patient).

Symptom event monitors (also known as post-event or non-looping) can be a small hand-held device (put in a pocket) or one worn on the wrist like a watch. They only start recording when activated, and some can't go back from that (but some can). They do not require leads, but the device has to be pressed against the chest to get a recording.

Both Loop and Symptom monitors can send data via telephone.

Implantable devices are very small loop recorders that are put into the subcutaneous tissue in the chest wall and can record up to 3 years. They can be monitored remotely, but typically can only show one lead (view).

Mobile Cardiac Outpatient Telemetry (MCOT) monitors continuously analyze the electrocardiogram (ECG) and transmit events real time.

### Coding

**Effective January 1, 2023**, the following CPT codes have been **deleted**:

- **0497T**: External patient-activated, physician- or other qualified health care professional-prescribed, electrocardiographic rhythm derived event recorder without 24 hour attended monitoring; in-office connection
- **0498T**: External patient-activated, physician- or other qualified health care professional-prescribed, electrocardiographic rhythm derived event recording without 24 hour attended monitoring; review and interpretation by a physician or other qualified health care professional per 30 days with at least one patient-generated triggered event

### Examples of Cardiac Monitoring Devices and Procedural Coding (not all inclusive):

For a complete description of the codes, see the Coding section of the Medical Policy.

Cardiac Event Monitoring Device	Product Name	CPT Codes
External Ambulatory Event Monitors	<ul style="list-style-type: none"> <li>• Zio® Event Card (iRhythm Technologies, Inc., San Francisco, CA)</li> <li>• REKA E100™ (REKA Health, San Diego, CA)</li> </ul>	93268 93270 93271 93272
<ul style="list-style-type: none"> <li>• Noncontinuous devices with memory</li> <li>• Autoactivated or patient-activated</li> </ul>		(See *Note below)

Cardiac Event Monitoring Device	Product Name	CPT Codes
Implantable Ambulatory Event Monitors	• Reveal® Insertable Loop Recorder (Medtronic Inc., Minneapolis, MN)	33285
	• Continuous “memory loop” devices	33286
Mobile Outpatient Cardiac Telemetry (MCOT)	• CardioNet Mobile Cardiac Outpatient Telemetry™ (MCOT™) (CardioNet, Inc., Conshohocken, PA)	93228 93229
	• HEARTLink™ II system (Cardiac Telecom Corporation, Greensburg, PA)	(See **Note below)
	• Vital Signs Transmitter (VST™) Monitor (Biowatch Medical, Columbia, SC)	
	• Lifestar Ambulatory Cardiac Telemetry (ACT) system (LifeWatch Technologies, Ltd., Rehovot, Israel)	
Continuous Monitoring Devices with Longer Recording Periods	• Zio® Patch (iRhythm Technologies, Inc., San Francisco, CA)	93241-93248
	• BodyGuardian® Remote Monitoring System (Preventice®, Inc., Minneapolis, MN)	

**\*Note:** CPT code (93268) represents a bundled CPT code including all components of ambulatory event monitoring, including ECG analysis of all the recorded strips during a 30-day period. CPT codes (93270, 93271, and 93272) represent unbundling of CPT code 93268.

The following CPT codes represent an implantable cardiac event recorder:

- **33285:** Insertion, subcutaneous cardiac rhythm monitor, including programming
- **33286:** Removal, subcutaneous cardiac rhythm monitor

The interpretation of the electrocardiograms (ECGs) recorded with ambulatory event monitors may be coded as follows:

- **93268:** External patient and, when performed, auto activated electrocardiographic rhythm derived event recording with symptom-related memory loop with remote download capability up to 30 days, 24-hour attended monitoring; includes transmission, review and interpretation by a physician or other qualified health care professional

The above CPT code represents a bundled CPT code including all components of ambulatory event monitoring, including ECG analysis of all recorded strips during a 30-day period.

Other CPT codes that can be used for ambulatory event monitoring represent unbundling of the 93268 code. For example, CPT code 93270 describes the connection, recording, and disconnection of an external device; CPT code 93271 describes the transmission download and analysis; and 93272 describes the physician review and interpretation of the ECG strips. Ambulatory event monitoring services may supply the monitoring, receipt of transmissions, and analysis of the ECGs (i.e., CPT codes 93271 and 93272), but the provider supplies the hook-up and disconnection of the device (i.e., CPT code 93270). If this is the case, the unbundled codes may be used. It should also be noted that CPT code 93272 (physician review and interpretation) applies to all ECGs transmitted during a 30-day period; therefore, billing for each individual transmitted strip is not warranted.

There are specific CPT codes for mobile outpatient cardiac telemetry:

- **93228:** External mobile cardiovascular telemetry with electrocardiographic recording, concurrent computerized real time data analysis and greater than 24 hours of accessible ECG data storage (retrievable with query) with ECG triggered and patient selected events transmitted to a remote attended surveillance center for up to 30 days; review and interpretation with report by a physician or other qualified health care professional

- **93229:** External mobile cardiovascular telemetry with electrocardiographic recording, concurrent computerized real time data analysis and greater than 24 hours of accessible ECG data storage (retrievable with query) with ECG triggered and patient selected events transmitted to a remote attended surveillance center for up to 30 days; technical support for connection and patient instructions for use, attended surveillance, analysis and transmission of daily and emergent data reports as prescribed by a physician or other qualified health care professional

**\*\*Note:** CPT codes (93228 and 93229) can only be reported once per 30 days of service.

The following Category I CPT codes will **replace Category III CPT codes 0295T-0298T** for devices with longer recording capabilities:

- **93241:** External electrocardiographic recording for more than 48 hours up to 7 days by continuous rhythm recording and storage; includes recording, scanning analysis with report, review and interpretation
- **93242:** External electrocardiographic recording for more than 48 hours up to 7 days by continuous rhythm recording and storage; recording (includes connection and initial recording)
- **93243:** External electrocardiographic recording for more than 48 hours up to 7 days by continuous rhythm recording and storage; scanning analysis with report
- **93244:** External electrocardiographic recording for more than 48 hours up to 7 days by continuous rhythm recording and storage; review and interpretation
- **93245:** External electrocardiographic recording for more than 7 days up to 15 days by continuous rhythm recording and storage; includes recording, scanning analysis with report, review and interpretation
- **93246:** External electrocardiographic recording for more than 7 days up to 15 days by continuous rhythm recording and storage; recording (includes connection and initial recording)
- **93247:** External electrocardiographic recording for more than 7 days up to 15 days by continuous rhythm recording and storage; scanning analysis with report
- **93248:** External electrocardiographic recording for more than 7 days up to 15 days by continuous rhythm recording and storage; review and interpretation

The following Category III CPT code is used to report remote programming of a subcutaneous cardiac rhythm monitor which is a new technology that provides physicians the ability to remotely program the settings and alerts to the subcutaneous cardiac rhythm monitor device.

- **0650T:** Programming device evaluation (remote) of subcutaneous cardiac rhythm monitor system, with iterative adjustment of the implantable device to test the function of the device and select optimal permanently programmed values with analysis, review and report by a physician or other qualified health care professional

The following HCPCS code represents a proactive diagnostic technology that monitors a patient's hearts electrical activity for changes that may indicate an Acute Coronary Syndrome event related to blockage of a coronary artery.

- **C1833:** Monitor, cardiac, including intracardiac lead and all system components (implantable)

## Description

Various devices are available for outpatient cardiac rhythm monitoring. These devices differ in the types of monitoring leads used, the duration and continuity of monitoring, the ability to detect arrhythmias without patient intervention, and the mechanism of delivering the information from patient to clinician. These devices may be used to evaluate symptoms suggestive of arrhythmias (e.g.,

syncope, palpitations), and may be used to detect atrial fibrillation (AF) in patients who have undergone cardiac ablation of AF or who have a history of cryptogenic stroke.

## Related Policies

- N/A

## Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## 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. Food and Drug Administration product codes include: DSH, DXH, DQK, DSI, MXD, MHX.

## Rationale

### 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 are discussed.

Arrhythmias are an important potential cause of syncope or near syncope, which in some cases may be described as dizziness. An electrocardiogram (ECG) is generally indicated whenever there is suspicion of a cardiac cause of syncope. Some arrhythmic causes will be apparent on ECG. However, for patients in whom an ECG is not diagnostic, longer monitoring may be indicated. The 2009 joint guidelines from the European Society of Cardiology and 3 other medical specialty societies suggested that, in individuals with clinical or ECG features suggesting an arrhythmic syncope, ECG monitoring is indicated; the guidelines also stated that the "duration (and technology) of monitoring should be selected according to the risk and the predicted recurrence rate of syncope."<sup>1</sup> Similarly, guidelines from the National Institute for Health and Care Excellence (2014) on the evaluation of transient loss of consciousness, have recommended 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.<sup>2</sup> 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 1 to 2 weeks, an external event recorder is recommended; and if the frequency is less than once every 2 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.<sup>3</sup>

### **Atrial Fibrillation Detection**

AF is the most common arrhythmia in adults. It may be asymptomatic or be associated with a broad range of symptoms, including lightheadedness, palpitations, dyspnea, and a variety of more nonspecific symptoms (e.g., fatigue, malaise). It is classified as paroxysmal, persistent, or permanent based on symptom duration. Diagnosed AF may be treated with antiarrhythmic medications with the goal of rate or rhythm control. Other treatments include direct cardioversion, catheter-based radiofrequency- or cryo-energy-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.<sup>4</sup>

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.<sup>5,6</sup> 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 a 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 24 to 72 hours.

Traditionally, most Holter monitors have 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 to 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. Devices 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	<ul style="list-style-type: none"> <li>• Zio® Event Card (iRhythm Technologies)</li> <li>• REKA E100™ (REKA Health)</li> </ul>
Continuous recording devices with longer recording periods	Devices continuously worn and continuously record via $\geq 1$ cardiac leads and store data longer than traditional Holter (14 days)	<ul style="list-style-type: none"> <li>• Zio®XT Patch and ZIO ECG Utilization Service (ZEUS) System (iRhythm Technologies)</li> </ul>
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 <i>preceding</i> 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).	<ul style="list-style-type: none"> <li>• Patient-triggered: Explorer™ Looping Monitor (LifeWatch Services)</li> <li>• Auto-triggered: LifeStar AF Express™ Auto-Detect Looping Monitor (LifeWatch Services)</li> <li>• Auto-triggered or patient-triggered: King of Hearts Express® AF (Card Guard Scientific Survival)</li> </ul>
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	<ul style="list-style-type: none"> <li>• Auto-triggered or patient-triggered: Reveal® XT ICM (Medtronic) and Confirm Rx Insertable™ Cardiac Monitor (Abbott)</li> <li>• Auto-triggered: BioMonitor, Biotronik)</li> </ul>
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	<ul style="list-style-type: none"> <li>• CardioNet MCOT™ (BioTelemetry)</li> <li>• LifeStar Mobile Cardiac Telemetry (LifeWatch Services)</li> <li>• Zio AT(iRhythm)</li> </ul>

ECG: electrocardiogram.

There are also devices that combine features of multiple classes. For example, the LifeStar ACT Ex Holter (LifeWatch Services) is a 3-channel Holter monitor, but is converted to a mobile cardiac telemetry system if a diagnosis is inconclusive after 24 to 48 hours of monitoring. The BodyGuardian® Heart Remote Monitoring System (Preventice Services) is an external auto-triggered memory loop device that can be converted to a real-time monitoring system. The eCardio Verité™ system (eCardio) can switch 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 Zio Patch, can record 2 channels for 14 to 40 days.

### **Literature Review**

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the 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 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 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 (e.g., dizziness, syncope or near syncope, palpitations) is discussed. Specific arrhythmias may be relatively nonspecific in terms of the symptoms they cause. However, the diagnosis of some arrhythmias has well-defined management implications that are known to improve outcomes, such as the use of an implantable cardioverter defibrillator in individuals with potentially lethal arrhythmias, or antiarrhythmic drugs or pulmonary vein isolation for the treatment of atrial fibrillation (AF). Therefore, 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.

## **Auto-Activated External or Continuous Ambulatory Event Monitoring for Patients With Arrhythmia Symptoms**

### **Clinical Context and Test Purpose**

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

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

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

### ***Populations***

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

### ***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***

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

### ***Outcomes***

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

### **Study Selection Criteria**

For the evaluation of clinical validity of auto-activated 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.

### Review of Evidence

#### Systematic Review

Hoefman et al (2010) published a systematic review on diagnostic tools for detecting cardiac arrhythmias.<sup>7</sup> 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, auto-triggered event recorders, and implantable loop recorders (ILRs). The yield varied among devices, with auto-trigger devices providing the highest range of detection (72% to 80%), followed by patient-activated devices (17% to 75%), and Holter monitors (33% to 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.<sup>8</sup> 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.

Turakhia et al (2013) evaluated the diagnostic yield of the Zio Patch.<sup>9</sup> Data from the manufacturer were used to identify 26,751 first-time users of the device. The most common clinical indications were palpitations (40.3%), 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 1 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. The overall yield was significantly higher when comparing the total monitored period (62.2%) with the first 48 hours (43.9%;  $p < 0.001$ ). These data confirmed previous studies that had shown that while a substantial proportion of arrhythmias in symptomatic patients can be detected within a 48-hour period of monitoring, 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.<sup>10</sup> Included were patients referred for evaluation of a suspected cardiac arrhythmia at a single institution. For the detection of atrioventricular block, sinus pause, polymorphic ventricular tachycardia, supraventricular tachycardia (SVT), 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 1 only detected by the Holter monitor. 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 might have clinical significance if its performance is similar in nonresearch 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.<sup>11</sup> 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, 1766 (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 1468 (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.<sup>12</sup> The median time to the first detected paroxysmal AF event was 24.9 hours (interquartile range [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 2 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.<sup>13</sup> 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 3209 children included in a manufacturer registry.<sup>14</sup> Patient age ranged from 1 month to 17 years. Indications for monitoring included palpitations (n=1138 [35.5%]), syncope (n=450 [14.0%]), unspecified tachycardia (n=291 [9.1%]), paroxysmal 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 referred for palpitations, 6.7% referred for syncope, 14.8% referred for tachycardia, 22.7% referred for paroxysmal SVT, and 6.5% referred for chest pain.

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

**Table 2. Single-Center Studies Reporting on Zio Patch Diagnostic Yield**

Study	Population	Monitoring Indication Indication (%)	Main Findings
Eisenberg et al (2014) <sup>15</sup>	524 consecutive patients evaluated in an academic EP practice	<ul style="list-style-type: none"> <li>Surveillance for unspecified arrhythmia or palpitations (47)</li> <li>Known/suspected AF (30)</li> <li>Syncope (8)</li> <li>Bradycardia surveillance (4)</li> <li>Tachycardia surveillance (5)</li> <li>Chest pain (2)</li> </ul>	<ul style="list-style-type: none"> <li>Significant arrhythmias detected in 297 (57%)</li> <li>66% had 1st arrhythmia detected within 2 days of monitoring</li> <li>25% of patient-triggered events associated with clinically significant arrhythmias</li> </ul>

Study	Population	Monitoring Indication	Main Findings
Schreiber et al (2014) <sup>16</sup>	174 patients with symptoms suggestive of arrhythmia seen in an ED	<ul style="list-style-type: none"> <li>Palpitations 44.8)</li> <li>Syncope (24.1)</li> <li>Unspecified arrhythmias detected in the ED (11.5)</li> </ul>	<ul style="list-style-type: none"> <li>&gt;1 significant arrhythmia other than chronic AF (<math>\geq 4</math> beats VT, paroxysmal AF, <math>\geq 4</math> beats SVT, <math>\geq 3</math>-second pause, 2nd-degree Mobitz II or 3rd-degree AV block, or symptomatic bradycardia) detected in 83 (47.7%)</li> <li>Median time to arrhythmia detection: <ul style="list-style-type: none"> <li>Any arrhythmia: 1.0 day (IQR, 0.2 to 2.8)</li> <li>VT: 3.1 days</li> <li>Sinus pause: 4.2 days</li> <li>Significant heart block: 5.8 days</li> </ul> </li> </ul>
Mullis et al (2019) <sup>17</sup>	59 consecutive patients seen in an outpatient EP clinic	PVCs	<ul style="list-style-type: none"> <li>Median of minimum 24-hour PVC burden: 4.5% (IQR, 2.6% to 11.2%)</li> <li>Median of maximum 24-hour PVC burden: 16.2% (IQR, 11.7 % to 26.2%)</li> <li>Mean 24-hour PVC burden: 9.0% (IQR, 6.4% to 17.9%)</li> <li>Median difference between maximum 24-hour PVC burden and minimum 24-hour burden: 2.45-fold (IQR, 1.68- to 5.55-fold)</li> </ul>
Reed et al (2018) <sup>18</sup>	86 patients evaluated in an ED	Syncope	<ul style="list-style-type: none"> <li>9/86 (10.5%) had a symptomatic significant arrhythmia endpoint (95% CI, 4.0 to 16.9)</li> </ul>

AF: atrial fibrillation; AV: atrioventricular; CI: confidence interval; ED: emergency department; EP: electrophysiology; IQR: interquartile range; PVC: premature ventricular contraction; 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.<sup>19</sup> 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.<sup>20</sup> 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; 7 addressed long-term AEMs and 5 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 100,000 patients, have compared the diagnostic yield of automatic and patient-activated arrhythmia recordings and reported an improved yield with auto-triggering devices.<sup>21,22,23</sup>

### **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 monitors indicates that such devices typically detect greater numbers of arrhythmias during extended follow-up compared with 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 3 months postprocedure, 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 3 months postablation, 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.<sup>24,25</sup> However, the presence of recurrent episodes of AF is a predictor of future thromboembolic events. In a large observational study of 565 patients postablation, Chao et al (2011) found the 2 major predictors of thromboembolism were the CHADS<sub>2</sub> score and the presence of recurrent episodes of AF.<sup>26</sup>

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

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

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

### ***Populations***

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

### ***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 recording activity continuously and can store data longer than the Holter monitor.

### ***Comparators***

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

### ***Outcomes***

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

### **Study Selection Criteria**

For the evaluation of clinical validity of auto-activated 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).

### **Review of Evidence**

#### **Randomized Controlled Trial**

In a prospective, randomized study, Kapa et al (2013) compared ILRs with conventional transtelephonic recorders in the assessment of arrhythmia burden after catheter ablation.<sup>27</sup> Forty-four patients were enrolled and randomized; all patients received the ILR postablation. Six patients were excluded due to requests for device removal or loss to follow-up. During the first 6 months after ablation, all subjects underwent conventional monitoring that consisted of twice daily, 1-minute pulse rate assessments by the patient and 3, 30-day transtelephonic monitoring periods. At 6 months postablation, patients were allocated to the randomization arm (on a 1:1 basis at initial enrollment) of either the ILR (transmission of data every 31 days) or conventional monitoring (twice daily, 1-minute pulse rate assessment, 1 transtelephonic recording for 30 days at month 11). At 6 months postablation, conventional monitoring detected AF in 7 (18%) of 38 patients and the ILR confirmed AF in all of these patients. ILR monitoring also detected AF in an additional 11 (29%) patients. During the subsequent 6-month period, 5 of 18 patients in the conventional monitoring arm refused ongoing monitoring due to discomfort and lifestyle restrictions; of the remaining 13, 5 (38%) had a recurrence

of AF. In the ILR group, 5 (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 Study

Reporting on the prospective 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.<sup>28</sup> Patients were instructed to keep a standardized diary record of arrhythmia symptoms. Asymptomatic AF recurrences were defined as implantable cardiac monitor (ICM) events lasting 2 minutes or longer, without a corresponding diary entry. Based on diary reporting of symptoms, 29 (58%) of 50 patients were arrhythmia-free after ablation; based on monitor recordings from intermittent (every 3 month) ECG or Holter monitor, 28 (56%) patients were arrhythmia-free postablation. 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 observational studies have followed patients who stopped anticoagulation after a comprehensive evaluation, which included ambulatory monitoring, that indicated the patient had a low-risk for recurrent episodes. These patients experienced a low subsequent rate of thromboembolic events. In 1 study, Themistoclakis et al (2010) evaluated 3355 patients from 5 clinical centers, of whom 2692 discontinued anticoagulation at 3 to 6 months postablation and 663 continued anticoagulation medication.<sup>29</sup> During a mean follow-up of 28 months, 2 (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%). In addition, the adverse event rate of major hemorrhage was lower for patients who discontinued anticoagulation (0.04%) compared with those who continued (2%;  $p<0.001$ ).

### 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 Ambulatory Cardiac Monitoring for Patients With Atrial Fibrillation following Ablation

Evidence includes an RCT and several observational studies that make a strong indirect argument that long-term monitoring for asymptomatic episodes of AF with AEMs will lead to changes in management with 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. In addition, patients discontinuing anticoagulants experienced fewer major hemorrhages. These changes in management based on ambulatory monitoring are likely to improve outcomes. Because different long-term monitoring devices were used across the studies, the specific type of monitoring associated with the best outcomes is not established.

### **Long-term Ambulatory Cardiac Monitoring for Patients with Cryptogenic Stroke**

#### **Clinical Context and Test Purpose**

Approximately 5% of patients with cryptogenic stroke will have AF diagnosed on ECG and/or telemetry monitoring in the hospital. Patients with a history of cryptogenic stroke who have had AF detected, are typically treated with anticoagulants. Studies comparing the use of continuous telemetry monitoring at the bedside with Holter monitoring for patients hospitalized for stroke or transient ischemic attack (TIA) have reported inconclusive results as to which is the preferred method for AF detection.<sup>30,31</sup> Longer term ambulatory event monitoring has been shown to identify additional patients with asymptomatic episodes, with rates of detection estimated at 6% to 26% of patients.<sup>5,32,33</sup>

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

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

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

#### ***Populations***

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

#### ***Interventions***

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

#### ***Comparators***

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

#### ***Outcomes***

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

#### **Study Selection Criteria**

For the evaluation of clinical validity of auto-activated 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.

### Review of Evidence

#### 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 4 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), ELR, and ILR.<sup>34</sup> In total, 50 studies with 11658 patients met the inclusion criteria. Studies were mixed in their patient composition: 22 (28%) included only cryptogenic stroke cases, 4 (5%) stratified events into cryptogenic and noncryptogenic, and 53 (67%) included unselected patient populations. The proportion of patients diagnosed with poststroke AF during the ambulatory phases was 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%), ELR (16.2%; 95% CI, 0.3% to 24.6%), or ILR (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.<sup>35</sup> Thirty-two studies were selected: 18 studies included patients with ischemic stroke only, 1 study 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%); among selected patients, it was 13.4% (95% CI, 9.0% to 18.4%). In cryptogenic strokes, new AF was detected in 15.9% of patients (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 nonimplantable loop recording, and MCOT) was 14.7% (95% CI, 10.7% to 19.3%).

The Kishore et al (2014) 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 their relation to the preceding stroke uncertain. 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 (Table 3). Two were small pilot trials. 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.<sup>36</sup> There were no cases of AF detected in either group (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 7 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, an ELR device (Table 3).<sup>37</sup> 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 (Table 4).

Sanna et al (2014) reported on results from the Cryptogenic Stroke and underlying times Fibrillation (CRYSTAL AF) trial, an RCT that evaluated whether long-term monitoring with ICMs in patients who had cryptogenic stroke would lead to changes in anticoagulant management and/or improved outcomes (Table 3).<sup>38,39</sup> 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 6-month follow-up, 2 were lost to follow-up, 5 died, and 18 exited the trial before 6 months. Crossover occurred in 12 patients in the ICM group and 6 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) (Table 4). Median time from randomization to detection of AF was 41 days (IQR, 14 to 84 days) in the ICM group and 32 days (IQR, 2 to 73 days) in the control group. Most AF episodes in the ICM group were asymptomatic (74%) compared with 33% 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.<sup>40</sup> 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 Atrial Fibrillation in Patients with Cryptogenic Stroke 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 (Table 3).<sup>41</sup> 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 1 or more ECGs and 1 or more 24-hour Holter monitors. In total, 572 patients were randomized to an ELR (ER910AF Cardiac Event Monitor, Braemar) or to a 24-hour Holter monitor. Among intervention group subjects, 82% completed at least 3 weeks of monitoring. AF was detected in 45 (16.1%) of 280 patients in the intervention group compared with 9 (3.2%) of 277 patients in the control group (risk difference, 12.9 percentage points; 95% CI, 8.0 to 17.6; p<0.001) (Table 4). At 90-day follow-up, patients in the intervention group (18.6%) were more likely to be treated with anticoagulants than those in 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.<sup>42</sup> 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=0.026).

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

Study	Country	Sites	Dates	Participants	Interventions (n)	
					Active	Comparator
Kamel et al (2013) <sup>36</sup> .	United States	1	2009-2011	Cryptogenic ischemic stroke or high-risk TIA	MCOT (20)	Standard (20)
Higgins et al (2013) <sup>37</sup> .	United Kingdom	2	2010-2011	Transient or persistent symptoms of acute TIA	ELR (50)	Standard (50)
Sanna et al (2014) <sup>39</sup> , & Brachmann et al (2016) <sup>40</sup> .	Canada, Europe, United States	55	2009-2012	Cryptogenic ischemic stroke or TIA	ILR (221)	Standard (220)
Gladstone et al (2014) <sup>41</sup> .	Canada	16	NR	Cryptogenic ischemic stroke or TIA	ELR (280)	Standard (277)
Kaura et al (2019) <sup>42</sup> .	United Kingdom	2	NR	Cryptogenic ischemic stroke or TIA	Zio Patch (60)	Standard (60)

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

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

Study	FU	AF Detection		p-value	Additional Findings
		AEM, %	Standard, %		
Kamel et al (2013) <sup>36</sup> .	90 days	0	0	NS	<ul style="list-style-type: none"> <li>MCOT identified atrial tachycardia in 2 patients (1 incorrectly labeled as AF by telemetry software)</li> <li>MCOT identified 2 nonsustained ventricular tachycardia</li> </ul>
Higgins et al (2013) <sup>37</sup> .	14 days 90 days	18 22	28	<0.05 0.09	<ul style="list-style-type: none"> <li>No difference between groups for recurrent stroke, TIA, or mortality</li> </ul>
Sanna et al (2014) <sup>39</sup> ; Brachmann et al (2016) <sup>40</sup> .	6 months 12 months 3 years	8.9 12.4 30	1.4 2.0 3.0	<0.001 <0.001 <0.001	<ul style="list-style-type: none"> <li>Percent patients on oral anticoagulation therapy significantly higher in ILR group vs. standard group</li> <li>At 3-year follow-up, recurrent stroke or TIA occurred in 20 patients in ILR group and in 24 in standard group</li> </ul>
Gladstone et al (2014) <sup>41</sup> .	90 days	16.1	3.2	<0.001	<ul style="list-style-type: none"> <li>Atrial premature beats was identified in a regression model as a potential predictor of AF detection</li> </ul>
Kaura et al (2019) <sup>42</sup> .	90 days	16.3	2.1	0.026	<ul style="list-style-type: none"> <li>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=0.05)</li> </ul>

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 devices, including ILRs,<sup>6,43,44</sup> and continuous monitors with longer recording periods,<sup>45</sup> along with a pilot study evaluating the Zio Patch for AF detection poststroke.<sup>46</sup>

### 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 compared with 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. Because different long-term monitoring devices were used across the studies, the specific type of monitoring associated with the best outcomes is not established.

**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 the absence of screening; incremental benefit of earlier versus later treatment for stroke when AF is detected; and potential harms of over-diagnosis.

Assessing the prevalence of asymptomatic AF is difficult because of the lack of symptoms. Approximately one-third of all patients with AF are estimated to be asymptomatic.<sup>47</sup> Studies have suggested that most paroxysmal episodes of AF are asymptomatic.<sup>48,49</sup> 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<sup>50,51</sup> while in a systematic review of 12 studies (total N=99,996 patients), Ganesan et al (2016) found that the risks of thromboembolism and all-cause mortality were higher with nonparoxysmal than with paroxysmal AF.<sup>52</sup> 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.<sup>53</sup> This RCT showed that systematic and opportunistic screening detected similar rates of AF and both were superior to standard care. The mechanisms of how and when to screen for AF in unselected populations have not been well-studied.

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

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

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

### ***Populations***

The relevant population of interest is asymptomatic individuals with risk factors 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 comparators are no additional evaluation or standard care. Standard care may include an ECG and/or pulse palpation.

### ***Outcomes***

To assess 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 auto-activated 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.

### **Review of Evidence**

#### **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.<sup>54,55,56</sup> 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.<sup>57</sup>

#### **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 (Zio Patch) for patients with risk factors for AF.<sup>58</sup> The study included 75 patients older than age 55 years 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 at moderate- to

high-risk of stroke (CHA<sub>2</sub>DS<sub>2</sub>-VAsC scores  $\geq 2$ ). After a mean follow-up of 7.6 days, AF was detected in 4 (5.3%) subjects, all of whom had CHA<sub>2</sub>DS<sub>2</sub>-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 to 84 years of age and free of clinically-recognized cardiovascular disease.<sup>59</sup> A total of 1122 participants completed 1 or 2 monitoring episodes using the Zio Patch. The mean age of participants at the time of monitoring was 75 (standard deviation, 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.<sup>57</sup> 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 CHA<sub>2</sub>DS<sub>2</sub>VAsC 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 one year among the actively monitored groups combined vs the matched observational controls. For the primary endpoint, at 4 months follow-up, 3.9% of the immediate group and 0.9% of the delayed group had newly diagnosed AF (absolute difference, 3.0%; 95% confidence interval [CI], 1.8% to 4.1%). For the secondary endpoint, at 1 year follow-up, 6.7 per 100 person-years in the monitored group and 2.6 per 100 person-years in the control group had newly diagnosed AF. At one year, patients who were actively monitored were more likely to initiate anticoagulants, and have more cardiology visits and more primary care visits. There were no differences in emergency room visits or hospitalizations between the monitored and unmonitored groups after one year.

Steinhubl et al (2021) reported 3-year outcomes for the observational cohort.<sup>60</sup> 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.<sup>54,55,56</sup>



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).<sup>54</sup> Patients were 65 years and older, asymptomatic, with CHA<sub>2</sub>DS<sub>2</sub>-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.<sup>55</sup> 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.

Svensden et al (2021) reported results of the LOOP trial.<sup>56</sup> 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.

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

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
Halcox et al (2017) <sup>54</sup>  REHEARSE-AF  ISRCTN10709813	UK	1	2015-2017	65 years and older, asymptomatic, with CHA2DS2-VASc scores of 2 or higher.	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 = 500  N = 501  Followed by general practitioners
Gladstone et al (2021) <sup>55</sup>  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)
Svensden et al (2021) <sup>56</sup>  LOOP Trial  NCT02036450	Denmark	4	2014 to 201	Eligibility criteria: Ages 70 to 90 years, with at least one of four conditions: hypertension, diabetes, previous stroke, or heart failure  Exclusions: atrial fibrillation, a history of atrial fibrillation, a pacemaker, anticoagulation medicine, or contraindication to anticoagulation.	N = 1501  Continuous ECG monitoring via automated remote transmissions with daily physician review of all transmissions. If atrial fibrillation lasting at least 6 min was detected, the participant was contacted and initiation of oral anticoagulation was	N = 4503  Annual interview with a study nurse and standard contact with the participant's general practitioner)

Study; Trial	Countries	Sites	Dates	Participants	Interventions
					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) <sup>54</sup> ,	19/500 (3.8%)	5/501 (1.0%)	HR 3.9 (1.4 to 10.4)	.007
Gladstone et al (2021) <sup>55</sup> ,	23/434 (5.3%)	2/422 (0.5%)	RR 11.2 (2.7 to 47.1)	.001
Svensden et al (2021) <sup>56</sup> ,	477/1501 (31.8%)	550/4503 (12.2%)	HR 3.17 (2.81 to 3.59)	<.0001
LOOP Trial				
NCT02036450				

CI: confidence interval; HR: hazard ratio; RR: relative risk.

**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
Svensden et al (2021) <sup>56</sup> ,						
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 <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Duration of Follow-up <sup>e</sup>
Halcox et al (2017) <sup>54</sup> ,	4. Race not reported; majority of participants were of White				1 year insufficient duration to draw conclusions on

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Duration of Follow-up <sup>e</sup>
	European ethnicity				health outcomes.
Gladstone et al (2021) <sup>55</sup> ,	4. 94% White, 1.5% Black				6 months was insufficient duration to draw conclusions on health outcomes.
Svensden et al (2021) <sup>56</sup> , 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

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> 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.

<sup>b</sup> 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.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

<sup>d</sup> 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.

<sup>e</sup> 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 <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
Halcox et al (2017) <sup>54</sup> ,		1. Not blinded			4. Not powered to detect differences in health outcomes	
Gladstone et al (2021) <sup>55</sup> ,		1. Not blinded			4. Not powered to detect differences in health outcomes	
Svensden et al (2021) <sup>56</sup> , 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.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

<sup>b</sup> Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication;

4. Other.

<sup>d</sup> 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.

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

<sup>f</sup> 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 for Patients With Symptoms of Arrhythmia**

#### **Clinical Context and Test Purpose**

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

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

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

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

#### ***Populations***

The relevant population of interest is 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 auto-activated. 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 auto-activated 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).

### **Review of Evidence**

#### **Systematic Reviews**

Solbiati et al (2017) conducted a systematic review and meta-analysis on the diagnostic yield of ILRs in patients with unexplained syncope.<sup>61</sup> 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%;  $I^2=80%$ ). 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.

Burkowitz et al (2016) conducted a systematic review and meta-analysis of ILRs in the diagnosis of syncope and the detection of AF.<sup>62</sup> For syncope diagnosis, the review identified 3 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, 4.17; 95% CI, 2.57 to 6.77;  $I^2=14%$ ). The RCTs (Da Costa et al [2013],<sup>63</sup> Farwell et al [2004],<sup>64</sup> and Krahn et al [2001]<sup>65</sup>) 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.<sup>66</sup> Reviewers included 16 studies (N=1770 patients): 3 RCTs and 13 observational studies. For ILR-monitored patients, the median monitoring duration was 365 days (range, 50 to 569 days), while for wearable device-monitored patients, the median monitoring duration was 14 days (range, 4 to 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 2 strategies for evaluating syncope: an experimental strategy involving the early use of an ILR and a conventional evaluation strategy excluding an ILR (see Table 10).<sup>67</sup> The trial included patients who had a single syncope (if severe and recent) or at least 2 syncopes in the past 12 months. The syncope had to be unexplained at the end of clinical examination and who had 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 2 (5%) cases of atrioventricular block, 4 (10%) cases of sinus node disease, one (2.5%) case of AF, one (2.5%) case of ventricular fibrillation, and 3 (8%) other tachycardias. In the conventionally managed group, 8 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 (Table 10).<sup>63</sup> 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 1 arrhythmia detected, with a significant difference in the 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 ( $\leq 1$  episode per month) unexplained palpitations--: an ILR strategy (n=26) and a conventional strategy (n=24) including 24-hour Holter, 4 weeks of ambulatory ECG monitoring with an external recorder, and an electrophysiologic study if the 2 prior evaluations were negative) (see Table 10).<sup>68</sup> 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 5 (21%) subjects, after a mean time to diagnosis of 36 days, based on external ECG monitoring in 2 subjects and electrophysiologic studies in 3 subjects. In the ILR group, a diagnosis was made in 19 subjects after a mean time to diagnosis of 279 days (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 (Table 5).<sup>64</sup> 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;  $p < 0.001$ ) (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 to 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) (Table 10).<sup>65</sup> Eligible patients had a 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**

Study	Country	Sites	Dates	Participants	Interventions (n)	
					Active	Comparator
Podoleanu et al (2014) <sup>67</sup>	France	13	2004-2008	Single recent syncope or 2 in past 12 months	ILR (39)	Standard (39)
Da Costa et al (2013) <sup>63</sup>	France	Multiple, NS	2005-2010	Single syncope	ILR (41)	Standard (37)
Giada et al (2007) <sup>68</sup>	Italy	Multiple, NS	NR	Unexplained palpitations	ILR (26)	Standard (24)
Farwell et al (2004) <sup>64</sup>	England	1	2000-2001	$\geq 2$ unexplained syncope in	ILR (103)	Standard (98)



					Interventions (n)		
					past 12 months		
Krahn et al (2001) <sup>65</sup> ,		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 trial.

**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) <sup>67</sup> ,	14 months	18 (46)	2 (5)	<0.001	<ul style="list-style-type: none"> <li>Advanced cardiology tests performed less frequently in ILR group vs. standard (p=0.05)</li> <li>No difference in quality of life</li> </ul>
Da Costa et al (2013) <sup>63</sup> ,	27 months <sup>a</sup>	15 (37)	4 (11)	0.02	<ul style="list-style-type: none"> <li>Earlier diagnosis in ILR group permitted earlier pacemaker implantation. However, earlier implantation did not improve survival (potentially due to small sample).</li> </ul>
Giada et al (2007) <sup>68</sup> ,	≥12 months	19 (73)	5 (21)	<0.001	<ul style="list-style-type: none"> <li>9 of 19 patients with negative results with standard care crossed over to ILR and 6 of them received a diagnosis</li> </ul>
Farwell et al (2004) <sup>64</sup> ,	≥6 months	34 (33)	4 (4)	<0.001	<ul style="list-style-type: none"> <li>ECG-directed therapy was initiated quicker in the ILR group</li> <li>No difference in syncopal episodes, mortality, or quality of life</li> </ul>
Krahn et al (2001) <sup>65</sup> ,	12 months	14 (52)	6 (20)	0.012	<ul style="list-style-type: none"> <li>Crossover offered to patients with negative results</li> <li>1 of 6 switching to ELR was diagnosed and 8 of 13 switching to ILR was diagnosed (p=0.07)</li> </ul>

ECG: electrocardiogram; FU: follow-up; ILR: implantable loop recorder; RCT: randomized controlled trial.

<sup>a</sup> Mean.

### Observational Studies

Multiple observational studies compared the diagnostic yield of ICMs to the Holster monitor and reported high rates of arrhythmia detection.<sup>69,70,71,72,73,74</sup> Several observational studies reported management outcomes following diagnoses, such as anticoagulation initiation or cardiac procedures.<sup>75,76,77,78</sup>

### Safety of Implantable Loop Recorders

Mittal et al (2015) reported on safety outcomes related to the use of an ILR, based on data from 2 studies, the Reveal LINQ Usability study and the Reveal LINQ Registry.<sup>79</sup> 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 postmarketing surveillance registry, with a planned enrollment of at least 1200. 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, 2 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 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****Section Summary: Implantable Loop Recorders for Patients with Symptoms of Arrhythmia**

Several RCTs have reported high rates of arrhythmia detection with the use of ILRs 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 MCOT to ambulatory cardiac monitoring 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 is 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 auto-activated 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).

**Review of Evidence****Randomized Controlled Trials**

An RCT by Rothman et al (2007) compared MCOT with standard event monitors (Table 12).<sup>80</sup> This trial involved 305 patients randomized to the LOOP recorder or to MCOT (CardioNet) and monitored for up to 30 days. Patients were recruited from 17 centers. Investigators and patients were not blinded to randomization assignment. Monitor strips and diagnoses were reviewed by an electrophysiologist blinded to the monitoring device assignment. Most patients in the LOOP recorder group had a patient-triggered event monitor. Only a subset of patients (n=50) had auto-trigger devices, thus precluding comparison between MCOT and auto-trigger devices. Analyses were conducted on patients completing at least 25 days of monitoring. The primary endpoint was either confirmation or exclusion of arrhythmic cause of the patient's symptoms. Arrhythmias were classified as either clinically significant or clinically insignificant. The diagnostic endpoint (confirmation or exclusion of arrhythmic cause of symptoms) was significantly different between the 2 groups (Table 13). 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. 1 patient), and ventricular tachycardia defined as more than 3 beats and rate greater than 100 (14 patients vs. 2 patients). These differences were thought to be clinically significant rhythm disturbances and the likely causes of the patients' symptoms. In this trial, median time to diagnosis in the total study population was 7 days in the MCOT group and nine days in the LOOP group (Table 13). 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) <sup>80</sup>	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) <sup>80</sup>	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).<sup>81</sup> Patients were diagnosed with palpitations, syncope and collapse, AF, tachycardia, and/or TIA. Patients given the MCOT were monitored for an average of 20 days and patients given the AT-LER were monitored an average of 27 days. The diagnostic yield using MCOT was significantly higher than that using AT-LER for several events: 128% higher for AF, 54% higher for bradycardia, 17% higher for ventricular pause, 80% higher for SVT, and 222% higher for ventricular tachycardia. Mean time to diagnosis for each asymptomatic arrhythmia was shorter for patients monitored by MCOT than by AT-LER. There was no discussion of management changes or health outcomes based on monitoring results.

Kadish et al (2010) evaluated the frequency with which events transmitted by MCOT represented emergent arrhythmias, thereby indirectly assessing the clinical utility of real-time outpatient monitoring.<sup>82</sup> 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% (5459) 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 of 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.<sup>83,84,85,86</sup> One study (Joshi et al [2005]) described the outcomes of a consecutive case series of 100 patients.<sup>83</sup> 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 resulted in an increased diagnostic yield, but there was no discussion of its unique features (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, Favilla et al (2015) evaluated a retrospective cohort of 227 patients with cryptogenic stroke or TIA who underwent 28 days of monitoring with MCOT.<sup>87</sup> AF was detected in 14% (31/227) of patients, of whom 3 reported symptoms at the time of AF. Oral anticoagulation was initiated in 26 (84%) patients diagnosed with AF. Of the remaining 5 (16%) not on anticoagulation therapy, 1 had a prior history of gastrointestinal bleeding, 3 were unwilling to accept the risk of bleeding related to the use of anticoagulants, and 1 failed to follow-up.

Miller et al (2013) retrospectively analyzed paroxysmal AF detection rates among 156 patients evaluated with MCOT within 6 months of a cryptogenic stroke or TIA.<sup>33</sup> 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 AF by standard monitoring.<sup>86</sup> In this study, 13 (23%) of 56 patients with cryptogenic stroke had AF detected by MCOT. Twenty-seven asymptomatic AF 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.<sup>88</sup> 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.<sup>89</sup> 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 3 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.<sup>90</sup> The smartwatch system uses an algorithm to enable rhythm analysis of the photoplethysmographic signals. The population consisted of 508 hospitalized patients who had interpretable ECG and photoplethysmographic recordings. The photoplethysmographic algorithm compared with the cardiologists' diagnoses had a sensitivity of 94% and a specificity of 98%. A limitation of the study was that many of the recordings were excluded due to insufficient signal quality (148 of 672). The investigators concluded that detection of AF is feasible with a smartwatch, though signal quality issues need to be resolved and a broader population needs to be tested.

### **Clinically Useful**

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

### **Direct Evidence**

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

### **Chain of Evidence**

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

**Section Summary: Mobile Cardiac Outpatient Telemetry for Patients with Symptoms of Arrhythmia**

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

**Summary of Evidence****Ambulatory Event Monitoring**

For individuals who have signs and/or symptoms suggestive of arrhythmia(s) who receive patient- or auto-activated 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 (OS) and morbid events. The RCT and the observational studies have consistently shown that continuous monitoring with longer recording periods 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 an improvement in the net health outcome.

For individuals who have AF following ablation who receive long-term ambulatory cardiac monitoring, the evidence includes one RCT comparing ambulatory event monitoring with standard care and several observational studies. Relevant outcomes are OS, 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 postablation 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 one type of monitor preferable over another. The evidence is sufficient to determine that the technology results in an 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 OS, morbid events, medication use, and treatment-related morbidity. RCTs evaluating a long-term AF monitoring strategy poststroke 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 one type of monitor preferable over another. The evidence is sufficient to determine that the technology results in an 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 auto-activated implantable ambulatory event monitoring, the evidence includes RCTs comparing implantable loop recordings (ILRs) with shorter term monitoring, usually 24- to 48-hour Holter monitoring, and many observational studies. Relevant outcomes are OS, morbid events, medication use, and treatment-related morbidity. Studies assessing prolonged ILRs 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 ILR when longer monitoring is needed. The evidence is sufficient to determine that the technology results in an 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 OS and morbid events. The available evidence has suggested that outpatient cardiac telemetry is at least as good at detecting arrhythmias as ambulatory event monitoring. However, studies have not evaluated whether the real-time monitoring feature of outpatient cardiac telemetry leads to reduced cardiac events and mortality. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

### **Supplemental Information**

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

### **Clinical Input From Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

### **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 on mobile cardiac outpatient telemetry and new devices. There was no consensus whether mobile cardiac outpatient telemetry is medically necessary. While reviewers agreed that mobile cardiac outpatient telemetry 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 1 physician specialty society and 4 academic medical centers (5 reviews) while this policy was under review in 2009. There were differences among reviewers on outpatient cardiac telemetry, with some reviewers concluding it had a role in certain subsets of patients (e.g., in those with sporadic atrial fibrillation). Other reviewers commented that the value of this technology should be considered in both providing a diagnosis and in making treatment decisions. At times, excluding arrhythmia as a cause of a patient's symptoms is an important finding.

## Practice Guidelines and Position Statements

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

## International Society for Holter and Noninvasive Electrocardiology/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.<sup>91</sup> Below are 2 summary tables from the consensus statement, detailing advantages and limitations of ambulatory electrocardiogram techniques (see Table 14) and recommendations for the devices that are relevant to this evidence review (see Table 15).

**Table 14. Advantages and Limitations of Ambulatory ECG Techniques, International Society for Holter and Noninvasive Electrocardiology/HRS**

ECG Monitoring Technique	Advantages	Limitations
Holter monitoring	<ul style="list-style-type: none"> <li>Records and documents continuous 3- to 32-lead ECG signal simultaneously with biologic signals during normal daily activities</li> <li>Physicians familiar with analysis software and scanning services</li> </ul>	<ul style="list-style-type: none"> <li>Frequent noncompliance with symptom logs and event markers</li> <li>Frequent electrode detachments</li> <li>Signal quality issues due to skin adherence, tangled wires, dermatitis</li> <li>Absence of real-time data analysis</li> <li>Poor patient acceptance of electrodes</li> </ul>
Patch ECG monitors	<ul style="list-style-type: none"> <li>Long-term recording of <math>\geq 14</math> days</li> <li>Excellent patient acceptance</li> </ul>	<ul style="list-style-type: none"> <li>Limited ECG from closely spaced electrodes, lacking localization of arrhythmia origin</li> <li>Inconsistent ECG quality due to body type variations</li> </ul>
External loop recorders	<ul style="list-style-type: none"> <li>Records only selected ECG segments marked as events either automatically or manually by patient</li> <li>Immediate alarm generation on event detection</li> </ul>	<ul style="list-style-type: none"> <li>Single-lead ECG, lacking localization of arrhythmia origin</li> <li>Cannot continuously document cardiac rhythm</li> <li>Requires patient to wear electrodes continuously</li> </ul>
Event recorders	<ul style="list-style-type: none"> <li>Records only selected ECG segments after an event is detected by patient</li> <li>Immediate alarm generation at event detected by patient</li> <li>Well-tolerated by patient</li> </ul>	<ul style="list-style-type: none"> <li>Single-lead ECG, lacking localization of arrhythmia origin</li> <li>Cannot continuously document cardiac rhythm</li> <li>Diagnostic yield dependent on patient ability to recognize correct symptom</li> </ul>
Mobile cardiac telemetry	<ul style="list-style-type: none"> <li>Multilead, so higher sensitivity and specificity of arrhythmia detection</li> </ul>	<ul style="list-style-type: none"> <li>Long-term patient acceptance is reduced due to requirement of daily electrode changes</li> </ul>

ECG Monitoring Technique	Advantages	Limitations
	<ul style="list-style-type: none"> <li>Streams data continuously; can be programmed to autodetect and autosend events at prescribed time intervals</li> <li>Immediate alarm generation on event without patient interaction</li> </ul>	

ECG: electrocardiogram; HRS: Heart Rhythm Society.

**Table 15. Select Recommendations for Ambulatory ECG and External Monitoring or Telemetry, International Society for Holter and Noninvasive Electrocardiology/HRS**

Recommendation	COR <sup>a</sup>	LOE <sup>b</sup>
<b>Selection of ambulatory ECG</b>		
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; HRS: Heart Rhythm Society.

<sup>a</sup> COR definitions: I: strong recommendation; IIa: benefit probably exceeds risk.

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

### 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<sup>4</sup>, on the management of patients with atrial fibrillation (AF).<sup>92</sup> 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 on the evaluation and management of patients with syncope<sup>93</sup> and patients with ventricular arrhythmias<sup>94</sup>. Cardiac monitoring recommendations are summarized below in Tables 16 and 17.

**Table 16. Cardiac Monitoring Recommendations, AHA/ACC/HRS**

Recommendation	COR <sup>a</sup>	LOE <sup>b</sup>
Choice of a specific cardiac monitor should be determined on the basis of frequency and nature of syncope events. <sup>93</sup>	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. <sup>93</sup>	IIa	B-NR
To evaluate selected ambulatory patients with syncope of suspected arrhythmic etiology, an implantable cardiac monitor can be useful. <sup>93</sup>	IIa	B-R
Ambulatory electrocardiographic monitoring is useful to evaluate whether symptoms including palpitations, presyncope, or syncope, are caused by ventricular arrhythmia <sup>94</sup> .	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. <sup>92</sup>	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.

<sup>a</sup> COR definitions: I: strong recommendation; IIa: benefit probably exceeds risk.

<sup>b</sup> 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 17. Patient Selection Recommendations by Cardiac Rhythm Monitor, AHA/ACC/HRS**

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

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

### Heart Rhythm Society et al

A consensus document on catheter and surgical ablation for AF was published in 2012 by HRS, the European Heart Rhythm Association, and the European Cardiac Arrhythmia Society<sup>95</sup>, and updated in 2017.<sup>96</sup> This document did not contain formal practice guidelines, but provided general recommendations based on literature review and expert consensus. Use of ambulatory event monitors postablation was addressed in 2 sections of the document. First, in the section discussing use of anticoagulation following ablation, the following statement was made:

"Patients in whom discontinuation of systematic anticoagulation is being considered based on patient values and preferences should consider undergoing continuous or frequent ECG [electrocardiogram] monitoring to screen for AF recurrence."

In the section on postoperative rhythm monitoring of patients who are postablation, the following statements were made:

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

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

### European Heart Rhythm Association

The European Heart Rhythm Association (2009) published guidelines on the use of diagnostic implantable and external loop recorders.<sup>97</sup> For the indications that the Association considered established at the time of publication, the guidelines made the following statements about indications for implantable and external recorders (see Table 18).

**Table 18. Guidelines on Use of Diagnostic ILRs and ELRs**

Recommendation	COR	LOE
"ILR [implantable loop recorder] is indicated: <ul style="list-style-type: none"> <li>• "In an early phase of evaluation of patients with recurrent syncope of uncertain origin who have:</li> </ul>	I	A

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

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

**American Academy of Neurology**

The American Academy of Neurology updated its guidelines on the prevention of stroke in patients with nonvalvular AF (NVAF).<sup>98</sup> These guidelines made the following recommendations on the identification of patients with occult NVAF:

A1. "Clinicians might obtain outpatient cardiac rhythm studies in patients with cryptogenic stroke without known NVAF, to identify patients with occult NVAF (Level C).

A2. 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)."

**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).<sup>99</sup>

**Medicare National Coverage**

The Centers for Medicare & Medicaid Services (2004) implemented a national coverage determination for electrocardiographic services.<sup>100</sup> This national coverage determination includes descriptions of the Holter monitor and event recorders (both external loop recorders and implantable loop recorders). Ambulatory cardiac monitors are covered when there is documentation of medical necessity. Indications for use include detection of symptomatic transient arrhythmias and determination of arrhythmic drug therapy (to either initiate, revise, or discontinue the therapy).

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 19.

**Table 19. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment Date	Completion Date
<i>Ongoing</i>			

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03072693	Daily Ambulatory Remote Monitoring System vs Conventional Therapy for the Post-Discharge Management of Acute Decompensated Heart Failure	876	Apr 2023
NCT04126486 <sup>a</sup>	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	240	Sep 2022
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 2025
NCT03940066	Evaluation of AmbulatoryMonitoring of Patients After High-risk Acute Coronary Syndrome Using Two Different Systems: Biomonitor-2 and Kardia Mobile	150	Dec 2022
<i>Unpublished</i>			
NCT03221777	Atrial Fibrillation Occurring Transiently With Stress (AFOTS): Understanding the Risks of Recurrent AF. Study in Non-cardiac Surgery and in Medical Illness Patients	276	Oct 2021 (Recruiting; last update Sep 2020)
NCT04556240 <sup>a</sup>	RECORD-VP: Real-time Evaluation of Cardiac Outpatient Recording Device With VitalPatch RTM	500	Nov 2020 (Recruiting; last update Sep 2020)

<sup>a</sup> Denotes industry involvement

NCT: national clinical trial.

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## Documentation for Clinical Review

### Please provide the following documentation:

- History and physical and/or cardiology consultation report including:
  - Clinical justification for device
  - Description and frequency of symptoms
  - Name and type of device including vendor name
  - Documentation of prior trial of Holter monitor or external ambulatory event monitor if applicable
  - History of AF including (if applicable):
    - Past catheter ablation history
    - Anticoagulation status and plan for discontinuation if applicable

### Post Service (in addition to the above, please include the following):

- Ambulatory monitor report

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.*

*The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.*

Type	Code	Description
CPT®	0497T	External patient-activated, physician- or other qualified health care professional-prescribed, electrocardiographic rhythm derived event recorder without 24 hour attended monitoring; in-office connection <i>(Deleted code effective 1/1/2023)</i>
	0498T	External patient-activated, physician- or other qualified health care professional-prescribed, electrocardiographic rhythm derived event recording without 24 hour attended monitoring; review and interpretation by a physician or other qualified health care professional per 30 days with at least one patient-generated triggered event <i>(Deleted code effective 1/1/2023)</i>
	0650T	Programming device evaluation (remote) of subcutaneous cardiac rhythm monitor system, with iterative adjustment of the implantable device to test the function of the device and select optimal permanently programmed values with analysis, review and report by a physician or other qualified health care professional
	33285	Insertion, subcutaneous cardiac rhythm monitor, including programming

Type	Code	Description
	33286	Removal, subcutaneous cardiac rhythm monitor
	93228	External mobile cardiovascular telemetry with electrocardiographic recording, concurrent computerized real time data analysis and greater than 24 hours of accessible ECG data storage (retrievable with query) with ECG triggered and patient selected events transmitted to a remote attended surveillance center for up to 30 days; review and interpretation with report by a physician or other qualified health care professional
	93229	External mobile cardiovascular telemetry with electrocardiographic recording, concurrent computerized real time data analysis and greater than 24 hours of accessible ECG data storage (retrievable with query) with ECG triggered and patient selected events transmitted to a remote attended surveillance center for up to 30 days; technical support for connection and patient instructions for use, attended surveillance, analysis and transmission of daily and emergent data reports as prescribed by a physician or other qualified health care professional
	93241	External electrocardiographic recording for more than 48 hours up to 7 days by continuous rhythm recording and storage; includes recording, scanning analysis with report, review and interpretation
	93242	External electrocardiographic recording for more than 48 hours up to 7 days by continuous rhythm recording and storage; recording (includes connection and initial recording)
	93243	External electrocardiographic recording for more than 48 hours up to 7 days by continuous rhythm recording and storage; scanning analysis with report
	93244	External electrocardiographic recording for more than 48 hours up to 7 days by continuous rhythm recording and storage; review and interpretation
	93245	External electrocardiographic recording for more than 7 days up to 15 days by continuous rhythm recording and storage; includes recording, scanning analysis with report, review and interpretation
	93246	External electrocardiographic recording for more than 7 days up to 15 days by continuous rhythm recording and storage; recording (includes connection and initial recording)
	93247	External electrocardiographic recording for more than 7 days up to 15 days by continuous rhythm recording and storage; scanning analysis with report
	93248	External electrocardiographic recording for more than 7 days up to 15 days by continuous rhythm recording and storage; review and interpretation
	93268	External patient and, when performed, auto activated electrocardiographic rhythm derived event recording with symptom-related memory loop with remote download capability up to 30 days, 24-hour attended monitoring; includes transmission, review and interpretation by a physician or other qualified health care professional
	93270	External patient and, when performed, auto activated electrocardiographic rhythm derived event recording with symptom-related memory loop with remote download capability up to 30 days, 24-hour attended monitoring; recording (includes connection, recording, and disconnection)
	93271	External patient and, when performed, auto activated electrocardiographic rhythm derived event recording with symptom-

Type	Code	Description
		related memory loop with remote download capability up to 30 days, 24-hour attended monitoring; transmission and analysis
	93272	External patient and, when performed, auto activated electrocardiographic rhythm derived event recording with symptom-related memory loop with remote download capability up to 30 days, 24-hour attended monitoring; review and interpretation by a physician or other qualified health care professional
HCPCS	C1764	Event recorder, cardiac (implantable)
	C1833	Monitor, cardiac, including intracardiac lead and all system components (implantable)
	E0616	Implantable cardiac event recorder with memory, activator, and programmer
	G2066	Interrogation device evaluation(s), (remote) up to 30 days; implantable cardiovascular physiologic monitor system, implantable loop recorder system, or subcutaneous cardiac rhythm monitor system, remote data acquisition(s), receipt of transmissions and technician review, technical support and distribution of results

### Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
04/05/2007	BCBSA Medical Policy adoption
12/18/2009	Policy revision without position change. Title change from Ambulatory Events Monitors and Mobile Outpatient Cardiac Telemetry.
01/15/2010	Coding Update
03/13/2012	Coding Update
04/05/2013	Policy revision with position change
03/28/2014	Policy revision with position change
09/30/2014	Policy revision with position change
12/31/2014	Policy revision with position change
08/31/2015	Policy revision with position change
07/01/2016	Policy revision without position change
07/01/2017	Policy revision without position change
02/01/2018	Coding update
07/01/2018	Policy revision without position change
02/01/2019	Coding update
07/01/2019	Policy revision without position change
09/01/2019	Policy revision without position change
03/01/2020	Coding update
07/01/2020	Annual review. Policy statement, guidelines and literature updated.
01/01/2021	Coding update
07/01/2021	Annual review. No change to policy statement. Policy guidelines and literature updated. Coding update.
03/01/2022	Coding update
07/01/2022	Annual review. Policy statement, guidelines and literature updated.
03/01/2023	Coding update
07/01/2023	Annual review. No change to policy statement. Literature review updated.

## Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

## Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: [MedPolicy@blueshieldca.com](mailto:MedPolicy@blueshieldca.com)

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*

**Appendix A**

POLICY STATEMENT (No changes)	
BEFORE	AFTER
<p><b>Ambulatory Event Monitors and Mobile Cardiac Outpatient Telemetry 2.02.08</b></p> <p><b>Policy Statement:</b></p> <ul style="list-style-type: none"> <li>I. 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 (see Policy Guidelines section) may be considered <b>medically necessary</b> in <b>any</b> of the following situations:                             <ul style="list-style-type: none"> <li>A. Infrequent symptoms (less frequently than every 48 hours) suggestive of cardiac arrhythmias (i.e., palpitations, dizziness, presyncope, or syncope)</li> <li>B. History of atrial fibrillation (AF) and prior catheter ablation, and in whom discontinuation of systemic anticoagulation is being considered</li> <li>C. History of cryptogenic stroke with a negative standard workup for AF including a 24-hour Holter monitor (see Policy Guidelines section)</li> </ul> </li>   <li>II. The use of implantable ambulatory event monitors, either patient-activated or auto-activated, may be considered <b>medically necessary</b> in <b>any</b> of the following situations:                             <ul style="list-style-type: none"> <li>A. Recurrent symptoms (i.e., palpitations, dizziness, presyncope, or syncope) and a negative prior evaluation with external ambulatory event monitors</li> <li>B. Prior history of cryptogenic stroke and concern for AF</li> <li>C. Prior atrial fibrillation (AF) with ablation, and concern for possible recurrent AF (see Policy Guidelines section)</li> </ul> </li>   <li>III. The following are considered <b>investigational</b>:                             <ul style="list-style-type: none"> <li>A. Outpatient cardiac telemetry (also known as mobile cardiac outpatient telemetry) for evaluating infrequent symptoms (less frequently than every 48 hours) suggestive of cardiac arrhythmias (i.e., palpitations, dizziness, presyncope, syncope)</li> </ul> </li> </ul>	<p><b>Ambulatory Event Monitors and Mobile Cardiac Outpatient Telemetry 2.02.08</b></p> <p><b>Policy Statement:</b></p> <ul style="list-style-type: none"> <li>I. 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 (see Policy Guidelines section) may be considered <b>medically necessary</b> in <b>any</b> of the following situations:                             <ul style="list-style-type: none"> <li>A. Infrequent symptoms (less frequently than every 48 hours) suggestive of cardiac arrhythmias (i.e., palpitations, dizziness, presyncope, or syncope)</li> <li>B. History of atrial fibrillation (AF) and prior catheter ablation, and in whom discontinuation of systemic anticoagulation is being considered</li> <li>C. History of cryptogenic stroke with a negative standard workup for AF including a 24-hour Holter monitor (see Policy Guidelines section)</li> </ul> </li>   <li>II. The use of implantable ambulatory event monitors, either patient-activated or auto-activated, may be considered <b>medically necessary</b> in <b>any</b> of the following situations:                             <ul style="list-style-type: none"> <li>A. Recurrent symptoms (i.e., palpitations, dizziness, presyncope, or syncope) and a negative prior evaluation with external ambulatory event monitors</li> <li>B. Prior history of cryptogenic stroke and concern for AF</li> <li>C. Prior atrial fibrillation (AF) with ablation, and concern for possible recurrent AF (see Policy Guidelines section)</li> </ul> </li>   <li>III. The following are considered <b>investigational</b>:                             <ul style="list-style-type: none"> <li>A. Outpatient cardiac telemetry (also known as mobile cardiac outpatient telemetry) for evaluating infrequent symptoms (less frequently than every 48 hours) suggestive of cardiac arrhythmias (i.e., palpitations, dizziness, presyncope, syncope)</li> </ul> </li> </ul>

POLICY STATEMENT (No changes)	
BEFORE	AFTER
<ul style="list-style-type: none"> <li>B. Outpatient cardiac telemetry (also known as mobile cardiac outpatient telemetry) for any other condition, disease or symptoms</li> <li>C. Ambulatory event monitors, including outpatient cardiac telemetry and mobile applications for monitoring asymptomatic individuals with risk factors for arrhythmia</li> <li>D. Ambulatory event monitors, including outpatient cardiac telemetry and mobile applications for monitoring the effectiveness of antiarrhythmic medications</li> <li>E. Ambulatory event monitors, including outpatient cardiac telemetry and mobile applications for detection of myocardial ischemia by detecting ST-segment changes</li> </ul>	<ul style="list-style-type: none"> <li>B. Outpatient cardiac telemetry (also known as mobile cardiac outpatient telemetry) for any other condition, disease or symptoms</li> <li>C. Ambulatory event monitors, including outpatient cardiac telemetry and mobile applications for monitoring asymptomatic individuals with risk factors for arrhythmia</li> <li>D. Ambulatory event monitors, including outpatient cardiac telemetry and mobile applications for monitoring the effectiveness of antiarrhythmic medications</li> <li>E. Ambulatory event monitors, including outpatient cardiac telemetry and mobile applications for detection of myocardial ischemia by detecting ST-segment changes</li> </ul>