International Journal of Cardiology xxx (xxxx) xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Enhanced detection of cardiac arrhythmias utilizing 14-day continuous ECG patch monitoring

Chih-Min Liu [a,b], Shih-Lin Chang [a,b,*], Yung-Hsin Yeh [c], Fa-Po Chung [a,b], Yu-Feng Hu [a,b], Chung-Chuan Chou [c], Kuo-Chun Hung [c], Po-Cheng Chang [c], Jo-Nan Liao [a,b], Yi-Hsin Chan [c], Li-Wei Lo [a,b], Lung-Sheng Wu [c], Yenn-Jiang Lin [a,b], Ming-Shien Wen [c], Shih-Ann Chen [a,b,d]

[a] Heart Rhythm Center, Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[b] Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan
[c] Cardiovascular Division, Chang-Gung Memorial Hospital, Chang-Gung University College of Medicine, Taoyuan, Taiwan
[d] Cardiovascular Center, Taichung Veterans General Hospital, Taichung, Taiwan

ARTICLE INFO

Article history:
Received 8 November 2020
Received in revised form 28 February 2021
Accepted 8 March 2021
Available online xxxx

Keywords:
14-day electrocardiogram monitor
Arrhythmia
Electrocardiography
Medical device
24-h Holter

ABSTRACT

Background: To evaluate the performance of a single-lead, 14-day continuous electrocardiogram (ECG) patch for the detection of arrhythmias compared to conventional 24-h monitoring.
Methods: This prospective clinical trial enrolled patients suspected of arrhythmias but not diagnosed by 12-lead ECGs. Each patient underwent a 24-h Holter and 14-day ECG patch simultaneously. Seven types of arrhythmias were classified: supraventricular tachycardia (SVT, repetitive atrial beats >4 beats), irregular SVT without P wave (>4 beats), AF/AFL (irregular SVT without P wave ≥30 s), pause ≥3 s, atrioventricular block (AVB; Mobitz type II, third-degree, two to one or high degree AVB), ventricular tachycardia (VT), and polymorphic VT.
Results: A total of 158 patients were recruited (mean wear time:12.3 ± 3.2 days). The overall arrhythmia detection rate was higher with 14-day ECG patches (59.5%) compared to 24-h Holter (19.0%, $P < 0.001$). Up to 87.2% of arrhythmias recorded with 14-day ECG patches were not associated with symptoms. The 14-day ECG patch was associated with higher detection rates compared to the 24-h Holter in patients with SVT (52.5% versus 15.8%, $P < 0.001$), irregular SVT without P wave (12.7% versus 4.4%, $P = 0.002$), AF/AFL (9.5% versus 3.8%, $P = 0.042$), and critical arrhythmias (pause ≥3 s, AVB, VT, polymorphic VT) (16.5% versus 2.5%, $P < 0.001$). The 14-day ECG patch detected more than 2 types of arrhythmias in 5.1% of patients. No serious adverse events in patients wearing the 14-day ECG patch were reported.
Conclusions: The 14-day ECG patch outperformed 24-h Holter to detect overall, asymptomatic, critical and multiple arrhythmias. It is safe and has the potential to identify individuals with hidden arrhythmias, especially those with critical arrhythmias.

1. Introduction

Cardiac arrhythmias encompass any slow, fast, irregular, or abnormal heart rhythms, and may be caused by a multitude of mechanisms. Some arrhythmias such as supraventricular tachycardia (SVT), atrial fibrillation (AF), atrial flutter (AFL), ventricular tachycardia (VT), atrioventricular block (AVB), and pause can be serious and life-threatening and lead to stroke, heart failure and even cardiac death. [1] Symptomatic arrhythmias can affect patients' lifestyle, quality of life, and daily activities. [1,2] The global prevalence and cost of the most common arrhythmias, such as AF, are expected to surge owing to factors such as economic growth, an aging population, and increased prevalence of risk factors in Western countries and the Asian population. [3,4]

Ambulatory electrocardiographic (ECG) monitoring (AEM) is the standard of care to screen symptomatic adults at high-risk of atrial and ventricular arrhythmias. [5,6] However, direct comparison between proprietary AEM monitors has been associated with observed variations in diagnostic yield even when the arrhythmia occurs during identical monitoring periods. [7,8] Conventional 24-h monitoring devices (Holter monitors) limit the mobility of participants and often do not detect symptomatic or clinically meaningful arrhythmias because of the relatively short monitoring time. [9,10] Beyond the detection of symptomatic arrhythmia events, there is a growing body of evidence that subclinical arrhythmias are often missed by conventional 24-h monitoring devices. [10] Recent technologic advances in ECG recorders include miniaturization and more efficient energy use that has facilitated the development of wearable biosensors designed to be unobtrusive and

* Corresponding author at: Heart Rhythm Center, Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Road, Beitou Dist., Taipei City 112, Taiwan.
E-mail address: slchang4@vghtpe.gov.tw (S.-L. Chang).

https://doi.org/10.1016/j.ijcard.2021.03.015
0167-5273/

comfortable to enable long-term cardiac arrhythmia recording. [2] These advanced technologies, such as the Zio cardiac arrhythmia recording system, can allow for greater comfort, extended periods of ECG monitoring, and higher detection rates compared with traditional Holter monitoring. However, most of the studies were merely focusing on AF. [11–13] The present study aimed to evaluate the performance of a 14-day continuous ECG patch monitor in the detection of clinically significant arrhythmia events over the total wear time of the devices in the clinical setting.

2. Methods

2.1. Patient enrollment and study population

This open-label prospective study was approved by the institutional review board (IRB) of Chang Gung Medical Foundation and Veterans General Hospital (No. SIGEZYZ20170828). The number of clinical trial registry was NCT03602742 (Clinical Trial Registration: https://clinicaltrials.gov/ct2/show/NCT03602742). Patients suspected of arrhythmias were recruited from the cardiology outpatient department between June 2017 and December 2018. All of the participants signed written informed consent before enrollment into the study. Eligible participants met all of the following criteria: (1) aged 20 years or older; (2) visited the outpatient clinic with suspected arrhythmias but not documented by 12-lead ECGs; (3) assigned to wear 24-h Holter monitors for suspected arrhythmias and associated signs and symptoms, such as fatigue, palpitation, lightheadedness, dizziness, syncope or nearly syncope, chest tightness, feeling of paused, or irregular heartbeats as judged by physicians; and (4) able to communicate with the investigators, and to understand and comply with the requirements of the study, including being willing to wear ECG monitor up to 14 days.

Participants with any of the following conditions were excluded from study participation: (1) did not have a 12-lead ECG test result at study onset; (2) previously confirmed any arrhythmias such as SVT, AF, AFL, VT, AVB, or pause ≥3 s; (3) had skin-related issues that could put patients at risk, interfere with study evaluations, or prevent meeting the requirements of the study; (4) currently taking medication or receiving any treatment for arrhythmia within 2 weeks prior to the screening visit; (5) currently enrolled in another trial or participated in a previous clinical trial which may interfere with the study data within 2 weeks prior to the screening visit; (6) pregnant; and (7) presented with hyperhidrosis.

Data regarding clinical variables, including vital signs, medical history and co-morbidities, were obtained from outpatient medical records.

2.2. Use of monitoring devices

Eligible patients were instructed to simultaneously wear a traditional 24-h Holter monitor (GE Healthcare SEER™1000, Philips 1810 Holter, Medilog®AR4 Plus) and the 14-day ECG patch (EZYPRO®, Sigknow Biomedical Co., Ltd., Taipei, Taiwan). Both devices were set up and initiated at the same time, allowing for a direct comparison between the two devices during the first 24-h monitoring period. The 24-h Holter monitor was removed after 24 h, while the 14-day ECG patch continuously monitored and recorded arrhythmic events of subjects during the 14-day wear time. The 14-day ECG patch was removed after 14 days.

The EZYPRO® cardiac arrhythmia monitoring patch is a Conformité Européenne (CE) and Taiwan Food and Drug Administration (FDA)-approved continuously monitoring ECG recorder indicated for up to 14 days of use in asymptomatic adults or those who suffer from transient symptoms. It is a single-use, lightweight (31 g), waterproof, single-lead ECG device without external leads or wires and attainable for constant ECG recordings for up to 14 days. It continuously records heart rhythms with an event recording function that allows the patient to self-record any symptomatic event. The self-record function was explained in detail to all study participants before the start of the study. The 14-day ECG patch was applied to the subject's left chest on clean, dry, hair-free skin surface via its adhesion patch. The upper and lower bounds of the patch were placed across from the clavicle to the 3rd intercostal area and the left and right bounds of the patch were placed across from the sternum to the left mid-clavicular line (Fig. 1A).

After completing the 14-day ECG patch recording, the subjects returned to the hospital to remove the 14-day ECG patch, and the medical staff sent the ECG recorder back to the Sigknow analysis center for data processing and analysis. However, the ECG information recorded by Holter is analyzed by respective software (Philips, Oxford, or GE) in each hospital. Of them, one hundred and fourteen (72.2%) Holter recordings were analyzed by Philips Zymed 1810 Holter Software, 38 (24.0%) Holter recordings were analyzed by Oxford Medilog Cardiology information system V2.4 Software, 6 (3.8%) patients were analyzed by GE Multi Area Reliability Simulation (MARS) Software.

The 14-day ECG patch utilized self-developed automatic ECG analysis algorithm software (wearable ECG system-ECG recorder, EZYPRO® ECG analysis system), which CE and Taiwan FDA have approved in clinical application for preliminary ECG analysis. The EZYPRO® ECG analysis system (Sigknow Biomedical Co., Ltd.) included signal preprocessing, heartbeat, and rhythm classification. In signal preprocessing, the bandpass filter was used to eliminate motion artifacts and high-frequency interference. Noise analysis can be assisted by software filtering function, demyoelectronic function, and G-sensor to discriminate symptoms or noises. And then, morphology-based features were used for heartbeat classification, and heart rate irregularity was used for heart rhythm classification. The trained and qualified technician analyzed and edited all the ECG data and selected the arrhythmia strips to be present in the preliminary report. Finally, the report was reviewed and confirmed by at least one cardiologist in each hospital (Supplementary Fig. 1). Based on the complexity of ECG tracings, the analysis time of each ECG report is about 2.5 to 6 h.

2.3. Arrhythmia events measurement

The arrhythmic events were defined as the previous publication, 2015 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) and 2019/2020 European Society of Cardiology (ESC) guidelines. [7,14–17] A patient was considered to have an arrhythmia if any one of seven types of arrhythmias were detected: SVT (defined as repetitive atrial beats or tachycardias >4 beats with atrial rates above 100 beats per minute, except irregular SVT without discernible P wave), irregular SVT without discernible P wave (>4 beats), pause ≥3 s, AVB (Mobitz type II, third-degree, two to one or high degree AVB), VT (>4 beats), or polymorphic VT (Supplementary Fig. 2). Among ECG tracings with irregular SVT without discernible P wave, a duration of at least 30 s was further defined as AF or AFL. Critical arrhythmias were defined as the cardiac arrhythmias that included a pause ≥3 s, AVB, VT, or polymorphic VT which could be life-threatening. The data was collected and documented by the investigators and analyzed using the 14-day EZYPRO® analysis system. Arrhythmia events that were recorded by the patient's self-activated function were collected and compared between the 14-day ECG patch and 24-h Holter monitor.

2.4. Assessment of skin irritation

Skin irritation was assessed after the removal of the 14-day ECG patch using an 8-point scale (0 = no evidence of irritation; 1 = minimal erythema, barely perceptible; 2 = definite erythema, readily visible;

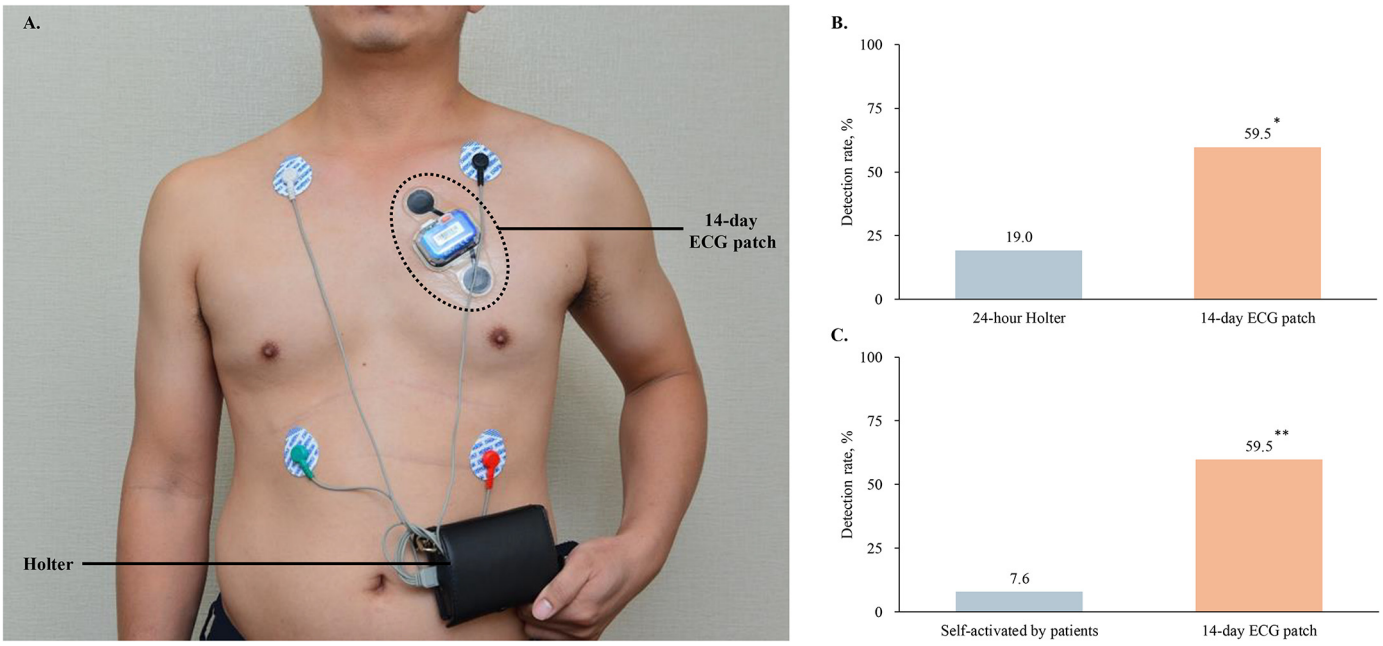

Fig. 1. The cardiac ECG monitors and the detection rates of arrhythmic events in patients with any one of the seven types of arrhythmias. **A.** The 14-day ECG patch cardiac monitor and 24-h Holter monitor. **B.** The overall detection rate among 14-day ECG patch and 24-h Holter. **C.** The detection rate among self-activated recorded events and total events detected by a 14-day ECG patch. Abbreviation: ECG, electrocardiogram. *Indicate statistically significant difference between 14-day ECG patch and 24-h Holter. **Indicate statistically significant difference between self-activated recorded events and total events.

minimal edema or minimal papular response; 3 = erythema and papules; 4 = definite edema; 5 = erythema, edema, and papules; 6 = vesicular eruption; 7 = strong reaction spreading beyond the test site).

2.5. Primary endpoint

The primary goal of the study was to compare the performance between the14-day ECG patch and a 24-h Holter monitor in the detection of arrhythmias over total wear time.

2.6. Secondary endpoints

The secondary endpoints included: (1) rate of asymptomatic arrhythmias over the 14-day total wear time; (2) occurrence rate of specific types of arrhythmias, including individual arrhythmia and critical arrhythmias, between the 14-day ECG patch and 24-h Holter monitor devices; (3) detection rate of the number of types of arrhythmias between 14-day ECG patch and 24-h Holter monitor devices over the total wear time; (4) safety issues in terms of adverse events (including serious adverse events and skin irritation) over the study period. The serious adverse events were defined as a skin irritation response score ≥ 6.

2.7. Statistical analysis

Categorical variables were presented as numbers and percentages, while continuous variables were presented as mean and standard deviation. McNemar's tests were used to compare the matched pairs of data from the 24-h Holter and 14-day ECG patch monitor. Continuous and categorical variables were compared using the student's *t*-test and Pearson's chi-square test with Yates' correction, respectively. All *P* values were 2-sided, and values of $P < 0.05$ indicated statistical significance. All statistical analyses were performed in R Studio (version 1.2.1) utilizing the R statistical language version 3.6.0. All charts were also produced in R Studio.

3. Results

3.1. Participant demographics

A total of 158 eligible participants met the enrollment criteria. Patient demographics and clinical characteristics are summarized in Table 1. The mean wear time and mean analyzable data of the 14-day ECG patch were 12.3 ± 3.2 days and 11.4 ± 3.6 days, respectively. 78.5% of patients wore the 14-day ECG patch for >10 days. One hundred and twelve (70.9%) patients completed 14-days of monitoring and 46 (29.1%) patients did not. For those who cannot wear 14-day ECG patch for 14 days or close to 14 days, the reasons included itchy skin, local sweating resulting in the 14-day ECG patch to detach early, needs to take a plane or take other examinations to avoid interference,

Table 1
Participant baseline characteristics.

Variables	Total ($N = 158$)
Wear days	12.3 ± 3.2
Analyzable days	11.4 ± 3.6
Sex	
Female, n (%)	80 (50.6)
Male, n (%)	78 (49.4)
Age, years	55.2 ± 17.2
BMI, kg/m^2	24.4 ± 4.1
Heart rate, beats/min	75.8 ± 9.2
Blood pressure, mmHg	
Systolic	128.4 ± 19.3
Diastolic	79.8 ± 13.8
Medical history	
Hypertension, n (%)	40 (25.3)
Diabetes mellitus, n (%)	14 (8.9)
CHF, n (%)	3 (1.9)
Stroke, n (%)	5 (3.2)
Transient ischemic attack, n (%)	1 (0.6)

Values are numbers (percentage) or mean ± standard deviation.
Abbreviation: BMI, body mass index; CHF, congestive heart failure.

subjects requesting for interpreting ECG data early, and early removal of the 14-day ECG patch due to emergencies (such as syncope for first aid).

3.2. 14-day ECG patch and 24-h Holter monitor detection performance

The percentage of unanalyzable ECG data per day in 14-day ECG patch was constant during the first day to the fourteenth day from 1.58 to 5.95% (Supplementary Fig. 3). The quality of ECG data was consistent and stable during the recordings of 14 days.

3.2.1. All arrhythmias

A total of 94 (59.5%) patients had an arrhythmia (any 1 of the 7 types of arrhythmias). The arrhythmia detection rate was significantly greater with the 14-day ECG patch than the 24-h Holter monitor (14-day ECG patch versus 24-h Holter: 59.5% versus 19.0%, $P < 0.001$) (Fig. 1B).

3.2.2. Asymptomatic arrhythmias

Twelve (7.6%) patients were self-aware and activated the 14-day ECG patch recorder due to symptoms of the arrhythmic events, significantly lower than the total arrhythmic events recorded by the 14-day ECG patch (self-activated versus total events: 7.6% versus 59.5%, $P < 0.001$) (Fig. 1C). Among the 94 patients in whom arrhythmias were detected, 82 (87.2%) patients were unaware of the occurrence of arrhythmic events and did not activate the recorder.

3.2.3. The specific type of arrhythmias

The 14-day ECG patch identified a significantly greater occurrence rate of arrhythmias in patients with SVT (52.5% versus 15.8%, $P < 0.001$), irregular SVT without discernible P wave (12.7% versus 4.4%, $P = 0.002$), and critical arrhythmias (16.5% versus 2.5%, $P < 0.001$) compared with 24-h Holter monitor, respectively

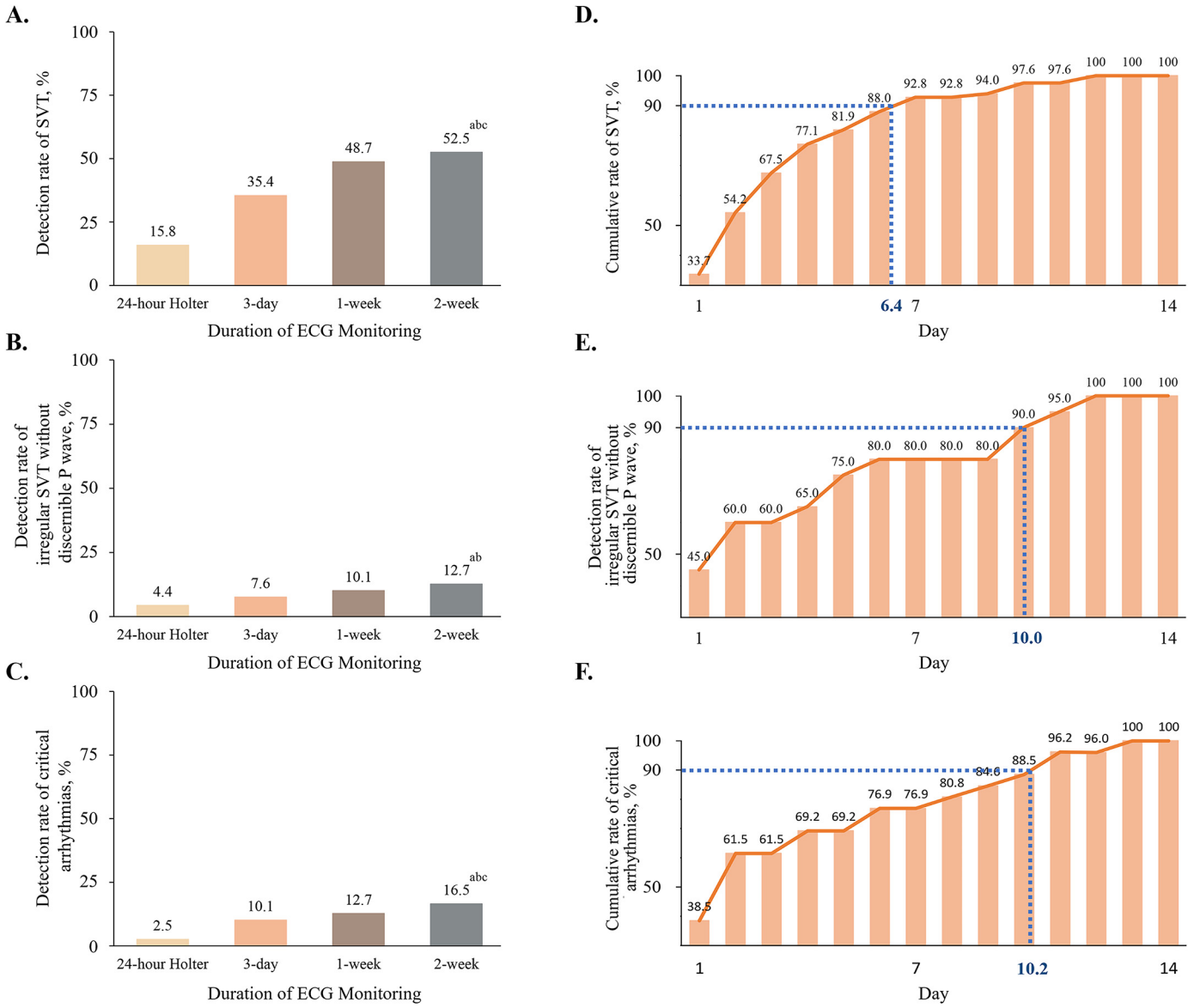

Fig. 2. The detection and cumulative rates of arrhythmias among participants with the 14-day ECG patch and 24-h Holter. **A.** The detection rate for SVT. **B.** The detection rate for irregular SVT without discernible P wave. **C.** The detection rate for critical arrhythmias. **D.** The cumulative rate of SVT identified by 14-day ECG patches according to wear time. **E.** The cumulative rate of irregular SVT without discernible P wave identified by 14-day ECG patches according to wear time. **F.** The cumulative rate of critical arrhythmias identified by 14-day ECG patches according to wear time. The critical arrhythmias included pause ≥3 s, AVB (Mobitz type II, third-degree, two to one or high degree AVB), VT, or polymorphic VT which could be life-threatening. Abbreviation: AVB, atrioventricular block; ECG, electrocardiogram; SVT, supraventricular tachycardia; VT, ventricular tachycardia. [a] Indicates the comparison between 2-week ECG monitoring and 24-h Holter ($P < 0.05$). [b] Indicates the comparison between 2-week and 3-day ECG monitoring ($P < 0.05$). [c] Indicates the comparison between 2-week and 1-week ECG monitoring ($P < 0.05$).

(Fig. 2A-2C). Among episodes of irregular SVT without discernible P wave, there were 85.7% (6/7) and 75.0% (15/20) patients with events longer than 30 s in 24-h Holter and 14-day ECG patch, respectively, which were defined as AF or AFL. In general, the 14-day ECG patch also recognized higher AF/AFL (9.5% versus 3.8%, $P = 0.042$) episodes in comparison with 24-h Holter (Supplementary Fig. 4). Increased wear time was associated with significantly greater arrhythmia detection. For SVT recorded using the 14-day ECG patch, an increased occurrence of SVT was detected over 2-weeks compared with 3-days (2-week versus 3-day: 52.5% versus 35.4%, $P < 0.001$) and 1-week monitoring (2-week versus 1-week: 52.5% versus 48.7%, $P = 0.041$) (Fig. 2A), respectively. For irregular SVT without discernible P wave recorded using the 14-day ECG patch, an increased occurrence of irregular SVT without discernible P wave was detected over 2-weeks compared with 3-days (2-week versus 3-day: 12.7% versus 7.6%, $P = 0.013$). However, the occurrence of irregular SVT without discernible P wave was similar to 2-week monitoring when compared to 1-week (2-week versus 1-week: 12.7% versus 10.1%, $P = 0.133$) (Fig. 2B). Among episodes of irregular SVT without discernible P wave, however, the occurrence of AF/AFL was similar to 2-week monitoring when compared with 3-days (2-week versus 3-day: 9.5% versus 7.0%, $P = 0.413$) and 1-week (2-week versus 1-week: 9.5% versus 8.9%, $P = 0.846$), respectively (Supplementary Fig. 4). For critical arrhythmias recorded using the 14-day ECG patch, an increased occurrence of critical arrhythmias was detected over 2-weeks compared with 3-days (2-week versus 3-day: 16.5% versus 10.1%, $P = 0.004$) and 1-week (2-week versus 1-week: 16.5% versus 12.7%, $P = 0.041$), respectively (Fig. 2C).

Further analysis was performed to determine the wear time (days) required for the 14-day ECG patch to detect most of the arrhythmias (above 90%). The detection rate for SVT was greater than 90% when wear time was longer than 6.4 days (Fig. 2D). For irregular SVT without discernible P wave and critical arrhythmias, the detection rate was greater than 90% when wear time was longer than 10.0 and 10.2 days, respectively (Fig. 2E and F).

3.2.4. Number of arrhythmic types

The 14-day ECG patch detected a significantly higher occurrence rate of arrhythmias in patients with one type of arrhythmia (41.8% versus 15.2%, $P < 0.001$), two types of arrhythmias (12.7% versus 3.8%, $P = 0.004$), and three or four arrhythmias (5.1% versus 0.0%, $P = 0.013$) compared to the 24-h Holter monitoring, respectively (Supplementary Fig. 5). The 14-day ECG patch monitor detected patients with three (3.8%) and four types of arrhythmias (1.3%), while the 24-h Holter monitor did not identify any patients with more than two types of arrhythmias (Supplementary Fig. 5).

3.3. Adverse events associated with 14-day ECG patch monitoring

There were no serious adverse events reported during the study. The mean skin irritation score was 1.5 ± 0.8 for the 14-day ECG patch. Most patients wearing the 14-day ECG patches had barely perceptible erythema (43.6%) or visible erythema and minimal edema/papular response (34.8%). The range of skin irritation scores for the 14-days ECG patch was 0–3 (Table 2).

3.4. Satisfaction survey

The satisfaction survey for the overall satisfaction during wear time was conducted in each patient after the study. A total of 155 (98.1%) patients fulfilled the questionnaires. There was a higher percentage of patients who were satisfied with 14-day ECG patch compared to 24-h Holter (14-day ECG patch versus 24-h Holter: 91.6% versus 69.0%, $P < 0.001$) (Supplementary Fig. 6).

Table 2
Adverse events of continuous 14-day ECG patch monitoring.

Variables	Total (N = 158)
[a]Serious adverse events	0
Skin irritation response score, mean	1.5 ± 0.8
0 (No evidence of irritation)	17 (10.8)
1 (Minimal erythema, barely perceptible)	69 (43.6)
2 (Definite erythema, readily visible; minimal edema or minimal papular response)	55 (34.8)
3 (Erythema and papules)	17 (10.8)
4 (Definite edema)	0
5 (Erythema, edema, and papules)	0
6 (Vesicular eruption)	0
7 (Strong reaction spreading beyond test site)	0

Values are numbers (percentage) or mean ± standard deviation.
Abbreviation: ECG, electrocardiogram.
[a] The serious adverse events were defined as scores of skin irritation response ≥6.

4. Discussion

4.1. Main findings

The 14-day ECG patch demonstrated a higher detection rate of SVT, irregular SVT without discernible P wave, AF/AFL, and critical arrhythmias and is capable of detecting multiple arrhythmias compared with a 24-h Holter monitor because of prolonged recording time. Among patients with arrhythmias, most of them (87.2%) were asymptomatic or displayed very mild symptoms and were unable to recognize by themselves. Among those patients with recorded arrhythmias, most of the arrhythmias (up to 90%) can be detected if ECG recording was prolonged above 11 days. The extended, up to 14 days, recording time is necessary for the detection of arrhythmias in patients who are suspected of arrhythmias, but were not recorded using a 24-h Holter monitor. There was also no serious adverse event in patients wearing the 14-day ECG patch.

4.2. 14-day continuous ECG monitoring detected hidden arrhythmias

Previous publications have reported 20%–30% of individuals with AF were asymptomatic, [18] and a substantial number of these patients were undiagnosed and untreated. [19,20] Early detection and treatment of AF are critical to reducing the considerable morbidity and mortality associated with such a prevalent condition. [21] While recent evidence has demonstrated that extended monitoring may be useful to detect arrhythmias in high-risk populations, such as those with a history of ischemic stroke, these studies focused primarily on identifying AF. [22,23] There is a paucity of empirical evidence describing the impact and diagnostic yield of extended and continuous monitoring for other clinically meaningful arrhythmias in addition to AF.

Compared with other existing methods for cardiac monitoring that primarily focused on detection of AF, [24] the 14-day ECG patch can detect at least 7 distinct types of arrhythmias. The present study reported the detection rates for various arrhythmias over a 14-day recording period, including SVT, irregular SVT without discernible P wave, AF/AFL, VT, polymorphic VT, AVB, and pause. By a thorough literature review, previous studies have reported incremental detection of clinically relevant arrhythmic events when the duration of monitoring was greater than 24 h as part of a 14-day monitoring period (e.g., Zio, Cardiostat or Nuvant patches). [24–28] In addition to similar results of enhanced arrhythmic detection rates, we have expanded on previous findings and comprehensively raised several issues to demonstrate the importance of extended ECG monitoring up to 14 days with novelty. Firstly, the detection rates of SVT and critical arrhythmias were significantly higher in 2-weeks than 1-week recordings. Most (up to 90%) of the recorded arrhythmias can be detected if ECG recording was expanded

between 7 and 14 days. Secondly, continuous recording is better than self-activated recording because above 50% of patients were asymptomatic. Thirdly, our study also demonstrated that a 14-day ECG patch was able to detect the occurrence of 3 or 4 different types of arrhythmias in 5.1% of all participants. The 24-h Holter monitor, however, did not detect more than 2 different types of arrhythmias in any participants. For the first time, our results suggested that prolonged ECG monitoring up to 14-days allows for the comprehensive detection of multiple and concurrent arrhythmias.

According to the 2017 ACC-AHA-HRS Task Force on Clinical Practice Guidelines and 2018 ESC Guidelines on syncope, the performance of noninvasive prolonged ECG monitoring (external or implantable) in patients with recurrent unexplained syncope was recommended to support and guide diagnosis. [29,30] Similarly, our extended 14-day continuous ECG monitoring resulted in a greater detection rate of critical arrhythmias, including pause, which is the primary cause of cardiogenic syncope. Based on these findings, we recommend prolonged ECG monitoring for 14 days in patients suspected of arrhythmias, but who were not monitored using a 24-h Holter. The extended monitoring provides additional opportunity to detect hidden arrhythmias and to allow patients to receive potentially life-saving therapy.

4.3. Continuous ECG recording is superior to self/patient-activated event recording

Prolonged ambulatory ECG monitoring provides incremental detection of potentially clinically relevant arrhythmic events that were not identified utilizing ECG monitoring in a short period. [25] The recording mode of the device, whether patient-activated or automatic/continuous affects the detection yield of arrhythmic events. Reiffel et al. reported that the diagnostic yield of an arrhythmic event using an auto-triggered memory loop recorder is at least 2 times greater than that of a patient-activated event recorder (36% versus 17%). [9] Our study also demonstrated that greater than 50% of participants with arrhythmias were not identified using the self-activated recording, which may be due to several reasons. Firstly, patients have to be aware of the symptoms of arrhythmias in order to self-activate and asymptomatic arrhythmias often go unnoticed. Secondly, patients who are aware of their symptoms may not be able to initiate the recording at the time of event onset. This may be due to several factors, one of which is consideration regarding patient mobility. These are the primary disadvantage of a self-activated event recorder compared with a continuous ECG monitor, which collectively pose risks that may lead to missed diagnoses.

4.4. 14-day of continuous ECG monitoring did not compromise patient compliance

Previous studies have suggested that traditional 24-h Holter monitoring is not sufficiently long enough to detect many types of arrhythmias. [11–13,31–33] The development of an ECG patch allows for continuous long-term uninterrupted cardiac recording and provides improved arrhythmia detection rates and greater convenience compared with other recording options. Patient compliance during long-term continuous monitoring has to be taken into consideration when evaluating the performance of such devices, as compliance is a fundamental indicator of the user experience and it can also affect arrhythmia detection rate. Chua et al. has reported that the single-lead 14-day ECG patch can be tolerated well and allowed for prolonged continuous monitoring than the 24-h Holter monitor in adults. [34] Bolourchi et al. also addressed that because of the wireless design and ability to shower, the 14-day ECG patch comes into favor with children suspected of arrhythmias. [35] However, the performance of such devices has been evaluated mostly in the United Kingdom and the United States, where the climate and humidity are different from that of Asian countries. A systemic review of 13 studies reported that the prescribed recording time was 14 days with the Zio patch, however the actual patient unweighted mean wear time was 10.4 days (weighted: 9.5 days; media ranging from 5 to 14 days). [36] Compared with other continuous monitoring options, the 14-day ECG patch in the present study demonstrated higher patient compliance. In our study, a total of 78.5% of the patients wore the patch for more than 10 days, with an average wear time of 12.3 days. In addition, there were no serious adverse events during the total wear time in the present study. Overall, these results suggest that the 14-day ECG patch is safe and tolerable for patients to wear for a prolonged period, thus providing continuous monitoring and improved probability for accurate recording of arrhythmias.

4.5. Limitations

Data on clinical outcomes following monitoring in the participants were not available, so the direct clinical impact from the detection of arrhythmias identified by monitors in our study could not be delineated. Although all the patients wore 24-h Holter and 14-day ECG patches, the skin irritation score was only recorded after take-off of the 14-day ECG patch but not after take-off of the 24-h Holter device. The skin irrigation score cannot be compared between 24-h Holter and 14-day ECG patch. Even though the satisfaction measurement is higher for 14-day ECG patch, we did not investigate the question about the willing to re-wear both devices if needed. In the main text, we analyzed the detection rate of irregular SVT without discernible P wave between 24-h Holter and 14-day ECG patch. However, the clinical significance remained unknown. Although a retrospective study demonstrated that short irregular SVT without P wave (< 30 s) likely represented early stages of AF or atrial myopathy and was associated with incident AF and ischemic stroke, [17] further prospective studies are required to validate this finding.

5. Conclusions

The 14-day ECG patch outperformed 24-h Holter monitoring in the detection of overall, asymptomatic, critical, and multiple arrhythmias. It is a safe option for extended ECG monitoring and provides the opportunity to identify individuals with hidden arrhythmias, especially those with critical arrhythmias. The extended recording time, up to 14 days with the 14-day ECG patch is necessary for the detection of arrhythmias in patients suspected of arrhythmias who were not identified using 24-h Holter monitors.

Sources of funding

This work was supported by grants from the Szu-Yuan Research Foundation of Internal Medicine and Taipei Veterans General Hospital (Grant No.: V109C-001).

Declaration of Competing Interest

None.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.03.015.

References

[1] G.Y.H. Lip, F.R. Heinzel, F. Gaita, J.R.G. Juanatey, J.Y. Le Heuzey, T. Potpara, et al., European Heart Rhythm Association/Heart Failure Association joint consensus

document on arrhythmias in heart failure, endorsed by the Heart Rhythm Society and the Asia Pacific Heart Rhythm Society, EP Europace. 18 (2015) 12–36.
[2] E. Fung, M.R. Järvelin, R.N. Doshi, J.S. Shinbane, S.K. Carlson, L.P. Grazette, et al., Electrocardiographic patch devices and contemporary wireless cardiac monitoring, Front. Physiol. 6 (2015) 149.
[3] S.S. Chugh, R. Havmoeller, K. Narayanan, D. Singh, M. Rienstra, E.J. Benjamin, et al., Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study, Circulation. 129 (2014) 837–847.
[4] F. Rahman, G.F. Kwan, E.J. Benjamin, Global epidemiology of atrial fibrillation, Nat. Rev. Cardiol. 11 (2014) 639–654.
[5] J. Liao, Z. Khalid, C. Scallan, C. Morillo, M. O'Donnell, Noninvasive cardiac monitoring for detecting paroxysmal atrial fibrillation or flutter after acute ischemic stroke: a systematic review, Stroke. 38 (2007) 2935–2940.
[6] D.G. Katritsis, G.C. Siontis, A.J. Camm, Prognostic significance of ambulatory ECG monitoring for ventricular arrhythmias, Prog. Cardiovasc. Dis. 56 (2013) 133–142.
[7] P.M. Barrett, R. Komatireddy, S. Haaser, S. Topol, J. Sheard, J. Encinas, et al., Comparison of 24-hour Holter monitoring with 14-day novel adhesive patch electrocardiographic monitoring, Am. J. Med. 127 (2014) 95.e11-7.
[8] W.M. Smith, F. Riddell, M. Madon, M.J. Gleva, Comparison of diagnostic value using a small, single channel, P-wave centric sternal ECG monitoring patch with a standard 3-lead Holter system over 24 hours, Am. Heart J. 185 (2017) 67–73.
[9] J.A. Reiffel, R. Schwarzberg, M. Murry, Comparison of autotriggered memory loop recorders versus standard loop recorders versus 24-hour Holter monitors for arrhythmia detection, Am. J. Cardiol. 95 (2005) 1055–1059.
[10] J. Wiesel, M. Spinelli, Subclinical atrial fibrillation and the risk of stroke, N. Engl. J. Med. 366 (2012) 1351 author reply 2-3.
[11] M.A. Rosenberg, M. Samuel, A. Thosani, P.J. Zimetbaum, Use of a noninvasive continuous monitoring device in the management of atrial fibrillation: a pilot study, Pacing Clin. Electrophysiol. PACE. 36 (2013) 328–333.
[12] A. Kaura, L. Sztriha, F.K. Chan, J. Aeron-Thomas, N. Gall, B. Piechowski-Jozwiak, et al., Early prolonged ambulatory cardiac monitoring in stroke (EPACS): an open-label randomised controlled trial, Eur. J. Med. Res. 24 (2019) 25.
[13] S. Pradhan, J.A. Robinson, J.K. Shivapour, C.S. Snyder, Ambulatory arrhythmia detection with ZIO® XT patch in pediatric patients: a comparison of devices, Pediatr. Cardiol. 40 (2019) 921–924.
[14] J. Brugada, D.G. Katritsis, E. Arbelo, F. Arribas, J.J. Bax, C. Blomström-Lundqvist, et al., 2019 ESC Guidelines for the management of patients with supraventricular tachycardia. The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC), Eur. Heart J. 41 (2020) 655–720.
[15] R.L. Page, J.A. Joglar, M.A. Caldwell, H. Calkins, J.B. Conti, B.J. Deal, et al., 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the heart rhythm society, J. Am. Coll. Cardiol. 67 (2016) 1575–1623.
[16] G. Hindricks, T. Potpara, N. Dagres, E. Arbelo, J.J. Bax, C. Blomström-Lundqvist, et al., 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS), Eur. Heart J. 42 (2021) 373–498.
[17] L.S.B. Johnson, A.P. Persson, P. Wollmer, S. Juul-Möller, T. Juhlin, G. Engström, Irregularity and lack of p waves in short tachycardia episodes predict atrial fibrillation and ischemic stroke, Heart Rhythm. 15 (2018) 805–811.
[18] M. Zoni-Berisso, F. Lercari, T. Carazza, S. Domenicucci, Epidemiology of atrial fibrillation: European perspective, Clin. Epidemiol. 6 (2014) 213–220.
[19] N. Lowres, L. Neubeck, J. Redfern, S.B. Freedman, Screening to identify unknown atrial fibrillation. A systematic review, Thromb. Haemost. 110 (2013) 213–222.
[20] A. Kishore, A. Vail, A. Majid, J. Dawson, K.R. Lees, P.J. Tyrrell, et al., Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis, Stroke. 45 (2014) 520–526.
[21] J.J. You, D.E. Singer, P.A. Howard, D.A. Lane, M.H. Eckman, M.C. Fang, et al., Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines, Chest. 141 (2012) e531S-e75S.
[22] A.C. Flint, N.M. Banki, X. Ren, V.A. Rao, A.S. Go, Detection of paroxysmal atrial fibrillation by 30-day event monitoring in cryptogenic ischemic stroke: the Stroke and Monitoring for PAF in Real Time (SMART) registry, Stroke. 43 (2012) 2788–2790.
[23] D.J. Gladstone, M. Spring, P. Dorian, V. Panzov, K.E. Thorpe, J. Hall, et al., Atrial fibrillation in patients with cryptogenic stroke, N. Engl. J. Med. 370 (2014) 2467–2477.
[24] N.R. Jones, C.J. Taylor, F.D.R. Hobbs, L. Bowman, B. Casadei, Screening for atrial fibrillation: a call for evidence, Eur. Heart J. 41 (2020) 1075–1085.
[25] M.D. Solomon, J. Yang, S.H. Sung, M.L. Livingston, G. Sarlas, J.C. Lenane, et al., Incidence and timing of potentially high-risk arrhythmias detected through long term continuous ambulatory electrocardiographic monitoring, BMC Cardiovasc. Disord. 16 (2016) 35.
[26] C. Dussault, H. Toeg, M. Nathan, Z.J. Wang, J.F. Roux, E. Secemsky, Electrocardiographic monitoring for detecting atrial fibrillation after ischemic stroke or transient ischemic attack: systematic review and meta-analysis, Circ. Arrhythm. Electrophysiol. 8 (2015) 263–269.
[27] E. Korompoki, A. Del Giudice, S. Hillmann, U. Malzahn, D.J. Gladstone, P. Heuschmann, et al., Cardiac monitoring for detection of atrial fibrillation after TIA: a systematic review and meta-analysis, Int. J. Stroke 12 (2017) 33–45.
[28] M.P. Turakhia, D.D. Hoang, P. Zimetbaum, J.D. Miller, V.F. Froelicher, U.N. Kumar, et al., Diagnostic utility of a novel leadless arrhythmia monitoring device, Am. J. Cardiol. 112 (2013) 520–524.
[29] M. Brignole, A. Moya, F.J. de Lange, J.C. Deharo, P.M. Elliott, A. Fanciulli, et al., 2018 ESC Guidelines for the diagnosis and management of syncope, Eur. Heart J. 39 (2018) 1883–1948.
[30] W.K. Shen, R.S. Sheldon, D.G. Benditt, M.I. Cohen, D.E. Forman, Z.D. Goldberger, et al., 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the heart rhythm society, Circulation. 136 (2017) e60–e122.
[31] R.C. Seet, P.A. Friedman, A.A. Rabinstein, Prolonged rhythm monitoring for the detection of occult paroxysmal atrial fibrillation in ischemic stroke of unknown cause, Circulation. 124 (2011) 477–486.
[32] P. Higgins, P.W. MacFarlane, J. Dawson, G.T. McInnes, P. Langhorne, K.R. Lees, Noninvasive cardiac event monitoring to detect atrial fibrillation after ischemic stroke: a randomized, controlled trial, Stroke. 44 (2013) 2525–2531.
[33] D. Schreiber, A. Sattar, D. Drigalla, S. Higgins, Ambulatory cardiac monitoring for discharged emergency department patients with possible cardiac arrhythmias, West. J. Emerg. Med. 15 (2014) 194–198.
[34] S.K. Chua, L.C. Chen, L.M. Lien, H.M. Lo, Z.Y. Liao, S.P. Chao, et al., Comparison of arrhythmia detection by 24-hour Holter and 14-day continuous electrocardiography patch monitoring, Acta Cardiol. Sin. 36 (2020) 251–259.
[35] M. Bolourchi, E.S. Silver, D. Muwanga, E. Mendez, L. Liberman, Comparison of Holter with Zio patch electrocardiography monitoring in children, Am. J. Cardiol. 125 (2020) 767–771.
[36] M. Yenikomshian, J. Jarvis, C. Patton, C. Yee, R. Mortimer, H. Birnbaum, et al., Cardiac arrhythmia detection outcomes among patients monitored with the Zio patch system: a systematic literature review, Curr. Med. Res. Opin. 35 (2019) 1659–1670.