frontiers | Research Topics

Wearable devices for cardiac rhythm monitoring, volume II

Edited by
Emma Svennberg, David Duncker and Dominik Linz

Published in
Frontiers in Cardiovascular Medicine

FRONTIERS EBOOK COPYRIGHT STATEMENT

The copyright in the text of individual articles in this ebook is the property of their respective authors or their respective institutions or funders. The copyright in graphics and images within each article may be subject to copyright of other parties. In both cases this is subject to a license granted to Frontiers.

The compilation of articles constituting this ebook is the property of Frontiers.

Each article within this ebook, and the ebook itself, are published under the most recent version of the Creative Commons CC-BY licence. The version current at the date of publication of this ebook is CC-BY 4.0. If the CC-BY licence is updated, the licence granted by Frontiers is automatically updated to the new version.

When exercising any right under the CC-BY licence, Frontiers must be attributed as the original publisher of the article or ebook, as applicable.

Authors have the responsibility of ensuring that any graphics or other materials which are the property of others may be included in the CC-BY licence, but this should be checked before relying on the CC-BY licence to reproduce those materials. Any copyright notices relating to those materials must be complied with.

Copyright and source acknowledgement notices may not be removed and must be displayed in any copy, derivative work or partial copy which includes the elements in question.

All copyright, and all rights therein, are protected by national and international copyright laws. The above represents a summary only. For further information please read Frontiers' Conditions for Website Use and Copyright Statement, and the applicable CC-BY licence.

ISSN 1664-8714
ISBN 978-2-8325-4612-3
DOI 10.3389/978-2-8325-4612-3

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Wearable devices for cardiac rhythm monitoring, volume II

Topic editors

Emma Svennberg — Karolinska University Hospital, Sweden

David Duncker — Hannover Heart Rhythm Center, Department of Cardiology and Angiology, Hannover Medical School, Germany

Dominik Linz — Maastricht University Medical Centre, Netherlands

Citation

Svennberg, E., Duncker, D., Linz, D., eds. (2024). *Wearable devices for cardiac rhythm monitoring, volume II*. Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-8325-4612-3

Table of contents

05 Continuous Heart Rate Monitoring for Automatic Detection of Life-Threatening Arrhythmias With Novel Bio-Sensing Technology
Ehud Chorin, Aviram Hochstadt, Arie Lorin Schwartz, Gil Matz, Sami Viskin and Raphael Rosso

10 A novel blood pressure monitoring technique by smart HUAWEI WATCH: A validation study according to the ANSI/AAMI/ISO 81060-2:2018 guidelines
Lili Wang, Hong Xian, Jiajun Guo, Weihao Li, Jiaqi Wang, Qing Chen, Xiaoyu Fu, Hongbao Li, Qin Chen, Wei Zhang and Yucheng Chen

16 The role of digital health in the cardiovascular learning healthcare system
Ragasnehith Maddula, James MacLeod, Tyson McLeish, Sabrina Painter, Austin Steward, Generika Berman, Abdulaziz Hamid, Mohamed Abdelrahim, Jeffrey Whittle and Sherry Ann Brown for the Connected, Health Innovation Research Program (C.H.I.R.P.), Cardiology Oncology Innovation Network (COIN), Cardio-Oncology Artificial Intelligence Informatics Precision (CAIP) research team investigators

29 An implantable loop recorder or smartphone based single-lead electrocardiogram to detect arrhythmia in adults with congenital heart disease?
Maarten A. Koole, Dirkjan Kauw, Kirsten M. Kooiman, Joris R. de Groot, Danielle Robbers-Visser, Igor I. Tulevski, Barbara J. Mulder, Berto J. Bouma and Mark J. Schuuring

37 Wrist-worn device combining PPG and ECG can be reliably used for atrial fibrillation detection in an outpatient setting
Harri Juhani Saarinen, Atte Joutsen, Kirsi Korpi, Tuomas Halkola, Marko Nurmi, Jussi Hernesniemi and Antti Vehkaoja

46 Assessing physical activity with the wearable cardioverter defibrillator in patients with newly diagnosed heart failure
Konstantinos Iliodromitis, Zsuzsanna Balogh, Filippos Triposkiadis, Spyridon Deftereos, Dimitrios Vrachatis, Nana-Yaw Bimpong-Buta, Fabian Schiedat and Harilaos Bogossian

54 Six-lead electrocardiography compared to single-lead electrocardiography and photoplethysmography of a wrist-worn device for atrial fibrillation detection controlled by premature atrial or ventricular contractions: six is smarter than one
Justinas Bacevicius, Neringa Taparauskaite, Ricardas Kundelis, Daivaras Sokas, Monika Butkuviene, Guoste Stankeviciute, Zygimantas Abramikas, Aiste Pilkiene, Ernestas Dvinelis, Justina Staigyte, Julija Marinskiene, Deimile Audzijoniene, Marija Petrylaite, Edvardas Jukna, Albinas Karuzas, Vytautas Juknevicius, Rusne Jakaite, Viktorija Basyte-Bacevice, Neringa Bileisiene, Ignas Badaras, Margarita Kiseliute, Gintare Zarembaite, Modestas Gudauskas, Eugenijus Jasiunas, Linda Johnson, Vaidotas Marozas and Audrius Aidietis

67 Photoplethysmography-documented atrial fibrillation in the first week after catheter ablation is associated with lower success rates
Martin Manninger, Astrid N. L. Hermans, Andrei-Antonio Caracioni, Ursula Rohrer, Anna-Sophie Eberl, Kevin Vernooy, Andreas Zirlik, Dominik Linz and Daniel Scherr

75 Searching for atrial fibrillation post stroke: is it time for digital devices?
Olivier Piot and Céline Guidoux

82 Real-time heart rate variability according to ambulatory glucose profile in patients with diabetes mellitus
Sung Il Im, Soo Jin Kim, Su Hyun Bae, Bong Joon Kim, Jung Ho Heo, Su kyoung Kwon, Sung Pil Cho, Hun Shim, Jung Hwan Park, Hyun Su Kim and Chul Ho Oak

90 Smart devices to measure and monitor QT intervals
Leendert J. Hoek, Jan Leendert P. Brouwer, Adriaan A. Voors and Alexander H. Maass

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 14 July 2021
doi: 10.3389/fcvm.2021.707621

Continuous Heart Rate Monitoring for Automatic Detection of Life-Threatening Arrhythmias With Novel Bio-Sensing Technology

Ehud Chorin[1], Aviram Hochstadt[1], Arie Lorin Schwartz[1], Gil Matz[2], Sami Viskin[1] and Raphael Rosso[1]*

[1] Department of Cardiology, Tel Aviv Sourasky Medical Center and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel, [2] CardiacSense, Tel Aviv, Israel

Aims: Assessing the effectiveness of novel bio-sensing technology (CardiacSense), for accuracy and reliability of automatic detection of life-threatening arrhythmias.

Methods and Results: This prospective study consisted of Eighteen patients (13 males and 5 females, mean age 59.4 ± 21.3 years) undergoing induction of ventricular tachycardia/fibrillation or provocation of transient ventricular asystole. We tested the detection of provoked ventricular arrhythmias by a wrist-worn watch-like device which uses photoplethysmography (PPG) technology to detect the cardiac rhythm. We used simultaneous electrocardiographic (ECG) recordings as gold standard for arrhythmia definition and confirmation of beat-to-beat detection. A total of 1,527 QRS complexes were recorded simultaneously by ECG and PPG. The overall correlation between the ECG (R-R intervals) and the PPG (G-G intervals) was high, with a correlation coefficient of $R = 0.949$ ($p < 0.001$). The device accurately detected all events of mimicked life endangering arrhythmias, including five events of transient (adenosine-induced) ventricular asystole as well as seven episodes of monomorphic ventricular tachycardia and 6 events of ventricular fibrillation.

Conclusion: This proof-of-concept study suggests that wearable devices using PPG technology, currently used to detect atrial fibrillation, may also have a role as automatic detectors of life-threatening arrhythmias.

Keywords: cardiac arrest, automatic arrhythmia detectors, photoplethysmography, ECG, sudden cardiac death

OPEN ACCESS

Edited by:
Daniel M. Johnson, The Open University, United Kingdom

Reviewed by:
David Duncker, Hannover Medical School, Germany
Andrew D. Blaufox, Cohen Children's Medical Center, United States
Mark J. Schuuring, Amsterdam University Medical Center, Netherlands

****Correspondence:***
Ehud Chorin
udichorin5@gmail.com

Specialty section:
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

Received: *10 May 2021*
Accepted: *21 June 2021*
Published: *14 July 2021*

Citation:
Chorin E, Hochstadt A, Schwartz AL, Matz G, Viskin S and Rosso R (2021) Continuous Heart Rate Monitoring for Automatic Detection of Life-Threatening Arrhythmias With Novel Bio-Sensing Technology. Front. Cardiovasc. Med. 8:707621. doi: 10.3389/fcvm.2021.707621

INTRODUCTION

Out of hospital sudden cardiac death (SCD) is very common worldwide and accounts for more than 5% of all crude mortality in the United States (1). Despite advances in the treatment and prevention of heart disease, the outcome of patients experiencing sudden cardiac arrest (SCA) remains poor, with rates of survival to hospital discharge ranging from 1.3 to 20.7% (2).

A major predictor of prognosis in SCA is response time, provision of cardiopulmonary resuscitation and a witnessed event (3). It is therefore imperative to shorten as much as possible the time to detection of SCA for an immediate initiation of CPR and preforming defibrillation as soon as possible (4). This need is emphasized in the American Heart Association cardiopulmonary

resuscitation guidelines as the first link in the "out of hospital chain of survival" is "recognition of cardiac arrest and activation of the emergency response system" (4). Improving this link is crucial and most approaches are focused on public education of recognizing a cardiac arrest and initiating CPR (4). However, a vast percentage of SCA occurs during sleep or unwitnessed, thus making bystander early recognition impossible and significantly lowering chances of CPR success (5).

A continuous heart-rate monitoring device, comfortable enough to be worn all of the time and reliable enough to detect potentially life-threatening arrhythmias, could trigger the alarm that would start the chain of survival thus offering a better prognosis when a SCA occurs. We report here of our study with such a device, that uses photplatysmogrphy (PPG) technology, tested on patients with induced arrhythmias in a controlled setting as surrogate for life-threatening ventricular arrhythmias. Of note, heart-monitors using PPG technology are already in use for the detection of atrial fibrillation (6–11). However, to the best of our knowledge, this is the first time that the ability of a PPG-based "heart-watch" for detecting potentially life-threatening arrhythmias is reported.

METHODS

Study Design and Patient Selection

This is a single-center, prospective study, assessing the effectiveness of novel bio-sensing technology (CardiacSense), for accuracy and reliability of automatic detection of life-threatening arrhythmias. The same PPG devices have been used to continuously detect sinus rhythm in ambulatory volunteers (7) and for the automatic detection of atrial fibrillation in patients at rest (6).

The study-group consisted of consecutive patients undergoing electrophysiological studies (EPS) or defibrillator implantation [with ventricular tachycardia/fibrillation (VT/VF) induction] or ablation procedures that included adenosine injection (provoking transient ventricular asystole). The study was approved by our Institutional Review Board (IRB number TLV 0066-16). All patients provided informed consent. Importantly, all the electrophysiologic studies performed during the course of the study, and all the attempts to provoke arrhythmias during the course of these procedures, were clinically indicated. For example, intravenous injection of high doses of adenosine (invariably provoking transient ventricular asystole due to sinus arrest or transient atrioventricular block) is standard practice during ablation of atrial fibrillation to test for pulmonary vein reconnection.

The Bio-Sensing Technology (CardiacSense)

The CardiacSense is a wrist-worn watch-like device, specifically designed to detect cardiac arrhythmias. PPG is a simple optical technique that can be used to detect blood volume changes in the microvascular bed of tissues. Using this technology, it is possible to accurately detect the pulse rate and pulse pressure on a beat-by-beat basis. PPG is used for atrial fibrillation detection by other manufacturers, including the Apple Watch (8–11).

The algorithm that detects a life-threating arrhythmia is based on two parameters: The first is the length of the RR interval (recorded as simultaneous interval between consecutive PPG signals, termed G-G interval), in order to detect episodes of predefined extreme bradycardia or tachycardia. The second, uses the signal to noise ratio of the PPG measurements, which correlates with the pulse pressure and thus correlate with cardiac output and tissue perfusion pressure. Prospective participants underwent simultaneous, continuous PPG (CardiacSense watch placed on the wrist) and ECG recordings during the entire procedure. The ECG recording was the gold standard used for analyzing the simultaneous PPG recording. Specifically, all cardiac intervals in ECG recordings (denoted as R-R interval) are compared with the quasi-simultaneous (delayed by a few milliseconds) PPG signals (denoted as G-G intervals) (**Figure 1**). Time to detection of cardiac arrest was set arbitrarily at 8 s to prevent false negative alert due to effect of rapid pacing or ventricular extrastimulation at the time of VT provocation during the EPS procedures.

Statistics

All data is summarized and displayed as number (and percentage) for categorical variables. Differences between RR and GG intervals was compared using the paired sample *t*-test. Accuracy was determined using the Pearson correlation test. Significant *p*-values were considered when $p < 0.05$. All calculations were done using SPSS v.24 from IBM, Armonk, Virginia.

RESULTS

Study Population

Eighteen patients (13 males and 5 females, mean age 59.4 ± 21.3 years) participated in the study of simulated cardiac arrest events that were recorded with simultaneously with PPG and ECG (**Table 1**). The events simulating life-threatening arrhythmias included seven events of VT during electrophysiological studies, seven events of induced VF during defibrillator implantation and five events of transient ventricular asystole provocation adenosine injection.

Detection of Ventricular Tachycardia and Ventricular Fibrillation by the Device

During electrophysiological studies and defibrillation threshold testing (DFT), 7 VT events and 6 VF events were induced, all of which were detected by the PPG algorithm. Representative examples are shown in **Figure 1**. However, the VF events and one event of fast monomorphic (presumably hypotensive) VT, were detected as "asystole" rather than as very rapid tachyarrhythmias.

Detection of Asystole by the Device

Adenosine test provoked 5 transient ventricular asystole events, all of which were detected by the PPG algorithm. Representative examples are shown in **Figure 1D**.

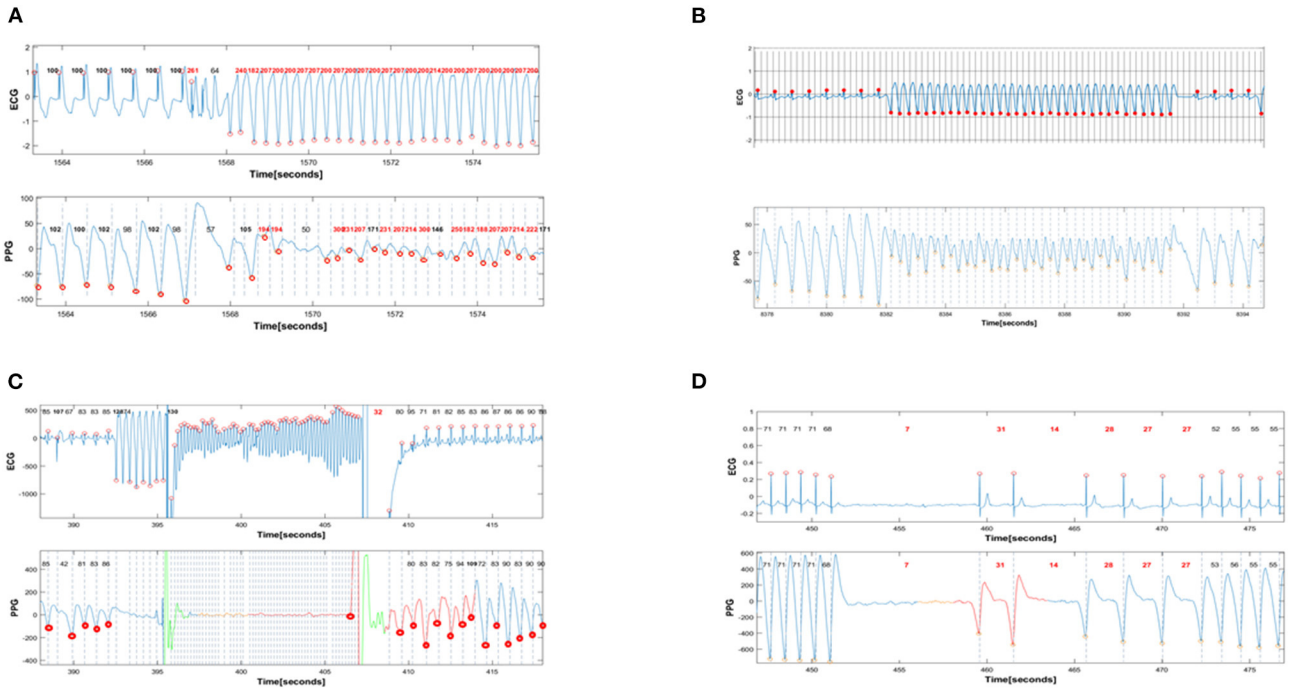


FIGURE 1 | Simultaneous PPG and ECG recordings during provoked arrhythmias. In all panels, the red dots denote the timing of automatic detection of a QRS complex (R-R intervals) or a PPG signal (G-G intervals). The interval between red dots dictates the R-R (and G-G) interval that is automatically detected and annotated as beat-to-beat heart rate in beats/min. **(A)** shows the induction of monomorphic VT with programmed ventricular stimulation. The first 6 complexes are ventricular paced beats with a basic cycle length of 600 msec. All these beats are appropriately detected by PPG, with a heart rate of 100 beats/min in the ECG recorder and 98 −102 betas/min in the PPG recorder. Then there are 3 beats of ventricular extrastimulation with very short coupling interval. Only one of these 3 extrastimuli is detected by PPG. This is followed by an induced fast sustained VT (ventricular rate 210 beats/min). Except for the initial 9 beats of VT, almost all subsequent cardiac beats are also detected with a rate >200/min by PPG signals. **(B)**: Spontaneous ventricular tachycardia with a rate of 215 beats/min that terminates spontaneously after 10 s. All sinus complexes and all VT complexes detected by the ECG are also detected by PPG. Note the immediate decrement and subsequent alternans in PPG amplitude during VT, reflecting the reduced cardiac output during VT. Nevertheless, there is appropriate detection of VT by the PPG recorder. **(C)**: Induction of VF during ICD implantation. During sinus rhythm, eight beats of ventricular pacing are followed by a low energy shock delivered on the T-wave to induce VF that is eventually terminated by the ICD shock. The VF is falsely detected as "asystole" by PPG. **(D)**: Induced transient complete AV block provoked by adenosine and leading to 9 s of ventricular asystole. The prolonged ventricular asystole, as well as shorter subsequent pauses, are correctly detected by PPG.

TABLE 1 | Baseline characteristics, $n = 18$.

Variable	
Age–mean (SD)	59.4 (21.3)
Male gender	13 (72.2)
DM	4 (22.2)
HTN	8 (44.4)
EF% mean (SD)	48.63 (12.71)
AF	6 (33.3)
Brugada syndrome	3 (16.6)
DFT after ICD implant	5 (27.7)

Measuring Accuracy of the PPG Detection or RR Interval Length

A total of 1,527 QRS complexes were recorded simultaneously by ECG and PPG during EPS, out of which 522 (34.2%) were recorded during procedures involving adenosine testing for provocation of asystole, 320 (20.1%) during procedures involving VF provocation and 685 (44.9%) during VT provocation. The overall correlation between the R-R and the G-G intervals was high, with a correlation coefficient of $R = 0.949$ ($p < 0.001$). There was a small but statistically significant difference between RR and GG intervals: the former being, as a group, shorter than the simultaneously recorded G-G intervals by 16.9 ± 209 msec, $p = 0.002$. Of note, these results do not apply to the VF and rapid VT episodes that appeared as "asystole" in the PPG recorder.

Measuring Accuracy of Cardiacsense Detection Algorithm

Out of the 18 events of cardiac arrest, all were detected by the PPG algorithm yielding a sensitivity of 100%. However, all VF episodes and one episode of rapid monomorphic VT were detected as "asystolic arrest" (rather than tachyarrhythmia-related arrest) due to absence of minimal amplitude PPG signals during tachyarrhythmias causing low- or no cardiac output.

DISCUSSION

This proof-of-concept study suggests that wearable devices using PPG technology, currently used to detect atrial fibrillation (6–11),

may also have a role as automatic detectors of life-threatening arrhythmias. PPG-based heart-watches, like the Apple watch, have already been used to detect atrial fibrillation in large-scale studies (9, 11). We therefore speculated that the same devices could prove to be of use for the automatic detection of life-threatening ventricular arrhythmias.

Automatic arrhythmia detectors could draw the attention of household members (or individuals nearby in public places) with visual and audible alarms. The device could not only alert bystanders to an event of serious nature but could also instruct them to preform CPR, as this is often delayed even in populated settings. Furthermore, automatic arrhythmia detectors could communicate via mobile phone or Wi-Fi with Emergency Medical Services, providing them with PPG recordings of the event and with the patient's exact location. Automatic detectors of life-threatening arrhythmias could ultimately be designed to interact with drone networks delivering automatic external defibrillator (EAD) devices. A remaining concern remains the issue of false alarms.

The possibility of excessive false alarms must be addressed. With the newest generation of the Apple-Watch, which offers the possibility of ECG confirmation after automatic detection of atrial fibrillation by PPG sensors (also available in the device tested here), there were no events of false-positive detection of atrial fibrillation (9). To our knowledge, the Apple-Watch has not been used for detection of life-threatening arrhythmias. In a recent study of healthy volunteers who tested the present PPG-signal detector (using simultaneous Holter recordings as gold standard) while walking and/or performing daily activities, 0.7% of PPG recorded beats could not be matched to ECG re- corded beats and were considered false-detected (7). The issue of false alarms has been addressed by investigators of the wearable defibrillator, where a false alarm could actually trigger a painful inappropriate shock (12). When the wearable defibrillator senses a fast cardiac rhythm in the "VF zone," it sounds an audible alarm. True VF is assumed to lead within seconds to loss unconsciousness. In contrast, patients with false-positive detection of VF can press a "shock-hold" button that will prevent the delivery of inappropriate shock for as long as the patient remains consiuous thus holding the button. Similar strategies for dealing with potential false alarm detections could be adopted for devices like CardiacSense. In the event of an automatic detection of a "life-threatening arrhythmia," the patient would be prompted (by vibratory alarm) to perform an ECG via the same watch (as done in the Apple Watch). This ECG would prove or disprove the arrhythmia detection.

Our study has several limitations. The number of arrhythmic events tested was small. However, as a proof of concept, and knowing that each ECG signal triggers cardiac output that, in turn, triggers a PPG signal, it is fairly clear that additional arrhythmic events will add little information. A more important limitation relates to the fact that all patients were studied while resting, sedated, in a supine position. It remains to be demonstrated that arrhythmia detection is reliable in ambulatory and active patients. However, this particular PPG sensor has been shown to detect cardiac rhythm with fair accuracy in ambulatory patients in sinus rhythm (6). Finally, hypotensive VT and all VF events were misdiagnosed as "bradyasystolic arrest." The last limitation is acceptable because the sequence of events that should follow any alarms triggered by "cardiac arrest detection," regardless of the arrhythmia causing it, should ultimately lead to the deployment of AEDs designed to distinguish between shockable and non-shockable ventricular arrhythmias during cardiac arrest.

CONCLUSION

The results of this proof-of-concept study suggest that PPG-based arrhythmia detectors, currently in use for the detection of atrial fibrillation, could be of use of the immediate detection of life-threatening arrhythmias.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Tel Aviv Medical Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EC, AH, AS, GM, SV, and RR have all participated in the data acquisition, study design, and writing of the research. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Chugh SS, Jui J, Gunson K, Stecker EC, John BT, Thompson B, et al. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. Community. *J Am Coll Cardiol.* (2004) 44:1268–75. doi: 10.1016/j.jacc.2004.06.029
2. Nichol G, Stiell IG, Laupacis A, Pham B, Maio VJ, Wells GA. A cumulative meta-analysis of the effectiveness of defibrillator-capable emergency medical services for victims of out-of-hospital cardiac arrest. *Ann Emerg Med.* (1999) 34:517–25. doi: 10.1016/S0196-0644(99)80054-7
3. Sasson C, Rogers MA, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes.* (2010) 3:63–81. doi: 10.1161/CIRCOUTCOMES.109.889576
4. Iwami T, Nichol G, Hiraide A, Hayashi Y, Nishiuchi T, kajino K, et al. Continuous improvements in "chain of survival"

increased survival after out-of-hospital cardiac arrests: a large-scale population-based study. *Circulation.* (2009) 119:728–34. doi: 10.1161/CIRCULATIONAHA.108.802058
5. Kuisma M, Jaara K. Unwitnessed out-of-hospital cardiac arrest: is resuscitation worthwhile? *Ann Emerg Med.* (1997) 30:69–75. doi: 10.1016/S0196-0644(97)70114-8
6. Hochstadt A, Chorin E, Viskin S, Schwartz AL, Lubman N, Rosso R. Continuous heart rate monitoring for automatic detection of atrial fibrillation with novel bio-sensing technology. *J Electrocardiol.* (2019) 52:23–7. doi: 10.1016/j.jelectrocard.2018.10.096
7. Hochstadt A, Havakuk O, Chorin E, Schwartz AL, Merdler I, Laufer M, et al. Continuous heart rhythm monitoring using mobile photoplethysmography in ambulatory patients. *J Electrocardiol.* (2020) 60:138–41. doi: 10.1016/j.jelectrocard.2020.04.017
8. Marcus GM. The apple watch can detect atrial fibrillation: so what now? *Nat Rev Cardiol.* (2020) 17:135–6. doi: 10.1038/s41569-019-0330-y
9. Seshadri DR, Bittel B, Browsky D, Houghtaling P, Drummond CK, Desai MY, et al. Accuracy of apple watch for detection of atrial fibrillation. *Circulation.* (2020) 141:702–3. doi: 10.1161/CIRCULATIONAHA.119.044126
10. Wasserlauf J, You C, Patel R, Valys A, Albert D, Passman R. Smartwatch performance for the detection and quantification of atrial fibrillation. *Circ Arrhythm Electrophysiol.* (2019) 12:e006834. doi: 10.1161/CIRCEP.118.006834
11. Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, et al. Large-scale assessment of a smartwatch to identify atrial fibrillation. *N Engl J Med.* (2019) 381:1909–17. doi: 10.1056/NEJMoa1901183
12. Adler A, Halkin A, Viskin S. Wearable cardioverter-defibrillators. *Circulation.* (2013) 127:854–60. doi: 10.1161/CIRCULATIONAHA.112.146530

Conflict of Interest: GM designed the detection algorithm for CardiacSense. SV is Chief Medical Officer for the cardiac arrhythmia section at CardiacSense.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2021 Chorin, Hochstadt, Schwartz, Matz, Viskin and Rosso. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 11 October 2022
DOI 10.3389/fcvm.2022.923655

Check for updates

OPEN ACCESS

EDITED BY
Pietro Amedeo Modesti,
University of Florence, Italy

REVIEWED BY
Fabio Angeli,
University of Insubria, Italy
Joseph Schwartz,
Stony Brook University, United States

*CORRESPONDENCE
Wei Zhang
weizhanghx@163.com
Yucheng Chen
chenyucheng2003@163.com

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Hypertension, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 19 April 2022
ACCEPTED 26 September 2022
PUBLISHED 11 October 2022

CITATION
Wang L, Xian H, Guo J, Li W, Wang J, Chen Q, Fu X, Li H, Chen Q, Zhang W and Chen Y (2022) A novel blood pressure monitoring technique by smart HUAWEI WATCH: A validation study according to the ANSI/AAMI/ISO 81060-2:2018 guidelines. *Front. Cardiovasc. Med.* 9:923655. doi: 10.3389/fcvm.2022.923655

COPYRIGHT
© 2022 Wang, Xian, Guo, Li, Wang, Chen, Fu, Li, Chen, Zhang and Chen. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

A novel blood pressure monitoring technique by smart HUAWEI WATCH: A validation study according to the ANSI/AAMI/ISO 81060-2:2018 guidelines

Lili Wang[1,2†], Hong Xian[3†], Jiajun Guo[1], Weihao Li[1], Jiaqi Wang[1], Qing Chen[4], Xiaoyu Fu[4], Hongbao Li[4], Qin Chen[4], Wei Zhang[5*] and Yucheng Chen[1*]

[1]Department of Cardiology, West China Hospital, Sichuan University, Chengdu, Sichuan, China, [2]Department of Cardiology, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, National Center for Cardiovascular Diseases, Beijing, China, [3]Department of Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan, China, [4]Huawei Device Co., Ltd., Shenzhen, China, [5]West China Biomedical Big Data Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Background: Given the rapid innovation of wearable technology, additional physical indicators can be detected, and blood pressure (BP) has become the focus of many emerging medical-device manufacturers. This study aimed to validate the accuracy of the newly developed HUAWEI WATCH in BP monitoring, according to the American National Standards Institute/Association for the Advancement of Medical Instrumentation/International Organization for Standardization (ANSI/AAMI/ISO 81060-2:2018) guidelines.

Materials and methods: The same arm sequential BP measurement was applied. One validation included four reference BP measurements taken simultaneously by two independent observers using a mercury sphygmomanometer, alternating with three test-watch measurements. Each test-watch measurement was compared against the average of the previous and subsequent reference BP readings. Two criteria were required for validation: (1) a mean BP difference of 5 mm Hg or less, with a standard deviation (SD) of 8 mm Hg or less for systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the 255 pairs of measurements, and (2) an SD for the of 85 averaged BP differences within the threshold defined by the mean test-reference BP difference listed in the ANSI/AAMI/ISO 81060-2:2018 guidelines.

Results: The mean age of the 85 participants was 48 ± 18 years (range: 21–85), and 53 (62.4%) were male. The mean differences between the test and reference BPs were -0.25 ± 5.62 mm Hg and -1.33 ± 6.81 mm Hg for

SBP and DBP, respectively (according to Criterion 1). The mean differences between the test BPs and reference BPs were -0.25 ± 5.00 mm Hg and -1.33 ± 6.31 mm Hg for SBP and DBP, respectively, according to Criterion 2.

Conclusion: Blood pressure measurement using the HUAWEI WATCH showed excellent consistency with reference BPs, and fulfilled both validation criteria of the guidelines, show its promise as a wearable device for BP self-monitoring.

KEYWORDS

smart watch, blood pressure, digital health, wearable device, validation

Introduction

Hypertension is one of the most important preventable causes of premature morbidity and mortality. It affects more than 1 billion persons globally, and accounts for 10 million deaths worldwide per annum (1). The accurate measurement of blood pressure (BP) is essential in the management of hypertension, which requires a standardized procedure and a validated device.

Out-of-office BP measurement is widely used and recommended by both European and American guidelines (2, 3), for the following reasons. Out-of-office BP measurements are usually lower than conventional office BP measurements, which may reduce or eliminate the "white-coat" effect. Out-of-office BP measurements provide BP data that are more reproducible, which may be helpful in detecting "masked hypertension." Out-of-office self-monitoring BP may have a beneficial effect on medication adherence and BP control (4–6). Out-of-office BP is more closely related to hypertension-mediated organ damage (7), and it is a better predictor of cardiovascular morbidity and mortality than office measurements of BP (8). Out-of-office BP measurements are typically taken early in the morning and at bedtime, as daytime BP level is often overlooked. Although recent studies have found that daytime stress at the workplace may increase BP, the prevalence of hypertension has been found to be high at the workplace, while awareness and control of it is poor (9, 10). Therefore, a portable BP device that can monitor BP anywhere and anytime may help to improve the condition.

Wearable devices are widespread, and an increasing number of adults are using smartwatches or wrist-worn fitness bands. Many physical indicators, such as heart rate, heart rhythm, electrocardiogram, oxygen saturation, and sleep can be detected using wearable devices (11), but BP cannot be accurately measured using a wearable device. Watch-based BP measurement equipment can be a great convenience to the user. The newly developed HUAWEI WATCH (HUAWEI Technologies Co. Ltd., Shenzhen, China) is equipped with a BP measuring function, and to our knowledge, it is the first smartwatch equipped with a BP measurement function. Therefore, the present study aimed to validate the accuracy of the HUAWEI WATCH in BP monitoring according to the guidelines of the American National Standards Institute/Association for the Advancement of Medical Instrumentation/International Organization for Standardization (ANSI/AAMI/ISO 81060-2:2018) (12).

Materials and methods

Study subjects

This study was conducted and reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. This study was approved by the ethics committee of our institution, and all of the participants gave their informed consent to participate. The clinical trial registration number is ChiCTR2000040197. Participants were recruited as volunteers, and the inclusion criterion was age ≥18 years. The exclusion criteria were: (i) arrhythmia, inaudible phase V Korotkoff sounds to determine the DBP, (ii) inability to cooperate with blood pressure measurements, and (iii) a wrist circumference of <13.0 cm or >20.0 cm.

Features of the device

The newly developed HUAWEI WATCH is equipped with a BP measuring function (**Figure 1**). The BP measurement of the WATCH is based on oscillometry, which involves using a micro-pump and a detachable cuff. Two cuffs of different sizes are provided to accommodate different wrist circumferences.

The measurement range of the HUAWEI WATCH is 60–230 mm Hg for systolic BP (SBP) and 40–160 mm Hg for diastolic BP (DBP). It analyzes the pulse wave detected during

FIGURE 1
Illustration of the HUAWEI WATCH.

inflation using an algorithm for determining the SBP and DBP; the algorithm is proprietary and cannot be disclosed at this time.

Blood pressure validation

The same arm sequential BP measurement was applied in accordance with the ANSI/AAMI/ISO 81060-2:2018 guidelines. The measurements were taken in a quiet room, after a 5-min rest period. During the process, the participants remained quiet with their legs uncrossed in a sitting position. One validation included four reference BP measurements (R1-R4), alternating with three test-watch measurements (R1-T1-R2-T2-R3-T3-R4), as shown in **Figure 2**.

The reference BP measurements were taken simultaneously by two independent observers using a Y-tube and a calibrated mercury sphygmomanometer. Participants' SBP was determined based on phase I Korotkoff sounds heard by the observer, and DBP was determined based on phase V disappearance of the Korotkoff sounds. A third observer served as a supervisor who checked the BP readings of the two observers. Any pair of SBP or DBP observations with a difference greater than 4 mm Hg was excluded, and another group of measurements was performed. Measurements of BP using the mercury sphygmomanometer were recorded as the average value of the BPs measured by the two observers. The reference BPs was recorded as the average value of the previous and subsequent BP readings by the mercury sphygmomanometer. If the previous and subsequent reference SBP readings differed by more than 12 mm Hg, or the DBP readings differed by more than 8 mm Hg, all data from the participants were excluded as cases of "Reference BP variations."

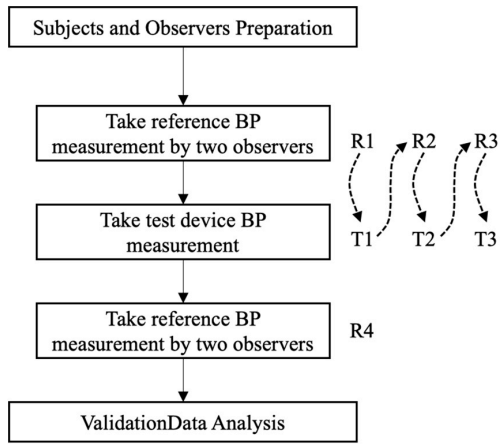


FIGURE 2
The same arm sequential BP measurement process.

Participants' BP was measured with their left wrist positioned at the level of the heart, and the time between each set of BP measurements was at least 60 s.

Statistical analysis

Normally distributed continuous variables are expressed as mean ± standard deviation (SD), and categorical variables are expressed as number and percentage. Data were analyzed in accordance with Criteria 1 and 2 of the ANSI/AAMI/ISO 81060-2:2018 guidelines. For Criterion 1, each test BP reading minus the reference BP reading by a mercury sphygmomanometer were calculated, for a total of three differences for each participant. The mean and SD of the difference was calculated to fulfill the Criterion 1 requirement for a mean BP difference of 5 mm Hg or less for 255 pairs of measurements, and an SD of 8 mm Hg or less for SBP and DBP. For Criterion 2, a difference was defined as the mean of the three test SBPs or DBPs, as measured by the HUAWEI WATCH minus the mean values of the three reference SBPs or DBPs. A total of 85 pairs of BP differences were calculated to fulfill Criterion 2; the SDs of the 85 pairs of BP differences were required to be within the threshold defined by the mean test-reference BP difference listed in the ANSI/AAMI/ISO 81060-2:2018 (see **Table 1** for SBP and DBP). The data were analyzed using SPSS 26.0 (IBM Corp., Armonk, NY, USA) on software, version 3.8.8 (G. van Rossum). Data analyses were conducted in February 2022.

Results

In total, 107 participants were screened, 22 were excluded, and 85 sets of valid measurements were analyzed to comprise

TABLE 1 Characteristics of the study participants.

Age, years	48 ± 18
Men: women, n	53:32
Height, cm	169.9 ± 8.0 (147.0–183.0)
Weight, kg	62.8 ± 13.7 (36.0–96.0)
Wrist circumference, mm (range)	162.13 ± 15.64 (128.00–197.00)
Distribution of SBPs	
≥160 mm Hg, n (%)	7 (8.3%)
140–160 mm Hg, n (%)	11 (12.9%)
100–140 mm Hg, n (%)	47 (55.3%)
≤100 mm Hg, n (%)	20 (23.5%)
Distribution of DBPs	
≥100 mm Hg, n (%)	8 (9.4%)
85–100 mm Hg, n (%)	9 (10.6%)
60–85 mm Hg, n (%)	60 (70.6%)
≤60 mmHg, n (%)	8 (9.4%)

SBP, systolic blood pressure; DBP, diastolic blood pressure.

TABLE 2 Validation results in accordance with Criterion 1 and Criterion 2 of the guidelines.

	SBP	DBP
Criterion 1	-0.25 ± 5.62	-1.33 ± 6.81
Criterion 2	-0.25 ± 5.00	-1.33 ± 6.31

SBP, systolic blood pressure; DBP, diastolic blood pressure.

the final participant group. The participants' mean age was 48 ± 18 years (range: 21–85 years), 53 (62.3%) were men, 32 (37.7%) were women, and the gender distribution fulfilled the guideline's 30% criterion. Participants' mean height was 169.9 ± 8.0 cm (range: 147.0–183.0 cm), their mean weight was 62.8 ± 13.7 kg (range: 36.0–96.0 kg), and their mean wrist circumference was 162.13 ± 15.64 mm (range: 130.00–197.00 mm). The characteristics of the 85 participants are summarized in Table 1. Distribution of the reference BPs fulfilled the criterion stated in the guidelines, with high (≥160 mm Hg), medium (≥140 mm Hg), and low (≤100 mm Hg) percentages of 8.3% (meeting the 5% criterion), 21.1% (20% criterion), and 23.5% (5% criterion), respectively, for the reference SBPs. The high (≥100 mm Hg), medium (≥85 mm Hg), and low (≤60 mm Hg) percentages were respectively, 9.4% (meeting the 5% criterion), 20.0% (20% criterion), and 9.4% (5% criterion), respectively, for reference DBPs, as shown in Table 1.

The mean differences between the test-watch and reference BPs were −0.25 ± 5.62 mm Hg for SBP and −1.33 ± 6.81 mm Hg for DBP, in accordance with Criterion 1. The results are presented in Table 2. The Bland–Altman analysis showed a bias of −0.25 with limits of agreement ranging from −11.27 to 10.54 mm Hg for SBP (Figure 3A) and a bias of −1.33 with limits of agreement from −14.56 to 12.02 for DBP (Figure 3B). The mean differences between the test-watch and reference BPs were −0.25 ± 5.00 mm Hg for SBP and −1.33 ± 6.31 mm Hg for DBP in accordance with Criterion 2 (Table 2). These results fulfilled the ANSI/AAMI/ISO 81060−2:2018 validation criteria of ≤5 ± ≤8.0 mm Hg for Criterion 1, and SDs of <6.95 mm Hg for SBP and <6.82 mm Hg for the DBP for Criterion 2.

Discussion

In the present study, we validated the performance of the HUAWEI WATCH's monitoring of BP in accordance with the ANSI/AAMI/ISO 81060-2:2018 guidelines. The results showed that the HUAWEI WATCH fulfilled Criteria 1 and 2 of the guidelines, indicating that it could be a reliable and convenient device in the daily self-monitoring of BP.

Usually, BP measurements (or self-monitored BP measurements) are taken in the home, typically in the morning and at bedtime, thereby overlooking daytime BP levels. Given the research findings that BP levels increase

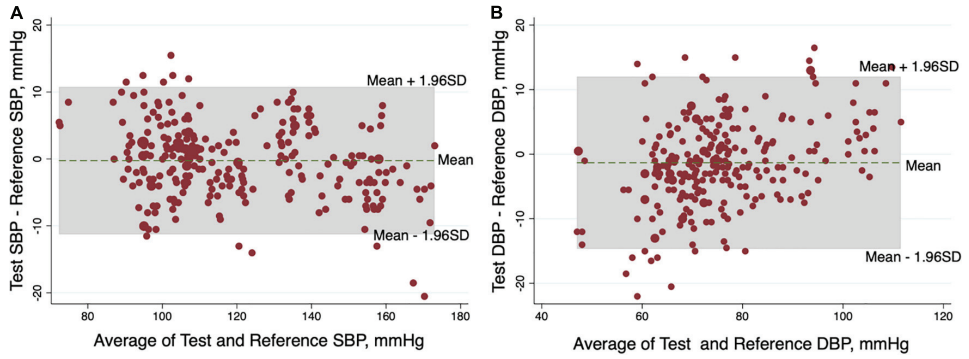


FIGURE 3
Bland-Altman plots of the differences between the test blood pressures (BPs) by HUAWEI WATCH and the reference BPs by mercury sphygmomanometer for the systolic blood pressure (SBP) **(A)** and diastolic blood pressure (DBP) **(B)**.

throughout the day, and that daily variability of BP is a predictor of future cardiovascular events (13), the awareness of daytime BP measurements has increased through research findings on daytime BP, especially at the workplace. A recent clinical trial found that the prevalence of hypertension was high among the working population in China, but the rates of awareness, treatment, and control of BP were unacceptably low, indicating there is substantial room for improvement in the diagnosis and treatment of hypertension among employees at the workplace (9). Another study found that workplace-based interventions, which improved hypertension control, appeared to be more effective than usual care (10). However, a previous study with similar findings demonstrated that BP measured in the workplace was more closely related to left ventricular mass index than was BP measured in a clinic (14). A sphygmomanometer is not a convenient measurement tool in the workplace; it is a heavy and cumbersome instrument. However, a portable and compact device, such as a watch-type of wearable BP monitor is ideal in workplace settings.

The Omron HEM-6410T-ZM and Omron HEM-6410T-ZL were the first wristwatch types of wearable BP monitors. The mean differences between the test and reference SBPs were −0.9 and −1.1 mm Hg for the two devices, respectively; the mean differences for the DBPs were 2.4 and 0.3 mm Hg, and both devices fulfilled the validation criteria of the ANSI/AAMI/ISO81060-2:2018 guidelines (15). The mean differences between the test and reference BPs were −0.25 and −1.33 mm Hg for the SBP and DBP, respectively, for the HUAWEI WATCH, which was smaller than the Omron watch-type wearable BP monitor. In addition, the range of the wrist-circumferences accommodated by the Omron watch-type wearable BP monitors were very narrow (16–21.5 cm). In our study, the wrist circumference of many of the participants was below 16 cm; thus, the HUAWEI WATCH, which has a wrist circumference of 13–20 cm, was suitable for more participants. The HUAWEI WATCH enables consumers to measure their BP frequently, throughout their activities of daily living, and most importantly, the HUAWEI WATCH is a smartwatch-based BP monitor, equipped with other functions, and therefore, more consistent with the needs of today's society.

Limitations

One study limitation is that the HUAWEI WATCH was validated using participants' left wrist at heart level; hence, further validation is needed in future studies.

Conclusion

In conclusion, BP measurements using the HUAWEI WATCH were consistent with the reference BPs and fulfilled both of the guidelines' validation criteria, thereby showing its promise as a wearable device for BP self-monitoring.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by West China Hospital, Sichuan University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YC: concept and design. LW, JG, WL, JW, HX, QingC, QinC, HL, and XF: acquisition, analysis, and interpretation of the data. LW, HX, JG, WL, and JW: drafting of the manuscript. YC and WZ: critical revision of the manuscript. LW, HX, JG, and WL: statistical analysis. LW, JG, WL, QingC, QinC, HL, and XF: administrative, technical, or material support. WZ and YC: supervision. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the Joint Innovation Project of West China Hospital-Huawei Ltd: 'Validation of Wrist-type Blood Pressure monitoring devices' (No. HX-H2012260) and 'Exploring and constructing a multi-index data management mode for comprehensive evaluation services for the elderly based on the application of wearable technology' (No. 2021YFS0080). It received funding from Huawei Device Co., Ltd. This funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

Conflict of interest

Authors QingC, XF, HL, and QinC were employed by Huawei Device Co., Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. *JAMA*. (2017) 317:165–82.

2. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J*. (2018) 39:3021–104.

3. Whelton PK, Carey RM, Aronow WS, Casey DE Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol*. (2018) 71:2199–269. doi: 10.1161/HYP.0000000000000075

4. McManus RJ, Mant J, Haque MS, Bray EP, Bryan S, Greenfield SM, et al. Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized clinical trial. *JAMA*. (2014) 312:799–808. doi: 10.1001/jama.2014.10057

5. McManus RJ, Mant J, Bray EP, Holder R, Jones MI, Greenfield S, et al. Telemonitoring and self-management in the control of hypertension (TASMINH2): a randomised controlled trial. *Lancet*. (2010) 376:163–72. doi: 10.1016/S0140-6736(10)60964-6

6. Tucker KL, Sheppard JP, Stevens R, Bosworth HB, Bove A, Bray EP, et al. Self-monitoring of blood pressure in hypertension: a systematic review and individual patient data meta-analysis. *PLoS Med*. (2017) 14:e1002389. doi: 10.1371/journal.pmed.1002389

7. Bliziotis IA, Destounis A, Stergiou GS. Home versus ambulatory and office blood pressure in predicting target organ damage in hypertension: a systematic review and meta-analysis. *J Hypertens*. (2012) 30:1289–99. doi: 10.1097/HJH.0b013e3283531eaf

8. Ward AM, Takahashi O, Stevens R, Heneghan C. Home measurement of blood pressure and cardiovascular disease: systematic review and meta-analysis of prospective studies. *J Hypertens*. (2012) 30:449–56. doi: 10.1097/HJH.0b013e32834e4aed

9. Shen Y, Wang X, Wang Z, Zhang L, Chen Z, Zhu M, et al. Prevalence, awareness, treatment, and control of hypertension among Chinese working population: results of a workplace-based study. *J Am Soc Hypertens*. (2018) 12:311–22.e2. doi: 10.1016/j.jash.2018.01.013

10. Wang Z, Wang X, Shen Y, Li S, Chen Z, Zheng C, et al. Effect of a workplace-based multicomponent intervention on hypertension control: a randomized clinical trial. *JAMA Cardiol*. (2020) 5:567–75. doi: 10.1001/jamacardio.2019.6161

11. Sim I. Mobile devices and health. *N Engl J Med*. (2019) 381:956–68. doi: 10.1056/NEJMra1806949

12. International Organization for Standardization. *ISO 81060-2:2018. Non-Invasive Sphygmomanometers-Part 2: Clinical Investigation of Intermittent Automated Measurement Type*. Geneva: ISO (2018).

13. Chowdhury EK, Owen A, Krum H, Wing LM, Nelson MR, Reid CM, et al. Systolic blood pressure variability is an important predictor of cardiovascular outcomes in elderly hypertensive patients. *J Hypertens*. (2014) 32:525–33. doi: 10.1097/HJH.0000000000000028

14. Devereux RB, Pickering TG, Harshfield GA, Kleinert HD, Denby L, Clark L, et al. Left ventricular hypertrophy in patients with hypertension: importance of blood pressure response to regularly recurring stress. *Circulation*. (1983) 68:470–6. doi: 10.1161/01.CIR.68.3.470

15. Kuwabara MHK, Hishiki Y, Kario K. Validation of two watch-type wearable blood pressure monitors according to the ANSI/AAMI/ISO81060-2:2013 guidelines: Omron HEM-6410T-ZM and HEM-6410T-ZL. *J Clin Hypertens (Greenwich)*. (2019) 21:853–8. doi: 10.1111/jch.13499

frontiers | Frontiers in Cardiovascular Medicine

TYPE Opinion
PUBLISHED 03 November 2022
DOI 10.3389/fcvm.2022.1008575

Check for updates

OPEN ACCESS

EDITED BY
June-Wha Rhee,
City of Hope National Medical Center, United States

REVIEWED BY
Paul Cheng,
Stanford Health Care, United States

*CORRESPONDENCE
Sherry Ann Brown
shbrown@mcw.edu

†These authors share first authorship

SPECIALTY SECTION
This article was submitted to Cardio-Oncology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 01 August 2022
ACCEPTED 07 October 2022
PUBLISHED 03 November 2022

CITATION
Maddula R, MacLeod J, McLeish T, Painter S, Steward A, Berman G, Hamid A, Abdelrahim M, Whittle J and Brown SA (2022) The role of digital health in the cardiovascular learning healthcare system.
Front. Cardiovasc. Med. 9:1008575.
doi: 10.3389/fcvm.2022.1008575

COPYRIGHT
© 2022 Maddula, MacLeod, McLeish, Painter, Steward, Berman, Hamid, Abdelrahim, Whittle and Brown. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

The role of digital health in the cardiovascular learning healthcare system

Ragasnehith Maddula[1†], James MacLeod[1†], Tyson McLeish[1], Sabrina Painter[2], Austin Steward[1], Generika Berman[3], Abdulaziz Hamid[1], Mohamed Abdelrahim[1], Jeffrey Whittle[4] and Sherry Ann Brown[5*] for the Connected, Health Innovation Research Program (C.H.I.R.P.), Cardiology Oncology Innovation Network (COIN), Cardio-Oncology Artificial Intelligence Informatics Precision (CAIP) research team investigators

[1]Medical College of Wisconsin, Milwaukee, WI, United States, [2]Zilber School of Public Health, University of Wisconsin-Milwaukee, Milwaukee, WI, United States, [3]Medical College of Wisconsin, Green Bay, WI, United States, [4]Division of Internal Medicine, Medical College of Wisconsin, Milwaukee, WI, United States, [5]Cardio-Oncology Program, Division of Cardiovascular Medicine, Medical College of Wisconsin, Milwaukee, WI, United States

KEYWORDS

digital health, digital medicine, health innovation, learning healthcare system, artificial intelligence, cardio-oncology, wearables, health technology

Introduction

Modern medicine has undergone immense transformation in the past decade with the discovery, innovation, and development of novel health systems and advanced patient care brought forth by technological progress. Synchronously, developments in technology have created what many call, a "paradigm shift" in the way society interacts with technology, as well as the impact and ubiquity of technology in our livelihood (3). This transformation is influencing medicine and modern science in many aspects. One example is the adoption of digital health which includes "disruptive technologies that provide digital and objective data accessible to both caregivers and patients" (3); according to the Food and Drug Administration (FDA) these disruptive technologies include mobile health (mHealth), health information technology, wearable devices, telehealth and telemedicine and personalized medicine (2).

Digital health represents an important aspect of health for the future, and when applied to medical practice, can be termed digital medicine. Initiatives in digital medicine are leading healthcare and traditional models of medicine to evolve and address the changing dynamic of patient-physician relationships and overall clinical outcomes (4). In digital medicine, hardware and software tools power technology that supports the practice of medicine, such as disease prevention and treatment for

individuals and populations. While electronic health record (EHR), registry, and claims data will predominate in the near term, they cannot provide a complete picture of the various factors that influence a patient's cardiac health. As a result, technologies that can provide an accurate account from outside of hospitals and clinics will become more important in the cardiovascular learning healthcare system (2). As mentioned by an American Heart Association (AHA) Scientific Statement, the absence of defined procedures for analysis and application of the clinical uses of digital health technologies remains a large hurdle (5). This problem is being addressed, however, as the American College of Cardiology (6) and the FDA (2, 7) have recently released preliminary guidelines on this topic. The process of amassing relevant data to further shape guidelines will take time.

This review explores the role of digital health and how we can maximize benefits for patients and the health system in general in the context of a learning healthcare system (LHS). The Agency for Healthcare Research and Quality defines a LHS as one in which observational data generated within the system are synthesized with scientific evidence from outside the system to provide patients with safer, more efficient, and higher quality healthcare (1). The AHA released a scientific statement on LHS in 2017 (5), which includes how health information technology and health data can be leveraged to ensure that "evidence informs practice and practice informs evidence" (8). This integration includes high quality data from the literature which is then woven into routine practice. Dissemination of evidence-based information and responsiveness to feedback also allows LHS usage to improve work environments for employees (1). In a LHS, the component technologies of digital health are outlined and contextualized to illustrate their impact on enabling patients to understand and visualize medical prognosis in a user-friendly manner (9). By understanding the motive, expectations, and development of digital health, we will better understand the direction in which disruptive technologies continue to revolutionize medicine (3).

Recent events have amplified the necessity of digital and connected health offerings. The coronavirus disease of 2019 (COVID-19) has accelerated accessibility, adoption, and efficacy of these offerings (10). However, barriers still exist in assessing these technologies and ensuring integration is done in an equitable way. Working with industry to conduct robust studies on clinical efficacy of various products can give confidence to health care providers recommending their use and will begin to build a body of evidence to continue the growth of insurance coverage for digital health. In an effort to contribute to and guide the growth of this body of evidence, this review outlines the role of digital health in the LHS, delineates challenges in system implementation and notes considerations that should be made to ensure equitable, and patient centered integration into the pre-existing system.

Digital health in the pandemic

The COVID-19 pandemic caused a rapid shift toward telemedicine, mHealth and digital health due to restrictions made on elective procedures and regular clinics visits (11). This paved the way for physicians, health care providers, and patients to maintain communication safely through digital means (11, 12). The scope of digital health includes technologies in the form of mobile applications, eHealth, and wearables [e.g., Electrocardiogram (ECG) monitors, blood pressure sensors] to health diaries and instructional videos for patient care. The facilities and infrastructure that have used digital health in the pandemic have consequentially benefited large patient populations considered immunocompromised or at-risk (13). Some hospital systems took initiative to reduce potential exposures and transmission by integrating artificial intelligence (AI) into their pre-hospital triage procedures, including employing an AI-based COVID-19 screener tool used to assess patient risk and lower the volume of abandoned calls on their COVID-19 hotline (14). These tasks were traditionally performed by clinical staff and the transition to AI allowed for a reduction in the consumption of resources.

In 2021, the use and value of remote patient monitoring (RPM) through wearables to enhance virtual patient care had accelerated to protect individuals from exposure and continue providing optimal care and monitoring (14). RPM provides patient data to clinicians outside the healthcare facility, which is essential because continuous access to real-time physiological data improves physician oversight of patient health. The use of RPM has accelerated since COVID-19 started, from 7 million patients using RPM in 2016 to over 23 million in 2020 (15). The number of patients utilizing remote health monitoring tools is estimated to increase to 30 million by 2024 (16). In cardiology, digital health has become an immensely growing component in transforming cardiac medicine. There are many benefits to digital medicine. However, there are challenges that will need to be addressed for digital medicine to fulfill its potential. Such challenges include adoption and implementation especially regarding under-resourced populations potentially being left behind (15).

Through the lens of the ongoing global pandemic, telemedicine has provided adequate medical support to thousands of patients. Telemedicine increases access to healthcare for patients across communities and can provide a cheaper alternative to modern healthcare when physical visitations may not be required for all patients. Combined with lowered costs, for both patients and the healthcare system, telemedicine a category of digital health, provides an efficient alternative for non-emergency situations, while also expanding the reach to underserved communities that may not have accessible facilities for healthcare nearby (16, 17). By bridging the gap between quality health care and populations in need,

clinical outcomes and overall health in patients can improve through many forms of digital health (18).

Need for digital health

While there was a robust expansion in the usage of digital health technologies during the pandemic to expand access to healthcare, there are other utilities for digital health. The usage of digital health is commonly associated with increased access to healthcare. However, digital health is needed in a LHS to enhance the clinician-patient relationship in several ways. Digital health interventions promote effective clinical care. An example of this is the CardioMEMs system. In the CardioMEMs system (St. Jude Medical, St. Paul, MN), cardiac catheterization is used to permanently implant a "wearable" pressure sensor in the pulmonary artery that communicates with an external data collection device to send pulmonary artery pressure, pressure waveforms, and heart rate data to a secure cloud-based website, allowing early detection of worsening heart failure (5, 19). In initial clinical trials, patients with New York Heart Association class III heart failure who received the device experienced a 37% reduction ($P < 0.0001$) in heart failure hospitalizations over a 15-month mean follow-up period (5, 19). This system is one of the most successful and early applications of digital health in cardiology. Digital health interventions within cardiovascular care have been crucial in assessing the effect of health technologies in improving patient health self-management and outcomes, with one particular study observing patients with acute myocardial infarctions presenting with a predominantly higher level of patient activation in self-management as well as fewer 30-day readmissions (20). Other digital health interventions have been implemented and studied for several cardiovascular health applications, such as heart failure diagnosis and management, risk assessment, cardiac rehabilitation, and peripheral vascular disease management, with promising results (21). Digital health tools have the capability to attenuate risk factors throughout disease processes such as cancer, during prehabilitation, habilitation, and rehabilitation (22). Physicians in many fields are increasingly considering implementing digital health solutions into their practice. The AMA "Physicians' Motivations and Key Requirements for Adopting Digital Health Adoption and attitudinal shifts from 2016 to 2022" study outlines improving health outcomes, work efficiency, and diagnostic ability as key drivers for physicians considering implementing digital health into their practice (23). Notably, about 3 in 5 physicians say technology can help address key needs with chronic disease patients, preventative care and automating administrative tasks (23).

Incorporating digital health tools into a LHS will lead to stronger patient-physician relationships and increased personalization of care, as patients can transmit RPM and mHealth data which provides insight into the day-to-day factors that influence cardiovascular health and disease. In addition, when patients use digital health tools to transmit real-time, objective clinical and subjective data, they are empowered because they are more involved in their care and the decisions their providers make (5). For example, patient portals empower patients with self-service functions such as appointment scheduling, secure messaging with providers, access to test results, and personal health information. In addition, patient portals are beginning to integrate with digital platforms that provide RPM-centered functions, establishing infrastructure for alert and referral systems based on vital signs, biomarker tracking and other critical biometrics (23, 24). This change has enhanced the patient-physician relationship by streamlining workflow and allowing patients and providers to rapidly establish lines of communication with one another when there are changes in a patient's condition. An example of this combined digital health workflow is a patient using a blood pressure device and uploading their results to an integrated patient portal digital platform. The patient's physician can review this information, and communication about the results can occur *via* secure patient portal messaging or a scheduled telemedicine visit. For patients with an increased risk for severe COVID illness, all aspects of care can be addressed through a digital health-centered workflow without the patient having to leave the safety of their own home (23, 24). Trust is fostered with more regular interactions between patients and providers, including the use of secure messaging, patient portals, mHealth apps, and other digital health tools.

There is a need for healthcare providers to manage an incredible amount of clinical information as healthcare delivery systems become increasingly more complex. An increased demand for clinicians to manage these clinical data can lead to inconsistencies between data reporting between providers or health systems, uninterpretable data, or missing data (24). The LHS will benefit from the use of AI-based digital health tools that integrate EHR across practices to provide structure to EHR data that are otherwise organized on a practice-to-practice basis. AI tools also provide us with a means to extract actionable clinical data that is buried amongst irrelevant clinical data. As the AHA LHS statement outlines, collaboration of medicine and technology will be a necessary foundation in the future to improve the quality, access, and effectiveness of patient care through technological advances. A LHS integrates and evolves the current healthcare system to use health data to apply scientific discovery at the point of care and uses insights from said clinical care to inform future care (5). Further, as efficiency is optimized, digital health can improve cost and utilization in healthcare. For example, the CardioMEMS heart failure system was found to be cost effective compared with the standard of care treatment (25). Additionally, a study analyzing healthcare utilization associated with digital health intervention in asthma treatment

demonstrated a reduction in hospitalizations and emergency department visits (26). Integration of digital technologies into existing EHR systems may increase productivity and cost-effectiveness of these systems by enhancing existing EHR strengths in chronic and medical care management and communication efficiency between and within organizations (27). Limited healthcare resources necessitates advancements that create better health outcomes at a lower cost; The described digital health technologies show that these goals are achievable.

Vast range of potential technologies

Improvement in healthcare practices is predicated on the integration of technology through all aspects of medicine. We are embarking on an era of digital medicine that has enabled progress in patient care due to the ability of technology to reduce costs, improve access, collect data and personalize medicine for patients (28). Wearables (e.g., ECG monitors, blood pressure sensors, etc.), digital health diaries, and electronic instructional modules have started to transform how we deal with disease by improving management and maintenance (29). Mobile applications can increase access to various demographics and integrate mobile health into regular clinical practice (**Figure 1**) (30–32). The increased integration of technology in medicine not only stems from the consistent advancements in technology but also from the growing scope of practices that can be improved. The full potential of digital medicine is still unexplored due to the vast range of available technologies. Initially, technology integration in healthcare focused on patient monitoring and charting to optimize patient care. Digital technology is now involved in numerous sectors of medicine, including diagnostics, health information technology, mobile health, telemedicine, and wearable devices (5). Digital health interfaces with or includes variations of telemedicine and biometric tracking, as well as digital applications that diagnose, augment treatment, and increase access to resources for medical conditions, especially those related to preventive care and mental health (7, 28). The expounding potential of medicine stems from personalized care, where patient data, genetic testing and wearable devices can create individualized treatment plans to cater to unique needs. Technology that categorizes and captures the characteristics of patient populations, specifically high-cost patients, can direct allocation of resources and tailor interventions to optimize care (33). The US Institute of Medicine has two imperatives that each kind of health focused technology must address. The first requires technology to be informational and the second requires technology to provide value (34). Being informational is defined as helping providers and patients navigate the increased scientific body of knowledge and complexity of the medical system. The technology or digitization can contribute to the second imperative value, where there is a lack of cost transparency or a mismatch of incentives. An example of a company that claims to fit both imperatives has developed technology to simplify healthcare plans for seniors by using software to guide physician recommendations based on what is covered by Medicare and other insurance plans. The technology empowers providers with AI-driven personalized insights at the point of care.

The vast range of potential technologies is evident by the smart wearable products available on the market today. Each device collects distinct biological measurements that are conducive to various cardiovascular clinical applications. Wearable activity sensors are advantageous to clinicians to provide accurate daily data of patient physical activity levels as an active lifestyle is a critical component of promoting cardiovascular health. This can be accomplished through data capture by accelerometers, Global Positioning System (GPS) devices or barometers. Accelerometers measure the linear acceleration of movement along triaxial planes, which is useful for tracking step count, speed, and sedentary time (21). GPS can coordinate distance traveled while barometers can measure the stair count of exercise. Wearable heart rate and rhythm sensors are pragmatic approaches to detecting daily hemodynamic changes in patients for clinical monitoring through ECG or photoplethysmography sensors. ECG sensors track cardiac electrical activity and monitor patients for potential electrolyte abnormalities and arrhythmias. Photoplethysmography sensors can evaluate heart rate, blood pressure (BP) and cardiac output through measurement of changes in microvascular blood volume. BP sensors are necessary to predict, monitor, and track the potential for the development and progression of hypertension by providing clinicians with comprehensive tools for treatment. An example of this is an oscillometer, which is a blood pressure measurement device worn on the wrist that displays readings through a smartwatch monitor. The use of various sensors has diversified wearable approaches, as they can be worn through clothing and shoe embedded sensors, smartwatches, smart bands, chest straps, ECG patches and medical earbuds (21).

Another frontier of technology that manifests promise in the field of digital health is the rise of AI-based applications, especially in the field of cardiology. Advances in deep learning aspects of AI-based systems have propelled the use of this technology in clinical cardiovascular treatment. AI, and more specifically, precision medicine, have been used in concordance with clinicians to provide advanced frameworks for developing cardiovascular therapeutics through alternative approaches to cardiovascular risk stratification and phenotyping heart failure (35). AI has been integral in maximizing the efficiency of association studies, developing the expansion of precision medicine and the potential to improve patient care through this novel framework of capabilities (35). The AHA statement on learning healthcare systems highlights the utility of predictive analytics in understanding patient and environmental data

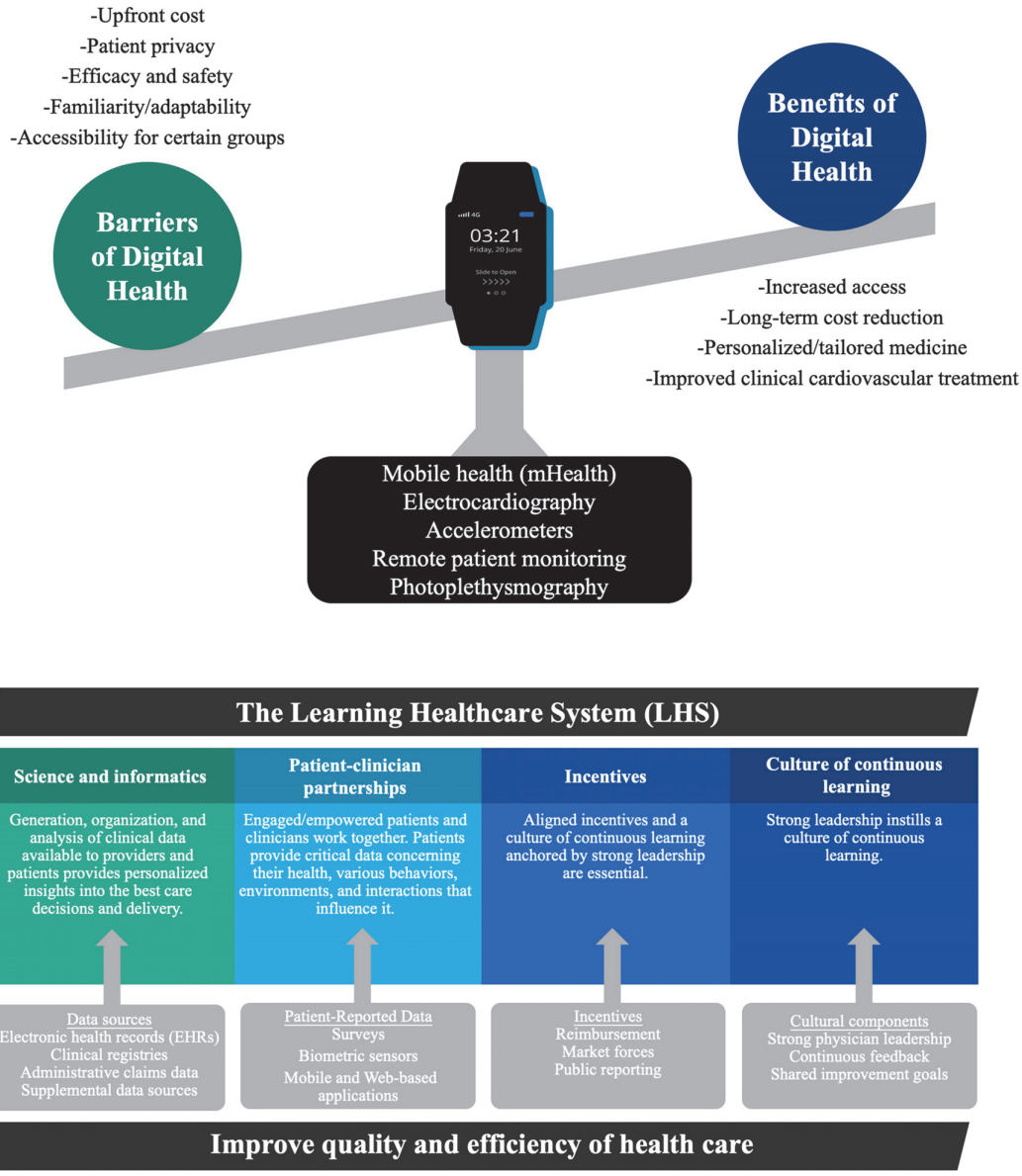


FIGURE 1
Digital health architecture and pillars of the learning healthcare system. The digital health architecture provides clinicians with insight into patients' health and lifestyle outside of healthcare settings. Patient-reported data is recorded with: mobile health (mHealth), biometric sensors (including wearables), and web-based applications. The four key components of the learning healthcare system are data sources, patient-reported surveys, incentives, and cultural components to bolster novel findings and improve quality of care. Templates from Infograpia were used in these graphics.

to maximize benefits in individual and population health, in conjunction with EHRs (5). Beyond integrating commercial technologies, applications in which predictive analytics would be useful in a LHS include evaluating high-cost patient care, anticipating readmissions, predicting adverse events and projecting the trajectory of diseases, further enhancing the integration between digital technologies and healthcare systems in improving modern medicine (5). An example of this is mobile health (mHealth), which includes the use of newly developed smartphone-connected applications in resource-limited areas to assist in diagnosing rheumatic and heart diseases (36). A trial of this technology in mHealth clinics in India demonstrated that patients randomized to mHealth diagnostic assessments were associated with a lower risk of hospitalization and/or death on follow-up (15% vs. 28%) (36). This substantiates the potential and necessity for digital health within clinical frameworks and in providing optimal patient care. The most important component to successful digital health integration is adherence

from not only clinicians but patients as well. The exponential advancement and integration of technology in all parts of our lives has strengthened openness of Americans to digital health integration. The positive perceptions of digital health among Americans can be shown by 50% of American adults switching from in-person to telehealth appointments in the past year and the growth of 7 million patients in 2016 using remote devices for monitoring their health to over 23 million users in 2020 (37). Overall, the integration of a vast array of technologies in health care is not a possibility but an inevitability, which provides a positive outlook for the future of healthcare.

Digital health for patient education and engagement

Patient education and medical literacy have steadily improved since the influx of disruptive technology in recent decades. This is in part due to the immense troves of information available on the internet, as well as applications and databases that have allowed patients to understand more colloquially medical terminology, prognosis, and treatment options (3, 38). With increased accessibility to medical information online, modern medicine has had to adapt to the increase in curiosity and need for clarity for patients seeking better understanding of their health and complications (39). Patient education has taken many forms, such as education on nutrition, health hygiene, and maintaining healthy habits, or on methods for tracking personal biometrics to understand one's health. Innovative and interactive technologies, such as ECG wearables, health diaries, telemonitoring, blood pressure sensors, and several others have expanded the scope of health management, for patients as well as healthcare professionals. The process of incorporating digital health technologies into daily practice among providers and patients is gradually becoming commonplace (18, 38). Several studies have evaluated the impacts of integrating digital health technologies as a method of patient education and engagement in their health management, particularly with medication adherence, health practices and improving clinical or laboratory outcomes. Voice recognition technologies used in the medical management of patients with chronic heart failure showed a potential to better control sodium intake, improved Minnesota Living with Heart Failure (MLHFQ) scores, as well as greater quality of life, highlighting the importance of self-management in the long term prognosis of cardiovascular disease (40). Medication adherence and lifestyle modifications, which have a critical role in cardiovascular disease management, were shown to be positively influenced by mobile phone-based interventions through short messaging services in addition to virtual training, face-to-face counseling, electronic pillboxes and home monitors (41, 42). This natural evolution has increased the visibility of health information, substantially increasing the decision-making power of patients regarding their own health, as opposed to the traditional model of medicine heavily reliant on physician responsibility.

Digital health has also begun to incorporate advanced technologies in AI in various aspects of medicine, importantly in understanding biomarker progression in patients, and establishing a system that expedites the referral process and mitigates emergency situations when they do arise (18). Immediate alerts and telemonitoring subsequently improve overall health outcomes as physician, and patient oversight is increased, along with understanding of biodata and evaluating paths of treatment and intervention (42).

The prevalence of digital health today can also be attributed to the improvements and innovations in user experience with health technologies. With improved user interfaces, patients are now able to quickly understand how the technology works to facilitate incorporation into their daily lives. Adherence to medications and treatment plans have also been improved, as trackers and sensors, along with app monitoring and reminders have improved patient adherence, while also allowing providers to maintain oversight. This component of medicine has always been difficult to oversee, as patients may not always keep track of their medications and dosage intervals, leading to reduced adherence and worse outcomes. For example, in individuals with asthma, sensors have been incorporated into inhalers to track inhaler usage, and also to determine location of patients to understand environmental triggers and factors leading to asthma exacerbation (43). These applications improve the quality of care, help providers understand factors that trigger negative responses, and further improve the healthcare process by treating patients using multifaceted measures and approaches. Insights suggested by health technologies contribute to the overall transformation of healthcare by introducing new parameters and perspectives not previously incorporated in medicine. By doing so, providers and patients can take better measures for interventions, and preemptive measures to reduce future complications.

Assessing health technologies

While digital health technologies have already begun changing lives for the better, there are many, often overlooked, pitfalls of apps and technologies. Proper evaluation of a technology's utility and clinical impact is necessary to ensure that clinical care and patient well-being are not compromised in the name of convenience, higher billings, or expediting clinical workflow. Data breaches, false measurements and assessments, and exacerbation of the very health issues being treated are all potential side effects (44, 45). While we amass clinical data regarding new health technologies, patterns of risks and benefits will become clearer as well as which technologies are most efficacious. We are starting to understand the benefits of these technologies but there

remains a large gap between their development and precise evidence-based implementation into clinical practice (46). Just like with any medication, we must first prove the efficacy of a new technology, act directly to minimize harm potential and ensure that there are no more beneficial standards of care in place. Only then should a physician feel comfortable prescribing or recommending an application, software, or hardware device to their patient. Regulation of digital health technologies is carried out by the FDA and is an evolving process. Their Digital Health Center of Excellence marks the beginning of a comprehensive digital health approach providing regulatory guidance to digital health companies and education for stakeholders through a pool of digital health resources (2). They also have released draft guidance documents for the use of remote patient monitoring with digital health technologies. Their guidance document, Digital Health Technologies for Remote Data Acquisition in Clinical Investigations released in January 2022, provides non-binding recommendations on the use of digital health technologies to acquire clinical investigation data remotely (7). This document will help direct the research necessary for physician guidance on implementing digital health. Beyond the FDA, the American College of Cardiology's Best Practices for Consumer Cardiovascular Technology Solutions framework emphasizes four key metrics in assessing a product: ease of use and retention, accuracy, clinical outcomes, and clinical workflow integration (6). Their guide has several use cases that outline barriers to digital health implementation in specific patient scenarios, and potential solutions where possible. This document serves as a key first step to aid physicians in feeling confident when recommending digital health technologies. This framework does not, however, rectify the need for long term evaluation of patient satisfaction and clinical outcomes in relation to digital health. Guidance documents like these can help direct physicians through the process of incorporating digital health into their practice, but just like the rest of medicine, a comprehensive evidence-based pool of peer-reviewed research will guide practice.

Several groups are beginning to recognize the need for digital health and leveraging technology to substantially advance modern healthcare. Universities in the United States and independent organizations, including the AHA and American Medical Association have set up initiatives and centers for the furthering of digital medicine (23, 47). These programs seek to make medicine more precise and promote integration of medicine and the digital world. The Stanford Center for Digital Health promotes interprofessional collaboration and aid for researching medical technology (48, 49). The Digital Medicine Society is an organization for experts from various fields to aid in the furthering of digital health. They achieve this goal through research, communication and education and community building (49). Assessing the feasibility and clinical efficacy of specific technologies is a cornerstone and foundation to integrating digital health into standard practice across all specialties. By understanding the nuances in measurement, analysis and representation of clinical data in the medical setting requires several parameters to which technology companies along with medical institutions must abide to in concurrence with medical guidelines and scientific society statements. Preventive cardiology continues to be bolstered by the influx of integrative digital health technologies aimed to improve medical monitoring and risk management. Feasibility studies on blood pressure management have shown improvements in patient engagement with BP monitoring in those with acute myocardial infarctions (AMI), as well as those with previous cardiovascular disease and hypertension management post-AMI (50). Validation studies are crucial in not only evaluating the integration of digital health technologies into standard care, but also in assessing the intrinsic validity of measurement tools such as blood pressure and heart rate monitoring devices, where high correlation between manual measurements and wearables shows promising potential particularly in ambulatory medical management (51). Clinical trials and innovative research programs have also become more notable in understanding the holistic impact disruptive technologies such as smart scales measuring fluid and hemodynamic status, AI-based self-management platforms, and smartphone applications, can have in clinical management as well as quality of life in patients with chronic conditions such as heart failure (52). The Connected Health Innovation Research Program (C.H.I.R.P.) started at the Medical College of Wisconsin, extends this growing interest in integrating digital health technologies through research partnerships with innovators, academic institutions, and clinicians to properly assess the utility and adoptability of technologies before integration into cardiovascular care (53). Objective evaluation of parameters such as adoptability and clinical integrity, through retrospective and prospective analysis, play an integral role in confirming adherence to medical guidelines, as well as evaluate the feasibility of introducing new technologies into the traditional model of clinical medicine to improve clinical outcomes through various avenues, not limited to patient education and enhanced patient-physician relationships in the decision-making process (53). Therefore the desire for digital health integration in patient care continues to accelerate through these initiatives and dedicating efforts to research this possibility further.

While we navigate the use of technologies in the medical system, it has become clear that the public is open to their implementation. MSI International, a leading global strategic market research firm, recently found that 4 out of 5 Americans are open to embracing remote monitoring of their health. According to their study of 300 Americans carried out in May 2021, respondents were receptive to allowing physician remote monitoring of their: blood pressure (70%), heart rate (68%),

blood sugar (66%) and blood oxygen (65%) (37). This promising result shows that the bottleneck of implementation is most likely specific high quality research guiding physician prescription, recommendation, and insurance coverage of the technologies.

Complications and barriers of digital health

Digital health, although widely welcomed, is not without barriers or difficulties. Indeed, patients and health care professionals are becoming more comfortable with technology integration into healthcare. However, not all patients will be able to adapt and transition to digital medicine which may at times limit care that deviates from the traditional model of medicine. The World Heart Federation recently released a roadmap to digital health in cardiology (54). In this document several complications and barriers to digital health implementation are discussed. These include health system, health workforce, patient and technological roadblocks (54). The organization also offers solutions to these roadblocks focused on regulation, education and investment in the future of digital health.

We need to be cognizant of potential barriers to adoption of these systems, including perceived usefulness and ease of use from both the physician and patient's perspectives, design and technical concerns, data privacy concerns, familiarity with the technology, risk-benefit assessment, and communication between health workers and patients (47). Additionally, some patients or patient populations cannot afford costs related to digital health which may not yet be covered by their insurance or may have limited use for certain technologies due to disability (55). While some patients easily accept and appreciate digital health in their standard healthcare, others may be unable to understand and quickly adapt to new technologies. Studies have shown that senior patients, who are often less familiar with newer technologies and yet could sometimes benefit the most, may face difficulty and consequently refuse to use these technologies even if advised (56). Measures will need to be put in place to allocate resources and infrastructure for patient education with these technologies. Optimizing resources, infrastructure, and patient literacy and engagement may help improve adherence, efficacy of technological products, and ultimately improvement in clinical outcomes. The CardioMEMS heart failure system is an applicable example of an effective form of healthcare technology that has yet to be disseminated into everyday healthcare practice despite its evident benefits (22). As previously mentioned, the adoption of digital medicine within everyday practice is influenced by a complex range of factors that stem from not only the technology itself but from healthcare providers, governing institutions and the patients receiving care. Many factors influence consumer use of digital health, including cost of utilization and security concerns that may limit the patient's eagerness to try new and unfamiliar technology. These factors and others can lead to technologies that have not evolved quickly enough to supply suitable care for a large and medically diverse population. It seems that the most influential factor for the adoption of digital health within everyday healthcare practice is one that we cannot control, which is time itself. The evolution of technology and the growing comfort of this technology with patients and healthcare providers take ample time to ensure long-term implementation into healthcare practice. Despite this revelation, our call to action is for more in depth research that can identify the factors that influence the speed of technology adoption in healthcare to ensure patients receive the most up to date healthcare treatment.

Systems of validation and oversight are needed to ensure health technologies distributed to patient populations collect and provide data that are reliable, accurate, and equitable. Like drug therapies and other types of medical interventions, patient consent in clinical trials evaluating digital health products must employ regulatory processes, ensuring that the safety and health of the patient remain of the utmost priority. Protecting patient privacy is a major barrier to the application of digital health as well. User consent is an ethical concern of digital health as most users do not read the terms of use of the applications (57). Ensuring transparency regarding what data is collected and who can access patient data when taking informed patient consent is a key challenge in digital health adoption (58). The various domains of digital health create data that needs protection, this requires digital health platforms that include anonymization technologies (58). Data breaches can leave patients and institutions vulnerable and can pose major difficulties. The use of multiple digital health technologies could compromise a patient's protected health information leading to serious consequences such as fraud. Understanding these barriers and complications with incorporating digital health will help reduce patient non-adherence as well as maintain the level of quality healthcare expected in digital health. There needs to be further research into what digital health strategies influence health outcomes and the cost-effectiveness of service delivery (59).

Learning healthcare system: Data and digital health

Data sources for learning healthcare systems

A LHS as described by the AHA (5) references four main sources of digital data for the improvement of care:

EHR data, clinical registry data, administrative claims data, and supplemental data sources. The AHA outlines the use of EHR, clinical registry, and administrative claims data in detail. The document states that these methods leave out one crucial environment of health: patient health outside of the healthcare delivery setting. Patient health information from outside of the healthcare system arguably represents the majority of potentially actionable data and is a crucial untapped aspect of patient health. Newer data collection technologies such as wearables and implantable trackers provide a more comprehensive view of a patient's health leading to preventive rather than reactive medicine. One of the greatest challenges outlined by the AHA LHS statement for these technologies is recent naissance and thus lack of standardized methods for analysis and use. Programs that incorporate supplemental data sources help determine their most efficacious uses and viability. While EHR, registry, and claims data will predominate in the near term, they cannot provide a complete perspective on the various factors that influence a patient's cardiac health; so technologies that g ive an accurate account from outside of hospitals and clinics will increasingly contribute to the cardiovascular learning healthcare system (5). As a result, the learning healthcare system for cardio-oncology will need to develop, integrate, and eventually act on supplemental data sources that can provide critical insights into previously untapped aspects of patient health (5).

Digital health in learning healthcare systems

LHSs are reliant on four key elements to improve quality and efficiency of health care: science and informatics, patient-clinician partnerships, incentives, and a culture of continuous learning (**Figure 1**). Digital health in a LHS increases connectivity between the patient and healthcare professionals, providing easier access to information regarding real-world patient physiology, forging a progressive partnership between the patient and clinician and enhancing engagement of patients in their care. Online care delivery platforms such as patient portals can inform, engage, and empower patients in shared decision making to improve autonomy and clinician-patient trust (60). Patient portals give access to online medical consultations, previous after-visit notes, pharmaceutical information, scheduling, and messaging services to connect to their care team for non-emergency questions (60). This gives patients a more prominent role in their care and makes them key contributors to the LHS.

LHS applicable supplemental data sources can be broadly classified as patient-reported data or environmental data (5). Environmental data includes data on patients' living environments and the impact these environments have on their health (61). Patient-reported data includes information about a patient's health status (e.g., symptoms, functional status, and quality of life) (61) and physiological measurements (e.g., blood pressure, volume status), which can be collected using traditional methods of inquiry (e.g., questionnaires) or newer data collection methods such as implantable medical devices (e.g., CardioMEMs) and wearables (e.g., FitBit) (5). Collecting and integrating data from these and other domains enables a more comprehensive assessment of an oncology patient's cardiac health and may improve the ability of the learning healthcare system to proactively anticipate and respond to cardiac health declines or improvements. Supplemental data sources are in their infancy, and additional work is required to develop methods for their collection, analysis, and use (5). Numerous early initiatives that collect and use cardiovascular patient-reported data have demonstrated promise in studies of atrial fibrillation, hypertension, and heart failure (5). For example, studies have shown the accuracy and feasibility of detecting atrial fibrillation and pediatric tachyarrhythmias using sensors integrated into smartphones (32, 62, 63). Studies have also shown promise with remote monitoring of implantable cardioverter-defibrillators and pacemakers (5). This has also been the case with medication adherence (5).

Disparities and health equity

Racial and ethnic health disparities are prevalent in the United States. These disparities stem from systemic racism and are caused by poor socio-economic outcomes such as decreased financial security, lower educational attainment, and less access to health care. As a result, individuals from marginalized backgrounds bear a greater disease burden. This is apparent in oncology, cardiology, and cardio-oncology, where historically disadvantaged groups experience a higher incidence of cancer occurrence, cardiovascular disease, and cardiotoxicity from cancer therapies (64). African Americans die at a higher rate from cardiovascular disease than non-Hispanic Whites (NHWs) (64). Black women are disproportionately affected by breast cancer mortality and have been shown to be 41% more likely to die of breast cancer than NHW women. (65). Furthermore, Black women with breast cancer are 25% more likely to die from cardiovascular disease than NHW women (66). Even after controlling for cardiovascular risk factors, Black women are twofold more likely to develop cardiotoxicity from trastuzumab use than NHW women (66). Yet, disparities are not limited to the incidence of disease. Risk factors contributing to cardiovascular disease processes weigh more heavily on racial and ethnic minorities. Hypertension has a higher prevalence in African Americans than Caucasians, and is

often undertreated in these populations (66, 67). Additionally, African Americans experience earlier onset of diabetes and obesity than Caucasians.

Digital health has the potential to reduce health disparities through the implementation of digital tools in a LHS. Within the LHS, data could be collected about user access to healthcare with metrics like broadband access and visit satisfaction for virtual visits. The LHS could be used to track the impact of improving access to digital tools for underserved groups. Digital tools like "hot-spotting" could also be used to identify underserved healthcare areas where additional resources or programming can be applied to impact social determinants of health, which could contribute heavily to the prevention of disease. Underserved patients with conditions that can be managed with remote monitoring could also receive both technology and education on how to use these tools. Further, modern communication technologies could be used to distribute educational materials specific to these patients to improve engagement. A LHS can use digital meeting rooms to facilitate new community group meetings or to allow individuals to attend existing meetings remotely to make attendance more convenient and improve participation in the patient-provider dialogue described in the AHA learning healthcare system statement (5).

Through the incorporation of digital health tools into the LHS, health disparities can be further studied through clinical research. As we incorporate digital health tools into the LHS, it is appropriate to leverage these tools to better understand racial and ethnic health disparities through clinical research. This research must focus on equitable representation of racial and ethnic minorities in clinical research, such as incorporating data from diverse populations in pre-clinical studies and increasing marginalized group participation in clinical trials (64). Engaging marginalized groups in clinical research through digital health tools is promising, as these tools are being used by racial and ethnic minorities (17). For example, there was increased usage of telemedicine services among African Americans and other marginalized groups during the COVID-19 pandemic (68). However, marginalized groups still face several challenges with respect to using digital health tools such as lower health literacy and reduced internet access and conducting digital health research and incorporating digital health interventions into the care of these groups should focus on increasing accessibility (68). Clearly more than just incorporation of digital tools into the LHS and clinical research engagement is needed to address the health disparities that racial and ethnic minorities face. Efforts need to be made to dismantle structural racism, engage the community, and improve access to cardio-oncology services (64).

Conclusion

Digital health, in many present and future forms, continues to become increasingly relevant in modern medicine. By understanding the importance, capabilities, and limitations of digital health, innovators in healthcare can continue working toward refining how we utilize technology in medicine. In addition, as we have seen in the past year, telemedicine and digital health have the opportunity to provide an economical alternative to providing quality care with increased access to many patient populations (16, 17, 32, 68, 69). With this understanding, we can recognize that digital health will remain an integral aspect of the new era in medicine and the successful implementation of a LHS as described by the AHA.

While digital data are already highly integrated into the EHR, clinical registry, and administrative claims branches of the LHS data systems, digital health has enormous potential to mold the supplementary data branch by providing reports on patient health outside the healthcare setting. The production and research of digital health tools will revolutionize the healthcare system and the quality of care we can provide. While digital health tools continue to be developed and show promise, they outpace the rate that research on the efficacy of these tools can be conducted. Indeed, studies have shown that digital health interventions can improve medication adherence, provide remote data to inform accurate diagnoses and monitor pre-pathological states, among other benefits. However, more steps must be taken to implement digital health interventions into evidence-based clinical practice. To make this a reality in modern patient care, providers must feel comfortable recommending these technologies and guidelines, such as the ACC Best Practices for Consumer Cardiovascular Technology Solutions (8, 9). In addition, design concerns, such as providing appropriate patient education, and technical concerns, such as data breaches, must be addressed. Research must be conducted on the benefits and risks of digital health interventions before widespread implementation. Although this field of study is still in its early stages, we have an advantage in terms of designing studies to accurately represent the population and determine optimal ways to increase access to combat racial and ethnic disparities.

Author contributions

RM and SAB: conception and design. RM, JM, TM, SP, AS, GB, AH, JW, and SAB: drafting of the manuscript. RM, JM, TM, SP, AS, GB, AH, and SAB: interpretation of data. RM, JM, TM, SP, AS, GB, AH, MA, JW, and SAB: critical revision. All authors have read and approved the final manuscript.

Funding

This publication was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Nos. UL1TR001436 and KL2TR001438.

Acknowledgments

We are grateful to all members of the Connected Health Innovation Research Program (C.H.I.R.P.), Cardiology Oncology Innovation Network (COIN), and Cardio-Oncology Artificial Intelligence Informatics and Precision (CAIP) Research Team Investigators for local, regional, national and global partnership in this work.

Conflict of interest

All of our authors are involved in digital health research, none of which inappropriately restricts or limits our analyses or publications. SAB serves as an advisor for HeartIn and NutriSense. SAB has not received compensation or research support for any work related to this project.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Author disclaimer

This article's contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

References

1. AQRH,. *About Learning Health Systems Agency for Healthcare Research and Quality2019*. (2019). Available online at: https://www.ahrq.gov/learning-health-systems/about.html (accessed December 20, 2021).

2. FDA. *FDA Digital Health Center of Excellence U.S. Food & Drug Administration2021 [updated 11/23/2021*. (2021). Available online at: https://www.fda.gov/medical-devices/digital-health-center-excellence (accessed December 20, 2021).

3. Meskó B, Drobni Z, Bényei É, Gergely B, Győrffy Z. Digital health is a cultural transformation of traditional healthcare. *mHealth*. (2017) 3:38.

4. Murray E, Hekler EB, Andersson G, Collins LM, Doherty A, Hollis C, et al. Evaluating digital health interventions: key questions and approaches. *Am J Prevent Med*. (2016) 51:843–51.

5. Maddox TM, Albert NM, Borden WB, Curtis LH, Ferguson TB, Kao DP, et al. The learning healthcare system and cardiovascular care: a scientific statement from the American Heart Association. *Circulation*. (2017) 135:e826–57. doi: 10.1161/CIR.0000000000000480

6. CES. *Best Practices for Consumer Cardiovascular Technology Solutions. American College of Cardiology: Consumer Technology Association*. Arlington, VA: CES (2022).

7. FDA. *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations. FDA Guidance Documents: Food and Drug Administration*. White Oak, MD: FDA (2022).

8. Greene SM, Reid RJ, Larson EB. Implementing the learning health system: from concept to action. *Ann Intern Med*. (2012) 157:207–10.

9. Inkster B, O'Brien R, Selby E, Joshi S, Subramanian V, Kadaba M, et al. Digital health management during and beyond the COVID-19 pandemic: opportunities, barriers, and recommendations. *JMIR Ment Health*. (2020) 7:e19246. doi: 10.2196/19246

10. Kadakia K, Patel B, Shah A. Advancing digital health: FDA innovation during COVID-19. *NPJ Digit Med*. (2020) 3:161.

11. Peek N, Sujan M, Scott P. Digital health and care in pandemic times: impact of COVID-19. *BMJ Health Care Inform*. (2020) 27:e100166.

12. Maeder, A, Bidargaddi N, Williams P. Contextualising digital health contributions to fighting the COVID-19 pandemic. *J Int Soc Telemed EHealth*. (2020) 8:1–5.

13. Petracca F, Ciani O, Cucciniello M, Tarricone R. Harnessing digital health technologies during and after the COVID-19 pandemic: context matters. *J Med Internet Res*. (2020) 22:e21815. doi: 10.2196/21815

14. Lai L, Wittbold KA, Dadabhoy FZ, Sato R, Landman AB, Schwamm LH, et al. Digital triage: novel strategies for population health management in response to the COVID-19 pandemic. *Healthc (Amst)*. (2020) 8:100493. doi: 10.1016/j.hjdsi.2020.100493

15. Brewer LC, Fortuna KL, Jones C, Walker R, Hayes SN, Patten CA, et al. Back to the future: achieving health equity through health informatics and digital health. *JMIR Mhealth Uhealth*. (2020) 8:e14512. doi: 10.2196/14512

16. Snoswell CL, Taylor ML, Comans TA, Smith AC, Gray LC, Caffery LJ. Determining if telehealth can reduce health system costs: scoping review. *J Med Internet Res*. (2020) 22:e17298.

17. Shea S, Weinstock RS, Teresi JA, Palmas W, Starren J, Cimino JJ, et al. A randomized trial comparing telemedicine case management with usual care in older, ethnically diverse, medically underserved patients with diabetes mellitus: 5 year results of the IDEATel study. *J Am Med Inform Assoc*. (2009) 16:446–56. doi: 10.1197/jamia.M3157

18. Lupton D. *Beyond Techno-Utopia: Critical Approaches to Digital Health Technologies*. (Vol. 4). Basel: MDPI (2014).

19. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet*. (2011) 377:658–66. doi: 10.1016/S0140-6736(11)60101-3

20. Marvel FA, Spaulding EM, Lee MA, Yang WE, Demo R, Ding J, et al. Digital health intervention in acute myocardial infarction. *Circ Cardiovasc Qual Outcomes*. (2021) 14:e007741.

21. Bayoumy K, Gaber M, Elshafeey A, Mhaimeed O, Dineen EH, Marvel FA, et al. Smart wearable devices in cardiovascular care: where we are and how to move forward. *Nat Rev Cardiol*. (2021) 18:581–99. doi: 10.1038/s41569-021-00522-7

22. Brown SA. Preventive cardio-oncology: the time has come. *Front Cardiovasc Med*. (2019) 6:187.

23. American Medical Association. *Physicians' Motivations and Key Requirements for Adopting Digital Health Adoption and attitudinal shifts from 2016 to 2022. American Medical Association*. (2022). Available online at: https://www.ama-assn.org/system/files/ama-digital-health-study.pdf (accessed Sepetember 9, 2022).

24. Kahn MG, Brown JS, Chun AT, Davidson BN, Meeker D, Ryan PB, et al. Transparent reporting of data quality in distributed data networks. *EGEMS (Wash DC).* (2015) 3:1052.

25. Schmier JK, Ong KL, Fonarow GC. Cost-effectiveness of remote cardiac monitoring with the CardioMEMS heart failure system. *Clin Cardiol.* (2017) 40:430–6.

26. Merchant R, Szefler SJ, Bender BG, Tuffli M, Barrett MA, Gondalia R, et al. Impact of a digital health intervention on asthma resource utilization. *World Allergy Organ J.* (2018) 11:28.

27. Atasoy H, Greenwood BN, McCullough JS. The digitization of patient care: a review of the effects of electronic health records on health care quality and utilization. *Annu Rev Public Health.* (2019) 40:487–500.

28. Topol EJ. Transforming medicine via digital innovation. *Sci Transl Med.* (2010) 2:16cm4.

29. Frederix I, Caiani EG, Dendale P, Anker S, Bax J, Böhm A, et al. ESC e-cardiology working group position paper: overcoming challenges in digital health implementation in cardiovascular medicine. *Eur J Prev Cardiol.* (2019) 26:1166–77. doi: 10.1177/2047487319832394

30. Feroz A, Jabeen R, Saleem S. Using mobile phones to improve community health workers performance in low-and-middle-income countries. *BMC Public Health.* (2020) 20:49.

31. Liu P, Astudillo K, Velez D, Kelley L, Cobbs-Lomax D, Spatz ES. Use of mobile health applications in low-income populations: a prospective study of facilitators and barriers. *Circ Cardiovasc Qual Outcomes.* (2020) 13:e007031.

32. Haberman ZC, Jahn RT, Bose R, Tun H, Shinbane JS, Doshi RN, et al. Wireless smartphone ECG enables large-scale screening in diverse populations. *J Cardiovasc Electrophysiol.* (2015) 26:520–6. doi: 10.1111/jce.12634

33. Zhang Y, Grinspan Z, Khullar D, Unruh MA, Shenkman E, Cohen A, et al. Developing an actionable patient taxonomy to understand and characterize high-cost medicare patients. *Healthc (Amst).* (2020) 8:100406. doi: 10.1016/j.hjdsi.2019.100406

34. Institute of Medicine (US) Roundtable on Evidence-Based Medicine. *The Healthcare Imperative: Lowering Costs and Improving Outcomes: Workshop Series Summary*. Washington, DC: National Academies Press (2010).

35. Mathur P, Srivastava S, Xu X, Mehta JL. Artificial intelligence, machine learning, and cardiovascular disease. *Clin Med Insights Cardiol.* (2020) 14:1179546820927404.

36. Bhavnani SP, Sola S, Adams D, Venkateshvaran A, Dash PK, Sengupta PP, et al. A randomized trial of pocket-echocardiography integrated mobile health device assessments in modern structural heart disease clinics. *JACC Cardiovasc Imaging.* (2018) 11:546–57. doi: 10.1016/j.jcmg.2017.06.019

37. MSI International Study. *Americans View Remote Monitoring of Health Favorably [Press Release]*. CISION2021. London: Savanta (2021).

38. Lupton D. Critical perspectives on digital health technologies. *Sociol Compass.* (2014) 8:1344–59.

39. Vayena E, Haeusermann T, Adjekum A, Blasimme A. Digital health: meeting the ethical and policy challenges. *Swiss Med Wkly.* (2018) 148:w14571.

40. Lee H, Park JB, Choi SW, Yoon YE, Park HE, Lee SE, et al. Impact of a telehealth program with voice recognition technology in patients with chronic heart failure: feasibility study. *JMIR Mhealth Uhealth.* (2017) 5:e127. doi: 10.2196/mhealth.7058

41. Palmer MJ, Machiyama K, Woodd S, Gubijev A, Barnard S, Russell S, et al. Mobile phone-based interventions for improving adherence to medication prescribed for the primary prevention of cardiovascular disease in adults. *Cochrane Database Syst Rev.* (2021) 3:CD012675.

42. Gallagher BD, Moise N, Haerizadeh M, Ye S, Medina V, Kronish IM. Telemonitoring adherence to medications in heart failure patients (TEAM-HF): a pilot randomized clinical trial. *J Card Fail.* (2017) 23:345–9. doi: 10.1016/j.cardfail.2016.11.001

43. Su JG, Barrett MA, Henderson K, Humblet O, Smith T, Sublett JW, et al. Feasibility of deploying inhaler sensors to identify the impacts of environmental triggers and built environment factors on asthma short-acting Bronchodilator use. *Environ Health Perspect.* (2017) 125:254–61. doi: 10.1289/EHP266

44. Plante TB, Urrea B, MacFarlane ZT, Blumenthal RS, Miller ER, Appel LJ, et al. Validation of the instant blood pressure smartphone app. *JAMA Intern Med.* (2016) 176:700–2.

45. Tan T, Kuek A, Goh SE, Lee EL, Kwok V. Internet and smartphone application usage in eating disorders: a descriptive study in Singapore. *Asian J Psychiatr.* (2016) 19:50–5. doi: 10.1016/j.ajp.2015.11.007

46. Bhavnani SP. Digital health: opportunities and challenges to develop the next-generation technology-enabled models of cardiovascular care. *Methodist Debakey Cardiovasc J.* (2020) 16:296–303. doi: 10.14797/mdcj-16-4-296

47. Schorr EN, Gepner AD, Dolansky MA, Forman DE, Park LG, Petersen KS, et al. Harnessing mobile health technology for secondary cardiovascular disease prevention in older adults: a scientific statement from the American Heart Association. *Circ Cardiovasc Qual Outcomes.* (2021) 14:e000103. doi: 10.1161/HCQ.0000000000000103

48. Seninger C. *Stanford Medicine Center for Digital Health*. (2020). Available online at: http://med.stanford.edu/cdh.html (accessed February 25, 2022).

49. Digital Medicine Society (DiMe) 2020 Available online at: https://www.dimesociety.org/index.php/about-us-main (accessed February 25, 2022).

50. Shan R, Ding J, Weng D, Spaulding EM, Wongvibulsin S, Lee MA, et al. Early blood pressure assessment after acute myocardial infarction: insights using digital health technology. *Am J Prev Cardiol.* (2020) 3:100089. doi: 10.1016/j.ajpc.2020.100089

51. Moon JH, Kang MK, Choi CE, Min J, Lee HY, Lim S. Validation of a wearable cuff-less wristwatch-type blood pressure monitoring device. *Sci Rep.* (2020) 10:19015. doi: 10.1038/s41598-020-75892-y

52. Victoria-Castro AM, Martin M, Yamamoto Y, Ahmad T, Arora T, Calderon F, et al. Pragmatic randomized trial assessing the impact of digital health technology on quality of life in patients with heart failure: design, rationale and implementation. *Clin Cardiol.* (2022) 45:839–49. doi: 10.1002/clc.23848

53. Maddula R, MacLeod J, Painter S, McLeish T, Steward A, Rossman A, et al. Connected health innovation research program (C.H.I.R.P.): a bridge for digital health and wellness in cardiology and oncology. *Am Heart J Plus Cardiol Res Pract.* (2022) 20:100192.

54. Tromp J, Jindal D, Redfern J, Bhatt A, Séverin T, Banerjee A, et al. World heart federation roadmap for digital health in cardiology. *Glob Heart.* (2022) 17:61.

55. Radcliffe E, Lippincott B, Anderson R, Jones M. A pilot evaluation of mhealth app accessibility for three top-rated weight management apps by people with disabilities. *Int J Environ Res Public Health.* (2021) 18:3669. doi: 10.3390/ijerph18073669

56. Levine DM, Lipsitz SR, Linder JA. Trends in seniors' use of digital health technology in the United States, 2011-2014. *JAMA.* (2016) 316:538–40. doi: 10.1001/jama.2016.9124

57. Vayena E, Mastroianni A, Kahn J. Caught in the web: informed consent for online health research. *Sci Transl Med.* (2013) 5:fs6–6. doi: 10.1126/scitranslmed.3004798

58. Manteghinejad A, Javanmard SH. Challenges and opportunities of digital health in a post-COVID19 world. *J Res Med Sci.* (2021) 26:11. doi: 10.4103/jrms.JRMS_1255_20

59. Greaves F, Joshi I, Campbell M, Roberts S, Patel N, Powell J. What is an appropriate level of evidence for a digital health intervention? *Lancet.* (2019) 392:2665–7.

60. Jung C, Padman R. Disruptive digital innovation in healthcare delivery: the case for patient portals and online clinical consultations. In: Agarwal R, Selen W, Roos G, Green R editors. *The Handbook of Service Innovation*. London: Springer London (2015). p. 297–318.

61. Rumsfeld JS, Alexander KP, Goff DC, Graham MM, Ho PM, Masoudi FA, et al. Cardiovascular health: the importance of measuring patient-reported health status: a scientific statement from the American Heart Association. *Circulation.* (2013) 127:2233–49.

62. Ferdman DJ, Liberman L, Silver ESA. Smartphone application to diagnose the mechanism of pediatric supraventricular tachycardia. *Pediatr Cardiol.* (2015) 36:1452–7. doi: 10.1007/s00246-015-1185-6

63. McManus DD, Lee J, Maitas O, Esa N, Pidikiti R, Carlucci A, et al. A novel application for the detection of an irregular pulse using an iPhone 4S in patients with atrial fibrillation. *Heart Rhythm.* (2013) 10:315–9.

64. Fazal M, Malisa J, Rhee JW, Witteles RM, Rodriguez F. Racial and ethnic disparities in cardio-oncology: a call to action. *JACC CardioOncol.* (2021) 3:201–4. doi: 10.1016/j.jaccao.2021.05.001

65. Centers for Disease Control and Prevention (CDC). Vital signs: racial disparities in breast cancer severity–United States, 2005-2009. *MMWR Morb Mortal Wkly Rep.* (2012) 61:922–6.

66. Prasad P, Branch M, Asemota D, Elsayed R, Addison D, Brown S-A. Cardio-oncology preventive care: racial and ethnic disparities. *Curr Cardiovasc Risk Rep.* (2020) 14:18. doi: 10.1188/21.CJON.S1.36-41

67. Iacopo F, Branch M, Cardinale D, Middeldorp M, Sanders P, Cohen JB, et al. Preventive cardio-oncology: cardiovascular disease prevention in cancer patients and survivors. *Curr Treat Opt Cardiovasc Med.* (2019) 23:2–3.

68. Campos-Castillo C, Anthony D. Racial and ethnic differences in self-reported telehealth use during the COVID-19 pandemic: a secondary analysis of a US survey of internet users from late March. *J Am Med Inform Assoc.* (2021) 28:119–25. doi: 10.1093/jamia/ocaa221

69. Suran M. Increased use of medicare telehealth during the pandemic. *JAMA.* (2022) 327:313.

frontiers | Frontiers in Cardiovascular Medicine

TYPE Brief Research Report
PUBLISHED 06 January 2023
DOI 10.3389/fcvm.2022.1099014

Check for updates

OPEN ACCESS

EDITED BY
David Duncker,
Hannover Medical School, Germany

REVIEWED BY
Sebastian Feickert,
Department for Cardiology
and Conservative Intensive Care Unit,
Germany
Eimo Martens,
Technical University of Munich,
Germany

*CORRESPONDENCE
Mark J. Schuuring
✉ M.J.Schuuring-19@umcutrecht.nl

SPECIALTY SECTION
This article was submitted to
Cardiac Rhythmology,
a section of the journal
Frontiers in Cardiovascular Medicine

RECEIVED 15 November 2022
ACCEPTED 13 December 2022
PUBLISHED 06 January 2023

CITATION
Koole MA, Kauw D, Kooiman KM,
de Groot JR, Robbers-Visser D,
Tulevski II, Mulder BJ, Bouma BJ and
Schuuring MJ (2023) An implantable
loop recorder or smartphone based
single-lead electrocardiogram
to detect arrhythmia in adults with
congenital heart disease?
Front. Cardiovasc. Med. 9:1099014.
doi: 10.3389/fcvm.2022.1099014

COPYRIGHT
© 2023 Koole, Kauw, Kooiman,
de Groot, Robbers-Visser, Tulevski,
Mulder, Bouma and Schuuring. This is
an open-access article distributed
under the terms of the Creative
Commons Attribution License (CC BY).
The use, distribution or reproduction in
other forums is permitted, provided
the original author(s) and the copyright
owner(s) are credited and that the
original publication in this journal is
cited, in accordance with accepted
academic practice. No use, distribution
or reproduction is permitted which
does not comply with these terms.

An implantable loop recorder or smartphone based single-lead electrocardiogram to detect arrhythmia in adults with congenital heart disease?

Maarten A. Koole[1,2,3], Dirkjan Kauw[4], Kirsten M. Kooiman[1], Joris R. de Groot[1], Danielle Robbers-Visser[1], Igor I. Tulevski[2], Barbara J. Mulder[1], Berto J. Bouma[1] and Mark J. Schuuring[1,5,6]*

[1]Department of Cardiology, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands, [2]Cardiology Centers of the Netherlands, Amsterdam, Netherlands, [3]Department of Cardiology, Rode Kruis Ziekenhuis Beverwijk, Beverwijk, Netherlands, [4]Department of Cardiology, Haga Teaching Hospital, The Hague, Netherlands, [5]Netherlands Heart Institute, Utrecht, Netherlands, [6]Department of Cardiology, UMC Utrecht, Utrecht, Netherlands

Background: The European Society of Cardiology (ESC) guidelines for the management of adult congenital heart disease (ACHD) recommend screening in patients at risk for arrhythmic events. However, the optimal mode of detection is unknown.

Methods: Baseline and follow-up data of symptomatic ACHD patients who received an implantable loop recorder (ILR) or who participated in a smartphone based single-lead electrocardiogram study were collected. The primary endpoint was time to first detected arrhythmia.

Results: In total 116 ACHD patients (mean age 42 years, 44% male) were studied. The ILR group (n = 23) differed from the smartphone based single-lead electrocardiogram group (n = 93) in having a greater part of males and had more severe CHD and (near) syncope as qualifying diagnosis. In the smartphone based single-lead electrocardiogram group history of arrhythmia and palpitations were more frequent (all $p < 0.05$). Monitoring was performed for 40 and 79 patient-years for the ILR- and smartphone based single-lead electrocardiogram group, respectively. Arrhythmias occurred in 33 patients with an equal median time for both groups to first arrhythmia of 3 months (HR of 0.7, p = 0.81). Furthermore, atrial fibrillation occurred most often (n = 16) and common therapy changes included medication changes (n = 7) and implantation of pacemaker or Implantable Cardioverter Defibrillator (ICD) (N = 4). Symptoms or mode of detection were not a determinant of the first event.

10.3389/fcvm.2022.1099014

Conclusion: Non-invasive smartphone based single-lead electrocardiogram monitoring could be an acceptable alternative for ILR implantation in detecting arrhythmia in symptomatic ACHD patients in respect to diagnostic yield, safety and management decisions, especially in those without syncope.

KEYWORDS

arrhythmias, congenital heart disease, electrocardiography, telemedicine, implantable loop recorder, cardiology, pacemaker, eHealth

1. Introduction

1.1. Adult congenital heart disease

Congenital heart disease has a worldwide prevalence of ∼9 per 1000 newborns. Nowadays, the number of adult congenital heart disease (ACHD) patients exceeds the number of children with congenital heart disease and the population of ACHD patients is still increasing by 5% per year (1, 2). These ACHD patients are under lifelong surveillance in specialized centers. Although their prognosis has significantly improved compared to only a few decades ago, these patients are not cured. Data from the Dutch National CONCOR registry showed that the median age of death is 49 years and that two third of adult patients with CHD die from a cardiac cause (3–6). One of the most common causes of death is sudden cardiac death (19%), which occurs at a median age of 39 years (3, 4, 7). It is estimated that 1 out of 6 ACHD patients develops bradycardias or tachyarrhythmia during life, that often precede syncope and/or sudden death (3). Over one-third of tetralogy of Fallot (ToF) patients develop symptomatic atrial tachyarrhythmia by adulthood, 10% develop high-grade ventricular arrhythmia, and 5% require a pacemaker implantation for surgically acquired atrioventricular block or sinus node dysfunction. After Senning or Mustard repairs for Transposition of the Great Arteries (TGA), loss of sinus rhythm occurs in 60% of patients in the 20-year period after surgery (8).

1.2. Arrhythmia detection

The European Society of Cardiology (ESC) guidelines recommend periodical screening in symptomatic ACHD patients, without arrhythmia documentation at presentation, evaluation for arrhythmia (1). Subgroups of patients who are at increased risk are identified in the guideline. In patients with pacemakers or implantable cardioverter defibrillators (ICDs), device interrogation is used to screen for arrhythmias (9, 10). In patients without implantable device, short term screening is commonly performed with Holter studies, and prolonged screening with Implantable Loop Recorders (ILR). However, smartphone based single-lead electrocardiogram solutions may provide new alternatives (11, 12). Mobile devices for heart rhythm monitoring, defined as ambulant diagnostics, is rapidly evolving as wearables, mobile health applications (apps) and smartphone possibilities are improving, and increasing in number (13–15). ACHD patients seem particularly eligible to benefit from these alternative solutions, as these patients have a higher burden of arrhythmia compared to the general population and having their first arrhythmia at younger age. So they are generally well motivated to apply eHealth. However, data on smartphone based single-lead electrocardiogram are scarce. Therefore, the study aimed to explore whether smartphone based single-lead electrocardiogram can be a good alternative to ILR in detecting arrhythmia.

2. Methods

2.1. Study data

Baseline and follow-up data were collected of two cohorts of ACHD patients with symptoms which could be caused by arrhythmia. One cohort were patients who participated in a smartphone based single-lead electrocardiogram study and the other cohort are patients gathered by a retrospective chart review of patients with an ILR. Indications for ILR implantation were symptoms which could be related to arrhythmia. The smartphone based single-lead electrocardiogram group of patients participated in a prospective study in two medical centers in the Netherlands (Haga Teaching Hospital and Amsterdam UMC, location AMC). The study protocol required routine evaluation of heart rhythm using a wireless pocket-sized single lead EKG recording device that could record a 30 s single lead EKG (Kardia, AliveCor). After a 1-week run-in period, a single lead EKG was recorded once every week. Patients could perform extra measurements in case of symptoms. Data of events were sent by the application of the smartphone to our telemedicine center and within 48 h judged by specialized nurses. Data of the ILR were read as

soon as possible after an event at our outpatient clinic. All patients were explained to contact a physician directly in case of emergency. Detailed description of the study has been published elsewhere (15). A retrospective chart review has been performed to collect ILR data of all symptomatic ACHD patients having an ILR implanted between 2003 and 2019 (Amsterdam UMC, location AMC).

2.2. Study criteria

The smartphone based single-lead electrocardiogram study ACHD patients were eligible for inclusion if they met the following inclusion criteria: palpitations within the last 3 years (with or without arrhythmia diagnosis) or HF NYHA class ≥ II, and possession of a smartphone. Patients with impaired cognition, as assessed by their treating physician, tremors or patients with an insurance not covering costs of the smartphone based single-lead electrocardiogram program, were excluded. Patients were recruited from the outpatient clinic and clinical wards. Enrollment in this study followed after informed consent for the use of their clinical data was acquired. The local medical ethics committees of both institutions issued a waiver for this study. This included a waived consent for the retrospective chart review, because data were processed anonymously by the investigator.

2.3. Study outcome

The primary endpoint was time to first arrhythmia detected (AF, SVT, VT, sinus node defect, or AV block) in both study groups. Device implantation and change in medication were not an outcome but also registered as a result of detecting arrhythmia for both groups. Data were analyzed with Kaplan-Meier survival curves and Cox proportional hazard analysis (SPSS version 28, IBM, Armonk, New York, NY, USA). Chi-square test or independent *t*-test were used to assess differences between patient-groups.

3. Results

3.1. Baseline characteristics

In total 116 ACHD patients were studied, see **Table 1**. Mean age was 42 years and 44% were male. There were 25 (22%) patients with mild CHD, 45 (39%) patients with moderate CHD, and 46 (39%) patients with severe CHD. The rate of hypertension (*n* = 16, 14%) or coronary artery disease was low (*n* = 7, 6%). The ILR group consisted of 23 patients and the smartphone based single-lead electrocardiogram consisted of 93 patients.

TABLE 1 Baseline characteristics.

	All	ILR	Smartphone ECG	*p*
	N = 116	*N* = 23	*N* = 93	
Age, years	42	44	42	0.573
Male, *N* (%)	51 (44)	17 (74)	34 (37)	**0.001**
Severity of CHD				
Mild, *N* (%)	25 (22)	3 (23)	22 (24)	**0.020**
Moderate, *N* (%)	45 (39)	5 (22)	40 (93)	
Severe, *N* (%)	46 (39)	15 (65)	31 (33)	
Medical history				
Cardiac surgery, *N* (%)	92 (79)	17 (74)	75 (81)	0.475
Non-cardiac surgery, *N* (%)	54 (47)	5 (22)	49 (53)	**0.007**
Coronary artery disease, *N* (%)	7 (6)	2 (9)	5 (5)	0.559
Arrhythmia, *N* (%)	91 (78)	10 (43)	81 (87)	< **0.01**
Heart failure, *N* (%)	22 (19)	3 (13)	19 (20)	0.418
Hypertension, *N* (%)	16 (14)	1 (4)	15 (16)	0.142
Systemic EF < 40%, *N* (%)	6 (5)	0	6 (6)	0.208
Subpulmonic EF < 40%, *N* (%)	4 (3)	1 (4)	3 (3)	0.399
NYHA class				
I, *N* (%)	90 (78)	16 (70)	74 (80)	0.303
≥ 2, *N* (%)	26 (22)	7 (30)	19 (20)	
Arrhythmia symptoms, *N* (%)	95 (82)	19 (83)	76 (82)	0.921
Palpitations, *N* (%)	78 (67)	8 (35)	70 (75)	< **0.01**
Dyspnea, *N* (%)	12 (10)	2 (9)	10 (11)	0.772
(Near) syncope, *N* (%)	18 (16)	15 (65)	3 (3)	< **0.01**
Medication				
Antiarrhythmic agents, *N* (%)	52 (45)	7 (30)	45 (48)	0.121
Diuretics, *N* (%)	13 (11)	3 (13)	10 (11)	0.701
Anticoagulation, *N* (%)	45 (39)	7 (30)	38 (41)	0.358

N, number; EF, ejection fraction; ILR, implantable loop recorder; CHD, congenital heart disease; NYHA, New York heart association. Bold values represent the significant values.

The ILR group (*n* = 23) differed from the smartphone based single-lead electrocardiogram group (*n* = 93) in having a greater part of males. They had more severe CHD and (near) syncope (65 vs. 3%) as qualifying symptom of possible arrhythmia. In the smartphone based single-lead electrocardiogram group history of arrhythmia and suffering from palpitations were more frequent.

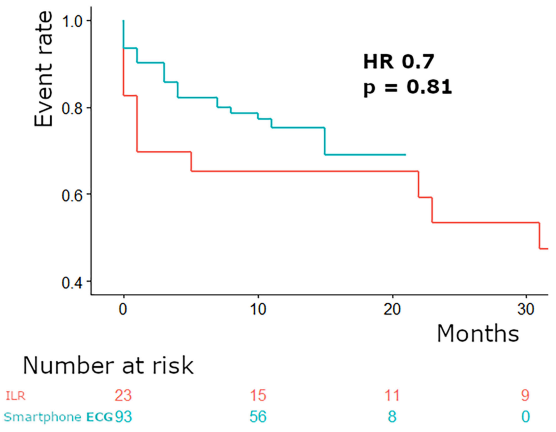


FIGURE 1
Time to first arrhythmia.

3.2. Monitoring details

In total patients were monitored for 119 patient years. Monitoring was performed for 40 and 79 patient years, respectively, in the ILR and smartphone based single-lead electrocardiogram groups. The median time to first arrhythmia was 92 (16–233) days for the complete study cohort, for the ILR group 40 (15–681) days and for the smartphone based single-lead electrocardiogram group 102 (21–232) days (p = 0.80, HR of 0.7) (**Figure 1** and **Table 2**). Arrhythmias occurred in 33 patients, of which 11 (48%) were documented in the ILR group and 22 (24%) in the smartphone based single-lead electrocardiogram group (p = 0.021). In both groups atrial fibrillation was the most frequently documented arrhythmia and no patient died.

3.3. Changes in patient management

Arrhythmia detection led to the important care changes, displayed in **Figure 2**. In the ILR group device implantation to treat arrhythmia was performed in four patients (three pacemaker and one ICD) and medication changes were performed in two patients (start of beta-blocker). Furthermore, in the ILR group a wait and see strategy was chosen in five patients. In the smartphone based single-lead electrocardiogram group ablation was performed in one patient and electrical cardioversion was performed in three patients. In five patients monitored with smartphone based single-lead electrocardiogram medication changes were performed, including start of a direct oral anticoagulant, start of amiodarone, and both start and increase of beta blocker. In one patient it was decided to perform additional Holter monitoring and in 12 patients no change in management was initiated.

3.4. Determinants of the first arrhythmia event

The mode of detection (HR 0,688 95% CI 0.3–1.6, 0,371) appeared not to be associated with the first detection of arrhythmia in the study period (HR 3.2, 95% CI 1.5–6.8, p = 0.002). The use of anti-arrhythmic drugs was associated with an arrhythmia event because patients with anti-arrhythmic drugs are at high risk of arrhythmia.

4. Discussion

4.1. Principal findings

Rhythm monitoring is important in ACHD patients as they are at high risk for arrhythmic and brady-arrhythmic events, but with the currently expanded possibilities of diagnostics no optimal diagnostic strategy has been defined yet. To our knowledge this is the first study that performed a comparison of ILR and smartphone based single-lead electrocardiogram for heart rhythm monitoring in ACHD patients. Smartphone based single-lead electrocardiogram seems to be a reasonable non-invasive alternative diagnostic tool for symptomatic patients instead of an invasive ILR for detecting arrhythmia.

4.2. Diagnostic yield of ambulatory rhythm monitoring in ACHD patients

Our findings of a high burden of arrhythmia in selected ACHD patients is comparable to the literature. Dodeja et al. evaluated traditional ILR monitoring in ACHD patients and showed a useful adjunct with clinically relevant events in 41% of patients (9). Schultz et al. performed a retrospective cohort study on remote ambulatory monitoring in 307 ACHD patients with symptoms, a history of arrhythmia or screening due to an increased risk. Their 14-day screening detected arrhythmia in 153 (50%) ACHD patients. Management changes, including medication changes (30%), further testing or imaging (10%), and procedures (6%), were made based on results of these prolonged monitoring strategy (16). Huntgeburth et al. performed a single center, retrospective observational study in which all CHD-patients with an ILR who were under care of the German Heart Center Munich between February 2015 and January 2019 were identified (17). The authors found a considerable complementary diagnostic value of ILR for the detection and differentiation of benign and malignant arrhythmias. Huntgeburth et al. concluded that ILR implantation should be considered in patients with CHD of any complexity who need medium or long-term arrhythmia monitoring, especially if short-term Holter monitoring cannot provide sufficient diagnostic certainty.

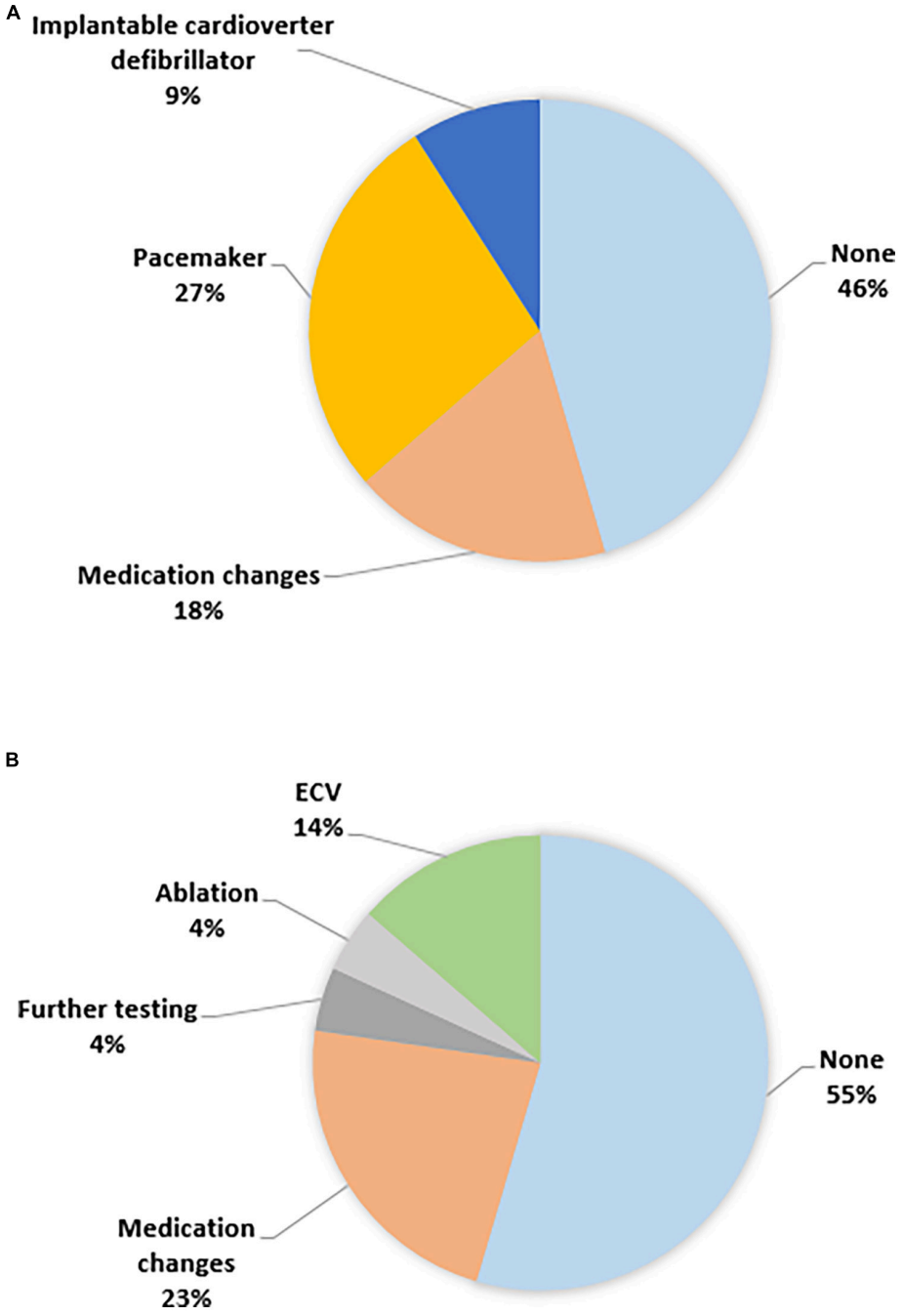


FIGURE 2
Care changes **(A)** ILR and **(B)** smartphone ECG.

4.3. Smartphone based single-lead electrocardiogram for heart rhythm monitoring in ACHD patients

Smartphone based single-lead electrocardiogram is a promising tool to improve care and detect arrhythmia in ACHD patients (18–21). Smartphone based single-lead electrocardiogram has been shown to enable early detection of recurrences and new diagnosis of arrhythmia, which led to swift therapeutic response or remote reassurance. Furthermore, smartphone based single-lead electrocardiogram was well accepted in ACHD patients with high adherence and positive patient experience (15, 22). The risk of ILR implantation such as need for re-implantation, wound dehiscence or device

10.3389/fcvm.2022.1099014

TABLE 2 Details on monitoring.

A				
	All	ILR	Smartphone ECG	*p*
	N = 116	*N* = 23	*N* = 93	
Median time to first arrhythmia, days (IQR)	92 (16–233)	40 (15–681)	102 (21–232)	0.801
Median monitoring time per patient, days (IQR)	322 (148–428)	567 (40–1217)	317 (188–399)	**0.045**
B				
Details on first arrhythmia				
	All	ILR	Smartphone	*p*
	N = 116	*N* = 23	*N* = 93	
Arrhythmia occured, *N* (%)	33 (28)	11 (48)	22 (24)	**0.021**
Atrial fibrillation, *N* (%)	16 (14)	2 (9)	14 (15)	0.428
Supraventricular tachycardia, *N* (%)	14 (12)	6 (26)	8 (9)	**0.021**
Ventricular tachycardia, *N* (%)	1 (1)	1 (4)	0	**0.043**
Sinus node defect, *N* (%)	2 (2)	2 (9)	0	**0.004**
Atrioventricular block, *N* (%)	0	0	0	1.000

N, number; IQR, interquartile ranges; ILR, implantable loop recorder. Bold values represent the significant values.

erosion of 1–9% can be avoided (17, 23, 24). Smartphone based single-lead electrocardiogram as a non-invasive diagnostic tool has no such risk of surgical complications. In our analysis smartphone based single-lead electrocardiogram proofed to be an effective tool in detecting arrhythmia. In our study there was a lower rate of arrhythmia detection in the smartphone based single-lead electrocardiogram group, potentially due to the fact that this group had less patients with severe ACHD. Although ILR is better at detecting arrhythmias in patients because the window of measurement is continuous, it has the before mentioned disadvantage of being an invasive tool. So, we suggest in symptomatic patients, if symptoms occur on daily basis, 24 Holter monitoring for diagnosing arrhythmia is a good option. If symptoms occur less frequently smartphone based single-lead electrocardiogram could be an alternative option and save the ILR for patients where no diagnosis could be found with these modalities and for whom detecting arrhythmia is important to their prognosis. Furthermore, new wearables with smart algorithms can monitor patients continuous and alert patient and physician if arrhythmia is detected (25, 26).

4.4. Prolonged rhythm monitoring in acquired heart disease patients

Diagnostic yield of prolonged monitoring is also well established in AF screening in cryptogenic stroke patients (27). Longer durations of monitoring were associated with the highest diagnostic yield in these patients (28, 29). However, the optimal monitoring method and duration of monitoring is unclear (30–32). Solbiati et al. performed a systematic Cochrane review on ILR performance and concluded that available data are non-conclusive. The authors therefore recommended further research on ILR with clinically relevant outcomes (33). Our study suggests our smartphone based single-lead electrocardiogram protocol compared to ILR can be a good alternative in detecting arrhythmia in patients with symptoms other than syncope. Especially if these complaints are less frequent than once a day for which 24–48-h Holter monitoring is still a good alternative option.

4.5. Future directions

Beside clinical effectiveness other aspects of implementation include amongst others: cost evaluation, governance, patient, and technological factors. Studies on costs of smartphone based single-lead electrocardiogram are scarce. In the first study that compared eHealth with the standard outpatient clinic setting it was suggested that eHealth was likely cost-effective (34). That study was performed in patients who suffered from acute myocardial infarction. Hypothetically, smartphone based single-lead electrocardiogram is more cost-effective than ILR because it saves on the costs of implantation and explantation, but if wearables for heart rhythm monitoring use a service center with medical personnel, the costs for this solution could also become significant. Furthermore, health system governance, health provider, patient and technological factors may complicate implementation. However, tools to identify barriers to implementing digital health and recommendations for overcoming them are increasingly available (35–37).

4.6. Limitations

Our study was limited by a combination of two datasets, without randomization of patients between the two monitoring strategies. Moreover, short arrhythmia and asymptomatic arrhythmia or bradycardias may remain unnoticed in both groups. Despite we screened all ACHD patients visiting our outpatient clinic between 2003 and 2019 for having an

ILR, the number of patients we found having an ILR was much smaller compared to the smartphone based single-lead electrocardiogram group. We postulate that the threshold for using an invasive diagnostic tool to find arrhythmia in symptomatic patients is higher compared to non-invasive Holter monitoring. The decision to implant an ILR to detect arrhythmia was most often reserved for ACHD patients with unexplained syncope or cerebral vascular accident after unsuccessful period of Holter monitoring. However, in the emerging field of non-invasive wearable heart rhythm monitoring solutions we are the first to report a comparison in this high-risk patient population. Matching was not performed in the study. The smartphone based single-lead electrocardiogram has a significantly higher number of patients with a history of previous arrhythmia. Previous arrhythmia could make arrhythmia recurrence more likely than no previous arrhythmia. However, arrhythmia could also make arrhythmia recurrence less likely because of the treatment with anti-arrhythmic drugs. Potentially this could have introduced bias the process of arrhythmia detection.

5. Conclusion

Non-invasive smartphone based single-lead electrocardiogram monitoring could be an acceptable alternative in detecting arrhythmia in symptomatic ACHD patients instead of an ILR in respect to diagnostic yield, safety and management decisions, especially in those patients without syncope.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Amsterdam UMC. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MK, BB, and MS drafted the manuscript, which was critically revised and edited by BM, DR-V, DK, IT, JG, and KK. All authors agree to be accountable for all aspects of the work.

Conflict of interest

IT was shareholder in ventures supplying hardware and software implemented in the methods of this study.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller G-P, et al. 2020 ESC Guidelines for the management of adult congenital heart disease. *Eur Heart J.* (2021) 42:563–645. doi: 10.1093/eurheartj/ehaa554

2. Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* (2019) 73:e81–192. doi: 10.1016/j.jacc.2018.08.1029

3. Koyak Z, Harris L, de Groot JR, Silversides CK, Oechslin EN, Bouma BJ, et al. Sudden cardiac death in adult congenital heart disease. *Circulation.* (2012) 126:1944–54. doi: 10.1161/CIRCULATIONAHA.112.104786

4. van der Velde ET, Vander VET, Vriend JWJ, Mannens MMAM, Uiterwaal CSPM, Brand R, et al. CONCOR, an initiative towards a national registry and DNA-bank of patients with congenital heart disease in the Netherlands: rationale, design, and first results. *Eur J Epidemiol.* (2005) 20:549–57. doi: 10.1007/s10654-005-4264-9

5. Zomer AC, Vaartjes I, Uiterwaal CSPM, van der Velde ET, van den Merkhof LFM, Baur LHB, et al. Circumstances of death in adult congenital heart disease. *Int J Cardiol.* (2012) 154:168–72.

6. van der Bom T, Zomer AC, Zwinderman AH, Meijboom FJ, Bouma BJ, Mulder BJM. The changing epidemiology of congenital heart disease. *Nat Rev Cardiol.* (2011) 8:50–60.

7. Vehmeijer JT, Koyak Z, Leerink JM, Zwinderman AH, Harris L, Peinado R, et al. Identification of patients at risk of sudden cardiac death in congenital heart disease: the PRospEctiVE study on implaNTable cardIOverter defibrillator therapy and suddeN cardiac death in Adults with Congenital Heart Disease (PREVENTION-ACHD). *Heart Rhythm.* (2021) 18:785–92. doi: 10.1016/j.hrthm.2021.01.009

8. Bouma BJ, Mulder BJM. Changing landscape of congenital heart disease. *Circ Res.* (2017) 120:908–22. doi: 10.1161/CIRCRESAHA.116.309302

9. Dodeja AK, Thomas C, Daniels CJ, Kertesz N, Kamp A. Detection of arrhythmias in adult congenital heart disease patients with LINQTM implantable loop recorder. *Congenit Heart Dis.* (2019) 14:745–51. doi: 10.1111/chd.12815

10. Dussault C, Toeg H, Nathan M, Wang ZJ, Roux J-F, Secemsky E. Electrocardiographic monitoring for detecting atrial fibrillation after ischemic stroke or transient ischemic attack: systematic review and meta-analysis. *Circ Arrhythm Electrophysiol.* (2015) 8:263–9. doi: 10.1161/CIRCEP.114.002521

11. Jensen MT, Treskes RW, Caiani EG, Casado-Arroyo R, Cowie MR, Dilaveris P, et al. ESC working group on e-cardiology position paper: use of commercially available wearable technology for heart rate and activity tracking in primary and secondary cardiovascular prevention—in collaboration with the European Heart Rhythm Association, European Association of Preventive Cardiology, Association of Cardiovascular Nursing and Allied Professionals, Patient Forum, and the Digital Health Committee. *Eur Heart J Digit Health.* (2021) 2:49–59. doi: 10.1093/ehjdh/ztab011

12. Schuuring MJ, Kauw D. How to initiate eHealth in congenital heart disease patients? *Eur Heart J Digit Health.* (2020) 1:83–6. doi: 10.1093/ehjdh/ztaa012

13. Svennberg E, Tjong F, Goette A, Akoum N, Di Biase L, Bordachar P, et al. How to use digital devices to detect and manage arrhythmias: an EHRA practical guide. *Europace.* (2022) 24:979–1005. doi: 10.1093/europace/euac038

14. Cowie MR, Bax J, Bruining N, Cleland JGF, Koehler F, Malik M, et al. e-Health: a position statement of the European Society of Cardiology. *Eur Heart J.* (2015) 37:63–6. doi: 10.1093/eurheartj/ehv416

15. Kauw D, Koole MAC, Winter MM, Dohmen DAJ, Tulevski II, Blok S, et al. Advantages of mobile health in the management of adult patients with congenital heart disease. *Int J Med Inform.* (2019) 132:104011. doi: 10.1016/j.ijmedinf.2019.104011

16. Schultz KE, Lui GK, McElhinney DB, Long J, Balasubramanian V, Sakarovitch C, et al. Extended cardiac ambulatory rhythm monitoring in adults with congenital heart disease: arrhythmia detection and impact of extended monitoring. *Congenit Heart Dis.* (2019) 14:410–8. doi: 10.1111/chd.12736

17. Huntgeburth M, Hohmann C, Ewert P, Freilinger S, Nagdyman N, Neidenbach R, et al. Implantable loop recorder for monitoring patients with congenital heart disease. *Cardiovasc Diagn Ther.* (2021) 11:1334–43. doi: 10.21037/cdt-20-677

18. Schuuring MJ, Mischie AN, Caiani EG. Editorial: digital solutions in cardiology. *Front Cardiovasc Med.* (2022) 9:873991. doi: 10.3389/fcvm.2022.873991

19. Duncker D, Svennberg E. Editorial: wearable devices for cardiac rhythm monitoring. *Front Cardiovasc Med.* (2022) 9:951769. doi: 10.3389/fcvm.2022.951769

20. Abu-Alrub S, Strik M, Ramirez FD, Moussaoui N, Racine HP, Marchand H, et al. Smartwatch electrocardiograms for automated and manual diagnosis of atrial fibrillation: a comparative analysis of three models. *Front Cardiovasc Med.* (2022) 9:836375. doi: 10.3389/fcvm.2022.836375

21. Pengel LKD, Robbers-Visser D, Groenink M, Winter MM, Schuuring MJ, Bouma BJ, et al. A comparison of ECG-based home monitoring devices in adults with CHD. *Cardiol Young.* (2022) [Online ahead of print]. doi: 10.1017/S1047951122002244

22. Koole MAC, Kauw D, Winter MM, Dohmen DAJ, Tulevski II, de Haan R, et al. First real-world experience with mobile health telemonitoring in adult patients with congenital heart disease. *Neth Heart J.* (2019) 27:30–7. doi: 10.1007/s12471-018-1201-6

23. Lim WY, Papageorgiou N, Sukumar SM, Alexiou S, Srinivasan NT, Monkhouse C, et al. A nurse-led implantable loop recorder service is safe and cost effective. *J Cardiovasc Electrophysiol.* (2019) 30:2900–6. doi: 10.1111/jce.14206

24. Bezzerides VJ, Walsh A, Martuscello M, Escudero CA, Gauvreau K, Lam G, et al. The real-world utility of the LINQ implantable loop recorder in pediatric and adult congenital heart patients. *JACC Clin Electrophysiol.* (2019) 5:245–51. doi: 10.1016/j.jacep.2018.09.016

25. Avram R, Ramsis M, Cristal AD, Nathan V, Zhu L, Kim J, et al. Validation of an algorithm for continuous monitoring of atrial fibrillation using a consumer smartwatch. *Heart Rhythm.* (2021) 18:1482–90. doi: 10.1016/j.hrthm.2021.03.044

26. Garikapati K, Turnbull S, Bennett RG, Campbell TG, Kanawati J, Wong MS, et al. The role of contemporary wearable and handheld devices in the diagnosis and management of cardiac arrhythmias. *Heart Lung Circ.* (2022) 31:1432–49. doi: 10.1016/j.hlc.2022.08.001

27. Dilaveris PE, Antoniou CK, Caiani EG, Casado-Arroyo R, Climent AM, Cluitmans M, et al. ESC Working Group on e-Cardiology Position Paper: accuracy and reliability of electrocardiogram monitoring in the detection of atrial fibrillation in cryptogenic stroke patients : in collaboration with the Council on Stroke, the European Heart Rhythm Association, and the Digital Health Committee. *Eur Heart J Digit Health.* (2022) 3:341–58. doi: 10.1093/ehjdh/ztac026

28. Wachter R, Gröschel K, Gelbrich G, Hamann GF, Kermer P, Liman J, et al. Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AFRANDOMISED): an open-label randomised controlled trial. *Lancet Neurol.* (2017) 16:282–90. doi: 10.1016/S1474-4422(17)30002-9

29. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med.* (2012) 366:120–9. doi: 10.1056/NEJMoa1105575

30. Kishore A, Vail A, Majid A, Dawson J, Lees KR, Tyrrell PJ, et al. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. *Stroke.* (2014) 45:520–6. doi: 10.1161/STROKEAHA.113.003433

31. Albers GW, Bernstein RA, Brachmann J, Camm J, Easton JD, Fromm P, et al. Heart rhythm monitoring strategies for cryptogenic stroke: 2015 diagnostics and monitoring stroke focus group report. *J Am Heart Assoc.* (2016) 5:e002944. doi: 10.1161/JAHA.115.002944

32. Steinberg JS, Varma N, Cygankiewicz I, Aziz P, Balsam P, Baranchuk A, et al. 2017 ISHNE-HRS expert consensus statement on ambulatory ECG and external cardiac monitoring/telemetry. *Heart Rhythm.* (2017) 14:e55–96. doi: 10.1016/j.hrthm.2017.03.038

33. Solbiati M, Costantino G, Casazza G, Dipaola F, Galli A, Furlan R, et al. Implantable loop recorder versus conventional diagnostic workup for unexplained recurrent syncope. *Cochrane Database Syst Rev.* (2016) 4:CD011637. doi: 10.1002/14651858.CD011637.pub2

34. Treskes RW, van den Akker-van Marle ME, van Winden L, van Keulen N, van der Velde ET, Beeres S, et al. The box-eHealth in the outpatient clinic follow-up of patients with acute myocardial infarction: cost-utility analysis. *J Med Internet Res.* (2022) 24:e30236. doi: 10.2196/30236

35. Tromp J, Jindal D, Redfern J, Bhatt A, Séverin T, Banerjee A, et al. World heart federation roadmap for digital health in cardiology. *Glob Heart.* (2022) 17:61. doi: 10.5334/gh.1141

36. Kauw D, Huisma PR, Medlock SK, Koole MAC, Wierda E, Abu-Hanna A, et al. Mobile health in cardiac patients: an overview on experiences and challenges of stakeholders involved in daily use and development. *BMJ Innovat.* (2020) 6:1–8. doi: 10.1136/bmjinnov-2019-000418

37. Treskes RW, Wildbergh TX, Schalij MJ, Scherptong RWC. Expectations and perceived barriers to widespread implementation of e-Health in cardiology practice: results from a national survey in the Netherlands. *Neth Heart J.* (2019) 27:18–23. doi: 10.1007/s12471-018-1199-9

frontiers | Frontiers in Cardiovascular Medicine

TYPE Clinical Trial
PUBLISHED 09 February 2023
DOI 10.3389/fcvm.2023.1100127

Check for updates

OPEN ACCESS

EDITED BY
Emma Svennberg,
Karolinska University Hospital,
Sweden

REVIEWED BY
Rachel Van Der Velden,
Maastricht University Medical Center,
Netherlands
Hani Sabbour,
Cleveland Clinic Abu Dhabi,
United Arab Emirates

*CORRESPONDENCE
Harri Juhani Saarinen
harri.saarinen@fimnet.fi

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Cardiac Rhythmology, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 16 November 2022
ACCEPTED 19 January 2023
PUBLISHED 09 February 2023

CITATION
Saarinen HJ, Joutsen A, Korpi K, Halkola T, Nurmi M, Hernesniemi J and Vehkaoja A (2023) Wrist-worn device combining PPG and ECG can be reliably used for atrial fibrillation detection in an outpatient setting. *Front. Cardiovasc. Med.* 10:1100127. doi: 10.3389/fcvm.2023.1100127

COPYRIGHT
© 2023 Saarinen, Joutsen, Korpi, Halkola, Nurmi, Hernesniemi and Vehkaoja. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Wrist-worn device combining PPG and ECG can be reliably used for atrial fibrillation detection in an outpatient setting

Harri Juhani Saarinen[1*†], Atte Joutsen[2,3,4†], Kirsi Korpi[1,5], Tuomas Halkola[5], Marko Nurmi[5], Jussi Hernesniemi[1,2,4] and Antti Vehkaoja[2,4,5]

[1]Heart Hospital, Tampere University Hospital, Tampere, Finland, [2]Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland, [3]Department of Medical Physics, Tampere University Hospital, Tampere, Finland, [4]Finnish Cardiovascular Research Center, Tampere University, Tampere, Finland, [5]PulseOn Oy, Espoo, Finland

Aims: The aim was to validate the performance of a monitoring system consisting of a wrist-worn device and a data management cloud service intended to be used by medical professionals in detecting atrial fibrillation (AF).

Methods: Thirty adult patients diagnosed with AF alone or AF with concomitant flutter were recruited. Continuous photoplethysmogram (PPG) and intermittent 30 s Lead I electrocardiogram (ECG) recordings were collected over 48 h. The ECG was measured four times a day at prescheduled times, when notified due to irregular rhythm detected by PPG, and when self-initiated based on symptoms. Three-channel Holter ECG was used as the reference.

Results: The subjects recorded a total of 1,415 h of continuous PPG data and 3.8h of intermittent ECG data over the study period. The PPG data were analyzed by the system's algorithm in 5-min segments. The segments containing adequate amounts, at least ~30 s, of adequate quality PPG data for rhythm assessment algorithm, were included. After rejecting 46% of the 5-min segments, the remaining data were compared with annotated Holter ECG yielding AF detection sensitivity and specificity of 95.6 and 99.2%, respectively. The ECG analysis algorithm labeled 10% of the 30-s ECG records as inadequate quality and these were excluded from the analysis. The ECG AF detection sensitivity and specificity were 97.7 and 89.8%, respectively. The usability of the system was found to be good by both the study subjects and the participating cardiologists.

Conclusion: The system comprising of a wrist device and a data management service was validated to be suitable for use in patient monitoring and in the detection of AF in an ambulatory setting.

Clinical Trial Registration: ClinicalTrials.gov/, NCT05008601.

KEYWORDS

atrial fibrillation, wearable sensors, photoplethysmography, electrocardio graphy, ambulatory

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia diagnosed in clinical practice with increasing numbers forecast due to the worldwide aging of large generations (1) AF results from chaotic activation of multiple origins in the atrial muscle of the heart. AF predisposes patients to embolic stroke and anticoagulation medication should be considered if the CHA_2DS_2VASc score of

the patient is one or higher. One in three to four patients with ischemic stroke, and over 80% of those with ischemic stroke of cardioembolic type, also had atrial fibrillation (2). There is also evidence of an association between AF and cognitive dysfunction ranging from mild impairment to overt dementia (3, 4). This makes recognizing and diagnosing AF critical. On the other hand, the brief paroxysms of AF can be very difficult to detect, and in some patients, AF may be asymptomatic. The European Society of Cardiology guidelines for the diagnosis and management of AF recommend that a minimum of 30 s single-lead electrocardiogram (ECG) with irregular rhythm without discernible repeating P waves is required for the diagnosis of AF (5, 6).

Inexpensive, convenient, and reliable means to diagnose AF could improve the prevention AF related stroke and death and also the development of cognitive dysfunctions. The paroxysmal nature of AF episodes may limit the use of conventional 12-lead ECG recorded on demand by health care practitioners. Implantable loop recorders are better suited for other purposes than diagnosing AF as they are invasive and expensive. Modern wearable devices such as smart watches and smart phones can be used to screen the heart rhythm for anomalies almost continuously (smart watches) or intermittently (smart phones) *via* photoplethysmography (PPG), but recorded ECG is still required for a diagnosis. Some of the new smart watches feature both optical cardiac rhythm monitoring and a capability to record a single-lead ECG tracing. However, certified medical devices featuring both modalities and intended for clinical use have so far been lacking.

The objective of this study was to validate the performance of the PulseOn Arrhythmia Monitor System (PulseOn Oy, Espoo, Finland) consisting of a wrist-worn device and a data visualization cloud service, the PulseOn Data Management Service, intended to be used by medical professionals in detecting AF in an outpatient setting for 48 h.

2. Materials and methods

The intended purpose of the PulseOn Arrhythmia Monitor System is to assist in the diagnosis, screening, and monitoring of cardiac arrhythmias, especially atrial fibrillation. The system consists of a wrist-worn device and a secure cloud-based data management service. The wrist device optically monitors the user's pulse rate to detect any heartbeat irregularity and is used to take intermittent single-lead (Lead I) ECG measurements between the arms. The wrist device stores the measured data, which is later transferred to the data management service where it can be analyzed by medical professionals. The device is intended to be used inside and outside the hospital environment. The usage period of the system may vary from days to several weeks. A descriptive, observatory clinical investigation was conducted to validate the system's performance (clinical trial NCT05008601).

2.1. Study population

According to the performance results of earlier clinical feasibility studies, an estimated half of the obtained data was sinus rhythm and the other half AF data. Using 0.1 as the probability of type I error and 80% power level, the required amount of data was estimated as 500 h based on a non-inferiority approach (7). However, due to several uncertainties in estimated values, the target subject number was set at 30 instead of the minimum 11 for 48-h recordings.

The targeted subject number was based on the primary study objective of showing the sensitivity of the PPG based arrhythmia detection algorithm in detecting atrial fibrillation when the analysis is made in 5-min windows. Subjects were recruited who met the inclusion criteria: age $\geq$ 18 years and prior diagnosis of AF alone or AF with concomitant atrial flutter were recruited. Patients with pacemakers were excluded. Thirty-eight subjects were assessed for eligibility, seven were excluded and 31 included in the monitoring (Figure 1).

2.2. Wrist device and data management service

The wrist device used in the PulseOn Arrhythmia Monitor System includes both reflective mode wrist PPG with yellow-colored LEDs as well as stainless steel dry electrodes to enable Lead I ECG measurement when the recording loop is closed by placing the contralateral palm on the wrist device (Figure 2). The device continuously measures PPG from the patient's wrist to analyze the beat-to-beat heart rate for possible cardiac rhythm irregularities. When irregular rhythm is detected, the device notifies the patient to take a 30-s ECG recording for further analysis. The exact duration of the recording is 35 s of which 30 s are shown to the healthcare professional. The notifications can also be scheduled to take place 1–4 times a day. In addition, the patient can self-initiate recordings whenever there is a need, e.g., if they experience arrhythmia symptoms. The PPG-based inter-beat-intervals (IBI), the heart rhythm status based on the IBIs and recorded ECGs are stored in the internal memory of the wrist device. In normal operation, the wrist device can store up to 6 months of data to its internal memory.

The data can be transferred *via* a gateway to a server or, as in this study, be downloaded at the clinic when the wrist device is returned. The data analysis and patient rhythm assessment are done by the PulseOn Data Management Service through a web browser user interface. The Data Management Service includes ECG analysis algorithms (Cardiolund AB, Lund, Sweden) that process the measured ECG signals and flag signals showing signs of arrhythmia (Figure 3). The service features three views: a monthly overview, a more detailed weekly view, as well as an ECG signal view. The ECG view shows the measured ECG signals including beat specific markings overlaid on the signal, RR-intervals in milliseconds and the labeling of each recording made by the algorithms. The markings include *Short*, *Long and Very long RR-intervals, Supraventricular extrasystoles (SVES), Ventricular extrasystole (VES), Tachycardia, Fast, Slow*, Bigeminy, and Trigeminy. The labels for the whole 30-s record comprise *Possible arrhythmia, Inadequate quality, No rhythm deviation, Pause/AVblock II, Fast regular, Fast regular and wide QRS, Fast/Slow episode, Bigeminy, Trigeminy, Wide QRS, > 5 SVES, and > 5 VES.*

The device and the silicone wrist strap are easy and quick to clean between patients using common cleaning agents. The device is classified as waterproof up to 1 m and the battery lasts for more than 7 days without recharging. In longer studies, the patient is given an easy-to-operate charging dock.

This current validation was performed for the CE approval of the PulseOn Arrhythmia Monitor System as a class IIa medical device for its intended purpose according to the regulation (EU) 2017/745 of the European Parliament and of the Council on Medical Devices.

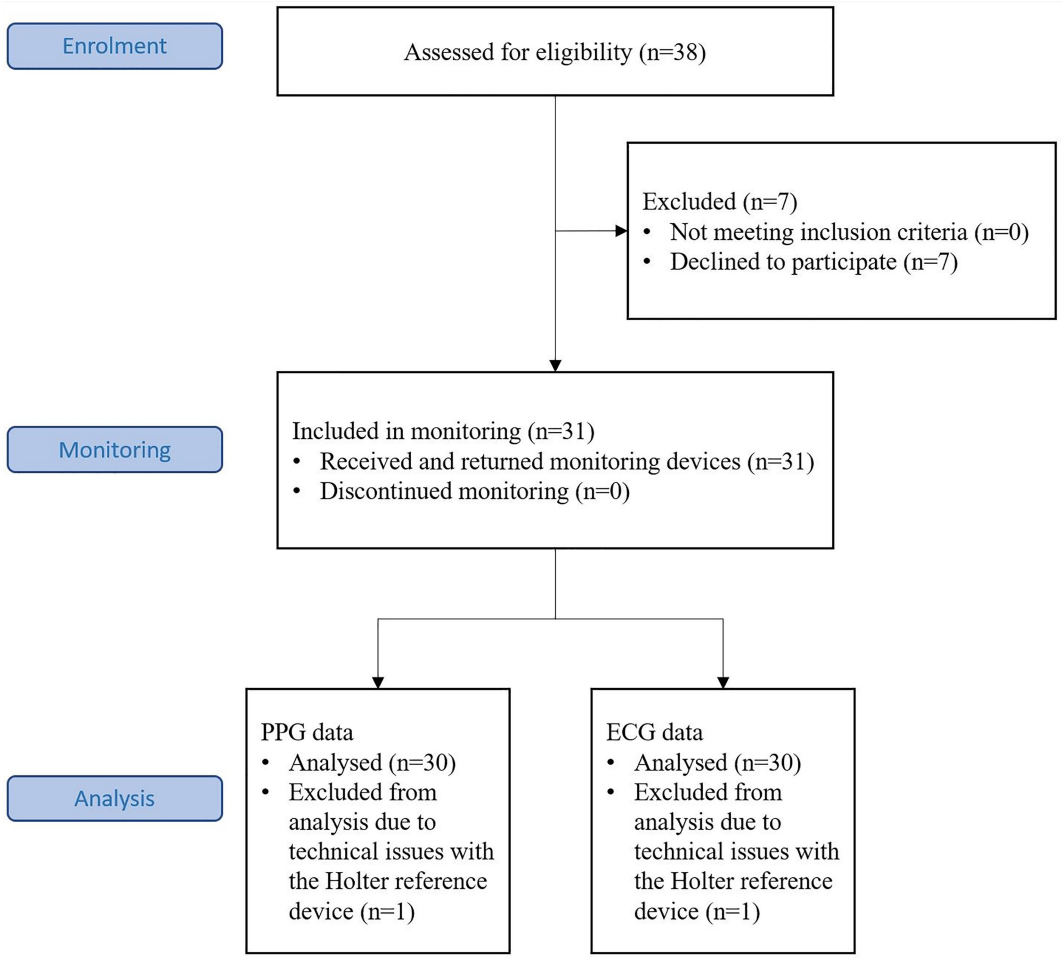


FIGURE 1
The Consort flow diagram for the trial.

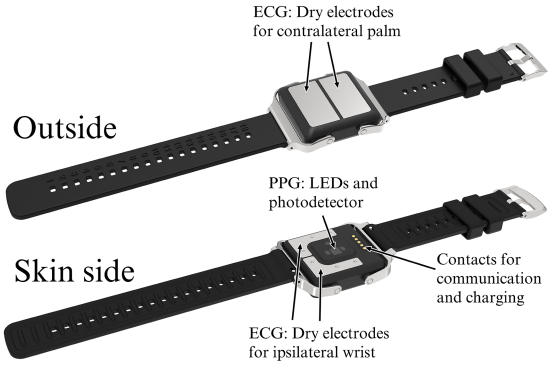


FIGURE 2
The PulseOn Arrhythmia Monitor wrist device outside (above) and skin side (below) with details.

2.3. Data collection

The subjects were asked to simultaneously wear two different devices for cardiac rhythm monitoring: the PulseOn wrist device and a three-channel Holter device (Faros 360, Bittium Biosignals Oy, Oulu, Finland) with disposable Ag/AgCl gel electrodes (Ambu Blue Sensor L-OO-S, Ambu A/S, Ballerup, Denmark). The Holter device was used to obtain reference information on the heartbeat intervals and rhythm status of the subjects. The subjects wore the devices continuously during the 48-h study period. Six individual devices of both types were circulated among the subjects. Data collection was started during an outpatient visit. The data were collected during the subjects` normal daily activities.

In addition to the continuous PPG recording of heartbeat intervals, the subjects were instructed to collect 30-s ECG recordings in three cases: first, if the device gave a timed reminder to take a recording (four times a day at 8:00, 12:00, 16:00, and 20:00); second, if the device gave an arrhythmia notification based on the PPG monitoring; and third, if the subject experienced arrhythmia symptoms. Thus, at least four intermittent ECG recordings were taken daily.

2.4. Signal analysis

Two experienced cardiologists investigated the collected ECG data. The reference Holter-recordings were annotated by a cardiologist (HJS) blind to the wrist device data using Darwin2 Holter analysis software (Schiller Americas, Doral, FL, United States). In addition to the standard hour by hour statistical Holter report, the precise time points for the beginning and ending of the arrhythmia episodes were marked and used in the estimation of the sensitivity and specificity of both the automated

FIGURE 3
ECG view of PulseOn Data Management Service.

PPG and the ECG analysis algorithms. Another cardiologist (KK) assessed the cardiac rhythm from the wrist device ECG recordings blind to the reference data. HJS also assessed the rhythm using the wrist device ECG recordings. This assessment was done after a significant amount of time (approximately 6 months) had elapsed since annotating the Holter-recordings to retain objectivity regarding the assessment. The cardiologists' wrist device ECG appraisals were used for data quality assessment and to determine how many subjects showing AF in the Holter-recordings could be correctly classified visually using only the wrist device data.

The evaluation of the PPG-based arrhythmia detection was made using 5-min data segments. The 5-min analysis window length has earlier been used by Zhang et al. (8) and Chang et al. (9). If more than 30 consecutive heartbeats were classified as arrhythmia or regular rhythm, the whole segment was appropriately labeled as arrhythmia or regular rhythm, arrhythmia having priority if both rhythm types were found in the segment. Those 5-min segments during which the arrhythmia analysis algorithm had not been able to make a rhythm assessment, e.g., due to too much movement, were labeled as undetermined and excluded from the sensitivity/specificity analysis. The same 30 consecutive heartbeat threshold is used by the wrist device to give irregular rhythm notification.

2.5. Usability

After the 48-h recording, the subject returned the wrist device and completed a usability questionnaire. Fourteen items on the questionnaire included the subject's impressions of the clarity of the device's notifications (four items), comfort when wearing the device (six items), possible skin irritation (one item), ease of recording a 30 s ECG (two items), and an overall grade for the device. The scale was 1–5 in 10 questions and binary (Yes/No) in four questions. Open-ended comments were invited to supplement the structured questions.

The cardiologists KK and HJS were interviewed about how they felt about using the PulseOn Data Management Service for reviewing the wrist device ECG data.

2.6. Statistical analysis

The performance of the PulseOn Arrhythmia Monitor System was assessed by comparing the wrist device PPG segments and ECG records labeled by the wrist device and Data Management Service algorithms with the cardiologists' Holter ECG manual annotations. The wrist device data were scored as seen in Table 1. Sensitivity and specificity were calculated from these results.

The accuracy of the IBIs estimated from the PPG signal was evaluated by first aligning the IBIs with the reference RR-intervals obtained from the ECG signal and then calculating the average of the absolute of the difference between the corresponding intervals. This metric is often called mean absolute error. Only the IBIs marked "reliable" by the PPG analysis algorithm were considered.

2.7. Consent and ethical considerations

The study followed the ethical principles of the Declaration of Helsinki, and each study subject gave written informed consent. The study protocol was approved by the Research Ethics Board of Tampere University Hospital (decision number R20087) and the national competent authority Fimea. The study was registered in the open clinical trial database ClinicalTrials.gov (NCT05008601).

3. Results

Thirty-one volunteer subjects aged from 32 to 83 years were recruited from the patient base of Tampere Heart Hospital, Finland. One of the subjects was excluded after the data collection because of a technical problem with the reference Holter data (Figure 1). Two recordings were terminated prematurely at 31 and 32 h of data collection due to wrist device software failure. The recordings until the time of termination were reviewed, found to be intact, and included in the material. Of the final 30 subjects eight were female and 22 were male. The median age was 65 (IQR: 57–71) years. The

TABLE 1 The data labels used in scoring the wrist device's data.

Label in ECG	Label in PPG	Label in Holter	Result
Possible arrhythmia	Arrhythmia	Atrial fibrillation	True positive
Possible arrhythmia	Arrhythmia	Sinus rhythm	False positive
No rhythm deviation	Regular rhythm	Sinus rhythm	True negative
No rhythm deviation	Regular rhythm	Atrial fibrillation	False negative

diagnoses were: Paroxysmal AF: 21 subjects, Persistent AF: three subjects, Chronic AF: one subject, Paroxysmal AF and Typical AFL: three subjects, Persistent AF and Typical AFL: one subject, and Unspecified AF and AFL: one subject. The recordings were performed between March and June 2021. None of the subjects was hospitalized during the study period.

A total of 1,416 h of wrist device data were collected from the 30 subjects included, corresponding on average to 47 h 12 min per subject. Reference Holter ECG data were collected simultaneously, and totaled 1,438 h. Based on the cardiologists' annotations, 150 h (10%) of the Holter data was of low but analyzable signal quality due to artifacts. Of the Holter data, 371.8 h (25.9%) showed AF and 50.7 h (3.5%) AFL. No adverse events occurred during the study.

3.1. PPG performance

The PPG dataset included 16,980 5-min data segments. Of these segments, 7,828 (46%) were labeled as *undetermined* by the algorithm due to inadequate data quality. Of all the day time (8:00–22:00), segments 69% were labeled as *undetermined*. In the night-time (22:00–8:00), only 21% were labeled as *undetermined*. The above segments were discarded from the sensitivity/specificity analysis. The remaining 9,152 segments (54%) were of adequate quality for rhythm analysis. Of these, 2,419 were labeled as arrhythmia and 6,733 as regular rhythm. After matching the annotated Holter ECG with the PPG, a sensitivity/specificity analysis was conducted for each subject and the whole data set (Table 2).

The sensitivity and specificity of the 5-min based PPG atrial fibrillation detection were, respectively, 95.6 and 99.2%. The mean absolute error of the PPG inter-beat-interval estimation averaged over the whole dataset was 26.6 ms.

One study subject had a diagnosis of unspecified AF with concomitant atrial flutter whose rhythm was very stable most of the time but occasionally became irregular. This subject was considered to be non-AF in the analysis. Stable flutter rhythm is not detectable with PPG technology that utilizes heartbeat interval regularity analysis. The irregular rhythm periods however produced PPG-based arrhythmia notifications and caused 23 out of the total 55 *false positive* labels in Table 2.

3.2. ECG performance

The subjects recorded a total of 457 30-s ECG measurements using the wrist device. The number of ECG measurements per subject over the 48-h study period varied between 7 and 28. The prescheduled measurements were 47%, the PPG triggered were 23%, and the self-initiated were 30% of all the ECG segments.

TABLE 2 Confusion matrix of PPG-based atrial fibrillation detection.

	Positive prediction	Negative prediction	Total
Actual atrial fibrillation	True positives 2,364	False negatives 110	2,474
Actual non-AF rhythm	False positives 55	True negatives 6,623	6,678
Total	2,419	6,733	9,152

TABLE 3 Confusion matrix of ECG-based AF detection.

	Positive prediction	Negative prediction	Total
Actual atrial fibrillation	True positives 173	False negatives 4	177
Actual non-AF rhythm	False positives 24	True negatives 211	235
Total	197	215	412

Of the 457 30-s ECG segments, the algorithm labeled 44 (10%) as inadequate quality. These segments were excluded from the subsequent analysis. In addition, the cardiologists KK and HJS, respectively, labeled 24 (5%) and 5 (1%) of the remaining ECG segments as inadequate quality. These segments were included in the analysis of automatic ECG algorithm performance as the system as such was under evaluation. The algorithm identified 413 (90%) of the segments as analyzable quality. Based on the visual assessment of only the wrist device ECG data, the cardiologists were able to correctly classify all the subjects having episodes of AF during the measurement period. None of the subjects who were in sinus rhythm throughout the whole measurement period were incorrectly assessed as having arrhythmia episodes.

Fifteen subjects did not have any episodes of AF or AFL during the recording. Five of these had atrial tachycardia episodes of less than 30 s, thus not meeting the criteria for AF. Seven subjects had episodes of paroxysmal AF during the recording, seven subjects were in continuous AF and one in continuous AFL throughout the whole recording. However, both cardiologists found the aforementioned subject who had stable atrial flutter rhythm with periods of irregularities challenging to interpret. Flutter waves are often poorly visible in Lead I ECG making it difficult to assess atrial flutter (6). Neither of the cardiologists was confident about their analyses, however, assessing the subject as being either in AF or in mixed AF and flutter rhythm. On an ECG segment level, the algorithm labeled 197 segments as *Possible arrhythmia* indicating primarily AF and 215 either as *No rhythm deviation* indicating sinus rhythm or with any other of the labels listed below. Sensitivity and specificity were calculated based on the confusion matrix of Table 3 showing 97.7% sensitivity and 89.8% specificity.

The Data Management System labels the 30-s ECG records with one of the following labels: *Possible arrhythmia, Inadequate quality, No rhythm deviation, Pause/AVblock II, Fast regular, Fast regular and wide QRS, Fast/Slow episode, Bigeminy, Trigeminy, Wide QRS, >5 SVES, and >5 VES*. In the above analysis only the label *Possible arrhythmia* was considered to indicate AF, which yields the results in Table 3. If any label, excluding *Inadequate quality* and *No rhythm deviation*, is considered to indicate AF, the sensitivity becomes 100.0% and specificity 84.26% (Table 4). This approach can be considered justified because in clinical use, the cardiac rhythm is always visually confirmed from the ECGs and the labels of the automatic analysis can be used attract the attention of the clinician performing the assessment.

Further, if atrial flutter is considered together with atrial fibrillation the results become 99.5% sensitivity and 87.6% specificity.

TABLE 4 Confusion matrix of ECG-based cardiac arrhythmia detection.

	Positive prediction	Negative prediction	Total
Actual atrial fibrillation	True positives 177	False negatives 0	177
Actual non-AF rhythm	False positives 37	True negatives 198	235
Total	214	198	412

3.3. Usability

Test subject feedback based on the questionnaire was received from 25 out of the 30 subjects. The average of the overall grade was 4.6 out of a maximum of five. The averages of the clarity of notifications was 4.2, wear comfort was 4.1, and ease of ECG recording was 4.6. The average of skin irritation was 1.4 (1 = no irritation, 5 = severe irritation). Thirteen percent of the subjects found notifications occasionally disturbing, 25% percent had to adjust the wrist strap tightness, 91% felt they knew what the correct tightness should be, and 4% felt uncomfortable and had to switch the device to another wrist. The comments in the subjects' own words included generally positive remarks as well as comparisons, according to which the wrist device was preferred to the Holter.

Both cardiologists gave similar types of positive feedback on the usability of the PulseOn Data Management Service: the user interface of the Data Management Service supports the cardiologist's work well, it is logically organized, has well-functioning review tools and the web browser interface responds promptly to the user's commands. However, it should be noted that KK has had minor involvement in the design work of the Data Management Service and is a part-time employee of PulseOn Oy.

4. Discussion

The main finding of this study was that the wrist device investigated and the PulseOn Data Management Service evaluated can be reliably used to detect and diagnose AF in an ambulatory setting in daily life. The usability of the wrist device, comfort wearing it, and ease of ECG recording were rated good by the study subjects. Little to no skin irritation was experienced. The cardiologists found the Data Management Service to be well functioning for its purpose.

4.1. Photoplethysmogram

Our results in the PPG-based atrial fibrillation detection (sensitivity 95.6% and specificity 99.2%) are in line with those of earlier studies. Similar methodology has been previously used by four groups in five studies. Zhang et al. used the Samsung Galaxy Active 2 watch over 4 weeks on 53 patients and compared AF detection to continuous patch ECG. The sensitivity and specificity of the device were 90.8 and 93.0%, respectively, (8). Chang et al. recruited 200 participants who underwent 24 h of simultaneous Holter ECG monitoring and continuous PPG recording using a Garmin Forerunner 945 smartwatch. AF detection sensitivity and specificity were 97.1 and 86.8%, respectively, (9). The Philips Cardio and Motion Monitoring Module was used in two 24-h studies with 20 and 27 patients with Holter reference. The respective AF detection sensitivities and specificities of the two studies were 98.4 and 98.0% (10) and 100 and 96% (11). Wasserlauf et al., studied 24 patients who had an insertable loop recorder and wore an Apple Watch with Kardiaband during daytime for an average of 110 days. In their study, AF episodes of ≥1 h were detected with a sensitivity 97.5% per episode. Considering the total duration of all the AF episodes detected (loop recorder 1127.1 h, watch 1101.1 h) sensitivity and specificity were 97.7 and 98.9%, respectively, (12).

In our study, the PPG algorithm labeled 46% of the 5-min segments as *undetermined* because of inadequate data quality. The inadequate segments were recorded mostly in the day time. In the night-time, the artifacts were reduced as the subjects were resting. The amount of inadequate data is comparable with the previous studies: 42% calculated from Chang et al. (9), 24–57.6% as reported by Eerikäinen et al. (10) and 56% as reported by Bonomi et al. (11).

In addition to the above long-term studies with ambulatory outpatients, there have been several short-term studies with hospital inpatients. In these studies, the patients have been sitting or lying down, and are therefore not easily comparable with the free-living conditions of the outpatients. Nevertheless, the following results of the 21 studies reviewed reflect the current state of the art in using PPG for AF detection. Median number of patients was 60, median recording duration 10 min, median sensitivity 97.03% (range 84.10–100%) and specificity 96.00% (56.64–99.90%). (13–33)

The largest published studies on wrist-worn PPG devices and AF detection in normal daily living are those by Perez et al. using the Apple Watch on 419,297 (34) and Guo et al. using Huawei's technology on 187,912 participants (35). In the Apple study, the detected AFs were subsequently confirmed by using ECG patches. In the Huawei study, the confirmation was by using clinical evaluation, electrocardiogram, or 24-h Holter monitoring. The positive predictive values for the Apple and Huawei technologies were 0.84 and 0.916, respectively.

There are numerous mobile software applications that utilize smart watch or smart phone flash and camera sensor to assess pulse rate variability, but accuracy is usually tested in restricted conditions. Clearly, diagnosing AF requires very high specificity to avoid situations where patients are treated with lifelong anticoagulative medications and suffer bleeding risk as a result of incorrectly diagnosed AF. The measured PPG should only be used as an indication for further evaluation: ECG visually assessed by a qualified doctor is required for initial diagnosis. However, PPG monitoring could be efficacious in monitoring the AF burden on patients with already diagnosed AF or after catheter ablation (6).

4.2. Electrocardiogram

The results of the ECG performance of the wrist device (sensitivity 97.7% and specificity 89.8%) were also on par with the results in the recent literature. Hermans et al. compared long-term intermittent AliveCor Kardia recording including automatic analysis to Holter heart rhythm monitoring for the detection of AF recurrence after cardiac ablation therapy in 115 patients. The patients made 30-s ECG recordings three times a day and whenever experiencing symptoms during a 4-week period. The sensitivity obtained was 95.3% and the specificity 97.5% (36). Karregat et al. invited 205 primary care patients aged ≥65 years with a negative 12-lead ECG to wear a Holter monitor for 2 weeks and to use a MyDiagnostick single-lead ECG device three times a day for 60 s ECG recordings. The sensitivity and specificity results of AF detection were 66.7 and 68.8%, respectively, (37). Svennberg et al. used the Zenicor device in an AF screening study on 3,209 persons. The study did not have a reference device, but the performance of the ECG

analysis algorithm used by Zenicor was compared to manual interpretation of the same ECGs. The outcomes were 97.8% sensitivity and 88.2% specificity (38). The AliveCor Apple iPhone cover with Lead I ECG measurement (iECG) was used in two long-term studies by two different groups. The number of patients in the studies were 60 and 42 and the study durations were 1 and 4 weeks. In the first study, the reference methods were a cardiologist's interpretation of the iECG in combination with the noise-reduced iECG, and 12-lead ECG or Holter monitoring. The second study used the Pacetrack transtelephonic monitor to record ECG. The respective sensitivity and specificity results were 100 and 97% (39), and 94.6 and 92.9% (40).

Ten recent short-term inpatient studies were also reviewed. As with the PPG short-term studies, these provide a snapshot of the patient's situation and provide limited information on the performance in the actual use environment. Median of the ECG recording duration was 30 s, median number of patients 144 and median sensitivity 93.0% (range 75.0–100.0%) and specificity 95.0% (84.0–95.7%) (41–50).

In the present study, the wrist device ECG was recorded using stainless steel dry electrodes. Ten percent of the ECG segments were labeled as inadequate quality by the algorithm with an additional 5 and 1% by the cardiologists. The physicians' subjective judgment on the adequacy of the quality of the ECG records for rhythm assessment was based on their prior experience with single lead ECG interpretation and the clinical context. In the Holter using disposable Ag/AgCl electrodes, 10% of the data were assessed as low quality due to artifacts. The stainless steel dry electrodes can record diagnostic level data, and in long-term use they compare with the Holter data quality. However, it must be noted that due to the ECG recording method of the wrist device, subjects are instructed to remain still during measurement, whereas the continuous Holter data includes both low activity and high activity periods.

There is usually a trade-off between sensitivity and specificity when monitoring a medical condition. Technical adjustments in algorithms or methods toward high sensitivity may cause lowered specificity and vice versa as can be seen in our study when comparing the performance in the cases where (A) only the label *Possible Arrhythmia* or (B) any cardiac event labeled by the algorithm was accepted as positive prediction (Tables 3, 4). However, diagnosis never relies solely on just algorithm classification. A trained medical professional always reviews the data before treatment decisions are made.

In a device with its intended purpose to detect AF it is important to optimize for high sensitivity to correctly detect all patients with AF. False positives may lead to further unnecessary investigations but constitute a lower burden on society than false negatives, which can cause strokes with high treatment and rehabilitation costs and in the worst-case lead to patient death. It must be noted, however, that only AF can be reliably diagnosed using Lead I ECG. Depending on the subject the flutter waves of AFL cannot necessarily be distinguished in Lead I. This is because during AFL Lead I is in most subjects low amplitude or isoelectric for the atrial activity (51). Further, more ECG channels are needed to diagnose other arrhythmias, but ambulatory single-lead monitoring can provide information to trigger subsequent evaluation, e.g., 12-lead ECG or Holter.

The coronavirus pandemic that started in late 2019 has restricted travel and accelerated the use of telehealth. Wearable technology affords an opportunity for continuous heart rhythm assessment. The increasing popularity of wearable technology capable of detecting AF alongside the development of direct acting oral anticoagulants has also sparked new research interest. Could patients with paroxysmal AF under continuous heart rhythm monitoring be treated with direct acting oral anticoagulants and exposed the risk of bleeding risk only intermittently when a sufficiently long period of AF is detected with by wearable device (52)? Obviously, this "pill-in-the-pocket" anticoagulation strategy still requires rigorous clinical investigation.

However, the use of smart devices to monitor heart rhythm may cause inequality among patients as these devices are not usually integrated into national health care systems or reimbursed, which makes them more readily available to people with better economic status and the high cost may impede their use.

The usual problem with consumer smart devices capable of cardiac rhythm monitoring is that their use is focused on the young and on those with high socioeconomic status and advanced interest in their health already, but the risk of AF starts to rise after the age of 55 (5). Smart devices have varied ECG recording methods. In those worn on the upper limb the contralateral limb is brought into contact with the device to record Lead I. In many devices, a crown button at the side of the device is pressed with a finger to form an electrical circuit for the recording. In the wrist device investigated, the recording is done by covering the whole anterior surface of the device where the dry electrodes are located with the palm of the opposite hand. This recording method may be easier for elderly users and the large skin-electrode contact area can even provide improved ECG signal quality for some subjects. The recorded data is transferred to the cloud for interpretation either post-hoc through a computer or automatically with a separate data gateway device. The gateway device can be positioned in the user's home, and will automatically send new recordings to the cloud when the user is near the gateway. This approach may be advantageous if the healthcare delivery process is arranged so that there is someone to observe the transferred data.

The key limitation of this study was that only subjects with a prior diagnosis of AF/AFL were included as an adequate number of relevant events were needed to validate the technical performance of the proposed system. The sample size was limited so the findings cannot be generalized without caution. Depending on the study design, PPG technology may have limitations; the irregular pulse notification of Apple Watch had only 41% sensitivity for AF in subjects who had recently undergone cardiac surgery (53). The group recorded 50 patients over 2 days. On telemetry AF was observed in 90 instances, and sinus rhythm was seen in 202 instances. Twenty-five of the 50 patients had ≥1 episodes of AF. In an earlier study, Tison et al. used Apple Watch to record 51 cardioversion patients for 20 min to achieve a sensitivity of 98.0% (21). Wasserlauf et al., recorded 24 patients with a history of paroxysmal AF over a mean duration of 110 days. Eighty-two episodes of AF ≥ 1 h were detected on the implantable loop recorder while the smartwatch was being worn, and the sensitivity was 97.7% (12). The three studies had different patient populations which may account for the variation in the results. However, the seemingly poor algorithm sensitivity in (53) may result from a lack of data due to subjects who have a low AF burden combined with some difficult to detect AF episodes leading to false negatives.

The standard ECG recording obtained with wrist devices is equivalent to ECG Lead I which is sub-optimal for the detection of P-waves and flutter waves. Atypical recording configurations could provide additional lead tracings more suitable for certain arrhythmias (6, 54). However, from the user point of view taking Lead I ECG between the arms is easy and thus practical.

The system investigated could be suitable for AF screening in older age groups due to its good usability, long battery life, signal quality, and

no need for a paired smart phone. Our next target is to investigate the performance of the PulseOn Arrhythmia Monitor System in a screening setting. In that study we will recruit subjects with AF risk factors but no prior diagnosis of AF or AFL. This study will also evaluate the suitability of the system for long-term use.

5. Conclusion

The PulseOn Arrhythmia Monitor System comprising the wrist device for PPG/ ECG recording and the Data Management Service has been validated. It was found that the system can reliably detect and diagnose AF in an ambulatory setting. The wrist device and the Data Management System were found easily usable by the study subjects and by the participating cardiologists.

Data availability statement

The datasets presented in this article are not readily available because study sponsor PulseOn Oy holds the rights to the data that support the findings of this study and therefore the availability is restricted. The data was used under license for the current study. However, the data is available from the authors representing the sponsor upon reasonable request. Requests to access the datasets should be directed to antti.vehkaoja@pulseon.fi.

Ethics statement

The studies involving human participants were reviewed and approved by Research Ethics Board of Tampere University Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

HS: methodology, investigation, data curation, writing—original draft, and writing—review and editing. AJ: methodology, formal analysis, writing—original draft, writing—review and editing, visualization, and funding acquisition. KK: investigation, data curation, and writing—review and editing. TH: software, formal analysis, data curation, and writing—review and editing. MN: software, formal analysis, and data curation. JH: methodology, project administration, and writing—review and editing. AV: conceptualization, methodology, resources, supervision, project administration, and writing—review and editing. All authors contributed to the article and approved the submitted version.

Funding

This study was financially supported by PulseOn Oy and partly supported by the Tampere University Faculty of Medicine and Health Technology doctoral program and the Tampere University Hospital Support Foundation, Tampere University Hospital project number MK355.

Acknowledgments

The authors would like to thank Ole Kirkeby of PulseOn Oy for the calculation of the optical beat-to-beat interval accuracy and optical arrhythmia detection sensitivity and specificity results.

An abstract summarizing the results has been presented as an ePoster at the European Society of Cardiology Congress in Barcelona, Spain, in August 2022 (55).

Conflict of interest

AV, KK, TH, and MN are employees of PulseOn Oy. KK is also a minority shareholder in PulseOn Oy.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Morillo, CA, Banerjee, A, Perel, P, Wood, D, and Jouven, X. Atrial fibrillation: the current epidemic. *J Geriatr Cardiol.* (2017) 14, 195–203. doi: 10.11909/j.issn.1671-5411.2017.03.011

2. Freedman, B, Potpara, TS, and Lip, GYH. Stroke prevention in atrial fibrillation. *Lancet.* (2016) 388:806–17. doi: 10.1016/S0140-6736(16)31257-0

3. Rivard, L, Friberg, L, Conen, D, Healey, JS, Berge, T, Boriani, G, et al. Atrial fibrillation and dementia: a report from the AF-SCREEN international collaboration. *Circulation.* (2022) 145:392–409. doi: 10.1161/CIRCULATIONAHA.121.055018

4. Kim, D, Yang, PS, Yu, HT, Kim, TH, Jang, E, Sung, JH, et al. Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: data from a population-based cohort. *Eur Heart J.* (2019) 40:2313–23. doi: 10.1093/eurheartj/ehz386

5. Hindricks, G, Potpara, T, Dagres, N, Arbelo, E, Bax, JJ, Blomström-Lundqvist, C, et al. Corrigendum to: 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European heart rhythm association (EHRA) of the ESC. *Eur Heart J.* (2021) 42:373–498. doi: 10.1093/eurheartj/ehaa612

6. Svennberg, E, Tjong, F, Goette, A, Akoum, N, di Biase, L, Bordachar, P, et al. How to use digital devices to detect and manage arrhythmias: an EHRA practical guide. *EP Europace.* (2022) 24:979–1005. doi: 10.1093/europace/euac038

7. Lenz, ST. Shein-Chung chow, Jun Shao, Hansheng Wang (2008): sample size calculations in clinical research, 2nd edition. *Stat Pap.* (2011) 52:243–4. doi: 10.1007/s00362-009-0218-8

8. Zhang, H, Zhu, L, Nathan, V, Kuang, J, Kim, J, Gao, JA, et al. Towards early detection and burden estimation of atrial fibrillation in an ambulatory free-living environment. *Proc ACM Interact Mob Wearable Ubiquitous Technol.* (2021) 5:1–19. doi: 10.1145/3463503

9. Chang, PC, Wen, MS, Chou, CC, Wang, CC, and Hung, KC. Atrial fibrillation detection using ambulatory smartwatch photoplethysmography and validation with simultaneous holter recording. *Am Heart J.* (2022):247. doi: 10.1016/j.ahj.2022.02.002

10. Eerikainen, LM, Bonomi, AG, Schipper, F, Dekker, LRC, Vullings, R, de Morree, HM, et al. Comparison between electrocardiogram- and photoplethysmogram-derived features for atrial fibrillation detection in free-living conditions. *Physiol Meas.* (2018) 39:084001. doi: 10.1088/1361-6579/aad2c0

11. Bonomi, AG, Schipper, F, Eerikäinen, LM, Margarito, J, van Dinther, R, Muesch, G, et al. Atrial fibrillation detection using a novel cardiac ambulatory monitor based on photoplethysmography at the wrist. *J Am Heart Assoc.* (2018) 7:e009351. doi: 10.1161/JAHA.118.009351

12. Wasserlauf, J, You, C, Patel, R, Valys, A, Albert, D, and Passman, R. Smartwatch performance for the detection and quantification of atrial fibrillation. *Circ Arrhythm Electrophysiol.* (2019) 12:e006834. doi: 10.1161/CIRCEP.118.006834

13. Gotlibovych, I, Crawford, S, Goyal, D, Liu, J, Kerem, Y, Benaron, D, et al. End-to-end deep learning from raw sensor data: Atrial fibrillation detection using Wearables. (2018)

14. Kashiwa, A, Koyama, F, Miyamoto, K, Kamakura, T, Wada, M, Yamagata, K, et al. Performance of an atrial fibrillation detection algorithm using continuous pulse wave monitoring. *Ann Noninvasive Electrocardiol.* (2019) 24:e12615. doi: 10.1111/anec.12615

15. Harju, J, Tarniceriu, A, Parak, J, Vehkaoja, A, Yli-Hankala, A, and Korhonen, I. Monitoring of heart rate and inter-beat intervals with wrist plethysmography in patients with atrial fibrillation. *Physiol Meas.* (2018) 39:065007. doi: 10.1088/1361-6579/aac9a9

16. Rezaei Yousefi, Z, Parak, J, Tarniceriu, A, Harju, J, Yli-Hankala, A, Korhonen, I, et al. Atrial fibrillation detection from wrist photoplethysmography data using artificial neural networks. In: IFMBE Proceedings. (2018)

17. Aschbacher, K, Yilmaz, D, Kerem, Y, Crawford, S, Benaron, D, Liu, J, et al. Atrial fibrillation detection from raw photoplethysmography waveforms: a deep learning application. *Heart Rhythm.* (2020) 1:3–9. doi: 10.1016/j.hroo.2020.02.002

18. Liao, MT, Yu, CC, Lin, LY, Pan, KH, Tsai, TH, Wu, YC, et al. Impact of recording length and other arrhythmias on atrial fibrillation detection from wrist photoplethysmogram using smartwatches. *Sci Rep.* (2022) 12:5364. doi: 10.1038/s41598-022-09181-1

19. Hochstadt, A, Chorin, E, Viskin, S, Schwartz, AL, Lubman, N, and Rosso, R. Continuous heart rate monitoring for automatic detection of atrial fibrillation with novel bio-sensing technology. *J Electrocardiol.* (2019):52. doi: 10.1016/j.jelectrocard.2018.10.096

20. Fallet, S, Lemay, M, Renevey, P, Leupi, C, Pruvot, E, and Vesin, JM. Can one detect atrial fibrillation using a wrist-type photoplethysmographic device? *Med Biol Eng Comput.* (2019) 57:477–87. doi: 10.1007/s11517-018-1886-0

21. Tison, GH, Sanchez, JM, Ballinger, B, Singh, A, Olgin, JE, Pletcher, MJ, et al. Passive detection of atrial fibrillation using a commercially available smartwatch. *JAMA Cardiol.* (2018) 3:409–16. doi: 10.1001/jamacardio.2018.0136

22. Bashar, SK, Han, D, Hajeb-Mohammadalipour, S, Ding, E, Whitcomb, C, McManus, DD, et al. Atrial fibrillation detection from wrist Photoplethysmography signals using Smartwatches. *Sci Rep.* (2019) 9:15054. doi: 10.1038/s41598-019-49092-2

23. Corino, VDA, Laureanti, R, Ferranti, L, Scarpini, G, Lombardi, F, and Mainardi, LT. Detection of atrial fibrillation episodes using a wristband device. *Physiol Meas.* (2017) 38:787–99. doi: 10.1088/1361-6579/aa5dd7

24. Nemati, S, Ghassemi, MM, Ambai, V, Isakadze, N, Levantsevych, O, Shah, A, et al. Monitoring and detecting atrial fibrillation using wearable technology. In: *Proceedings of the annual international conference of the IEEE engineering in medicine and biology society, EMBS.* (2016)

25. Dörr, M, Nohturfft, V, Brasier, N, Bosshard, E, Djurdjevic, A, Gross, S, et al. Eckstein J the WATCH AF trial: SmartWATCHes for detection of atrial fibrillation. *JACC Clin Electrophysiol.* (2019) 5:199–208. doi: 10.1016/j.jacep.2018.10.006

26. Väliaho, ES, Kuoppa, P, Lipponen, JA, Hartikainen, JEK, Jäntti, H, Rissanen, TT, et al. Martikainen TJ wrist band Photoplethysmography autocorrelation analysis enables detection of atrial fibrillation without pulse detection. *Front Physiol.* (2021) 12:654555. doi: 10.3389/fphys.2021.654555

27. Shashikumar, SP, Shah, AJ, Li, Q, Clifford, GD, and Nemati, S. "A deep learning approach to monitoring and detecting atrial fibrillation using wearable technology." in 2017 IEEE EMBS International Conference on Biomedical and Health Informatics, BHI 2017; (2017).

28. Chen, E, Jiang, J, Su, R, Gao, M, Zhu, S, Zhou, J, et al. A new smart wristband equipped with an artificial intelligence algorithm to detect atrial fibrillation. *Heart Rhythm.* (2020) 17:847–53. doi: 10.1016/j.hrthm.2020.01.034

29. Osca Asensi, J, Izquierdo de Francisco, MT, Cano Pérez, Ó, Sancho Tello de Carranza, MJ, Alberola Rubio, J, Planells Palop, C, et al. The RITHMI study: diagnostic ability of a heart rhythm monitor for automatic detection of atrial fibrillation. *Revista Española de Cardiología (English Edition).* (2021) 74:602–7. doi: 10.1016/j.rec.2020.05.034

30. Fan, YY, Li, YG, Li, J, Cheng, WK, Shan, ZL, Wang, YT, et al. Diagnostic performance of a smart device with photoplethysmography technology for atrial fibrillation detection: pilot study (pre-mafa II registry). *JMIR Mhealth Uhealth.* (2019) 7:e11437. doi: 10.2196/11437

31. Selder, JL, Proesmans, T, Breukel, L, Dur, O, Gielen, W, and van Rossum, AC. Allaart CP assessment of a standalone photoplethysmography (PPG) algorithm for detection of atrial fibrillation on wristband-derived data. *Comput Methods Prog Biomed.* (2020):197. doi: 10.1016/j.cmpb.2020.105753

32. Lemay, M, Fallet, S, Renevey, P, Sola, J, Leupi, C, Pruvot, E, et al. Wrist-located optical device for atrial fibrillation screening: a clinical study on twenty patients In: *Computing in Cardiology*. eds. A. Murray and C. D'Amico (UK/USA: IEEE) (2016).

33. Väliaho, ES, Kuoppa, P, Lipponen, JA, Martikainen, TJ, Jäntti, H, Rissanen, TT, et al. Wrist band photoplethysmography in detection of individual pulses in atrial fibrillation and algorithm-based detection of atrial fibrillation. *Europace.* (2019) 21:1031–8. doi: 10.1093/europace/euz060

34. Perez, MV, Mahaffey, KW, Hedlin, H, Rumsfeld, JS, Garcia, A, Ferris, T, et al. Large-scale assessment of a Smartwatch to identify atrial fibrillation. *N Engl J Med.* (2019) 381:1909–17. doi: 10.1056/NEJMoa1901183

35. Guo, Y, Wang, H, Zhang, H, Liu, T, Liang, Z, Xia, Y, et al. Mobile Photoplethysmographic technology to detect atrial fibrillation. *J Am Coll Cardiol.* (2019) 74:2365–75. doi: 10.1016/j.jacc.2019.08.019

36. Hermans, ANL, Gawalko, M, Pluymaekers, NAHA, Dinh, T, Weijs, B, van Mourik, MJW, et al. Luermans JGLM long-term intermittent versus short continuous heart rhythm monitoring for the detection of atrial fibrillation recurrences after catheter ablation. *Int J Cardiol.* (2021) 329:105–12. doi: 10.1016/j.ijcard.2020.12.077

37. Karregat, EPM, Van, GNV, Bouwman, AC, Uittenbogaart, SB, Himmelreich, JCL, Lucassen, WAM, et al. Screening for paroxysmal atrial fibrillation in primary care using Holter monitoring and intermittent, ambulatory single-lead electrocardiography. *Int J Cardiol.* (2021) 345:41:46. doi: 10.1016/j.ijcard.2021.10.021

38. Svennberg, E, Stridh, M, Engdahl, J, Al-Khalili, F, Friberg, L, Frykman, V, et al. Safe automatic one-lead electrocardiogram analysis in screening for atrial fibrillation. *Europace.* (2017) 19:euw286. doi: 10.1093/europace/euw286

39. Tarakji, KG, Wazni, OM, Callahan, T, Kanj, M, Hakim, AH, Wolski, K, et al. Using a novel wireless system for monitoring patients after the atrial fibrillation ablation procedure: the iTransmit study. *Heart Rhythm.* (2015) 12:554–9. doi: 10.1016/j.hrthm.2014.11.015

40. Lowres, N, Mulcahy, G, Gallagher, R, Ben Freedman, S, Marshman, D, Kirkness, A, et al. Self-monitoring for atrial fibrillation recurrence in the discharge period post-cardiac surgery using an iPhone electrocardiogram. *Eur J Cardiothorac Surg.* (2016) 50:44–51. doi: 10.1093/ejcts/ezv486

41. Haverkamp, HT, Fosse, SO, and Schuster, P. Accuracy and usability of single-lead ECG from smartphones—a clinical study. *Indian Pacing Electrophysiol J.* (2019) 19:145–9. doi: 10.1016/j.ipej.2019.02.006

42. Bumgarner, J, Lambert, C, Cantillon, D, Baranowski, B, Wolski, K, Hussein, A, et al. Assessing the accuracy of an automated atrial fibrillation detection algorithm using novel smartwatch technology among patients presenting for elective cardioversion. *J Am Coll Cardiol.* (2018) 71:A411. doi: 10.1016/S0735-1097(18)30952-5

43. Chan, NY, Choy, CC, Chan, CK, and Siu, CW. Effectiveness of a nongovernmental organization–led large-scale community atrial fibrillation screening program using the smartphone electrocardiogram: an observational cohort study. *Heart Rhythm.* (2018) 15:1306–11. doi: 10.1016/j.hrthm.2018.06.006

44. Desteghe, L, Raymaekers, Z, Lutin, M, Vijgen, J, Dilling-Boer, D, Koopman, P, et al. Performance of handheld electrocardiogram devices to detect atrial fibrillation in a cardiology and geriatric ward setting. *Europace.* (2017) 19:euw025. doi: 10.1093/europace/euw025

45. Doliwa, PS, Frykman, V, and Rosenqvist, M. Short-term ECG for out of hospital detection of silent atrial fibrillation episodes. *Scand Cardiovasc J.* (2009) 43:163–8. doi: 10.1080/14017430802593435

46. Lau, JK, Lowres, N, Neubeck, L, Brieger, DB, Sy, RW, Galloway, CD, et al. Freedman SB iPhone ECG application for community screening to detect silent atrial fibrillation: a novel technology to prevent stroke. *Int J Cardiol.* (2013) 165:193–4. doi: 10.1016/j.ijcard.2013.01.220

47. Haberman, ZC, Jahn, RT, Bose, R, Tun, H, Shinbane, JS, Doshi, RN, et al. Wireless smartphone ECG enables large-scale screening in diverse populations. *J Cardiovasc Electrophysiol.* (2015) 26:520–6. doi: 10.1111/jce.12634

48. Lowres, N, Neubeck, L, Salkeld, G, Krass, I, McLachlan, AJ, Redfern, J, et al. Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies: the SEARCH-AF study. *Thromb Haemost.* (2014) 111:1167–76. doi: 10.1160/TH14-03-0231

49. Williams, J, Pearce, K, and Benett, I. The effectiveness of a mobile ECG device in identifying AF: sensitivity, specificity and predictive value. *Br J Cardiol.* (2015) 22, 70–72. doi: 10.5837/bjc.2015.013

50. Lown, M, Yue, AM, Shah, BN, Corbett, SJ, Lewith, G, Stuart, B, et al. Screening for atrial fibrillation using economical and accurate technology (from the SAFETY study). *Am J Cardiol.* (2018) 122:1339–44. doi: 10.1016/j.amjcard.2018.07.003

51. Medi, C, and Kalman, JM. Prediction of the atrial flutter circuit location from the surface electrocardiogram. *Europace.* (2008) 10:786–96. doi: 10.1093/europace/eun106

52. Passman, R. "Pill-in-pocket" anticoagulation for atrial fibrillation: fiction, fact, or foolish? *Circulation.* (2021) 143:2211–3. doi: 10.1161/CIRCULATIONAHA.121.053170

53. Seshadri, DR, Bittel, B, Browsky, D, Houghtaling, P, Drummond, CK, and Desai, MY. Gillinov AM accuracy of apple watch for detection of atrial fibrillation. *Circulation.* (2020) 141:702–3. doi: 10.1161/CIRCULATIONAHA.119.044126

54. Ahmed, AS, Golden, KM, Foreman, JR, and Padanilam, BJ. Using a smartwatch to identify the morphology of atrial flutter. *HeartRhythm Case Rep.* (2020) 6:808–9. doi: 10.1016/j.hrcr.2020.06.021

55. Saarinen, H, Joutsen, A, Korpi, K, Hernesniemi, J, and Vehkaoja, A. Atrial fibrillation can be diagnosed using a combined wrist-worn photoplethysmography and electrocardiography. *Eur Heart J.* (2022) 43:417. doi: 10.1093/eurheartj/ehac544.417

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 12 May 2023
DOI 10.3389/fcvm.2023.1176710

Check for updates

OPEN ACCESS

EDITED BY
David Duncker,
Hannover Medical School, Germany

REVIEWED BY
Maura Zylla,
Heidelberg University Hospital, Germany
Henrike A.K. Hillmann,
Hannover Medical School, Germany

*CORRESPONDENCE
Konstantinos Iliodromitis
konstantinos.iliodromitis@gmail.com

†These authors have contributed equally to this work

RECEIVED 28 February 2023
ACCEPTED 24 April 2023
PUBLISHED 12 May 2023

CITATION
Iliodromitis K, Balogh Z, Triposkiadis F, Deftereos S, Vrachatis D, Bimpong-Buta N-Y, Schiedat F and Bogossian H (2023) Assessing physical activity with the wearable cardioverter defibrillator in patients with newly diagnosed heart failure.
Front. Cardiovasc. Med. 10:1176710.
doi: 10.3389/fcvm.2023.1176710

COPYRIGHT
© 2023 Iliodromitis, Balogh, Triposkiadis, Deftereos, Vrachatis, Bimpong-Buta, Schiedat and Bogossian. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Assessing physical activity with the wearable cardioverter defibrillator in patients with newly diagnosed heart failure

Konstantinos Iliodromitis[1,2]*, Zsuzsanna Balogh[1], Filippos Triposkiadis[3], Spyridon Deftereos[4], Dimitrios Vrachatis[4], Nana-Yaw Bimpong-Buta[1,2], Fabian Schiedat[5†] and Harilaos Bogossian[1,2†]

[1]Clinic for Cardiology and Electrophysiology, Evangelical Hospital Hagen-Haspe, Hagen, Germany, [2]School of Medicine, Witten/Herdecke University, Witten, Germany, [3]Department of Cardiology, Larissa University General Hospital, Larissa, Greece, [4]Medical School, National and Kapodistrian University of Athens, Athens, Greece, [5]Clinic for Cardiology, Marienhospital Gelsenkirchen Academic Hospital of the Ruhr University Bochum, Bochum, Germany

Background: The wearable cardioverter defibrillator (WCD), (LifeVest, ZOLL, Pittsburgh, PA, USA) is a medical device designed for the temporary detection and treatment of malignant ventricular tachyarrhythmias. WCD telemonitoring features enable the evaluation of the physical activity (PhA) of the patients. We sought to assess with the WCD the PhA of patients with newly diagnosed heart failure.
Methods: We collected and analyzed the data of all patients treated with the WCD in our clinic. Patients with newly diagnosed ischemic, or non-ischemic cardiomyopathy and severely reduced ejection fraction, who were treated with the WCD for at least 28 consecutive days and had a compliance of at least 18 h the day were included.
Results: Seventy-seven patients were eligible for analysis. Thirty-seven patients suffered from ischemic and 40 from non-ischemic heart disease. The average days the WCD was carried was 77.3 ± 44.6 days and the mean wearing time was 22.8 ± 2.1 h. The patients showed significantly increased PhA measured by daily steps between the first two and the last two weeks (Mean steps in the first 2 weeks: 4,952.6 ± 3,052.7 vs. mean steps in the last 2 weeks: 6,119.6 ± 3,776.2, p-value: < 0.001). In the end of the surveillance period an increase of the ejection fraction was observed (LVEF-before: 25.8 ± 6.6% vs. LVEF-after: 37.5 ± 10.6%, $p < 0.001$). Improvement of the EF did not correlate with the improvement of PhA.
Conclusion: The WCD provides useful information regarding patient PhA and may be additionally utilized for early heart failure treatment adjustment.

KEYWORDS

wearable cardioverter defibrillator, life vest, physical activity, ejection fraction, heart failure, sudden cardiac death, remote monitoring

Introduction

Heart failure with reduced ejection fraction (HFrEF) is a clinical condition associated with increased sudden cardiac death (SCD) risk (1–4). In the early phase of newly diagnosed HFrEF, reversible causes such as ongoing myocardial ischemia, tachyarrhythmias, or acute peri-myocarditis must be treated promptly. Furthermore,

despite swift initiation of the evidenced-based medical therapy for heart failure, titration of the of the disease-modifying drugs may be progressively achieved over longer periods (5). During this time frame, the SCD risk may be temporarily high, or cannot be determined. On the other hand, a prophylactic transvenous implantation of a cardioverter-defibrillator (ICD) in patients with severely reduced left ventricular ejection fraction (LVEF) in the early phase after an acute myocardial infarction lacks survival benefit (6, 7).

The wearable cardioverter defibrillator (WCD, LifeVest, ZOLL, Pittsburgh, PA, USA) is a device specifically designed for the temporary detection and treatment of ventricular tachyarrhythmias in patients during a vulnerable period for sudden arrhythmic death. The recently published European Guidelines for the prevention of SCD suggest that the surveillance with the WCD may be prophylactically considered in the early phase after acute myocardial infarction, whereas data on the beneficial effect of the WCD for patients with newly diagnosed non-ischemic cardiomyopathy are sparse (8). The device contains four non-adhesive electrodes positioned orthogonally around the waist (anterior-posterior & right-left), able to produce a two-lead filtered electrocardiogram (ECG) and three self-gelling defibrillation electrodes. This allows an effective and continuous arrhythmia detection from the WCD after combining data from both heart rate and QRS-complex morphology. All detected arrhythmic events are stored in the *LifeVest Network server* (https://lifevestnetwork.zoll.com) and the physician is automatically notified.

Furthermore, WCD has an incorporated accelerometer, which facilitates the counting of the steps, thus providing information about the patients' daily physical activity (PhA). The reliability of the WCD accelerometer as a tool for the assessment of PhA has been already successfully proven compared with the 6-minute-walking test (6MWT) (9).

Registries from Europe and the United States have thoroughly examined the feasibility and safety of the WCD during a vulnerable period for SCD in real world scenarios (10–15). Furthermore, the importance of patient risk stratification over time for SCD after initiation and optimization of heart failure treatment and the reduction of unnecessary ICD implantations has been previously demonstrated (16–18). The VEST-trial examined prospectively a potential benefit of the WCD in patients with reduced LVEF < 35% after AMI (19). The study showed no benefit in this population, however the wearing time with the device was much lower than anticipated (20).

Finally, data selected from the WCD are being stored and can be transmitted to the physician for offline analysis. Available data contain arrhythmic events, heart rate profile and the PhA of the patient in the form of daily steps (**Figure 1**).

In the present single-center, retrospective study we sought to evaluate the PhA of all patients with newly diagnosed severely reduced LVEF of either ischemic, or non-ischemic etiology, being telemonitored with the WCD until the end of the surveillance period. We also sought to identify clinical factors having an impact to the PhA of the patients.

Methods

Study population

A retrospective analysis of all patients treated with the WCD from January 2016 until October 2022 in our clinic was conducted. Inclusion criteria for the study were newly diagnosed non-valvular heart failure, with severely reduced LVEF less than 35% at the day of hospital discharge, of either ischemic, or non-ischemic etiology. Additional inclusion criteria were the duration of the bridging period with the WCD and the compliance to the treatment. Thus, a treatment with the WCD for at least 28 consecutive days and a minimum wearing time of the WCD of at least 18 h daily were prerequisite (**Figure 2**). Patients with primary electrical heart disease, or being bridged with WCD after removal of their implanted cardioverter defibrillator due to device infection were excluded from the study. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Physical activity estimation

All data for analysis were retrieved from the manufacturer database (LifeVest, ZOLL, Pittsburgh, PA, USA). The detection of either ventricular, or supraventricular episodes was noted. The endpoint of PhA was assessed by calculating the average number of daily steps in the first two weeks and comparing it to the average number of daily steps from the last two weeks prior to termination of the surveillance with the WCD. Additionally, we reported the initiation and/or modifications of all guideline recommended heart failure medications affecting the neurohumoral cycle of heart failure at the day of hospital discharge. Finally, we recorded and compared the change of the LVEF of each patient and correlated it with the PhA estimated with the WCD.

Evaluation of the left ventricular ejection fraction

LVEF evaluation was performed with 2D-transthoracic echocardiography using the modified Simpson's method. Transthoracic echocardiography was performed after reperfusion therapy and/or initiation of medical heart failure treatment (index event) prior to WCD therapy, as well as on scheduled follow-up prior to decision for termination of the WCD therapy.

Statistical analysis

The SPSS 29 (IBM SPSS Statistics) was used for all statistical analyses of this study. Continuous variables are shown as the mean ± standard deviation (SD). Categorical variables are presented as percentages. Pairwise comparisons of continuous variables were performed using the paired t-test. Factors affecting the results were examined with multivariate linear regression

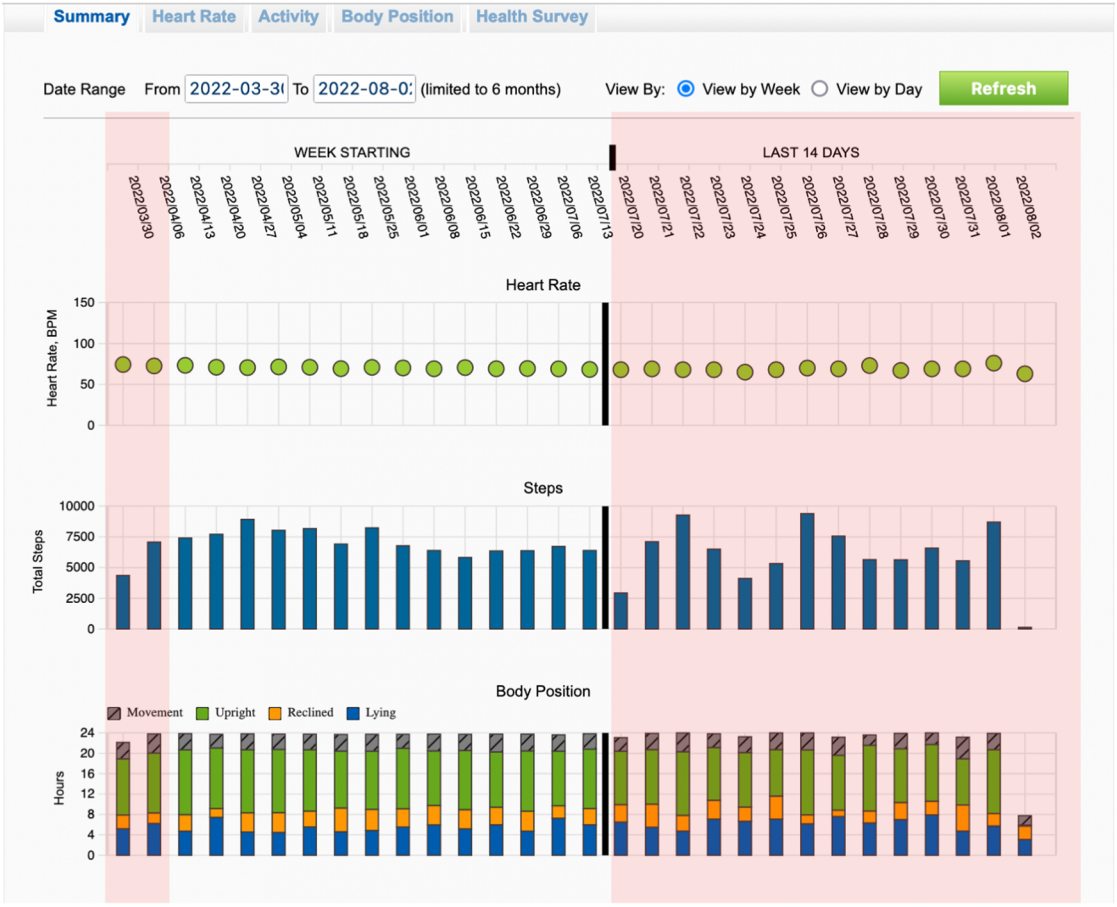


FIGURE 1
Recordings of the trends from wearable cardioverter defibrillator during the entire surveillance period. Highlighted with red color are the first two weeks and the last 14 days of the total wearing period.

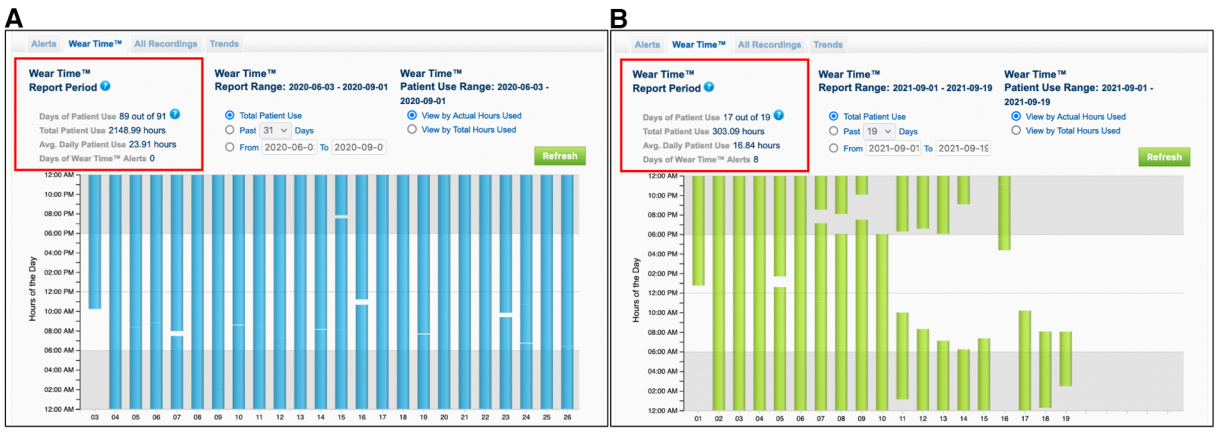


FIGURE 2
Recordings from the wearing time of the wearable cardioverter defibrillator from two different patients. Patient (**A**) shows a very compliance to the WCD therapy with an average wearing time of 23.91 h per day. Patient (**B**) shows a low compliance to the WCD therapy with an average wearing time of 16.84 h per day, resulting to early termination of the surveillance and exclusion from the study.

analysis. All of the statistical tests were two-sided at a significance level of 0.05.

Results

From January 2016 to October 2022 a total of 136 patients had been treated with the WCD. Inclusion criteria were fulfilled in 77 patients, who were included in the analysis. Fifty-five patients were males (70.5%) and the mean age of the study population was 63.7 ± 11.7 years. WCD therapy without further device implantation was terminated in 50 patients (64.9%). In particular, 44 of the patients showed an improvement of their left ventricular function with a LVEF over 35%, whereas six patients denied a permanent device implantation despite no adequate LVEF improvement under heart failure medication at the end of the follow-up. A transvenous one-chamber cardioverter defibrillator (ICD) was implanted in 18 patients (23.4%) and a biventricular cardioverter defibrillator (CRT-D) in 9 patients (11.7%). Episodes of non-sustained ventricular tachycardia were recorded in four individuals (5.2%), all of whom showed no improvement of their LVEF (Table 1).

The average days that our study population carried the WCD was 77.3 ± 44.6 days and the average daily wearing-time of the WCD was 22.8 ± 2.1 h. An improvement of the LVEF was noted at the end of the surveillance period with the WCD (LVEF-before: 25.8 ± 6.6% vs. LVEF-after: 37.5 ± 10.6%, $p < 0.001$).

TABLE 1 Demographic data.

Study population (n = 77)		n	%
Males		55	71.4
Females		22	28.6
Age (years)		63.7 ± 11.7	
Body mass index (BMI—kg/m²)		28.9 ± 5.7	
Comorbidities		**n**	**%**
Ischemic Cardiomyopathy		37	48.1
Non-ischemic Cardiomyopathy		40	51.9
Atrial Fibrillation		30	39
Paroxysmal		7	9.1
Persistent		14	18.2
Permanent		9	11.7
Coronary Heart Disease		47	61.4
Chronic obstructive pulmonary disease		15	19.5
Diabetes mellitus		22	28.6
Arterial hypertension		57	74
Overweight (BMI >25 kg/m²)		53	68.8
Arrhythmic events and Outcome		**n**	**%**
Non sustained ventricular tachycardia		4	5.2
Sustained ventricular tachycardia		0	0
Ventricular fibrillation		0	0
ICD Implantation		18	23.4
CRT-D Implantation		9	11.7
No device implantation		50	64.9
Improvement of LVEF >35%		44	57,1

LVEF, left ventricular ejection fraction; ICD, implantable cardioverter defibrillator; CRT-D, cardiac resynchronization therapy defibrillator.

Furthermore, the PhA of the patients increased significantly in the last two weeks of surveillance, compared to the first two weeks (mean steps first two weeks: 4,952.6 ± 3,052.7 vs. mean steps last two weeks: 6,116.6 ± 3,776.2, $p < 0.001$) (Table 2).

Multivariate regression analysis was used to evaluate the factors affecting the change of the left ventricular ejection fraction (Δ-LVEF). Included factors in the model were the type of cardiomyopathy (ischemic vs. non-ischemic), the wearing time of the WCD in hours, the length of duration the WCD was carried in days and the initiation of each of the guideline recommended heart failure medications (B-Blockers, Angiotensin Converting Enzyme (ACE)-Inhibitors, Angiotensin-1 (AT-1) receptor blockers, Sacubitril/Valsartan, Mineralcorticoid Receptor Antagonists (MRAs) and Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors (Table 3). The only factor that was associated with LVEF improvement was Sacubitril/Valsartan (Table 4).

Additionally, multivariate regression analysis was used to evaluate the factors affecting the change of the physical activity measured in daily steps (Δ-Steps). Included factors in the model were all previously mentioned plus the Δ-LVEF. The only factors associated with improvement in physical activity were wearing

TABLE 2 Follow-up Data.

		First two weeks	Last two weeks	P-value
Average daily steps		4,952.6 ± 3,052.7	6,119.6 ± 3,776.2	<0.001
Average heart rate		73.1 ± 11.1	71.4 ± 10.6	ns
		Beginning of follow-up	**End of follow-up**	**P-value**
Left ventricular ejection fraction (%)		25.8 ± 6.6	37.5 ± 10.7	<0.001
Δ-Steps	1,167.1 ± 2,455.9			
Δ-LVEF (%)	11.6 ± 10.6			
Wearing Time (hours)	22.8 ± 2.1			
Days carried	77.3 ± 44.6			

Δ-Steps, Improvement of physical activity measured in daily steps; Δ-LVEF, Improvement of left ventricular ejection fraction.

TABLE 3 Overview of medical treatment for heart failure.

	Prior index event (n)	%	After index event (n)	%
B-Blockers	31	40,3	75	97,4
ACE-Inhibitors	18	23,4	19	24,7
AT-1 Receptor Blockers	15	19,5	8	10,4
Sacubitril/ Valsartan	4	5,2	50	64,9
MRAs	12	15,6	65	84,4
SGLT2-Inhibitors	5	6,5	34	44,2

ACEs, angiotensin converting enzyme; AT-1, angiotensin-1; MRAs, mineralcorticoid receptor antagonists, SGLT2, sodium-glucose cotransporter-2.

TABLE 4 Factors potentially associated with improvement of left ventricular ejection fraction (Δ-LVEF). Results of multivariate regression analysis.

	Unstandardized Coefficients	Standardized Coefficients		t	*P* Value	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	−34.706	17.534		−1.979	0.052	−69.704	0.292
Type of heart failure	−2.841	2.369	−0.135	−1.199	0.235	−7.570	1.887
Wearing time (hours)	0.964	0.570	0.189	1.693	0.095	−0.173	2.101
Days carried	0.042	0.026	0.177	1.595	0.115	−0.011	0.095
B-Blockers	8.345	7.406	0.126	1.127	0.264	−6.437	23.127
ACEi	12.080	7.121	0.496	1.697	0.094	−2.132	26.293
ARBs	5.404	8.030	0.157	0.673	0.503	−10.623	21.432
Sacubitril/valsartan	15.323	7.132	0.697	2.148	0.035	1.087	29.559
MRAs	1.905	3.296	0.066	0.578	0.565	−4.673	8.484
SGLT-2i	−1.730	2.457	−0.082	−0.704	0.484	−6.634	3.174

Type of heart failure: ischemic vs. nonischemic; ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; MRAs, mineralocorticoid receptor antagonists; SGLT-2i, sodium-glucose cotransporter-2 inhibitors.

time of the WCD and the length of duration the WCD was carried (Table 5).

Discussion

The WCD is a non-invasive option for the treatment of malignant ventricular tachyarrhythmias during a temporary period with increased risk for SCD. Also, the WCD allows daily remote telemonitoring of the patient's PhA during the entire surveillance period.

Currently, the 6*M*WT is a well-established and simple medical tool for the evaluation of functional capacity among patients with heart failure (21, 22). Results from Burch AE. et al. showed that the WCD-guided 6MWT provides similar step counts compared to clinician-guided 6MWT, suggesting the reliability and accuracy of step counts with the WCD (9). However, a limitation of the clinical 6MWT remains its applicability in every-day and out-of-hospital settings, as well as its continuity in real life during the entire day and over longer periods. On the contrary, high adherence during the entire day, which is a prerequisite of an effective WCD therapy, enables more accurate and representative assessment of PhA in patients with HFrEF.

The high wearing time compliance with an average daily wearing time of the WCD of 22,8 ± 2.1 h per day was aligned with the average wearing time of previous studies (10–13, 23) assuring a careful daily telemonitoring of the patients. Additionally, the average wearing days that our population carried the WCD was 77.3 ± 44.6 days. Tripp C. et al. examined the PhA with the WCD in a large cohort of patients after acute myocardial infarction (24). Results from that study showed a significant increase of the PhA from the beginning of the prescription of WCD to the end of the therapy. Furthermore, they showed a negative relationship between wearing time over 20 h per day and PhA. Our results confirm their first finding, showing a positive correlation between incremental PhA measured by daily steps and wearing days of the WCD. This may be attributed to a general improvement of health condition. On the contrary, we report a positive correlation between prolonged wearing time and increased PhA. We assume that this may be the result of improved familiarization with the WCD and increased confidence of the patient to exercise after the index event, as none of the administered medical substances were

TABLE 5 Factors potentially associated with improvement of physical activity (Δ-steps). Results of multivariable regression analysis.

	Unstandardized Coefficients		Standardized Coefficients	t	*P* value	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	−7,403.588	4,378.612		−1.691	0.096	−16,145.770	1,338.594
Type of heart failure	426.845	581.195	0.087	0.734	0.465	−733.548	1,587.239
Change in LVEF	7.474	29.654	0.032	0.252	0.802	−51.731	66.679
Wearing Time (hours)	300.357	141.208	0.253	2.127	0.037	18.427	582.287
Days carried	13.830	6.518	0.251	2.122	0.038	0.816	26.845
B-Blockers	2,756.052	1,814.530	0.180	1.519	0.134	−866.775	6,378.878
ACEi	−2,094.027	1,765.064	−0.370	−1.186	0.240	−5,618.091	1,430.037
ARBs	−1,349.070	1,955.594	−0.169	−0.690	0.493	−5,253.539	2,555.399
Sacubitril/valsartan	−2,022.073	1,789.791	−0.395	−1.130	0.263	−5,595.506	1,551.360
MRAs	−442.009	801.970	−0.066	−0.551	0.583	−2,043.194	1,159.176
SGLT-2i	50.226	598.536	0.010	0.084	0.933	−1,144.789	1,245.241

Type of heart failure: ischemic vs. nonischemic; LVEF, left ventricular ejection fraction; ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; MRAs, Mineralocorticoid receptor antagonists, SGLT-2i, Sodium-glucose cotransporter-2 inhibitors.

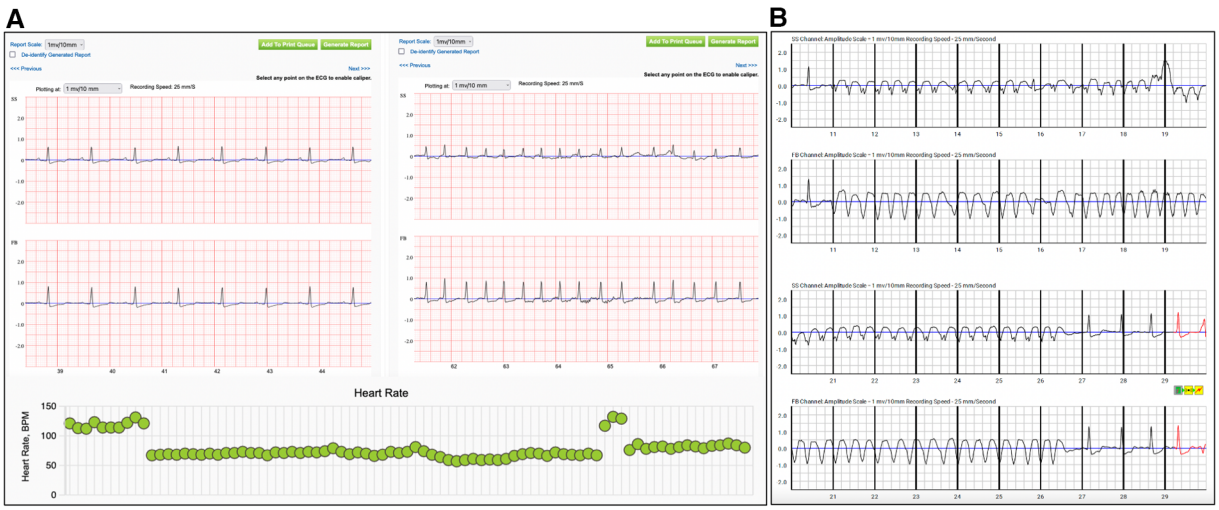


FIGURE 3
Recordings of alerts from the wearable cardioverter defibrillator during the surveillance period. Patient (**A**) reported worsening of dyspnea, with the electrocardiographic confirmation of atrial fibrillation. In the lower panel are depicted the daily heart rate trends from the same patient, with a sudden increase of the heart rate suggestive for an arrhythmic event. (SS: side-side electrodes, FB: front-back electrodes) Recording from the wearable cardioverter defibrillator of an episode of non-sustained ventricular tachycardia in patient (**B**) with non-ischemic cardiomyopathy. (SS: side-side electrodes, FB: front-back electrodes).

correlated with the improvement of PhA. Similar results have been published by Hillmann et al., examining the PhA with the WCD in a cohort of patients with both ischemic and non-ischemic cardiomyopathy (25), showing a significant increase of the step count between the first and last week of surveillance.

A novel element from the findings of our study is the lack of correlation between the improvement of the LVEF and the PhA of the patients. During the surveillance period with the WCD, a statistically significant improvement of the LVEF was recorded. The analysis of the applied medication showed, a positive correlation between the sacubitril/valsartan initiation and LVEF improvement. None of the remaining prescribed evidenced-based and recommended heart medication did correlate with the improvement of PhA. Moreover, the improvement of the PhA of the patients did not correlate with the improvement of the LVEF. These results are in accordance with previous studies highlighting the limited value of LVEF as a marker for physiological assessment, as this may vary depending on the loading condition of the patient (preload and afterload) and the myocardial contractility (26–28).

Thus, high adherence to WCD therapy, patient familiarization and education with the device facilitate a high quality daily telemonitoring of PhA. This may lead to early physician interference in cases of patients with good WCD compliance and gradually reduced PhA for the adjustment of the applied medical therapy and avoid unnecessary hospital admissions (**Figure 3**). None of them showed improvement of their LVEF during the bridging period with the WCD. Although these events may not be enough for conclusions, it highlights the importance of careful interrogation of all available recordings provided from WCD for more accurate, non-invasive risk stratification of the patients.

Limitations

The retrospective design of the current study remains a limitation. Furthermore, the inclusion criteria for the study population may introduce selection bias in the results, however high compliance to the WCD is prerequisite for effective therapy and the extraction of valid results. Finally, alternative ways for the calculation of PhA, such as steps per hour wearing time, might have been more descriptive.

Conclusion

The WCD provides useful information regarding the PhA in patients with heart failure, who are having good compliance.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in

accordance with the national legislation and the institutional requirements.

Author contributions

KI, FT, and HB contributed to conception and design of the study. KI and ZB organized the database. FT performed the statistical analysis. KI wrote the first draft of the manuscript. KI, ZB, FT, SD, DV, FS, NYBB and HB wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

The costs for the open access publication of the manuscript have been covered by research grants of the company ZOLL CMS GmbH.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor DD declared a past co-authorship with the author HB.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Solomon SD, Zelenkofske S, McMurray JJ, Finn PV, Velazquez E, Ertl G, et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med.* (2005) 352(25):2581–8. doi: 10.1056/NEJMoa043938

2. Busk M, Maeng M, Kristensen SD, Thuesen L, Krusell LR, Mortensen LS, et al. Timing, causes, and predictors of death after three years' follow-up in the danish multicenter randomized study of fibrinolysis versus primary angioplasty in acute myocardial infarction (DANAMI-2) trial. *Am J Cardiol.* (2009) 104(2):210–5. doi: 10.1016/j.amjcard.2009.03.014

3. Beggs SAS, Jhund PS, Jackson CE, McMurray JJV, Gardner RS. Non-ischaemic cardiomyopathy, sudden death and implantable defibrillators: a review and meta-analysis. *Heart (British Cardiac Society).* (2018) 104(2):144–50. doi: 10.1136/heartjnl-2016-310850

4. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med.* (2016) 375(13):1221–30. doi: 10.1056/NEJMoa1608029

5. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* (2021) 42(36):3599–726. doi: 10.1093/eurheartj/ehab368

6. Steinbeck G, Andresen D, Seidl K, Brachmann J, Hoffmann E, Wojciechowski D, et al. Defibrillator implantation early after myocardial infarction. *N Engl J Med.* (2009) 361(15):1427–36. doi: 10.1056/NEJMoa0901889

7. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med.* (2004) 351(24):2481–8. doi: 10.1056/NEJMoa041489

8. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, et al. 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J.* (2022) 43(40):3997–4126. doi: 10.1093/eurheartj/ehac262

9. Burch AE, Scherr D, Rieth A, Griffin J, Bianco NR, Odeneg T, et al. Wearable cardioverter defibrillator-guided 6-min walk test performed at home is accurate and reliable: rESULTS OF THE TRENDS STUDY. *J Cardiopulm Rehabil Prev.* (2020) 40 (2):E14–e7. doi: 10.1097/HCR.0000000000000441

10. Kutyifa V, Moss AJ, Klein H, Biton Y, McNitt S, MacKecknie B, et al. Use of the wearable cardioverter defibrillator in high-risk cardiac patients: data from the prospective registry of patients using the wearable cardioverter defibrillator (WEARIT-II registry). *Circulation.* (2015) 132(17):1613–9. doi: 10.1161/CIRCULATIONAHA.115.015677

11. Feldman AM, Klein H, Tchou P, Murali S, Hall WJ, Mancini D, et al. Use of a wearable defibrillator in terminating tachyarrhythmias in patients at high risk for sudden death: results of the WEARIT/BIROAD. *Pacing and Clin Electrophysiol: PACE.* (2004) 27(1):4–9. doi: 10.1111/j.1540-8159.2004.00378.x

12. Chung MK, Szymkiewicz SJ, Shao M, Zishiri E, Niebauer MJ, Lindsay BD, et al. Aggregate national experience with the wearable cardioverter-defibrillator: event rates, compliance, and survival. *J Am Coll Cardiol.* (2010) 56(3):194–203. doi: 10.1016/j.jacc.2010.04.016

13. Wäßnig NK, Günther M, Quick S, Pfluecke C, Rottstädt F, Szymkiewicz SJ, et al. Experience with the wearable cardioverter-defibrillator in patients at high risk for sudden cardiac death. *Circulation.* (2016) 134(9):635–43. doi: 10.1161/CIRCULATIONAHA.115.019124

14. Masri A, Altibi AM, Erqou S, Zmaili MA, Saleh A, Al-Adham R, et al. Wearable cardioverter-defibrillator therapy for the prevention of sudden cardiac death: a systematic review and meta-analysis. *JACC Clinical Electrophysiol.* (2019) 5 (2):152–61. doi: 10.1016/j.jacep.2018.11.011

15. Garcia R, Combes N, Defaye P, Narayanan K, Guedon-Moreau L, Boveda S, et al. Wearable cardioverter-defibrillator in patients with a transient risk of sudden cardiac death: the WEARIT-France cohort study. *Europace.* (2021) 23(1):73–81. doi: 10.1093/europace/euaa268

16. Dreher TC, El-Battrawy I, RÖger S, Rosenkaimer SL, Gerhards S, Kuschyk J, et al. Comparison of the outcome of patients protected by the wearable cardioverter defibrillator (WCD) for <90 wear days versus ≥90 wear days. *In Vivo.* (2020) 34 (6):3601–10. doi: 10.21873/invivo.12205

17. Duncker D, König T, Hohmann S, Bauersachs J, Veltmann C. Avoiding untimely implantable cardioverter/defibrillator implantation by intensified heart failure therapy optimization supported by the wearable cardioverter/defibrillator-the PROLONG study. *J Am Heart Assoc.* (2017) 6(1). doi: 10.1161/JAHA.116.004512

18. Mueller-Leisse J, Brunn J, Zormpas C, Hohmann S, Hillmann HAK, Eiringhaus J, et al. Extended follow-up after wearable cardioverter-defibrillator period: the PROLONG-II study. *ESC Heart Fail.* (2021) 8(6):5142–8. doi: 10.1002/ehf2.13586

19. Olgin JE, Pletcher MJ, Vittinghoff E, Wranicz J, Malik R, Morin DP, et al. Wearable cardioverter-defibrillator after myocardial infarction. *N Engl J Med.* (2018) 379(13):1205–15. doi: 10.1056/NEJMoa1800781

20. Olgin JE, Lee BK, Vittinghoff E, Morin DP, Zweibel S, Rashba E, et al. Impact of wearable cardioverter-defibrillator compliance on outcomes in the VEST trial: as-treated and per-protocol analyses. *J Cardiovasc Electrophysiol.* (2020) 31(5):1009–18. doi: 10.1111/jce.14404

21. Demers C, McKelvie RS, Negassa A, Yusuf S. Reliability, validity, and responsiveness of the six-minute walk test in patients with heart failure. *Am Heart J.* (2001) 142(4):698–703. doi: 10.1067/mhj.2001.118468

22. Du H, Wonggom P, Tongpeth J, Clark RA. Six-Minute walk test for assessing physical functional capacity in chronic heart failure. *Curr Heart Fail Rep.* (2017) 14 (3):158–66. doi: 10.1007/s11897-017-0330-3

23. Blockhaus C, Guelker JE, Feyen L, Bufe A, Seyfarth M, Shin DI. Telemonitoring potential of wearable cardioverter-defibrillators during the follow-up of patients with heart failure. *J Cardiovasc Dev Dis.* (2022) 9(6):175–85. doi: 10.3390/jcdd9060175

24. Tripp C, Burch AE, Erath JW, Hain A, Sears SF. Physical activity in adults with wearable cardioverter defibrillators in the post-myocardial infarction period. *J Cardiopulm Rehabil Prev.* (2020) 40(3):164–6. doi: 10.1097/HCR.0000000000000454

25. Hillmann HAK, Hohmann S, Mueller-Leisse J, Zormpas C, Eiringhaus J, Bauersachs J, et al. Feasibility and first results of heart failure monitoring using the

wearable cardioverter-defibrillator in newly diagnosed heart failure with reduced ejection fraction. *Sensors (Basel*. (2021) 21(23). doi: 10.3390/s21237798

26. Triposkiadis F, Butler J, Abboud FM, Armstrong PW, Adamopoulos S, Atherton JJ, et al. The continuous heart failure spectrum: moving beyond an ejection fraction classification. *Eur Heart J*. (2019) 40(26):2155–63. doi: 10.1093/eurheartj/ehz158

27. Triposkiadis F, Starling RC. Chronic heart failure: diagnosis and management beyond LVEF classification. *J Clin Med*. (2022) 11(6). doi: 10.3390/jcm11061718

28. Konstam MA, Abboud FM. Ejection fraction: misunderstood and overrated (changing the paradigm in categorizing heart failure). *Circulation*. (2017) 135 (8):717–9. doi: 10.1161/CIRCULATIONAHA.116.025795

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 09 June 2023
DOI 10.3389/fcvm.2023.1160242

Check for updates

OPEN ACCESS

EDITED BY
Dominik Linz,
Maastricht University Medical Centre,
Netherlands

REVIEWED BY
Laurent Pison,
East Limburg Hospital, Belgium
David Zweiker,
Klinik Ottakring, Austria

*CORRESPONDENCE
Justinas Bacevicius
justinas.bacevicius100@gmail.com

RECEIVED 06 February 2023
ACCEPTED 26 May 2023
PUBLISHED 09 June 2023

CITATION
Bacevicius J, Taparauskaite N, Kundelis R, Sokas D, Butkuviene M, Stankeviciute G, Abramikas Z, Pilkiene A, Dvinelis E, Staigyte J, Marinskiene J, Audzijoniene D, Petrylaite M, Jukna E, Karuzas A, Juknevicius V, Jakaite R, Basyte-Bacevice V, Bileisiene N, Badaras I, Kiseliute M, Zarembaite G, Gudauskas M, Jasiunas E, Johnson L, Marozas V and Aidietis A (2023) Six-lead electrocardiography compared to single-lead electrocardiography and photoplethysmography of a wrist-worn device for atrial fibrillation detection controlled by premature atrial or ventricular contractions: six is smarter than one.
Front. Cardiovasc. Med. 10:1160242.
doi: 10.3389/fcvm.2023.1160242

COPYRIGHT
© 2023 Bacevicius, Taparauskaite, Kundelis, Sokas, Butkuviene, Stankeviciute, Abramikas, Pilkiene, Dvinelis, Staigyte, Marinskiene, Audzijoniene, Petrylaite, Jukna, Karuzas, Juknevicius, Jakaite, Basyte-Bacevice, Bileisiene, Badaras, Kiseliute, Zarembaite, Gudauskas, Jasiunas, Johnson, Marozas and Aidietis. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Six-lead electrocardiography compared to single-lead electrocardiography and photoplethysmography of a wrist-worn device for atrial fibrillation detection controlled by premature atrial or ventricular contractions: six is smarter than one

Justinas Bacevicius[1,2]*, Neringa Taparauskaite[1,2], Ricardas Kundelis[1,2], Daivaras Sokas[3], Monika Butkuviene[3], Guoste Stankeviciute[1], Zygimantas Abramikas[1,2], Aiste Pilkiene[1], Ernestas Dvinelis[1,2], Justina Staigyte[1,2], Julija Marinskiene[1,2], Deimile Audzijoniene[1,2], Marija Petrylaite[1,2], Edvardas Jukna[1,2], Albinas Karuzas[1,2], Vytautas Juknevicius[1,2], Rusne Jakaite[1,2], Viktorija Basyte-Bacevice[1], Neringa Bileisiene[1,2], Ignas Badaras[1,2], Margarita Kiseliute[1], Gintare Zarembaite[1], Modestas Gudauskas[1,2], Eugenijus Jasiunas[4], Linda Johnson[5], Vaidotas Marozas[3,6] and Audrius Aidietis[1,2]

[1]Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania, [2]Center of Cardiology and Angiology, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania, [3]Biomedical Engineering Institute, Kaunas University of Technology, Kaunas, Lithuania, [4]Center of Informatics and Development, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania, [5]Department of Clinical Sciences, Malmö, Lund University, Lund, Sweden, [6]Electronics Engineering Department, Kaunas University of Technology, Kaunas, Lithuania

Background: Smartwatches are commonly capable to record a lead-I-like electrocardiogram (ECG) and perform a photoplethysmography (PPG)-based atrial fibrillation (AF) detection. Wearable technologies repeatedly face the challenge of frequent premature beats, particularly in target populations for screening of AF.

Objective: To investigate the potential diagnostic benefit of six-lead ECG compared to single-lead ECG and PPG-based algorithm for AF detection of the wrist-worn device.

Methods and results: From the database of DoubleCheck-AF 249 adults were enrolled in AF group ($n = 121$) or control group of SR with frequent premature ventricular (PVCs) or atrial (PACs) contractions ($n = 128$). Cardiac rhythm was monitored using a wrist-worn device capable of recording continuous PPG and simultaneous intermittent six-lead standard-limb-like ECG. To display a single-lead ECG, the six-lead ECGs were trimmed to lead-I-like ECGs. Two diagnosis-blinded cardiologists evaluated reference, six-lead and single-lead ECGs as "AF", "SR", or "Cannot be concluded". AF detection based on six-lead ECG, single-lead ECG, and PPG yielded a sensitivity of 99.2%, 95.7%, and 94.2%, respectively. The higher number of premature beats per minute was associated with false

positive outcomes of single-lead ECG (18.80 vs. 5.40 beats/min, $P < 0.01$), six-lead ECG (64.3 vs. 5.8 beats/min, $P = 0.018$), and PPG-based detector (13.20 vs. 5.60 beats/min, $P = 0.05$). Single-lead ECG required 3.4 times fewer extrasystoles than six-lead ECG to result in a false positive outcome. In a control subgroup of PACs, the specificity of six-lead ECG, single-lead ECG, and PPG dropped to 95%, 83.8%, and 90%, respectively. The diagnostic value of single-lead ECG (AUC 0.898) was inferior to six-lead ECG (AUC 0.971) and PPG-based detector (AUC 0.921). In a control subgroup of PVCs, the specificity of six-lead ECG, single-lead ECG, and PPG was 100%, 96.4%, and 96.6%, respectively. The diagnostic value of single-lead ECG (AUC 0.961) was inferior to six-lead ECG (AUC 0.996) and non-inferior to PPG-based detector (AUC 0.954).

Conclusions: A six-lead wearable-recorded ECG demonstrated the superior diagnostic value of AF detection compared to a single-lead ECG and PPG-based AF detection. The risk of type I error due to the widespread use of smartwatch-enabled single-lead ECGs in populations with frequent premature beats is significant.

KEYWORDS

wearable, smartWatch, multiple-lead ECG, telemedicine, mHealth, remote monitoring, digital

Introduction

Atrial fibrillation (AF) is an arrhythmia that can lead to various cardiovascular events including ischemic stroke and heart failure, especially if undiagnosed or not treated adequately (1). AF is the most common arrhythmia in the world with the latest approximate prevalence of 60 million patients and contributes to >8 million disability-adjusted life years (2). While the prevalence of this disease increases, there is still a high percentage of undiagnosed cases (3, 4). This includes asymptomatic patients and patients who experience symptoms but the diagnosis of AF is not confirmed with a standard 12-lead electrocardiogram (ECG). As undiagnosed AF may pose potential risks to the patient and, in case of adverse cardiovascular events, additional burden to the health care system (5), early AF diagnosis and management is of crucial importance (6). To reduce the number of undiagnosed AF cases, systematic screening for AF should be considered in individuals aged ≥75 years (7). In addition, the new practical guide of the European Heart Rhythm Association (EHRA) upgraded the consensus statement to "may be beneficial" in individuals aged ≥65 years with comorbidities increasing the risk of stroke (as systematic screening by intermittent ECG) and in patients aged ≥65 years without comorbidities or <65 years with comorbidities (as opportunistic screening) (8).

Increasing numbers of wearable technologies facilitate the detection of AF in asymptomatic or undiagnosed symptomatic individuals and establish a clear hierarchy of diagnostic methods for AF screening. As a rule of thumb, photoplethysmography-based (PPG) devices are preferred to pulse palpation. However, if PPG screening is indicative of AF, only an ECG-based method should be used to confirm the diagnosis of AF and is preferred over PPG-based devices (8).

The key factor for high diagnostical accuracy for AF detection using a wearable device is the sufficient quality of ECG. When artifacts are present, conventional multiple-lead-ECG Holter monitoring demonstrates additional vectors of electrical activity and subsequently increases the chances of correct interpretation (9). However, the situation is different in a real-life setting, i.e., artifacts, noise, and the presence of other concomitant arrhythmias with irregular heart contractions, such as premature beats, are the most common challenges for AF detection in wearable-recorded ECGs (10).

Most current smartwatches share a common feature of recording a lead-I-like ECG. Our scientific group has introduced the first wrist-worn device, which combines a PPG-based algorithm for AF screening and intermittent 6-lead ECG recorded with no wires for AF confirmation (11). Whether multi-lead ECG recorded using a wrist-worn device brings an additional benefit for AF detection compared to single-lead ECG is unknown. The aim of this study is to compare the performance of single-lead and six-lead ECGs obtained using the wrist-worn device as well as the automatic PPG-based AF detector.

Materials and methods

Study design

This was a single-center, non-randomized substudy of DoubleCheck-AF with a prospective case-control model. A regional bioethics committee approved it with registration No. 158200-18/7-1052-557. The study is registered at ClinicalTrials.gov (NCT04281927).

Patients were recruited from both inpatient and outpatient wards of Cardiology Department at Vilnius University Hospital Santaros Klinikos at any time of the day. All the participants gave written informed consent before enrolment. Adult patients (18 to 99 years) diagnosed with AF or sinus rhythm (SR) with frequent PVCs or PACs were included in the study. Patients in SR with frequent PVCs and PACs were selected as a control group. Individuals with at least one ectopic beat in 2 min were classified as SR with frequent PVCs or PACs. Patients who did

not give informed consent, had paced ventricular beats, other arrhythmias or stable SR were excluded from the study.

A sample of 435 patients was collected in the original DoubleCheck-AF study. For analysis of 2×2 contingency tables [degree of freedom (df) = 1], medium effect size ($w = 0.3$), α error probability = 0.05, and power $(1 - \beta) = 0.95$, we needed a sample size of 145 patients. In the current substudy, after the exclusion of the control subgroup of stable SR, the remaining subjects ($n = 249$) were sufficient to match the required sample size.

Measurements

Cardiac rhythm was monitored using a wrist-worn device, detailly described by Bacevicius et al. (11), which provides continuous PPG-based AF monitoring and an intermittent, on-demand, six-lead ECG. Synchronously, reference ECG was registered using a validated Holter monitor (Bittium Faros, Bittium, Finland).

The PPG signals are analyzed using an embedded AF detector (12), which structure is inspired by the rhythm-based detector used for ECG signals (13). The algorithm relies on the analysis of peak-to-peak intervals using 8-beat long sliding window and includes blocks of signal quality assessment, peak-to-peak interval characterization, and suppression of non-AF rhythms such as ectopic beats, bigeminy, and respiratory sinus arrhythmia.

The main specifications of the wearable device are as follows. The sampling rate of the PPG signal is 100 Hz, the amplitude resolution is 18 bits, and the bandwidth is 0–50 Hz. The device can record green, red, and infrared light channels, although only the green channel was used in this application.

The recorded ECG leads are similar to standard Einthoven-like limb leads, as they are measured by contact of three electrodes to the skin: two electrodes are on the outer surface (one electrode on top of the device enclosure, another electrode on the bracelet), and the third electrode is placed on the inner surface next to the PPG sensor (**Figure 1**). Additional three ECG leads (Goldberger augmented limb leads aVR, aVL, and aVF) were calculated from Einthoven leads I, II, and III. The sampling rate of the ECG is 500 Hz, the amplitude resolution is 24bit, and the bandwidth is 0–130 Hz. Both PPG and ECG, were recorded in the device's 8GB local flash memory using a secure GDF (General Data Format) (14).

In order to display equivalent episodes of arrhythmia in a single-lead ECG, the six-lead wearable-recorded ECG was trimmed to a width of lead-I-like ECG (**Figure 2**). Thus, the accuracy of both methods was not influenced by any potential difference in the complexity of recording as it was exactly the same episode of arrhythmia. Reference ECG, single-lead ECG, and six-lead ECG from each patient were evaluated by two independent diagnosis-blinded cardiologists as "AF", "SR", or "Cannot be concluded". In case of disagreement, a third cardiologist was asked to evaluate the case to make the final diagnosis.

Data analysis

Continuous variables were reported as mean with standard deviation or median with interquartile range. Categorical variables were presented as counts and percentages. Detection performance was evaluated using sensitivity, specificity and accuracy. Due to the great dependence on the prevalence of disease, positive or negative predictive value were not evaluated. An independent sample Student's T-test or Mann-Whitney U test was applied to quantitative data. When the expected values in any of the cells of a contingency table were ≥5, a Chi-square test was applied for categorical data. Otherwise, a two-tailed Fisher's exact test was selected. Cramer's V was used to measure the association between the results of investigated diagnostic method and reference. Cohen's kappa was used to measure inter-rater agreement. Data was processed using the statistical package for the social sciences (27.0, SPSS Inc., Chicago, IL, USA).

FIGURE 1
Acquiring of single-lead ECG (left panel) and six-lead ECG without any wires (right panel) with the use of the prototype device. The configuration of electrodes is displayed elsewhere (11).

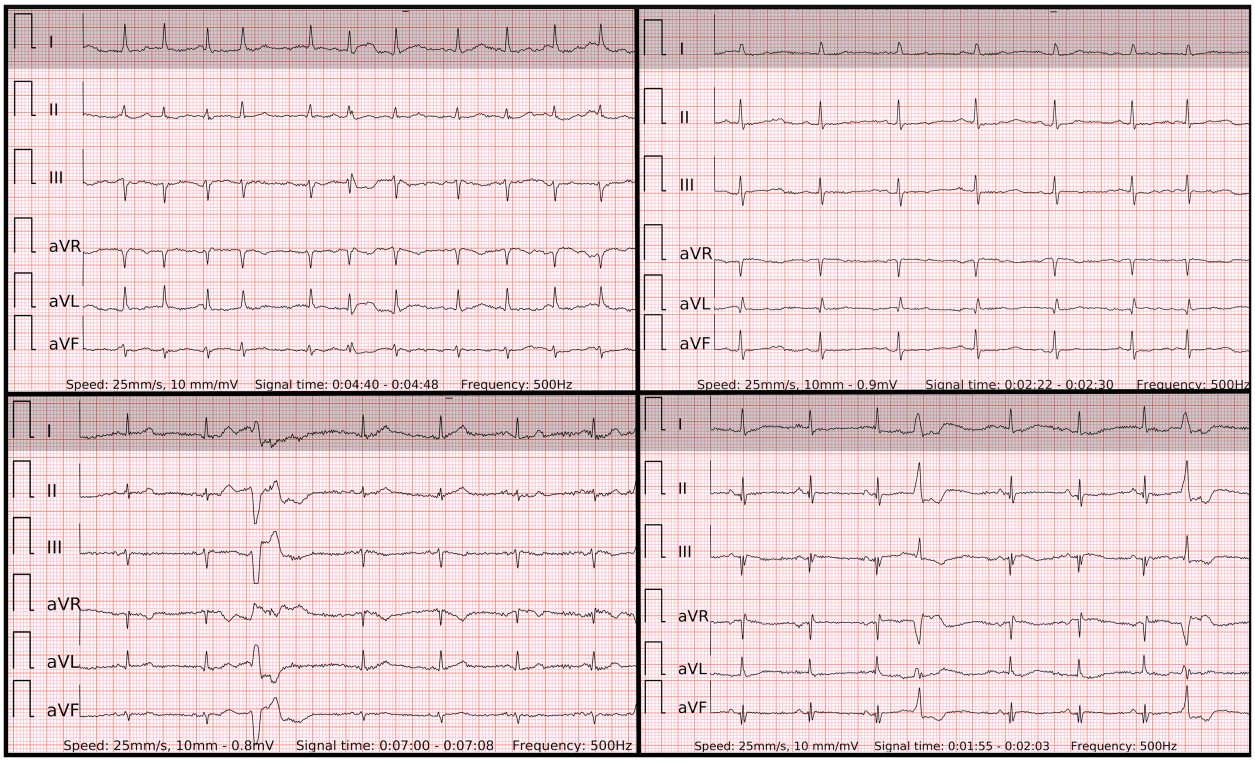


FIGURE 2
The 6-lead ECGs recorded by the wearable device with the examples of atrial fibrillation (top left panel); SR with frequent premature atrial contractions (top right panel); SR with frequent premature ventricular contractions with superior axis (lower left panel); SR with frequent premature ventricular contractions with inferior axis (lower right panel).

Results

In this substudy of the DoubleCheckAF trial, the initial assessment group for eligibility constituted 435 patients (**Figure 3**), of which 123 patients with stable SR were excluded. In addition, 12 recordings with duplicates or other similar issues of data logistics were excluded. Among the rest of the recordings, 1.3% (4/300) were with missing ECG signal of the prototype wrist-worn device and 8.3% (25/300) were with insufficient ECG quality of the prototype wrist-worn device. The final analysis included 249 patients, i.e., 121 patients with AF and 128 patients in the control group of SR with frequent premature beats, which consisted of dominant PVCs ($n = 88$) or PACs ($n = 40$).

In the control subgroup of SR with PACs and PVCs, the burden of premature beats per minute constituted a total of 5.5 beats/min (3, 13.9) and 6.7 beats/min (2.7, 16.4), respectively (**Table 1**). Patients with frequent PVCs were more likely to present with bigeminy/trigeminy (31.8%, 28/88) and less likely with runs of ≥3 beats (5.7%, 5/88) compared to patients with frequent PACs (7.5%, 3/40, and 17.5%, 7/40, respectively). These parameters represent not only just discrete single premature beats in both control subgroups but also the grouped extrasystoles or very frequent bigeminy/trigeminy episodes, which cause high irregularity.

In the group of AF the median duration of an ECG and the median number of six-lead or single-lead ECG recordings per patient was 166.5 s (130, 222.5) and 1 recording (1, 1), respectively.

In the control group of frequent PACs/PVCs the median duration of an ECG and the median number of six-lead or single-lead ECG recordings per patient was 156 s (125.5, 209.8) and 1 recording (1, 2), respectively.

Accordingly, the duration of PPG signal per patient was 1,358 seconds (892, 2,206) in patients with AF and 1,113 seconds (915.8, 1,718.8) in patients with frequent premature beats.

Single-lead ECG, six-lead ECG and PPG-based algorithm for AF detection when controlled by SR with PACs and PVCs

When compared to the control group, AF detection based on six-lead ECG, single-lead ECG, and PPG-based detector yielded a sensitivity of 99.2% (95% CI: 95.4–100), 95.7% (95% CI: 90.3–98.6), and 94.2% (95% CI: 88.4–97.6), respectively (**Table 2**). Due to type I error, the specificity of the same diagnostic tools was 98.4% (95% CI: 94.4–99.8), 92.5% (95% CI: 86.2–96.5) and 94.5% (95% CI: 89.1–97.8), respectively. The six-lead ECG demonstrated the highest overall accuracy with 98.4% (95% CI: 89.1–97.8), followed by the PPG-based detector with 94.5% (95% CI: 90.9–97) and single-lead ECG with 92.5% (95% CI: 88.4–95.5).

False positive cases were more common for single-lead ECG (9/120, 7.5%) or tended to be more common for PPG-based detector

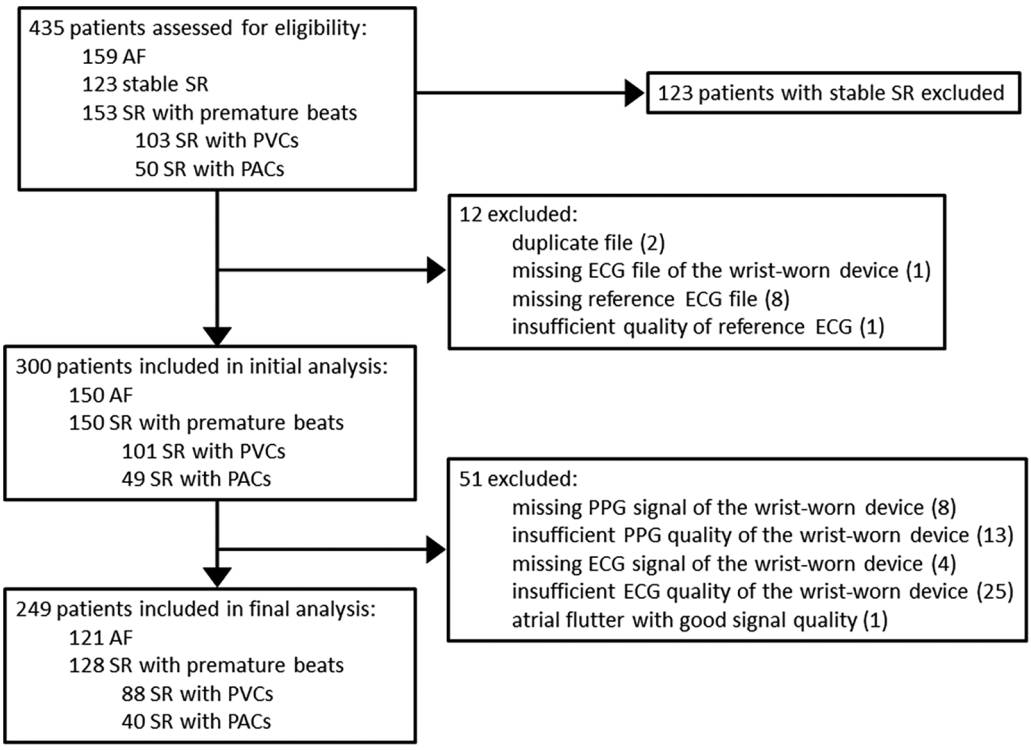


FIGURE 3
Flow chart of patients. AF, atrial fibrillation; SR, sinus rhythm; PVC, premature ventricular contraction; PAC, premature atrial contraction; ECG, electrocardiography; PPG, photoplethysmography.

TABLE 1 Baseline characteristics.

Characteristic	AF ($n = 121$)	SR with frequent premature contractions ($n = 128$)	
		SR with frequent PACs ($n = 40$)	SR with frequent PVCs ($n = 88$)
Age (years), mean ± SD	65.6 ± 11.2	70.9 ± 11.6	65.7 ± 15.0
Male, *n* (%)	64 (52.9)	20 (50)	49 (55.7)
Paroxysmal: persistent: permanent AF	101:14:6	NA	NA
Type and frequency of premature contractions			
Cases with frequent runs of ≥3 PACs/PVCs, *n* (%)	0 (0)	7 (17.5)	5 (5.7)
Cases with frequent bigeminy/trigeminy episodes, *n* (%)	0 (0)	3 (7.5)	28 (31.8)
PACs, median beats/min (IQR)	< 0.5	5.4 (2.6, 12.8)	<0.5
PVCs, median beats/min (IQR)	<0.5	<0.5	5.6 (2.4, 16.4)
Total, median beats/min (IQR)	<0.5	5.5 (3, 13.9)	6.7 (2.7, 16.4)
$CHADS_2VASc$ risk score (categorical)			
0–1, *n* (%)	37 (30.6)	1 (7.1)[a]	0 (0)[b]
2–4, *n* (%)	64 (52.9)	8 (57.1)[a]	13 (76.5)[b]
≥5, *n* (%)	20 (16.5)	5 (35.7)[a]	4 (23.5)[b]
$CHADS_2VASc$ risk score (quantitative), mean ± SD	2.7 ± 1.7	4 ± 2.1[a]	3.6 ± 1.2[b]
HAS-BLED score, mean ± SD	0.9 ± 0.8	1 ± 0.7[a]	1.7 ± 1.2[b]
OAC, *n* (%)	91 (75.2)	10 (25)	13 (14.8)
DOAC, *n* (%)	67 (55.4)	6 (15)	9 (10.2)
Warfarin, *n* (%)	23 (19)	4 (10)	4 (4.5)
LMWH, *n* (%)	1 (0.8)	0 (0)	0 (0)

AF, atrial fibrillation; SR, sinus rhythm; PVC, premature ventricular contraction; PAC, premature atrial contraction; OAC, oral anticoagulant; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; IQR, interquartile range.
[a]Calculated for patients with a history of AF, thus the denominator is 14.
[b]Calculated for patients with a history of AF, thus the denominator is 17.

TABLE 2 Diagnostic measures of the wrist-worn device for AF detection controlled by SR with PVCs/PACs.

Measure	Single-lead ECG	Six-lead ECG	PPG-based detector
Sensitivity[a], % (95% CI)	95.7 (90.3–98.6)	**99.2** (95.4–100)	94.2 (88.4–97.6)
Specificity[a], % (95% CI)	92.5 (86.2–96.5)	**98.4** (94.4–99.8)	94.5 (89.1–97.8)
Accuracy[a], % (95% CI)	92.5 (88.4–95.5)	**98.4** (96.0–99.6)	94.5 (90.9–97)
False positive cases, *n* (%)	**9/120 (7.5)**	2/127 (1.6)	7/128 (5.5)
False negative cases, *n* (%)	5/117 (4.3)	1/119 (0.8)	**7/121 (5.8)**
Cannot be concluded by a physician, *n* (%)	**12/249 (4.8)**	3/249 (1.2)	NA
Cramer's *V*, PACs subgroup	0.803, $P < 0.001$	**0.950**, $P < 0.001$	0.823, $P < 0.001$
Inter-rater agreement, PACs subgroup[b]	0.803, $P < 0.001$	**0.950**, $P < 0.001$	NA
Cramer's *V*, PVCs subgroup	0.918, $P < 0.001$	**0.990**, $P < 0.001$	0.903, $P < 0.001$
Inter-rater agreement, PVCs subgroup[b]	0.918, $P < 0.001$	**0.990**, $P < 0.001$	NA
AUC, PACs subgroup (95% CI)	0.898 (0.849–0.946)	**0.971** (0.948–0.994)	0.921 (0.881–0.962)
AUC, PVCs subgroup (95% CI)	0.961 (0.935–0.987)	**0.996** (0.988–1.00)	0.954 (0.926–0.982)
PACs/PVCs in false positive cases, median beats/min (IQR)	18.8 (11.6, 22.6)	**64.3** (41.2, 87.4)	13.2 (10, 41.2)

AF, atrial fibrillation; SR, sinus rhythm; PVC, premature ventricular contraction; PAC, premature atrial contraction; IQR, interquartile range. Both wearable-recorded ECGs were interpreted manually by diagnosis-blinded cardiologists. The PPG-based AF detector operated automatically.
[a]Calculated for the overall control group of SR with PACs and PVCs.
[b]Measured as Cohen's kappa.
The highest values are in bold.

(7/128, 5.5%) compared to six-lead ECG (2/127, 1.6%) ($P = 0.02$ and $P = 0.08$, respectively).

The higher number of premature beats per minute was the main factor associated with false positive cases in comparison to true negative cases for each diagnostic method, namely the single-lead ECG (18.80 vs. 5.40 beats/min, $P < 0.01$), the six-lead ECG (64.3 vs. 5.8 beats/min, $P = 0.018$) and the PPG-based detector (13.20 vs. 5.60 beats/min, $P = 0.05$) (Figure 4). Of note, six-lead ECG was the most robust tool as it required 3.4 times more premature beats to result in a false positive outcome compared to single-lead ECG and 4.9 times more premature beats compared to the PPG-based detector. A single-lead ECG

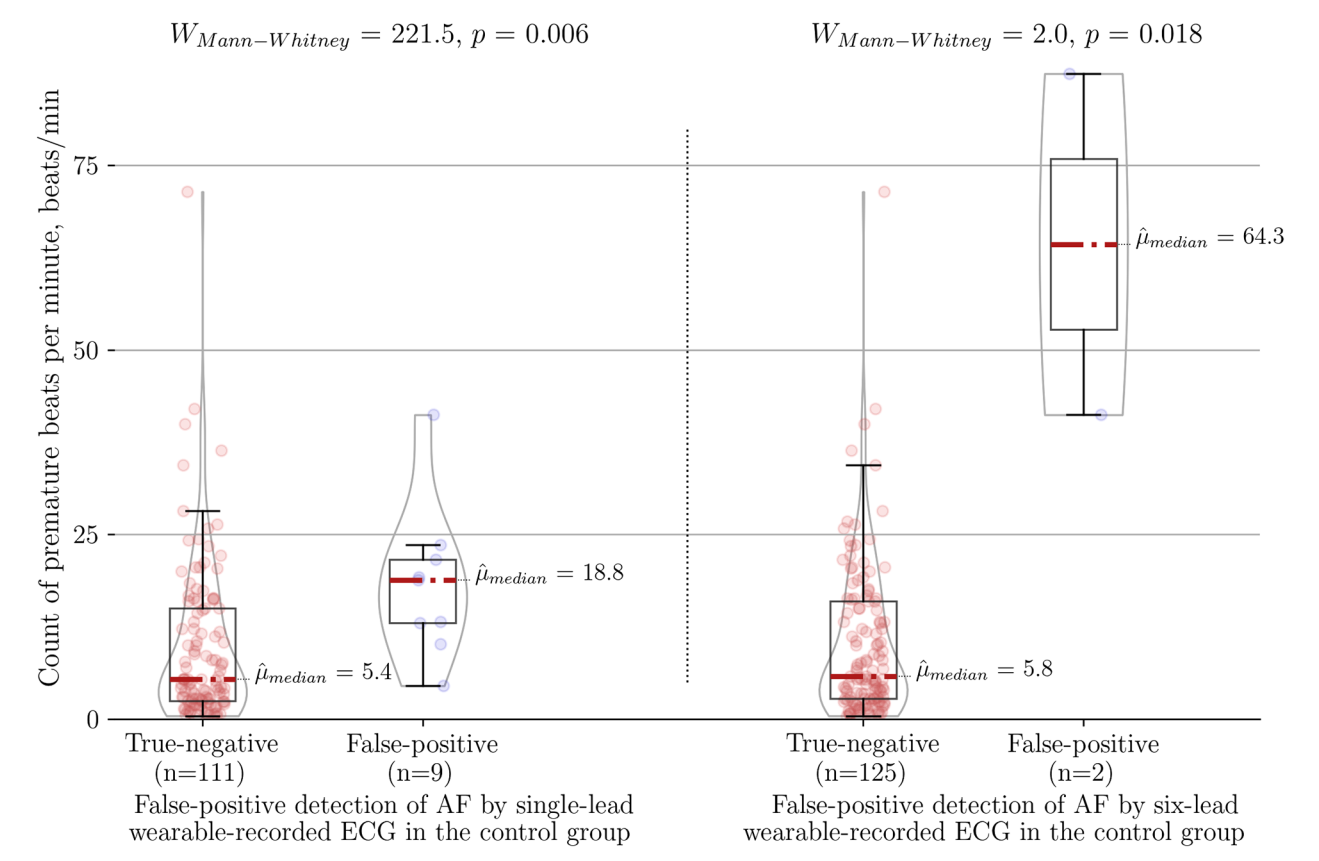


FIGURE 4
Association between count of premature beats per minute and type I error of the wearable-recorded single-lead ECG (left panel) vs. six-lead ECG (right panel) in the control group of SR with frequent premature beats. AF, atrial fibrillation.

(12/249) was more frequently labeled "Cannot be concluded" than six-lead ECG (3/249) ($P = 0.01$).

There was no trend of AF with higher rates of beats per minute in false negative cases. The median beats per minute in false negative cases of PPG-based detector (7/121) was 92 bpm (58, 116). Accordingly, in a single false negative case of six-lead ECG (1/119) the median was 76 bpm and in 5 cases of single-lead ECG the median was 92 bpm (92, 94).

Single-lead ECG, six-lead ECG, and PPG-based algorithm for AF detection when controlled by SR with frequent PACs

When compared to the control subgroup of PACs, the specificity of AF detection by six-lead ECG, single-lead ECG, and PPG-based detector dropped to 95% (95% CI: 83.1–99.4), 83.8% (95% CI: 68–93.8), and 90% (95% CI: 76.3–97.2), respectively (**Figure 5**). Interestingly, further analysis of single-lead ECGs (AUC 0.898; Cramer's V association 0.803, $P < 0.001$; inter-rater agreement Cohen's kappa 0.803, $P < 0.001$) showed lower diagnostic value not only compared to six-lead ECG (AUC 0.971; Cramer's V association 0.950, $P < 0.001$; inter-rater agreement Cohen's kappa 0.950, $P < 0.001$), but also lower than PPG-based detection (AUC 0.921; Cramer's V association 0.823, $P < 0.001$).

Single-lead ECG, six-lead ECG, and PPG-based algorithm for AF detection when controlled by SR with frequent PVCs

When compared to the control subgroup of PVCs, the specificity of AF detection by six-lead ECG, single-lead ECG, and PPG-based detector yielded a specificity of 100% (95% CI: 95.9–100), 96.4% (95% CI: 89.8–99.3), and 96.6% (95% CI: 90.4–99.3), respectively (**Figure 5**). In this case the diagnostic value of single-lead ECG (AUC 0.961; Cramer's V association 0.918, $P < 0.001$; inter-rater agreement Cohen's kappa 0.918, $P < 0.001$) was lower compared to six-lead ECG (AUC 0.996; Cramer's V association 0.990, $P < 0.001$; inter-rater agreement Cohen's kappa 0.990, $P < 0.001$), but non-inferior to PPG-based detector (AUC 0.954; Cramer's V association 0.903, $P < 0.001$).

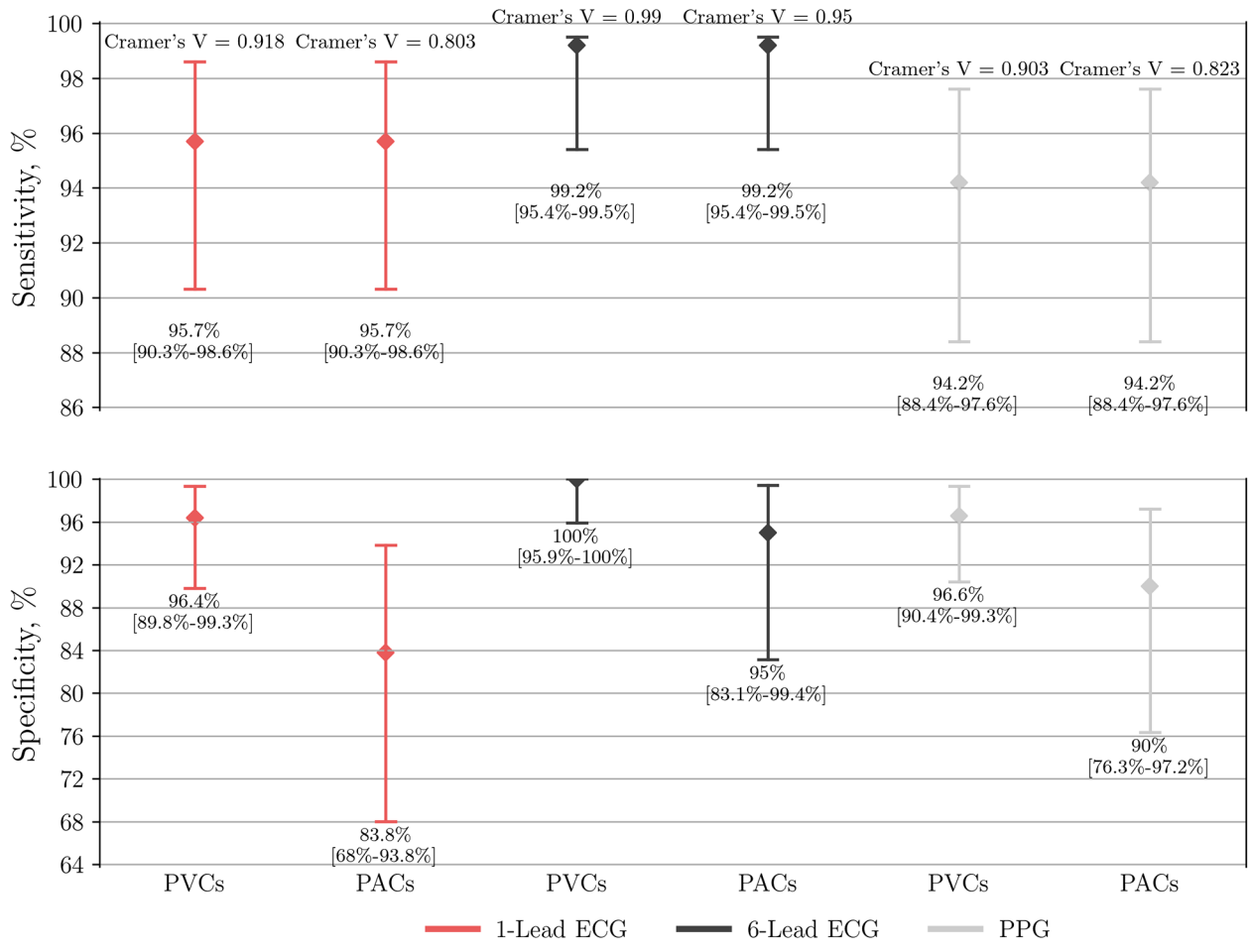


FIGURE 5
Performance of single-lead ECG ($n = 237$), six-lead ECG ($n = 246$) and the PPG-based algorithm ($n = 249$) to detect AF. The group of AF is compared to either a control subgroup of SR with frequent PVCs or PACs. PPG, photoplethysmography; ECG, electrocardiography; AF, atrial fibrillation; SR, sinus rhythm; PVC, premature ventricular contraction; PAC, premature atrial contraction.

Discussion

Major findings

This study investigates the diagnostic accuracy of the first wrist-worn device with a PPG-based AF detector and intermittent simultaneous six-lead standard-limb-like ECG for manual rhythm confirmation by a physician. The main focus of the current analysis is a head-to-head comparison of single-lead and six-lead ECGs as well as the automatic PPG-based AF detector of the same wearable device. Major findings are: (1) comparing to any control subgroup of SR with premature beats (PACs or PVCs) the diagnostic value of six-lead ECG was significantly superior to single-lead ECG and PPG-based AF detector both regarding type I and type II errors. (2) The sensitivity of single-lead ECG was slightly higher compared to PPG-based detector in both control subgroups. (3) Single-lead ECG demonstrated lower specificity not only vs. six-lead ECG but also vs. PPG-based automatic AF detection when controlled by a subgroup of frequent PACs. (4) The specificity of single-lead ECG and PPG-based detector were equivalent when controlled by a subgroup of frequent PVCs. (5) The number of premature beats per minute was the main factor associated with false positive cases compared to true negative cases for all diagnostic tools. (6) Six-lead ECG was the most robust tool as it required 3.4 times more premature beats to result in a false positive outcome compared to single-lead ECG and 4.9 times more premature beats compared to the PPG-based detector. (7) Based on previous findings, the widespread use of single-lead ECGs recorded by smartwatches significantly increases the risk of type I error in populations with frequent premature contractions.

It is important to emphasize the choice of the control group in this study, which included SR with frequent premature contractions. Stable SR was excluded from the control group, which is in contrast to the vast majority of other mHealth studies (15–18). This choice was based on the DoubleCheck-AF trial, in which it was demonstrated that stable SR as an isolated control subgroup does not sufficiently challenge the specificity of diagnostic tools (11).

Why six is smarter than one: impact of electrode contact in wearables and relation to the topographic anatomy of sinus node

The concept of an original Einthoven's triangle, generated by the contact of three electrodes and described by prof. W. Einthoven, explains why certain ECG leads of modern mHealth technologies maintain or decline the signal quality (19). In case of recording a single-lead ECG (i.e., lead-I-like in smartwatches), one insufficient contact on the left or right arm causes absence of ECG or artifacts which complicate the interpretation of ECG. In case of recording a six-lead ECG with three electrodes, one insufficient contact results in artifacts of two involved leads while leaving the third lead unaffected. This is the main practical reason why a wearable-recorded six-lead ECG outperformed the single-lead ECG to accurately differentiate AF and SR with frequent premature beats.

Another reason of the better performance of six-lead ECG vs. single-lead ECG relates to the location of the sinus node in the right atrium (RA). Chen X. et al. (20) performed the 3D electroanatomical mapping and investigated the earliest atrial activation (EAA), which represent the exit site of sinus node, in a population of patients with AF who were scheduled for superior vena cava (SVC) isolation. The EAA in a majority of patients with AF was located above the RA SVC junction 72/136 (52.9%), especially in a subgroup of persistent AF with a proportion of 26/43 (60.5%). Of those with EAA below RA SVC (64/136 (47.1%), the high position of EAA in RA was predominant and constituted 60/64 (93.8%). As a consequence, the high location of sinus node exit in individuals with AF or SR transfers to relevant wearable-recorded ECG features. The axis of *P* wave in SR is predominantly inferior and slightly less leftward. Accordingly, one of the main standard-limb-lead ECG features of SR is that the *P* wave amplitude in lead II comes out bigger than in lead I. Therefore, the usual *P* wave in lead-I-like ECG of smartwatches is not as apparent as in lead-II-like ECG. Suppose we put this small but relevant difference in *P* wave amplitude together with artifacts, which are quite common for all wearable-recorded ECGs. In that case, it partly explains why single-lead ECG was inferior to six-lead ECG to detect AF in the current study. In addition, even if a smartwatch is used to record a single-lead-II-like ECG (21, 22), it would arguably still be unable to outperform the six-lead ECG. Any single-lead ECG inevitably lacks the possibility to simultaneously check the reproducibility of suspected *P* waves throughout each of the six leads and exclude the mimicking artifacts.

These hypotheses are partly supported by another study of 220 patients (15), where manual interpretation of lead-II-like ECG by either Withings or Apple Watch (correct classification 54%) was numerically superior to the manual interpretation of lead-I-like ECG by Withings (28%, $P = 0.076$) or Apple Watch (33%, $P = 0.246$) for detection of atrial flutter. In addition, the six-lead ECG of Kardia 6l was the most accurate method for a correct diagnosis of atrial flutter in 63% of all cases ($P < 0.001$ compared to Withings and Apple Watch). Of note, no control group of SR patients with frequent PACs/PVCs was included.

ECG examples of false negative, false positive and inconclusive cases in single-lead vs. six-lead ECGs

When the ECG signal has no major artifacts (**Figure 2**) presumably even one beat of PQRST complexes in any single-lead ECG could be sufficient to differentiate AF from SR with premature beats. However, the decisive real-world difference in diagnostic accuracy lies in ECGs with lower signal quality. In fact, artifacts are common not only in wearable-recorded ECGs but also in conventional ambulatory ECG monitoring. El-Sherif et al. (9) reported artifacts in 4.8% (48/1,000) and

misinterpretations in 3.5% (35/1,000) of recordings in ambulatory ECG monitoring or telemetry. Of them, most artifacts were misclassified as pseudo-ventricular tachycardia or pseudo-AF/atrial flutter due to movement-generated repetitive waves, which hide real QRS or *P* waves. In addition, most misinterpretations were pseudo-ventricular tachycardia due to high rates of SVT/AF with bundle branch block.

In our study, the sensitivity of six-lead ECG was superior to single-lead ECG. The lower ECG signal quality was predominantly present in isolated leads, such as lead-I-like. Occasionally the ECG recordings presented with repetitive artifacts in the usual location of *P* waves, also, R-R intervals were rather regularly-irregular, mimicking SR with PACs (**Figure 6**) in single-lead ECGs. These factors typically led to false negative outcomes in patients with AF in single-lead ECG and true positive detection in six-lead ECG. Interestingly, there was no trend of AF with higher rates of beats per minute in false negative cases as the median of beats per minute did not reach 100 bpm.

The specificity of six-lead ECG was superior to single-lead ECG due to similar reasons. Firstly, likely poor contact on one of the electrodes led to a distorted ECG signal on two leads (one of which was usually lead-I-like ECG) of Einthoven's triangle. However, the remaining third lead stayed unaffected. Secondly, the amplitude of the *P* wave in lead-I-like appeared smaller compared to the *P* wave in lead-II-like ECG. Therefore, the six-lead ECG allowed to avoid false positive outcomes as opposed to single-lead ECG in both control subgroups of SR with frequent PACs (**Figure 7**) and PVCs (**Figure 8**). Few cases (2/127) with runs of PACs resulted in false positive outcome in both six-lead and single-lead ECGs, presumably due to the small amplitude of abnormal *P* waves and irregular R-R intervals during fast bursts of runs of PACs (**Figure 9**).

These ECG examples illustrate why of all three diagnostic tools the six-lead ECG was the most refractory to frequent premature contractions as well as the least likely to be labeled "Cannot be concluded". As a future prospect, six-lead ECG has an additional advantage of potentially reconstructing the axis of both QRS complex and *P* wave. Although this is out of the scope of current study and no precordial leads are displayed, it could help identify the approximate location of arrhythmias with rare clinical presentation, such as existing ECG algorithms for idiopathic ventricular tachycardia/PVC or atrial tachycardia (23, 24).

Results of other wearable devices with six-lead ECG for AF detection

To the best of our knowledge, there are two wearable devices capable of recording six-lead ECG with no wires:

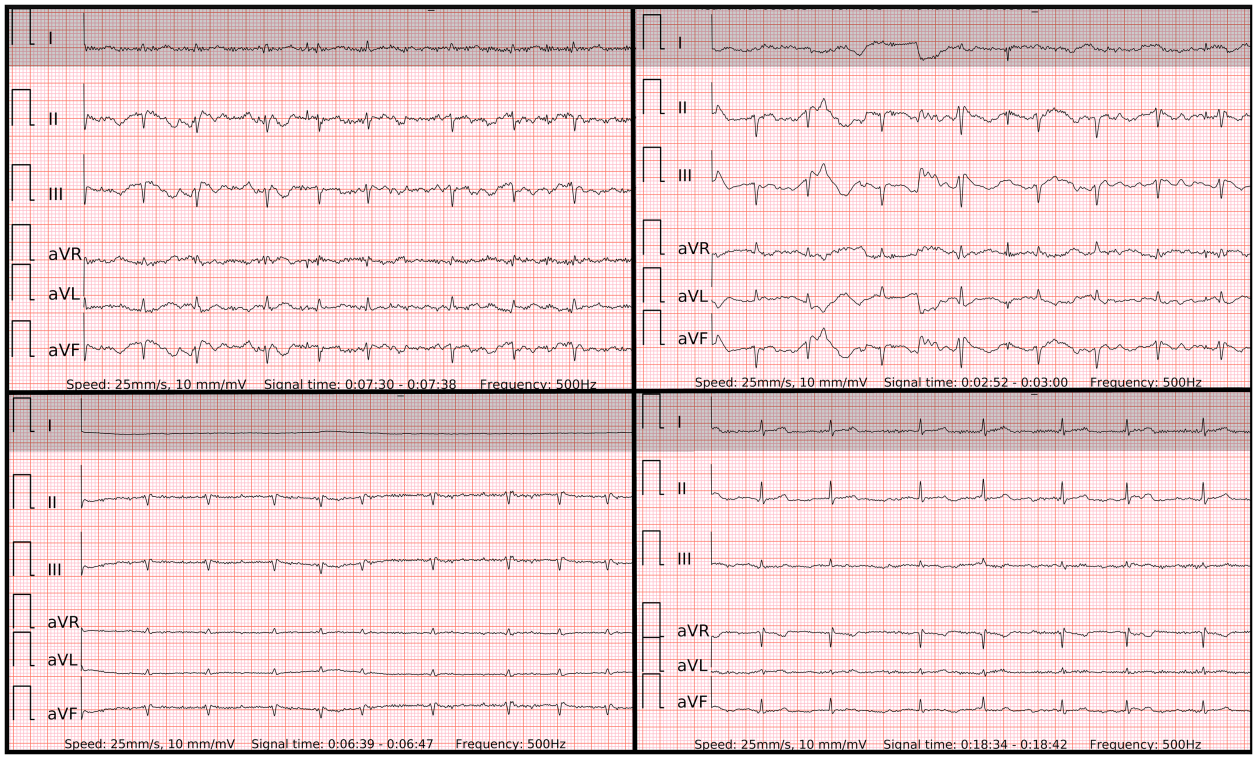


FIGURE 6
Problematic recordings of AF. False if interpreted by single lead-I-like ECGs (marked in gray) vs. correct if interpreted by six-lead ECGs. Top left panel: false negative due to artifacts mimicking P' of runs of PACs in single-lead ECG, true positive in six-lead ECG with no reproducible *P* waves; Top right panel: cannot be concluded due to low amplitudes in single-lead ECG, true positive in six-lead ECG; Lower left panel: cannot be concluded due to isoelectric signal in single-lead ECG, true positive in six-lead ECG with no reproducible *P* waves; Lower right panel: false negative due to artifacts mimicking P' of PACs and pseudo *regularly*-irregular R-R intervals in single-lead ECG, true positive in six-lead ECG with no reproducible *P* waves.

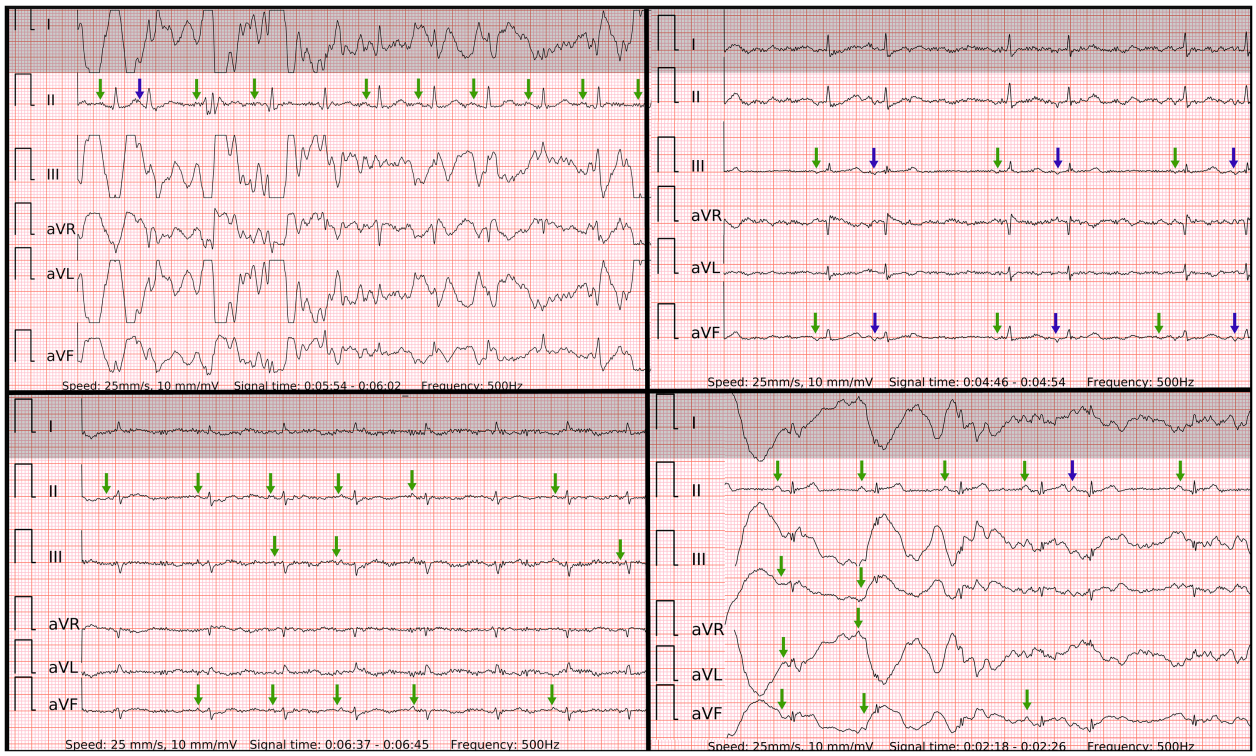


FIGURE 7
Problematic recordings of SR with PACs. False if interpreted by single lead-I-like ECGs (marked in gray) vs. correct if interpreted by six-lead ECGs. Top left panel: cannot be concluded due to artifacts in single-lead ECG, true negative in six-lead ECG with reproducible *P* waves of SR (green arrows) and *P'* of PAC on the T wave (blue arrow); Top right panel: false positive due to artifacts masking small *P* waves and mimicking f waves in single-lead ECG, true negative in six-lead ECG with reproducible *P* waves of SR (green arrows) and P' of PACs (blue arrows); Lower left panel: false positive due to artifacts masking small *P* waves and mimicking f waves in single-lead ECG, true negative in six-lead ECG with reproducible *P* waves of SR (green arrows); Lower right panel: cannot be concluded due to artifacts in single-lead ECG, true negative in six-lead ECG with reproducible *P* waves of SR (green arrows) and P' of PAC after the T wave (blue arrow);.

Kardia Mobile 6l (KM) and Istel HR 2000 (IS). Both of them essentially work as event recorders, which provide intermittent six-lead ECG for opportunistic screening of AF. In contrast to the wrist-worn device used in this study, they have no PPG-based AF detector for continuous screening of AF (12).

Krzowski et al. (16) analyzed 98 patients with a head-to-head comparison of KM and IS after manual interpretation by physicians. For diagnosing SR, KM yielded a sensitivity of 88.1% and a specificity of 89.7%. IS yielded 91.5% and 84.6% sensitivity and specificity, respectively. The sensitivity of KM in detecting AF was higher than IS (86.4% vs. 77.3%), but their specificity was comparable (97.4% vs. 98.7%). Notably, the control group in this study included patients with only SR and no premature contractions.

Scholten et al. (15) presented reproducible results in line with our findings. The manual interpretation of KM six-lead ECG was superior (sensitivity 98.9%, specificity 96.7%) to manual interpretations of single-lead ECG of Withings (sensitivity 95.4%, specificity 94.9%) and Apple Watch (sensitivity 96.2%, specificity 94.4%) for AF detection. Importantly, there was no dedicated control group of SR with premature beats, only patients with stable SR after electrical cardioversion were included in the control group.

These studies produce comparable results, which support the idea of six-lead ECG diagnostic superiority to single-lead ECG for AF detection. Nevertheless, the above-mentioned studies were not designed to include a dedicated control group of patients in SR with frequent premature contractions.

Limitations

Several limitations apply to the study. Firstly, it is a substudy of DoubleCheckAF, which originally was not intended for recording a single-lead ECG. In order to display a single-lead ECG, the six-lead wearable-recorded ECG was trimmed to a width of lead-I-like ECG. However, there is also an advantage to it as the accuracy of both diagnostic tools was not influenced by any potential difference in the complexity of recording since it was exactly the same episode of arrhythmia. Secondly, as outlined in **Figure 3** some patients were excluded due to issues with data logistics, insufficient signal quality and other reasons. This could cause additional costs or visits for patients in real-life conditions. Thirdly, since the participants in the presented study were White the performance of PPG detector could not be generalized for other skin pigmentations. Finally, all recordings were done in a hospital after a short explanation by a physician. As highlighted

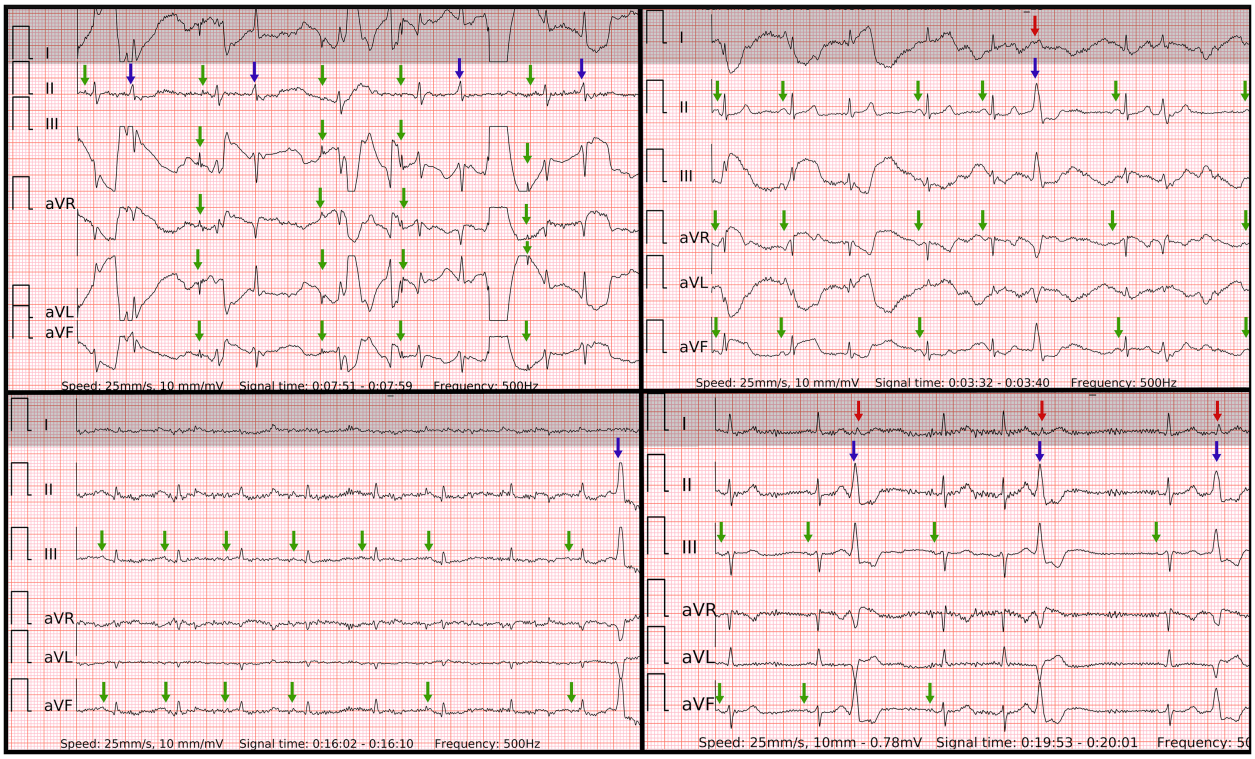


FIGURE 8
Problematic recordings of SR with PVCs. False if interpreted by single lead-I-like ECGs (marked in gray) vs. correct if interpreted by six-lead ECGs. Top left panel: cannot be concluded due to artifacts in single-lead ECG, true negative in six-lead ECG with reproducible *P* waves of SR with some artifacts (green arrows) and QRS of PVC or aberrancy (blue arrow); Top right panel: false positive due to artifacts masking small *P* waves and mimicking f waves as well as pseudo irregularly-irregular R-R intervals due to barely visible QRS of PVC (red arrow) in single-lead ECG, true negative in six-lead ECG with reproducible *P* waves of SR (green arrows) and big QRS of PVC with inferior axis (blue arrow); Lower left panel: cannot be concluded due to artifacts and small amplitudes in single-lead ECG, true negative in six-lead ECG with reproducible *P* waves of SR (green arrows) and QRS of PVC with inferior axis (blue arrow); Lower right panel: cannot be concluded due to artifacts and unclear irregularity type of R–R intervals due small QRS of PVCs (red arrows) in single-lead ECG, true negative in six-lead ECG with reproducible *P* waves of SR (green arrows), regularly-irregular R–R intervals and QRS of bigeminy/trigeminy PVCs with inferior axis (blue arrows).

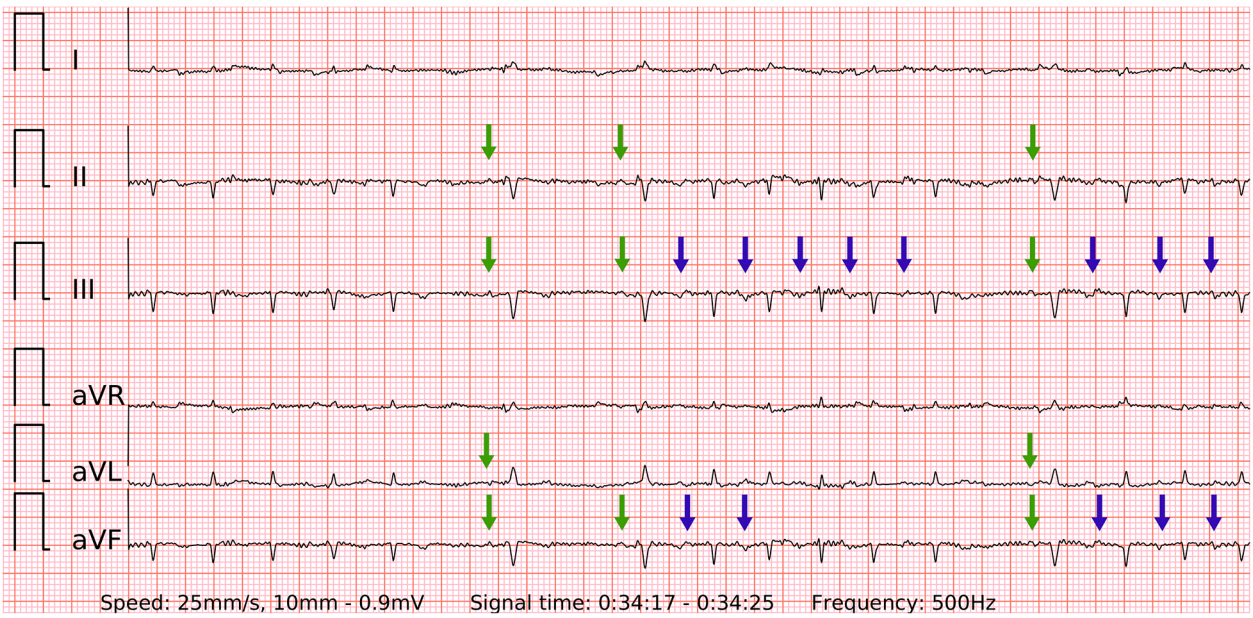


FIGURE 9
A problematic recording of SR with runs of PACs. A rare example of false positive in both single-lead and six-lead ECGs. Presumably due to the small amplitude of abnormal P' waves (blue arrows) and lightly irregular R-R intervals during fast bursts of runs of PACs. The *P* waves of SR are visible and reproducible (green arrows), but overwhelmed by the previous findings.

by the EHRA practical guide the implementation of wearables requires improved digital health literacy among patients and healthcare personnel (8). In an outpatient setting the users have to move up the learning curve, and hence the real-world accuracy may differ, particularly when starting to use a new device.

Conclusions

A six-lead ECG recorded by a wearable with no wires demonstrated the superior diagnostic value of AF detection compared to a single-lead ECG and automatic PPG-based AF detection when controlled by patients with any type of frequent premature contractions. The performance of a single-lead ECG was inferior to a PPG-based AF detector when controlled by patients with frequent PACs and non-inferior when controlled by patients with frequent PVCs. The risk of type I error due to the widespread use of single-lead ECGs of smartwatches in populations with frequent premature beats is significant.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Vilnius regional bioethics committee approved the study with registration No. 158200-18/7-1052-557. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JB, AA, VM were responsible for design and general execution of the study. JB, NT, RK, GS, ZA, AP, ED, DA, MP, JM, JS, NB, IB, MK, GZ, MG, EJ were involved in search or inclusion of patients and data collection or monitoring. AK, VJ, RJ analysed the recorded data. DS, MB were involved in technological description of the device, illustrations and reviewing. EJ was involved in statistical analysis. JB wrote the initial manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the European Regional Development Fund (01.2.2-LMT-K-718-03-0027) under grant agreement with the Research Council of Lithuania (LMTLT).

Conflict of interest

JB, DS, MB, VM, AA hold patent for the technology. JB received travel grants from Abbot, consults Teltonika Telemedic, received travel grants from Biosense Webster.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *Br Med J*. (2016) 354:i4482. doi: 10.1136/bmj.i4482

2. Elliott AD, Middeldorp ME, Van Gelder IC, Albert CM, Sanders P. Epidemiology and modifiable risk factors for atrial fibrillation. *Nat Rev Cardiol*. (2023) 20:404–17. doi: 10.1038/s41569-022-00820-8

3. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: an increasing epidemic and public health challenge. *Int J Stroke*. (2021) 16(2):217–21. doi: 10.1177/1747493019897870

4. Turakhia MP, Shafrin J, Bognar K, Trocio J, Abdulsattar Y, Wiederkehr D, et al. Estimated prevalence of undiagnosed atrial fibrillation in the United States. *PLoS One*. (2018) 13(4):e0195088. doi: 10.1371/journal.pone.0195088

5. Ringborg A, Nieuwlaat R, Lindgren P, Jönsson B, Fidan D, Maggioni AP, et al. Costs of atrial fibrillation in five European countries: results from the euro heart survey on atrial fibrillation. *EP Europace*. (2008) 10(4):403–11. doi: 10.1093/europace/eun048

6. Kahwati LC, Asher GN, Kadro ZO, Keen S, Ali R, Coker-Schwimmer E, et al. Screening for atrial fibrillation: updated evidence report and systematic review for the US preventive services task force. *JAMA*. (2022) 327(4):368–83. doi: 10.1001/jama.2021.21811

7. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, 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*. (2021) 42(5):373–498. doi: 10.1093/eurheartj/ehaa612

8. Svennberg E, Tjong F, Goette A, Akoum N, Di Biase L, Bordachar P, et al. How to use digital devices to detect and manage arrhythmias: an EHRA practical guide. *EP Eur*. (2022) 24(6):979–1005. doi: 10.1093/europace/euac038

9. El-Sherif N, Turitto G. Ambulatory electrocardiographic monitoring between artifacts and misinterpretation, management errors of commission and errors of omission. *Ann Noninvasive Electrocardiol*. (2015) 20(3):282–9. doi: 10.1111/anec.12222

10. Tooley JE, Perez MV. Role of digital health in detection and management of atrial fibrillation. *Heart*. (2022) 108(11):834–9. doi: 10.1136/heartjnl-2020-318262

11. Bacevicius J, Abramikas Z, Dvinelis E, Audzijoniene D, Petrylaite M, Marinskiene J, et al. High specificity wearable device with photoplethysmography and six-lead electrocardiography for atrial fibrillation detection challenged by frequent premature contractions: doubleCheck-AF. *Front Cardiovasc Med*. (2022) 6(9):869730. doi: 10.3389/fcvm.2022.869730

12. Sološenko A, Petrėnas A, Paliakaitė B, Sörnmo L, Marozas V. Detection of atrial fibrillation using a wrist-worn device. *Physiol Meas*. (2019) 40(2):025003. doi: 10.1088/1361-6579/ab029c

13. Petrėnas A, Marozas V, Sörnmo L. Low-complexity detection of atrial fibrillation in continuous long-term monitoring. *Comput Biol Med*. (2015) 65:184–91. doi: 10.1016/j.compbiomed.2015.01.019

14. Daukantas S, Marozas V, Drosatos G, Kaldoudi E, Lukosevicius A. General data format security extensions for biomedical signals. In: Eskola H, Väisänen O, Viik J, Hyttinen J, editors. *EMBEC & NBC 2017*. Singapore: Springer (2018). p. 731–4. (IFMBE Proceedings).

15. Scholten J, Jansen WPJ, Horsthuis T, Mahes AD, Winter MM, Zwinderman AH, et al. Six-lead device superior to single-lead smartwatch ECG in atrial fibrillation detection. *Am Heart J*. (2022) 253:53–8. doi: 10.1016/j.ahj.2022.06.010

16. Krzowski B, Skoczylas K, Osak G, Żurawska N, Peller M, Kołtowski Ł, et al. Kardia Mobile and ISTEL HR applicability in clinical practice: a comparison of kardia Mobile, ISTEL HR, and standard 12-lead electrocardiogram records in 98 consecutive patients of a tertiary cardiovascular care centre. *Eur Heart J Digit Health*. (2021) 2(3):467–76. doi: 10.1093/ehjdh/ztab040

17. Scholten J, Mahes A, De Groot JR, Winter MM, Zwinderman AH, Keijer JT, et al. A comparison of over-the-counter available smartwatches and devices for electrocardiogram based detection of atrial fibrillation. *Eur Heart J*. (2021) 42 (Supplement_1):ehab724.3047. doi: 10.1093/eurheartj/ehab724.3047

18. Mannhart D, Lischer M, Knecht S, du Fay de Lavallaz J, Strebel I, Serban T, et al. Clinical validation of 5 direct-to-consumer wearable smart devices to detect atrial fibrillation. *JACC Clin Electrophysiol*. (2023) 9(2):232–42. doi: 10.1016/j.jacep.2022.09.011

19. Einthoven W. Die galvanometrische registrirung des menschlichen elektrokardiogramms, zugleich eine beurtheilung der anwendung des capillar-elektrometers in der physiologie. *Pflügers Archiv*. (1903) 99(9):472–80. doi: 10.1007/BF01811855

20. Chen X, Lu Y, Liu Y, Chen Q, Chen H, Ju W, et al. Three-dimensional electroanatomic mapping characteristics of superior vena cava myocardial sleeve and sinoatrial node in patients with atrial fibrillation. *Front Cardiovasc Med*. (2022) 7(9):902828. doi: 10.3389/fcvm.2022.902828

21. Ploux S, Strik M, Caillol T, Ramirez FD, Abu-Alrub S, Marchand H, et al. Beyond the wrist: using a smartwatch electrocardiogram to detect electrocardiographic abnormalities. *Arch Cardiovasc Dis*. (2022) 115(1):29–36. doi: 10.1016/j.acvd.2021.11.003

22. Behzadi A, Sepehri Shamloo A, Mouratis K, Hindricks G, Arya A, Bollmann A. Feasibility and reliability of SmartWatch to obtain 3-lead electrocardiogram recordings. *Sensors*. (2020) 20(18):5074. doi: 10.3390/s20185074

23. Kistler PM, Chieng D, Tonchev IR, Sugumar H, Voskoboinik A, Schwartz LA, et al. P-Wave morphology in focal atrial tachycardia: an updated algorithm to predict site of origin. *JACC Clin Electrophysiol*. (2021) 7(12):1547–56. doi: 10.1016/j.jacep.2021.05.005

24. Al'Aref SJ, Ip JE, Markowitz SM, Liu CF, Thomas G, Frenkel D, et al. Differentiation of papillary muscle from fascicular and mitral annular ventricular arrhythmias in patients with and without structural heart disease. *Circ Arrhythm Electrophysiol*. (2015) 8(3):616–24. doi: 10.1161/CIRCEP.114.002619

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 22 June 2023
DOI 10.3389/fcvm.2023.1199630

Check for updates

OPEN ACCESS

EDITED BY
Antonio Sorgente,
EpiCURA, Belgium

REVIEWED BY
Linda Johnson,
Lund University, Sweden
Vassil B. Traykov
Tokuda Hospital, Bulgaria

*CORRESPONDENCE
Martin Manninger
martin.manninger-wuenscher@medunigraz.at

†These authors have contributed equally to this work

RECEIVED 03 April 2023
ACCEPTED 09 June 2023
PUBLISHED 22 June 2023

CITATION
Manninger M, Hermans ANL, Caracioni A-A, Rohrer U, Eberl A-S, Vernooy K, Zirlik A, Linz D and Scherr D (2023) Photoplethysmography-documented atrial fibrillation in the first week after catheter ablation is associated with lower success rates.
Front. Cardiovasc. Med. 10:1199630.
doi: 10.3389/fcvm.2023.1199630

COPYRIGHT
© 2023 Manninger, Hermans, Caracioni, Rohrer, Eberl, Vernooy, Zirlik, Linz and Scherr. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Photoplethysmography-documented atrial fibrillation in the first week after catheter ablation is associated with lower success rates

Martin Manninger[1,2]*, Astrid N. L. Hermans[2], Andrei-Antonio Caracioni[†1], Ursula Rohrer[1], Anna-Sophie Eberl[1], Kevin Vernooy[2], Andreas Zirlik[1], Dominik Linz[2†] and Daniel Scherr[1,2†]

[1]Division of Cardiology, Department of Internal Medicine, Medical University of Graz, Graz, Austria, [2]Department of Cardiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, Maastricht, Netherlands

Aims: To test the feasibility of postprocedural photoplethysmography (PPG) rhythm telemonitoring during the first week after atrial fibrillation (AF) ablation and its predictive value for later AF recurrence.
Methods: PPG rhythm telemonitoring during the first week after the ablation procedure was offered to a total of 382 consecutive patients undergoing AF ablation. Patients were instructed to perform 1 min PPG recordings by a mobile health application 3 times per day and in case of symptoms. Clinicians assessed the PPG tracings via a secured cloud and the information was remotely integrated into the therapeutic pathway via teleconsultation (TeleCheck-AF approach).
Results: 119 patients (31%) agreed to perform PPG rhythm telemonitoring after ablation. Patients included in the TeleCheck-AF approach were younger compared to those who declined participation (58 ± 10 vs. 62 ± 10 years, $p < 0.001$). Median follow up duration was 544 (53–883) days. 27% of patients had PPG tracings suggestive of AF in the week following the ablation. In 24% of patients, the integration of PPG rhythm telemonitoring resulted in a remote clinical intervention during teleconsultation. During follow-up of one year, 33% of patients had ECG-documented AF recurrences. PPG recordings suggestive of AF in the week after ablation were predictive of late recurrences ($p < 0.001$).
Conclusion: PPG rhythm telemonitoring during the first week after AF ablation often triggered clinical interventions. Due to its high availability, PPG-based follow-up actively involving patients after AF ablation may close a diagnostic and prognostic gap in the blanking period and increase active patient-involvement.

KEYWORDS
atrial fibrillation, atrial fibrillation ablation, blanking period, remote rhythm monitoring, mHealth, photoplethysmography

Introduction

Atrial fibrillation (AF) ablation is an established treatment option able to decrease AF burden, progression and AF-related complications (1, 2). Traditionally, a two- to three-month blanking period is used before assessing the long-term outcome of AF ablations accounting for potential pro-arrhythmic effects of the ablation procedure (3). However, multiple studies revealed a correlation between early recurrences during the blanking-

period and long-term outcomes (4, 5). Until now, implantable loop recorders, ECG mHealth devices or ECG Holter monitoring of variable duration have been used for rhythm monitoring during follow-up in clinical trials, and the feasibility of novel rhythm monitoring technologies, such as photoplethysmography (PPG) in this clinical setting remains unclear (6).

First clinical experience with the PPG technology in this patient population around AF ablation was collected in 40 AF centres within the TeleCheck-AF project and early adopters of this PPG technology saw a great potential for monitoring post-ablation patients (7–10). Additionally, a recent practical guide by the European Heart Rhythm Association (EHRA) on the use of mobile health technologies proposes, that particularly patient populations with already diagnosed AF without the need of ECG confirmation are best suited for using PPG technology for rhythm telemonitoring as an alternative for ECG technology (11). However, data on feasibility and prognostic implications of PPG rhythm telemonitoring directly after AF ablation are absent.

In this pragmatic single-centre observational study, we report on inclusion rates, adherence and motivation using an approach of PPG-based rhythm telemonitoring within the first week after AF ablation and assess its predictive value for later clinical ECG-documented AF recurrences.

Materials and methods

Study population

Consecutive patients undergoing AF ablation between June 1st 2020 and December 15th 2021 at the Medical University of Graz were offered the opportunity to perform PPG telemonitoring within the first week after being discharged from hospital.

This study was approved by the local ethics committee and all patients gave informed consent for inclusion in the ablation registry and, if applicable, telemonitoring within the TeleCheck-AF initiative.

Telemonitoring

Within 1 week before the ablation procedure, patients presented at the outpatient clinic for informed consent and preliminary exams including lab testing, transthoracic echocardiography, transoesophageal echocardiography and/or computed tomography scans. During this outpatient clinic appointment, patients were given the opportunity to perform telemonitoring within the TeleCheck-AF initiative during the first week after being discharged from the hospital.

Patients received an information sheet including a QR code for activation of the FibriCheck® app (Qompium, Hasselt, Belgium) on their smartphone and the study coordinator's telephone number. Patients then either self-installed the app or, upon request, were assisted by study coordinators. After installation of the app, patients were connected to the clinician's telemedicine portal (see schematic **Figure 1**). Patients were instructed to perform a 1-minute rhythm recording using their smartphone's camera and light source three times per day and in case of symptoms. Patients were included in the study if they installed the app within the first two days after the ablation and performed at least one measurement. Clinicians assessed the tracings via a secured cloud and contacted the patients if therapeutic steps were indicated.

Motivation and adherence

Motivation was defined as the proportion of days the patient performed at least the required number of measurements (3). Adherence was defined as proportion of performed measurements over the total number of required measurements over a duration of 6 complete days (first and last half days not counted, 3 measurements per day over a duration of 6 days = 18 measurements required, can be >100% if more measurements than necessary were performed).

Ablation procedure

Ablation procedures were performed on the day of hospital admission. Patients received oral anticoagulation for at least four weeks prior to the procedure. In case of insufficient anticoagulation, transoesophageal echocardiography was performed prior to the procedure to rule out left atrial thrombus. All procedures were performed under conscious (radiofrequency or cryo ablations) or deep sedation (pulsed field ablations) using fentanyl and propofol.

In case of a first procedure, pulmonary vein isolation was either performed with radiofrequency ablation (CARTO 7, ablation catheter: QDOT Micro or Thermocool SmartTouch, mapping catheter: Lasso or PentaRay, Biosense Webster), cryo-ablation (Arctic Front Advance and Achieve catheter, Medtronic) or pulsed field ablation (Farawave 31/35 mm, Boston Scientific). Pulmonary vein isolation was verified with entrance and exit-block pacing of all pulmonary veins.

In case of a repeat procedure, a 3D electroanatomic mapping system was used (CARTO 7, Biosense Webster). After transseptal puncture, a multielectrode mapping catheter (PentaRay, Biosense Webster) was used to map the left atrium. In case of AF, cardioversion was performed before mapping. If cardioversion was unsuccessful, the left atrium was mapped in AF. Gaps in the antral pulmonary vein isolation were closed using radiofrequency ablation (Thermocool SmartTouch, Biosense Webster).

Additional ablation of the cavotricuspid isthmus was performed in case of typical right atrial flutter documented either prior to or during the procedure. Further ablation was performed in case of persistent AF at the operator's discretion.

Anticoagulation was restarted on the day of the procedure for at least three months after the ablation and was continued thereafter according to the patients' risk profile.

In case of previously prescribed antiarrhythmic drug therapy, it was continued for three months after the procedure.

10.3389/fcvm.2023.1199630

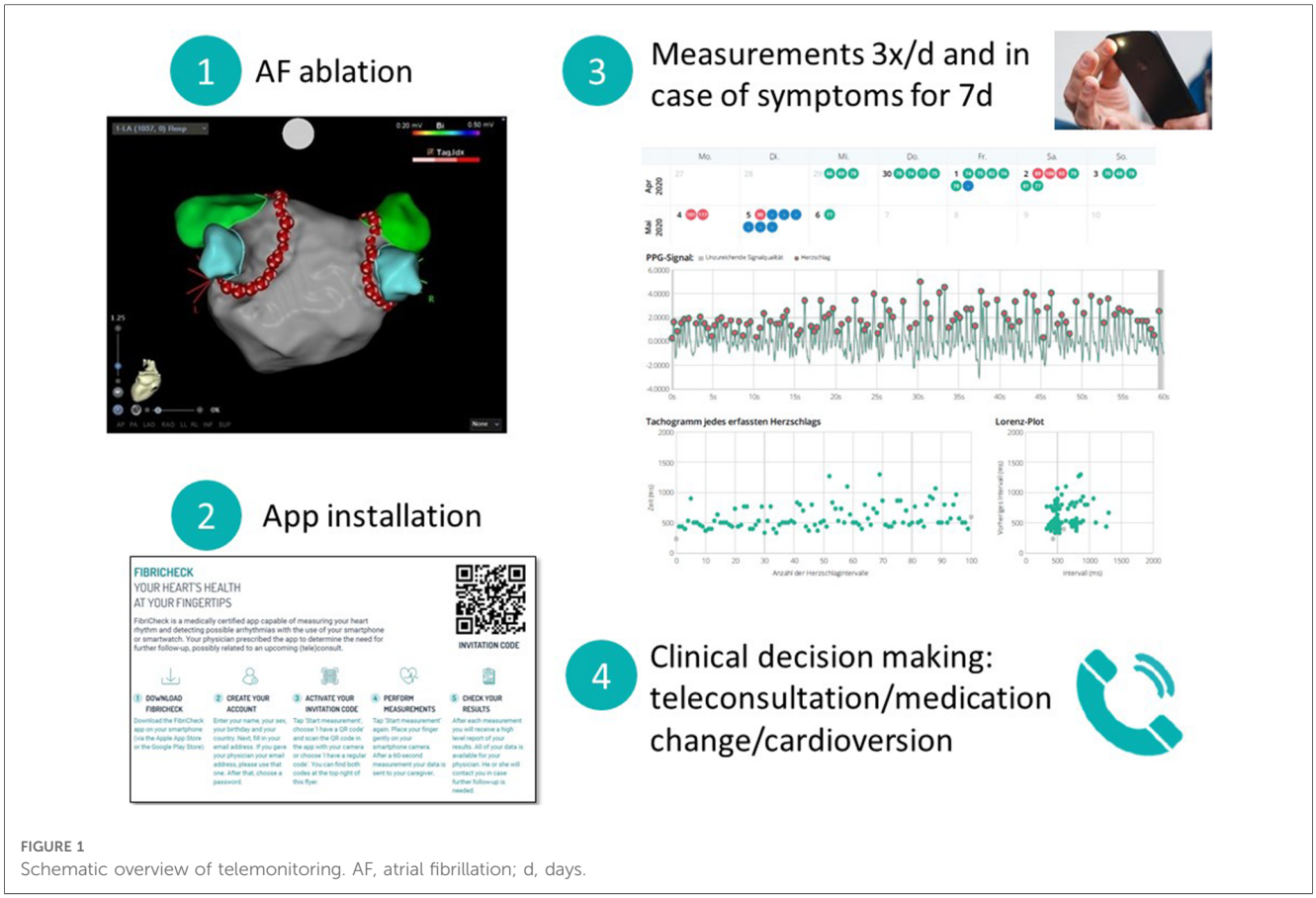


FIGURE 1
Schematic overview of telemonitoring. AF, atrial fibrillation; d, days.

Follow-up

Patients were followed up with 24 h Holter monitoring at our institution or their referring physicians 3, 6 and 12 months after the procedure. After the 12-month follow-up visit, patients were followed up with a yearly 24 h Holter ECG at their referring physician. Between regular visits, patients were encouraged to seek ECG or Holter monitoring in case of symptoms suggesting AF recurrences.

Data processing and statistical analyses

Continuous variables are presented as mean ± SD, median (range). Categorical variables are presented as percentages (%) and counts. Two-group comparisons of continuous variables were performed by Student's t tests if normally distributed or with Wilcoxon ranksum tests if the normality assumption was violated according to Shapiro-Wilk tests or visual inspection of normal probability plots. Categorical variables were compared by Chi-square tests or Fisher's exact tests. Time to first arrhythmia recurrence was calculated without a blanking period and plotted using the Kaplan-Meier product-limit method with comparisons performed by logrank statistics. Two-tailed p values < 0.05 were considered to indicate statistical significance.

Baseline characteristics were complete in all patients. Statistical analyses were performed using SPSS 23.0 (IBM, Armonk, NY).

Results

Out of 382 consecutive patients undergoing AF ablation between June 1st 2020 and December 31st 2021, 119 patients (31%) performed telemonitoring after ablation. Patients undergoing telemonitoring were younger compared to those who declined (58 ± 10years vs. 62 ± 10years, $p = 0.001$, **Table 1**). CHA_2DS_2-VASc scores, gender, types of AF, presence of atrial flutter and number of previous ablations were comparable between both groups.

TABLE 1 Baseline characteristics of patients with atrial fibrillation (AF) performing vs. patients declining photoplethysmography (PPG) rhythm telemonitoring.

	No PPG monitoring ($n = 263$)	PPG monitoring ($n = 119$)	P
Age (years)	62 ± 10	58 ± 10	**0.001**
Females	34%	33%	0.9
CHA_2DS_2-VASc	2 (0–9)	1 (0–6)	0.03
AF type			
–Paroxysmal	67%	62%	0.28
–Persistent	30%	37%	
–Longstanding persistent	6%	1%	
Typical atrial flutter (%)	30%	32%	0.64
Prior ablations	0 (0–3)	0 (0–3)	0.34

Bold values denote significance level $P < 0.01$.

Patient characteristics (telemonitoring group)

Thirty-four percent of included patients were female, median CHA_2DS_2-VASc-Score was 1 (0–6). 62% of patients had paroxysmal AF, 37% had persistent AF and 1% had longstanding persistent AF. One out of four patients (24%) had already undergone previous AF ablations. Most patients (89%) underwent radiofrequency ablations, 7% underwent cryo-ablation and 4% pulsed field ablation. Median follow up duration was 544 (53–883) days. One patient died 53 days after the ablation due to cerebral haemorrhage associated with a direct anticoagulant the patient already received for more than one year prior to the ablation.

Adherence to PPG rhythm telemonitoring during one week after AF ablation and resulting clinical interventions

Of those patients downloading and activating the PPG app, the median motivation was 33.3% and the median adherence was 77.8%. Motivation and adherence were higher in patients with PPG tracings of atrial tachyarrhythmias in comparison to patients without atrial tachyarrhythmias, 66.6% vs. 33.3% ($p < 0.05$) and 105.6 vs. 78% ($p < 0.05$), respectively.

32 patients (27%) recorded a median of 5 (1–58) tachycardia tracings in the week following the ablation (**Figure 2**). 30 patients had recordings suggestive of AF, 7 patients had recordings suggestive of AF as well as non-AF tachyarrhythmias and 2 patients recorded only non-AF tachyarrhythmia tracings suggestive of atrial tachycardia or atrial flutter. Complete Holter follow-up (at 3/6/12 months after ablation) was available in 89.9% of patients without documented arrhythmia recurrence.

Telemonitoring triggered clinical interventions in 24% of patients ($n = 29$, **Figure 3**): amiodarone was started in 8% ($n = 10$), class I antiarrhythmic drugs were up titrated in 7% ($n = 8$), electrical cardioversion was scheduled in 5% ($n = 6$), antiarrhythmic drugs were reduced due to symptomatic bradycardia in 3% of patients ($n = 4$).

Association between early PPG-documented and ECG-documented AF recurrence after AF ablation

During follow-up, 40 (34%) patients had ECG-documented AF recurrences after a median time of 146 (7–564) days. Twenty percent of the recurrences ($n = 8$) were documented on regular follow-up Holters, 80% ($n = 32$) were documented during patient-initiated ECG recordings. PPG recordings suggestive of AF in the week after ablation were predictive of late recurrences ($p < 0.001$, **Figure 4**).

The majority of patients neither had early PPGs suggestive of AF, nor late ECG documented AF recurrences ($n = 70$, 59%), 19% ($n = 23$) had both PPGs suggestive of AF and late ECG documented AF recurrences, 14% ($n = 17$) had just late ECG documented AF recurrences and only 8% ($n = 9$) had early PPG AF recurrences during the initial blanking period without later AF recurrences. Sensitivity and specificity of early PPG AF

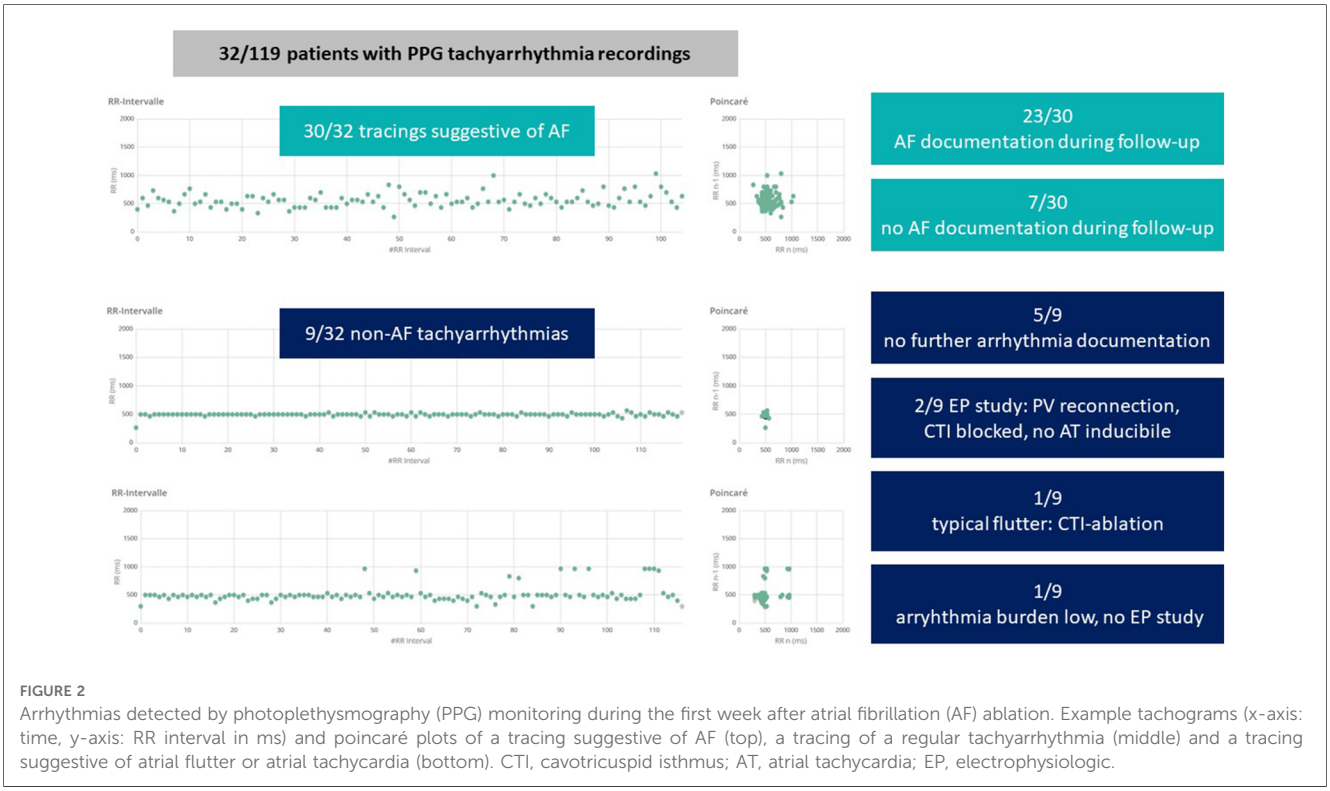


FIGURE 2
Arrhythmias detected by photoplethysmography (PPG) monitoring during the first week after atrial fibrillation (AF) ablation. Example tachograms (x-axis: time, y-axis: RR interval in ms) and poincaré plots of a tracing suggestive of AF (top), a tracing of a regular tachyarrhythmia (middle) and a tracing suggestive of atrial flutter or atrial tachycardia (bottom). CTI, cavotricuspid isthmus; AT, atrial tachycardia; EP, electrophysiologic.

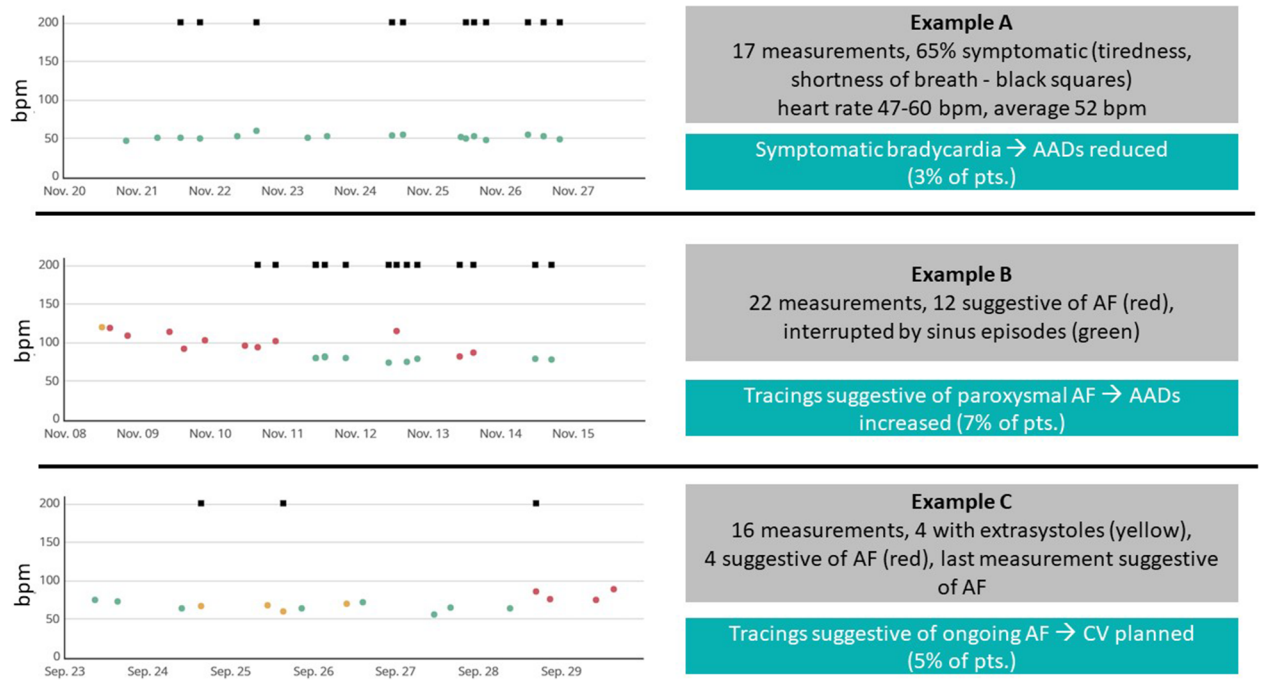


FIGURE 3
Sample tracings and clinical interventions. Examples of 7-day recordings during the PPG monitoring period. Each point marks one recording (green: regular rhythm, yellow: warning, red: suggestive of atrial fibrillation—AF), squares at the top of each recording mark, whether the patient was symptomatic during the recording. bpm, beats per minute; AAD, antiarrhythmic drug.

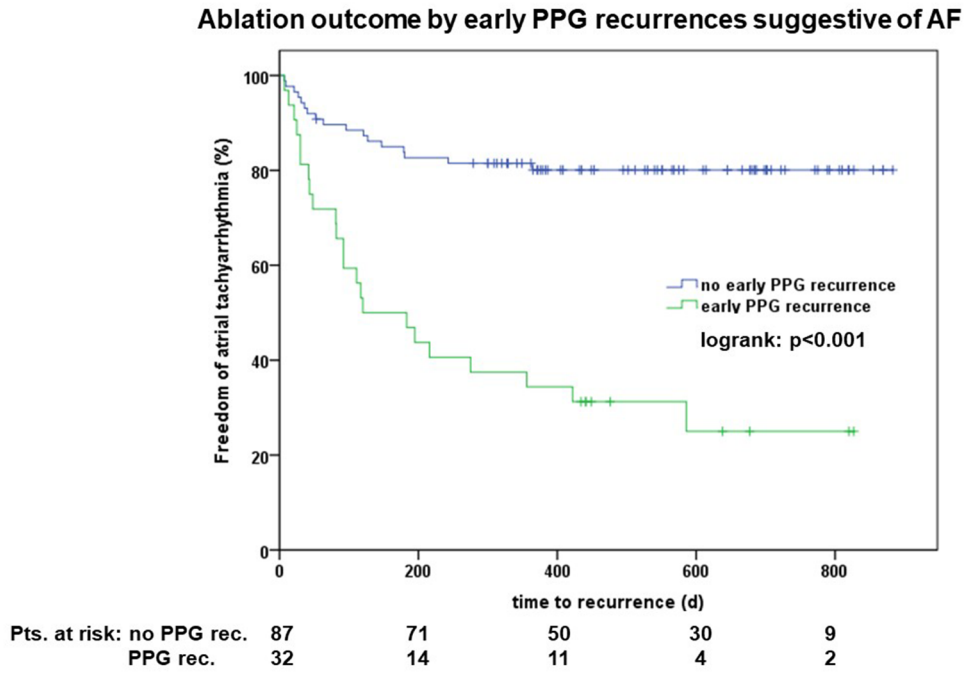


FIGURE 4
Outcome of patients with vs. without early photoplethysmography (PPG) documented arrhythmias suggestive of atrial fibrillation (AF).

recordings as predictors of late ECG documented AF recurrence were 65.4 and 83.0%, respectively. The positive predictive value was 89.7%, the negative predictive value was 71.9%.

Most of patients (5 out of 9 patients) with early non-AF tachyarrhythmias PPG recordings had no ECG documentations of AF or any other atrial tachyarrhythmia during follow-up

(Figure 3). One patient with ECG-documented symptomatic AF recurrence underwent a second AF ablation procedure showing reconnection of pulmonary veins as well as inducible typical atrial flutter and underwent re-do PVI and CTI ablation. Two patients with non-AF tachyarrhythmias underwent repeat procedures showing pulmonary vein reconnection but blocked CTI lines, no atrial tachyarrhythmias were inducible in these patients. One patient refused a repeat procedure because of a significantly reduced arrhythmia burden.

Most patients with ECG documented recurrences underwent redo-ablations ($n = 17$, 43%) or were scheduled for redo-ablations ($n = 8$, 20%). Rhythm control strategy was abandoned in 10% of patients; they were either switched to medical rate control therapy ($n = 3$) or underwent pace and ablate procedure ($n = 1$). Nine patients (22.5%) refused repeat ablations because their symptomatic AF burden was significantly lower and in only two patients (5%) episodes were only documented within the traditional blanking period of three months and required no further intervention.

Discussion

Holter ECGs are commonly used for follow-up of patients after AF ablation. The use of novel rhythm monitoring devices may overcome limitations of serial ECGs in this clinical scenario. However, concerns have been raised whether these devices are useful in the post-ablation setting, since they were not validated within this patient population which is prone to develop atrial tachyarrhythmias other than AF (11). Here, we demonstrate that intermittent PPG rhythm telemonitoring within the first week after AF ablation using a pragmatic onboarding approach has the potential to close a diagnostic gap during follow-up. Within our patient cohort, an approach of pragmatic PPG rhythm telemonitoring often led to clinical interventions. Most importantly, early PPG-documented AF recurrences within the first week after AF ablation were closely associated with the clinically established ECG-documented long-term rhythm outcomes.

Early arrhythmia recurrences are attributed to atrial and pericardial inflammatory changes induced by the ablation procedure. Traditionally, a 90-day blanking period is used until antiarrhythmic effects of the ablation-induced myocardial scarring take effect (3). This blanking period is commonly used in clinical studies investigating long-term effects of catheter ablation (12–15). However, there is an increasing number of studies highlighting the correlation between recurrences during the blanking period and recurrences after the blanking period while a meta-analysis suggests an optimal blanking period of 4 weeks (4, 5, 16). Importantly, follow-up strategies have been significantly different between the included studies. While multiple studies use implanted cardiac devices to monitor patients after ablation (12), conventional follow-up approaches including repetitive ECGs, Holter recordings and symptom-driven rhythm monitoring are most commonly used in patients outside of clinical trials. We could demonstrate that early PPG-documented recurrences during the first week after ablation were highly predictive of the freedom of atrial tachyarrhythmias after a median follow-up of approximately 1.5 years. This is in line with other trials, meta-analyses and physician-based surveys questioning the benign nature of early atrial tachyarrhythmias recurrences after ablation (17–19).

Novel rhythm monitoring devices might help switching follow-up strategies to a more patient-centred approach allowing low-threshold, long-duration monitoring enabling symptom-rhythm correlation. For example, a prior study has shown that 2 weeks of intermittent monitoring using single-lead ECG devices was superior in detecting AF recurrences and resulted in higher patient convenience than short continuous Holter monitoring (20). Another study demonstrated how single-lead ECG monitoring can be implemented into follow-up of these patients with AF detection rates comparable to standard clinical follow-up (21). PPG monitoring has not been assessed within this patient cohort, but the fact that it requires no specific hardware, but uses the patient's smartphone, is promising for application in everyday clinical practice outside of clinical trials (22). Due to limited ambulatory capacities during the COVID-19 pandemic, several European centres collected experience on using on-demand digital devices for follow-up of patients after ablation (7). Of note, the total inclusion rate of 31% in this single centre study was relatively low in our series of consecutive patients and younger patients were more willing to participate in the study. These two observations differ from the overall results of the complete TeleCheck-AF analysis (23). This may be attributed to the pragmatic onboarding approach or clinical scenario specific factors including general scepticism towards the technology, the timepoint of inclusion during the long preparatory outpatient visit prior to ablation, or limited digital literacy. Additionally, motivation and adherence to perform the recommended number of measurements was lower than in the total TeleCheck-AF cohort (23). However, the higher motivation and adherence in those patients who recorded arrhythmias might reflect the importance of the symptom-driven recordings in this specific clinical scenario post PVI. Personal assistance during the installation process and close monitoring of adherence including measurement reminders might enhance patient acceptance, adherence, and motivation.

One potential limitation of the PPG rhythm telemonitoring is the detection of non-AF tachyarrhythmias. We previously described a structured stepwise approach on how to deal with specific PPG tracings which highlights combining specific tachogram and poincaré plot patterns with the patient's history to choose which further diagnostics steps to take (24). In this study, the prevalence of non-AF tachyarrhythmias was low and most of the documented arrhythmias were only documented within the first week after ablation. There was only one single patient with detection of a previously non-documented clinically relevant arrhythmia (typical right atrial flutter). If, however, tracings suggestive of AF were recorded, these were highly predictive of future AF recurrences, which is also in line with a sub-study of the CIRCA-DOSE trial (18).

While AF ablation procedures have become more standardized, safe, and reproducible within the past years, days spent in hospital have decreased within most centres. Same-day discharge has shown to be feasible and safe with the use of standardized protocols (25). However, early paroxysmal and persistent recurrences as well as side effects of antiarrhythmic drugs might develop within the first days after hospital discharge. On-demand

remote monitoring using novel rhythm monitoring devices might facilitate patient-involvement as well as interaction between the patient and health care providers. Indeed, clinical interventions were performed in 1 of 4 patients based on PPG recordings. These interventions included medication changes as well as scheduling for early cardioversions. This type of monitoring might reduce the time to intervention, increase patient satisfaction and positively influence patient outcomes.

In summary, we believe that future applications of PPG monitoring could be (1) monitoring early after discharge, (2) patient-initiated monitoring in case of symptoms and (3) structured periodic monitoring.

Limitations

The current study describes results from a single centre and included only a limited number of patients in different stages of AF undergoing different ablation strategies. Therefore, results may not be generalizable to all AF patients and ablation centres. The study design relies on accurate recordkeeping and may include bias; therefore, these findings need to be confirmed in a larger randomized controlled trial.

Episodes recorded during PPG monitoring were not validated by simultaneous ECG. However, ECG validation might not be necessary in this patient population with diagnosed AF. This is underlined by the fact that unvalidated PPG tracings suggestive of AF were predictive of later ECG documented AF recurrences.

Despite extensive efforts to detect asymptomatic AF/AT recurrences, true recurrence rates may have been underestimated by a lack of continuous AF monitoring. Predictive value of PPG might have been overestimated by patients from this cohort seeking for ECG documentation more thoroughly.

Conclusion

A pragmatic approach of PPG rhythm telemonitoring during the first week after AF ablation often triggered clinical interventions in patients actively involved in monitoring. In this cohort, PPG recordings suggestive of AF in the week after ablation were predictive of late ECG-documented recurrences, while recurrence of non-AF PPG documented episodes was rare. Due to its high availability, a structured, PPG-based follow-up actively involving patients after AF ablation may close a diagnostic and prognostic gap and increase active patient-involvement.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics committee, Medical University of Graz. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MM: conceptualized the study, performed data analysis and wrote the manuscript. AH, AC, UR and AE: included patients and assisted in data analysis. KV, AZ, DL and DS: conceptualized the study and actively contributed to the manuscript. DL and DS: contributed equally as senior authors. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, 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): the task force for the diagnosis and management of atrial fibrillation of the European society of cardiology (ESC) developed with the special contribution of the European heart rhythm association (EHRA) of the ESC. *Eur Heart J.* (2021) 42:373–498. doi: 10.1093/eurheartj/ehaa612

2. Kuck KH, Lebedev DS, Mikhaylov EN, Romanov A, Gellér L, Kalējs O, et al. Catheter ablation or medical therapy to delay progression of atrial fibrillation: the randomized controlled atrial fibrillation progression trial (ATTEST). *EP Europace.* (2021) 23:362–369a. doi: 10.1093/europace/euaa298

3. Gottlieb LA, Dekker LRC, Coronel R. The blinding period following ablation therapy for atrial fibrillation. *JACC Clin Electrophysiol.* (2021) 7:416–30. doi: 10.1016/j.jacep.2021.01.011

4. Onishi N, Kaitani K, Nakagawa Y, Inoue K, Kobori A, Nakazawa Y, et al. The association between late-phase early recurrence within the blanking period after atrial fibrillation catheter ablation and long-term recurrence: insights from a large-scale multicenter study. *Int J Cardiol.* (2021) 341:39–45. doi: 10.1016/j.ijcard.2021.07.053

5. Saglietto A, Ballatore A, Xhakupi H, Rubat Baleuri F, Magnano M, Gaita F, et al. Evidence-based insights on ideal blanking period duration following atrial fibrillation catheter ablation. *EP Europace*. (2022) 24(12):1899–08. doi: 10.1093/europace/euac098

6. Elgendi M. On the analysis of fingertip photoplethysmogram signals. *Curr Cardiol Rev*. (2012) 8:14–25. doi: 10.2174/157340312801215782

7. Gawałko M, Duncker D, Manninger M, van der Velden RMJ, Hermans ANL, Verhaert DVM, et al. The European TeleCheck-AF project on remote app-based management of atrial fibrillation during the COVID-19 pandemic: centre and patient experiences. *EP Europace*. (2021) 23:1003–15. doi: 10.1093/europace/euab050

8. Linz D, Pluymaekers NAHA, Hendriks JM. TeleCheck-AF for COVID-19. *Eur Heart J*. (2020) 41:1954–5. doi: 10.1093/eurheartj/ehaa404

9. Pluymaekers NAHA, Hermans ANL, van der Velden RMJ, den Uijl DW, Vorstermans B, Buskes S, et al. On-demand app-based rate and rhythm monitoring to manage atrial fibrillation through teleconsultations during COVID-19. *Int J Cardiol Heart Vasc*. (2020) 28:100533. doi: 10.1016/j.ijcha.2020.100533

10. Pluymaekers NAHA, Hermans ANL, van der Velden RMJ, Gawałko M, den Uijl DW, Buskes S, et al. Implementation of an on-demand app-based heart rate and rhythm monitoring infrastructure for the management of atrial fibrillation through teleconsultation: TeleCheck-AF. *Europace*. (2021) 23:345–52. doi: 10.1093/europace/euaa201

11. Svennberg E, Tjong F, Goette A, Akoum N, Di Biase L, Bordachar P, et al. How to use digital devices to detect and manage arrhythmias: an EHRA practical guide. *EP Europace*. (2022) 24:979–1005. doi: 10.1093/europace/euac038

12. Andrade JG, Champagne J, Dubuc M, Deyell MW, Verma A, Macle L, et al. Cryoballoon or radiofrequency ablation for atrial fibrillation assessed by continuous monitoring: a randomized clinical trial. *Circulation*. (2019) 140:1779–88. doi: 10.1161/CIRCULATIONAHA.119.042622

13. Reddy VY, Dukkipati SR, Neuzil P, Natale A, Albenque JP, Kautzner J, et al. Randomized, controlled trial of the safety and effectiveness of a contact force-sensing irrigated catheter for ablation of paroxysmal atrial fibrillation: results of the TactiCath contact force ablation catheter study for atrial fibrillation (TOCCASTAR) study. *Circulation*. (2015) 132:907–15. doi: 10.1161/CIRCULATIONAHA.114.014092

14. Kuck KH, Brugada J, Fürnkranz A, Metzner A, Ouyang F, Chun KRJ, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med*. (2016) 374:2235–45. doi: 10.1056/NEJMoa1602014

15. Reddy VY, Dukkipati SR, Neuzil P, Anic A, Petru J, Funasako M, et al. Pulsed field ablation of paroxysmal atrial fibrillation. *JACC Clin Electrophysiol*. (2021) 7:614–27. doi: 10.1016/j.jacep.2021.02.014

16. Willems S, Khairy P, Andrade JG, Hoffmann BA, Levesque S, Verma A, et al. Redefining the blanking period after catheter ablation for paroxysmal atrial fibrillation: insights from the ADVICE (adenosine following pulmonary vein isolation to target dormant conduction elimination) trial. *Circ Arrhythm Electrophysiol*. (2016) 9:e003909. doi: 10.1161/CIRCEP.115.003909

17. Bordignon S, Barra S, Providencia R, de Asmundis C, Marijon E, Farkowski MM, et al. The blanking period after atrial fibrillation ablation: an European heart rhythm association survey on contemporary definition and management. *EP Europace*. (2022) 24(10):1684–90. doi: 10.1093/europace/euac131

18. Steinberg C, Champagne J, Deyell MW, Dubuc M, Leong-Sit P, Calkins H, et al. Prevalence and outcome of early recurrence of atrial tachyarrhythmias in the cryoballoon vs irrigated radiofrequency catheter ablation (CIRCA-DOSE) study. *Heart Rhythm*. (2021) 18:1463–70. doi: 10.1016/j.hrthm.2021.06.1172

19. Calkins H, Gache L, Frame D, Boo LM, Ghaly N, Schilling R, et al. Predictive value of atrial fibrillation during the postradiofrequency ablation blanking period. *Heart Rhythm*. (2021) 18:366–73. doi: 10.1016/j.hrthm.2020.11.020

20. Hermans ANL, Gawalko M, Pluymaekers NAHA, Dinh T, Weijs B, van Mourik MJW, et al. Long-term intermittent versus short continuous heart rhythm monitoring for the detection of atrial fibrillation recurrences after catheter ablation. *Int J Cardiol*. (2021) 329:105–12. doi: 10.1016/j.ijcard.2020.12.077

21. Lambert CT, Patel D, Bumgarner JM, Kanj M, Cantillon D, Saliba W, et al. Atrial fibrillation future clinic. Novel platform to integrate smart device electrocardiogram into clinical practice. *Cardiovasc Digit Health J*. (2021) 2:92–100. doi: 10.1016/j.cvdhj.2021.02.002

22. Hillmann HAK, Soltani S, Mueller-Leisse J, Hohmann S, Duncker D. Cardiac rhythm monitoring using wearables for clinical guidance before and after catheter ablation. *JCM*. (2022) 11:2428. doi: 10.3390/jcm11092428

23. Gawałko M, Hermans AN, van der Velden RM, Betz KVM, Verhaert D, Hillmann HA, et al. Patient motivation and adherence to an on-demand app-based heart rate and rhythm monitoring for atrial fibrillation management: data from the TeleCheck-AF project. *Eur J Cardiovasc Nurs*. (2022) 22(4):412–24. doi: 10.1093/eurjcn/zvac061

24. van der Velden RMJ, Verhaert DVM, Hermans ANL, Duncker D, Manninger M, Betz K, et al. The photoplethysmography dictionary: practical guidance on signal interpretation and clinical scenarios from TeleCheck-AF. *Eur Heart J Digit Health*. (2021) 2:363–73. doi: 10.1093/ehjdh/ztab050

25. Deyell MW, Leather RA, Macle L, Forman J, Khairy P, Zhang R, et al. Efficacy and safety of same-day discharge for atrial fibrillation ablation. *JACC Clin Electrophysiol*. (2020) 6:609–19. doi: 10.1016/j.jacep.2020.02.009

frontiers | Frontiers in Cardiovascular Medicine

TYPE Review
PUBLISHED 27 July 2023
DOI 10.3389/fcvm.2023.1212128

Check for updates

OPEN ACCESS

EDITED BY
Emma Svennberg,
Karolinska University Hospital, Sweden

REVIEWED BY
Henrike A. K. Hillmann,
Hannover Medical School, Germany
Linda Johnson,
Lund University, Sweden
Martin Manninger,
Medical University of Graz, Austria

*CORRESPONDENCE
Olivier Piot
o.piot@ccn.fr

RECEIVED 25 April 2023
ACCEPTED 13 July 2023
PUBLISHED 27 July 2023

CITATION
Piot O and Guidoux C (2023) Searching for atrial fibrillation post stroke: is it time for digital devices?
Front. Cardiovasc. Med. 10:1212128.
doi: 10.3389/fcvm.2023.1212128

COPYRIGHT
© 2023 Piot and Guidoux. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Searching for atrial fibrillation post stroke: is it time for digital devices?

Olivier Piot[1]* and Céline Guidoux[2]

[1]Department of Cardiac Arrhythmia, Centre Cardiologique du Nord, Saint-Denis, France, [2]Department of Neurology and Stroke Unit, Bichat Hospital, Assistance Publique–Hôpitaux de Paris, Paris, France

The detection of atrial fibrillation (AF) in patients with cryptogenic stroke (CS) is an essential part of management to limit the risk of recurrence. However, in practice, not all patients who need AF screening are screened, or are screened with significant delays. The disparities of access to examinations, their costs as well as the increasing workload require an evolution of practices both in terms of organization and the type of equipment used. The ubiquity and ease of use of digital devices, together with their evaluation in large population and their expected lower cost, make them attractive as potential alternatives to current equipment at all stages of patient management. However, reliability and accuracy of each digital device for the detection of paroxysmal AF in CS patients should be established before consideration for inclusion in clinical practice. The aim of this short analysis is therefore to review the current practical issues for AF detection in post stroke patients, the potential benefits and issues using digital devices in stroke patients and to position the different digital devices as alternative to standard equipment at each stage of stroke patient pathway. This may help to design future studies for the evaluation of these devices in this context. Under this condition, the time for digital devices to detect AF after stroke seems very close.

KEYWORDS

atrial fibrillation, stroke, screening, digital devices, connected tools

Introduction

One quarter of all ischemic strokes (IS) and transient ischemic attacks (TIAs) are of cardioembolic origin, with atrial fibrillation (AF) being the main cause. In 20 to 30% of cases, AF is known before the stroke (1). For the remaining patients, the search for asymptomatic paroxysmal atrial fibrillation should be performed as soon as the patient arrives at the stroke center. ECG at the time of admission and more prolonged ECG monitoring can detect new AF in approximately one quarter of patients with IS (2). Identification of AF allows optimization of secondary prevention treatment by instituting oral anticoagulant therapy, which can reduce the risk of stroke recurrence by up to two thirds (3). In current practice, a main issue is that the screening strategy is based not only on scientific recommandations but also on local resources.

Detection of atrial fibrillation begins on admission of a stroke patient with a 12-lead ECG, followed by repeated ECGs, scope monitoring or telemetry during hospital stay and a Holter ECG of at least 24 h (4). Long-term cardiac rhythm monitoring is recommended in patients with cryptogenic stroke (CS) and negative initial workup (4). The longer the duration of monitoring, the higher the percentage of AF diagnosis, around 30% at 3 years for patients with implantable loop recorder (ILR) (5). Many barriers complicate the current pathway of detecting AF in stroke

patients. Despite some issues, the advantages of digital devices make them a serious alternative to improve AF detection in this high-risk population.

Current pathway for stroke patients to detect AF

When a patient is admitted to a stroke unit, tests are performed to determine the cause(s) of the stroke. The patient has an ECG on arrival and is continuously monitored by a cardiac monitor during their stay in the intensive care unit (ICU). After the ICU, the patient is transferred to a conventional neurological inpatient unit and monitoring continues. At this stage, the screening strategy is agreed between neurologists and cardiologists to determine the appropriate tests for the patient. However, the fluidity of this assessment depends on local organization, and the issues of this screening are threefold: the availability of monitoring equipment, the selection of patients to be proposed for long-term monitoring, and the level of benefit expected for the patients. Usually, inpatient monitoring during conventional hospitalization can be telemetry or, in case telemetry is not available, ECG Holter (more or less prolonged). However, if there is a strong suspicion of AF and depending on the local organization, ILR may be discussed before discharge. Outside of this case, after hospitalization and depending on the data from the first monitoring, ambulatory long-term monitoring is discussed using ILRs as well as mobile cardiac outpatient telemetry (MCOT), external loop recorders (ELRs) placed after ILRs in recent guidelines (6) (**Figure 1**).

Current practical issues for AF detection in post stroke patients

Main barriers

Many practical barriers exist in screening for AF in patients post-stroke. Economic issues may limit telemetry monitoring in neurology departments. The availability of Holter devices and event recorders is not always high. Appointment times for 24-h Holter ECGs and even more for external loop recorders are often long. This results in many patients not receiving the necessary tests for AF detection. This is not a recent problem: the Ontario Stroke Registry for patients managed between 2003 and 2013 found a 30% rate of 24-h Holter ECGs performed and less than 1% for longer Holter duration (7) whereas this was not the case for cardiac ultrasound. AF detection is far from optimal today too, with a use of ECG monitoring in around 10% of post IS patients in a Danish nationwide cohort, not correlated with risk factors of AF raising the appropriateness of screening (8). The use of ILR in daily practice is limited to a subset of patients, estimated at 15% in a US cohort of nearly 13,000 patients with CS (9).

French experience

A recent national survey of vascular neurologists and heads of stroke units in France (10, 11) was conducted using structured online questionnaires. The objective was to evaluate the methodology of AF screening and to analyze (qualitatively and quantitatively) the availability and current use of AF screening in stroke units. Regarding the availability of cardiac rhythm screening, continuous cardiac monitoring during hospitalization of a stroke

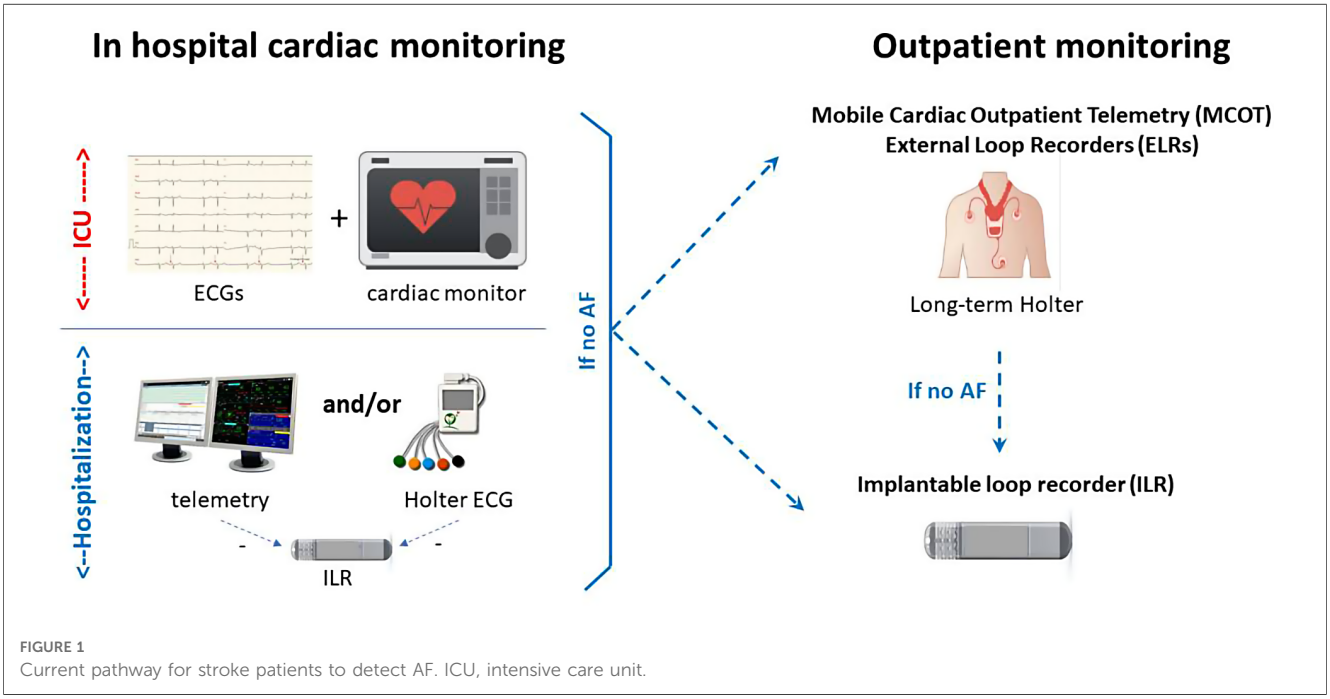


FIGURE 1
Current pathway for stroke patients to detect AF. ICU, intensive care unit.

patient is considered necessary by 90% of neurologists, but only 1/3 of them have continuous cardiac recording monitoring (outside the intensive care unit.). In-hospital AF screening also relies, to a variable extent among centers, on initial and then repeated ECG (29%), and 24-h Holter ECG (70%). All vascular neurologists in this study considered ambulatory cardiac monitoring to be of great interest or necessity. When the 24-h Holter recording is initially normal and AF is strongly suspected, additional prolonged monitoring is suggested. 75% of neurologists request noninvasive ambulatory monitoring for at least 7 days, and more than half request ILR. The accessibility of ambulatory monitoring modalities is ranked as follows: fairly easy for 24/48h-Holter ECG (85%) and ILR (68%); fairly difficult/impossible for 3–7 days Holter ECG (51%), 8–21 days Holter ECG (75%), or e-ECG tools (99%). It is noteworthy that the ambulatory 24-h Holter ECG is obtained within one week to one month after the stroke in 70% of cases. The main barriers to developing monitoring capabilities in the SUs are lack of manpower (80%), effective network with cardiologists (56%), familiarity with techniques (42%); and cost of technical equipment (44%). This survey shows the lack of a uniform strategy regarding the methods used and their access for AF screening. These results call for the harmonization of practices and the promotion of a plan to improve AF detection (patient selection, tools, and prioritization of examinations) after an IS in France.

Selection of patients for the screening strategy

Age, patient's cardiovascular risk factors, atheromatous disease are predictive factors for AF after stroke. The CHAD2DS2-VASC score includes these parameters (4, 12). Echocardiographic features and biomarkers—left atrial dilatation, BNP and pro-BNP (2)—and stroke due to proximal occlusion of an intracerebral artery (and therefore associated with significant neurological deficit on the NIHSS score) (13) are also predictive of AF after stroke. AF risk prediction scores have been evaluated to determine which patients with cryptogenic stroke should be offered priority for long-term monitoring. These composite scores are based on clinical, ECG, echocardiographic, and/or biological parameters to predict AF after IS but their lack of sensitivity and specificity make them difficult to use in clinical practice (14–17).

On the other hand, although the benefit of anticoagulation in secondary prevention is widely recognized (4), it is not certain that this benefit is present for patients with a very limited AF burden and it is therefore not certain that there is a need to detect very short and very rare episodes of AF (18–20). It is sometimes difficult to establish a link between stroke and AF episodes detected very long after its occurrence (21).

Potential benefits and issues using digital devices in stroke patients

Digital devices to monitor heart rhythm can be divided in two ways (**Table 1**). First according to the technology used to evaluate heart rhythm, devices are electrocardiogram (ECG)-based or non ECG based including photoplethysmography (PPG). Using a non ECG based device needs confirmation via ECG and clinician oversight to confirm AF diagnosis. Second according to the mode of heart rhythm recording, the devices are wearables such as smartwatch using PPG, patches, biotextiles, belts or non-wearables such as handheld ECG, smartwatch ECG, contactless video PPG (22). The use of digital devices in the context of stroke patients therefore seems interesting because of the availability and low cost of the equipment with remote monitoring capability as well as their ease of use in hospitals, rehabilitation centers or at home and their acceptability by patients and healthcare professionals (HCP) (23). Age is not a barrier to the use of these devices in large studies (20, 24, 25). In a recent survey, more than 85% of HCP agreed that reimbursement should be applied for the clinical use of digital devices, also in the post-stroke setting (26). However, it is important to emphasize that digital devices are not yet included in the recommendations on AF detection after stroke. The lack of evaluation and of a general framework of requirements as for ambulatory ECG systems (27) make general recommendations difficult (28, 29). It is indeed essential to know for each device its sensitivity and specificity in terms of detection and diagnostic algorithms (29, 30). For example, validation studies using Holter ECG as controls reveal that chest belt devices have superior performance (accuracy of >0.90) compared to PPG-based wrist-worn devices (highly variable accuracy range, 0.36–0.99) (22). However, given the limitations in terms of access to care, budgetary constraints, and the incomplete level of evidence for cardiac rhythm monitoring after stroke, it seems essential to evaluate the benefit of using these digital devices to address these concerns. Conventional monitoring combines admission 12-lead ECG, repeated ECGs, scope monitoring and/or telemetry in the neurovascular unit, then Holter ECG from 24 h to 7 days, and finally, depending on the estimated probability of AF, long-term monitoring, preferably with ILR (1, 6). At each stage of monitoring, digital devices could play an alternative or even substitute role (**Table 2**).

TABLE 1 Digital devices to monitor heart rhythm, according to their technology and the mode of heart rate recording. Using a non ECG-based device needs confirmation via ECG.

	Wearable	Non wearable
ECG-based	Patch, vest (biotextiles), belt	Handheld ECG, smartwatch-ECG
Non ECG-based (including PPG)	Smartwatch-PPG	Contactless video PPG

PPG, photoplethysmography.

Digital devices as alternative to standard equipment at each stage of stroke patient pathway

The 12-lead ECG on admission is mandatory to detect AF and sometimes conduction disorders or to suspect underlying heart

TABLE 2 Current pathway of stroke patient with equipment use for AF detection, and potential alternative by digital devices.

Stroke patient's pathway	Current monitoring	Digital devices as possible alternative
Admission in stroke unit	12-lead ECGs	1. ECGs acquired through wearable devices (ex: patch-type wireless 12-lead ECG) 2. Systematically digitized ECG [AF prediction in sinus rhythm (AI) and/or ECG marker of atrial cardiopathy]
Stroke unit and neurology department	Serial ECGs Scope monitoring Telemetry In patient 24-h Holter	1. PPG-based monitoring device—Wearable wireless devices (watch)HD video camera in room, cameras from smartphone/tablets 2. ECG-based monitoring devices (handheld devices or wearable wireless devices such as biotextiles, belt, watch)
Outpatient shot term	24-h/7 days Holter	1. Adhesive single-use patch: up to 14 days of continuous recording with a single or two leads ECG 2. ECG recordings through connected devices (handheld, watch)
Outpatient long term	MCOT External loop recorder	1. Sequential ECG recordings through wearable devices (watch) or continuous ECG recording (biotextile) 2. Continuous PPG-based with wearable devices or smartphone/tablet cameras
Outpatient very long term	Implanted loop recorder	Initial phase to better select patient for ICM implantation or alternative? 1. Sequential ECG recordings through wearable devices 2. Continuous PPG-based wearable devices or smartphone/tablet cameras

disease. AF detection rate is around 7.7% in stroke patients without known AF (1). Simplification of ECG acquisition and digital processing could provide potential benefits in clinical practice. New systems are currently developed such as a patch-type wireless 12-lead ECG (31) allowing a layperson to acquire a 12-lead ECG in a median time of 3 min. Currently, digital processing of ECGs seems mandatory to store them, transfer them for analysis by a cardiologist directly or after triage through a dedicated algorithm (32). Using artificial intelligence algorithms (33) or particular ECG measurement (34), recent publications suggest a potential value of ECG analysis in sinus rhythm to predict AF occurrence and/or stroke risk. A higher level of evidence is needed but these potential uses reinforce the need for routine ECG digitization in daily practice (**Figure 2**).

Classically, four different types of monitoring are used on stroke units and neurology wards to detect AF providing a 5.1% rate of AF detection: serial electrocardiography, continuous inpatient ECG monitoring, continuous inpatient cardiac telemetry and in-hospital Holter monitoring (1). Serial electrocardiography could be performed in an easier mode than a standard ECG machine using a single-lead connected device with a high sensibility and specificity (35). In the SPOT-AF study, patients were monitored using a smartphone-enabled handheld ECG (iECG) during routine nursing observations, and underwent 24-h Holter monitoring according to local practice. AF was detected in 25/294 (8.5%) by iECG, and 8/294 (2.8%) by 24-h Holter recordings (non-randomized comparison) (36). Other techniques could be evaluated by comparison to scope monitoring and telemetry such as continuous photoplethysmography (PPG)-based wearable devices providing a cheap and leadless solution easier to handle in daily practice. Using facial video cameras from smartphone or tablets for measurement of pulse rate and AF detection is

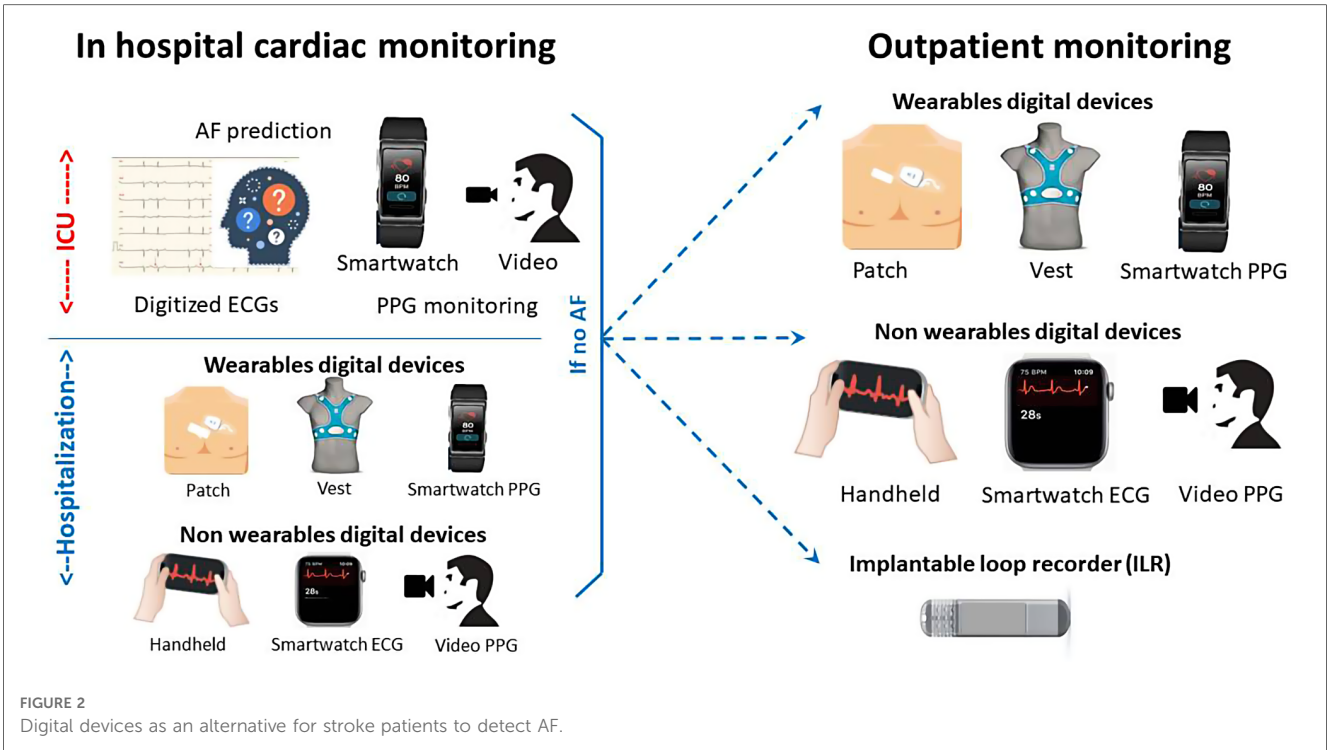


FIGURE 2
Digital devices as an alternative for stroke patients to detect AF.

currently under evaluation (37). However it is important to remember that detection of AF based on PPG currently requires confirmation of AF by ECG (29). Finally, continuous ECG monitoring is taking part of bedside AI-based predictive analytics monitoring (38) that could be useful for post stroke patient management in the future.

Ambulatory Holter monitoring from 24 h to 7 days provides a 10.7% rate of AF detection (1). Digital devices such as single ECG patch monitor providing up to 14 days of recording have been developed to replace conventional Holter ECG with leads. A randomized controlled trial of 116 patients following stroke showed superiority compared to a 24-h Holter monitor (detection of 1 participant in the Holter monitor group compared to 8 participants in the patch group) (39). This patch is currently recommended by the National Institute for Health and Care Excellence in the UK as an option for people with suspected cardiac arrhythmias who would benefit from ambulatory ECG monitoring for 24 h. Another approach currently under investigation is the continuous monitoring of PPG-based rhythm for weeks after stroke: in the Liverpool Huawei stroke study effectiveness, cost-effectiveness and patient and staff acceptability of using Huawei smart wearables to detect AF following IS during four weeks post discharge will be determined in 1,000 stroke patients (40). Signals will be analyzed through remote monitoring and patients with suspected AF will be referred to a cardiologist. In the multicenter CryptoAF study (41), another wearable device, a textile wearable holter monitoring, have been tested up to 90 days, detecting a high percentage of AF, although a significant number of patients did not complete the monitoring. A self-screening procedure using a patch-ECG could be also an interesting approach as recently demonstrated in individuals aged more than 65 years from the general population of Norway (42).

Ambulatory long-term monitoring using MCOT, ELRs and ILRs provides a 16.9% rate of AF detection (1). External monitoring is sometimes proposed before ILR. The randomized CANDLE-AF study will evaluate a 72-h single-patch monitor to standard strategy and to an event-recorder-type device in 600 IS patients without any history of AF (43). Single-patch monitor arm will repeat monitoring at 1, 3, 6, and 12 months, event-recorder-type arm will repeat monitoring twice daily for 12 months. Recent studies have shown the superiority of ILR on ELR in post-stroke AF detection (44). ILR is preferred upon MCOT and ELRs in recent guidelines (6). A predischarge nurse-led implantation of ICM has been the subject of specific patient pathway leading to short delay (45) but the follow-up and analysis of electrograms remain a significant workload despite the development of remote monitoring and the use of artificial intelligence algorithms (46). Moreover, the cost of ILR is quite high, although below the limit of acceptability for cost-effectiveness (47, 48). The constant loop recording of ECG of ILR for around three years explain its high yield of AF diagnosis compared to other techniques. Recently, in a sub-study of LOOP study in 590 patients aged more than 70 years followed for 3 years, different types of sequential screenings from 10-second ECG recording every day for 14 days to annual 30-day monitoring were applied. Even with the more intense screenings, more than 4 in 10 patients with AF and around one in six with underlying ≥24-h episodes will go undetected (49). Except particular case (50), it seems unlikely that any connected tools used in a sequential way could provide a high AF diagnostic yield such as ILRs. However, combination of continuous PPG-based monitoring with wearables devices such as belts, watch or ring-types and sequential ECG-based monitoring with the same wearable devices could be an interesting alternative to compare to ILR. This combination is currently being investigated in the Heartline randomised trial in people over 65 years-old using a smartwatch connected to a smartphone compared to using a smartphone app only (51).

The detection of AF in patients with CS is an essential part of management to limit the risk of recurrence. In practice, not all patients who need AF screening do so, or with significant delays. The disparities of access to examinations, their costs as well as the increasing workload require an evolution of practices both in terms of organization and the type of equipment used. The ubiquity and ease of use of digital devices, together with their evaluation in large population and their expected lower cost, make them attractive as potential alternatives to current equipment at all stages of patient management. However, reliability and accuracy of each device for the detection of paroxysmal AF in patients with CS must be established before inclusion in clinical practice is considered as well as the actual impact on workload. Under this condition, the time for digital devices to detect AF after stroke seems very close (52).

Author contributions

OP: conception, writing cardiology part CG writing neurology part both review and correction. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors thank ADREC (Association Dionysienne de Recherche et d'Enseignement Cardiologique) for its support.

Conflict of interest

OP: Research grant and honorary from Abbott, Medtronic, BMS-Pfizer. CG: Research grant and honorary from Abbott, consultant for Medtronic, BMS-Pfizer and Boston Scientific.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Sposato LA, Cipriano LE, Saposnik G, Ruíz Vargas E, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol.* (2015) 14:377–87. doi: 10.1016/S1474-4422(15)70027-X

2. Schnabel RB, Haeusler KG, Healey JS, Freedman B, Boriani G, Brachmann J, et al. A white paper of the AF-SCREEN international collaboration: searching for atrial fibrillation poststroke. *Circulation.* (2019) 140:1834–50. doi: 10.1161/CIRCULATIONAHA.119.040267

3. Ntaios G, Papavasileiou V, Diener HC, Makaritsis K, Michel P. Nonvitamin-K-antagonist oral anticoagulants in patients with atrial fibrillation and previous stroke or transient ischemic attack: a systematic review and meta-analysis of randomized controlled trials. *Stroke.* (2012) 43:3298–304. doi: 10.1161/STROKEAHA.112.673558

4. Hindricks G, Potpara T, Fagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation. *Eur Heart J.* (2021) 42:373–498. Eur Heart J. 2020;**42**:373–498. doi: 10.1093/eurheartj/ehaa612

5. Lau CP, Siu CW, Yiu KH, Lee KL, Chan YH, Tse HF. Subclinical atrial fibrillation and stroke: insights from continuous monitoring by implanted cardiac electronic devices. *Europace.* (2015) 17(Suppl 2):ii40–6. l 2:ii40–6. doi: 10.1093/europace/euv235

6. Rubiera M, Aires A, Antonenko K, Lémeret S, Nolte CH, Putaala J, et al. European stroke organisation (ESO) guideline on screening for subclinical atrial fibrillation after stroke or transient ischaemic attack of undetermined origin. *Eur Stroke J.* (2022) 7(3):VI. doi: 10.1177/23969873221099478

7. Edwards JD, Kapral MK, Fang J, Saposnik G, Gladstone DJ. Investigators of the registry of the Canadian stroke network. Underutilization of ambulatory ECG monitoring after stroke and transient ischemic attack: missed opportunities for atrial fibrillation detection. *Stroke.* (2016) 47:1982–9. doi: 10.1161/STROKEAHA.115.012195

8. Lyckhage LF, Hansen ML, Butt JH, Hilmar Gislain G, Gundlund A, Wienecke T. Time trends and patient selection in the use of continuous electrocardiography for detecting atrial fibrillation after stroke: a nationwide cohort study. *Eur J Neurology.* (2020) 11:2191–201. doi: 10.1111/ene.14418

9. Yaghi S, Ryan MP, Gunnarsson CL, Irish W, Rosemas SC, Neisen K, et al. Longitudinal outcomes in cryptogenic stroke patients with and without long-term cardiac monitoring for atrial fibrillation. *Heart Rhythm O2.* (2022) 3:223–30. doi: 10.1016/j.hroo.2022.02.006

10. Guidoux C, Sibon I, Alamowitch S, Godeneche G, Guillon B, Timsit S, et al. Société française de NeuroVasculaire (SFNV) stroke and AF group. Capacities of atrial fibrillation detection after stroke: a French nationwide survey. *Eur Heart J.* (2022) 42(Supplement_1):ehab724.2076. doi: 10.1093/eurheartj/ehab724.2076

11. Gaillard N, Sibon I, Alamovitch S, Godeneche G, Guillon B, Timsit S, et al. Capacities of atrial fibrillation detection after stroke: a French nationwide survey. *Eur Stroke J.* (2021) 6(suppl ESOC Abstracts):3–568. doi: 10.1177/23969873211034932

12. Fauchier L, Clementy N, Pelade C, Collignon C, Nicolle E, Lip GYH. Patients with ischemic stroke and incident atrial fibrillation. *Stroke.* (2015) 46(9):2432–7. doi: 10.1161/STROKEAHA.115.010270

13. Fontaine L, Sibon I, Raposo N, Albucher JF, Mazighi M, Rousseau V, et al. ASCOD Phenotyping of stroke with anterior large vessel occlusion treated by mechanical thrombectomy. *Stroke.* (2021) 52(12):e769–72. doi: 10.1161/STROKEAHA.121.035282

14. Kwong C, Ling AY, Crawford MH, Zhao SX, Shah NH. A clinical score for predicting atrial fibrillation in patients with cryptogenic stroke or transient ischemic attack. *Cardiology.* (2017) 138:133–40. doi: 10.1159/000476030

15. Uphaus T, Weber-Krüger M, Grond M, Toenges G, Jahn-Eimermacher A, Jauss M, et al. Development and validation of a score to detect paroxysmal atrial fibrillation after stroke. *Neurology.* (2019) 92:e115–24. doi: 10.1212/WNL.0000000000006727

16. Suissa L, Bertora D, Lachaud S, Mahagne MH. Score for the targeting of atrial fibrillation (STAF): a new approach to the detection of atrial fibrillation in the secondary prevention of ischemic stroke. *Stroke.* (2009) 40:2866–8. doi: 10.1161/STROKEAHA.109.552679

17. Kneihsl M, Bisping E, Scherr D, Mangge H, Fandler-Höfler S, Colonna I, et al. Predicting atrial fibrillation after cryptogenic stroke via a clinical risk score-a prospective observational study. *Eur J Neurol.* (2022) 29:149–57. doi: 10.1111/ene.15102

18. Tsvigoulis G, Triantafyllou S, Palaiodimou L, Mac Grory B, Deftereos S, Körhman R, et al. Prolonged cardiac monitoring and stroke recurrence: a meta-analysis. *Neurology.* (2022) 98:e1942–52. doi: 10.1212/WNL.0000000000200227

19. Sposato LA, Chaturvedi S, Hsieh CY, Morillo CA, Kamel H. Atrial fibrillation detected after stroke and transient ischemic attack: a novel clinical concept challenging current views. *Stroke.* (2022) 53:e94–103. doi: 10.1161/STROKEAHA.121.034777

20. Ko D, Dai Q, Flynn DB, Bosch NA, Helm RH, Monahan KM, et al. Meta-analysis of randomized clinical trials comparing the impact of implantable loop recorder versus usual care after ischemic stroke for detection of atrial fibrillation and stroke risk. *Am J Cardiol.* (2022) 162:100–4. doi: 10.1016/j.amjcard.2021.09.013

21. Chen LY, Chung MK, Allen LA, Ezekowitz M, Furie KL, McCabe P, et al. Atrial fibrillation burden: moving beyond atrial fibrillation as a binary entity: a scientific statement from the American heart association. *Circulation.* (2018) 137:e623–44. doi: 10.1161/CIR.0000000000000568

22. Svennberg E, Tjong F, Goette A, Akoum N, Di Biase L, Bordachar P, et al. How to use digital devices to detect and manage arrhythmias: an EHRA practical guide. *Europace.* (2022) 24:979–1005. doi: 10.1093/europace/euac038

23. Bonini N, Vitolo M, Imberti JF, Marco Proietti M, Romiti GF, Boriani G, et al. Mobile health technology in atrial fibrillation. *Expert Rev Med Devices.* (2022) 19 (4):327–40. doi: 10.1080/17434440.2022.207000

24. Fabritz L, Connolly DL, Czarnecki E, Dudek D, Guasch E, Haase D, et al. Smartphone and wearable detected atrial arrhythmias in older adults: results of a fully digital European case finding study. *Eur Heart J Digital Health.* (2022) 3:610–6. doi: 10.1093/ehjdh/ztac067.eCollection

25. Svennberg E, Friberg L, Frykman V, Al Khalili F, Engdahl J, Rosenqvist M. Strokestop study. *Lancet.* (2021) 398:1498–506. doi: 10.1016/S0140-6736(21)01637-8

26. Boriani G, Svennberg E, Guerra F, Linz D, Casado-Arroyo R, Malaczynska-Rajpold K, et al. Reimbursement practices for use of digital devices in atrial fibrillation and other arrhythmias: a European heart rhythm association survey. *Europace.* (2022) 24(11):1834–43. doi: 10.1093/europace/euac142

27. Medical Electrical Equipment—Part 2-47: Particular Requirements for The Basic Safety And Essential Performance Of Ambulatory Electrocardiographic Systems. ANSI/AAMI/IEC 60601-2-47:2012 (R2016).

28. Dilaveris PE, Antoniou CK, Caiani EG, Casado-Arroyo R, Climent AM, Cluitmans M, et al. ESC Working group on e-cardiology position paper: accuracy and reliability of electrocardiogram monitoring in the detection of atrial fibrillation in cryptogenic stroke patients. *Eur Heart J Digital Health.* (2022) 3:341–58. doi: . org/10.1093/ehjdh/ztac026

29. Varma N, Cygankiewicz I, Turakhia MP, Heidbuchel H, Hu YF, Chen LY, et al. 2021 ISHNE/HRS/EHRA/APHRS expert collaborative statement on mHealth in arrhythmia management: digital medical tools for heart rhythm professionals: from the international society for holter and noninvasive electrocardiology/heart rhythm society/European heart rhythm association/Asia-pacific heart rhythm society. *Circ Arrhythm Electrophysiol.* (2021) 14:e009204. doi: 10.1161/CIRCEP.120.009204

30. Brandes A, Stavrakis S, Freedman B, Antoniou S, Boriani G, Camm AJ, et al. Consumer-led screening for atrial fibrillation: frontier review of the AF-SCREEN international collaboration. *Circulation.* (2022) 146:1461–74. doi: 10.1161/CIRCULATIONAHA.121.058911

31. Yoon S, Kim T, Kang E, Heo S, Chang H, Seo Y, et al. Feasibility of patch-type wireless 12-lead electrocardiogram in laypersons. *Sci Rep.* (2023) 13:4044. doi: 10.1038/s41598-023-31309-0

32. Hannun AY, Rajpurkar P, Haghpanahi M, Tison GH, Bourn C, Turakhia MP, et al. Cardiologist-level arrhythmia detection and classification in ambulatory electrocardiograms using a deep neural network. *Nat Med.* (2019) 25:65–9. doi: 10.1038/s41591-018-0268-3

33. Attia ZI, Noseworthy PA, Lopez-Jimenez F, Asirvatham SJ, Deshmukh AJ, Gersh BJ, et al. An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. *Lancet.* (2019) 394:861–7. doi: 10.1016/S0140-6736(19)31721-0

34. Kamel H, Soliman EZ, Heckbert SR, Kronmal RA, Longstreth WT Jr., Nazarian S, et al. P-wave morphology and the risk of incident ischemic stroke in the multi-ethnic study of atherosclerosis. *Stroke.* (2014) 45:2786–8. doi: 10.1161/STROKEAHA.114.006364

35. Campo D, Elie V, de Gallard T, Bartet P, Morichau-Beauchant T, Genain N, et al. Atrial fibrillation detection with an analog smartwatch: prospective clinical study and algorithm validation. *JMIR Form Res.* (2022) 6:e37280. doi: 10.2196/37280

36. Yan B, Tu H, Lam C, Swift C, Ho MS, Mok VCT, et al. Nurse led smartphone electrographic monitoring for 33. Atrial fibrillation after ischemic stroke: SPOT-AF. *J Stroke.* (2020) 22:387–95. doi: 10.5853/jos.2020.00689

37. Barde K, Tsouri G, Page A, Pham T, Lutz M, Hall B, et al. Measurements of pulse rate using facial video cameras from smart devices in patients diagnosed with atrial fibrillation. *J Electrocardiol.* (2023) 78:58–64. doi: 10.1016/j.jelectrocard.2023.01.006

38. Monfredi OJ, Moore CC, Sullivan BA, Keim-Malpass J, Fairchild KD, Loftus TJ, et al. Continuous ECG monitoring should be the heart of bedside AI-based predictive analytics monitoring for early detection of clinical deterioration. *J Electrocardiol.* (2023) 76:35–8. doi: 10.1016/j.jelectrocard.2022.10.011

39. Kaura A, Sztriha L, Chan FK, Aeron-Thomas J, Gall N, Piechowski-Jozwiak B, et al. Early prolonged ambulatory cardiac monitoring in stroke (EPACS): an open-label randomised controlled trial. *Eur J Med Res.* (2019) 24(1):25. doi: 10.1186/s40001-019-0383-8

40. Harrison SL, Buckley BJR, Zheng Y, Hill A, Hlaing T, Davies R, et al. Evaluation of huawei smart wearables for detection of atrial fibrillation in patients following ischemic stroke: the liverpool-huawei stroke study. *Am Heart J.* (2023) 257:103–10. doi: 10.1016/j.ahj.2022.12.004

41. Pagola J, Juega J, Francisco-Pascual J, Rodriguez M, Dorado C, Martinez R, et al. Intensive 90-day textile wearable holter monitoring: an alternative to detect paroxysmal atrial fibrillation in selected patients with cryptogenic stroke. *Heart Vessels*. (2023) 38:114–21. doi: 10.1007/s00380-022-02141-9

42. Sandberg LE, Halvorsen S, Berge T, Grimsmo J, Atar D, Fensli R, et al. Fully digital self-screening for atrial fibrillation with patch electrocardiogram. *Europace*. (2023) 25:1–11. doi: 10.1093/europace/euad075

43. Jung S, Lee HA, Kang IS, Shin SH, Chang Y, Woo Shin D, et al. Clinical implications of atrial fibrillation detection using wearable devices in patients with cryptogenic stroke (CANDLE-AF) trial: design and rationale. *Front Cardiovasc Med*. (2022) 9:837958. doi: 10.3389/fcvm.2022.837958

44. Buck BH, Hill MD, Quinn FR, Butcher KS, Menon BK, Gulamhusein S, et al. Effect of implantable vs prolonged external electrocardiographic monitoring on atrial fibrillation detection in patients with ischemic stroke: the PER DIEM randomized clinical trial. *JAMA*. (2021) 325:2160–8. doi: 10.1001/jama.2021.6128

45. Dulai R, Hunt J, Veasey RA, Biyanwila C, O'Neill B, Patel NJ. Immediate implantable loop recorder implantation for detecting atrial fibrillation in cryptogenic stroke. *Stroke Cerebrovasc Dis*. (2023) 32:106988. doi: 10.1016/j.jstrokecerebrovasdis.2023.106988

46. Quartieri F, Marina-Breysse M, Pollastrelli A, Paini I, Lizcano C, Lillo-Castellano JM, et al. Artificial intelligence augments detection accuracy of cardiac insertable cardiac monitors: results from a pilot prospective observational study. *Cardiovasc Digital Health J*. (2022) 3:201–11. doi: 10.1016/j.cvdhj.2022.07.071

47. Chew DS, Rennert-May E, Spackman E, Mark DB, Exner DV. Cost-effectiveness of extended electrocardiogram monitoring for atrial fibrillation after stroke: a systematic review. *Stroke*. (2020) 51:2244–8. doi: 10.1161/STROKEAHA.120.029340

48. Sawyer LM, Witte KK, Reynolds MR, Mittal S, Grimsey Jones FW, Rosemas SC, et al. Cost-effectiveness of an insertable cardiac monitor to detect atrial fibrillation in patients with cryptogenic stroke. *J Comp Eff Res*. (2021) 10:127–41. doi: 10.2217/cer-2020-0224

49. Diederichsen SZ, Haugan KJ, Kronborg C, Graff C, Højberg S, Køber L, et al. Comprehensive evaluation of rhythm monitoring strategies in screening for atrial fibrillation: insights from patients at risk monitored long term with an implantable loop recorder. *Circulation*. (2020) 141:1510–22. doi: 10.1161/CIRCULATIONAHA.119.044407

50. Wouters F, Gruwez H, Vranken J, Ernon L, Mesotten D, Vandervoort P, et al. Will smartphone applications replace the insertable cardiac monitor in the detection of atrial fibrillation? The first comparison in a case report of a cryptogenic stroke patient. *Front Cardiovasc Med*. (2022) 9:839853. doi: 10.3389/fcvm.2022.839853

51. Gibson CM, Steinhubl S, Lakkireddy D, Turakhia MP, Passman R, Jones WS, et al. Does early detection of atrial fibrillation reduce the risk of thromboembolic events? Rationale and design of the heartline study. *Am Heart J*. (2023) 259:30–41. doi: 10.1016/j.ahj.2023.01.004

52. Kalarus Z, Mairesse GH, Sokal A, Boriani G, Średniawa B, Casado-Arroyo R, et al. Searching for atrial fibrillation: looking harder, looking longer, and in increasingly sophisticated ways. An EHRA position paper. *Europace*. (2023) 25:185–98. doi: 10.1093/europace/euac144

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 16 November 2023
DOI 10.3389/fcvm.2023.1249709

Check for updates

OPEN ACCESS

EDITED BY
Daniel M. Johnson,
The Open University, United Kingdom

REVIEWED BY
Swapna Ravi,
Gundersen Health System, United States
Ahmed F. El-Yazbi,
Alexandria University, Egypt

*CORRESPONDENCE
Hyun Su Kim
✉ kim.hyunsu100@gmail.com
Chul Ho Oak
✉ oaks70@hanmail.net

†These authors have contributed equally to this work

RECEIVED 29 June 2023
ACCEPTED 01 November 2023
PUBLISHED 16 November 2023

CITATION
Im SI, Kim SJ, Bae SH, Kim BJ, Heo JH, Kwon Sk, Cho SP, Shim H, Park JH, Kim HS and Oak CH (2023) Real-time heart rate variability according to ambulatory glucose profile in patients with diabetes mellitus.
Front. Cardiovasc. Med. 10:1249709.
doi: 10.3389/fcvm.2023.1249709

COPYRIGHT
© 2023 Im, Kim, Bae, Kim, Heo, Kwon, Cho, Shim, Park, Kim and Oak. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Real-time heart rate variability according to ambulatory glucose profile in patients with diabetes mellitus

Sung Il Im[1†], Soo Jin Kim[1†], Su Hyun Bae[1], Bong Joon Kim[1], Jung Ho Heo[1], Su kyoung Kwon[2], Sung Pil Cho[3], Hun Shim[3], Jung Hwan Park[3], Hyun Su Kim[1*] and Chul Ho Oak[4*]

[1]Division of Cardiology, Department of Internal Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Republic of Korea, [2]Division of Endocrinology, Department of Internal Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Republic of Korea, [3]MEZOO, Won Ju, Republic of Korea, [4]Division of Pulmonology, Department of Internal Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Republic of Korea

Background: Autonomic neuropathy commonly occurs as a long-term complication of diabetes mellitus (DM) and can be diagnosed based on heart rate variability (HRV), calculated from electrocardiogram (ECG) recordings. There are limited data on HRV using real-time ECG and ambulatory glucose monitoring in patients with DM. The aim of this study was to investigate real-time HRV according to ambulatory glucose levels in patients with DM.
Methods: A total of 43 patients (66.3 ± 7.5 years) with DM underwent continuous real-time ECG monitoring (225.7 ± 107.3 h) for HRV and ambulatory glucose monitoring using a remote monitoring system. We compared the HRV according to the ambulatory glucose profile. Data were analyzed according to the target in glucose range (TIR).
Results: There were no significant differences in the baseline characteristics of the patients according to the TIR. During monitoring, we checked ECG and ambulatory glucose levels (a total of 15,090 times) simultaneously for all patients. Both time- and frequency-domain HRVs were lower when the patients had poorly controlled glucose levels (TIR < 70%) compared with well controlled glucose levels (TIR > 70%). In addition, heart and respiratory rates increased with real-time glucose levels ($P < 0.001$).
Conclusions: Poorly controlled glucose levels were independently associated with lower HRV in patients with DM. This was further substantiated by the independent continuous association between real-time measurements of hyperglycemia and lower HRV. These data strongly suggest that cardiac autonomic dysfunction is caused by elevated blood sugar levels.

KEYWORDS

heart rate variability, glucose level, real-time monitoring, electrocadiography, autonomic dysfunction

Introduction

Heart rate variability (HRV) is the fluctuation in the time interval between adjacent heartbeats (1). Cardiac autonomic function can be noninvasively assessed by calculating HRV, which reflects the interaction of the sympathetic and parasympathetic parts of the autonomic nervous system (ANS) on the sinus node. HRV indexes neurocardiac function

and is generated by heart-brain interactions and dynamic nonlinear ANS processes. HRV is an emergent property of the interdependent regulatory systems that operate at different timescales to help us adapt to environmental and psychological challenges. HRV reflects the regulation of autonomic balance, blood pressure (BP), gas exchange, and gut, heart, and vascular tone, which refers to the diameter of the blood vessels that regulates BP (2).

Type 2 diabetes mellitus (DM) is increasingly prevalent worldwide and is associated with an increase in obesity and metabolic syndrome (3). The number of people with DM is predicted to double within the next three decades (4). Besides macrovascular and microvascular complications, the leading causes of death in DM are cardiovascular complications. Cardiovascular mortality is associated with cardiac autonomic neuropathy, which is frequently associated with DM (5).

Screening for cardiac autonomic neuropathy is recommended for the diagnosis of DM, particularly in patients with a history of poor glycemic control, macro and microvascular complications, and increased cardiovascular risk. Although standard cardiovascular reflex tests remain the gold standard for the assessment of cardiovascular autonomic neuropathy, one of the easiest and most reliable ways to assess cardiac autonomic neuropathy is by measuring HRV. HRV is the variation between two consecutive beats; the higher the variation, the higher the parasympathetic activity (6). A high HRV reflects the fact that an individual can constantly adapt to microenvironmental changes. Therefore, low HRV is a marker of cardiovascular risk (7). Conveniently, the measurement of HRV is non-intrusive and pain-free (1). Although the evaluation of HRV in DM has been assessed in several studies, conflicting results have been reported (2, 3, 6). Moreover, there is no consensus on the decreased levels of HRV parameters in patients with DM. Furthermore, despite the link between HRV and DM severity (8), there are limited data on the association between HRV parameters and glucose levels using real-time electrocardiogram (ECG) and ambulatory glucose monitoring in patients with DM. Therefore, we aimed to simultaneously check HRV and glucose levels in patients with DM to identify the most explanatory variables for autonomic dysfunction according to the glucose level.

Methods and methods

Participants

We recruited 83 patients (mean age, 65.5 ± 6.2 years) with DM from endocrinology out-patient clinic during their usual follow-up. The participants were recruited between October 2021 and December 2021. All patients were screened for medication use and medical conditions.

The inclusion criteria were age > 18 years, type 2 DM, and treatment with oral antidiabetic agents. The main exclusion criteria were pregnancy, neurological disease, heart failure, chronic liver or renal failure (known chronic liver disease or stage 3 advanced chronic kidney disease), uncontrolled DM, thyroid disorder, or treatment that could influence HRV parameters.

In our study, normal candidates (40 patients) without DM were included as controls. Five patients who were lost to follow-up or had incomplete monitoring were excluded from the study. Before HRV measurements, patients answered a questionnaire on personal information and lifestyle habits (e.g., smoking, alcohol consumption, coffee drinking, and exercise).

Finally, total 38 patients (16 men and 22 women; mean age: 66.3 ± 7.5 years) who completed the HRV measurements and glucose monitoring were included in the analysis.

Ethical statement

The study protocol was approved and the requirement for informed consent of individual patients was approved by the Ethics Committee of Kosin University Gospel Hospital (IRB No. 2022-06-016). Written informed consent was obtained from all patients. This study was conducted according to the principles of the latest version (2013) of Declaration of Helsinki.

Data collection

After ECG and chest radiography, the cardiovascular status of each patient was evaluated using echocardiography and blood laboratory data from the initial visit, as determined by the attending physicians. From the database, the following information were collected: (1) patient data, including sex, age, height, and weight; (2) cardiovascular risk factors, including hypertension (use of antihypertensive agents, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥ 90 mmHg on admission) and DM (use of oral hypoglycemic agents or insulin, or glycosylated hemoglobin ≥6.5%); (3) cardiovascular disease status, including structural heart disease, congestive heart failure, or a history of a disabling cerebral infarction or transient ischemic attack; and (4) use of medication.

ECG monitoring device

Hicardi® (MEZOO Co., Ltd., Wonju-si, Gangwon-do, Korea) is an 8 g, 42 × 30 × 7 mm (without disposable electrodes) wearable ECG monitoring patch device certified as a medical device by the Ministry of Food and Drug Safety of Korea (**Supplementary Figure S1**). This wearable device monitors and records single-lead ECGs, respiration, skin surface temperature, and activity. The ECG signal is recorded with a 250 Hz sampling frequency and 14-bit resolution.

The data from the wearable patch were transferred through Bluetooth Low Energy to a mobile gateway, which was implemented as a smartphone application. The mobile gateway transmitted the data to a cloud-based monitoring server.

After informed consent was obtained from the patient, a wearable patch was attached to the left sternal border. The ECG

signals and the above-mentioned data were continuously recorded, and all ECG signals were reviewed by a cardiologist via a cloud-based monitoring server.

HRV parameters

HRV analysis was performed in the time and frequency domains of the wearable ECG recordings according to international guidelines (9).

On average, 225.7 ± 107.3 h of ECG were recorded per patient, and the HRV analysis was performed by excerpting the previous five-minute segment from the time of glucose measurement.

To calculate the HRV parameters, RR intervals must be computed from the wearable ECG recordings. The following steps were performed to obtain the RR interval time series. First, R-peaks were detected using the geometric angle between two consecutive samples of the ECG signal (10). Detected R-peaks were then used to generate an RR interval time series. To remove the abnormal intervals caused by ectopic beats, arrhythmic events, missing data, and noise, intervals below 80% or above 120% of the average of the last six intervals were excluded. The time-domain parameters were calculated from the RR interval time series.

Second, the RR interval time series was resampled at 4 Hz using linear interpolation. The resulting series was detrended by eliminating linear trends. After detrending, the power spectral density for the RR interval time series was estimated using the Burg autoregressive model, where the order of the model was 33.

In the time domain, we analyzed the RR intervals, standard deviations of RR intervals, square root of the mean squared difference of successive RR intervals, and percentage of adjacent NN intervals differing by more than 50 ms (NN50).

In the frequency domain, we analyzed low frequency (LF, 0.04–0.15 Hz), an index of both sympathetic and parasympathetic activity, and high frequency (HF, 0.15–0.4 Hz), representing the most efferent vagal (parasympathetic) activity to the sinus node. Very low frequency (VLF; 0.003–0.04 Hz) partially reflects thermoregulatory mechanisms, fluctuations in the activity of the renin–angiotensin system, and the function of peripheral chemoreceptors. The LF/HF ratio, that is, sympathovagal balance, was also calculated.

Continuous glucose monitoring

Assessment of glucose status

For continuous glucose monitoring, we used FreeStyle Libre 14 day system®, a continuous glucose monitoring device with real-time alarm capability indicated for the management of DM. The flash glucose-sensing technology used was the FreeStyle LibreTM, which is a sensor-based flash glucose-monitoring system (Abbott Diabetes Care, Witney, UK). The sensor was worn on the back of the arm for up to 14 days, and glucose data were automatically stored every 15 min. Real-time glucose levels can be obtained as often as every minute by scanning the sensor with a reader. Data were transferred wirelessly by radio-frequency identification from the sensor to the reader's memory, which stored historical sensor data for 90 days. Data can be uploaded using the device software to generate summary glucose reports. The target in glucose range (TIR) was 70–180 mg/dl. We analyzed the data according to glucose control and TIR of <70% or >70%. For these individuals, fasting glucose levels and information about DM medication were used to determine glucose metabolism status. Glucose metabolism status was defined according to the 2006 World Health Organization criteria as normal glucose metabolism or type 2 diabetes (11).

Statistical analysis

All continuous variables are expressed as mean ± standard deviation (SD), depending on the distribution. For continuous data, statistical differences were evaluated using the Student's *t*-test or Mann–Whitney *U* test, depending on the data distribution. Categorical variables are presented as frequencies (percentages) and were analyzed using the χ^2 test. One-way ANOVA analysis of variance was used to compare the differences between groups according to TIR and DM. To determine whether any of the variables were independently related to HRV according to the glucose levels, a multivariate analysis of variables with a *P*-value <0.05 in the univariate analysis was performed using linear logistic regression analysis. All correlations were calculated using the Spearman's rank correlation test. All statistical analyses were conducted using the SPSS statistical software (version 19.0 (SPSS Inc., Chicago, IL, USA), and statistical significance was set at $P < 0.05$ (two-sided).

Results

A total of 38 patients (age, 66.3 ± 7.5 years) with DM underwent continuous real-time ECG monitoring (225.7 ± 107.3 h) for HRV and ambulatory glucose monitoring using a remote monitoring system. We compared the HRV according to the ambulatory glucose profile. Ambulatory glucose levels were checked every 15 min in all patients during real-time ECG monitoring.

During monitoring, we checked a total of 15,090 ECG data points for HRV and ambulatory glucose levels simultaneously for all patients. There are baseline characteristics and medication in **Tables 1**, **2**. We analyzed the data according to the TIR. There were no significant baseline differences in patient characteristics except for the mean glucose level according to the TIR (**Supplementary Table S1**). No significant difference in baseline medication, according to the TIR, was observed (**Supplementary Table S2**).

Both time- and frequency-domain HRVs were lower in patients with poorly controlled glucose levels (TIR < 70%) than in those with normally controlled glucose levels (TIR > 70%; **Table 3**).

In addition, heart and respiratory rates increased according to real-time glucose levels ($P < 0.001$) in all patients with DM (**Figure 1**).

TABLE 1 Baseline characteristics in patients with DM.

Total patients = 38	
Variable	
Mean glucose level (mg/dl)	175.4 ± 74.6
Age (years)	65.4 ± 6.6
Sex (%), male	20 (52.6)
DM (%)	38 (100)
HTN (%)	30 (78.9)
Hyperlipidemia (%)	30 (78.9)
CAD (%)	12 (31.6)
CVA (%)	8 (21.1)
CHF (%)	3 (7.9)
CMP (%)	0 (0)

DM indicates diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; CVA, cerebrovascular accident; CHF, congestive heart failure; CMP, cardiomyopathy.

TABLE 2 Baseline medications in patients with DM.

Total patients = 38	
Variable	
Medications	
BB (%)	10 (26.3)
CCB (%)	21 (55.3)
ARB/ACEi (%)	24 (63.2)
Diuretics (%)	7 (18.4)
Statin (%)	32 (84.2)
Aspirin/clopidogrel (%)	18 (47.4)
DM medications	
Insulin (%)	14 (36.8)
Metformin (%)	23 (60.5)
Sulfonylurea (%)	21 (55.3)
sGLT inhibitor (%)	15 (39.4)
DPP-4 inhibitors (%)	16 (42.1)

DM indicates diabetes mellitus; BB, beta-blocker; CCB, calcium channel blocker; ARB, angiotensin receptor blocker; ACEi, angiotensin converting enzyme inhibitor; sGLT inhibitor, sodium-glucose transport protein 2 inhibitor; DPP-4 inhibitor, Dipeptidyl peptidase 4 inhibitor.

TABLE 3 HRV measures according to TIR in patients with DM.

HRV			
Time domain	TIR < 70%	TIR > 70%	*P*-value
SDNN, ms	40.5 ± 38.5	48.1 ± 43.1	<0.001
RMSSD, ms	7.9 ± 6.9	10.0 ± 9.2	<0.001
SDSD, ms	7.9 ± 6.9	10.1 ± 9.2	<0.001
NN50, count	14.6 ± 40.7	25.3 ± 55.6	<0.001
pNN50, %	1.0 ± 2.9	1.8 ± 4.0	<0.001
Frequency domain			
Total Power, N.U. $*10^5$	5.5 ± 0.3	8.2 ± 0.3	<0.001
VLF, N.U. $*10^5$	3.7 ± 0.3	4.7 ± 0.2	0.019
LF, N.U. $*10^5$	1.2 ± 0.3	2.3 ± 0.5	<0.001
HF, N.U. $*10^5$	0.6 ± 0.1	1.3 ± 0.3	<0.001

*HRV indicates heart rate variability; TIR, target in glucose range; DM, diabetes mellitus; SDNN, standard deviation of NN intervals; RMMSD, root mean square of successive RR interval differences; SDSD, standard deviation of differences between adjacent NN intervals; NN50, number of NN intervals differed by more than 50 ms; pNN50, ratio of NN50; Total power, 5 min total power in frequency range ≤0.4 Hz; VLF, power in very low frequency range ≤0.04 Hz; LF, power in low frequency range 0.04–0.15 Hz; HF, power in high frequency range 0.15–0.4 Hz; N.U., normalized unit.

As shown in Figure 2, continuous measures of glycemia (plasma glucose levels) were linearly associated with HRV (time domain, SDNN (A); frequency domain, HF (B); $P < 0.001$). Both HRV (time, frequency domains) decreased according to increased continuous monitored glucose level.

As shown in Figure 3, we compared the frequency-domain HRV (LF and HF) according to DM and TIR. The patients with DM had a lower HRV than those without DM (LF, $P < 0.001$; HF, $P < 0.001$). DM patients with TIR < 70% had a lower HRV than those with TIR > 70% (LF, $P < 0.001$; HF, $P < 0.001$).

Discussion

In this study, we simultaneously evaluated heart rate and HRV according to glucose levels in patients with DM. The results of the current study demonstrated that poorly controlled DM is associated with lower HRV. The amount by which HRV was lower in patients with DM with TIR < 70% (compared to those with TIR > 70%) was approximately 2/3 in both the time and frequency domains. In addition, continuous measures of glycemia (plasma glucose levels) were linearly associated with HRV, suggesting a graded decline in HRV with worsening glucose tolerance. Heart and respiratory rates increased according to real-time glucose levels in all patients with DM. These associations were independent of the major cardiovascular risk factors (7). Therefore, our results support the concept that cardiac autonomic dysfunction occurs when poorly controlled glucose levels are measured in real time before checking long-term glucose level predictors such as HbA1c and C-peptide levels and may play a role in the development of cardiovascular diseases earlier in the course of type 2 DM.

Cardiac autonomic dysfunction is a complication of DM that carries an approximately fivefold increased risk of mortality in adults (2). Damage to the autonomic innervations of the heart and blood vessels can lead to lethal arrhythmias and sudden cardiac death (12). Hyperglycemia is thought to be associated with abnormal signaling of autonomic neurons via accumulation of advanced glycation end products, activation of polyol pathway, and ischemia induced atrophy of the autonomic nerve fibers innervating the cardiac and vascular tissues (13).

Previous studies suggested the involvement of sympathetic activation in early metabolic dysfunction in triggering perivascular adipose tissue inflammation via increased uncoupling protein-1 expression and augmented hypoxia, which could allow unmitigated augmentation of inflammation driven by hyperglycemia as type 2 DM develops, at which time brainstem involvement would evoke further autonomic dysfunction (14–16).

Both divisions of the ANS are typically affected, with parasympathetic impairment preceding the sympathetic dysfunction (6). Loss of HRV is one of the earliest manifestations

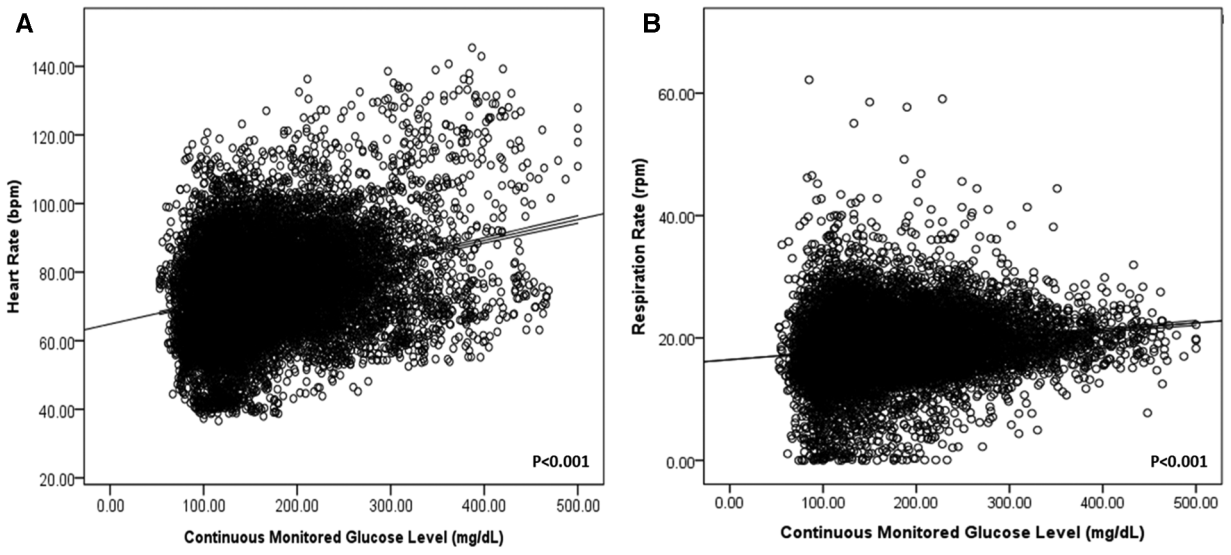


FIGURE 1
Heart rate (A) and respiration rate (B) according to continuously monitored glucose levels in patients with DM.

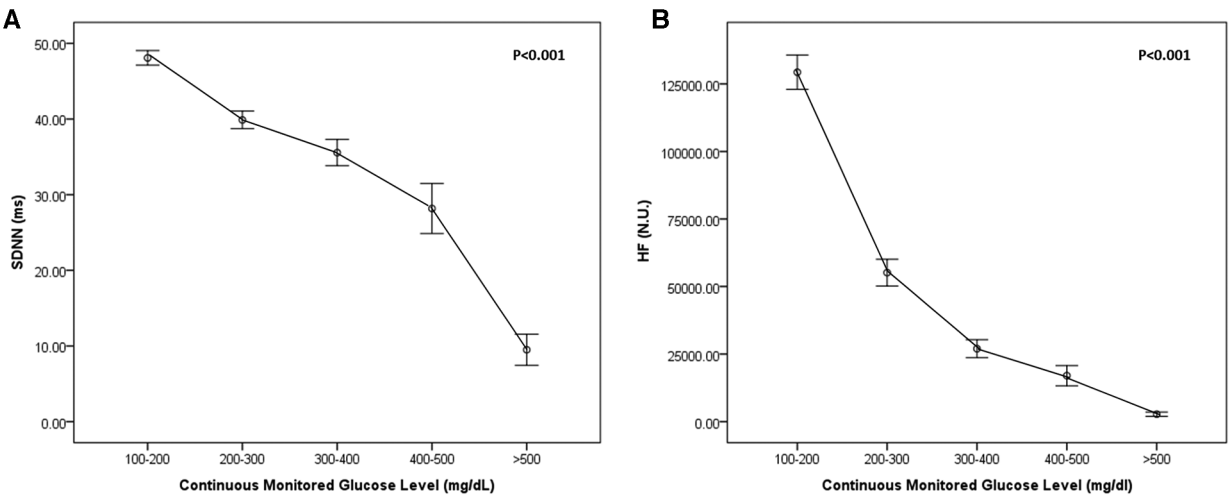


FIGURE 2
Heart rate variability (HRV) according to continuously monitored glucose level in the time domain [SDNN, (A)] and frequency domain [HF, (B)].

of this process. In the Framingham Heart Study, HRV was found to be inversely associated with the risk of mortality (17). Similarly, the Atherosclerosis Risk in Communities study found that decreased HRV was independently associated with the risk of developing coronary heart disease (18) and lower HRV was also associated with the total burden of cerebral small vessel disease (CSVD) and each of the magnetic resonance image markers of CSVD in patients with DM (19).

Adaptation to stress is characterized by an increase in sympathetic activity and a decrease in parasympathetic activity, inducing a state of alertness (20). Interestingly, common diseases such as depression, metabolic syndrome, and cancer; smoking habit; and obesity are associated with a decrease in parasympathetic activity and activation of sympathetic activity (7, 21).

One explanation is that DM is a metabolic disease responsible for cardiac autonomic neuropathy, which affects both sympathetic and parasympathetic fibers. DM has a negative influence on almost all HRV parameters, indicating that it leads to cardiac autonomic dysfunction (22, 23).

We demonstrated that an increase in heart rate was associated with higher glucose levels and a decrease in HRV (HF and LF). Although no study has previously assessed this relationship in patients with DM, conflicting results have been reported in the general population, with either high BP associated with an increase in all spectral parameters or a decrease in HRV (24, 25). It has also been suggested that a decrease in autonomic nervous function precedes the development of clinical hypertension (26). However, in our study, there was no

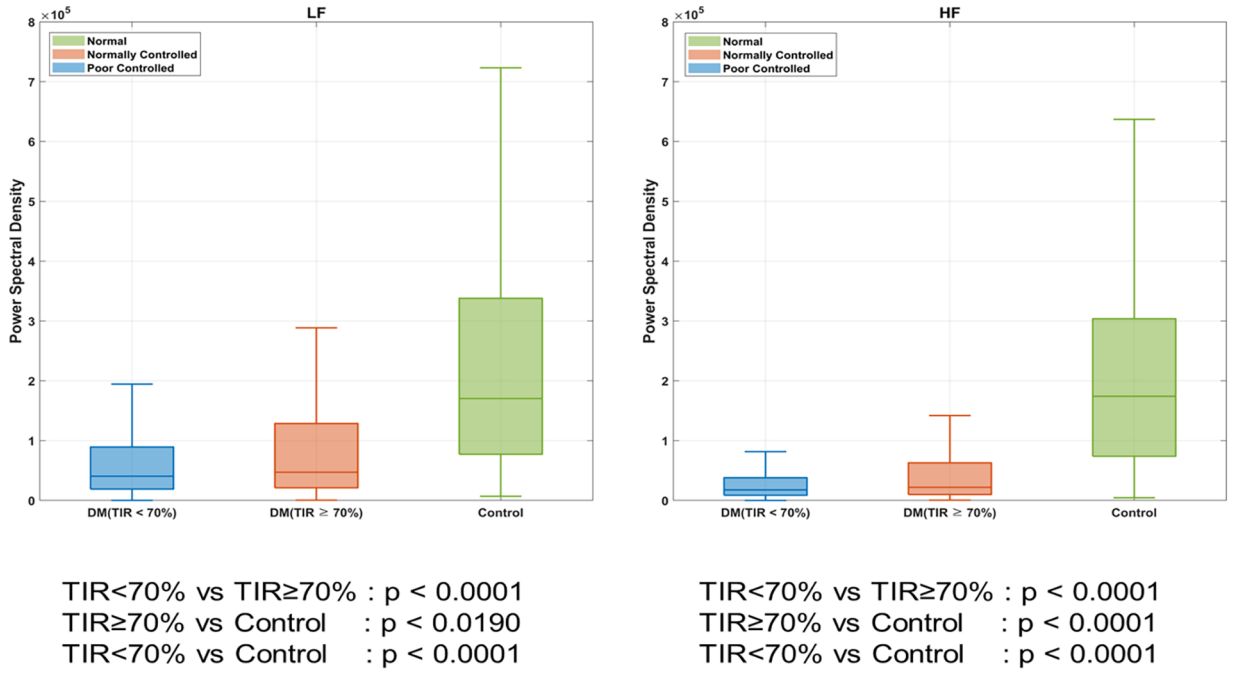


FIGURE 3
Heart rate variability (HRV) according to DM. *DM indicates diabetes mellitus; TIR, target in glucose range.

significant difference in HRV according to hypertension. Moreover, although age and sex may have a minor role in HRV parameters compared with the variables linked to DM, a previous study demonstrated a decrease in both LF and HF with age and in males (27, 28). In our study also, HRV was decreased with age and in males.

To the best of our knowledge, this is the first study to simultaneously investigate the HRV and glucose levels in patients with DM using a remote monitoring system for a long duration (225.7 ± 107.3 h, continuously). Importantly, in contrast to previous population-based studies (9, 29), we found that virtually all time- and frequency-domain measures of HRV, either as a composite score or as individual measures, were associated with worsening glucose tolerance. This may be explained by the fact that we used a more accurate 14 days remote-monitoring ECG-derived HRV as opposed to HRV derived from short-term ECG recordings. In addition, we were able to adjust for a large series of potential confounders, including real-time glucose level, respiration, and physical activity, objectively measured in a live studio at our institute using a remote monitoring system.

Our study has some limitations that must be addressed. First, the relatively small sample size was a limiting factor in generalizing the findings to the DM population. However, it was sufficient to identify significant correlations between HRV and glucose levels in individuals with DM using a remote system for HRV and continuous glucose monitoring, checked 15,090 times simultaneously during the monitoring. Despite the small number of patients, our analysis demonstrated significant and interesting relationships, particularly between the HRV parameters and glucose levels associated with DM. Hence, the results of our study should be considered hypothesis-generating, and future prospective studies are warranted to confirm these results. Second, in the present study, we only evaluated patients with DM aged <75 years. Although a previous study (30) in patients with DM and prediabetes and healthy participants and another study (27) that investigated the impact of sex and age on HRV demonstrated that HRV indices significantly increased with the participants' age, we do not know whether older adults with DM aged >75 years have similar or worse HRV patterns than older healthy individuals. Third, the health status of the controls was not detailed in our study, which could have influenced the HRV parameters. This may also have minimized the differences in HRV between patients with DM and controls. Fourth,

In conclusion, poorly controlled glucose levels are independently associated with lower HRV in patients with DM. This was further substantiated by the independent continuous association between real-time measurements of hyperglycemia and lower HRV. These data strongly suggest that cardiac autonomic dysfunction is caused by elevated blood sugar levels.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Kosin University Gospel Hospital (IRB No. 2022-06-016). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

Data curation: SC, HS, JP. Formal analysis: SC, SI. Methodology: SB, SK, BK, JH. Supervision: HK, SI. Validation: CO. Visualization: SI, SC. Writing - original draft: SI. Writing - review & editing: SI, SK. All authors contributed to the article and approved the submitted version.

Funding

The study was supported by Korea Health Industry Development Institute (KHIDI 20210048001).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1249709/full#supplementary-material

References

1. Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. *Front Public Health*. (2017) 5:258. doi: 10.3389/fpubh.2017.00258

2. Shah AS, El Ghormli L, Vajravelu ME, Bacha F, Farrell RM, Gidding SS, et al. Heart rate variability and cardiac autonomic dysfunction: prevalence, risk factors, and relationship to arterial stiffness in the treatment options for type 2 diabetes in adolescents and youth (TODAY) study. *Diabetes Care*. (2019) 42:2143–50. doi: 10.2337/dc19-0993

3. Motairek I, Al-Kindi S. Ameliorating cardiovascular risk in patients with type 2 diabetes. *Endocrinol Metab Clin North Am*. (2023) 52:135–47. doi: 10.1016/j.ecl.2022.07.002

4. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF diabetes atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. (2022) 183:109119. doi: 10.1016/j.diabres.2021.109119

5. Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, Gudbjornsdottir S, et al. Excess mortality among persons with type 2 diabetes. *N Engl J Med*. (2015) 373:1720–32. doi: 10.1056/NEJMoa1504347

6. Sudo SZ, Montagnoli TL, Rocha BS, Santos AD, de Sa MPL, Zapata-Sudo G. Diabetes-induced cardiac autonomic neuropathy: impact on heart function and prognosis. *Biomedicines*. (2022) 10(12):3258. doi: 10.3390/biomedicines10123258

7. Benichou T, Pereira B, Mermillod M, Tauveron I, Pfabigan D, Maqdasy S, et al. Heart rate variability in type 2 diabetes mellitus: a systematic review and meta-analysis. *PLoS One*. (2018) 13:e0195166. doi: 10.1371/journal.pone.0195166

8. Gerritsen J, Dekker JM, TenVoorde BJ, Kostense PJ, Heine RJ, Bouter LM, et al. Impaired autonomic function is associated with increased mortality, especially in subjects with diabetes, hypertension, or a history of cardiovascular disease: the hoorn study. *Diabetes Care*. (2001) 24:1793–8. doi: 10.2337/diacare.24.10.1793

9. Meyer ML, Gotman NM, Soliman EZ, Whitsel EA, Arens R, Cai J, et al. Association of glucose homeostasis measures with heart rate variability among hispanic/latino adults without diabetes: the hispanic community health study/study of latinos (HCHS/SOL). *Cardiovasc Diabetol*. (2016) 15:45. doi: 10.1186/s12933-016-0364-y

10. Song MH, Cho SP, Kim W, Lee KJ. New real-time heartbeat detection method using the angle of a single-lead electrocardiogram. *Comput Biol Med*. (2015) 59:73–9. doi: 10.1016/j.compbiomed.2015.01.015

11. Deckers JG, Schellevis FG, Fleming DM. WHO diagnostic criteria as a validation tool for the diagnosis of diabetes mellitus: a study in five European countries. *Eur J Gen Pract*. (2006) 12:108–13. doi: 10.1080/13814780600881268

12. Ewing DJ, Boland O, Neilson JM, Cho CG, Clarke BF. Autonomic neuropathy, QT interval lengthening, and unexpected deaths in male diabetic patients. *Diabetologia*. (1991) 34:182–5. doi: 10.1007/BF00418273

13. Verrotti A, Loiacono G, Mohn A, Chiarelli F. New insights in diabetic autonomic neuropathy in children and adolescents. *Eur J Endocrinol*. (2009) 161:811–8. doi: 10.1530/EJE-09-0710

14. Rafeh R, Viveiros A, Oudit GY, El-Yazbi AF. Targeting perivascular and epicardial adipose tissue inflammation: therapeutic opportunities for cardiovascular disease. *Clin Sci*. (2020) 134:827–51. doi: 10.1042/CS20190227

15. Vinik AI, Erbas T, Casellini CM. Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. *J Diabetes Investig*. (2013) 4:4–18. doi: 10.1111/jdi.12042

16. Bakkar NZ, Mougharbil N, Mroueh A, Kaplan A, Eid AH, Fares S, et al. Worsening baroreflex sensitivity on progression to type 2 diabetes: localized vs. systemic inflammation and role of antidiabetic therapy. *Am J Physiol Endocrinol Metab*. (2020) 319:E835–51. doi: 10.1152/ajpendo.00145.2020

17. Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, et al. Impact of reduced heart rate variability on risk for cardiac events. The framingham heart study. *Circulation*. (1996) 94:2850–5. doi: 10.1161/01.cir.94.11.2850

18. Liao D, Carnethon M, Evans GW, Cascio WE, Heiss G. Lower heart rate variability is associated with the development of coronary heart disease in individuals with diabetes: the atherosclerosis risk in communities (ARIC) study. *Diabetes*. (2002) 51:3524–31. doi: 10.2337/diabetes.51.12.3524

19. Qiu Q, Song W, Zhou X, Yu Z, Wang M, Hao H, et al. Heart rate variability is associated with cerebral small vessel disease in patients with diabetes. *Front Neurol*. (2022) 13:989064. doi: 10.3389/fneur.2022.989064

20. Hufnagel C, Chambres P, Bertrand PR, Dutheil F. The need for objective measures of stress in autism. *Front Psychol*. (2017) 8:64. doi: 10.3389/fpsyg.2017.00064

21. Lin KD, Chang LH, Wu YR, Hsu WH, Kuo CH, Tsai JR, et al. Association of depression and parasympathetic activation with glycemic control in type 2 diabetes mellitus. *J Diabetes Complications*. (2022) 36:108264. doi: 10.1016/j.jdiacomp.2022.108264

22. Tantawy A E, Anwar G, Esmail R, Zekri H, Mahmoud S, Samir N, et al. Cardiac autonomic neuropathy linked to left ventricular dysfunction in type 1 diabetic patients. *Cardiovasc Endocrinol Metab*. (2022) 11:e0272. doi: 10.1097/XCE.0000000000000272

23. Liu L, Wu Q, Yan H, Chen B, Zheng X, Zhou Q. Association between cardiac autonomic neuropathy and coronary artery lesions in patients with type 2 diabetes. *Dis Markers*. (2020) 2020:6659166. doi: 10.1155/2020/6659166

24. Askin L, Cetin M, Turkmen S. Ambulatory blood pressure results and heart rate variability in patients with premature ventricular contractions. *Clin Exp Hypertens*. (2018) 40:251–6. doi: 10.1080/10641963.2017.1356846

25. de Andrade PE, do Amaral JAT, Paiva LDS, Adami F, Raimudo JZ, Valenti VE, et al. Reduction of heart rate variability in hypertensive elderly. *Blood Press*. (2017) 26:350–8. doi: 10.1080/08037051.2017.1354285

26. Schroeder EB, Liao D, Chambless LE, Prineas RJ, Evans GW, Heiss G. Hypertension, blood pressure, and heart rate variability: the atherosclerosis risk in communities (ARIC) study. *Hypertension*. (2003) 42:1106–11. doi: 10.1161/01.HYP.0000100444.71069.73

27. Reardon M, Malik M. Changes in heart rate variability with age. *Pacing Clin Electrophysiol*. (1996) 19:1863–6. doi: 10.1111/j.1540-8159.1996.tb03241.x

28. Pavithran P, Madanmohan T, Nandeesha H. Sex differences in short-term heart rate variability in patients with newly diagnosed essential hypertension. *J Clin Hypertens*. (2008) 10:904–10. doi: 10.1111/j.1751-7176.2008.00052.x

29. Ziegler D, Voss A, Rathmann W, Strom A, Perz S, Roden M, et al. Increased prevalence of cardiac autonomic dysfunction at different degrees of glucose intolerance in the general population: the KORA S4 survey. *Diabetologia*. (2015) 58:1118–28. doi: 10.1007/s00125-015-3534-7

30. Coopmans C, Zhou TL, Henry RMA, Heijman J, Schaper NC, Koster A, et al. Both prediabetes and type 2 diabetes are associated with lower heart rate variability: the maastricht study. *Diabetes Care*. (2020) 43:1126–33. doi: 10.2337/dc19-2367

frontiers | Frontiers in Cardiovascular Medicine

TYPE Review
PUBLISHED 27 November 2023
DOI 10.3389/fcvm.2023.1172666

Check for updates

OPEN ACCESS

EDITED BY
Alessandro Zorzi,
University Hospital of Padua, Italy

REVIEWED BY
Nuryani Nuryani,
Sebelas Maret University, Indonesia
Fatima El-Hamad,
University of Adelaide, Australia

*CORRESPONDENCE
Alexander H. Maass
✉ a.h.maass@umcg.nl

RECEIVED 23 February 2023
ACCEPTED 06 November 2023
PUBLISHED 27 November 2023

CITATION
Hoek LJ, Brouwer JLP, Voors AA and Maass AH (2023) Smart devices to measure and monitor QT intervals.
Front. Cardiovasc. Med. 10:1172666.
doi: 10.3389/fcvm.2023.1172666

COPYRIGHT
© 2023 Hoek, Brouwer, Voors and Maass. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Smart devices to measure and monitor QT intervals

Leendert J. Hoek[1,2], Jan Leendert P. Brouwer[1], Adriaan A. Voors[2] and Alexander H. Maass[2]*

[1]ICON plc, Early Development Services, Groningen, Netherlands, [2]Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands

Careful observation of the QT interval is important to monitor patients with long QT syndrome and during treatment with potentially QT-prolonging medication. It is also crucial in the development of novel drugs, in particular in case of a potential side effect of QT prolongation and in patients with increased risk of QT prolongation. The 12-lead electrocardiogram (ECG) is the gold standard to evaluate cardiac conduction and repolarization times. Smartwatches and smart devices offer possibilities for ambulatory ECG recording and therefore measuring and monitoring the QT interval. We performed a systematic review of studies on smartwatches and smart devices for QTc analysis. We reviewed PubMed for smartwatches and smart devices that can measure and monitor the QT interval. A total of 31 studies were included. The most frequent devices were (1) KardiaMobile 6L, a Food and Drug Administration-approved device for QTc analyses that provides a 6-lead ECG, (2) an Apple Watch, a smartwatch with an integrated ECG tool that allows recording of a single-lead ECG, and (3) the Withings Move ECG ScanWatch, an analog watch with a built-in single-lead ECG. The KardiaMobile 6L device and the Apple Watch provide accurate measurements of the QT interval, although the Apple Watch is studied in standard and non-standard positions, and the accuracy of QT measurements increased when the smartwatch was moved to alternative positions. Most studies were performed on patients, and limited results were available from healthy volunteers.

KEYWORDS
QTc, QT interval, smartwatch, smart device, ECG

Introduction

In 1957, Jervell and Lange-Nielsen described a case of a family in which QT prolongation was found in multiple children and who subsequently died in infancy without any evidence of cardiac pathology at autopsy (1). Descriptions of young individuals with prolonged QT intervals and a history of loss of consciousness and ventricular fibrillation were published in the following years (2, 3). As a result, physicians showed increased awareness and recognized the importance of QT interval evaluation, acknowledging that abnormal QT prolongation may predispose to ventricular arrhythmia and sudden cardiac death. In 1964, Selzer and Wray described cases of ventricular tachycardia in the context of a prolonged QT interval in patients prescribed with Quinidine (4). The typical morphology of ventricular tachycardia was coined Torsades de Pointes (TdP) by Dessertenne (5). Congenital long QT syndrome (LQTS) is a familial cardiac ion channelopathy. Incomplete penetrance and variability in genetic expression lead to a heterogeneous phenotype. Classifying this condition clinically can be challenging (6). Those patients requiring regular QT interval monitoring are the mutation carriers, especially at a younger age. An increase in the QT interval can have therapeutic consequences, such as drug treatment with beta-blockers or pacemaker implantation. The diagnosis of LQTS partly depends on the QT

interval, at rest or during recovery from the exercise stress test. Furthermore, T-wave morphology and clinical and family history are a part of the Scoring System for Clinical Diagnosis of Long QT Syndrome (7). In 1988, it was found that Prenylamine (Segontin) was associated with QT prolongation and sudden cardiac death. This resulted in Prenylamine being the first drug to be withdrawn from the market due to QT prolongation associated with sudden cardiac death (8). Additional classes of medications were linked to ventricular arrhythmias and cardiac death in the following years. Some of these agents were thereafter withdrawn by the Food and Drug Administration (FDA) (9). Due to these events, the pharmaceutical industry and government regulators became aware that careful evaluation of the QT interval during the development of a new compound devolvement program is crucial. There are still drugs on the market that have been associated with prolongation of the QT interval, such as patients with a need for psychotropic medications, and are linked with lethal ventricular arrhythmias (10). Monitoring the QT interval in patients prescribed this kind of medication could be of additional value. The ICH E14 guidance for industry mentions that other ways of obtaining a high-quality ECG can be used to collect ECGs for QT/QTc collection (11, 12). The gold standard for evaluating cardiac conduction and repolarization times is the 12-lead electrocardiogram (ECG), which is usually registered for seconds or minutes. For longer monitoring, Holter analysis can provide QT analysis for several days. The disadvantage of using a 12-lead ECG is that this also entails practical difficulties, including that the 12-lead ECG is just a single time point recording. Continuous monitoring is of added value in some situations. That way, patients can be monitored at home and possible QT prolongation after medication with possible effects on the QT time can be objectified more safely and easily. Other technologies have been developed to measure conduction times, including the QT interval. The reliability of these different devices is actively being investigated. The European Heart Rhythm Association has published a position paper on using digital devices to detect and manage arrhythmias (13). They conclude that for QT interval monitoring, studies are scarce and more studies are needed before these devices can be safely used on patients. Previous reviews on ECG monitoring systems were performed in the era before ECG recordings could be performed with smartwatches and therefore did not include QTc monitoring using these devices (14, 15). Other reviews on the use of smartwatches were related to detecting atrial fibrillation (16). To the best of our knowledge, this is the first review on using smartwatches to monitor QT intervals. This systematic review of the literature about the use of smartwatches and smart devices for QTc analysis is intended to provide an overview of the current literature regarding the use of these devices in analyzing QT intervals and to explore how these devices could change the landscape of QTc analysis.

Materials and methods

We reviewed PubMed (https://pubmed.ncbi.nlm.nih.gov) for studies published on the use of smart devices for QTc analysis until September 30, 2022. For reporting and methodology, the updated 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines were used (17). Terms "QTc" and "smart device," "QT interval" and "smart device," "QTc" and "smartwatch," "QT interval" and "smartwatch," "QTc" and "Apple Watch," "QT interval" and "Apple watch," "QTc" and "device," "QT interval" and "device," "device" and "TQT," and "smartwatch" and "TQT" were used to identify studies examining the use of smart devices for QT analysis. Bibliographies of selected articles were manually reviewed for additional studies. Only original research articles published in English were considered for review. Eligibility of the articles was determined based on the screening of titles and abstracts. Articles that did not publish about methods and/or devices for QT analysis, implantable devices, 12-lead ECG monitoring, bed-side ECG monitoring; pediatric studies; non-human studies; and studies about telemetric monitoring were excluded.

Results

The initial search identified 1,071 studies. After screening titles, 43 articles were considered for further review. After reviewing the 43 articles, 12 articles were further excluded. The search strategy is shown in **Figure 1**. The search identified studies conducted until September 2022. The most frequently studied device was AliveCor's KardiaMobile ($N = 16$). Five studies examined the Apple Watch. Another smart watch (SW), the Withings Move ECG ScanWatch, was examined in three studies. A graphic representation of the three most studied devices is shown in **Figure 2**. In addition to the above-mentioned devices, a single publication was found for eight other devices an overview of the studied devices is shown in **Table 1**. Agreement between devices and 12-lead ECG was performed through Bland–Altman analysis in several studies and in a descriptive manner in some other publications.

KardiaMobile 6L

KardiaMobile 6L (AliveCor Inc., Mountain View, CA, USA) is a wireless mobile ECG (mECG) device that can directly record a 6-lead ECG, which consists of leads I, II, and III and also augmented Vector Left (aVL), augmented Vector Foot (aVF), and augmented unipolar right arm lead (aVR). It is a small (9.0 cm × 3.0 cm × 0.72 cm) device that consists of three electrodes each on both the top surface and the bottom surface. Electrodes on the top surface make contact with both thumbs, and electrodes on the bottom surface make contact with either the left knee or the left ankle. KardiaMobile 6L can subsequently be connected to the corresponding application through Bluetooth on mobile devices such as tablets and smartphones to record a 30-s 6-lead mECG. It then provides an automated assessment of heart rate and heart rhythm (18). The FDA guidance allows using KardiaMobile 6L to measure QT intervals in patients with COVID-19 (19). Sixteen studies examined AliveCor's KardiaMobile 6L. Kleiman

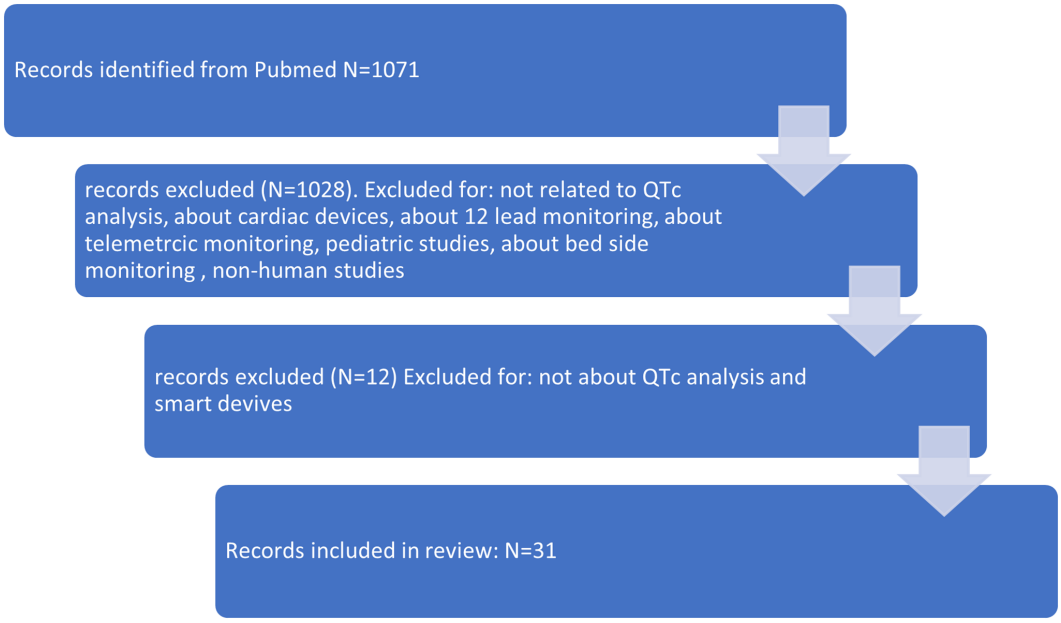


FIGURE 1
Search strategy.

et al. (20) compared interval duration measurements (IDMs) between 6-lead ECGs recorded with AliveCor's KardiaMobile 6L and standard 12-lead ECGs. Interpretable 12-lead and 6-lead recordings were available for 685 out of 705 (97%) eligible patients. The mean difference between the QTc measured on the 6-lead and 12-lead ECGs was −2.6 ms (95% CI −4.1 to −1.1 ms). The absolute difference of <10 ms was present in 44.3%, ≤10 and <20 ms in 32.9%, ≤20 and <30 ms in 10.3%,

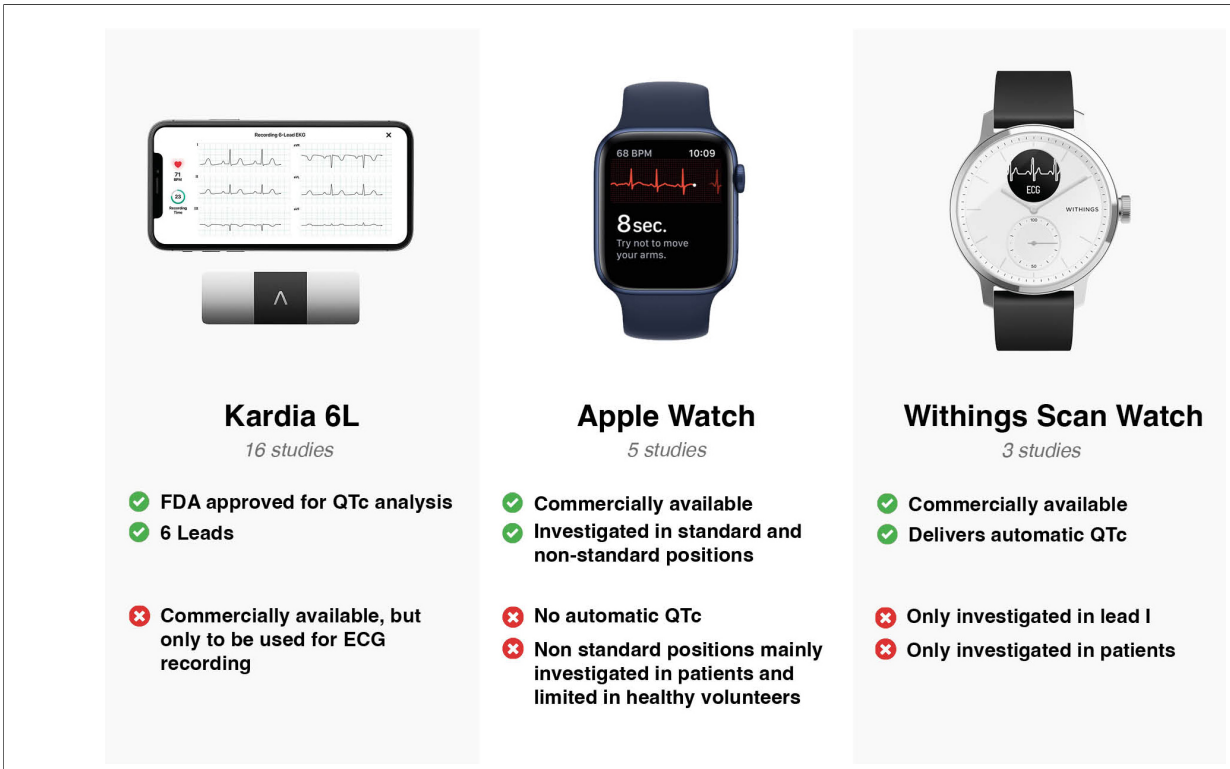


FIGURE 2
Graphical representation of most studied devices.

TABLE 1 Table with an overview of studied devices.

KardiaMobile 6L						
Aim	*N*	Setting	Device	Leads	Outcome	Reference
Comparison of interval duration measurements between standard 12 lead ECGs and 6 Lead ECGs recorded with KardiaMobile 6L	705	Patients referred to the Genetic Heart Rhythm Clinic	KardiaMobile	ECG leads I, II, III, aVL, aVR, and aVF	Mean difference between the QTc measured on the 6-lead and 12-lead ECGs was −2.6 ms (95% CI −4.1 to −1.1 ms)	(20)
To access the accuracy of KardiaMobile 6L in measuring the QTc	234	Patients visiting the cardiology clinic for any indication	KardiaMobile	ECG leads I, II, III, aVL, aVR, and aVF	Mean absolute difference in QTc values between the modalities using lead I was 14 ± 13 ms ($r = 0.783$; <0.001). Mean absolute difference in lead II QTc between the modalities was 12 ± 9 ms ($r = 0.856$, $p < 0.001$)	(18)
To access the feasibility of obtaining recordings using the KardiaMobile 6L and to qualitative compare with standard 12-lead ECG recordings	4	COVID-19-positive patients or patients requiring ECG monitoring	KardiaMobile	ECG leads I, II, III, aVL, aVR, and aVF	KardiaMobile 6L had the ability to provide contactless ECGs with acceptable QT/QTc interval measurements	(21)
To describe the usefulness of telemonitoring for management of QT-prolonging drugs	70	COVID-19-positive patients receiving hydroxychloroquine, azithromycin, or lopinavir/ritonavir	KardiaMobile	ECG leads I, II, III, aVL, aVR, and aVF	Intraclass correlation coefficient points to a good agreement in the measurements of QTc interval	(22)
To investigate the KardiaMobile 6L to record and measure the QTc	13	Multidrug-resistant tuberculosis and non-tuberculous mycobacterium	KardiaMobile	ECG leads I, II, III, aVL, aVR, and aVF	Mean percentage difference between the automated 12-lead and manually calculated AliveCor readings was 3%. The correlation between the automated QTc and AliveCor QTc was evaluated with Pearson's correlation coefficient = 0.43 ($p > 0.05$)	(23)
To evaluate the agreement and clinical precision of Kardia Mobile 1l to measure the QTc interval and compare it to the 12-lead ECG	128	Patients with a presumed or confirmed diagnosis of COVID-19	KardiaMobile 1l	Single-lead ECG	Values of the QTc interval were practically the same for both devices (442.45 ± −40.5 vs. 441.65 ± 40.3 ms, $p = 5.15$)	(24)
To evaluate the feasibility of QTc monitoring with a KardiaMobile 6L	227	182 patients with COVID-19 and 45 healthy patients	KardiaMobile 6L	ECG leads I, II, III, aVL, aVR, and aVF	No differences were observed between the monitoring strategies in QTc prolongation ($p = 0.864$). In the control group, all but one ECG registry with the smart device allowed QTc measurement, and mean QTc did not differ between both techniques ($p = 0.612$), displaying a moderate reliability [ICC 0.56 (0.19–0.76)]	(25)
To access the reliability of using AliveCor tracings (KardiaMobile 1l) and compare them to the QTc on standard ECGs	5	Patients on dofetilide for atrial fibrillation	KardiaMobile	Single-lead ECG	No significant difference between the AliveCor QTc and ECG QTc for any of the five patients (all ± 20 ms)	(26)
To determine the accuracy of different ECG-based devices to detect atrial fibrillation, QRS morphology, and ECG intervals compared with 12-lead ECG	176	Patients with congenital heart disease	KardiaMobile	ECG leads I, II, III, aVL, aVR, and aVF	QTc duration accuracy was acceptable in 74% of KardiaMobile 6L. QTc interval of KardiaMobile 6L compared to the 12-lead ECG illustrates limits of agreements, which were independent of the QTc interval	(27)
To train and validate an artificial intelligence-enabled 12-lead algorithm to determine the QTc and test this algorithm on tracings acquired from a KardiaMobile 6L	686	Patients with genetic heart disease	KardiaMobile	ECG leads I, II, III, aVL, aVR, and aVF	Difference between DNN-predicted QTc values derived from mECG tracings and those annotated from 12-lead ECGs by a QT expert (−0.45 ± 24.73 ms) and a commercial core ECG laboratory (10.52 ± 25.64 ms) was nominal	(33)
To describe the implementation of a remote trial in which self-collected ECG measurements were recorded on KardiaMobile 6L	231	Patients with SARS-CoV-2	KardiaMobile	ECG leads I, II, III, aVL, aVR, and aVF	QT interval can be efficiently measured and verified within a remote clinical trial paradigm	(34)
To compare the KardiaMobile 6L with the 12-lead ECG	1,015	Unselected cardiac inpatients and outpatients	KardiaMobile	ECG leads I, II, III, aVL, aVR, and aVF	Mean differences between KardiaMobile 6L and the 12-lead ECG for QT and QTc were small; the AUC was >75% for QT but less for QTc, although overall >60%	(28)

(*Continued*)

TABLE 1 Continued

KardiaMobile 6L						
Aim	*N*	Setting	Device	Leads	Outcome	Reference
To examine and compare the level of similarity between KardiaMobile 6L ECG and 12-lead ECG	30	Healthy athletes	KardiaMobile	ECG leads I, II, III, aVL, aVR, and aVF	Relatively high levels of agreement between the mean 6-lead and 12-lead measurements for QTc, with the 6l readings slightly but significantly shorter on average. The difference in the QTc intervals was 391 vs. 401 ms ($p = 0.003$)	(29)
Comparison of KardiaMobile 6L and 12-lead ECG recordings	100	Cardiac patients	KardiaMobile	ECG leads I, II, III, aVL, aVR, and aVF	QT intervals measured by the KardiaMobile device were significantly different (shorter) than those observed in the standard ECG method: 393 vs. 400 ms ($p < 0.001$)	(30)
To determine the accuracy of QT measurement in a KardiaMobile 1l and compared it with a 12-lead ECG	125	Patients with non-acute indication in primary care	KardiaMobile	Single-lead ECG	Mean QTcB interval was 393 ± 25 ms in 1-lead ECGs and 392 ± 27 ms in lead I of the 12-lead ECGs, with a mean difference of 1 ± 21 ms. Comparing QTcB of 1-lead ECGs with those of lead II of 12-lead ECGs showed a mean difference of 8 ± 22 ms	(31)
To provide a brief overview of a protocol for monitoring the QT interval using KardiaMobile 6L	81	Patients with SARS-CoV-2	KardiaMobile	ECG leads I, II, III, aVL, aVR, and aVF	Portable wireless devices may represent a quick and useful alternative for QT interval monitoring	(32)
Apple Watch						
To compare the feasibility and reliability using the Apple Watch to calculate a QT interval to those of using a standard ECG to calculate a QT interval	119	100 patients admitted to Cardiology division 19 healthy subjects	Apple Watch	Leads I, II, and V2	There was agreement among the QT intervals of I, II, and V2 leads and the QT mean using the smartwatch and the standard ECG with Spearman's correlations of 0.886, 0.881, 0.793, and 0.914 ($p < 0.001$), respectively	(38)
To access the accuracy of interval measurements on Apple Watch tracings in comparison to lead I on a 12-lead ECG	43	Healthy volunteers	Apple Watch	Lead I of Apple Watch and lead I of 12-lead ECG	Mean difference (d) of −11.27 ± 22.9 ms for the QT interval ($r = 0.79$) and −11.67 ± 27 ms for the QTc interval ($r = 0.57$)	(39)
To compare the smartwatch-recorded QT and QTc assessed using AccurKardia's AccurBeat platform with the 12-lead ECG	50	Healthy volunteers	Apple Watch	Lead I Apple Watch and ECG leads I and II of 12-lead ECG	The Bland–Altman plot results found that 96% of the average QTc interval measurements between the platform and QTc intervals from the 12-lead ECG were within the 95% confidence limit of the average difference between the two measurements, with a mean difference of −10.5 (95% LoA −71.43 to 50.43). A total of 94% of the average QT interval measurements between the platform and the 12-lead ECG were within the 95% CI of the average difference between the two measurements, with a mean difference of −6.3 (95% LoA −54.54 to 41.94)	(40)
To validate the use of the Apple Watch for QT measurement	100	100 patients in sinus rhythm from outpatient or emergency departments	Apple Watch	Apple Watch lead I, lead II, and AW-LAT (simulated lead V6)	Compared with the 12-lead ECG, the median absolute error in QTc was 18 ms for AW-I, 20 ms for AW-II, and 16 ms for AW-LAT	(41)
To demonstrate the use of an Apple Watch to monitor QT prolongation	1	One patient with COVID-19	Apple Watch	Apple Watch lead I	Very similar waveform morphology and QT measurements compared to lead I of the 12-lead ECG	(42)
Withings ScanWatch						
To compare automated QTc measurements using a single-lead ECG of a Withings ScanWatch with manual measured QTc from a 12-lead ECG	367	Patients referred to a tertiary hospital for cardiac work-up	Withings ScanWatch	Smartwatch lead I	Disagreement for QTc measurements between the SW-AI and the manual measurements by the cardiologist using the 12-lead ECG was <15 ms in 38% cases and >20 ms in 54, and 29% of measurements had a disagreement >30 ms. In 12 patients (7%), the difference between the QTc intervals was greater than the LoA	(43)

(*Continued*)

TABLE 1 Continued

KardiaMobile 6L						
Aim	*N*	Setting	Device	Leads	Outcome	Reference
To compare QTc duration measured on Withings ScanWatch compared with those measured on 12-lead ECGs	85	Patients with COVID-19 who were prescribed hydroxychloroquine-azithromycin therapy	Withings ScanWatch	Smartwatch lead I	Bland–Altman analysis resulted in a bias of 6.6 ms (95% LoA −59 to 72 ms) comparing automated QTc measurements (SW-ECG) with manual QTc measurement (12-lead ECG). In 12 patients (6.9%) the difference between the two measurements was greater than the LoA	(44)
To determine the accuracy of different ECG-based devices to detect atrial fibrillation, QRS morphology, and ECG intervals compared with 12-lead ECG	176	Patients with congenital heart disease	Withings ScanWatch	Smartwatch lead I	In the Withings ECG, the QTc interval was more frequently (49%) over- or underestimated by more than 40 ms compared to both Eko DUO (30%) and KardiaMobile 6L (26%) ($p < 0.001$ for both comparisons)	(27)
Other devices						
To evaluate the diagnostic accuracy of a patient-operated ECG device compared with a 12-lead ECG	508	Patients with an indication for 12-lead ECG recording	Omron HeartScan	Single-lead, position chest electrode C4	Linear correlation (r^2) between the patient-operated ECG system and the standard ECG was 0.89 for QTc	(45)
To evaluate the ease of device use and quality of transmitted ECG tracings for QT interval measurement	31	Adult heart transplant recipients	HeartOne, Aerotel medical systems	Lead II	89% of the ECGs were acceptable quality for QT interval measurement	(46, 47)
To access the diagnostic accuracy of a single-lead portable ECG device for measuring QT intervals in comparison with a 12-lead ECG	101	Adult patients visiting the outpatient department with an indication for a 12-lead ECG recording	HeartCheck	Single-lead portable ECG Lead I	The mean QTc interval measured was 430.6 (SD ± 31.1) ms for the 12-lead ECG and 396.7 (SD ± 47.5) ms for the single-lead ECG. The difference of the QTc intervals between the two measurements was substantially outside the definition of perfect agreement of 10 ms difference or less. Only seven (6.9%) ECG recordings demonstrated perfect agreement	(47)
To evaluate ECG signal quality and ECG parameters measured with a 12-lead ECG acquisition T-shirt	30	Healthy subjects	12-lead ECG acquisition shirt	12 leads	QTc intervals obtained with the smart T-shirt were highly comparable to the ones measured with Holter	(48)
To evaluate the accuracy of a Smartphone Home Monitor for assessing the QTc as compared to the 12-lead ECG	124	99 healthy volunteers and 25 hospitalized patients receiving sotalol or dofelitide	Smartphone heart monitor	Leads I and II	In healthy volunteers the ASHM QT demonstrated a very good agreement (bias = 4 ms; standard deviation of bias = 11 ms) with the GE 12-lead ECG, using the Bland–Altman method of measurement agreement. In the hospitalized patients, the automated GE and ASHM QTc measurements based on lead I demonstrated a reasonable agreement (bias = 3 ms; standard deviation of bias = 46 ms) using the Bland–Altman method	(49)
To explore whether automated QTc measurements by BodyGuardian are sufficiently reliable compared to manual measurements on 12-lead Holter recordings	36	20 LQTS patients and 16 healthy controls	BodyGuardian	Lead II	QTc automatically measured by BG was 445 ± 47 ms, and the QTc manually measured was 446 ± 41 ms. The disagreement between BG and manual measurement was <15 ms in 57% of cases 34% of measurements had a disagreement >20 ms	(50)
To evaluate the diagnostic accuracy of a handheld bipolar ECG event recorder	52	52 patients admitted to the cardiology department	Beurer ME 80 device	Reconstruct 9 leads I, II, III, and V1–V6	Diagnosis of a prolonged QTc was inaccurate due to the inherent difficulties with measuring this interval because of lower signal quality and non-simultaneous tracings that make it difficult to align the waveforms	(51)
To evaluate the accuracy, usability, and diagnostic capabilities of a single-lead ECG device	144	94 patients cardiac patients and 50 asymptomatic controls	ECG check	Lead I	No significant differences were found in QT intervals between the two modalities	(52)

DNN, deep neural network; AW, apple watch; LAT, lateral; ICC, intraclass correlation.

≤30 and <40 ms in 7.5%, ≤40 and <50 ms in 2.8%, and ≥50 ms in 2.2%. The authors concluded that 6-lead recordings with this KardiaMobile 6L can provide high-quality ECG recordings that may be useful in clinical medicine and during clinical trials. Bergeman et al. (18) studied the accuracy of the KardiaMobile 6L device for assessment of QT intervals in 234 outpatients visiting a cardiology clinic for any indication. Due to artifacts, it was impossible to perform QTc measurement in any lead in 16 mECGs (7%). In all 12-lead ECGs, QTc measurement was possible. Lead II was the most accurate lead. The mean (±SD) absolute difference in QTc values between mECGs and 12-lead ECGs was 12 ± 9 ms ($r = 0.856$; $p < 0.001$) in lead II. The absolute difference between QTc values was <10 ms in 55% of the subjects. A mean QTc ≥480 ms in lead II on the 12-lead ECG was found in six subjects. The sensitivity and specificity for mECG QTc prolongation in lead II were 80% and 99%, respectively ($n = 203$). The authors concluded that using a 6-lead mECG enables measuring the QT interval with good accuracy compared with the standard 12-lead ECG. Frisch et al. (21) published a case series of four patients in which they assessed the feasibility of obtaining mECG recordings using the KardiaMobile 6L device. Acceptable QT/QTc interval measurements were performed. Abellas-Sequeiros et al. (22) published a research letter about QT interval monitoring in patients with COVID-19 with KardiaMobile 6L. Seventy patients were enrolled, and tracings obtained with KardiaMobile 6L were of sufficient quality to provide an accurate QT interval measurement in 69 of them (98.6%). The device proved useful for ECG monitoring in these patients, detecting ECG abnormalities significant enough to promote a change in treatment in 17.4% of them. Puranik et al. (23) investigated the AliveCor device to monitor the QT interval in patients with multidrug-resistant tuberculosis and non-tuberculous mycobacterium. For 13 patients, a comparison was made between an automated QTc readout from the 12-lead ECG, and the mean QTc value was calculated from each patient's respective AliveCor device tracing (lead II). The AliveCor device underestimated the QTc compared to the corresponding 12-lead QTc readout in 12 of 13 cases (92%). In this study, not all patients had a same-day comparison with a 12-lead ECG. Marín et al. (24) evaluated the agreement and clinical precision of the KardiaMobile single-lead device (KM-1l). In this study, performed on 128 patients with a confirmed or presumed diagnosis of COVID-19, QTc of ECG recordings obtained with the KM-1l device were compared to QTc obtained with the standard 12-lead ECG. Values of the QTc interval were almost the same for the KM-1l device and the 12-lead ECG (442.45 ± −40.5 vs. 441.65 ± 40.3 ms, $p = 0.15$). An excellent agreement and no statistically significant differences in the QTc interval measurement was found in this study. It was demonstrated that the KM-1l device has adequate precision and agreement compared to the standard 12-lead ECG. Minquito-Carazo et al. (25) evaluated the feasibility of QTc monitoring with KardiaMobile 6L in 63 COVID-19 patients receiving therapies that could interfere with the QT interval. QTc could be measured in lead II in 84.5% of the registries. In a control group, 12- and 6-lead ECGs were recorded for 45 healthy subjects. It was found that KardiaMobile 6L showed similar diagnostic feasibility for measurement of the QT interval to the standard 12-lead ECG, with moderate reliability. Chung and Guise (26) assessed, in five patients receiving dofetilide for atrial fibrillation, the feasibility of tracings for QTc obtained with the AliveCor device compared to QTc from the standard ECG. No significant difference was found in this study. Pengel et al. (27) compared different devices for ECG monitoring to the standard 12-lead ECG to examine the accuracy of these devices in adults with congenital heart disease. ECG intervals were manually evaluated for these devices. A difference in the QT interval of >40 ms compared to the 12-lead ECG was considered clinically unacceptable. A total of 176 patients were enrolled in this study. In 26%, the QTc difference was >40 ms compared to the standard 12-lead ECG. Azram et al. (28) compared KardiaMobile 6L with the 12-lead ECG in 1,015 unselected cardiac inpatients and outpatients. The QT interval was closely accurate to the gold standard 12-lead ECG. Orchard et al. (29) present data from 30 healthy athletes who underwent a KardiaMobile 6-lead ECG recording and a subsequent 12-lead ECG recording. The difference in the QTc interval was not significant. Koltowski et al. (30) compared KardiaMobile 6L and 12-lead ECGs for a group of 100 consecutive cardiac patients. QT intervals were significantly ($p < 0.001$) shorter in the KardiaMobile 6-lead ECG than in the 12-lead ECG. Beers et al. (31) determined the accuracy of QT measured by KM-1l in 125 patients. These patients had a non-acute indication for a 12-lead ECG. The authors concluded that KM-1l ECGs measured the QT interval accurately compared to standard 12-lead ECGs. Gonzales et al. (32) validated QT intervals measured by KardiaMobile 6L and a conventional ECG in a study on 50 SARS-CoV2 patients. They found a very good correlation between the KardiaMobile 6L device and the 12-lead ECG. The authors showed that the implementing a monitoring protocol can identify patients who are prone to prolong the QT interval and that such devices may represent an alternative for QT interval monitoring. Giudicessi et al. (33) trained and validated an artificial intelligence (AI)-enabled 12-lead ECG algorithm to determine the QTc. They prospectively tested this algorithm on tracings recorded from a mobile ECG device (equivalent to the AliveCor KardiaMobile 6L). A strong agreement appeared between manually evaluated and AI-predicted QTc values (−1.76 ± 23.14 ms). Mayfield et al. (34) described implementing a fully randomized clinical trial with cardiac monitoring. ECG collection was performed with the KardiaMobile 6L device. The authors demonstrated that remote QT interval monitoring can be efficiently performed.

Apple Watch

Apple Watch Series 3 can record pulse frequency. It uses photoplethysmography located on the back of the watch (35). Apple Watch Series 4 (Apple Inc., Cupertino, CA, USA) has an integrated ECG tool with which a single-lead ECG can be recorded. The negative electrode is placed in the crown, and the

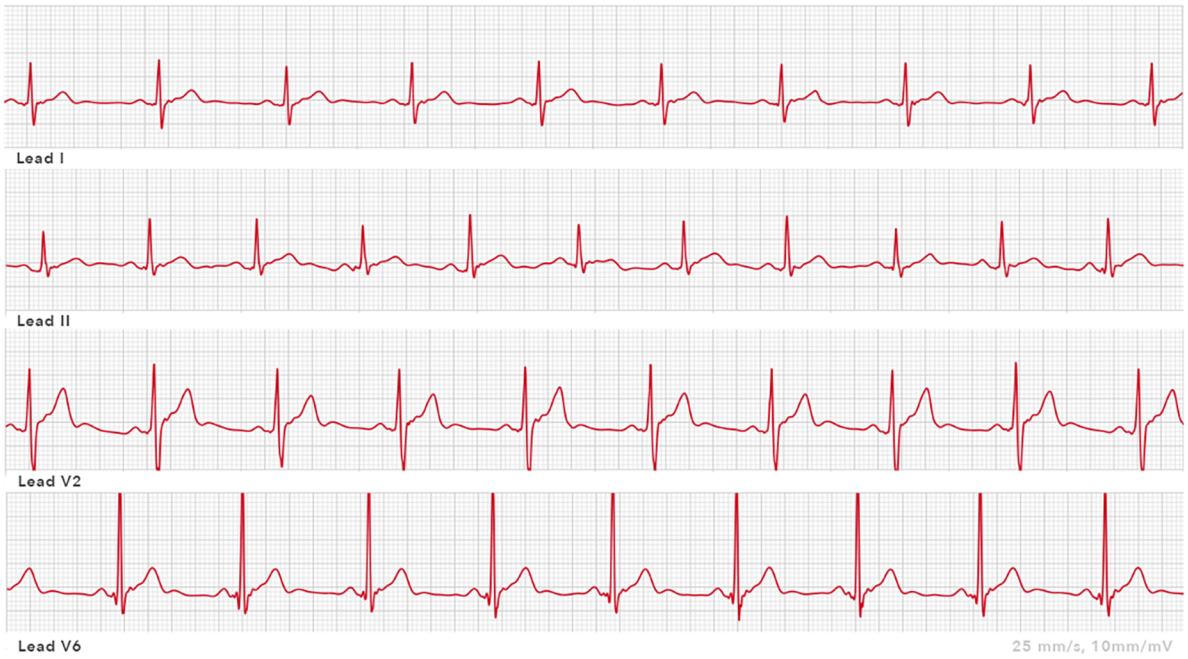


FIGURE 3
ECG leads recorded by an Apple Watch: lead I Apple Watch ECG 25 mm/s, 10 mm/mV (smartwatch worn on the left wrist); lead II Apple Watch ECG 25 mm/s, 10 mm/mV (smartwatch on left lower abdomen); lead V2 Apple Watch ECG 25 mm/s, 10 mm/mV (smartwatch at the site of V2); and lead V6 Apple Watch ECG 25 mm/s, 10 mm/mV (smartwatch at the site of V6).

positive electrode is located on the back of the watch. A bipolar ECG lead, the simulated lead I, can be derived by recording the voltage difference over time between the watch's back electrode on the left arm wrist and the right index finger on the crown (36, 37). Electrocardiograms can be stored on a smart device mobile application (mApp). Afterward, PDFs can be generated from obtained ECGs. An example of an ECG obtained with an Apple Watch from standard and non-standard positions is shown in **Figure 3**. This wearable SW contains possibilities to detect atrial fibrillation. Apple Watch has received FDA approval for the detection of atrial fibrillation. Five studies examined the Apple Watch in the context of QT interval measurements. Spaccarotella et al. (38) assessed in 119 patients, admitted to the cardiology division, the feasibility and reliability of the obtained QT interval examined in leads I, II, and V2 using an Apple Watch. Lead I was recorded in the standard SW position with the watch on the left wrist. For leads II and V2, the SW was placed in non-standard positions. Lead II was recorded with the SW on the left lower abdomen; for obtaining lead V2, the SW was placed in the fourth intercostal space left parasternal. For all these above-mentioned leads, the right index finger was placed on the crown. The authors calculated an average of the QT interval in all of the above-mentioned leads (I, II, V2) using Bazett's, Fidericia's, and Framingham's formulas. A strong agreement was found between the QT intervals measured in the different leads compared to standard 12-lead ECGs, so the authors concluded that the Apple Watch can accurately measure the QT interval compared with the standard ECG. Saghir et al. (39) compared the accuracy of interval electrocardiographic interval measurements on Apple Watch ECG tracings to lead 1 on 12-lead ECGs in 43 volunteers. There were no inconclusive readings. Strong agreement, defined as mean difference (d) <20 ms, was found in 65.1% of the QT measurements and 48.8% of the QTc measurements. Moderate agreement, defined as d <40 ms, was found in 86% of the QT intervals and 74.4% of the QTc measurements. Chokshi et al. (40) compared the SW-recorded QT and QTc assessed using AccurKardia's AccurBeat platform with the conventional 12-lead ECG. This study consisted of 50 healthy participants. All analyzable complexes of the 12-lead ECG were in leads I and II. The AccurBeat platform annotates ECGs and can also diagnose arrhythmias using AI-based techniques. More than 90% of the average QT interval measurements between the platform and the QT intervals from the 12-lead ECG were within the 95% CI. The authors concluded that QT and QTc intervals obtained by the Apple SW coupled with the platform are comparable to those from a 12-lead ECG. Strik et al. (41) investigated using the Apple Watch for QT measurement, including using non-standard SW positions, in an unselected outpatient population ($N = 100$). Apple Watch lead I was obtained with the watch on the left wrist, and lead II was obtained with the watch on the left ankle. Furthermore, the simulated lead V6 was recorded with the watch on the left lateral chest. Adequate QT measurements were observed in 85% of the patients when the SW was worn on the left wrist. This number of adequate measurements increased to 94% when the SW was moved to alternative positions. Chinitz et al. (42) published a case report about a physician in home isolation due to a COVID-19 infection. She was prescribed hydroxychloroquine

and considered at moderate risk for drug-associated QT prolongation. Recordings from the Apple Watch rhythm strips were transmitted to a cardiologist. After treatment, a 12-lead ECG was performed in the hospital, which showed a very similar waveform morphology and QT measurement to lead I from the Apple Watch.

Withings Move ECG ScanWatch

The Withings ScanWatch (SW, Withings SA, Issy les Moulineaux, France) is an analog watch with an in-built single-lead ECG. It offers, without manual measurement of the SW-ECG or the need for any other software, an automated analysis of the corrected QT interval (43). An artificial intelligence QTc (AI-QTc) is systematically measured from the smartwatch ECG (SW-ECG). After performing the SW-ECG, it is transmitted for assessment to the Cardiologs platform. The AI-QTc is calculated by a deep convolutional neural network that identified both the onset of QRS complexes and the offset of subsequent T waves in the SW-ECG. Finally, to remove extreme and anomalous values, the AI-QTc of the SW-ECG was calculated as the median QTc over all beats (44). A total of three studies examined this SW. In two studies, the agreement between manual QTc measurement by a 12-lead ECG and the AI-QTc of the SW-ECG was tested. Another study examined the accuracy of different ECG-based devices, including the Withings ScanWatch, compared to the 12-lead standard ECG on several tasks. Mannhart et al. (43) compared automated QTc measurements of the Withings ScanWatch with manually measured QTc from a 12-lead recorded ECG. A total of 317 patients referred for cardiac work-up were enrolled in this study. Two blinded cardiologists manually interpreted the QT interval of a 12-lead ECG by assessing lead II or V5/V6 with Bazett's formula. In 177 patients (56%), the AI algorithm was able to automatically measure the QTc. A 6.6 ms bias [with 95% limit of agreement (LoA) of −59 and 72 ms] was reported comparing manual measurements and QTc calculated by the SW-AI. There was a disagreement between the measurements of <15 ms in 38% of the cases, >20 ms in 54% of the cases, and >30 ms in 29% of the cases. There was a substantial difference, defined as greater than the LoA, between the QTc intervals in 7% of the cases. The authors concluded that this SW-AI algorithm tends to underestimate the QTc interval; furthermore, the use of single-lead SW-ECG for QTc monitoring could be feasible, but further validation is needed. Maille et al. (44) assessed a group of 85 patients with COVID-19. These patients underwent hydroxychloroquine–azithromycin therapy, which is known as a drug that interferes the QT interval. The authors compared the AI-QTc with a manually measured QTc on a 12-lead ECG, measured in leads I and II or V5. This study showed the AI-QTc tends to overestimate QTc compared to the standard 12-lead ECG. At baseline, there was a difference of less than 50 ms between the two measurements in 97% of the patients. On days 6 and 10, there was a difference of less than 50 ms in 96% and 98% of the patients, respectively. The authors concluded that fair agreement was observed between AI and 12-lead ECGs. Pengel et al. (27) compared different devices for ECG monitoring to the standard 12-lead ECG to examine the accuracy of these devices in adults with congenital heart disease. ECG intervals were manually evaluated for these devices. A difference in the QT interval of >40 ms compared to the 12-lead ECG was considered clinically unacceptable. A total of 176 patients were enrolled in this study. In all patients, Withings ScanWatch ECGs were recorded. In 84% of the patients, the QT interval could be assessed and identified. The authors concluded that QTc was underestimated and QTc duration accuracy was acceptable in only 51% of Withings ECGs. In 49%, the QTc difference was >40 ms, assessed by a physician, compared to the 12-lead ECG.

Other devices

Kaleschke et al. (45) evaluated the diagnostic accuracy of another device (Omron HeartScan HCG-80) in 508 patients with an indication for 12-lead ECG and compared it to that of a standard 12-lead ECG. This study showed a linear correlation of continuous ECG parameters (with also QTc measurement) between Omron HeartScan and the 12-lead ECG in the study population ($R^2 = 0.89$). Carter et al. (46) evaluated the feasibility and compliance with daily home ECG monitoring of the QT interval in 31 heart transplant patients using the HeartOne (Aerotel Medical Systems, Holon, Israel) device. During the study period, 644 ECGs were successfully received; of these, 569 ECGs (89%) were acceptable for QTc measurement. Bekker et al. (47) assessed the diagnostic accuracy of a single-lead ECG recorder (HeartCheck) for measuring QTc prolongation. The authors concluded an inferior diagnostic accuracy of this device to measure QTc intervals in cardiology patients to the gold-standard 12-lead ECG. Fouassier et al. (48) evaluated the quality of signals measured with a 12-lead acquisition smart T-shirt (Cardioskin) or a 12-lead Holter recording in 30 healthy subjects. All measured parameters, including QTc, were comparable to the ones obtained with the Holter. Garabelli et al. (49) compared QT interval readings between a Smartphone Home Monitor (SHM) and a 12-lead ECG in 99 healthy volunteers and 25 patients receiving sotalol or dofetilide. An AliveCor-designed prototype was used that allowed the recording of various leads. A very good agreement in QT interval measurements was shown between the Smartphone Home Monitor and the 12-lead ECG in healthy volunteers. However, just a reasonable agreement was demonstrated in patients. Castelletti et al. (50) investigated whether automated QTc measurements obtained by BodyGuardian (BG), a wearable remote monitor system, were reliable compared to manual measurements in 20 patients with long QT syndrome and 16 healthy controls. Measurements of the QT interval obtained by BG were very similar to the manual measurements. Nigolian et al. (51) evaluated the diagnostic accuracy of the Beurer ME 80 device (Ulm, Germany) in 52 patients. It was difficult to recognize the waveforms due to technical issues such as lower signal quality and non-simultaneous tracings. Because of this, it was not possible to measure the QT interval, so diagnosis of

prolonged QTc was inaccurate. Haverkamp et al. (52) investigated the accuracy and usability of single-lead ECG obtained by ECG Check in 94 cardiac patients admitted to the hospital and 50 asymptomatic controls. No significant differences were found in QT intervals.

Discussion

Measuring and monitoring QTc intervals are frequently performed in the early phases of novel drug development programs and in daily clinical practice during antiarrhythmic drug initiation. The golden standard for QTc analyses is the 12-lead ECG, but it is not practical to monitor QTc intervals over a longer period of time. During the last few years, many wearable devices that can measure QTc intervals have become available. Only three of them have been adequately compared to 12-lead ECG measurements. Two of these are commercially available smartwatches (Apple Watch and Withings ScanWatch) with possibilities for ECG and QTc measurements. When an SW is worn on the wrist, which is common practice, the device can only provide lead I recording, which has significant limitations. Historically, measurement of conduction intervals is preferably performed in lead II (53), which is not possible when the watch is worn on the wrist. Furthermore, Cheung et al. (54) suggested that the acquisition of accurate and reproducible QTc values is only possible after obtaining multiple leads. However, this limitation can be overcome by performing recording at non-standard positions. This can be done by placing the SW in other places and positions on the body, which improved the accuracy of the Apple Watch from 85% to 94%. The Withings ScanWatch was only studied using a single lead position. The benefit of this Withings ScanWatch is the automated analysis of the corrected QT interval remotely without needing third-party software or manual measurement of SW-ECG. However, this is limited by the finding that the automated algorithm was able to measure QTc in only 56% of cases (43). On the other hand, a fair agreement was found between the QTc interval durations measured manually on a standard 12-lead ECG and assessed by AI on single-lead SW recordings (44). At this time, the Apple Watch does not offer an automated QTc measurement; addition of this feature might be desirable in the future. A cardiology-focused digital health company (AccurKardia) had developed a device diagnostic platform (AccurBeat) to analyze Apple Watch-generated ECGs. It was found that a total of 94% of the average QT interval measurements by the platform and the 12-lead ECG were within the 95% CI of the average difference (40). Some studies have shown that manual measurement is even more accurate (48). However, manual QT interval assessment is time-consuming and tedious, and, even when performed by experts, the discrepancy between manual QTc measurements is wide, ranging from 34 to 80 ms (55). Furthermore, the QT interval is a dynamic parameter due to sympathovagal interaction in diurnal variation (56). The best-studied device was KardiaMobile 6L, an FDA-approved device for QTc analyses in COVID-19 patients that provides a 6-lead ECG. Two studies examined the earlier version of the KMobile-1l device. Most studies found good accuracy between the QTc measurements of the Kardia device and 12-lead ECG. One study found KardiaMobile 6L underestimated the QTc compared to the corresponding 12-lead QTc. However, this was a small study and not all recordings were taken on the same day. In addition to good accuracy, another great advantage of KardiaMobile 6L is that multiple lead recordings were obtained, which improves accuracy. ECG registration time was found to be significantly lower with KardiaMobile 6L compared with the 12-lead ECG, which suggests good usability. A disadvantage of KardiaMobile 6L is that it can only be used to make ECG recordings and offers no other functionalities. Smartwatches offer many functionalities, including the option for ECG recordings. Many households already own an SW, increasing the potential availability of measurements with these devices. Only a single study provided information on their accuracy in measuring QTc intervals from a few other devices. Other studies only described the feasibility and compliance of these devices. Omron HeartScan HCG-801-E, CardioSkin, BodyGuardian, ECG Check, and HeartOne showed comparable QTc results to 12-lead ECGs. The QTc analysis results of Beurer ME 80 and HeartCheck were inferior compared to the 12-lead ECG. QTc measurements by the Smartphone Home Monitor demonstrated very good agreement with the 12-lead ECG in healthy volunteers and reasonable agreement in patients. We note that some of these other investigated devices clearly showed promising results, but hardly anyone had these devices at home, which makes using such a device for monitoring the QTc interval in households less practical. Most studies were performed on patients, either with COVID-19 or various cardiac diseases. Garabelli et al. (49) showed important differences in the accuracy of the same device between patients and healthy volunteers, with very good agreement in healthy volunteers and reasonable agreement in hospitalized patients. This finding suggests that it is recommended for phase 1 studies only to use a device that has also been studied on healthy people. There are clear advantages in monitoring QTc intervals using a smart device. Remote monitoring offers the opportunity to reduce the duration of confinement and might reduce the study burden on the participants as well as the costs of the study. Remote monitoring can also be promising for patients who are prescribed QT-prolonging medications. Another advantage is the potential reduction of the ecological footprint. Because many people already own an SW, no extra material needs to be manufactured for this. Furthermore, less paper is used than if all these ECGs were produced in the traditional way. In addition, less travel, and therefore less CO_2 emissions, is required because patients have the option of sending an ECG to their doctor from the home. This is an assumption and needs further investigation. However, it can be argued that home measurement of QT intervals may allow for a reduction in time and resources for travel. A potential limitation of using smart devices for measurement of the QT interval is the fact that one of the parts of the Schwartz score, the recommended method for diagnosing prolonged QT intervals, includes measurement of the QT interval after exercise testing (7). Measurement of the QT interval using a smart device after exercise testing has not yet been investigated.

Future studies need to focus on several issues. Safety and adequate alerting in case of QT prolongation need to be prospectively studied. Healthy volunteers have been underrepresented in the presented studies. In addition, many studies were conducted during the COVID-19 pandemic. Conducting studies during the COVID-19 pandemic has its limitations, which should be taken into account. Another limitation of the studies comparing 12-lead ECG to SW-ECG is inconsistent criteria for what is considered an acceptable difference between the two measurements. QT intervals, even if corrected for heart rate, are not only prone to change by drug therapy but also by circadian rhythms and vagal and sympathetic tone. This needs to be taken into account when designing future studies. If you think about an optimal situation, a wearable device should be able to transmit ECGs via remote monitoring to the treating physician for periodic QT analysis but also be able to transmit alerts in case of QT prolongation exceeding a certain threshold or in case of proarrhythmic events such as self-limiting TdP.

Conclusions

Smartwatches and smart devices offer possibilities for monitoring the QT interval and could be of great additional value. Compared to a 12-channel ECG, patients can record an ECG themselves, which is also possible at home. Results differ from device to device, but some devices can provide comparable results with the gold standard 12-lead ECG and allow adequate QT measurements. Given that smartwatches are already owned by many people and offer additional functionalities, these are promising devices. However, it is recommended to not only measure the QT interval from standard lead I but also at least from lead II and preferably one of the precordial leads. Further studies are needed to evaluate and validate QTc monitoring in healthy subjects and patients. While much research has been done into detecting atrial fibrillation with an SW, this review proves that reliable measurement of the QT interval is also possible. This can have an important impact on drug safety monitoring and monitoring of patients at risk for QT prolongation and offers opportunities in drug research. These devices have the potential to lead to future clinical applications in the evaluation of any drug-induced arrhythmogenicity related to prolongation of the QT interval, needing close monitoring of QT intervals. Before they can be used in daily clinical practice for antiarrhythmic drug initiation, alerts for QT prolongation or arrhythmic events need to be prospectively studied.

Author contributions

The first version of the manuscript was written by LH and revised and approved by JB, AV, and AM. All authors contributed to the article and approved the submitted version.

Conflict of interest

Authors LH and JB were employed by ICON plc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval and sudden death. *Am Heart J.* (1957) 54:59–68. doi: 10.1016/0002-8703(57)90079-0

2. Romano C, Gemme G, Pongiglione R. [Rare cardiac arrythmias of the pediatric age. II. Syncopal attacks due to paroxysmal ventricular fibrillation. (Presentation of 1st case in Italian pediatric literature)]. *Clin Pediatr (Bologna).* (1963) 45:656–83. Available at: https://pubmed.ncbi.nlm.nih.gov/14158288/ (Accessed February 14, 2023).

3. Ward OC. A new familial cardiac syndrome in children. *J Ir Med Assoc.* (1964) 54:103–6.

4. Selzer A, Wray HW. Quinidine syncope. Paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias. *Circulation.* (1964) 30:17–26. doi: 10.1161/01.CIR.30.1.17

5. Dessertenne F. [Ventricular tachycardia with 2 variable opposing foci]. *Arch Mal Coeur Vaiss.* (1966) 59:263–72.

6. Lankaputhra M, Voskoboinik A. Congenital long QT syndrome: a clinician's guide. *Intern Med J.* (2021) 51:1999–2011. doi: 10.1111/IMJ.15437

7. *Table 1. [Scoring system for clinical diagnosis of long QT syndrome]. GeneReviews®—NCBI Bookshelf.* Available at: https://www.ncbi.nlm.nih.gov/books/NBK1129/table/rws.T.scoring_system_for_clinical_diagno/ (Accessed February 14, 2023).

8. Meanock CI, Noble MIM. A case of prenylamine toxicity showing the torsade de pointes phenomenon in sinus rhythm? *Postgrad Med J.* (1981) 57:381–4. doi: 10.1136/PGMJ.57.668.381

9. Fung M, Thornton A, Mybeck K, Wu JH-H, Hornbuckle K, Muniz E. Evaluation of the characteristics of safety withdrawal of prescription drugs from worldwide pharmaceutical markets—1960 to 1999. *Drug Inf J.* (2001) 35:293–317. doi: 10.1177/009286150103500134

10. Beach SR, Celano CM, Sugrue AM, Adams C, Ackerman MJ, Noseworthy PA, et al. QT prolongation, Torsades de pointes, and psychotropic medications: a 5-year update. *Psychosomatics.* (2018) 59:105–22. doi: 10.1016/J.PSYM.2017.10.009

11. Shah RR, Morganroth J. ICH E14 Q & A (R1) document: perspectives on the updated recommendations on thorough QT studies. *Br J Clin Pharmacol.* (2013) 75:959–65. doi: 10.1111/J.1365-2125.2012.04442.X

12. Darpo B, Ferber G. The new S7B/E14 question and answer draft guidance for industry: contents and commentary. *J Clin Pharmacol.* (2021) 61:1261–73. doi: 10.1002/JCPH.1880

13. Svennberg E, Tjong F, Goette A, Akoum N, di Biase L, Bordachar P, et al. How to use digital devices to detect and manage arrhythmias: an EHRA practical guide. *Europace.* (2022) 24:979–1005. doi: 10.1093/EUROPACE/EUAC038

14. Bansal A, Joshi R. Portable out-of-hospital electrocardiography: a review of current technologies. *J Arrhythm.* (2018) 34:129–38. doi: 10.1002/JOA3.12035

15. Serhani MA, El Kassabi HT, Ismail H, Navaz AN. ECG monitoring systems: review, architecture, processes, and key challenges. *Sensors (Basel)*. (2020) 20 (6):1796. doi: 10.3390/S20061796

16. Wong KC, Klimis H, Lowres N, Von Huben A, Marschner S, Chow CK. Diagnostic accuracy of handheld electrocardiogram devices in detecting atrial fibrillation in adults in community versus hospital settings: a systematic review and meta-analysis. *Heart*. (2020) 106:1211–7. doi: 10.1136/HEARTJNL-2020-316611

17. Moher D, Liberati A, Tetzlaff J, Altman DG, Group PRISMA. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Open Med*. (2009) 3:e123–30.

18. Bergeman AT, Pultoo SNJ, Winter MM, Somsen GA, Tulevski II, Wilde AAM, et al. Accuracy of mobile 6-lead electrocardiogram device for assessment of QT interval: a prospective validation study. *Neth Heart J*. (2022) 31(9):340–7. doi: 10.1007/S12471-022-01716-5

19. New FDA Guidance Allows Use of KardiaMobile 6L to Measure QTc in COVID-19 Patients. Alivecor. Available from: https://alivecor.com/press/press_release/new-fda-guidance-allows-use-of-kardiamobile-6l-to-measure-qtc-in-covid-19-patients/

20. Kleiman R, Darpo B, Brown R, Rudo T, Chamoun S, Albert DE, et al. Comparison of electrocardiograms (ECG) waveforms and centralized ECG measurements between a simple 6-lead mobile ECG device and a standard 12-lead ECG. *Ann Noninvasive Electrocardiol*. (2021) 26:e12872. doi: 10.1111/ANEC.12872

21. Frisch DR, Frankel ES, Farzad DJ, Woo SH, Kubey AA. Initial experience in monitoring QT intervals using a six-lead contactless Mobile electrocardiogram in an inpatient setting. *J Innov Card Rhythm Manag*. (2021) 12:4433–40. doi: 10.19102/ICRM.2021.120301

22. Abellas-Sequeiros M, Lozano-Granero C, García-Sebastián C, Franco-Díez E, Hernández-Madrid A, Moreno-Planas J, et al. Monitoring of QTc interval in patients with COVID-19. First experience with a portable ECG-recording device. *Cardiol J*. (2021) 28:483–5. doi: 10.5603/CJ.A2021.0033

23. Puranik S, Harlow C, Martin L, Coleman M, Russell G, Park M, et al. Monitoring prolongation of QT interval in patients with multidrug-resistant tuberculosis and non-tuberculous mycobacterium using mobile health device AliveCor. *J Clin Tuberc Other Mycobact Dis*. (2021) 26. doi: 10.1016/J.JCTUBE.2021.100293

24. Marín OMM, García PÁA, Muñoz VOM, Castellanos RJC, Cáceres ME, Santacruz PD. Portable single-lead electrocardiogram device is accurate for QTc evaluation in hospitalized patients. *Heart Rhythm O2*. (2021) 2:382–7. doi: 10.1016/J.HROO.2021.06.005

25. Minguito-Carazo C, Echarte-Morales J, Benito-González T, del Castillo-García S, Rodríguez-Santamarta M, Sánchez-Muñoz E, et al.. QT interval monitoring with handheld heart rhythm ECG device in COVID-19 patients. *Glob Heart*. (2021) 16 (1):42. doi: 10.5334/GH.916

26. Chung EH, Guise KD. QTC intervals can be assessed with the AliveCor heart monitor in patients on dofetilide for atrial fibrillation. *J Electrocardiol*. (2015) 48:8–9. doi: 10.1016/J.JELECTROCARD.2014.10.005

27. Pengel LKD, Robbers-Visser D, Groenink M, Winter MM, Schuuring MJ, Bouma BJ, et al. A comparison of ECG-based home monitoring devices in adults with CHD. *Cardiol Young*. (2023) 33(7):1129–35. doi: 10.1017/S1047951122002244

28. Azram M, Ahmed N, Leese L, Brigham M, Bowes R, Wheatcroft SB, et al. Clinical validation and evaluation of a novel six-lead handheld electrocardiogram recorder compared to the 12-lead electrocardiogram in unselected cardiology patients (EVALECG cardio). *Eur Heart J Digit Health*. (2021) 2:643–8. doi: 10.1093/EHJDH/ZTAB083

29. Orchard JJ, Orchard JW, Raju H, la Gerche A, Puranik R, Semsarian C. Comparison between a 6-lead smartphone ECG and 12-lead ECG in athletes. *J Electrocardiol*. (2021) 66:95–7. doi: 10.1016/J.JELECTROCARD.2021.03.008

30. Koltowski L, Balsam P, Glowczynska R, Rokicki JK, Peller M, Maksym J, et al. Kardia Mobile applicability in clinical practice: a comparison of Kardia Mobile and standard 12-lead electrocardiogram records in 100 consecutive patients of a tertiary cardiovascular care center. *Cardiol J*. (2021) 28:543–8. doi: 10.5603/CJ.A2019.0001

31. Beers L, van Adrichem LP, Himmelreich JCL, Karregat EPM, de Jong JSSG, Postema PG, et al. Manual QT interval measurement with a smartphone-operated single-lead ECG versus 12-lead ECG: a within-patient diagnostic validation study in primary care. *BMJ Open*. (2021) 11. doi: 10.1136/BMJOPEN-2021-055072

32. González NT, Acosta LÁ, Miranda DV, Plasencia AI, Cáceres VB, Zambrano MR, et al. QT interval measurement with portable device during COVID-19 outbreak. *Int J Cardiol Heart Vasc*. (2020) 30:100644. doi: 10.1016/J.IJCHA.2020.100644

33. Giudicessi JR, Schram M, Bos JM, Galloway CD, Shreibati JB, Johnson PW, et al. Artificial intelligence-enabled assessment of the heart rate corrected QT interval using a mobile electrocardiogram device. *Circulation*. (2021) 143:1274–86. doi: 10.1161/CIRCULATIONAHA.120.050231

34. Mayfield JJ, Chatterjee NA, Noseworthy PA, Poole JE, Ackerman MJ, Stewart J, et al. Implementation of a fully remote randomized clinical trial with cardiac monitoring. *Commun Med*. (2021) 1:62. doi: 10.1038/S43856-021-00052-W

35. Foster KR, Torous J. The opportunity and obstacles for smartwatches and wearable sensors. *IEEE Pulse*. (2019) 10:22–5. doi: 10.1109/MPULS.2018.2885832

36. Samol A, Bischoff K, Luani B, Pascut D, Wiemer M, Kaese S. Recording of bipolar multichannel ECGs by a smartwatch: modern ECG diagnostic 100 years after einthoven. *Sensors (Basel)*. (2019) 19(13):2894. doi: 10.3390/S19132894

37. Avila CO. Novel use of Apple Watch 4 to obtain 3-lead electrocardiogram and detect cardiac ischemia. *Perm J*. (2019) 23. doi: 10.7812/TPP/19-025

38. Spaccarotella CAM, Migliarino S, Mongiardo A, Sabatino J, Santarpia G, de Rosa S, et al. Measurement of the QT interval using the Apple Watch. *Sci Rep*. (2021) 11:10817. doi: 10.1038/S41598-021-89199-Z

39. Saghir N, Aggarwal A, Soneji N, Valencia V, Rodgers G, Kurian T. A comparison of manual electrocardiographic interval and waveform analysis in lead 1 of 12-lead ECG and Apple Watch ECG: a validation study. *Cardiovasc Digit Health J*. (2020) 1:30–6. doi: 10.1016/J.CVDHJ.2020.07.002

40. Chokshi S, Tologonova G, Calixte R, Yadav V, Razvi N, Lazar J, et al. Comparison between QT and corrected QT interval assessment by an Apple Watch with the AccurBeat platform and by a 12-lead electrocardiogram with manual annotation: prospective observational study. *JMIR Form Res*. (2022) 6:e41241. doi: 10.2196/41241

41. Strik M, Caillol T, Ramirez FD, Abu-Alrub S, Marchand H, Welte N, et al. Validating QT-interval measurement using the Apple Watch ECG to enable remote monitoring during the COVID-19 pandemic. *Circulation*. (2020) 142:416–8. doi: 10.1161/CIRCULATIONAHA.120.048253

42. Chinitz JS, Goyal R, Morales DC, Harding M, Selim S, Epstein LM. Use of a smartwatch for assessment of the QT interval in outpatients with coronavirus disease 2019. *J Innov Card Rhythm Manag*. (2020) 11:4219–22. doi: 10.19102/ICRM.2020.1100904

43. Mannhart D, Hennings E, Lischer M, Vernier C, de Lavallaz JdF, Knecht S, et al. Clinical validation of automated corrected QT-interval measurements from a single lead electrocardiogram using a novel smartwatch. *Front Cardiovasc Med*. (2022) 9. doi: 10.3389/FCVM.2022.906079

44. Maille B, Wilkin M, Million M, Rességuier N, Franceschi F, Koutbi-Franceschi L, et al. Smartwatch electrocardiogram and artificial intelligence for assessing cardiac-rhythm safety of drug therapy in the COVID-19 pandemic. The QT-logs study. *Int J Cardiol*. (2021) 331:333–9. doi: 10.1016/J.IJCARD.2021.01.002

45. Kaleschke G, Hoffmann B, Drewitz I, Steinbeck G, Naebauer M, Goette A, et al. Prospective, multicentre validation of a simple, patient-operated electrocardiographic system for the detection of arrhythmias and electrocardiographic changes. *Europace*. (2009) 11:1362–8. doi: 10.1093/EUROPACE/EUP262

46. Carter EV, Hickey KT, Pickham DM, Doering LV, Chen B, Harris PRE, et al. Feasibility and compliance with daily home electrocardiogram monitoring of the QT interval in heart transplant recipients. *Heart Lung*. (2012) 41:368–73. doi: 10.1016/J.HRTLNG.2012.02.012

47. Bekker CL, Noordergraaf F, Teerenstra S, Pop G, van den Bemt BJF. Diagnostic accuracy of a single-lead portable ECG device for measuring QTc prolongation. *Ann Noninvasive Electrocardiol*. (2020) 25(1):e12683. doi: 10.1111/ANEC.12683

48. Fouassier D, Roy X, Blanchard A, Hulot JS. Assessment of signal quality measured with a smart 12-lead ECG acquisition T-shirt. *Ann Noninvasive Electrocardiol*. (2020) 25(1):e12682. doi: 10.1111/ANEC.12682

49. Garabelli P, Stavrakis S, Albert M, Koomson E, Parwani P, Chohan J, et al. Comparison of QT interval readings in normal sinus rhythm between a smartphone heart monitor and a 12-lead ECG for healthy volunteers and inpatients receiving sotalol or dofetilide. *J Cardiovasc Electrophysiol*. (2016) 27:827–32. doi: 10.1111/JCE.12976

50. Castelletti S, Dagradi F, Goulene K, Danza AI, Baldi E, Stramba-Badiale M, et al. A wearable remote monitoring system for the identification of subjects with a prolonged QT interval or at risk for drug-induced long QT syndrome. *Int J Cardiol*. (2018) 266:89–94. doi: 10.1016/J.IJCARD.2018.03.097

51. Nigolian A, Dayal N, Nigolian H, Stettler C, Burri H. Diagnostic accuracy of multi-lead ECGs obtained using a pocket-sized bipolar handheld event recorder. *J Electrocardiol*. (2018) 51:278–81. doi: 10.1016/J.JELECTROCARD.2017.11.004

52. Haverkamp HT, Fosse SO, Schuster P. Accuracy and usability of single-lead ECG from smartphones—a clinical study. *Indian Pacing Electrophysiol J*. (2019) 19:145–9. doi: 10.1016/J.IPEJ.2019.02.006

53. Postema P, Wilde A. The measurement of the QT interval. *Curr Cardiol Rev*. (2014) 10:287–94. doi: 10.2174/1573403X10666140514103612

54. Cheung CC, Davies B, Gibbs K, Laksman ZW, Krahn AD. Multilead QT screening is necessary for QT measurement: implications for management of patients in the COVID-19 era. *JACC Clin Electrophysiol*. (2020) 6:878–80. doi: 10.1016/J.JACEP.2020.04.001

55. Viskin S, Rosovski U, Sands AJ, Chen E, Kistler PM, Kalman JM, et al. Inaccurate electrocardiographic interpretation of long QT: the majority of physicians cannot recognize a long QT when they see one. *Heart Rhythm*. (2005) 2:569–74. doi: 10.1016/J.HRTHM.2005.02.011

56. Murakawa Y, Inoue H, Nozaki A, Sugimoto T. Role of sympathovagal interaction in diurnal variation of QT interval. *Am J Cardiol*. (1992) 69:339–43. doi: 10.1016/0002-9149(92)90230-V

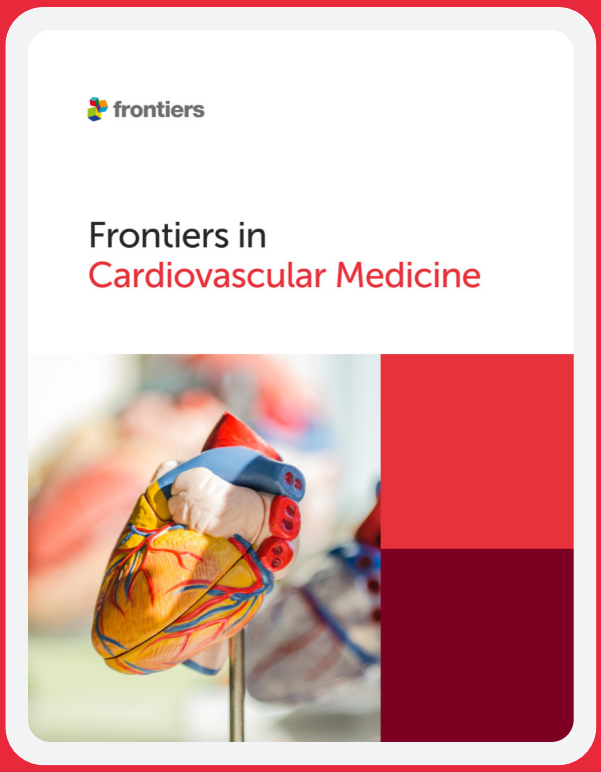
Frontiers in
Cardiovascular Medicine

Innovations and improvements in cardiovascular treatment and practice

Focuses on research that challenges the status quo of cardiovascular care, or facilitates the translation of advances into new therapies and diagnostic tools.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact