WEARABLE DEVICES FOR CARDIAC RHYTHM MONITORING

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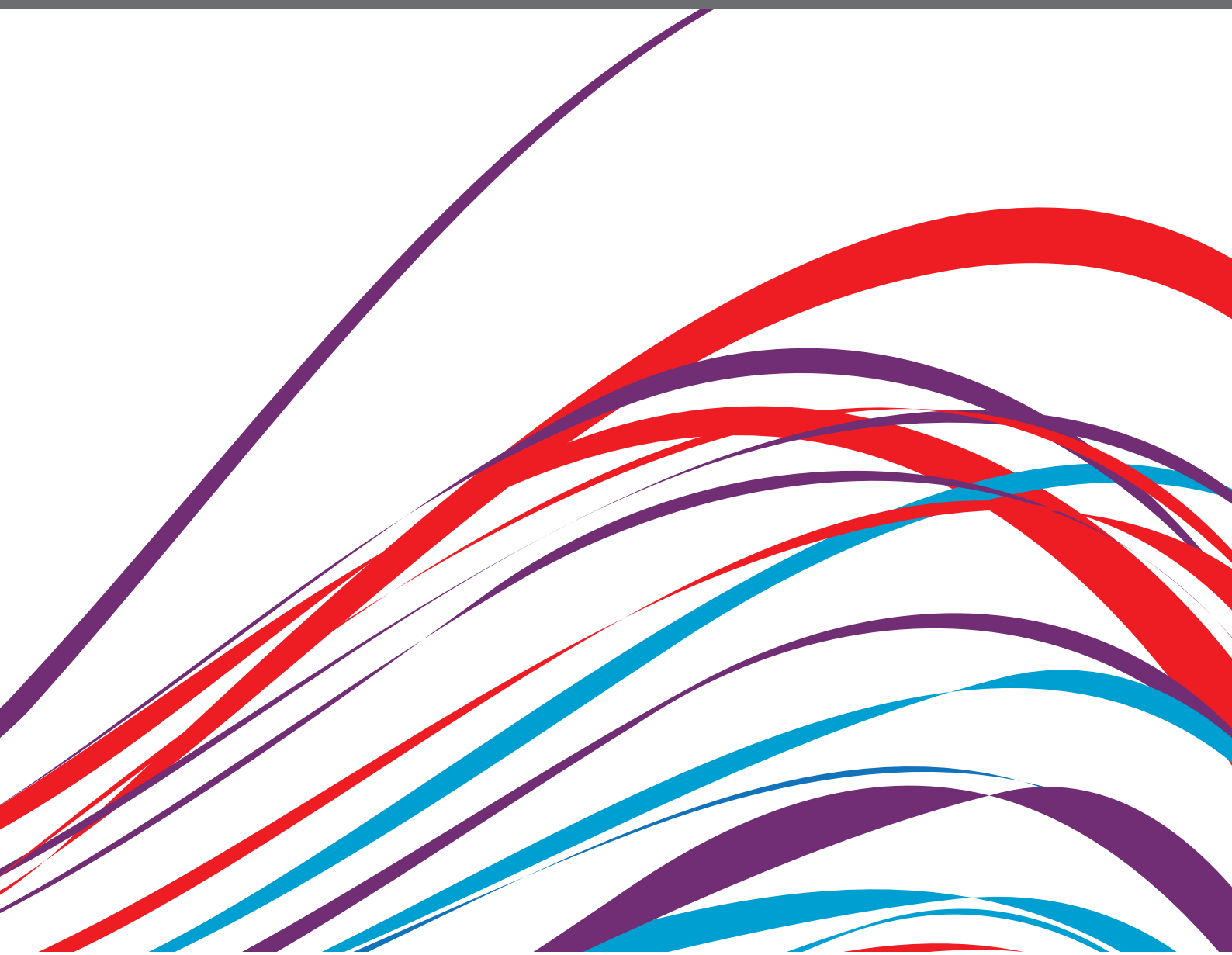

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WEARABLE DEVICES FOR CARDIAC RHYTHM MONITORING

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EDITORIAL
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Editorial: Wearable Devices for Cardiac Rhythm Monitoring

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Keywords: mobile health (mHealth), wearable device, atrial fibrillation, screening, rhythm monitoring

Editorial on the Research Topic

Wearable Devices for Cardiac Rhythm Monitoring

New wearable technologies for cardiac rhythm monitoring are gaining more importance in clinical routine in the field of cardiology and electrophysiology - by physicians as well as patients. These include, but are by far not restricted to, smartphone-based electrocardiogram (ECG) or photoplethysmograpy (PPG), finger-ECG, smartwatches, smart garments and more. This opens new horizons for mobile (m) Health-based patient care, mHealth-enhanced teleconsultations, but also mass screening for heart rhythm disorders.

The current Research Topic includes new research on these technologies covering methodological aspects on wearable single- and multiple-lead ECG or PPG devices as well as clinical implementation of digital devices (**Figure 1**).

Xintarakou et al. present an elaborated review about smart wearables for monitoring and management of cardiac arrhythmias. The sensitivity and specificity of PPG-based devices in detecting AF is very good. Interpreting the PPG waveforms and tracings, however, requires some training (1). The INTERPRET-AF study by Gruwez et al. show that the accuracy of physicians interpreting PPGs is quite high and that using all available information from the PPG signal, the tachogram, the Poincaré plot and an automated algorithm increases the diagnostic accuracy and is comparable to a single lead ECG or 12-lead ECG. However, a call for training and education of PPG tracings and validity and limitations of interpretation should be made as this is rare in cardiological curricula, except in the recently updated curricula by the German Cardiac Society (2).

NEW DEVICES

Comparative studies on different devices are rare. Abu-Alrub et al. compared recording quality of three single-lead smartwatches in 100 patients with atrial fibrillation vs. 100 patients in sinus rhythm. Diagnosing AF is possible using various ECG smartwatch models, but differences in diagnostic accuracy of the related automated algorithms were noted.

An electronic-textile-based ECG monitoring was evaluated by Teferra et al. showing an effective option for continuous cardiac monitoring implemented into textiles.

Combining digital devices with machine learning algorithms represents a unique opportunity for individualized approaches or early identification of patients at risk. Luongo et al. evaluated a machine learning algorithm using a single-lead Holter ECG to identify patients with AF-induced cardiomyopathy. In clinical routine this could be a time and cost-efficient discriminator for general practitioners performing Holter ECG to identify patients requiring referral to a cardiologist.

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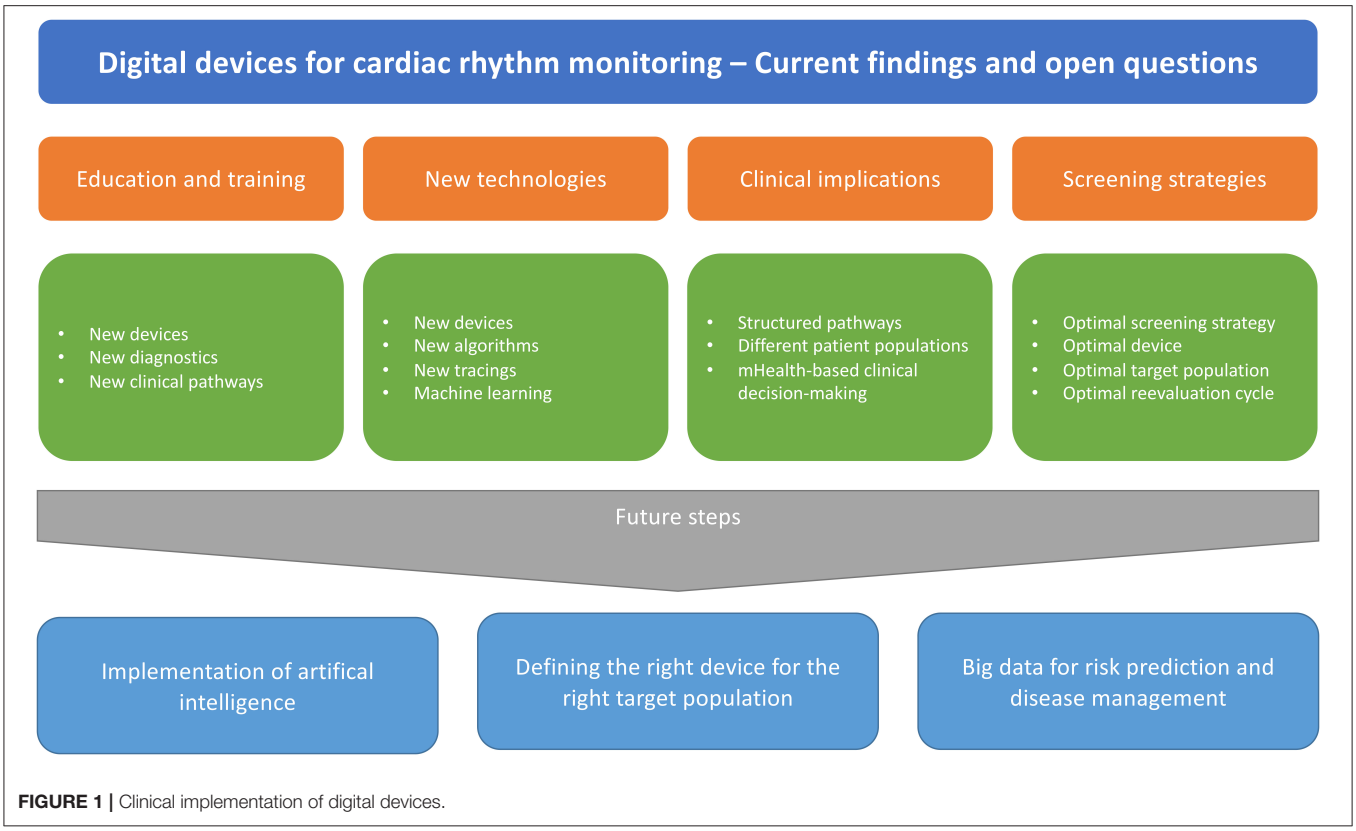

FIGURE 1 | Clinical implementation of digital devices.

CLINICAL IMPLICATIONS

Still, these new technologies require validation in clinical settings and a substantiated choice of the appropriate method using the appropriate device for the patient or user (3, 4). The DoubleCheck-AF validation study from Bacevicius et al. prospectively evaluated a wrist-worn device providing both continuous PPG-based rhythm monitoring and simultaneous 6-lead ECG. The study confirms a high specificity of the underlying algorithm to detect atrial fibrillation and to differentiate atrial fibrillation from other differential diagnoses, like frequent premature contractions.

The optimal screening strategy remains to be found (5). Following important screening trials like the STROKESTOP study (6), current consensus documents extended their recommendations on target populations and settings for screening for atrial fibrillation (3). Furthermore, the implementation of systematic screening for AF to achieve long-term reduction in a combined outcome of mortality, stroke, and severe bleeding is supported by current evidence (7), but will require establishment of clear diagnostic patient pathways.

The DoubleCheck-AF study opens the door for new screening strategies using PPG-based technology as the initial screening device and extending with ECG-based devices in case of irregular pulse notifications Bacevicius et al.. Fabritz et al. present the study design of the investigator-initiated multicenter Smart in OAC – AFNET 9 study which will include 1,000 unselected individuals of 65 years or older on wearable-based screening for PPG-detected atrial arrhythmias.

In post stroke patients, searching for AF is of utmost importance and strongly recommended (3, 8). Wouters, Gruwez, Vranken, Ernon, et al. present a nice case report of a patient simultaneously monitored by an implantable loop recorder and a PPG device.

In preliminary results from the REMOTE trial, Wouters, Gruwez, Vranken, Vanhaen, et al. present their initial results from 39 patients monitored with an implantable loop recorder and a PPG-based device. Interestingly, using the implantable loop recorder as the gold standard compared to a PPG-based monitoring, they identified limitations of the mHealth technology, but also registered false-positive recordings by the implantable loop record requiring revision by a physician.

For patients after cryptogenic stroke, the CANDLE-AF study will clarify the role of a single-lead patch ECG for the early detection of AF (Jung et al.).

In a novel outlook on use of wearables, patients after coronary bypass surgery used a digital device to study the relationship between heart rate variability and pulse rate variability (Chen et al.).

Digital devices not only measure the cardiac rhythm, but can also be used for further risk stratification and clinical decision-making. In a sub-study from the TeleCheck-AF project (9), Hermans et al. analyzed the patient responses to an app-based 10-item questionnaire on risk factors. They found that self-reported

mHealth-based assessment of AF risk factors is feasible, but still bears the risk of over- or underreporting. This sets the stage for new approaches to mHealth-based clinical pathways.

CONCLUSIONS AND FUTURE PERSPECTIVES

Wearable devices for cardiac rhythm monitoring are common. For practical implementation it is key that health care professionals learn about the benefits and pitfalls of new devices, how to interpret the tracings, but also how to integrate this knowledge in practical patient pathways. Further studies are needed to identify the optimal target populations, the best screening settings, establish gold standards, and identify appropriate interventions.

AUTHOR CONTRIBUTIONS

DD and ES drafted the work and revised it critically for important intellectual content. Both authors approved publication of the content and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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ORIGINAL RESEARCH
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Accuracy of Physicians Interpreting Photoplethysmography and Electrocardiography Tracings to Detect Atrial Fibrillation: INTERPRET-AF

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Aims: This study aims to compare the performance of physicians to detect atrial fibrillation (AF) based on photoplethysmography (PPG), single-lead ECG and 12-lead ECG, and to explore the incremental value of PPG presentation as a tachogram and Poincaré plot, and of algorithm classification for interpretation by physicians.

Methods and Results: Email invitations to participate in an online survey were distributed among physicians to analyse almost simultaneously recorded PPG, single-lead ECG and 12-lead ECG traces from 30 patients (10 in sinus rhythm (SR), 10 in SR with ectopic beats and 10 in AF). The task was to classify the readings as 'SR', 'ectopic/missed beats', 'AF', 'flutter' or 'unreadable'. Sixty-five physicians detected or excluded AF based on the raw PPG waveforms with 88.8% sensitivity and 86.3% specificity. Additional presentation of the tachogram plus Poincaré plot significantly increased sensitivity and specificity to 95.5% ($P < 0.001$) and 92.5% ($P < 0.001$), respectively. The algorithm information did not further increase the accuracy to detect AF (sensitivity 97.5%, $P = 0.556$; specificity 95.0%, $P = 0.182$). Physicians detected AF on single-lead ECG tracings with 91.2% sensitivity and 93.9% specificity. Diagnostic accuracy was also not optimal on full 12-lead ECGs (93.9 and 98.6%, respectively). Notably, there was no significant difference between the performance of PPG waveform plus tachogram and Poincaré, compared to a single-lead ECG to detect or exclude AF (sensitivity $P = 0.672$; specificity $P = 0.536$).

Conclusion: Physicians can detect AF on a PPG output with equivalent accuracy compared to single-lead ECG, if the PPG waveforms are presented together with a tachogram and Poincaré plot and the quality of the recordings is high.

Keywords: atrial fibrillaiton, single-lead ECG, PPG (photoplethysmography), digital health, electrocardiography

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INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with an estimated number of 30–100 million patients worldwide (1). Currently, the prevalence of AF in Europe is approximated between 2 and 4% and is expected to double from 2010 to 2060 as a result of the increasing burden of risk factors such as hypertension, diabetes, and aging of the population (2, 3). AF is associated with significant morbidity including a 5-fold risk to develop stroke, increased heart failure rate, frequent hospitalizations and impaired quality of life, resulting in an overall 3.5-fold increase in mortality (3). According to the 2020 European Society of Cardiology (ESC) guidelines, the diagnosis of AF should be made on a standard 12-lead ECG or a $\geq$30 s single-lead ECG, showing an irregularly irregular rhythm, with no discernible P-waves preceding the QRS complexes (3). However, frequent or long term ECG monitoring is cumbersome and photoplethysmography (PPG) has emerged as a non-intrusive modality to monitor the heart rate and rhythm. A variety of mobile devices, including smartphones and smartwatches, enable PPG-based heart rhythm monitoring through their built-in cameras and/or photodetectors (4). PPG is an optical measurement technique, based on a pulse volume signal resulting from the propagation of blood pressure waves along arterial blood vessels (5). The data collected by PPG-based smartphone applications can also be used to generate a PPG waveform and various graphs that represent the interval between consecutive heartbeats to facilitate physician interpretation of the PPG output. Several algorithms have been developed to use PPG information to detect AF with a high sensitivity and specificity (6). However, data on the performance of physicians to accurately detect AF based on PPG output is lacking. This study aims to, to systematically determine and compare the accuracy of qualitative PPG, single-lead ECG and 12-lead ECG analysis by physicians to differentiate between AF and non-AF rhythms. Secondly, this study aims to explore the incremental value of PPG presentation as a tachogram and Poincaré plot, and of algorithm classification for interpretation by physicians. Thirdly, this study aims to evaluate the influence of prior PPG experience.

METHODS

Study Design

In this prospective comparative study, cardiologists, electrophysiologists and cardiology fellows were invited via email to qualitatively analyse PPG, single-lead ECG, and 12-lead ECG recordings (each temporally related in the same patients) via three separate surveys. Demographic and professional characteristics were collected from all subjects. The study was performed between March 2020 and November 2020. The protocol complies with the Declaration of Helsinki and was approved by the local ethics committee (Ziekenhuis Oost-Limburg, Genk, Belgium). The study was registered at clinicaltrials.gov (NCT04374344).

Survey Construction

The presented heart rhythm recordings were collected from a pre-existing dataset containing almost simultaneously recorded PPG, single-lead ECG and 12-lead ECG waveforms of patients that visited the outpatient cardiology department of the hospital 'Ziekenhuis-Oost Limburg'. A 60-s PPG waveform using FibriCheck® (Qompium NV, Hasselt, Belgium), a 30-s single-lead ECG representing lead one using KardiaMobile® (AliveCor, Mountain View, USA) and 10-s standard 12-lead ECG using General Electric MAC 5500HD/VU360® (Boston, Massachusetts, USA) were collected consecutively during an outpatient consultation. The recordings from patients with sinus rhythm (SR), SR with ectopic atrial or ventricular beats and AF were exported as three separate datasets. Thirty patients were selected from the dataset based on the following criteria: sufficient quality of the PPG waveform according to the FibriCheck® algorithm, sufficient quality of the single-ECG recording according to the KardiaMobile® algorithm and visually classified as high-quality PPG, single-lead ECG and 12-lead ECG recordings by two blinded medical technicians. To provide the reference diagnosis, the 12-lead ECG recordings were additionally reviewed by two independent cardiologists. In case of disagreement, a third cardiologist was consulted. As a result, the collected data included high-quality recordings from 10 patients with a regular rhythm, 10 patients with SR with ectopic beats and 10 patients with AF.

These recordings were used to construct three separate surveys (**Figure 1**), in which the participating physicians were asked to classify the heart rhythm as 'regular rhythm,' 'one or more ectopic/missed heartbeats,' 'atrial flutter,' 'atrial fibrillation,' 'unreadable,' or 'other' via a multiple-choice question formulation. The first survey consisted of PPG data only. For each of the 30 patients, the heart rhythm recording was shown as a PPG waveform (**Figure 1A**). Subsequently, additional information was added stepwise in the second and third presentation of the PPG rhythm recording. The second presentation consisted of the waveform with the corresponding 60-s tachogram (visualising the duration of peak-to-peak intervals of the waveform) and Poincaré plot (visualises the randomness of the heart rhythm by plotting the peak-to-peak interval relative to the previous peak to peak interval) (**Figure 1B**). In the third presentation, the FibriCheck® algorithm information was added to the PPG waveform with the plots (**Figure 1C**). The algorithm information was provided by the proprietary algorithm classifying each measurement as normal (i.e., regular rhythm, green), warning (i.e., possible non-AF irregularity, orange), or urgent (i.e., possible AF, red) and providing the average heart rate during the 60-s measurement. The second and third survey consisted of the single-lead and 12-lead ECG recordings of these 30 patients, respectively.

Survey Conduction

Physicians with a FibriCheck® dashboard account were invited to participate in the study and were requested to share the invitation with their colleagues. Only upon completion of the first survey, access was provided to the second and third survey presenting single-lead ECG and 12-lead ECG recordings, respectively. There were no time-limits to complete the survey and no feedback was given during or after

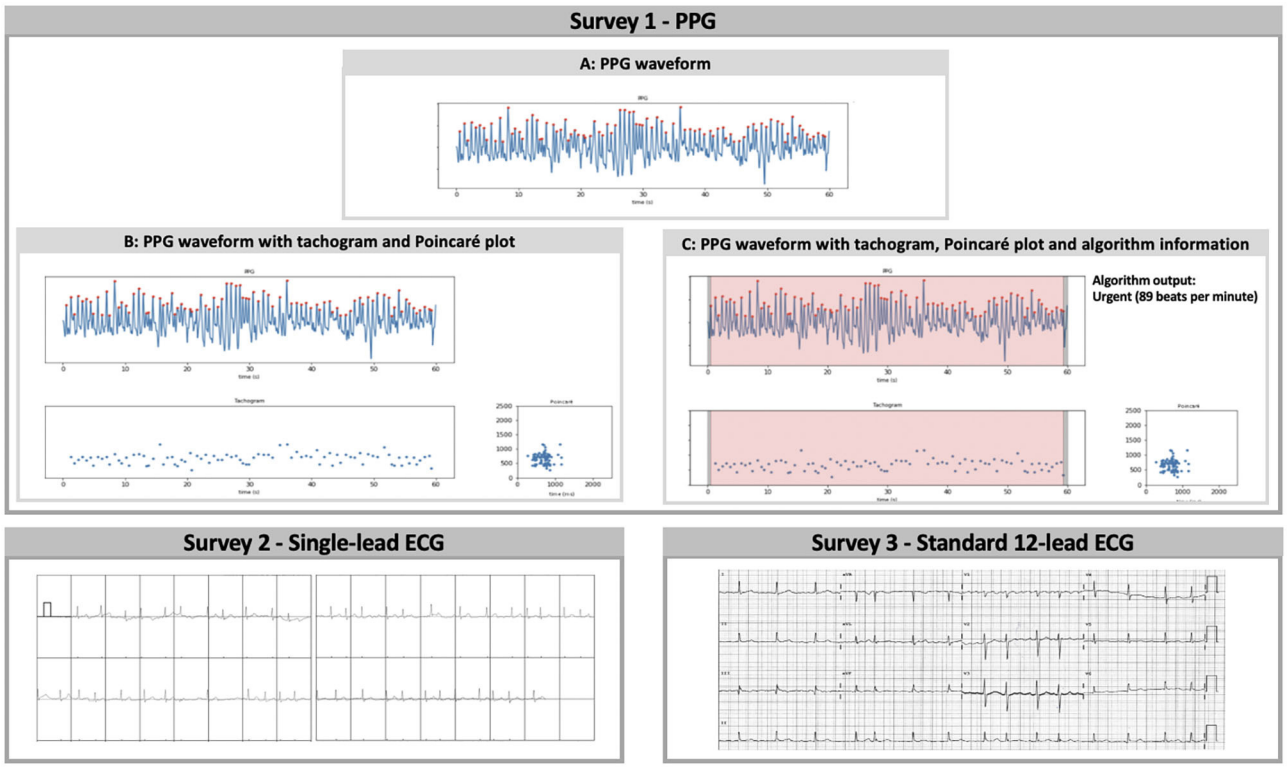

FIGURE 1 | Survey 1: **(A)** PPG waveform, **(B)** PPG waveform with tachogram and Poincaré plot, and **(C)** PPG waveform with tachogram, Poincaré plot, and algorithm information were separately and consecutively shown for qualitative analysis in the first survey. The tachogram shows the duration of each peak-to-peak interval in milliseconds, while the Poincaré plot visualises the randomness of the heart rhythm by plotting each interval on the *x*-axis (ms) vs. the preceding interval on the *y*-axis (ms). The proprietary algorithm classified measurements with sufficient signal quality as normal (regular rhythm, green), warning (possible non-AF irregularity, orange), or urgent (possible AF, red). Survey 2: The performance of single-lead ECG analysis was assessed via the second survey. The vertical dashes underneath the QRS-complexes represent potential heartbeats detected by the Kardiamobile® algorithm. Survey 3: Finally, subjects were invited to qualitatively analyse traditional 12-lead ECG recordings in the third survey. PPG, photoplethysmography; ECG, electrocardiography.

completing the surveys. Incomplete surveys were excluded from the analysis.

Statistical Analysis

For the dichotomous comparison, 'atrial fibrillation' and 'atrial flutter' answers were regarded as AF, and 'regular rhythm' and 'one or more ectopic/missed heartbeats' answers were regarded as non-AF. Recordings labelled as 'unreadable' were handled as false positive or false negative, as appropriate. If a tracing was labelled 'other' the physician was requested to specify the diagnosis in a blank text space. These diagnoses were handled as AF or non-AF as appropriate. Two-by-two contingency tables were constructed including all answers to the various PPG representations, single-lead ECG and 12-lead ECG with respect to the reference diagnosis. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of AF detection were calculated as mean with 95% confidence interval (CI). The PPVs and NPVs were estimated based on an expected AF prevalence of 6% in a population aged >65 years old (7). Additionally, PPVs were calculated for a hypothetical prevalence of 2 and 33%. These calculations were performed using the sensitivities and specificities derived from this study in the formula:

$$PPV = \frac{sensitivity\ x\ prevalence}{(sensitivity\ x\ prevalence) + ((1 - specificity)\ x\ (1 - prevalence))}$$

Sensitivities and specificities were compared with the Obuchowski-Rockette's ANOVA approach with Jackknife covariance estimation and Benjamini-Hochberg correction (8, 9). The sensitivity and specificity, which were modelled separately, were dependent variables in the Obuchowski-Rokkett's ANOVA approach. The technique was an independent variable. The advantage of the Obuchowski-Rokkett's ANOVA approach was that it takes the correlation structure in the data into account via a random effect for reader and a random effect for the test-reader interaction. The results of the various PPG presentations were compared reciprocally. The results of the PPG presentation with plots were compared against single-lead ECG and 12-lead ECG results. The latter were also compared reciprocally. Solely paired data were used in these comparisons. The influence of prior experience on the performance of physicians was analysed using a generalised linear mixed model.

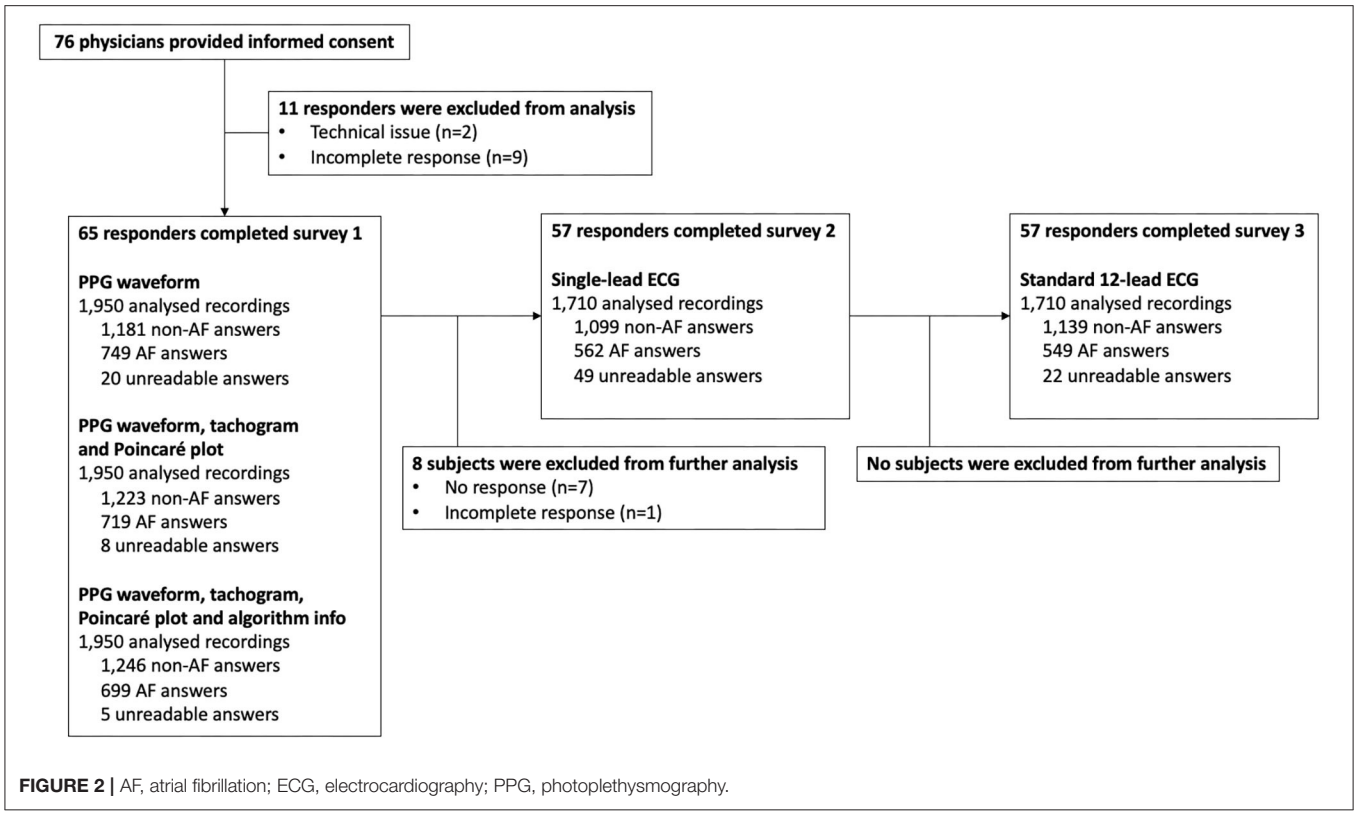

FIGURE 2 | AF, atrial fibrillation; ECG, electrocardiography; PPG, photoplethysmography.

Sensitivity and specificity were modelled separately, as dependent variables. As independent variables, experience, technique and the interaction between both were used in the model. The model also accounts for the correlation in the data through a random effect for patient and reader and allows the covariance of both random effects to differ according to the technique. All statistical analyses were 2-sided, and the level of significance was set at 5%. *P*-values were corrected for multiple testing using the Benjamini-Hochberg correction (10). SPSS Statistics 25.0 (IBM, Chicago, IL, USA) was used for descriptive analysis (participant characteristics), RStudio 3.6.3 (RStudio, Boston, USA) was used to perform the Obuchowski-Rockette's ANOVA approach using the R package MRMCaov (9) and the GLIMMIX procedure in SAS 9.4 (SAS, North-Carolina, USA) was used to perform the generalised linear mixed model.

RESULTS

Study Population

A total of 76 surveys were started of which 11 had to be excluded as a result of technical issues and/or incompleteness (**Figure 2**). Complete responses, eligible for analysis, were obtained from 30 cardiologists, 26 electrophysiologists, and 9 cardiology fellows (**Table 1**). Afterwards, the single-lead ECG survey and 12-lead ECG survey were completed by 57 subjects, resulting in a total number of 1,950, 1,710, and 1,710 interpreted recordings, respectively (**Figure 2**). The participating physicians originated from 33 centres in 9 European countries. 47.7% of them had prior experience with manual PPG analysis.

TABLE 1 | Characteristics of the study population.

	Medical professionals ($n = 65$)
Age, years (Q1–Q3)	38 (34–47)
Current profession	
Cardiologist	30 (46.2%)
Electrophysiologist	26 (40.0%)
Cardiology fellow	9 (13.8%)
Use PPG in clinical practice	43 (66.2%)
Experience in manual PPG analysis	31 (47.7%)

PPG, Photoplethysmography; Q1, 25th percentile; Q3, 75th percentile.

Performance of Photoplethysmography Analysis

Data on accuracy is summarised in **Table 2**. The classification of PPG waveforms alone provided a total of 1,699 (87.1%) correct answers. This yielded a sensitivity of 88.8% (95% CI 86.1–91.1%) and specificity of 86.3% (95% CI 84.3–88.1%) to detect AF. When the corresponding tachogram and Poincaré plot were added in the next step, 182 (9.3%) answers were adjusted; 153 (84.1%) were successfully corrected, whilst 29 (15.9%) were incorrectly adjusted. The sensitivity and specificity to detect AF both increased significantly to 95.5% (95%; CI 93.7–97.0%; $P < 0.001$) and 92.5% (95%; CI 90.9–93.8%; $P = 0.002$), respectively (**Figure 3**). When the FibriCheck® algorithm output was provided subsequently, 57 (2.9%) answers were

TABLE 2 | Accuracy metrics of the qualitative PPG, single-lead ECG, and 12-lead ECG analysis.

	PPG waveform	PPG waveform + Tachogram + Pointcaré plot	PPG waveform + Tachogram + Pointcaré plot + Algorithm info	Single-lead ECG	12-lead ECG
N physicians	65	65	65	57	57
N qualitatively analysed recordings	1,950	1,950	1,950	1,710	1,710
N unreadable answers (n AF; n non-AF)*	20 (1.0%) (14; 6)	8 (0.4%) (8; 0)	5 (0.3%) (5; 0)	49 (2.9%) (21; 28)	22 (1.2%) (20; 2)
Sensitivity, % (95% CI)	88.8 (86.1–91.1)	95.5 (93.7–97.0)	97.5 (96.0–98.6)	91.2 (88.6–93.4)	93.9 (91.6–95.7)
Specificity, % (95% CI)	86.3 (84.3–88.1)	92.5 (90.9–93.8)	95.0 (93.7–96.1)	93.9 (92.3–95.2)	98.6 (97.7–99.2)
PPV**, % (95% CI)	29.3 (26.5–32.2)	44.7 (40.1–49.5)	55.5 (49.6–61.2)	48.7 (43.0–54.4)	81.0 (72.4–87.4)
NPV**, % (95% CI)	99.2 (99.0–99.3)	99.7 (99.6–99.8)	99.8 (99.7–99.9)	99.4 (99.2–99.5)	99.6 (99.5–99.7)
Accuracy, % (95% CI)	87.1 (85.6–88.6)	93.5 (92.3–94.5)	95.9 (94.9–96.7)	93.0 (91.7–94.2)	97.0 (96.1–97.8)

PPG, photoplethysmography; ECG, electrocardiography; N, number; AF, atrial fibrillation; CI, confidence interval; (*) Number of readings classified as unreadable by the subjects. n-AF: number of AF recordings classified as unreadable. N non-AF: number of non-AF recordings classified as unreadable; (**) Estimated based on an AF prevalence of 6%.

adjusted, 51 (89.5%) were successfully corrected, whilst 7 (10.5%) were incorrectly adjusted. The engendered increase in sensitivity to 97.5% (95% CI 96.0–98.6%; $P = 0.556$) and specificity to 95.0% (95% CI 93.7–96.1%; $P = 0.182$) for AF were not statistically significant.

The accuracy to detect AF by physicians who reported to be experienced with PPG analysis was not significantly different from the performance of physicians without prior PPG experience for any of the PPG presentations ($P > 0.37$ for sensitivity, $P > 0.62$ for specificity). The average proportion of correct answers in the PPG survey was 93.3% per participating physician (61.1% minimum; 90.0% 1st quartile; 95.6% 3th quartile; 100% maximum).

Electrocardiography vs. Photoplethysmography Recordings to Detect AF

The mean sensitivity for AF detection based on a single-lead ECG and 12-lead ECG were 91.2% (CI 88.6–93.4%) and 93.8% (95% CI 91.5–95.7%), respectively. There was no significant difference among both, neither when compared to qualitative analysis of the PPG waveforms with plots. The mean specificity for AF detection based on single-lead ECG and 12-lead ECG was 93.9% (95% CI 92.3–95.2%) and 98.6% (95% CI 97.7–99.2%), respectively. The specificity of 12-lead ECG was significantly higher ($P = 0.035$), while for single-lead ECG the specificity was similar ($P = 0.536$) compared to PPG waveforms with corresponding RR-tachograms and Poincaré plots.

Extrapolating Survey Results to a Hypothetical AF Screening Program

The performance was calculated in a hypothetical population with AF prevalence of 6% (**Table 2**). The overall accuracy for the raw PPG waveform (87.1%; CI 85.6–88.6) increased numerically when the tachogram and Poincaré plot were provided (93.5%; CI 92.3–94.5) and further increased when the algorithm output was provided (95.9%; CI 94.9–96.7), which was comparable to single-lead ECG (93.0%; 91.7–94.2) but numerically lower than 12-lead ECG (97.0%; 96.1–97.8). A similar trend was observed for the PPV. The raw PPG waveform resulted in the lowest PPV (29.3%; 26.5–32.2), which increased when the plots were provided (44.7%; CI 40.1–49.5%) and when the algorithm output was provided (55.5%; CI 49.6–61.2). This is numerically comparable to single-lead ECG (48.7%; CI 43.0–54.4%), but lower than 12-lead ECG (81.0%; CI 72.4–87.4%). The NPV was above 99.2% for all PPG and ECG outputs.

DISCUSSION

Main Findings

This study evaluated the performance of cardiologists and cardiology fellows to differentiate between AF and non-AF rhythms based on PPG, single-lead ECG and 12-lead ECG recordings. The main finding is that physicians can detect AF on a PPG output with equivalent accuracy compared to single-lead ECG in high-quality recordings. To achieve this performance level, a tachogram and Poincaré plot should be provided to facilitate the interpretation of the PPG waveform. These results were consistent in physicians with and without prior PPG experience.

What Is the Best Way to Present PPG Waveforms to Improve Interpretability?

PPG is new in the clinical toolbox for rhythm monitoring and many physicians are still unfamiliar with the interpretation of PPG outputs. In our study, 53% of the cardiologists and cardiology fellows had no prior experience with manual PPG

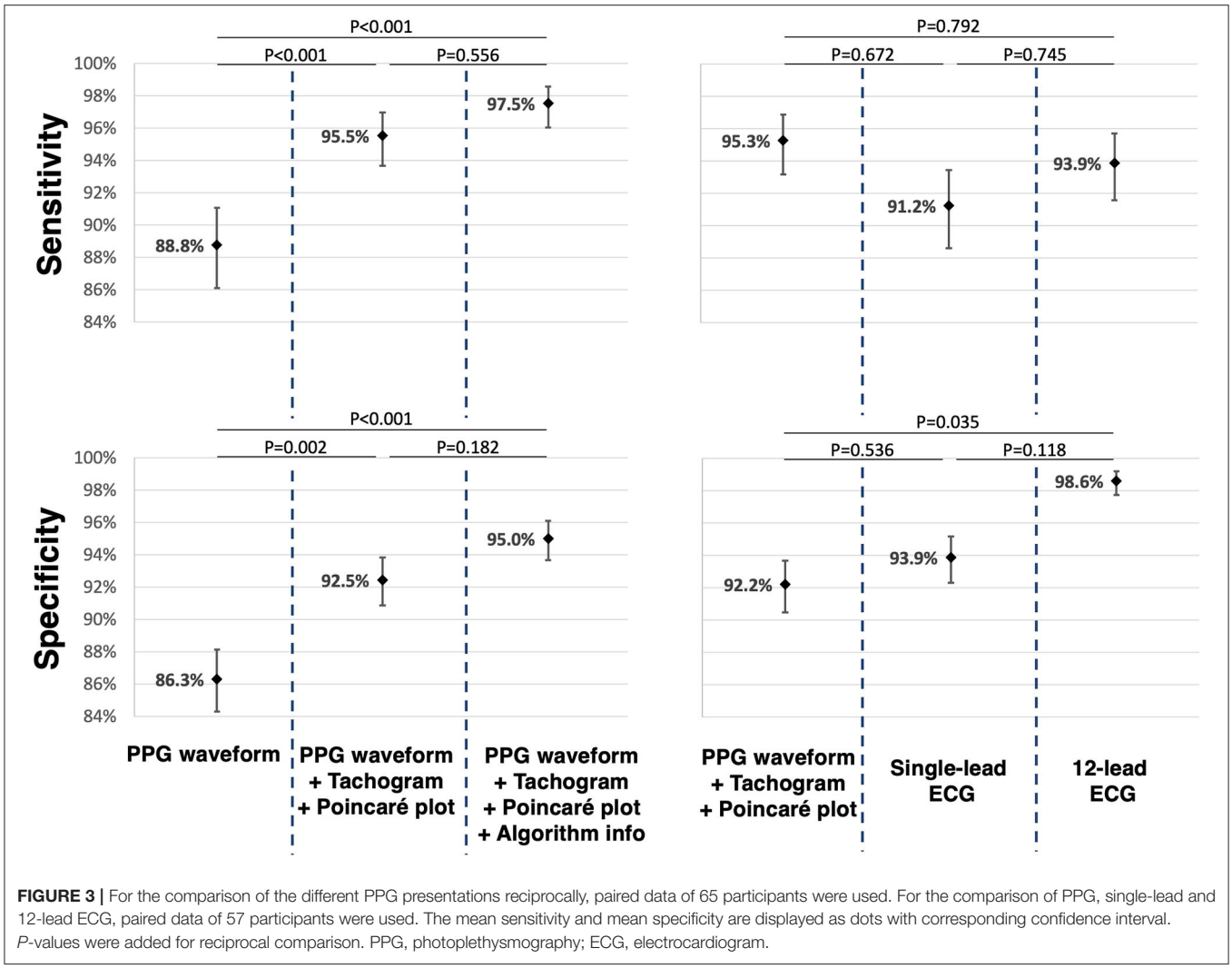

FIGURE 3 | For the comparison of the different PPG presentations reciprocally, paired data of 65 participants were used. For the comparison of PPG, single-lead and 12-lead ECG, paired data of 57 participants were used. The mean sensitivity and mean specificity are displayed as dots with corresponding confidence interval. *P*-values were added for reciprocal comparison. PPG, photoplethysmography; ECG, electrocardiogram.

analysis. This study was designed to evaluate the incremental value of a tachogram and Poincaré plot to the interpretation of a PPG waveform. The performance of physicians to detect AF improved significantly when the PPG waveform was accompanied by the plots. This demonstrates that physicians used the heart rate irregularity presented by these plots as additional information to the PPG morphology and indicates the importance of these plots in PPG analysis.

This presentation of PPG results was also adopted in the PPG dictionary paper by van der Velden et al., and should be used to define and to benchmark the presentation of PPG outputs to interpret PPG signals in clinical practice and for further research (11). Interestingly, the accuracy did not further improve, when the physicians were provided with the FibriCheck® algorithm results in addition to the PPG waveform with plots. It should be noted that the accuracy of the algorithm by itself was not evaluated in this study. The accuracy of the FibriCheck® app has been described in literature with a reported sensitivity of 96% and specificity of 97% to detect AF (12). Potentially, a combined approach of the algorithm classification and manual overreading may result in even better performance and reduce workload, which warrants further study. To compare PPG vs. single-lead ECG, we compared the benchmark presentation (a PPG waveform with plots) against single-lead ECG without providing the algorithm results of either technology. Of note, we did not investigate the accuracy of single-lead ECG combined with the corresponding tachogram and Poincaré plot, which may also have implications for the representation of 12-lead and single-lead ECG recording.

Photoplethysmography: AF Detection vs. AF Diagnosis

Current guidelines state that when AF is suspected by an automated algorithm, confirmation on an ECG tracing is always required. While the use of a single-lead ECG is a class I recommendation in the ESC 2020 guidelines, the use of PPG alone to establish the diagnosis is not accepted, even when overread by a physician (3). This accords with the general feeling among cardiologists as 83% would diagnose AF based on a single-lead ECG, but only 27% would make the diagnosis based on

a PPG output (13). Theoretically, single-lead ECG has some advantages over PPG, such as the ability to evaluate the presence of a p-wave, the QRS width and the QT interval. However, these advantages did not result in a superior performance to detect AF in our study. Particularly if the PPG waveform is combined with the corresponding tachogram and Poincaré plot, physicians could accurately interpret the recordings and detect AF, regardless of prior PPG experience. However, it should be noted that a higher number of different morphologies and other arrythmias could influence these results when applied in clinical practice. Whether the disparity between the general feeling among cardiologist and our study results derive from ignorance toward PPG or superior evaluation of other morphologies and arrythmias with ECG in clinical practice remains to be demonstrated. Currently, PPG is already being used in clinical practice for remote rhythm management in patients who are already diagnosed with AF. By example, in the TeleCheck-AF project on-demand PPG-based rate and rhythm monitoring was used around teleconsultation in 40 centers in Europe during the COVID-19 pandemic (14–16). In this context PPG technology is used to detect, but not diagnose AF. The provided results of this INTERPRET-AF study should trigger further discussion whether every AF episode detected with PPG still needs to be confirmed with ECG documentation to allow the diagnosis of AF in a patient.

Clinical Implications and Implications for AF Screening

Patients with AF detected with PPG and an automated analysis algorithm should have their PPG output reviewed by a physician. To optimise the accuracy, the output should be presented as a PPG waveform with the corresponding tachogram and Poincaré plot for physician review. This is the new benchmark presentation and the results of this study demonstrate that AF can be detected on this presentation with similar accuracy as on a single-lead ECG trace, but lower specificity then a 12-lead ECG. That is, for measurements of high-quality. As alluded to before, according to current guidelines, ECG confirmation is required to make the diagnosis of AF. However, ECG confirmation may become obsolete as physicians can detect AF on the PPG benchmark presentation with similar accuracy as demonstrated in these results. This is of particular interest in AF screening. The feasibility of PPG based screening for AF has been demonstrated by large scale screening trials that used smartphones to record a 60-s PPG waveform at home (17). In our study, a smartphone was used to generate 60-s of PPG data in the hospital. PPG measurements with a smartphone at home or in the hospital are considered equivalent as the patient is aware when a measurement is made and instant feedback is provided when the measurement is of insufficient quality, allowing the patient to make a new measurement and avoid motion artefacts until the required quality is attained. Similarly, in real-life conditions, the quality assessment is performed by the algorithm before a rhythm classification is performed. In all (>5.5 million) 60-s PPG segments recorded with the FibriCheck application up to August 2021, only 8.2% of the measurements were of insufficient quality (data provided by Qompium NV, Hasselt, Belgium). Measurements of insufficient quality are disregarded and will not be presented to the physician for interpretation. By contrast, screening trials that adopted a smartwatch-based approach can sample more frequent PPG measurements (up to a continuous measurement) (18). However, wearable devices (smartwatches) perform PPG measurements while the patient is unaware and unable to avoid motion artefacts. Hence, this approach does not always result in a high-quality measurement and the classification of insufficient quality measurements is more relevant to PPG deriving wearables. It should be noted, that our study design does not allow extrapolation of these results to measurements of insufficient quality. Both the smartphone- and smartwatch-approach require additional hardware to make a confirmatory ECG documentation of the arrythmia. By contrast, screening programs that use single-lead ECG to screen for AF do not require confirmatory testing to diagnose AF according to current guidelines (19). This study challenges that inequality and suggests that in the absence of other arrythmias, single-lead ECG is not superior to PPG to detect AF when a high-quality PPG waveform is presented with a tachogram and Poincaré plot. Due to the nature of screening, it is likely that confirmational testing of any kind remains indispensable. Hence, this study should open the debate whether confirmatory testing will be possible with PPG as it is with single-lead ECG.

Despite the high sensitivity and specificity of PPG and single-lead ECG for AF detection, the PPV for both drastically declines in populations with a lower AF prevalence. In the setting of AF screening, most studies reported an AF detection rate between 2 and 10%, which is far less than the AF prevalence of 33% in the PPG and ECG dataset presented to the participants in this study (20). To simulate the setting of AF screening in an elderly population, the diagnostic metrics of this study were re-calculated for a hypothetical AF prevalence of 6%. In this simulation, PPG with plots, single-lead ECG and 12-lead ECG all had a very high NPV above 99.2%, but the PPV was moderate for PPG with plots, and for single-lead ECG (44.7 and 48.7%, respectively), suggesting that these detection methods may generate a high number of false positive (FP) diagnoses in AF screening. **Figure 4** illustrates how the PPV decreases as the AF prevalence decreases. This highlights the need for confirmational testing after AF detection in a screening program. It has previously been shown that the PPV of handheld single-lead ECG is less than the 12-lead ECG gold standard (between 61.9 and 87.0%), even when interpreted by electrophysiologists in a population with a high AF prevalence (11.9%) (21). However, this is the first study to directly compare PPG and single-lead ECG, suggesting that PPG might be as appropriate as single-lead ECG to confirm AF (if a high-quality PPG output is reviewed by a physician on a waveform with tachogram and Poincaré plot). It will be important to confirm these findings in out-of hospital settings with more morphologies and other arrythmias before enabling smartphones to both detect and confirm AF with PPG.

The purpose of repetitive PPG measurements to confirm AF is to increase the PPV and to lower the false positive rate. There are several reasons why PPG is a suitable tool to fulfil this goal. One, because PPG does not require additional hardware, PPG can

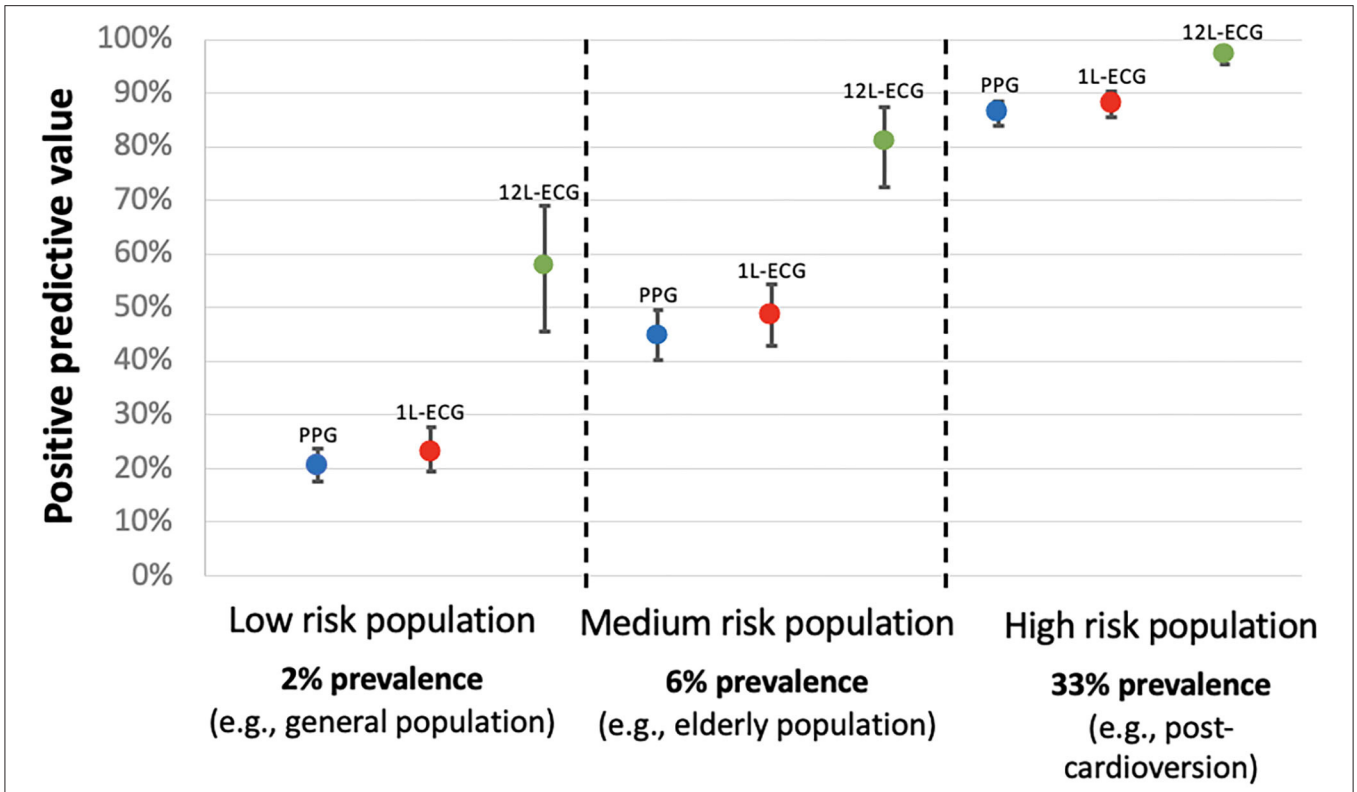

FIGURE 4 | Positive predictive value for AF detection according to the AF prevalence in the targeted population. 1L-ECG, single-lead electrocardiogram; 12L-ECG, 12-lead electrocardiogram; PPG, photoplethysmography (in this context refers to photoplethysmography waveform with tachogram and poincaré plot).

easily be used with repetitive measurements which by itself is a strong mechanism to improve specificity and reduce the number of false positives. Two, combining AF detection algorithms and manual interpretation can decrease the false positive rate in PPG and single-lead ECG screening strategies (17). In this study, the algorithm output did not significantly improve the accuracy, however the algorithm did guide physicians to correct their response in 51 cases. Three, advances in deep learning algorithms will likely continue to improve the robustness of PPG algorithms and ECG algorithms resulting in increased an PPV and fewer false positives (5).

Further larger studies also focusing on the real-life performance of physicians to interpret PPG waveforms and the non-inferiority of treatment of ECG- vs. PPG-detected AF on AF outcomes are required to clarify the predictive values in population screening. Both PPG and single-lead ECG based screening with both algorithms as well as physician interpretation should be validated in real-world setting with appropriate AF prevalence and where AF detection is complicated by other cardiac arrythmias and artefacts that were not included in the current validation studies.

LIMITATIONS

We acknowledge several limitations to this survey-based study approach. One, the number of responders, participating in the study, was limited. Despite, statistical power was attained as a result of the high number of questions per subject. Two, there may be a selection bias, as the invited physicians were mainly physicians with an existing FibriCheck® dashboard. However, according to our survey results, almost half of the responders did not have prior PPG experience. Three, the tracings chosen for PPG and ECG represent an artificial population and may limit extrapolation to real-world use. Therefore, the prevalence was adjusted in the PPV and NPV calculation. Four, this study only evaluated the differentiation between AF and non-AF rhythms as a dichotomous classification and did not take a broader differential diagnosis into account. Five, only high-quality measurements performed in the cardiology department were selected in the survey, limiting the extrapolation to wearable devices (smartwatches) performing PPG measurements while the patient is unaware and unable to avoid motion artefacts. Six, only measurements of 30 patients were included in the survey. These findings should be confirmed in a larger population with more morphologies and arrythmias.

CONCLUSION

Physicians can detect AF on a high-quality PPG output with equivalent accuracy compared to single-lead ECG, even without prior PPG training. To achieve this performance level, a tachogram and Poincaré plot should be provided to facilitate the interpretation of the PPG waveform. Such rhythm interpretation

is even as sensitive as 12-lead ECG to detect AF. However, it remains that 12-lead ECG is more specific, and thus results in a higher positive predictive value and fewer false positives. This is the first paper to describe a method of PPG presentation that should be used for future benchmarking studies. Subsequent studies should be conducted in real world settings to confirm or disprove the findings suggested by this study, that high-quality PPG recordings might be as suitable as single-lead ECG to diagnose AF.

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 Comité Medische Ethiek, Ziekenhuis Oost-Limburg. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SE and TP were involved in data collection. SE, HG, LP, PV, and PH were involved in the statistical analysis. HG wrote the initial manuscript. All authors read, reviewed, and edited the manuscript in the subsequent revision rounds.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.734737/full#supplementary-material

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Relationship Between Heart Rate Variability and Pulse Rate Variability Measures in Patients After Coronary Artery Bypass Graft Surgery

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Background: Heart rate variability (HRV) and pulse rate variability (PRV) measures are two kinds of physiological indices that can be used to evaluate the autonomic nervous function of healthy subjects and patients with various kinds of illness.

Purpose: In this study, we compared the agreement and linear relationship between electrocardiographic signals (ECG)-derived HRV and photoplethysmographic signals (PPG)-derived right hand PRV (R-PRV) and left hand PRV (L-PRV) measures in 14 patients over 1 year after coronary artery bypass graft (CABG) surgery.

Method: The ECG and PPG signals of the patient were recorded simultaneously for 10 min in a supine position. The last 512 stationary RR intervals (RRI) and peak-to peak intervals (PPI) of pulse wave were derived for data analysis. Bland-Altman plot was used to assess the agreement among HRV and both hand PRV measures, while linear regression analysis was used to examine the relationship among corresponding measures of HRV, R-PRV, and L-PRV.

Result: The results revealed significant differences in total power (TP), very low-frequency power (VLF), low-frequency power (LF), high-frequency power (HF), and normalized VLF (VLFnorm) among HRV, R-PRV, and L-PRV. Bland-Altman plot analysis showed good agreements in almost all measures between R-PRV and L-PRV, except insufficient agreement was found in LF/HF. Insufficient agreements were found in root mean square successive difference (RMSSD), normalized HF (HFnorm), and LF/HF indices between HRV and L-PRV, and in VLFnorm, HFnorm, and LF/HF indices between HRV and R-PRV. Linear regression analysis showed that the HRV, R-PRV, and L-PRV measures were all highly correlated with one another ($r = 0.94 \sim 1$; $p < 0.001$).

Conclusion: Though PRV measures of either hand are not surrogates of HRV measures, they might still be used to evaluate the autonomic nervous functions of CABG patients due to the moderate to good agreements in most time-domain and frequency-domain HRV measures and the strong and positive correlations among HRV and both hands PRV measures in CABG patients.

Keywords: autonomic nervous modulation, heart rate variability, pulse rate variability, coronary artery bypass graft, photoplethysmographic assessment

INTRODUCTION

Heart rate (HR) variability (HRV) refers to the fluctuation of HR responses around the mean HR. The underlying mechanisms to modulate cardiac-related activation are related to autonomic nervous activities and other physiological system regulations (1–3). The temporal and spectral components of HRV can be used to identify the sympathovagal interaction in various pathophysiological conditions, such as acute myocardial infarction (4, 5), prediction of morbidity and mortality (6), identification of septic patients in the intensive care unit (7), and prediction of severity for septic patients in the emergency department (8).

In clinical practice, the health practitioners frequently use palpation technique to determine the pulses rate (PR) of the patients. Recently, wearable devices are frequently used to facilitate PR evaluation for health monitoring. For example, smartwatches and smartphones with built-in photoplethysmographic (PPG) sensors have been extensively used to evaluate the daily change in cardiovascular responses (9). These biomarkers can be further applied to clinical diagnosis, e-health management, and exercise adaptation (10). Thus, PPG assessment of pulse provides convenient and friendly facilitation to monitor cardiovascular health in general and clinical populations.

The PPG detection from different body regions has been reported in recent HRV and PR variability (PRV) studies (11, 12). However, this alternative use of HRV and PRV to assess cardiac-related health is controversial. Previous studies comparing measures between blood pressure waveforms and HRV demonstrated that both methods were reliable to assess cardio-related changes in sympathovagal interaction (13, 14). In a clinical study, moderate to good agreement between HRV and PRV during 1 min deep breath controlled at 6 times per minute and a standard 5 min short-term record has been reported in clinical patients with gynecological and pain medicine practice (15). Conversely, a discrepancy between PRV and HRV measures has been reported in cold exposure (11), spectral analysis (16), during obstructive sleep apnea events (17), and healthy subjects (18). The discrepancy between HRV and PRV measures is related to the blood contents and the structure of the radial artery on the arterial pulse wave propagation (19). The difference in experimental conditions might also play a role, such as ambient temperature (20), respiratory control (21), body position (22).

Pathological studies have shown that patients after coronary artery bypass graft surgery (CABG) have significantly reduced sensitivity in HRV modulation (23). Thus, the HRV assessment can be used to do risk stratification and to monitor the recovery of cardiac health after CABG surgery. However, conventional ECG recording may not be obtainable in CABG patients during home-based recovery. Since PPG technology via smartphone and wearable devices has been widely used nowadays to monitor HRV and PRV, the PRV measures of either hand may be the alternative method to monitor the autonomic nervous function in patients with cardiovascular diseases (24).

This study aimed to investigate (1) the limits of agreement between ECG-derived HRV and both hands PPG-derived PRV measures in patients after CABG surgery; (2) the correlations among measures of HRV and both hands PRV in CABG patients.

MATERIALS AND METHODS

Subjects

Fourteen patients after CABG surgery over 1 year were recruited in this study. All patients were requested to refrain from alcohol or caffeine ingestion 24 h prior to participation in the study. Exclusion criteria included atrial fibrillation, frequent premature ectopic complexes, the use of class I antiarrhythmic medication, and myocardial infarction within the last 6 months. This study has been approved by the Institute Review Board of Taipei Veterans General Hospital. The experimental procedures were introduced to the patients, and written informed consents were obtained prior to the study. This study was undertaken in accordance with the Declaration of Helsinki.

Heart Rate and Pulse Rate Variabilities

After 5 min rest in a supine position, the ECG and PPG signals of the patient were recorded simultaneously using the PowerLab 16sp with 16 channels (ML795 PowerLab/16SP, ADInstruments, Sydney, Australia) for 10 min. Three self-adhesive ECG electrodes were placed onto the chest parallel to the longitudinal heart axis for ECG recording. The pulse wave signals were recorded at the index fingertip of both hands via infrared PPG probes (MLT1020; ADInstruments, CO Springs, CO, USA). A custom-written program was used to collect ECG and PPG signals (MathWorks Inc., Natick, Massachusetts, USA). An analog-to-digital converter with a sampling rate of 400 Hz was set for data acquisition.

A peak detection algorithm was developed to detect the peaks of the R waves in the QRS complexes in the ECG tracing using a

TABLE 1 | Demographics and clinical characteristics of the patients receiving CABG.

Age (yrs)	63.5 (55.5 ∼ 66.3)
Gender	
Male	9 (64.3)
Female	5 (35.7)
Body height (cm)	162 (157 ∼ 168)
Body weight (kg)	64.1 (57.3 ∼ 80.0)
Body mass index (kg/m^2)	25.1 (22.1 ∼ 27.0)
History	
Previous myocardial infarction	5 (35.7)
Hypertension	11 (78.6)
Diabetes mellitus	6 (42.9)
Hyperlipidemia	4 (28.6)
Medication	
Beta-Blocker	5 (35.7)
Calcium antagonist	9 (64.3)
Nitrates	12 (85.7)
Angiotensin-Converting enzyme inhibitor	6 (42.9)
Digitalis	2 (14.3)
Aspirin	10 (71.4)

Data are presented as median and interquartile range (IQR, 25 ∼ 75%) or number (percentage). CABG, coronary artery bypass graft surgery.

wavelet-based method along with multiscale differential operator (25). The length of the interval between successive peaks of R waves in the QRS complexes was defined as the RR interval (RRI) of that pair of R waves. The highest peak of the pulse wave following the R wave in the QRS complex was detected using a similar peak detection algorithm. The length of the interval between successive peaks of pulse waves in the PPG tracing was defined as the peak-to-peak intervals (PPI) of pulse waves. The last 512 stationary RRI and PPI were used for subsequent data analysis.

Both time-domain and frequency-domain measures of HRV and both hands PRV were compared. Time-domain measures included mean RRI (Mn), heart rate (HR), standard deviation and root mean square successive difference (RMSSD) of RRI or PPI (SDNN), and coefficient of variation of RRI or PPI (CVNN = SDNN/Mn). Frequency-domain measures were the individual powers in the power spectra of HRV and PRV. The power spectra of RRI and PPI were analyzed via fast Fourier transformation (FFT). Direct current components were excluded before computing the powers of individual frequency bands in the power spectra using FFT. The area-under-the-curve of the spectral peaks within the range of 0.01–0.4, 0.01–0.04, 0.04–0.15, and 0.15–0.4 Hz were calculated as the total power (TP), very low-frequency power (VLF), low-frequency power (LF), and high-frequency power (HF), respectively. The normalized high-frequency power (HFnorm = HF/TP) was used as the index of vagal modulation (26); the normalized low-frequency power (LFnorm = LF/TP) as the index of sympathetic and vagal modulation (27); and the low-/high-frequency power ratio (LF/HF) as the index of sympathovagal balance. The very low-frequency power (VLF) was used as the index of renin-angiotensin-aldosterone system and vagal withdrawal (28, 29).

In FFT, the best known use of the Cooley–Tukey algorithm is to divide the transform into two pieces of size $n/2$ at each step. The number of samples used in the FFT is therefore limited to power-of-two sizes, though any factorization can be used in general. Therefore, a sample size of 2^n is often used in FFT. In this study, $2^9 = 512$ RRI were used so that the ECG and PPG recording time can be restricted to within 10 min if the heart rate of the study subject is not <52 beats per minute. A long recording time of ECG and PPG might result in instability in the ECG and PPG tracing due to drowsiness, agitation, body movement, etc. The RRI and PPI thus obtained might not be stationary anymore.

Statistical Analyses

Data are presented as the median and interquartile range (IQR, 25 ∼ 75%). Variance of different measures among HRV, and both hand PRV were compared using Friedman repeated-measures analysis of variance (ANOVA) on ranks. All pairwise comparisons were further processed using the Tukey test. Additionally, the agreement between the HRV and PRV measures was assessed using Bland-Altman plots (30). Bias was calculated based on the average value of the difference between measures. The ratio of half difference between upper and lower 95% confidence limits to the mean of all pairwise measurement means (MPM) was calculated. A ratio <0.1 was defined as good agreement; a ratio between 0.1 and 0.2 was defined as moderate agreement; and a ratio >0.2 was defined as insufficient agreement (31). Linear regression analysis was performed to determine the relationship between common measures of HRV and both hands PRV. All statistical analyses were performed using SigmaPlot 13 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographics and Clinical Profiles

Fourteen patients recruited in this study had a mean age of 59.5 years, and 9 (64.3%) of them were male. The demographics, clinical profiles, and current medication are presented in **Table 1**.

Comparisons Among HRV, Left Hand PRV, and Right Hand PRV

The results revealed significant differences in TP, VLF, LF, HF, and VLFnorm among HRV, right hand PRV (R-PRV), and left hand PRV (L-PRV) (**Table 2**). Pairwise comparisons showed that the VLF, HF, and VLFnorm of R-PRV were significantly greater than those of HRV, whereas the LF of L-PRV was significantly greater than that of HRV.

Bland-Altman Analysis

Table 3 shows the results of Bland-Altman analysis among HRV, L-PRV, and R-PRV. Good agreements were observed in Mn, SDNN, CVNN, TP, VLF, and VLFnorm; moderate agreements were found in LF, HF, and LFnorm; while insufficient agreements were observed in RMSSD, HFnorm, and LF/HF between HRV and L-PRV (**Figure 1**).

TABLE 2 | Comparisons among HRV, L-PRV, and R-PRV measures in patients after CABG.

Parameters	HRV		L-PRV		R-PRV		
	Median (IQR)	CV (%)	Median (IQR)	CV (%)	Median (IQR)	CV (%)	*P*-value
Time-domain variables							
Mn (ms)	783.7 (747.9 ∼ 843.6)	8.1	783.7 (747.9 ∼ 843.6)	8.1	783.7 (747.9 ∼ 843.6)	8.1	0.779
SDNN (ms)	28.6 (19.4 ∼ 35.9)	59.2	28.5 (18.3 ∼ 36.1)	58.1	28.6 (18.4 ∼ 36.0)	58.3	0.863
CVNN (%)	0.03 (0.02 ∼ 0.04)	53.5	0.03 (0.02 ∼ 0.05)	52.4	0.03 (0.02 ∼ 0.05)	52.3	0.223
RMSSD (ms)	18.1 (11.2 ∼ 46.4)	92.0	21.9 (10.6 ∼ 45.9)	89.1	20.9 (10.7 ∼ 45.4)	90.1	0.865
Frequency-domain variables							
TP (ms^2)	271.2 (92.5 ∼ 467.6)	139.7	277.4 (95.0 ∼ 511.1)	138.0	278.9 (98.8 ∼ 516.6)	138.1	0.033#
VLF (ms^2)	66.9 (34.2 ∼ 83.5)	81.0	66.9 (34.5 ∼ 83.6)	81.7	67.6 (35.4 ∼ 84.1)*	81.2	0.024#
LF (ms^2)	56.6 (28.2 ∼ 198.3)	138.1	59.5 (30.3 ∼ 196.6)*	138.6	57.5 (33.5 ∼ 196.1)	139.0	0.011#
HF (ms^2)	40.6 (16.2 ∼ 335.5)	173.8	62.2 (20.4 ∼ 336.7)	170.1	61.3 (20.9 ∼ 331.9)*	170.1	0.042#
VLFnorm (nu)	30.6 (11.5 ∼ 48.3)	70.4	33.1 (11.6 ∼ 47.4)	68.1	32.6 (11.8 ∼ 45.9)*	68.2	0.030#
LFnorm (nu)	27.9 (19.4 ∼ 37.3)	60.7	29.1 (18.8 ∼ 36.3)	59.8	29.3 (18.2 ∼ 35.6)	60.9	0.807
HFnorm (nu)	32.1 (12.5 ∼ 61.9)	65.7	30.6 (17.0 ∼ 61.5)	61.1	31.6 (19.2 ∼ 61.5)	60.4	0.257
LF/HF	0.7 (0.4 ∼ 2.7)	127.1	0.8 (0.5 ∼ 2.2)	131.8	0.8 (0.4 ∼ 1.9)	140.7	0.318

*Data are presented as median (interquartile range, IQR: 25 ∼75%). CABG, coronary bypass graft surgery; HRV, heart rate variability; PRV, pulse rate variability; L-PRV, left hand PRV; R-PRV, right hand PRV; CV, coefficient of variation; Mn, mean RR interval; SDNN, standard deviation of RR intervals; CVNN, coefficient of variation of RR intervals; RMSSD, root mean square of successive difference; TP, total power; VLF, very low-frequency power; LF, low-frequency power; HF, high-frequency power; VLFnorm, normalized VLF; LFnorm, normalized LF; HFnorm, normalized HF; LF/HF, low-/high- frequency power ratio; bpm, beats per minute; ms, millisecond; nu., normalized unit. *Significant difference vs. HRV. #Significant difference in group comparison.*

TABLE 3 | Bland-Altman analysis of measuring variables among HRV, L-PRV, and R-PRV in patients after CABG.

Parameters	HRV vs. L-PRV			HRV vs. R-PRV			R-PRV vs. L-PRV		
	MPM	Ratio	Agreement	MPM	Ratio	Agreement	MPM	Ratio	Agreement
Mn (ms)	797.2 ±64.7	1.39×10^{-4}	Good	797.2 ±64.7	1.19×10^{-4}	Good	797.2 ±64.7	6.71×10^{-5}	Good
SDNN (ms)	31.7 ±18.6	0.076	Good	31.6 ±18.6	0.063	Good	31.7 ±18.4	0.035	Good
CVNN (%)	3.9 ±2.1	0.076	Good	3.9 ±2.1	0.065	Good	3.9 ±2.1	0.037	Good
RMSSD (ms)	34 ±30.7	0.203	Insufficient	33.9 ±30.8	0.170	Moderate	33.8 ±30.2	0.082	Good
TP (ms^2)	455.9 ±632.9	0.092	Good	455.7 ±633	0.088	Good	461.3 ±636.8	0.022	Good
VLF (ms^2)	78.2 ±63.6	0.035	Good	78.3 ±63.5	0.030	Good	78.6 ±64	0.012	Good
LF (ms^2)	139.6 ±193.0	0.142	Moderate	139.3 ±192.9	0.135	Moderate	142 ±197	0.023	Good
HF (ms^2)	238.2 ±409.3	0.137	Moderate	238.2 ±409.5	0.128	Moderate	240.7 ±409.4	0.036	Good
VLFnorm (nu)	35.9 ±22.3	0.026	Good	35.8 ±22.3	0.268	Insufficient	70.7 ±43.4	0.017	Good
LFnorm (nu)	30.8 ±18.5	0.179	Moderate	30.7 ±18.6	0.168	Moderate	30.9 ±18.6	0.039	Good
HFnorm (nu)	36.8 ±23	0.434	Insufficient	37 ±23	0.40	Insufficient	37.3 ±22.6	0.055	Good
LF/HF	1.8 ±2.4	0.739	Insufficient	1.9 ±2.5	0.689	Insufficient	1.7 ±2.4	0.275	Insufficient

MPM is presented as mean and standard deviation, and ratio as 0.5× (range of LA)/MPM. CABG, coronary bypass graft surgery; HRV, heart rate variability; PRV, pulse rate variability; MPM, mean of pairwise means. Ratio = 0.5 (range of LA)/MPM. Mn, mean RR interval; SDNN, standard deviation of RR intervals; CVNN, coefficient of variation of RR intervals; RMSSD, root mean square of successive difference; TP, total power; VLF, very low-frequency power; LF, low-frequency power; HF, high-frequency power; VLFnorm, normalized VLF; LFnorm, normalized LF; HFnorm, normalized HF; LF/HF, low-/high- frequency power ratio; bpm, beats per minute; ms, millisecond; nu, normalized unit.

The comparison between HRV and R-PRV revealed good agreements in Mn, SDNN, CVNN, TP, and VLF; moderate agreement in RMSSD, LF, HF, and LFnorm; and insufficient agreement in VLFnorm, HFnorm, and LF/HF between HRV and R-PRV (**Figure 2**).

In the comparison between the measures of R-PRV and L-PRV, good agreements were observed in almost all measures, except for insufficient agreement found in LF/HF (**Figure 3**).

Linear Regression Analysis

Figure 4 shows the linear correlations among the RRI, left hand PPI, and right hand PPI in a representative patient. There are very significant and strong positive correlations among RRI and both hands PPI in that study subject, indicating that both hand PPI is associated strongly and positively with the RRI. As demonstrated in **Table 4**, there were significant and strong positive correlations among all measures of HRV, R-PRV, and L-PRV (r ranged from 0.943 to 1, $p < 0.01$).

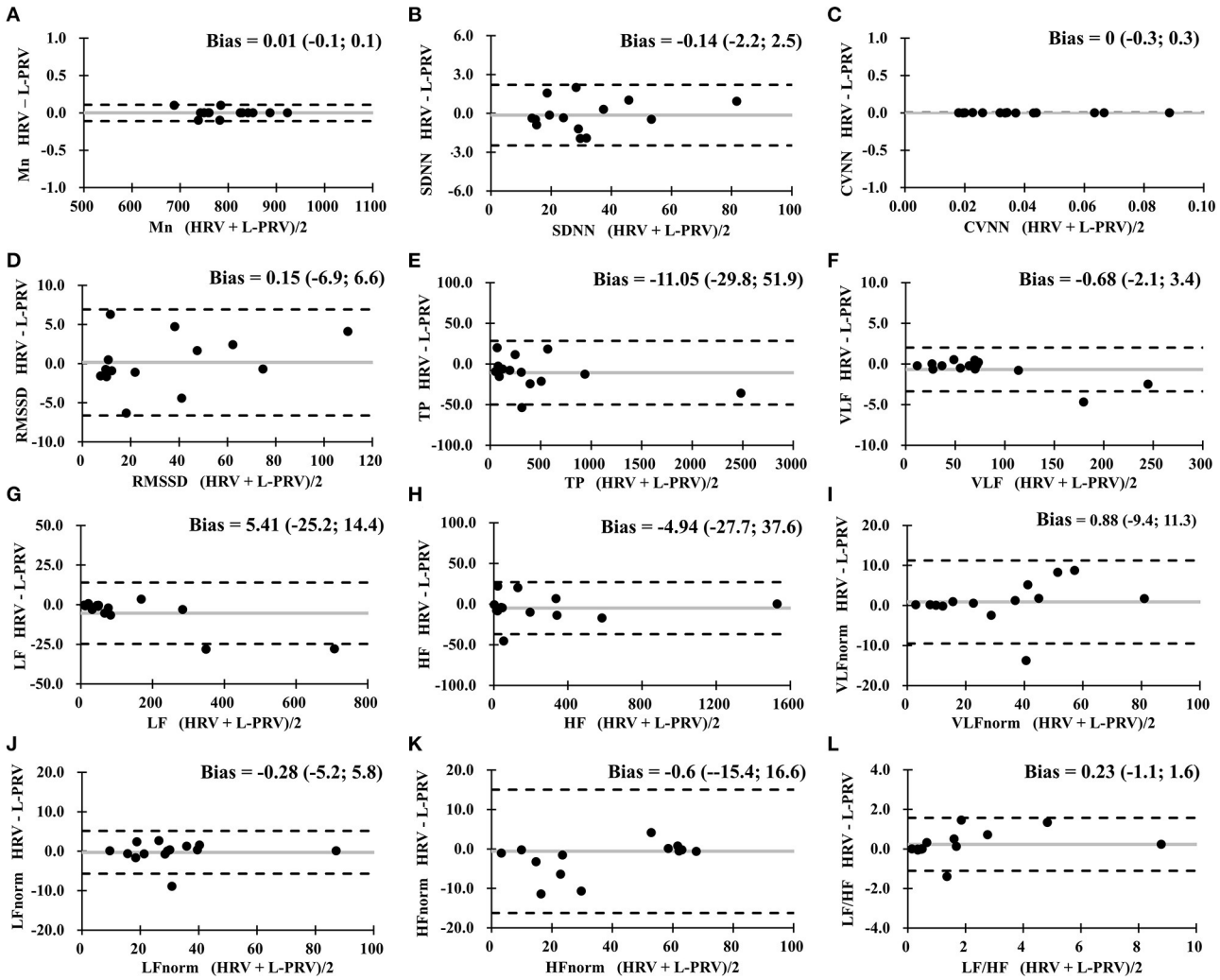

FIGURE 1 | Bland-Altman analysis between HRV measures and L-PRV measures. Gray lines indicate the bias between the measures. **(A)** Mn, mean RR interval; **(B)** SDNN, standard deviation of normal RR intervals; **(C)** CVNN, coefficient of variation of normal RR intervals; **(D)** RMSSD, root mean square of successive difference; **(E)** TP, total power; **(F)** VLF, very low-frequency power; **(G)** LF, low-frequency power; **(H)** HF, high-frequency power; **(I)** VLFnorm, normalized VLF; **(J)** LFnorm, normalized LF; **(K)** HFnorm, normalized HF; **(L)** LF/HF, low-/high- frequency power ratio; L-PRV, left hand pulse rate variability.

DISCUSSION

This study investigated the agreement and correlation of time-domain and frequency-domain HRV indices between ECG-derived HRV and finger PRV (right and left hands) in CABG patients after 1 year of surgery. The primary finding was that both hands PRV cannot be used as the surrogate of HRV as evidenced by (1) insufficient agreement in RMSSD, HFnorm, and LF/HF between HRV and L-PRV, and (2) insufficient agreement in VLFnorm, HFnorm, and LF/HF between HRV and R-PRV. Clearly, there was insufficient agreement in LF/HF between HRV measures and PRV measures of either hand. The secondary finding was that both hands PRV measures have a near perfect correlations with HRV measures, indicating that both hand PRV measures can also be used to evaluate autonomic nervous modulation in CABG patients. If the latter finding is true, then the PRV of either hand can be used as a user-friendly and low-cost (i.e., smartphone and smartwatch) option for the regular evaluation and monitoring of autonomic nervous function in CABG patients and possibly in patients with other cardiovascular diseases.

In this study, the Friedman test revealed significant differences in TP, VLF, LF, HF, and VLFnorm among HRV, R-PRV, and L-PRV. Overestimation of HRV variables in VLF, LF, HF, and VLFnorm of R-PRV was observed when PRV was used to compare to HRV. It seems such observation only occurred in frequency-domain HRV indices.

The limits of agreements were found to be of a moderate to good levels in Mn, SDNN, CVNN, TP, VLF, LF, HF, and LFnorm, while an insufficient agreement was found in RMSSD, VLFnorm, HFnorm, and LF/HF between HRV and both hand PRV. Our previous study supported such findings

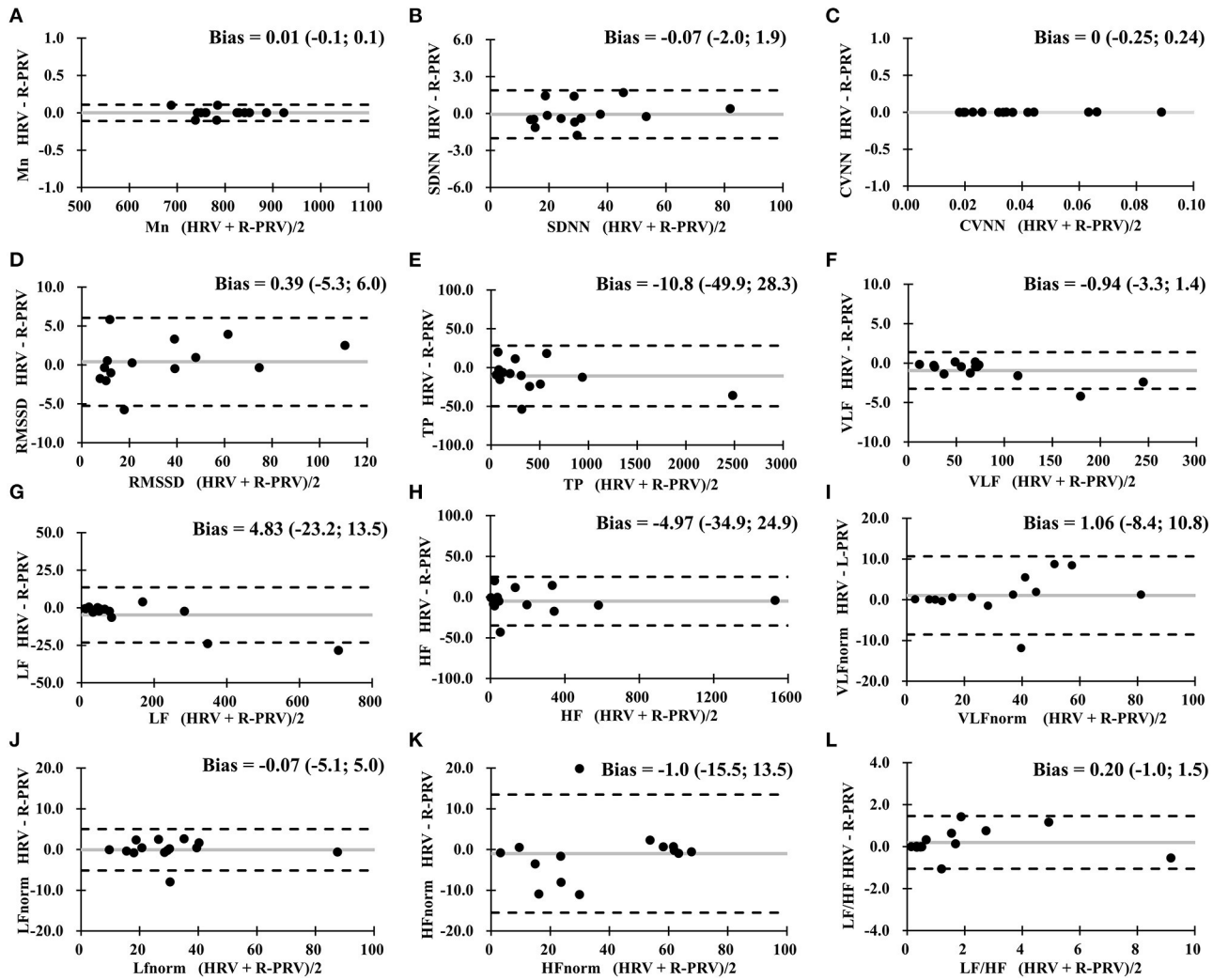

FIGURE 2 | Bland-Altman analysis between HRV measures and R-PRV measures. Gray lines indicate the bias between the measures. **(A)** Mn, mean RR interval; **(B)** SDNN, standard deviation of normal RR intervals; **(C)** CVNN, coefficient of variation of normal RR intervals; **(D)** RMSSD, root mean square of successive difference; **(E)** TP, total power; **(F)** VLF, very low-frequency power; **(G)** LF, low-frequency power; **(H)** HF, high-frequency power; **(I)** VLFnorm, normalized VLF; **(J)** LFnorm, normalized LF; **(K)** HFnorm, normalized HF; **(L)** LF/HF, low-/high- frequency power ratio; R-PRV, right hand pulse rate variability.

where a poor agreement was found between both hand PRV and ECG-derived HRV in healthy adults (18). Furthermore, pathological conditions such as obstructive sleep apnea (17) and blood pressure hypertension or hypotension (32) could potentially lead to a large measurement bias between the PRV and HRV. Conversely, moderate to good agreements between HRV and PRV have been reported in 343 clinical patients with gynecological and pain medicine practice during deep breath and normal breath conditions (15). The controversial findings may be related to methodological considerations (signal processing, identification of fiducial points, sample rate etc…) and physiological conditions (arterial vessel, respiratory activity, recording site etc…) among the studies (12).

In term of the time-domain HRV indices, RMSSD showed insufficient agreement between HRV and PRV of either hand. In HRV measures, the RMSSD is a strong indicator of vagal tone (33) and is considered a primary biomarker to identify autonomic adaptation in responses to psychological (34) and physiological stimuli (35). It was assumed that pathological conditions could play a role in affecting the limits of agreement between PRV and HRV. Mejía-Mejía et al. (32) showed that hospitalized patients in an intensive care unit have the largest bias error in RMSSD between PRV and HRV measures, compared to others time-domain indices such as SDNN, RRI, and pNN50. Furthermore, Khandoker et al. (17) reported a significant difference in RMSSD when PRV and HRV were recorded during 2 min obstructive sleep apnea events. The inaccuracy measures of RMSSD between PRV and HRV was also identified in healthy adults (18). The poor accuracy of measures between PRV and HRV may be related to the

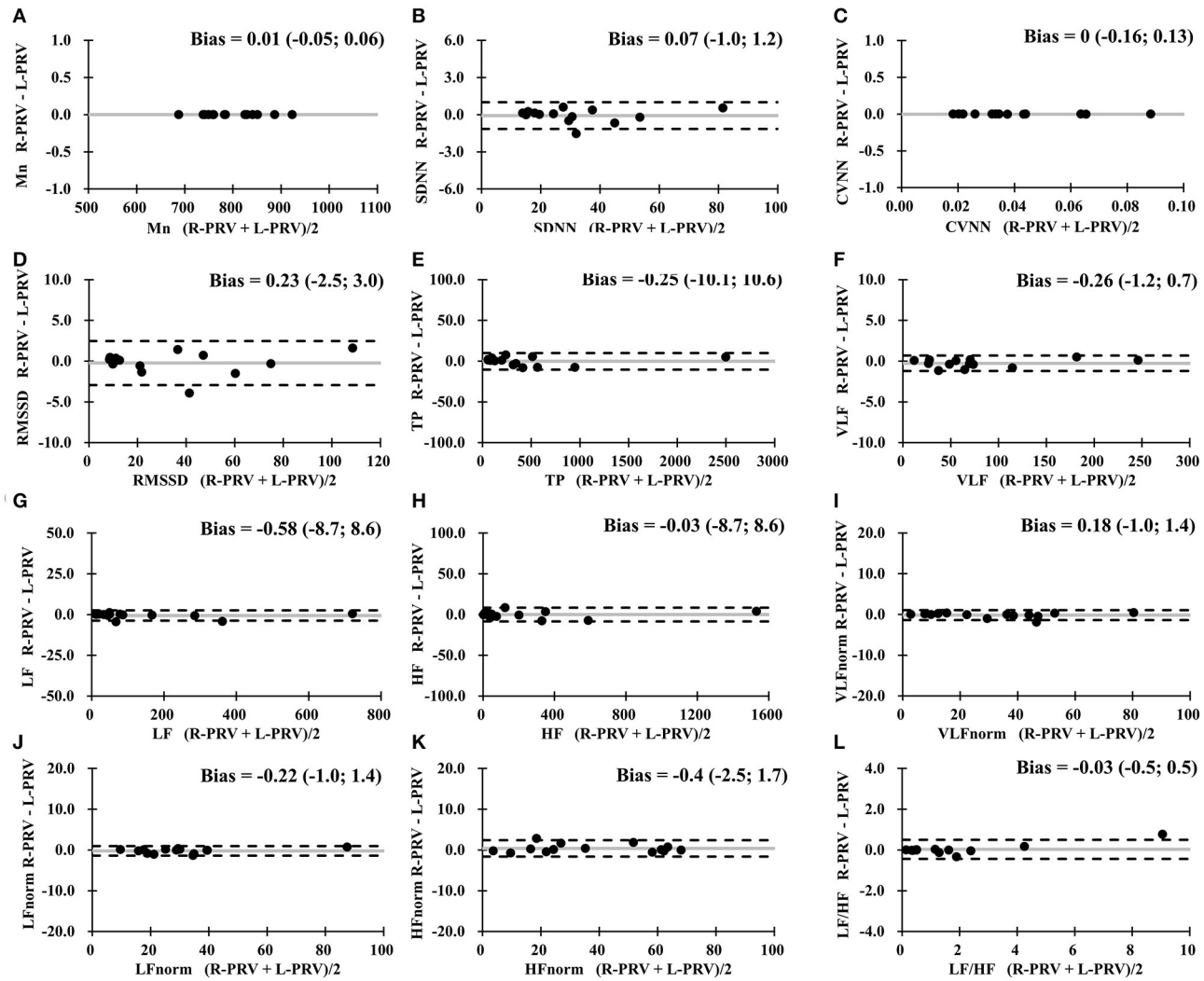

FIGURE 3 | Bland-Altman analysis between R-PRV measures and L-PRV measures. Gray lines indicate the bias between the measures. **(A)** Mn, mean RR interval; **(B)** SDNN, standard deviation of normal RR intervals; **(C)** CVNN, coefficient of variation of normal RR intervals; **(D)** RMSSD, root mean square of successive difference; **(E)** TP, total power; **(F)** VLF, very low-frequency power; **(G)** LF, low-frequency power; **(H)** HF, high-frequency power; **(I)** VLFnorm, normalized VLF; **(J)** LFnorm, normalized LF; **(K)** HFnorm, normalized HF; **(L)** LF/HF, low-/high- frequency power ratio; L-PRV, left hand pulse rate variability; R-PRV, right hand pulse rate variability.

association of mathematical calculation and fiducial points of measures.

Interestingly, large measurement errors were observed in HFnorm and LF/HF when right or left hand PRV was compared to the ECG-derived HRV. These two HRV variables provide an essential view to understanding the vagal activation and sympathovagal balance in health status (33). The high-frequency component of HRV is known to be caused by respiration. The effect of respiration on the variation in RRI and PPI might be different because of the intervening radial artery. The time for the pulse wave to travel from the heart to the index fingertip of either hand through the radial artery might be affected by respiration, leading to a greater effect of respiration on the higher frequency component of PRV. The greater impact of respiration on PPI might be the reason why the lower-frequency components agree better than the higher-frequency components between HRV and PRV. Further explorations of these factors are warranted to validate this speculation.

Although autonomic modulation is similar between PRV and HRV, these two measures are not surrogates of each other due to insifficuint agreement found in RMSSD, HF, and LF/HF. Recent studies provide solid evidence to support the profound effects of cardiac and vascular mechanisms on PPG recording, suggesting distinctive features between HRV and PRV (19). Another factor contributing to the difference between HRV and both hand PRV might be the variation in time used by the blood to travel from the heart to the radial artery. Nevertheless, the accuracy of both hand PRV measures as the surrogate of HRV estimation is not convincing in CABG patients. A potential risk to underestimate/overestimate the HRV values by using either

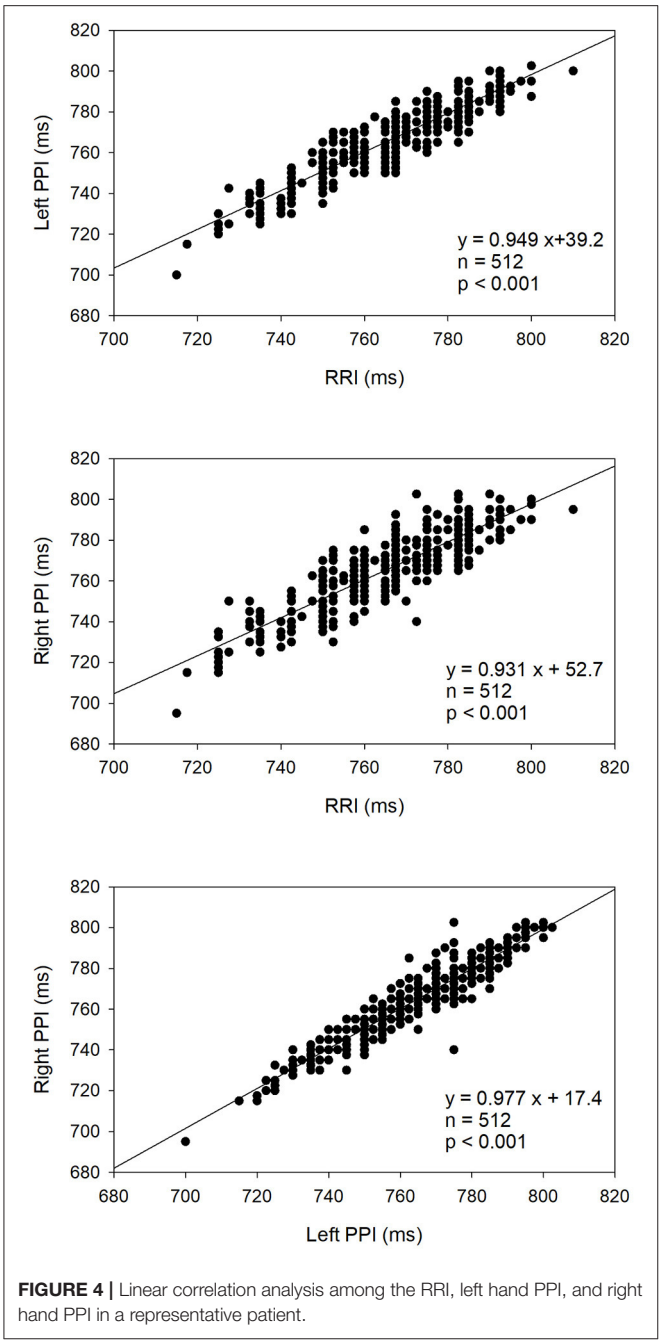

FIGURE 4 | Linear correlation analysis among the RRI, left hand PPI, and right hand PPI in a representative patient.

TABLE 4 | Linear regression analysis among HRV, L-PRV, and R-PRV measures in patients after CABG.

Parameters	HRV vs. L-PRV	HRV vs. R-PRV	L-PRV vs. R-PRV
Mn (ms)	1 < 0.01	1 < 0.01	1 < 0.01
SDNN (ms)	0.998 < 0.01	0.999 < 0.01	1 < 0.01
CVNN (%)	0.998 < 0.01	0.998 < 0.01	0.999 < 0.01
RMSSD (ms)	0.994 < 0.01	0.996 < 0.01	0.999 < 0.01
TP (ms^2)	1 < 0.01	1 < 0.01	1 < 0.01
VLF (ms^2)	1 < 0.01	1 < 0.01	1 < 0.01
LF (ms^2)	1 < 0.01	1 < 0.01	1 < 0.01
HF (ms^2)	0.999 < 0.01	0.999 < 0.01	1 < 0.01
VLFnorm (nu)	0.974 < 0.01	0.978 < 0.01	1 < 0.01
LFnorm (nu)	0.989 < 0.01	0.990 < 0.01	1 < 0.01
HFnorm (nu)	0.943 < 0.01	0.951 < 0.01	0.999 < 0.01
LF/HF	0.963 < 0.01	0.967 < 0.01	0.998 < 0.01

Data are presented as r and p-values. CABG, coronary bypass graft surgery; HRV, heart rate variability; PRV, pulse rate variability; L-PRV, left hand PRV; R-PRV, right hand PRV; Mn, mean RR interval; SDNN, standard deviation of RR intervals; CVNN, coefficient of variation of RR intervals; RMSSD, root mean square of successive difference; TP, total power; VLF, very low-frequency power; LF, low-frequency power; HF, high-frequency power; VLFnorm, normalized VLF; LFnorm, normalized LF; HFnorm, normalized HF; LF/HF, low-/high- frequency power ratio; bpm, beats per minute; ms, millisecond; ms^2, millisecond squared; nu, normalized unit.

hand PRV should be noted (15). We speculate that measurement error may occur when PRV measures of either hand are used as a surrogate of HRV in CABG patients.

To identify the limits of agreement on ipsilateral hand PRV, the R-PRV, and L-PRV were used for comparison in our study. Previously Wong et al. (18) reported asymmetry in PRV modulation between both hands in healthy seniors, as observed by RMSSD, TP, HF, HFnorm, and LF/HF variables. Conversely, our finding only revealed insufficient agreement in LF/HF between both hands PRV. The difference in the accuracy of hand PRV measures between healthy seniors and CABG patients might be related to the structure of radial artery, the asymmetry of cardiovascular anatomy in the thorax, and the less sensitivity of vagal-related control over arterial modulation after CABG surgery (23). Thus, using hand PRV measure as an independent biomarker to evaluate the overall cardiovascular function in the target population should be considered.

As demonstrated in **Table 4**, near perfect and perfect correlations were identified in all pairwise comparisons. The results of linear correlation demonstrated a strong link between both hand PRV and HRV measures for the evaluation of autonomic nervous function in CABG patients. In particular, this finding was associated with a similar coefficient of variance in intra-subject comparisons, as shown in **Table 2**. Our findings were in line with previous reports, which showed significant strong positive correlations between PRV and HRV in healthy adults (11, 18, 34) and in patients with hypoglycemia syndrome (35).

The discrepancy of 5 min short-term records in RMSSD, VLFnorm, HFnorm, and LF/HF variables found in the present study may be influenced by two physiological factors. The first factor is related to vascular determinants present in both hands PRV but not in ECG-derived HRV. The hemodynamic functions are mainly determined by the quality and structure of blood vessels, vascular stiffness after the left ventricle contraction, and the viscosity and osmolarity of the blood. Measuring arterial responses at the fingertips may be potentially influenced by these physiological factors during PPG assessment (12, 19). The second factor is related to the discrepancy in biosignal transmission between ECG and both hands PRV. The information transmitted from the R wave of ECG to the subsequent peak of pulse wave may be affected by respiratory control, stiffness of radial artery, constituents of

blood, medication, and multiple chronic diseases. The CABG patients in this study had more than one chronic disease and used many kinds of medication, including cardiovascular medicine. Previous studies examining cardiovascular waveforms in patients with cardiovascular diseases supported this conjecture (36–38).

In CABG, reverse segments of the great saphenous vein or the pedicle graft of the left internal mammary artery were harvested and bridged between the coronary artery distal to the stenotic lesion and ascending aorta. In this study, all patients received CABG surgery with the graft taken from their internal mammary artery or great saphenous vein. None of them received grafts from their radial arteries. Therefore, the quality of PPG signals taken from the radial arteries of both hands were not affected by the CABG surgery in this study.

The practical implication of the current study highlights the feasibility of using PRV for interpreting cardiac health in CABG patients. The advancement of PRV recordings is the result of the widespread use of built-in PPG sensors (i.e., smartphone, smartwatch, or pulse oximeter etc.). The PRV recorded from the fingertip is easily assessable and convenient as a daily routine (10). This routine process may be used as a diagnostic tool to reduce the mortality rate of coronary events or a clinical evaluation for postoperative care (39). Recently, a clinical study demonstrated that the high quality of smartphone-based PPG recordings provided a similar level of sensitivity and accuracy in diagnosing atrial fibrillation by physicians (40). Thus, future studies are recommended to use PRV signals to identify subsequent changes in cardiovascular functions in patients after CABG surgery.

This study has several limitations. Firstly, more patients after CABG surgery are needed to validate our findings in this small-scale study. Secondly, the extension of the findings of this study to patients with other kinds of cardiovascular disease needs further evidence to verify as only CABG patients were recruited in the current study. Thirdly, only post-surgical HRV and PRV measures in the CABG patients were taken over a 1 year period. The results of this study may not be applicable to patients during the recovery phase after CABG surgery in the hospital setting and during home-based recovery phase within a year. Future studies should compare the accuracy between HRV and both hands PRV measures in other kinds of cardiovascular disease and CABG patients within 1 year after surgery. Fourthly, this study was carried on using short-term spectral HRV/PRV analysis, which is subject to the variation in the physiological and psychological conditions and the medications of the patients. Finally, this study was a cross-sectional investigation. The outcomes of this study are not comparable to longitudinal measures between HRV and PRV in CABG patients. Cautions should be exercised in the interpretation of the experimental data.

CONCLUSION

Both hand PRV measures cannot be used as the surrogate of ECG-derived HRV measures in CABG patients due to insufficient agreements in RMSSD, HFnorm, and LF/HF indices which are essential in the evaluation of autonomic nervous function in short-term HRV analysis. The use of PRV measures to monitor cardiac-related health in patients after CABG surgery over 1 year should be done with caution. However, the use of PRV of either hand for the evaluation of autonomic nervous function might be warranted in CABG patients and possibly other kinds of cardiovarscular diseases because of good agreement in most time-domain and frequency-domain HRV measures and the strong positive correlations among HRV and both hand PRV measures in CABG patients.

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 Institute Review Board of Taipei Veterans General Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Y-SC contributed to the study conceptualization, investigation, and writing (including reviewing and editing) of the manuscript. Y-YL contributed to the methodology, data acquisition, statistical analysis, and writing (including reviewing and editing) of the manuscript. C-CS contributed to the surgery, primary care and recruitment of CABG patients, administration, and writing (including reviewing and editing) of the manuscript. C-DK contributed to the study conceptualization, project administration, methodology, supervision, data interpretation, and writing (including reviewing and editing) of the manuscript. All authors contributed to the article and approved the submitted version.

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Preliminary Analysis of a Wireless and Wearable Electronic-Textile EASI-Based Electrocardiogram

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Background: With cardiovascular disease continuing to be the leading cause of death and the primary reason for hospitalization worldwide, there is an increased burden on healthcare facilities. Electronic-textile (e-textile)-based cardiac monitoring offers a viable option to allow cardiac rehabilitation programs to be conducted outside of the hospital.

Objectives: This study aimed to determine whether signals produced by an e-textile ECG monitor with textile electrodes in an EASI configuration are of sufficient quality to be used for cardiac monitoring. Specific objectives were to investigate the effect of the textile electrode characteristics, placement, and condition on signal quality, and finally to compare results to a reference ECG obtained from a current clinical standard the Holter monitor.

Methods: ECGs during different body movements (yawning, deep-breathing, coughing, sideways, and up movement) and activities of daily living (sitting, sitting/standing from a chair, and climbing stairs) were collected from a baseline standard of normal healthy adult male using a novel e-textile ECG and a reference Holter monitor. Each movement or activity was recorded for 5 min with 2-min intervals between each recording. Three different textile area electrodes (40, 60, and 70 mm^2) and electrode thicknesses (3, 5, and 10 mm) were considered in the experiment. The effect of electrode placement within the EASI configuration was also studied. Different signal quality parameters, including signal to noise ratio, approximate entropy, baseline power signal quality index, and QRS duration and QT intervals, were used to evaluate the accuracy and reliability of the textile-based ECG monitor.

Results: The overall signal quality from the 70 mm^2 textile electrodes was higher compared to the smaller area electrodes. Results showed that the ECGs from 3 and 5 mm textile electrodes showed good quality. Regarding location, placing the "A" and "I" electrodes on the left and right anterior axillary points, respectively, showed higher signal quality compared to the standard EASI electrode placement. Wet textile electrodes showed better signal quality compared to their dry counterparts. When compared to the traditional Holter monitor, there was no significant difference in signal quality, which indicated textile monitoring was as good as current clinical standards (non-inferior).

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Conclusion: The e-textile EASI ECG monitor could be a viable option for real-time monitoring of cardiac activities. A clinical trial in a larger sample is recommended to validate the results in a clinical population.

Keywords: ambulatory cardiac monitoring, EASI ECG, electronic-textile electrodes, Holter monitoring, smart fabrics, wearable device, wearable sensors

INTRODUCTION

Cardiovascular Disease (CVD) is the number one non-communicable disease and the highest cause of death worldwide, with an estimated life loss of 17.92 million people in 2015 (1). This number is predicted to rise to 23.6 million by 2030 (2). Heart attack and stroke are the most common events constituting more than 85% of the CVD incidents in 2017 (1, 3).

Population aging in developed countries increases the demand for available health care. At the same time, the prevalence of CVD is also higher in this older age group, placing increased pressure on the medical system (4). A study published in 2019 reported that long-term ambulatory ECG monitoring could play a vital role in detecting the onset of ventricular dysrhythmias and atrial fibrillation (5). Ventricular dysrhythmias are the prominent factors indicating heart failure, stroke, and cardiac death. Electronic-textile-based cardiac monitoring offers a viable option (6) for long-term ambulatory monitoring outside of the hospital premises.

Electronic textiles, also known as e-textiles, are defined as "fabrics that have electronics and interconnections woven into them (7)." In the field of cardiology, researchers have developed e-textile sensors that can monitor the cardiac activities of patients while they are engaging in their day-to-day life (8) or in hospital settings (9). These e-textile ECG electrodes produce signals of acceptable quality (10) and are resistant to repeated washing in aqueous solutions without losing their properties (11, 12). However, an e-textile ECG monitor with a diagnostics capability is yet to be reported (8).

The 12-lead ECG has superior dependability and is considered the gold standard for diagnostic ECG (13). However, the conventional Holter monitor has ECG lead wires and 10 sticky electrodes, making it less comfortable for extended ambulatory monitoring. A wireless ECG monitor based on an EASI electrode configuration (14) was implemented to address this issue. This ECG monitor has a reduced number of leads (three base ECG leads; V_{AI}, V_{ES}, and V_{AS}) and only five electrodes to realize the equivalence of a 12-lead ambulatory cardiac monitor.

OBJECTIVES

This research focused on the testing and evaluation of ECG signals during activities of daily living with an e-textile ECG monitor with textile electrodes in an EASI configuration. The objectives of the experiments were to:

1. Examine the effect of the textile electrode characteristics (area and thickness) on signal quality
2. Investigate the effect of electrode placement on signal quality
3. Examine the effect of electrode condition due to sweating on signal quality; and
4. Compare the performance of the e-textile ECG monitor to that of a traditional Holter monitor.

MATERIALS AND METHODS

The E-Textile ECG Monitor

An ECG monitor consisting of a smart ECG vest, textile electrodes, and miniature ECG hardware with a Java-based real-time ECG viewer and data logger was designed. The ECG hardware weighs 152 g and has a built-in Bluetooth module that can transmit data up to a maximum distance of 100 m. The ECG monitor measures ECG using textile sensors and wiring embedded within a garment. The ECG vest has a lining covering made of a modified commercial t-shirt from K-mart (a local department store). The smart ECG vest is shown in **Figure 1**.

Electrodes are placed in an EASI configuration according to Feild et al. (14): (i) electrode "E" on the lower sternum at the fifth intercostal space; (ii) electrode "A" on the same level as the "E" electrode on the left mid-axillary line; (iii) electrode "I" on the same level as the "E" electrode on the right mid-axillary line; (iv), and electrode "S" at the top of the sternum, on the manubrium.

Data Collection Protocol

The experiment was divided into two phases. During the first phase, ECGs during daily living activities (yawning, coughing, deep breathing, sitting/standing from a chair, lying on a bed in a supine position, making a call using a mobile phone, and climbing stairs) were collected from an e-textile ECG monitor to address Research Objectives 1–3. In the latter phase, the identical setups in the first stage were used to acquire ECG simultaneously from the proposed e-textile ECG monitor and a reference standard 3-leads Holter monitor (SEER light ambulatory ECG from General Electric) to answer Research Objective.

Each movement or activity was recorded for 5 min, with 2-min intervals between each recording. After each session, the lining covering of the ECG vest and the textile electrodes were replaced before the new test was conducted.

Participants

Ethics approval to collect ECG based on the data collection protocol outlined in section Data Collection Protocol from healthy adult participants was obtained from the Flinders University Social and Behavioral Research Ethics Committee (SBREC: project code – 8490). Due to the outbreak of COVID-19 pandemic, it was not possible to collect data from members of the public. However, the protocol was adapted to a COVID

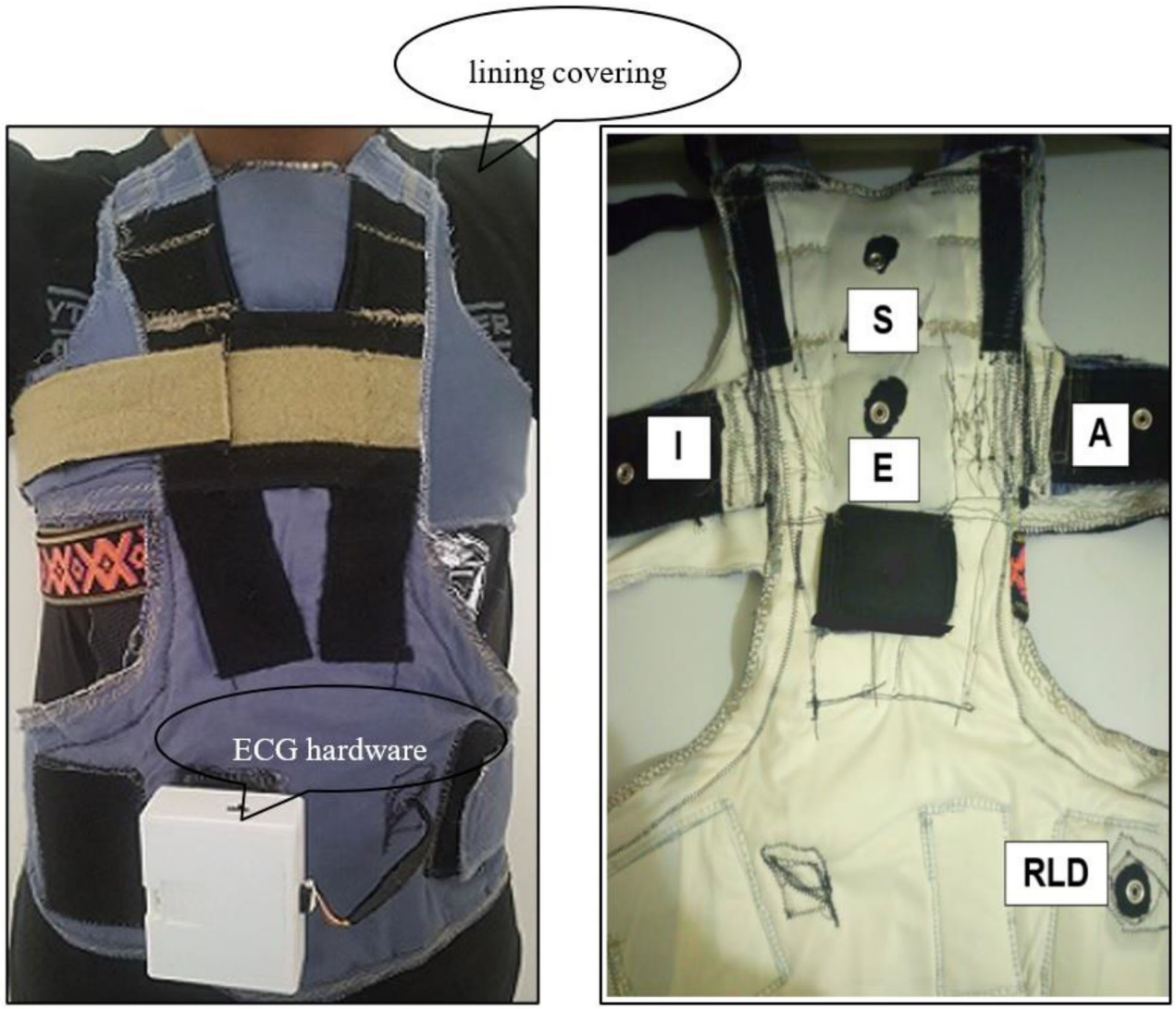

FIGURE 1 | The e-textile ECG vest with textile electrodes and embedded wiring (right) the EASI electrodes attachment site on the smart ECG vest (RLD—the reference Right Leg Drive electrode) (left).

safe version, and data were collected from a single healthy male volunteer (age 34, BMI 22.5 kg/m^2).

Signal Quality Index (SQI) Parameters

The following parameters were defined to evaluate the accuracy and reliability of the e-textile ECG monitor.

Signal to Noise Ratio (SNR)

Signal to Noise Ratio (SNR) measures the relative power between the desired signal and unwanted interference. SNR is one of the parameters used extensively in signal processing (15–17). SNR is defined in (1):

The equations should be inserted in editable format from the equation editor.

$$f(x) = 10 \log 10 \frac{\sum_{i=1}^{N} x(i)^2}{\sum_{i=1}^{N} \left(x(i) - x_r(i)\right)^2} \quad (1)$$

Where x(i) – clean / filtered ECG signal and $x_r(i)$ – the raw ECG signal.

The higher the SNR value, the better the energy content in the e-textile ECG. For example, a lower SNR requires complex signal processing algorithms to reduce and remove noise (18).

Approximate Entropy

Approximate entropy (ApEn) is a statistical method used to determine the dynamic nature (randomness) of a noisy time-series signal (19). Given the variable nature of the ECG signal,

the ApEn (2) of the collected data was used to study irregularities in the acquired ECG (20)[1]:

$$ApEn\,(S_N,m,r) = \ln \frac{C_m\,(r)}{C_{m+1(r)}} \quad (2)$$

Where: $C_m(r)$ – the prevalence of repetitive patterns of length m in S_N; S_N – sequence of length N; m – pattern length and r – similarity criteria.

The ApEn is interpreted differently in different disciplines. For example, lower ApEn in heart rate variability (HRV) analysis might indicate underlying pathology. However, the ApEn in the context of this study refers to the complexity and randomness of the acquired ECG, where a higher ApEn value signifies increased noise (21). The ApEn analysis was conducted for a minimum of 1,000 data points based on a similarity criterion of 0.2 and a pattern length of 2, as recommended by Pincus and Goldberger (21).

The Baseline Power Signal Quality Index

The baseline power signal quality index (basSQI) (3) is used to examine ECG noise artifact in the low-frequency region (f $\leq$ 1 Hz) as a result of deep breathing, coughing, yawning, and various body movements (16). The higher the value of basSQI, the better the signal quality. Clifford et al. (22) showed that a good quality signal had a basSQI value of 0.996 while a poor-quality ECG signal scored a basSQI value of 0.5. Therefore, a basSQI $\geq$ 0.95 was considered the minimum acceptable baseline low-frequency noise in this study.

$$basSQI = 1 - \frac{\int 0^1 P\left(f\right) df}{\int_0^{40} P\left(f\right) df} \quad (3)$$

QRS Duration and QTc Intervals

The clinical importance of the QRS duration (23, 24) and QT intervals (25, 26) to diagnose and predict possible cardiac abnormalities are well-established concepts. For an ECG monitor to have a diagnostic application, it should be able to acquire a signal with QRS duration and QT intervals equivalent to the standard 12-lead ECG (27). The QT_C was calculated based on the following formula (4) (27):

$$\mathbf{QTc} = \frac{QT}{\sqrt{RR}} \quad (4)$$

Where: RR is the time between two consecutive R peaks on the ECG tracing.

In the study, the QRS duration (normal QRS, NQRS: 0.08 – 0.12 s; long QRS, LQRS: $>$ 0.12 s) and the corrected QT interval (QT_C; short QT: $<$ 0.36 s; long QT: $>$ 0.45 s) were used to evaluate the performance of the textile ECG monitor against the reference Holter monitor. If the values between the two systems were different, this was assumed to be a result of noise, so signals were then filtered using a MATLAB-based 2nd order high pass Butterworth filter (fc = 0.67 Hz) to remove the noise, and the results were again compared.

[1] Available at: https://archive.physionet.org/physiotools/ApEn/.

Three peak detection algorithms [Pan and Tompkins, State-Machine, and Multilevel Teager Energy Operator (MTEO)] from BioSigKit (28), a MATLAB toolkit for Bio-Signal analysis, were used to detect the Q, R, S, and T waves of the acquired ECG.

Electrode Characteristics

The relation between the noise introduced during a series of controlled movements and activities of daily living and the textile electrodes surface area was studied. Custom textile electrodes (**Figure 2**) of different contact surface areas (40, 60, and 70 mm^2) were produced in the Medical Device Research Institute laboratory at Flinders University, South Australia. These were constructed from squares of silver-plated nylon conductive fabric (Adafruit Industries, New York, U.S.) sewn onto 3 mm thick Statfree® conductive polyurethane foam. Then, ECGs were acquired from these textile electrodes to investigate the effect of electrode surface area on signal quality. The thickness of the electrodes was kept at 3 mm throughout this study.

In a second experiment, the effect of electrode thickness (padding of the textile electrodes) on ECG signal transduction was assessed. 60 mm^2 squares of silver-plated nylon conductive fabric were sewn onto 3, 5, and 10 mm thick Statfree® conductive polyurethane foam to produce padded textile-electrodes of 3, 5, and 10 mm thickness. ECGs were collected with the standard EASI electrode configuration throughout the experiment.

Electrode Placement

Optimal electrode placement remains an active area of research in cardiac monitoring (8, 29). As the textile electrodes are not attached to the skin firmly, it is possible for the textile electrodes to move during certain activities. It was, therefore, necessary to study the effect of electrode position on signal quality. The lateral electrodes (A and I) were more likely to be knocked or moved during activity. Hence, we wanted to see the effect of varying the electrode position. Therefore, in the experiment, the positions of the two textile sensors at "A" and "I" were varied into three positions—anterior axillary, mid-axillary, and posterior-axillary and at the level of the "E"-electrode while keeping the "E" and "S" electrodes at their defined positions. Throughout the experiment, 70 mm^2 textile electrodes of 3 mm thickness were used.

Electrode Condition

An experiment was conducted to investigate the effect of moisture from sweating on signal quality. Signals from "wet" and "dry" electrodes were also compared to those from standard commercial Ag/AgCl electrodes.

An initial ECG was obtained with the participant in a relaxed seated position. The electrodes were considered to be dry for this measurement since the effect of sweating was minimal over this time. Once ECG acquisition from the dry textile electrodes was complete, the volunteer performed casual walking for 5 min wearing the smart ECG vest to induce sweating. ECG was then collected from the "wet" textile electrodes during different body movements and activities of daily living.

Before the start of each movement/activity, the subject rested for 5 min and was given a fresh hand towel to use to dry body sweating. Then, the textile electrodes used in the previous test

FIGURE 2 | The e-textile ECG electrodes; left—front view (user side), middle—back view with male snap fastner (attached to the ECG vest) and right—textile electrode attachment female snap fastner on the ECG vest.

were replaced with new dry textile electrodes. For the entire test duration, the standard EASI configuration and 3 mm thick, 70 mm^2 textile electrodes were used to collect ECG.

Finally, ECGs from wet-gel electrodes (Nissha Medical Technologies, NY, United States) were collected using the e-textile ECG monitor during different body movements (yawning, deep breathing, sideways, and up movements) and activities of daily living (sitting/standing from a chair and climbing stairs) and signal quality was compared to that of the 3 mm thick 60 mm^2 textile electrodes.

Comparing the E-Textile ECG to the Traditional Holter Monitor

ECG was acquired simultaneously from the e-textile ECG monitor (using 3 mm thick, 70 mm^2 textile electrodes) and from a reference standard 3-lead Holter monitor (SEER light ambulatory ECG from General Electric Healthcare, Chicago, Illinois, U.S.; using wet-gel commercial electrodes). According to the reference Holter monitor user documentation, channel one is the reference lead and is used to acquire modified V5 (mV5). A modified V1 (mV1) is obtained through channel two. It is possible to collect either modified V3 (mV3), modified aVF (maVF), or modified Z (mZ) ECG based on the lead placement connected to channel three (30)[2]. The modified maVF arrangement was selected as the lead placement during the maVF ECG does not coincide with any of the EASI ECG electrode positions.

Data Analysis

ECG from the e-textile monitor was sampled at 4,000 samples per second (sps), recorded at 200 sps with a frequency range from 0 to 100 Hz at −3 dB level, and wirelessly transmitted to a host PC. Data were analyzed using MATLAB^{TM} 2017Ra software (The MathWorks Inc., Natick, MA, U.S.).

The ECG collected from the SEER Holter monitor was exported to MIT Signal Format upon completing the experiments. The data were then converted to an excel file (CSV UTF comma delimited—*.csv) and Text (Tab delimited—*.txt) format using a MATLAB script for ease of manipulation. According to the header file, the ECG from the Holter monitor was recorded at 125 Hz. However, the proposed textile ECG monitor has a recording frequency of 200 samples per second. Therefore, the Holter EC was resampled to match the 200 Hz rate of the textile ECG.

To retain as much low-frequency noise as possible while removing the DC offset from the inadequate skin-electrode interface and the electrode half-cell potential (31), a first-order Butterworth high pass filter (Fc = 0.067 Hz) was used to block the zero-frequency interference into the acquired ECG signal.

Statistical Analysis

Wilcoxon Signed-Rank Test is the non-parametric form of the paired-sample *t*-test used to analyze samples where the data has unknown distribution. The Wilcoxon Test ranks the absolute values of the differences between the paired data in the two samples. It computes statistical values based on the number of negative and positive differences. If the resulting *p*-value is small ($p < 0.05$), it is safe to assume that the two samples have different distributions and reject the null hypothesis (32). In cardiac research, previous studies (13) validated the Wilcoxon Signed-Rank Test as a practical statistical tool to analyze ECG. As a result, the Wilcoxon Signed-Rank Test was used to compare results throughout the experiment. A *p*-value of < 0.05 was considered statistically significant.

RESULTS

Results from the e-textile ECG experiments are presented in four themes below (A) Textile electrode characteristic, (B) Electrode placement, (C) Electrode condition, and (D) Comparison between the e-textile ECG monitor and the commercial Holter monitor.

[2]Available at: http://apps.gehealthcare.com/servlet/ClientServlet.

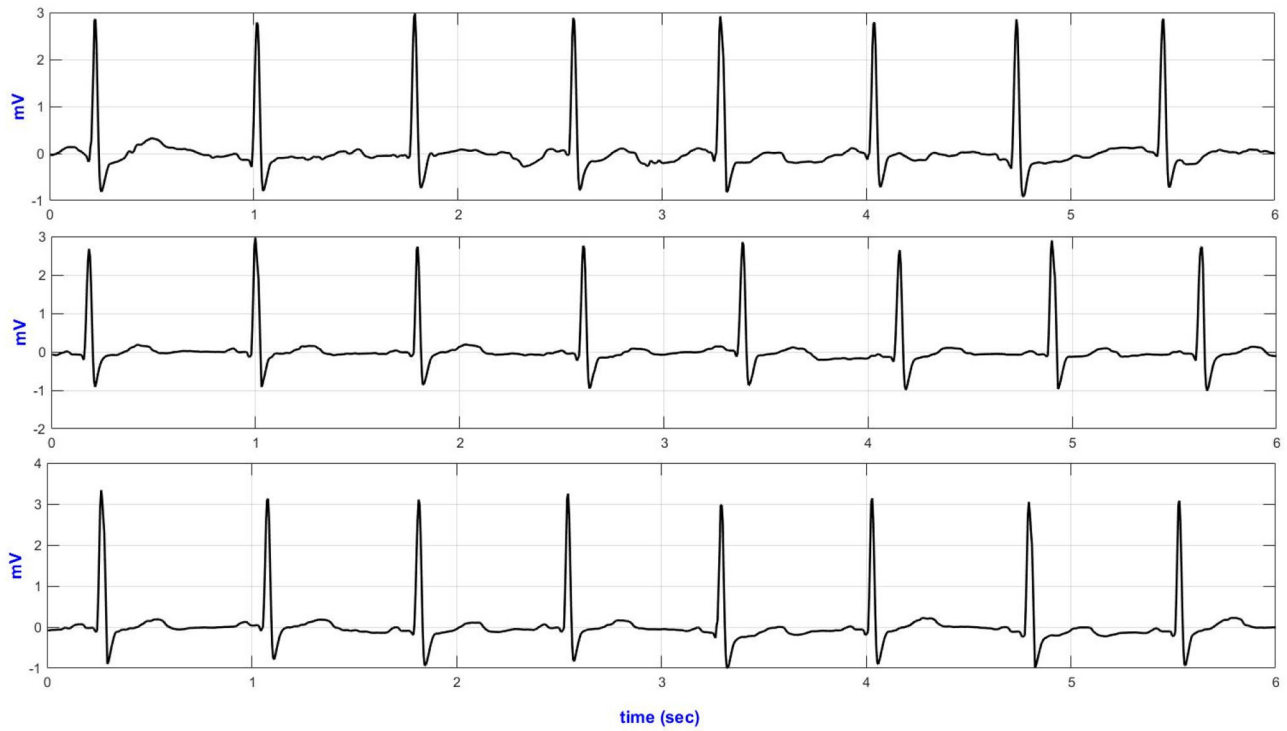

FIGURE 3 | Lead-II representative ECG traces from different size textile electrodes acquired during climbing stairs (top–40 mm^2; middle–60 mm^2 and bottom–70 mm^2 textile electrodes).

Textile Electrode Characteristic

Effect of Electrode Area on Signal Quality

Figure 3 illustrates representative ECG strips from different size textile electrodes. **Table 1** presents the SQI (ApEn, basSQI, and SNR) analysis results of experiments conducted to investigate the effect of electrode surface area on motion artifact.

The ECG from the 70 mm^2 textile electrodes showed lower ApEn during yawning, deep breathing, and up movement and climbing stairs. In contrast, the ECG from the 60 mm^2 textile electrodes showed lower ApEn during coughing. The ECG acquired from the 70 and 60 mm^2 textile electrodes did not show significant ApEn difference during sideways movement, sitting/standing from a chair and climbing stairs.

Table 1 also compares the SNR values of the ECGs obtained from textile electrodes of three different surface areas (40, 60, 70 mm^2). During deep breathing, the lead-II ECG from the 60 mm^2 showed increased SNR. Acquiring ECG through the 70 mm^2 textile sensors showed higher SNR compared to the smaller area textile electrodes.

Effect of Electrode Thickness (Electrode Padding) on Signal Quality

The signal quality parameters were computed to examine the influence of electrode thickness on the ECG signal quality during different body movements and activities of daily living. The results are presented in **Table 2**. As shown in **Table 2**, the ECG collected from the 10 mm thick textile electrodes performed poorly for all movements and activities (higher ApEn, lower basSQI, and lower SNR).

Electrode Placement

Figure 4 presents the temporal plots of lead-II ECG acquired during sideways movement.

The basSQI, average R-peak amplitude and average ECG power were calculated to assess the power characteristics of the acquired ECG and are summarized in **Table 3**. Placing the textile electrodes far from the heart, on the posterior-axillary lines, reduced the amplitude of the collected ECG. Therefore, even though the medial placement showed higher noise in the low-frequency range, the basSQI values were better compared to the posterior placement (**Table 3**).

ApEn analysis was conducted to confirm that the higher power content of the ECG acquired from the anterior axillary lines is, in fact, mainly from the ECG signal, and the results are summarized in **Table 3**. The anterior axillary electrode placement resulted in lower randomness in the acquired signal for the entire experiment. On the other hand, the ECG obtained from the medial-axillary lines showed a higher noise level for every test involving hand movement (sideways, up, sitting/standing from a chair, and climbing stairs).

Electrode Condition

Effect of Sweating on Signal Quality

The ApEn analysis results presented in **Table 4** revealed that the ECG collected from dry textile electrodes exhibited

TABLE 1 | Results of SQI analysis based on lead-II ECGs from different size textile electrodes (40, 60, and 70 mm^2).

Body movement / activities	ApEn descriptive statistics (Mean ± SD)			basSQI			SNR		
	40 mm^2	60 mm^2	70 mm^2	40 mm^2	60 mm^2	70 mm^2	40 mm^2	60 mm^2	70 mm^2
Yawning	**0.063 ± 0.0081***	0.049 ± 0.0049*	0.043 ± 0.0030	0.9661	***0.9312***	0.9946	5.2402	5.4238	6.2582
Deep Breathing	**0.048 ± 0.0078***	0.046 ± 0.0067*	0.041 ± 0.0040	0.9791	0.9780	0.9840	5.7759	8.0175	7.7144
Coughing	**0.048 ± 0.0081**	0.036 ± 0.0067*	0.044 ± 0.0039	0.9950	0.9920	0.9692	6.3124	7.3790	7.6144
Sideways	**0.061 ± 0.0063***	0.055 ± 0.0080	0.055 ± 0.0055	0.9852	0.9880	0.9876	6.4403	7.8228	11.7176
Up	**0.198 ± 0.0251***	0.121 ± 0.0182*	0.098 ± 0.0155	***0.7760***	0.9895	0.9937	5.6869	6.9605	7.2274
Sitting/Standing	**0.049 ± 0.0057***	0.046 ± 0.0063	0.043 ± 0.0029	0.9812	0.9921	0.9943	7.8956	7.9628	9.1100
Stairs	**0.060 ± 0.0091***	0.046 ± 0.0063	0.045 ± 0.0029	0.9828	0.9968	0.9921	7.8110	7.4803	8.7859

Sideways, moving the hands sideways and moving them back to the midline horizontally; up, raise arms above the head and moving them back; sitting / standing, sitting / standing from a chair; stairs, climbing stairs; ApEn, Approximate entropy; basSQI, baseline power signal quality index; SNR, Signal to Noise Ratio; Bold italic - Red, moderate to intense lower frequency noise (basSQI<0.95); Bold, higher ApEn value.

**Statistically significant ($p < 0.05$) compared to the ECG from the 70 mm^2 textile electrodes.*

TABLE 2 | Results of SQI analysis based on lead-II ECGs acquired from 3, 5, and 10 mm thick Textile electrodes.

Body movement / activities	ApEn descriptive statistics (Mean ± SD)			basSQI			SNR		
	Thickness of the textile electrodes								
	3 mm	5 mm	10 mm	3 mm	5 mm	10 mm	3 mm	5 mm	10 mm
Yawning	0.043 ± 0.0030	0.048 ± 0.0075	**0.053 ± 0.0065***	0.9680	0.9624	***0.9138***	8.0865	5.7944	1.8421
Deep breathing	0.040 ± 0.0039	0.050 ± 0.0055*	**0.054 ± 0.0061***	0.9863	0.9655	***0.9182***	7.9564	5.7428	2.7611
Coughing	0.043 ± 0.0048	0.049 ± 0.0050*	**0.074 ± 0.0096***	0.9709	0.9559	***0.8619***	7.6567	5.8650	2.9173
Sideways	0.054 ± 0.0057	0.061 ± 0.0068	**0.080 ± 0.0077***	0.9921	0.9655	***0.8074***	11.4961	6.9296	1.9336
Up	0.096 ± 0.0202	0.146 ± 0.0205*	**0.175 ± 0.0316***	0.9942	0.9712	***0.9279***	7.2397	6.2622	3.8354
Sitting/standing	0.042 ± 0.0031	0.053 ± 0.0043*	**0.081 ± 0.0102***	0.9953	0.9743	***0.8727***	8.4876	7.5886	4.2407
Stairs	0.046 ± 0.0025	0.056 ± 0.0043*	**0.124 ± 0.0158***	0.9926	0.9692	***0.8028***	8.7658	6.2901	3.8456

Sideways, moving the hands sideways and moving them back to the midline horizontally; up, raise arms above the head and moving them back; sitting / standing, sitting / standing from a chair; stairs, climbing stairs; ApEn, Approximate entropy; basSQI, baseline power signal quality index; SNR, Signal to Noise Ratio; Bold italic - Red, moderate to intense lower frequency noise (basSQI < 0.95); Bold, higher ApEn value.

**Statistically significant ($p < 0.05$) compared to the ECG from the 3 mm textile electrodes.*

higher randomness (higher ApEn) compared to the ECGs from wet textile sensors. The basSQI and SNR computation results of the ECG from dry and wet textile electrodes (**Table 4**) showed that the ECG acquired from the wet textile electrodes showed reduced noise in the low-frequency region.

Comparison Between the Textile Electrodes and the Disposable Wet-Gel Electrodes

Quantitative signal quality parameters, including ApEn, basSQI, and SNR, were computed, and the results are presented in **Table 4**. The ECGs from the commercial wet-gel electrodes exhibited higher randomness (ApEn) and lower basSQI values compared to the wet-textile electrodes. However, ECGs from the commercial wet-gel electrodes showed higher SNR during deep breathing, sitting/standing from a chair, and climbing stairs (**Table 4**). **Figure 5** presents a representative ECG acquired during up movement.

Comparison Between the E-Textile ECG Monitor and the Commercial Holter Monitor

Six seconds of representative ECG trances from the Holter and textile-based ECG are presented in **Figure 6**. Increased body movement (e.g., climbing stairs, **Figure 6**) forced the ECG to drift away from the isoelectric line.

Table 5 compares the quantitative signal quality parameters. The Holter ECG revealed an increased interference in the low-frequency region of the ECG acquired, especially during sitting/standing activities (basSQI = 0.8067), lying on a bed (basSQI = 0.8687), climbing stairs (basSQI = 0.8874), and making a phone call from a mobile phone (basSQI = 0.9325). The significantly higher ApEn values of the ECGs from the reference ambulatory monitor (**Table 5**) supported the increased randomness of the Holter ECGs compared to the ECGs from the proposed textile-based ECG monitor.

The SNR analysis (**Table 5**) further confirmed the higher baseline drifts within the reference Holter monitor during the two activities (sitting/standing from a chair and climbing stairs)

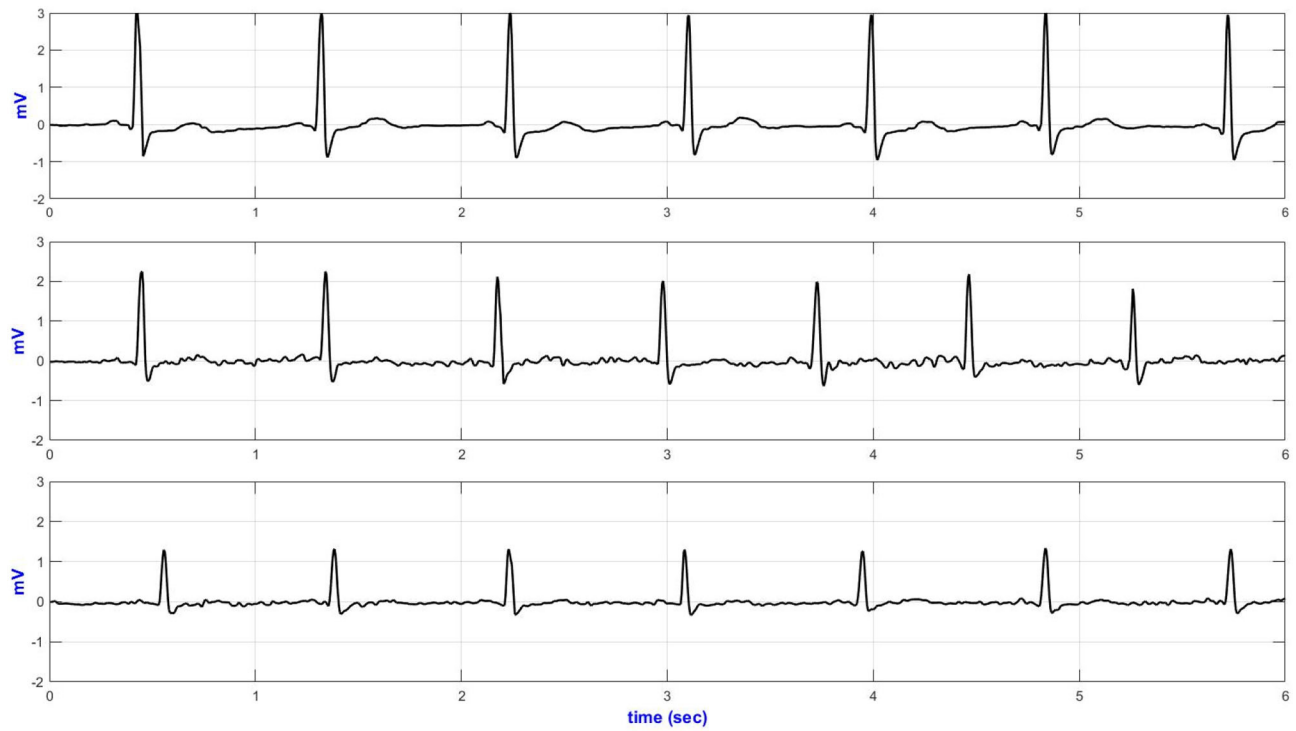

FIGURE 4 | Lead-II representative sideways ECG (top—Anterior; middle—medial and bottom—posterior AI electrodes placement).

compared to the ECG acquired from the proposed textile-based ECG monitor during the same sequence of body movements. However, the textile ECGs collected during sideways movement showed lower signal power.

Table 6 summarizes the QRS duration and QTc measurements from ECGs collected from both the reference Holter monitor and the proposed textile-based ECG monitor. There was no difference in the number of normal QRS intervals between the two systems. However, the QT_C measures were different between the two systems when the subject was sitting in a chair. For the signals from the Holter monitor, 58 of the 262 QT_C intervals were identified as long QT_C (>0.45 s), and one was a short QT_C interval (<0.36 s). However, 261 of the 262 QT_C intervals from the textile-based ECG were detected as normal (**Table 6** top). For both the Holter monitor and the textile-based ECG, one QT_C interval was missing. The ECG was then denoised using a 2nd order high pass Butterworth filter (fc = 0.67 Hz) in a MATLAB environment and the QT_C intervals were computed again. All 58 QT_C intervals identified as long QT_C within the reference ambulatory monitor were classified as normal QT_C after denoising. Moreover, the missed T-wave was recovered in both the Holter and textile ECGs (**Table 6** bottom).

DISCUSSION

The aim of this study was to determine whether signals produced by an e-textile ECG monitor with textile electrodes in an EASI configuration are of sufficient quality to be used for cardiac monitoring. Specific objectives were to investigate the effect of the textile electrode characteristics, placement, and condition on signal quality, and finally to compare results to a reference ECG obtained from a current clinical standard the Holter monitor.

Textile Electrode Characteristic

The relation between the size of the electrodes and the ECG quality was studied. Results showed that the bigger the textile electrodes' size, the better the signal quality and the lower the approximate entropy (randomness of the signal). This finding is in agreement with that reported by Ueno et al. (33). Throughout the experiment, the ECG from the 70 mm^2 resulted in a higher peak ECG signal for all body movements and daily activities except for deep breathing, where the ECG collected *via* the 60 mm^2 textile electrodes showed slightly higher SNR. The increased ECG amplitude and higher signal power for an increased electrode area also agree with previous studies (34–36).

In a previous study, Cömert and Hyttinen (37) used a 4 mm thick cushion padding structure to support their textile electrodes. The authors showed that the electrode support structure and padding increased the stability of the skin-electrode interface and distributed the compressive force uniformly across the electrode. Moreover, a soft support structure has been shown to produce less noise as it allows the textile electrode to follow the underlying anatomy (37). In this study, 3, 5, and 10 mm thick textile electrodes were constructed using a soft support structure made of Statfree® conductive polyurethane foam.

TABLE 3 | Summary of the ECG characteristics based on "AI" electrodes placement.

Body movement / activities	basSQI			Average R-wave amplitude (mV)			Average ECG power (mW)			ApEn descriptive statistics (Mean ± SD)		
	Electrode placement											
	Ant	Med	Post	Ant**	Med	Post	Ant	Med	Post	Ant	Med	Post
Yawning	0.990	0.986	***0.872***	3.08	1.89	1.13	269.1	105.3	41.3	0.039 ± 0.009	0.044 ± 0.011	**0.060 ± 0.008***
Deep breathing	0.988	0.987	***0.923***	3.15	2.01	1.23	258.1	105.4	40.6	0.039 ± 0.005	0.044 ± 0.007	**0.056 ± 0.009***
Coughing	0.995	0.998	0.992	3.27	2.12	1.35	304.6	140.5	59.1	0.032 ± 0.005	0.038 ± 0.005*	**0.062 ± 0.006***
Sideways	0.992	0.990	0.965	3.04	2.07	1.26	221.1	110.2	43.2	0.039 ± 0.004	**0.159 ± 0.035***	0.139 ± 0.031
Up	0.993	0.992	0.964	2.89	1.93	1.24	228.8	119.6	49.4	0.074 ± 0.001	**0.384 ± 0.059***	0.168 ± 0.027*
Sitting/standing	0.998	0.984	0.972	3.16	2.26	1.38	275.3	138.4	55.5	0.039 ± 0.005	**0.067 ± 0.011***	0.065 ± 0.009
Stairs	0.998	0.991	0.981	3.08	1.89	1.13	269.1	105.3	41.3	0.038 ± 0.004	**0.087 ± 0.013***	0.074 ± 0.006*

Sideways, moving the hands sideways and moving them back to the midline horizontally; up, raise arms above the head and moving them back; sitting / standing, sitting / standing from a chair; stairs, climbing stairs; basSQI, baseline power signal quality index; ApEn, approximate entropy; Ant, AI electrodes placed at the left and right anterior axillary lines, respectively; Med, AI electrodes placed at the left and right medial axillary lines, respectively; Post, AI electrodes placed at the left and right posterior axillary lines, respectively; Bold italic - Red, moderate to intense lower frequency noise (basSQI < 0.95); Bold, higher ApEn value.

***Higher R-wave amplitude.*

**Statistically significant ($p < 0.05$) compared to the ECG from the Anterior AI textile electrodes placement.*

TABLE 4 | SQI analysis results of lead-II ECG from textile electrodes and commercial wet-gel electrodes using textile ECG monitor.

Body movement / activities	ApEn descriptive statistics (Mean ± SD)			basSQI			SNR		
	Dry textile electrodes	Wet textile electrodes	Wet-gel electrodes	Dry textile electrodes	Wet textile electrodes	Wet-gel electrodes	Dry textile electrodes	Wet textile electrodes	Wet-gel electrodes
Yawning	**0.059 ± 0.004***	0.038 ± 0.006	**0.058 ± 0.005***	***0.9051***	0.9822	0.9614	4.6507	7.6812	6.6747
Deep breathing	**0.051 ± 0.006***	0.047 ± 0.004	0.039 ± 0.006	***0.9060***	0.9900	0.9860	3.8205	7.1519	7.6097
Sideways	**0.057 ± 0.007***	0.045 ± 0.005	**0.061 ± 0.010**	0.9858	0.9932	0.9701	6.7089	11.8897	7.7883
Up	**0.181 ± 0.019***	0.094 ± 0.012	**0.186 ± 0.019***	0.9633	0.9944	***0.9447***	6.4031	8.3891	7.6526
Sitting/standing	**0.067 ± 0.006***	0.043 ± 0.003	**0.063 ± 0.010***	***0.9044***	0.9953	0.9581	6.9461	9.1111	9.3364
Stairs	**0.075 ± 0.005***	0.045 ± 0.003	0.059 ± 0.007*	***0.9313***	0.9926	0.9733	6.9189	8.9621	9.6773

*Sideways, moving the hands sideways and moving them back to the midline horizontally; up, raise arms above the head and moving them back; sitting / standing, sitting / standing from a chair; stairs, climbing stairs; ApEn, Approximate entropy; basSQI, baseline power signal quality index; SNR, Signal to Noise Ratio; Bold italic - Red, moderate to intense lower frequency noise (basSQI < 0.95); Bold, higher ApEn value; *Statistically significant ($p < 0.05$) compared to the ECG from the wet textile electrodes.*

Throughout the trial, ECG signals from the 3 and 5 mm textile electrodes showed higher signal power, lower randomness, and decreased motion artifact aligning with Comert and Hyttinen's 2015 study (37), where they showed a positive relationship between electrode padding and signal quality using a 4 mm thick padding. In another study, Cömert et al. (38) examined the effect of different thicknesses and types of padding using 6, 9, 13, 14, and 16 mm thick electrodes where the padding was made of two different grades of SunMate memory foam and Poron XRD impact protection cushion. The authors reported the positive effect of padding on signal quality. However, the padding that resulted in the best ECG quality was not clearly stated.

In this study, increasing the padding thickness beyond 5 mm showed decreased signal quality. For example, during climbing stairs, the ECG from the 10 mm thick textile sensors performed worst. This may be a result of the thicker textile electrodes (thicker padding, e.g., 10 mm thick textile electrodes) shifting position and sliding when subjected to movement more so than the thinner (e.g., 3 and 5 mm) textile electrodes. Moreover, Cömert et al. (38) used a different technique to acquire the ECG (electrode was placed on the upper arm and was subjected to different magnitude pressure from 5 to 25 mmHg) and a different material to make the support structure. In our experiment, the electrodes were placed along the EASI configuration, and the support structure was made of Statfree® conductive polyurethane foam. Hence, it is difficult to compare the results directly.

Electrode Placement

Based on the EASI configuration, placing the "A" and "I" electrodes at the anterior axillary line showed a lower ApEn. At the same time, during sideways and up movement, the medial axillary and posterior "AI" placement showed higher randomness (an increased ApEn) in the acquired ECG. As the hands were moved side to side (sideways) and raised above the head and then moved back (up movement), there was a high chance of the arms touching the electrodes placed under the armpit and on the posterior axillary lines, resulting in an unstable skin-electrode interface. This continuous impedance-change induced low-frequency interference in the acquired ECGs.

Moreover, moving the electrodes from the anterior-axillary to the posterior-axillary line diminished the R-wave ECG amplitude, reduced the power contained within the acquired ECG, and increased low-frequency noise. From an electrophysiology perspective, where the body is assumed to be a volume conductor (39), the further the sensors from the source (the heart), the higher the impedance of the volume conductor (39, 40). Therefore, it is unsurprising that the amplitude of the ECG collected with the AI electrodes on the medial axillary line is greater than the ECG collected at the posterior axillary line.

Electrode Condition

Wet textile electrodes (from sweating) were compared to dry counterparts. They were found to perform better as the dry textile electrodes drift easily, change position, and are susceptible to motion artifact during physical activities. Moreover, the performance of the wet textile electrodes was comparable to that of commercial wet-gel electrodes. Previous studies support this result. Pani et al. (41) used poly (3,4-ethylene dioxythiophene): poly (styrene sulfonate) textile electrodes to compare dry textile electrodes, wet textile electrodes, and commercial Ag/AgCl electrodes during different daily activities. The authors showed that the dry textile electrodes performed poorly, especially during physical activities. However, the wet textile electrodes were as good as the Ag/AgCl commercial electrodes. When evaluated based on a QRS detector, the wet textile electrodes performed better than the commercial Ag/AgCl electrodes.

Marozas et al. (34) compared commercial Ag/AgCl electrodes to wet textile electrodes in exercise ECG. The authors concluded that the textile electrodes showed significant noise in the low-frequency band (0–0.67 Hz) while textile electrodes are less prone to broadband noise (0–250 Hz) compared to the Ag/AgCl electrodes. We did not see the same level of low-frequency noise; however, results cannot be directly compared as we did not experiment on exercise ECG. Also, Marozas et al. (34) used three electrodes placed on the thorax area 25 cm apart, where in our case we used the EASI electrode configuration. However, the analog front-end of our hardware has been carefully designed to minimize low-frequency distortion, which might be why we did not observe intense low-frequency noise from the wet textile electrodes.

Comparison Between the E-Textile ECG Monitor and the Commercial Holter Monitor

The performance of the textile-based ECG monitor was compared against the traditional Holter monitor. Channel one (modified V5) from the Holter monitor and the V5 ECG from the textile-based ECG monitor were used to analyze the data. In the time domain plots, there was no significant difference between the ECGs acquired from the Holter monitor and the textile-based ECG monitor. Even from the noisy recording, it was possible to identify the QRS complexes. The main problem seen on the time traces were baseline drift. In both the Holter monitor and the textile-based ECG monitor the motion artifact within the QRS band (5–15 Hz) was minimal as confirmed by the SQI values. However, the ECGs from the Holter monitor showed an increased low-frequency noise, and hence lower basSQI values during a phone call, sitting / standing from a chair, lying on a bed, and climbing stairs.

In summary, compared to the body movements (e.g., deep breathing), the daily activities (e.g., sitting / standing from a chair) resulted in greater low-frequency interference within the ECG acquired from the Holter monitor. The reference ambulatory monitor and the smart ECG vest were used simultaneously. In this regard, for an increased activity like sitting / standing from a chair, the smart ECG vest might be touching the Holter lead wires and hence introducing an increased noise within the Holter ECG.

The precise delineation of the QRS duration and QT_C interval is important to detect cardiac episodes. In this regard, the QRS durations and the QT_C intervals were extracted from the Holter ECGs and the textile-based ECGs, and the results compared.

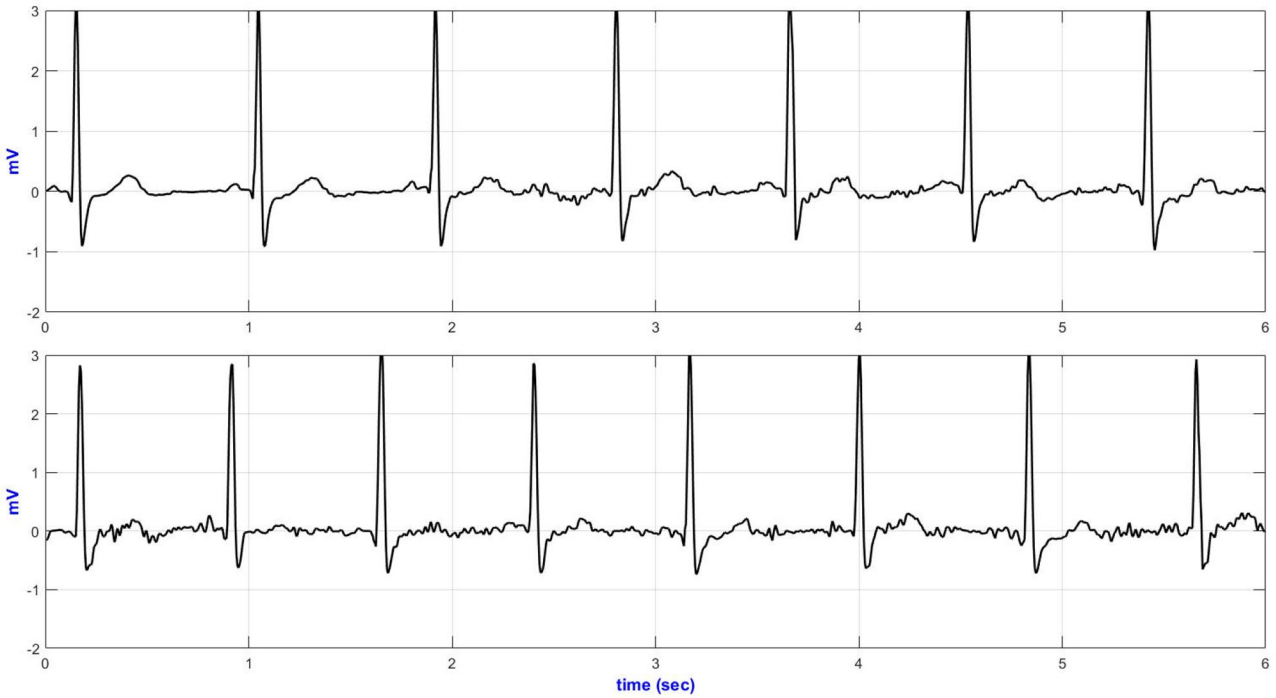

FIGURE 5 | Lead-II representative ECG during up movement (top—wet textile electrodes and bottom—commercial wet-gel electrodes).

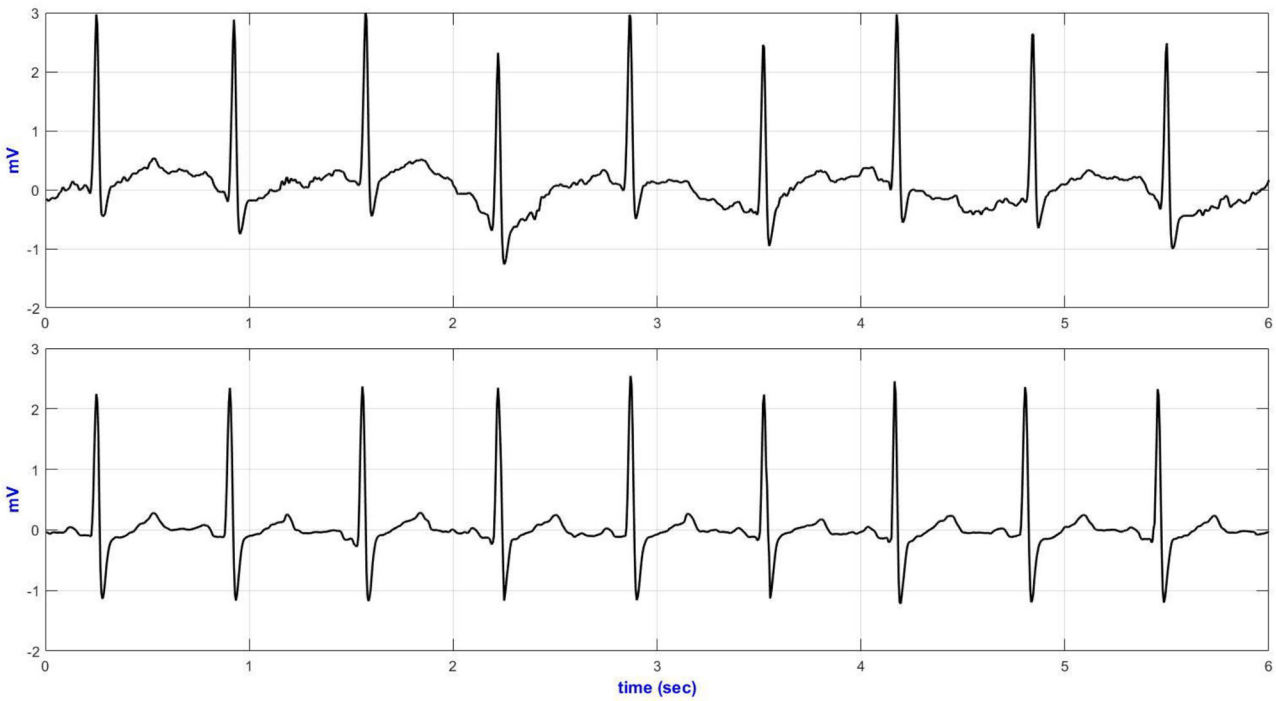

FIGURE 6 | V5 representative ECG during climbing stairs (top—Holter ECG and bottom—textile ECG monitor).

TABLE 5 | SQI analysis results of lead V5 ECG from the reference Holter monitor (using wet-gel commercial electrodes) and the textile ECG monitor (using textile electrodes).

Body movement / activities	ApEn descriptive statistics (Mean ± SD)		basSQI		SNR	
	Holter monitor	Textile ECG monitor	Holter monitor	Textile ECG monitor	Holter monitor	Textile ECG monitor
Deep breathing	**0.1385 ± 0.0245***	0.1268 ± 0.0126	0.9818	0.9898	20.1131	18.7119
Coughing	**0.1590 ± 0.0197***	0.1328 ± 0.0093	0.9639	0.9890	15.3232	16.8440
Sideways	**0.1665 ± 0.0520**	0.1459 ± 0.0329	0.9896	0.9904	13.6312	18.4488
Up	**0.1138 ± 0.0114**	0.1097 ± 0.0063	0.9862	0.9911	15.5721	16.0624
Sitting	**0.1294 ± 0.0274***	0.1143 ± 0.0102	0.9896	0.9867	16.0861	18.1898
A phone call	**0.1842 ± 0.0191***	0.1244 ± 0.0156	***0.9325***	0.9920	14.6479	15.3835
Sitting / standing	**0.1803 ± 0.0353***	0.1400 ± 0.0184	***0.8067***	***0.9287***	9.1645	16.2594
Lying on a bed	**0.1442 ± 0.0222***	0.1126 ± 0.0052	***0.8687***	0.9924	13.7291	15.0579
Stairs	**0.17871 ± 0.0224***	0.1268 ± 0.0126	***0.8874***	0.9970	11.9310	17.0698

Sideways, moving the hands sideways and moving them back to the midline horizontally; up, raise arms above the head and moving them back; sitting / standing, sitting / standing from a chair; stairs, climbing stairs; ApEn, Approximate entropy; basSQI, baseline power signal quality index; SNR, Signal to Noise Ratio; Bold italic - Red, moderate to intense lower frequency noise (basSQI < 0.95); Bold, higher ApEn value.
**Statistically significant ($p < 0.05$) compared to the ECG from the Textile ECG monitor.*

TABLE 6 | Summary of the QRS duration and QT_C intervals of ECG from the Holter monitor and textile-based ECG monitor during different body movements and activities of the daily living.

Body movement / activities	Reference Holter ECG (mV5)					Textile based ECG (V5)				
	QRS duration		QT_C			QRS duration		QT_C		
	NQRS	LQRS	NQT_C	SQT_C	LQT_C	NQRS	LQRS	NQT_C	SQT_C	LQT_C
Deep breath	333	0	332	1	0	333	0	333	0	0
Coughing	159	0	159	0	0	159	0	159	0	0
Sideways	147	0	146	1	0	147	0	146	0	1
Up	140	0	140	0	0	140	0	140	0	0
Sitting	261	1	202	1	58	262	0	261	0	0
A phone call	82	0	79	3	0	82	0	82	0	0
Sitting / standing	78	0	77	1	0	78	0	77	0	1
Lying on a bed	70	0	70	0	0	70	0	69	1	0
Stairs	160	0	158	0	2	160	0	160	0	0

Body movement / activities	QT_C after the ECGs were denoised									
	Reference Holter ECG (mV5)					Textile based ECG (V5)				
	QRS duration		QT_C			QRS duration		QT_C		
	NQRS	LQRS	NQT_C	SQT_C	LQT_C	NQRS	LQRS	NQT_C	SQT_C	LQT_C
Sitting	262	0	261	1	0	262	0	262	0	0

Sideways, moving the hands sideways and moving them back to the midline horizontally; up, raise arms above the head and moving them back; sitting / standing, sitting / standing from a chair; stairs, climbing stairs; QT_C, corrected QT interval; NQRS, number of the normal (0.08–0.12 s); LQRS, long QRS (>0.12 s) durations; NQT_C, number of the normal (0.36–0.45 s); SQT_C, short (<0.36 s); LQT_C, long QT_C (>0.45 s) intervals, respectively. The textile-based ECG showed higher accuracy compared to the reference Holter monitor.

Based on the QRS and QT_C analysis, there was no significant difference between the Holter monitor and the textile-based ECG monitor. However, the textile-based ECG monitor showed higher accuracy than the Holter monitor for the ECG collected when the participant sat quietly. Previous studies showed that ECGs acquired during upright position showed a decreased amplitude in the ST-segments (42), T (43), and Q (44) waves. Moreover, Yokus and Jur (45) compared the textile and wet-commercial electrodes and reported that ECGs collected from textile electrodes during sitting showed a higher SNR. As a result, sitting ECGs from the Holter monitor might be prone to low-frequency noise that affects the lower amplitude Q and T waves. The peak detection algorithm might be an additional contributing factor (34, 46).

LIMITATIONS

The major limitation of our study is that data were only collected from a single healthy participant. Even though ethics approval was obtained from the Flinders University Social and Behavioral Research Ethics Committee (SBREC: project code – 8490), it was not possible to recruit and collect data from more participants or cardiac patients due to the outbreak of the COVID-19 pandemic. As a result, given a unisex design of the ECG vest, the effect of different body sizes, body hair, skin type, and gender on ECG quality and the presence or absence of skin irritation due to textile electrodes were not studied.

CONCLUSION AND IMPLICATIONS FOR FURTHER RESEARCH

This study reports on the testing and evaluation of a wireless and wearable EASI-based e-textile ECG monitor. Optimal electrodeposition remains an active area of research for quality ECG transduction. In this regard, the best electrodeposition for the EASI configuration was studied, where the results could be extended for the traditional EASI lead system ECG. Placing the "A" and "I" electrodes on the left and right anterior axillary point, respectively, showed higher signal quality compared to the standard EASI electrode placement.

The preliminary results revealed that there was no significant signal quality difference between the traditional Holter monitor and the e-textile ECG monitor. The standard ambulatory monitor utilizes sticky wet-gel electrodes where the ECG quality deteriorates over time due to the drying of the gel interface. Moreover, the ECG lead wires reduced the comfort of the users. On the other hand, the textile-based ECG monitor has embedded wires and textile electrodes.

The use of the EASI configuration combined with the wearable and wireless design of the e-textile ECG monitor could support long-term ambulatory monitoring of cardiac patients and increase access to cardiac rehabilitation *via* telemonitoring. The intuitive design of the ECG vest will significantly reduce the time needed to train the users. No assistance is required to put on/off the smart ECG vest. Therefore, it will also lower diagnosis errors due to misplaced electrodes. Further research is needed to validate the e-textile ECG monitor in a larger trial and on a cardiac population.

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 Flinders University Social and Behavioral Research Ethics Committee (SBREC: Project Code – 8490). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MT conceived the original idea, contributed to the study design, analyzed the data, and wrote the manuscript with support from DH, RC, and KR. All authors contributed to the data analysis, interpretation, and to drafting the article.

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Self-Reported Mobile Health-Based Risk Factor and CHA_2DS_2-VASc-Score Assessment in Patients With Atrial Fibrillation: TeleCheck-AF Results

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Introduction: The TeleCheck-AF approach is an on-demand mobile health (mHealth) infrastructure incorporating mobile app-based heart rate and rhythm monitoring through teleconsultation. We evaluated feasibility and accuracy of self-reported mHealth-based AF risk factors and CHA_2DS_2-VASc-score in atrial fibrillation (AF) patients managed within this approach.

Materials and Methods: Consecutive patients from eight international TeleCheck-AF centers were asked to complete an app-based 10-item questionnaire related to risk factors, associated conditions and CHA_2DS_2-VASc-score components. Patient's medical history was retrieved from electronic health records (EHR).

Results: Among 994 patients, 954 (96%) patients (38% female, median age 65 years) completed the questionnaire and were included in this analysis. The accuracy of self-reported assessment was highest for pacemaker and anticoagulation treatment and lowest for heart failure and arrhythmias. Patients who knew that AF increases the stroke risk, more often had a 100% or ≥80% correlation between EHR- and app-based

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results compared to those who did not know (27 vs. 14% or 84 vs. 77%, $P = 0.001$). Thromboembolic events were more often reported in app (vs. EHR) in all countries, whereas higher self-reported hypertension and anticoagulant treatment were observed in Germany and heart failure in the Netherlands. If the app-based questionnaire alone was used for clinical decision-making on anticoagulation initiation, 26% of patients would have been undertreated and 6.1%—overtreated.

Conclusion: Self-reported mHealth-based assessment of AF risk factors is feasible. It shows high accuracy of pacemaker and anticoagulation treatment, nevertheless, displays limited accuracy for some of the CHA_2DS_2-VASc-score components. Direct health care professional assessment of risk factors remains indispensable to ensure high quality clinical-decision making.

Keywords: atrial fibrillation, mobile health, photoplethysmography, risk factors, thromboembolic risk

INTRODUCTION

According to the current European Society of Cardiology (ESC) guidelines (1) for the diagnosis and management of atrial fibrillation (AF), treatment of AF incorporates heart rate or rhythm control, stroke prevention with appropriate anticoagulation therapy, and management of comorbidities, risk factors or lifestyle modification. The presence and combination of specific risk factors may trigger the prescription and frequent adjustment of medical therapies, e.g., anticoagulation, to prevent stroke, based on the CHA_2DS_2-VASc-score.

Traditionally, individual risk factors are assessed by structured face-to-face history taking during outpatient visits. During the coronavirus disease 2019 (COVID-19) pandemic, scheduled face-to-face outpatient consultations were frequently converted into teleconsultations (2). To support AF management through teleconsultations, a new mobile health (mHealth) approach was made available to several European AF centers within the large TeleCheck-AF project. This mHealth approach incorporated teleconsultations coupled with remote on-demand photoplethysmography (PPG)-based heart rate and rhythm monitoring (FibriCheck®) (3–6). Within the TeleCheck-AF project, patients were invited to fill in a 10-item questionnaire via the mobile phone app focusing on AF risk factors required to guide comprehensive AF management and estimate thromboembolic risk by the CHA_2DS_2-VASc-score. Although app-based questionnaires have been used previously in mHealth infrastructures (7, 8), the accuracy of self-reported data collected with a mobile app compared to clinical health records and possible consequences for clinical decision-making on the initiation of anticoagulation has not been investigated, yet.

Within the TeleCheck-AF project, we evaluated the feasibility and accuracy of a remote mobile app-based self-reported assessment of AF risk factors and CHA_2DS_2-VASc-score.

MATERIALS AND METHODS

Project Design

The TeleCheck-AF project has been previously described in more detail (4). In brief, TeleCheck-AF is an international, multicenter on-demand mHealth infrastructure, initially dedicated to allowing the continuity of comprehensive AF management and to support integrated care through teleconsultation during the COVID-19 pandemic. It involves a structured teleconsultation ("Tele") preceded by an app-based on-demand heart rate, rhythm, and symptom monitoring infrastructure ("Check") to guarantee comprehensive AF management ("AF"). The retrospective data collection from the participating TeleCheck-AF centers was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committees of the participating centers.

Patient Population

From April 2020 to April 2021, patients (≥18 years) scheduled for teleconsultation in 40 European AF outpatient clinics were managed within the TeleCheck-AF project. Individuals were eligible if they had a smartphone and were able to operate the remote on-demand heart rate, rhythm, and symptom monitoring mobile phone application system after instructions. A subgroup of these 40 centers participated in the retrospective analysis. Eight centers with the highest contribution in patient recruitment (recruited at least 25 patients) were included in this specific app-based AF risk factor assessment analysis (Maastricht University Medical Center+, Maastricht, the Netherlands; Radboud University Medical Center, Nijmegen, the Netherlands; Rijnstate, Arnhem, the Netherlands; Hannover Heart Rhythm Center, Hannover, Germany; University Hospital Cologne, Cologne, Germany; Medical University of Graz, Graz, Austria; Liverpool Heart and Chest Hospital, Liverpool, United Kingdom; Medical University of Warsaw, Warsaw, Poland).

Project Procedures

At least 1 week prior to a scheduled (tele)consultation appointment, patients were provided with a mHealth prescription in the form of a temporary QR code and short instruction for the Conformité Européenne (CE)-marked app-based heart rate, rhythm, and symptom monitoring (FibriCheck, Qompium, Hasselt, Belgium) using PPG technology through the built-in camera of a mobile phone (4). Patients were instructed to record a 60-s PPG measurement and specify their symptoms, if

any, three times daily and in case of symptoms for 7 consecutive days prior to their teleconsultation. Once the first measurement was performed, patients received a separate automatic app notification to complete a short mobile phone app-based 10-item questionnaire with closed-ended questions (yes or no) provided in different languages related to patient-reported AF risk factors presented in **Supplementary Table 1**. A reminder to complete the questionnaire automatically popped up after the following four app-based heart rate, rhythm, and symptom recordings (five times in total).

Data Collection

The results of the questionnaire were collected in the FibriCheck cloud, an CE marked and secured online database, only accessible to authorized physicians, and afterwards exported for each center participating in the retrospective per-patient analysis.

A standardized electronic case record form was provided to all centers participating in the retrospective per-patient analysis of the TeleCheck-AF population. Baseline clinical characteristics (demographics and medical history) were retrieved from patients' electronic health records (EHR) at time of start app-based heart rate and rhythm monitoring. Each patient-reported app-based AF risk factor was compared with the corresponding EHR-based risk factor information, available in **Supplementary Table 1**. This process was blinded, as responsible physicians were not aware of the patient's response regarding the mHealth questionnaire.

Using the app-based AF risk factor information and EHR-based AF risk factor information, we calculated the app-based and EHR-based CHA_2DS_2-VASc-score, respectively. The potential risk for OAC undertreatment was defined as the number of patients that would not have been treated with appropriate anticoagulation if only the app-based risk factor questionnaire would have been used [patients with app-based CHA_2DS_2-VASc-score 0 (male), 1 (female) and EHR-based CHA_2DS_2-VASc-score $\geq$ 1 (male), $\geq$2 (female)] according to current ESC guidelines (1). The potential risk for OAC overtreatment was defined as the number of patients that would have been prescribed with anticoagulants without meeting indication criteria, if only the app-based risk factor questionnaire would have been used [patients with app-based CHA_2DS_2-VASc-score $\geq$1 (male), $\geq$2 (female) and EHR-based CHA_2DS_2-VASc-score 0 (male), 1 (female)].

Statistical Analysis

All continuous variables were pretested for normal distribution using the Shapiro-Wilk test and assessed as non-parametric variables therefore presented as median (interquartile range [IQR]) and categorical variables as numbers (n) with percentages (%). Differences in continuous parameters were compared using non-parametric Wilcoxon signed-rank test or Mann-Whitney U test as applicable. For the comparison of categorical data, the McNemar's test or Chi-square test was used. For sensitivity and specificity comparison between participating countries, the McNemar's test was used. To determine predictors of app- and EHR agreement, multiple logistic regression analysis, using the stepwise backward procedure (with α level of 0.05) was performed, including all variables that reached significance in univariate analysis with continuous variables (age) assessed every 10 units (**Supplementary Table 2**). Finally, accuracy of app-based AF risk factor assessment was estimated by receiver operating characteristic (ROC) analysis, reporting sensitivity and specificity. Statistical significance was assumed at a 5% level. For database management and statistical analysis, IBM SPSS Version 25 (IBM Corporation, Somers, New York, USA) was used.

RESULTS

In eight of the most active TeleCheck-AF centers, 994 consecutive AF patients were available in the database. Out of these patients, 954 (96%) patients (363 female, age 65 [57–71] years) completed the mobile app-based 10-item questionnaire and were included in this analysis. No statistically significant difference was observed between patients who completed the questionnaire compared to those who did not complete it regarding baseline characteristics, except older age (65 years [57–71] vs.61 years [52–69], $P = 0.046$) (**Supplementary Table 3**).

Agreement Between EHR and App-Based Parameters

The agreement between the mobile app-based 10-item questionnaire and the EHR is presented in **Table 1**. There were no statistically significant differences between EHR and app-based reported sex and age. Patients more often reported having a pacemaker in the mobile app (4.1 vs. 2.6% in EHR, $P = 0.001$). Arrhythmias (89.2 vs. 97.5%, $P < 0.001$), and in particular AF (69.3 vs. 90.2%, $P < 0.001$) were less often reported, whereas heart failure was more frequently reported (24.0 vs. 14.3%, $P < 0.001$) in the mobile app-based questionnaire compared to the EHR. Vascular disease was reported in 13.5% of patients in the mobile app, while vascular disease was mentioned by 15.7% of patients in the EHR ($P = 0.057$). There was a significant difference in the number of patients who had a medical history of TIA and/or CVA in the mobile app-based questionnaire compared to the EHR (25.9 vs. 8.9%, $P < 0.001$). A total of 274 (29.3%) patients reported hypertension in the mobile app-based questionnaire and as much as 461 (49.3%) patients had a diagnosis of hypertension in EHR ($P < 0.001$). The number of patients with diabetes mellitus was similar in the mobile app-based questionnaire and EHR (11.8 vs. 9.9%, $P = 0.097$). Anticoagulation treatment was similarly reported in both app and EHR (79.8 vs. 80.3%, $P = 0.649$). Overall, the sensitivity and specificity of the mobile app-based assessment was highest for pacemaker therapy and anticoagulant treatment, and lowest for vascular disease or heart attacks and arrhythmias. Noteworthy, arrhythmias including AF were not only less often reported but also more often inappropriately reported resulting in the lowest specificity (**Table 2**).

Patients With vs. Without Overall Full Agreement

One-fifth of patients ($n = 196$ [22.7%]) completed the app-based questionnaire in 100% agreement with EHR. Those patients were younger (63 [56–70] vs.66 [57–72] years, $P = 0.014$), were more often diagnosed with AF (94.9 vs. 89.8%, $P = 0.033$) and more frequently treated with AF ablation

TABLE 1 | Demographics and 10-item questionnaire compared to electronic health record-based results.

App-based question	App-based results	EHR-based results	*P*-value
Demographics			
Female sex	369 (38.7%)	363 (38.1%)	0.210
Age (years), median [IQR]	65 [57–71]; *n = 895*	65 [57–71]; *n = 895*	0.213
Questionnaire parameters			
Did you know atrial fibrillation increases the risk of stroke?	630 (66.1%); *n = 953*	NA	NA
Do you have a pacemaker?	38 (4.1%); *n = 932*	24 (2.6%); *n = 932*	0.001
Were you ever diagnosed with cardiac arrhythmias?	828 (89.2%); *n = 928*	905 (97.5%); *n = 928*	<0.001
Are you (or were you before) diagnosed with or treated for atrial fibrillation or AF?	644 (69.3%); *n = 929*	838 (90.2%); *n = 929*	<0.001
Are you (or were you before) treated for heart failure or pulmonary edema?	224 (24.0%); *n = 934*	134 (14.3%); *n = 934*	<0.001
Are you (or were you before) treated for vascular disease in your legs or aorta? Or did you ever suffer from a heart attack?	126 (13.5%); *n = 936*	147 (15.7%); *n = 936*	0.057
Did you ever suffer from thrombosis or a stroke, with or without serious consequences (CVA or TIA)?	242 (25.9%); *n = 935*	83 (8.9%); *n = 935*	<0.001
Are you (or were you before) treated for hypertension?	274 (29.3%); *n = 935*	461 (49.3%); *n = 935*	<0.001
Are you (or were you before) treated for diabetes?	110 (11.8%); *n = 936*	93 (9.9%); *n = 936*	0.097
Do you take anticoagulants?	743 (79.8%); *n = 931*	748 (80.3%); *n = 931*	0.649
Thromboembolic risk			
CHA_2DS_2-VASc-score 0 (if male), 1 (if female)	204 (23.9%); *n = 853*	197 (23.1%); *n = 853*	0.468
CHA_2DS_2-VASc-score 1 (if male), 2 (if female)	176 (20.6%)	220 (25.8%)	0.002
CHA_2DS_2-VASc-score ≥ 2 (if male), ≥3 (if female)	473 (55.5%)	436 (51.1%)	0.004

AF, atrial fibrillation; CVA, cerebrovascular accident; EHR, electronic health record; IQR, interquartile range; NA, non-applicable; TIA, transient ischemic attack. Number provided after the semicolon indicates the total number of patients available for that variable.

TABLE 2 | Sensitivity and specificity of app-based with electronic health record-based results.

App-based question	Sensitivity	Specificity
Do you have a pacemaker?	0.958	0.983
Were you ever diagnosed with cardiac arrhythmias?	0.898	0.348
Are you (or were you before) diagnosed with or treated for atrial fibrillation or AF?	0.724	0.593
Are you (or were you before) treated for vascular disease in your legs or aorta? Or did you ever suffer from a heart attack?	0.403	0.787
Are you (or were you before) treated for heart failure or pulmonary edema?	0.551	0.943
Did you ever suffer from thrombosis or a stroke, with or without serious consequences (CVA or TIA)?	0.723	0.786
Are you (or were you before) treated for hypertension?	0.497	0.905
Are you (or were you before) treated for diabetes?	0.591	0.935
Do you take anticoagulants?	0.945	0.803

*Abbreviations: see **Table 1**. The heatmap scale reflects the highest agreement between app- and EHR-based results (green) and the lowest agreement (red).*

therapy (63.3 vs. 38.5%, $P < 0.001$) to restore heart rhythm as compared to those whose responses on questionnaire were not in full agreement (**Supplementary Table 2**). Moreover, patients with 100% agreement had less comorbidities such as coronary artery disease, diabetes or hypertension. Additionally, they had lower thromboembolic risk and were less often treated with cardiovascular medications. Patients who reported awareness that AF increased the risk of stroke were more likely to have a 100% agreement (27 vs. 14%, $P = 0.001$) and ≥80% agreement (84 vs. 77%, $P = 0.001$) between EHR and app-based results compared to those who did not (**Figure 1**). Predictors for 100% app-EHR agreement were previous AF ablation therapy (odds ratio [OR] 2.40, 95% coincidence interval [CI] 1.64–3.51) and AF knowledge (OR 2.30, 95% CI 1.51–3.52), whereas coronary artery disease (OR 0.28, 95% CI 0.13–0.61), hypertension (OR 0.41, 95% CI 0.28–0.61) and beta-blocker therapy (OR 0.64, 95% CI 0.44–0.94) decreased this agreement (**Supplementary Table 4**).

Country Differences

In patients from all countries, hypertension was less frequently reported in the mobile app-based questionnaire compared to the EHR, while thromboembolic events such as TIA and/or CVA were more often reported. Some important country disparities between app- vs. EHR-based results were observed. Whereas, patients in Germany more often reported anticoagulant usage in the mobile app, Austrian patients reported such treatment less frequently. In addition, in contrary to German patients, Dutch patients more frequently declared having heart failure in app-based assessment (**Supplementary Table 5**).

Age Differences

Dividing patients into different age groups showed increasing tendency in anticoagulation usage and decreasing heart failure as well as vascular disease agreement between mobile app and EHR within patients aged between 30 and 80 years (**Supplementary Figure 1**).

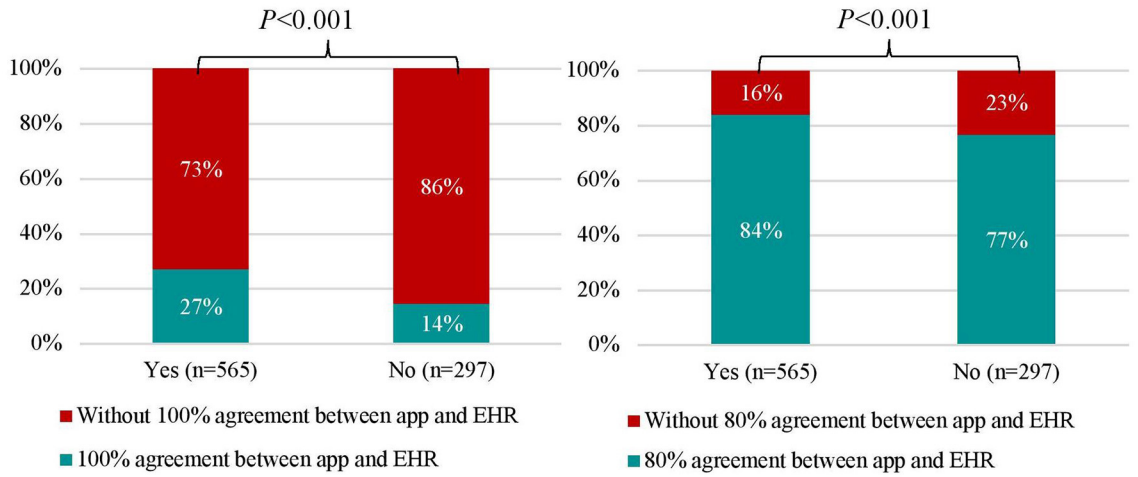

FIGURE 1 | Comparison between patients with and without 100% and ≥80% agreement between electronic health record- and app-based results and patients' knowledge about atrial fibrillation as a risk for stroke. Abbreviations: see **Table 1**.

Assessment of Thromboembolic Risk and Anticoagulation

CHA_2DS_2-VASc-scores were determined based on information derived from the mobile app and by information derived from the EHR. Compared to the CHA_2DS_2-VASc-score derived from data in the EHR, the mobile app-based assessment of the CHA_2DS_2-VASc-score identified a lower proportion of patients with a high thromboembolic risk and CHA_2DS_2-VASc-score ≥ 2 (if male), ≥3 (if female) (51.1 vs. 55.5%, $P = 0.004$) (**Table 1** and **Figure 2**). Compared to the results from the EHR, the app-based assessment would have resulted in a different indications for OAC in one-fifth (22%) of patients with EHR-based CHA_2DS_2-VASc-score ≥2 (if male) and ≥3 (if female), half (46%) of patients with EHR-based CHA_2DS_2-VASc-score 1 (if male) and 2 (if female) and quarter (26%) of patients with EHR-based CHA_2DS_2-VASc-score 0 (if male) and 1 (if female) (**Figure 3A**). Compared to the CHA_2DS_2-VASc-score derived from data in the EHR, the app-based assessment of the CHA_2DS_2-VASc-score would have resulted in a different indications for OAC in 6.1% of patients with EHR-based CHA_2DS_2-VASc-score ≥1 (if male) and ≥2 (if female) and 26% of patients with EHR-based CHA_2DS_2-VASc-score 0 (if male) and 1 (if female) (**Figure 3B**). The proportion of patients with a CHA_2DS_2-VASc-score ≥1 (if male) and ≥2 (if female) based on the mobile app and the EHR was comparable (**Supplementary Figure 2**).

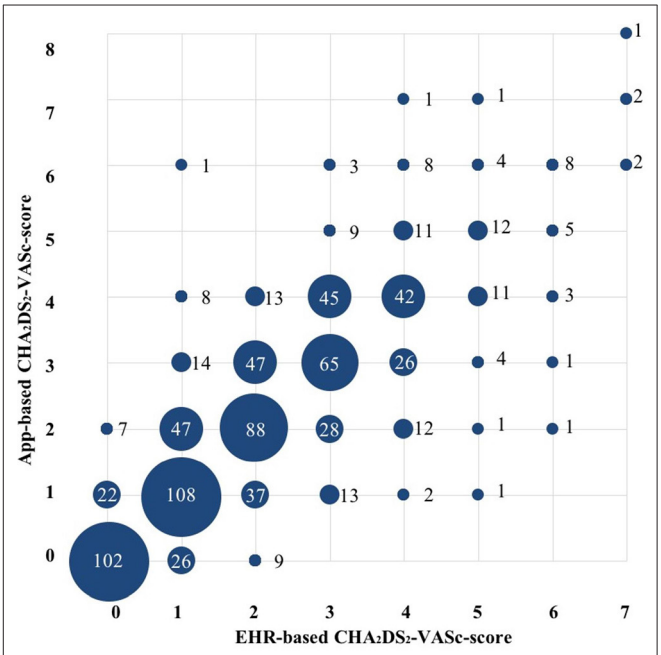

FIGURE 2 | Comparison between electronic health record- and app-based CHA_2DS_2-VASc score ($n = 853$). Size of the circles represent the numbers of patients (also mentioned as numbers). Abbreviations: see **Table 1**.

DISCUSSION

Surveys for AF risk factor assessment have been used in previous mHealth studies (7, 9–11). To the best of our knowledge, the present analysis of the real-world European mHealth TeleCheck-AF project conducted in numerous Telehealth-AF centers is the first assessing and validating the accuracy of remote self-reported AF risk factors and CHA_2DS_2-VASc-scores by patients, based on an app-based 10-item questionnaire in comparison with EHR data. Although blood pressure and physical activity data (12) can be directly incorporated into mobile apps by immediate data transfer from the measurement device, some other AF risk factors are filled in by patients and herein, we present the first study on accuracy of patient self-reported risk factor documentation.

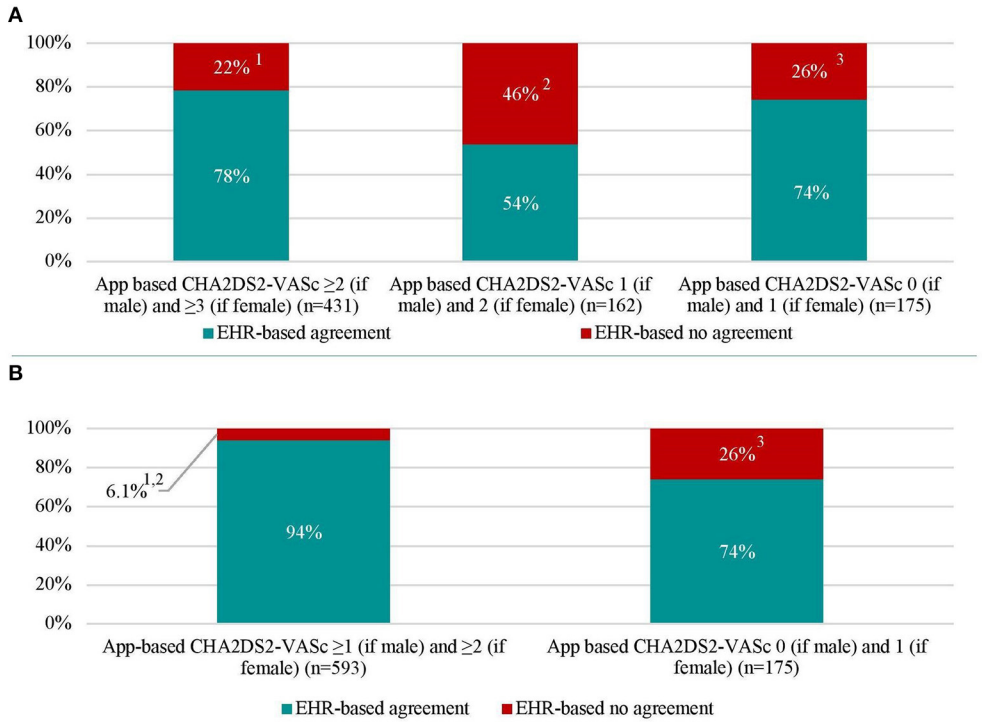

FIGURE 3 | Thromboembolic (CHA_2DS_2-VASc) score in patients with atrial fibrillation based on electronic health record- and app-based results ($n = 768$). **(A)** represents recommended (App-based CHA_2DS_2-VASc ≥2 [if male] and ≥3 [if female]), to be considered (App-based CHA_2DS_2-VASc 1 [if male] and 2 [if female]), and not recommended (App-based CHA_2DS_2-VASc 0 [if male] and 1 [if female]) indications for oral anticoagulation with percentages of agreement and disagreement with electronic health record indications. **(B)** represents recommended and to be considered indications for oral anticoagulation were merged. Abbreviations: see **Table 1**.[1]EHR-based CHA_2DS_2-VASc 0 (if male) and 1 (if female) in 2.8% of patients, CHA_2DS_2-VASc 1 (if male) and 2 (if female) in 19% of patients. [2]EHR-based CHA_2DS_2-VASc 0 (if male) and 1 (if female) in 15% of patients, CHA_2DS_2-VASc ≥2 (if male) and ≥3 (if female) in 31% of patients. [3]EHR-based CHA_2DS_2-VASc ≥2 (if male) and ≥3 (if female) in 5.1% of patients, CHA_2DS_2-VASc 1 (if male) and 2 (if female) in 21% of patients.

We demonstrated that collection of patient self-reported AF risk factors by an app-based 10-item questionnaire is feasible. In a real-world setting within the TeleCheck-AF project, most patients completed the app-based questionnaire. Within this physician-initiated and patient-centered setting, all patients were provided a standard instruction to guide them through the installation and activation process of the app (4). Additionally, after installation of the app, pop-up messages were provided to remind patients to complete the questionnaire. The high completion rate of >90% demonstrates that a reminder-based questionnaire with a limited number of closed-ended questions is feasible making it an important tool for further digital studies. We found that older patients were more concordant in completing the app-based questionnaire. Moreover, compared to younger patients, these patients showed a higher agreement between app-based and EHR-based assessment of anticoagulation usage but lower agreement between app-based and EHR-based heart failure assessment. This suggests that age should not be a limitation for innovative solutions such as mHealth questionnaires. However, other factors such as lower health literacy, lower education and lower income,which was not specifically determined in TeleCheck-AF, may represent barriers for digital health usage and mHealth equity (13).

To determine the accuracy of app-based risk factors and CHA_2DS_2-VASc-score, we compared the information provided by patients via the app with the patient characteristics retrieved from the EHR completed by the treating physician and used to decide on patient management and treatment in the respective outpatient clinics of the participating TeleCheck-AF centers. Despite an acceptable accuracy of app-based AF risk factor assessment compared to EHR, there are still differences between mobile app and EHR. Possibly, the formulation and wording of questions enclosed in the 10-item questionnaire even in countries with same language (AF named as both, "voorkamerfibrilleren" and "boezemfibrilleren") may explain some of the discrepancy observed (14). Furthermore, as TeleCheck-AF is an international mHealth project, language/country-specific differences in app-based questionnaire translations may also play a role in the differences between mobile app-based and EHR-based risk factor assessment. The difference between countries could also be explained by the different settings in which the TeleCheck-AF protocol was used in these countries (for example in Germany more often used in for pulmonary vein isolation follow up). Accordingly, Germany and Austria, which share German as a common language, document similar pattern of accuracy of app-based and EHR-based results.

Likewise, in the Netherlands, a particularly high accuracy was observed, which may reflect the effect of more intense patient education in the dedicated AF outpatient clinics, which was not present in other countries participating in TeleCheck-AF. Whether better patient instruction and easier language use may improve the accuracy of app-based AF risk factor assessment warrants further studies. In general, a direct health care professional-patient contact, either as face-to-face consultation or teleconsultation, to critically check patient self-reported app-based statements regarding their medical-history and risk factors remains indispensable.

Differences between self-reported app-based AF risk factors and the EHR-based risk factors may support the treating health care provider to identify gaps in knowledge and awareness of the patients about their own risk factors. In a recent meta-analysis including 21 studies that assessed AF patients' knowledge about their medications and condition, the main AF-related knowledge gap and misconception was the fact that AF can be asymptomatic and can predispose to heart failure (15). This is in line with our results where patients underreported arrhythmias and overreported heart failure in the app-based questionnaire. Incorporating this information on possible knowledge gaps of our patients in traditional face-to-face consultations or teleconsultations can help to guide a personalized patient education. There is a growing number of mobile applications, educational platforms and websites (www.afibmatters.org) dedicated to improve patients' knowledge about AF (16) and compliance for treatment with anticoagulation. Based on our study, patient knowledge about AF as a risk factor for stroke was independently associated with higher agreement between EHR and app-based results. This adds to the result of recent studies suggesting, that a better knowledge about AF and associated treatment options increases the acceptance of adverse events associated with treatment and disease (17), anticoagulation adherence (18), symptom management and quality of life (19).

In addition to the above discussed limited accuracy of some of the app-based risk factors and the app-derived CHA_2DS_2-VASc-score, a purely digital assessment of AF patients does not incorporate factors such as frailty, kidney function and potential bleeding risk, which also need to be considered for the initiation of OAC treatment. In TeleCheck-AF, without considering clinical OAC contraindications and OAC indications other than AF, 26% of patients would be exposed to a potential risk for OAC undertreatment and 6% of patients to a potential risk for OAC overtreatment if only the app-based risk factor questionnaire would have been used for the clinical decision on the initiation of OAC (20). Whether this would be acceptable for the initiation of OAC in a purely digital AF management setting or whether the results could be used for future digital trials to describe patient characteristics needs to be further discussed with all involved stakeholders, including patients. Noteworthy, proper risk factor (CHA_2DS_2-VASC score) assessment is crucial in AF screening to identify high thromboembolic risk population.

In TeleCheck-AF, we used a 7 day on-demand mHealth approach. The completion of the 10-item questionnaire was just a spot assessment of the risk factors. However, risk differs due to individual temporally dynamic risk factors and may change over time. Therefore, close patient monitoring may make sense to regularly re-evaluate burden of AF as well as current risk factors (21, 22). App-based risk factor monitoring has potential for longitudinal risk factor assessment to evaluate treatment response and the development of new risk factors early. Including the possibility for frequent re-assessment of risk analysis over time by mHealth apps may allow future longitudinal analyses and assessments of risk factors which could be used to detect deterioration of risk factors at an early time point. Possibly, a structured longitudinal re-evaluation of risk scores may result in a better guideline adherence over time and guide individualized risk factor management programs. Therefore, the ideal setting may be longitudinal app-based questionnaire validated by physicians with the help of patient records during the teleconsultation.

Limitations

Our study has several limitations. Firstly, there may be selection bias, as it includes only patients who were willing to use the mobile app in this real-life setting. Therefore, there should be caution in generalizing our findings to all patients with AF, especially living in non-wealthy countries. Secondly, due to the retrospective, observational character of this study, we were not able to determine the causal relationship between patient characteristics and completion of the 10-item questionnaire as well as the 100% agreement between mobile app and EHR. Thirdly, definitions of CHA_2DS_2-VASc-score components were fairly differently defined in app and EHR. Vascular disease was defined as peripheral artery disease or myocardial infarction in the app, but in the EHR, percutaneous coronary intervention and coronary artery bypass graft were included as well. In addition, hypertension in app was based on medication, although some hypertensive drugs such as angiotensin converting enzyme inhibitors may be given for other indications. This would have influenced the results, and these factors (vascular disease and hypertension) were also the components that varied the most. Finally, the timing of mobile app usage during the course of AF may have influenced app-based patient's knowledge concerning AF as newly diagnosed AF patients may be less aware of their disease than after a few months and few visits to the physician.

CONCLUSION

App-based AF risk factor assessment is feasible. It shows high accuracy of pacemaker and anticoagulation treatment assessment, but limited accuracy for the assessment of some of the traditional AF risk factors as components of the CHA_2DS_2-VASc-score. As such, a direct doctor-patient contact remains indispensable to maintain high quality clinical-decision making, especially to prevent over- or undertreatment with prescribed anticoagulation. Whether app-based risk factor assessment can be incorporated in personalized patient education and longitudinal guidance of risk factor modification programs requires future studies.

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 Medical Research Ethics Committee of Maastricht University Medical Center (METC2020-1337). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AH, MG, HH, MM, DD, and DL were responsible for conception and design of the study. AH, MG, and HH were part of the data analysis committee and drafted the manuscript. All authors contributed substantially to data acquisition, data interpretation, critical revising of the manuscript for important intellectual content, to the final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.757587/full#supplementary-material

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Smartwatch Electrocardiograms for Automated and Manual Diagnosis of Atrial Fibrillation: A Comparative Analysis of Three Models

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Aims: The diagnostic accuracy of proprietary smartwatch algorithms and the interpretability of smartwatch ECG tracings may differ between available models. We compared the diagnostic potential for detecting atrial fibrillation (AF) of three commercially available smartwatches.

Methods: We performed a prospective, non-randomized, and adjudicator-blinded clinical study of 100 patients in AF and 100 patients in sinus rhythm, patients with atrial flutter were excluded. All patients underwent 4 ECG recordings: a conventional 12-lead ECG, Apple Watch Series 5®, Samsung Galaxy Watch Active 3®, and Withings Move ECG® in random order. All smartwatch ECGs were analyzed using their respective automated proprietary software and by clinical experts who also graded the quality of the tracings.

Results: The accuracy of automated AF diagnoses by Apple and Samsung outperformed that of Withings, which was attributable to a higher proportion of inconclusive ECGs with the latter (sensitivity/specificity: 87%/86% and 88%/81% vs. 78%/80%, respectively, $p < 0.05$). Expert interpretation was more accurate for Withings and Apple than for Samsung (sensitivity/specificity: 96%/86% and 94%/84% vs. 86%/76%, $p < 0.05$), driven by the high proportion of uninterpretable tracings with the latter (2 and 4% vs. 15%, $p < 0.05$).

Conclusion: Diagnosing AF is possible using various smartwatch models. However, the diagnostic accuracy of their automated interpretations varies between models as does the quality of ECG tracings recorded for manual interpretation.

Keywords: electrocardiogram, atrial fibrillation, wearable, arrhythmia, diagnosis

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice but often remains undiagnosed. The ability to record an ECG tracing that is equivalent to lead I at any time and as often as desired is a relatively new feature of select smartwatches, creating opportunities to diagnose cardiac abnormalities such as AF (1–4). Recent guidelines recognize the potential value of smartwatch-based ECGs for diagnosing AF (5). Apple, Inc (Cupertino, CA, USA) released the first smartwatch to receive FDA approval for automated detection of AF, but smartwatches from competitors such as Samsung (Seoul, South Korea) and Withings (Issy les Moulineaux, France) can similarly record ECG tracings and warn wearers when AF is detected (6). The process of recording an ECG, analyzing it to generate an automated diagnosis of AF, and providing options to transmit these results to the wearer's physician(s) are similar between smartwatch manufacturers. However, their diagnostic algorithms are proprietary and not made available for analysis. The diagnostic accuracy of these algorithms and the ability of healthcare professionals to correctly interpret smartwatch-based ECGs may differ between commercially available smartwatches. Given this technology's widespread and growing use, mass screening for AF using various smartwatch-based technologies may effectively soon occur, the results of which will require clinical decisions on the part of healthcare professionals. Critical evaluation of the relative diagnostic strengths and weaknesses of commercially-available smartwatch technologies is therefore critical. The primary objective of our study was to compare the diagnostic performance of smartwatch ECGs from three companies (Apple, Samsung, and Withings), specifically their ability to accurately differentiate sinus rhythm (SR) from AF using either their automated algorithms or through review of recorded smartwatch ECG tracings.

METHODS

This was a prospective, non-randomized, and blinded clinical study of 100 consecutive patients in sinus rhythm who had undergone an AF ablation procedure in the previous 6 months and 100 consecutive patients in persistent or permanent AF who were referred for catheter ablation. All patients were ≥18 years of age and provided informed consent. Patients with atrial flutter, permanent pacemakers or implantable cardioverter-defibrillators were excluded. All patients had 12-lead ECGs performed, which served as the reference standard for the diagnosis of AF or sinus rhythm. Immediately after the 12-lead ECG was performed, 30-s ECG tracings using an Apple Watch Series 5® (Apple Inc, Cupertino, CA, USA), Samsung Galaxy Watch Active 3® (Samsung, Seoul, South Korea), and Withings Move ECG® (Withings, Issy-les-Moulineaux, France) were recorded in random order and after providing standardized instructions. These smartwatches' automated AF-detection algorithms yield one of several possible results, including "sinus rhythm," "atrial fibrillation," "low heart rate," "high heart rate," "poor recording" or "inconclusive recording." All smartwatch ECG recordings were saved as PDF documents for offline analysis, anonymized, randomized and each automatic diagnosis was removed before distribution to two blinded electrophysiologists who independently interpreted each tracing and assigned one of three possible diagnoses: AF, SR, or unclassified (unable to differentiate between AF and SR). In addition, the quality of smartwatch ECG tracings was classified as good, poor but interpretable (e.g., presence of artifacts but differentiating between AF and SR was deemed possible), and uninterpretable. In case of disagreements between the two experts, a third cardiac electrophysiologist reviewed the tracing and made the final diagnosis.

Statistical Analysis

For each of the three smartwatch models, sensitivity, specificity, positive predictive values and negative predictive values were calculated for automated and physician-interpreted smartwatch ECGs. Classifications were not binary as ECGs could be non-classified (i.e., inconclusive automated diagnoses or uninterpretable ECG tracings as per reading physicians) therefore two analyses were undertaken. In the first analysis, unclassified ECGs were considered false positives (when the patient was in SR) or false negatives (when the patient was in AF), yielding "worst-case-scenario" estimates (7). In the second approach, unclassified ECGs were excluded from the analysis. Kappa (κ) coefficients for interobserver agreement were assessed for the three models. Analysis of variance (ANOVA) tests were used to compare percentages between the three groups. All analyses were performed using SPSS software ver. 22.0 (IBM, Armonk, NY, USA) with a two-tailed alpha level of 0.05 to define statistical significance.

RESULTS

In total, 200 patients were enrolled (100 in SR, 100 in AF). Their mean age was 62 ± 7 years and 56% were male. Standard 12-lead and smartwatch ECGs from all the three models could be recorded in all patients, generating 200 12-lead ECGs and 600 single-lead smartwatch ECGs available for analysis. Representative examples of smartwatch ECGs from each model in a patient in AF is shown in **Figure 1**.

Automated Diagnosis Using the Apple Smartwatch

Of the 100 patients in SR, 86 ECG recordings were correctly diagnosed as SR, 1 incorrectly as AF, and 13 were not classified (3 due to poor recording, 3 due to a heart rate of <50 beats/min, and 7 due to inconclusive recordings). Of the 100 patients in AF, 87 ECG recordings were correctly diagnosed as AF, 7 incorrectly as SR, and 6 were not classified (1 due to poor recording, 1 due to a heart rate of <50 beats/min, 1 due to a heart rate of >150 beats/min, and 3 due to inconclusive recording). When considering non-classified ECGs as false results, sensitivity was 87% (95%-CI 79–93%) and specificity 86% (95%-CI 78–92), positive predictive value (PPV) was 86% and negative predictive value (NPV) was 87 %. When excluding unclassified ECGs from the analysis, sensitivity was 99% (95%-CI 94–100%) and

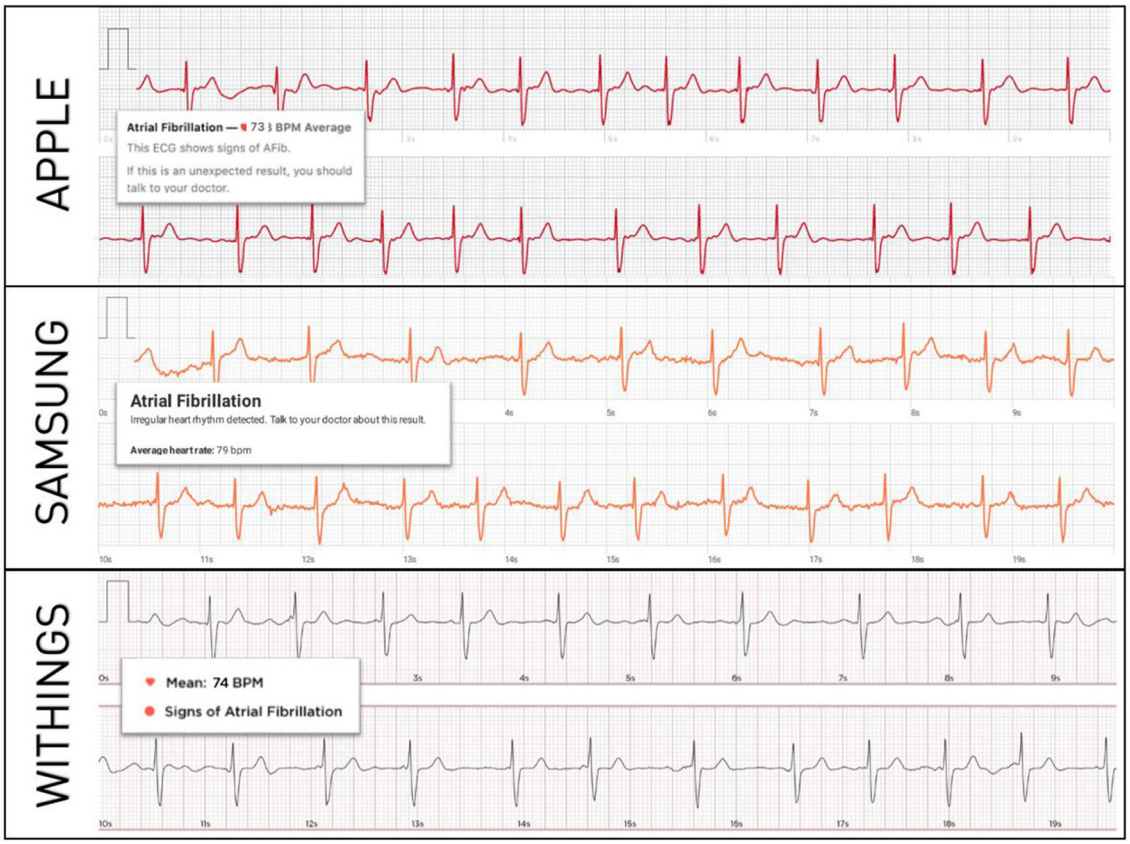

FIGURE 1 | Representative examples of smartwatch ECGs in the same patient with confirmed AF. The diagnosis of AF is correctly made by each smartwatch's automated algorithm.

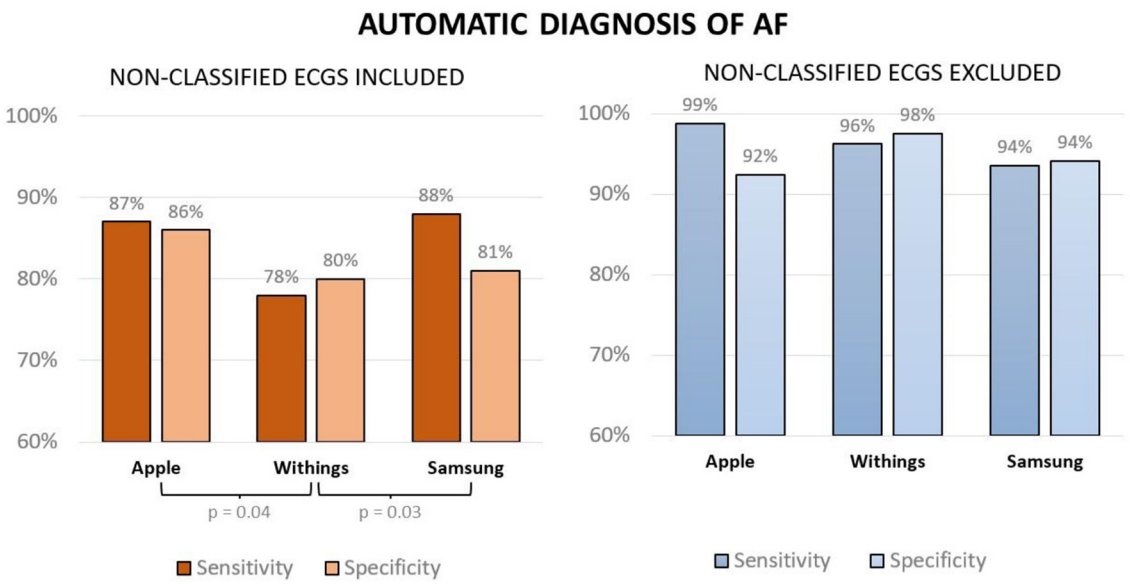

FIGURE 2 | Sensitivity and specificity of smartwatch-based automated diagnoses of AF when considering unclassified ECGs as false results (left panel) and when excluding unclassified ECGs (right panel).

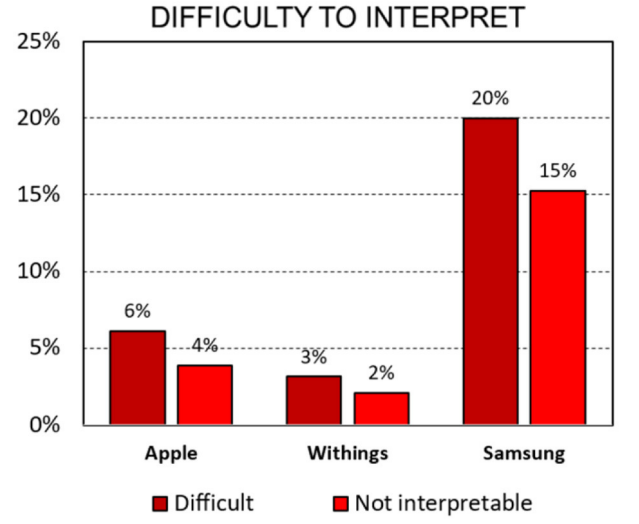

FIGURE 3 | Percentage of *difficult* or *uninterpretable* smartwatch ECGs according to the experts ($p < 0.05$ for ANOVA analysis).

specificity 93% (95%-CI 85–97%), PPV was 93% and NPV was 99%.

Automated Diagnosis Using the Samsung Smartwatch

Of the 100 patients in SR, 81 ECG recordings were correctly diagnosed as SR, 6 incorrectly as AF, and 13 were not classified (2 due to poor recording, 1 due to a heart rate of <50 beats/min, and 10 due to inconclusive recordings). Of the 100 patients in AF, 88 ECG recordings were correctly diagnosed as AF, 5 incorrectly as SR, and 7 were not classified (all 7 were considered inconclusive). When considering unclassified ECGs as false results, sensitivity was 88% (95%-CI 80–94%) and specificity 81% (95%-CI 72–88%), PPV was 82% and NPV was 87%. When excluding unclassified ECGs, sensitivity was 94% (95%-CI 87–98%) and specificity 94% (95%-CI 87–98%), PPV was 95% and NPV was 93%.

Automated Diagnosis Using the Withings Smartwatch

Of the 100 patients in SR, 80 ECG recordings were correctly diagnosed as SR, 3 incorrectly as AF, and 17 were not classified (1 due to poor recording, 3 due to a heart rate of <50 beats/min, 1 due to a heart rate >100 beats/min, and 12 due to inconclusive recordings). Of the 100 patients in AF, 78 ECG recordings were correctly diagnosed as AF, 2 incorrectly as SR, and 20 were not classified (all were labeled as inconclusive). When considering non-classified ECGs as false results, sensitivity was 78% (95%-CI 68–86%) and specificity 80% (95%-CI 71–87%), PPV was 80% and NPV was 78%. When excluding non-classified ECGs, sensitivity was 96% (95%-CI 90–99%) and specificity 98% (95%-CI 92–100%), PPV was 98% and NPV was 96%.

Comparison Across Smartwatch Models

We presented the results separately for SR and AF since inconclusive diagnoses may differ between rhythms. All automated smartwatch algorithms had high sensitivity and specificity for the diagnosis of AF even when considering unclassified tracings as false results (**Figure 2**). However, the Withings smartwatch had lower sensitivity and specificity relative to Apple ($p = 0.02$ for comparison of sensitivity and specificity between Withings and Apple) and Samsung models ($p = 0.03$ compared with Withings) when unclassified ECGs were considered false results, possibly due to the higher proportion of unclassified ECGs with this smartwatch (19 vs. 10% and 10% respectively, $p < 0.05$).

Manual Diagnosis by Electrophysiologists

Cardiac electrophysiologists exhibited high agreement for the differentiation between AF and SR with high inter-observer reproducibility for the three models (Apple $\kappa = 0.96$, Samsung $\kappa = 0.92$, Withings $\kappa = 0.94$). With 20% of tracings deemed difficult to interpret and 15% deemed uninterpretable, ECGs recorded with the Samsung smartwatch were more challenging for the electrophysiologists relative to the other models (**Figure 3**, Apple: 6% difficult and 4% uninterpretable; Withings: 3% difficult and 2% uninterpretable, ANOVA $p < 0.05$). When excluding uninterpretable ECGs, the sensitivity and specificity were high for all three models: 95% sensitivity and 90% specificity for Apple (PPV 90%, NPV 96%), 98% sensitivity and 88% specificity for Withings (PPV 89%, NPV 98%), and 99% sensitivity and 94% specificity for Samsung (PPV 93%, NPV 99%). When considering unclassified tracing as false results, the results were as follows: 94% sensitivity and 84% specificity for Apple (PPV 84%, NPV 94%), 96% sensitivity and 86% specificity for Withings (PPV 88%, NPV 95%), and 86% sensitivity and 76% specificity for Samsung (PPV 78%, NPV 85%) (**Figure 4**).

DISCUSSION

Direct access to wearable devices equipped with portable ECG technology is now widespread. This feature may prove useful for detecting symptomatic and asymptomatic AF, thus creating opportunities to intervene. Previous studies have always investigated a single model, mostly focusing on optical sensors and connected ECG wristbands (8–11). However, the relative diagnostic value of available smartwatch models is poorly known. Our results show that the accuracy of automated algorithms for the diagnosis of AF vary between smartwatch models as does the quality of ECG tracings recorded for offline interpretation by healthcare professionals.

Automated Diagnoses: Sinus Rhythm vs. Atrial Fibrillation

Algorithm-based automated AF diagnoses may have undesired consequences. A less-than-perfect screening test used in a population with low pre-test probability of cardiac arrhythmias

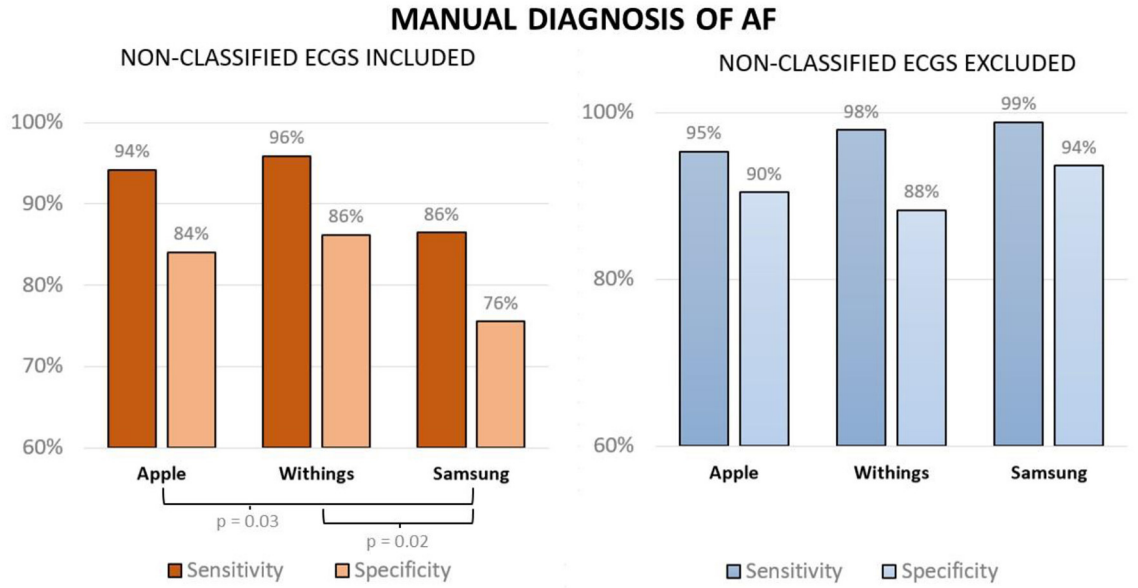

FIGURE 4 | Sensitivity and specificity of expert-interpreted smartwatch ECGs for the diagnosis of AF when considering unclassified ECGs as false results (left panel) and when excluding unclassified ECGs (right panel).

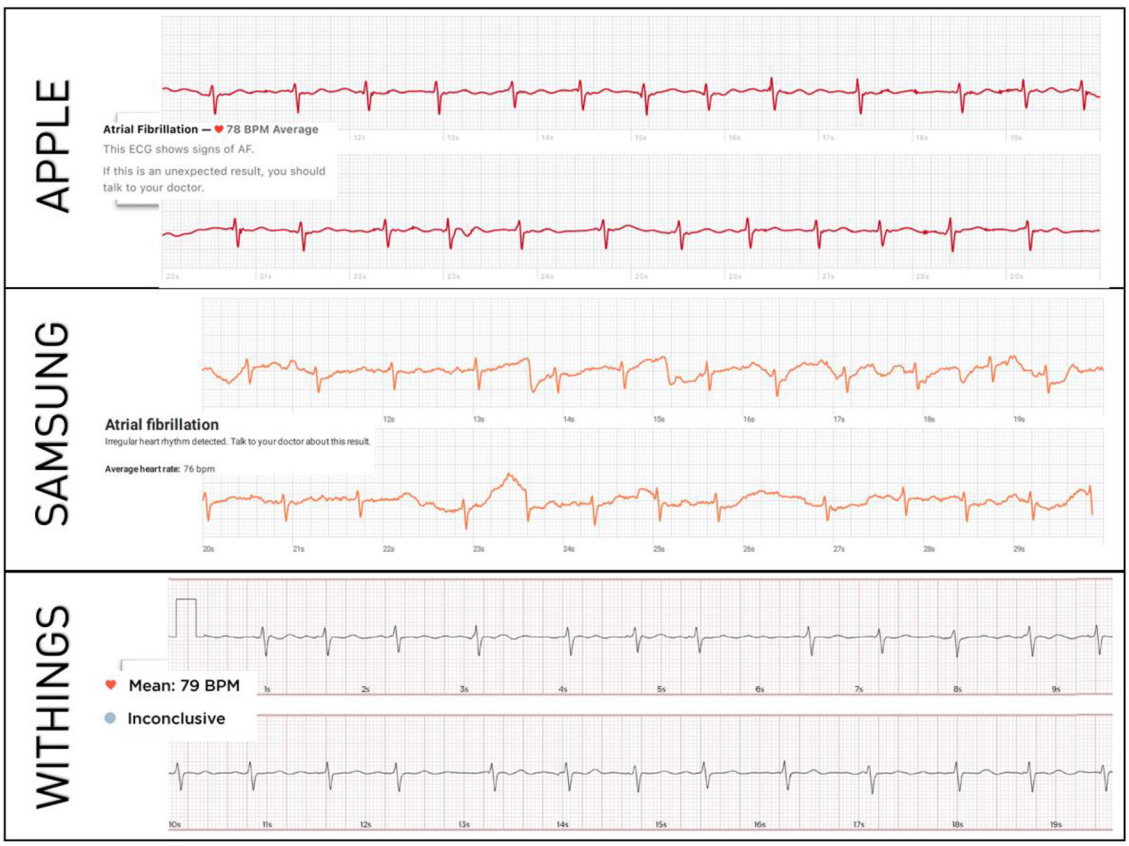

FIGURE 5 | Smartwatch ECGs in the same patient with confirmed AF. Although the Samsung ECG was classified as difficult to interpret due to artifact, its automated algorithm correctly diagnosed AF. In contrast, the Withings ECG is of high quality but its automated algorithm failed to diagnose AF.

translates into a modest post-test probability of disease. False positives can be associated with anxiety, unnecessary medical testing, and even potentially inappropriate treatments. On the other hand, false negatives (diagnoses of SR or inconclusive rhythm when the patient is in AF) can falsely reassure the patient and lead to diagnostic and therapeutic delay. The results of our study show that the sensitivities and specificities of all three algorithms are high. While the Withings algorithm is associated with a slightly but significantly lower sensitivity, this may be due to the higher proportion of ECGs reported as inconclusive with this smartwatch. Inconclusive rhythm classifications may occur in several circumstances: if the heart rate is too high (depending on the model), the heart rate is too slow, the patient is in an arrhythmia other than AF, the tracing is of low quality and uninterpretable by the algorithm, or criteria are not met to classify the rhythm as SR or AF. The proportion of inconclusive tracings is expected to diminish as improvements in filtering, changes in algorithms, and widening of interpretable heart rate windows are implemented. For instance, the heart rate threshold above which AF is not diagnosed has been recently increased from 120 to 150 bpm in Apple smartwatches. The impact of inconclusive recordings may also be reduced with more patient practice, repeated recordings over time and alternative smartwatch positions (12–14). Artificial intelligence approaches may also improve the accuracy of automated diagnoses of smartwatches (15, 16). Alternative over-the-counter technologies to self-diagnose AF have also shown excellent accuracy among which ECG devices (such as AliveCor® 6L) and photoplethysmography-based smartphone apps (such as FibriCheck®) (17, 18). Smartwatches are expected to be more often used then mentioned alternative technologies as they are mostly acquired for non-medical purposes, not motivated by a healthcare professional.

Quality of the Tracings and Interpretation by Electrophysiologists

The product user manuals of the different smartwatches caution that the automated diagnosis (SR vs. AF) is provided only for information purposes and is not intended to replace the analysis of the tracing by a qualified health professional. Even though the accuracy of automated AF diagnoses is high, it remains imperative that a healthcare professional confirm the diagnosis before any therapeutic decision is made. The role for direct-to-consumer ECG tools in future guidelines will be defined by their feasibility and accuracy as shown in validation studies. Our study highlights that ECG tracing quality can differ between models with a direct impact on their diagnostic value. In our study, the quality of the tracings was lower using Samsung devices, which rendered ECG interpretation more difficult (the example shown in **Figure 5** was classified as difficult to interpret). In fact, for this model, the automated diagnosis of AF outperformed offline ECG interpretation by experts. This may be due to differences in the criteria used to diagnose AF between smartwatch algorithms and physicians. For existing devices, automated AF diagnoses are schematically based on the exclusion of heart rates that are too fast or too slow (with different thresholds used across models), on the irregularity of QRS complexes, and the absence of repetitive patterns associated with extrasystoles. A perfectly stable rhythm will therefore usually be classified as sinus rhythm and an irregular rhythm as AF without a dedicated analysis of atrial activity. In contrast, although the above features are considered by electrophysiologists, direct analysis of atrial activity is considered an essential component of the diagnosis of AF—a criterion that generally requires an ECG tracing without excessive artifact or baseline wander for at least a few seconds. Without this confirmation, physicians may be reluctant to diagnose AF even if suspected.

Study Limitations

This was a single-center study of 200 patients, half of whom had AF and half of whom had undergone atrial ablation. The accuracy of these devices in a larger population with or without cardiovascular risk factors or previous cardiac interventions remains to be shown. Participants were instructed on how to use the smartwatch prior to obtaining each recording and their ability to record each tracing was directly observed. The performance of the algorithms and the quality of the recorded tracings may be less accurate in an ambulatory setting without this instruction. However, none of the patients who participated in our study had previously used these smartwatches. While examiners were blinded to the concomitant automatic diagnosis and to the manual diagnosis of the smartwatch ECGs of the other models in the same patient, they were not blinded to the smartwatch model as each model features distinct characteristics on the ECG which make the manufacturer identifiable. More in-depth information about filters and algorithms would facilitate the comprehension of differences in performance between the smartwatch models but unfortunately this information is not made publically available by the manufacturers.

CONCLUSION

Diagnosing AF is possible using various ECG smartwatch models. Our study demonstrates that there exist differences in the diagnostic accuracy of their automated algorithms and in the quality of ECG tracings recorded, the latter of which influences the ability of healthcare professionals to make a manual diagnosis of AF.

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 Bordeaux University Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SA-A, NM, HM, and SB: collection of tracings and inclusion of patients. MS, FR, SP, and HR: writing of the article. PB and MH: concept and approval of the study. All authors contributed to the article and approved the submitted version.

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Machine Learning Using a Single-Lead ECG to Identify Patients With Atrial Fibrillation-Induced Heart Failure

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Aims: Atrial fibrillation (AF) and heart failure often co-exist. Early identification of AF patients at risk for AF-induced heart failure (AF-HF) is desirable to reduce both morbidity and mortality as well as health care costs. We aimed to leverage the characteristics of beat-to-beat-patterns in AF to prospectively discriminate AF patients with and without AF-HF.

Methods: A dataset of 10,234 5-min length RR-interval time series derived from 26 AF-HF patients and 26 control patients was extracted from single-lead Holter-ECGs. A total of 14 features were extracted, and the most informative features were selected. Then, a decision tree classifier with 5-fold cross-validation was trained, validated, and tested on the dataset randomly split. The derived algorithm was then tested on 2,261 5-min segments from six AF-HF and six control patients and validated for various time segments.

Results: The algorithm based on the spectral entropy of the RR-intervals, the mean value of the relative RR-interval, and the root mean square of successive differences of the relative RR-interval yielded an accuracy of 73.5%, specificity of 91.4%, sensitivity of 64.7%, and PPV of 87.0% to correctly stratify segments to AF-HF. Considering the majority vote of the segments of each patient, 10/12 patients (83.33%) were correctly classified.

Conclusion: Beat-to-beat-analysis using a machine learning classifier identifies patients with AF-induced heart failure with clinically relevant diagnostic properties. Application of this algorithm in routine care may improve early identification of patients at risk for AF-induced cardiomyopathy and improve the yield of targeted clinical follow-up.

Keywords: atrial fibrillation, heart failure, machine learning, ECG, RR intervals, diagnostic tool

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in human kind, affecting approximately eight million patients in the European Union (1). Fibrillatory activity in the atria not only promotes atrial thrombus formation and systemic thromboembolism, but also leads to irregular and often rapid ventricular activation.

AF and heart failure share many common risk factors, predispose to each other, and often coexist (2). AF can occur concomitantly with heart failure without causative relation, and restoration of sinus rhythm in these patients results in only modest improvements of left ventricular systolic dysfunction (LVSD). In a potentially large subset of patients with AF and heart failure however, sinus rhythm restoration leads to drastic improvements or normalization of LVSD (3–6) within days to weeks.

It is currently not fully understood why certain patients develop severe heart failure symptoms and LVSD during AF (AF-induced heart failure; AF-HF). Current guidelines emphasize the importance of AF in this context, and recommend routine clinical follow-up in AF patients to recognize cardiac deterioration early (1). The most established modality to detect heart failure in this patient group remains echocardiography, unfortunately including all its limitations with regard to the equipment and training of the examiner that is required. Given the ever-increasing prevalence of AF in the European population, easily applicable screening tools to identify patients at risk are desirable to tailor patient care and reduce costs for health care systems.

Machine learning-based algorithms are an emerging tool in diagnosis and risk prediction and have shown promising results in the field of cardiology (7). A feature-based machine learning algorithm can lead to a clear interpretation of the results as clinical algorithms do. However, to develop a performant feature-based classifier a careful selection of features that have been recognized as relevant in the analysis of heart rhythms should be made.

We hypothesize that specific patterns of ventricular beat-to-beat variations and arrhythmia characteristics in AF are associated with the clinical phenotype of AF-HF, potentially enabling early prediction of AF-patients at risk to develop heart failure.

In the following manuscript, we show the methods and procedures used to implement a classification between patients with AF-HF and control group patients (in AF but without risk of developing heart failure) using 5-min RR signals acquired during daylight hours (from 8 a.m. to 10 p.m.). In addition, an analysis of the influence of the circadian cycle on classification performance was performed.

METHODS

Study Protocol

This prospective observational study was approved by the local institutional review board, and patients gave informed consent. Inclusion criteria were persistent (lasting 7 days to 12 months) or long-persistent (lasting >12 months) AF at study screening, absence of left- or right-sided significant valvulopathies (moderate or severe), and absence of relevant coronary artery disease as evidenced using coronary angiography or non-invasive imaging within 12 months of screening. Patients younger than 18 years and those with a history of ischemic heart disease requiring revascularization with or without myocardial infarction were excluded.

All study participants underwent standard 12-lead ECG, 24 h Holter single-lead ECG, and transthoracic echocardiography within 24 h from study inclusion (**Supplementary Figure 3**). Details on echocardiographic assessment of LVEF are provided in the **Supplementary Material**. Patients with LVEF >50% in AF were considered as control group. Patients with an initial LVEF ≤40% in AF were scheduled for electro-cardioversion on the next working day and underwent additional clinical follow-up including repeat echocardiography at day 40. As the current study focuses on AF-induced heart failure, only patients who experienced an absolute improvement of LVEF of 15% or more within 40 days in sinus rhythm remained in the study for further analysis (6). Patients who either experienced AF-recurrence within 40 days from cardioversion or who experienced an improvement in LVEF of <15% despite sinus rhythm were excluded from this study ($n = 6$ and $n = 3$, respectively).

The primary endpoint was the determination and validation of an algorithm to identify AF-HF patients from 5-min Holter ECG segments recorded during daytime (8 a.m. to 10 p.m.). Secondary endpoints were the performance of the feature set for nighttime (10 p.m. to 8 a.m.) and full-day times (8 a.m. to 8 a.m.).

ECG Data Extraction

Consecutive RR-intervals (RR) were extracted from the single-lead 24 h Holter ECG raw data set using the Cardioday software (Getemed Medizintechnik, Teltow, Germany) with a 128 Hz-sampling rate. Prior to extraction, the complete data set was manually screened, and noise or artifacts were excluded by two senior electrocardiogram-analysts. Relative RR-intervals (relRR) were calculated as a percentage of the current RR-interval N with respect to the previous RR-interval N-1. Based on the conventional short-term recording standards (8), intervals were grouped in segments of 5 min each, resulting in a total of 10,234 segments. Two-thousand one hundred-four AF-HF and 2,301 control group daytime segments (recorded between 8 a.m. to 10 p.m.) were analyzed. Moreover, a full-day set and a night set (from 10 p.m. to 8 a.m.) were analyzed to check the circadian differences in performance. The full-day set comprised 5,266 segments in the AF-HF group, and 4,968 segments in the control group group, whereas the night set comprised 3,162 AF-HF, and 2,667 control group segments.

Feature Extraction

Fourteen features were extracted from the signals (8 from RR, and 6 from relRR series) using several clinical heart rate variability (HRV), and advanced biosignal processing parameters to derive information regarding the regularity and complexity of the time series: the mean RR and mean relRR intervals ($\overline{RR}$ and $\overline{relRR}$), time between all adjacent heartbeats; the standard

deviation of the RR and relRR intervals (*SDRR* and $SDRR_{rel}$) to measure how these intervals vary over time; the root mean square of successive differences between heartbeats ($RMSSD_{RR}$ and $RMSSD_{relRR}$) reflecting the beat-to-beat variance in heart rate (HR) (9); the deceleration capacity (*DC*) providing a measure of cardiac vagal modulation; the deceleration reserve (*DR*) to measure the balance between deceleration and acceleration capacity emphasizing asymmetric growing, decaying HR trends, and non-stationarity (10); the Shannon entropy of the RR and relRR series ($ShanEn_{RR}$ and $ShanEn_{relRR}$) to assess the complexity of the signals based on information theory; the sample entropy ($SampEn_{RR}$ and $SampEn_{relRR}$) measuring the complexity of the time series (9); and spectral entropy ($SpecEn_{RR}$ and $SpecEn_{relRR}$) indicating the spectral complexity of these time series (11). More information regarding the feature extraction methods is provided in the **Supplementary Material**.

Feature Selection and Evaluation

A greedy forward selection technique was implemented to select the optimal feature set out of the 14. This algorithm started with an empty feature set and added, in each iteration, the feature which led to the highest classification performance increase assessed using the accuracy of a decision tree classifier (see Section Feature Selection and Evaluation for details about the classifier). The algorithm stopped when performance based on the validation set (subset of data utilized to tune the algorithm's parameters) could not be further increased. Candidate features to be added to the set were only added if the correlation coefficient with any of the already included features was < 0.6. The correlation threshold was optimized looking for the best compromise between redundant information and physiological explanation only deleting the features that have similar values' distributions and that are expression of the same physiological behavior.

Shapley calculation was implemented to analyze a posteriori the importance of the features selected for classification once the model was trained (12). The Shapley calculation was run 1,000 times with random samples to calculate the standard deviation (SD).

Machine-Learning Classification

A decision tree classifier was implemented for binary classification (AF-HF vs. control group) for the daytime set. The decision tree algorithm was selected due to its simplicity and explainability. The decision tree was trained, and applied using the MATLAB functions fitctree, and predict, respectively. Similar analyses were performed using different machine learning algorithms and with different segment lengths (see **Supplementary Material**).

The multi-feature classification was performed with the feature set selected as described in Section Feature Selection and Evaluation. Five-fold cross-validation was performed by randomly dividing the dataset into a training set, validation set, and test set with 32, 8, and 12 patients in each set, respectively (**Figure 1**). Training and validation sets were recalculated at each iteration while the test set was excluded and used only once on the final classifier. The final classifier was obtained by re-training it with all the data (training + validation sets). This approach allowed us not to include RR series from the same patient in different sets, and not to use the test set during algorithm development, thus avoiding overfitting on the data. The classes were always balanced between the two groups, however for shrewdness the Prior model parameter in the MATLAB fitctree function was set to uniform. Sensitivity, specificity, and positive predictive value (PPV) were calculated considering the AF-HF group as positive, and the control group group as negative. The choice of these performance metrics is motivated by their extensive use in the clinical and biomedical engineering fields regarding machine learning approaches applied to biomedicine and being considered basic concepts of this field.

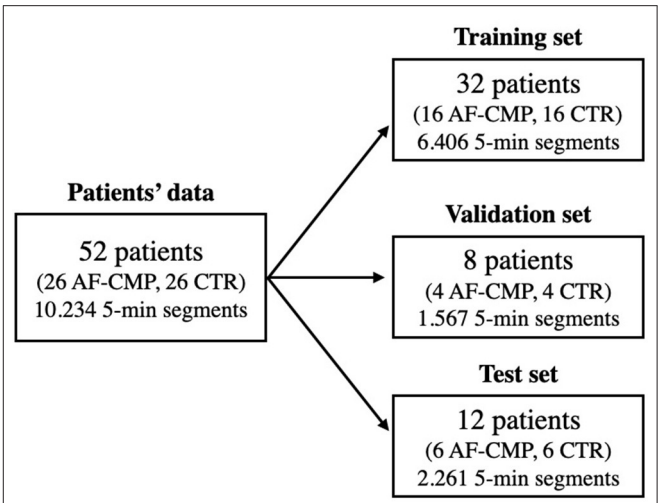

FIGURE 1 | Flow chart showing the dataset division of the 52 patients' signals into training, validation, and test sets, respectively. The number of all 5-min segments acquired from the patients is reported as well. Control group (CTR).

Moreover, a decision tree single-feature classification was implemented with each individual feature of the set to compare their individual classification power against that of the multi-feature classifier.

Regarding the full-day set, and the nighttime set, we first computed classifiers using the feature set extracted for the daytime set. Then, we implemented two new classifiers where the feature sets were optimized for the full-day, and nighttime set by greedy selection (see Section Feature Selection and Evaluation), respectively.

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0 for macOS (IBM Corporation, Armonk, New York), or GraphPad Prism version 8 for macOS (GraphPad Software, La Jolla, California). Normally distributed data are expressed as mean ± SD, skewed data are expressed as median (interquartile range). Intergroup comparisons were performed using student's *t*-test, or Mann-Whitney-test depending on normality.

Classifier performance was evaluated using accuracy (ACC), sensitivity, specificity, and PPV. Accuracy was also calculated for

TABLE 1 | Descriptive patient characteristics.

	All $n = 52$	AF-HF $n = 26$	CTR $n = 26$	p-value
Age (years)	68.3 (11.7)	70.48 (11.83)	66.3 (11.54)	0.204
Male sex	26 (50)	18 (69.2)	17 (65.5)	1.000
BMI (kg/m^2)	29.1 (4.9)	29.59 (5.84)	28.74 (4.03)	0.416
Systolic blood pressure (mmHg)	135.7 (21.1)	132.4 (22.66)	139 (19.25)	0.264
Diastolic blood pressure (mmHg)	87.42 (13.1)	85.81 (13.77)	89.04 (12.49)	0.380
NYHA stages				<0.001
NYHA I	8 (15)	1 (3.8)	7 (26.9)	
NYHA II	10 (19)	2 (7.7)	8 (30.8)	
NYHA III	19 (36.5)	9 (34.6)	10 (38.5)	
NYHA IV	15 (28.8)	14 (53.8)	1 (3.8)	
Diabetes	7 (13.5)	0 (0)	7 (26.9)	0.01
Hypertension	35 (67)	17 (65.4)	18 (69.2)	1.000
Hyperlipidemia	26 (50)	12 (46.2)	14 (53.8)	0.782
Medications				
ß blocker	37 (71)	19 (73.1)	18 (69.2)	1.000
ACE inhibitors	22 (42.3)	16 (61.5)	6 (23.1)	0.011
ATRA	10 (19.2)	4 (84.6)	6 (76.9)	0.726
Mineralcorticoid receptor blocker	14 (26.9)	12 (46.2)	2 (7.7)	0.004
Diuretics	21 (40.4)	13 (50)	8 (30.8)	0.160
Digoxin	2 (3.8)	0 (0)	2 (7.7)	0.490
Antiarrhythmics (class 1c and class 3 cumulative)	19 (36.5)	16 (61.5)	3 (11.5)	<0.001
Echocardiography				
LVEF	44.8 (15.9)	29.25 (6.78)	59.15 (2.64)	<0.001
LVESD (mm)	39 (9.9)	45.67 (8.78)	31.9 (4.75)	0.004
LVEDD (mm)	52 (7.0)	55.48 (7.80)	49.92 (5.03)	<0.001
LAD (mm)	45 (6.4)	48.54 (4.86)	42.38 (6.4)	<0.001
LAV (ml)	96.4 (27.4)	106.84 (18.13)	75.6 (31.17)	0.002
LAVI (ml/kg/BW)	49 (9.6)	51.94 (7.35)	42.38 (11.47)	0.017
ECG				
Resting heart rate in 12-lead ECG	93.4 (24.2)	104 (23.9)	82.6 (19.5)	0.001
Mean heart rate in 24 h- ECG	85.3 (17.2)	91.6 (16.6)	78.7 (15.4)	0.006
QRS width (ms)	93.3 (16.0)	95.1 (19.2)	91.4 (12.2)	0.407

Control group (CTR), body mass index (BMI), New York Heart Association (NYHA), angiotensin converting enzyme (ACE), angiotensin type 1 receptor antagonist (ATRA), left ventricular ejection fraction (LVEF), left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), left atrial diameter (LAD), left atrial volume (LAV), left atrial volume index (LAVI). Values are given as mean (± standard deviation) or number (%).

each individual patient in the test set (ACCi, with i as test set patient ID, **Table 2**) by counting how many segments belonging to the same patient were correctly classified with respect to their total number.

The comparison between the feature distributions, and AF-HF, and control group groups was done using the Wilcoxon rank sum test (one-tailed, $p < 0.05$ considered significant).

RESULTS

Patient Characteristics

A total of 52 patients (26 with AF-HF and 26 control group) were included in the study. All patients were in persistent or long-persistent AF at study inclusion. Descriptive data of study participants are given in **Table 1**. Patients with AF-HF had higher NYHA stages, higher average heart rates, and were more often on ACE inhibitors and aldosterone antagonists, as well as on antiarrhythmics.

Feature Selection and Algorithm Performance to Detect Atrial Fibrillation-Induced Heart Failure

Splitting the longitudinal Holter ECG data into intervals of 5 min each and selecting only segments recorded during daytime (8 a.m. to 10 p.m.) resulted in a total of 4,405 segments (2,104 segments for AF-HF and 2,301 segments for control group). Greedy forward selection on these data led to a feature set composed of three out of the 14 features extracted in total: $SpecEn_{RR}$, $relRR$, and $RMSSD_{relRR}$.

TABLE 2 | Number of segments and accuracy for each individual patient in the test set (%) for the daytime dataset.

Test set patient ID	No. of segments	Class	ACC_P_i
1	72	AF-HF	76.19
2	77	AF-HF	56.10
3	85	AF-HF	57.14
4	64	AF-HF	81.43
5	78	AF-HF	43.80
6	99	AF-HF	17.81
7	85	CTR	85.39
8	88	CTR	92.13
9	112	CTR	96.34
10	78	CTR	97.06
11	96	CTR	93.59
12	66	CTR	85.19

Patients who were correctly classified over all segments (ACC_Pi > 50%) are highlighted in green. Patients who got misclassified over all segments (ACC_P_i < 50%) are highlighted in red. Control group (CTR).

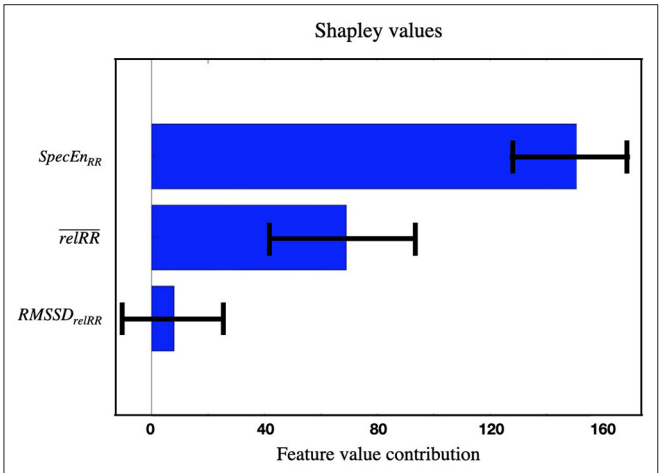

FIGURE 2 | Shapley feature importance calculation on the three features selected for the daytime binary classification AF-HF vs. control group. The shapley calculation was run 1,000 times with random samples to calculate the SD (error bars in the plot).

Evaluation of the relative contribution of each feature to the overall classification demonstrated the highest contribution for $SpecEn_{RR}$, followed by $\overline{relRR}$ and $RMSSD_{relRR}$ (**Figure 2**). In the **Supplementary Material** the $SpecEn_{RR}$ values' distribution is shown for the control group and AF-HF groups.

Application of the decision tree classifier with this feature set on the patients in the test set (475 AF-HF, and 525 control group 5-min segments from six AF-HF, and six control group patients, respectively) yielded an overall accuracy to correctly assign a given 5-min segment to AF-HF or control group of 73.5%, with a specificity of 91.4%, sensitivity of 64.7%, and PPV of 87.0% (**Figure 3**). When applying a 50% threshold on the fraction of segments correctly classified for a given patient, 10 out 12 patients (83.3%) were correctly assigned to AF-HF or control group (6/6 patients in the control group group and 4/6 in the AF-HF group; **Figure 3**). The accuracy achieved for each individual patient in the daytime test set is given in **Table 2**. Similar results have been achieved using other machine learning algorithms (see **Supplementary Material**).

Circadian Performance Differences on the Classification

The decision tree classifiers derived from Holter recordings during daytime as described above ($\overline{relRR}$, $RMSSD_{relRR}$, and $SpecEn_{RR}$) yielded an accuracy of only 56.5% when applied on all available 5-min-segments (recorded between 8 a.m. and 8 a.m. the next day, $n = 2{,}261$), and 49.3% for segments recorded during nighttime (10 p.m. to 8 a.m., $n = 1{,}261$).

An optimized feature set for all segments (recorded between 8 a.m. and 8 a.m. the next day) based on the greedy forward selection was composed of 10 features out of the 14 extracted ($ShanEn_{RR}$, $RMSSD_{relRR}$, $ShanEn_{relRR}$, $\overline{RR}$, DR, $SampEn_{RR}$, $SpecEn_{RR}$, DC, $SpecEn_{relRR}$, and $SDRR$). The classifier retrained on this optimized feature set yielded an improved accuracy on all segments of the test set of 60.5%, specificity, and sensitivity of 64.2%, and 57.3%, respectively, and a PPV of 62.2%. With respect to the total number of segments for each patient, 10/12 patients (83.3%) were classified correctly (5/6 control group patients, and 5/6 AF-HF patients, table in the **Supplementary Material**).

Optimization for segments recorded during nighttime (10 p.m. to 8 a.m.) led to a feature set that comprised four features out of the 14 extracted features (DC, $SDRR$, $SpecEn_{relRR}$, and $RMSSD_{relRR}$). The classifier retrained on this optimized feature set yielded a nighttime test set accuracy of 50.4%, specificity of 47.6%, sensitivity of 53.2%, and PPV of 50.7%, and 7/12 patients (58.3%) were classified correctly (3/6 control group patients, and 4/6 AF-HF patients). The difference in accuracy between the three different classifiers is visually shown in the **Supplementary Material**, whereas an overview of the performance that the decision tree classifier achieved in the different datasets using the respective feature sets is shown in **Figure 4**.

DISCUSSION

The current study reports three main findings: First, patients with AF-HF differ from control group patients without heart failure with regard to heartbeat entropy ($SpecEn_{RR}$) and beat-to-beat variation ($\overline{relRR}$ and $RMSSD_{relRR}$) during AF. Second, incorporation of these individual features in a machine learning algorithm correctly stratifies the majority of test patients to AF-HF or control group. And third, circadian analysis of algorithm performance demonstrates superior discriminative properties during daytime.

Heart Rate in AF and Development of LVSD–The Fast and the Furious?

Epidemiological studies demonstrate that heart failure and AF predispose to each other, and often co-exist (13). AF may worsen heart failure symptoms in patients with various underlying

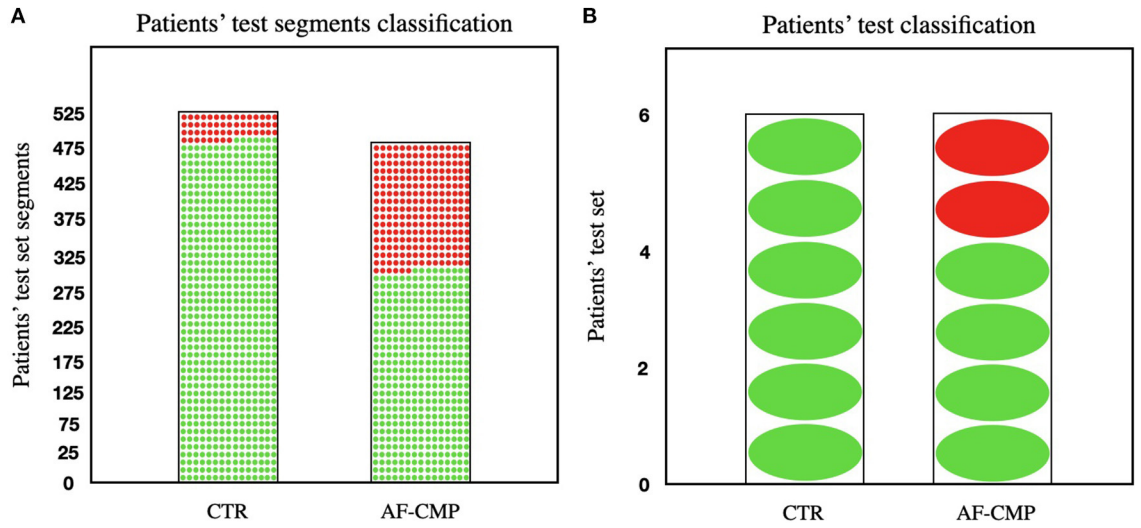

FIGURE 3 | (A) Visual representation of the number of segments in the test set that were correctly classified for both control group and AF-HF groups (91.4% and 64.7% of the segments correctly classified for each group, respectively). **(B)** Visual representation of the number of individual patients in the test set that were correctly classified for both control group and AF-HF groups (100% and 83.3% of the patients correctly classified for each group, respectively). The red dots represent segments/patients misclassified; the green dots represent segments/patients correctly classified. Control group (CTR).

cardiomyopathies such as ischemic or valvular heart disease ("AF-associated" cardiomyopathy) or serve as the only causative reason for LVSD (AF-HF). The pathophysiology of AF-HF is not entirely understood, and proposed mechanisms include immunological alterations (14) as well as abnormalities in energy metabolism or calcium handling (15).

Rapid ventricular heart rates during AF are often being associated with AF-HF. As such, rapid atrial pacing is a common model to induce LVSD in animals, and heart rate control was shown to be non-inferior to rhythm control in older heart failure trials (16). However, average heart rates below 100 bpm in AF may equally lead to severe forms of AF-HF (6), demonstrating that heart rate alone is likely not a suitable discriminator for AF-HF in clinical practice.

In the current study, we investigated various features that describe entropy, variability but also beat-to-beat heart rate in patients with AF-HF. The most important features for discrimination of patients with AF-HF from control group patients were all related to entropy and variability ($SpecEn_{RR}$, $RMSSD_{relRR}$, and $\overline{relRR}$). This finding is in line with the clinical observation that arrhythmia-induced heart failure occurs not only in the context of chronic tachycardia but also with frequent premature atrial or ventricular contractions (15).

Machine-Learning for Patient Stratification

For the current study, fourteen features commonly used for the analysis of heart rate variability and regularity were extracted from 5-min RR-series segments. The 5-min intervals were chosen following the recommendation given by the European Society of Cardiology and the North American Society of Pacing and Electrophysiology regarding the standardization of physiological and clinical studies (8). The decision tree classifiers for binary classification of AF-HF vs. control group achieved a clinically useful specificity and positive predictive value of 91.4 and 87.0%, respectively, using only three features ($SpecEn_{RR}$, $\overline{relRR}$, and $RMSSD_{relRR}$). The most important contribution to the algorithm's performance was given by $SpecEn_{RR}$ (**Figure 2**), with lower $SpecEn_{RR}$ values corresponding to decreased spectral complexity (the number of frequencies of which the signal is composed) in patients with AF-HF.

Remarkably, the abovementioned features that were automatically selected for the classifier are relatively novel, and the scientific literature reporting on their application in patients with AF is scarce. In this context, spectral entropy was previously shown to predict outcomes in AF patients, and to discriminate between persistent, and long-standing AF (17). In patients with sinus rhythm, analysis of spectral entropy was successfully used to discriminate healthy patients from patients with heart failure (18). In line with our findings, heart failure in this study was associated with lower a spectral entropy.

$\overline{relRR}$ has been proposed as a robust, simple, and reliable measure of heart rate variability, aiming to overcome the shortcomings of conventional measures of HRV, with $RMSSD_{relRR}$ being a direct derivative (19). $\overline{relRR}$ was successfully applied in machine learning algorithms to differentiate atrial fibrillation from sinus rhythm (20). To our knowledge, the current study is the first clinical evaluation of the performance of these parameters for stratification of AF-induced heart failure.

In contrast to the good performance of the algorithm when derived from and applied to RR-intervals recorded during the day, application of the algorithm to data recorded at nighttime performed significantly worse even after optimization of the feature set. It is possible that influences of factors such as physical activity, or autonomic nervous

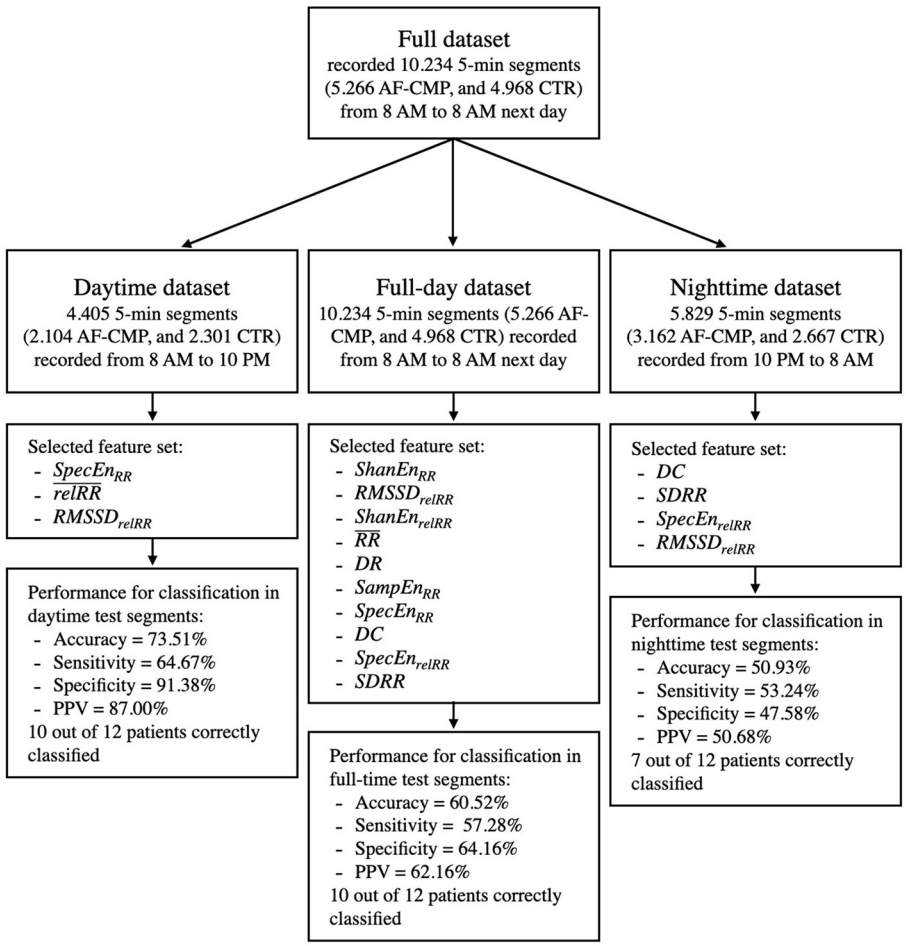

FIGURE 4 | Overview of the decision tree classifier performance on the optimal feature sets selected from the different datasets utilized in this work. Control group (CTR).

tone, and the concentration of catecholamines in serum are pronounced during the day and blunted at night, although the current study does not allow to draw causative relations in this context.

FUTURE PERSPECTIVE

Current clinical guidelines (1) emphasize the association of heart failure, and AF both during the initial diagnostic workup for new-onset AF, as well as during follow-up: they request a baseline echocardiogram in patients with new-onset AF, and they recommend regular clinical follow-up for the development of heart failure in patients with known AF. The algorithm reported in the current study may be particularly useful for the latter part, i.e., detection of LVSD in patients with AF. Due to its high specificity, and positive predictive value, it can act as an indicator, and trigger for prompt clinical follow-up to detect, and manage heart failure early, and potentially reduce mortality (21). In this context, the general applicability of the algorithm to all kinds of 5-min samples of RR intervals without the need for more than one lead (such as data derived from pulse wave analysis, oximetry derived heart rate or single-lead smart watch recordings) might enable the translation to a variety of wearables, and pocket ECG monitors.

LIMITATIONS

The current study was restricted to the analysis of beat-to-beat intervals that were extracted from a single-lead ECG. This approach is however potentially also applicable to any device offering beat-to-beat annotations of the cardiac cycle, which may include widely applicable devices such as e.g., photo-plethysmography in smart phones although this will require additional validation. While the performance of the current algorithm is superior when applied on daytime-datasets, the impact of varying physiological conditions during daytime such as physical activity or mental stress, is beyond the scope of the current study. Also, we cannot comment on the influence of

pertinent baseline medications on the performance of the current algorithm, though its applicability on a real-world patient cohort likely adds to its external validity.

CONCLUSION

The current work demonstrates that machine learning with the simple input of beat-to-beat intervals from a single-lead ECG allows discriminating AF patients with, and without AF-induced heart failure with diagnostic properties that are immediately clinically applicable. Given the ever-increasing prevalence of AF, the algorithm described in this study may allow to identify patients who require cardiological care earlier and render the clinical follow-up more cost-effective.

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 Institutional Review Board of the University of Freiburg. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FR, CA, LM, F-JN, TA, AJ, and BM-E were involved in data collection. GL, DN, MR, OD, RS, and AL were involved in the machine learning application. GL and BM-E wrote the initial manuscript. All authors read, reviewed, and edited the manuscript in the subsequent revision rounds.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.812719/full#supplementary-material

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REVIEW
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Remote Cardiac Rhythm Monitoring in the Era of Smart Wearables: Present Assets and Future Perspectives

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Remote monitoring and control of heart function are of primary importance for patient evaluation and management, especially in the modern era of precision medicine and personalized approach. Breaking technological developments have brought to the frontline a variety of smart wearable devices, such as smartwatches, chest patches/straps, or sensors integrated into clothing and footwear, which allow continuous and real-time recording of heart rate, facilitating the detection of cardiac arrhythmias. However, there is great diversity and significant differences in the type and quality of the information they provide, thus impairing their integration into daily clinical practice and the relevant familiarization of practicing physicians. This review will summarize the different types and dominant functions of cardiac smart wearables available in the market. Furthermore, we report the devices certified by official American and/or European authorities and the respective sources of evidence. Finally, we comment pertinent limitations and caveats as well as the potential answers that flow from the latest technological achievements and future perspectives.

Keywords: smart wearable devices, remote monitoring, sensors, arrhythmia detection, heart rate, cardiac function

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INTRODUCTION

Heart rhythm disorders are dominant public health issues, affecting more than 2% of the adult population. Their incidence is comparable to that of other major cardiovascular diseases, such as stroke, acute myocardial infarction and non-ischemic cardiomyopathy (1, 2). Cardiac rhythm abnormalities significantly increase with advancing age (1), so that the gradual aging of the world population has led to a sharp rise in the prevalence of cardiac arrhythmias, a phenomenon that is expected to intensify in the upcoming decades (3).

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting approximately 46.3 million people worldwide. According to recent studies, in 2017, 10 million Europeans were suffering from AF, while, in the United States the number of the patients is expected to rise from 6 to 16 million, by 2050 (4, 5). The lifetime risk of AF is estimated at about 35% for Caucasians and 20% for African Americans (6). Even though sometimes asymptomatic (7), the disease causes significant morbidity, as it increases up to five times the risk of stroke (8), accounting for approximately one-third of all ischemic strokes (9, 10). Nevertheless, early arrhythmia diagnosis and initiation of anticoagulation treatment can lead to 64% stroke reduction (11).

Other rhythm disturbances, such as conduction disorders, bradyarrhythmias, supraventricular and ventricular tachycardias, induce significant morbidity and mortality, with related socioeconomic impact. These types of arrhythmias often result in patient hospitalization, while affected patients may experience severe symptoms, such as fatigue or syncope, as well as life-threatening events, or even sudden cardiac death (1).

Based on the above, early detection of cardiac arrhythmias is of paramount importance, in order to improve patient management. Timely diagnosis allows the implementation of appropriate interventions, either pharmacological or interventional, in order to prevent adverse effects, reducing morbidity and mortality. In the recently issued guidelines for the management of AF, the European Society of Cardiology recommends opportunistic screening in individuals aged ≥65 years to detect asymptomatic AF (12). Traditional methods of arrhythmia screening, such as electrocardiography (ECG) and continuous ambulatory Holter monitoring are mainly hampered by the limited period of rhythm recordings. Consequently, these tools are not useful for the screening of asymptomatic patients and the detection of paroxysmal arrhythmias, such as AF. Implantable loop recorders have drawbacks as well, since their cost may hinder their implementation in certain healthcare systems. Moreover, adverse events, such as skin erosion, infections, device oversensing or undersensing can limit their effectiveness (13).

Recently, rapid technological advances have led to the development of wearables with built-in micro-detectors, that can provide real-time monitoring of the vital signs and heart rate. Such devices can detect cardiac arrhythmias (14, 15), with varying accuracy, that depends on device type and detection method (16, 17).

The purpose of this review is to provide thorough insights into "smart" wearables, capable of cardiac rhythm monitoring, presenting the latest data derived from major clinical trials. The devices certified by the United States Food and Drug Administration (FDA), or CE-marked by the European Union authorities, are summarized, contributing to a comprehensive perception of the existing knowledge. Finally, legitimate concerns, based on literature evidence and future perspectives, are discussed, highlighting the limitations that need to be addressed and the aspects of potential development during the following years.

METHODS

The comprehensive review of the literature was achieved through screening of the Pubmed, Google Scholar and ClinicalTrials.gov databases from 1989 to January 2022, focusing mainly on articles published over the last decade. The searching procedure was based on several key terms regarding devices ("smart wearable devices" OR "smartwatches" OR "patches" OR "wristbands") and heart conditions ("arrhythmia monitoring" OR "heart rhythm disorders" OR "cardiac diseases"), combined with Medical Subject Headings (MeSH). The first evaluation of the literature was based on the title and the abstract of each paper, while all the articles written in language other than English, or having included animal subjects, were dismissed. The reference section of the detected review articles was also probed and assessed, contributing to the overall selection of the literature. Finally, the Healthskouts Solutions Library for certified apps was used, as an additional source of certified smart wearable devices.

WEARABLE DEVICES TO MONITOR HEART RATE AND CARDIAC RHYTHM

Technological advancements have allowed heart rate sensors to be incorporated into numerous commercially available wearables. The spectrum of these devices ranges from smart accessories to sensors embedded into clothing and shoes. Patches, in particular, are leadless, wearable devices, that are attached to the patient's chest and provide ambulatory ECG monitoring over several days to weeks (18–21). Fitness bands and smartwatches are wrist-worn devices, able to track heart rate in real time (22–26). Heart rate sensors have also been integrated into accessories, such as rings (27, 28), necklaces (29), earbud headphones (30–32), chest straps (31, 33–35), footwear (36), glasses (37), even into textiles (38). **Table 1** summarizes the most commonly used, FDA certified or/and CE-marked wearables to monitor heart rate, while **Table 2** presents the essential technical specifications of each device.

Wearable devices rely on photoplethysmography (PPG) or single lead ECG tracings to detect heart rate. PPG is a non-invasive, optical technique that detects beat-to-beat alterations in the skin capillary bed volume (39). It utilizes a light source, usually a light-emitting diode, to shine light on the skin and a photodetector to measure the intensity of the non-absorbed light. Green light is most frequently used to minimize motion artifacts (40). Light attenuation correlates with the beat-to-beat volume changes of the microvasculature, caused by the peripheral pulse, thus allowing for heart rate assessment (39–41). Specific algorithms can identify heart rhythm irregularities, such as AF, based on fluctuations of the beat-to-beat interval (42–44). PPG technology is widely incorporated into the majority of the wearables used to monitor heart rhythm. On the other hand, patches use leadless electrodes and a sensor to obtain a single lead ECG, when attached to the patient's skin (45). Captured ECG tracings are reviewed to detect heart rhythm disturbances, either by automated algorithms, or by physicians (44). Of note, certain wearables, such as the Apple Watch series 4, or later, provide heart rhythm monitoring via both a PPG sensor and a single lead ECG (46). The latter can be recorded by wearing the Apple Watch and holding a finger of the opposite hand on the digital crown, creating an electric circuit that correspond to lead I of the 12-lead ECG. **Figure 1** shows the recording of sinus rhythm by both a smartwatch and a chest patch.

The accuracy of the various wearables to monitor heart rate and detect cardiac arrhythmias is highly dependent on both the type of the device and the method of detection in use. In general, PPG-based heart rate measurements from wrist-worn devices show high agreement with those derived from simultaneous ECG

TABLE 1 | Wearable devices for heart rate and rhythm monitoring, certified by FDA or CE marked by the European authorities.

Device type	Manufacturer	Product name	Cardiac function measurements	Other measurements	Certification	Official website
Watch	Apple	Apple Watch series 7	HR, ECG	SpO2, physical activity, sleep tracker	FDA Certified, CE-marked	https://www.apple.com
Watch	Empatica	EmbracePlus	HR, HR variability	SpO2, skin temperature, respiratory rate, seizures detection	FDA Certified, CE-marked	https://www.empatica.com
Watch	Fitbit	Sense, Versa 2, Versa 3	HR, ECG	physical activity, sleep tracker, skin temperature, SpO2	FDA Certified, CE-marked	https://www.fitbit.com/global/us/home
Watch	Omron	HeartGuide	HR, BP	physical activity, sleep tracker	FDA Certified	https://omronhealthcare.com
Watch	Samsung	Galaxy Watch 4, Galaxy Watch Active2	HR, ECG	physical activity, VO2 max, fall detection	FDA Certified, CE-marked	https://www.samsung.com/global/galaxy/
Watch	Verily Life Sciences	Verily Study Watch	HR, ECG	electrodermal activity, inertial movements	FDA Certified	https://verily.com/solutions/study-watch/
Watch	Withings	Scanwatch	HR, ECG	SpO2, physical activity, sleep tracker	FDA Certified, CE-marked	https://www.withings.com/us/en/
Wristband	Biobeat	BB-613WP Wrist Monitor	HR, HR variability, BP stroke volume, cardiac output, cardiac index	SpO2, physical activity, respiratory rate, systemic vascular resistance, skin temperature	FDA Certified, CE-marked	https://www.bio-beat.com
Wristband	Empatica	Empatic E4	HR, HR variability	SpO2, skin temperature, respiratory rate, seizures detection	FDA Certified, CE-marked	https://www.empatica.com
Wristband	Fitbit	Charge 5, Luxe, Ace 3, Inspire 2	HR, ECG	physical activity, sleep tracker, skin temperature, SpO2	FDA Certified, CE-marked	https://www.fitbit.com/global/us/home
Chest monitor	Biobeat	BB-613WP Chest Monitor	HR, ECG, HR variability, BP, stroke volume, cardiac output, cardiac index	SpO2, physical activity, respiratory rate, systemic vascular resistance, skin temperature	FDA Certified, CE-marked	https://www.bio-beat.com
Patch	Bardy Diagnostics	BardyDx CAM	HR, ECG	None	FDA Certified, CE-marked	https://www.bardydx.com
Patch	BioTelemetry	ePatch	HR, ECG	None	FDA Certified, CE-marked	https://www.gobio.com
Patch	BioTelemetry	MCOT	HR, ECG	None	FDA Certified	https://www.gobio.com
Patch	Icentia	CardioSTAT	HR, ECG	None	CE-marked	https://www.icentia.com
Patch	InfoBionic	MoMe Kardia	HR, ECG	None	FDA Certified, CE-marked	https://infobionic.com
Patch	iRhythm	Zio Patch	HR, ECG	None	FDA Certified, CE-marked	https://www.irhythmtech.com
Patch	LifeSignals	WiPatch (1A Biosensor, 1AXe Biosensor, 1AX Biosensor)	HR, ECG	respiratory rate	FDA Certified, CE-marked	https://lifesignals.com
Patch	MediBioSense	Vital Patch, MBS HealthStream, MCM (Mobile Cardiac Monitoring)	HR, HR variability, ECG,	physical activity, respiratory rate, body temperature, fall detection, body posture	FDA Certified, CE-marked	https://www.medibiosense.com
Patch	Peerbridge Health	Peerbridge Cor	HR, ECG	None	FDA Certified	https://peerbridgehealth.com/for-physicians/
Patch	Preventice Solutions	BodyGuardian MINI	HR, ECG	None	FDA Certified, CE-marked	https://www.preventicesolutions.com/patients/body-guardian-heart
Patch	Rooti Medical	RootiRX	HR, ECG	skin temperature	FDA Certified	https://www.rootilabs.com
Patch	Samsung SDS	S-Patch	HR, ECG	None	CE-marked	https://www.samsungsds.com/en/cardio/cardio.html
Patch	Vpatch Cardio	Vpatch	HR, ECG	None	FDA Certified, CE-marked	https://www.vpatchcardio.com
Chest strap	NimbleHeart	Physiotrace Smart	HR, ECG	None	FDA Certified	https://www.nimbleheart.com
Chest strap	Qardio	QardioCore	HR, HR variability, ECG	physical activity, respiratory rate, skin temperature	FDA Certified, CE-marked	https://www.qardio.com

(Continued)

TABLE 1 | Continued

Device type	Manufacturer	Product name	Cardiac function measurements	Other measurements	Certification	Official website
Chest strap/clothing	Equivital	eqO2+lifemonitor	HR, ECG, R-R interval	respiratory rate, skin temperature, galvanic skin response	FDA Certified, CE-marked	https://www.equivital.com
Chest strap/clothing	Medronic	Zephyr BioHarness	HR, ECG	physical activity, respiratory rate, skin temperature, body posture	FDA Certified	https://www.zephyranywhere.com/system/components
Chest strap/clothing	Nanowear	SimpleSense	HR	physical activity, respiratory rate, lung volume	FDA Certified	https://www.nanowearinc.com/simplesense
Chest strap/clothing	Nuubo	Nuubo System	HR, ECG	None	FDA Certified, CE-marked	https://www.nuubo.com/en-us
Clothing	HealthWatch Technologies	Master Caution	HR, ECG	respiratory rate, skin temperature, body posture	FDA Certified, CE-marked	https://healthwatchtech.com
Smart accessory	Ōura	Oura Ring	HR	SpO2, skin temperature, sleep tracking	FDA Certified	https://ouraring.com
Smart accessory	toSense	CoVa 2	HR, HR variability, ECG, stroke volume, cardiac output	chest fluids, respiratory rate	FDA Certified	https://www.tosense.com

BP, blood pressure; CE mark, Conformité Européene mark; ECG, electrocardiogram; FDA, Food and Drug Administration; HR, heart rate; SpO2, peripheral oxygen saturation; VO2 max, maximal oxygen consumption.

tracings (34), although deviations have been reported in AF patients with high heart rates (47). Depending on the device model and the form of physical activity, the error in heart rate measurements by PPG ranges from 1.8 to 8.8% (24). Regarding AF detection, wearables using PPG signals are reported to have an accurary of 95–97% (48–50). In case of inconclusive readings, the diagnostic accuracy can be improved in devices providing ECG tracings, when the latter are interpreted by a trained physician (17, 44, 51). Patches show a consistently high accuracy in arrhythmia detection, comparable with that of ECG Holter monitors (52, 53).

WEARABLES FOR DETECTION OF ATRIAL FIBRILLATION

Table 3 summarizes the clinical trials and studies, which were conducted to evaluate the heart rhythm monitoring-oriented features of several smart wearable devices, cited in Section Wearables for Detection of Atrial Fibrillation.

Smartwatches/Wristbands

Smartwatches and wristbands are the most popular type of wearable devices, holding the dominant share of the global market, with a projected compound annual growth rate of 20% until 2026 (77). Inevitably, the wide spread of smartwatches that incorporate heart rhythm sensors among the population, raises queries about their role in AF screening and diagnosis (50), which is still controversial (78). At the same time, major studies are conducted, in order to define the accuracy of different smartwatch models to detect AF (50).

Apple Watch

The Apple Heart Study was one of the primary and most important studies regarding ambulatory ECG monitoring with the use of a wearable device (68). By recruiting 419,297 individuals without clinical history of AF, the authors examined the abnormalities of cardiac rhythm detected by the Apple Watch, in relation to AF detection, using an ECG patch, which was offered to those patients who received an irregular pulse notification from the device. Despite the limited number of the participants who finally returned the ECG patches and completed the study, the notification algorithm of the device had a positive predictive value of 84% to identify AF (95% confidence interval, 76% to 92%). In addition, a greater proportion of individuals older than 65 years was notified due to an irregular pulse, thus identifying a specific population group that could potentially benefit the most from AF screening with a smart wearable. Other studies with more restricted sample sizes have also assessed the accuracy of the Apple smartwatch to distinguish between AF and sinus rhythm, with comparable and promising results, regarding sensitivity and specificity of the embedded diagnostic algorithm (44, 64). However, physicians' involvement is necessary to provide an accurate diagnosis in unclassified recordings, which account for a significant proportion of the total tracings (51).

TABLE 2 | Main technical specifications of the smart wearable devices listed in **Table 1**. Presented information is derived either from the official website of the respective company, or from the user guide document, detected through the search engine UserManual.wiki.

Devices	Sensor type	ECG channels	Measurement range (accuracy)*	Battery type	Recording time	Service life
Apple Apple Watch series 7	Accelerometer, altimeter, ambient light sensor, blood oxygen sensor, electrical heart sensor, emergency SOS, gyroscope, optical heart sensor	1	HR: 30–210 bpm (accuracy not provided)	Rechargeable lithium-ion battery	18 h	∼ 3 years
Empatica EmbracePlus	Accelerometer, electrodermal activity sensor, gyroscope, skin temperature sensor (thermometer)	not recorded	Not provided	Rechargeable lithium-ion battery	48+ h	2 years
Fitbit Sense, Versa 2, Versa 3	Accelerometer, altimeter, ambient light sensor, blood oxygen sensor, electrical heart sensor, electrodermal activity sensor, gyroscope, optical heart sensor, skin temperature sensor (thermometer)	1	HR: 20–220 bpm (accuracy not provided)	Rechargeable lithium-ion polymer battery	6 days	1–3 years
Omron HeartGuide	Oscillometric pulse sensors for blood pressure measurement	Not recorded	SBP: 60–230 mmHg (± 3 mmHg), DBP: 40–160 mmHg (± 3 mmHg), HR: 40–180 bpm (± 5 %)	Rechargeable lithium-ion polymer battery	8 times/day	1–2 years
Samsung Galaxy Watch 4, Active2	Accelerometer, ambient light sensor, barometer, bioelectrical impedance analysis sensor, electrical heart sensor, geomagnetic sensor, gyroscope, optical heart sensor	1	Not provided	Rechargeable lithium-type battery	Not provided	Not provided
Verily life sciences verily study watch	Electrical heart sensor, electrodermal activity sensor, inertial movement sensor	1	Not provided	Rechargeable lithium-ion battery	7 days	Not provided
Withings Scanwatch	Accelerometer, multi-wavelength PPG heart rate/SpO2 sensor	1	HR: 30–210 bpm (accuracy not provided)	Rechargeable lithium-type battery	∼30 days	Not provided
Biobeat BB-613WP Wrist Monitor	PPG sensor	not recorded	SBP: 60–250 mmHg (± 5 mmHg) DBP: 40–150 mmHg (± 5 mmHg) HR: 40–240 bpm (± 3 %)	Non-rechargeable lithium manganese dioxide	3 days	3 years
Empatica Empatic E4	Accelerometer, electrodermal activity sensor, PPG sensor, skin temperature sensor (infrared thermopile)	Not recorded	Not provided	Rechargeable lithium-ion battery	24–48 h	Not provided
Fitbit Charge 5, Luxe, Ace 3, Inspire 2	Accelerometer, ambient light sensor, blood oxygen sensor, electrical heart sensor, electrodermal activity sensor, optical heart rate monitor, skin temperature sensor (thermometer), vibration motor	1	BP: 30–220 bpm (accuracy not provided)	Rechargeable lithium-ion polymer battery	7 days	Not provided

(Continued)

TABLE 2 | Continued

Devices	Sensor type	ECG channels	Measurement range (accuracy)*	Battery type	Recording time	Service life
Biobeat BB-613WP Chest Monitor	PPG sensor	1	SBP: 60–250 mmHg (± 5 mmHg) DBP: 40–150 mmHg (± 5 mmHg) HR: 40–240 bpm (± 3 %)	Rechargeable lithium-ion polymer battery	6 days	3 years
Bardy Diagnostics BardyDx CAM	ECG electrodes	1	No range limitation	Not rechargeable lithium primary (coin cell) battery	7 days	2 years
BioTelemetry ePatch	ECG electrodes	1, 2, or 3	No range limitation	Rechargeable lithium-ion battery	5 days	2 years
BioTelemetry MCOT	ECG electrodes	2	No range limitation	Rechargeable lithium-ion battery	Not provided	3 years
Icentia CardioSTAT	ECG electrodes	1	No range limitation	Not provided	14 days	18 months
InfoBionic MoMe Kardia	ECG electrodes	2	No range limitation	Rechargeable lithium-ion battery	24 h	Not provided
iRhythm Zio Patch	ECG electrodes	1	No range limitation	2 lithium manganese dioxide coin cells gateway battery 1 lithium polymer cell battery	14 days	One-time use
LifeSignals WiPatch (1A Biosensor, 1AXe Biosensor, 1AX Biosensor)	ECG electrodes 1AX Biosensor: accelerometer, skin temperature sensor, gyroscope	2	HR: 30–250 bpm (± 3 bpm)	zinc-air battery (1A Biosensor), lithium-manganese dioxide battery (1AXe Biosensor, 1AX Biosensor)	3 days (1A Biosensor), 7 days (1AXe Biosensor), 5 days (1AX Biosensor	One-time use
MediBioSense Vital Patch, MBS HealthStream, MCM (Mobile Cardiac Monitoring)	accelerometer, ECG electrodes, skin temperature sensor	1	HR: 30–200 bpm (< ± 5 bpm)	Zinc Air battery	7 days	Not provided
Peerbridge Health Peerbridge Cor	ECG electrodes	2	No range limitation	Not provided	7 days	Not provided
Preventice Solutions BodyGuardian MINI	accelerometer, ECG electrodes	1–3	No range limitation	Rechargeable lithium-ion battery	16 days	Not provided
Rooti Medical RootiRX	ECG electrodes skin temperature sensor	1	No range limitation	Rechargeable lithium-ion polymer battery	7 days	1 years
Samsung SDS S-Patch	ECG electrodes	1	No range limitation	Not rechargeable lithium primary (coin cell) battery	5 days	2 years
Vpatch Cardio Vpatch	ECG electrodes	3	No range limitation	Not rechargeable lithium primary (coin cell) battery and rechargeable lithium-ion battery	7 days	5 years
NimbleHeart Physiotrace Smart	ECG electrodes	1	No range limitation	Not provided	Not provided	Not provided
Qardio QardioCore	ECG electrodes	1	SBP + DBP: 40-250 mmHg (± 3 mmHg), HR accuracy: ± 5 %	Rechargeable lithium-ion battery	24 h	2 years
Equivital eqO2+lifemonitor	accelerometer ECG electrodes breathing rate sensor skin temperature sensor	2	HR: 25-240 bpm (accuracy not provided)	Not provided	48 h	Not provided
Medronic Zephyr strap/clothing	accelerometer ECG electrodes breathing rate sensor skin temperature sensor	1	HR: 25-240 bpm (± 1 bpm)	Rechargeable lithium-ion polymer battery	12–28 h	Not provided

(Continued)

TABLE 2 | Continued

Devices	Sensor type	ECG channels	Measurement range (accuracy)*	Battery type	Recording time	Service life
Nuubo Nuubo System	accelerometer ECG sensor	2	Not provided	Rechargeable battery	30 days	Not provided
HealthWatch Technologies Master Caution	ECG sensor breathing rate sensor skin temperature sensor	3–12	Not provided	Rechargeable or disposable battery	12–48 h	Not provided
Ōura Oura Ring	accelerometer PPG sensor negative temperature coefficient sensor for body temperature	Not recorded	Not provided	Rechargeable Lipo battery	4-7 days	Not provided
toSense CoVa 2	ECG sensor breathing rate sensor skin temperature sensor	1	Not provided	Not provided	Not provided	Not provided

**As reported by the manufacturer.*

bpm, beats per minute; DBP, diastolic blood pressure; ECG, electrocardiogram; HR, heart rate; mmHg, millimeters of mercury; PPG, photoplethysmography; SBP, systolic blood pressure; SpO2, peripheral oxygen saturation.

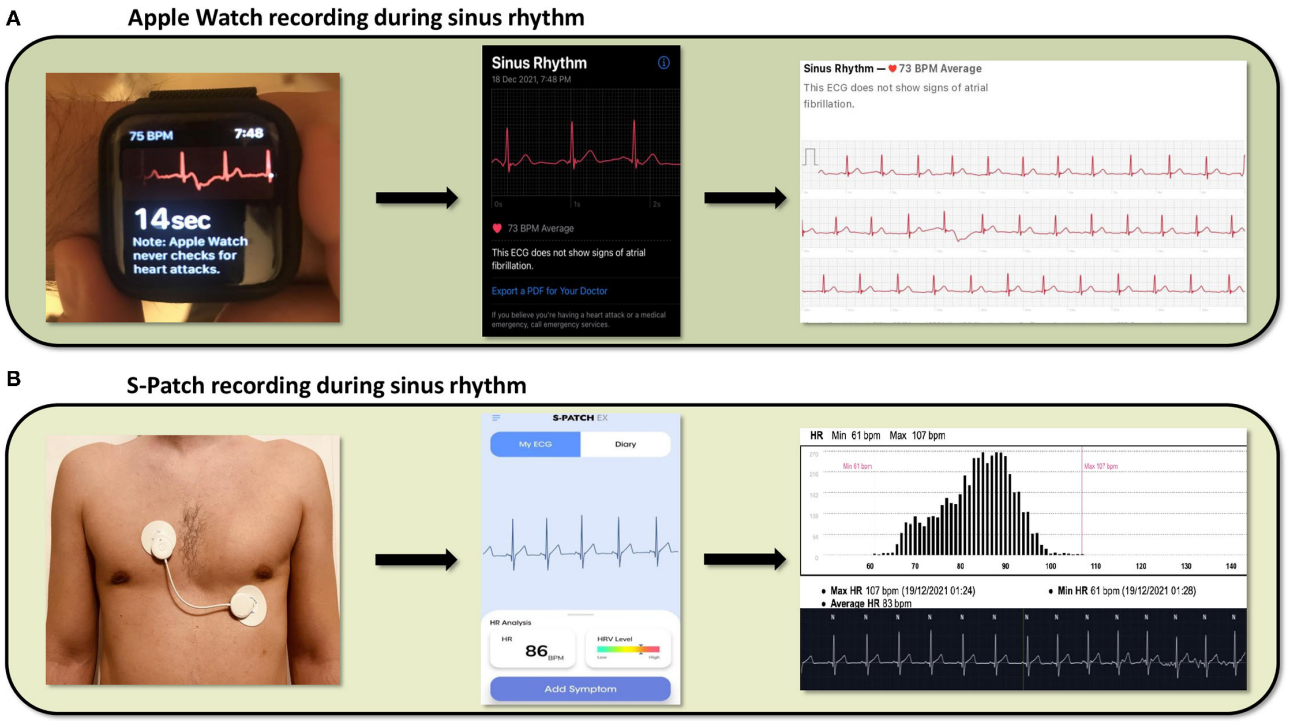

FIGURE 1 | Cardiac rhythm recordings derived from a smartwatch (Apple Watch) and a patch (S-Patch), **(A)** From left to right, the images show the process of data collection from an Apple Watch, the ECG presentation in the respective smartphone application and the final report, featuring a possible diagnosis, **(B)** From left to right, the images show the same process captured by the wearable S-Patch.

Fitbit Wearables

Recently, The Fitbit Heart Study (76) demonstrated a positive predictive value of 98% of the homonymous software algorithm to detect AF (79). The study enrolled more than 455,000 individuals, without history of AF, while an irregular heart rhythm was detected only in 4,728 (1%). The median population age was 47 years and people aged 65 years or older accounted for 12% of the total cohort. Among this elderly group of participants, the positive predictive value was also high (97%), encouraging the application of this technology to individuals older than 65 years of age, who usually have more comorbidities and are at greater risk of stroke.

Fitbit and Apple smartwatches have also been compared with the standard ECG, concerning the accuracy of the PPG technology to estimate heart rate. Two studies that included 102 and 32 participants, respectively, recorded a total of more

TABLE 3 | Comprehensive presentation of clinical trials and studies, conducted to evaluate the function and cardiac features of the wearable smart devices.

References	Device type	Device name	Used technology (PPG vs ECG)	Number of recruited patients	Mean age (years)	Median monitoring time	Findings
Rothman et al. (54)	patch	MCOT	ECG	305	56	25–30 days	The MCOT is superior to standard cardiac loop recorder regarding cardiac arrhythmia diagnosis
Tayal et al. (55)	patch	MCOT	ECG	56	66 ± 11	21 days	The MCOT showed high detection rate of AF in symptomatic patients after cryptogenic TIA/stroke
Miller et al. (56)	patch	MCOT	ECG	156	68.5	up to 30 days	The increased duration of monitoring with the MCOT is associated with a higher rate of paroxysmal AF detection
Rosenberg et al. (52)	patch	ZioPatch	ECG	74	64.5 ± 8.1	10.8 ± 2.8 days	Comparable estimation of the AF burden during the first 24 h between ZioPatch and Holter monitor. The longer recording duration achieved with ZioPatch resulted to increased diagnostic accuracy
Barrett et al. (57)	patch	ZioPatch	ECG	146	64	11 days	More arrhythmia events were detected with the ZioPatch compared to standard Holter monitor
Derkac et al. (58)	patch	MCOT, AT-LER	ECG	78,510	not provided	20 days: MCOT, 30 days: AT-LER	The MCOT showed higher diagnostic yield for arrhythmia detection compared to the AT-LER
Smith et al. (59)	patch	CAM	ECG	50	54.8 ± 17.8	24 h	Higher diagnostic accuracy and increased patient's comfortability are detected with the use of the CAM compared to standard 3-channel Holter monitor
Bumgarner et al. (44)	wrist-wearable	Apple Watch	ECG (Kardia Band technology)	100	68 ± 11	single tracing	The Kardia Band technology demonstrated 93% sensitivity and 84% specificity, regarding AF detection, compared to 12-lead ECG
Koshy et al. (60)	wrist-wearable	Fitbit smartwatch, Apple Watch	PPG	102	68 ± 15	30 min	Both smart devices showed a higher tendency to underestimated heart rate when AF was the leading cardiac rhythm
Rho et al. (61)	patch	ZioPatch (Zio-XT), CAM	ECG	29	73.1 ± 7.1	7 days	The CAM demonstrated more episodes of arrhythmia in combination with more accurate ECG recording. Patients' compliance was sufficient with both devices
Selvaraj et al. (62)	patch	VitalPatch	ECG	57	35 ± 11	not provided	The VitalPatch demonstrated a promising performance regarding physiological activity remote monitoring
Steinhubl et al. (63) (NCT02506244)	patch	iRhythmZio	ECG	2,659	72.4	up to 4 weeks	The intensive monitoring of high-risk patients, with a chest patch, contributes to increased rate of AF diagnosis
Tison et al. (64)	wrist-wearable	Apple Watch	PPG	9,750	42	20 min	The combination of smartwatch PPG technology and deep neural network, demonstrated 98% sensitivity and 90.2% specificity to identify AF, compared to standard 12-lead ECG
Ding et al. (65)	wrist-wearable	Samsung Simband 2	PPG	40	71	42 min	Data received from the wearable device, analyzed by a real-time algorithm, demonstrated high sensitivity (98.2%), specificity (98.1%) and accuracy (98. 1%) for irregular pulse detection
Guo et al. (66)	wrist-wearable	Honor Band, Huawei Watch	PPG	246,541	35	14 days	The PPG technology of the wearable devices could detect AF with a PPV of 91.6%
Kaura et al. (67)	patch	ZioPatch	ECG	116	70	14 days	Prolonged monitoring with the chest-patch was superior to the shorten Holter monitoring, regarding the detection of paroxysmal AF

(Continued)

TABLE 3 | Continued

References	Device type	Device name	Used technology (PPG vs ECG)	Number of recruited patients	Mean age (years)	Median monitoring time	Findings
Nault et al. (53)	patch	CardioSTAT	ECG	213	67 ± 11	24 h	The CardioSTAT showed high accuracy for AF diagnosis but moderate accuracy for atrial flutter diagnosis, compared to a Holter monitor
Pasadyn et al. (34)	wrist-wearable, chest strap	Apple Watch, Fitbit Iconic, Garmin Vivosmart HR, Tom Tom Spark 3, Polar H7	PPG	50	29	2 min	The Polar H7 chest strap demonstrated the highest accuracy to monitor heart rate among all wearables compared with the standard ECG
Perez et al. (68) (NCT03335800)	wrist-wearable, app	Apple Heart Study App and Apple Watch	PPG	419,927	41 ± 13	117 days	The individual tachogram demonstrated a PPV of 71% to detect AF, while the PPV of the irregular pulse notification was 84%
Al-Kaisey et al. (47)	wrist-wearable	Fitbit smartwatch, Apple Watch	PPG	32	68 ± 12	21 ± 1.3 h	Both devices demonstrated underestimation of the heart rate during AF
Inui et al. (69)	wrist-wearable	Apple Watch, Fitbit Charge	PPG	40	71	2 weeks	The work mode of the Apple Watch showed greater precision and accuracy to detect AF and measure heart rate, compared to the Fitbit wearable
Karunadas et al. (70)	patch	WebCardio	ECG	141	44.41	∼24 h	Comparable accuracy of arrhythmia detection was observed between the WebCardio patch and the Holter monitor. However, 1st degree AV block and PVCs could both be detected more accurately with the patch
Nachman et al. (71)	wrist-wearable	Biobeat BB-613WP	PPG	1,480	35.1 ± 23.8	single tracing	The device demonstrated agreement of 94.9% and 96.5% for hypertension and normal pressure, respectively, with the reference sphygmomano-meter-based device
Rajakariar et al. (51)	wrist-wearable	Apple Watch	ECG (Kardia Band technology)	218	67 ± 16	30 seconds	The Kardia Band technology demonstrated 94.4% sensitivity, 81.9% specificity and a PPV of 54.8% to detect AF. Improved diagnostic accuracy was observed with the combination of the device with an expert's interpretation
Schuurmans et al. (72)	wrist-wearable	Empatica E4	PPG	15	15	∼5 min	Empatica E4 is comparable to the gold standard recording method for heart rate estimation
Avram et al. (73)	wrist-wearable chest patch	Samsung Galaxy Active 2, Biotel ePatch	PPG and ECG	204	62 ± 11.6	4 weeks	The collaborative function of the PPG and ECG sensors of the smart devices demonstrated high sensitivity (96.9%) and specificity (99.3%) for irregular heart rhythm monitoring
Caillol et al. (74)	wrist-wearable	Apple Watch	ECG	256	66 ± 6	single tracing	The Apple Watch was accurate to detect bradyarrhythmias and tachyarrhythmias, beyond AF and demonstrated high specificity but low sensitivity to detect ischemic heart disease
Ha et al. (75) (NCT02793895)	patch	SEEQ, CardioSTAT	ECG	336	67.4	30 days	Increased rate of postoperative AF detection in patients at high risk of stroke, by 17.9%, was observed using a 30 days continuous ambulatory cardiac rhythm monitoring system
Lubitz et al. (76)* (NCT04380415)	wrist-wearable	Fitbit fitness tracker or smartwatch	PPG	455,699	47	not provided	An irregular heart rhythm detection by the Fitbit device had a PPV of 98.2% for AF diagnosis

AF, atrial fibrillation; AT-LER, Autotrigger Looping Event Recorder; AV, atrioventricular; CAM, Carnation ambulatory monitoring; ECG, electrocardiogram; MCOT, Mobile cardiac outpatient telemetry; PPG, photoplethysmography; PPV, positive predictive value; PVCs, premature ventricular contractions.

**At the time of writing "The Fitbit Heart Study" had demonstrated its main outcomes only as a conference presented abstract.*

than 91,000 heart rate values and showed that both devices underestimate heart rate during AF, especially when a rapid ventricular response of 100 beats per minute or faster occurs (47, 60). In addition, more accurate recordings were observed during night-time, when the physical activity is usually reduced, thus avoiding movement artifacts (47). In terms of direct comparison, the Apple Watch has a slightly superior diagnostic performance, compared to Fitbit smartwatches, closer to that of the gold standard ECG (34, 69).

Other Smartwatches/Wristbands

Many other companies have also launched smartwatches capable of heart rhythm detection, using either a PPG sensor or a combination of PPG and single-lead ECG. Two recent studies have shown high reliability of the AF detecting algorithms embedded into Samsung smart devices (65, 73). According to the findings, PPG sensor enhanced with a warning signal, prompting for an ECG recording, significantly increased the sensitivity for AF detection to 96.9% and the specificity to 99.3%. Thus, the high rate of specificity makes these wearables even more efficient for screening of the general population. Additionally, the algorithm was able to determine AF burden, a parameter associated with the risk of ischemic stroke and systemic cardioembolic events (73, 80). The Scanwatch by Withings, is a device able of recording 1-lead ECG tracings and is under evaluation in two ongoing clinical trials (NCT04493749, NCT04041466), regarding AF detection, compared with the standard 12-lead ECG. Finally, Huawei smart watches were used for the screening of patients included in the mobile Atrial Fibrillation II programme (mAFA-II programme), a two-phase trial, aiming to examine the optimization of AF screening and management through the integration of wearable PPG-based technologies (81). The early phase, called the Huawei Heart Study, assessed the effectiveness of smart wearables to detect AF, demonstrating a positive predictive value of 91.6% (66). The late phase, known as the mAFA II trial, investigated the value of a holistic care approach in AF patients, including the AF Better Care pathway (ABC pathway), combined with mobile smart technologies (82). However, these wearables have been certified only by the Chinese National Medical Products Administration.

Other wearables are able to track dominant factors of cardiovascular function, associated with arrhythmia initiation and development, even though they do not feature specific AF detection algorithms. The E4 wristband and EmbracePlus smartwatch by Empatica, in particular, assess the heart rate variability, a measure of the autonomic nervous systems related to AF development (83, 84). Schuurmans et al. validated the performance of Empatica E4 wristband in assessing heart rate variability, underlying the need for the user to remain still, in order to achieve accurate measurements (72). The HeartGuide smartwatch by Omron and the BB-613WP wristband by BioBeat Technologies feature blood pressure measurement, physical activity and sleep tracking, in addition to heart rate measurement (71, 85). Since the above are considered factors for AF development, these devices could potentially contribute to improved patient monitoring, individualized arrhythmia treatment and potentially reduction of AF burden (86).

Patches

Wearable ECG patch monitors are appealing for AF detection, given their potential to store ECG tracings for a longer time, compared to conventional 24-h ECG Holter monitors. In general, patches provide an attractive alternative to conventional ambulatory Holter ECG monitoring for AF detection. They are easy to use and apply (63), less cumbersome than a Holter monitor (53, 57) and they interfere less with everyday activities, due to their leadless nature. Patients have reported to find patches comfortable and to prefer them over traditional Holter monitors (57), resulting in higher compliance. They can be worn for several days, rendering them ideal for mid-term rhythm monitoring, which increases the diagnostic yield of AF (63, 67). Physicians, on the other hand, believe that patch monitors provide definite diagnosis more often than a Holter monitor (57).

ZioPatch

The ZioPatch (iRhythm Technologies, USA) is a leadless, adhesive cardiac monitor, that is placed on the anterior chest wall by a technician, or easily self-applied by the patient, to provide up to 14 days of continuous ECG monitoring (87). After the completion of the monitoring period, the device is mailed back to the data processing center for the captured tracings to be processed, using an FDA cleared algorithm to detect potential arrhythmic episodes. Trained technicians review and classify the detected arrhythmias to generate a report that is then reviewed by the ordering physician (18). In a study by Rosenberg et al., the ZioPatch detected all AF episodes recorded in a 24-h ECG Holter monitor and reported similar AF burden rates, in patients simultaneously wearing both devices (52). In the mSToPS trial, 2,659 individuals at high risk of AF were randomly assigned to an immediate, 4-month, monitoring period that featured a total of 4 weeks of ZioPatch application, or to delayed monitoring, comprising of 4 months of usual of care, before starting a 4-month monitoring period, using the ZioPatch for a total of 4 weeks (88). At the end of first 4-months, the incidence of newly diagnosed AF was 4 times higher in the immediate monitoring group, compared to those allocated to usual of care for the corresponding time period. Over a 1-year follow-up period, 6.7 new AF cases per 100 person-years were detected in the total population of actively monitored participants, compared to 2.6 new AF diagnosis per 100 person-years in a matched observational control group. Active monitoring was also associated with increased likelihood of anticoagulant and antiarrhythmic therapy initiation, cardioversion procedures, ablation and increased health care resources utilization (63). ZioPatch was also found to be superior to short-term ECG Holter monitoring in detecting AF in patients after an ischemic stroke or transient ischemic attack (67). It should be noted that time to first AF detection with the use of the ZioPatch (and long-term rhythm monitoring in general) is inversely proportional to patient's AF burden; the higher the arrhythmic burden, the shorter the time to AF detection will be (18). The median duration to first AF detection reported in the mSToPS trial was 2 days (63).

Carnation Ambulatory Monitor

The Carnation Ambulatory Monitor (CAM, BardyDx, USA) is an adhesive patch monitor that is placed along the sternum for

optimized P-wave capture. Improved P-wave clarity is associated with more accurate rhythm identification, compared to standard Holter monitoring (59). In a small study comparing the Carnation Ambulatory Monitor with the ZioPatch, in patients undergoing cardiac rhythm monitoring with the two devices for 7 days, patients with AF episodes during the monitoring period were successfully identified by both patches (61).

Mobile Continuous Outpatient Telemetry

The Mobile Continuous Outpatient Telemetry (MCOT) (BioTelemetry Inc, USA) consists of a sensor, an adhesive patch and a monitor and can be used for medium-term heart rhythm monitoring. The sensor is attached on the patch, which is then placed on the patient's chest. Each patch lasts for approximately 5 days, before it is replaced by a new one, until the desired monitoring period is complete. The sensor captures a two-lead ECG tracing, using the patch embedded electrodes. Data are transmitted via Bluetooth to the monitor, which constantly analyses the ECG, using algorithms based on pre-specified criteria. If a heart rhythm disorder is detected, or the patient marks a symptom, the monitor instantly transmits the ECG tracing to the central monitoring station and the referring physician is notified (89). Thus, the device offers near continuous, real-time, heart rhythm monitoring, that is only interrupted for sensor recharging. The MCOT monitor is able of detecting AF (89) with a higher diagnostic yield, compared to loop event recorders, especially for asymptomatic AF episodes (54, 58). In studies assessing extended rhythm monitoring in patients with cryptogenic stroke, AF was diagnosed in 17–23% of the participants using the MCOT system, with the rates of AF detection constantly increasing within the monitoring period (55, 56). The device has also been studied in patients undergoing radiofrequency ablation for AF, to detect arrhythmia recurrences during the follow-up period (90). A non-telemetry version of this monitor, the ePatch (BioTelemetry Inc, USA), is also commercially available. The device can be worn for up to 14 days and needs to be sent back to the manufacturer for data acquisition and review (91).

CardioSTAT

The CardioSTAT (Icentia Inc, Canada) is a single-lead device, worn on the upper chest to provide up to 14 days of heart rhythm monitoring through a lead I–like electrode configuration. In a validation study by Nault et al., the agreement between CardioSTAT and Holter monitor readings on AF detection was very high (53). In patients following cardiac surgery, a high-risk population for arrhythmic events, post-operative AF detection was increased by more than ten times, when individuals were continuously monitored with the CardioSTAT patch, compared to those assigned to usual care (75).

WiPatch

The WiPatch sensors (LifeSignals Inc, USA) are worn on the upper left part of the chest and record a two-lead ECG, for up to 72 h. Data are automatically transmitted to a connected mobile device and then uploaded to a cloud server for storage and analysis. Similar AF detection rates were reported in ambulatory patients monitored for 24 h, simultaneously by both a Holter ECG and a WiPatch (70).

VitalPatch

The VitalPatch (MediBioSense Ltd, UK) is another peel-and-stick device, capable of real-time heart rate monitoring. The device consists of a patch and a relay device (either a tablet or a phone). A single-lead ECG tracing is continuously recorded by a biosensor embedded in the patch, which is worn on the upper-left chest. Acquired data are transmitted to the relay device, analyzed and then sent to a central workstation. Apart from heart rate and single-lead ECG, VitalPatch also records data regarding heart rate variability, respiratory rate, body temperature and body motion, while it can also detect falls, providing a holistic telemonitoring of physiological measurements and body activity (62). Recently, the device was updated with arrhythmia detection, including AF, but clinical data are still lacking.

Clothing and Accessories

The integration of heart rate sensors into textiles and accessories has led to the development of a wide variety of devices, that can track heart rate and/or record ECG. Accessories, such as rings (27, 28), headphones (30, 32), and footwear (36) are reported to be reliable in heart rate measurements, even though their accuracy can be compromised during high intensity exersice (31). Another monitoring system features a devices that resembles a necklace (CoVa monitoring system) (29), which, not only monitors heart rate and ECG in real-time, but also provides information regarding stroke volume, cardiac output and fluid status, providing an holistic hemodynamic assessement of heart failure patients, rather than merely cardiac rhythm monitoring. Chest straps, like the Zephyr BioHarness (33, 35, 92–94), the Polar H7 (30, 34, 95) and the EQ02 Lifemonitor (96, 97) provide a wide range of biomeasurments and are used mainly in athlete training, even though the Polar H7 chest strap has been utilized as an AF screening tool, with high accuracy (98). Sensors embedded in clothing, such as the Nuubo vest (99, 100) and the Master Caution shirt (101), allow for continuous ECG monitoring, fascilitating arrhythmia detection. In a study by Pagola et al., prolonged patient monitoring, using the Nuubo vest, after a cryptogenic stroke, led to the diagnosis of AF in 20% of the participants (102). In general, smart clothing and accessories reliably provide a wide variety of biomeasurements, including heart rate, but validation as diagnostic tools for arrhythmia detection is lacking for most of the products under this category.

ARRHYTHMIAS OTHER THAN AF

Although all the large-scale studies conducted on the use of smartwatches as diagnostic and monitoring tools focus on AF, data in the literature demonstrate their potential contribution to the detection of arrhythmias other than AF (50). The spectrum of the heart rhythm disorders that can be detected with wearable devices is outlined in **Table 4**.

TABLE 4 | Heart rhythm disorders identified by wearable devices and the respective modality used to detect them.

Heart rhythm disorders	Smart wearable modality
Tachycardias	
Sinus tachycardia	ECG
Supraventricular tachycardia	ECG
Ventricular tachycardia/fibrillation	ECG
Bradycardias	
Sinus bradycardia	ECG
Pause	PPG, ECG
Ectopy	
Supraventricular premature complexes	ECG
Ventricular premature complexes	ECG
Irregular rhythms	
Atrial fibrillation	PPG, ECG
Atrioventricular conduction disorders	
First degree AV block	ECG
Second degree AV block	ECG
Complete AV block	ECG
Other	
QT interval assessment	ECG

AV, atrioventricular; PPG, photoplethysmography; ECG, electrocardiogram.

Smartwatches/Wristbands

Bradyarrhythmias and tachyarrhythmias can be identified with the use of smartwatches (74). The Apple Watch has been used in the detection of ventricular arrhythmias in two patients suffering from arrhythmogenic right ventricular cardiomyopathy and episodes of non-sustained ventricular tachycardia (VT), respectively, enabling physicians to correlate the reported symptoms with the underlying cause, which would otherwise remain undiagnosed (103). Captured single-lead ECG tracings of ventricular tachycardia in a patient with structural heart disease, or pre-excited AF with rapid ventricular response in an otherwise healthy young individual, using an Apple Watch, have also been reported (104). In patients wearing the Apple Watch, episodes of supraventricular tachycardia (SVT), such as atrioventricular reentrant and atrioventricular nodal reentry tachycardia have been recognized, as well (105, 106). Furthermore, researchers suggest an alternative use of these wrist wearables, by placing the sensor either at both upper extremities or at the abdomen and the chest in order to receive a more comprehensive recording that best resembles the standard 12-lead ECG. As a result, differential diagnosis between AF and atrial flutter could be facilitated. Furthermore, abnormalities associated with sudden cardiac arrest in young adults with ventricular pre-excitation, Brugada ECG pattern, arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy or long-QT syndrome can also be detected (107, 108).

Patches

Apart from AF, patches that monitor heart rhythm can identify a series of other clinically significant arrhythmias, being a useful tool in the diagnostic work-up of patients with symptoms such as palpitations, syncope or presyncope. Supraventricular tachycardia was the most common rhythm disorder identified in a large cohort of individuals monitored with the ZioPatch (18, 52), as well as in patients with symptoms of arrhythmia discharged from the emergency department (109). Prolonged rhythm monitoring with wearables other than the ZioPatch is also associated with an increased rate of SVT diagnosis (55, 56, 70, 89). Patches providing clear identification of the P-wave facilitate further classification of the detected SVTs (61). Côté et al., have reported two cases of Wolff-Parkinson-White syndrome with intermittent pre-excitation, not present in 12-lead ECG, in children monitored with the CardioSTAT patch, who were complaining of palpitations (110).

Among participants actively monitored in the mSToPS trial, the detection of significant pauses and high degree atrioventricular block, along with runs of non-sustained VT, resulted in increased rates of pacemaker and implantable defibrillator implantations (63). In comparative studies, the MCOT patch was superior to a loop event recorder in detecting bradycardia, cardiac pauses, sustained or symptomatic SVT, asymptomatic high ventricular rates and runs of VT (54, 58). In patients undergoing transcatheter aortic valve replacement (TAVR), prolonged, patch-based, rhythm monitoring, prior to the procedure, can detect significant bradyarrhythmias in one-fifth of the patients, some of which may require a change of treatment (111). Following TAVR, Tian et al., identified patients with late high degree atrioventricular block, using the BodyGuardian patch (Preventice Solutions, Inc, USA) (112). The same patch was also found to reliably assess the QT interval, both in healthy individuals and long QT syndrome patients and could be used to remotely monitor patients in risk of QT interval prolongation and arrhythmias (113).

LIMITATIONS

Despite the variety of benefits associated with wearable technology, several limitations have to be overcome in order to establish their role as medical devices for cardiac rhythm monitoring and diagnosis, in everyday clinical practice. **Figure 2** summarizes the main limitations and future perspectives, concerning the growing population of smart wearables.

Smartwatches and wristbands are practical and able to track heart rhythm during every possible physical activity, using a semi-continuous PPG sensor, with or without intermittent ECG tracings, when available. Consequently, they lack the ability of continuous rhythm monitoring and require the cooperation of the user in order to achieve a reliable recording and capture the required data (12). Due to this operation mode, recording of paroxysmal arrhythmias may be missed, preventing accurate diagnosis and targeted management. In addition, the necessity for patient's alertness precludes monitoring during episodes with associated loss of consciousness, that could reveal malignant underlying arrhythmias, while the concomitant reduction of the peripheral blood pressure may weak the pulse signal, affecting the quality of the PPG signal (69). In view of this, in the WATCH AF trial, a high dropout rate of record files due to inadequate quality

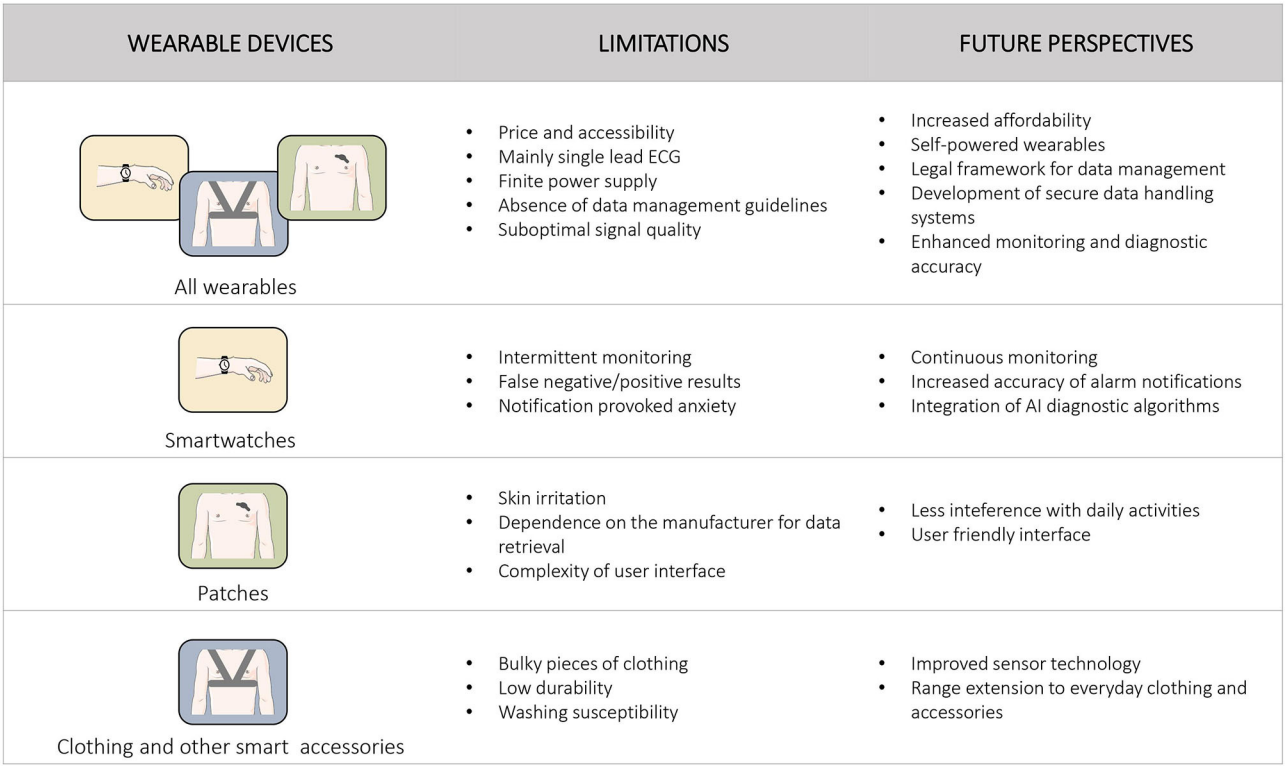

FIGURE 2 | Main limitations and future perspectives of wearable devices for heart rhythm monitoring are presented. Specific information for each category of wearable devices is presented separately.

of the signal was observed, thus restricting the applicability of a smartwatch monitor in everyday practice (48). Smartwatches often demonstrate false positive results, occasionally leading to overdiagnosis and overtreatment of patients. At the same time, pathological signals and repeated notifications provoke intense anxiety to the user, often affecting both his physical and mental health (12).

On the other hand, wearable patches provide continuous rhythm recording during the application period, without requiring the active involvement of the user. Nonetheless, they manifest caveats that also restrict their applicability. Some patients may experience skin irritation, which is the most common adverse reaction of adhesive patch monitors (54, 63, 87). Noise recording could render the rhythm tracing uninterpretable, especially when single-lead patches are used (53). Another limitation is the fact that certain devices, such as the ZioPatch and the CardioSTAT, have to be mailed back to the manufacturer for data collection and analysis. This process could result in significant turnaround times between the end of the monitoring period and arrhythmia detection. Moreover, there is a clear dependance on the device company for data retrieval and analysis for most patch monitors, while the cost of using these devices is not negligible. Finally, user interface is quite complex for people who are not particularly familiar with handling novel technological platforms, excluding its utilization by elderly patients and non-familiarized physicians (114).

The integration of sensors into garments overcomes some of the drawbacks listed above, such as the need for the user to operate certain devices. On the other hand, incorporating electronics into fabric results in bulky, inflexible pieces of clothing. Moreover, the lifespan of smart clothing may be limited, affected by low durability and washing susceptibility.

Most of the wearables that capture ECG tracings provide data equivalent only to one of the 12 leads of the traditional ECG, thus limiting their value in detecting more complex arrhythmias and cardiac disorders (74). Furthermore, despite the significant progress observed in the field of lithium battery lifetime, power supply is still of finite duration, demanding repeated recharging and resulting to intervals of monitoring interruption (14). Besides that, the great abundance of sensitive data collected through these new technologies, require the development of strict policies to ensure safe storage, transparency, privacy and security of users' personal data (14, 115). Additionally, the crucial challenge of pricing and accessibility of smart wearables is still under discussion. Their consideration as medical devices establishes new standards that require the normalization of economic inequalities, in order to avoid health disparity. Moreover, the involvement of the public and private insurance systems in device reimbursement is unclear and is yet to be determined (14, 116).

Wearable devices have evidence-based credentials that establish their role as a screening tool for the detection of

cardiac arrhythmias, especially AF, affecting decision making in patient pharmacological treatment. However, the benefit derived from the initiation of anticoagulation, based on AF diagnosis by wearable devices screening, has not been confirmed. In fact, despite the increased diagnostic rate of AF episodes, in high-risk individuals, in the STROKESTOP trial (117, 118) and the LOOP study (119), the LOOP study failed to show any added benefit, regarding the endpoint of stroke or systemic embolism, after initiation of preventive anticoagulation (119). These results imply that not all AF episodes in asymptomatic patients pose the same thromboembolic risk and underscore the need for further evaluation, in order to determine the exact role of AF screening and indicate specific AF characteristics and/or AF patient groups that derive potential benefit from oral anticoagulation initiation.

FUTURE PERSPECTIVES

Undoubtedly, novel technologies bear the potential to shift the paradigm of disease diagnosis and patient management. The ideal wearable device for heart rhythm monitoring should be easy to use, even by the elderly and less familiarized patients, not interfere with daily activities and provide continuous and accurate real-time heart rhythm monitoring. Most commercially available wearables are capable of continuous monitoring for several days, providing they have sufficient power. Use of self-powered technology would, theoretically, allow for uninterrupted, extended use of cardiac monitoring devices (120). Wearables with integrated mobile network access could instantaneously transmit data to central analysis stations, circumventing the need of a transmitting device, and potential data loss if the patient is not within the range of the latter, when a clinically significant arrhythmia appears (70). This would grant real-time surveillance of the heart rhythm, which is of outmost importance in high-risk patients, such as those in risk of ventricular arrhythmias.

Further improvement of the diagnostic accuracy has the potential to transform wearables, such as smartwatches, from screening and pre-diagnostic tools to diagnostic modalities. The integration of artificial intelligence algorithms in basic medical tools, such as the 12-lead ECG, has demonstrated promising results, regarding the early and accurate detection of structural heart disorders, thus extending beyond the field of arrhythmia diagnosis (121, 122). The combination of this technological advancement with wearable devices could improve the reliability of their measurements and provide prognostic features for the detection of subclinical cardiac conditions (123). Advances in deep learning technologies and their application in the diagnostic algorithms will certainly further increase their diagnostic accuracy (124, 125). Moving away from validation studies, clinical trials pursuing hard endpoints, such as cardiovascular mortality or stroke, are essential to facilitate wider acceptance of wearables from clinicians, their implementation in everyday clinical practice and to support device reimbursement from insurance companies.

As wearable devices become more affordable and reach an increasingly number of consumers, a plethora of sensitive health data are anticipated to be generated. There is a clear necessity for an integrated system to collect and safely store personal information, in a way that will ensure users' privacy. Clear legal regulations, along with an ethical framework, under which personal data are collected and handled, are essential (126). Data processing should target accurate diagnosis and provide the attending physician with clinically meaningful information. In this way, integrated data handling systems could translate to improved patient management, with personalized healthcare interventions and better utilization of health care resources.

CONCLUSIONS

Wearable devices are a new reality in monitoring and management of cardiac arrhythmias. Pertinent caveats, such as signal quality, connectivity issues, battery life limitations, sub-optimal diagnostic accuracy and data security and storage, need to be addressed, in order to enable their full utilization as medical devices. However, advanced technological developments contribute to rapid improvement and accomplishment of future intentions and are expected to establish the role of smart wearables as important tools in the emerging era of telehealth, remote patients' control, personalized and precision medicine.

AUTHOR CONTRIBUTIONS

ST, AX, VS, DA, and PV: conception of the theme and design. AX and VS: data collection and preparation of the draft manuscript. ST: editing. ST and PV: final revision and supervision. All authors approved the final version of the manuscript.

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Remote Design of a Smartphone and Wearable Detected Atrial Arrhythmia in Older Adults Case Finding Study: Smart in OAC – AFNET 9

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Introduction: Screening for atrial fibrillation and timely initiation of oral anticoagulation, rhythm management, and treatment of concomitant cardiovascular conditions can improve outcomes in high-risk populations. Whether wearables can facilitate screening in older adults is not known.

Methods and Analyses: The multicenter, international, investigator-initiated, single-arm case-finding Smartphone and wearable detected atrial arrhythmia in older adults case finding study (Smart in OAC – AFNET 9) evaluates the diagnostic yield of a validated, cloud-based analysis algorithm detecting atrial arrhythmias via a signal acquired by a smartphone-coupled wristband monitoring system in older adults. Unselected participants aged ≥65 years without known atrial fibrillation and not receiving oral anticoagulation are enrolled in three European countries. Participants undergo continuous pulse monitoring using a wristband with a photo plethysmography (PPG) sensor and a telecare analytic service. Participants with PPG-detected atrial arrhythmias will be offered ECG loop monitoring. The study has a virtual design with digital consent and teleconsultations, whilst including hybrid solutions. Primary outcome is the proportion of older adults with newly detected atrial arrhythmias (NCT04579159).

Discussion: Smart in OAC – AFNET 9 will provide information on wearable-based screening for PPG-detected atrial arrhythmias in Europe and provide an estimate of the prevalence of atrial arrhythmias in an unselected population of older adults.

Keywords: atrial fibrillation, screening, wearable, digital consent, stroke, telemedicine, digital cardiology, photo plethysmography

INTRODUCTION

Atrial fibrillation (AF) is often only diagnosed in the context of a first stroke [up to 10% of unselected stroke survivors (1)]. Earlier initiation of anticoagulation could prevent strokes and systemic embolism, and reduce cardiovascular mortality in patients (2).

Recent controlled clinical trials demonstrate that population-based screening for AF and subsequent initiation of oral anticoagulation can reduce stroke in elderly populations (3, 4). These trials also illustrate a relatively high number needed to screen and that a relevant proportion of those invited to screening do not use patient-operated ECGs (3) or implanted monitors (4). Thus, simpler methods to screen for AF are desirable. Many consumer devices, most notably smartphones and smartwatch/wearable-based devices (5–7), enable near-continuous heart rhythm monitoring with reasonable precision (8–10). Such technologies could offer an additional, potentially simpler way of screening for atrial arrhythmias. So far, these promising technologies have mainly been evaluated in younger, tech-savvy early adopters (5), while the biggest clinical need for AF screening is in unselected elderly populations (11). Older adults, however, may face barriers in uptake, use and adherence to smartphone and app based screening offers. To advance the use of consumer electronics for AF screening, there is a need to evaluate the uptake, usability, and diagnostic yield of atrial arrhythmias in older adults with and without prior knowledge of wearable technologies.

The Smartphone and wearable detected atrial arrhythmia in Older Adults Case finding study (Smart in OAC – AFNET 9) will therefore evaluate the usability of a fully digital PPG-based detection system for atrial arrhythmias in an unselected population of older adults. The study will furthermore evaluate communication channels designed to offer PPG-based arrhythmia screening to older adults. This case finding study will also fully adhere to European privacy regulations.

METHODS AND ANALYSIS

Study Design

Smart in OAC – AFNET 9 is an investigator-initiated, single-arm, international, multicentre case-finding study in an at-risk population without previously known atrial fibrillation using a low-threshold, digitally enhanced screening platform (**Figure 1**). The primary objective of Smart in OAC – AFNET 9 is to determine the ability of a wearable-based PPG-based screening to detect atrial arrhythmias in older adults. Within the limitations of a controlled trial requiring consent, the system is designed for simplicity (**Figure 1**). We will estimate the detection rate of atrial arrhythmias using a validated PPG analysis system using a consumer electronic wearable in a structured, digital screening process offered to individuals aged 65 years or older. The study has been approved by the local Ethics Committees in all participating sites.

Participants

Smart in OAC – AFNET 9 aims to reach out to unselected participants aged 65 years or older without previously known AF and not on oral anticoagulation and can provide informed consent. During enrolment, we rely on self-reported information provided by the participants. Several communication channels are used to reach the target population. It is planned to advertise the study using newspaper adverts and television, media that are commonly used by older adults. Study centres will additionally explore ways of approaching participants directly, suitable to the region's cultural and regulatory peculiarities, e.g., those seen during routine health checks including vaccination appointments. The routes of contact will be described and evaluated during the study aiming to identify routes that enable equitable access to the screening tool.

Study Intervention

Participants will be offered participation in the study using an online consent form. Paper versions are available if required by local ethics regulations. Participants who consent to the study will be provided with a wristband (Corsano 287, MMT SA, Switzerland) coupled to an existing smartphone (operating system requirements Apple iOS version 12.2 or higher or Android 8.0 or higher). The wristband contains a PPG sensor that couples to the participant's smartphone via Bluetooth. Initiation of the study requires installation of the Corsano Preventicus Smart app on the smartphone. The PPG is recorded from the wristband automatically after pairing the wristband to the smartphone. Data is first stored in the wristband and automatically uploaded via smartphone to Preventicus Telecare® cloud. The first pairing activation can be done by the participants themselves following in-app guidance. In-person support is provided via the local study teams and by trained staff at Preventicus. Once the monitoring is activated and the wristband coupled to the smartphone, the system enables continuous monitoring of heart rhythm using a wristband with a PPG sensor coupled with a smartphone app and a validated cloud based

Abbreviations: AA, atrial arrhythmia; AF, atrial fibrillation; ECG, electrocardiogram; PPG, pulse plethysmography.

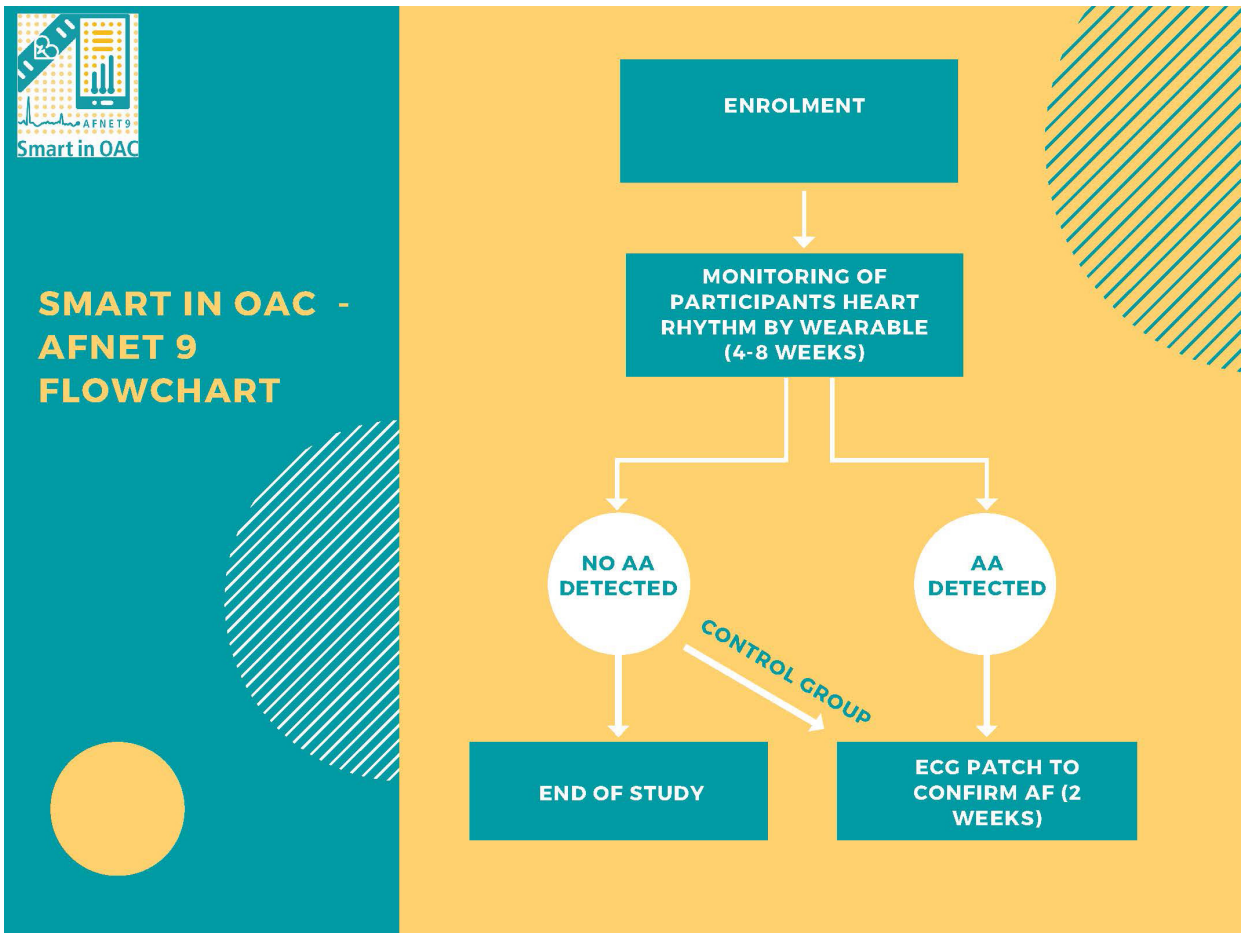

FIGURE 1 | Study flow chart.

analytic service [Preventicus Heartbeats®, Jena, German[1] (9)]. The wearable technology records passively around the clock, operating for up to 5 days without re-charging, and determines the length of atrial arrhythmia (AA) episodes and the AA burden per day using a fully automated, cloud-based transmission and analysis service. Participants are asked to wear the wristband and use the system for 4 weeks, including nights, with a possibility to extend monitoring up to 8 weeks. This screening duration was chosen by the steering committee as likely to be biologically meaningful in terms of stroke risk, as very rare atrial arrhythmias detected by long screening durations will be associated with a lower stroke risk than atrial arrhythmias detected during one to two months of screening (11–13).

All signals will be centrally analysed by the Preventicus Telecare service using Preventicus Heartbeats®. Preventicus is ISO 13485 certified. Preventicus Heartbeats® is a cloud-based and device-agnostic analytic service for plethysmographic (PPG), accelerometric (ACC), and ECG raw data. It is a CE class IIa certified medical product for heart rate and rhythm analysis based on either 1.5 min measurements with smartphone camera, or continuous and passive raw PPG recordings from wearables. More than 10 million analyses have been performed so far with the analytic service; it has been comprehensively validated (14–17). The algorithm showed an accuracy of ∼96% and a positive predictive value of ∼99% for AF in the "WatchAF" and "Detect AF Pro" trials with more than 1200 participants (9, 18). To quantify which arrhythmias will be classified as atrial arrhythmia in the study, ECG beat annotations containing over 150,000 min of rhythm recordings from 341 subjects available in seven open databases available from PhysioNet were used (see **Supplementary Table 1**) to obtain 1-minute-long beat-to-beat segments that were evaluated using the AF-detection algorithm used in the study. The minute-wise comparison of ground truth arrhythmias and AA detection by the algorithm demonstrates good sensitivity and specificity for AF (see **Supplementary Table 2**). These analyses were furthermore compiled to provide a subject-wise picture of the arrhythmias contained. This evaluation demonstrates that the algorithm comprises atrial fibrillation. In addition to PPG-detected atrial arrhythmias, the investigational product also uses raw PPG data to detect other abnormalities with irregular beat-to-beat intervals and accurately differentiates them against sinus rhythm and AA (19).

[1]www.preventicus.com

When an atrial arrhythmia episode is detected and verified by the Preventicus Telecare service, participants are offered a 14-day external loop recorder Holter ECG (CardioMem® CM 100 XT) (**Figure 1**). If the participant agrees to receive the ECG device remotely, the necessary equipment and instructions for use at home will be mailed. The study sites will provide the ECG loop device to the participant and collect additional health data. Participants will be informed about the results of the measurements and about whether further actions are to be taken depending on their results. Participants with clinically confirmed atrial fibrillation will be offered a clinical visit at the study site to determine their best management.

Data Collection

Smart in OAC – AFNET 9 will collect all data remotely via the consumer electronic device enhanced with the smart wristband. During the enrolment, the participants provide information on data such as name, mobile number, date of birth, known AF and current oral anticoagulation and there is an option to fill in an EQ-5D-5L electronically (**Table 1**). A participant ID is assigned automatically. In participants with atrial arrhythmias detected by the PPG, additional information on cardiovascular conditions will be requested and further data such as repeat information on quality of life based on the EQ-5D-5L will be collected.

As technical difficulties could impair enrolment and adherence for the oldest participants, we plan technical support in local languages not only at inclusion, but also during follow-up to address any potential pairing and software issues. The app's design for this study was specifically designed and adapted for ease of use, including enhanced contrast and enlarged font size for improved use in older adults.

Adherence to the screening programme and duration of PPG monitoring will be recorded as secondary outcome. If participants discontinue participation, the information gathered until discontinuation will be analysed.

Due to the device-agnostic certification, the Preventicus analysis service can be coupled with different wearables, provided they transmit PPG and ACC raw data (and optionally ECG data) to the cloud service in a standardised way. In the present study, the Corsano 287 wearable PPG wristband is used for this purpose. It is manufactured and provided by MMT SA (Switzerland[2]), an ISO 13485 certified medical product manufacturer. The core module of Corsano 287 has been previously used with over 150,000 modules sold and has CE medical device certification under EU-MDR standards. The wearables provide an up to 5 days recharge cycle and are suitable for continuous PPG and ACC raw data capturing including transfer to cloud service via Bluetooth 5.0 using the participants smartphone.

Data and information technology safety and data security requirements are met. Preventicus data management and data protection comply with General Data Protection Regulation. Personal data (declarations of consent, contact information, etc.) are stored exclusively in Preventicus Caresafe (i.e., a platform for the study centres to manage the digital enrolment modalities. The data in the Caresafe are end-to-end encrypted, so that Preventicus and Corsano Health B.V. (manufacturer of the app) and MMT (manufacturer of the wearable) are not able to gain access to personal data.

[2]www.mmt.ch

Sample Size and Statistical Analyses

The prevalence of AA in elderly populations was ca. 30–40% when continuous monitoring is applied for 2–3 years using implantable loop recorders (4, 20, 21). Integrating the estimated effects of shorter monitoring times (1 month), considering that the wearable will not be used 24/7 by all participants, and based on the known effects of intermittent and shorter ECG monitoring on detection rates of short AA (7, 22), we estimate a detection rate of AA of 3–6% in the screening population. This estimated rate is higher than observed in STROKESTOP, where only very short intermittent monitoring was applied (30 s twice a day for a few weeks) (23).

A sample size of 1,000 participants undergoing PPG screening will allow us to estimate a rate of detection of 5% with a precision of 2.8% (width of the two-sided 95% Clopper Pearson confidence interval, PASS 16.0.3). For 750 participants, the precision is 3.3%, for 500 participants 4%.

Details will be set out in a statistical analysis plan. The primary analysis will be based on the full analysis data set, consisting of all participants that consented to screening and provided at least one data point. For the analysis of the demographics and baseline characteristics, descriptive statistics will be used. The proportion of participants that consent to participate in screening or not will be estimated with corresponding two-sided 95% Wald confidence interval. The detection rate of AA will be calculated together with the corresponding two-sided 95%-confidence interval.

Primary Outcome

The primary outcome parameter of this study is the prevalence of PPG-detected atrial arrhythmias calculated as number of participants with AA detected by the wearable in relation to all included participants.

Secondary Outcomes

Secondary outcomes include a description of the enrolment routes and comparison of clinical characteristics between enrolment routes, proportion of participants who underwent monitoring as a proportion of the participant invited, and the duration of monitoring per participant. Regional differences of AA prevalence within the European study sites in terms of AA prevalence and differences by route of invitation and enrolment will be evaluated. All processes and procedures will be evaluated to extract information on usability, including exclusions due to lack of smartphone ownership or digital capability. Further information collected for key secondary analyses is provided in **Table 1**.

Adverse Events

This observational study uses approved technologies based on tested consumer electronics in an approved indication, evaluating the feasibility of its use to screen an at-risk population at large scale in a low-threshold access setting. Thus, Smart in OAC –

TABLE 1 | Primary outcome and key secondary outcomes of Smart in OAC – AFNET 9.

1. Primary Outcome
The primary endpoint is the proportion of participants with newly detected atrial arrhythmias within 4 weeks of device use of all participants included in the study. It will be reported with a two-sided 95% Clopper-Pearson confidence interval.
2. Key Secondary Outcomes
Proportion of participants with atrial arrhythmias detected at any time, including those with atrial arrhythmias detected within the full time of recording will be reported with a two-sided 95% Clopper-Pearson confidence interval
Time from completed enrolment to the first positive screening, taking death as competing risk into account will be analysed using Aalen–Johansen curves.
Regional differences of atrial arrhythmia prevalence (diagnostic yield), differences by route of invitation and enrolment will be compared using a logistic regression model
Differences by route of invitation and enrolment will be compared using a logistic regression model
Compliance: The compliance of participants with protocol with regards to the measurement procedure of the app and wearable will be presented descriptively. This will include reasons to discontinue the monitoring prematurely, and reasons for withdrawal of consent. The duration of screening per participant will be plotted. Proportion of participants with atrial arrhythmias contacting the study centre (personal visit or remote),as recommended. Number of participants wearing the 14 day Tele ECG patch after detection of atrial arrhythmias; Compliance of participants using the app/wearable: percentage of active users after two weeks, histogram of analysable data recorded.
Detection of AF: Number of participants with clinically confirmed arrhythmias (sub-analysis: AF) during Holter ECG, documented clinically or by event-recorder. We will add clinical evidence as available. The agreement of ECG-based detection of AF will be accessed by cross-tabulating both methods and quantified using the proportion of concordant diagnoses in the ECG subpopulation.

AFNET 9 is a low-risk study. Adverse events related to the study procedures (e.g., side effects of the wearable, in this case a wristband) will be prospectively collected and reported.

DISCUSSION

Smart in OAC – AFNET 9 will provide information on the usability and diagnostic yield of screening for atrial arrhythmias in unselected older adults. The results will address the open question whether structured AF screening programmes using short-term ECG recordings or implanted rhythm monitors can be supplemented or replaced by consumer-electronic based arrhythmia screening. While a growing majority of older adults in the UK (24) and in Germany (25) now use a smartphone, the feasibility of the study part will also assess the extent to which digital exclusion might limit access to this technology in older adults.

The results will provide robust information on the prevalence of PPG-detected arrhythmias in older adults. Smart in OAC – AFNET 9 will evaluate and validate pathways for participant recruitment and follow-up and thus generate robust information for the planning of an outcome trial. Thereby, the study will provide data on different methods to reach out to such populations to offer arrhythmia screening and on characteristics of participants with PPG-detected arrhythmias.

ETHICS STATEMENT

Smart in OAC – AFNET 9 is registered at https://clinicaltrials.gov/ct2/show/NCT04579159. Ethics have been granted (Hamburg 2020-10260-BO-ff, Dresden (Markkleeberg) EK-BR-95/21-1, Barcelona HCB/2021/0255, Krakow/Nowy Sasz 298/KBL/OIL/2020, Birmingham, UK IRAS 292218). The protocol of the study is published with this manuscript. The results of the trial will be published after trial completion and statistical analysis. A list of secondary analyses and publications will be provided by the steering committee of the trial based on the statistical analysis plan. The steering committee will be responsible for decisions regarding additional analyses and access to data.

AUTHOR CONTRIBUTIONS

LF, RS, and AZ wrote the manuscript. RS, PK, LF, AZ-H, DH, EC, and KJ designed the protocol. AZ, DD, EG, LF, TH, US, and RS planned the study. KJ, EC, AZ-H, LF, RS, and EG designed the patient-friendly information and prepared ethics applications. All authors made critical comments on the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.839202/full#supplementary-material

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CASE REPORT
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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

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Background and Case: This case report exemplifies the clinical application of non-invasive photoplethysmography (PPG)-based rhythm monitoring in the awakening mobile health (mHealth) era to detect symptomatic and asymptomatic paroxysmal atrial fibrillation (AF) in a cryptogenic stroke patient. Despite extensive diagnostic workup, the etiology remains unknown in one out of three ischemic strokes (i.e., cryptogenic stroke). Prolonged cardiac monitoring can reveal asymptomatic atrial fibrillation in up to one-third of this population. This case report describes a cryptogenic stroke patient who received prolonged cardiac monitoring with an insertable cardiac monitor (ICM) as standard of care. In the context of a clinical study, the patient simultaneously monitored his heart rhythm with a PPG-based smartphone application. AF was detected simultaneously on both the ICM and smartphone application after three days of monitoring. Similar AF burden was detected during follow-up (five episodes, median duration of 28 and 34 h on ICM and mHealth, respectively, $p = 0.5$). The detection prompted the initiation of oral anticoagulation and AF catheter ablation procedure.

Conclusion: This is the first report of the cryptogenic stroke patient in whom PPG-based mHealth was able to detect occurrence and burden of the symptomatic and asymptomatic paroxysmal AF episodes with similar precision as ICM. It accentuates the potential role of PPG-based mHealth in prolonged cardiac rhythm monitoring in cryptogenic stroke patients.

Keywords: atrial fibrillation, cryptogenic stroke, mobile health, case report, insertable cardiac monitor (ICM)

INTRODUCTION

The etiology of stroke remains unknown in one-third of all ischemic stroke patients despite extensive diagnostic workup (i.e., cryptogenic stroke) (1). Prolonged cardiac monitoring can reveal the often asymptomatic atrial fibrillation (AF) in 12–33% patients using insertable cardiac monitors (ICMs) (2, 3). These patients are almost three times as likely to suffer from a recurrent stroke as non-AF-related stroke patients (4). Since oral anticoagulation can only be initiated after AF diagnosis, this has significant implications for secondary prevention (5).

According to the European Society of Cardiology (ESC) guidelines, prolonged cardiac monitoring is recommended in cryptogenic stroke and transient ischemic attack (TIA) patients since it increases the detection rate of AF by a factor of six (2, 5). The ongoing REMOTE study on cryptogenic stroke patients with implanted ICMs [approved by the medical ethics committees (Ziekenhuis Oost-Limburg, Genk, Belgium and Hasselt University, Hasselt, Belgium): 19/0093U, ClinicalTrials.gov Identifier: NCT05006105] investigates the added value of photoplethysmography (PPG)-based mobile health (mHealth) in AF detection using spot-check and semi-continuous measurements on the smartphone or smartwatch, respectively. The FibriCheck® application (Qompium NV, Hasselt, Belgium) was used as a tool in this study. This app has both CE mark and FDA approval. It is qualified to detect AF in patients with medical-grade precision (sensitivity and specificity are 96 and 97%, respectively) (6, 7). This case report presents the detection of symptomatic and asymptomatic, paroxysmal AF episodes with a minimum duration of approximately 19 h in a cryptogenic stroke patient enrolled in the REMOTE study using an mHealth smartphone application.

CASE DESCRIPTION

A 59-year old male with a past medical history of arterial hypertension, a sedentary lifestyle, and who was a former smoker woke up with aphasia and headache. His medication regimen consisted of chlortalidone 50 mg, quinapril 20 mg, and atenolol 25 mg. He presented to the emergency department the next day with normal vital parameters and word-finding difficulties, resulting in a National Institutes of Health Stroke Scale (NIHSS) on admission of one.

Diagnostic Assessment

Initial labs showed no electrolyte or metabolic disturbances; glycemia was 129 mg%. The electrocardiogram (ECG) was normal except mild sinus bradycardia of 52 bpm. A computed tomography (CT) scan of the brain indicated recent ischemia in the left temporoparietal cortex. The CT angiography of the carotid arteries showed no cause of the stroke. Brain magnetic resonance imaging confirmed recent ischemia with diffusion restriction in the corticosubcortical posterior temporal area of 47 mm, with a stroke volume of 20 ml in the left middle cerebral artery area (M3). Both gray and white matter were affected. Another focal area of diffusion restriction was distinguished in the paramedian right occipital lobe. There was no hemorrhagic transformation. The EEG did not demonstrate signs of epilepsy.

The transesophageal echocardiogram could not confirm a cardiac source of emboli. Cardiac monitoring during 67 h on the stroke unit could not detect AF. HbA1c was normal, 5.7%. The LDL cholesterol level was 79 mg/dl; total cholesterol was 145 mg/dl. The thrombophilia screening panel, including anti-cardiolipin and lupus anticoagulant, was negative. The patient was sent home on dual antiplatelet therapy with acetylsalicylic acid 80 mg and clopidogrel 75 mg during three weeks and was told to continue only clopidogrel 75 mg after that. Furthermore, atorvastatin 40 mg was initiated. After hospital discharge, a 24-h blood pressure monitor showed no hypertension. A seven-day ECG Holter showed no AF episodes or pauses. However, 82 bradycardia events, 235 ventricular ectopic beats, and 481 supraventricular ectopic beats were detected.

Long-Term Cardiac Monitoring

The stroke was finally defined as cryptogenic due to a negative seven-day ECG Holter. As a result, an ICM was indicated for prolonged cardiac rhythm monitoring to detect asymptomatic AF. Furthermore, the patient was included in the clinical double-blind REMOTE study in which ICMs are compared to PPG-based mHealth on either a smartphone or smartwatch. An ICM was inserted seven weeks after the stroke to monitor the heart rhythm continuously until battery end-of-service (i.e., average duration of three years). The patient was randomized to the smartphone monitoring group and was asked to perform two one-minute spot-checks using the FibriCheck® application each day, and additional spot-checks could be performed in case of symptoms during a period of 6 months. This application uses the PPG signal, which is interpreted and classified by an algorithm. After an offline validation, the result was available for the researcher, yet blinded for both patient and caregiver.

Detection of Atrial Fibrillation

The use of mHealth was initiated on the day of ICM insertion. The time to first AF detection was three days. This first AF episode with rapid ventricular response was detected on both ICM and mHealth. The ICM reported an AF episode lasting 28 h. During this period, five mHealth spot-checks were performed. All of them were identified as AF; only one of these episodes was reported to be symptomatic. The initially cryptogenic stroke was now considered to be caused by cardioembolism due to AF. Since this first AF episode occurred during the weekend, it took five days before the cardiologist switched from antiplatelet to anticoagulation therapy based on the ICM data (i.e., mHealth was blinded for both patient and caregiver). Six weeks after ICM insertion, bisoprolol 5 mg was initiated.

Due to the patient's young age, the absence of structural cardiac disorders, and the paroxysmal nature of this AF, an ablation procedure was performed to isolate the pulmonary veins. After the ablation, flecainide 100 mg was initiated. No AF was detected in the six weeks following the ablation, resulting in the cessation of flecainide 100 mg and bisoprolol 5 mg. He continued to use edoxaban 60 mg, chlortalidone 25 mg, atorvastatin 40 mg,

TABLE 1 | Duration of the AF episodes based on ICM and PPG-based mHealth.

AF episode number	AF duration (ICM)	AF duration (mHealth)	*p*-value
1	28 h 22 min	36 h 18 min	
2	28 h 44 min	41 h 24 min	
3	26 h 14 min	26 h 46 min	
4	20 h 4 min	18 h 51 min	
5	37 h 14 min	34 h 19 min	
Total AF duration	140 h 38 min	157 h 38 min	
Median [IQR] AF duration	28 h 22 min [23 h 9 min–32 h 59 min]	34 h 19 min [22 h 49 min–38 h 51 min]	0.5

AF, atrial fibrillation; ICM, insertable cardiac monitor; mHealth, mobile health. P-value was obtained via a Wilcoxon signed-rank test.

and quinapril 20 mg. Neither mHealth nor ICM detected AF within 8 months after ablation.

Comparison Between Insertable Cardiac Monitor and Photoplethysmography-Based Mobile Health

Before the ablation procedure, five AF episodes were detected on both the ICM and mHealth application. The durations of these AF episodes are presented in **Table 1**. The AF duration detected by the mHealth application was estimated as follows (**Figure 1**); the time between the last green spot-check (i.e., no AF) and the first red spot-check (i.e., AF) divided by two, plus the time between the first and last red spot-check, plus the time between the last red spot-check and the first green spot-check divided by two. The duration of the AF episodes thus calculated with mHealth (*mdn* = 34 h 19 min), was not significantly different from the ICM-registered episodes (*mdn* = 28 h 22 min, $Z = -0.674$, $p = 0.5$). The AF burden was calculated as the proportion of time the patient was in AF during a monitoring period (8). The overall AF burden between ICM insertion until ablation was 8% according to the ICM and 9% based on mHealth.

Over a period of 180 days (i.e., 6 months), 230 measurements were performed using a smartphone. Simultaneously, the ICM collected 4,320 h of continuous data. Compliance was defined as the total number of spot-checks performed, divided by the total number of recommended spot-checks. Motivation was defined as the number of days with at least two daily spot-checks divided by the number of days. The compliance to the mHealth application prior to ablation was 88%, the motivation was 56%. After ablation, this decreased to a compliance of 46% and a motivation of 35%. Despite the moderate motivation of this patient to perform spot-checks, all AF episodes were detected by the mHealth application, with a similar AF burden as the continuous monitoring of an ICM. It is important to note that no other arrhythmias were detected using the mHealth application before or after the AF episodes. Furthermore, only three AF spot-checks (19%) were symptomatic (i.e., palpations and dizziness); two of these were recorded within the same hour.

This patient was found to have primarily asymptomatic paroxysmal AF episodes after suffering a cryptogenic stroke. The AF episodes were concurrently detected by an ICM and a PPG-based mHealth smartphone application with an artificial intelligence algorithm to detect AF. The application detected all AF episodes identified by the ICM (**Figure 2**). Moreover, there were no false-positive mHealth recordings.

FIGURE 1 | Visualization of the estimated duration of an atrial fibrillation episode measured by spot-checks. The time between the last green spot-check (no AF) and the first red spot-check (AF) divided by two, plus the time between the first and last red spot-check, plus the time between the last red spot-check and the first green spot-check divided by two.

DISCUSSION

This case report discusses the first head-to-head comparison between continuous cardiac monitoring using an ICM and spot-check PPG-based rhythm monitoring in a cryptogenic stroke patient. The time until AF detection in this cryptogenic stroke patient using PPG-based mHealth was equal to the ICM, the gold standard for AF monitoring. Furthermore, despite a tremendous difference in data quantity, PPG-based mHealth was able to detect paroxysmal AF with a similar AF burden as the ICM in a cryptogenic stroke patient. During the third and fourth AF episodes, only one mHealth recording was performed. Nevertheless, the duration of these episodes was very similar between ICM and mHealth. However, the most accurate estimation of AF episode duration with mHealth is expected to be achieved when performing recordings frequently and regularly.

This case exemplifies a real-world clinical application of PPG-based rhythm monitoring in the awakening mHealth era. The detection of AF after cryptogenic stroke has a tremendous impact on treatment strategy and clinical outcomes. Therefore, the ESC recommends long-term cardiac monitoring using an ICM in cryptogenic stroke and TIA patients (5). Despite the clinical evidence of ICMs as demonstrated in the CRYSTAL-AF study and the recommendations in the guidelines, the use of long-term cardiac follow-up in these patients is not yet standard of care and thus underutilized (2, 9).

Compared to ICMs, PPG-based rhythm monitoring has some advantages. It is non-invasive, less expensive, and can be used anywhere, anytime (10, 11). Furthermore, it allows context and

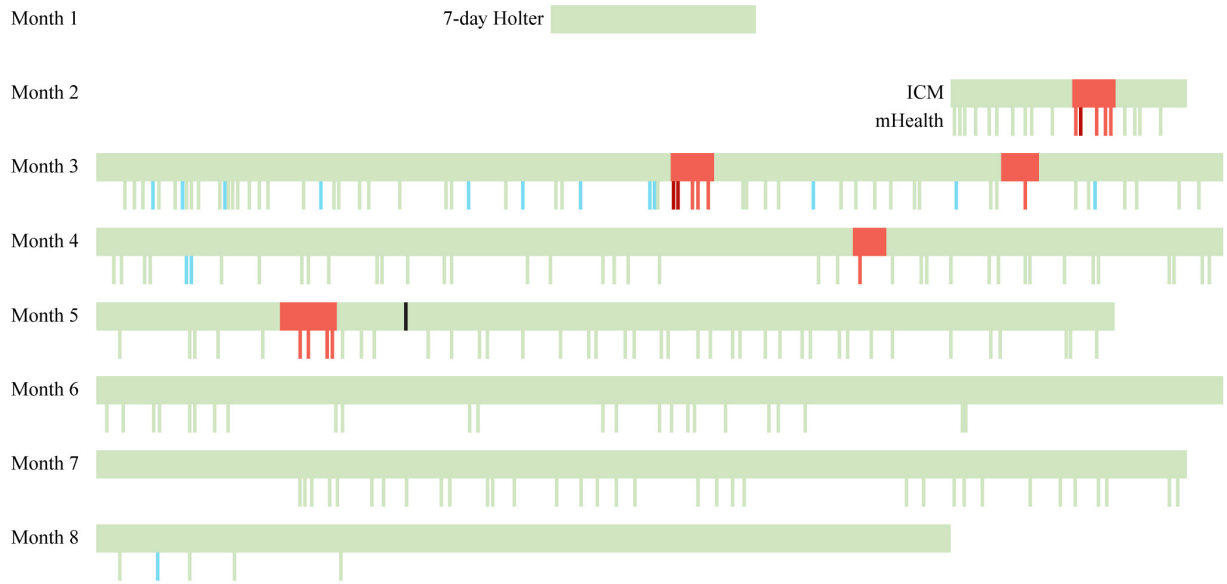

FIGURE 2 | Timeline of continuous and spot-check measurements performed by ICM and mHealth. A seven-day ECG Holter was used in the first month. At the end of the second month, the ICM was inserted, and the use of PPG-based mHealth was initiated. Green bars indicate a sinus rhythm, red bars indicate an AF episode, dark red bars indicate a symptomatic AF episode as reported in the mHealth app, blue bars indicate insufficient data quality, and the black bar indicates the ablation. ICM, insertable cardiac monitor; mHealth, mobile health.

symptom reporting by the patient (12). Moreover, it identifies AF when it lasts at least 30 s of a 1-min recording, whereas multiple ICM devices require at least 2 min of AF (9, 13, 14). More PPG-based mHealth approaches are being developed, which can pave the path toward their use in cryptogenic stroke or TIA patients' follow-up and secondary prevention (15).

In this case report, PPG-based mHealth was used on a smartphone by performing spot-check measurements. Consequently, longer AF episodes, similar to those detected in this patient, are more likely to be identified by two spot-check recordings per day. On the other hand, short AF episodes might have been missed when performing only two one-minute recordings in 24 h. Nevertheless, smartwatches can offer semi-continuous rhythm monitoring, approximating the continuous nature of ICMs (14). Further research is necessary to determine the duration of AF episodes that can be detected with spot-check or semi-continuous rhythm monitoring.

The Apple Heart Study, the Fitbit Heart Study, and the Huawei Heart Study already illustrated the potential of PPG-based rhythm monitoring using smartwatches to detect AF in a more general population. However, these studies used mHealth as a screening tool for primary prevention. As such, these studies were not performed in a cryptogenic stroke or TIA population. Moreover, a 24-h Holter or 7-day Holter was used to confirm AF. Therefore, there was only a limited time window where both PPG and ECG were used concurrently. This is in large contrast with ECG monitoring using an ICM with concurrent PPG monitoring for 6 months (16–18). In addition, spot-check recordings performed with a smartphone differ from semi-continuous rhythm monitoring performed with a smartwatch. When using a phone, the patient is stationary and aware that a measurement is being recorded. Moreover, these recordings can be performed when the patient experiences symptoms such as palpations. On the other hand, using a smartwatch, recordings are performed when the patient is performing its daily activities, resulting in data that is more prone to motion artifacts. Finally, another mHealth tool that detects AF but uses ECG instead of PPG is the AliveCor KardiaMobile. Compared with the PPG-based mHealth used in the REMOTE study, the AliveCor demonstrated equivalent diagnostic performance. However, a significant limitation of the hand-held ECG device is the necessity to purchase additional hardware (19).

Study Limitations

A limitation in this case report is blinding the PPG-based mHealth results during the study. This has two consequences. First, if the results were unblinded, a recording that is suspicious for AF might prompt the patient to perform more recordings. This could improve the estimation of the AF episode duration. Second, no action nor time to action can be attributed to the detection of AF by the mHealth tool. Furthermore, the ESC guidelines state that when AF is detected by a screening tool such as mHealth, a confirmation of AF should be obtained using an ECG recording. Therefore, this confirmation is necessary to diagnose AF, and thus, to initiate anticoagulant therapy (5). However, it could be debated that in this high-risk population (i.e., secondary prevention of cryptogenic stroke patients), AF detected by PPG-based rhythm monitoring is sufficient to start therapy. However, more research is necessary to substantiate this decision. Secondly, this case report compares the detection of AF between mHealth and ICM in only one patient, limiting the

extrapolation to the broader population. Therefore, the ongoing REMOTE study is essential to collect more data and provide more insight. Finally, short AF episodes may still be missed given the nature of intermittent monitoring using PPG-based mHealth. However, the clinical relevance of short AF episodes requires further investigation (8).

CONCLUSION

This is the first report of the cryptogenic stroke patient in whom PPG-based mHealth was able to detect occurrence and burden of paroxysmal AF episodes with similar precision as ICM. ICM is the most performant rhythm monitoring device but is expensive, invasive, and currently underutilized. This case demonstrated the feasibility of implementing PPG-based mHealth monitoring as a low-cost and non-invasive tool. The potential role of PPG-based mHealth in prolonged cardiac rhythm monitoring in cryptogenic stroke patients should be validated in larger patient population.

Patient Perspective

A questionnaire was conducted after using mHealth and indicated an equal sense of safety and reliability of both mHealth and ICM. Furthermore, the smartphone app was reported to be interesting, supportive, and easy to learn.

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 Comité Medische Ethiek, Ziekenhuis Oost-Limburg and Hasselt University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PV contributed to the diagnosis and treatment of this patient. FW collected the data, performed the statistical analysis, and drafted this manuscript. All authors read, reviewed, and edited the manuscript.

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Clinical Implications of Atrial Fibrillation Detection Using Wearable Devices in Patients With Cryptogenic Stroke (CANDLE-AF) Trial: Design and Rationale

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Background: Although many electrocardiography wearable devices have been released recently for the detection of atrial fibrillation (AF), there are few studies reporting prospective data for wearable devices compared to the strategy of the existing guidelines in the detection of atrial fibrillation (AF) after cryptogenic stroke. A tiny single-patch monitor is more convenient than a conventional Holter monitor recording device and, therefore, longer duration of monitoring may be acceptable.

Methods and Design: The CANDLE-AF study is a multicenter, prospective, randomized controlled trial. Patients with transient ischemic attack or ischemic stroke without any history of AF will be enrolled. The superiority of the 72-h single-patch monitor to standard strategy and non-inferiority of the 72-h single-patch monitor to an event-recorder-type device will be investigated. 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. The enrollment goal is a total of 600 patients, and the primary outcome is the detection of AF which continues at least 30 s during study period. The secondary outcome is the rate of changes from antiplatelet to anticoagulant and major adverse cardiac and cerebrovascular events within 1 year.

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Conclusions: The results of CANDLE-AF will clarify the role of a single-lead patch ECG for the early detection of AF in patients with acute ischemic stroke. In addition, the secondary outcome will be analyzed to determine whether more sensitive AF detection can affect the prognosis and if further device development is meaningful. (cris.nih.go.kr KCT0005592).

Keywords: atrial fibrillation, wearable device, single-lead ECG, rhythm monitoring, ischemic stroke, cryptogenic stroke

INTRODUCTION

For stroke patients, the American/European Stroke Society recommends 24–72 h rhythm monitoring for detecting atrial fibrillation (AF) as well as additional monitoring with long-term noninvasive monitors or implantable loop recorders (ILRs) if the cause of the stroke is unclear (1–4). The recently issued European Society of Cardiology 2020 AF guideline (3) recommends intensive electrocardiogram (ECG) monitoring in high-risk patients older than 75 years (Class of recommendation: IIa). ILRs can monitor the ECG rhythm 24 h a day for more than 3 years and can detect AF considerably more often than stepwise additional monitoring including 24-h Holter, which is the guideline-based standard method (12.2% vs. 2.0% and 30% vs. 3% in 12 and 36 months, respectively, after cryptogenic stroke; $n = 221$ vs. 220; $p < 0.001$) (5–7). However, because ILR insertion is an invasive procedure, not all patients receive ILR monitoring. The Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) (8) showed that early rhythm control of AF improved major clinical outcomes. Therefore, the development of a convenient, effective, noninvasive ECG monitor is valuable for diagnosing post-stroke AF.

Although the accuracy, sensitivity, and specificity of single-lead ECG recording have improved (9), few prospective studies have compared the AF-detection rates between different types of single-lead ECG recorders in patients with cryptogenic stroke. Studies such as the Apple Heart Study (10), REHEARSE-AF (REmote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation) (11), and the SCREEN-AF (SCREENing for Atrial Fibrillation) (12) proved the usefulness of single-lead ECG, their results were based on data from the general population and not data that was specifically obtained from patients with an ischemic stroke or transient ischemic attack (TIA). In 2020, a study of nurse-led monitoring during stroke (SPOT-AF) demonstrated the feasibility and efficacy of a single-lead ECG recorder for post-stroke AF detection (13). A prospective study for comparing the event recorder (2 times daily) with a 7-day Holter monitor is ongoing (14).

According to the 2020 guideline of the European Society of Cardiology (3), single-lead ECG recording using a wearable device can be used for confirming a diagnosis of AF (Class of recommendation: Ia). A recent systematic review and meta-analysis suggested a noninvasive rhythm-monitoring strategy prior to invasive monitoring (15). Against this background, we designed a trial that compares a single-lead patch to an event-type recorder and standard care, respectively. We aimed to determine whether a single-lead patch-type ECG recorder is superior to the standard methods and to ascertain the non-inferiority of single-lead ECG patch recorder to an event recorder for early detection of AF in high-risk patients who have experienced an acute stroke and, thereby, facilitate an early switch from antiplatelet to anticoagulant medication based on the findings and other clinical conditions. Consequently, in this study, we intend to 1) reveal the clinical utility of a single-lead patch ECG for AF detection in patients who have experienced acute stroke; 2) identify whether single-patch ECG monitoring has possibility to be another widely used monitoring method for the detection of AF after cryptogenic stroke; and 3) explore, as a pilot study, the effect of the difference in the detection rate of AF on the recurrence of TIA or ischemic stroke and major adverse cardiovascular and cerebrovascular events (composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death) in patients with AF after stroke.

MATERIALS AND METHODS

Trial Design

The Clinical implications of Atrial fibrillatioN Detection using a wearabLE device in patients with cryptogenic stroke (CANDLE-AF) study is a multicenter, prospective, open-label, randomized, controlled trial for detecting AF in post-stroke patients who have not been previously diagnosed with AF (reg. no. cris.nih.go.kr KCT0005592). Following the detection of AF in patients with cryptogenic stroke, we will conduct a superiority trial of single-lead patch ECG monitoring against standard monitoring and a non-inferiority trial of single-lead patch ECG monitoring against event-recorder type monitoring.

Primary Objectives

For 12 months, this trial will investigate the superiority and non-inferiority of a 3-day continuous single-lead ECG patch in the detection of AF after stroke or TIA in comparison with the conventional strategy (guideline-based group) and event-recorder type monitoring, respectively.

Secondary Objectives

In each group, we will evaluate the rate of change from antiplatelet therapy to anticoagulants following AF detection and the rate of major adverse cardiovascular or cerebrovascular events, which include all-cause mortality, stroke or TIA, and all-cause hospitalization and major adverse cardiovascular events

(composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death). As the treatment policy will be changed in accordance with the detection of AF, we will assess the change in the incidence of recurrent stroke within 6 months/12 months of the initial stroke in each group.

Study Population and Randomization

Seven tertiary hospitals with stroke units in South Korea will participate in this trial and these centers represent a full coverage of all levels of care, including state-of-art tests, monitoring, imaging equipment, the latest treatment policies of specialists, and intensive care units. All patients who first visit the department of neurology with a stroke or TIA without history of AF at the time of admission and if no AF was detected during monitoring of the hospital stay will be enrolled in this study after obtaining voluntary informed consent. In this study, by referring to the inclusion criteria used in CRYSTAL-AF (16), the minimum symptoms required for inclusion by TIA were established: speech or language deficit, weakness of an arm or leg, or hemianopsia. As an inclusion criterion, history of AF was established as a person who did not have AF at the time of admission and who had no prior AF diagnosis. A surface ECG at hospitalization will be used as the screening test to check for pre-existing AF. During the hospital stay, continuous ECG monitoring will be performed through telemonitoring. Before being discharged, all enrolled participants will be randomized to the: 1) the standard treatment group, 2) the single-lead ECG patch group, and 3) the event-recorder group. The exclusion criteria are described in **Figure 1**. We performed block randomization using random number generator function of Excel (Microsoft, USA). The randomization ratio is 1:1:1.

Two Types of Single-Lead ECG Monitors

A recently developed wearable device for the detection of arrhythmia, the adhesive single-lead ECG patch (mobiCARE-MC100 TM, Seers Technology, Seongnam-si, Gyeonggi-do, Republic of Korea), which comprises a light chest patch weighing 9.2 g without any other additional parts, allows long-term continuous ECG monitoring and is relatively more comfortable than standard Holter monitoring (**Figure 2A**). In a study comparing this single-lead patch monitor and Holter by wearing them simultaneously for 24 h, most patients did not feel discomfort with single-lead patch monitor (17). Based on these results, it is thought that the single-lead patch was more comfortable than the Holter. Monitoring is possible for up to 72 h when the patch is used once, and it is possible to continue the monitoring even when the battery has been replaced. Patients can check their ECG through a mobile phone application and the ECG will be automatically transmitted to a core laboratory. This single-lead ECG patch uses an artificial intelligence-based algorithm to systematically classify and analyze data to improve diagnostic accuracy. Furthermore, this device has an advantage in terms of signal accuracy because it has excellent ability to remove motion artifacts that may be mistaken for a heartbeat. According to a comparative study where a Holter monitor and the abovementioned single-lead ECG patch were simultaneously attached to non-arrhythmic patients, the intraclass correlation coefficients for total QRS complexes, ventricular ectopic beats, and supraventricular ectopic beats of the two devices were 0.991, 0.999, and 0.966, indicating that the performance of the two devices did not differ significantly (17).

An event recorder-type ECG device based on a smartphone (Kardia Mobile TM, Alivecor Inc., San Francisco, CA, USA) has been developed (**Figure 2B**) and can enable the patient to measure and transmit the heart rhythm for a specific number of times a day and has superior AF-detection ability when compared to routine care in non-AF patients (11). In our study, in addition to the superiority of the single-lead patch to standard monitoring, we intend to demonstrate the non-inferiority of the single-lead ECG patch type monitoring to the event-recorder type of monitoring.

The server to which the ECG is transmitted is managed by the manufacturer of each device, and access to the data is restricted to those authorized to handle the data related to patient care and this study by IRB approval. The device manufacturers had no role in the trial design, data accrual, or analysis.

ECG Monitoring

All participants will receive ECG monitoring for at least 24 h in the stroke unit and a separate 12-lead ECG recording will be performed. In a simulation study using CRYSTAL-AF trial data (18), simulated intermittent monitoring data in the 12 months after a cryptogenic stroke, although AF detection doubles at 2 months, showed that a 30-day event recorder (sensitivity of 22.8%) and a quarterly repeated 7-day Holter monitor (sensitivity of 20.8%) have the highest sensitivity among various short-term or periodic monitoring strategies. In the EMBRACE (19) trial, a study using an external loop recorder for 30 days, AF was found in 42 (14.8%) of 284 patients within 4 weeks, 21 (7.4%) patients were detected within the first week. Based on this, we thought that it would be more cost-effective to monitor only once every 3 months than to monitor 2 or 3 months respectively. On the other hand, it is unclear whether AF found in monitoring after 1 year has a causative role for index stroke (15). This is because risk factors for stroke or factors that stroke patients usually have, such as metabolic disease and old age, may be the cause of AF found by longer monitoring (20). For 1 year monitoring, it is also reasonable to try quarterly monitoring for 3, 6, 9, and 12 months. However, considering the patients', 1, 3, 6, and 12 months of monitoring were planned for 6 and 12 months. Therefore, the 3-day single-lead patch group will receive for 72 h of monitoring within 1 month and at 3, 6, and 12 months. The event-recorder group will start monitoring at 7 days after the stroke and monitoring will be repeated twice daily for 12 months. For the standard treatment group, 24-h Holter monitors as a minimum will be initially performed, and the decision to perform subsequent tests is left to the physician's choice preferably according to the latest guidelines (3, 21). Study ECG data from the standard group will be analyzed by trained physicians and the ECG data from both wearable devices will be transmitted to a cardiac core laboratory for analysis. For single-patch devices, all AFs automatically detected by the software in 72-h ECG recordings are visually supervised by experts to ensure that the AF diagnosis is accurate. In case

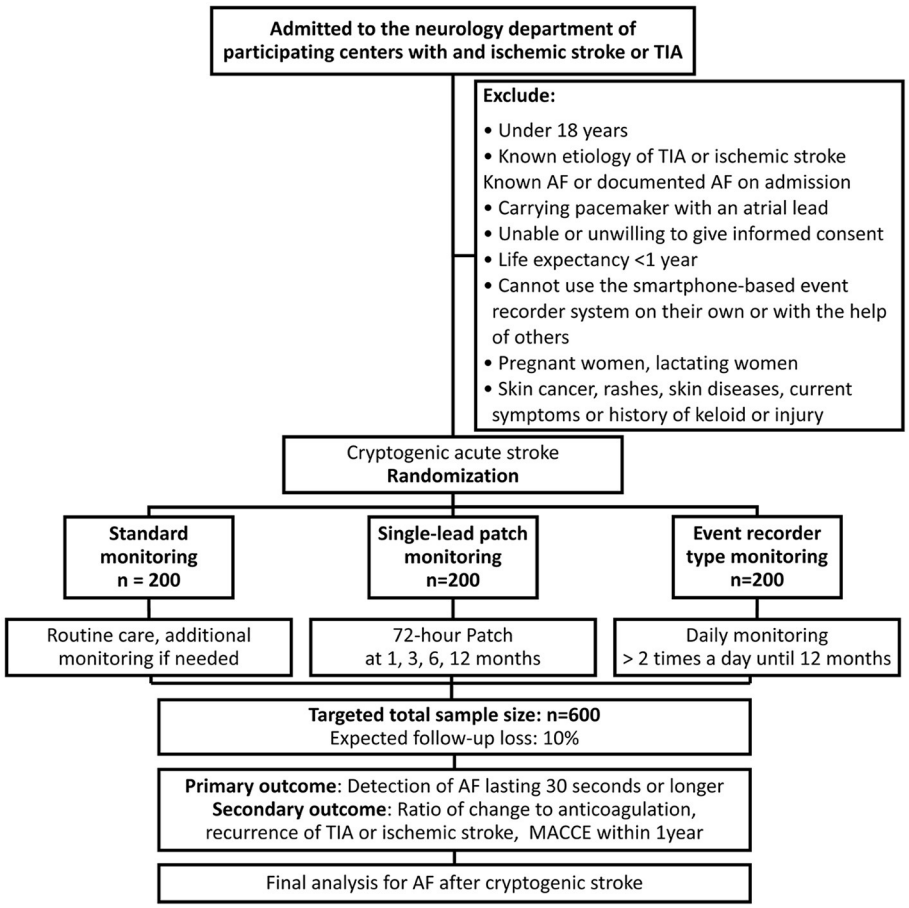

FIGURE 1 | Flow chart of the study design. AF, atrial fibrillation; TIA, transient ischemic attack; MACCE, major adverse cardiovascular and cerebrovascular events (composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death).

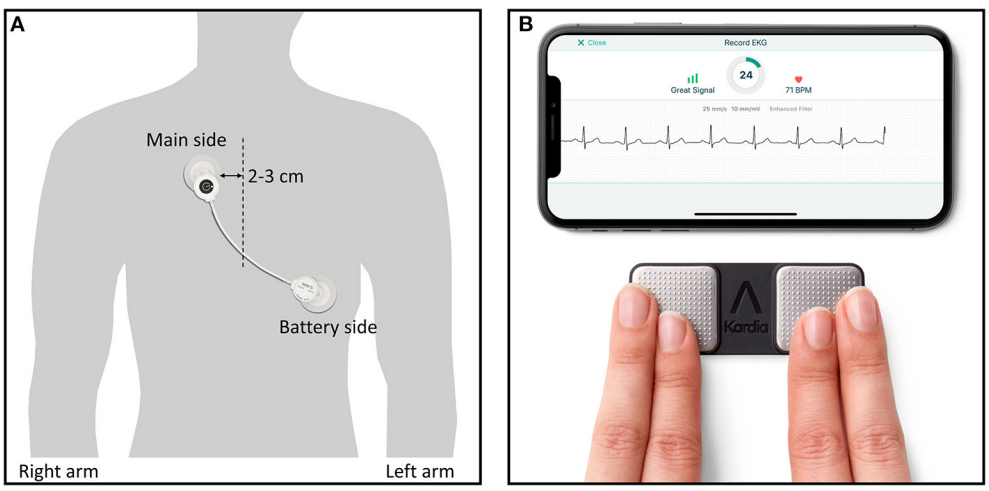

FIGURE 2 | Two types of wearable devices in this study. **(A)** Single-lead ECG monitor (mobiCARE-MC100 TM) which is attached by replaceable adhesive ECG electrodes, **(A)** Single-lead event recorder type monitor (KardiaMobile systemTM) being used with finger of right and left hand touching the respective electrode and showing sample ECG rhythm in mobile phone display. Copyright with permission from Seers Technology **(A)** and Alivecor **(B)**.

TABLE 1 | Summarization of CANDLE-AF study protocol.

	Enrollment	Hospital discharge	0 month	3 months	6 months	12 months
Standard group			On-demand additional evaluation			
Smartphone-based monitoring group	Randomization	24-h Holter	Daily 2 times of monitoring by smartphone-based monitor			
Single-lead patch monitoring group			72-h single-lead patch #1	72-h single-lead patch #1	72-h single-lead patch #1	72-h single-lead patch #1

of single-patch device, all detected AF by software automatically in 72-h ECG recordings will be visually inspected by experts to ensure that they were consistent with AF episodes. The results of the core laboratory analysis, if indicated, will be communicated telephonically to the individual participant and the patient's physician as soon as possible but no later than 3 weeks after detection by the enrolling study center. The study-specific definition of clinical AF is a recording of AF lasting 30 s or longer on an ECG, as defined in the 2020 European Society of Cardiology guideline for the diagnosis and management of AF (3) (**Table 1**).

Clinical Monitoring

For 12 months following hospitalization, the detection of AF recorded on the device, all-cause mortality, all-cause rehospitalization, and change to anticoagulation will be recorded at the outpatient visit or through a telephone call. The prevalence of stroke, cardiovascular disease, diabetes, hypertension, and heart failure will be ascertained using the International Classification of Diseases-10 code corresponding to the diagnosis in the medical record. Sex, age, and the results of general blood tests, biochemical tests, myocardial enzyme levels, echocardiography, and brain imaging tests performed during the hospitalization period will be recorded. It is intended to be used as a covariate when comparing differences in primary or secondary outcomes.

Study Duration, Interim Analyses, and Early Termination

The difference in the detection rate of AF is the primary outcome. The device-based monitoring will be stopped when AF is detected. The secondary outcome is the rate of changes from antiplatelet to anticoagulant, major adverse cardiac and cerebrovascular events (composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death), and occurrence of major bleeding (fatal or overt bleeding with a drop in hemoglobin level of at least 2 g/dL or requiring transfusion of at least 2 units packed blood cells, or critical anatomical site hemorrhage (e.g., intracranial, retroperitoneal) within 1 year. For secondary outcome, the follow-up period is 12 months. Changes in antiplatelet and anticoagulant therapy will not affect clinical study discontinuation. Monitoring and follow-up will be terminated early if a skin disease occurs due to the patch, if the patient no longer wants to participate, or if it is impossible for the patient to participate due to causes, such as hospitalization due to a serious disease or death. When discontinuation or drop-out occurs, all data of the participants that were recorded up to that time point will be used, and patient data up to the point of interruption in the intention-to-treat strategy will be used for statistical analysis. If the participant does not want their data to be used, all of their data will be discarded and not used in the statistical analysis.

Sample-Size Estimates

The sample-size calculation is based on the primary endpoint: "the detection probability for each group." The detection probability was assumed as standard treatment: 2.5%, smartphone recorder: 8.5%, single-lead device: 14.5%, based on the SPOT-AF trial (13) and a previous assessment of a simulation in the CRYSTAL-AF trial (18). Non-inferiority margin was assumed to be 2.3% conservatively based on the difference in expected detection rates between single-lead device (14.5%) and smartphone-based device (8.5%) (13, 18). First, for determining the single-lead device's superiority to standard strategy at a significance level (alpha) of 5%, power (1-beta) of 80%, and margin of 2.3%, we calculated that 108 participants are needed in each group, assuming a 10% drop-out rate. 2, to prove the single-lead monitor's non-inferiority to the event recorder with a significance level (alpha) of 5%, power (1-beta) of 80%, and margin of 2.3%, each group needs 200 patients with a 10% drop-out rate. For randomization, each group will recruit 200 participants by applying the results of the pair with the greater number of participants (**Figure 1**). The sample-size calculation was performed using the Power and Sample Size website (http://powerandsamplesize.com/Calculators/Compare-2-Proportions/2-Sample-Non-Inferiority-or-Superiority, accessed November 22, 2021). Because it is an intention-to-treat study, we plan to conduct analyzes including drop-out cases except which the subject wants to remove the data.

Statistical Analysis

The CANDLE-AF trial will use an intention-to-treat analysis that includes all participants according to randomization. It is hypothesized that, regarding the AF-detection rate, the 72-h single-patch monitoring will be superior to standard care and non-inferior to the event-recorder type of monitoring. For the baseline variables, bivariate relationships will be investigated using chi-square or Fisher's exact tests and Student's *t*-tests or Wilcoxon rank sum tests. All continuous variables will be represented as mean or median with standard deviation or interquartile range, respectively. And according to the results of the normality test performed by the Shapiro-Wilk test, the *t*-test is performed for data following the normal distribution, otherwise

the Mann-Whitney U test will be performed. Categorical and dichotomized variables will be described as percentages and analyzed using Fisher's exact test.

The primary outcome will be compared between the 72-h monitoring group and each control arm using the chi-square test or Fisher's exact tests. Unadjusted outcome effect sizes will be estimated as odds ratios with 95% confidence intervals as appropriate. In addition, for the time to the first documented AF episode during the 12-month observation period, Kaplan–Meier curves will be calculated for each arm and compared using a log-rank test. Moreover, we will compare the total major adverse cardiovascular or cerebrovascular events and the rate of change from antiplatelet to anticoagulant therapy following AF detection, as well as the incidence of recurrent strokes. All analyses will evaluate the effectiveness through multivariate analysis, taking other factors into account in a progressive model. In multivariate analysis, age, hypertension, heart failure, valvular disease, history of myocardial infarction, thyroid insufficiency, obesity, chronic obstructive pulmonary disease, chronic kidney disease, and smoking, which are known independent risk factors for Afib (22–27), are planned to be used as covariate. The Statistical Package for the Social Sciences (SPSS version 26.0, IBM SPSS Statistics, Armonk, New York, USA) will be used for statistical analyses. $P < 0.05$ will be considered statistically significant.

Current Status

The CANDLE-AF trial is planned to complete the 3-year enrollment period for the prespecified 600 participants from the 7 participating centers. The first participant was enrolled in November 2020, and∼ 100 patients were enrolled by the end of November 2021. Enrollment may be completed in late 2023, and the primary results of the CANDLE-AF trial will be available by early or mid-2024.

Ethical Conduct

The study protocol was approved by the Independent Ethics Committee of the Ewha Womans' University Mokdong Hospital, Seoul, Korea (EUMC 2020-08-004-004), and all participating centers obtained approval from their corresponding ethics committees. All study procedures comply with the principles of Good Clinical Practice and the Declaration of Helsinki. Only patients who have provided written informed consent based on sufficient explanation will be included.

DISCUSSION

Several types of ECG monitoring strategies after cryptogenic stroke have been investigated, and most studies have proved that longer monitoring has a higher AF-detection rate. Martin et al. (28) reported the results of 72-h Holter compared to 24-h Holter in cryptogenic stroke (2.50 vs. 4.30%, total $n = 1{,}135$). A German prospective randomized study with 7-day continuous ECG monitoring in a stroke unit (29) showed a detection rate of 7.69%, which is significantly greater than the 2.83% of 24-h Holter monitoring. In studies using 10-day Holter (FIND-AF trial; Finding Atrial Fibrillation in Stroke–Evaluation of Enhanced and Prolonged Holter Monitoring) (21) and a 30-day external loop recorder (EMBRACE trial) (19), the detection rates were 14% ($n = 398$) and 16.1% ($n = 572$), respectively. In the PER DIEM study (Post-Embolic Rhythm Detection with Implantable vs External Monitoring), 1-year ILR was better than 30-day ELR: 15.3% vs. 4.7% (RR 3.29) (30). Use of ILR for 3 years confirmed AF-detection rates of up to 41.4% (31).

However, the conventional Holter is uncomfortable and difficult to use for a long time, and ILRs can be used comfortably for a long time but are invasive. Then, there have been limitations to extensive long-term ECG monitoring. Moreover, a recently published large study showed that 7 days of monitoring was not long enough to make a significant difference compared to conventional strategies (standard vs. 7-day Holter until discharge in the stroke unit, 4.0% vs. 5.8%; total $n = 3\,465$) (32).

To overcome these limitations, monitoring methods for AF have undergone technological advances, and novel devices have been developed that may improve their feasibility, comfort, and cost-effectiveness. The current spectrum of devices and methods for AF involves intermittent rhythm-monitoring strategies using blood pressure monitors and handheld devices and continuous ECG recordings of variable durations through wearable, dry-electrode belts, and adhesive patches (20, 33).

The single-lead ECG patch (mobiCARE-MC100 TM) allows continuous monitoring and transmission to the core laboratory and is relatively comfortable because of the lightweight design. An event recorder-type ECG device based on a smartphone (KardiaMobile systemTM) that can measure and transmit the ECG predetermined intervals has also been developed. Each of these monitoring tools has advantages and disadvantages; however, they are more likely to detect AF compared to the conventional strategy. In patients over 65 years of age with elevated CHADS-VASc score ($\geq$ 2) without AF, REHEARSE-AF (REmote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation) (11) reported a 3.9-fold increase (3.8%, 19/500 vs. 1.0%, 5/500) in the AF detection rate by using the smartphone-based event-recorder type system twice weekly over 12 months, compared to routine care. A trial comparing event-recorder-type ECG with the standard guidelines for post-stroke patients also showed superiority for AF detection (8.5% vs. 2.8%, total $n = 588$) (34).

This trial is conducted to prove that the single-lead patch monitoring device is superior to the methods in the existing guidelines and is non-inferior to the event-recorder-type device. As a design for efficient research performance, the interval of use of single-lead patch devices was determined by referring to the period of high detection rate revealed in the previous ILR study for patients with cryptogenic stroke (6). If AF can be detected noninvasively and conveniently but sensitively, physicians could have more chances to reduce the embolic event rates and improve the prognosis of stroke patients. In addition, with this trial, we plan to monitor the patients' long-term outcomes; therefore, we expect additional information on whether more AF findings will lead to better patient outcomes. We hope to suggest better monitoring guidelines for post-stroke patients to detect more AF cases.

Recurrent TIA or ischemic stroke in 3 years showed no significant difference in the standard group and ILR group (9% vs. 11%, total $n = 441$; $p = 0.64$) (5, 6). The Find-AF-randomized trial demonstrated no significant difference in recurrent stroke at 12 months in subclinical AF patients of 10-day Holter monitoring group and control group (3.7% in 200 patients vs. 5.4% in 198 patients; $p = 0.46$) (21). As such, there have been several attempts to elucidate the relationship between the more sensitive detection of silent AF after cryptogenic stroke and the prognosis, but there were no results showing a clear difference.

Study Limitations

In this study, we will monitor AF after cryptogenic stroke using three types of devices. Although we will randomize the enrolled patients, this trial is an open-label trial because of the differences in the shape of the device and the format of the result sheet. Therefore, it is difficult to completely rule out detection bias in the diagnosis of AF detection. In addition, the follow-up will be carried out for only 1 year. Thus, the trial does not compare long-term outcomes according to differences in the detection rates of AF. If there is a significant difference in the AF-detection rates, further study will be needed to compare the long-term outcomes. Several single-lead patch ECG recording devices have been validated for AF detection, but single-lead patch device which we used in this study has not yet been validated for AF detection. Although this is a limitation of our study, we are trying to secure specificity by examining all detected AFs by experts. Another limitation is that the control arm is "usual standard treatment arm" without a structural unified diagnostic protocol and that may vary among doctors and thus may create a bias both in favor or against the suggested treatment strategy.

CONCLUSION

More frequent and longer ECG monitoring by convenient devices after stroke has the potential to be used as a non-invasive, inexpensive, and effective way to increase AF detection, which could improve the secondary prevention of recurrent stroke.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Independent Ethics Committee of the Ewha Womans' University Mokdong Hospital, Seoul, Korea (EUMC 2020-08-004-004). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JP: conceptualization. JP and SJ: methodology. SJ: writing—original draft and visualization. SJ and HL: statistical methodology. SJ, IK, D-HK, SS, YC, DW, T-JS, M-SP, YK, HN, JH, T-HK, HY, JL, SH, HW, J-KP, S-YR, CK, Y-SL, JD and JP: writing—review and editing. All authors contributed to the article and approved the submitted version and take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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High Specificity Wearable Device With Photoplethysmography and Six-Lead Electrocardiography for Atrial Fibrillation Detection Challenged by Frequent Premature Contractions: DoubleCheck-AF

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Background: Consumer smartwatches have gained attention as mobile health (mHealth) tools able to detect atrial fibrillation (AF) using photoplethysmography (PPG) or a short strip of electrocardiogram (ECG). PPG has limited accuracy due to the movement artifacts, whereas ECG cannot be used continuously, is usually displayed as a single-lead signal and is limited in asymptomatic cases.

Objective: DoubleCheck-AF is a validation study of a wrist-worn device dedicated to providing both continuous PPG-based rhythm monitoring and instant 6-lead ECG with no wires. We evaluated its ability to differentiate between AF and sinus rhythm (SR) with particular emphasis on the challenge of frequent premature beats.

Methods and Results: We performed a prospective, non-randomized study of 344 participants including 121 patients in AF. To challenge the specificity of the device two control groups were selected: 95 patients in stable SR and 128 patients in SR with frequent premature ventricular or atrial contractions (PVCs/PACs). All ECG tracings were labeled by two independent diagnosis-blinded cardiologists as "AF," "SR" or "Cannot be concluded." In case of disagreement, a third cardiologist was consulted. A simultaneously recorded ECG of Holter monitor served as a reference. It revealed a high burden of ectopy in the corresponding control group: 6.2 PVCs/PACs per minute, bigeminy/trigeminy episodes in 24.2% (31/128) and runs of ≥3 beats in 9.4% (12/128) of patients. AF detection with PPG-based algorithm, ECG of the wearable and combination of both yielded sensitivity and specificity of 94.2 and

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96.9%; 99.2 and 99.1%; 94.2 and 99.6%, respectively. All seven false-positive PPG-based cases were from the frequent PVCs/PACs group compared to none from the stable SR group ($P < 0.001$). In the majority of these cases (6/7) cardiologists were able to correct the diagnosis to SR with the help of the ECG of the device ($P = 0.012$).

Conclusions: This is the first wearable combining PPG-based AF detection algorithm for screening of AF together with an instant 6-lead ECG with no wires for manual rhythm confirmation. The system maintained high specificity despite a remarkable amount of frequent single or multiple premature contractions.

Keywords: wrist-worn device, multiple-lead portable ECG, telemedicine, mhealth, remote monitoring, digital health

INTRODUCTION

Atrial fibrillation (AF) is closely associated with an ageing population and its prevalence is expected to double by 2060 to 17.9 million in the European Union alone (1). Consequently, the burden of thromboembolic events, heart failure, bleeding and other major implications may arise. Health care resources must adapt to large-scale early diagnosis and individualized state-of-the-art treatment. To comply with it, the European Society of Cardiology upgraded the recommendation class for systematic electrocardiography (ECG) screening to detect AF in individuals aged ≥75 years, or those at high risk of stroke from 'may be considered' (class IIb) to 'should be considered' (class IIa) (2). Opportunistic screening for AF by pulse taking or ECG rhythm strip in patients ≥65 years of age remains 'recommended' (class I). The problem of insufficient examination for AF is also relevant to secondary prevention. As revealed by an international survey, in 40% of European countries only conventional ECG without long-term cardiac monitoring is the most common method to exclude AF after transient ischemic attack (3).

Accelerated by the Covid-19 pandemic (4) new wearable technologies have the potential to expand the availability of medical care (5, 6), reduce health inequities in remote areas (7) and integrate into the workflow of dedicated AF teams (8). However, clinicians need to assess the cost-effectiveness, regulatory approval, specific clinical applications, patient expectations, data logistics and other issues of each mobile health (mHealth) tool (9). As implied by the World Health Organization, the cost of finding a case (including the diagnosis and the treatment of the diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole (10). We are convinced that major real-world flaws of wearables are driven by false-positive cases, which require numerous additional resources.

In the DoubleCheck-AF study we present a wrist-worn device dedicated to providing both extensive photoplethysmography-based (PPG) rhythm monitoring and reliable decision establishment with a wearable 6-lead limb-like ECG. The aim of this paper was to evaluate whether the described system has an acceptable ability to differentiate between AF and sinus rhythm (SR) when challenged by a substantial group of patients with premature ventricular or atrial contractions (PVCs/PACs), that are often underestimated in clinical trials.

MATERIALS AND METHODS

Study Design and Recruitment

DoubleCheck-AF is a single-center, non-randomized validation study with a prospective case-control model. It was carried out in accordance with the Declaration of Helsinki. A regional bioethics committee approved the study with registration No. 158200-18/7-1052-557. All enrolled patients provided a written informed consent. The study is registered at ClinicalTrials.gov (NCT04281927).

Patients were recruited from inpatient and outpatient wards of Cardiology Department at Vilnius University Hospital Santaros Klinikos. Inclusion criteria were adult patients (18 to 99 years) with a current ECG-based diagnosis of AF, sinus rhythm (SR) or SR with frequent PVCs/PACs (at least one ectopic beat in 2 min). Subjects with a regular pulse wave despite AF (e.g., paced ventricular beats) or with other arrhythmia as well as those who refused to sign or could not give an informed consent were excluded.

Measurements

The wrist-worn device integrates two types of sensors: PPG for continuous screening of AF and on-demand 6-lead ECG with no wires for rhythm confirmation (**Figure 1**).

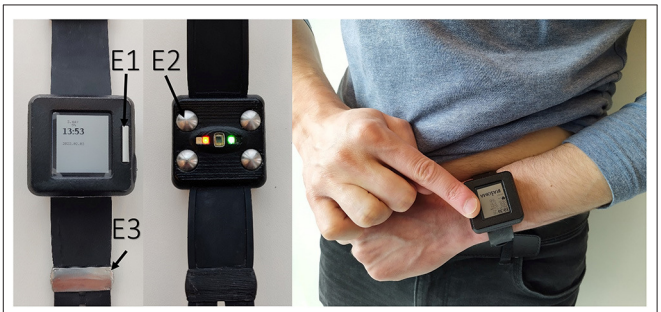

FIGURE 1 | Prototype of the wearable device (left panel); acquiring of 6-lead ECG without any wires (right panel).

The automatic PPG-based algorithm indicates whether AF is suspected as described previously (11, 12). An embedded PPG sensor uses a green light-emitting diode and a photodetector to continuously measure changes in blood flow. The algorithm relies on the analysis of peak-to-peak intervals, extracted using an adaptive threshold for peak detection. The AF detector has several solutions to reduce the false alarm rate, including filtering of ectopic beats, bigeminy suppression, sinus arrhythmia suppression and continuous signal quality assessment. The latter analyses each detected PPG pulse, identifies artifacts and enables reliable long-term monitoring for AF. The algorithm for AF detection is flexible with respect to the briefest duration of possible AF episode (12). In this study, the algorithm was tuned to detect as short AF episodes as 30 s, accounting to the clinical definition of the minimal duration of paroxysmal AF. Therefore, the PPG-based algorithm triggers the AF alarm after an average duration of 30 s in AF if the condition of sufficient signal quality index is met (11). It should be noted that the duration from the onset of AF to the alarm may vary depending on the heart rate irregularity. That is, the alarm can be triggered as soon as after 5 s in case of highly irregular AF, but no later than after 1 min in case of AF with very low irregularity of heartbeats. Once the PPG-based algorithm detects a possible AF episode, it triggers a vibration alarm for the user.

Following the alarm notification, a wearable 6-lead ECG is acquired (**Figure 2**). During our study, even if no notification occurred in at least 1 min of wearing it, an ECG was recorded as well to confirm the rhythm and investigate the method.

The device has three electrodes: two on the outer surface and one on the inner surface next to the PPG sensor (**Figure 1**). The wearable ECG was recorded by touching one electrode on the upper surface with the right index finger and holding another electrode on the left upper abdomen under the rib cage (**Figure 1**). In this way, the Einthoven leads I and II were measured. The lead III was calculated according to Kirchhoff's law. Goldberger augmented limb leads aVR, aVL and aVF were also calculated from the measured leads. ECG strips were registered at the intervals of contact between the electrodes and the patient's body. The sudden drop in bioimpedance recorded in a separate channel helped to detect ECG recording events in the continuous multichannel signal. All signals were recorded in a file within the internal memory of the device using a secure GDF (General Data Format) (13). Manual ECG rhythm assessment was performed using dedicated software based on the presence or absence of P-waves and the regularity of QRS complexes.

Diagnostic measures of both PPG-based and wearable ECG-based AF detection methods were calculated separately. Alternatively, the methods were also evaluated together as a "double-check" system for detection of AF. In the latter strategy an embedded PPG-based detector ensures continuous monitoring for AF episodes. If it suspects AF and alarms the patient, only then a matched wearable 6-lead ECG is included in further data analysis for diagnosis confirmation. Such approach does not correct false-negative cases of the PPG algorithm, i.e., sensitivity, but may add great value in reducing the number of false-positive cases of the PPG algorithm, i.e., improving specificity.

All participants used the wearable to record at least a total of 2 min of PPG and 2 min of 6-lead standard-limb-like ECG. In addition, each subject was simultaneously monitored with a validated ECG Holter monitor (eMotion Faros, Kuopio, Finland), which recorded a continuous 3-lead ECG. The ECG of Holter monitor served as a gold standard test for cardiologists to verify the heart rhythm and provide a comparable reference to the PPG-based algorithm and wearable 6-lead ECG of the studied device.

Data Analysis

Two independent diagnosis-blinded cardiologists labeled all ECG tracings as "AF," "SR" or "Cannot be concluded." In case of disagreement, a third diagnosis-blinded cardiologist was consulted. The ECG tracings of the studied device and the gold standard Holter have a different number of leads (I, II, III, aVR, aVL, aVF – like vs. three leads, respectively). Therefore, they were presented to cardiologists as separate data sets rather than merged into one. Continuous variables were reported as mean with standard deviation or median with interquartile range. Categorical variables were presented as counts and percentages. For diagnostic performance evaluation we applied standard measures such as sensitivity, specificity, accuracy, positive likelihood ratio and negative likelihood ratio. Due to the great dependence on the prevalence of disease, positive or negative predictive values 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 $\geq$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 results of investigated diagnostic methods and reference. Data was processed using the statistical package for the social sciences (27.0, SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 435 patients were assessed for eligibility in a single center between March 2019 and September 2019. As presented in detail (**Figure 3**), we excluded 15 subjects due to logistical errors (duplicates or missing data files). After the initial analysis of PPG tracings, 8 patients were excluded due to missing PPG signals and 13 due to insufficient PPG quality. Regarding the wearable ECG method, we excluded 11 subjects due to missing ECG signals and 43 due to insufficient ECG quality. One patient was excluded due to typical atrial flutter instead of AF. Therefore, the final sample size constituted 344 patients. Our analysis included 121 patients with AF, predominantly paroxysmal, 95 patients with stable SR and 128 patients with SR and frequent premature contractions (**Table 1**). The latter group consisted of individuals with dominant PVCs ($n = 88$) or PACs ($n = 40$). To meet a threshold for a sufficient frequency of at least one extrasystole per 2 min, a Holter ECG of validated device was thoroughly examined. The real burden of PVCs/PACs exceeded the threshold to a large extent and comprised a median of 6.2 (16.1–2.8) premature beats per minute. Importantly, almost a quarter of this group (31/128, 24.2%) had episodes of bigeminy

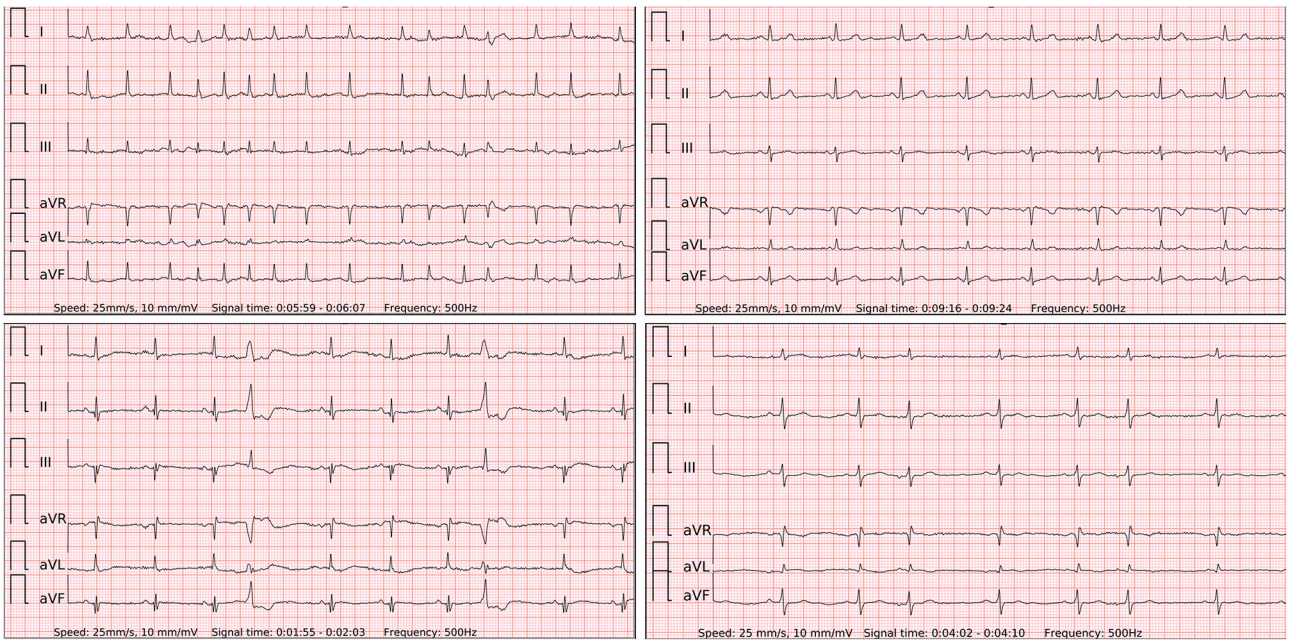

FIGURE 2 | The 6-lead ECGs recorded by the wearable device with the examples of atrial fibrillation (top left panel); stable sinus rhythm (SR) (top right panel); SR with frequent premature ventricular contractions (lower left panel); SR with frequent premature atrial contractions (lower right panel).

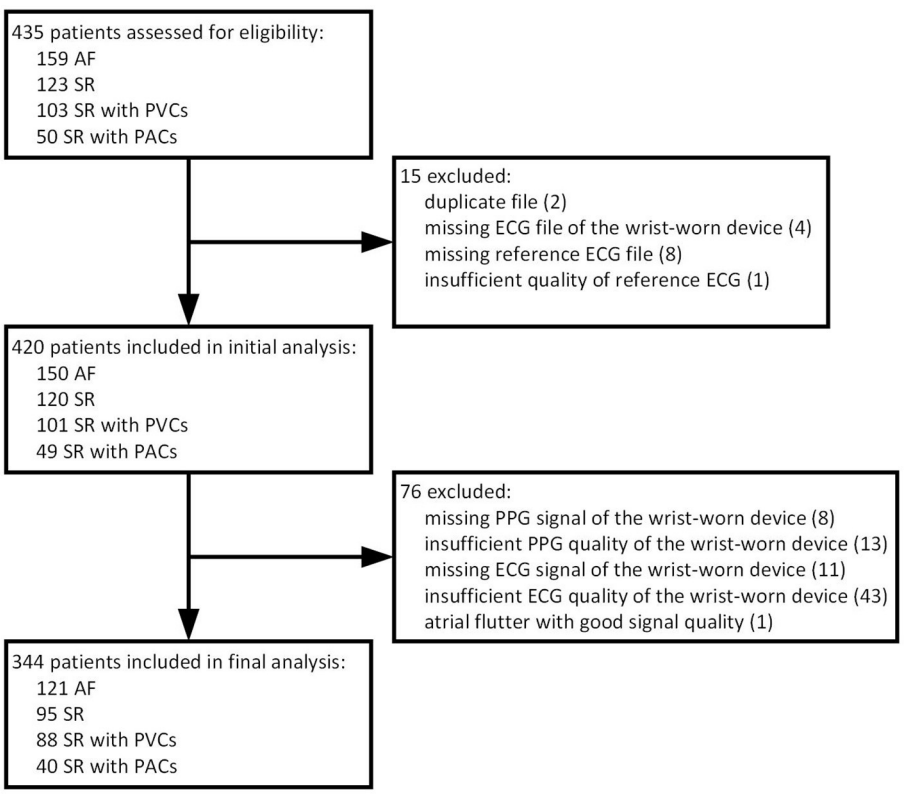

FIGURE 3 | Flow chart of patients. AF, atrial fibrillation; SR, sinus rhythm; PVC, premature ventricular contraction; PAC, premature atrial contraction; ECG, electrocardiography; PPG, photoplethysmography.

TABLE 1 | Baseline characteristics.

Characteristic	AF ($n = 121$)	Stable SR ($n = 95$)	SR with frequent premature contractions ($n = 128$)
Age (yrs.), mean ± SD	65.6 ± 11.2	64.0 ± 13.8	67.3 ± 14.2
Male, *n* (%)	64 (52.9)	55 (57.9)	69 (53.9)
Paroxysmal: persistent: Permanent AF	101:14:6	NA	NA
Type and frequency of premature contractions			
Dominant PVC: dominant PAC type	NA	NA	88:40
Cases with frequent runs of ≥3 PACs/ PVCs, *n* (%)	0 (0)	0 (0)	12 (9.4)
Cases with frequent bigeminy/ trigeminy episodes, *n* (%)	0 (0)	0 (0)	31 (24.2)
PVCs, median beats/min (IQR)	<0.5	<0.5	6.7 (16.4–2.6)
PACs, median beats/min (IQR)	<0.5	<0.5	5.5 (14.6–2.9)
Total, median beats/min (IQR)	<0.5	<0.5	6.2 (16.1–2.8)
$CHADS_2VASc$ risk score (categorical)			
0–1, *n* (%)	37 (30.6)	4 (18.2)[a]	1 (3.2)[b]
2–4, *n* (%)	64 (52.9)	14 (63.6)[a]	21 (67.7)[b]
≥5, *n* (%)	20 (16.5)	4 (18.2)[a]	9 (29)[b]
$CHADS_2VASc$ risk score (quantitative), mean ± SD	2.7 ± 1.7	3.1 ± 1.4[a]	3.8 ± 1.7[b]
HAS-BLED score, mean ± SD	0.9 ± 0.8	0.8 ± 0.6[a]	1.4 ± 1.0[b]
OAC, *n* (%)	91 (75.2)	19 (20)	23 (18)
DOAC, *n* (%)	67 (55.4)	15 (15.8)	15 (11.7)
Warfarin, *n* (%)	23 (19)	4 (4.2)	8 (6.3)
LMWH, *n* (%)	1 (0.8)	0 (0)	0 (0)

[a]*Calculated for patients with a history of AF, thus the denominator is 22.* [b]*Calculated for patients with a history of AF, thus the denominator is 31. 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.*

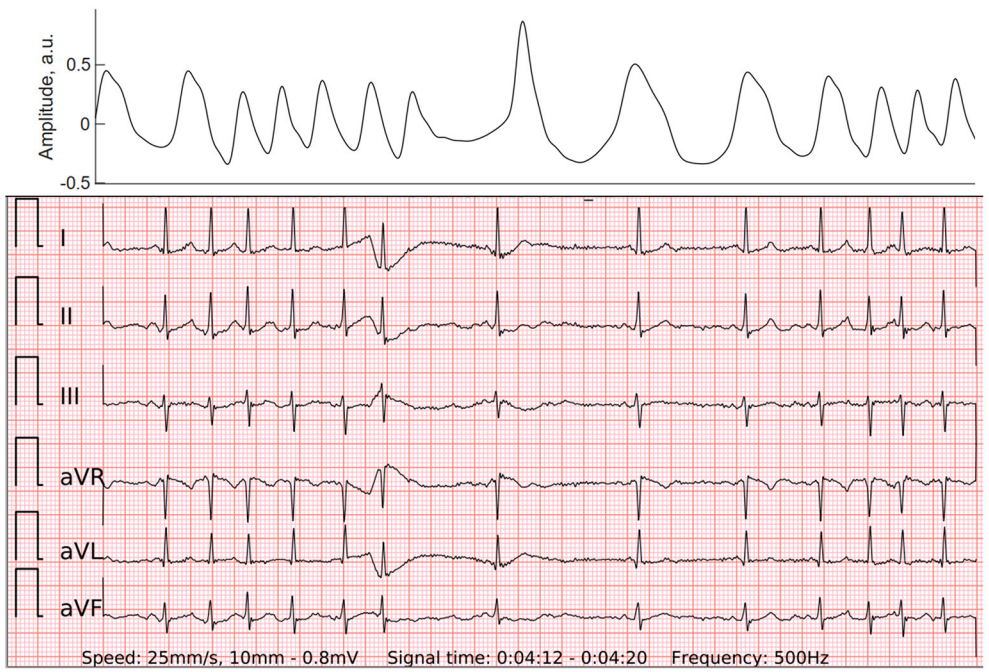

FIGURE 4 | PPG (top panel) and wearable 6-lead ECG (lower panel) of the atrial run, which may also be called "micro-AF". By definition, it is a sudden onset of irregular tachycardia with episodes of ≥5 consecutive supraventricular beats and total absence of P-waves, lasting less than 30 s (16).

TABLE 2 | Diagnostic measures of automated PPG-based algorithm for AF detection.

Measure	AF vs. stable SR group ($n = 216$)	AF vs. both SR groups including frequent PVCs/PACs ($n = 344$)
Sensitivity (%), (95% CI)	94.2 (88.4–97.6)	94.2 (88.4–97.6)
Specificity (%), (95% CI)	100 (96.2–100)	96.9 (93.6–98.7)
Accuracy (%), (95% CI)	99.9 (98.2–100)	96.8 (94.4–98.4)
LR (+), (95% CI)	-	30.01 (14.46–62.31)
LR (-), (95% CI)	0.06 (0.03–0.12)	0.06 (0.03–0.12)

AF, atrial fibrillation; SR, sinus rhythm; PVC, premature ventricular contraction; PAC, premature atrial contraction; LR (+), positive likelihood ratio; LR (-), negative likelihood ratio.

or trigeminy and almost a one-tenth (12/128, 9.4%) had runs of ≥3 PACs/PVCs which were often irregular (**Figure 4**). The mentioned arrhythmogenicity parameters reflect the significant pressure we have put on both the PPG algorithm and the ECG of the device to differentiate between SR and AF.

Performance of the Automated PPG-Based Algorithm of the Device for AF Detection

The total duration of the PPG recordings of 344 individuals was 8933.8 min, averaging 26.0 ± 29.9 min per patient. The PPG-based detector embedded in the wrist-worn device analyzed the rhythm and successfully detected AF with a sensitivity of 94.2%, specificity of 100% and accuracy of 99.9% when AF was compared to the stable SR group (**Table 2**). In addition, if we included patients with frequent PVCs/PACs into the control group, it resulted in seven false-positive cases (three due to frequent PVCs and four due to frequent PACs) compared to none in stable SR group ($P < 0.001$). Consequently, sensitivity, specificity, and accuracy dropped to 94.2, 96.9, and 96.8%, respectively. As anticipated, the median of premature beats per minute in our false-positive cases of the PPG-based algorithm reached 13.2 (IQR 41.2–10), ($n = 7$) and tended to be higher compared to the burden of ectopy in the rest of cases in the group of SR with frequent PVCs/PACs, which comprised 5.6 (IQR 16–2.5), ($n = 121$) ($P = 0.053$) (**Figure 5**). In contrast, among false-positive cases subgroup none of the patients had bigeminy/trigeminy episodes (0 of 7, $P = 0.124$) and only a minority had frequent runs of ≥3 PACs/PVCs (2 of 7, $P = 0.073$).

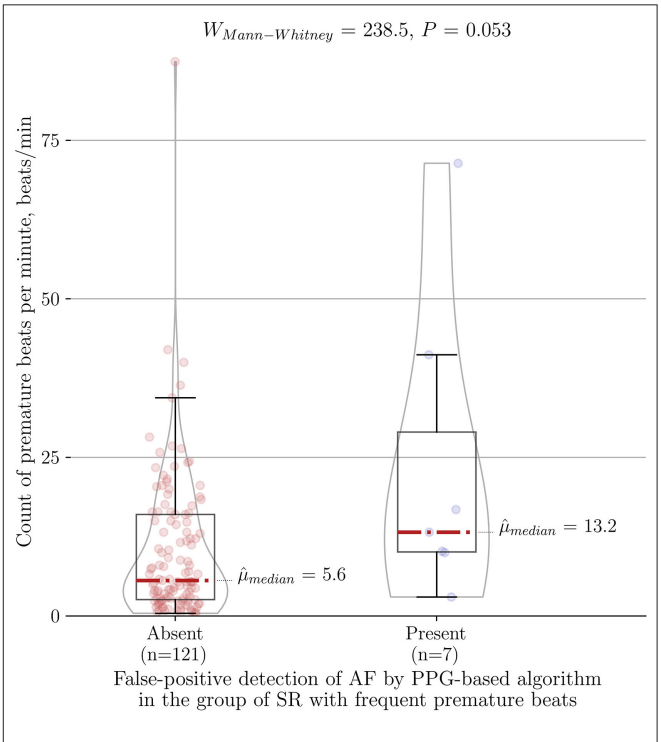

FIGURE 5 | Association between count of premature beats per minute and type I error of the PPG-based algorithm for AF detection in the control group of SR with frequent premature beats ($n = 128$). PPG, photoplethysmography; AF, atrial fibrillation; SR, sinus rhythm.

Performance of the 6-Lead-ECG of the Device for AF Detection When Assessed by Independent Cardiologists

When three diagnosis-blinded cardiologists assessed wearable ECG recordings ($n = 344$), three of them were classified as "Cannot be concluded" ($n = 3$). The rest of the tracings ($n = 341$) yielded a sensitivity of 99.2%, a specificity of 100% and an accuracy of 100% when comparing the AF group vs. the stable SR group (**Table 3**). Extending the control group with all SR patients including frequent PVCs/PACs led to a sensitivity of 99.2, a specificity of 99.1, and an accuracy of 99.1%. Similarly to PPG-based AF detection results, the group of SR with frequent premature contractions here added two false-positive cases and thus slightly decreased the specificity. However, the difference of type I error due to inclusion of patients with frequent PVCs/PACs was not significant compared to the stable SR group ($P = 0.065$).

Performance of the Integrated System of the PPG-Based Algorithm and the 6-Lead-ECG of the Device for AF Detection

The model of integrated "double-check" system with both methods together, as described in the measurements section, yielded a sensitivity of 94.2, a specificity of 100, and an accuracy of 99.9% when differentiating between AF vs. stable SR (**Table 4**). Furthermore, comparing AF vs. all patients with SR including frequent PVCs/PACs led to a sensitivity of 94.2, a specificity of 99.6% and an accuracy of 99.5%. Of seven initially false-positive cases by the PPG-based algorithm, the diagnosis-blinded

TABLE 3 | Diagnostic measures of the 6-lead ECG of the device for the detection of AF.

Measure	AF vs. stable SR group ($n = 214$)	AF vs. both SR groups including frequent PVCs/PACs ($n = 341$)
Sensitivity (%), (95% CI)	99.2 (95.4–100)	99.2 (95.4–100)
Specificity (%), (95% CI)	100 (96.2–100)	99.1 (96.8–99.9)
Accuracy (%), (95% CI)	100 (-)	99.1 (97.4–99.8)
LR (+), (95% CI)	-	110.07 (27.70–437.41)
LR (-), (95% CI)	0.01 (0.00–0.06)	0.01 (0.00–0.06)

AF, atrial fibrillation; SR, sinus rhythm; PVC, premature ventricular contraction; PAC, premature atrial contraction; LR (+), positive likelihood ratio; LR (-), negative likelihood ratio.

TABLE 4 | Diagnostic measures of the system combining monitoring with an automated PPG-based algorithm together with the 6-lead wearable ECG confirmation.

Measure	AF vs. stable SR group ($n = 216$)	AF vs. both SR groups including frequent PVCs/PACs (n 344)
Sensitivity (%), (95% CI)	94.2 (88.4–97.6)	94.2 (88.4–97.6)
Specificity (%), (95% CI)	100 (96.2–100)	99.6 (97.5–100)
Accuracy (%), (95% CI)	99.9 (98.2–100)	99.5 (98.0–100)
LR (+), (95% CI)	-	210.10 (29.71–1485.76)
LR (-), (95% CI)	0.06 (0.03–0.12)	0.06 (0.03–0.12)

AF, atrial fibrillation; SR, sinus rhythm; PVC, premature ventricular contraction; PAC, premature atrial contraction; LR (+), positive likelihood ratio; LR (-), negative likelihood ratio.

cardiologists were able to correct the diagnosis to SR in six of them ($P = 0.012$). The system of both methods demonstrated a high Cramer's V association (0.949, $P < 0.001$) (**Figure 6**).

DISCUSSION

To our knowledge, this is the first study of a wearable that offers a combination of continuous PPG for screening of AF together with the possibility of recording an intermittent 6-lead standard-limb-like ECG without any wires for rhythm confirmation by a physician. The authors evaluated the performance of the device with particular emphasis on the challenge of ectopic contractions that is often underestimated. Frequent premature beats reduced the specificity of the PPG algorithm and should be routinely considered when realistically evaluating emerging mHealth technologies. Furthermore, the 6-lead ECG with high sensitivity and specificity despite frequent ectopic contractions added great value to reduce type I errors of the PPG-based algorithm and integrate into one system of both methods.

Impact of Premature Contractions on the PPG-Based Algorithm for AF Detection

The PPG-based AF detection algorithms are increasingly used in wearables and apps. However, there is a lack of device validation studies that comprehensively test the algorithms on patients with frequent premature contractions. Choosing a stable SR control group underrepresents real-world settings. Subsequently, some physicians express a low trust in the specificity of wearables in daily practice. It may contribute to denying reimbursement of wearable diagnostics, reported in a recent survey by as much as 36% (194/539) of respondents worldwide (14). Therefore, we dedicated a distinct control group and reported a comprehensive analysis of premature contractions as beats per minute, cases with frequent runs of PACs/PVCs or bigeminy/trigeminy episodes. To compare different technologies and acquire reproducible results such standard of reporting is highly needed. One of our key findings is that frequent PVCs/PACs reduce the specificity of the PPG-based AF detection algorithm as all seven false-positive cases were from this group in contrast to none from the stable SR group. The authors further investigated what qualitative and quantitative characteristics of premature beats were associated with type I error of the PPG-based algorithm. Interestingly, cases with bigeminy/trigeminy episodes as well as frequent runs of $\geq$3 PACs/PVCs did not reduce the diagnostic accuracy of the algorithm. Such finding could be explained by a dedicated bigeminy suppression in the algorithm. However, a type I error of the PPG-based algorithm had a tendency to be associated with a higher burden of premature beats per minute (**Figure 5**).

Frequent premature contractions seem to be a specificity lowering factor for Apple Watch PPG-based notification for irregular rhythm detection. A recent substudy of participants with an irregular pulse notification on the Apple Watch and no AF observed on ECG patch revealed other atrial or ventricular arrhythmias (mostly ectopic beats) in 40% of participants (15). This is important to acknowledge when applying similar PPG-based apps or devices for wide population research such as Apple Heart Study (5) or TeleCheck-AF project (4). Even if it is considered a screening measure it may potentially cause harmful effects for an individual with many PVCs/PACs, e.g., unnecessary visits, interventions, anxiety. The authors are strongly convinced that in the field of wearables with a continuous PPG algorithm for the screening of AF, specificity is of critical importance. Since an individual is unobtrusively monitored for a prolonged period

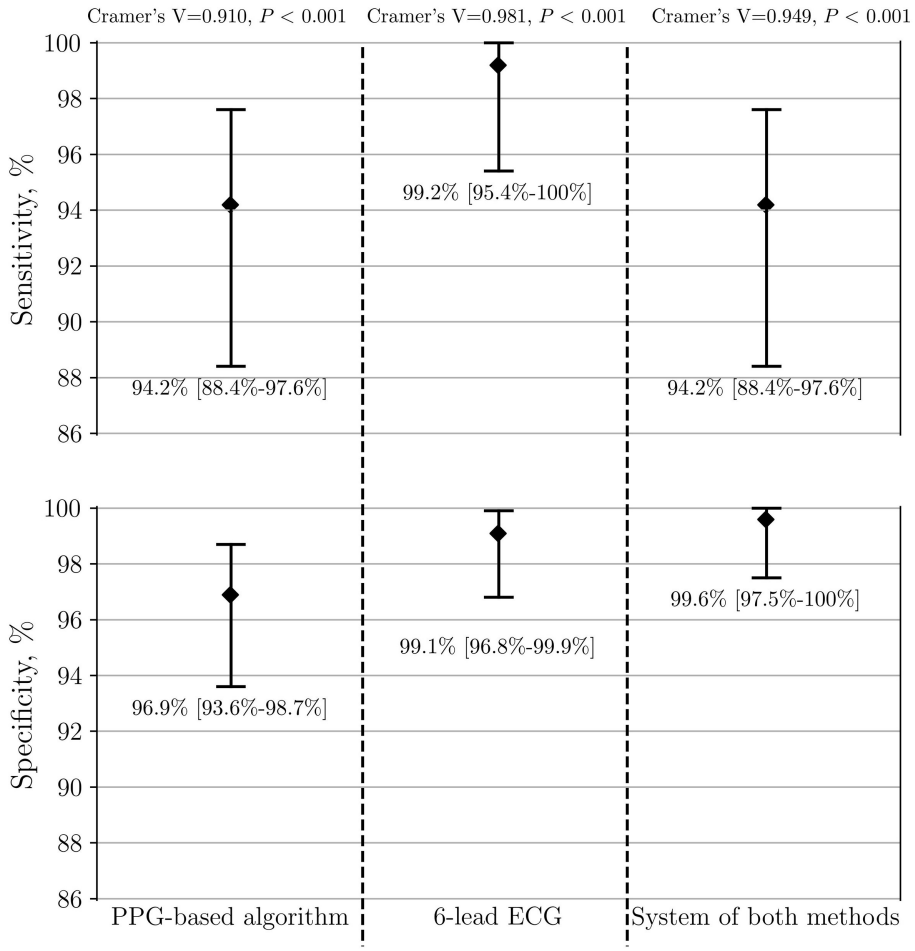

FIGURE 6 | Performance of PPG-based algorithm, 6-lead ECG and the system of both methods to detect AF ($n = 341$). The group of AF is compared to both control SR groups, including patients with frequent PVCs/PACs. PPG, photoplethysmography; ECG, electrocardiography; AF, atrial fibrillation; SR, sinus rhythm; PVC, premature ventricular contraction; PAC, premature atrial contraction.

of time, there is a high chance of arrhythmia detection and, thus, novel technologies should be in line with the principle of "first, do no harm."

Impact of Premature Contractions on the ECG of the Wearable for AF Detection

The effect of premature beats on the ECG-based AF detection was minor in our study. The 6-lead ECG of the wearable significantly reduced type I errors of the PPG-based algorithm. Both false-positive wearable ECG cases were particular tracings of SR with multiple and irregular runs of PACs. These episodes may arguably represent the initial stage of the development of AF or an undiagnosed conventional AF. The STROKESTOP study group from Karolinska Institute coined the term 'micro-AF' for this phenomenon. By definition, it is a sudden onset of irregular tachycardia with episodes of ≥5 consecutive supraventricular beats and total absence of P-waves, lasting less than 30 s (16). In a large-scale AF screening study of 7,173 individuals micro-AF was related to a higher risk of AF (HR 4.3; 95% CI 2.7–6.8) and death (HR 2.0; 95% CI 1.1–3.8) (17). Furthermore, a single false-negative case in our study presented with f-waves which occasionally organized and imitated regularly irregular P-waves. Hence it gave the diagnosis-blinded cardiologists a hard time to differentiate it from SR with PACs. Interestingly, short strips of reference Holter ECG corresponding to these two false-positive and one false-negative cases were also falsely recognized as AF and SR, respectively. Only after thorough examination of long reference Holter ECG tracings cardiologists were able to confirm the diagnosis of these challenging cases. It suggests that diagnostic measures of a 6-lead-ECG of the wearable without any wires could be non-inferior to regular 3-lead Holter ECG recordings.

Impact of Premature Contractions on Automated ECG Algorithm for AF Detection

The impact of frequent PVCs/PACs on the accuracy of automated ECG algorithms in available devices is likewise important.

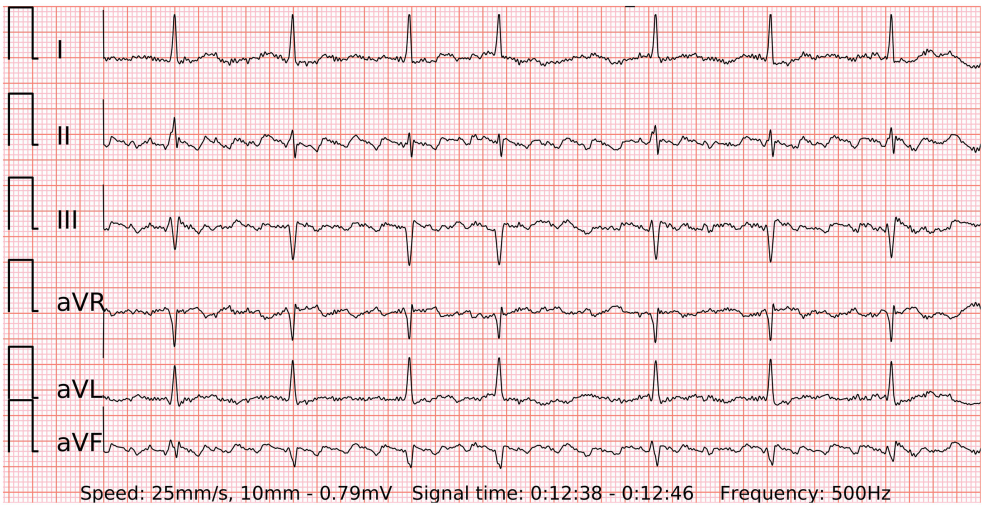

FIGURE 7 | A 6-lead ECG of typical counterclockwise atrial flutter with variable atrioventricular conduction recorded by the wearable device.

Although implantable loop recorders are considered a reliable tool for prolonged monitoring with great compliance, their algorithm for arrhythmia detection from a single-lead ECG has been reported to produce substantial numbers of false-positive results. In a prospective study of 559 participants, the incidence of false-positive transmissions was as high as 46% (201/440) for patients with AF surveillance indication for implantable loop recorder (18). Among the different categories of false-positive cases in scheduled and alert transmissions the proportion of falsely diagnosed AF was 50 and 32%, respectively. The paramount etiology of false-positive cases in alert transmissions was premature ventricular or atrial ectopy (52%). The average workload to review one false-positive transmission and make a decision after consulting electrophysiologists was estimated between 30 and 45 min.

Impact of Premature Contractions on PPG-Based Algorithm vs. ECG for AF Detection

Although the 6-lead ECG of the wearable in our study tended to perform better compared to the automatic PPG algorithm (sensitivity 99.2 vs. 94.2%, specificity 99.1 vs. 96.9%), the difference was not statistically significant as the confidence intervals overlapped. Similarly, Gruwez et al. (19) compared detection of AF from a single-lead ECG vs. PPG waveform after manual interpretation by physicians. Despite the small number of participants ($n = 30$) it was a commendably rare example of a distinguished SR group with extrasystoles. The lone PPG waveform yielded a rather small sensitivity of 88.8% and a specificity of 86.3%. Only after adding tachogram and Poincaré plot the PPG-based detection increased the sensitivity to 95.5% ($P < 0.001$) and the specificity to 92.5% ($P < 0.001$). Then it did not show any significant difference from the sensitivity and the specificity of single-lead ECG manual interpretation for the detection of AF, 91.2% ($P = 0.67$) and 93.9% ($P = 0.54$), respectively. Whether the equivalent outcome would occur after comparing the manual PPG interpretation with the 6-lead ECG of our wearable remains to be investigated. Although the PPG algorithm appears to be a suitable method for screening, current AF guidelines remain restricted to only a standard 12-lead ECG or ECG strip with AF of at least 30 s (including wearable-recorded ECGs) to establish the diagnosis by the physician (2). In our study both methods are predominantly assigned to these two different purposes, i.e., the PPG-based algorithm is assigned for screening of AF and the 6-lead ECG is assigned for rhythm confirmation. Therefore, both methods work synergistically in the wrist-worn device.

Limitations

The generalizability of this study might be limited to the involved population. As outlined in a comprehensive review (20), the accuracy and cost-effectiveness of mHealth technologies for AF detection depend greatly on given incidence, risk profile, type of AF and other characteristics. For instance, all the participants in the presented study were White. Diverse skin pigmentation may alter the results of PPG-based AF detection. Predefined groups of patients with AF and SR may hypothetically produce bias. Patients with atrial flutter were beyond the scope of this study and may present with different patterns of the pulse wave, though the wearable 6-lead ECG seems to be a promising diagnostic tool for future investigations in such subjects (**Figure 7**). A part of recordings was not analyzed due to presented reasons (**Figure 3**) and may cause additional costs or visits for the patients in real-life conditions. Furthermore, the results were derived from an analysis of short-term in-hospital recordings. Diagnostic measures of the device in outpatient settings may differ. In particular, the quality of PPG has been reported to decrease significantly during most daily activities but has a reasonably good quality for analysis during sleep (21). Therefore, it can be

anticipated that the accuracy of AF screening should be higher during the sleep state.

CONCLUSIONS

This is a validation study of the prototype of the wearable device that offers a combination of a PPG-based AF detection algorithm for the screening of AF and an instant 6-lead ECG without any wires for rhythm confirmation. The system maintained high specificity for AF detection despite a remarkable amount of frequent single or multiple premature contractions in the control group. The ability of the device to accurately detect AF in long-term screening and allow the physician to confidently diagnose the arrhythmia without further testing remains to be investigated.

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 with registration No. 158200-18/7-1052-557. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JB, AA, and VM were responsible for design and general execution of the study. JB, ZA, ED, DA, MP, JM, JS, and NB were involved in search and inclusion of patients. AK, VJ, RJ, and AS analyzed the recorded data. AS, DS, AP, MB, BP, SD, and AR implemented the algorithm and technological solutions of the device. EJ was involved in statistical analysis. JB wrote the initial manuscript. All authors reviewed and edited the manuscript.

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BRIEF RESEARCH REPORT
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The Potential and Limitations of Mobile Health and Insertable Cardiac Monitors in the Detection of Atrial Fibrillation in Cryptogenic Stroke Patients: Preliminary Results From the REMOTE Trial

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Aim: This paper presents the preliminary results from the ongoing REMOTE trial. It aims to explore the opportunities and hurdles of using insertable cardiac monitors (ICMs) and photoplethysmography-based mobile health (PPG-based mHealth) using a smartphone or smartwatch to detect atrial fibrillation (AF) in cryptogenic stroke and transient ischemic attack (TIA) patients.

Methods and Results: Cryptogenic stroke or TIA patients (n = 39) received an ICM to search for AF and were asked to use a blinded PPG-based mHealth application for 6 months simultaneously. They were randomized to smartphone or smartwatch monitoring. In total, 68,748 1-min recordings were performed using PPG-based mHealth. The number of mHealth recordings decreased significantly over time in both smartphone and smartwatch groups ($p < 0.001$ and $p = 0.002$, respectively). Insufficient signal quality was more frequently observed in smartwatch (43.3%) compared to smartphone recordings (17.8%, $p < 0.001$). However, when looking at the labeling of the mHealth recordings on a patient level, there was no significant difference in signal quality between both groups. Moreover, the use of a smartwatch resulted in significantly more 12-h periods (91.4%) that were clinically useful compared to smartphone users (84.8%) as they had at least one recording of sufficient signal quality. Simultaneously, continuous data was collected from the ICMs, resulting in approximately 6,660,000 min of data (i.e., almost a 100-fold increase compared to mHealth). The ICM algorithm detected AF and other cardiac arrhythmias in 10 and 19 patients, respectively. However, these were only confirmed after adjudication by the remote monitoring team in 1 (10%) and 5 (26.3%) patients, respectively. The confirmed AF was also detected by PPG-based mHealth.

Conclusion: Based on the preliminary observations, our paper illustrates the potential as well as the limitations of PPG-based mHealth and ICMs to detect AF in cryptogenic stroke and TIA patients in four elements: (i) mHealth was able to detect AF in a patient in which AF was confirmed on the ICM; (ii) Even state-of-the-art ICMs yielded many false-positive AF registrations; (iii) Both mHealth and ICM still require physician revision; and (iv) Blinding of the mHealth results impairs compliance and motivation.

Keywords: atrial fibrillation, cryptogenic stroke, insertable cardiac monitor (ICM), mobile health, cardiac rhythm monitoring

INTRODUCTION

Cryptogenic stroke and transient ischemic attack (TIA) patients have no determined etiology at discharge and comprise about 35% of all ischemic stroke and TIA patients (1, 2). The most important risk factor for cryptogenic stroke is sub-clinical atrial fibrillation (AF) (3, 4). AF often remains undetected due to its often paroxysmal and asymptomatic nature (5). Mortality and stroke recurrence are twice as likely to occur in AF-related strokes compared to non-AF strokes. As such, they entail a higher burden on the patient and the healthcare system (6).

The risk of stroke in AF can be considerably reduced by oral anticoagulation (OAC) (6). However, according to current guidelines, AF should be documented for at least 30 s to warrant OAC therapy initiation (7). Insertable cardiac monitors (ICMs) are subcutaneously inserted and can reliably estimate the incidence and duration of AF episodes (i.e., AF burden) for up to 3 years (8). Moreover, the CRYSTAL-AF study demonstrated the superiority of ICMs vs. no prolonged rhythm monitoring (9). However, due to its invasive nature and high cost, the state-of-the-art ICM technology remains underutilized in the follow-up of cryptogenic stroke patients (9, 10).

Rapid progress in mobile technology supported the use of mobile devices in medical and public health practice, defined as mobile health (mHealth) (11). More specifically, novel smartphone and smartwatch applications have emerged as a non-invasive, inexpensive, and reliable alternative to detect AF (12, 13). In addition, mHealth allows the patient to perform numerous measurements in daily life without medical hardware. As such, mHealth could become a useful, long-term, less invasive add-on or alternative to ICMs in the detection of AF (14). Smartphone apps are very user-friendly as no additional device is necessary to detect AF. These apps (i.e., FibriCheck® and Preventicus® Heartbeats) use the photoplethysmography (PPG) principle (i.e., optical technique that detects blood volume changes) to perform spot-check rhythm monitoring (12, 13, 15, 16). On the other hand, smartwatches can detect AF by semi-continuous rhythm monitoring in an unobtrusive way using PPG (i.e., FibriCheck® on a Fitbit®) (12, 17). Alternatively, electrodes implemented in the digital crown and back of the watch can be used to monitor the electrocardiogram (ECG) with point measurements (12). Several large companies (i.e., Apple®, Fitbit®, and Samsung®) have produced smartwatches that use both PPG and ECG (18–20). To our knowledge, PPG-based rhythm monitoring with a smartphone or smartwatch has not directly been compared to long-term continuous cardiac monitoring using an ICM in cryptogenic stroke or TIA patients. Although the digitization of healthcare was already in progress, the coronavirus 2019 (COVID-19) pandemic accelerated the shift toward mHealth and remote monitoring (21, 22). However, the ongoing REMOTE study encountered challenges still to be met. This paper elucidates the opportunities and limitations of using ICMs and PPG-based mHealth in cryptogenic stroke and TIA patients.

METHODS

This prospective, single-center, interventional, randomized trial compared the blinded use of PPG-based mHealth using a smartphone or smartwatch to guideline-recommended ICMs in cryptogenic stroke or TIA patients.

The study was started in September 2020, and the enrollment is ongoing. The protocol is in accordance with the Declaration of Helsinki and was approved by the medical ethics committees (i.e., Ziekenhuis Oost-Limburg, Genk, Belgium and Hasselt University, Hasselt, Belgium; 19/0093U). The study was registered at clinicaltrials.gov (NCT05006105).

Study Population

The data presented in this paper were collected from cryptogenic stroke and TIA patients enrolled between September 2020 and 2021. The enrollment and randomization are presented in **Figure 1**. Inclusion and exclusion criteria are presented in the **Supplementary Table 1**. Inclusion criteria were diagnosis of cryptogenic ischemic stroke or TIA, the patient or its legal representative is willing to sign the informed consent, and the patient is 18 years or older. Exclusion criteria were history of AF or atrial flutter, life expectancy of less than 1 year, not qualified for ICM insertion, indication or contraindication for permanent OAC at enrollment, untreated hyperthyroidism, myocardial infarction or coronary bypass grafting less than 1 month before stroke onset, presence of patent foramen ovale (PFO) and it is or was an indication to start OAC according to the European Stroke Organization guidelines, inclusion in another clinical trial that would affect the objectives of this study, not able to understand the Dutch language, and the patient or partner is not in possession of a smartphone.

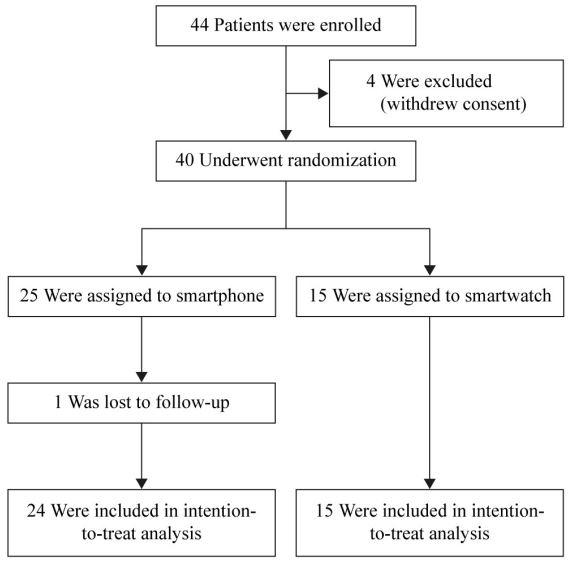

FIGURE 1 | Flowchart of enrollment and randomization. ICM, insertable cardiac monitor.

Study Design

This study aimed to compare PPG-based mHealth and ICM-derived data in cryptogenic stroke or TIA patients. Patients used the mHealth tool (i.e., FibriCheck®, Qompium NV, Hasselt, Belgium) for 6 months starting from the day of ICM insertion. The subjects were randomized in a 1:1 manner to use either a smartphone or smartwatch to perform PPG-based rhythm monitoring. Patients in the smartphone group were asked to perform 2 1-min measurements each day and in case of symptoms. Subjects in the smartwatch group were asked to continuously wear the smartwatch, which performed semi-continuous measurements (i.e., automatic recording of 1 min, every 3 min). These patients were also allowed to perform recordings using their smartphones. The adjudication of the mHealth recordings was based on the mHealth algorithm followed by a Qompium physician overreading in case of irregularities detected by the FibriCheck® algorithm. The results of the PPG-based rhythm monitoring recordings were blinded for both patient and caregiver during the study. Remote monitoring of irregularities detected by the ICM algorithm was conducted every weekday by a dedicated remote monitoring team, according to the usual clinical care. Labeling of the ICM data was performed in two steps. First, the ICM device algorithm identified episodes of heart rhythm irregularity potentially consistent with AF or other arrhythmias. Subsequently, these episodes were adjudicated by a dedicated remote monitoring team.

To determine the adherence to the protocol in the smartphone group, two parameters were specified. Compliance describes to what extent the patient performed the expected number of recordings. It was calculated as the total number of performed spot-checks divided by the total number of recommended spot-checks (i.e., two measurements each day during 180 days). Motivation gives more information about the regularity or consistency with which the recordings were performed. It was calculated as the number of days with at least two daily spot-checks divided by the number of days on which the application should be used (i.e., 180 days when a patient completed the 6-month follow-up or fewer in case follow-up was still ongoing). As there was no minimal recommended number of measurements per day for the smartwatch group, the compliance and motivation were not calculated for these patients. Therefore, the number of recordings per day was calculated.

Data Collection

Demographic and clinical characteristics of the subjects were obtained from the electronic medical record (HIX, Chipsoft, Netherlands) and the device dashboards (Biotronik, Germany; Medtronic, Ireland; Qompium, Belgium) and collected in the electronic case report form (Castor EDC, Netherlands).

Statistical Analysis

Sample size calculations were performed by CenStat (Hasselt University). Since we did not expect an increased AF detection rate by mHealth compared to ICMs, non-inferiority testing was chosen. Based on literature, we assumed an AF detection rate after 6 months of 20% and 15% by ICM and mHealth, respectively (9, 23, 24). The non-inferiority margin was set at 0.07 to achieve an improved AF detection compared to a 7-day Holter (25). Since a control method (i.e., ICM) was compared with two other methods (i.e., PPG-based mHealth on smartphone and smartwatch), a Bonferroni-correction was applied. A total sample size of 225 patients is expected to achieve 80% power, including a drop-out rate of 10%.

Data analysis was performed using the Statistical Package for Social Sciences release 28.0 (IBM® SPSS® Inc., Chicago, IL, United States). A $p < 0.05$ was considered statistically significant unless specified otherwise. The Shapiro–Wilk statistic assessed the normality of the continuous data. The continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR) when appropriate. Discrete variables are presented as absolute numbers and percentages (%). An intention-to-treat analysis was used to compare demographic and clinical characteristics between the smartphone and smartwatch groups. These analyses were performed using the Pearson's Chi-Square test, Fisher's exact test, Mann–Whitney U test, Likelihood Ratio, or independent *t*-test. The mHealth measurements were analyzed using Pearson's Chi-Square test and Fisher's exact test, based on which device was used to perform the recording. Finally, the Friedman test and *post-hoc* Sign test with Bonferroni correction applied were performed to compare the compliance, motivation, and the number of recordings performed over time.

RESULTS

Forty-four cryptogenic stroke or TIA patients were enrolled. Due to the COVID-19 pandemic, four patients withdrew consent.

One patient was lost to follow-up. Therefore, 39 subjects were considered in the analyses (**Figure 1**).

Study Population

The demographic and clinical characteristics of the included subjects are presented in **Table 1**. There were no significant differences in the demographic characteristics between the smartphone and the smartwatch groups.

Arrhythmia Detection and Annotation of Insertable Cardiac Monitors

The ICMs collected continuous data, resulting in approximately 111,000 h, or 6,660,000 min of data. The ICM algorithm detected 259 potential AF episodes in 10 different patients. After adjudication, these episodes were labeled as AF (5, 1.9%, all in 1 patient), sinus rhythm (200, 77.2%, in 8 patients), ectopic beats (40, 15.4%, in 3 patients), oversensing (1, 0.4%), or noise (2, 0.8%, in 1 patient); 11 episodes (4.3%, in 2 patients) were not labeled.

Besides AF, the ICM algorithm also identified other relevant arrhythmias such as pause (221, 7.4%), tachycardia or tachyarrhythmia (tachy, 83, 2.8%), atrial tachycardia (AT, 2,653, 88.8%), high ventricular rate (14, 0.5%), and bradycardia or bradyarrhythmia (brady, 17, 0.6%) episodes. The remote monitoring team adjudicated only 349 of these other relevant arrhythmia episodes. The labeling of the arrhythmias by the ICM device algorithm and their adjudication by the remote monitoring team as either disapproved (i.e., the algorithm-generated label was inappropriate) or confirmed (i.e., the label was appropriate) is presented per patient in **Table 2**.

TABLE 1 | Demographic and clinical characteristics.

Characteristic	Smartphone group (n = 24)	Smartwatch group (n = 15)
Age, years	63.0 ± 12.6	68.7 ± 9.3
Sex, male	19 (79.2%)	8 (53.3%)
BMI, kg/m^2	26.9 [24.3 – 29.2]	28.4 [23.9 – 30.1]
PFO	7 (29.2%)	5 (33.3%)
Index event		
Stroke	15 (62.5%)	9 (60.0%)
TIA	9 (37.5%)	6 (40.0%)
Prior stroke	0 (0.0%)	3 (20.0%)
Prior TIA	3 (12.5%)	0 (0.0%)
Score on NIH Stroke Scale*	1 [0.5 – 3]	1 [0 – 2]
Hypertension	17 (70.8%)	9 (60.0%)
Diabetes	3 (12.5%)	2 (13.3%)
Hypercholesterolemia	14 (58.3%)	7 (46.7%)
Current smoker	9 (37.5%)	3 (20.0%)
CHA_2DS_2-VASc score**	4 [3 – 5]	4 [3 – 5]
Mean time between index event and ICM insertion, days	77.5 [62.0 – 112.3]	88.0 [63.0 – 144.0]

*BMI, body mass index; ICM, insertable cardiac monitor; PFO, patent foramen ovale; TIA, transient ischemic attack. *Score on National Institutes of Health Stroke Scale ranges from 0 to 42; higher score indicates more severe neurologic deficits. **CHA_2DS_2-VASc score ranges from 0 to 9; higher score indicates an increased risk of stroke.*

Arrhythmia Detection and Annotation of mHealth

The subjects performed a total of 68,748 1-min recordings using PPG-based mHealth; 5,030 (7.3%) using a smartphone, and 63,718 (92.7%) using a smartwatch. All patients randomized to the smartwatch group also performed recordings on their smartphone, either temporary or permanent. More than half of the subjects (n = 26) reported symptoms during 350 (0.5%) recordings. The mHealth recordings were labeled sinus rhythm (n = 38,819), insufficient signal quality (n = 28,509), suspicious for AF (n = 101), or other arrhythmias (i.e., ectopic beats) (n = 1,315), presented per patient in **Table 2**. Four measurements showed no result. There was a significant difference in the mHealth recordings' labeling between the smartphone and smartwatch groups ($p < 0.001$) for all labels (i.e., sinus rhythm, insufficient signal quality, suspicious for AF, and other arrhythmias). More specifically, sinus rhythm, suspicious for AF, and other arrhythmias were more present in the smartphone group, whereas insufficient signal quality was more prevalent in smartwatch users. However, when looking at the labeling of the mHealth recordings on a patient level, there was only a significant difference for the labels suspicious for AF and other arrhythmias between both groups ($p = 0.02$ and $p < 0.001$, respectively). The patient in which AF was detected and adjudicated as such by the ICM, also performed mHealth recordings using a smartphone. These recordings were labeled as suspicious for AF.

For both smartphone and smartwatch groups, there were 4,809 periods of 12 h in which at least one measurement was performed using mHealth. In 4,133 (85.9%) of these periods, at least 1 recording had sufficient signal quality to be evaluated and was, therefore, clinically useful. There was a statistically significant difference between smartphone- and smartwatch-performed recordings ($p < 0.001$). Using a smartphone, 3,362 (84.8%) out of the 3,965 12-h periods had at least 1 measurement performed with sufficient signal quality. On the other hand, 771 (91.4%) out of the 844 12-h periods were clinically useful when using a smartwatch.

Compliance, Motivation, and Number of Measurements Performed With mHealth

The compliance and motivation of using mHealth were determined for the patients in the smartphone group. This resulted in a compliance of 60.4% ± 23.0% and a motivation of 40.6% ± 22.4%. Both compliance and motivation decreased after the 1st month ($p < 0.001$) (**Figures 2A,B**). *Post-hoc* analysis with Sign test was conducted with a Bonferroni correction applied, resulting in a significance level set at $p < 0.0033$ to compare differences between the different months.

The total monitoring duration of all patients in the smartwatch group was 1,123 days. On 357 (31.8%) days, no measurements were performed. In theory, 480 out of 1,440 min were expected

TABLE 2 | Number of patients with a cardiac arrhythmia detected by insertable cardiac monitor and labeling of the mHealth recordings per patient performed with smartphone or smartwatch.

Insertable cardiac monitor		
Label	**Disapproved**	**Confirmed**
Atrial fibrillation (*n* = 10)	9 (90.0%)	1 (10.0%)
Pause (*n* = 8)	6 (75.0%)	2 (25.0%)
Tachycardia/tachyarrhythmia (*n* = 7)	6 (85.7%)	1 (14.3%)
Atrial tachycardia (*n* = 1)	1 (100%)	0 (0.0%)
High ventricular rate (*n* = 2)	1 (50.0%)	1 (50.0%)
Bradycardia/bradyarrhythmia (*n* = 1)	0 (0.0%)	1 (100%)
Photoplethysmography-based mobile health		
Label	**Smartphone (*n* = 39)**	**Smartwatch (*n* = 15)**
Sinus rhythm	38 (97.4%)	15 (100%)
Insufficient signal quality	32 (82.1%)	14 (93.3%)
Other arrhythmias	16 (41.0%)	14 (93.3%)
Suspicious for atrial fibrillation	4 (10.3%)	6 (40.0%)

Data presented as n (%).

to be monitored using PPG-based mHealth daily. However, only a median of 19.5 [3 – 146.5] minutes per day were monitored. Due to technical issues, 6 (40.0%) patients eventually used their smartphones to perform the recordings, resulting in a reduction of performed measurements per day. As such, there was a statistically significant difference (p = 0.002) over the months in the median number of measurements performed in the smartwatch group (**Figure 2C**). *Post-hoc* analysis with Sign test was conducted with a Bonferroni correction applied, resulting in a significance level set at $p < 0.0083$. Median [IQR] number of measurements per day in month 1, 2, 3, and 4 were 57 [2 – 178], 3 [1 – 4], 2 [0 – 3], and 0 [0 – 2], respectively. There was a statistically significant reduction in the number of measurements performed in the 3rd month compared to the 1st month (p = 0.008).

DISCUSSION

This paper presents the opportunities and limitations of using PPG-based mHealth compared to ICMs in cryptogenic stroke and TIA patients.

Both Insertable Cardiac Monitor and Photoplethysmography-Based mHealth Detected Atrial Fibrillation in the Same Patient

Only five AF episodes detected by the ICM algorithm in one patient were confirmed after physician revision. The confirmed AF episodes were also detected by PPG-based mHealth on a smartphone. The number of patients in which AF was detected, is lower than expected. However, not all patients have already been monitored for 6 months. Overall, the median time between index event and ICM insertion was 81 (62 – 117) days. This is two to three times longer compared to other studies (9, 23). In real-life, this intermediate period could be bridged by using mHealth applications.

State-of-the-Art Insertable Cardiac Monitors Yield False-Positive Atrial Fibrillation Registrations, and Together With mHealth Requires Adjudication

Remarkable was the substantial proportion of false-positive AF episodes reported by the state-of-the-art ICMs. After revision by dedicated remote monitoring nurses or cardiologists, most of these retained "AF episodes" were redefined as sinus rhythm, ectopic beat, noise, or oversensing. As such, 259 AF episodes detected by the ICM had to be revised by a physician. On the other hand, 101 PPG-based mHealth recordings detected AF and could require a second revision by a physician. This was also the case for other non-AF arrhythmias selected by the ICM algorithm, likewise, often judged as inappropriately labeled. As such, 2,988 other arrhythmias were detected by the ICM and required physician revision. PPG-based mHealth detected 1,315 other arrhythmias that could demand a second revision. Consequently, ICMs require an even higher workload to revise cardiac rhythm irregularities compared to PPG-based mHealth.

Differences Between Smartphones and Smartwatches

The proportions of the different labels were significantly different between smartphone- and smartwatch-performed recordings. More arrhythmias were detected in the smartphone group compared to the smartwatch group. This might be because recordings were more often performed when patients experienced symptoms, whereas while using a smartwatch, most recordings were performed unconsciously. The most interesting finding was that insufficient signal quality was significantly more present in recordings performed with a smartwatch compared to a smartphone. This result may be explained because recordings performed with a smartwatch (i.e., passive measurements) are more sensitive to motion artifacts since patients are mostly unaware when a measurement is being recorded. In contrast, the patient has to perform a recording using a smartphone actively, and thus, is more likely to remain still during the measurement.

However, when looking at the labeling of the mHealth recordings on a patient level, there was no significant difference in signal quality between both groups. Furthermore, to establish if this would impair the physician to evaluate the heart rhythm of a patient twice daily, the number of 12-h periods with at least one recording of sufficient quality was determined. This demonstrated that the use of a smartwatch resulted in significantly more 12-h periods that were clinically useful compared to smartphone users. This is due to the increased amount of measurements performed with a smartwatch compared to a smartphone. As such, the chances of

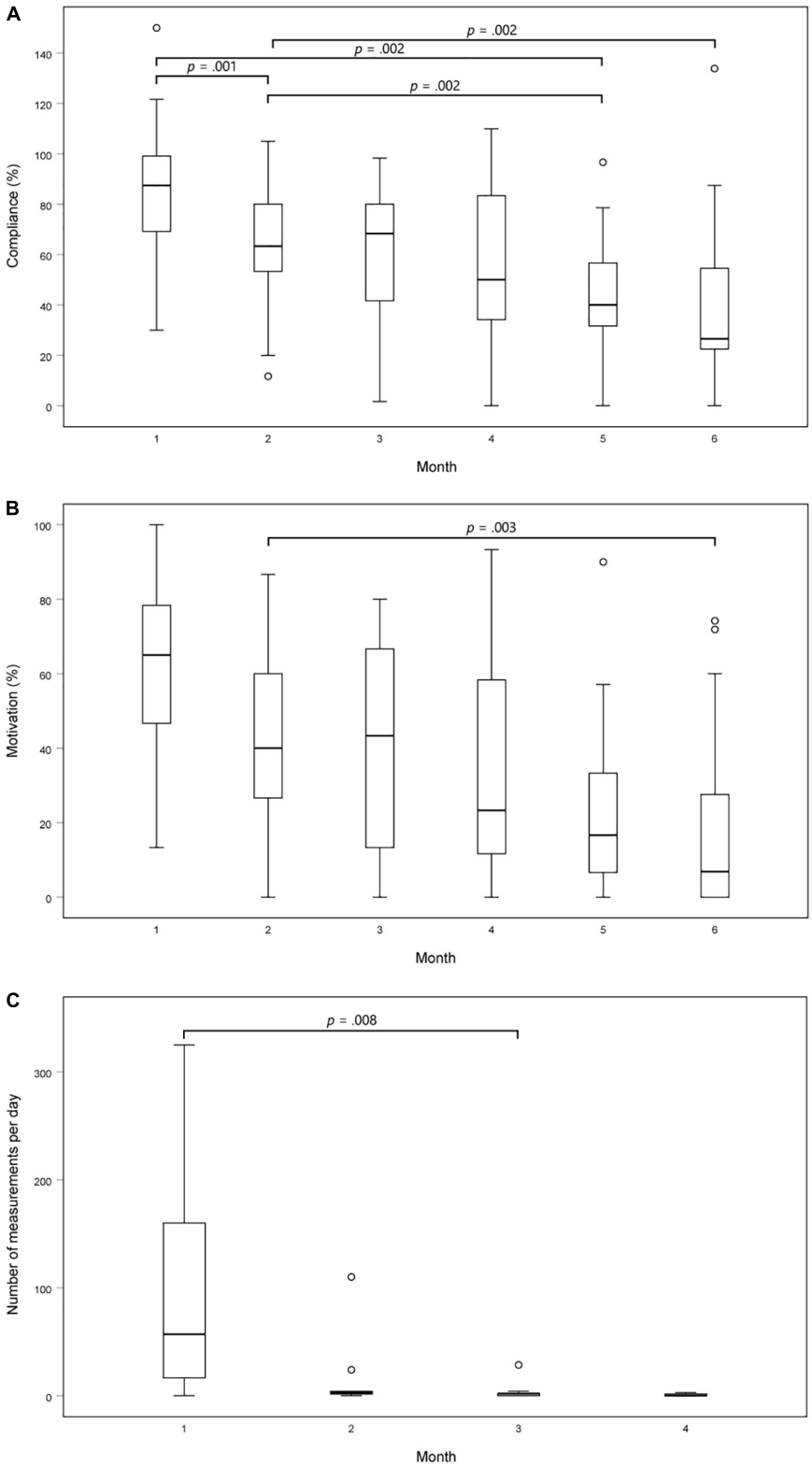

FIGURE 2 | Adherence to the protocol over time. **(A)** Compliance of using PPG-based mHealth on a smartphone over time. This was calculated as the total number of spot-checks performed divided by the total number of recommended spot-checks (i.e., two measurements each day); **(B)** Motivation of using PPG-based mHealth on a smartphone over time. This was calculated as the number of days with at least two daily spot-checks divided by the number of days on which the application should be used; **(C)** Number of recordings performed per day using mHealth on a smartwatch over time. *P*-values were calculated using a Friedman test and *post-hoc* Sign test with Bonferroni correction applied.

having at least one valuable recording are higher compared to when only two measurements are performed using a smartphone.

Blinding of the mHealth Results Impairs Compliance and Motivation

Thus far, there was limited information about long-term compliance and motivation of PPG-based mHealth prescribed in a cryptogenic stroke or TIA population. However, it has been demonstrated to generate good compliance and motivation in other populations (24, 26). Since we could not compute the compliance and motivation for the smartwatch group, this group cannot be compared with the smartphone group. However, it is noteworthy that this adherence to the protocol reduced significantly over time in both groups. Overall, patients in the smartphone group became less compliant and motivated to perform two measurements each day over time. This can be a result of the blinding of the measurements' results. Lack of feedback might impair the patient's motivation to perform two recordings daily.

Strengths and Limitations of mHealth Using a Smartwatch

The emergence of novel medical smartphone and smartwatch applications underscores the value of mHealth in a hyperconnected digital world and exemplifies the digital transformation in healthcare (13, 27, 28). The added value of PPG-based mHealth performed on smartwatches is the possibility to perform semi-continuous measurements, approximating the continuous nature of ICMs. In this study, a recording was performed automatically every 3 min. In theory, this results in 480 measurements performed each day. On average, only a mere 20 recordings were performed daily. Similar to the smartphone group, the number of measurements performed per day decreased significantly over time. This is because patients did not continuously wear the watch as it needed to recharge almost daily due to this strenuous measurement schedule. Moreover, some technical problems occurred in this group. An inactive measurement schedule caused most technical issues. Another but less prevalent technical issue was a disruption in the Bluetooth connection between the watch and the phone. As such, the recordings could not be uploaded to the cloud. Since only a limited number of recordings could be saved on the watch, this might have led to data loss.

Besides technology issues, a reduced number of measurements could also be due to the operator. In this study, cryptogenic stroke or TIA patients were included. Memory dysfunction is often present in this population (29). However, patients received daily reminders to perform recordings or wear their watch.

As a result, the number of recordings performed per day in the smartwatch group decreased considerably over time compared to what was expected. This could theoretically affect the sensitivity of the smartwatch, particularly for detecting short-lived episodes of AF in paroxysmal AF patients. Nevertheless, PPG-based mHealth used in this study was programmed to identify AF when the duration exceeds 30 s. ICMs, in contrast, require at least 2 min of AF to minimize false positives (12, 23). On the other hand, there is no consensus on the threshold of AF episode durations that are clinically relevant, especially in stroke patients (30). However, a study performed by Singer et al. confirmed the direct and transient association between AF and stroke while using an AF duration threshold of 5.5 h. Furthermore, they found that AF episodes with a duration of more than 23 h were associated with the most significant increased stroke risk (31). Therefore, two discrete mHealth spot-check recordings per day using a smartphone or smartwatch should be sufficient to detect clinically relevant AF episodes.

Study Limitations

A head-to-head comparison between PPG-based mHealth and ICMs in the detection of AF could not be described due to a limited amount of data. Therefore, these preliminary data analyses focused on detecting the different arrhythmias and their adjudication by the remote monitoring team. A limitation of this study is the blinding of the PPG-based mHealth results for both patient and caregiver. Mainly because it diminishes the compliance and motivation of patients to perform the recommended number of recordings per day. However, this was necessary to ensure that all clinical decision-making was solely based on the findings from the state-of-the-art ICMs, as recommended by current guidelines. Another limitation to the widespread implementation of mHealth is the fact that particularly smartwatch technology has not yet been widely adopted, especially not in the older population. This would require a care system in which hospitals provide a smartwatch to either bridge the period between index event and ICM insertion or replace ICMs in those who refuse to have an ICM inserted. Finally, a reduction in stroke recurrence after an optimized AF detection strategy is yet still to be demonstrated (23). However, it is known that stroke recurrence is twice as likely to occur in AF-related strokes (6). Furthermore, several studies have already suggested a decrease in stroke recurrence risk in cryptogenic stroke patients who received OAC after AF detection on ICM (9, 32). Nevertheless, there are still many unanswered questions about the clinical relevance of short AF episodes and whether using PPG-based mHealth might be sufficient to detect longer AF episodes.

CONCLUSION

This paper indicated the potential of PPG-based mHealth using smartphones and smartwatches to detect AF in a cryptogenic stroke and TIA population while presenting the constraints from both ICM and PPG-based mHealth on smartwatches. PPG-based mHealth was able to detect AF in a patient in which AF was confirmed on the ICM. However, even state-of-the-art ICMs yielded many false-positive AF registrations. Consequently, both mHealth and ICMs still require deliberation by trained nurses or cardiologists. Besides technical issues, blinded mHealth also suffered from a reduction in compliance and motivation with long-term use. More data is necessary to compare the results of both cardiac monitoring methods.

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 the Comité Medische Ethiek, Ziekenhuis Oost-Limburg, and Hasselt University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FW and DVa were involved in the data collection. FW performed the statistical analysis and drafted this manuscript. All authors read, reviewed, and edited the manuscript and contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.848914/full#supplementary-material

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