

## 2017 ISHNE-HRS expert consensus statement on ambulatory ECG and external cardiac monitoring/telemetry

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### Abstract

Ambulatory ECG (AECG) is very commonly employed in a variety of clinical contexts to detect cardiac arrhythmias and/or arrhythmia patterns which are not readily obtained from the standard ECG. Accurate and timely characterization of arrhythmias is crucial to direct therapies that can have an important impact on diagnosis, prognosis or patient symptom status. The

rhythm information derived from the large variety of AECG recording systems can often lead to appropriate and patient-specific medical and interventional management. The details in this document provide background and framework from which to apply AECG techniques in clinical practice, as well as clinical research.

**KEYWORDS** ambulatory ECG monitoring; event monitor; Holter; loop recorder; telemetry; transtelephonic (Heart Rhythm 2017; ■:e1–e39)

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## 1. Introduction

Ambulatory ECG (AECG)<sup>1</sup> telemetry is typically used to evaluate symptoms such as syncope, dizziness, chest pain, palpitations, or shortness of breath, which may correlate with intermittent cardiac arrhythmias. Additionally, AECG is used to evaluate patient response to initiation, revision, or discontinuation of arrhythmic drug therapy and to assess prognosis in specific clinical contexts. The purposes of this statement were (1) to review how contemporary AECG devices acquire and process ECG signals and how they should be interpreted; (2) to review appropriate utilization of these devices in the management of cardiovascular disease; and (3) to promote standards that will improve the accuracy and appropriate use of the AECG in clinical practice.

The writing group recognizes that technical details of the processing and recording of AECGs may be unfamiliar to some clinicians. Accordingly, a major purpose of this document was to provide clinicians with insight concerning current technology and its implications for clinical interpretation. Moreover, evolving technologies permit integration of cardiac data with other monitored variables, extending traditional applications.

This document builds upon previous published professional society guidelines from 1999 to 2009 (Brignole et al., 2009; Crawford et al., 1999; Drew et al., 2004; Kadish et al., 2001), and focuses most intently on the evolution and advancement of AECG technology and its impact on clinical decision making and practice.

## 2. Methodology of Document Preparation

The writing committee consisted of experts in the field representing the International Society for Holter and Noninvasive Electrocardiology (ISHNE) and Heart Rhythm Society (HRS). The authors performed exhaustive literature searches to develop and ultimately provide recommendations regarding appropriate technology for AECG monitoring and its clinical applications. The final recommendations were reviewed by all writing committee members, and each member voted for inclusion with the vote threshold set at 80%. Recommendation classes and level of evidence presented in this document follow 2014 ACC/AHA standards (Jacobs, Anderson & Halperin, 2014) with recent modifications.

## 3. Section 1: Modalities, Technology, and Equipment

### 3.1. Ambulatory ECG monitoring techniques and systems

External AECG serves to detect, document, and characterize abnormal cardiac activity during ordinary daily activities, extending the role of ECG recording beyond the bedside 10-s standard 12-lead resting ECG (Crawford et al., 1999;

Kadish et al., 2001). AECG technology is noninvasive, easy to use, relatively inexpensive, and readily available.

Pioneering work by Norman “Jeff” Holter led to the first prototype of “mobile” cardiac telemetry device, requiring 85 pounds of equipment, worn on his back while riding a stationary bicycle and used a radio-ECG (circa 1947) (Del Mar, 2005; Kennedy, 2006). Modern AECG devices are light and inconspicuous, and through continuous beat-to-beat ECG monitoring, automatic arrhythmia detection and wireless transmission of data in near real time improve diagnostic yield and provide enormous improvements in efficiency and ease of use (Charitos et al., 2012; Hanke et al., 2009; Locati et al., 2016; Mittal, Movsowitz, & Steinberg, 2011; Reiffel, Schwarzberg, & Murry, 2005; Rosenberg, Samuel, Thosani, & Zimetbaum, 2013; Rothman et al., 2007; Vasamreddy et al., 2006).

Miniaturization of instrumentation is progressing rapidly in concert with evolution of microelectronic circuits (Soundarapandian & Berarducci, 2009) accompanied by evolution of wireless networking technologies and in particular the emergence of secure Smart Bluetooth (ver. 4.2) optimized for medical applications. Some AECG devices also feature multiple biological signal sensors that allow for simultaneous recording of multilead ECGs along with respiratory rate, peripheral oxygen saturation, physical activity, skin temperature, arterial pulse pressure, and other parameters, to provide the comprehensive evaluation of patients with complex disorders, such as heart failure or sleep apnea syndromes (Locati, 2002). These sensors extend AECG functions from simply ECG to include ambulatory vital signal monitoring.

Challenges persist for both manufacturers and clinicians to provide reliability and functionality, yet handle transmissions and analyze and store large amounts of data securely. In asymptomatic patients and situations when abnormalities occur infrequently, AECG devices capable of very long recording periods of up to several weeks and even months can be used. Poor tolerability of wire-electrode systems (especially when recording is prolonged) and adverse skin reactions challenge patient compliance. Table 1 and Figure 1 summarize some characteristics of modern AECG monitoring devices.

#### 3.1.1. Continuous single and multilead external recorders wire-lead transmission (Holter monitors)

Ambulatory ECG recorders are typically small, lightweight devices (200–300 gm) that use soft wire patient cables and standard wet gel electrodes worn continuously to record ECG data. Recordings may be in 2-channel (two independent bipolar leads), 3-channel, 12-channel, or EASI lead formats. Although traditionally used for 24–48 hr, some newer generation devices permit recording periods up to 30 consecutive days.

Traditional AECG recorders require active patient participation. Patients may manually record in a diary or mark the occurrence of symptoms by pressing a built-in switch on the recorder. AECG data are analyzed postrecording on a dedicated workstation.

<sup>1</sup>Synonymously termed Holter and continuous ECG monitoring. We have elected to consistently use “AECG” for this document.

**Table 1** Characteristics of ambulatory cardiac monitoring devices

Duration of recording	<1 min	24–48 hr	3–7 days	1–4 weeks	≤36 months
Types of recorder	External event recorder Smartphone-based recorder	Standard Holter recorder Mobile cardiac telemetry	Patch/Vest/Belt recorder Mobile cardiac telemetry Event loop recorder	Patch/Vest/Belt recorder External loop recorder Mobile cardiac telemetry	Implantable loop recorder
Modality of recording					
Event recording	✓	✓	✓	✓	✓
Continuous recording		✓	✓	✓	
Autotrigger recording			✓	✓	✓
Number of recording leads					
1 lead (2 electrodes)	✓	✓	✓	✓	✓
2 leads (3 electrodes)		✓	✓	✓	
3 leads (5–7 electrodes)		✓	✓	✓	
12 leads (10 electrodes)		✓			
Type of recording system					
Adhesive wired electrodes		✓	✓	✓	
Patch/Vest/Belt wireless system			✓	✓	
Built-in electrodes	✓				✓
Available analyses					
Arrhythmia analysis	✓	✓	✓	✓	✓
ST analysis		✓	✓	✓	
HRV—Heart rate variability		✓	✓	✓	
QT dynamicity		✓	✓	✓	
HRT—Heart rate turbulence		✓	✓	✓	
HDR—Holter-derived respiration		✓	✓	✓	
QRS late potentials		✓			
P-wave averaging		✓			
T-wave variability		✓			
Activity level		✓	✓	✓	

Frequency of symptoms should dictate the type of recording: longer term ECG monitoring is required for more infrequent events. Correlation (or lack of) of symptoms and arrhythmias is key. The most appropriate clinical workflow may include a continuous (short-term 24 hr and up to 7 days) AECG monitoring, which if unsuccessful, is followed by intermittent external loop recording (long-term from weeks to months). For those patients remaining undiagnosed after prolonged noninvasive monitoring, implantable loop recorders (ILR) may be necessary.

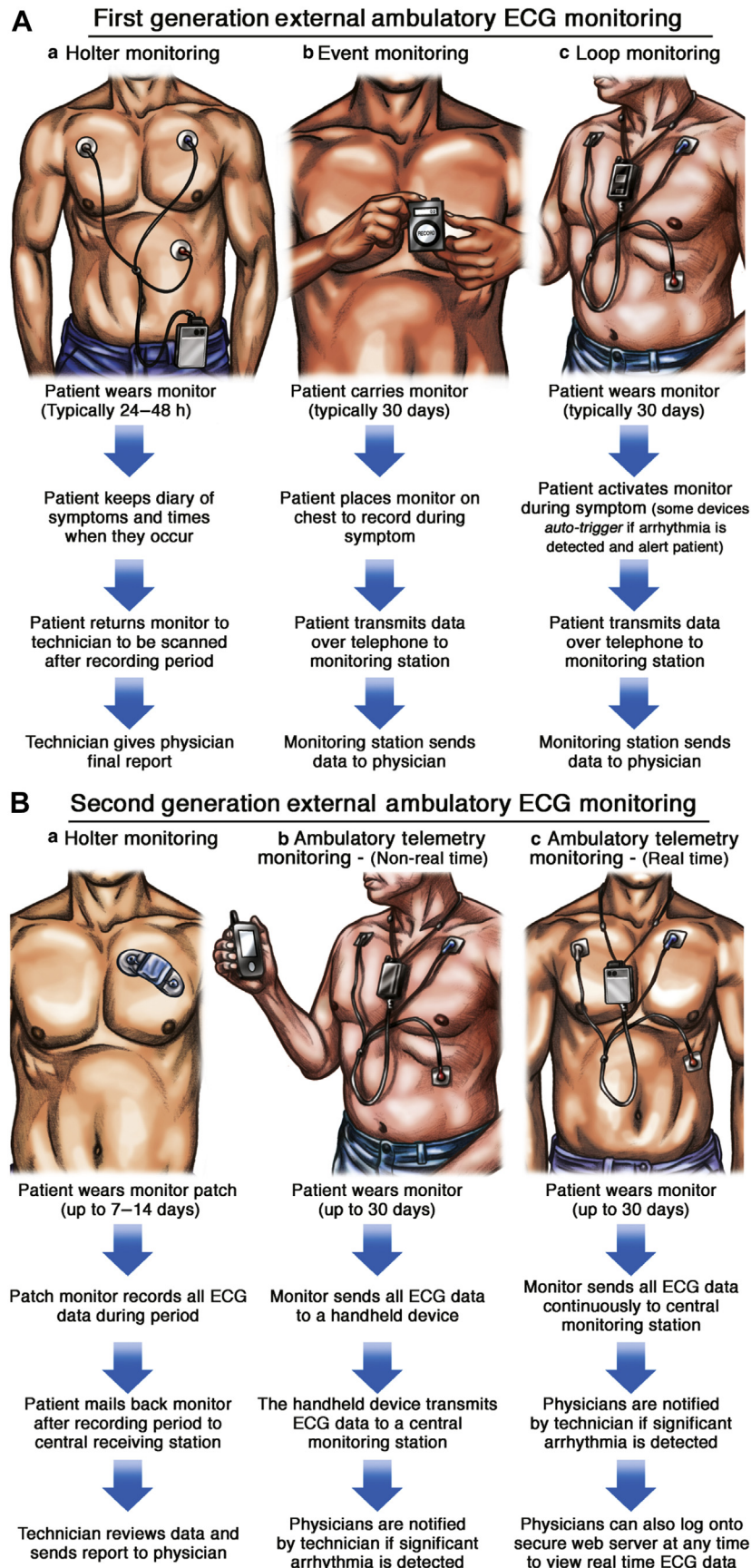
### 3.1.2. Continuous single- or two-lead external recorders with wireless transmission (patch ECG monitors)

Wearable adhesive “patch ECG monitors” constructed with embedded electrodes, with wireless data transmission, are a new class of AECG recording devices (Lobodzinski, 2013; Lobodzinski & Laks, 2012). These on-skin wearable devices, which remove the need for patient cable wires and discrete electrodes, can record 1- or 2-lead electrogram from two closely spaced electrodes worn continuously for up to 14 days. A compact, lightweight patch affixed over the patient’s left pectoral region is comfortable to wear and does not interfere with patients’ daily routines as it is water resistant and can remain on the patient during showering and exercise. Patients can press a button to mark symptomatic episodes. Proprietary algorithms diagnose cardiac rhythms based on beat-by-beat QRS detection. Up to 7–14 days of ambulatory monitoring yields a high rate of arrhythmia identification (Rosenberg et al., 2013; Turakhia et al., 2013). Newer patch ECG monitors are also capable of recording body temperature, patient activity, respiration, and galvanic skin reflex (Ajami & Teimouri, 2015). Adhesive ECG patch devices with embedded electrodes and sensor shirts featuring

textile electrodes (sometimes called “textrodes”) are better accepted by the patients and improve compliance with extended monitoring (Lobodzinski, 2013; Lobodzinski & Laks, 2008, 2012; Perez de Isla et al., 2011).

### 3.1.3. Intermittent external patient- or event-activated recorders (external loop recorders)

Intermittent autotriggered loop recorders are typically single bipolar lead devices. Loop recording is generally performed over longer periods, ranging from weeks to months. Continuous memory-loop recorders are often equipped with an autotrigger function that captures the “prior-to-event to postevent” portion of the ECG signal into the device memory. Intermittent loop recorders can be either external devices (“external loop recorder” or ELR) or implantable devices (“implantable loop recorder” or ILR) (Brignole et al., 2009). Both ELR and ILR record ECG tracings lasting from few seconds to several minutes (in some cases up to 1 hr, to include the onset and offset of arrhythmias) and can detect both symptomatic and asymptomatic arrhythmias (by means of autotrigger functions). ELR and ILR detect,



**Figure 1** Types of AECG monitors currently available in clinical practice. (A) Holter, event, and loop monitoring; (B) patch-type extended Holter and ambulatory telemetry monitoring AECG, ambulatory external electrocardiographic; ECG, electrocardiographic. Figure illustration by Craig Skaggs. Reproduced with permission from [Mittal et al. \(2011\)](#).



record, and store the occurrence of infrequent specific rhythm disorders (such as pauses, bradycardia, supraventricular, and ventricular arrhythmias). ELRs need to be worn continuously by the patient and are attached to the chest by a variety of carrier systems that include wire electrodes. Upon event detection, ECG data are stored for a pre-defined amount of time prior to the event (looping memory) and a period of time after the activation. As documented by SYNARR-Flash study, prolonged 4-week ELR monitoring has a high yield for evaluation of syncope and palpitations (Locati et al., 2016).

#### 3.1.4. Intermittent external patient- or automatically activated postevent recorders (external event recorders)

Simpler nonlooping postevent recorders are not worn continuously. Rather, these portable devices with built-in electrodes are applied directly on the chest (or held by both hands) to record a very brief duration single-lead ECG signal during symptoms. Recently, new smartphone-based ECG recording systems have been developed (Haberman et al., 2015). These record a single-lead electrogram from closely spaced stainless steel electrodes embedded into the smartphone-holding case (also see Section 9). Patient-activated postevent recorders have the potential to transmit the “near-real-time” event ECG data, provided patients recognize symptoms and activate the recording in a timely fashion. The event data are transmitted usually via digital cell phone networks directly to the data monitoring center for immediate analysis. Notification alarms are also generated and sent directly to the caregivers.

#### 3.1.5. External real-time cardiac telemonitoring systems—mobile cardiac telemetry

Mobile cardiac telemetry (MCT) devices combine the benefits of AECG recorders, ELRs, and nonlooping event recorders. Often, these are single-lead electrogram recording devices embedded either in a patch, necklace pendant, or a chest belt carrier, as well as conventional ECG electrodes. Worn continuously, these devices are capable of real-time streaming, transmitting a loop, or a single-event electrogram directly to the reading center via a wireless link. Newest iterations can connect to any WiFi access point to transfer data.

The MCT data are processed in a reading center on the back end of the monitoring system. The arrhythmic events are analyzed by trained technicians, and alarms are distributed to the caregivers. MCT devices are also equipped with real-time signal processing algorithms providing detection of cardiac arrhythmias. Some MCTs use a multilead standard 3-channel Holter-like recording wire-electrode systems (Rothman et al., 2007; Tsang & Mohan, 2013).

#### 3.1.6. Selection of appropriate technologies

The selection of appropriate technology has to take into account diagnostic power, monitoring, and risk stratification accuracy with consideration about cost-effectiveness,

patient acceptance, degree of automaticity, and local availability and experience, as well as, symptom frequency, the overall patient clinical condition, and the probability of life-threatening arrhythmia (Tables 1 and 2). MCT provides the benefit of real-time, comprehensive data without requiring the patient to participate in the process of data transmission. Unlike AECG recorders, these devices allow immediate transmission of information; compared with looping event recorders, they gather more information and allow remote data transfer while overcoming the technical challenges of data transmission. This large amount of real-time data affords a higher diagnostic yield than standard devices but places a potential burden on the clinician who must be available to review large amounts of information (e.g., daily) at any time of the day or night. Conversely, standard AECG monitoring devices and loop recorders are inexpensive and readily available. The need for ECG resolution may direct choice of Holter versus patch electrodes. Major advantages and limitations of AECG techniques are summarized in Table 3.

### 3.2. AECG signal acquisition, processing, and interpretation

There have been major advances in recording and signal processing techniques resulting in enhanced recording fidelity and more sophisticated analysis software (Kennedy, 2006).

#### 3.2.1. Electrodes for AECG applications

Virtually, all wire and embedded electrodes used by AECG monitoring devices utilize wet gel electrodes. These are nonpolarizable electrode types, with a silver–silver chloride (AgCl) element coated with an ionically active gel. Polarizable silver electrodes (textile electrodes) embedded in the shirt/vest carrier are also now available (Lobodzinski & Laks, 2008; Perez de Isla et al., 2011). All ECG monitoring electrodes must comply with ANSI/AAMI EC12:2000 (R 2010) standard and are subject to regulatory oversight (Guidance for Industry and Food and Drug Administration Staff, 2011). AECG signal recording artifacts persist with the newer electrodes, especially those due to motion and impaired skin–electrode interface (see section below) (Keller & Lemberg, 2007; Knight et al., 1999, 2001; Krasnow & Bloomfield, 1976; Márquez, Colín, Guevara, Iturralde, & Hermosillo, 2002).

Selection of optimal monitoring electrodes for AECG applications is of critical importance to signal fidelity (Ackermans et al., 2012; Lobodzinski & Laks, 2012; Locati, 2002; Zimetbaum & Goldman, 2010; Zimetbaum, Kim, Josephson, Goldberger, & Cohen, 1998). Optimal electrode application includes the following: (1) shaving the skin if necessary; (2) removing dead skin cells by rubbing the area with a rough paper or cloth; (3) using electrodes from air tight packages; and (4) paying attention to expiration dates on the electrodes packages (Kligfield et al., 2007).

**Table 2** Estimated diagnostic yield of different AECG recording modalities

Duration of recording	Type of recorder	Palpitations (%)	Syncope (%)	Cryptogenic stroke (%) (Silent AF)
<60 s	Event recorder	50–60	Not applicable	Not applicable
24–48 hr	Standard Holter	10–15	1–5	1–5
3–7 days	Patch/Vest/Belt Recorder/MCT/ELR	50–70	5–10	5–10 (?)
1–4 weeks	ELR/Patch/Vest/Belt Recorder/MCT	70–85	15–25	10–15 (?)
≤36 months	ILR	80–90	30–50	15–20 (?)

MCT, mobile cardiac telemetry; ELR, external loop recorder; ILR, implantable loop recorder.

### 3.2.2. Holter lead configurations

Ideally, all AECG devices should use 12-lead configuration. Due to technological, patient acceptance, and economic reasons, however, only few AECG monitors have 12-lead system capabilities. A 12-lead Holter lead system shown in [Figure 2a](#) uses a quasi-standard Mason-Likar lead system. The arm electrodes are placed in the infraclavicular fossae medial to the deltoid insertions, and the left leg electrode is placed midway between the costal margin and iliac crest in the left anterior axillary line. More recent applications of the Mason-Likar monitoring position place the arm electrodes over the outer clavicles and the right leg electrode (body potential reference) at the sternum. The precordial electrodes are placed in the standard positions ([Drew & Finlay, 2008](#); [Welinder, Wagner, Maynard, & Pahlm, 2010](#)). When 12-lead AECG monitors are not available, a “pseudo-standard” lead system may be used. These are usually either 2-channel/7-electrode frontal plane configurations.

The EASI lead system ([Figure 2b](#)) is a reduced 5-electrode system that uses the E, A, and I electrodes from the Frank lead system and adds an “S” electrode at the top of the mid sternum, along with a body reference electrode to provide orthogonally oriented signals. This eliminates the need to determine intercostal spaces and avoids the breast. EASI lead system makes use of the transformation coefficient matrix that produce synthesized 12-lead ECGs. EASI is well suited for AECG applications because of the absence of limb electrodes, which usually produce signal artifacts in active subjects.

Most patch ECG monitors, ELR, event recorders, and MCT monitors available today feature only a single lead derived from two closely spaced embedded or wired electrodes ([Lobodzinski, 2013](#); [Lobodzinski & Laks, 2012](#)). A variety of single-lead configurations are only possible in wire-electrode systems, the most common being a chest-modified  $V_5$  (CM5), a chest-modified  $V_3$  (CM3), and a modified inferior lead. Specific lead configurations can be chosen in specific situations (e.g., in case of a patient undergoing AECG monitoring for ischemia, the AECG lead configuration should be chosen to mimic those leads with the greatest ST-segment change during exercise).

Ambulatory ECGs recorded with torso placement of the extremity electrodes cannot be considered equivalent to standard ECGs for all purposes and should not be used interchangeably with standard ECGs for serial comparison ([Papouchado, Walker, James, & Clarke, 1987](#)). For example, a 12-lead ECG is the diagnostic test of choice for long QT syndrome (LQTS), rather than an AECG.

### 3.2.3. AECG processing

All modern AECG instrumentation today is digital and subject to regulatory guidelines ([Guidance for Industry and Food and Drug Administration Staff, 2003](#)). The front end is typically a highly integrated system on the chip (SoC) responsible for surge protection (defibrillator shock), analog-to-digital conversion, digital filtering, and calibration. The processing flow of the AECG signal starts with the bio-potential signal acquisition front-end subsystem of the monitor. Common-mode rejection ratio, or CMRR, is one of the most important performance parameters for ECG system applications and is subject to regulatory approval. A driven right leg circuit or “DRL” circuit is an electric circuit that is added to ECG signal amplifiers to reduce common-mode interference. SoC provide multichannel, simultaneous sampling, 24-bit, delta-sigma ( $\Delta\Sigma$ ) analog-to-digital converters (ADCs) with built-in programmable gain amplifiers capable of resolving signals as small as pico volts. Unfortunately, the patient’s body can also act as an antenna which picks up electromagnetic interference, especially 50/60 Hz noise from electrical power lines. This interference signal induces voltages much greater than the ECG signal itself, thus making it very challenging to measure. right leg driver circuitry is used to eliminate interference noise by actively canceling the interference signal ([Winter & Webster, 1983](#)).

The AECG digital signal must then be amplified and low-pass filtered in SoC to prevent aliasing errors. Next, the digital AECG is band-pass and notch filtered to eliminate or suppress low-frequency noise caused by baseline wander, respiration, and higher frequency noise caused by muscle tremors and induced electromagnetic interference. Once amplified, filtered, and smoothed, the analysis of the AECG can proceed. The end result of this operation is the delineation of the AECG into P, QRS, and T waveforms. Global waveform measurements, such as duration, amplitudes, ratios, are derived from individual lead data or from mathematical combinations of simultaneously acquired individual lead data and stored in the measurement matrix. The accuracy of the waveform classification highly depends on the redundancy of the information contained in a multilead system. Generally speaking, the higher the number of the leads the higher the complex detection precision.

### 3.2.4. Mobile cardiac telemetry ECG data transmission

The MCT devices use either packet-oriented mobile data service on the 2G and 3G cellular communication system

**Table 3** Advantages and major limitations of AECG techniques

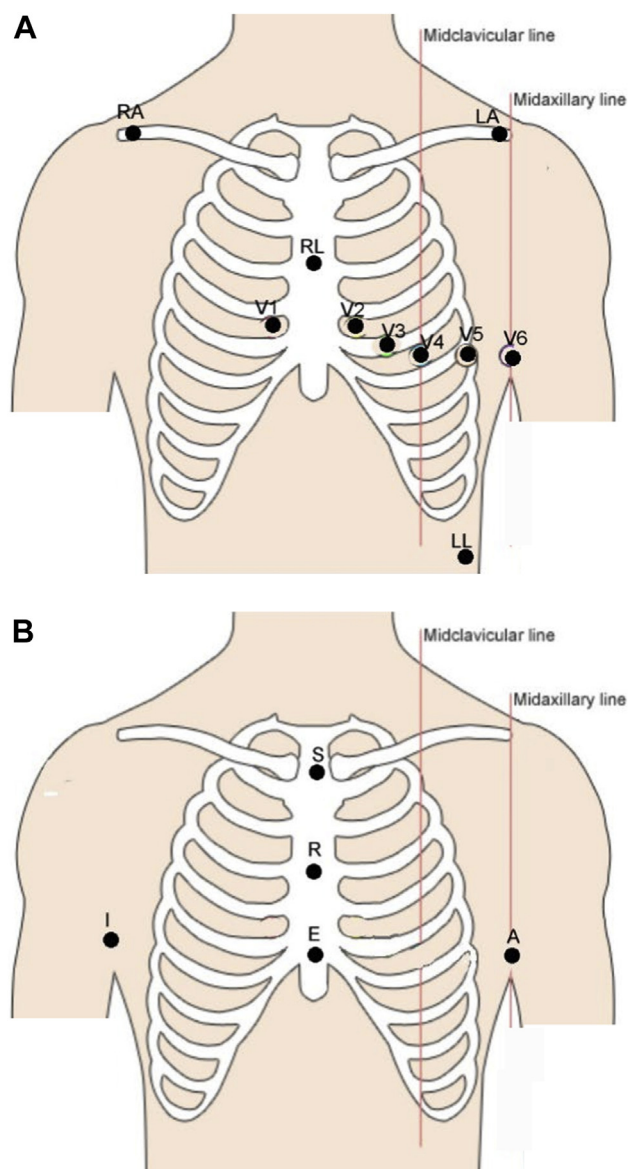
ECG monitoring technique	Advantages	Limitations
Holter monitoring	<ul style="list-style-type: none"> <li>• Ability to record and document continuous 3- to 12-lead ECG signal simultaneously with a variety of other biological signals during normal daily activities</li> <li>• Familiarity of physicians with analysis software programs and a wide availability of third-party scanning services that outsource the equipment and generate preliminary diagnostic reports</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 artifacts, wire entanglements, and occasional skin dermatitis caused by electrode gels</li> <li>• Absence of real-time data analysis</li> <li>• Poor patient acceptance of wire-electrode systems</li> </ul>
Patch ECG monitors	<ul style="list-style-type: none"> <li>• Long-term recording of 14 days or longer</li> <li>• Excellent patient acceptance</li> </ul>	<ul style="list-style-type: none"> <li>• Records a limited ECG from closely spaced electrodes comprising a time series of P-, Q-, R-, ST-, and T-wave sequence with lower voltage amplitudes without information on their spatial orientation, thus lacking localization ability of arrhythmia origin</li> <li>• Inconsistent optimal ECG signal quality due to varying body types</li> </ul>
External loop recorders	<ul style="list-style-type: none"> <li>• Records only selected ECG segments of fixed duration marked as events either automatically or manually by the patient</li> <li>• Immediate alarm generation upon event detection</li> </ul>	<ul style="list-style-type: none"> <li>• Records a single-lead ECG sequence without information on spatial orientation of P, Q, R, ST, and T waves, thus lacking localization ability of arrhythmia origin; P waves may not be visible</li> <li>• No capability to continuously document cardiac rhythm</li> <li>• Requires patients to wear electrodes continuously during the recording period</li> </ul>
Event recorders	<ul style="list-style-type: none"> <li>• Records only selected ECG segments of fixed duration after an event is detected by the patient</li> <li>• Immediate alarm generation upon the event detection</li> <li>• Well-tolerated by the patient</li> </ul>	<ul style="list-style-type: none"> <li>• Single-lead devices do not indicate the origin of many arrhythmias</li> <li>• No capability to continuously document cardiac rhythm</li> <li>• Diagnostic yield of event recorders is highly dependent on patient's ability to recognize correct symptom</li> </ul>
Mobile cardiac telemetry	<ul style="list-style-type: none"> <li>• Multilead MCT devices can record pseudo-standard, 3-lead electrocardiogram, hence has a much higher sensitivity and specificity of arrhythmia detection as compared to single-lead devices</li> <li>• Can stream the data continuously to caregivers; often combines the functionality of traditional 3-lead Holter event and loop recorder, for example, programmed to autodetect and autosend events at certain time (e.g., 1 every 10 min)</li> <li>• Immediate alarm generation upon an event detection without patient interaction or manual activation</li> </ul>	<ul style="list-style-type: none"> <li>• Electrode-wire MCTs require daily electrode changes, and thus, patient acceptance is reduced for long-term monitoring applications</li> </ul>

(GPRS) or a combination of Bluetooth with a Wi-Fi 802.11 b/g/n relay station (Engel et al., 2011). GPRS uses powerful algorithms and encryption techniques on security controls that include subscriber identity confidentiality, subscriber identity authentication, user data confidentiality on physical connections, connectionless user data confidentiality, and signaling information element. The MCTs that use Bluetooth security feature transmit data via relay (smartphone, tablet, and dedicated transmission device) to the remote reading centers. The newly announced Smart Bluetooth low-energy protocol used by the latest MCT devices also features robust security measures. The weakest link in relay type of AECG

data transmission is the HTTPS data transmission protocol widely used over the Internet.

### 3.2.5. AECG analysis and interpretation

Many ECG processing algorithms exist today. Most are proprietary, and very few data are available regarding their documented clinical accuracy. The developers usually use the annotated MIT-BIH ECG and arrhythmia databases available on [physionet.org](http://physionet.org) to tune their algorithms (George & Roger, 2001). All AECG data are processed in an off-line fashion using specialized computer workstations, whereas MCT and



**Figure 2** Holter lead configurations. (A) Mason-Likar 12-lead system for continuous ECG monitoring. Electrode placements are as follows: RA: 2nd intercostal space right side midclavicular, LA: 2nd intercostal space left side midclavicular, LL below 8th intercostal left side midclavicular line, RL: upper sternum, V<sub>1</sub>: 4th right intercostal space at the sternal border, V<sub>2</sub>: 4th left intercostal space at the sternal border, V<sub>3</sub>: between V<sub>2</sub> and V<sub>4</sub>, V<sub>4</sub>: 5th left intercostal space at the midclavicular line, V<sub>5</sub>: 5th left intercostal space at the anterior axillary line, V<sub>6</sub>: 5th left intercostal space at the midaxillary line; (B) EASI reduced leads system. EASI is a reduced lead system suitable for continuous ECG monitoring. It is an alternative to both the commonly used 5-electrode monitoring system and the traditional 10-electrode Mason-Likar 12-lead ECG system. The EASI lead configuration enables continuous reconstructed 12-lead ECG ambulatory monitoring using only five electrodes. The EASI 12-lead ECG is derived from a set of four recording electrodes and one reference electrode. The placement of these leads is as follows: E: lower extreme of the sternum, A: left mid-axillary line, same transverse line as E, S: sternal manubrium, I: right mid-axillary line, same transverse line as E, R: fifth electrode is the body potential reference and can be placed anywhere on the torso.

patch ECG data are always processed in dedicated reading centers. Processing algorithms detect and document abnormal rhythms or conduction abnormalities, and provide

a quantitative analysis of supraventricular and ventricular rhythm disorders (the so-called “arrhythmic burden”). Additional algorithms can also analyze multiple parameters of the ECG signals, such as assessment of ST-segment shifts, heart rate variability (HRV), QT dynamics and T-wave variability, T-wave alternans (TWA), heart rate turbulence (HRT) (Hoefman, Weert, Reitsma, Koster, & Bindels, 2005; Joshi, et al., 2005; Salleh et al., 2017).

### 3.2.6. Pitfalls in the interpretation of arrhythmias detected by AECG and MCT

Two main categories of ECG artifacts are recognized. One group includes those related to body movement, temporary impairment of skin–electrode contact, loose electrode connections, dysfunctional leads, skeletal myopotentials, and ambient noise. These can generate deflections that can simulate a variety of arrhythmias and are thus termed, pseudo-atrial arrhythmias, for example, atrial flutter or fibrillation (Figure 3a), or pseudo-ventricular tachyarrhythmia (Figure 3b,c). A second group of artifacts is probably related to intermittent impairment of electrode contact or recorder problems in older recording systems that can result in tape slowing or intermittent stoppage (Krasnow & Bloomfield, 1976; Márquez et al., 2002). These artifacts result in pseudo-pauses that can simulate sinus arrest, pacemaker malfunction, or high-degree atrioventricular conduction block. The majority of artifacts can be recognized from simultaneous multichannel ECG.

In contrast to the role of the more common AECG artifacts, failure by the technician or clinician to recognize a genuine arrhythmia episode in the ECG recording may lead to potentially more serious implications (El-Sherif & Turitto, 2015). This problem is significantly more common on the hospital cardiac telemetry service and highlights the need of improved training in the detection and interpretation of AECG of the technical and clinical staff who make up this service (See Section 6).

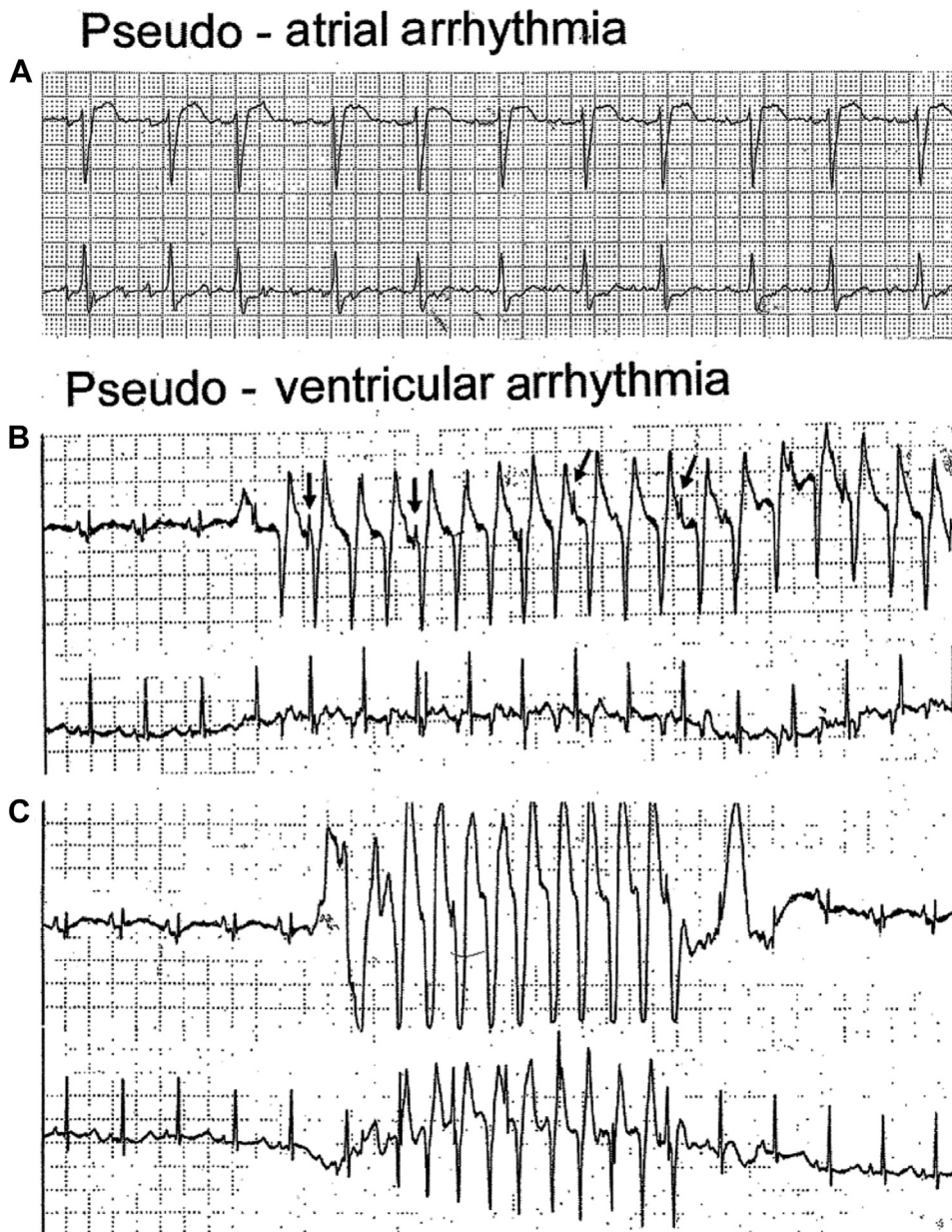
The clinical implication of misinterpretation of AECG recordings could result in errors of commission and errors of omission. Errors of commission include, but are not confined to, recommending the wrong medication or potentially harmful and unnecessary interventional procedures such as cardiac catheterization, electrophysiological study, or implantation of arrhythmia devices (Krasnow & Bloomfield, 1976). Errors of omission include failure to properly address patients with potentially serious arrhythmic events.

## 4. Section 2: Clinical Indications—Diagnostics

### 4.1. Syncope

Syncope (loss of consciousness from either sudden or gradual but persistent decrease of blood flow to the brain as a consequence of low cardiac output) may be due to primary electrical problems (bradycardia/tachycardia) or hemodynamic causes. The role of the AECG is to identify (Watanabe et al., 2014) bradyarrhythmias (e.g., sinus pauses, periods





**Figure 3** Examples of ECG artifacts (A) The bottom channel shows recording artifact that may simulate atrial flutter/fibrillation. However, careful analysis of the upper channel shows sinus rhythm with clear P waves. The presence of an irregular rhythm secondary to both sinus arrhythmia and occasional premature atrial beats adds to difficulty in making the correct diagnosis from the recording in the bottom channel alone. Figures (B and C) are two distinct examples of artifacts from the same Holter recording that may simulate ventricular tachyarrhythmia. In both tracings, the artifacts are more prominent in one of the two illustrated channels but not the other, making correct interpretation feasible. Normal QRS complexes are marked by arrows at the channel with prominent artifacts. Reproduced with permission from [El-Sherif & Turitto \(2015\)](#).

of atrioventricular [AV] block), or tachyarrhythmias (e.g., sustained VT).

Several guidelines, scores, and recommendations for the diagnosis and management of patients with syncope have been published in the last decade ([Ammirati, Colivicchi, & Santini, 2000](#); [Baranchuk et al., 2005](#); [Brignole et al., 2001](#); [Cerrone & Priori, 2009](#); [Colivicchi et al., 2003](#); [Locati, Vecchi, Vargiu, Cattafi, & Lunati, 2014](#); [Morillo & Baranchuk, 2004](#); [Moya, Sutton, & Ammirati, 2009](#); [Sheldon et al., 2006](#)). Most provide recommendations on

the need for hospital admission and the nature of further diagnostic workup to identify or exclude high-risk causes of syncope. A significant number of low-risk patients are unnecessarily admitted for further investigation, and a role for outpatient use of AECG can be offered as an alternative.

Symptom/rhythm correlation remains the cornerstone of the diagnostic efforts in syncope to confirm the involvement of the cardiac electrical system in the origin of syncope ([Morillo & Baranchuk, 2004](#)). The choice of monitoring modality depends on the frequency of events. Sometimes a

single surface 12-lead ECG may be enough to establish the connection between the symptom and the cardiac rhythm (e.g., complete heart block); however, more often extended monitoring is necessary as at the time of the evaluation the cause of syncope remains elusive because of its transient and intermittent nature (Baron-Esquivias et al., 2010). The pediatric population represents a specific challenge, especially the very young who may be unable to verbalize symptoms or comply with complex instructions; these young patients may require more automated recording systems tailored to the individual circumstance.

#### 4.1.1. Bradycardias that can be detected by AECG

1. Transient and paroxysmal high-degree AV block: AECG allows detection of a sudden interruption of AV conduction without slowing of the sinus discharge. The latter would suggest a vagal or neurocardiogenic mechanism rather than primary disease of the electrical conductive system (and suggest avoidance of pacemaker implantation).
2. Sinus node dysfunction (Dąbrowski & Piotrowicz, 1988; Makowski & Kramarz 2013): Defects of sinus automaticity include sinoatrial block, sinus bradycardia, tachy/brady syndrome, sinus pauses, and postconversion asystole (usually associated with atrial fibrillation [AF]). It is strongly recommended to establish symptom/rhythm correlation, as formalized cutoffs are arbitrary although a sinus rate <40 bpm is considered potentially causative in a symptomatic patient (Epstein et al., 2013). A variety of AECG recorders can indicate whether sinus node competency is inadequate to match the metabolic demands of the individual patient and produce symptoms. The specifics of monitor selection depend on the frequency and nature of symptoms.

#### 4.1.2. Tachycardias that can be detected by ambulatory telemetry

1. Supraventricular tachycardias are a rare cause of syncope, with exceptions in the setting of heart failure or cardiomyopathy, or during postconversion sinus pause. They are diagnosed by the presence of a narrow complex rhythm with QRS complex similar to that of sinus rhythm in most cases. A variety of mechanisms exist and some have unique patterns and initiation sequences. In some patients, supraventricular tachycardias produce QRS aberration and present as a wide complex tachycardia. As AECGs do not usually have the full array of ECG leads, the aberrantly conducted rhythm may be challenging to identify as supraventricular in origin.
2. Ventricular tachycardias include ventricular tachycardias (monomorphic and polymorphic), ventricular fibrillation, and torsade de pointes. AECG monitoring is only one component of the investigation and most useful if recorded during symptoms. Many patients with

depressed left ventricular function will be candidates for implantable cardioverter defibrillator (ICD) based on left ventricular ejection fraction (LVEF), and others may require electrophysiological study for programmed stimulation to elicit VT.

An AECG monitor is used in many patients who have unexplained syncope. The strategy of AECG recording is based on two objectives: (1) capture of a serious arrhythmic event that is sufficient to explain syncope, can imply the possibility of even more serious arrhythmic events, or is in and of itself sufficient to warrant treatment or intervention; and (2) correlate the presence of recurrent symptoms with an arrhythmic event that can guide therapy, or equally importantly, demonstrate the absence of arrhythmia during recurrent symptoms, effectively excluding an arrhythmic basis for syncope. For example, the first objective may be met when periods of higher grade AV block are observed, particularly in setting of bundle branch block (e.g., Type II 2o AV block or transient 3o AV block). When pursuing the second objective, one study of short-term Holter monitoring found that symptoms correlated with a documented arrhythmia in 4% and occurred without an arrhythmia on the monitor in 17% (Morillo & Baranchuk, 2004).

The type of recorder and the duration of recording should be tailored to the individual patient's history, but in general, the diagnostic yield is limited and dependent on the frequency of clinical symptoms. Extended recordings may improve diagnostic yield. In 1 trial, the overall probability of obtaining a symptom–rhythm correlation increased from 22% to 56% for 48-hr Holters compared to 1 month of ECG loop recording (Sivakumaran et al., 2003). In another study, the median time for recording a symptom–rhythm correlation was 16 days for patients assigned a loop recorder as their first diagnostic strategy and symptom–rhythm correlation was obtained in 87% of patients by 1 month of monitoring (Bass et al., 1990). Much longer monitoring using ILRs can further improve the diagnostic yield for syncope, as high as 85% in some studies (Cotter et al., 2013).

Although exercise-induced arrhythmias are typically worked up via an exercise treadmill examination, there may be value in using AECG recording, especially for adolescents. This may facilitate recordings during more natural activities and also stimulate levels of exertion not achieved in an artificial environment, enhancing symptom–rhythm correlation.

## 4.2. Palpitations

Palpitations are the most frequent indication for AECG, and one of the main reasons why AECG was originally developed. Up to 20% of outpatients present with palpitations and most of the cases have benign causes (Kroenke, Arrington, & Mangelsdorff, 1990). Although a detailed history, physical examination, and 12-lead ECG are sufficient to make a definitive diagnosis in up to one-third of patients with palpitations, in the remainder AECG is the most cost-effective clinical tool (Weber & Kapoor, 1996).

Ambulatory ECG monitoring for symptom–ECG correlation is indicated for the following groups of patients with unexplained palpitations: (1) when history, physical examination, and 12-lead ECG suggest a possibility of arrhythmia; (2) in the setting of diagnosed structural heart disease, family history of sudden cardiac death (SCD), or inherited channelopathy with known risk of arrhythmia; (3) when patients need reassurance and specific explanation of their symptoms, and (4) when symptoms warrant therapy and specifics of treatment are dependent on a formal arrhythmic diagnosis (e.g., ablation, antiarrhythmic therapy).

Ambulatory ECG monitoring is the key tool for the diagnosis of unexplained, well-tolerated recurrent palpitations. Clinical presentation and frequency of palpitations should be taken into consideration when selecting the device (Crawford et al., 1999; Mittal, 2015; Raviele et al., 2011). Traditional AECG monitor (24–48 hr) is indicated for patients who experience frequent palpitations every day, or can reliably reproduce symptoms (e.g., positional or exertional palpitations). It is important for a patient to keep a diary recording the time of palpitations. The relevance of identified spontaneous arrhythmias to the palpitations is variable and could be low (Lok & Lau, 1996; Zeldis, Levine, Michelson, & Morganroth, 1980). Loop event recorders and interactive ECG applications that save and transmit ECG only when the patient activates the monitor are suitable for patients with infrequent and unpredictable palpitations. Such devices provide better correlation with symptoms, but require that the patient be vigilant and capable of activating the recording in time. Continuous-loop recorders provided higher diagnostic yield, as compared to 24-hr Holter, and have proved to be more cost-effective (Fogel, Evans, & Prystowsky, 1997). It has been shown that 2 weeks of ECG monitoring provide the best balance between diagnostic yield and associated cost (Zimetbaum et al., 1998). The diagnostic yield of AECG directly correlates with the duration of AECG monitoring and depends on the percentage of “accurate reporters” in the studied population. Typically, diagnosed rhythms reflect prevalence of arrhythmias in the studied populations (Table 2).

### 4.3. Chest pain and coronary ischemia

Ambulatory ECG monitoring can be utilized to diagnose the etiology of chest pain (both atherosclerotic coronary artery disease and Prinzmetal’s variant angina), identify episodes of atypical chest pain that do not have an apparent manifestation on the surface ECG, and assess the magnitude of “ischemic burden,” the product of duration of ischemia and the magnitude of ST-segment depression. The majority of episodes of ambulatory ischemia in patients with coronary disease are asymptomatic, and therefore objective ECG monitoring, such as with the AECG, can be used to identify the severity of ischemia during daily activities (Birnbaum et al., 2014).

For a diagnosis of ischemia, ST-segment depression of at least 0.5–1.0 mV (0.5–1.0 mm) lasting for at least 1 min

before returning to normal should be seen (Conti, Bavry, & Petersen, 2012). Reported rates of ST-depression sensitivity (62%) and specificity (61%) as detected by continuous ECG in patients with angiographically defined chest pain and known coronary artery disease are similar to those derived from an exercise treadmill test (67% and 65%, respectively) using similar lead positions. With AECG monitoring, nearly one-half of patients with stable coronary artery disease exhibit transient ST-segment depressions that likely represent ischemic events (Pepine, Geller, & Knatterud, 1994; Smith, Amsterdam, & Balady, 2000). This has important prognostic information, potentially beyond the findings obtained during an exercise treadmill test. In one study, after multivariable adjustment, only ST-segment depression during AECG monitoring, and not ST-segment depression during exercise testing, significantly predicted worse outcomes (Rocco et al., 1988). In patients with unstable coronary syndromes, silent ischemia can predict both short-term and long-term risk (Gibson et al., 2009; Gottlieb, Weisfeldt, Ouyang, Mellits, & Gerstenblith, 1987; Langer, Singh, Freeman, Tibshirani, & Armstrong, 1995; Patel et al., 1997; Scirica et al., 2009).

Ambulatory ECG monitoring has also been utilized to diagnose and manage patients with the rare syndrome of Prinzmetal’s variant angina, but confirmation of adequate therapeutic prevention of vasospasm episodes has been primarily based on provocative testing in the cardiac catheterization laboratory (Bayés de Luna et al., 2014; Waters, Szlachcic, Theroux, Dauwe, & Mizgala, 1981).

In patients suffering ST elevation myocardial infarction (STEMI), early reperfusion via percutaneous coronary intervention (PCI) remains the critical therapeutic intervention. As PCI resources are only available in specific institutions, prehospital diagnosis has specific practical advantages: directing emergency transport to the optimal facility, bypassing the emergency department, and preparation at the receiving facility for emergent PCI and associated treatment. The emergency transport system must be capable of recording a 12-lead ECG and transmitting the ECG to a center that can provide skilled confident interpretation. The Danish health system has formally implemented such a system for several years, processing about 4,000 ECGs per year, and observed that 81% of prehospital diagnoses of STEMI underwent emergent PCI resulting in an acceptable low “false-positive” rate (Clemmensen et al., 2013). This rapid triage system has been associated with a decline in 30-day mortality rates, confirming technical feasibility and suggesting measurable clinical impact.

### 4.4. Special considerations for pediatric patients

AECG in pediatric patients bears special consideration. Indications are similar to adult patients, largely predicated upon symptom frequency and duration, and also for risk stratification and assessing treatment efficacy.

Palpitations are a common presenting symptom. Arrhythmia correlation during AEGM was noted in



10%–15% of pediatric patients experiencing palpitations. Conversely, sinus tachycardia is identified in nearly 50% of patients with the same symptoms (Dick, McFadden, Crowley, & Rosenthal, 1979; Fyfe, Holmes, Neubauer, & Feldt, 1984; Goldstein, Hesslein, & Dunnigan, 1990; Karpawich, Cavitt, & Sugalski, 1993). In one single-center experience of 495 pediatric patients, transtelephonic electrocardiographic event monitors (TTMs) yielded a useful diagnosis in 48% (Saarel et al., 2004). Conversely, >50% patients in this study failed to transmit a single, legible ECG while symptomatic, highlighting the limitation of patient-activated equipment in the pediatric population. This is compounded by age-related compliance: Most young children (<5 years) are unable to comply with event triggered monitoring. Clinicians have circumvented this issue by allowing parents, caregivers, or even teachers to provide the activation. Of course, in time-sensitive events, this is not always plausible which remains a major limitation of this equipment.

The evaluation of syncope creates a diagnostic challenge with patient-activated AECG. Temporary loss of consciousness precludes patient triggered activation. As such, clinicians recommend outpatient cardiac telemetry with continuous recording independent of patient activation. In some circumstances, ILRs may ensure capture of syncopal events. A cardiac cause of chest pain is extremely unlikely in the pediatric population. In a large prospective study, <5% of patients were identified as having a cardiac cause of their chest pain (Selbst, Ruddy, Clark, Henretig, & Santulli, 1988). Therefore, AECG has low diagnostic yield but has utility to exclude cardiac- or rhythm-related etiologies to symptoms as a means of providing reassurance to patients and families.

AECG can be useful for risk assessment. In asymptomatic patients with Wolff–Parkinson–White, recent guidelines favor exercise stress testing to detect beat-to-beat loss of pre-excitation (Pediatric and Congenital Electrophysiology Society [PACES] et al., 2012). This may be accomplished with AECG though typically lead analysis and electrogram quality are inferior to those obtained during 12-lead rhythm strip evaluation during formal stress testing. AECG is a relatively routine portion of serial evaluation in pediatric patients with congenital heart disease (CHD). For example, AECG is a class I recommendation for patients with repaired CHDs or for patients with significant residual, hemodynamic abnormalities (Crawford et al., 1999). In adult patients with CHDs, AECG is considered as a class IIa for monitoring of arrhythmias and/or conduction disturbances (Baumgartner et al., 2010; Khairy et al., 2014). The finding of nonsustained ventricular tachycardia is considered a significant risk factor for sudden death in patients with hypertrophic cardiomyopathy (HCM) (Elliott et al., 2014; Gersh et al., 2011). Indications for pacemaker implantations in patients with congenital complete heart block are largely predicated on the presence of prolonged pauses, low average heart rates, or complex ventricular ectopy on Holter monitoring (Epstein et al., 2013).

Despite important limitations in the pediatric patient, AECG has become a standard diagnostic tool for rhythm

assessment. As technology improves and devices become more compatible and less cumbersome for our “smaller” population (e.g., patch technologies with continuous monitoring), the utilization of these devices and their diagnostic power will undoubtedly increase.

## 5. Section 3: Clinical Indications—Prognosis and Risk Stratification

Ambulatory ECG detection of transient arrhythmias, electrical perturbations, or autonomic disturbances has been used for risk stratification although its value varies according to clinical context. In the absence of structural and/or electrical heart disease, the prognostic value of these recordings is generally weak or absent.

### 5.1. Ischemic heart disease and postinfarction patients

Premature ventricular complexes (PVCs) and nonsustained (NS) VT have long been associated with increased risk in patients recovering from acute MI. The nature of MI care has changed dramatically in recent years, so more contemporary analyses are germane to guiding modern care. In patients with non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS), the development of NSVT ( $\geq 3$  beats,  $\geq 100$  bpm) beyond the first 48 hr after admission signifies the presence of increased mortality risk. Continuous 7-day ECG monitoring in NSTEMI-ACS patients in the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-elevation ACS-Thrombolysis In Myocardial Infarction (MERLIN-TIMI) 36 trial recorded at least one episode of NSVT in more than half of the patients in the overall cohort. Moreover, both short and longer NSVT episodes (4–7 or  $\geq 8$  beats) were significantly associated with 2.3- to 2.8-fold increased annual SCD risk, especially when associated with the presence of myocardial ischemia irrespective of the presence of prior myocardial infarction (Scirica et al., 2010). While short-lasting NSVT episodes occurring within the first 48 hr after admission did not carry the same risk, similar episodes that occurred beyond 48 hr were associated with significant (2.9- to 3.7-fold) annual SCD risk. The failure to link an effective therapeutic intervention following these AECG findings has probably limited its utilization in clinical practice.

In the late (>24 hr) postacute MI inpatient period, the detection of NSVT episodes has been associated with a higher rate of sustained VT and with subsequent increased mortality (Cheema, Sheu, Parker, Kadish, & Goldberger, 1998; Pires et al., 2001). Following discharge, NSVT has limited prognostic significance in post-MI patients. NSVT detection among MI survivors yielded low prognostic value for subsequent mortality and no prognostic value when only arrhythmic events were considered (Hohnloser et al., 1999). Although the presence of NSVT in 24-hr ECG recording was an independent predictor of adverse prognosis in the Autonomic Tone and Reflexes After Myocardial Infarction trial and raised interest in Holter monitoring for



risk stratification (La Rovere et al., 2001), in the current era in which post-MI patients are adequately reperfused and treated with beta-blockers, NSVT may not serve as an independent predictor of long-term mortality especially when other covariates such as LVEF are taken into account (Bloch et al., 2010; Hofsten, Wachtell, Lund, Molgaard, & Egstrup, 2007; Katritsis, Siontis, & Camm, 2013). Therefore, AECG is currently not commonly used.

After hospital discharge following MI, left ventricular scarring and remodeling may yield a suitable electrophysiological substrate for the genesis of both nonsustained and sustained ventricular arrhythmias. Although post-MI studies published in the early 1980s and 1990s identified frequent PVCs and NSVT as strong independent predictors of arrhythmia risk and SCD in MI survivors with left ventricular dysfunction (Doval et al., 1996), in the modern era, the independent predictive value of NSVT is not established (Buxton et al., 2007; Katritsis et al., 2013; Maggioni et al., 1993; Makikallio et al., 2005; Singh, Fisher, Carson, & Fletcher, 1998; Teerlink et al., 2000). This discrepancy could be explained by the extreme temporal variability of NSVT in different patient populations in association with the wide range in the timing of Holter recordings.

On the other hand, NSVT was shown to be a significant predictor of SCD in post-MI patients with a relatively preserved ejection fraction (LVEF > 35%), independently of diabetes mellitus, age, and LVEF (Makikallio et al., 2005). NSVT accompanied by inducibility of sustained VT during programmed ventricular stimulation was associated with an increased risk of SCD (Buxton et al., 1999; Moss et al., 1996). Following the Multicenter Unsustained Tachycardia Trial (MUSTT) (Buxton et al., 1999), there is a role for AECG for NSVT detection in post-MI patients with LVEF 35%–40% as electrophysiologically guided ICD implantation improves survival (Epstein et al., 2013; Priori et al., 2015).

In conclusion, in patients with prior MI treated with reperfusion and beta-blockers, NSVT is not an independent predictor of long-term mortality when other covariates such as LVEF are taken into account. Across studies of ischemic heart failure patients, the predictive value of irregular ventricular activity in ambulatory Holter recordings remains debatable. However, prolonged (>8 beats) and rapid (>120 beats per minute) episodes of NSVT may justify further exploration of the SCD risk by use of noninvasive or even invasive measures. The detection of any NSVT in patients with borderline EF (e.g., 35%–40%) might prompt further risk stratification and determination of need for ICD using EPS.

## 5.2. Nonischemic dilated cardiomyopathy

Nonischemic dilated cardiomyopathy (NIDCM) may be the consequence of a variety of causes, including virus-mediated and autoimmune disease, as well as toxic and metabolic, inherited, and tachycardia-induced conditions. Tachycardiomyopathy may result from atrial arrhythmias with rapid and/or irregular ventricular response or frequent

ventricular ectopy. In such cases, AECG monitoring is useful to evaluate heart rate or frequency and complexity of ectopy in order to establish diagnosis and/or indications for invasive therapeutic treatment as ablation (Baman et al., 2010; Pedersen et al., 2014).

Patients with NIDCM die mostly from SCD or heart failure progression (Okutucu & Oto, 2010). Theoretically, AECG monitoring may be considered as a tool in risk stratification of SCD by detection of NSVT episodes and evaluation of other Holter-based risk markers. However, in contradistinction to what is reported in patients with ischemic cardiomyopathy, the prognostic value of AECG in NIDCM is rather low and remains controversial (Goldberger et al., 2007, 2014; Pedersen et al., 2014).

The incidence of NSVT in patients with NIDCM varied from 33% to 79% (Doval et al., 1996; Katritsis et al., 2013; Okutucu & Oto, 2010). Iacoviello et al. (2007) found that NSVT was associated with threefold higher risk of arrhythmic events during follow-up and that prognostic value of NSVT was enhanced by a combination with low LVEF and abnormal QT dynamics. In Marburg Cardiomyopathy study (Grimm, Christ, Bach, Müller, & Maisch, 2003), NSVT evaluated alone was not associated with an increased risk of arrhythmic events; however, when combined with low LVEF, the risk was eightfold higher. A meta-analysis by de Sousa et al. (2008) showed that the presence of NSVT was a statistically significant predictor, independent of LVEF, of SCD in patients with NIDCM and depressed LVEF. A more recent meta-analysis by Goldberger et al. (2014) based on 45 studies encompassing over 6,000 patients concluded that NSVT evaluated alone was a significant risk predictor (OR = 2.92,  $p < .001$ ) of an arrhythmic endpoint defined as sudden or arrhythmic death, cardiac arrest, documented ICD therapy, and documented VT/VF. The negative predictive value of NSVT was as high as 90%; however, its positive predictive value was only 20%. This study summarized the prognostic role of multiple risk stratifiers and found that the best predictors of unfavorable outcome were TWA, left ventricular end diastolic diameter, EPS, signal averaged ECG, LVEF, QRS duration, and NSVT. None of the markers of autonomic dysfunction such as baroreflex sensitivity, HRV, and HRT was found to be statistically significant. Overall, the data regarding NSVT are weak and do not support routine use of noninvasive techniques in this population.

## 5.3. Hypertrophic cardiomyopathy

An unfavorable clinical course in HCM is related to an increased risk of SCD, progressive heart failure, and complications attributable to AF. HCM is the most common cause of SCD in young people, notably athletes (Maron et al., 2014).

Syncope and palpitations are among the most commonly reported complaints in patients with HCM (Elliott et al., 2014; Finocchiaro et al., 2012; Gersh et al., 2011; Monserrat et al., 2003). Syncopal episodes may be caused by conduction disturbances, paroxysmal atrial arrhythmias with rapid ventricular rate, LV outflow tract obstruction or

neurally mediated events, and most ominously, potentially lethal ventricular arrhythmias. Up to 30% of HCM patients present with NSVT episodes on Holter monitoring (Adabag et al., 2005; Monserrat et al., 2003). The frequency is related to the degree of myocardial fibrosis (Adabag et al., 2008). As syncope is considered a risk factor for SCD in patients with HCM, careful workup including ECG, exercise test, and AECG should be performed. ACCF/AHA guidelines published in 2011 recommended 24-hr AECG monitoring, while 2014 ESC guidelines recommend longer 48-hr AECG monitoring in patients at their initial clinical assessment to detect atrial and ventricular arrhythmias (Class IB) (Elliott et al., 2014; Gersh et al., 2011).

Paroxysmal supraventricular arrhythmias (including AF) are observed in up to 38% of patients with HCM (Elliott et al., 2014; Gersh et al., 2011) and are poorly tolerated, contributing to syncopal episodes or heart failure. According to ESC guidelines, HCM patients with left atrium diameter  $\geq 45$  mm, which is considered as a risk predictor for AF and stroke, should undergo 48 hr AECG every 6–12 months to detect AF even if asymptomatic (Elliott et al., 2014).

Ambulatory ECG monitoring is an essential part of SCD risk stratification in patients with HCM, especially in younger subjects. Nevertheless, NSVT is characterized by high negative (95%) but low positive predictive values (Adabag et al., 2005). Recently, published ESC guidelines recommend that the probability of sudden death at 5 years should be estimated based on the HCM Risk-SCD formula (O'Mahony et al., 2014). This “prognostic index” integrates detected NSVT with structural abnormalities and family history of SCD, unexplained syncope and age (class IB) (Elliott et al., 2014). 48-hr AECG monitoring to detect NSVT, defined as  $\geq 3$  PVCs at heart rate  $\geq 120$  bpm, together with clinical history and echocardiogram are considered as a first-line recommended assessment. Long NSVT episodes observed on AECG prior to an ICD implantation predicted appropriate ICD therapy during follow-up (Francia et al., 2014). An index of NSVT severity (heart rate  $\times$  length in beats/100  $> 28$ ) was associated with over fivefold higher risk of ICD intervention. If medical therapy is used to treat ventricular arrhythmias, AECG can be repeated.

During follow-up, AECG monitoring should be repeated in the case of any symptoms suggestive of arrhythmia or routinely every 1–2 years to evaluate evidence of NSVT episodes (class IIa) or to detect asymptomatic AF episodes (class IIb) (Gersh et al., 2011). ESC guidelines (Elliott et al., 2014) recommend longer recordings (48-hr) in all subjects and more frequent monitoring (every 6–12 months) in patients with a sinus rhythm and left atrium dimension  $\geq 45$  mm.

#### 5.4. Arrhythmogenic right ventricular dysplasia/ Cardiomyopathy

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is associated with a risk of SCD and/or

progressive heart failure. Patients with ARVD/C may be asymptomatic or present with palpitations, dizziness, or syncope, potentially related to frequent ventricular ectopy or ventricular tachycardia episodes. Importantly, SCD may be the first manifestation of disease, especially in young athletes (Corrado et al., 2008).

According to the 2010 revised Task Force criteria (Marcus et al., 2010), ARVD/C is diagnosed based on a multidimensional scoring system. Major arrhythmic criteria for diagnosis and risk stratification include the presence of nonsustained or sustained VT of LBBB morphology with superior axis. Minor criteria include nonsustained or sustained VT of RV outflow tract morphology, LBBB with inferior or unknown axis, and presence of  $>500$  VPBs per 24 hr. Therefore, the initial evaluation of all patients suspected for ARVD/C should include 24-hr AECG monitoring. Extension of monitoring duration to capture arrhythmias may be considered. Significant day-to-day variability in PVC burden is noted in patients with ARVD/C, but Camm et al. (2015) reported that 24-hr AECG was sufficient to document the required Task Force criterion of over 500 PVCs in nearly 90% of cases, and extension of monitoring to 96 hr increased the number of correct classification to 95.5%.

AECG has a role in patients already treated with an ICD. NSVT or PVC burden  $>1,000/24$  hr may predict appropriate ICD discharge, the latter PVC burden associated with over threefold higher risk of ICD discharge (Bhonsale et al., 2011). Identification of atrial arrhythmias is important as it may herald inappropriate ICD therapy, and is associated with a higher risk of heart transplantation and cardiac mortality in patients with ARVD/C (Saguner et al., 2014).

AECG monitoring should be performed during evaluation of all first-degree relatives of patients with ARVD (Marcus et al., 2010). Episodes of VT with right ventricular origin pattern or more than 200 PVCs/24 hr are suggestive of familial involvement. There is no consensus on the frequency of serial re-assessment of subjects suspected for ARVD/C, but yearly assessment is reasonable. Documented electrical abnormalities, such as abnormal ECG and/or Holter, may precede structural changes during a 4-year follow-up in a cohort of ARVD/C relatives (te Riele et al., 2013). Complex ventricular arrhythmia may be observed even when the surface ECG is normal (te Riele et al., 2014).

#### 5.5. Wolff–Parkinson–White syndrome

Ambulatory ECG monitoring is potentially useful for evaluation of accessory pathway conduction properties in patients with Wolf–Parkinson–White syndrome. The risk of sudden death is related to rapid conduction across the pathway, particularly during AF, if the anterograde refractory period is short. During continuous ambulatory recordings, intermittent preexcitation or sudden loss of preexcitation with sinus rate acceleration is suggestive of “low risk,” for example, those that have a shortest pre-excited RR interval during AF  $>250$  ms (Skanes, Obeyesekere, & Klein, 2015). AECG may also be helpful in identifying patients with

WPW who have nonsustained runs of AF (Santinelli et al., 2009).

### 5.6. Inherited primary arrhythmic diseases

Cardiac channelopathies constitute a heterogeneous group of inherited diseases such as long and short QT syndromes, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), early repolarization syndrome, and idiopathic VF, which are often caused by mutations in genes coding ion channels or regulatory proteins. They are characterized by lack of evident structural heart disease and high risk of sudden death due to ventricular tachyarrhythmias (Priori et al., 2013). Surface ECG is a prerequisite in diagnosing these conditions and in predicting their risk of dying suddenly. Phenotype ECG expression in channelopathies is variable; therefore, AECG monitoring may be useful in assessment of transient electrical changes suggestive of a disease. However, in patients with inherited primary arrhythmia syndromes the most important role of AECG is attributed to detection of arrhythmias and risk stratification. It should be emphasized that HRS/EHRA/APHRS consensus on inherited primary arrhythmia syndromes (Priori et al., 2013) underlines the role of exhaustive evaluation of the origin of syncope episodes in patients with channelopathies. Syncope is considered a significant risk marker of SCD.

#### 5.6.1. Long QT syndrome

The long QT syndrome (LQTS) is a hereditary channelopathy characterized by QT prolongation and propensity to syncope, cardiac arrest, or sudden death in association with torsade de pointes polymorphic VT that might deteriorate to ventricular fibrillation (Zareba & Cygankiewicz, 2008). Recent guideline revisions suggest the diagnosis of LQTS is based on the presence of risk score  $\geq 3$  points and/or the presence of a prolonged QTc  $\geq 480$  ms interval on repeated ECGs or pathogenic mutation (Priori et al., 2015). The risk score increases in relation to significantly prolonged QTc, torsade de pointes arrhythmias, and syncope. QT measurements are based on surface ECG; however, AECG may reveal transient prolongation of QT interval and/or inappropriate QT adaptation to heart rate. Repolarization abnormalities are frequently related to periods with abrupt changes in heart rate. In case of progressively increasing or decreasing RR intervals, the QT interval shows a linear correlation with heart rate within physiological limits. However, in case of abrupt RR changes, the QT does not change adequately (Merri et al., 1992). It is also documented that RR changes in the form of “short-long” cycles may precede the onset of VT in patients with LQTS (Locati et al., 1995). AECG may be helpful in illustrating T-wave abnormalities, evaluation of R on T phenomenon, capture of T-wave alternans (an ominous finding), detection of nonsustained or sustained VT (especially torsade de pointes), in addition to identifying QT interval prolongation itself. While no doubts exist in subjects with QTc  $> 500$  ms, those with QTc  $< 500$  ms are frequently referred for exercise ECG testing and

24-hr Holter monitoring. The presence of QTc  $> 500$  ms at heart rates  $< 100$  beats per minute during exercise testing or Holter recordings may be indicative of LQTS, whereas values below 500 ms are within physiological range (Molnar et al., 1996). Findings of inappropriate QT adaptation to heart rate or even transient QT prolongation would be clinically useful findings.

Whether AECG monitoring is required for establishing diagnosis or help in therapeutic decisions such as ICD implantation or drug titration remains unresolved. The 12-lead ECG remains the gold standard for diagnosis, however. During follow-up, AECG can be used to assess efficacy of drug therapy and its potential adverse effects such as bradycardia. Regarding noninvasive ECG risk stratification, one may consider use of AECG for detection of increased QT variability/dispersion, which are considered markers of electrical instability and therefore related to higher risk of SCD.

#### 5.6.2. Short QT syndrome

Short QT syndrome diagnosed in patients with QTc  $\leq 340$  ms is a cardiac channelopathy associated with consistently shortened QT interval and a predisposition to AF and SCD in patients with no structural heart disease (Priori et al., 2015). Clinical manifestation of short QT syndrome may vary from totally asymptomatic to SCD as the first symptom. In the largest database of short QT syndrome patients, history of syncope was found in 24% of subjects, and the initial symptom in 14%. Palpitations were experienced by 31% of patients and were attributed to documented AF or atrial flutter in the majority of cases (Giustetto et al., 2006). AECG in short QT syndrome is useful in identification of the cause of syncope and palpitations, particularly in detection of AF episodes, but has little role in diagnosis or guiding protective therapy.

#### 5.6.3. Brugada syndrome

Brugada syndrome is a primary inherited electrical condition characterized by abnormal repolarization pattern in the right precordial ECG leads and predisposition to life-threatening ventricular arrhythmias. The ECG diagnosis depends on a pattern of J-point elevation of 2 mm with coved ST-segment elevation and inverted T wave in V<sub>1</sub>–V<sub>2</sub>, classified as the type 1 morphology (Priori et al., 2013, 2015), occurring spontaneously or after provocative testing. The ECG of patients with Brugada syndrome is highly variable and can fluctuate over time from type 1 to other types, or even normalize, and vice versa. Therefore, some have suggested the 12-lead AECG may be useful to reveal the transient Brugada ECG pattern in patients who are suspected of harboring Brugada syndrome. Recently, Cerrato et al. (2015) analyzed the prevalence of Brugada pattern type 1 in 12-lead 24-hr AECG recordings in a series of 251 patients from the Brugada Registry, including 30% of patients with spontaneous and 70% of drug-induced type 1 patterns. They found that “spontaneous” but intermittent ECG type 1 pattern could be detected in 20% of patients who were



identified primarily from a “drug-induced” group. Transient Brugada pattern was observed predominantly in the afternoon hours, from 12 p.m. to 6 p.m. The authors suggested that 12-lead AECG monitoring may be used as a screening test to avoid drug challenge as a first-line diagnostic procedure. It has also been reported that a 12-lead Holter recording with V<sub>1</sub>–V<sub>2</sub> electrodes displaced to the third intercostal space is more sensitive for detection of the ECG type 1 pattern than repeated 12-lead ECGs or Holters with conventionally placed leads (Shimeno et al., 2009). Additionally, the AECG could be used to assess for other arrhythmias or ECG patterns that may be supportive of the diagnosis of BS in asymptomatic subjects such as AF, ST-T wave alternans, spontaneous LBBB, and PVCs.

Lifesaving therapy, that is, ICD implantation, is available for Brugada syndrome, but because the diagnosis can prove elusive in symptomatic patients, extended AECG recording with and without special lead positions can be considered in patients with unexplained syncope when a suspicion of Brugada syndrome exists (e.g., based on family history, characteristic trigger [fever, specific medications]).

#### 5.6.4. Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia is a rare but highly lethal inherited channelopathy characterized by exercise- or emotion-induced palpitations and/or syncope in early adolescence, in subjects with no structural heart disease. SCD risk in CPVT is related to adrenergic-induced bidirectional and polymorphic ventricular tachycardia. As resting surface ECG is not helpful for the diagnosis of suspected CPVT, further electrocardiographic evaluation and provocative testing should be pursued. These tests may include AECG monitoring to assess the presence of ventricular tachyarrhythmia during daily activities and emotional stress, and above all exercise stress test to evaluate relationship of ventricular arrhythmia with increased catecholamines. Ventricular ectopy usually appears at a heart rate of 110–130 bpm and tends to aggravate in number and complexity with an increasing heart rate. Adrenergically induced atrial arrhythmias are also common.

Ambulatory ECG could be recommended as a measure of efficacy of drug treatment in patients with CPVT. Prior HRS/EHRA/APHRs statements recommended periodic AECG monitoring and exercise tests to determine the heart rate at which ventricular arrhythmia occurs and to evaluate the efficacy of arrhythmia suppression, although the presence of asymptomatic PVCs on Holter monitoring does not imply an unfavorable prognosis (Hayashi et al., 2009; Priori et al., 2013).

#### 5.6.5. Early repolarization syndrome

Following the publication by Haïssaguerre et al. (2008), more attention is being paid to the early repolarization pattern that had for years been considered a benign ECG finding. Several studies have documented that J-point elevation in the inferior and/or lateral leads is frequently observed in patients with

idiopathic VF. Nevertheless, such an ECG pattern may also be observed in up to 31% of the general population (Macfarlane et al., 2015; Maury & Rollin, 2013; Rosso et al., 2008). According to HRS/EHRA/APHRs consensus (Priori et al., 2013), AECG monitoring may contribute to documentation of early repolarization pattern especially during bradycardia in survivors of VF, although the vast majority is accomplished via standard ECG. Increase in J-point elevation amplitude preceding ventricular arrhythmias has been reported in ICD patients with electrical storm (Nam et al., 2010).

#### 5.6.6. Idiopathic ventricular fibrillation

Idiopathic ventricular fibrillation is a diagnosis by exclusion, defined as a resuscitated cardiac arrest, preferably with ECG documentation of VF, in subjects in whom cardiac, respiratory, metabolic, and toxicological etiologies have been excluded. Detailed analysis of cardiac arrest victims should include personal and family history, electrocardiology (surface ECG, signal averaged ECG and AECG), imaging techniques to rule out structural heart disease, provocative tests, electrophysiological study, ventricular biopsy, and genetic testing. Holter monitoring has been suggested in evaluation of first-degree relatives of idiopathic VF victims.

### 5.7. Dialysis and chronic kidney disease

The prevalence of chronic kidney disease is increasing, and it is now present in at least 15% of the adult population (Coresh et al., 2003). End-stage renal disease (ESRD) is characterized by extremely high mortality (20% per year), and up to 100 times higher rate of cardiovascular death, as compared to the general population (Foley, 2003). SCD is the most common cause of death in dialysis patients (Cheung et al., 2004). Fluctuations of electrolytes and fluid, a chronic inflammatory state, preserved systolic function, but left ventricular hypertrophy with diastolic dysfunction, silent myocardial ischemia, and repetitive myocardial injury from dialysis-induced myocardial stunning contribute to the substrate for SCD (Bleyer et al., 2006).

However, data on the rate of asymptomatic cardiac arrhythmia in patients with ESRD between dialysis sessions are limited. Previous 24–48 Holter ECG studies reported conflicting findings regarding cardiac arrhythmia burden and ECG markers of SCD during and after dialysis. Burton, Jefferies, Selby, and McIntyre (2009) showed that PVCs and VT were more common during hemodialysis than in the subsequent monitored period, and were associated with myocardial stunning. Silent myocardial ischemia was diagnosed on Holter in 22% of dialysis patients, and strongly associated with VT/VF during and after dialysis (Mohi-uddin et al., 2005). Interestingly, silent myocardial ischemia did not correlate with significant coronary heart disease and was thought to be due to microvascular disease and coronary spasm. Dynamic ECG observations included a progressive increase in QRS voltage and heart rate, decrease in T-wave amplitude, and increased occurrence of arrhythmia during



dialysis (Rodriguez-Fernandez et al., 2012). Green et al., (2012) reported that microvolt TWA increased during dialysis, but did not find association between TWA and cardiovascular outcomes during 2.6 years of follow-up. Recently, an association between higher serum hemoglobin level and frequency of PVCs during dialysis was shown, which might explain the detrimental effect of high hemoglobin level on hemodialysis patients (Saygi et al., 2011). Poulidakos et al. (2013) showed that T-wave morphology undergoes uniform rate-dependent changes during the dialysis procedure, whereas QRS-T angle changes differ from person to person, and correlated with the level of parathyroid hormone.

Recently, Buiten et al. (2014) showed that the dialysis procedure itself is associated with the development of AF. Patients receiving peritoneal dialysis showed significantly fewer episodes of AF. AF onset was more frequent on the days of the hemodialysis procedure, and during the dialysis procedure itself. Therefore, AECG monitoring during dialysis could help with the earlier diagnosis of AF in asymptomatic patients, which may prompt appropriate AF management including anticoagulant therapy.

### 5.8. Neurological and muscular diseases

Perturbation of the balance of the autonomic nervous system can be studied by AECG, particularly through the analysis of HRV. Reduced HRV is generally associated with an elevated sympathetic tone or reduced parasympathetic activity. Activation of the autonomic nervous system can contribute to the genesis of a variety of arrhythmias, including both brady- and tachyarrhythmias. A strong link between epilepsy and cardiac arrhythmias has been described. Recordings during seizures report that sinus tachycardia just prior to the seizure is common, with both atrial and ventricular ectopy also observed. However, life-threatening arrhythmias and sudden death in epileptic patients are uncommon, with a rate of approximately two in a thousand. It is possible that the same cellular mechanisms triggering cardiac arrhythmias may be responsible for cerebral epilepsy.

Myotonic dystrophy is a progressive genetic condition that primarily affects skeletal muscle but has important cardiac complications (Groh et al., 2008). A variety of bradyarrhythmias have been observed, including sinus node dysfunction, bundle branch block, and the entire spectrum of AV blocks. Patients may also experience AF and sustained VT. Sudden death is reportedly due to asystole and ventricular fibrillation, and some patients may benefit from pacemaker or ICD. AECG may be used to detect arrhythmias to guide device and medical management, but there is little published data to guide its specific use in this clinical context.

### 5.9. Sleep apnea

Sleep apnea syndrome is a common breathing disorder that affects 2%–4% of the population, with men being affected almost twice as often as women (Baranchuk et al., 2008). The condition has well-defined associations with increased cardiovascular morbidity and mortality, arrhythmia, daytime

hypersomnolence, motor vehicle accidents, and neurocognitive dysfunction, yet it is grossly underdiagnosed (Hersi, 2010).

Recent studies have shown that cardiac arrhythmias and conduction disorders are common in patients with sleep apnea (Hersi, 2010; Todd et al., 2010). The mechanisms of this association include autonomic imbalance, systemic and pulmonary hypertension, intermittent hypoxia, and inflammation. All these conditions facilitate structural and electrical remodeling, which is considered to be the electrical substrate for a variety of arrhythmias (Baranchuk, 2012).

The cornerstone for the diagnosis of sleep apnea is polysomnography, during which a variety of cardiac arrhythmias (AV block, sinus pauses, NSVT, and paroxysmal AF) can be detected (Monahan et al., 2009). Because polysomnography is not universally available and can be logistically cumbersome, screening larger populations at risk would be advantaged by simpler and less expensive diagnostic tests. It has been proposed that the Holter monitor may fill this role. Additional information beyond what is typical for Holter recordings include a description from the patient about hours of sleep. Some commercial systems include apnea analysis algorithms that use: (1) breathing-related changes in sinus rhythm, that is, sinus arrhythmia, modulated by the ANS; and/or (2) changes in R-wave amplitude modified by respiratory movement of the chest wall resulting in subtle shift of the distance between ECG electrodes. More validation of these techniques is needed.

### 5.10. Athletes and precompetition screening

Arrhythmia monitoring of the athlete is, in some ways, distinct from utilization of monitoring in other circumstances. For the athlete, symptoms suspicious of an arrhythmia, rarely, can be a premonitory sign of SCD and may indicate an otherwise potentially serious but treatable condition or arrhythmia. On the other hand, undue restriction for suspicious but benign symptoms may be unwarranted.

A stepwise approach to evaluating the athlete should be considered. First, it is important to understand historical features of the symptoms involved and if they are related to specific competitive or physical activities. Second, it is important to rule out important cardiovascular disease that may be present concomitantly or be the initiator of the arrhythmia.

An ECG and other noninvasive tests are performed to determine the presence of any underlying structural process that could be involved and require restriction from athletics. On the ECG, there may be obvious features that point to a specific arrhythmogenic substrate. However, for many competitive athletes, the sport itself is required to initiate the symptom and potentially the arrhythmia. Furthermore, any symptom and/or arrhythmia may not necessarily be reproducible. Thus, the AECG is one of several subsequent steps in evaluating the patient depending on the sport, the athlete, the circumstances of the symptoms, and the presence of comorbidities as well as family history.

Ambulatory ECG monitoring for the athlete is specifically useful when (1) the athlete is not already restricted due to a diagnosed cardiovascular condition; (2) there is no other way to secure a diagnosis or cause for the symptoms with any certainty; and (3) participation in athletics causes the symptoms and may facilitate the arrhythmia diagnosis. ECG monitoring can be used to secure an initial diagnosis or as a surveillance tool to ascertain that an arrhythmia is eliminated by therapy. AECG should be considered to correlate symptoms (e.g., syncope, palpitations) with arrhythmia. In addition, it may be helpful in asymptomatic patients when the initial screening ECG suggests high-density or complex ventricular ectopy to quantify the ventricular arrhythmia burden (Zipes et al., 2015). Very frequent ventricular ectopy may suggest the presence of underlying heart disease (Biffi et al., 2002). In addition, some known heart conditions (e.g., congenital aortic stenosis, low-risk cardiomyopathy) and baseline ECG abnormalities (e.g., AV block, bundle branch block) may be further worked up with AECG (Pelliccia et al., 2005).

The type of monitoring depends on symptom frequency, severity, duration, and type of circumstances surrounding the symptoms. In addition, the type of monitoring depends on the type of athletic participation and the arrhythmia and symptom being assessed. There is no one best monitoring technique, and individualized decisions are needed.

Rhythm disturbances, by themselves, do not necessarily elicit symptoms, and some rhythm disturbances can occur with or without symptoms. On the other hand, patients may have multiple rhythm disturbances and recording an asymptomatic rhythm disturbance does not necessarily imply high risk.

## 6. Section 4: Holter-Based Markers of Autonomic Nervous Tone and Repolarization

Candidate selection for ICD therapy could be improved. Implantation according to current guidelines results in appropriate therapy in only about 20% of patients with ICDs. In addition, current indications neglect the vast majority of patients vulnerable to SCD who have relatively preserved LVEF. Accounting for the multifactorial pathogenesis of SCD including structural substrate, autonomic dysfunction, and repolarization abnormalities may improve specificity.

### 6.1. Heart rate variability

Heart rate variability is one of the oldest Holter-based risk stratification tools as well as the most extensively used. It detects autonomic nervous system tone based on beat-to-beat RR intervals. Studies have demonstrated the correlation of depressed HRV with risk of mortality including cardiovascular death but not with SCD (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Sassi et al., 2015; Wellens et al., 2014).

Measurement of HRV is performed in the frequency and time domains as well as by nonlinear techniques.

Frequency-domain parameters require data stationarity and typically employ short-term recordings under controlled conditions but can also be performed over 24 hr from 5-min segments averaged over the entire period. Time-domain parameters measure changes in NN intervals often based on long-term recordings, typically 18 hr encompassing morning and night. Standard deviation of all NN intervals (SDNN) is the oldest, the simplest, and the most frequently used time-domain HRV parameter. Nonlinear HRV analysis is believed to be less dependent on preprocessing and to express better the complexity of RR changes (Perkiomaki et al., 2000). The methodology of HRV measurement is summarized in a report of the Task Force of ESC/NASPE and in recently published joint position statement by e-Cardiology Working Group of ESC/EHRA/APHRS (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Sassi et al., 2015).

Decreased HRV values have been consistently reported in post-MI infarction and heart failure patients (Bigger et al., 1992; Kleiger et al., 1987; La Rovere et al., 2003, 2012; Makikallio et al., 2005). The clinical relevance of abnormal HRV, namely, increased sympathetic tone and/or decreased vagal activity, as a predictor of overall mortality was appreciated as early as in the 1980s, when Kleiger et al. (1987) first reported that SDNN <50 ms was associated with fivefold higher mortality in postmyocardial infarction patients compared to those with SDNN > 50 ms. Multiple studies have consistently confirmed the prognostic value of HRV in predicting overall mortality and heart failure progression (La Rovere et al., 2003, 2012). Recent studies, performed in modern postmyocardial infarction cohorts treated with beta-blockers and early reperfusion, have reported conflicting results. The REFINE study failed to demonstrate the usefulness of decreased SDNN in predicting cardiac death or resuscitated cardiac arrest in 322 acute postmyocardial infarction patients with LVEF <50% (Exner et al., 2007). By contrast, the CARISMA trial investigators reported that in 312 patients evaluated at 6 weeks after an acute myocardial infarction, SDNN, very low frequency (VLF), high frequency (HF), and fractal scaling component independently predicted all-cause mortality and arrhythmic events documented by an ILR (Huikuri et al., 2009). In heart failure patients, decreased HRV has been documented as a potent marker of heart failure progression and identified patients in need of heart transplantation or with elevated risk for death due to pump failure. The GISSI Holter substudy in a contemporary population of heart failure patients showed that SDNN, VLF, LF, and detrended fluctuation analysis were independent risk predictors for cardiovascular death, while VLF and LF were associated with sudden death or appropriate ICD discharge (La Rovere et al., 2012).

Despite data linking decreased HRV with increased mortality, randomized trials in patients stratified for ICD implantation based on this parameter failed to demonstrate the usefulness of HRV in predicting benefit from ICD therapy (Hohnloser et al., 2004; Steinbeck et al., 2009). Patients with impaired HRV at enrollment were more likely to die

from heart failure progression than from arrhythmic causes. In fact, HRV algorithms are currently implemented in cardiac resynchronization therapy (CRT) devices to identify heart failure exacerbation (Landolina et al., 2008). Additionally, the DEFINITE trial showed that preserved HRV, defined as SDNN >100 ms, identified patients without sudden death or ICD shocks during a 3-year follow-up (Rashba et al., 2006). Most commercial Holter systems are equipped with software for automated analysis of time- and frequency-domain HRV measures.

## 6.2. Heart rate turbulence

Heart rate turbulence analyzes the baroreceptor-mediated response of the sinus node to premature ventricular beats composed of an early acceleration and subsequent deceleration and is an indicator of baroreceptor sensitivity (Schmidt et al., 1999; Bauer et al., 2008). Changes in RR intervals following PVCs are subtle and require dedicated software for calculation. Only Holter recordings with  $\geq 5$  PVCs are considered reliable for HRT calculation. Detailed HRT methodology is summarized in the ISHNE-sponsored consensus document (Bauer et al., 2008).

Abnormal HRT parameters have been documented in various subsets of patients following myocardial infarction, or patients with heart failure or other cardiac and noncardiac diseases such as diabetes, obstructive sleep apnea, or connective tissue diseases (Barthel et al., 2003; Bauer et al., 2008; Cygankiewicz et al., 2008; Exner et al., 2007; Huikuri et al., 2009; Schmidt et al., 1999). Clinical and ECG covariates such as age, LVEF, NYHA class, heart rate, number of PVCs, pharmacotherapy, and invasive therapeutic strategies influence HRT results (Bauer et al., 2008; Cygankiewicz, 2013).

The initial evidence of the usefulness of abnormal HRT to stratify risk for all-cause mortality (Schmidt et al., 1999) in postmyocardial infarction was confirmed in patients receiving guideline-directed medical therapy and early revascularization by PCI (Barthel et al., 2003; Exner et al., 2007; Makikallio et al., 2005). The FINGER (FINland and GERmany Postinfarction) study documented that only abnormal turbulence slope (TS) and NSVT were significantly associated with an increased risk of SCD; patients with abnormal slope had almost threefold higher risk than those with normal slope (Makikallio et al., 2005). The REFINE (The Risk Estimation Following Infarction Noninvasive Evaluation) trial reported that abnormal HRT analyzed at 10–14 weeks after myocardial infarction predicted the primary endpoint of cardiac death or resuscitated cardiac arrest in post-MI patients with LVEF <50% (Exner et al., 2007). Abnormal TS evaluated at 6 weeks after MI identified patients with LVEF <40% who were at risk for arrhythmic events such as ventricular fibrillation or symptomatic VT during the 24-month follow-up (Huikuri et al., 2009). Combined analysis from REFINE and CARISMA studies reported that in acute postmyocardial infarction patients, absence of an increase in TS values was associated

with sevenfold to 10-fold higher risk of life-threatening arrhythmias during a 2-year follow-up (Huikuri et al., 2010). In patients with heart failure, abnormal HRT is associated with an increased risk of all-cause mortality and heart failure progression. Moreover, both the MUSIC and GISSI-HF trials, which enrolled ambulatory patients with mild-to-moderate heart failure, documented that abnormal TS predicts not only total mortality but also SCD and/or appropriate ICD discharge (Cygankiewicz et al., 2008; La Rovere et al., 2012). Abnormal HRT seems to be particularly useful in identifying high-risk patients among those with LVEF >30% (Bauer et al., 2008; Cygankiewicz et al., 2009; La Rovere et al., 2012) and is frequently evaluated in risk scores that combine assessment of arrhythmogenic substrate (low LVEF), repolarization instability (e.g., TWA), and abnormal autonomic nervous system tone (HRV). The REFINE study showed that patients with both abnormal HRT and TWA had a fourfold higher risk of arrhythmic events, while the MUSIC study documented that a combination of abnormal TS, decreased SDNN, and increased repolarization dynamicity (QT/RR) was associated with the highest risk of sudden death in patients with heart failure and LVEF >35%. The value of combined risk stratification including HRT was also observed in GISSI-HF trial (Cygankiewicz et al., 2009; Exner et al., 2007; La Rovere et al., 2012).

## 6.3. QT variability and dynamics

QT variability (QTV) measures variations in the length rather than in the morphology of the QT interval to assess duration of repolarization. There are approximately 15 different QTV measures. Technical difficulties in QTV assessment include identification of the end of the T wave, differences among leads, and effects of T-wave amplitude. QTV studies are performed at constant heart rates to avoid the need for heart rate correction. Importantly standardization is lacking including technical requirements, recording duration, most suitable leads, and means to deal with effects of the autonomic nervous system, respiration, circadian influences, and medications. QTV studies have enrolled  $\sim 3,500$  individuals. Important limitations include the facts that (1) normative QTV values have not been established; (2) there are no agreed cutpoints indicating elevated risk; and (3) QTV studies do not provide evidence of its capacity to guide therapy.

Different methodological approaches have been proposed to evaluate the long-term rate dependence of QT interval. The principal and better established methods are as follows: (1) the circadian profile of the rate-corrected QT interval (QTc); (2) long-term evaluation of the QT-RR relationship; and (3) the QT variability index. Some of these methods have been implemented on commercial Holter systems, and they are becoming available for routine clinical use.

QT-RR dynamicity, that is, the relationship between QT-interval duration and the immediately preceding RR interval, reflects action potential duration dependence on cycle length.



Analysis of the QT-RR relationship requires recordings at different heart rates, making 24-hr Holter monitoring recordings suitable. QT-RR dynamicity can be altered in patients with ischemic heart disease, congenital, and acquired LQTSs, where the QT-RR pattern differs according to genotypes, and the Brugada syndrome (Chevalier et al., 2002s; Cygankiewicz et al., 2008; Fujiki et al., 2004; Jensen et al., 2005). Patients with altered QT dynamics may have a greater incidence of malignant arrhythmias (Jackman et al., 1988; Moss & Schwarz, 1982; Roden, 1991).

The QTV Index measures repolarization lability by calculating the ratio of repolarization variability to HRV. Specifically, it assesses beat-to-beat variability of the duration of the QT interval and U wave with concomitant evaluation of the circadian rate-adjusted QTV and RR interval variability (Berger et al., 1997). Increased QTV index is associated with both all-cause mortality and cardiovascular mortality in patients with acute myocardial infarction or heart failure and in resuscitated cardiac arrest (Dobson et al., 2013).

Recent ESC guidelines on ventricular arrhythmias and SCD do not recommend noninvasive risk stratification in the early postinfarction phase (Priori et al., 2015) given the limited sensitivity and positive predictive values of various Holter-based parameters to improve SCD risk stratification, including quantitative analysis of T-wave alternans (Gold et al., 2008; Kentta et al., 2014; Verrier et al., 2011; Verrier et al., 2013; Chow et al., 2008; Zipes et al., 2006; Nieminen et al., 2014; Uchimura-Makita et al., 2014). However, efforts to improve this continue, since sudden death occurs largely in subjects in whom left ventricular ejection fraction has proven insufficient for risk stratification. A recurring theme is that the use of the multiparameter approach incorporating indicators of autonomic tone and repolarization abnormality holds the greatest promise. The absence of randomized clinical trials to assess the capacity of these parameters to guide therapeutic interventions to prevent SCD is a major deficiency.

## 7. Section 5: Clinical Indications—Pretreatment Arrhythmia Assessment and Documentation of the Efficacy and Safety of Pharmacological and Nonpharmacological Therapy in Specific Clinical Contexts

### 7.1. Ventricular arrhythmias

#### 7.1.1. PVC monitoring

AECG facilitates detection, quantification, and morphology assessment for the evaluation of the overall PVC burden as a potential cause of “tachycardiomyopathy” (Baman et al., 2010) and correlation between symptoms and ECG findings, for example, intense physical activity or emotional stress (Cantillon, 2013; Zipes et al., 2006). AECG may be analyzed for relationship between ventricular arrhythmia and preceding heart rate and repolarization changes (e.g., transient QT prolongation) or ischemia (Diem et al., 2002; Lewis et al., 1983). These factors are important for

directing (and assessing efficacy and safety of therapy) (Aliot et al., 2009; Cantillon, 2013; Katritsis et al., 2013; Pedersen et al., 2014). Three-channel AECGs are suitable for detection and quantification of ventricular arrhythmia burden. However, 12-channel recorders more reliably diagnose PVC origin (and reveal aberrant supraventricular conduction as a cause for wide complexes), useful for decisions regarding catheter ablation.

#### 7.1.2. Suppression of ventricular arrhythmia by pharmacotherapy

Treatment of ventricular arrhythmias is sometimes utilized for relief of symptoms and/or suppression of frequent PVCs that cause left ventricular dysfunction (Pedersen et al., 2014). Data from 1980s on the value of Holter monitoring in evaluation of efficacy of antiarrhythmic drugs indicated that suppression of arrhythmia should be considered when a reduction of 75% in isolated or coupled PVCs and 90% in VT episodes had been achieved. However, these observations were based on repetitive 24-hr Holter recordings. More recent data suggest that 24-hr monitoring is not sufficient to reliably confirm suppression of arrhythmia due to poor reproducibility (Reis Mdo et al., 2014).

Most antiarrhythmic drugs also exert negative chronotropic and dromotropic effects. Routine AECG for detection of sinus node automaticity and/or AV conduction disturbances prior to drug administration or during follow-up should be performed in patients with symptoms suggestive of bradycardia–tachycardia syndrome or in those with clinical suspicion of side effects related to decrease in automaticity and conduction. Significant bradycardia in patients requiring heart rate lowering drugs may warrant pacemaker implantation. AECG monitoring may be useful in patients who receive antiarrhythmic drugs to detect transient excessive QT prolongation (especially those that occur postpause), worrisome patterns of ventricular ectopy (tight-coupled or at the peak of the T wave), or asymptomatic episodes of torsade de pointes VT. In some cases, hospitalization with continuous ECG telemetry to detect excessive QT prolongation may be recommended during drug initiation (Drew et al., 2012; Moss et al., 2001).

#### 7.1.3. Efficacy of ablation procedure

Catheter ablation of ventricular arrhythmias has become a widely used therapeutic approach. In symptomatic patients with frequent PVCs, catheter ablation is recommended as class IIa indication (Level of Evidence B), particularly for those with left ventricular dysfunction and no other detectable cause of ventricular impairment (Aliot et al., 2009). The efficacy of catheter ablation for ventricular arrhythmia is assessed immediately during and shortly after a procedure. EHRA/HRS consensus on Catheter Ablation of Ventricular Arrhythmias (Aliot et al., 2009) recommends surveillance of VT recurrences after catheter ablation. In patients without an ICD, symptomatic arrhythmia should be documented by a surface 12-lead ECG or by AECG monitoring. In order to



detect asymptomatic recurrence of arrhythmias after ablation, the following optional screening modalities at 6-month intervals were recommended: (1) AECG monitoring for 4 weeks around the follow-up interval, including symptom-triggered recordings and weekly transmissions for asymptomatic episodes; (2) 24- to 72-hr Holter monitoring; or (3) 30-day auto-triggered event monitoring or AECG. According to EHRA/HRS consensus, a minimum follow-up of 6–12 months with regular monitoring of arrhythmia is required to assess the efficacy of ablation.

## 7.2. Atrial fibrillation

### 7.2.1. ECG recording modalities

As symptoms during AF are largely nonspecific (or absent), extended AECG recording is helpful to clarify the need for additional treatment (such as pacemaker), to help reassure the patient, and to predict long-term prognosis (Kennedy, 2015). In addition, other arrhythmic causes of symptoms, such as atrial flutter, atrial tachycardia, atrial ectopy, and others can usually be differentiated from AF, especially with multilead recordings (Mittal et al., 2011). Notably, AF may be triggered by other arrhythmias, for example, AVRT or AVNRT, especially in younger patients, and it is important to document this before selecting appropriate treatment (Calkins et al., 2012; Sauer et al., 2006). Some patients exhibit very-high-density atrial ectopy that can serve as AF triggers as well, and 24-hr recordings that contain >1,000 atrial premature beats may be candidates for ablation of these “focal triggers” (Calkins et al., 2012).

The definition of AF has been set as a minimum of 30 s (Calkins et al., 2012), but this is not based on any data analysis of AF duration and patient outcome. In clinical practice, this severe definition may give way to one that also takes account of AF frequency, duration, and symptom status. Duration and frequency of events vary greatly among patients with AF. Therefore, the choice of AECG to capture AF episodes will be determined by duration and continuity of recording (Mittal et al., 2011). AECG can quantify atrial and repetitive ectopy, shortest and longest duration of AF, burden of AF, the heart rate during AF, and pattern of initiation and termination of AF. Short-duration 24- to 72-hr Holter recordings are best suited for patients with very frequent paroxysms of AF or persistent AF. For less frequent episodes, patient-activated event and loop recorders can be used for several weeks at a time. These devices are particularly useful to capture ECG recordings during symptomatic events and clarify the arrhythmic basis for unexplained or ambiguous symptoms, especially if infrequent. Autotriggered devices have higher diagnostic yield than standard 24-hr Holter monitors and 30-day loop recorders (Reiffel et al., 2005). Although these monitors can detect the onset of an arrhythmia such as AF, their algorithms are not designed to include the offset of the arrhythmia. Thus, information about the burden of AF cannot be consistently ascertained. Patch monitors and MCT are the most complete outpatient ECG recording and increase the likelihood for detecting AF, and can provide accurate

representation of AF burden for the duration of recording (Barrett et al., 2014; Rosenberg et al., 2013; Rothman et al., 2007; Turakhia et al., 2013; Schreiber et al., 2014).

Reliance on symptoms alone (by patient or physician) may be misleading—both over and underestimating the presence of AF (Charitos et al., 2014). This has important implications for assessing treatment effects including interventional ablation (Calkins et al., 2012; Joshi et al., 2009; Steinberg et al., 2014). Indeed, catheter ablation may increase the proportion of AF events that are asymptomatic, probably by alteration of cardiac neural element (Hindricks et al., 2005). As most patients do not have an implanted device, extended AECG facilitates accurate AF quantification and associated ventricular rates.

### 7.2.2. Cryptogenic stroke

Twenty-five percent of ischemic strokes remain unexplained after an initial thorough evaluation including 12-lead ECG and in-hospital telemetry monitoring and full neurological workup, that is, “cryptogenic stroke” (Wolf et al., 1987). AF and associated thrombus formation is the most common cardioembolic source of ischemic stroke (Liao et al., 2007). Because the formal diagnosis of AF leads to an effective medical intervention with chronic oral anticoagulation (rather than aspirin), it is critical to identify AF in patients with cryptogenic stroke (Hart & Halperin, 2001). Postdischarge AECG recording after cryptogenic stroke has particular utility (Marini et al., 2005) although AF detection is sensitive to the patient selection process, the definition of AF, and the duration of monitoring. The minimal duration of AECG monitoring is uncertain, and 30-day recordings have identified as high as a 20% prevalence of AF (Kishore et al., 2014). A recent randomized clinical trial involving 572 patients compared 30-day AECG monitoring to 24- to 48-hr Holter recording and found the respective yield to be 16.1% versus 3.2% for AF >30 s and 9.9% versus 2.5% for AF >2.5 min, with a resultant increase in prescription of anticoagulant therapy (Gladstone et al., 2014). If detection is thought to require more prolonged monitoring, AECG may be limited by noncompliance and an ILR may be more effective with a sixfold increased detection rate of AF >30 s at 6 months of follow-up in a trial that used a control group with little AECG monitoring (Sanna et al., 2014). The optimal AF detection strategy and monitoring duration are undefined and definitive recommendations will depend on cost-efficacy, patient acceptance and compliance, clarification of AF definitions, and demonstration of enhanced stroke reduction by a specific approach.

### 7.2.3. Acute treatment assessment—“pill-in-the-pocket” approach

An alternative to emergency department treatment for patients with infrequent but disabling AF is the “pill-in-the-pocket” strategy (Alboni et al., 2004). AECG monitoring can provide important efficacy and safety data in the outpatient setting, that is, confirmation of AF occurrence and

absence of spontaneous termination prior to using the antiarrhythmic drug, or after therapy has been self-administered, confirmation of success or failure that may require alternative management strategies. Possible complications (e.g., posttermination pauses) can also be captured by AECG.

#### 7.2.4. Posttreatment assessment—pharmacologic therapy

##### *Rate control*

These measures provide symptom relief by slowing of ventricular rate through AV nodal blockade, with target ranges no higher than 80 at rest and an average <100–110 on Holter monitoring (class IIA and class IIb recommendation, respectively) (January et al., 2014; Wyse et al., 2002; Van Gelder et al., 2010). Additional AECG monitoring to correlate rate with residual symptoms should be individualized and may require extended ECG recording, for example, in patients with heart failure and/or ventricular dysfunction.

##### *Rhythm control*

The goal of a rhythm control strategy is to suppress or reduce the prevalence of AF associated with symptoms. Therefore, it may be reasonable to perform AECG to confirm the presence or absence of AF, particularly if residual symptoms are ambiguous or resting ECGs have been inconclusive.

##### *Safety of pharmacotherapy*

Outpatient monitoring with AECG may be used when starting antiarrhythmic drugs that do not require hospitalization for initiation. Class IC drugs (e.g., flecainide, propafenone) can transform AF into atrial flutter with 1:1 AV conduction or aggravate preexisting conduction abnormalities causing QRS prolongation or patterns of AV block. Class III antiarrhythmic drugs risk torsade de pointes, which may be pre-saged by increasing QT intervals (particularly postpause), prominent U waves, TWA, and greater prevalence of ventricular ectopy. If outpatient initiation has been selected (not permitted by FDA for dofetilide, but not prohibited for sotalol), then AECG recording during dose initiation and titration may be reasonable (Zimetbaum, 2012). Many antiarrhythmic drugs (e.g., amiodarone, dronedarone) may aggravate sinus or AV node dysfunction. Presence of significant bradyarrhythmia and/or correlation with symptoms may be confirmed with prolonged ECG recording.

##### *Posttreatment assessment—ablation therapy*

Many centers advocate early follow-up ECG recording. Monitoring postprocedure is mandatory to assess success and determine future management. Complete absence of AF is considered a very favorable finding. Recurrence in the early “blinking period” may require treatment, for example, cardioversion to prevent progressive adverse electrical remodeling, and facilitate detection of non-AF atrial tachyarrhythmias, or revelation of undiagnosed bradyarrhythmias that may warrant adjustment of medications or consideration of permanent pacing. Very early AF events in the first 2 weeks may predict long-term failure (Joshi et al., 2009), and AF during the blinking period may indicate

greater likelihood of need for additional procedures or drugs (Arya et al., 2010). Heightened surveillance during the early weeks following ablation may help manage patient expectations, provide reassurance regarding underlying rhythms when patients experience subtle or ambiguous symptoms, and aid in decision making for discontinuation of antiarrhythmic drug when the blanking period concludes. HRS guidelines suggest (1) ECG recordings at all clinic visits, (2) 24-hr Holter at 1 year, and (3) “event recording regularly and at the time of symptoms,” continuing monitor use from 3 to 12 months following ablation of paroxysmal AF. For persistent AF, this document suggests 24-hr Holters each 6 months and event-driven ECG monitoring. However, reimbursement may be problematic for prolonged or frequent ECG monitoring (Calkins et al., 2012).

### 7.3. Drug trials and safety (QT and arrhythmia evaluation)

Drug-induced QT prolongation has been recognized as a side effect of many commonly used medications. A prolonged QT interval predisposes to the development of ventricular tachyarrhythmias such as torsade de pointes and ventricular fibrillation, which could cause syncope, cardiac arrest, or SCD (Haverkamp et al., 2000; Moss, 1999; Zareba et al., 1995). Medications representing numerous classes of drugs have been shown to cause QT prolongation, usually via the mechanism of blocking IKr potassium current. The vast majority of older patients take several drugs, so an interaction of two or more drugs might increase the risk of QT prolongation and proarrhythmia. A standard 12-lead ECG is used in daily clinical practice to evaluate QT prolongation, whereas telemetry monitoring, event recorders, or Holter monitoring are utilized to assess arrhythmias.

Development of new compounds by the pharmaceutical industry requires assessment of potential proarrhythmic effect at early stages of preclinical and clinical investigations. Phase I and phase II clinical studies (if properly designed with ECG monitoring incorporated) provide an opportunity to identify the effect of the tested drug on QT duration. In many cases, the thorough QT study (International Conference on Harmonisation, 2005) is required, which consists of careful monitoring of ECG parameters on therapeutic and suprathreshold doses of a tested drug and during administration of moxifloxacin, an antibiotic with known QT prolonging effect considered as the positive control. Drugs with QT prolongation with upper confidence interval below 10 ms do not raise concerns regarding their QT-related safety, whereas drugs causing QT prolongation exceeding 10 ms, but especially 20 ms, might require additional safety measures or might not be allowed to enter the market. Until recently, thorough QT studies have been conducted utilizing standard 12-lead ECG recordings with time schedule reflecting plasma concentration and/or drug metabolism. Increasing usage of digital high-resolution, 12-lead AECG recordings is currently heading toward more frequent utilization allowing for extraction of ECG signal from

ongoing recordings that in addition to snapshots of the definitive 12-lead ECGs provide an insight into continuous assessment of arrhythmias (Sarapa et al., 2004).

Recent data from five thorough QT studies (Ferber et al., 2015) utilized access to continuous Holter recordings to further decrease variability in QT measurements by analyzing a larger number of beats. This approach demonstrated that Holter monitoring in early phase I and II studies could provide effective assessment of QT prolongation with smaller sample sizes without conducting separate and costly thorough QT studies (Darpo et al., 2015). This approach could be further enhanced by drug exposure to QT response analysis empowered by continuous Holter monitoring (Darpo et al., 2015).

#### 7.4. Ambulatory ECG monitoring in patients with cardiac implantable devices

AECG monitoring plays an essential role in establishing indications for pacemaker implantation. In some cases, it is useful for evaluation of already implanted patients although current era implantable electronic devices (pacers, ICDs, and CRTs) have sophisticated remote monitoring capabilities that are able to evaluate electrical properties of the device itself and also arrhythmias (Andrikopoulos et al., 2010; Barold, 1998; Dubner et al., 2012; Mittal et al., 2014; Mittal & Steinberg, 2012; Ritter, 2013; Varma & Auricchio, 2013; Varma & Ricci, 2013). Nevertheless, AECG may be helpful for arrhythmia analyses needed for correct device programming to deliver appropriate therapy, to avoid inappropriate intervention, or to detect device malfunction.

##### 7.4.1. Indications for implantation and evaluation prior to implantation

AECG may be considered in CRT candidates suspected of transient LBBB. In patients with AF scheduled for CRT implantation, careful analysis of ventricular rate response is required prior to implantation to ensure future efficiency of biventricular pacing treatment. In those with poorly controlled ventricular response, AV node ablation may be helpful following CRT implantation (Brignole et al., 2013; Epstein et al., 2013). Even with well-controlled ventricular rates and high percentage of biventricular pacing capture, intermittent loss of LV capture, or the presence of frequent fusion and/or pseudofusion beats may compete with pacing and presage inadequate response to CRT as shown in a careful 12-lead Holter study (Kamath et al., 2009).

AECG monitoring may provide valuable advice regarding the type of implanted device in terms of single versus dual chamber. DDD pacing with minimal ventricular pacing algorithms is preferred in sick sinus syndrome. Detection of frequent, even asymptomatic, episodes of atrial arrhythmias and/or bradyarrhythmias in patients referred for an ICD implantation suggests that a dual chamber device should be preferred as this subgroup may require permanent pacing when antiarrhythmic drugs are administered during follow-up, or for tracking of tachyarrhythmia burden.

##### 7.4.2. Evaluation during follow-up

Advances in technology and clinical experience acquired over the past decades indicate that routine ECG monitoring after implantation is not necessary. Myopotential inhibition, cross talk, and pacemaker-mediated tachycardia, which constitute the major abnormalities in Holter recordings performed in pacemaker patients, are infrequently encountered, and may be detected and notified by remote monitoring, if and when they occur. However, AECG may be useful to correlate symptoms suggestive of arrhythmias or device malfunctioning. For example, AECG may also be helpful in patients with devices to assess upper rate pacemaker behavior with exercise, that is Wenckebach or 2:1 AV block, and the device could be reprogrammed accordingly.

AECG monitoring can be performed in patients with symptoms suggestive of device malfunctioning such as intermittent loss of capture or sensing abnormalities that may lead to clinically significant pauses or tachyarrhythmias in patients in whom routine interrogation does not reveal the reason for corresponding clinical symptoms. Notably, other causes of syncopal episodes are frequently observed in patients with pacemakers. In one report, only 4.9% of patients were found to have pacemaker dysfunction as a cause of syncope (DeCicco et al., 2014; Ofman et al., 2013).

Evaluation of atrial and ventricular arrhythmia by device software and retrieved diagnostics may not always be complete (Kumor et al., 2010). Atrial arrhythmias may be characterized and quantified by AECG to guide proper treatment. Patients in whom arrhythmia counters show frequent PVCs may be treated with ablation procedure, which may be directed by a 12-lead AECG to evaluate exact morphology of PVCs and/or VT episodes. Furthermore, slow VT episodes below detection threshold can only be assessed externally. Even though the results of randomized clinical trials have provided the optimal programming of primary prevention ICD devices (Moss et al., 2012; Wilkoff et al., 2016), AECG monitoring and exercise testing may be useful in individual optimization of ICD settings in some difficult cases.

Benefit from CRT depends mostly on the effectiveness of biventricular pacing and programming should assure the maximum (>98%) of biventricular pacing (Wilkoff et al., 2016). According to the 2012 EHRA/HRS expert consensus on CRT (Daubert & Saxon, 2012), long-term AECG monitoring may be recommended to document ventricular or atrial arrhythmia that might not have been detected by a device or for reassurance of proper arrhythmia classification. AECG should be recommended to evaluate the presence of pacing fusion and pseudofusion beats. The presence of fusion and pseudofusion complexes may lead to overestimation of biventricular pacing by a CRT device (Kamath et al., 2009; Pysno-Prokopowicz et al., 2016). Kamath et al. (2009) documented that in a small sample of CRT patients with AF and over 90% biventricular pacing as shown by a device interrogation, analysis of 12-lead Holter monitoring revealed high prevalence (53%) of patients with fusion and pseudofusion beats and lesser CRT response. Therefore, such an



evaluation should be recommended especially in nonresponders or in those who initially responded to CRT and then deteriorated during follow-up.

As the number and chronicity of implantable devices increase, the number of patients undergoing explants for device problems and/or infections is increasing. The need for reimplantation has to be established even before explantation, and therefore, monitoring of symptoms and ECG with a device programmed at a pacing rate below the patient's intrinsic rate is recommended. Both European and American guidelines underline that after device removal, careful reassessment of indications for reimplantation should be performed on an individual basis to determine risk–benefit ratios (Habib et al., 2009; Wilkoff et al., 2009).

## 8. Section 6: Hospital-Based Cardiac Telemetry and Continuous Rhythm Monitoring

Hospital-based cardiac telemetry and continuous rhythm monitoring are important hospital resources for the detection and treatment of cardiac arrhythmias. Though utilized worldwide, there is a surprisingly dearth of evidence for their application regarding selection of at-risk candidates and alarm management, but recent recognition of harms associated with alarm fatigue.

### 8.1. Technical aspects

Hardwired continuous cardiac rhythm monitoring systems involve connections to monitoring equipment by cable using either digital or analog signals for data transfer. These are utilized within intensive care units with immobilized critically ill patients. Cardiac telemetry refers to remote monitoring with wireless data transfers using a radiofrequency signal, typically applied on medical or surgical hospital wards to allow patient ambulation. Hospital-based monitoring most commonly involve three, five, or six leads, and less commonly 12 leads. Fewer leads simplify connections and nursing workflow, and add less bulk, but attenuate ability for myocardial ischemia detection with continuous ST-segment monitoring (Drew & Krucoff, 1999).

Competency is required in both the afferent and efferent communication limbs of continuous cardiac rhythm monitoring. Attention to skin preparation, electrode placement, and equipment connections represents a critical first step. Incorrect electrode placement was found in 26% in one study, but improved with educational interventions (Pettersen et al., 2014) with immediate direct impact on signal quality of monitoring (reducing noise artifact). Arrhythmia recognition requires both dutiful attention to the clinical alarms and also sufficient knowledge to delineate true arrhythmia events from noise artifact. False positives may lead to inappropriate medical interventions (Knight et al., 1999). Responsibility of arrhythmia recognition and notification/escalation is not standardized and varies among hospitals from nursing, to monitoring technicians and even nonclinical personnel in some instances. Efferent communication includes rhythm-specific

treatment responses by the primary clinical service, designated rapid response or code teams.

### 8.2. Alarm fatigue

Nominal alarm default settings are designed to be highly sensitive so as to not miss a clinically important event, but can also demonstrate poor specificity. Alarm fatigue is defined as desensitization from a high alarm volume with a low yield of clinically relevant findings and has potentially serious adverse clinical consequences (Sendelbach & Funk, 2013). True events may be missed when a large volume of false alarms systematically desensitizes responders. Deliberate but dangerous reactions include rendering clinical alarms inaudible, inappropriate use of alarm suspension features and adjustments of alarm parameters to indiscriminately silence alarms. The underlying problem in both scenarios is that between 72% and 99% of hospital alarms have no immediate clinical relevance (Atzema et al., 2006; Chambrin et al., 1999; Lawless, 1994; Siebig et al., 2010; Tsien & Fackler, 1997). Telemetry findings can be low yield and altered management in only 7% of cases in one study evaluating over 2,000 non-ICU patients (Estrada et al., 1995). Conversely, serious adverse events including death have resulted from alarm fatigue, and these are likely heavily under-reported (Pennsylvania Patient Safety Authority, 2008). In recognition, a 2014 national patient safety goal was issued by the Joint Commission requiring hospitals to establish effective alarm management policies by 2016 (The Joint Commission, 2014).

Addressing alarm fatigue may improve clinical outcomes. Simply improving skin preparation with fine sandpaper and daily electrode replacement reduced alarms by 46% (Clochesy et al., 1991; Cvach et al., 2012; Pettersen et al., 2014). Empiric adjustments of the default heart rate settings (upper limit 130–135 bpm and lower limit of 40–45 bpm) safely reduced clinical alarms in a general medical surgical ward (Burgess, 2009).

### 8.3. Standardized cardiac telemetry

Patient selection may be important. Monitoring low-risk patients who are unlikely to experience cardiac arrhythmias may yield a disproportionate ratio of false alarms including noise artifact and ECG lead failures. For example, arrhythmia yield was only 1.5% in one study of “low-risk” hospitalized patients admitted with chest pain and normal or nonspecific ECG findings (Hollander et al., 1997). The AHA practice guidelines in 2004 (Drew et al., 2004) omitted many commonly applied telemetry indications including stroke evaluation, hypoxemic respiratory disorders, proarrhythmic acid/base disorders, and exposures to pro-arrhythmic drugs (dofetilide, sotalol) or illicit substances (cocaine, amphetamines, alcohol intoxication) (Henriques-Forsythe et al., 2009). In one discouraging report of nearly 9,000 patients evaluated longitudinally, 20% of non-ICU cardiac arrests occurred in unmonitored patients (Schull & Redelmeier, 2000). It is unknown whether standardized indications can



result in a safe decrease in clinical alarms by pruning back a low-risk patient population. Importantly, cardiac event rates stratified by telemetry indication have not yet been reported, leaving institutions to wonder about the relative yield within each category. Future research is needed to provide event rates stratified by telemetry indication and outcomes associated with standardization.

#### 8.4. Centralized monitoring

Dedicating “watchers” for continuous rhythm monitoring has been previously associated with an improvement in the fidelity of true rhythm recognition events in prior studies, including reduction in sustained ventricular tachycardia events—presumably owing to earlier interventions for non-sustained events (Cantillon et al., 2016; Funk et al., 1997; Stukshis et al., 1997). However, the feasibility of continuous human monitoring of multiple screens is questionable and costly, pulling nurses away from direct patient care and education (Drew et al., 2004). Automated electronic alarms hold promise; however, heavy reliance on these has generated alarm fatigue.

An innovative solution pioneered by the Cleveland Clinic was to create a dedicated off-site monitoring facility (Central Monitoring Unit) to provide continuous 24/7 monitoring for its main campus and key regional hospitals. Advantages include less distraction from normal hospital activity, centralization of staffing and monitoring resources, and access to and standardization of monitoring practice across multiple hospitals. In this model, one monitoring technician provides surveillance of up to 48 patients continuously, inclusive of cardiac as well pulse oximetry, respiratory rate, blood pressure, and ventilator alarms for step-down units, as well as intracranial pressure monitoring for neurological step-down units in conjunction with the patient’s electronic medical record. Lead technicians (i.e., watchers for the watchers) are available to aid in real-time complex arrhythmia interpretation and direct further management. Communication with nursing staff via direct mobile phone or use of a Crisis Phone for emergencies prevents delays in notification of an alarm or change, with direct communication with rapid response teams when needed. Monitoring technician educational backgrounds commonly include cardiac arrhythmia recognition training as a Certified Cardiographic Technician or Certified Rhythm Analysis Technician. While promising, central monitoring outcomes and feasibility have not yet been published.

Telemonitoring has potential advantages in ICU/urgent care settings for rapid responses for managing acutely decompensated patients. This can reduce frequency of unnecessary transfers and thus decrease hospital cost. Immediate response to emergencies can be facilitated, for example, when a physician is not at the bedside. A single click of a button will connect the nurse to the doctor. There is a lower mortality and morbidity with a decreased length of stay in hospitals that have adopted the so-called E-ICU. There are two types of E-ICU systems: centralized and decentralized. The former consists of a central hub of intensivist and

well-trained critical care nurses connected to a two-way audio and video capable of instructing the bedside nurse. The decentralized version is a more personal way of being connected to the remote computers via an outside Internet connection. For example, a patient in circulatory shock can receive immediate interpretation of bedside telemetry and echocardiogram. E-ICU may provide supervision for resident physicians during procedures. Overall, E-ICU has advantages for rural hospitals, decreases transfer to tertiary care hospitals, permits adherence to best critical care practices, and improves patient outcomes.

### 9. Section 7: Telemetered Cardiac Rehabilitation

Telerehabilitation is a technique by which skilled rehabilitation services can be delivered in the home and community-based setting, potentially increasing accessibility and adherence to rehabilitation processes.

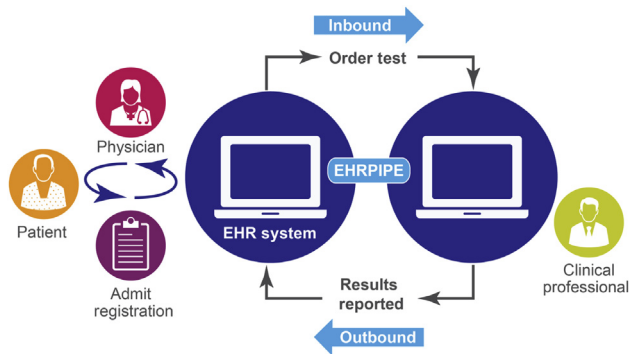
Home-based cardiac rehabilitation programs were introduced in the early 1980s using ECG transtelephonic monitoring and were found to be efficacious and safe (Fletcher et al., 1984). Transtelephonic exercise monitoring was as efficacious as hospital-based standard rehabilitation programs in improving functional capacity (Shaw et al., 1998) and provided clinically significant improvements in risk factors and exercise capacity at the end of 4 weeks following cardiac surgery (Zutz et al., 2007). The virtual cardiac rehabilitation program included on-line intake forms, scheduled one-to-one chat sessions, and weekly education sessions. Thus, integrated telemedicine services by providing surveillance, education, psychological support, and interactive motivational tools have the potential to monitor cardiovascular risk factors and to significantly affect morbidity and mortality on a large scale (Piotrowicz & Piotrowicz, 2013).

Home-based telemonitored cardiac rehabilitation is also feasible and safe in patients suffering from heart failure (Kouidi et al., 2006; Piotrowicz et al., 2010; Smart et al., 2005). Following an 8-week training program, significant improvements were observed in NYHA class, peak oxygen consumption, 6-minute walking test distance, and quality of life scores. In addition, no worrying signs or symptoms were observed during training, nor it was necessary to stop rehabilitation urgently in any patient. However, the evidence for the value of telemedicine in managing chronic heart failure is not yet definitive (Wootton, 2012). While a Cochrane Collaboration review and meta-analysis reported that telemedicine (structured telephone support or telemonitoring) significantly reduced heart failure-related hospitalizations (Inglis et al., 2011), these results were not confirmed by two subsequent large randomized controlled trials (Chaudhry et al., 2010; Koehler et al., 2011).

### 10. Section 8: Data Management, Reimbursement, and Legal Considerations

#### 10.1. Integration with the electronic health record

There is increasing interest in integrating reports emanating from AECG monitoring systems with the patient’s electronic



**Figure 4** Electronic Health Record (EHR) integration workflow. The EHR contains information about the patient, which is captured at registration. In this example, the practice is using a third-party provider for ambulatory electrocardiographic monitoring. The EHRPipe is an interface of interrogation engine that serves as a bidirectional bridge between this provider and the EHR system (courtesy of ScottCare, Inc.).

health record (EHR). This requires an interface (preferentially a bidirectional interface) based upon the Health Level Seven (HL7) information exchange standard, which provides the framework for the exchange, integration, sharing, and retrieval of electronic health information (Figure 4). Most commonly, a PDF is created to “display” the data acquired by an AECG system for an event or over a prespecified monitoring period (e.g., event, daily, weekly, and/or end of monitoring summary report). The PDF file can be manually attached to a patient’s EHR; alternatively, an automatic interface can directly integrate the PDF file into the EHR. In this scenario, the clinician receives a message within the EHR that a test result is available for review. The PDF can then be accessed either directly from within the message or through a URL link incorporated within the message.

## 10.2. Reimbursement

In the USA, individual insurance carriers define the frequency of monitoring as well as the indications for monitoring. The Centers for Medicare and Medicaid Services (CMS) has a national coverage determination (NCD 20.15) for ECG services; this document was implemented on December 10, 2004 (<http://www.cms.gov/medicare-coverage-database/details/nccdetails.aspx?NCDId=179&ncover=1&DocID=20.15&searchType=Advanced&bc=IAA AABAABAAA&>). CMS defines AECG services as those “rendered in an outpatient setting over a specified period of time, generally while a patient is engaged in daily activities, including sleep.” AECG devices are intended to provide the physician with documented episodes of arrhythmia, which may not be detected using a standard 12-lead EKG. Table 4 summarizes the 2014 national average reimbursement in the United States for the various types of AECG monitoring devices. Since 2011, there has been a significant decline in reimbursement for all AECG services.

In the European Union (EU), there is considerable disparity among member countries. In Northern European

countries, health coverage is usually more robust. In Southern European healthcare systems, there are co-payments, but many benefits are not covered by the public system, which leads to development of private medical systems funded via direct payments or the purchase of additional insurance. Examples of reimbursement models in Europe are presented in Table 5.

## 10.3. Legal considerations

Currently available autotriggered loop recorders and ambulatory cardiovascular telemetry systems have the capability of wireless data transfer to an independent diagnostic testing facility via a cellular network. As a result, practices must ensure that they have a mechanism in place to handle incoming data on a 24/7/365 basis to ensure that potentially life-threatening arrhythmias are rapidly identified and treated. As patients are monitored for up to a month at a time, a significant amount of ECG data accumulates for physician review. Vendors have established nominal physician notification criteria; these often overestimate the clinical significance of captured arrhythmias and generate needless calls to physicians and/or Emergency Medical Services. Therefore, it is highly recommended that practices develop specific notification criteria to prevent being inundated by after hour calls related to nonurgent arrhythmic detections. Table 6 outlines an example of notification criteria that have been developed to minimize unnecessary calls to patients and after hour calls to physicians yet ensure patient safety in the event a life-threatening arrhythmia is detected. It is hoped that these types of robust criteria can minimize the legal liability to a practice by minimizing the likelihood that they will fail to respond to clinically important AECG information.

Heterogeneity among European countries makes it difficult to generalize legal ramifications. In some, there are already available legal solutions but in most these are under development. The Green Paper on mobile health (mHealth) announced in the eHealth Action Plan 2012–2020 may produce a common platform (European Commission, 2014). Its objective is to launch a broad stakeholder consultation on existing barriers and issues related to mHealth deployment and help identify the right way forward to unlock mHealth potential to maintain and improve patients’ health and well-being and encourage their empowerment.

## 11. Section 9: Emerging Technologies

### 11.1. Use of smartphone technology for AECG recording

Smartphone-based AECG is a potentially disruptive technology, blurring the traditional models of prescribed device and physician interpretation, and also definitions of patient versus consumer. Already, over 50 million Americans wear a connected device to track activity and that number is expected to grow to over 160 million with the recent introduction of the “smart” watches. Almost all activity sensors include heart rate and some chest-worn body sensors

**Table 4** 2014 CPT codes for AECG monitoring, Medicare fee schedule, and approved indications

Technology	CPT	Description	Reimbursement <sup>a</sup>	Indications
Holter monitors (up to 48 hr; up to twice every 6 months)	93224	External electrocardiographic recording up to 48 hr by continuous rhythm recording and storage; includes recording, scanning analysis with report, physician review, and interpretation (global)	\$91.71 (23%)	<ul style="list-style-type: none"> <li>• Detection of transient episodes of cardiac dysrhythmias, permitting correlation of these episodes with current cardiovascular symptomatology;</li> <li>• Detection of abnormalities of cardiac rhythm or electrocardiographic morphology associated with symptoms of syncope, near syncope, palpitations, chest pain suggestive of cardiac ischemia, shortness of breath on exertion, and recurrent congestive heart failure where arrhythmia is the suspected cause;</li> <li>• Evaluation of arrhythmias in the patient with documented coronary artery disease, including the assessment of the immediate postmyocardial infarction patient;</li> <li>• Detection of arrhythmias (such as atrial fibrillation) in patients with acute stroke or TIAs;</li> <li>• Assessment of patients with implanted pacemakers or defibrillators, but only when patients have symptoms suggestive of arrhythmia not revealed by the standard ECG or defibrillator event recordings, or by analysis of the pacemaker or defibrillator devices;</li> <li>• Monitoring the effectiveness of antiarrhythmic therapy</li> </ul>
	93225	... recording (includes connection, recording, and disconnection)	\$26.87 (24%)	
	93226	... scanning analysis with report	\$37.97 (27%)	
	93227	... physician review and interpretation	\$26.87 (12%)	
Event monitors (up to 30 days; no defined frequency limit)	93268	External patient and, when performed, autoactivated electrocardiographic rhythm-derived event recording with symptom-related memory loop with remote download capability up to 30 days, 24-hr attended monitoring; transmission of data and physician review and interpretation of the data (global)	\$205.26 (34%)	<ul style="list-style-type: none"> <li>• No defined guidelines</li> </ul>
	93270	... recording (includes connection, recording, and disconnection)	\$9.31 (52%)	
	93271	... transmission download and analysis	\$170.52 (36%)	
	93272	... physician review and interpretation	\$25.43 (12%)	
Mobile cardiovascular telemetry (up to 30 days; once every 6 months)	92229	Wearable mobile cardiovascular telemetry with electrocardiographic recording, concurrent computerized real-time data analysis, and >24-hr 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 physician prescribed transmission of daily and emergent data reports	\$669.17 (22%)	<ul style="list-style-type: none"> <li>• Detection, characterization, and documentation of symptomatic transient arrhythmias, when the frequency of the symptoms is limited and use of a 24-hr ambulatory ECG is unlikely to capture and document the arrhythmia;</li> <li>• Regulation of antiarrhythmic drug dosage, when needed to assess efficacy of treatment;</li> <li>• To ensure the absence of atrial fibrillation prior to the discontinuation of anticoagulation therapy;</li> <li>• To monitor patients who have had surgical or ablative procedures for arrhythmias</li> </ul>

(Continued)



**Table 4** (Continued)

Technology	CPT	Description	Reimbursement <sup>a</sup>	Indications
	93228	Wearable mobile cardiovascular telemetry with electrocardiographic recording, concurrent computerized real-time data analysis and >24 hr 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; physician review and interpretation with report	\$26.51 (08%)	

AECG, ambulatory electrocardiography; CPT, current procedural terminology.

<sup>a</sup>Numbers in parenthesis reflect decline in reimbursement since 2011.

Adapted with permission from [Mittal et al. \(2011\)](#).

include ECG. The ability to record an ECG is increasingly seen as an important requirement in the biometric monitoring of elite athletes.

For heart rhythm monitoring, some technologies partner sensors into smartphone casing to record an ECG tracing which can be interpreted by the patient or transmitted to a physician. These therefore function as patient-activated intermittent nonlooping AECGs. For AF, these have been applied for screening and for monitoring response to therapy (at time of writing, one such device has received FDA clearance for this purpose). They may be particularly useful in pediatric populations. For elite athletic screening, such single-lead AECG recordings have been shown to be equivalent to 12-lead ECG screening for detection of rate and rhythm

disturbances and for assessment of conduction intervals ([Haberman et al. 2015](#); [Lowres et al., 2014](#); [Nguyen et al., 2015](#); [Tarakji et al., 2015](#)). Newer implantable cardiac implantable electronic devices (e.g., ICDs) may relay their data directly via smartphone apps. This may facilitate remote monitoring of these devices that has been recommended as standard of follow-up care. This removes the current transceiver that has been a traditional impediment to remote monitoring implementation due to phone incompatibility, lack of portability, and cost.

Given the almost ubiquitous presence of smartphones, downloadable healthcare apps have the potential to be widely used and for unrestricted periods of time, with ability to transmit data over cellular networks or WiFi, that is, breaking the

**Table 5** Reimbursement models in Europe

Germany	For outpatients, the statutory insurances pay a flat fee/patient/quarter of the year, currently approximately 64 EUR, as long as at least an echo is performed in addition to physical examination and ECG, regardless of additional ambulatory tests or treatments
Italy	The range of reimbursement for Holter ECG monitoring is 63.02–72.95 EUR
Hungary	The National Health Service of Hungary pays the reimbursement to the Institute, which performs the ECG The categories are as follows: 1. Resting 12-lead ECG—308 points (1.54 EUR) 2. 24-hr ambulatory Holter ECG monitoring—3,120 points (15.6 EUR) 3. Ambulatory transtelephonic ECG monitoring a. Acute cases or postoperative monitoring—3,000 points (15 EUR) b. Elective monitoring—1,502 points (7.51 EUR)
Norway	Cardiologists who have a contract with the regional healthcare company can also obtain a contract with the NHS. This contract makes it possible to obtain reimbursements for each consultation and for procedures performed according to a national scheme (“Normaltariffen”), which is negotiated yearly. The AECG is reimbursed by NHS with the sum of approximately 41 Euros
France	For most services, patients make a direct payment and are reimbursed afterward, with the exception of laboratories, pharmacies, hospitals, and outpatient clinics. Patients do not need a referral from their general practitioner to consult a specialist and have free choice of doctor Complementary Health Insurance is at the level of 100%
Poland	The National Health Service pays the reimbursement to the Institute, which performs the ECG The categories are as follows: 1. Cardiologic consultation—6 points (12.72 EUR) 2. Cardiologic consultation with echocardiography—10 points (21.2 EUR) 3. Cardiologic consultation with AECG or ABPM—13 points (27.56 EUR)
Greece	The cost of Holter monitoring in the outpatient clinic is 6 and 40 EUR with and without the public healthcare insurance cover, respectively For patients admitted at the Emergency Department who require further investigation, there is no cost for Holter monitoring during hospitalization

**Table 6** Physician notification criteria for ambulatory cardiovascular telemetry

## Emergency criteria:

1. The vendor will always call the patient for ascertainment of symptoms and to obtain a follow-up recording (regardless of time of day and whether the recording with automatically or patient triggered)
2. This is the only situation that the vendor will place a call to the patient
3. If the patient presents with an ECG meeting emergency notification criteria and the physician cannot be reached, the vendor will activate emergency medical services (EMS)
4. ECG recordings that meet criteria for emergency notification may include the following:
  - a. Sustained, regular, wide complex tachycardia at  $\geq 160$  bpm
  - b. Prolonged asystole

## 24-hr notification criteria:

1. The vendor will notify the physician's office, or the on-call physician, when a patient transmits a recording that meets 24-hr notification criteria
2. ECG recordings that meet criteria for 24-hr notification include the following:
  - Sustained, regular, wide complex tachycardia at  $< 160$  bpm
  - Sustained, regular, supraventricular tachycardia  $\geq 150$  bpm if reported by the patient as being associated with symptoms (manually triggered), otherwise office-hour notification
  - Pause  $\geq 4$ -s if reported by the patient as being associated with symptoms (manually triggered), otherwise office-hour notification
  - Type II second-degree or third-degree atrioventricular (AV) block, whether or not associated with symptoms
  - All reported syncopal episodes
  - All observed pacemaker malfunction episodes
  - All reported or observed ICD discharges
  - Sustained bradycardia (heart rate  $\leq 30$  bpm) if reported by the patient as being associated with symptoms (manually triggered), otherwise office-hour notification

## Office hour (9 a.m.–5 p.m. 7 days a week) notification criteria:

1. The vendor will notify the physician's office the same day if recorded between the hours of 9 a.m. and 5 p.m., or the following day if obtained after 5 pm
2. ECG recordings that meet criteria for office hour notification include the following:
  - Atrial fibrillation and/or flutter
    - i. New onset (as documented by the vendor) with a duration  $\geq 30$  s
    - ii. Ventricular response  $\geq 150$  bpm for  $\geq 60$  s
  - Wide complex tachycardia  $\geq 120$  bpm lasting between 3 beats and 30 s and not meeting EMS or 24-hr notification criteria
  - Type I second-degree AV block

traditional model of AECG monitoring. AECG may be coupled with other sensors via Bluetooth, for example, to capture blood pressure or oxygen saturation, and for monitoring comorbidities. Together with this versatility comes a set of challenges regarding validation of recordings, increased onus on the physician for interpretation of large volumes of transmissions (without established reimbursement), data storage, and security. However, there are potential benefits of involving patients in their healthcare process, increasing their engagement and compliance with medical therapies and follow-up management.

### 11.2. Wearable cardioverter defibrillator

The wearable cardioverter defibrillator (WCD) is playing a more prominent role in the management of patients as a bridge or temporary substitute for ICDs. Current WCDs have embedded remote monitoring capability. This online remote patient management system allows clinicians to monitor data downloaded from a patient's WCD. The patient downloads through the base station/battery charger. The device connects to it with Bluetooth and is then encrypted and sent wirelessly via cellular networks to the secure network website where it is archived for review. The patient receives a confirmation on the screen once a download is

completed. Information on the network can be accessed anytime and the dashboard page allows clinicians to triage multiple patients based on customized settings. Examples of events that can trigger alerts include the following: shock treatments, patient-initiated ECG recordings, and detected arrhythmia where no treatment was given (e.g., short runs of VT). Importantly, bradycardic events and AF can also be discovered. Clinicians can elect to be notified when a patient triggers an alert. ECGs may be captured by manual recording or automatically delivered from an event (i.e., SVT, NSVT, asystole). A 2-channel ECG can be viewed online. Some of these recorded events may support ICD implantation. Apart from continuous arrhythmia monitoring, the remote monitoring system can chart compliance (wear time on a daily basis), patient activity, and orthopnea, potentially important for heart failure management (Kutyifa et al., 2015).

## 12. Section 10: Future Needs

The rapid pace of evolution of AECG devices, along with evolving changes in indications, duration, and intensity of monitoring, have resulted in several key knowledge gaps and unmet needs.

### 12.1. Education and regulatory oversight of consumer-grade wearables

Mobile smartphone devices have enabled a new class of consumer-grade wearable monitoring devices, colloquially referred to as “wearables.” With few exceptions, almost all wearable devices have entered the consumer or retail space, generally with no medical regulatory oversight or approval. Although most of these devices are designed to measure heart or pulse rate rather than rhythm, the sensitivity and specificity for heart rate, let alone, arrhythmia detection, are poorly defined, and there is limited information on the agreement of these devices with medical-grade lead-based ECG monitors (Parak & Korhonen, 2014). Still, patients may bring these data to their clinician, and clinicians may even rely or recommend the use of these tools for heart rate detection as means for rhythm surveillance. A regulatory framework of these consumer-grade devices used in a clinical context, coupled with clinician education about risks and limitations, is necessary to avoid inappropriate reliance on consumer-grade wearables and to ensure that medically approved AECG monitoring is used when appropriate.

### 12.2. Decision support for data interpretation and precision medicine

As the wear time of AECG devices increases due to technological enhancements, the yield of detected arrhythmias is expected to increase proportionally. For example, patients wearing a patch-based ECG monitor for up to 14 days, the yield of AF beyond 48 hr (the traditional Holter monitor duration) is substantial (Barrett et al., 2014; Turakhia et al., 2015). Finally, devices vary in their definitions of arrhythmias, including AF, and sustained and NSVT. As newer devices detect shorter and shorter arrhythmia episodes over longer monitoring periods, the clinical significance of these episodes may be uncertain and clinicians may struggle with decision making for treatments such as anticoagulation. Improved decision models are needed to help guide clinicians. Large datasets derived from population of patients with noninvasive or implantable monitors, linked to clinical events from EHR, may be useful to provide more robust, individually tailored estimates of long-term and short-term risk of events and potential benefits and harms of therapies (Inglis et al., 2011). Novel analytical techniques, such as machine learning, may help to identify patterns of risk not readily apparent simply based on arrhythmia burden or standard multivariate regression techniques, particularly if framed using a Bayesian rather than frequentist statistical methodology. Similar techniques may also be useful to help clinicians more accurately risk stratify and triage various conditions based on inpatient telemetry, such as syncope.

### 12.3. Data management and integration in EMR or adjacent EMR platforms

Most of the current monitoring solutions provide the data and interpretation to clinicians in the form of a report rather than

structured or raw data. These reports, while clinically useful, are generally freestanding digital documents that are scanned or imported into the EMR as image or media. These data generally cannot be overlaid with other structured EMR data, such as vital signs, laboratory data, or medications. As a result, the synthesis of the AECG data with other EMR data must be actively performed by the clinical service or practice, leaving great potential for human error. As a result, methods to import structured ambulatory ECG data into the EMR should be a high priority. Solutions exist for implantable devices (Medtronic, Mounds View, MN; Geneva Health Care, National City, CA), and there is a pressing need to develop or extend similar technology to the noninvasive monitoring space, particularly as indefinite noninvasive continuous monitoring is likely to emerge.

## 13. Section 11: Conclusions and Recommendations

Accurate and timely diagnosis of arrhythmias is crucial to direct therapies that can make an important impact on patient care and healthcare utilization. The rhythm information derived from the large spectrum of AECG recording systems can often lead to appropriate and patient-specific medical and interventional management. The details in this document provide background and framework from which to apply AECG techniques in clinical practice, as well as clinical research. AECG is very commonly used in a variety of clinical contexts, for a variety of clinical purposes, and involves a variety of clinical personnel. There needs to be an understanding of the strengths and limitations of the AECG per se, and also of the specifically implemented technique, in order to optimize the impact that these results have on patient care. The committee used all published studies and relevant unpublished information, but was hampered by the relative absence of controlled trials or those that correlated detected arrhythmia with long-term outcome. The Recommendations<sup>2</sup> that follow represent the consensus of the writing committee.

<sup>2</sup>The consensus recommendations in this document use the commonly used class I, IIa, IIb, and III classifications and the corresponding language according to the most recent statement of the ACC. Class I is a strong recommendation, denoting benefit greatly exceeding risk. Class IIa is a somewhat weaker recommendation, denoting benefit probably exceeding risk, and class IIb denotes benefit equivalent or possibly exceeding risk. Class III is a recommendation against a specific treatment, because either there is no net benefit (benefit is equal to the risk) or there is net harm (risk outweighs the benefit). Level A denotes the highest level of evidence, usually from multiple clinical trials with or without registries. Level B evidence is of a moderate level, either from randomized trials (B-R) or well-executed nonrandomized trials (B-NR). Level C evidence is from weaker studies with significant limitations (e.g., randomized or nonrandomized observations or registry; studies with limitations of design or execution; meta-analyses of such studies; physiological or mechanistic studies in human subjects), and level E is simply a consensus of experts opinion based on clinical experience when evidence is insufficient, vague, or conflicting.



	Class of recommendation	Level of evidence
<b>A. Selection of AECG</b>		
24- to 48-hr Holter monitoring is recommended when frequent symptomatic events are anticipated to occur within the recording window	Class I	LOE: B-NR
Extended AECG monitoring (e.g., 15–30 days) is recommended when symptomatic event frequency is less than daily, or uncertain	Class I	LOE: B-R
12-lead Holter monitoring is recommended for qualitative analysis of QRS morphology (e.g., PVC, CRT), ST-segment patterns (Brugada syndrome, ischemia), and QT dynamics	Class I	LOE: C
Continuous monitoring (1–14 days) is indicated to facilitate quantification and trending of arrhythmia burden and patterns (e.g., ventricular ectopy, sinus tachycardia)	Class I	LOE: B-NR
<b>B. Specific conditions</b>		
A strategy of AECG monitoring is recommended for unexplained syncope, when a tachycardic or bradycardic etiology is suspected, or needs to be excluded	Class I	LOE: B-R
A strategy of AECG monitoring is recommended for unexplained palpitations	Class I	LOE: B-R
A strategy of AECG monitoring is indicated for evaluation of accessory pathway conduction properties in patients with Wolf–Parkinson–White syndrome and for monitoring for runs of atrial fibrillation	Class I	LOE: B-NR
A strategy of AECG monitoring is useful for detection and quantification of atrial fibrillation and associated ventricular rates, triggering arrhythmias (atrial ectopics, SVT, atrial flutter, and bradycardia), and postconversion pauses	Class IIa	LOE: B-NR
A strategy of extended AECG monitoring is recommended in patients with cryptogenic stroke to detect undiagnosed AF	Class I	LOE: B-R
A strategy of AECG monitoring is recommended in newly diagnosed nonischemic cardiomyopathy, if arrhythmia-induced ventricular dysfunction is suspected	Class I	LOE: B-NR
<b>C. Risk assessment</b>		
A strategy of AECG monitoring is reasonable for assessing efficacy of arrhythmia suppression either pharmacologically or interventionally	Class IIa	LOE: B-NR

(Continued)

	Class of recommendation	Level of evidence
The utility of AECG monitoring to characterize prognosis and risk stratification in patients with nonischemic cardiomyopathy may be considered	Class IIb	LOE: B-NR
A strategy of 24- to 48-hr Holter recording is useful in patients with healed MI and borderline EF of 35%–40% to detect NSVT and determine need for further risk stratification with EPS and need for ICD	Class IIa	LOE: B-R
A strategy of 24- to 48-hr Holter recording may be considered after acute MI to detect NSVT to predict increased risk of SCD, particularly in patient with reduced EF	Class IIb	LOE: B-NR
A strategy of AECG monitoring is recommended for detection of NSVT in patients with HCM for SCD risk stratification	Class I	LOE: B-NR
A strategy of AECG monitoring is recommended for quantification of ventricular ectopy and detection of NSVT in ARVD/C for diagnosis and risk stratification	Class I	LOE: B-NR
A strategy of AECG monitoring is recommended for outpatient initiation of some antiarrhythmic drugs, to detecting pro-arrhythmic adverse drug responses	Class I	LOE: C
AECG can be useful in CIED patients when symptoms suggest device malfunction if device interrogation is not definitive	Class IIa	LOE: B-NR

## Supporting Information

Additional Supporting Information may be found online in the Supplemental Materials tab for this article.

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