Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: https://www.tandfonline.com/loi/icmo20

Cardiac arrhythmia detection outcomes among patients monitored with the Zio patch system: a systematic literature review

Mihran Yenikomshian, John Jarvis, Cody Patton, Christopher Yee, Richard Mortimer, Howard Birnbaum & Mark Topash

To cite this article: Mihran Yenikomshian, John Jarvis, Cody Patton, Christopher Yee, Richard Mortimer, Howard Birnbaum & Mark Topash (2019) Cardiac arrhythmia detection outcomes among patients monitored with the Zio patch system: a systematic literature review, Current Medical Research and Opinion, 35:10, 1659-1670, DOI: 10.1080/03007995.2019.1610370

To link to this article: https://doi.org/10.1080/03007995.2019.1610370

CURRENT MEDICAL RESEARCH AND OPINION
2019, VOL. 35, NO. 10, 1659–1670
https://doi.org/10.1080/03007995.2019.1610370
Article FT-0146.R1/1610370

Taylor & Francis
Taylor & Francis Group

REVIEW

Cardiac arrhythmia detection outcomes among patients monitored with the Zio patch system: a systematic literature review

Mihran Yenikomshian[a], John Jarvis[a], Cody Patton[b], Christopher Yee[a], Richard Mortimer[a], Howard Birnbaum[a] and Mark Topash[c]

[a]Analysis Group Inc., Boston, MA, USA; [b]Analysis Group Inc., Menlo Park, CA, USA; [c]iRhythm Technologies Inc., San Francisco, CA, USA

ABSTRACT

Objective: Cardiac arrhythmias can be serious and life threatening, and can impose a significant burden on healthcare systems. Recent technological advances in ambulatory electrocardiogram recorders have led to the development of unobtrusive wearable biosensors which allow physicians to study patients' continuous cardiac rhythm data collected over multiple weeks. The objective of this systematic literature review was to summarize evidence on the clinical effectiveness of the Zio[1] patch, a long-term, continuous, uninterrupted cardiac monitoring system.

Methods: Findings from searches of MEDLINE, Embase and the Cochrane Central Register of Controlled Trials, as well as grey literature, were screened by two reviewers to identify studies reporting cardiac arrhythmia detection outcomes among patients monitored with Zio for an intended duration $\geq$7 days.

Results: Twenty-three publications (22 unique studies) were identified. The unweighted mean wear time was 10.4 days (median ranging from 5 to 14 days). The rate of arrhythmia detection increased with monitoring durations >48 h and continued to increase beyond 7 days of monitoring. Across the 22 studies, unweighted mean detection rates for atrial fibrillation (AF; $n = 15$), supraventricular tachycardia or supraventricular ectopy ($n = 15$), and ventricular tachycardia ($n = 15$) were 12.2%, 45.5% and 17.3%, respectively. Unweighted mean detection rates for chronic/sustained AF ($n = 5$) and paroxysmal AF ($n = 5$) were 5.6% and 23.3%, respectively.

Conclusion: Findings from the review suggest that long-term, continuous, uninterrupted monitoring with Zio results in longer patient wear times and higher cardiac arrhythmia detection rates compared with outcomes reported in previous reviews of short-duration (24–48 h) cardiac rhythm recording studies.

ARTICLE HISTORY
Received 22 March 2019
Revised 17 April 2019
Accepted 18 April 2019

KEYWORDS
Arrhythmias; cardiac; atrial fibrillation; cardiac monitoring; long-term monitoring; continuous monitoring; uninterrupted monitoring

Introduction

Cardiac arrhythmias encompass any slow, fast, irregular or abnormal heart rhythms, and can result from a multitude of mechanisms and causes. While not all cardiac arrhythmias are symptomatic or have prognostic significance, some can be serious and life threatening and can lead to stroke and heart failure, including atrial fibrillation (AF), sustained ventricular tachycardia (VT), ventricular fibrillation, supraventricular tachycardia (SVT), sinus bradycardia/pauses and atrioventricular (AV) block[1]. Symptoms associated with arrhythmias can have a clinical burden on patients, affecting their lifestyle and daily activities[1,2]. In addition, arrhythmias impose a substantial burden on healthcare systems; the economic burden of the most common arrhythmia, AF, is estimated to be as high as $26 billion annually in the US[3,4].

The electrocardiogram (ECG) is a primary tool for diagnosing cardiac arrhythmias; however, the standard 12-lead ECG does not allow for patient mobility. Ambulatory ECG has been limited to wearable multi-lead Holter recorders and wearable event recorders, which can be difficult to use and can interfere with activities of daily living[5]. Infrequent or asymptomatic arrhythmia events can go undetected during recording or monitoring interruptions that occur during activities that require removal of the device, such as recharging the battery or showering if the device is not waterproof. Furthermore, new research is beginning to discuss and measure the importance, value and impact of arrhythmia burden, which is the time an individual is in arrhythmia over the time the individual is being monitored[6]. In recent years, technological advances in ECG recorders such as miniaturization and more efficient energy uses have facilitated the development of wearable biosensors designed to be unobtrusive and comfortable for patients and to enable longer-term cardiac rhythm recording when compared with Holter recorders[2]. These advanced technologies can allow for greater comfort, longer periods of ECG recording and higher

CONTACT Mihran Yenikomshian Mihran.Yenikomshian@analysisgroup.com 111 Huntington Ave, 14th Floor, Boston, MA 02199, USA
Supplemental data for this article is available online at 10.1080/03007995.2019.1610370.

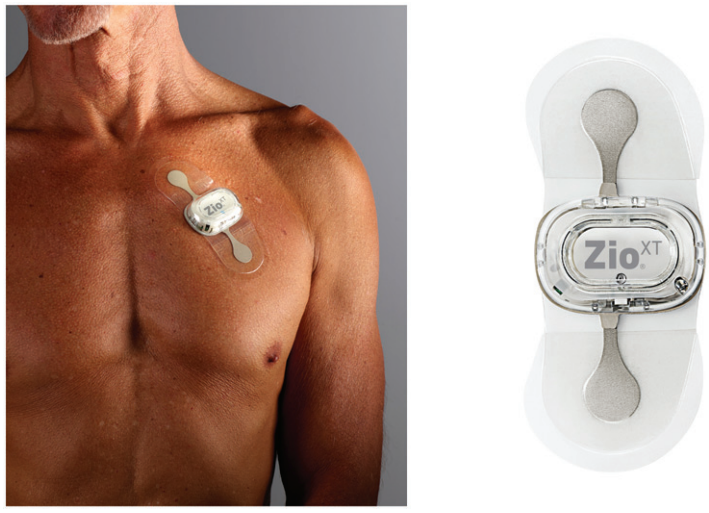

Figure 1. Placement of cardiac monitor patch. This cardiac arrhythmia recording system is a novel, single-lead, FDA-approved continuously recording ECG recorder indicated for use up to 14 days in asymptomatic patients or those who suffer from transient symptoms. (Images courtesy of iRhythm Technologies Inc., San Francisco, CA, USA).

detection rates than was previously possible with traditional Holter monitoring.

The Zio[1] cardiac arrhythmia recording system is a novel, single-lead, FDA-approved continuously recording ECG recorder indicated for use up to 14 days in asymptomatic patients or those who suffer from transient symptoms[7,8]. It is a single-use device that continuously records the electrical activity of the heart and that can be triggered by patients when they experience symptoms (see Figure 1)[9]. It is wireless and waterproof, allowing for uninterrupted recording during sleep, during light physical activity or when showering; overall, it offers improved patient comfort and adherence compared with Holter recording technology, which is the current standard of care[9]. Once patients have completed up to 14 days of recording, iRhythm's Zio ECG Utilization Service (ZEUS) processes and analyzes the ECG data, which is then reviewed by a certified cardiographic technician (CCT) before a detailed summary report is uploaded to a physician web-portal or into an electronic health record system and shared with patients' physicians[9]. While previous literature reviews of cardiac monitoring studies have compared arrhythmia detection among long-term monitoring (i.e. $\geq$7 days) and short-term monitoring (i.e. $\leq$72 h)[10] or separately evaluated outcomes by monitoring duration (i.e. $\leq$24 h, >24 h to $\leq$7 days, >7 days)[11], to the authors' knowledge no similar reviews have been conducted on the use of Zio specifically. Therefore, the objective of this systematic literature review was to gather and summarize the existing clinical evidence on diagnostic outcomes (e.g. cardiac arrhythmia detection rates) among patients whose cardiac rhythm was monitored with Zio for an intended long-term duration of $\geq$7 days.

Methods

Search strategy

A systematic literature search for recently published or released clinical data on the use of Zio among patients monitored for cardiac arrhythmias was conducted with methods guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines[12]. Databases searched included Embase, MEDLINE (including MEDLINE In-Process) and the Cochrane Central Register of Controlled Trials (all via OvidSP). Search terms related to Zio as well as long-term, continuous, uninterrupted, ambulatory recording of cardiac arrhythmias for the purpose of detecting, diagnosing or recording patients were applied (the full search strategy has been provided in Supplemental Appendix A). Electronic reviews of grey literature sources, including abstracts from several relevant conferences, and hand searches of referenced publications were also conducted. Searches were conducted in January 2019; no date restrictions were applied to database searches of published literature. Conference proceedings were restricted to the previous 2 years (2017 and 2018) in order to capture recent literature that may not have been published at the time of this review.

Study selection

Titles and abstracts of search results were screened by two independent reviewers. Studies evaluating patients monitored with Zio for intended durations of $\geq$7 days were included. No age restrictions were applied to screened patient populations. Studies were excluded if they did not include patients monitored with Zio and/or if they did not report relevant outcomes for cardiac arrhythmia detection rates. Only English-language records were included in the study selection. A complete list of inclusion and exclusion criteria is provided in Supplemental Appendix B. Studies meeting the inclusion criteria were subsequently assessed for inclusion based on full-text review. During both rounds of review, the two independent reviewers were required to agree on inclusion/exclusion as well as the reason for exclusion. Any disputes were resolved through discussion between reviewers or consultation with a third reviewer.

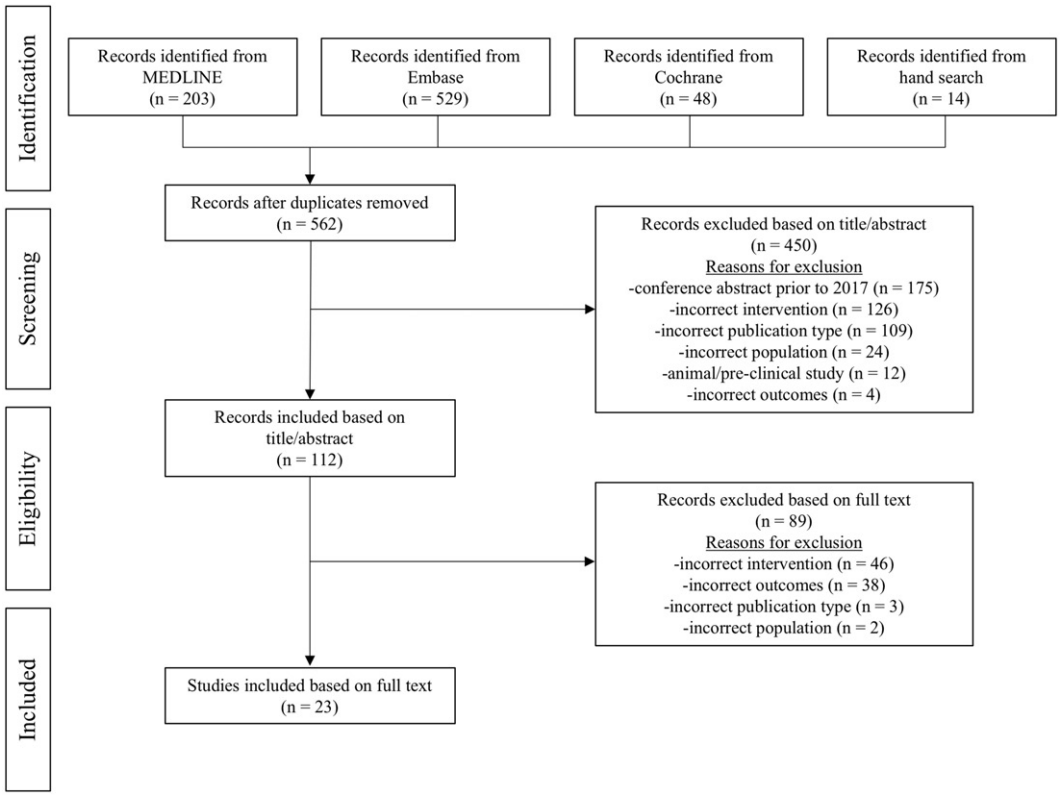

Figure 2. PRISMA flow diagram.

Data extraction

Full-text manuscripts or conference abstracts were obtained for each study meeting the inclusion criteria. Data from selected articles were extracted and verified for accuracy by two independent reviewers using a standardized extraction form, with any disagreements between the two reviewers adjudicated by consensus. Extracted data included study design and methodology, patient demographic/clinical characteristics, and relevant outcomes of interest.

Quality assessment

Published checklists were used to assess the quality and risk of bias of observational studies, retrospective database analyses and randomized controlled trials (RCTs)[13–15].

Data synthesis/statistical analysis

Data were synthesized descriptively by study authors across all included review studies. Microsoft Excel was used to generate a scatterplot figure. Numeric values were extracted directly from the cited studies if they were provided, or extracted from plots using a software tool (WebPlotDigitizer). A boxplot was generated in R (R version 3.4.2, RStudio version 1.1.392) using the ggplot2 library (version 2.2.1). Weighted mean detection rate outcomes were weighted by sample size; for a given arrhythmia, the detection rate reported by each study was multiplied by the study sample size, and the sum of these products was divided by the sum of the sample sizes of the studies. Due to the limited number of studies and heterogeneous patient populations, a meta-analysis was not conducted in association with this systematic review.

Results

Study characteristics

Our initial search strategy identified 780 publications, with an additional 14 publications identified from hand search. After removing duplicate publications, 562 records remained for title/abstract screening based on study eligibility criteria (eligibility criteria can be found in Supplemental Appendix B). Of these 562 studies, 112 publications were identified for detailed full-text review, 89 of which did not meet the systematic literature review inclusion criteria and were excluded. The remaining 23 publications (22 unique studies; 17 manuscripts and 6 conference abstracts) that met the eligibility criteria were included in the systematic literature review and relevant outcomes were extracted (refer to Figure 2 for the PRISMA study flow diagram).

Characteristics of included studies are reported in Table 1. Study designs varied between the 22 included studies. One study was an RCT that compared Zio with 24 h Holter recording[16]. Among the five included multi-arm prospective cohort studies, three compared Zio with 24 or 48 h Holter recording[17–19], one compared it with CAM by BardyDx[20] and one

compared it with 72 h Holter recording and E-patch by BioTelemetry[21]. Seven studies were single-arm prospective cohort studies[22–28] and 9 were single-arm retrospective cohort studies[29–38]. Nineteen studies (20 publications) reported outcomes among adult patients (defined as ≥18 years in 17 studies and ≥16 years in one study) and three studies reported outcomes among patients aged ≤18 years. Patient baseline characteristics were reported in all but one study[16]. Among the 19 studies that evaluated adult patients, the mean age was reported in 16 studies and ranged from 52.2 to 80 years old. Among these same 19 studies, the proportion of female patients ranged from 0 to 58.2% female. Nineteen studies (20 publications) were focused on US populations and three studies were conducted in the UK. Five studies included patient populations with previous stroke or transient ischemic attack (TIA), two studies included patients with previous heart failure, and nine studies included some patients with a previous diagnosis of AF.

Device wear time and analyzable data

A summary of studies reporting wear time and analyzable time for Zio is shown in Table 2. The prescribed wear time was 14 days in 21 of the 22 included studies, and 7 days in one study. The mean wear time was reported in 13 studies and ranged from 7.0 to 12.8 days, with an unweighted overall mean of 10.4 days (weighted: 9.5 days)[19,22,27–36,38]. The median wear time was reported in nine studies and ranged from 5.0 to 14.0 days (7.0–14.0 days among the eighteen studies evaluating adult patients)[17,23,25,26,28,30–32,37].

Five studies reported an unweighted mean of 96.4% (weighted: 96.6%; range: 92.6–98.6%) analyzable time, which refers to the amount of recording time that was free from electrical artifacts and other anomalies that would prevent the processing and analyzing of electrocardiogram signals by ZEUS[22,26,27,29,31].

Cardiac arrhythmia detection rates

Among the 22 included studies, seven studies reported cumulative cardiac detection rates over time among patients with a detected arrhythmia during the monitoring period (illustrated in Figure 3 and Figure 4). Overall, rates of cardiac arrhythmia detection increased with recording durations >48 h and continued to increase beyond 7 days of recording. A summary of the detection rates for cardiac arrhythmias can be found in Tables 3 and 4.

The most frequently reported arrhythmias were AF (15 studies), SVT or supraventricular ectopy (SVE; 15 studies), and VT (15 studies), followed by sinus pause (11 studies), atrioventricular block (9 studies), composite arrhythmias (8 studies, with varying composite definitions by study), paroxysmal AF (PAF; 6 studies), chronic/sustained AF (5 studies), and premature ventricular contractions (PVC; 4 studies). The unweighted mean detection rates for AF, SVT/SVE and VT were 12.2%, 45.5% and 17.3%, respectively (weighted: 13.5%, 44.9% and 17.1%). The unweighted mean detection rates for chronic/sustained AF and PAF were 5.6% and 23.3%, respectively (weighted: 7.2% and 17.3%). The unweighted mean detection rates for sinus pause, atrioventricular block and PVC were 3.8%, 1.4% and 47.4%, respectively (weighted: 1.8%, 1.2% and 81.6%, respectively). Two studies evaluated adult patients who were already diagnosed with PAF, while no other studies identified enrolled patients based on an enrollment criteria of prior AF diagnosis[19,29].

Only two studies identified in the literature review directly compared arrhythmia detection rates between Holter and patch monitoring during identical observation windows[17,19]. Of these, one study compared patch recording with 24 h Holter recording and found the same 24 h detection rates (33.7%); however, among patients who continued to wear Zio for up to 14 days, AF events were detected in 18 additional patients (total detection rate of 58.1%)[19]. In this same study, 21 patients (28.4%) had a change in clinical management, the most common being a change in antiarrhythmic medication for 13 patients[19]. In a separate non-RCT comparative study of 24 h Holter and 14 day patch recording, Zio identified significantly more overall arrhythmia events than Holter recording (96 vs. 61 events, respectively; $p < .001$), as well as a higher number of clinically significant non-SVT arrhythmia events (41 vs. 27 events, respectively, $p < .001$). When compared during the first 24 h of monitoring, Holter monitoring identified a higher number of overall arrhythmia events (61 vs. 52 events, respectively; $p = .013$) and clinically significant non-SVT arrhythmia events (27 vs. 24 events, respectively; $p = .083$); however, when compared over the total wear time, 14 day patch detected 60 of the 61 arrhythmia events identified by Holter monitoring, with no episode of AF/atrial flutter detected by the Holter monitor going undetected by Zio[17].

Furthermore, five studies (four observational and one RCT) evaluated patient populations with previous stroke and/or TIA at baseline[16,24,27,31,38]. One study that evaluated patients who were indicated for cardiac rhythm recording related to stroke or TIA reported an AF detection rate of 5.0% (0.6% chronic AF and 4.4% PAF)[31]. The study noted that 14.3% of PAF episodes occurred after 48 h of recording[31]. In an RCT of patients enrolled within 72 h of TIA or ischemic stroke, the odds of detecting PAF at 90 days (primary outcome) was significantly higher among patients monitored with Zio than 24 h Holter recording (16.3% vs. 2.1% detection rate, respectively; OR 8.9, 95% CI: 1.1–76.0; $p = .047$)[16].

Quality assessment

Quality assessment was conducted on all 23 included publications using a peer-reviewed checklists[13–15]. Among prospective and retrospective observational studies, most studies reported adequate information to meet the criteria for study relevance, credibility of the study design/data source, and interpretation of results. Among retrospective observational studies that used large databases for their analyses, study quality varied with respect to the research design, variable definitions and reporting of statistical analyses. This review also included one open-label clinical trial. Due to its open-label design, the risk of bias was assessed to

Table 1. Characteristics of included studies and patient populations.

First author, year; country	Study design (study//follow-up period)	Description of study population (*N*)	Age in years, mean (SD)	Female (%)	Previous stroke, HF, MI and/or diagnosis of AF, *n* (%)
Multi-arm studies					
Barrett, 2014; US[17]	Prospective cohort (04/2012–07/2012)	Patients referred for evaluation of cardiac arrhythmia and underwent simultaneous ambulatory ECG recording with a conventional 24 h Holter recorder and a 14 day adhesive patch monitor (146)	Median: 64 Range: [22–94]	58.2	NR
Chandratheva, 2017; UK[21]	Prospective cohort (09/2015)	Patients who after initial brain and vascular imaging had unknown etiology or etiology suggestive of cardioembolism (20)	61.4 (14.4)	40	NR
Kaura, 2017; UK[16]	RCT	Patients enrolled within 72 h of TIA or ischemic stroke event (90)	NR[a]	NR	TIA or ischemic stroke: 90 (100)
Rho, 2018; UK[20]	Prospective cohort (NR)	Patients referred to a community cardiology practice (29)	73.1 (7.1)	33.3	NR
Robinson, 2017; US[18]	Prospective cohort (10/2014–2/2016)	Patients ≤17 years who were prescribed a patch monitor (363)	Median 12.7 Range: [0.01–17]	50	NR
Rosenberg, 2013; US[19]	Prospective cohort (04/2011–05/2012)	Patients undergoing management of AF (74)	64.5 (8.1)	45.3	AF: 49 (67.1) PAF: 74 (100)
Single-arm studies					
Bolourchi, 2015; US[22]	Prospective cohort (01/2011–12/2013)	Children receiving their first adhesive patch monitors for clinical indications (3209)	12.5 (4.4)	56	NR
Eisenberg, 2014; US[38]	Retrospective cohort (05/2010–01/2013)	Patients from an electrophysiology practice who were prescribed Zio monitor (524)	56.7 (20.2)	56	AF: 155 (30) TIA: 6 (1)
Heckbert, 2018; US[23]	Prospective cohort (09/2017–10/2017)	Patients from the Multi-Ethnic Study of Atherosclerosis (946)	75 (8)	48.5	AF/flutter: 143 (15)
Loring, 2016; US[24]	Prospective cohort (2012–2015)	Patients receiving patch monitoring devices through the San Francisco Veterans Affairs Medical Center (694)	70 (12)	4.0	AF/flutter: 27 (27.0) Stroke/TIA: 22 (22.0)
May, 2018; US[37]	Retrospective cohort (11/2013–6/2016)	All patients aged 0–18 years who underwent patch monitoring ordered by one of six board-certified pediatric cardiologists (332)	Median: 13 IQR: [7–15]	54.4	Heart disease: 106 (28.4)
Narayanan, 2018; US[36]	Retrospective cohort (2016–2017)	Patients aged ≥75 enrolled in the Atherosclerosis Risk in Communities study (2260)	79 (5)	58	AF: 213 (9.4)
Norby, 2018[b]; US[35]	Retrospective cohort (2016–2017)	Patients aged enrolled in the Atherosclerosis Risk in Communities study who had no history of stroke and at least 2 days of patch monitoring (2152)	79 (5)	58	Stroke: 0 (0)
Reed, 2018; UK[25]	Prospective cohort (11/2015–6/2017)	Patients 16 years or over presenting within 6 hours of unexplained syncope in an emergency department (86)	62.8 (19.5)	47	HF: 5 (5.8) MI: 4 (4.7)
Rooney, 2018; US[34]	Retrospective cohort (6/2016–2/2017)	Patients enrolled in the Atherosclerosis Risk in Communities study who underwent cognitive testing (1116)	80 (5)	55	NR
Schreiber, 2014; US[26]	Prospective cohort (02/2011–02/2012)	Patients >18 years discharged from emergency department with symptoms of arrhythmia (174)	52.2 (21.0)	55	AF: 4 (2.3)
Schultz, 2019; US[33]	Retrospective cohort (06/2013–05/2016)	Patients >18 years of age with congenital heart disease (314)	Median: 31 IQR: [25–41]	61	AF: 32 (10)
Solomon, 2016; US[32]	Retrospective cohort (2011–2013)	Patients who were prescribed patch monitoring within the study period (122,454)	49.8% <65 35.6% 65–79 15.6% ≥80	53	NR
Steinhubl, 2018; US[27]	Prospective cohort (11/2015–1/2018)	Members of a large national health plan (2659)	72.4 (7.3)	38.6	Stroke: 369 (13.9) HF: 128 (4.8) MI: 147 (5.5)

(*continued*)

Table 1. Continued.

First author, year; country	Study design (study//follow-up period)	Description of study population (*N*)	Age in years, mean (SD)	Female (%)	Previous stroke, HF, MI and/or diagnosis of AF, *n* (%)
Tung, 2015; US[31]	Retrospective cohort (01/2012–06/2013)	Patients who underwent patch monitoring, with indication for monitoring related to stroke or TIA (1171)	67.9 (NR)	45	Stroke or TIA: 1171 (100)
Turakhia, 2013; US[30]	Retrospective cohort (01/2011–12/2011)	Patients who received monitoring with the patch (26,751)	60.2 (18.7)	54.5	AF: 6493 (24.3)
Turakhia, 2015; US[28]	Prospective cohort (05/2012–08/2013)	Patients with risk factors for AF, but no medical history or symptoms indicative of AF (75)	69 (8.0)	0	CHF: 13 (17) MI: 26 (35)
Wineinger, 2019; US[29]	Retrospective cohort (11/2014–09/2016)	Patients determined to have PAF (13,293)	69.4 (11.1)	40.3	PAF: 13,293 (100)

[a]All patients were over 18 years of age.
[b]Though the publications from Narayanan and Norby originated from the same study (Atherosclerosis Risk in Communities), they reported different *N* values, baseline characteristics and outcomes, and thus were not counted as duplicate publications.
Abbreviations. AF, Atrial fibrillation; CHF, Congestive heart failure; HF, Heart failure; IQR, Interquartile range; MI, Myocardial infarction; NR, Not reported; PAF, Paroxysmal atrial fibrillation; RCT, Randomized controlled trial; SD, Standard deviation; TIA, Transient ischemic attack.

be high with respect to allocation concealment, blinding or participants/researchers, and blinding of outcome assessment. However, risk of assessment was deemed to be low with regards to completeness of data reported, selective reporting or any other potential sources of bias[16]. Sixteen of the 23 included publications were conference abstracts, thus limiting the ability of reviewers to conduct a thorough quality assessment of these publications. Findings of the quality assessment for individual publications are reported in Supplemental Appendix C and Supplemental Appendix D.

Discussion

The present study is the first systematic literature review to evaluate cardiac arrhythmia detection rate outcomes among patients who underwent long-term, continuous, uninterrupted cardiac recording with Zio. This review included 23 publications of 22 unique studies that evaluated outcomes for patients whose cardiac rhythms were recorded with Zio, six of which were comparative studies (including one RCT) and 16 of which were single-arm cohort studies (prospective and retrospective).

Early detection and appropriate clinical management of cardiac arrhythmias is critical for reducing patient disease burden and improving patient quality of life. Long-term, continuous, uninterrupted cardiac recording may provide improved benefits for patients in detecting cardiac arrhythmias compared with current standard of care recording technologies. The prescribed recording time for 21 of the 22 included studies was 14 days with Zio, with an unweighted mean wear time of 10.4 days (weighted: 9.5 days) in the 13 studies that reported actual patient wear time with Zio.

Continuous ECG recording between 24 and 48 h with multi-lead Holter monitors is commonly utilized as an initial option for screening and detection of cardiac arrhythmias. While ECG recording with multi-lead monitors may provide advantages relative to single-lead monitors in certain cases (e.g. discriminating ventricular tachycardias from aberrant atrial rhythms), limitations in patient comfort/adherence and signal quality issues resulting from lead wire/electrode interaction within a 1–2 day recording window may result in lower arrhythmia detection rates and may necessitate repeat monitoring relative to single-lead devices. Other external longer duration monitoring technologies (e.g. external loop recorder, mobile cardiovascular telemetry [MCT]) may provide incremental detection benefits compared with Holter recording due to increased monitoring duration windows, but their use is limited by the need for patients to recharge/replace batteries, replace lead wire patches, or remove the device during activities such as showering or physical activity. Finally, despite promising initial results from implantable cardiac monitors in long-term arrhythmia detection, the invasive nature of these monitoring technologies may prevent their widespread use and they may not be an appropriate first-line cardiac monitoring option for most patients.

Compared with other existing and novel cardiac monitoring technologies which are primarily focused on AF

Table 2. Summary of studies reporting device wear time and analyzable time.

First author, year	Device(s)	Wear time, days				Analyzable time[a]		
		Prescribed	Mean (SD)	Median [IQR]	Range	Mean, %	Median, %	Median [IQR], days
Multi-arm studies								
Barrett, 2014[17]	24 h Holter	1		1.0	0.9–1.0			
	Zio	14		11.1	0.9–14.0			
Chandratheva, 2017[21]	72 h Holter	3						
	E-patch	3						
	Zio	14						
Kaura, 2017[16]	24 h Holter	1						
	Zio	14						
Rho, 2018[20]	CAM	7						
	Zio	7						
Robinson, 2017[18]	48 h Holter	1			NR			
	Zio	14			1–14			
Rosenberg, 2013[19]	24 h Holter	1	0.9 (0.08)		NR			
	Zio	14	10.8 (2.8)		4–14			
Single-arm studies								
Bolourchi, 2015[22]	Zio	14	7.8 (4.4)			92.6		
Eisenberg, 2014[38]	Zio	14	7 (2.6)		0.33–14			
Heckbert, 2018[23]	Zio	14		14 [13.2–14.0]			99.6	
Loring, 2016[24]	Zio	14						11.6 [10.8–13.8]
May, 2018[35]	Zio	14		5	1–14			
Narayanan, 2018[36]	Zio	14	12.5 (2.6)					
Norby, 2018[35]	Zio	14	12.5 (2.6)					
Reed, 2018[25]	Zio	14		13.6 [11.8–14.0]				
Rooney, 2018[34]	Zio	14	12.8 (2.4)					
Schreiber, 2014[26]	Zio	14		6.9 [5.8–9.2]		98.6		
Schultz, 2019[33]	Zio	14	9.5 (4.1)					
Solomon, 2016[32]	Zio	14	9.6 (4.0)	9.9 [6.8–13.8]				9.1 [6.4–13.1]
Steinhubl, 2018[27]	Zio	14	11.7 (4.1)			97.8		
Tung, 2015[31]	Zio	14	10.9	13.0 [7.2–14.0]		95.8	98.7	
Turakhia, 2013[30]	Zio	14	7.6 (3.6)	7.0 [5.9–9.3]			99	
Turakhia, 2015[28]	Zio	14	10.4 (4.5)	13 [7.8–14]			98	
Wineinger, 2019[29]	Zio	14	11.4			97.4		

[a]Analyzable time was defined as the amount of recording time that was free from electrical artifacts and other anomalies that would prevent interpreting the electrocardiogram signal. The numbers reported here appear as they were reported in the text of each study, either as a percentage of the total wear time, or as median and interquartile range in days.

Abbreviations. h, Hour; IQR, Interquartile range; SD, Standard deviation.

detection, Zio is able to detect up to 10 distinct classifications of heart arrhythmias[39]. Indeed, studies included in this systematic review reported detection rates for various arrhythmias, the most frequently reported being AF, SVT/SVE, VT and sinus pause. Overall, rates of cardiac arrhythmia detection increased for multiple arrhythmia subtypes with monitoring durations >48 h and continued to increase following 7 days of monitoring and greater. For one included study, repeat monitoring with Zio for a subset of study patients (up to 28 days of total recording) identified additional AF/flutter, AV block and sinus pause events that were not detected during the first 14 days of continuous recording. These findings are consistent with previous reviews which have reported greater rates of cardiac arrhythmia detection associated with longer monitoring durations[10,40].

Among the five multi-arm studies that compared cardiac arrhythmia detection rates between Zio and 24, 48 or 72 h Holter recording, detection rates were generally higher for patients monitored with Zio across a number of arrhythmias, particularly for AF and PAF. The reported rates of AF detection by Holter recording in these five studies were consistent with findings from previous literature reviews[11,41–43]. Notably, one study included in this review found that 53.4% of patients who experienced symptoms and marked the timing of the event (when the patient noticed symptoms) with Zio did not actually have an arrhythmia, suggesting the ability of long-term, uninterrupted, continuous monitoring to also rule out cardiac arrhythmias as the cause of symptomatic events[26]. Such patients have previously been shown to impose a substantial cost burden when repeat Holter recording failed to detect a clinical event or diagnose an underlying disease[44].

Results from the present study can also be placed in context with findings from previous systematic literature reviews of cardiac monitoring that have focused on AF detection. Across the 22 studies identified in the current review, 15 studies (16 publications) reported AF detection with a mean unweighted AF detection rate of 12.2% (weighted: 13.5%). Among studies limited to adult patient populations, the AF detection rates ranged from 3.5% to 58.1% for prescribed recording durations up to 14 days with an unweighted mean pooled rate of 12.7% (weighted: 14.7%). Two prior systematic reviews of monitoring durations ≥7 days following ischemic stroke or TIA have reported AF detection rates of 6%[11] and 15%[10]. Both studies reported that detection rate increased with longer monitoring durations[10,11], with one study reporting that mean AF detection rates for continuous ECG monitoring ≤72 h was markedly lower at 5.1%[10]. While differences

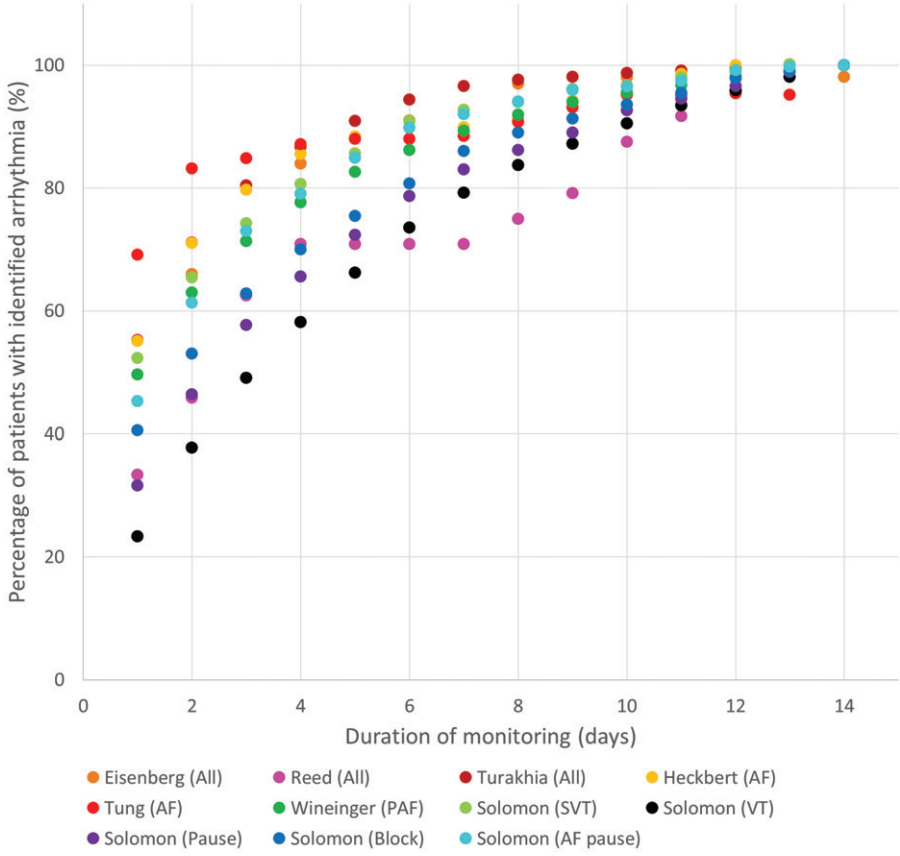

Figure 3. Cumulative arrhythmia detection rate over time, by study (among patients with a detected arrhythmia). Scatterplot shows cumulative percentages from studies that reported arrhythmia detection over the entire monitoring period. Data reported in this figure are restricted to patients who had a detected arrhythmia during the monitoring period (i.e. cumulative detection rate will reach 100% by the end of the monitoring period). The first author of each study is indicated in the figure legend, along with the type of arrhythmia in parentheses[23,25,29–32,38]. Studies varied in the types of arrhythmias that were monitored. Abbreviations. AF, Atrial fibrillation; PAF, Paroxysmal atrial fibrillation; SVT, Supraventricular tachycardia; VT, Ventricular tachycardia.

across reviews and the design of included studies preclude direct comparison of AF detection rates, the generally comparable or higher AF detection rates reported in the present review suggest the potential advantages in AF detection that may be derived from cardiac rhythm recording with Zio relative to other monitoring and recording modalities.

Finally, results from the current review also have important implications for findings from previous studies of the Zio technology that evaluated AF burden but did not focus on cardiac arrhythmia detection. In an analysis of 1965 Kaiser Permanente members diagnosed with PAF, patient AF burden (defined as the percentage of analyzable wear time in AF/atrial flutter during the cardiac monitoring period) greater than 11.4% was associated with a three-fold risk of thromboembolism among patients not taking oral anticoagulants[6]. Similarly, in an evaluation of 325 patients enrolled in the Atherosclerosis Risk in Communities (ARIC) study who were monitored with Zio, a correlation between higher AF burden and lower cognitive functioning was reported[45]. In addition to the potential arrhythmia detection benefits from cardiac monitoring with Zio, improved insights into patient AF burden may lead to enhanced clinical decision-making and long-term health outcomes. Indeed, one study reported a change in clinical management among patients studied with Zio, but not among those studied with 24 h Holter recording, after the longer duration of patch recording identified additional arrhythmias[19].

Limitations

The findings reported in the current systematic literature review are subject to several limitations. Most of the reviewed studies included cohorts that were selected based on patients having risk for arrhythmias, including AF, which is a potential source of bias. In particular, a subset of studies selected cohorts specifically based on AF risk and/or prior AF diagnosis. At the same time, heterogeneity in underlying risk factors and comorbidities existed across the different study populations, which could be a confounding factor contributing to the prevalence of cardiac arrhythmias and contribute to observed variation in arrhythmia detection rates. This heterogeneity complicates the ability to make direct comparisons across included studies, and precludes conducting a meta-analysis. Additionally, as the Zio cardiac arrhythmia detection algorithm continues to advance, it is possible that the arrhythmia detection rates observed in older studies may be underestimated relative to more recent studies. This also potentially limits the ability to directly compare arrhythmia

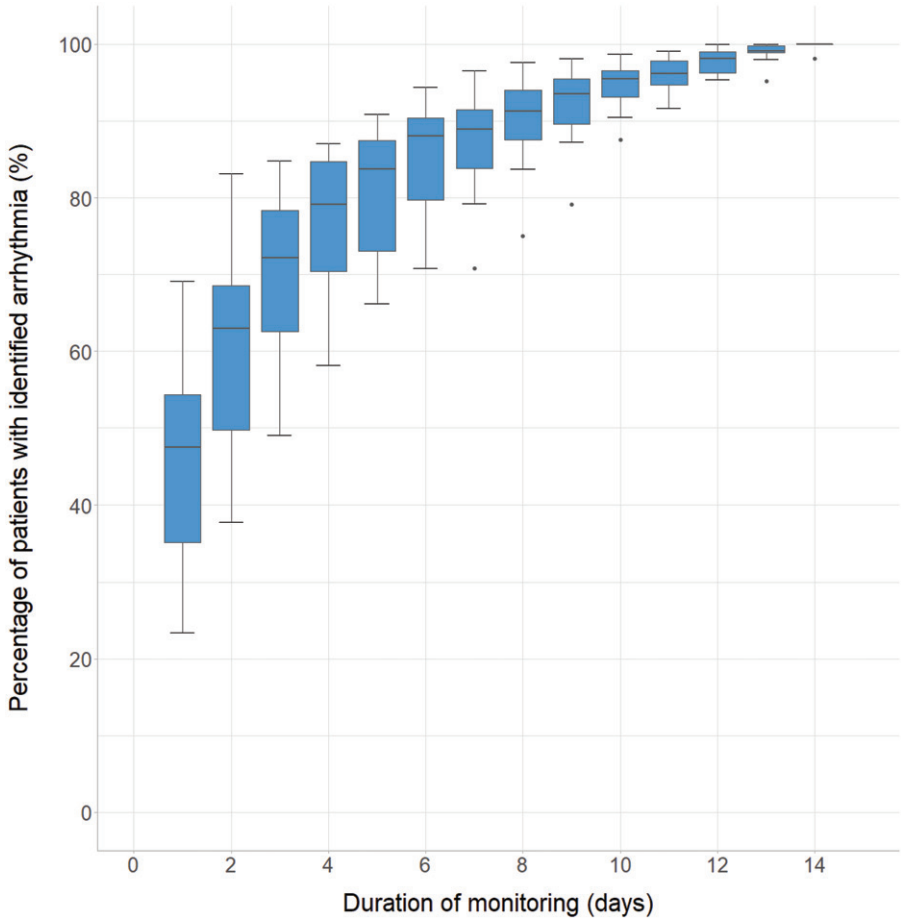

Figure 4. Cumulative arrhythmia detection rate over time, overall (among patients with a detected arrhythmia). The boxplot summarizes the cumulative arrhythmia detection across the studies shown in Figure 3. There is a set of box and whiskers for each day of monitoring. For each set of box and whiskers, the center horizontal line represents the median, and the top and bottom edges of the rectangle represent the 75th and 25th percentiles, respectively. The whiskers end at the minimum and maximum values for each day, excluding outliers. Outliers are shown as dots. Data reported in this figure are restricted to patients who had a detected arrhythmia during the monitoring period (i.e. cumulative detection rate will reach 100% by the end of the monitoring period).

Table 3. Mean arrhythmia detection rates across included studies.

	Number of studies	Total number of patients	Mean detection rate, %	
			Unweighted	Weighted[a]
AF	15	40,220	12.2	13.5
PAF	5	2033	23.3	17.3
Chronic/sustained AF	5	28,245	5.6	7.2
SVT/SVE	15	35,184	45.5	44.9
VT	15	155,441	17.3	17.1
Sinus pause	11	154,627	4.8	1.8
Atrioventricular block	9	154,086	1.6	1.2
PVC	4	1579	50.2	39.2

[a]The weighted mean detection rates were weighted by sample size; for a given arrhythmia, the detection rate reported by each study was multiplied by the study sample size, and the sum of these products was divided by the sum of the sample sizes of the studies.

Abbreviations. AF, Atrial fibrillation; PAF, Paroxysmal atrial fibrillation; PVC, Premature ventricular contraction; SVE, Supraventricular ectopy; SVT, Supraventricular tachycardia; VT, Ventricular tachycardia.

detection rates across studies conducted in different years. Furthermore, several studies had heterogeneous patient populations who were referred for cardiac monitoring for a variety of indications that were not specified. Since there is no standardized risk score across multiple cardiac arrhythmias, and because risk scores such as CHA_2DS_2-VAS_c and the Canadian Syncope Risk Score are specific to stroke and syncope, respectively, adjusting for arrhythmia risk across such populations is not currently possible. Overall, diverse etiologies of cardiac arrhythmias may have resulted from the variation in indications and cohort selection, resulting in differing arrhythmia detection rates across the included studies. Furthermore, this current review did not specifically aim to compare arrhythmia detection with Zio with other forms of cardiac monitoring, highlighting an important area for future research. Finally, the exclusion of studies that were not published in English may have overlooked studies conducted outside of English-speaking countries.

Table 4. Summary of studies reporting detection rates of cardiac arrhythmias.

First author, year	Type of device	Detection rate (%)								
		AF	Chronic or sustained AF	PAF	SVT or SVE	VT	Sinus pause	Block	PVC	Composite arrhythmias[a]
Multi-arm studies										
Barrett, 2014[17,b]	24 h Holter									41.8
	Zio									65.8
Chandratheva, 2017[21]	72 h Holter	0			20	5	0			
	E-patch	10								
	Zio	5			55	40	0			
Kaura, 2017[16]	24 h Holter	2.1		2.1		2.1				
	Zio	16.3		16.3		32.6				
Rho, 2018[20]	CAM	18.3			89.7	40.3		3.4	96.6	
	Zio	17.2			86.6	16.2		3.4	92.1	
Robinson, 2017[18,c]	48 h Holter				6.8	2.2		0.6		9.6
	Zio				9.6	1.9		0.8		12.4
Rosenberg, 2013[19]	24 h Holter	33.7	12.2	16.2						
	Zio	58.1	6.8	44.6	33.8	24.3	5.4	1.4		
Single-arm studies										
Bolourchi, 2015[22,d]	Zio	0.3			7.1	3.8	0.9	1.2		12.1
Eisenberg, 2014[38,e]	Zio	20		47	44	15	2.7		93	99.5
Heckbert, 2018[23]	Zio	7.3			88.6	34.6	3.0	3.0		
Loring, 2016[24]	Zio								14.6	
May, 2018[37]	Zio				3.6	0.6			0.9	
Narayanan, 2018[36]	Zio	8.1								
Norby, 2018[35]	Zio	8								
Reed, 2018[25,f]	Zio	3.5			2.3	17.4	7.0	1.2		27.9
Rooney, 2018[34]	Zio				95					
Schreiber, 2014[26]	Zio	6.3	2.3	4.0	38.5	8.1	2.3	1.1		
Schultz, 2019[33,g]	Zio				35	11	1.3			50
Solomon, 2016[32]	Zio					18.5	1.4	1.2		
Steinhubl, 2018[27]	Zio	5.1								
Tung, 2015[31]	Zio	5.0	0.6	4.4	70.2					
Turakhia, 2013[30,h]	Zio	17.3	7.5		45.9	12.3	3.7	1.4		60.3
Turakhia, 2015[28,i]	Zio	5.3	11		67	23	2.7		1.7	48
Wineinger, 2019[29]	Zio			100						

[a]Composite arrhythmias included detection of one or more arrhythmia subtypes identified during monitoring, which differed across studies; arrhythmia subtypes included in composite arrhythmia detection outcomes have been noted as follows for each study.
[b]Barrett, 2014: AF, AV block, polymorphic VT, sinus pause, SVT, VT.
[c]Robinson, 2017: AV block, SVT, VT.
[d]Bolourchi, 2015: AF, AV block, sinus pause, SVT, VT.
[e]Eisenberg, 2014: AF, bradycardia, non-sustained VT, PAC, PVC, sinus pause, SVT.
[f]Reed, 2018: AF, heart block, idioventricular rhythm, sinus pause, SVT, VT.
[g]Schultz, 2019: AF, atrial flutter, sinus pause, SVT, VT.
[h]Turakhia, 2013: AF, AV block, bradycardia, sinus pause, SVT, VT.
[i]Turakhia, 2015: AF, atrial tachycardia, PVC, sinus pause, SVE, VT; in this study, the detection rate of AF and atrial tachycardia were reported as a single number, listed above under "Chronic or sustained AF".
Abbreviations. AF, Atrial fibrillation; AV, Atrioventricular; h, Hour; PAC, Premature atrial contraction; PAF, Paroxysmal atrial fibrillation; PVC, Premature ventricular contraction; SVE, Supraventricular ectopy; SVT, Supraventricular tachycardia; VT, Ventricular tachycardia.

Conclusions

Long-term, continuous, uninterrupted external ambulatory cardiac rhythm recording with Zio for $\geq$7 days results in longer patient wear times and higher rates of cardiac arrhythmia detection compared with outcomes reported in previous reviews of short-term cardiac rhythm monitoring (24–48 h).

Notes

1. Zio is a registered trade name of iRhythm Technologies Inc., San Francisco, CA, USA

Transparency

Declaration of funding

This study was funded by iRhythm Technologies Inc.

Author contributions

M.Y., J.J., C.P., C.Y., R.M., H.B. and M.T. contributed to the study design and methodology. C.P., C.Y. and J.J. primarily contributed to study review and data extraction and all authors contributed to the critical review of the data as well as drafting of the manuscript. In addition, all authors approved the final manuscript and agree to be accountable for all aspects of the work.

Declaration of financial/other relationships

M.Y., J.J., C.P., C.Y., R.M. and H.B. have disclosed that they are employees of Analysis Group Inc., a company that received funding from iRhythm Technologies Inc. to conduct this study. M.T. has disclosed that he is an employee of iRhythm Technologies Inc. and owns stock/stock options in iRhythm Technologies Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. *CMRO* peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgements

The authors wish to thank Xcevio Zuluaga, Anshika Niraj, Khurram Ali and Jarrett Gorin of Analysis Group Inc. for their support in the study selection and data extraction processes.

References

[1] Olshansky B. Chapter 28 – Arrhythmias. In: Rakel D, editor. Integrative medicine. 4th ed. Atlanta (GA): Elsevier Inc.; 2018. p. 276–286.e3.
[2] Fung E, Jarvelin MR, Doshi RN, et al. Electrocardiographic patch devices and contemporary wireless cardiac monitoring. Front Physiol. 2015;6:149.
[3] Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014;129:837–847.
[4] Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. Nat Rev Cardiol. 2016;13:501.
[5] Sivakumaran S, Krahn AD, Klein GJ, et al. A prospective randomized comparison of loop recorders versus Holter monitors in patients with syncope or presyncope. Am J Med. 2003;115:1–5.
[6] Go AS, Reynolds K, Yang J, et al. Association of burden of atrial fibrillation with risk of ischemic stroke in adults with paroxysmal atrial fibrillation: The KP-RHYTHM study. JAMA Cardiol. 2018;3:601–608.
[7] iRhythm Technologies Inc. Zio XT indications, safety & warnings [Internet]. 2019 [cited 2019 Jan 29]. Available from: https://www.irhythmtech.com/zio_xt_precautions
[8] US Food and Drug Administration. August 2018 510(k) Clearances [Internet]. 2018 [cited 2019 Jan 29]. Available from: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/ucm619760.htm
[9] Lobodzinski SS, Laks MM. New devices for very long-term ECG monitoring. Cardiol J. 2012;19:210–214.
[10] Dussault C, Toeg H, Nathan M, et al. Electrocardiographic monitoring for detecting atrial fibrillation after ischemic stroke or transient ischemic attack: systematic review and meta-analysis. Circ Arrhythm Electrophysiol. 2015;8:263–269.
[11] Korompoki E, Del Giudice A, Hillman S, et al. Cardiac monitoring for detection of atrial fibrillation after TIA: a systematic review and meta-analysis. Int J Stroke. 2017;12:33–45.
[12] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.
[13] Berger ML, Martin BC, Husereau D, et al. A questionnaire to assess the relevance and credibility of observational studies to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value Health. 2014;17:143–156.
[14] Motheral B, Brooks J, Clark MA, et al. A checklist for retrospective database studies – report of the ISPOR Task Force on Retrospective Databases. Value Health. 2003;6:90–97.
[15] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
[16] Kaura AK, Lenane JL, Sztriha LS, et al. Early prolonged ambulatory cardiac monitoring in stroke (EPACS) – an open-label randomised controlled trial. Europace. 2017;19:i6.
[17] Barrett PM, Komatireddy R, Haaser S, et al. Comparison of 24-hour Holter monitoring with 14-day novel adhesive patch electrocardiographic monitoring. Am J Med. 2014;127:95.e11–e17.
[18] Robinson J, Snyder C. Ambulatory arrhythmia detection with Zio XT Patch in pediatric patients. Cardiol Young. 2017;27:S1–S653.
[19] Rosenberg MA, Samuel M, Thosani A, et al. Use of a noninvasive continuous monitoring device in the management of atrial fibrillation: a pilot study. Pacing Clin Electrophysiol. 2013;36:328–333.
[20] Rho R, Vossler M, Blancher S, et al. Comparison of 2 ambulatory patch ECG monitors: the benefit of the P-wave and signal clarity. Am Heart J. 2018;203:109–117.
[21] Chandratheva A, Pleming J, Dados A, et al. New versus conventional non invasive cardiac monitoring for atrial fibrillation detection in TIA clinic. Eur Stroke J. 2017;2:117.
[22] Bolourchi M, Batra AS. Diagnostic yield of patch ambulatory electrocardiogram monitoring in children (from a national registry). Am J Cardiol. 2015;115:630–634.
[23] Heckbert SR, Austin TR, Jensen PN, et al. Yield and consistency of arrhythmia detection with patch electrocardiographic monitoring: the Multi-Ethnic Study of Atherosclerosis. J Electrocardiol. 2018;51:997–1002.
[24] Loring Z, Hanna P, Pellegrini CN. Longer ambulatory ECG monitoring increases identification of clinically significant ectopy. Pacing Clin Electrophysiol. 2016;39:592–597.
[25] Reed MJ, Grubb NR, Lang CC, et al. Diagnostic yield of an ambulatory patch monitor in patients with unexplained syncope after initial evaluation in the emergency department: the PATCH-ED study. Emerg Med J. 2018;35:477–485.
[26] Schreiber D, Sattar A, Drigalla D, et al. Ambulatory cardiac monitoring for discharged emergency department patients with possible cardiac arrhythmias. WestJEM. 2014;15:194–198.
[27] Steinhubl SR, Waalen J, Edwards AM, et al. Effect of a home-based wearable continuous ECG monitoring patch on detection

of undiagnosed atrial fibrillation: the mSToPS randomized clinical trial. JAMA. 2018;320:146–155.
[28] Turakhia MP, Ullal AJ, Hoang DD, et al. Feasibility of extended ambulatory electrocardiogram monitoring to identify silent atrial fibrillation in high-risk patients: the Screening Study for Undiagnosed Atrial Fibrillation (STUDY-AF). Clin Cardiol. 2015;38: 285–292.
[29] Wineinger NE, Barrett PM, Zhang Y, et al. Identification of paroxysmal atrial fibrillation subtypes in over 13,000 individuals. Heart Rhythm. 2019;16:26–30.
[30] Turakhia MP, Hoang DD, Zimetbaum P, et al. Diagnostic utility of a novel leadless arrhythmia monitoring device. Am J Cardiol. 2013;112:520–524.
[31] Tung CE, Su D, Turakhia MP, et al. Diagnostic yield of extended cardiac patch monitoring in patients with stroke or TIA. Front Neurol. 2015;5:1–4.
[32] Solomon MD, Yang J, Sung SH, et al. Incidence and timing of potentially high-risk arrhythmias detected through long term continuous ambulatory electrocardiographic monitoring. BMC Cardiovasc Disord. 2016;16:35.
[33] Schultz KE, Lui GK, McElhinney DB, et al. Extended cardiac ambulatory rhythm monitoring in adults with congenital heart disease: arrhythmia detection and impact of extended monitoring. Congenit Heart Dis. 2019. [Epub ahead of print].
[34] Rooney MR, Norby FL, Koene RJ, et al. Excessive supraventricular ectopic activity and cognitive function: the Atherosclerosis Risk In Communities (ARIC) study. Circulation. 2018;136:A16492.
[35] Norby FL, Rooney MR, Gutierrez A, et al. Higher atrial fibrillation burden is independently associated with lower cognitive function: the Atherosclerosis Risk In Communities (ARIC) study. Heart Rhythm. 2018;15:S261.
[36] Narayanan MA, Norby FL, Rooney M, et al. Prevalence of subclinical atrial fibrillation in the elderly population: the Atherosclerosis Risk In Communities (ARIC) study. Heart Rhythm. 2018;15:S455.
[37] May JW, Carter EL, Hitt JR, et al. Clinical impact of a novel ambulatory rhythm monitor in children. Cardiol Young. 2018;28: 1134–1140.
[38] Eisenberg EE, Carlson SK, Doshi RN, et al. Chronic ambulatory monitoring: results of a large single-center experience. J Innov Card Rhythm Manag. 2014;5:1818–1823.
[39] Hannun AY, Rajpurkar P, Haghpanahi M, et al. Cardiologist-level arrhythmia detection and classification in ambulatory electrocardiograms using a deep neural network. Nat Med. 2019;25:65–69.
[40] Health Quality Ontario. Long-term continuous ambulatory ECG monitors and external cardiac loop recorders for cardiac arrhythmia: a health technology assessment [Internet]. 2017 [cited 2019 Jan 25]. Available from: http://www.hqontario.ca/evidence-to-improve-care/journal-ontario-health-technology-assessment-series
[41] Ramkumar S, Nerlekar N, D'Souza D, et al. Atrial fibrillation detection using single lead portable electrocardiographic monitoring: a systematic review and meta-analysis. BMJ Open. 2018;8:e024178.
[42] Kishore A, Vail A, Majid A, et al. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. Stroke. 2014;45:520–526.
[43] Seet RC, Friedman PA, Rabinstein AA. Prolonged rhythm monitoring for the detection of occult paroxysmal atrial fibrillation in ischemic stroke of unknown cause. Circulation. 2011;124:477–486.
[44] Arnold RJG, Layton A. Cost analysis and clinical outcomes of ambulatory care monitoring in Medicare patients: describing the diagnostic odyssey. JHEOR. 2015;5:161–169.
[45] Chen LY, Agarwal SK, Norby FL, et al. Persistent but not paroxysmal atrial fibrillation Is independently associated with lower cognitive function: ARIC study. J Am Coll Cardiol. 2016;67:1379–1380.