Detection and management of atrial fibrillation

DETECTION AND MANAGEMENT OF ATRIAL FIBRILLATION

STATE OF THE ART AND NOVEL APPROACHES

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CONTENTS

CHAPTER 1

General introduction

Definition and clinical features of atrial fibrillation

Atrial fibrillation (AF) is characterized by uncoordinated atrial electrical activation with consequent ineffective atrial contraction (1). AF is the most prevalent sustained cardiac arrhythmia (2), affecting more than 43 million people worldwide (1). AF is associated with morbidity such as heart failure and an increased risk of thromboembolic complications, mortality, and significantly increases burden to health care (3-12). Patients with AF are considered vulnerable and therefore monitoring of heart rate and rhythm is important and recommended to manage AF and prevent AF-related morbidity (1).

Detection and management of atrial fibrillation

Based on the current international AF guidelines of the European Society of Cardiology (ESC) (1), electrocardiogram (ECG)-documentation of an AF episode – either on a standard 12-lead ECG recording or a single/poly-lead ECG tracing of at least 30 seconds showing heart rhythm with absolutely irregular RR intervals and absence of P-waves – is required for the diagnosis of AF.

The goals of AF management are to alleviate patient symptoms, improve patient quality of life, and minimize the morbidity associated with AF such as stroke, heart failure and coronary artery disease (13-15). Therefore, the management of AF should be organized in an integrated care model (1). Integrated care is a patient-orientated approach, providing patients with coordinated and agreed personalized care and optimized treatment by an interdisciplinary team. Integrated AF management has a positive effect on the treatment burden of patients and patients' compliance to treatment (16). For integrated AF management, a comprehensive and structured approach is required based on the Atrial fibrillation Better Care (ABC) holistic pathway (17) (**Figure 1**). Adherence to the ABC pathway is associated with reduced risks of hospitalisation and clinical adverse events (18, 19). This pathway addresses three main components. The first component 'A' stands for 'avoid stroke' by optimizing stroke prevention with installing appropriate anticoagulation treatment to patients with a CHA2DS2-VASc score of ≥1 for males and ≥2 for females (17, 20). The CHA2DS2-VASc score is a validated scoring system used to estimate cardioembolic risk in patients with AF and includes the following parameters: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65-74 years and sex female (13).

The second component 'B' refers to 'better symptom management' (17). Patients with AF may have various symptoms (21-23), but its challenging to differentiate between AF-related symptoms and symptoms in AF (24). To improve symptom control, the identification of AF-related symptoms is important as it may identify patients who profit from rhythm control in regard to reduction in symptom burden. Thus, a symptom-focused management approach can help to guide personalized and joint decision making on either rate- or rhythm control.

The third component 'C' stands for 'cardiovascular and comorbidity risk reduction' (17). Part 'C' includes proactive detection and management of AF-associated risk factors and underlying concomitant diseases, such as coronary artery disease, vascular disease, hypertension, heart failure, diabetes mellitus, hyperthyroidism, obesity, chronic obstructive sleep apnoea, excessive alcohol consumption, physical inactivity, valvular heart disease, chronic pulmonary disease to prevent and smoking (25-30). Targeting these risk factors and underlying conditions as early as possible can reverse atrial remodelling and thus prevent or limit AF progression (30-37), and can improve the concomitant diseases themselves and in turn reduce strokes, symptom burden (symptoms in AF) and other cardiovascular adverse events (17, 28).

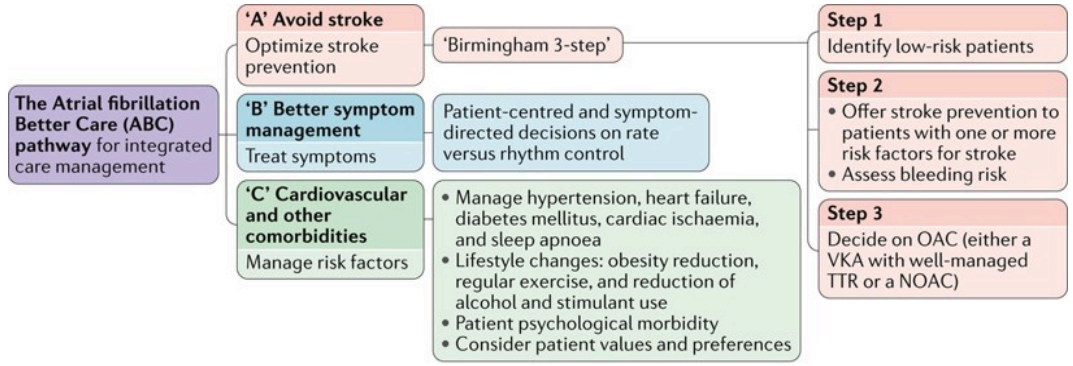

Figure 1. The Atrial fibrillation Better Care (ABC) pathway for integrated care management. *In the Birmingham 3-step for stroke prevention (38), step 1 is to identify low-risk patients (CHA2DS2-VASc score of 0 in men or 1 in women, with event rates of <1% per year) who do not require antithrombotic therapy. Step 2 is to offer stroke prevention to those with one or more risk factors for stroke. The SAMe-TT2R2 score can help to decide between a vitamin K antagonist (VKA) with good time in therapeutic range (TTR) or a non-VKA oral anticoagulant (NOAC; step 3). OAC, oral anticoagulation. Lip GYH. The ABC pathway: an integrated approach to improve AF management. Nat Rev Cardiol. 2017 Nov;14(11):627-628.*

Mobile health in atrial fibrillation detection and management

Novel mobile health (mHealth) solutions have been introduced to assist in the detection of AF as well as to support remote management of patients with AF (39-41), and the number is still growing. The use of such solutions in AF demonstrates improvements in patient behaviour, knowledge and quality of life (42). The diagnostic accuracy of mHealth devices differs with respect to the technology used. Some of the mHealth solutions use (single/poly-lead) ECGs, whereas others base their heart rhythm and rate assessment on photoplethysmography (PPG) (**Figure 2**). PPG technology is an optical technique that uses blood volume changes in the microvascular tissue bed that directly reflects pulse morphology. In PPG recordings, AF manifests as varying pulse-to-pulse intervals and pulse morphologies (43). The differences in technologies have important implications. ECG documentation, either on standard 12-lead ECG or on a single/poly-lead ECG tracing, is required to establish the diagnosis of AF (1). Although PPG technology cannot be used to confirm AF, it has an excellent accuracy to detect AF in both symptomatic and asymptomatic patients with a diagnosis of AF (44-46). Therefore, PPG technology can be of value in heart rhythm and rate assessment to support the management of patients diagnosed with AF (40).

Additionally, mHealth solutions using the same technology may collect data in different ways (intermittent vs continuous, spot vs longitudinal assessment) as well as different methods of measurement (handheld devices vs wearables vs implantable loop recorders), placement on the body and number of leads which could also influence the sensitivity and specificity for AF detection and management (**Figure 3**). Furthermore, the choice of mHealth solutions should be patient-tailored, considering clinical case, symptom frequency, expected duration of monitoring, local infrastructure, and patient's preference (47).

Clinical scenario – TeleCheck-AF project

During the coronavirus disease 2019 (COVID-19) pandemic, traditional face-to-face outpatient consultations in AF outpatient clinics were rapidly transferred into teleconsultations, which were initially conducted without any information on heart rhythm or rate of the patients. To guarantee the continuity of comprehensive AF management through teleconsultation during COVID-19, we

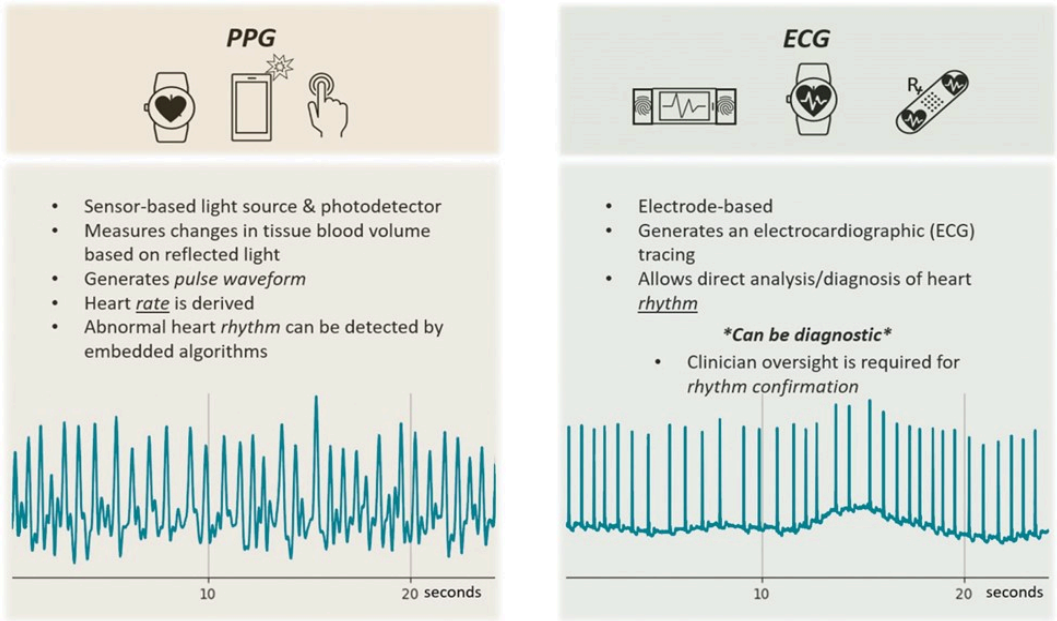

Figure 2. Comparison of photoplethysmography (PPG) vs. electrogram (ECG)-based techniques.
In the lower part of the figure an example of a registration from a patient with atrial fibrillation is shown. Svennberg E, et al. How to use digital devices to detect and manage arrhythmias: an EHRA practical guide. Europace. 2022 Jul 15;24(6):979-1005.

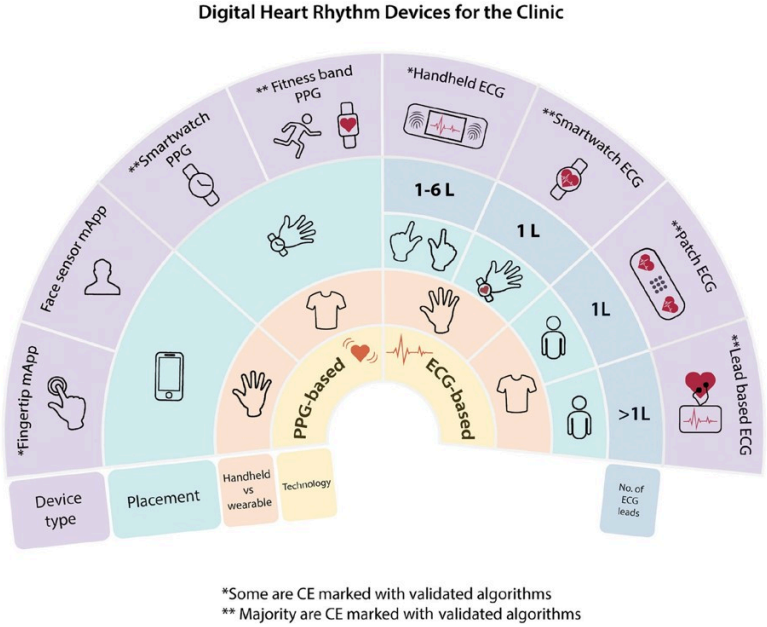

Figure 3. Overview of digital heart rhythm devices for the clinic.
Suggest reading the figure from the inner circle—devices have been divided into devices that provide photoplethysmography (PPG) or electrocardiogram (ECG), followed by the mode of handheld or wearable, and then placement on the body, number of leads, and device type. ECG, electrocardiogram; L, lead; mApp, mobile App; PPG, photoplethysmography. Svennberg E, et al. How to use digital devices to detect and manage arrhythmias: an EHRA practical guide. Europace. 2022 Jul 15;24(6):979-1005.

developed a remote on-demand mHealth infrastructure at the Maastricht Medical University Centre+ (MUMC+) to support AF teleconsultations: TeleCheck-AF. TeleCheck-AF incorporates three important components: (i) a structured teleconsultation ('Tele'); (ii) an app-based on-demand heart rhythm, rate and symptom monitoring infrastructure ('Check'); and (iii) comprehensive AF management ('AF') (48) (**Figure 4**). The TeleCheck-AF infrastructure is based on a CE-marked mobile app using PPG technology through the built-in camera allowing semi-continuous heart rhythm, rate and symptom monitoring of AF patients prior to the teleconsultation (49, 50). Patients were instructed to use the app three times per day and in case of symptoms to provide semi-continuous longitudinal information about heart rhythm, rate and symptoms. An mHealth prescription (QR-code) activates the mobile app for a limited predefined time period (usually seven days) and links the app to a secured and certified cloud accessible by the treating physician. Dependent on the clinical question and the physician preference, the using period of the mobile app can be adapted and controlled by providing respective QR-codes. The goal was to monitor hear rhythm, rate and symptoms remotely just around teleconsultations to allow a better assessment of the disease state of the patient and to support in treatment decisions (51).

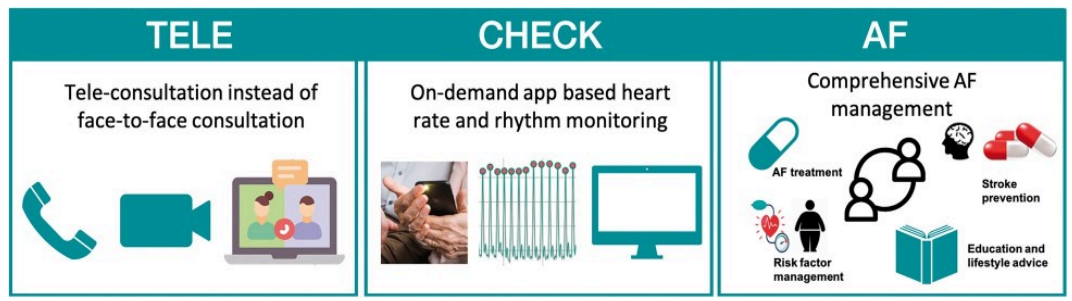

Figure 4. TeleCheck-AF steps.
Linz D, et al. TeleCheck-AF for COVID-19. Eur Heart J. 2020 Jun 1;41(21):1954-1955.

Aim and outline of this thesis

The main aim of this thesis is to evaluate the current state of art in AF detection and management as well as to develop and introduce novel AF detection and management approaches.

PART I. Atrial fibrillation detection and management: clinical challenges and gap of evidence

Part I of this thesis focuses on traditional AF detection and management and the associated clinical challenges and gaps of evidence. **Chapter 2** summarizes strategies for early AF detection and the transition to early AF management. The message generated from this review is that to allow early treatment, AF needs to be detected early and linked to a comprehensive work-up infrastructure. A detailed and structured assessment of symptoms and risk factors may help to guide this initial early management of the patients. However, the best way to assess AF-related symptoms and risk factors remains still unclear. This triggered us to investigate the association between symptoms and heart rhythm status (symptom-rhythm correlation) in patients with persistent AF, in accordance with current clinical practice using self-reported symptom reports collected during the outpatient AF clinic visits before and after electrical cardioversion (ECV). We used ECV as a diagnostic tool to evaluate symptom-rhythm correlation as it offers a before-after comparison. The results of this retrospective observational study are presented in **Chapter 3**.

PART II. Mobile health for (remote) atrial fibrillation detection and management

Part II of this thesis focuses on mHealth solutions to allow remote AF detection and management. In **Chapter 4** we discuss the importance of mHealth tools and strategies for the incorporation of

remote assessment of heart rate, rhythm and risk factors through allow comprehensive AF management through teleconsultation, particularly for patients who live remotely and far away from coordinating medical centres or during catastrophes, including coronavirus disease 2019 (COVID-19), when attendance of outpatient AF clinics or travelling to the hospital is not possible or undesirable. **Chapter 5** provides a systematic review about available mHealth solutions in AF detection and management. We noticed that the diagnostic accuracy of mHealth tools differs with respect to the type and technology used, as well as application setting, and study population. This reasoned us to investigate the utility of long-term intermittent ECG-based heart rhythm monitoring compared to short continuous ECG-based heart rhythm monitoring for the detection of AF recurrence after AF ablation, the results of this study are presented in **Chapter 6**. In **Chapter 7** we prospectively evaluate the accuracy of continuous PPG-based heart rate assessment during AF compared to continuous ECG monitoring as a reference.

PART III. Implementation and results of mobile health in atrial fibrillation detection and management

Part III describes the implementation and first results of a new mHealth infrastructure focusing on remote AF detection and management. Due to governmental restrictions and social distancing measures during the COVID-19 pandemic, face-to-face outpatient consultations were converted into teleconsultations. Although teleconsultation solutions can produce remote situations that are relatively similar to face-to-face interaction, the effective remote monitoring and management of AF patients is limited, mainly due to the absence of heart rate and rhythm information of the patient. As a response, we developed in the MUMC+ a new mHealth infrastructure to guarantee the continuity of comprehensive AF management through teleconsultation. This infrastructure is called the TeleCheck-AF approach and incorporates teleconsultations coupled with remote on-demand PPG-based heart rate and rhythm monitoring using a mobile app to allow the treating cardiologist, general practitioner or AF-nurse to comprehensively manage their AF patients through teleconsultation. **Chapter 8** describes the components and implementation of the TeleCheck-AF approach in an integrated and specialized AF clinic through teleconsultation. In **Chapter 9** we explain the coordination of the TeleCheck-AF approach and the implementation of this mHealth intervention in European centres. Subsequently, **Chapter 10** evaluates the patient motivation and adherence to this on-demand mobile app-based heart rate and rhythm monitoring infrastructure. Within the TeleCheck-AF project, we evaluate the feasibility and accuracy of a remote mobile app-based self-reported assessment of AF risk factors and CHA_2DS_2-VASc-score and those results are presented in **Chapter 11**. In addition, **Chapter 12** reports the results of a novel mobile app-based simultaneous symptom and heart rhythm monitoring approach to assess symptom-rhythm correlation, which has been developed within the TeleCheck-AF project. Finally, **Chapter 13** contains the general discussion of this thesis.

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PART I

Atrial fibrillation detection and management: clinical challenges and gap of evidence

CHAPTER 2

Early atrial fibrillation detection and the transition to comprehensive management

Linz D, Hermans A, Tieleman RG.
Europace. 2021 Apr 10;23(23 Suppl 2):ii46-ii51.

Abstract

Current atrial fibrillation (AF) guidelines recommend screening for AF in individuals above 65 years or with other characteristics suggestive of increased stroke risk. Several mobile health (mHealth) approaches are available to identify AF. Although most wearables or ECG machines include algorithms to detect AF, an ECG confirmation of AF is necessary to establish a suspected diagnosis of AF. Early detection of AF is important to allow early initiation of AF management, and early rhythm control therapy lowered risk of adverse cardiovascular outcomes among patients with early AF aged >75 or with a CHA2DS2-VASc score ≥2 and cardiovascular conditions in the EAST-AFNET 4 study. Strategies for early AF detection should be always linked to a comprehensive work-up infrastructure organized within an integrated care pathway to allow early initiation and guidance of AF treatment in newly detected AF patients. In this review article, we summarize strategies and mHealth approaches for early AF detection and the transition to early AF management including AF symptoms evaluation and assessment of AF progression as well as AF risk factors.

Keywords: Atrial fibrillation; Integrated care; Management; Mobile health; Screening.

Introduction

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder and affects 43.6 million patients across the world.1 The number of affected individuals is expected to double or triple within the next two to three decades following an increased AF incidence and ageing of European populations.2 Atrial fibrillation can be associated with significant symptoms, cognitive decline, and reduced quality of life. It doubles mortality and causes marked morbidity on a population level, even after adjustment for confounders.2

The timing of AF detection and restoration of normal sinus rhythm in AF patients can matter. Detection and treatment of AF before it becomes symptomatic can prevent the development of heart failure and stroke. Furthermore, preclinical and mechanistic clinical studies showed that AF is associated with electrophysiological and structural remodelling processes.3 A part of this remodelling process can be attributed to AF itself and AF can perpetuate its own progression to a more stable and treatment resistant disease state ('AF begets AF').4 Based on these pathophysiological considerations, early restoration of sinus rhythm should be effective in reducing the progression of AF and associated complications such as stroke, hospitalization, and heart failure.

However, several studies performed before 2002 did not show a clear reduction in the complications of AF through rhythm control, mainly by antiarrhythmic drugs, compared to rate control.5–9 Since 2002, the treatment AF catheter ablation has emerged as an important therapy for the treatment of AF. The recent EAST-AFNET 4 study revisited the question of rhythm and rate control and showed for the first time, that early rhythm control with antiarrhythmic drugs and ablation therapy in patients with early AF aged >75 or with a CHA2DS2-VASc ≥2 and cardiovascular conditions leads to a reduction in death, stroke, and cardiovascular events when compared with rate control.10

To allow early AF treatment and management, AF needs to be detected early and linked to a comprehensive work-up infrastructure. This paper focusses on strategies and mobile health (mHealth) approaches for early AF detection and the transition to early AF management including AF symptoms evaluation and assessment of AF progression as well as AF risk factors.

Early detection of atrial fibrillation

Current AF guidelines recommend screening of individuals above 65 years or with other characteristics suggestive of increased stroke risk.2 Atrial fibrillation screening in asymptomatic individuals aged <65 years with a low stroke risk is not justified, as the prevalence of AF in this population is low and the benefit of early treatment of asymptomatic AF remains unclear.11

Atrial fibrillation screening can be performed opportunistically or systematically and primary care, pharmacies, or community screening during special events may represent good settings for AF screening.2,11 In a recent meta-analysis, the efficacy of the different screening types (systematic vs. opportunistic or general practice vs. community screening) did not differ.12 More rigorous screening methods are needed and repeated rhythm assessments may be associated with significantly better effectiveness compared with single rhythm assessment.13 However, the appropriate frequency of rhythm monitoring is undefined.

For AF screening, different technologies and approaches are available: (semi-) continuous rhythm monitoring by cardiac implantable electronic devices (CIEDs), wearables (e.g. smart watches), handheld devices (e.g. AliveCor, MyDiagnostick, etc.) or app-based mHealth solutions using PPG technology through the smartphone's built-in camera (e.g. FibriCheck, Happitech, Preventicus,

etc.) have been developed and validated (Figure 1).2,14 Most of the devices and apps are CE marked and some of them are connected to secured and certified clouds, allowing remote access of the data by treating physicians or allied healthcare professionals. Importantly, based on the current international AF Guidelines of the ESC, a single-lead ECG recording of 30 s or longer or a 12-lead ECG of an AF episode is required to establish a definitive diagnosis of AF.2

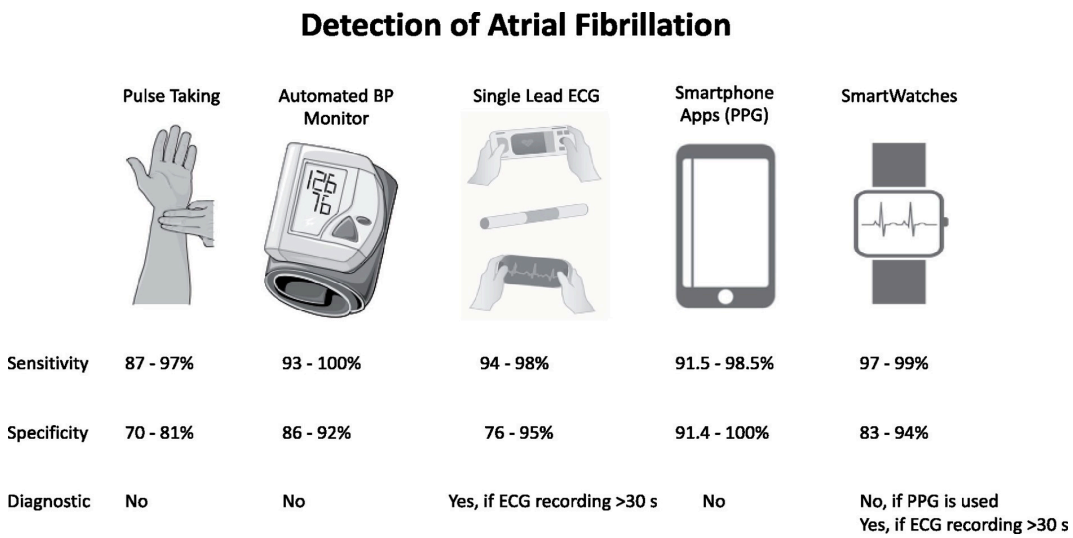

Figure 1. Technologies and approaches for atrial fibrillation screening.

Besides, there is increasing evidence for a relationship between atrial high-rate episodes (AHREs) and definitive diagnosis of AF. The ASSERT trial found that AHREs lasting >6 h have a high positive predictive value for ECG-confirmed AF.15 In addition, the ongoing NOAH-AFNET 6 trial will also provide information on the relationship between AHREs and clinically overt AF.16 Atrial high-rate episode detection suggestive for AF might therefore be used as a screening tool for AF.

Although some wearables or ECG machines include algorithms to detect AF, a standard 12-lead ECG recording or a single-lead ECG tracing of ≥30 s showing AF needs to be reviewed by a physician to establish a suspected diagnosis of AF.2 Positive screening results, which cannot be confirmed by an ECG documentation of AF, should be managed as negative screening results and no further actions are needed.

There are some large studies focusing on AF screening and the establishment of a definite AF diagnosis. In these studies, positive screening results were eventually confirmed using a less than 12-lead ECG tracing or a 12-lead ECG reviewed by an appropriately trained general practitioner or a cardiologist.12 The Apple Heart study included 419 297 self-enrolled smart-watch app users (mean age 40 years), of whom 0.5% received an irregular pulse notification (0.15% of those aged <40 years, 3.2% among those aged >65 years). Subsequent (notification-triggered) 1-week ECG patch monitoring revealed AF in 34% of monitored participants.17 The Huawei Heart study included 187 912 individuals (mean age 35 years, 86.7% male), of whom 0.23% received a 'suspected AF' notification. Of those effectively followed up, 87.0% were confirmed as having AF.18 In real life, a variety of consumer-facing wearables, devices, and apps are marketed directly to consumers to detect AF.19 However, the management of the resulting data is not defined, which complicates the clinical implementation and guidance of mHealth use by the treating physician. Additionally, widespread direct-to-consumer screening for asymptomatic AF may result in

unintended overutilization of healthcare resources owing to false-positive screening results and use of screening tools by users in whom they have not been adequately studied.20

In a recent survey of health care professionals initiated by the AF-SCREEN international collaboration, 57% of healthcare professionals advised wearables/apps for AF detection. However, the final decision to use these devices is frequently taken by the patient alone.21 The way when and how to perform measurements [(semi-) continuous vs. on-demand and ECG vs. PPG, respectively] are critically dependent on the clinical scenario and setting. As this is difficult for patients to judge, a physician-initiated or at least-guided approach appears to be necessary to allow the selection of the right tool for each patient.

Appropriate patient education and screening program organization with rapid clarification of the screening result may reduce anxiety induced by suspicion of abnormalities. Informing patients in a structured way about an AF screening event (why, when, and how to use the screening tool), may contribute to adequate collection of rhythm monitoring data [(semi-) continuous or on-demand] during such a program (Figure 2).

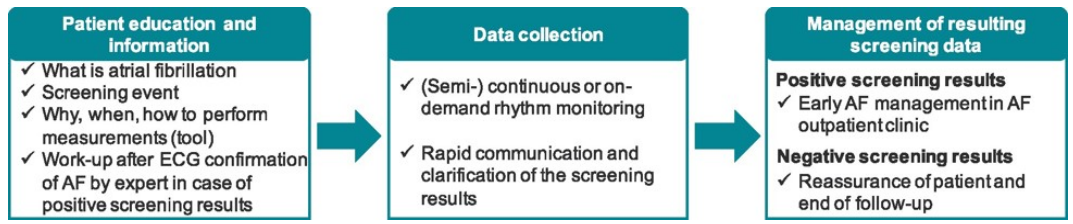

Figure 2. Organization of an atrial fibrillation screening program.
AF; atrial fibrillation

Assessment of the stage of atrial fibrillation-progression

Detection of AF within a screening program supports identification of previously unknown AF, but the screening result per se, even if confirmed by an ECG, does not inform about how long AF is already present, particularly if the patient is asymptomatic.

Early rhythm control therapy of AF to prevent the progression of AF from short-lasting self-terminating paroxysms towards more non-self-terminating sustained forms was associated with a lower risk of adverse cardiovascular outcomes than usual care among patients with early AF aged >75 or with a CHA2DS2-VASc ≥2 and cardiovascular conditions in the EAST-AFNET 4 study.10 Detailed and targeted history taking together with long-term rhythm monitoring at the time of AF diagnosis can provide a reference documentation to identify a progression of AF over time and may be useful to monitor the efficacy of rhythm control strategies. For the quantification of AF burden using semi-continuous rhythm monitoring devices, specific patient instructions about frequency and duration of monitoring are crucial to get information about AF triggers, AF burden (time spent in AF), diurnal AF patterns. Not just the way how intermittent AF-episodes initiate (trigger identification) but also the way how AF-episodes spontaneously stop (self-terminating AF) might provide helpful information about the stage of the natural time-course of AF and the underlying mechanisms in an individual patient. High AF burden indicates a more progressed disease. In patients with high or low AF burden, self-terminating short AF episodes suggest a predominant trigger dependent AF mechanism, while long stable AF episodes suggest a predominant structural substrate dependent AF mechanism. Also, the diurnal pattern of AF onset and termination may point towards specific mechanism (e.g. vagal AF or sleep apnoea-related AF in patients with predominant nocturnal AF episodes).22–25

Prevalence of AF progression varies with patient population and duration of follow-up but can be as high as 77% of patients progressing over 14 years.26 AF progression occurred in 13–15% of patients with recent-onset AF during 1-year follow-up.27 In another study in paroxysmal AF patients with 1 year Follow-up, changes in AF burden during the first 6 months compared to the last 6 months were studied. 62% patients remained stable, 22% showed progression to longer AF episode, 3% developed persistent AF, and 16% of patients showed AF regression.28 The HATCH score (heart failure, age, previous transient ischaemic attack or stroke, chronic obstructive pulmonary disease, and hypertension) is a simple tool to estimate the risk of AF progression in the near future.29 During 1 year of follow-up, ~50% of the patients with a HATCH score >5 progressed to persistent AF compared with only 6% of the patients with a HATCH score of 0.

Rhythm monitoring should be combined with echocardiographic assessment. Evaluation of atrial structural remodelling should eventually go beyond documentation of left atrial size. Left atrial function can be assessed by imaging (e.g. echocardiography or MRI). Atrial activation time determined by transthoracic Doppler tissue imaging can be used as an estimate of the total duration of atrial electrical activation.30 This so-called PA-tdi interval predicts the development of new-onset AF in sinus rhythm patients.31 Biomarkers and imaging such as late enhancement MRI may provide additional information about the underlying substrate and the stage of AF progression at the time point of AF detection.32

How to guide early atrial fibrillation management in newly detected atrial fibrillation patients

The transition from the consumer-lead screening scenario to a physician lead comprehensive early AF management scenario remains to be a challenge. For example, in patients with screening-detected AF in pharmacies, only 17% of patients received appropriate anticoagulation.33

In addition to the assessment of stroke risk (preferable by the CHA2DS2-VASc score) and initiation of anticoagulation, a structured assessment of symptoms and comorbidities of screen-detected or suspected AF cases is critical to allow early implementation of the Atrial fibrillation Better Care (ABC) holistic pathway (‘A’ Anticoagulation/Avoid stroke; ‘B’ Better symptom management; and ‘C’ Cardiovascular and Comorbidity optimization) recently introduced in the new AF guidelines.2 Antithrombotic treatment should not be initiated in patients with positive screening results before AF is diagnosed based on an ECG-confirmation. Just positive screening results which are confirmed by a standard 12-lead ECG recording or a single-lead ECG tracing of ≥30 s showing AF should lead to management of previously unknown AF. A summary of a possible symptom and risk factor assessment package for early AF management is summarized in Figure 3.

Assessment of symptom burden

Patients with AF report a wide variety and severity of symptoms. A detailed and structured assessment of symptoms may help to guide initial early management of the patients. It is widely recognized that many AF episodes are asymptomatic and that the relationship between AF symptoms and AF burden is weak.34 However, in case of symptomatic AF, the control of symptoms is central to improving the quality of life, a major objective of early AF management per society guidelines.2

The best way to assess and categorize symptoms in AF patients, and particularly how to determine AF-related symptoms in AF patients, remains unclear. There are different tools available: the EHRA score, in which symptoms are assessed by physicians by history taking35 or the CCS-SAF scale, which focuses on the combination of patient-reported AF-related symptoms (palpitations, dyspnoea, dizziness/syncope, chest pain, weakness/fatigue), the symptom-rhythm temporal correlation and the assessment of the effect of symptoms on function and quality of life.36 The

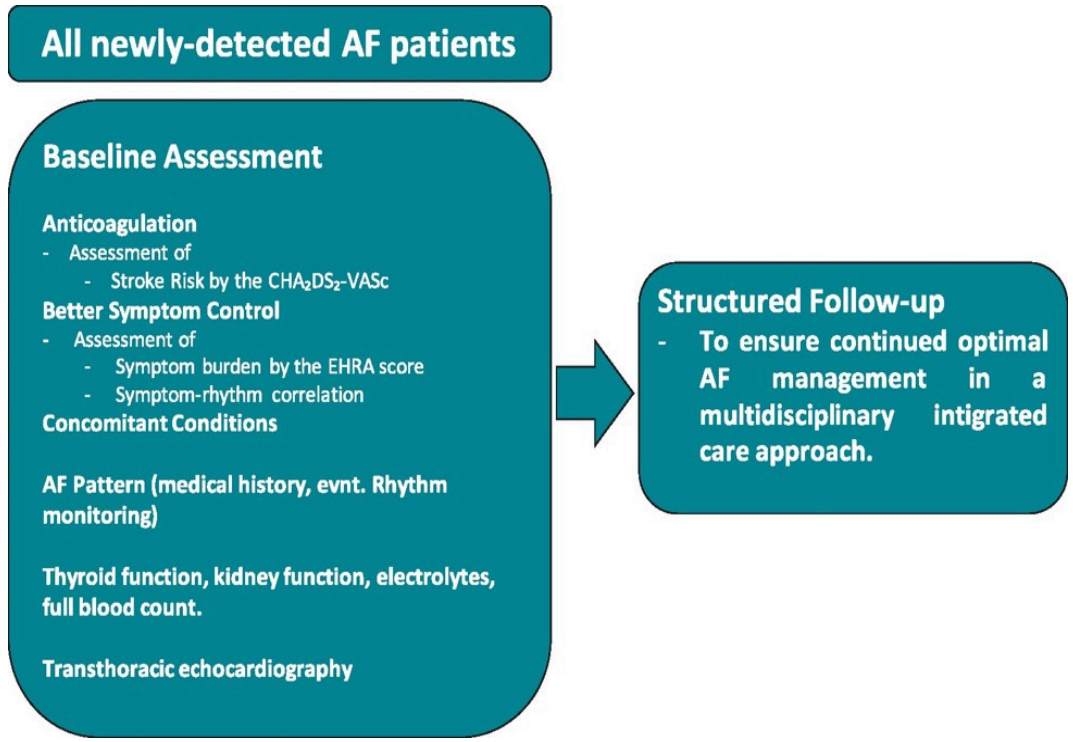

Figure 3. Assessment package for optimal atrial fibrillation management

initial assessment in these classification schemes consists of confirming that the reported symptoms are, in fact, associated with the presence of AF. This is particularly important in the case of paroxysmal AF, in which administering questionnaires in the absence of arrhythmic episodes may lead to underestimation of the illness burden for AF. Rhythm monitoring at the time point of symptom assessment is critical to distinguish between AF-related symptoms (AF-symptoms) and non-specific disease-related symptoms (symptoms in AF). The following approach may be helpful: in higher burden paroxysmal AF, a Holter ECG can be useful and in lower burden, event monitor/wearables can be applied. For persistent AF, electrical cardioversion (ECV) offers the opportunity to probe symptom-rhythm correlation. In patients in whom ECV is successful the time in sinus rhythm can be used to evaluate whether symptoms improve once sinus rhythm is restored (symptom-rhythm correlation), or whether symptom burden remains unaffected (no symptom-rhythm correlation). Additionally, often symptoms are interrogated only once in a structured way at baseline (spot-assessment). However, symptom severity and presentation may show visit-to-visit or even day-to-day variability.

Assessment of risk factors and comorbidities

Atrial fibrillation almost never comes alone. Assessment of risk factors and comorbidities represent an important component of early AF management.2 Structured testing for the presence of modifiable risk factors such as hypertension, metabolic syndrome/obesity, and sleep apnoea is important, as the so-called ‘up-stream therapy’ of these conditions may influence the outcome of rhythm control strategies.37 Sleep apnoea can be identified in 70% of all AF patients, but most patients reported low daytime sleepiness levels.22 The lack of excessive daytime sleepiness should not preclude patients from being investigated by objective measures (e.g. polygraphy) for the potential presence of concomitant sleep apnoea.38

Strict control of modifiable risk factors may improve arrhythmia-free survival.39,40 Goal-directed weight and risk factor management is associated with a lower progression to persistent AF (3% vs. 41% in patients who did not lose weight) and reversed the type of AF from persistent to paroxysmal or no AF in 88%.41 Recommendations in current AF guidelines pay particular attention to good BP control in AF patients with hypertension to reduce AF recurrences and risk of stroke and bleeding. Additionally, initiation of physical activity and weight-loss should be considered42,43 and optimal management of obstructive sleep apnoea may be considered,22 to reduce AF incidence, AF progression, AF recurrences, and symptoms. Importantly, the management of the continuum of unhealthy lifestyle, risk factor(s), and cardiovascular disease (often without specific threshold values), rather than focusing on one specific risk factor alone.

Implementation of early atrial fibrillation management

Active patient education is critical for the initiation but also for the success of early AF management.44 The patient's knowledge gaps about AF can be identified by validated questionnaires45 and online tailored education platforms43 or home-based education and learning programs46–48 can be effective in improving AF knowledge and impact AF outcomes. Informing about treatment options, goals, and success rates as well as of potential risks of possible interventions is important. The patient's perception of disease burden is important to assess. The patient's expectations should be realistic and otherwise corrected by the treating physician. The patient should be prepared for a longer treatment trajectory. Atrial fibrillation management does not stop with an intervention such as AF ablation. Patients need to learn how to live with their AF.

The implementation and early initiation of a comprehensive and structured AF management program should be best organized in an integrated care program.49–52 Integrated AF management programs, particularly in the setting of a nurse-led program, have been shown to improve patient care and AF outcomes.50,51 Also mHealth-supported remote programs may represent an alternative. In the Huawai study, 95.1% of those with identified AF, entered an integrated AF management program using a mobile AF App, streamlining integrated care of AF patients across all healthcare levels and among different specialties.18,52 Compared with usual care, implementation of the ABC pathway has been significantly associated with lower risk of all-cause death, composite outcome of stroke/major bleeding/cardiovascular death and first hospitalization, lower rates of cardiovascular events, and lower health-related costs.53

Recently, a new TeleCheck-AF program has been initiated across Europe. It consists of remote AF management through teleconsultation supported by an mHealth infrastructure, actively involving patients in the care process and providing comprehensive care by a multidisciplinary team.54 It incorporates three important components: (i) a structured teleconsultation ('Tele'), (ii) a CE-marked app-based on-demand heart rate and rhythm monitoring infrastructure ('Check'), and (iii) comprehensive AF management ('AF').55 Outcome data are not available yet.

Conclusion

Early treatment of AF has the potential of improving outcomes and quality of life in AF patients, by preventing the development of complications such as heart failure and stroke, and preventing progression of (the substrate of) the arrhythmia. To allow early treatment, AF needs to be detected early and linked to a comprehensive work-up infrastructure. mHealth approaches can support the early detection of AF and the transition to a structured AF management program which should be best organized in an integrated care pathway.

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CHAPTER 3

Clinical utility of rhythm control by electrical cardioversion to assess the association between self-reported symptoms and rhythm status in patients with persistent atrial fibrillation

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Abstract

Background: The best strategy to assess the association between symptoms and rhythm status (symptom-rhythm correlation) in patients with atrial fibrillation (AF) remains unclear. We aimed to determine the clinical utility of rhythm control by electrical cardioversion (ECV) to assess symptom-rhythm correlation in patients with persistent AF.

Methods: We used ECV to examine symptom-rhythm correlation in 81 persistent AF patients. According to current clinical practice, the presence of self-reported symptoms before ECV and at the first outpatient clinic follow-up visit (within 1-month) was assessed to determine the prevalence of a symptom-rhythm correlation (defined as self-reported symptoms present during AF and absent in sinus rhythm or absent in AF and yet relief during sinus rhythm). In addition, we evaluated symptom patterns around ECV.

Results: Only in 18 patients (22%), a symptom-rhythm correlation could be documented. Twenty-eight patients (35%) did not show any symptom-rhythm correlation and 35 patients (43%) had an unevaluable symptom-rhythm correlation as these patients were in symptomatic AF both at baseline and at the first outpatient AF clinic follow-up visit. Importantly, self-reported symptom patterns around ECV were intra-individually variable in 10 patients (12%) without symptom-rhythm correlation (of which 9 patients (11%) had AF recurrence) and in 2 patients (2%) with an unevaluable symptom-rhythm correlation.

Conclusions: In patients with persistent AF, symptom assessment around rhythm control by ECV, once before ECV and once within 1-month follow-up, rarely identifies a symptom-rhythm correlation and often suggests changes in symptom pattern. Better strategies are needed to assess symptom-rhythm correlation in patients with persistent AF.

Keywords: Atrial fibrillation; Electrical cardioversion; Symptom-rhythm correlation.

Introduction

Patient-tailored management of persistent atrial fibrillation (AF) relies on rate and/or rhythm control, antithrombotic treatment and management of concomitant cardiac diseases [1]. One of the main goals of AF rhythm control is amelioration of symptoms. Although a large proportion of patients with AF reports symptoms [2] , it often remains unclear whether all symptoms are related to AF or whether also other concomitant cardiovascular or non-cardiovascular conditions and risk factors contribute to overall symptom burden in an individual patient. Knowledge about the association between symptoms and rhythm status (symptom-rhythm correlation) has potential clinical implications as it may identify patients who profit from rhythm control in regard to reduction in symptom burden and improvement in quality of life. However, standardized strategies to assess symptom-rhythm correlation are currently not available [3].

Electrical cardioversion (ECV) offers the opportunity to probe symptom-rhythm correlation. In patients in whom ECV is successful the time in sinus rhythm can be used to evaluate whether symptoms improve once sinus rhythm is restored (symptom-rhythm correlation), or whether symptom burden remains unaffected (no symptom-rhythm correlation) [4].

In this retrospective observational cohort study, we determined the clinical utility of rhythm control by ECV to assess symptom-rhythm correlation in patients with persistent AF. Therefore, in accordance with current clinical practice, we used self-reported symptom reports collected during the outpatient AF clinic visits before and after ECV to (1) examine the prevalence of a symptom-rhythm correlation (defined as self-reported symptoms present during AF and absent in sinus rhythm or absent in AF and yet relief during sinus rhythm), and (2) assess the symptom patterns around ECV in patients with persistent AF.

Methods

Study design

This retrospective observational cohort study complies with the Declaration of Helsinki and was approved by the Institutional Review Board at the medical center (Committee reference number: NL 45118.068.13). Staff members of the independent Clinical Trial Center Maastricht performed the study monitoring and data management. All patients provided written informed consent.

Study population

Hemodynamic stable patients with persistent AF who underwent ECV in Maastricht University Medical Center (Maastricht, The Netherlands) were included in this study. Individuals were excluded if they were aged <18 years, were on antiarrhythmic drugs, previously underwent ablation therapy for AF or if the current episode of AF was classified as postoperative AF. Other exclusion criteria were the presence of a pacemaker unable to detect AF with a regular paced rhythm during AF, and a history of myocardial infarction within four weeks preceding recruitment into the study.

Data collection

Baseline clinical characteristics (demographics, concomitant cardiovascular conditions, and medication) were retrieved from patient medical records. Furthermore, we obtained the presence of self-reported symptoms and the predominant self-reported symptom type (symptom with highest self-reported symptom burden) of each individual patient before ECV and at the first outpatient AF clinic follow-up visit (within one month after ECV) from patient medical records. During structured history taking, the presence of the following symptoms and their symptom-

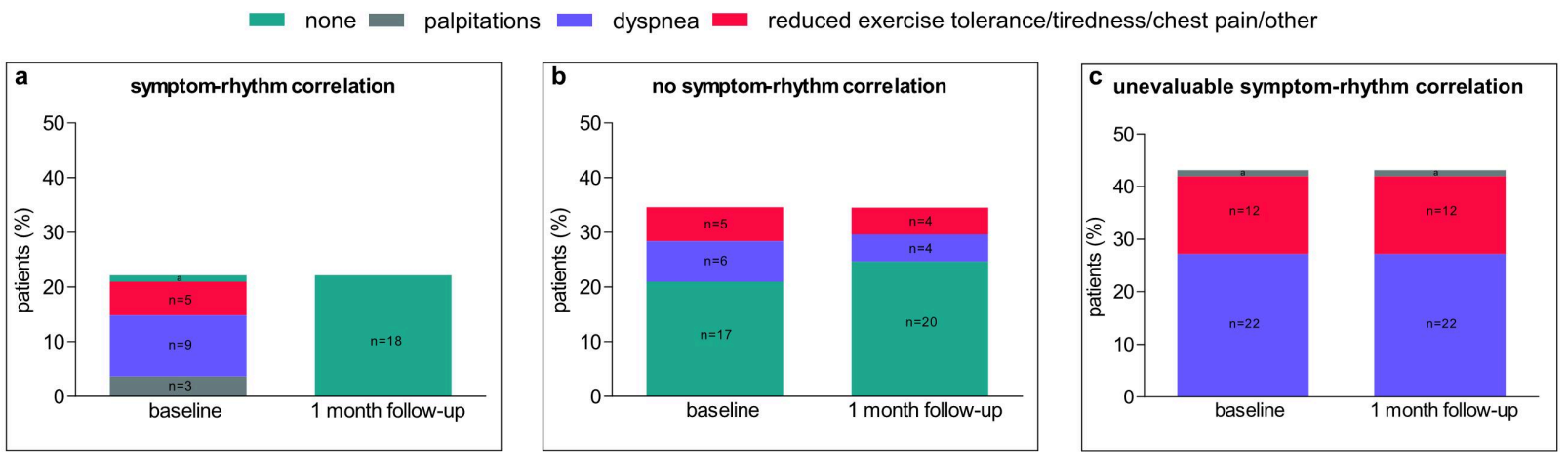

Figure 1. Symptom-rhythm correlation between baseline and 1-month follow-up in patients who underwent electrical cardioversion.
Panel a shows details regarding the variability in symptom pattern between baseline and one month follow-up of patients with a symptom-rhythm correlation (n = 18). Panel b shows details regarding the variability in symptom pattern between baseline and one month follow-up of patients without a symptom-rhythm correlation (n = 28). Panel c shows details regarding the variability in symptom pattern between baseline and one month follow-up of patients with an unevaluable symptom-rhythm correlation (n = 35). a n = 1

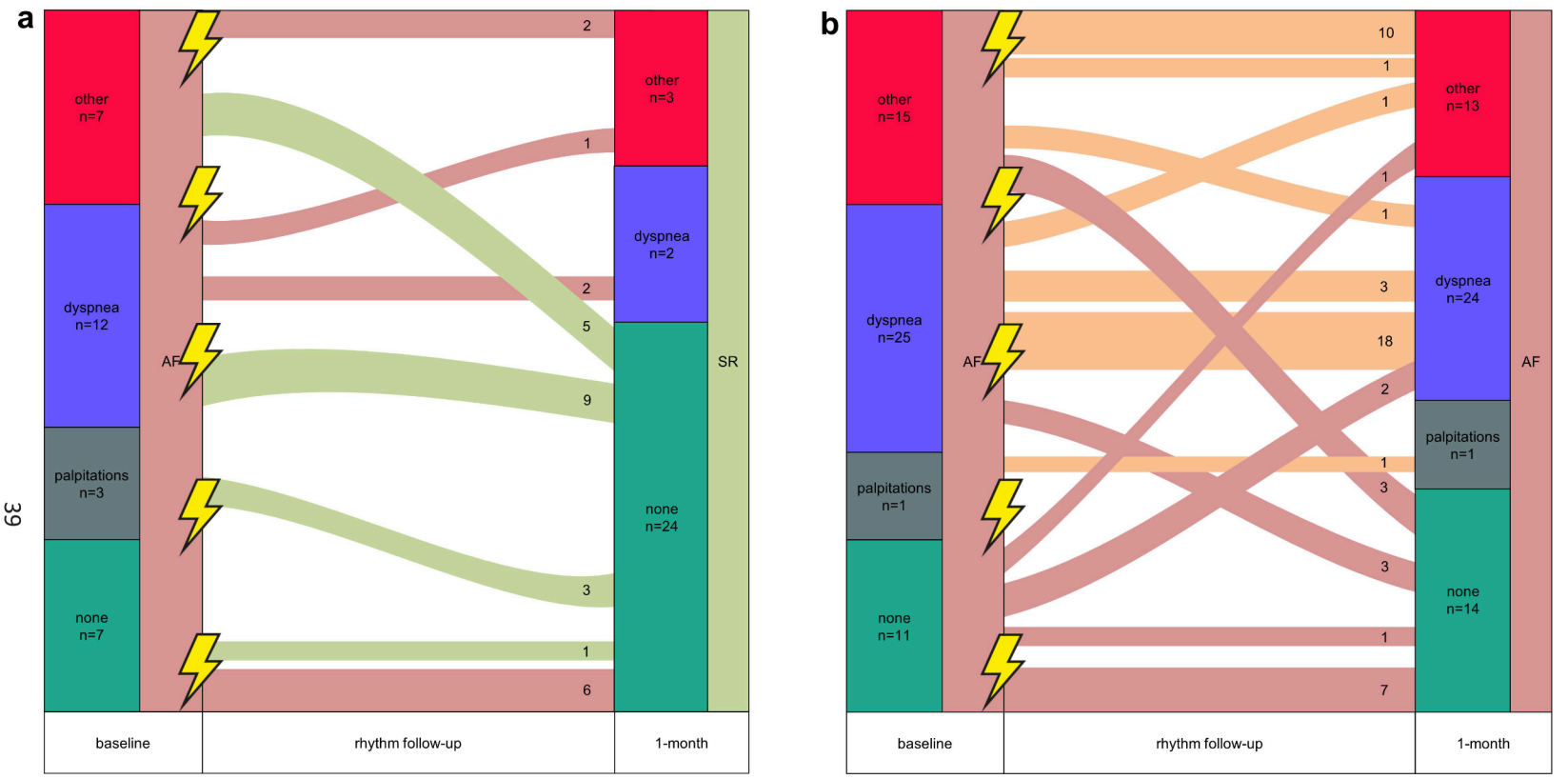

Figure 2. Symptom variability around electrical cardioversion per patient.
Shown is the symptom variability around electrical cardioversion (ECV) among patients without recurrence of atrial fibrillation (AF) (panel a) and with recurrence of AF (panel b). Other includes the following symptoms: reduced exercise tolerance, tiredness, chest pain, and others. The green lines indicate patients with a symptom-rhythm correlation around ECV (defined as self-reported symptoms present during AF and absent in sinus rhythm (SR) or absent in AF and yet relief during sinus rhythm). The red lines indicate patients without a symptom-rhythm correlation around ECV. The orange lines indicate patients with an unevaluable symptom-rhythm correlation around ECV. The lightning symbols are used to display the moment of ECV.

specific burden before and after ECV were interrogated by the attending physician without using a validated tool: palpitations, dyspnea, reduced exercise tolerance, tiredness, chest pain, and others. The presence of self-reported symptoms was determined to examine the prevalence of a symptom-rhythm correlation. Symptom-rhythm correlation was assessed by considering the association between self-reported symptoms and the rhythm status before and after ECV. Patients with symptoms prior to ECV and without symptoms in sinus rhythm as well as asymptomatic patients before ECV with yet symptom relief during sinus rhythm were defined as symptom-rhythm correlation. In persistent AF patients who perceived themselves as asymptomatic before ECV, ECV was performed to see if restoration and maintenance of sinus rhythm can 'unmask' a previously suppressed level of symptoms. The symptom-rhythm correlation was absent in patients with symptoms before ECV who remained symptomatic during sinus rhythm (regardless of changes in predominant symptom type) or in patients with symptoms prior to ECV and without symptoms in AF after ECV. Asymptomatic patients before ECV with or without symptoms in AF or sinus rhythm afterwards had no symptom-rhythm correlation as well. The symptom-rhythm correlation was unevaluable in patients who were symptomatic in AF before ECV and at the first outpatient AF clinic follow-up visit.

The predominant self-reported symptoms before and after ECV were collected to assess the symptom patterns around ECV. Intra-individually variable symptom patterns were defined as changes in predominant self-reported symptoms within patients around ECV.

Statistical analysis

All statistical analyses were performed using IBM SPSS 25.0 software (SPSS, Inc., Chicago, USA) and statistical significance was assumed at a 5% level. Histograms and Shapiro-Wilk tests were used to check for normality. Categorical variables were represented as numbers of patients (n) with percentages. Normally distributed continuous variables were reported as mean ± standard deviation (SD) and non-normal distributed continuous variables were presented as median with interquartile range (IQR). For the comparison of categorical data, the Pearson's chi-squared tests or alternatively Fisher's exact tests were used, as appropriate. Differences in continuous parameters were compared using one-way ANOVA and Kruskal-Wallis.

Results

Patients

A total of 81 patients were included in this analysis. The median age was 70 years (IQR, 64–75) and 19 patients (23%) were female. There were 51 patients (63%) with a first documented episode of AF and in 38 patients (47%) the current AF episode duration was ≤3 months (Table 1). Of all 81 persistent AF patients who underwent ECV, 63 were symptomatic (78%). ECV was performed in 18 additional persistent AF patients (22%) who perceived themselves as asymptomatic before ECV to see if restoration and maintenance of sinus rhythm can 'unmask' a previously suppressed level of symptoms. ECV was successful in 76 patients (94%), unsuccessful in 3 patients (4%), and 2 patients (2%) had immediate recurrence of AF (IRAF). Within one month after ECV, 52 patients (64%) had a documented recurrence of AF.

Symptom-rhythm correlation

The minority of patients (18 patients, 22%) displayed a symptom-rhythm correlation of which 17 (21 %) had symptoms prior to ECV and no symptoms in sinus rhythm and 1 (1%) was asymptomatic before ECV with yet symptom relief during sinus rhythm (in this patient, ECV 'unmasked' a previously suppressed level of symptoms) (Fig. 1 , panel a; Fig. 2 , panel a). Twenty-eight patients

Table 1. Baseline characteristics of the patients with, without and with unevaluable symptom-rhythm correlation.

		Symptom-rhythm correlation			
	Total	Yes	No	Unevaluable	P-value
	(n = 81)	(n = 18)	(n = 28)	(n = 35)	
Demographics					
Female	19 (23)	7 (39)	8 (29)	4 (11)	0.06
Age (years), median (IQR)	70 (64–75)	69 (61–76)	71 (64–75)	70 (67–75)	0.71
Body mass index (kg/m ^{2}), mean ± SD, (n = 80) [b]	29.2 ± 4.6	28.5 ± 5.7	29.4 ± 3.9	29.4 ± 4.7	0.74
First detected atrial fibrillation [b]	51/77 (66)	10/18 (56)	19/27 (70)	22/32 (69)	0.55
Duration current atrial fibrillation episode ≤ 3 months [b]	38/79 (48)	8/18 (44)	12/27 (44)	18/34 (53)	0.76
Previous electrical cardioversion	13 (16)	4 (22)	3 (11)	6 (17)	0.59
Previous antiarrhythmic medication	5 (6)	2 (11)	0 (0)	3 (9)	0.22
Concomitant cardiovascular conditions					
CHA_2DS_2-VASc score ≥ 2 [c]	65 (80)	13 (72)	23 (82)	29 (83)	0.62
Arterial hypertension	48 (59)	11 (61)	20 (71)	17 (49)	0.18
Stroke	7 (9)	1 (6)	3 (11)	3 (9)	1.00
Transient ischemic attack	8 (10)	0 (0)	2 (7)	6 (17)	0.15
Heart failure [b, d]	17/75 (23)	5/17 (29)	6/25 (24)	6/33 (18)	0.66
Obstructive sleep apnea syndrome	9 (11)	1 (6)	4 (14)	4 (11)	0.82
Medication					
Renin-angiotensin antagonists	42 (52)	12 (67)	14 (50)	16 (46)	0.34
Aldosterone antagonists	5 (6)	0 (0)	3 (11)	2 (6)	0.36
Anticoagulants	81 (100)	18 (100)	28 (100)	35 (100)	
Antiplatelets	5 (6)	2 (11)	1 (4)	2 (6)	0.71
Beta-blockers	69 (85)	17 (94)	26 (93)	26 (74)	0.07
Calcium channel blockers	17 (21)	3 (17)	7 (25)	7 (20)	0.78
Dihydropyridine [b]	13/17 (76)	2/3 (67)	7/7 (100)	4/7 (57)	0.18
Diuretics	31 (38)	7 (39)	10 (36)	14 (40)	0.94

Percentages may not total 100 because of rounding.
Values depicted as number of patients (n) with percentages unless indicated otherwise.
SD, standard deviation; IQR, interquartile range.
b Number of patients with available information is given since some patients had missing values.
c The CHA 2 DS 2 -VASc score is a well-established tool used for risk stratification of stroke in patients with atrial fibrillation, with scores ranging from 0 to 9 and a higher score corresponds to a greater risk. Congestive heart failure, hypertension, diabetes, vascular disease, an age of 65 years to 74 years and female gender are each allocated one point, and an age of more than 75 years and previous stroke or transient ischemic attack are each allocated two points [1] .
d Heart failure was defined as a left ventricular ejection fraction of less than 40%.

(35%) did not show any symptom-rhythm correlation (Fig. 1 , panel b; Fig. 2 , panel a and b) and 35 patients (43%) with relapse of AF had an unevaluable symptom-rhythm correlation as these patients were in symptomatic AF both at baseline and at the first outpatient clinic visit (Fig. 1 , panel c; Fig. 2 panel b). Baseline clinical characteristics of patients with and without symptom-rhythm correlation and of patients with an unevaluable symptom-rhythm correlation are reported in Table 1 . All patient characteristics were comparable. The findings hold true when we excluded patients with prior attempts of rhythm control (previous ECV or antiarrhythmic medication therapy) because of potential 'treatment expectation bias' (supplementary material online, Table S1).

Predominant self-reported symptoms

Before ECV, dyspnea was the most common symptom (n = 37, 46%), followed by reduced exercise tolerance (n = 16, 20%), tiredness (n = 5, 6%), palpitations (n = 4, 5%) and chest pain (n = 1, 1%). Twenty-two percent of patients (n = 18) reported no symptoms. Of the 29 patients with sinus rhythm after ECV, 24 (83%) were asymptomatic, 3 (10%) had reduced exercise tolerance and 2 (7%) had dyspnea at 1-month follow-up (Fig. 3 , panel a-d). In the 52 patients with a recurrence of AF after ECV, there were 14 patients (27%) without symptoms, 24 (46%) with dyspnea, 8 (15%) with reduced exercise tolerance, 3 (6%) with tiredness, 1 (2%) with palpitations, 1 (2%) with chest pain and 1 (2%) with other symptoms at one month (Fig. 3 , panel a-d). Importantly, self-reported symptom patterns around ECV were intra-individually variable in 10 patients (12%) without symptom-rhythm correlation (of which 9 patients (11%) had AF recurrence) and in 2 patients (2%) with an unevaluable symptom-rhythm correlation (Fig. 2 , panel a and b).

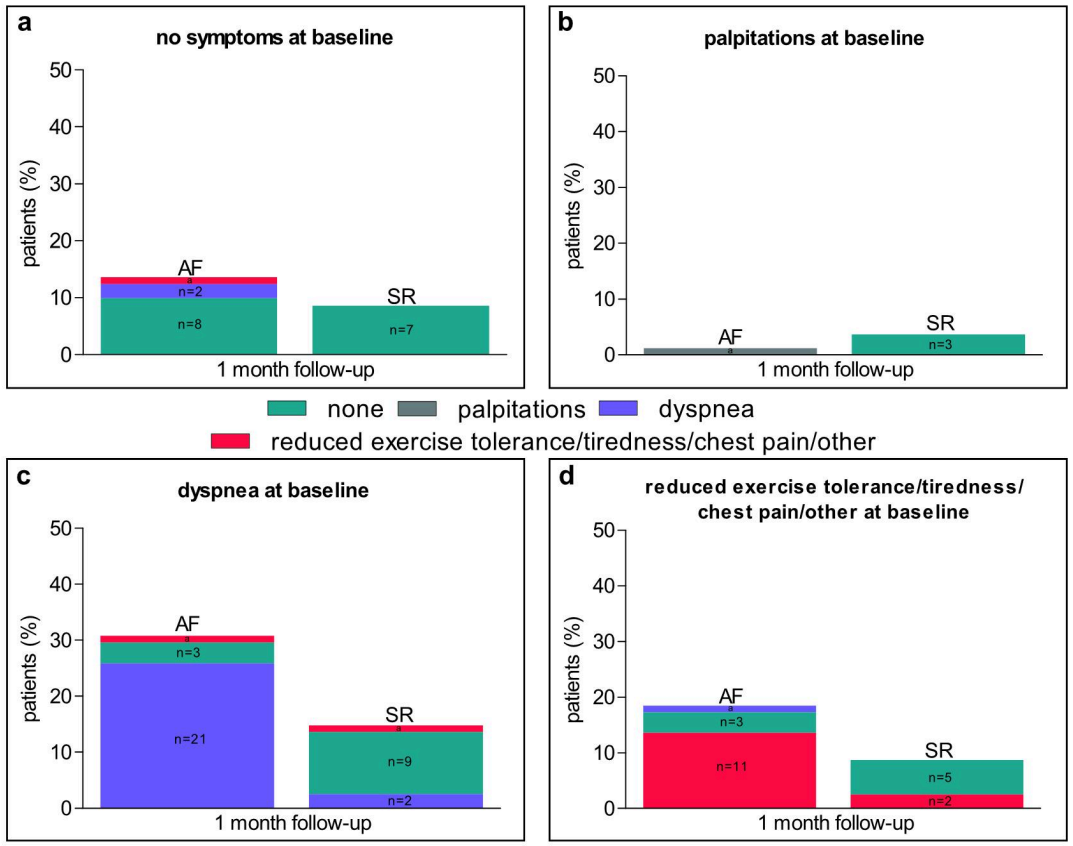

Figure 3. Symptom pattern before and after electrical cardioversion.
Shown is the symptom pattern between symptoms at baseline and symptoms at one month follow-up among 81 patients with and without recurrence of atrial fibrillation (AF). Panel a-d shows the percentage of patients with a specified baseline symptom and their symptoms at 1-month follow-up. a n = 1. SR, sinus rhythm.

Discussion

In this retrospective cohort study, the minority of patients showed a symptom-rhythm correlation (defined as predominant self-reported symptoms present during AF and absent in sinus rhythm or absent in AF and relief during sinus rhythm) around ECV. We found a high variability in self-reported symptoms before and after ECV in patients with AF recurrence.

Symptom-rhythm correlation and symptom pattern around electrical cardioversion

The low prevalence of symptom-rhythm correlation and the high remaining symptom burden after rhythm control by ECV do not support prior work showing that the majority of patients who were symptomatic in AF before ablation became asymptomatic in sinus rhythm after ablation [5, 6] . Additionally, patients with a successful ablation had greater reduction in symptoms compared to patients with an unsuccessful ablation [7, 8] . An explanation might be a different symptom perception in patients with paroxysmal and persistent AF, however invasive interventions per se may also lead to alterations in perception of AF caused by a placebo effect [8, 9, 10] . Moreover, patients' limited prior knowledge of AF, previous health experiences and interactions with health care providers may influence symptom perception as well [11] . In general, blinded sham-controlled studies may be needed to definitely rule out a placebo effect of rhythm-control, particularly if symptom-burden is one of the main outcome-measures.

The main goal of rhythm control strategies is amelioration of symptoms in AF patients. In regard to symptom control, the best responder to rhythm control (by pharmacological interventions, ECV or AF-ablation procedures) would be an AF patient who is predominantly symptomatic because of AF-related symptoms. Furthermore, severe symptomatic patients would have a higher likelihood of symptom improvement after the achievement of sinus rhythm compared to minimally symptomatic or asymptomatic patients [10] . Therefore, the assessment of the underlying pathophysiological condition mainly contributing to symptoms is important to guide the decision for rhythm versus rate control. Theoretically, in symptomatic patients without symptom-rhythm correlation, non-AF related factors such as cardiovascular or non-cardiovascular conditions and risk factors, which do not change after successful rhythm control, are likely contributing to overall symptom burden in an individual patient. However, in our study, the cardiovascular conditions and risk factors of patients with and without symptom-rhythm correlation as well as of patients with an unevaluable symptom-rhythm correlation were quite similar. Importantly, in addition to the amelioration of symptoms, recent studies also showed that rhythm control (AF ablation therapy and treatment with antiarrhythmic drugs) may also be associated with a reduction in cardiovascular outcomes, potentially even irrespective of improvement of symptoms and in asymptomatic patients [12, 13, 14] . Therefore, the role of systematic symptom-rhythm correlation assessment using ECV as a diagnostic tool to guide decision on rhythm control in patients with persistent AF needs to be investigated in future studies [10, 15] .

The assessment of symptom-rhythm correlation has potential clinical implications as it may identify patients likely profiting from rhythm control strategies to improve their symptom burden and quality of life. However, identifying a symptom-rhythm correlation in AF patients is challenging. The best way to determine symptom-rhythm correlation remains unclear. The high recurrence rate of AF within the first month is significantly limiting the diagnostic utility of ECV at one month. To enhance the performance of symptom-rhythm correlation assessment, the period in sinus rhythm after ECV may be lengthened by specific patient selection (e.g. smaller left atrial size) [16] or using temporary amiodarone or flecainide, which, however as such may affect symptom burden [4]. Besides, as it is established that ECV is associated with a 24-hour relapse gap of AF recurrence [17], symptom assessment at 24 h may give sufficient opportunity for an effective evaluation of changes in symptoms around ECV. Additionally, symptom burden was interrogated once at baseline and once at one month follow-up after ECV (in accordance with current clinical practice). A more longitudinal assessment of symptoms during simultaneous rhythm monitoring in persistent AF patients undergoing ECV may provide a more accurate approach to assess a symptom-rhythm correlation and to distinguish between AF-related symptoms (AF-symptoms) and unspecific disease-related symptoms (symptoms in AF). A better characterization and a better understanding of the mechanisms of symptoms in AF patients and symptom burden may help to obtain the

correct diagnosis, chose an appropriate treatment (rhythm control vs. rate control), and assess the actual result of a treatment. Additionally, the absence of a clear symptom-rhythm correlation may provide a plausible basis for a structured assessment and then for targeted and comprehensive management of co-morbidities contributing to symptom burden.

There was a high variability in self-reported symptoms before and after ECV in patients with AF recurrence. This heterogeneity in terms of symptom presentation suggests that symptoms in patients with AF may be the manifestation of multiple pathophysiologic mechanistic pathways [3]. Patients with first-detected AF are more symptomatic than patients with a longer history of AF [18] and even in highly symptomatic AF patients, asymptomatic episodes may occur [9] . Moreover, there are higher rates of atypical symptoms in elderly with AF [19] . Although most AF patients experience symptoms during AF episodes [2, 20] , symptom perception is highly variable [19] . Sociodemographic- and sex-specific factors as well as anxiety- and depression-related mechanisms may be involved in the type or severity of self-reported symptoms in AF patients [21] . Additionally, symptoms in AF patients related to certain comorbidities such as heart failure, obesity, diabetes, coronary artery disease, arterial stiffness, and sleep-disordered breathing may perpetuate and contribute significantly to the perception and judgement of the frequency and severity of AF-related symptoms as well [22, 23, 24, 25] . Therefore, additional studies evaluating the effect of specific concomitant non-cardiovascular and cardiovascular conditions and risk factors on overall symptom burden are needed.

Limitations

Several limitations of our study should be mentioned. First, the sample size of our study was relatively small and there may be selection bias, as we included only those patients who were not on antiarrhythmic drugs. Therefore, there should be caution in generalizing our findings to all patients with persistent AF, as results may differ in other patient populations. Second, the presence of symptoms and if present, the predominant self-reported symptoms around ECV were obtained retrospectively from patient medical records (in accordance with current clinical practice). Thus, there is a risk that the coverage of different symptoms is not as complete as in a questionnaire, diary or structured interview. Third, we just applied one technique to assess symptom-rhythm correlation, namely assessment of symptoms once before ECV and once at one month after ECV (spot-check symptom assessment). A more longitudinal assessment of symptoms during simultaneous rhythm monitoring around ECV may provide a more accurate approach to assess a symptom-rhythm correlation. Further studies are required to test the utility of such approach. Fourth, we presented symptom-rhythm correlation as a categorical variable (yes or no). But probably, symptom-rhythm correlation assessment is not that “black or white”, as also other concomitant cardiovascular or non-cardiovascular conditions and risk factors may contribute to overall symptom burden. A point to take also into account is that prior work suggested that the physician’s assessment of AF-specific symptoms is an underestimation of patients AF-specific symptoms, especially when they are mild, which may affect the variability in symptoms and thus the prevalence of symptom-rhythm correlation around ECV [26] .

Conclusions

In patients with persistent AF, spot-check-based symptom-rhythm correlation assessment around rhythm control by ECV, once before ECV and once at the first outpatient AF clinic follow-up visit (within one month after ECV), rarely identifies a symptom-rhythm correlation. Additionally, ECV often suggests changes in symptom pattern. Further research is warranted to identify more optimal strategies to assess symptom-rhythm correlation in patients with persistent AF and to establish the clinical implications of symptom-rhythm correlation assessment for AF management.

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Supplementary material

Table S1. Baseline characteristics of the patients without prior attempts of rhythm.

	Total (n=65)	Symptom-rhythm correlation Yes (n=13)	No (n=25)	Unevaluable (n=27)	P-value
Demographics					
Female	15 (23)	5 (39)	7 (28)	3 (11)	0.12
Age (years), median (IQR)	70 (64-75)	69 (59-75)	70 (64-75)	70 (66-74)	0.77
Body mass index (kg/m²), median (IQR)	29.05 (25.10-32.15)	29.03 (23.04-34.87)	29.35 (26.72-31.77)	28.68 (24.93-32.11)	0.85
First detected atrial fibrillation [b]	50/62 (81)	9/13 (69)	19/24 (79)	22/25 (88)	0.35
Duration current atrial fibrillation episode ≤3 months [b]	31/63 (49)	6/13 (46)	11/24 (46)	14/26 (54)	0.83
Concomitant cardiovascular conditions					
CHA_2DS_2-VASc score ≥2 [c]	52 (80)	9 (69)	20 (80)	23 (85)	0.50
Arterial hypertension	40 (62)	8 (62)	19 (76)	13 (48)	0.12
Stroke	6 (9)	0 (0)	3 (12)	3 (11)	0.64
Transient ischemic attack	6 (9)	0 (0)	1 (4)	5 (19)	0.13
Heart failure [b d]	15/61 (25)	4/13 (31)	5/22 (23)	6/26 (23)	0.84
Obstructive sleep apnea syndrome	7 (11)	1 (8)	4 (16)	2 (7)	0.59
Medication					
Renin-angiotensin antagonists	34 (52)	9 (69)	12 (48)	13 (48)	0.39
Aldosterone antagonists	4 (6)	0 (0)	3 (12)	1 (4)	0.41
Anticoagulants	65 (100)	13 (100)	25 (100)	27 (100)	
Antiplatelets	5 (8)	2 (15)	1 (4)	2 (7)	0.42
Beta-blockers	56 (86)	13 (100)	23 (92)	20 (74)	0.05
Calcium channel blockers	13 (20)	1 (8)	6 (24)	6 (22)	0.46
Dihydropyridine [b]	11/13 (85)	1/1 (100)	6/6 (100)	4/6 (67)	0.54
Diuretics	27 (42)	5 (39)	10 (40)	12 (44)	0.92

Percentages may not total 100 because of rounding. [a] Values depicted as number of patients (n) with percentages unless indicated otherwise. [b] Number of patients with available information is given since some patients had missing values. [c] The CHA_2DS_2-VASc score is a well-established tool used for risk stratification of stroke in patients with atrial fibrillation, with scores ranging from 0 to 9 and a higher score corresponds to a greater risk. Congestive heart failure, hypertension, diabetes, vascular disease, an age of 65 years to 74 years and female gender are each allocated one point, and an age of more than 75 years and previous stroke or transient ischemic attack are each allocated two points. [1 d] Heart failure was defined as a left ventricular ejection fraction of less than 40%. [e] IQR, interquartile range.

PART II

Mobile health for (remote) atrial fibrillation detection and management

CHAPTER 4

On-demand mobile health infrastructures to allow comprehensive remote atrial fibrillation and risk factor management through teleconsultation

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Abstract

Background: Although novel teleconsultation solutions can deliver remote situations that are relatively similar to face-to-face interaction, remote assessment of heart rate and rhythm as well as risk factors remains challenging in patients with atrial fibrillation (AF).

Hypothesis: Mobile health (mHealth) solutions can support remote AF management.

Methods: Herein, we discuss available mHealth tools and strategies on how to incorporate the remote assessment of heart rate, rhythm and risk factors to allow comprehensive AF management through teleconsultation.

Results: Particularly, in the light of the coronavirus disease 2019 (COVID-19) pandemic, there is decreased capacity to see patients in the outpatient clinic and mHealth has become an important component of many AF outpatient clinics. Several validated mHealth solutions are available for remote heart rate and rhythm monitoring as well as for risk factor assessment. mHealth technologies can be used for (semi-)continuous longitudinal monitoring or for short-term on-demand monitoring, dependent on the respective requirements and clinical scenarios. As a possible solution to improve remote AF care through teleconsultation, we introduce the on-demand TeleCheck-AF mHealth approach that allows remote app-based assessment of heart rate and rhythm around teleconsultations, which has been developed and implemented during the COVID-19 pandemic in Europe.

Conclusion: Large scale international mHealth projects, such as TeleCheck-AF, will provide insight into the additional value and potential limitations of mHealth strategies to remotely manage AF patients. Such mHealth infrastructures may be well suited within an integrated AF-clinic, which may require redesign of practice and reform of health care systems.

Background

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia and is associated with increased risk of heart failure, stroke, bleeding, acute coronary syndrome and severe adverse effects of antiarrhythmic drugs, all of which may lead to unplanned cardiovascular hospitalization, morbidity and mortality.[1] Management of AF risk factors and monitoring of vital parameters, particularly heart rate and rhythm, are important for the management of AF patients and prevention of AF-related morbidity.[2]

Remote monitoring by means of novel technologies provides an opportunity to bring the best standard of care and expertise to the patient rather than the patient having to visit an outpatient clinic. This may be particularly important for the management of patients who live remotely and far away from coordinating medical centers or during catastrophes, including coronavirus disease 2019 (COVID-19), when attendance of outpatient clinics or traveling to the hospital is not possible or undesirable.[3] Although new teleconsultation solutions can produce remote situations that are relatively similar to face-to-face interaction, the remote assessment of heart rate and rhythm as well as risk factors remains challenging.

In this review article, we discuss mobile health (mHealth) tools and strategies to remotely monitor heart rate and rhythm and incorporate AF risk factors assessment to allow comprehensive AF management through teleconsultation. Additionally, as a possible solution to improve remote AF care during the COVID-19 pandemic, we introduce the on-demand TeleCheck-AF mHealth approach that allows remote app-based assessment of heart rate and rhythm around teleconsultations.

Remote heart rate and rhythm monitoring

Different mHealth tools are available for remote heart rate and rhythm assessment. Until now, most tools are available within a patient-initiated paying-model which, together with the absence of reimbursement, complicates the clinical implementation and guidance of mHealth use by the treating physician. Additionally, the requirements on the way when and how to perform measurements (semi-continuous vs on-demand (Figure1) and electrocardiography (ECG) vs photoplethysmography (PPG), respectively) are critically dependent on the clinical scenario and setting. As this is difficult for patients to judge, a physician-initiated or at least -guided approach appears to be necessary to allow personalized mHealth use and the selection of the right tool for each patient.

To screen for AF, (semi-)continuous remote monitoring by cardiac implantable electronic devices (CIEDs), wearables (eg, smart watches), handheld devices (eg, AliveCor, MyDiagnostick, etc.) or app-based mHealth solutions using PPG technology through the smartphone's built-in camera (eg, FibriCheck) have been developed and validated (Figure 2). Smartwatches such as Fitbit and Apple Watch, equipped with PPG technology, are commonly used for semi-continuous heart rate and rhythm monitoring during day and night and have a valuable clinical effect by enabling AF detection in both symptomatic and asymptomatic patients.[4 , 5 , 6] Most of the devices are CE marked and some of them are connected to secured and certified clouds, allowing remote access of the data by treating physicians or allied healthcare professionals. PPG technology is not sufficient to diagnose AF. Based on the current international AF Guidelines of the European Society of Cardiology (ESC),[2] ECG-documentation of an AF episode is required for diagnosis. As most PPG algorithms are developed for AF screening scenarios, they operate in a high sensitivity mode, resulting in a higher number of false positive recordings.[7] Therefore, in the setting of AF screening, PPG-detected episodes suggestive of AF need to be confirmed by an ECG. Despite crucial differences between

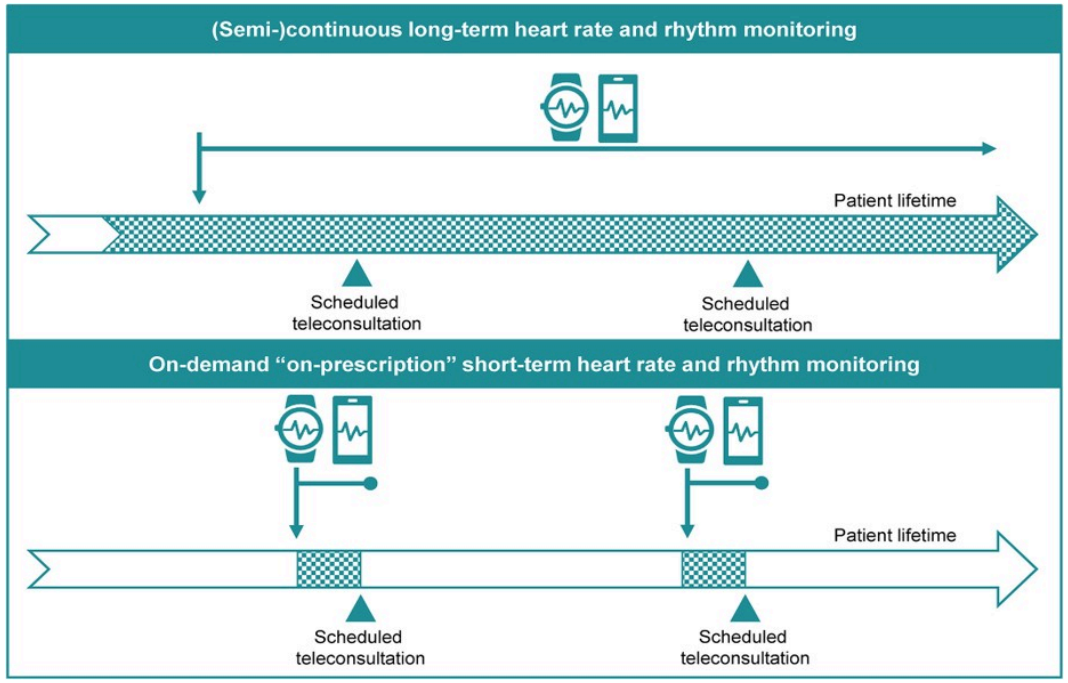

Figure 1. Remote heart rate and rhythm monitoring: (semi-)continuous longitudinal vs on-demand.

PPG and ECG technologies for heart rhythm monitoring, most of the PPG-based algorithms are validated to detect AF with a high sensitivity and specificity.[7] Additionally, there is already some data that PPG technology is nearly as accurate as ECG to detect AF.[8 , 9] In the validation studies for these devices, atrial high rate episodes (AHRE) from CIEDs have not been taken into account. Given the wide availability and low cost, PPG technology may represent an optimal screening tool to detect AF, which can then be confirmed by ECG technology afterwards in a second step.

Figure 2. Different mobile health devices.

While PPG technology has limitations to diagnose AF, the wide accessibility and low cost of this technology via smartphone apps makes it an interesting tool for remote heart rate and rhythm monitoring of patients who have already been diagnosed with AF. A temporary pre-determined on-demand approach, where heart rate and rhythm information are provided to the health care provider just before a scheduled appointment appears to fulfill most requirements to manage AF patients remotely through teleconsultation. This on-demand, rather than unfocused long-term monitoring enables an ideal remote consultation with helpful and crucial well-timed heart rate and rhythm information available for the treating physician, nurse or allied healthcare professional to steer management of patients with ECG-documented AF. For an on-demand mHealth approach, apps can be activated "on prescription" and linked to a secured cloud, which is accessible by the treating physician or nurse. Additionally, simultaneous monitoring of heart rhythm and symptoms provides information about symptom-rhythm correlation. On-prescription monitoring increases awareness with the patients who are better prepared for the remote consultation: patients know that symptom and rhythm evaluation is on the agenda during the consultation, together with discussions on necessary treatments. An on-demand monitoring approach also avoids unnecessary data load, which would require work-intensive and expensive data management infrastructures.

Remote assessment and management of AF risk factors

Management of risk factors is an important component of AF treatment. Despite convincing evidence for the need of risk factor management in AF patients,[10] it remains unclear, how best to assess risk factors and guide risk factor management and lifestyle modification in a remote setting.[11] Established risk factors are often assessed only once in a structured way at the time point when AF patients present for the first time in the AF-clinic (spot-assessment of risk factors). However, several AF risk factors may show a high visit-to-visit or even day-to-day variability and lifestyle components such as physical activity, diet and sleep behaviours may be variable over time. [11 , 12 , 13 , 14 , 15 , 16 , 17] This visit-to-visit or day-to-day variability does not just complicate the detection of AF risk factors but may also have a prognostic implication. High visit-to-visit variability in risk factors is associated with increased risk of incident new-onset AF, worse cardiovascular outcome and increased mortality.[18 , 19 , 20] Hence, assessment of risk factors requires a longitudinal and remote structured monitoring infrastructure (Figure 3). Additionally, longitudinal documentation of risk factors during a risk factor modification program may allow monitoring of the response to the intervention and adaptation and guidance as required to optimize the results.

For the implementation of remote and longitudinal assessment of risk factors and lifestyle components, mHealth applications and technologies such as activity trackers, Bluetooth-linked balances, blood pressure devices and diary apps to assess diet may provide the required infrastructures. Smartphone apps as well as smartwatches already provide longitudinal information about most lifestyle components and some risk factors. The smartphone app "Health Buddies application"[21] or a computer-animated application designed by Magnani et al.[22] resulted in increased adherence to oral anticoagulation and improved quality of life in AF patients. A meta-analysis of 51 randomized controlled trials demonstrated that compared with usual care, mHealth interventions in diabetes and hypertension management yielded significant mean differences in clinical outcomes including blood pressure, fasting blood glucose and HbA1c control and had positive effects on improving quality of life, satisfaction and self-efficacy.[23 , 24] However, until now, these apps are almost exclusively patient-initiated and not implemented in structured patient care pathways. Therefore, most of the apps remain as lifestyle products and have not found their way to clinical implementation.

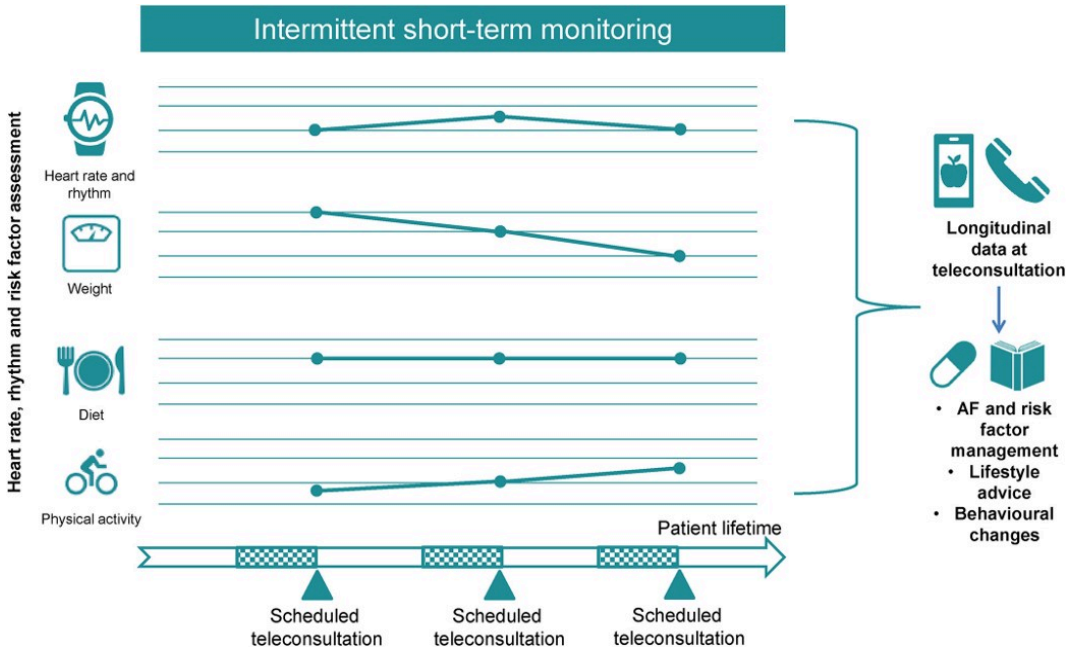

Figure 3. Intermittent short-term monitoring for longitudinal risk factor assessment.
The blue boxes indicate periods of intermittent short-term monitoring before scheduledteleconsultations.

Another emerging modifiable AF risk factor is sleep apnea.[25] Technologies implemented in implantable devices, on-contact biomotion sensors with actimetry, ballistic sensors or Doppler technology with radar frequencies can remotely monitor breathing during sleep.[26 , 27] Wearable devices with inbuilt pulse oximeters are now also becoming commercially available raising the prospect of routinely measuring the night-to-night variability of sleep disordered breathing severity by means of the oxygen desaturation index or determining hypoxic burden more broadly by newer validated algorithms.[17 , 28] Several clinical trials have demonstrated the feasibility of mHealth-based sleep apnea management compared with a more traditional in-person care model, suggesting non-inferiority in terms of adherence to continuous positive airway pressure treatment and compliance as well as functional outcomes such as satisfaction and cost-effectiveness.[29 , 30]

Technologies for longitudinal monitoring of lifestyle components and AF risk factors are available and may support a more complete remote assessment and management of AF patients in the future, once these tools can be implemented in existing clinical pathways or emerging mHealth approaches. In addition to the assessment of risk factors, mHealth infrastructures and apps can also be helpful in applying dedicated in-app coaching to improve lifestyle and control risk factors by behavioural changes.[31] Besides this, telemonitoring can also optimize medication adherence.[32]

Clinical implementation of teleconsultation and mHealth solutions in an integrated care approach

Integrated care has been recognized as a suitable approach to manage patients with chronic conditions and complex treatments, such as AF, in international guidelines of the ESC for the management of AF.[33 , 34] Implementation of teleconsultation and the use of mHealth solutions should be embedded within this integrated care approach, whilst adhering to the following four fundamental components:

1) The use of technology by means of eHealth or mHealth. This aims to support and guide the patient through the care process (eg, patient education and instruction) as well as the treatment team (smart technology to support decision making).[35] In fact, such technology solutions should support integrated care in terms of actively involving patients in their care process, collaboration within multidisciplinary teams, and provide guidance in the complex (shared) treatment decisions and coordination of care.

2) Active involvement of the patient is promoted through the mHealth solutions. The role of the patient in an mHealth infrastructure is crucial, as the treatment team relies on the patient to use the infrastructure and collect and provide data on vital parameters such as heart rate and rhythm as well as symptoms and potential risk factors. However, before patients can take on such a task, they should be educated and clearly instructed, so they understand what is expected from them.

3) The treatment may be provided by a multidisciplinary treatment team. This team consists of cardiologists, nurses, primary care physician and other specialists that might be involved in the management of AF, depending on the individual case. Infrastructure for such an approach might be available in terms of a specialized AF-clinic,[36] where cardiologists and specialized nurses would work closely with the patient, in a face to face setting or via teleconferencing, aiming to improve efficiency and outcomes.[37] Communication is key in such teams to assure that all team members understand their role and contribution, and that there is a designated care coordinator. Depending on the context this may be a nurse within the AF-clinic or administrative staff.

4) The final component of integrated care is the delivery of comprehensive treatment. Besides the management of AF (ie, heart rate and/or rhythm control strategy to improve symptoms) alone, it is crucial to determine the potential stroke risk and prescribe appropriate oral anticoagulation accordingly to prevent thromboembolic complications; management of precipitating factors (such as underlying cardiovascular conditions and modifiable risk factors) to reduce the cardiovascular burden to consequently reduce the AF burden.[33 , 38 , 39 , 40]

These four fundamentals form the basis of an integrated AF care approach and the use of mHealth solutions through teleconsultations, seamlessly fits within an AF-clinic as well as with the aims of integrated care: improving outcomes while preventing fragmentation of care. One possible pathway to implement an on-demand mHealth infrastructure for remote heart rate, rhythm and risk factor assessment to allow comprehensive AF management through teleconsultation is shown in Figure 4.

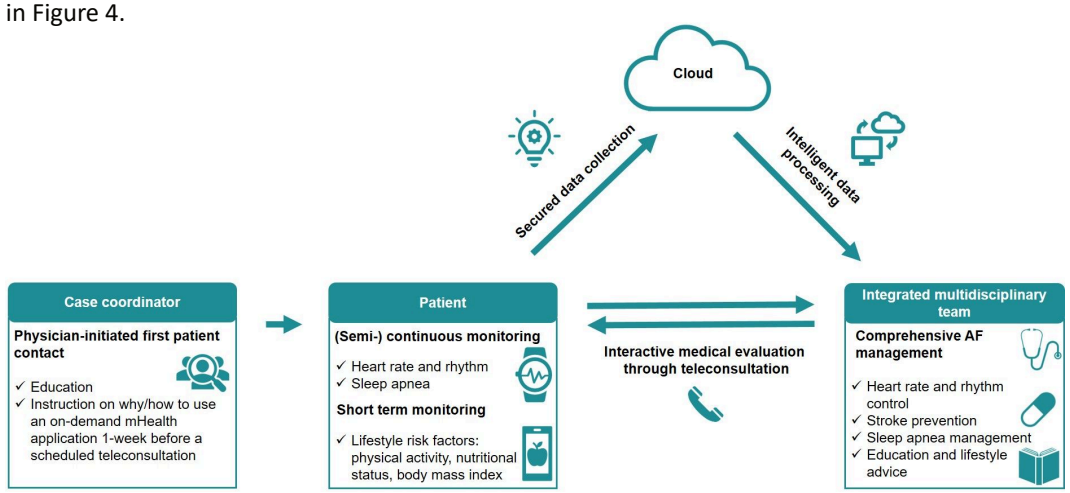

Figure 4. Remote heart rate, rhythm and risk factor assessment by the use of mobile health solutions through teleconsultation.

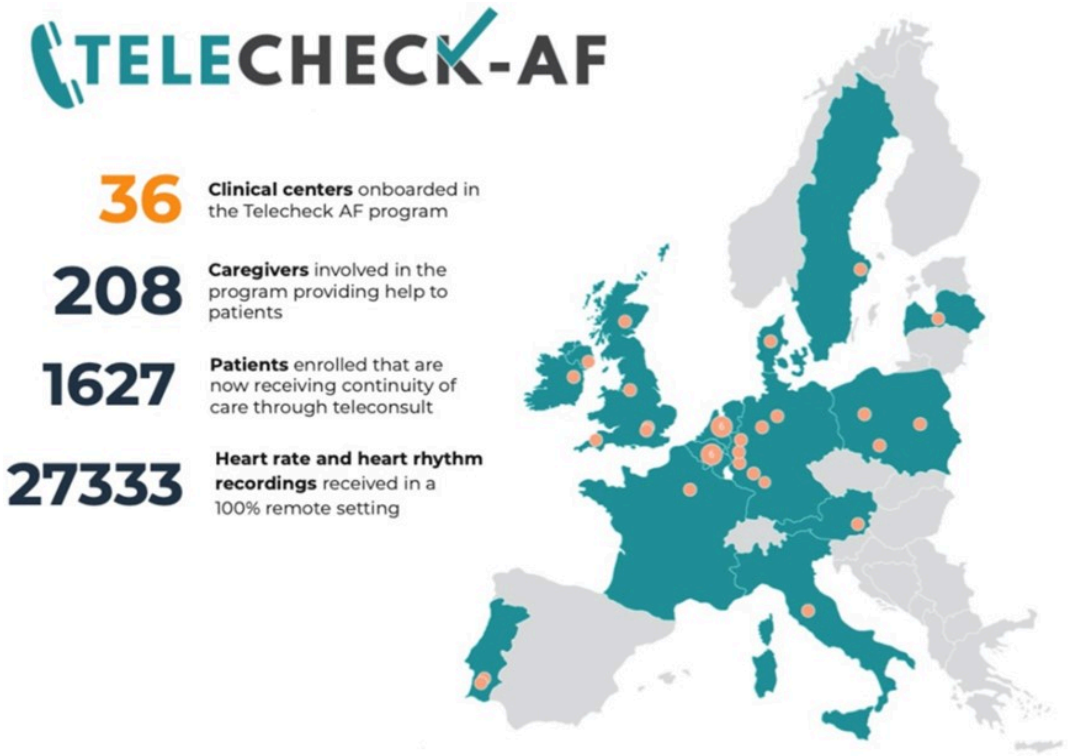

Figure 5. The TeleCheck-AF project

An example of an mHealth project to manage AF patients through teleconsultation during COVID-19

TeleCheck-AF is an on-demand mHealth intervention incorporating an app-based heart rate and rhythm monitoring infrastructure to allow remote AF management through teleconsultation. During the COVID-19 pandemic, it was made available in several European centres to keep AF patients out of the hospital (see Figure 5).[39 , 41 , 42] TeleCheck-AF involves a structured teleconsultation (“Tele”) preceded by an app-based on-demand heart rate and rhythm monitoring infrastructure (“Check”) to guarantee comprehensive AF management (“AF”).[39] The Conformité Européenne (CE)-marked PPG-based mobile phone app (www.fibricheck.com) allows semi-continuous heart rate and rhythm monitoring of AF patients for 7 days prior to and during the teleconsultation. One important advantage of TeleCheck-AF compared to other systems of telemonitoring is the on-demand mHealth approach.[43] It enables the physicians to use heart rate and rhythm data for treatment decisions and prevents unnecessary data collection which would be the case with continuous long-term heart rate and rhythm telemonitoring systems (eg, wearables devices or CIEDs), and which need to be managed afterwards requiring work-intensive and expensive data management infrastructures. Additionally, the on-demand heart rate and rhythm monitoring approach empowers patients to monitor their vital parameters and self-manage their condition. Patients are involved in making decisions about measurement time and number of measurements during the day, that depends in particular on the presence of symptoms. Furthermore, the TeleCheck-AF approach provides crucial information about symptom-rhythm correlation by simultaneous rhythm and symptom assessment to steer appropriate AF management. The TeleCheck-AF infrastructure can be combined with other available app-based risk factor assessment tools, to allow the comprehensive remote assessment and management of AF patients.

Further challenges for implementation of mHealth in clinical

Implementation of mHealth infrastructures require adaptation of existing care coordination and clinical pathways.[43] An important element for embedding mHealth in clinical practice is the accessibility of the recordings by other healthcare professionals. For this, a connection with the patients' electronic healthcare record is crucial. This connection facilitates automatic transmission of the recordings from the secured cloud to the electronic healthcare record of the patient and increases the accessibility of the data for other healthcare professionals. Additionally, many AF apps lack scientific validation and are written at excessively high reading-grade levels challenging users with limited health literacy. Although mHealth solutions for heart rate and rhythm monitoring are clinically established and used, apps for longitudinal risk factor assessment are not available and were therefore not yet incorporated in the TeleCheck-AF approach. Finally, a multi-disciplinary effort by regulatory agencies, healthcare organizations, and app stores is required to improve relevance, scientific validity, and readability of AF apps for AF patients.[44] Additionally, discussions with insurance companies about reimbursement of mHealth infrastructures and with different stakeholders to agree on security and privacy regulations are initiated in different countries.[31 , 45]

Conclusion

Health tools in the management of AF are becoming indispensable in current healthcare. Novel tools are able to remotely assess heart rate and rhythm and incorporate AF risk factor assessment to allow comprehensive AF management through teleconsultation. TeleCheck-AF is one, but not the only possible solution to improve remote AF care during the COVID-19 pandemic and will provide insight into the additional value and potential limitations of mHealth strategies to remotely manage AF patients. Such mHealth infrastructures may be well suited within an integrated AF-clinic, which may require redesign of practice and reform of health care systems.

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CHAPTER 5

Mobile health solutions for atrial fibrillation detection and management: a systematic review

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Abstract

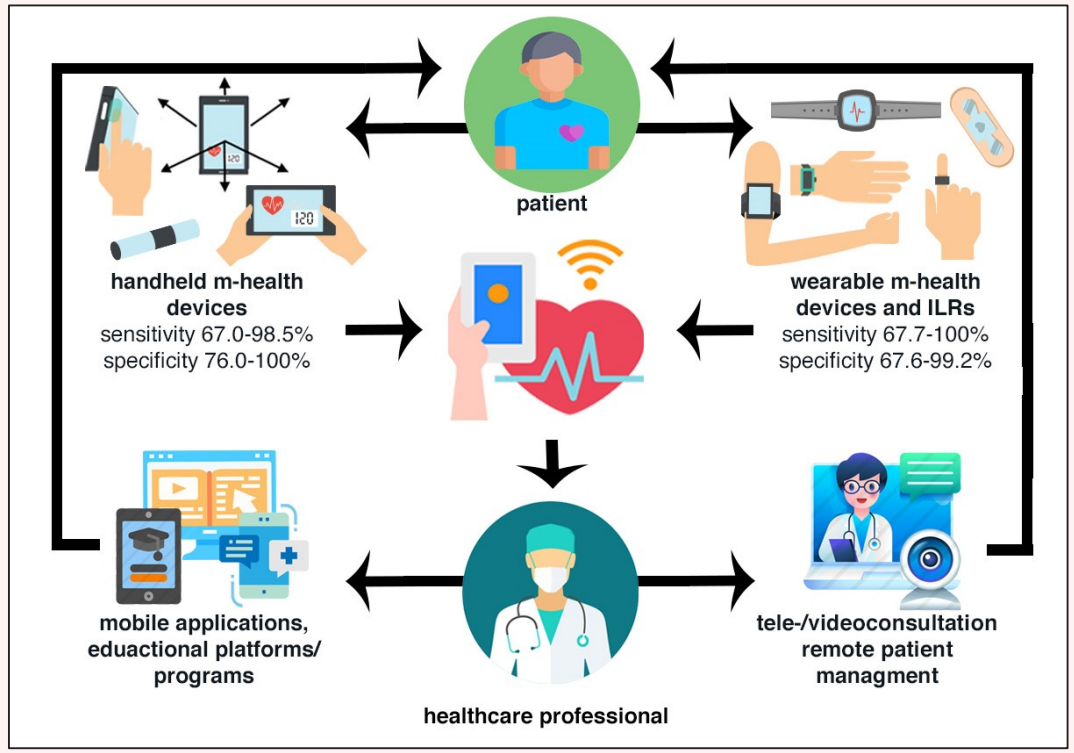
Aim: We aimed to systematically review the available literature on mobile Health (mHealth) solutions, including handheld and wearable devices, implantable loop recorders (ILRs), as well as mobile platforms and support systems in atrial fibrillation (AF) detection and management.

Methods: This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The electronic databases PubMed (NCBI), Embase (Ovid), and Cochrane were searched for articles published until 10 February 2021, inclusive. Given that the included studies varied widely in their design, interventions, comparators, and outcomes, no synthesis was undertaken, and we undertook a narrative review.

Results: We found 208 studies, which were deemed potentially relevant. Of these studies included, 82, 46, and 49 studies aimed at validating handheld devices, wearables, and ILRs for AF detection and/or management, respectively, while 34 studies assessed mobile platforms/support systems. The diagnostic accuracy of mHealth solutions differs with respect to the type (handheld devices vs wearables vs ILRs) and technology used (electrocardiography vs photoplethysmography), as well as application setting (intermittent vs continuous, spot vs longitudinal assessment), and study population.

Conclusion: While the use of mHealth solutions in the detection and management of AF is becoming increasingly popular, its clinical implications merit further investigation and several barriers to widespread mHealth adaption in healthcare systems need to be overcome. Mobile health solutions for atrial fibrillation detection and management: a systematic review.

Keywords: Atrial fibrillation; Systematic review; mHealth.



Graphic abstract. Mobile health solutions for atrial fibrillation detection and management: a systematic review.

Introduction

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia affecting more than 37 million people worldwide [1, 2]. According to current international guidelines, AF management should be organized in an integrated care model [3]. One important component of an integrated care model is usage of technology, such as mobile health (mHealth). mHealth is defined as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices" [4] which can engage patients in their treatment and support health care professionals (HCPs) to provide comprehensive and personalized diagnostic and therapeutic processes. Therefore, several handheld and wearable devices, implantable loop recorders (ILRs), mobile platforms, and support systems have been developed to support detection and integrated AF management. However, many of the available mHealth solutions are not clinically validated. Hence, caution is needed in their clinical use. To date, no systematic review has comprehensively evaluated the impact of the variety of mHealth tools developed for patients with AF and HCPs who manage this condition. In this systematic review article, we summarize the available literature on mHealth solutions including handheld and wearable devices, ILRs (Fig. 1), as well as mobile platforms and support systems in AF detection and management.

Methods

Search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [5]. The electronic databases PubMed (NCBI), Embase (Ovid), and Cochrane were systematically searched for articles published until 10 February 2021, inclusive. The main search strategy is available in Table S1 (supplementary material online).

Eligibility criteria

We included case–control, cohort, and cross-sectional studies that evaluated the effects of mHealth solutions designed to screen and monitor AF, enhance patient's and/or HCP's education of AF, improve communication between AF patients and HCPs, or to encourage active AF patient involvement in the management of their condition. Randomized and non-randomized controlled trials (RCTs) were only considered if demographic and outcome data were available. We excluded duplicates, published conference abstracts, case reports, studies without original data (e.g., reviews, commentaries, editorials), non-English written articles, and studies that only included routine methods of cardiac monitoring (pacemaker, cardiac resynchronization therapy, implantable cardioverter defibrillators). We included both invasive and non-invasive technologies since there is growing number of invasive tools that could be managed remotely by Bluetooth technology.

Data extraction

All identified studies were screened based on their title and abstract against the search criteria by two reviewers (A.N.L.H. and M.G.). The search was supplemented by manually screening the reference lists of the articles that were selected based on the search. The full texts of all articles were independently assessed by both reviewers and if they still met the eligibility criteria, the manuscript was included. Disagreements were resolved through assessment by a third reviewer (L.D.).

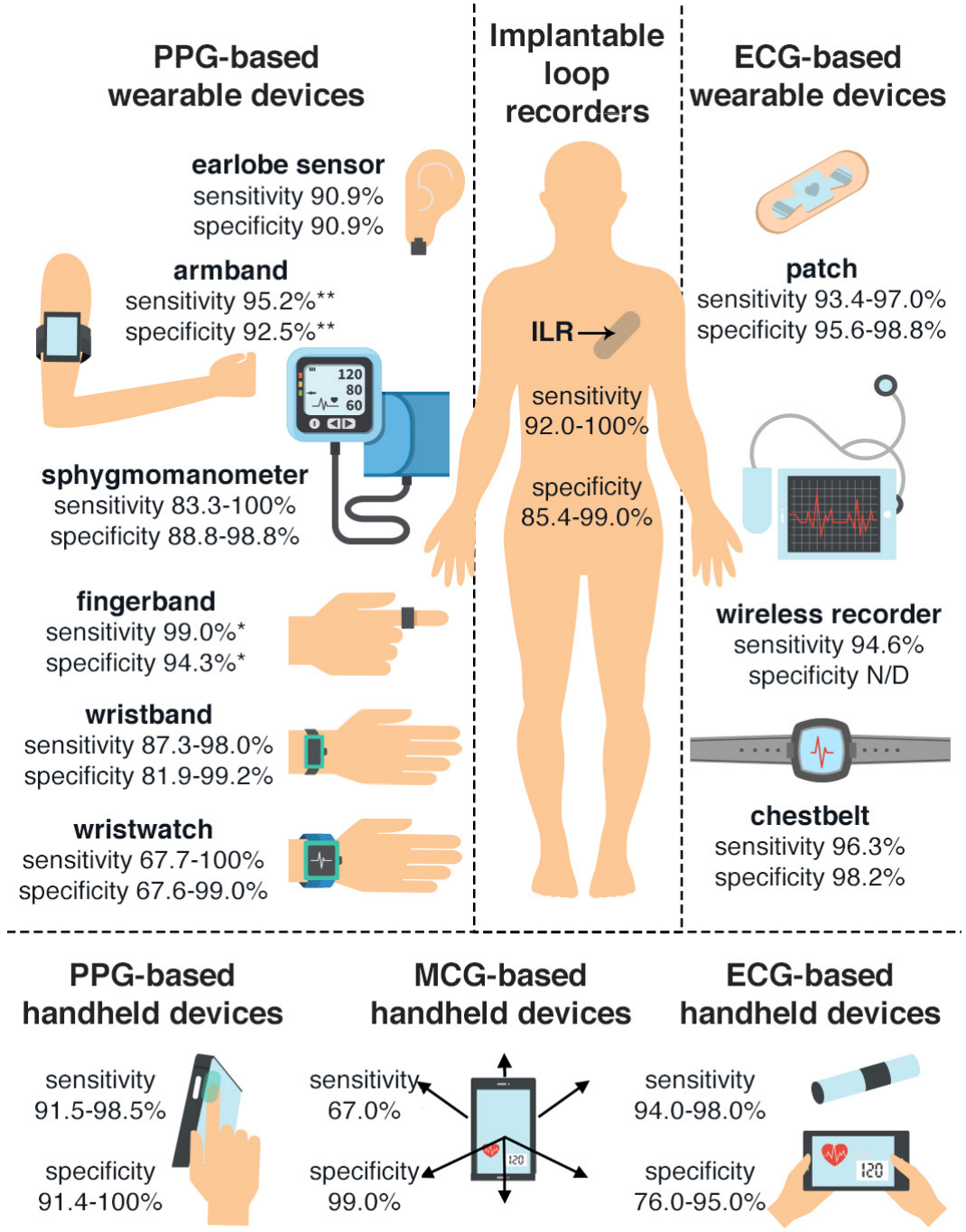


Figure 1. Presentation of mobile health devices and their sensitivity and specificity considering 12-lead electrocardiogram as the gold standard.
*This figure summarizes the literature as performed in this systematic review. Sensitivity and specificity range were given when an mHealth solution was clinically validated by > 1 study. *Single-lead electrocardiogram as the gold standard; **24-h Holter monitoring as the gold standard. ECG electrocardiography, MCG mechanocardiography, PPG photoplethysmography*

Data synthesis

Given that the included studies varied widely in their design, interventions, comparators, and outcomes, no synthesis was undertaken, and we undertook a narrative review.

Results

We identified 1483 studies (Fig. 2). After exclusion of duplicates (n = 407), non-English written articles (n = 19), studies with unsuitable study design (n = 501), not original data (n = 133), and articles without full text availability (n = 200), the titles, and abstracts of 223 articles were independently assessed for eligibility in their full text. Of these, 208 were deemed potentially relevant. A full list of the excluded studies after full-text reading and the reason for exclusion are provided in Table S8 (supplementary material online). Of the 208 studies included, 82, 46, and 49 studies aimed at validating handheld devices, wearables, and ILRs for AF detection and/or management, respectively, while 34 studies assessed mobile platforms/support systems (Fig. 3).

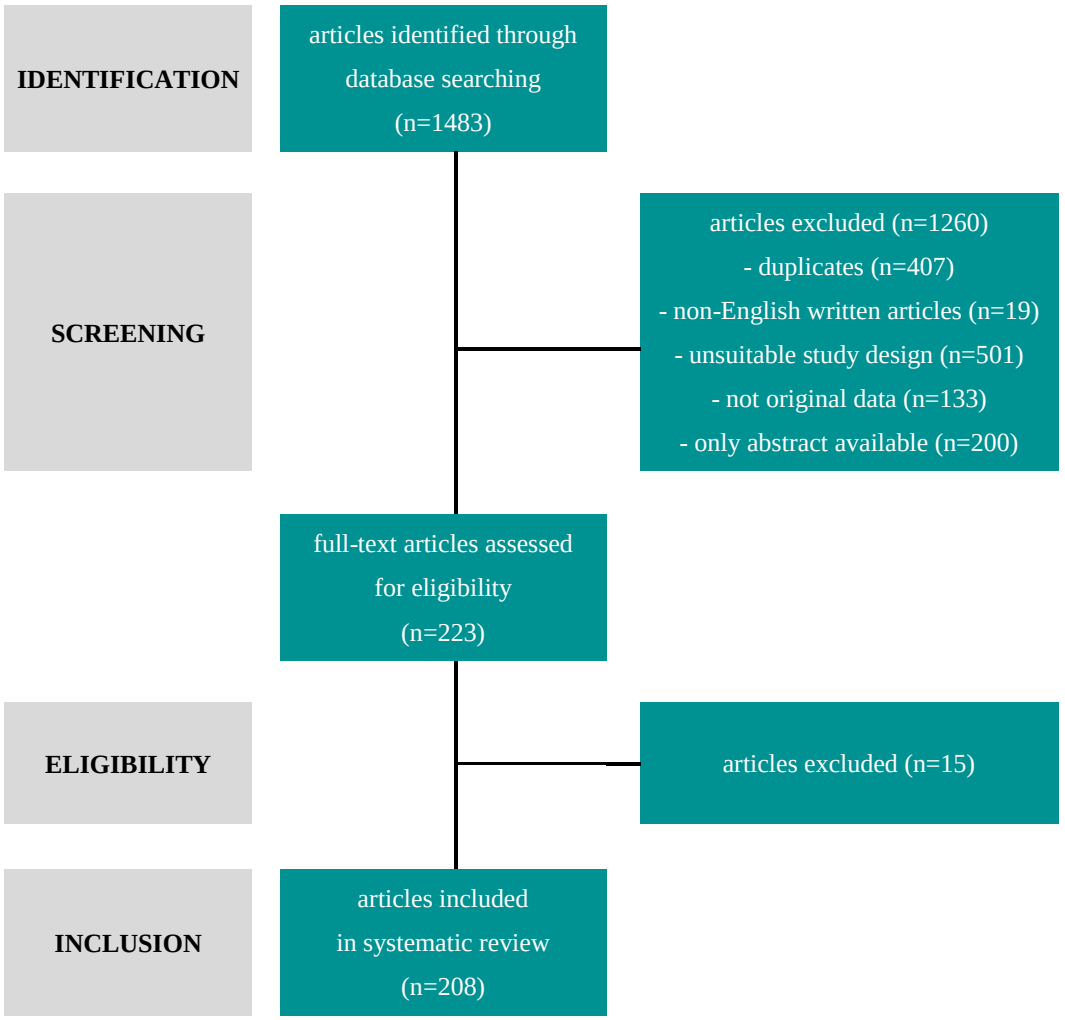


Figure 2. Flow diagram for study selection process.

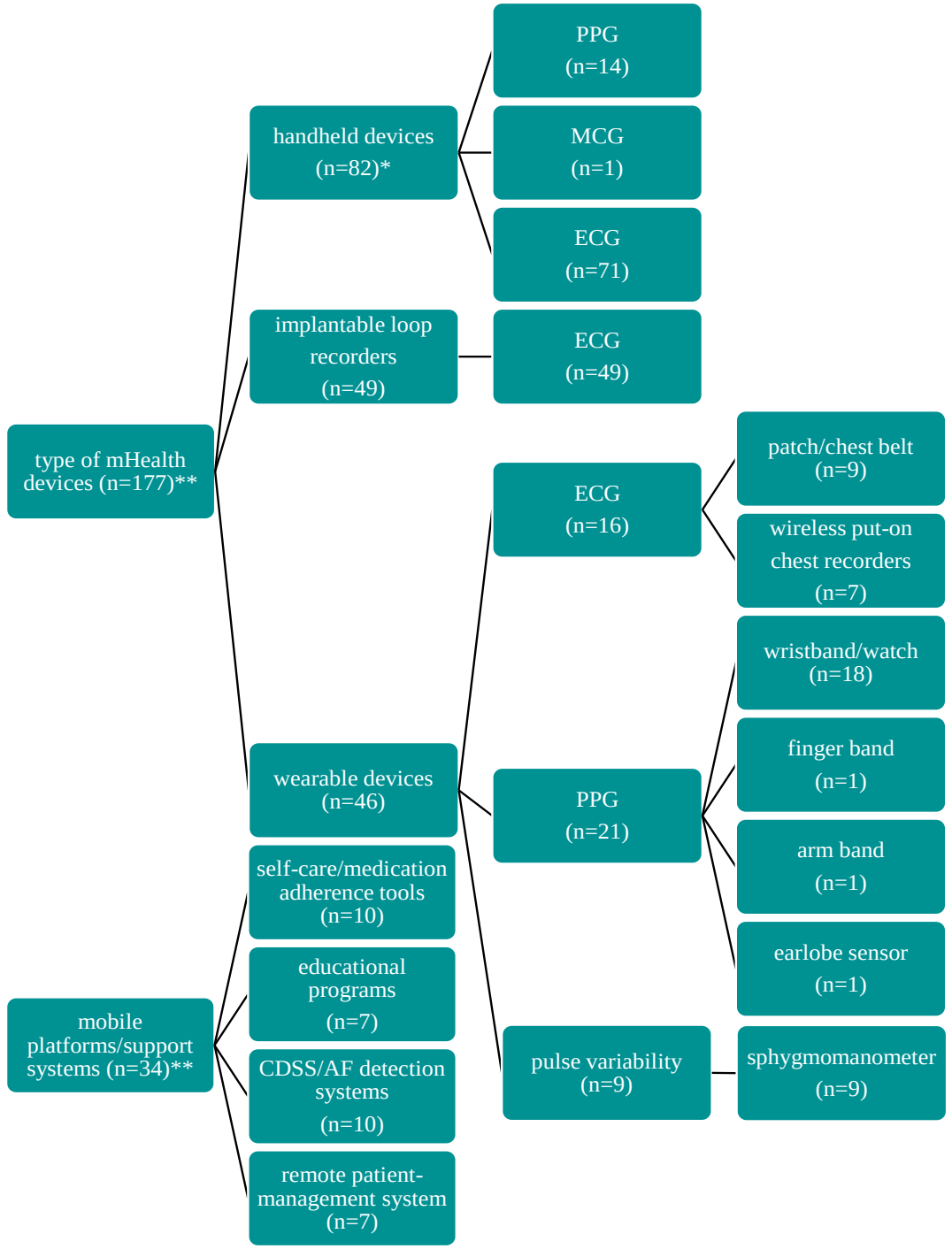


Figure 3. Type of mobile health solutions for atrial fibrillation detection and management.
**Numbers do not add up to 82 as 4 studies assessed in parallel PPG- and ECG-based device, **numbers do not add up to 208 as 3 studies assessed in parallel handheld device with mobile platforms/support systems (n = 1) and wearable devices (n = 2). AF atrial fibrillation, CDSS clinical decision system support, ECG electrocardiography, MCG mechanocardiography, mHealth mobile health, PPG photoplethysmography*

Handheld devices

A handheld device is a piece of computing equipment that can be used by holding in hand or touching it by a finger, activated by user and capable of detecting, analyzing and transmitting information concerning body signals with provided biofeedback. There are three technologies available to detect and monitor AF by a handheld device or mobile phone: photoplethysmography (PPG)-, electrocardiography (ECG)-, and mechanocardiography (MCG)-based devices [4]. Brief population characteristics of the studies on handheld devices, including their sensitivity and specificity, for AF detection and monitoring are presented in Table S2 (supplementary material online).

Photoplethysmography-based devices

PPG technology is an optical technique that uses blood volume changes in the microvascular tissue bed that directly reflects pulse morphology. In PPG recordings, AF manifests as varying pulse-to-pulse intervals and pulse morphologies [4].

Despite the availability of multiple PPG-based mobile apps, only a few have been validated. Clinical validation studies (n = 14) have been performed for FibriCheck [6–8], CardiioRhythm [9–11], Preventicus [12–16], and PULSE-SMART [17]. Majority (10 [71%]) of the studies were prospective cohort studies. One study (7.7%) was a RCT. Studies included between 88 and 10,000 participants with a mean age between 49 and 78 years, and with a percentage of females ranging from 35 to 100%. Only FibriCheck is currently cleared by the Food and Drug Administration (FDA) and Preventicus is in the FDA certification process. Both FibriCheck and Preventicus had Conformité Européenne (CE) approval. All mobile phone applications use the fingertip to measure PPG signals. Only CardiioRhythm can also derive PPG signals from the face. The duration of one PPG recording differs between the mobile applications: FibriCheck and Preventicus use 60-s recordings for heart rate and rhythm assessment, CardiioRhythm records for 20 s, and PULSE-SMART for up to 2 min. The Preventicus app also provides the option to extend measurements up to 5 min to enable less frequent arrhythmic events to be recorded more accurately. All apps provide the possibility to combine heart rhythm monitoring with symptom annotation and tracking. Secure cloud solution allowing PPG recordings storage and access for both patients and their HCPs is available for all four abovementioned apps. In the case of FibriCheck and Preventicus, there is the possibility for a medical team of experts to perform an evaluation of the measurements to exclude possible measurement errors and to verify heart rhythm disturbances from a medical-technical point of view. Additionally, they provide a structured and detailed report in a standardized format, which may be shared with HCPs and allows implementation in a digital patient record. Despite some feature differences, sensitivity and specificity for all aforementioned applications are high, with the highest sensitivity reported for PULSE-SMART (97.1%) and the highest specificity reported for Preventicus (98.1%). However, the sensitivity and specificity reported for the different devices are based on simultaneous disposable PPG and ECG recordings (from 1 to 6 repetitions). Data on the accuracy for longitudinal heart rhythm monitoring are lacking. The recording time (ranging from 20 s to 5 min) did not impact the accuracy to detect AF. Only one study compared a 1-min measuring period to a 5-min measuring period and demonstrated no impact on sensitivity and specificity, while the signal quality decreased from 93.3% (1-min test) to 67.7% (5-min test) [12]. Studies in which a 12-lead ECG was used as reference to assess the sensitivity and specificity of the respective app revealed a slightly higher range of sensitivity as compared to those where single-lead ECG was used as the reference (sensitivity: 93.1–98% vs 89.9–95.4%; specificity: 88–96.2% vs 85–99.6%). The highest sensitivity was observed among the elderly population (98%), whereas the highest specificity was observed among hospitalized patients at cardiology/geriatric wards (99.7%). The accuracy to detect AF was comparable for on-demand PPG-based handheld devices and continuous heart rate and rhythm monitoring by wearable PPG-based devices (e.g., wristbands)

(sensitivity: 95.4% vs 95%, specificity: 99.7% vs 99.7%, respectively) [13]. Moreover, the sensitivity to detect AF by PPG-based handheld devices seems to be equal to (both 98%) [7] or even higher (92.9% vs 71.4%) than ECG-based handheld devices with comparable specificity (88–97.7% vs 85–99.4%) [18].

Electrocardiography-based devices

MyDiagnostick [19, 20]1 [21–27] and KardiaMobile [7, 11, 16], [24, 28–75] represent the most widely used examples of ECG-based devices. Limited data are available for additional devices, such as DigiO2 Cardio Care ECG recorder [76], Zenicor-EKG [77–79], Card Guard [80], Sensor mobile 100 [81, 82], CardioBip [83, 84], and ECG check [85]. Overall, clinical validation studies (n = 71) have been performed, of which 54 (76%) were prospective cohort studies and 10 studies (14%) were RCTs. Studies included between 21 and 1,952,811 participants with a mean age between 40 and 79 years, and with a percentage of females ranging from 16 to 80%.

MyDiagnostick is a CE-marked, stick-shaped handheld device intended to detect AF within 45–60 s by holding both metallic handles. After recording, physicians can review, share, and store the ECG data by connecting the device via USB to a computer. Data can be analyzed by a standalone PC application or an internet-based web portal [27]. KardiaMobile is an FDA/CE-approved handheld tool that converts electrical ECG signals, from electrodes located on a metallic plate after 30-s finger touch to ultrasound signals, and transmits these signals to a smartphone as a single-lead ECG. Importantly, KardiaMobile 6L provides a third electrode which can be put on the left knee or ankle to imitate the 6 classic limb leads of a full 12-lead ECG. The recorded data are stored in an encrypted cloud accessible for the patient and HCP.

Most of the available studies regarding MyDiagnostick were performed for AF screening [19], [21–23, 25–27, 86, 87]; only one study used this device to monitor patients with recent-onset AF treated with cardioversion or rate control medication [20]. Overall diagnostic sensitivity and specificity ranged from 60.5 to 100% and 93 to 97.3%, respectively. The highest sensitivity was reported among patients admitted to cardiology outpatient clinics (100%) and specificity in those hospitalized in geriatric clinics (97%). In all analyzed studies, heart rate and rhythm measurements were performed at a single time with 12-lead ECG as gold standard for device accuracy.

The number of studies describing the diagnostic accuracy of KardiaMobile is almost five times higher compared to the studies on MyDiagnostick, which could explain the wide range of diagnostic sensitivity (38–100%) and specificity (29.2–100%) of KardiaMobile, potentially impacted by the heterogeneity of included patient groups. Most of the studies assessed accuracy of KardiaMobile to detect AF by 1–2 measurements at a single time point. Only three studies assessed sensitivity and specificity of KardiaMobile during more than one day, demonstrating a sensitivity of 94.6% and specificity of 92.9% in case of 4 measurements per day for 1 month [88], a sensitivity and specificity of 95.3% and 97.5% in case of 3 standard measurements per day and additional measurements in case of symptoms for 1 month [73], and a sensitivity of 38% in case of 2–3 measurements per day for 5 days [53]. Taking patient selection into account, the highest sensitivity and specificity were observed in elderly patients (aged ≥ 65 years). Higher sensitivity and specificity range were observed if a 12-lead ECG was used as gold standard compared to “expert” diagnosis (54.5–100% vs 38–100% and 65–100% vs 29.2–99%, respectively). To date, only one study has performed a direct comparison of MyDiagnostick and KardiaMobile for AF detection in both cardiology and geriatric wards showing suboptimal sensitivity and specificity values for both devices (cardiology ward: 81.8 and 94.2%, respectively, for MyDiagnostick; 54.5 and 97.5%, respectively, for KardiaMobile; geriatric ward: 89.5 and 95.7%, respectively, for MyDiagnostick; 78.9 and 97.9%, respectively, for KardiaMobile) [24].

Mechanocardiography-based devices

MCG-based apps record mechanical cardiac activity via accelerometers and gyroscopes, registering the tiny cardiogenic micro movements of the patient's chest for signal acquisition [4]. The data on this technology are limited; to date only one study has evaluated this method for AF detection. This study included 300 participants (median age 75, 44% women) and demonstrated a low sensitivity (67%) and high specificity (99%) when compared to 5-lead telemetry ECG [89]. Further studies are needed to establish this method for accurate AF detection.

Wearable devices

Wearables are lightweight, sensor-based devices, which are worn close to and/or on the surface of the skin, where they detect, analyze, and transmit information continuously or on-demand concerning body signals to an external device and provide biofeedback. These devices are becoming increasingly popular and encompass a wide range of PPG-based devices, including wristwatches/bands, armbands, fingerbands, and earlobe sensors, ECG-based devices, including patches, chest belts, and wireless recorders, as well as pulse variability-based devices, such as sphygmomanometers. Brief population characteristics of the studies on wearable devices are presented in Table S3 (supplementary material online).

Photoplethysmography-based wearables

Overall, clinical validation prospective cohort studies (n = 21) have been performed, included from 20 to 419,297 participants with a mean age between 41 and 76 years, and with a percentage of females ranging from 15 to 49%. Most studies using wristwatches/bands, armbands, and fingerbands incorporating PPG technology have focused on AF detection [90–105], and only a few on heart rate monitoring [106–110]. Most devices can be worn around the wrist, while Everion® is worn on the upper arm and CardioTracker as a ring on the finger. Apple Watch, Fitbit, and Empatica E4 were cleared by CE and the FDA, and CardiacSense is in the advanced stage of FDA and CE certification. A secure cloud solution allowing storage of PPG recordings and access for patients is available for Apple Watch, Fitbit, CardiacSense, Samsung Simband, Empatica E4, Gear Fit 2, Wavelet Health, Amazfit, Honor Band 4, Huawei Watch GT, and Honor Watch. In the case of Samsung Simband, there is the possibility to ask a medical team of experts about specific health questions and to perform an evaluation of the measurements to exclude possible measurement errors and to verify heart rhythm disturbances from a medical-technical point of view.

Overall sensitivity and specificity for all validated wristwatches/bands, armbands, and fingerbands are high and range from 67.7 to 100% and 60.7 to 100%, respectively, with the highest sensitivity of CardiacSense (100%) [93] and of Honor Band 4, Huawei Watch GT, and Honor Watch (100%) [97], and specificity of CM3 Generation-3 (100%) [95]. However, reported sensitivity and specificity are based on different monitoring periods that vary from 60 s [100] to 855 h [95]. Interestingly, despite differences in measurement times, the accuracy to detect AF using these wearables was comparable between all studies. Additionally, accuracy levels of the wristbands/watches [90–101, 105–110], fingerbands [102], and upper armbands [103] and PPG-based earlobe sensor [104] were similar. Studies in which a 24-h Holter monitor was used as a reference to assess the wearable's specificity for AF detection revealed a slightly higher range of specificity when compared to those where 12-lead ECG or single-lead ECG was considered the gold standard (84.9–100% vs 67.6–99% and 60.7–100%, respectively). Studies in which single-lead ECG was used as a reference to assess the wearable's sensitivity revealed a slightly higher range of sensitivity when compared to those where 24-h Holter or 12-lead ECG was considered as the gold standard (79–99% vs 71.6–95.2% and 67.7–100%, respectively). Two studies directly compared the diagnostic accuracy of PPG-based wristwatches/bands and ECG-based wristbands. The study by Chen found a higher sensitivity and

a lower specificity for wristwatches/bands using PPG compared to wristbands using ECG (88% vs 87.3% and 96.4% vs 99.2%, respectively) [99]. In contrast, in the study by Selder, PPG-based wristwatches/bands had a lower sensitivity and a similar specificity compared to ECG-based wristbands (79% vs 93% and 98% vs 98%, respectively) [100]. Further research is warranted to further investigate the diagnostic accuracy of PPG-based and ECG-based wristwatches/bands, armbands, and fingerbands in a selective high-risk population.

Electrocardiography-based wearables

Overall, clinical validation studies (n = 16) have been performed, of which 13 (81%) were prospective cohort studies with no RCTs. Studies included between 10 and 27,841 participants with a mean age between 53 and 66 years, and with a percentage of females ranging from none to 56%. Patch-based wearables record ECG signals without visible electrodes and lead wires. Eight studies focused on AF detection using patch-based devices, such as ZioXT [111–114], RhythmPad [115], and Firstbeat Bodyguard 2 [57], which were all CE approved. Only ZioXT was cleared by the FDA. Most patches provide single-lead or 3-lead ECG recordings and are attached to the patient's chest, whereas RhythmPad consists of 3 sensors placed around both arms and the right leg and records a 6-lead ECG. A patch can be used for uninterrupted heart rhythm monitoring for different time periods [from 10 s (RhythmPad) to 2 weeks or even longer (ZioXT)]. Several patches have the possibility to combine heart rhythm monitoring with symptom annotation, as they contain a trigger button that can be pressed when patients experience symptoms. A secure cloud solution allowing ECG recordings storage and access for both patients and HCPs is available for ZioXT, RhythmPad, and Firstbeat Bodyguard 2. Only ZioXT has the possibility to provide structured and detailed reports in a standardized format that could be shared with HCP and implemented in a digital patient record.

Two studies investigated the diagnostic accuracy of patches in AF detection [57, 115]. Overall diagnostic sensitivity and specificity of RhythmPad and Firstbeat Bodyguard 2 ranged from 93.4 to 96.3% and 96.8 to 98.8%, respectively, with the highest sensitivity of Firstbeat Bodyguard 2 (96.3%) and specificity of RhythmPad (98.8%). However, reported sensitivity and specificity levels are based on short continuous heart rhythm monitoring, ranging from 10 s to 2 min. Data on patches' long-term accuracy are lacking. The highest sensitivity was observed in patients above 65 years of age, whereas the highest specificity was observed in patients at high AF risk. Accuracy of both aforementioned patches was determined using 12-lead ECG as the gold standard. The accuracy level of ECG-patches is comparable with the sensitivity and specificity of ECG-based chest belt devices (ranging from 96.3 to 97% and 95.6 to 98.2%, respectively) [57, 116]. Additional research is needed to establish the accuracy level of patches in detection of AF.

Wireless recorders enable automatic arrhythmia detection and transmission of patient data files to service centers for immediate analysis and physician attention. ECG data of most wireless recorders are stored in an encrypted cloud. Transmission occurs without patient interaction. Wireless recorders can provide single-, 3-, or 12-lead ECG recordings. In several studies [117–122], wireless ECG recorders were used for short- and long-term continuous monitoring (ranging from 4 min to 24 h) and for long-term intermittent monitoring using single-lead ECG (ranging from 30 s daily for 4 weeks to 30 s twice daily for 6 months). Despite several ECG-based wireless recorders being available, only Medi-Trace 200 has been validated in clinical studies and had FDA and CE approval. The study of Lin revealed a high sensitivity of 94.6% and positive predictive value of 99.4% for Medi-Trace 200 in patients with and without a coded diagnosis of AF [117]. Additional research is warranted to establish the accuracy level of wireless ECG recorders in detection of AF in comparison to other wearable ECG- or PPG-based devices.

Pulse variability-based wearables

Overall, clinical validation prospective cohort studies (n = 9) have been performed that included between 73 and 2052 participants with a mean age between 58 and 80 years, and with a percentage of females ranging from 35 to 63%. Sphygmomanometers are automatic upper arm or wrist oscillometric blood pressure monitors, which can incorporate an algorithm for AF detection. Based on sphygmomanometer recordings, AF is concluded if at least two of three measurements show pulse irregularities. Nine studies focused on AF detection using sphygmomanometers [60, 123–130]. The Microlife BP [60, 124, 126–130] and OMRON [125, 130] have been validated in these clinical studies, and both have FDA and CE approval. Secure cloud solution allowing PPG recordings storage and access for patients and HCPs is available for both types of sphygmomanometers. In addition, they provide structured and detailed reports in a standardized format, which could be shared with HCPs and implemented in a digital patient record. Despite some differences in features, overall sensitivity and specificity for the validated sphygmomanometers are high, ranging from 83.3 to 100% and 88.8 to 98.8%, respectively. Most reported sphygmomanometers' sensitivity and specificity are based on single measurements (from 1 to 3 repetitions), and only Wiesel et al. provided long-term intermittent accuracy data of sphygmomanometer (4 repetitions per day for 30 days) [124]. Irrespective of measurement time, the accuracy levels of sphygmomanometers to detect AF were comparable. The study in which single-lead ECG was the reference to assess sphygmomanometer's accuracy [124] revealed a higher sensitivity and a slightly lower specificity as compared to those in which 12-lead ECG was considered as the gold standard (99.2% vs 94.6 and 92.9% vs 93.4%, respectively). A sphygmomanometer is a promising technology for the first step of AF screening. As hypertension is a major modifiable risk factor for AF, using a sphygmomanometer for AF detection would be valuable for the large number of hypertensive patients who monitor their blood pressure. To date, only one study examined the diagnostic accuracy of a sphygmomanometer in hypertensive patients. Therefore, additional research on accuracy of sphygmomanometer in AF detection in this specific population would be interesting.

Implantable loop recorders

ILRs are small devices inserted beneath the skin of the chest. Once implanted, the devices automatically capture continuous ECGs or can be activated manually by the patient if symptoms occur using optional external handheld patient devices or smartphone applications (Fig. 3). Wireless technology enables communication between the ILR and the clinician programmer, smartphone, or tablet. The information from the device is used to regularly inform the patient about abnormal heart rhythm, evaluate symptom–rhythm relations and, through manual activation, enable patients to self-management. ILR detection parameters, data storage, and methods of data transmission are presented in Table S4 (supplementary material online). The most frequently used ILRs are the Reveal [44, 131–172], BioMonitor [140, 173–175], and Confirm [146, 176, 177].

Overall, clinical validation studies (n = 49) have been performed, of which 30 (61%) were prospective cohort studies with 4 (8.2%) RCTs. Studies included between 30 and 1247 participants with a mean age between 49 and 76 years, and with a percentage of females ranging from 9 to 53%. Brief population characteristics of the ILR studies are presented in Table S5 (supplementary material online). Most of the included studies reported different lengths of follow-up, but most patients were diagnosed with AF within the first 6 months [150, 155, 167]. In a study by Healey, the AF detection rate roughly doubled by 6 months compared to 1 month (64% versus 34%) [176]. This is in line with the CRYSTAL-AF study where the AF detection rate increased from 8.9 to 12.4% and 30% at 6-, 12-, and 30-month follow-up, respectively [168]. Interestingly, most detected AF episodes were asymptomatic [145, 150, 164] and would probably have been missed without continuous ILR monitoring.

None of the studies provided comparative diagnostic test accuracy between a group of patients who were monitored with an ILR and a group that received standard monitoring. However, two studies [155, 158] used traditional AF detection data for a group of patients who were monitored for AF allowing the estimation of the diagnostic accuracy. The study of Choe found sensitivities of between 1.3%, from a single 24-h Holter monitor, and 20.8%, from quarterly 7-day Holter monitoring [158], which was confirmed in a study by Ziegler (24-h Holter monitor: 2.9%; quarterly 7-day Holter monitoring: 22.9%) [155]. Therefore, even the best-performing intermittent monitoring strategy detected less than one-third of the AF detected by ILR. Although ILR is often used as the gold standard to determine the diagnostic accuracy of other AF detection monitors, some studies [140, 157] reported an up to 90% false-positive rate for the Reveal and BioMonitor [140]. From 15% (subpectoral) to 46% (subcutaneous ILR localization Reveal) [157] of all AF episodes detected by the ILR algorithm were not subsequently verified as AF by a reviewing HCP. The mixed population diagnostic test accuracy studies suggest that the performance of the AF diagnosis algorithm in the Reveal XT and Reveal LINQ to diagnose AF improved over time. The study of Pürerfellner used the XPECT trial and Reveal LINQ usability study data sets and reanalized the data by a new ILR AF detection algorithm also incorporating the detection of P-waves [147]. They demonstrated that the accuracy of the Confirm DM2102 and Reveal LINQ improved by the adaptive P-sense algorithm (TruRhythm) to 100% sensitivity for AF detection, while the specificity varied (85.7% and 99.0%, respectively). Data on the diagnostic accuracy of the new version of the BioMonitor (BioMonitor 2-AF) and the Confirm (Confirm Rx) devices are still lacking (Table S4, supplementary material online). High-quality head-to-head clinical trials of the Reveal, BioMonitor, and Confirm are required to enable a direct comparison between the ILR in terms of clinical effectiveness.

Mobile platforms and support systems

The adoption and use of mobile devices (smartphones, watches or tablets) is widespread, with 88% of all users spending time in mobile applications [178]. Over 318 000 mobile applications are now available worldwide [179], including more than 500 dedicated to AF management [180]. Potential uses of those tools in daily practice include self-care/medication adherence tools [29, 181–189], educational programs [190–196], clinical decision support systems/AF detection systems [197–206], and remote patient–management systems [207–213]. Despite a widespread availability, most of the AF mobile platforms and support systems are not evaluated for effectiveness and lack regulatory oversight [214]. To date, only a minority of them are FDA/CE-approved (Table S6, supplementary material online) and/or evaluated in clinical studies Table S7 (supplementary material online). In a recent review of mobile applications for the detection and management of AF, the most common app functionalities were capturing and graphically displaying user self-reported and self-entered data (75%) and PPG waveform monitoring (92%). However, only 42% were scored above average for quality (MARS score ≥ 3.0) [180]. This highlights the need for clinically validated mobile applications to support patients and HCPs in the management of AF.

Self-care/medication adherence tools

Ten studies (60% prospective cohort studies and 40% RCTs) validated mobile app dedicated to comprehensive AF management, including between 10 and 2473 participants (mean age range: 59–69 years; female percentage range: 33–50%). The Health Buddies application was developed to improve adherence to oral anticoagulation in an elderly AF patients spelling out daily challenges for them and their grandchildren. Three-month study duration resulted in a mean increase in AF knowledge level of 5.8%, whereas anticoagulation adherence was as high as 99% [181]. Computer-animated application, designed by Magnani to improve patient education on AF, medication adherence and symptom management, significantly improved quality of life based on AF Effect on

Quality of life (AFEQT) score from 64 to 76%, and medication adherence based on the Morisky 8-item Medication Adherence Scale (MMAS-8) from 7.3 to 7.7 during relatively short time [29].

Several other applications have been developed to enhance patient education, improve communication between patients and HCP, and encourage active patient involvement. The mobile AF application (mAFA-II) trial [183, 215] reported that this holistic app-based management with dynamic risk monitoring and reassessment of the bleeding and thromboembolic risk scores reduced the risks of bleeding (mAFA vs usual care, 2.1% vs 4.3%) [188] and clinical adverse events, including thromboembolic events, rehospitalization, and all-cause death (1.9% vs 6.0%) [187], and increased total oral anticoagulation usage from 63 to 70% [188]. Continuous home monitoring with PPG technology via mAFA recognized AF with a positive predictive value (PPV) of 91.6% [216] suggesting feasibility of this approach for AF screening.

Based on available data, clinicians agreed that mobile applications facilitate AF patient's management with low decisional conflict [186, 213], whereas patients reported an improvement in their quality of life [29, 183, 213], AF- and procedure-related knowledge [186, 195], and medication adherence [29, 181, 183, 184, 186, 213].

Educational programs

Seven studies (2 [29%] prospective cohort studies and 5 [71%] RCTs) validated mobile app dedicated to comprehensive AF management, including from 12 to 720 participants (mean age range: 30–72 years; female percentage range: 24–82%). The OCULUS study was aimed to evaluate the effectiveness of the three-dimensional movie in teaching patients about AF associated consequences and stroke prevention. Patient AF risk and anticoagulation knowledge increased from 70 to 96% and from 22 to 83%, respectively, immediately after movie-based education and remained stable after 1 year [190]. Online tailored education of AF patients, requiring cardioversion or pulmonary vein isolation, improved their procedure knowledge from 65 to 75% based on the Jessa AF Knowledge Questionnaire (JAKQ), and this knowledge persisted at 6 (78%) and 12 (80%) weeks after the AF-related procedures [191]. EVICOAG, a Qstream spaced education platform comprising 12 case-based AF and anticoagulation learning scenarios, improved overall knowledge scores by 54% and use of the CHA2DS2-VASc and HAS-BLED scores among nurses during 6-week education [194]. Graded systematic exposure to online automated webinar dedicated for electrophysiologists improved their baseline identification of AF source on panoramic AF maps by 13% [195].

Clinical decision support systems/atrial fibrillation detection systems

Ten studies (30% prospective cohort studies and 60% RCTs) validated mobile app dedicated to comprehensive AF management, including from 60 to 13,379 participants (mean age range: 44–73 years; female percentage range: 23–44%). Discovery Link AFinder, a web-based application scanning all CareLink® Network transmissions to identify patients with AF among those with cardiac implantable electronic devices, enhanced AF detection sensitivity by 10% and improved oral anticoagulation optimal treatment by 6% [197]. A shared decision-making interaction, facilitated by Atrial Fibrillation Shared Decision Making (AFSDM) [199], Clinical Decision Support for AF (CDS-AF) [202], and Decision Analysis in Routine Treatment Study (DARTS) [205], decreased the rate of discordant antithrombotic therapy leading to improved medication adherence and patient satisfaction. AKENATON, an artificial intelligence tool to filter AF alerts, resulted in an 84% reduction in notification workload, while preserving patient safety [203].

Remote patient–management systems

Seven studies (2 [29%] prospective cohort studies and 5 [71%] RCTs) validated mobile app dedicated to comprehensive AF management including from 10 to 2281 participants (mean age range:

61–74 years; female percentage range: 32–48%). In a study by Shacham, instructions delivered by telephone to patients supported a conversion rate of almost 80% of AF episodes, whereas additional interventions by an attending physician within a mobile intensive care unit resulted in a conversion rate of only 70% [209]. Recently, the Characterizing AF by Translating its Causes into Health Modifiers in the Elderly (CATCH ME) Consortium, in collaboration with the European Society of Cardiology (ESC), has funded the creation of two applications for patients with AF and their HCPs. The patient application (myAF) aims to enhance patient education, self-management and interaction with HCPs, and the HCP application simplifies the choice of treatment and optimizes AF guideline adherence [217]. AF educational intervention within Integrated Management Program Advancing Community Treatment of AF (IMPACT-AF) trial [212] resulted in a significant increase in the proportion of oral anticoagulation use by AF patients and reduction in thromboembolic events during 12-month observation.

Conclusive remarks and perspectives

In this systematic review we have analyzed 208 studies. Compared to other systematic reviews that focused only on diagnostic accuracy of mHealth devices in screening for and detecting AF [218, 219], platforms, and programs to improve patients' knowledge of AF [220], we performed comprehensive summary of available mHealth devices, mHealth platforms, and mHealth applications for the screening, detection and management of AF for the first time.

The diagnostic accuracy of mHealth devices differs with respect to the type (handheld vs wearable vs ILR) and technology (ECG vs PPG-based devices) used. Based on the current international AF management guidelines of the ESC, ECG confirmation (even single-lead ECG of 30 s or more) is mandated for the diagnosis of AF [3]. PPG technology is not sufficient to diagnose AF based on current ESC guidelines [221]. However, there are already some data demonstrating that PPG technology is nearly as accurate as ECG to detect AF [18], [222]. The ongoing randomized-controlled Heartline Study (NCT04276441) will additionally investigate whether PPG-based devices could reduce thromboembolic events by early AF detection. Most of the ECG- and PPG-based algorithms are validated to detect AF with a high sensitivity and specificity, as most algorithms are developed for AF screening scenarios [223].

mHealth solutions with the same technologies may collect data in different ways (intermittent vs continuous, spot vs longitudinal assessment) as well as different methods of measurement (handheld vs wearable device) which could influence the sensitivity and specificity for AF detection [224]. In addition, AF burden and AF density, which both are gaining importance in the evaluation of AF treatment efficacy, can only be assessed by continuous longitudinal heart rhythm monitoring. Intermittent longitudinal heart rhythm monitoring, as provided by most mHealth handheld devices and wearables, may represent a surrogate variable of true AF burden and density. An important limitation in the utilization of user-controlled devices is the potential underdiagnosis of subclinical and asymptomatic arrhythmias, which do not trigger a rhythm documentation by the wearer. Since AF is often asymptomatic, especially in the early stages of paroxysmal AF, the use of mHealth devices in these subjects can only be applied with caution. Therefore, there is a need to perform head-to-head comparisons between handheld vs wearable devices, as their comparative effectiveness is limited, hence unclear.

To enable a smooth flow of information between the patient and the HCP, a shared infrastructure, in most cases a secured and certified cloud, is crucial to make patient data remotely available. A physician-initiated or at least guided approach appears to be necessary to allow personalized mHealth use and the selection of the right tool for each patient. Moreover, in addition to heart rate and rhythm monitoring, which can be performed by several mHealth solutions, the KardiaMobile and the Apple Watch allow a more detailed ECG interpretation incorporating QRS duration and QT interval analysis, [225–228] supraventricular tachycardia differentiation [229], and estimation of potassium levels by changes in T-wave morphologies [230].

Although mHealth solutions are becoming increasingly popular in the detection and management of AF, there are several barriers to widespread mHealth adaption in healthcare systems. Until reimbursement will not be provided by health insurances or the government, use of mHealth solutions will be limited to those patients who are willing to pay out-of-pocket for such a support, which may contribute to digital and mHealth inequity and fragmented care. Based on our review the studies which used randomly selected, mostly, low-risk population, reported the lowest accuracy for AF detection, whereas those focused on AF screening among high-risk and/or elderly population, reported the highest sensitivity and specificity for AF detection. Therefore, more targeted population selection and identifying those patients at higher risk of AF by using specific biomarkers [79] is a reasonable way to boost the pre-test, hence reduce false-positive results, especially among populations that are not represented by the usual risk scores (especially CHADS2 and CHA2DS2-VASc). Furthermore, more studies assessing therapeutic consequence results from an incidentally diagnosed AF in this population are on highly importance. Additionally, no standards for minimal requirements of validation studies and the format of data reports have been agreed on. This results in heterogeneous data collection processes with various devices and technologies of different reliability and validity complicating the implementation of mHealth-based results into healthcare system. Some infrastructures have been developed to manage the enormous amount of data supplied by mHealth tools to extract the most important data for the decision-making processes, but the concern over privacy is also legitimate. Sensitive health data of patients are exchanged through wireless networks and thus addressing the privacy and security concerns in the usage of mHealth apps is essential. Regulators must develop standards that the developers and all involved stakeholders need to adhere to in order to ensure data privacy and security in the healthcare system. Involvement of HCPs in the evaluation of functionality, usability, and security will enhance the trustworthiness of the apps and increase their adoption. A good mHealth policy should inform the users of what data are collected, how it is stored and used. This will enable users to weigh the benefits and risks of specific mHealth apps. All involved stakeholders, including HCPs, patients, mHealth companies, and health insurance companies, also need to discuss and agree on how best to use and implement mHealth solutions in clinical care in the future. Initiatives, such as the TeleCheck-AF project, that was introduced to keep AF patients' care during the coronavirus-2019 pandemic via teleconsultations coupled with heart rate and rhythm monitoring [231, 232], will help step-by-step to implement tailored mHealth solutions in clinical care pathways.

Strengths and limitations

This is the first systematic review of studies evaluating mHealth devices and applications in screening, detecting, and managing AF, aimed to support clinicians in choosing the appropriate way of monitoring patients and educating them in everyday practice, and to support researchers in finding research directions that should be extended.

Nonetheless, several limitations should be noted. The variation in interventions, settings, and study designs precluded meta-analyses. The methodological quality of the studies was suboptimal and prone to bias as most studies had an observational or quasi-experimental design and only a minority of studies were randomized control trials.

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Supplementary file

Table S1. Search strategy.

Electronic database	Search strategy
PubMed (NCBI)	(((((atrial fibrillation[MeSH Terms]) OR atrial fibrillation[Title]) OR AF[Title]) OR Afib[Title])) AND ((((((((((((((((((app) OR application-based) OR app-based) OR smartphone) OR smartphone-based) OR mobile health) OR mhealth) OR ehealth) OR ecardiology) OR telemedicine) OR wearable) OR digital treatment) OR alivecor) OR mydiagnostick) OR fibricheck) OR apple watch) OR myaf) OR remote monitoring)
Embase (Ovid)	(atrial fibrillation or AF or Afib).ti. and (app or app-based or application-based or smartphone-based or smartphone or mobile health or mhealth or ehealth or ecardiology or telemedicine or wearable or digital treatment or alivecor or mydiagnostick or fibricheck or apple watch or myaf or remote monitoring).ab.
Cochrane	(((MeSH descriptor: [Atrial Fibrillation] explode all trees) OR ((atrial fibrillation):ti OR (AF):ti OR (Afib):ti)) AND ((app) OR (app-based) OR (application-based) OR (smartphone) OR (smartphone-based) OR (mobile health) OR (mhealth) OR (ehealth) OR (ecardiology) OR (telemedicine) OR (wearable) OR (digital treatment) OR (alivecor) OR (mydiagnostick) OR (fibricheck) OR (apple watch) OR (myaf) OR (remote monitoring)))

Table S2. Baseline characteristic and outcomes of analyzed studies regrading handheld devices in patients with atrial fibrillation.

Study	Country	Design	Device	Type	Technology	Population	# included patients	Age (years)	Females	Monitoring time	AF rate	Sensitivity	Specificity	Reference test
PPG-based handheld devices														
Birkemeyer et al (1)	Germany	Case-control	Smartphone camera	Preventicus	PPG	Simulated group	10000	≥75-years	N/D	N/D	N/D	N/D	N/D	N/D
Brasier et al (2)	Germany Switzerland	Prospective single arm	Smartphone camera	Preventicus	PPG	Hospitalized (cardiology/ pulmonology ward)	592	78±13	45.3%	5min x 1 single-time	41.9%	89.9% (1min) 91.3% (3min) 91.5% (5min)	99.1% (1min) 98.7% (3min) 99.6%(5min)	single-lead ECG
Chan et al (3)	China	Prospective single arm	Smartphone camera	CardioRythm	PPG	With diabetes/ hypertension/elderly (≥65-years old)	1013	68.4±12.2	53.2%	20s x 1 single-time	2.76%	92.9%	97.7%	expert' diagnosis
Fan et al (4)	China	Prospective	Smartphone camera	Preventicus	PPG	Hospitalized (cardiology/ geriatric ward)	108	62 (mean)	41.7%	3 min x 1 single-time	48.1%	95.0%	99.7%	12-lead ECG
Guo et al (5)	China	RCT	Smartphone camera	mAFA	PPG	AF	3324 1646 (IC) 1646 (UC)	67 (mean) 67±15 (IC) 70±12 (UC)	38% 38% (IC) 38% ((UC)	N/D	N/D	N/D	N/D	N/D
Krivoshei et al (6)	Switzerland	Case-control	Smartphone camera	Preventicus	PPG	Ambulatory	80	78 (mean)	N/D	1 min x 1 single-time	50%	90%	85%	single-lead ECG
McManus et al (7)	USA	Prospective single arm	Smartphone camera	PULSE-SMART	PPG	Planned for ECV	121	66 (mean)	19%	2 min x 2 single-time	100%	97%	93.5%	12-lead ECG
Mutke et al (8)	Germany Switzerland	Prospective single arm	Smartphone camera Smartwatch	Preventicus	PPG	Data from DETECT-AF (2) and WATCH-AF(9)	1 101	N/D	N/D	N/D	46.7%	95.4%	91.6%	single-lead ECG
Proesmans et al (10)	Belgium	Prospective single arm	Smartphone camera	FibriCheck	PPG	Elderly (≥65-years old)	223	77±8	53.4%	1 min x 3 single-time	45.7%	95.3%	96.2%	12-lead ECG
Rozen et al (11)	USA	Prospective single arm	Smartphone camera	CardioRythm	PPG	Planned for ECV	98	67.7±10.5	24.5%	20s x 6 single-time	100%	93.1%	90.9%	12-lead ECG
Van Haelst (12)	The Netherlands	Prospective single arm	Smartphone camera	FibriCheck	PPG	Elderly (≥65-years old)	190	77.3±8.0	57.4%	1min x1 single-time	48.4%	98%	88%	12-lead ECG
Verbrugge et al (13)	Belgium	Prospective single arm	Smartphone camera	FibriCheck	PPG	General population	1179	49±14	42%	1min ≥1/day 7 days	1.1%	N/D	N/D	N/D
Yan et al (14)	China	Prospective single arm	Smartphone camera	CardioRythm	PPG	Hospitalized (cardiology ward)	217	70.3±13.9	28.6	20s x 3 single-time	34.6%	95%	96%	12-lead ECG
ECG-based handheld devices														
Battipaglia et al (15)	UK	Prospective single arm	Stick	MyDiagnostick	Single-lead ECG	General population	855	N/D	N/D	15s single-time	0.8%	100%*	100%*	Expert expertise
Desteghe et al (16)	Belgium	Prospective two arm	Stick	MyDiagnostick	Single-lead ECG	Hospitalized (cardiology/ geriatric ward)	320	67.9±14.6	43.1%,	1 min single-time	11.9% (cardiology ward) 36% (geriatric ward)	60.5% (PM; cardiology ward) 81.8% (no PM; cardiology ward) 81.8% (PM; geriatric ward) 89.5% (no PM; geriatric ward)	93.3% (PM; cardiology ward) 94.2% (no PM; cardiology ward) 96.1% (PM; geriatric ward) 95.7% (no PM; geriatric ward)	12-lead ECG
Jacobs et al (17)	The Netherlands	Prospective two arm	Stick	MyDiagnostick	Single-lead ECG	Influenza-vaccinated	1 952 811	77.4 (mean)	N/D	1min single-time	1.3%	N/D	N/D	N/D
Kaasenbrood et al (18)	The Netherlands	Prospective single arm	Stick	MyDiagnostick	Single-lead ECG	Influenza-vaccinated	3269	69.4±8.9	51%	1 min single-time	3.7% 5.9% (detected by device)	96%*	100%*	Expert expertise
Pluymaekers et al (19)	The Netherlands	Multicenter RCT	Stick	MyDiagnostick	Single-lead ECG	Planned for ECV	437	65±11	40%	1 min x 3 4 weeks	30% (RAF)	N/D	N/D	N/D

Study	Country	Design	Device	Type	Technology	Population	# included patients	Age (years)	Females	Monitoring time	AF rate	Sensitivity	Specificity	Reference test
Rivezzi et al (20)	Italy	Prospective single arm	Stick	MyDiagnostick	Single-lead ECG	Elderly (≥65-years old)	1820	50% aged 65-74 50% aged ≥75	53.4%	1 min single-time	5.5% 7.9% (detected by device0	94%*	100%*	12-lead ECG
Tavernier et al (21)	Belgium	Prospective single arm	Stick	MyDiagnostick	Single-lead ECG	Hospitalized (geriatric ward)	214	84±6	61.7%	1 min single-time	33%	88%	97%	12-lead ECG
Tieleman et al (22)	The Netherlands	Prospective single arm	Stick	MyDiagnostick	Single-lead ECG	Influenza-vaccinated	192	69.4±12.6	51.6%	1 min single-time	27.6%	100%	95.9%	12-lead ECG
Vaes et al (23)	Belgium	Prospective single arm	Stick	MyDiagnostick	Single-lead ECG	Primary care patients (84% with AF)	191	74.6±9.7	48%	1-2 min x 3 single-time	54%	94%	93%	12-lead ECG
Anderson et al (24)	USA	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	General population (health fair)	697	56±15	71%	30s x 1 single-time	2.3% (16/697)	N/D	N/D	N/D
Andrade et al (25)	Canada	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Elderly (≥65-years old) without prior AF	16 817	N/D	N/D	30s x 1 single-time	7% (1171/16817 detected by device0	69%*	N/D	12-lead ECG
Bumgarner et al (26)	USA	Prospective single arm	Plate attached to watch	KardiaMobile	Single-lead ECG	Planned for ECV	100	68.2±10.9	17%	30s x 1 single-time	N/D	93%	84%	12-lead ECG
Caceres et al (27)	USA	RCT	Plate	KardiaMobile	Single-lead ECG	Planned for ECV/AF-ablation	238 115 (IC) 123 (UC)	61.3±11.9 61.4±11.9 (IC) 61.2±11.8 (UC)	27% 27% (IC) 27% (UC)	30s 3x/week 6 months	55% 61% (IC) 49% (UC)	N/D	N/D	N/D
Chan et al (3)	China	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Elderly (≥65-years old)/ diabetic/ hypertensive	1013	68.4±12.2	53.2%	30s x 1 single-time	2.78% (28/1013)	71.4%	99.4%	Expert expertise
Chan et al (28)	China	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Elderly (≥65-years old) diabetic/ hypertensive	2052	67.8±10.6	54.2%	30s x 1 single-time	1.2% (24/2052)	66.7%	99.5%	12-lead ECG

Study	Country	Design	Device	Type	Technology	Population	# included patients	Age (years)	Females	Monitoring time	AF rate	Sensitivity	Specificity	Reference test
Chan et al (29)	China	Prospective two arm	Plate	KardiaMobile	Single-lead ECG	General population	13122	64.7±13.4	71.5%	30s x 1 single-time	1.8% (239/13122 detected by device)	98%	29.2%	Expert expertise
Chan et al (30)	China	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Elderly (≥50-years old)	10735	78.6±8.1	79.8%	30s x 1 single-time	2.3% (244/10735) 2.6% detected by device (282/10753)	75%	98.2%	Expert expertise
Chen et al (31)	China	Multicenter prospective single arm	Plate	KardiaMobile	Single-lead ECG	Elderly (≥65-years old)	4531	71.6±6.3	66%	30s x 1 single-time	4.0% (183/4531)	N/D	N/D	N/D
Cunha et al (32)	Portugal	Multicenter longitudinal	Plate	KardiaMobile	Single-lead ECG	General population (health fair)	205	66±15	64 %	30s x 1 single-time	22% (22/100) 22% (22/100 detected by device)	90.9%	97.4%	12-lead ECG
Desteghe et al (16)	Belgium	Prospective two arm	Plate	KardiaMobile	Single-lead ECG	Hospitalized (cardiological or geriatric ward)	320	67.9±14.6	43.1%,	30s x 1 single-time	11.9% (cardiology ward) 36% (geriatric ward)	36.8% (PM; cardiology ward) 54.5% (no PM; cardiology ward) 72.7% (PM; geriatric ward) 78.9% (no PM; geriatric ward)	96.1% (PM; cardiology ward) 97.5% (no PM; cardiology ward) 98.1% (PM; geriatric ward) 97.9% (no PM; geriatric ward)	12-lead ECG
Evans et al (33)	Kenya	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Hospitalized (internal, diabetic, ophthalmology, emergency, inpatient men's ward)	50	54.3±20.5	66%	30s x 1 single-time	8% (4/50)	100%	100%	12-lead ECG

Study	Country	Design	Device	Type	Technology	Population	# included patients	Age (years)	Females	Monitoring time	AF rate	Sensitivity	Specificity	Reference test
Godin et al (34)	Canada	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Elderly (≥65-years old) without prior AF	7585	35% aged ≥65	N/D	30s x 1 single-time	3.9%% (297/7585) 6.2% (471/7585 detected by device)	63%	N/D	Expert expertise
Goldenthal et al (35)	USA	RCT	Plate	KardiaMobile	Single-lead ECG	Planned for ECV/AF-ablation	238 115 (IC) 123 (UC)	61±12 61±12 (IC) 61±12 (UC)	23% 23% (IC) 22% (UC)	30s 1/day 6 months	50% (IC) 42% (UC)	N/D	N/D	N/D
Gropler et al (36)	Singapore	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Children	30	8.2 (0-17)	53%	30s x 1 single-time	0% 13% (4/30 detected by device)	N/D	87%	12-lead ECG
Grubb et al (37)	UK	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Elderly (≥65-years old) primary healthcare	1805	74.9±7.1	38.9%	30s x 1 single-time	5.1% (92/1805)	N/D	N/D	N/D
Gwynn et al (38)	Australia	Multicenter cross-sectional	Plate	KardiaMobile	Single-lead ECG	Mid-aged (≥45-years old)	619	N/D	56.1%	30s x 1 single-time	4.7% (29/619) 4.8% (30/619 detected by device0	85%*	65%*	12-lead ECG
Haberman et al (39)	USA	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Athletes/young adults/ hospitalized (cardiology ward)	381	35±20	51%	30s x 1 single-time	N/D	94.4%	99.4%	12-lead ECG
Halcox et al (40)	UK	RCT	Plate	KardiaMobile	Single-lead ECG	Elderly (≥65-years old) High stroke risk Without prior AF	1001 500 (IC) 501 (UC)	72.6±5.4 72.6±5.4 (IC) 72.6±5.4 (UC)	53.4% 51.8% (IC) 55.1% (UC)	30s, 2x/week 12 months	3.8% (19/500) 1.0% (5/501)	N/D	N/D	N/D
Hermans et al (41)	The Netherlands	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Post AF-ablation	115	64.0 (58.0-68.0)	30.4%	30s, 3x/day in case of symptoms, 4 weeks	25.2% (29/115)	95.3%	97.5%	≥24-h Holter
Hickey et al (42)	USA	RCT	Plate	KardiaMobile	Single-lead ECG	Cardiac electrophysiology and ambulatory care	46 23 (IC) 23 (UC)	55±10 (IC) 55±9 (UC)	29% (IC) 29% (UC)	30s >1/day (max 5 min/day) 6 months	61% (14/23; IC) 30% (7/23; UC)	N/D	N/D	N/D

Study	Country	Design	Device	Type	Technology	Population	# included patients	Age (years)	Females	Monitoring time	AF rate	Sensitivity	Specificity	Reference test
Kim et al (43)	Korea	Multicenter prospective single arm	Plate	KardiaMobile	Single-lead ECG	Elderly (≥60-years old)	2422	75.5±6.5	68.5%	40s x 1 single-time	3% (73/2422) 5.1% (124/2422 detected by device)	59%	N/D	12-lead ECG
Koltowski (44)	Poland	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Hospitalized (cardiology ward)	100	68±14.2	34%	30s x 1 single-time	N/D	92.8%	100%	12-lead ECG
Kropp et al (45)	USA	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	High AF risk; pharmacy customers	250	61.7±15.3	60%	30s x 1 single-time	3% 4% (10/250 detected by device)	N/D	N/D	N/D
Lown et al (46)	USA	Case-control	Plate	KardiaMobile	Single-lead ECG	Elderly (>65-years old) primary healthcare	418	73.9±6.1	N/D	30s x 1 single-time	19% (79/418 detected by device)	87.8%	98.81%	12-lead ECG
Lowres et al (47)	Australia	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Hospitalized (surgery)	42	69±9	20%	30s, 4x/day 4 weeks	24% (10/42 detected by device)	94.6%	92.9%	12-lead ECG
Lowres et al (48)	Australia	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Elderly (≥65-years old) pharmacy customers	1 000	76±7	56%	30-60s single-time	6.7% (67/1000)	98.5%	91.4%	12-lead ECG
Macniven et al (49)	Australia	Prospective single arm (on device's feasibility)	Plate	KardiaMobile	Single-lead ECG	Primary healthcare	18	N/D	N/D	N/D	N/D	N/D	N/D	N/D
Magnani et al (50)	USA	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	AF	31	68±11	39%	30s, 20 times over 30 days	N/D	N/D	N/D	N/D
Mutke et al (8)	Switzerland	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Data from DETECT-AF (2) and WATCH-AF(9)	1 101	N/D	N/D	30s x 1 single-time	46.7%	99.6%	97.4%	Expert expertise

Study	Country	Design	Device	Type	Technology	Population	# included patients	Age (years)	Females	Monitoring time	AF rate	Sensitivity	Specificity	Reference test
Orchard et al (51)	Australia	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Elderly (≥65-years old) without prior AF	1805	75.7	66%	30s x 1 single-time	3.7% (67/1805 detected by device)	N/D	N/D	N/D
Orchard et al (52)	Australia	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Elderly (>65-years old) primary healthcare	88	74.8±8.8	49%	30s x 1 single-time	19% (17/88)	N/D	N/D	N/D
Orchard et al (53)	Australia	RCT	Plate	KardiaMobile	Single-lead ECG	Elderly (≥65-years old) without prior AF primary health care	3103	75.1±6.8	36%	30s x 1 single-time	1.2% (36/3103)	97%	92%	12-lead ECG
Orchard et al (54)	Australia	Cross-sectional	Plate	KardiaMobile	Single-lead ECG	Elderly (≥65-years old) influenza-vaccinated	972	N/D	N/D	30s x 1 single-time	3.7% (36/972) 4.5% (44/972 detected by device)	95%	99%	Expert expertise
Rajakariar et al (55)	Australia	Prospective single arm	Plate attached to watch	KardiaMobile	Single-lead ECG	Hospitalized (medical, cardiac ward or ICU)	200	67±16	43.5%	30s x 1 single-time	19% (38/200)	94.4%	81.9%	12-lead ECG
Reed et al (56)	UK	RCT	Plate	KardiaMobile	Single-lead ECG	Hospitalized (emergency ward)	243 126 (IC) 117 (UC)	39.6±13.8 40±14 (IC) 39.1±13.5 (UC)	66.6% 59.2% (IC) 53.8% (UC)	30s x 1-2 90 days	6.5% (8/124) 0 (0/116)	N/D	N/D	N/D
Reed et al (57)	UK	Prospective single arm	Plate	KardiaMobile	Singe-lead ECG	Hospitalized (emergency ward)	68	45.8±15.1	441%	30s x 1-2 90 days	2 (3%)	N/D	N/D	N/D
Rischard et al (58)	France	Multicenter prospective single arm	Plate	KardiaMobile	Single-lead ECG	Hospitalized (cardiology ward)	1322	68.7±16.2	34.7%	30s x 1 single-time	20.8% (275/1322)	95%	86%	12-lead ECG
Rosenfeld et al (59)	USA	Multicenter prospective single arm	Plate	KardiaMobile	Single-lead ECG	High AF risk	772	65.2±15.4	67.5%	60s x 1 single-time	2.2% (17/670 detected by device)	N/D	N/D	N/D

Study	Country	Design	Device	Type	Technology	Population	# included patients	Age (years)	Females	Monitoring time	AF rate	Sensitivity	Specificity	Reference test
Savickas et al (60)	UK	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Elderly (≥65-years old) influenza-vaccinated	604	73 (69-78)	57.3%	30s x 1-2 single-time	4.3% (26/6040	92.3%	97.4%	12-lead ECG
Selder et al (61)	The Netherlands	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Ambulatory	233	58.4±14	48%	30s x 1 single-time	N/D	92%	95%	Expert expertise
Soni et al (62)	India	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	General population	2074	33.7% aged ≥66	52.2%	30s, 2-3x/day, 5 days	1.6% (33/2074) 4.2% (88/2074 detected by device)	38%	N/D	Expert expertise
Stavrakis et al (63)	USA	RCT	Plate	KardiaMobile	Single-lead ECG	Paroxysmal AF High stroke risk	58 29 (IC) 29 (IC)	62.5±12.2 (IC) 60.9±14.4 (UC)	43% 41% (IC) 45% (UC)	30s ≥1/day 7 days	62% (18/29)	N/D	N.D	N/D
Tarakji et al (64)	USA	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Planned for AF ablation	55	60±12	22%	30s x 1 single-time	N/D	100%	97%	Expert expertise
Van Haelst et al (12)	The Netherlands	Multicenter prospective single arm	Plate	KardiaMobile	Single-lead ECG	Elderly (>65-years old)	190	77.3±8.0	57.4%	30s x 1 single-time	48.4% (92/190)	98%	85%	12-lead ECG
Wasserlauf et al (65)	USA	Prospective two-arm	Plate attached to watch	KardiaMobile	Single-lead ECG	Paroxysmal AF with ICM	24	72.1±7.2	34.6%	30s x 1 single-time	N/D	100%	83.3%	ICM
Wegner et al (66)	Germany	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Hospitalized (cardiac ward)	99	64±15	38.4%	30s x 1 single-time	22% (22/99)	70%	69%	12-lead ECG
William et al (67)	USA	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	AF	52	68.1 (42.6-85.6)	32.7%	30s x 1 single-time	N/D	96.6%	94.1%	12-lead ECG
Williams et al (68)	UK	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	AF	95	N/D	N/D	30s x 1 single-time	31% (29/95)	93%	76%	12-lead ECG

Study	Country	Design	Device	Type	Technology	Population	# included patients	Age (years)	Females	Monitoring time	AF rate	Sensitivity	Specificity	Reference test
Yan et al (69)	Australia and China	Prospective two arm	Plate	KardiaMobile	Single-lead ECG	Post stroke/TIA	1079 785 (iECG) 294 (Holter +iECG)	66 (55-75) 64 (54-75) 68 (57-77)	38.6% 35.8% 45.9%	30s x 1 single-time	8.8% (69/785) 8.5% (25/294)	N/D	N/D	N/D
Zado et al (70)	USA	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Post-AF ablation	99	64±8	16%	30s x 2 30 days	16% (16/99)	N/D	N/D	N/D
Zaprutko et al (71)	Poland	Prospective single arm	Plate	KardiaMobile	Single-lead ECG	Elderly (≥65-years old) without prior AF pharmacy customers	525	73.7 ±6.5	68.2%	30s x 1 single-time	2.4% (12/490) 3.5% (17/490 detected by device)	100%	98.7%	Expert expertise
Aljuaid et al (72)	USA	Retrospective two-arm	Device	ECG check	Single-lead ECG	Post AF-ablation	90 45 (IC) 45 (UC)	66 (mean) 61.3±7.7 (IC) 60.9±7.4 (UC)	40% 37.8% (IC) 42.2% (UC)	30s, 1x/day 100 days	N/D	100%	97%	Expert expertise
Anczykowski et al (73)	Germany	Retrospective single arm	Device	Card Guard	Single-lead ECG	With symptoms of cardiac arrhythmia	790	54±18	60%	32s, ≥1/day 2-4weeks	14% (110/790)	N/D	N/D	N/D
Boriani et al (74)	World	Survey	Device/app	Several devices and applications	ECG and PPG	Healthcare professionals	588	N/D	N/D	N/D	N/D	N/D	N/D	N/D
Busch et al (75)	Germany	Retrospective two arm	Device	Sensor mobile 100	Single-lead ECG	General population	1678	54 (28-65)	N/D	30s, 2x/day 4 weeks	1.3% (21/1678) 2.6% (43/1678 detected by device)	N/D	N/D	12-lead ECG
Chen et al (76)	Taiwan	Prospective single arm	Device	DiGiO2	Single lead-ECG	General population	922	58.1±15	53.8%	15s x 1 single-time	2.4% (22/922)	95.5%	97.7%	Expert expertise

Study	Country	Design	Device	Type	Technology	Population	# included patients	Age (years)	Females	Monitoring time	AF rate	Sensitivity	Specificity	Reference test
Gudmundsdottir et al (77)	Sweden	RCT	Device	Zenicor	Single lead-ECG	Elderly (75/76-years old)	6868	(75-76)	N/D	30s x 1 single-time in case of SR and high AF risk: 30s 4x/day 2 weeks	8.1% (553/6688) known AF 0.5% (29/6315) newly detected AF 4.4% (164/3766) newly detected AF in 2 weeks	N/D	N/D	N/D
Gussak et al (78)	Serbia	Prospective single arm	Device	CardioBip	3 lead ECG	Post AF-ablation	25	51.5±2.8	16%	3x/day, 60 days +2x/day 30 days (at 6 month)	32% (8/25) 88% (22/25 detected by device)	100%*	24%*	12-lead ECG and 24-h Holter
Jaakkola et al (79)	Finland	Case-control	Device	Mechanocardiography	Mechanocardiography	Hospitalized (cardiology/internal ward)	300	74.8 (73.7-75.9)	44%	3min x 1 single-time	N/D	95.3 %	96%	Tele-ECG
Liu et al (80)	China	Prospective two arm	Device	Sensor mobile 100	Single-lead ECG	Post AF-ablation	92	54.4±9.8	78.3%	30s, 1x/day, 90 days	29.3% (27/92) 42.4% (39/92 detected by device)	N/D	N/D	12-lead ECG and 24-h Holter
Olsson et al (81)	Sweden	Retrospective single arm	Device	Zenicor	Single lead-ECG	Post stroke/TIA	370	66±12	47%	30s 2x/day 2 weeks	7.6% (27/356)	N/D	N/D	N/D
Svennberg et al (82)	Sweden	RCT	Device	Zenicor	Single lead-ECG	Elderly (75/76-years old)	7173	(75-76)	N/D	30s 2x/day 2 weeks	12.3% (884//7173) 9.3% (666/7173) known AF 3.0%(218/7173) newly detected AF	N/D	N/D	N/D
Vukajlovic et al (83)	Serbia	Prospective single arm	Device	CardioBip	3 lead ECG	Post AF-ablation	21	50.0±13.8	N/D	≤3/day 60 days	195 (4/21) 90% (19/21 detected by device)	N/D	N/D	12-lead ECG and 24-h Holter

Values are presented as median (interquartile range), (range), mean±standard deviation, or number with percentages.
*AF, atrial fibrillation; DM, diabetes mellitus; ECG, electrocardiogram; ECV, electrical cardioversion; HT, hypertension; IC, intervention care; UC, usual care ; N/D, no data; PM, pacemaker; PPG, photoplethysmography. *data counted based on available data*

Table S3. Baseline characteristic and outcomes of analyzed studies regrading wearable devices in patients with atrial fibrillation.

Study	Country	Design	Device	Type	Technology	Population	No. of patients	Age (years)	Females	Monitoring time (day)	AF rate	Sensitivity	Specificity	Reference test
PPG-based wearables														
Al-Kaisey et al (84)	Australia	Prospective single arm	Wristwatch	Fitbit Charge HR and Apple Watch Series 3	PPG	Referred for Holter monitoring	32	68±12	38%	24 hours	26 (81%)	N/D	N/D	24-hour Holter
Bonomi et al (85)	The Netherlands	Prospective single arm	Wrist device	CM3 Generation -3	PPG	1. Planned for ECV 2. Referred for Holter monitoring	1. 18 2. 34	1. 73.1±11.6 2. 67.4±12.1	1. 44% 2. 38%	1. 42 hours 2. 855 hours	1. 18 (100%) 2. 34 (100%)	1. 97% 2. 93%	1. 100% 2. 100%	1. Single-lead ECG 2. 24-hour Holter
Chen et al (86)	China	Prospective randomized	Wristband	Amazfit Health Band 1S	1. PPG 2. Single-lead ECG	Hospitalized / ambulatory	401	N/D	49.1%	1. 3 minutes 2. 60 seconds	150 (37%)	1. 88.00% 2. 87.33%	1. 96.41% 2. 99.20%	12-lead ECG
Conroy et al (87)	USA	Prospective single arm	Earlobe sensor	HeartSensor HRS-07UE	PPG	Planned for ECV	55	N/D	N/D	One time for >4 minutes	N/D	90.9%	90.9%	Single-lead ECG
Corino et al (88)	Italy	Prospective single arm	Wristband	Empatica E4	PPG	Hospitalized	70	N/D	49%	10 minutes	30 (43%)	75.4%	96.3%	N/D
Dörr et al (9)	Switzerland	Two-center prospective single arm	Wristband and wristwatch	Wavelet Health and Gear Fit 2	PPG	Hospitalized	508	76.4±9.5	44.3%	5 minutes	237 (46.7%)	93.7%	98.2%	Expert expertise based on single-lead ECG
Eerikäinen et al (89)	The Netherlands	Prospective single arm	Wrist device	CM3 Generation -3	PPG	1. Planned for ECV 2. Ambulatory	1. 18 2. 16	1. 75±11 2. 65±14	1. 44% 2. 37%	1. 1-hour before and after ECV 2. 24 hours	1. 18 (100%) 2. 4 (25%)	1. 92.3% 2. 71.6%	1. 60.7% 2. 84.9%	1. Single-lead ECG 2. 24-hour Holter
Guo et al (90)	China	Prospective single arm	Wristband and wristwatch	Honor Band 4, Huawei Watch GT and Honor Watch	PPG	Ambulatory	187 912	34.7±11.5	13.3%	60 seconds every 10 minutes for 14 days	227/262 (87%)	N/D	N/D	12-lead ECG and 24-hour Holter
Hochstadt et al (91)	Israel	Prospective single arm	Wristwatch	CardiacSense	PPG	Planned for ECV	20	74.1±8.7	25%	30 minutes before ECV and 10 minutes after ECV	20 (100%)	100%	93.1%	12-lead ECG
Huynh et al (92)	USA	Prospective single arm	Wristwatch	Apple Watch A1554	PPG	Obstructive sleep apnea	20	66±6.5	15%	60 seconds seven times	20 (100%)	N/D	N/D	12-lead ECG
Huynh et al (93)	USA	Prospective single arm	Wristwatch	Apple Watch	PPG	OSA in AF	20	66±6.5	15%	60 seconds every 10 seconds	20 (100%)	N/D	N/D	Telemetry
Inui et al (94)	Japan	Prospective single arm	Wristwatch and wristband	Apple Watch Series 3 and Fitbit Charge HR Wireless Activity	PPG	Hospitalized (cardiac surgery)	40	70.9±11.1	32%	Two weeks	20 (50%)	N/D	N/D	12-lead ECG
Jacobsen et al (95)	Germany	Prospective single arm	Upper armband	Everion®	PPG	AF	102	71.0±11.9	48%	24 hours	48 (47%)	95.2%	92.5%	24-hour Holter
Koshy et al (96)	Australia	Prospective single arm	Wristwatch	Apple Watch and Fitbit	PPG	Hospitalized	102	68±15	35%	1 minute every 15 seconds for 30 minutes	32 (31%)	N/D	N/D	ECG telemetry
Kwon et al (97)	Republic of Korea	Prospective single arm	Fingerband	CardioTracker	PPG	Persistent AF; planned for ECV	100	63.8±8.5	19%	15 minutes before and after ECV	100 (100%)	99.0%	94.3%	Single-lead ECG
Nemati et al (98)	USA	Retrospective single arm	Wristwatch	Samsung Simband	PPG	Hospitalized	36	N/D	N/D	(3.5-8.5) minutes	12 (33%)	97%	94%	Single-lead ECG
Perez et al (99)	USA	Prospective single arm	Wristwatch	Apple Watch	PPG	Without AF	419 297	41±13	42%	117 (113-186) days	153/450 (34%)	N/D	N/D	7-day ECG patch
Selder et al (100)	Belgium	Prospective single arm	Wristband	1. Wavelet Health with FibriCheck algorithm 2. KardiaBand	1. PPG 2. Single-lead ECG	Elderly	60	69.6±16.9	68%	Three times 1. 60 seconds 2. 30 seconds	6 (10%)	1. 79% 2. 93%	1. 98% 2. 98%	1. Single lead ECG 2. Expert expertise
Seshadri et al (101)	USA	Prospective single arm	Wristwatch	Apple Watch 4	PPG	Hospitalized (cardiac surgery)	50	61.4±10.4	28%	Six times	25 (50%)	N/D	N/D	6-lead telemetry
Tison et al (102)	USA	Multicenter prospective single arm	Wristwatch	Apple Watch	PPG	1. Ambulatory 2. Planned for ECV	1. 1617 2. 51	1. N/D 2. 66.1±10.7	1. N/D 2. 16%	1. N/D 2. 20 minutes	1. 64 (4%) 2. 51 (100%)	1. 67.7% 2. 98.0%	1. 67.6% 2. 90.2%	12-lead ECG

Study	Country	Design	Device	Type	Technology	Population	No. of patients	Age (years)	Females	Monitoring time (day)	AF rate	Sensitivity	Specificity	Reference test
Zhang et al (103)	China	Prospective single arm	Wristband and wristwatch	Honor Band 4, Huawei Watch GT and Honor Watch	PPG	Ambulatory	361	50 (36-62)	49.3%	60 seconds every 10 minutes for 14 days (band) and 45 seconds (watch)	31 (8.6%)	100%	99%	12-lead ECG
ECG-based wearables														
Fukuma et al (104)	Japan	Prospective single arm	Patch	T-shirt with a highly conductive material	Single-lead ECG	Low AF risk	100	52.5±5.4	0%	40 hours a week over 2 months	10 (10%)	N/D	N/D	Expert expertise
Heo et al (105)	USA	Prospective single arm	Patch	iRhythm Zio^{XT}	Single-lead ECG	Diabetic without prior AF	608	70.9±6.7	31.9%	2 weeks, twice	19 (3%)	N/D	N/D	Expert expertise
Lown et al (46)	UK	Multicenter prospective single arm	1. Chest belt 2. Patch	1. Polar-H7 2. Firstbeat Bodyguard 2	Single-lead ECG	Elderly (>65-years old)	418	N/D	N/D	1. 45 seconds 2. 2 minutes	79 (19%)	1. 96.3% 2. 96.3%,	1. 98.2% 2. 98.5%,	12-lead ECG
Reverberi et al (106)	Italy	Prospective single arm	Chest belt	Consumer-grade Bluetooth low-energy HR monitor with RITMIA^{TM} application	Single-lead ECG	Planned for ECV	95	66.2±10.7	21.1%	10 minutes	Pre- ECV, 92%; post-ECV 13%	97%	95.6%	12-lead ECG
Sabar et al (107)	UK	Prospective single arm	Patch	RhythmPad	6-lead ECG	High AF risk	750	(18-97)	51%	10 seconds	66 (10%)	AF detection, 93.4%; AF diagnosis 95.4%	AF detection, 96.8%; AF diagnosis, 98.8%	12-lead ECG
Steinhubl et al (108)	USA	Prospective randomized	Patch	Zio^{XT}	Single-lead ECG	High AF risk	2659	72.4±7.3	38.6%	4 weeks	53 (3.9%) vs 12 (0.9%)	N/D	N/D	Expert expertise
Torfs et al (109)	Belgium	Prospective single arm	Patch	N/D	3-lead ECG	1. Chronic AF 2. Planned for ECV	10	N/D	N/D	1. 24 hours 2. 2/3 hours	N/D	N/D	N/D	24-hour Holter
Turakhia et al (110)	USA	Prospective single arm	Patch	Zio^{XT}	Single-lead ECG	High AF risk	75	69±8.0	0%	2 weeks	4 (5.3%)	N/D	N/D	Expert expertise

Study	Country	Design	Device	Type	Technology	Population	No. of patients	Age (years)	Females	Monitoring time (day)	AF rate	Sensitivity	Specificity	Reference test
Wineinger et al (111)	USA	Retrospective single arm	Patch	Zio^{XT}	Single-lead ECG	Paroxysmal AF	13 293	69.4±11.1	40.3%	2 weeks	1 041 504 paroxysmal episodes >30 seconds	N/D	N/D	N/D
Atarashi et al (112)	Japan	Prospective randomized	Wireless recorder	Cardiophone^{TM}	Single-lead ECG	Paroxysmal AF/ AFL	123	N/D	21%	30 seconds daily for 4 weeks	95 (77%)	N/D	N/D	Expert expertise
Brunetti et al (113)	Italy	Prospective single arm	Wireless recorder	CardioVox P12	12-lead ECG	Hospitalized (emergency ward)	27 841	N/D	51%	N/D	3 249 (11.67%)	N/D	N/D	Expert expertise
Højager et al. (114)	Denmark	Prospective single arm	Wireless recorder	R.Test Evolution 4	ECG	High stroke risk; diabetes	200	66±0.7	41.5%	Every 2-3s; 5-7 days	21 (10.5%)	N/D	N/D	N/D
Kimura et al (115)	Japan	Prospective single arm	Wireless recorder	Cardiophone^{TM}	Single-lead ECG	Planned for AF ablation	30	59±9	13%	30 seconds twice daily for 6 months	30 (100%)	N/D	N/D	12-lead ECG and 24-hour Holter
Lin et al (116)	Taiwan	Prospective single arm	Wireless recorder	Medi-Trace 200	3-lead ECG	Hospitalized (cardiac ward, ICU)	30	N/D	N/D	6 minutes	20 (67%)	94.6%	N/D	12-lead ECG
Scalvini et al (117)	Italy	Prospective single arm	Wireless recorder	CG-7100	12-lead ECG	Primary healthcare	7 516	61±20	56%	N/D	719 (9%)	N/D	N/D	N/D
Wu et al (118)	Taiwan	Prospective single arm	Wireless recorder	CG-7100 and CG-2100	12-lead ECG (7100) and single-lead ECG (2100)	Cardiovascular disease	70	N/D	N/D	N/D	25 (36%)	N/D	N/D	N/D
Pulse variability-based wearables														
Chan et al (28)	China	Prospective single arm	Sphygmomanometer	Microlife WatchBP Office AFIB	Pulse beat interval algorithm	Diabetic or hypertensive	2052	67.8±10.6	54.2%	N/D	24 (1.2%)	83.3%	98.7%	12-lead ECG
Gandolfo et al (119)	Italy	Prospective single arm	Sphygmomanometer	Microlife BP3MQ1-2D	Pulse beat interval algorithm	Post stroke/TIA	207	77.7±11.34	50.2%	Three times	38 (18.4%)	89.5%	98.8%	12-lead ECG
Kearley et al (120)	UK	Prospective single arm	Sphygmomanometer	WatchBP	Pulse beat interval algorithm	Ambulatory	999	79.7 (75.1-99.8)	50.7%	One time	79 (7.9%)	94.9%	89.7%	12-lead ECG

Study	Country	Design	Device	Type	Technology	Population	No. of patients	Age (years)	Females	Monitoring time (day)	AF rate	Sensitivity	Specificity	Reference test
Marazzi et al (121)	Italy	Prospective single arm	Sphygmomanometer	1. Microlife® BP A200 Plus 2. OMRON® M6	Pulse beat interval algorithm	Hypertensive	503	67.0±10.5	45.7%	Three times	101 (20%)	1. 92% 2. 100%	1. 97% 2. 94%	12-lead ECG
Omboni et al (122)	Italy	Prospective single arm	Sphygmomanometer	Microlife WatchBP Office AFIB	Pulse beat interval algorithm	Ambulatory	220	57.5±15.3	48.6%	Three times	4 (1.8%)	N/D	N/D	Single-lead ECG
Stergiou et al (123)	Greece	Prospective single arm	Sphygmomanometer	Microlife BPA 100 Plus	Pulse beat interval algorithm	Hospitalized / ambulatory/ aged ≥35	73	70.5±10.6	34.2%	Three times	27 (37%)	100%	89%	12-lead ECG
Wiesel et al (124)	USA	Prospective single arm	Sphygmomanometer	Microlife BP monitor model BPM BP3MQ1-2D	Pulse beat interval algorithm	High AF risk	139	67 (26-89)	63%	Three times a day for 30 days	14 (10.1%)	99.2%	92.9%	Single-lead ECG
Wiesel et al (125)	USA	Prospective single arm	Sphygmomanometer	Microlife BP monitor model BP3MQ1-2D	Pulse beat interval algorithm	Ambulatory	405	73 (34-98)	49%	Three times	93 (23%)	96.8%	88.8%	12-lead ECG
Wiesel et al (126)	USA	Prospective single arm	Sphygmomanometer	Omron 712C	Pulse beat interval algorithm	Ambulatory	450	69 (31-99)	41%	Two times	54 (12%)	100%	91%	12-lead ECG

Values are presented as median (interquartile range), (range), mean±standard deviation, or number with percentages.
AF, atrial fibrillation; AFL, atrial flutter; ECG, electrocardiogram; ECV, electrical cardioversion; ICU, intensive care unit); N/D, no data; OSA, obstructive sleep apnea; PPG, photoplethysmography.

Table S4. Overview of the implantable cardiac monitor technologies under assessment.

Device features	BioMonitor 2-AF™ (Biotronik SE& Co. KG, Berlin, Germany)	Reveal LINQ™ (Medtronic plc, Minneapolis, MN, USA)	Reveal XT (Medtronic plc, Minneapolis, MN, USA)	Confirm Rx™ (Abbott Laboratories, Lake Bluff, IL, USA)
Standard components	• BioMonitor 2-AF device with flexible lead body • Insertion tools • SensingConsult™ (Biotronik SE & Co. KG) programmer, software	• Reveal LINQ device • Insertion tools • CareLink™ (Medtronic) programmer, software • MyCareLink™ monitor	• Reveal XT device • Insertion tools • CareLink™ (Medtronic) programmer, software	• Confirm Rx device • Insertion tools • Merlin™ (Abbott) programmer, software • myMerlin™ mobile app
Additional components		• Patient activity accelerometer • Triage and monitoring service (FocusOn™; Medtronic)		• Symptom annotator via app • Free technical support available via helpline or local staff
Patient activation	• Optional patient assistant device	• Patient assistant device as standard	• Optional patient assistant device	• Integrated™ in myMerlin app
Detection triggers and sensing parameters	• Atrial fibrillation (adjustable or pre-set functions to detect various atrial fibrillation characteristics) • Bradycardia • Sudden rate drop • Asystole • High ventricular rate	• Atrial tachyarrhythmia (including atrial fibrillation/ flutter) (exclusive algorithm) P-wave morphology discriminator algorithm • Bradyarrhythmia • Ventricular tachyarrhythmia • Pause episodes	• Atrial tachyarrhythmia (including atrial fibrillation/ flutter) (exclusive algorithm) • Bradyarrhythmia • Ventricular tachyarrhythmia • Pause episodes	• Atrial fibrillation (regularity, R–R variance and sudden onset) • Bradyarrhythmia • Tachyarrhythmia • Pause episodes • Transient loss of consciousness conditions • Epilepsy exclusion
Dimension	88.4 x15.2 x 6.2mm	44.8 x 7.2 x 4.0mm	95 x 62 x 8.0mm	49.0 x 9.4 x 3.1mm
Weight	10.1g	2.5 ± 0.5g	15g	3.0g
Device storage	• total duration of 60 min • 55 x 40s automatically activated episodes • 4 x 7.5 min patient-activated episodes	• total duration of 57 min • 27 min of automatically activated episodes • 30 min of patient-activated episodes	• total duration of 49.5 min • 27 min of automatically activated episodes • 22.5 min of patient-activated episodes	• total duration of 60 min • up to 250 atrial fibrillation episodes plus 250 auto-/patient-activated episodes of other arrhythmias
Estimated battery life	4 years	3 years	3 years	2 years
Telemetry	• via mobile phone network to Home Monitoring Service Centre	• via myCareLink™ monitor to a CareLink™ server using a mobile phone network	• via CareLink™ programmer to CareLink™ server	• via app to Merlin.net patient care network accessed by clinicians
Sensitivity	92%[127] – 100%[128]	97.4%[129] a – 100%*[130] a 98.4%[129] b 93.7%[129] c 97.3%[129] d 97.2%[129] e	96.1%[131] a – 96.1%*[130] a 98.1%[130] b 89.0%[130] c 85.2%[130] d 87.9%[130] e	100%[132] a 84.2%[132] b 96.4%[132] c 94.5%[132] d 95.6%[132] e
Specificity	67%[128]	97.0%[129] a – 99.0%*[130] a 99.5%[129] b 99.6%[129] c	85.4%[131] a – 90.0%*[130] a 98.5%[130] b 91.3%[130] c	85.7%[132] a 99.4%[132] b 99.4%[132] c 86.6%[132] d 98.2%[132] e
PPV	59% [127] – 83%[128]	92.5%[129] a – 97.4%*[130] a 97.2%[129] b 90.6%[129] c 74.8%[129] d 90.4%[129] e	79.3%[131] a – 84.9%*[130] a 91.9%[130] b 75.2%[130] c 38.8%[130] d 73.6%[130] e	64%[132] a 93.5%[132] b 63.3%[132] c 64.0%[132] d 60.7%[132] e
NPV	100%[128]	99.0%[129] a – 100%*[130] a	97.4%[131] a – 97.5%*[130] a	100%(132) a

Device features	BioMonitor 2-AF™ (Biotronik SE& Co. KG, Berlin, Germany)	Reveal LINQ™ (Medtronic plc, Minneapolis, MN, USA)	Reveal XT (Medtronic plc, Minneapolis, MN, USA)	Confirm Rx™ (Abbott Laboratories, Lake Bluff, IL, USA)
		99.7%[129] b 96.4%[129] c	99.7%[130] b 97.1%[130] c	98.4%[132] b 92.2%[132] c 76.4%[132] d 89.8%[132] e
Accuracy	N/A	97.1%[129] a – 99.3%*[130] a	89.3%[131] a – 92.2%*[130] a	N/A

**adaptive P-Sense algorithm. Diagnostic significance in BioMonitor and Confirm devices are reported for their earlier versions. a, patient based (gross); b, duration based (gross); c duration gross (patient average); d, episode based (gross); e episode gross (patient average).*
PPV, positive predictive value; N/A, non-available; NPV, negative predictive value.

Table S5. Baseline characteristic and outcomes of analyzed studies regrading implantable cardiac monitor in patients with atrial fibrillation.

Study	Country	Design	Device	No. of patients	Age (years)	Females	Population	Monitoring time (day)	Implantation after event (day)	Insertion to AF detection (day)	AF definition	AF rate
Asaithambi et al (133)	USA	Retrospective single arm	Reveal LINQ	234	72 [61-78]	45%	CS	536 [282-848]	4 [2-9]	94.5 [16-239]	N/D	20 (9%) (1mo) 47 (20%) (6mo) 57 (24%) (12mo) 68 (29%) (22mo)
Bergau et al (134)	Germany	Retrospective randomized	Reveal XT	30	67±10	44%	Post-AF ablation	1011±388	at the same day	N/D	≥30s	N/D
Bertelsen et al (135)	Denmark	RCT	Reveal LINQ	68	76.2±4.5	33.8%	Post-MRI	41 (36-43)	N/A	N/D	≥6min	32 (47%)
Carrazco et al (136)	USA	Prospective and retrospective single arm	Reveal LINQ (90%)/ XT (10%)	100	65.8 [28-93]	52.5%	CS	(240-540)	4.2±2.6	108 (0-514)	≥2min	25 (25%)
Choe et al (137)	International	ICM registry vs. simulated intermittent monitoring	Reveal XT	168	61.3± 11	32%	CS	>345	N/D	N/D	>30s	30 (18%)
Chorin et al (138)	USA	Retrospective single arm	Reveal LINQ Reveal XT	145	67 [53-70]	43%	CS	28 ± 12mo	N/D	7.4 ± 21.3 mo	≥2min	4 (2.8%) (1mo) 8 (5.5%) (6mo) 11 (7.6%) (12mo) 13 (9.6%) (24mo) 17 (12%) (36mo)
Christensen et al (139)	Denmark	Prospective single arm	Reveal XT	85	56.7 (mean)	45%	CS	569±310	107±117	109±48	>2min	14 (16%)
Ciconte et al (128)	Italy	Prospective single arm	BioMonitor	63	60.4±9.4	13.6%	AF-episodes/ management	N/D	N/D	N/D	>2min	39 (62%)
Cotter et al (140)	UK	Prospective single arm	Reveal XT	51	51±13.9	45.1%	CS	229±116	174±134	48 [34-118]	≥2min	13 (25%)
Dekker et al (141)	International	Prospective single arm	Reveal LINQ	121	57±11.4	25.6%	Pre/post AF-ablation	56 [37-174] (pre-) >180 (post ablation)	N/D	N/D	≥5min	28/71 (39%)
De With (142)	The Netherlands	RCT	Reveal LINQ	202	64±9	42%	Paroxysmal AF	183	N/D	N/D	≥2 min	139 (69%)
Diederichsen et al (143)	International	Prospective single arm	Reveal LINQ	597	76±4.0	43%	High stroke risk	1200 [1110-1260]	N/D	165 [42-510] 420 [144-780] 600 [192-900]	≥6min ≥5h ≥24h	209 (35%)

Study	Country	Design	Device	No. of patients	Age (years)	Females	Population	Monitoring time (day)	Implantation after event (day)	Insertion to AF detection (day)	AF definition	AF rate
Dion et al (144)	France	Prospective single arm	Reveal Plus	24	49±13.6	37.5%	CS	435 (mean)	90±30.3	N/D	≥30s	1 (4.2%)
Etgen et al (145)	Germany	Prospective single arm	Reveal XT	22	61.6 [51.9-71.3]	50%	CS	360	8.5 [6.5-10.5]	152.8 [61.6-244.1]	≥6min	6 (27%)
Forkmann et al (146)	Germany	Prospective single arm	Reveal LINQ	126	63±10	38.9%	Post AF-ablation	90 (ER) 360 (LR)	at the next day	N/D	≥30s	72 (57%) (ER) 57 (45%) (LR)
Haldar et al (147)	International	RCT	Reveal LINQ	120	62.3±9.6	36%	Post AF-ablation	22 (16-31) mo	0	N/D	≥30s	83 (73%)
Healey et al (148)	Canada	Prospective single arm	Confirm-AF	256	74±6	34.4%	High stroke risk	489±114	N/D	153±165	≥5min	31 (12.1% (1mo) 58 (22.3%) (6mo) 78 (30.5%) (12mo) 90 (35.2%) (18mo)
Hindricks et al (131)	International	Prospective single arm	Reveal XT	247	57±10	33.2%	High AF risk	N/D	N/D	N/D	≥2min	76 (37%)
Israel et al (149)	Germany	Prospective single arm	Reveal XT (87%)/ BioMonitor (13%)	123	65±9.0	39.8%	ESUS	381±165	20 (mean)	108±102	≥2min	8 (6.5%) (1mo) 15 (12%) (3mo) 21 (17%) (6mo) 29 (24%) (13mo)
Jorfida et al (150)	Italy	Prospective single arm	Reveal XT	54	67.8±9.4	42.6%	CS	435 (261-675)	108±60	162 [30-540]	≥5min	25 (46%)
Kitsiou et al (151)	Germany	Prospective single arm	Reveal XT	123	65±9	40%	ESUS	1095	20 (mean)	354 (mean)	≥2min	51 (41.4%)
Kusiak et al (152)	Poland	Prospective single arm	Reveal LINQ	29	55.6 (34-72)	31%	Post AF-ablation	90 (before) 180 (after)	N/D	N/D	≥2min	N/D
Lacour et al (153)	Germany	Retrospective single arm	BioMonitor 2-AF	19	61.3±13.0	42.1%	CS, HCM, SSS, syncope, AT, VT	42	N/D	N/D	N/D	1 (5.3%)
Lauschke et al (127)	International	Prospective single arm	BioMonitor	153	62.5±14.0	49%	Post AF-ablation	321±108	at the same day	N/D	≥2min	3/77 (3.9%)
Makimoto et al (154)	Germany	Prospective single arm	N/D	146	62±12	42.5%	ESUS	387 [283-552]	N/D	N/D	>30s	30 (21%)
Marks et al (155)	USA	Retrospective single arm	Reveal XT /LINQ	178	65 (mean)	52%	CS	384.1 ±218.9	5 (mean)	131.5 (median)	>2min	9 (5%) (1mo) 14 (16.2%) (12mo) 35 (19.6%) (30mo)

Study	Country	Design	Device	No. of patients	Age (years)	Females	Population	Monitoring time (day)	Implantation after event (day)	Insertion to AF detection (day)	AF definition	AF rate
Merce et al (156)	Spain	Prospective single arm	Reveal XT	14	65.4±10.9	28.6%	CS	870±177	<30	174 (mean)	N/D	5 (36%)
Muller et al (157)	Germany	Prospective single arm	Reveal XT	90	57.7±12.3	48%	CS	331±186	<60	40.7±42.2	≥30s	8 (9%) (1mo) 16 (18%) (6mo)
Nasir et al (158)	USA	Prospective single arm	Reveal LINQ(?)/ XT(?)	245	74.3±7.7	41.2%	High stroke risk	451±185	<30	141.3±139.5	≥6min	54 (22%)
Nölker et al (132)	International	Prospective single arm	Confirm DM2102	90	65.7± 9.6	39%	High AF/AF risk	N/D	N/D	N/D	≥2min	N/D
Pedersen et al (159)	Denmark	Prospective single arm	Reveal LINQ (72%)/ XT (28%)	105	65.4 [27.1-80.8]	54%	TIA	381 [371-390]	113 (30-294)	21 (5-146)	≥2min	7 (6.7%)
Poli et al (160)	Germany	Prospective single arm	Reveal LINQ (51%)/ XT (49%)	74	66.4±12.5	53.3%	CS	311±251	27±24	105±135	>2min	25 (34%)
Prabhu et al (161)	Australia	RCT	Confirm Reveal LINQ	68	(65-74)	9%	Post AF-ablation/medical rate control	6 months	At the procedure	N/D	>30s	average AF burden post-AF ablation was 1.6±5.0%
Purerfellner et al (130)	International	Enhanced AF algorithm detection using XPECT (131) and LINQ Usability Study (129)	Reveal LINQ (40%)/ XT (60%)	346	N/D	N/A	Post AF-ablation AF-management Syncope, CS high AF risk	N/D	N/D	N/D	≥2min	114 (33%)
Reiffel et al (162)	International	Prospective single arm	Reveal LINQ (69%)/XT(31%)	394	71.5±9.9	47.8%	High stroke risk	675±231	N/D	123 [41-330]	≥6min	6.2% (1mo) 20.4% (6mo) 27.1% (12mo) 29.3% (18mo) 33.6% (24mo) 40% (30mo)
Reinke et al (163)	Germany	Prospective single arm	Reveal XT	105	64.4±12.6	44%	CS	217[72.5-338]	0-28	N/D	≥30s	19 (18%)
Ritter et al (164)	Germany	Within-patient comparison of 7-day ECG vs. ICM	Reveal XT	60	63 [48.5-72]	43%	CS	382 [89-670]	13 [10-67]	64 (1-556)	≥30s	4 (6.7%) (1mo) 7 (12%) (3mo) 9 (15%) (6mo) 9 (15%) (12mo) 10 (17%) (21mo)
Romanov et al (165)	International	Prospective randomized	Reveal XT	60	62.5±6.5	20%	Post CABG	1080	at the same day	N/D	N/D	22 (37%)
Sanders et al (129)	International	Prospective single arm	Reveal LINQ	138	56.6±12.1	33%	Post AF-ablation AF-management Syncope, CS high AF risk	30	N/D	N/D	≥2min	38 (28%)

Study	Country	Design	Device	No. of patients	Age (years)	Females	Population	Monitoring time (day)	Implantation after event (day)	Insertion to AF detection (day)	AF definition	AF rate
Sanna et al (166)	International	Prospective randomized	Reveal XT	441 (221with ICM)	61.5±11.3	36.5%	CS	1080	38.1±27.6	41 [14-84](6mo) 84 (18-265) (12mo)	≥30s	(8.9%) (6mo) (12.4%) (12mo) (30%) (36mo)
Seow et al (167)	Singapore	Prospective single arm	Reveal LINQ	71	61.9±13.5	22.5%	CS	345±229	66 (median)	50 (median)	≥2min	9 (12.9%) (6mo) 11 (15.2%) (12mo)
Victor et al (168)	Spain	Prospective single arm	Reveal LINQ (86%)/XT (14%)	65	65.4±13.8	44.6%	ESUS	513±321	56 [28-109]	31 [11-59] 28 [20.5-117](XT) 31 [11-56] (LINQ)	≥30s (XT) ≥2min (LINQ)	19 (29%)
Wasserlauf et al (169)	USA	Within-patient comparison of AF-sensing watch vs. ICM	Reveal LINQ	24	72.1±7.2	34.6%	Syncope, AF-management, CS	110.3±35.7	N/D	N/D	N/D	N/D
Watson et al. (170)	USA	Retrospective single arm	Reveal LINQ	273	64.8±13.4	49.5%	CS CRAO	5.1 (max; CS) 3.6 (max; CRAO)	18 (median; CRAO) 21 (median; CS)	N/D	≥2min	64 (23%)
Wechselberger et al (171)	International	Prospective single arm	Reveal LINQ	419	65±10	43%	Post AF-ablation	450±180	at the same day	N/D	≥2min	227 (54%)
Xu et al. (172)	USA	Prospective single arm	Reveal LINQ	389	67 (mean)	46%	CS	542 days (median)	N/D	133 days (mean)	≥2min	102 (27.2%)
Yaeger et al (173)	USA	Unclear (ICM group within PENN AF Care Program)	Reveal XT	251	N/D	N/D	Post AF-ablation	30	at the same day	N/D	≥30s	90 (36%)
Ziegler et al (174, 175)	USA	ICM registry vs. simulated intermittent monitoring	Reveal LINQ	1 247	65.3±13.0	47%	CS	579±222	N/D	112 [35-293]	≥2min	4.6% (1mo) 12.2% (6mo) 16.3% (12mo) 21.5% (24mo)

Values are presented as median (interquartile range), (range), mean±standard deviation, or number with percentages.
AF, atrial fibrillation; AT, atrial tachyarrhythmia; CABG, coronary artery bypass graft; CS, cryptogenic stroke; ECG, electrocardiogram; ER, early recurrences; ESUS, embolic stroke of undetermined source; HCM, hypertrophic cardiomyopathy; ICM; implantable cardiac monitor; LR, late recurrences; mo; month; N/D, no data; SC, subcutaneous implantation; SP, subpectoral implantation; SSS, sick sinus syndrome; VT, ventricular tachyarrhythmia.

Table S6. Available FDA/CE-approved mobile applications.

Name	Company	FDA/ CE	Method, technology	Clinical application (selected)		Sensitivity	Specificity	PPV
				AF detection	Other			
Devices and mobile applications that are SPECIFIED in AF detection								
ECG App	Apple	FDA	smartwatch, PPG	yes	no	98,3%	99,6%	N/A
ECG Check	Cardiac Designs, Inc.	FDA, CE	ECG-handle device, ECG	yes	no	75%	97%	N/A
FibriCheck	Qompium nv	FDA, CE	smartphone's camera, PPG	yes	no	97%	94%	61.3%
Kardia	AliveCor, Inc.	FDA, CE	handle device, ECG	yes	no	89%	89%	89%
Microlife Connected Health	Microlife Corp.	CE	arm-worn device, MCG	yes	blood pressure	81-100%	89-99%	N/A
MoMe Kardia	InfoBionic, Inc.	FDA, CE	handle device, ECG	yes	no	N/A	N/A	N/A
myMerlin for Confirm Rx ICM	Abbott (formerly St. Jude Medical)	FDA, CE	implantable cardiac monitor	yes	no	97%	N/A	N/A
PatientCare; BodyGuardian Heart	Preventice, Inc.	FDA, CE	wearable patch ECG (chest)	yes	no	95.9%	N/A	99%
Peerbridge Cor	Peerbridge Health, Inc.	FDA	wearable patch ECG (chest)	yes	no	N/A	N/A	N/A
Verily Study Watch	Verily (Google Alphabet)	FDA	Smartwatch, PPG	yes	no	N/A	N/A	N/A
Eko Stethoscope CORE/DUO	Eko Devices, Inc.	FDA, CE	electronic stethoscope, MCG	yes	auscultation	99%	97%	NA
Name	**Company**	**FDA/ CE**	**Method, technology**	**Clinical application (selected)**				
Devices and mobile applications that COULD be used in AF detection (ECG feature)								
Health Mate	Withings France SA (formerly Nokia)	FDA, CE	arm-device, watch/mobile application	ECG, blood pressure, skin temperature, activity tracking, sleep tracking, respiratory tracking, women health				
Global ECG Management System (GEMS)	CardioComm Solutions, Inc.	FDA, CE	handle ECG device	ECG				
Qardio heart health	Qardio, Inc.	FDA, CE	arm-device, chest belt with sensors/mobile application	ECG, blood pressure, heart rate, respiratory rate, activity tracking, body composition, women health				
SimplECG	Nanowear, Inc.	FDA	bra or undershirt with sensors	ECG, blood pressure, heart rate, respiratory rate				
Master Caution	HealthWatch Technologies, Ltd.	FDA, CE	vest with sensors	ECG, heart rate, respiratory rate, skin temperature, body posture				
McKesson ECG Mobile	McKesson Corp.	FDA	wearable patch ECG (chest)	ECG				
Invision ECG system	InvisionHeart, Inc.	FDA	12-Lead ECG device	ECG				
Physiotrace Smart	NimbleHearth, Inc.	FDA	wearable patch ECG (chest)	ECG				
Rooti Rx	Rooti Labs, Ltd.	FDA	wearable patch ECG (chest)	ECG				
Smartheart	Shl Telemedicine, Ltd.	FDA, CE	ECG put-on chest device	ECG				
CoVa™ 2	toSense, Inc.	FDA	neck-worn sensor	ECG, stroke volume, cardiac output, chest fluid, heart rate, heart rate variability, respiration, skin temperature; remote monitoring portal access				
CADence IRONMAN	AUM Cardiovascular, Inc.	FDA	electronic stethoscope	auscultation (heart, lung), ECG, blood pressure				
No matching applications in AF detection used in "Heart/Circulatory System"								
Viz.ai	Viz.ai, Inc.	FDA, CE	mobile application	automatically identify suspected large vessel occlusion strokes on computed tomography angiogram imaging				
RhythmAnalytics	Biofourmis, Inc	FDA	arm-worn device	heart rate, skin temperature, respiratory rate, blood oxygenation, blood pulse wave, fitness trackers, sleep quality, heart rate variability, inter-beat-interval & a stress score				
StethoMe	StethoMe sp. z o.o.	CE	electronic stethoscope	auscultation (heart, lung), heart rate, respiration rate				
CareTaker	CareTaker, LLC	FDA, CE	hand-cuff device	blood, pressure, heart rate, respiration rate, oxygen saturation, arterial stiffness				

Name	Company	FDA/ CE	Method, technology	Clinical application (selected)
eMurmur ID	CSD Labs International Inc. d.b.a. eMurmur	FDA, CE	electronic stethoscope	auscultation (heart, lung), heart rate, respiration rate, health assistance (video-chat)
PhysioWave Pro	PhysioWave, Inc.	FDA	stand-on device	pulse wave velocity, pulse rate, body weight
Syndo Health	Syndo Health nv	CE	mobile application	blood pressure, fitness and body mass trackers, medication alerts, health educational tips, health assistance (chat)
Samsung Health	Samsung Electronics Co, Ltd.	FDA	mobile application	heart rate, oxygen saturation, stress, women health, fitness and body trackers
iHealth MyVitals	iHealthLabs, Inc.	FDA, CE	mobile application	blood pressure, scales, pulse oximeters, fitness and body mass trackers.
Masimo Professional or Personal Health	Masimo Corp.	FDA, CE	mobile application	heart rate, oxygen saturation, respiratory rate, respiratory effort index, pleth variability index, perfusion index

CE, Conformité Européenne; ECG, electrocardiogram; FDA, Food & Drug Administration; MCG, mechanocardiography; N/A, non-applicable; PPG, photoplethysmography; PPV, positive predictive value.

Table S7. Mobile applications and platforms supporting management of atrial fibrillation.

Study	Country	Design	Intervention	No. of patients	Age (years)	Females	%of AF patients	Study duration	Outcomes measured	Results
For patients										
Desteghe et al (176)	USA	Prospective single arm	Mobile app = Health Buddies - medication tracker, educational quizzes (grandparent) - healthy challenge tracker, educational games (grandchild) - communication with HCP - OAC refilling reminders	15 + grandchildren (n=20)	69.2 ±3.7	33%	100%	3 months	Patient AF knowledge (JAKQ) Patient drug adherence (MMAS-8) Patient motivation to use Mobile app feasibility, usability, satisfaction	• Patient AF knowledge: improved from 64.6+14.7% at baseline to 70.4+10.4% after 3 months (p = 0.09) • Medication adherence: 7.7±0.6 at baseline and 7.4±0.9 at end of study; electronic monitoring showed lower taking and regimen adherence than self-reported on app (taking adherence 88.6±15.4%) and regime adherence (81.8±18.7%); pill count adherence 94.5±9.2% • Motivation to use app: decreased towards end of study in both pts (p= 0.009) and grandchildren (p < 0.001). 87% of patients completed the 90-day contract • Mean days using app significantly higher in pts vs grandchildren (57.7±30.0% and 24.3±23.8%, respectively; p= 0.002) • App experience: rated positively on clarity (1.500), novelty (0.942) and stimulation (0.923) and attractiveness (0.859); efficiency (0.577) and dependability (0.481) received neutral rating
Magnani et al (50)	USA	Prospective single arm	Mobile app (animated character with speech, body gesture, facial expression) - AF education - symptom tracker - medication adherence - heart rate/rhythm monitoring (by ACK)	31	68±11	39%	100%	1 month	Patient QoL (AFEQT, HRQoL) Patient medication adherence (MMAS-8) Patient activation (PAM)	• Patient QoL: improved from 64.5±22.9 at baseline to 76.3±19.4 (p<0.01) • Patient drug adherence: improved from 7.3±0.9 to 7.7±0.5 (p=0.01) • Most of the participants found the relational agent useful, informative, and trustworthy
Ghanbari et al (177)	USA	Prospective single arm	Mobile app = miAfib - AF symptom tracker - affect tracker	10	ND	50%	100%	1 month	Patient engagement and acceptability Mobile app usability (5-ponit Likert scale)	• Patients found app easy to use (4.75 ± 0.46), intended to use it in the future (4.37 ± 1.06) and found it easy to integrate into daily routine (4.5 ± 1.07)
Guo et al (178)	China	RCT	Mobile application = mAFA - AF education - CDSS (CHA_2DS_2-VASc, HAS-BLED, SAMe-TT_2R_2 scores) - thromboprophylaxis guidance - patient event tracker - heart rhythm monitoring	3292 1646 (IC) 1646 (UC)	67 (mean) 67±15 (IC) 70±12 (UC)	38% 38% (IC) 38% (IC)	100%	291 days (mean)	Assessment of mobile application impact on long term outcomes	• Composite of ischemic stroke/systemic thromboembolism, death, and rehospitalization (1.9% in IC vs 6.0% in UC); HR 0.39 (95% CI 0.22-0.67); p<0.01 • Rehospitalization rate (1.2% in IC vs. 4.5% in UC); HR 0.32 (95% CI 0.17- 0.60); p<0.001
Guo et al (179)	China	RCT		1793 657 (IC) 1136 (UC)	64±24 N/D (IC) N/D (UC)	33% N/D (IC) N/D (UC)	100%	12 months	Assessment of mobile application impact on long term outcomes	• Bleeding events (2.1% in IC vs 4.3% in UC, p<0.01) • OAC use decreased significantly by 25% among AF patients receiving UC

Study	Country	Design	Intervention	No. of patients	Age (years)	Females	%of AF patients	Study duration	Outcomes measured	Results
Guo et al (180)	China	RCT	- blood pressure monitoring - symptom tracker - lifestyle trackers - medication adherence - self-care protocols - structured follow-up	209 113 (IC) 96 (UC)	67.4 ±10.6 70.9 ±17.4	42.5% 44.8%	100%	1 and 3 months	Patient AF knowledge (11-item AF questionnaire) Patient QoL (EQ-5D-Y) Patient drug adherence (Pharmacy Quality Alliance adherence measure) Patient OAC satisfaction (Anti-Clot Treatment Scale) Mobile app feasibility, usability, satisfaction	• Patient AF knowledge: improved vs. standard care (all p<0.05) • Patient QoL: increased vs. standard care at baseline (86.5 vs. 71.3), 1 month (87.6 vs. 70.1) and 3 months (87.2 vs. 69.9) (all p<0.05) • Patient drug adherence: increased vs. standard care at 1 month (0 (0–4) vs. 4 (0–11); p<0.001); 3 months (2 (0–4) vs.4 (0–11); p<0.001) • Patient anticoagulation satisfaction: standard care expressed more OAC burden (all p< 0.05); mAFA pts reported significantly more OAC benefit at 1 month only (p=0.013) • App usability: 90% reported app
Guo et al (181)	China	RCT		2473 1261 (IC) 1212 (UC)	67.0 (mean) (IC) 70.1 (mean) (UC)	38.0% (IC) 42.1% (UC)	100%	≥1 year	Stroke/thromboembolism All-cause death Rehospitalization App usability	• Lower composite outcome of ischaemic stroke/systemic thromboembolism, death, and rehospitalization in IC vs UC (HR 0.18, 95% CI: 0.13–0.25, *p*< 0.001) • App usability: 842 patients used mAFA, of which 70.8% had good management adherence, with the persistence of use of 91.7%
Hirschey et al (182)	USA	Prospective single arm	Mobile app - AF education - AF episodes tracker - AF triggers tracker -news from Cardiology Societies - medication reminders - heart rate monitoring - appointment reminder	12	59 [37-67]	42%	100%	1 month	Mobile app feasibility, usability, satisfaction	• App satisfaction (reported by 92% of participants), ease of use (100%), software bugs (58%), similarity to other apps used before (83%) • Perceptions of app usefulness: core needs of the patient segment, patient workflow while managing AF, app's ability to support the patient's evolving needs • Usability improvement: clarity of app instructions and design, software bugs
Manimaran et al (183)	UK	Prospective single arm	Mobile app = Ortus-iHealth (virtual arrhythmia clinic appointment via video call)	46	62 [23-86]	36%	100%	3 months	Mobile app feasibility, usability, satisfaction	• Patient activation: high satisfaction with installation and registration process (in 62% patients), sense of reminders (100%) and clinical letters (83%) usefulness, sense of cost- and time-effectiveness (80%)
Stephan et al (184)	Brazil	Prospective single arm	Mobile application - AF education - CDSS (CHA_2DS_2-VASc, HAS-BLED, SAMe-TT_2R_2 scores)	20	67.7 ±9.4	40%	100%	N/D	Patient AF knowledge Treatment decision conflict	• Patient AF knowledge: increased from 4.7±1.8 to 7.2±1.0, p<0.001 • Mobile app used resulted in low decisional conflict (11 ± 16/100 points in decisional conflict scale)

Study	Country	Design	Intervention	No. of patients	Age (years)	Females	%of AF patients	Study duration	Outcomes measured	Results
Balsam et al (185)	Poland	Prospective single arm	Educational program - AF education (video)	100	63±15	38%	62%	1 year	Patient AF knowledge (stroke risk, stroke reduction by drugs/OAC)	• Patient AF risk knowledge: increased from 22% (before), to 83% (immediately after), 79% (1 week after), 71% (1 year after movie) • Patient drugs knowledge: increased from 88% (before) to 100% (immediately after), 100% (1 week after), 97% (1 year after) • Patient OAC knowledge: increased from 70% (before) to 96% (immediately after), 92% (1 week after), 99% (1 year after)
Desteghe et al (186)	Belgium	RCT	Educational program - AF education (platform) 1. on-line tailored education group (group 1) 2. standard care with online access (group 2) 3. standard care only (group 3)	120 35 (gr.1) 36 (gr.2) 49 (gr.3)	68±10.2 62±10.1 (gr.1) 65±8.9 (gr.2) 74±7.6 (gr.3)	35% 23% (gr.1) 31% (gr.2) 47% (gr.3)	100%	12 months	Patient AF knowledge (JAKQ) Patient QoL (AFEQT) Patient experience/ opinion	• Group 1: significantly improved AF knowledge (75.0 [66.7–85.0] %; p= 0.001); knowledge persisted at 6 weeks (77.5 [65.0–85.0]%; p=0.010) and 12 weeks (80.0 [70.0–90.0] %; p< 0.001) after DCCV/PVI procedure • Group 2: no improvement in AF knowledge (65.0 [50.0–73.8]%; p=1.00); significant improvement between baseline and 6-week post-procedure (p= 0.010) and between hospitalization and 6-week post-procedure (p= 0.016) • Group 3: no knowledge improvement (p =0.248) • Group 1 and 2: significant increase in overall AFEQT score 6- and 12-week post-procedure compared to baseline and at hospitalization • Group 3: no significant difference in overall AFEQT score over time (p=0.082) • Usability: on-line platform rated positively on all aspects
Goni et al (187)	Spain	RCT	Educational program for Mediterranean diet enriched with extra virgin olive oil - phone contacts - web-based interventions with provision of dietary recommendations - access to web page, mobile app and printed resources	720 365 (IC) 355 (UC)	59.7±10.7 59.9±10.5 (IC) 59.6±10.9 (UC)	171 (24%) 82 (22.5%) (IC) 89 (25.1%) (UC)	N/D	2 years	14-item Mediterranean Diet Adherence Screener (MEDAS) questionnaire and a semi quantitative food frequency questionnaire	• Adherence to Mediterranean diet: higher improvement in IC compared with UC (net between-group difference: 1.8 points in the MEDAS questionnaire; p<.001)

Study	Country	Design	Intervention	No. of patients	Age (years)	Females	%of AF patients	Study duration	Outcomes measured	Results
Guhl et al (188)	USA	RCT	Educational program (animated character with speech, body gesture, facial expression) - AF education - AF symptom tracker - heart rhythm monitoring (by ACK)	120 61 (IC) 59 (UC)	72±9.1 72+10.6 (IC) 73+7.3 (UC)	52% 53% (IC) 51% (UC)	100%	1 month	Patient QoL (AFEQT) Patient experience/ opinion Patient daily activity Patient medication adherence	• Patient QoL: improved in IC (adjusted mean difference 4.5; 95% CI 0.6-8.3; p=0.03) compared with the UC • Patient daily activity: improved in IC (adjusted mean difference 7.1; 95% CI 1.8-12.4; p=0.009) compared with the UC • Patient medication adherence (3.5% in IC vs. 23.2% in UC; adjusted difference 16.6%; 95% CI 2.8%-30.4%; p<0.001). • Qualitative assessments of acceptability identified that participants found the relational agent useful, informative, and trustworthy
Carter et al (189)	Canada	RCT	Educational program - AF education via telephone	433 185 (UC) 228 (IC)	64±15 64±15 (IC) 64±15 (UC)	44% 43% (IC) 45% (UC)	100%	12 months	Assessment of AF knowledge on long term outcomes and OAC prescription	• Composite of death, cardiovascular hospitalization, and AF-related emergency department visits: 17.3% vs. 26.2% (IC vs. UC) OR 0.71 (95% CI 0.59 - 1.00); p=0.049 • Prescription of OAC increased in the $CHADS_2$ ≥2 group (88.4% in the IC vs. 58.5% in UC group, p<0.01).
Ferguson et al (190)	Australia	Prospecti ve single arm	Educational program - thromboprophylaxis guidance and AF education based on 12 case scenarios	74	88% aged<45	82%	N/D	6 weeks	Nurse AF and OAC knowledge Mobile app satisfaction	• There was a 54% mean improvement in knowledge levels post-intervention • Improvement in the use of the CHA_2DS_2-VASc (2.5–37.5%) and HAS-BLED (2.5–35%) tools to assess stroke and bleeding risk (p<0.01) • Mobile app satisfaction: very high satisfaction with the learning module (87%), with the content clarity (89%), ease in use (87%)
Mesquita et al (191)	Internatio nal	RCT	Educational program - online training for electrophysiologists regarding identification of AF driver sites	12 6 (IC) 6 (UC)	30 [28-32] 28 [26-30] (IC) 31 [30-33] (UC)	50% 50% (IC) 50% (UC)	100%	N/D	Impact of online training on identification of AF driver sites	• Baseline identification of AF termination sites increased from 35%±8% to 50.0%±8.2% (p=0.04) in training group, whereas no changes were observed in control group (37%±10% to 37.8%±10.5%, p=NS) • Training improved overall performance by 13.1%±3.6%, (p<0.001) while accuracy did not change for first- and second reads in the control group (2.7%±3.4%, p=0.439)
Cox et al (192)	Canada	RCT	CDSS - AF education - patient health record - thromboprophylaxis guidance - heart rate and rhythm control guidance - symptom tracker	11333 590 (IC) 543 (UC)	72+10 73+10 (IC) 72+9.9 (UC)	39.1% 60% (IC) 65% (UC)	100%	12 months	Assessment of CDS impact on long term outcomes	• Composite of unplanned emergency department visit or cardiovascular hospitalization 20.0% vs. 23.9% (IC vs. UC) HR 1.06 (95% CI 0.77 - 1.47); p=0.71 • Major bleeding 1.3% vs. 1.3% (IC vs. UC) HR 1.04 (95% CI 0.38 - 2.88); p=0.94

Study	Country	Design	Intervention	No. of patients	Age (years)	Females	%of AF patients	Study duration	Outcomes measured	Results
Eckman et al. (193)	USA	Prospecti ve single arm	CDSS - thromboprophylaxis guidance	65	66±10.5	35%	100%	1 month	Clinical decision support Patient AF knowledge Patient AF knowledge about personal stroke and bleeding risk Patient medication adherence (MMAS-8)	• Decisional conflict decreased from an average of 31 to 9; mean change was 22.3 (95% CI, 25.7 - 37.1) • Satisfaction with decision increased from 4.0 to 4.5 • Patient AF knowledge increased from 8.4 to 9.1 • Patient AF knowledge bout personal stroke and bleeding risk increased from 1 to 1.5 (p < 0.0001) • Patient medication adherence improved from 5.9 to 6.4 (p<0.0001).
Eckman et al. (194)	UK USA	RCT	CDSS - thromboprophylaxis guidance	1493 801 (IC) 692 (UC)	70 70 (IC) 70 (UC)	44% 44% 48%	100%	12 months	Clinical decision support	• Rate of discordant therapy decreased from 63% to 59% (p=0.02).
Hendriks et al (195)	The Netherlan ds	RCT	CDSS - AF management (thromboprophylaxis guidance, related treatment)	712 356 (IC) 356 (UC)	67±12 66±13 (IC) 67±12 (UC)	41.3% 44.7% (IC) 37.9% (UC)	100%	22 months (mean)	Comparison of AF nurse-led and routine clinical care	• Composite of cardiovascular hospitalization or cardiovascular death 14.3% vs. 20.8% (IC vs.UC) HR 0.65 (95% CI 0.45_0.93); p=0.017
Karlsson et al (196)	Sweden	RCT	CDSS - alert about high-risk patients left untreated	13379 7764 (IC) 6370 (UC)	59% of aged ≥75 58% (IC) 58% (UC)	43% 43% (IC) 43% (UC)	100%	12 months	Assessment of CDS impact on long term outcomes and guidelines adherence	• Adherence to guidelines increased from 70.3% (95% CI 62.9%–77.7%) to 73.0%, (95% CI 64.6%–81.4%) in IC and from 70.0% (95% CI 60.4%–79.6%) to 71.2% (95% CI 60.8%–81.6%) in UC, p = 0.013 • No difference in the incidence of stroke, transient ischemic attack, or systemic thromboembolism in the IC vs. UC (49 [95% CI 43–55] per 1,000 patients with AF in the IC compared to 47 [95% CI 39–55] per 1,000 patients with AF in UC, p= 0.64) • IC had a lower incidence of significant bleeding, with events in 12 (95% CI 9–15) per 1,000 patients with AF compared to 16 (95% CI 12–20) per 1,000 patients with AF in UC (p = 0.04)
Sheibani et al (197)	Iran	Prospecti ve single arm	CDSS - thromboprophylaxis guidance	10 HCP 373 pts	43.8 [33-58]	30%	100% (newly diagnosed)	6 months before and 6 months after interventi on	Provider adherence to OAC guidelines for AF	• CDSS improved adherence to guidelines for OAC for AF (from 48% to 65.5%, p < 0.0001)
Thomson et al (198) (DARTS-II)	UK	RCT	CDSS - thromboprophylaxis guidance	109 53 (IC) 56 (UC)	73 73±6.7 (IC) 74±6.2 (UC)	44% 43% (IC) 45% (UC)	100%	3 months	Clinical decision support	• Decision conflict was lower in IC vs. UC; mean difference -0.18 (95% CI -0.34 to -0.01) • Participants in IC not already on warfarin were much less likely to start warfarin than those in UC (25% vs. 93.8%); RR 0.27 (95% CI 0.11-0.63).

Study	Country	Design	Intervention	No. of patients	Age (years)	Females	%of AF patients	Study duration	Outcomes measured	Results
Wijtvielt et al (199)	The Netherlands	RCT	CDSS - AF management (thromboprophylaxis guidance, related treatment)	1374 671 (IC) 683 (UC)	64±10 64±10 (IC) 64±11 (UC)	44% 33% (IC) 35% (UC)	100%	37 months	Comparison of AF nurse-led and routine clinical care	• Composite of cardiovascular death and cardiovascular hospital admissions 9.7% per year vs. 11.6% per year (IC vs. UC) HR 0.85 (95% CI 0.69-1.04); p=0.12 • In a pre-specified subgroup analysis by center experience; HR 0.52 (95% CI 0.37–to 0.71) in four experienced centers and 1.24 (95% CI 0.94–1.63) in four less experienced centers (*p* for interaction <0.001).
Rosier et al (200)	France	Retrospective single arm	AF detection system - application filtering AF alerts	60	N/D	N/D	100%	9 months (mean)	Adequate classification of remote AF alerts	• 98% adequate classification of AF alerts • 84% reduction in the workload of remote monitoring of AF alerts
Zoppo et al (201)	Italy	Prospective single arm	AF detection system (AFinder web-based software)	472	69±10	23%	44%	24 months	AF detection via web-based software scanning of CIED data remote transmissions	• AFinder enhanced AF detection sensitivity by 10% • AFinder improved OAC optimal treatment by a factor of 6%
Shacham et al (202)	Israel	RCT	Remote patient-management system (remote management of PAF by telephonically transmitted recommendations (group A) or also included intervention by the attending physician (group B))	646 576 (gr.A) 160 (gr. B)	73±11	48%	100%	2-3 months	Remote AF management	• Group A: 79.5% of PAF episodes (1326/1667) were converted into sinus rhythm; mean heart rate decreased from 85±15 to 66±10 beats per minute (*p*<0.001). • Group B: 70% of PAF episodes (153/218) were converted into sinus rhythm; mean heart rate decreased from 92 ± 24 to 68 ± 21 beats per minute (*p*<0.001).
Stegman et al (203)	Germany	RCT	Remote patient management (daily transmission of body weight, blood pressure, heart rate/rhythm, oxygen saturation, and self-rated health status)	571 282 (IC) 289 (UC)	74+8.0 (IC) 74+8.1 (UC)	32% (IC) 30% (UC)	100%	12 months	Remote AF management on long term outcomes	• Days lost due to unplanned cardiovascular hospital admissions or all-cause death: 5.64%,(95% CI 3.81-7.48) in IC vs. 9.37% (95% CI 6.98-11.76) in UC group, ratio 0.60, P = 0.015). • All-cause mortality: 9.2% (95% CI 6.1–13.2) IC vs. 14.5% (95% CI 10.7–18.1) in the UC group (HR 0.60, CI 0.36–1.00, p= 0.050).

Study	Country	Design	Intervention	No. of patients	Age (years)	Females	%of AF patients	Study duration	Outcomes measured	Results
Jiang et al (204)	China	Prospective single arm	Remote patient-management system = HCFT-AF - AF education (for patient, HCP) - personal health record - AF symptom tracker - heart rate/rhythm monitoring - blood pressure monitoring - remote consultation	73	68±10.3	48%	100%	4 months	HCFT-AF program acceptability, feasibility, and usability	• HCFT-AF program satisfaction 5.21+1.43; ease of use 4.76+1.58, usefulness 5.45+1.40; overall usability 5.11+1.52 • Self-monitoring of blood pressure increased from 26% to 72% (p<0.001), heart rate from 8% to 52%(p<0.001), heart rhythm from 7% to 48%(p<0.001) • Healthy lifestyle: moderate physical activity increased from 22% to 42% (p=0.09), quitting or reducing alcohol intake from 51 to 73% (p=0.005), quitting or reducing smoking from 62% to 72% (p=0.04) • Low-salt, low-fat diet increased from 42% to 61% (p=0.04), more fruits or vegetables consumption increased from 25% to 76% (p<0.001) • 94% of indicated patients received OAC therapy
Goette et al (205)	Germany	RCT	Remote patient-management system=transtelephonic ECG transmission	225 214 (IC) 211 (UC)	61+11.2 (IC) 62+10.2 (UC)	38% (IC) 45% (UC)	100%	12 months	AF burden	•
Stewart et al (206)	Australia	RCT	Remote patient-management system - home visit and Holter monitoring 7-14 days after hospital discharge with additional telephone support	335 127 (IC) 137 (UC)	72±11 72±11 (IC) 71±12 (UC)	48% 50% (IC) 46% (UC)	100%	905 [773-1050] days	Comparison of AF nurse-led and routine clinical care	• Death or unplanned readmission 76% vs. 82% (IC vs. UC) HR 0.97 (95% CI 0.76 - 1.23); p=0.85
Vinereanu et al (207)	International	RCT	Remote patient-management system - AF education with regular monitoring and feedback to HCP	2281 1187 (IC) 1094 (UC)	70±11 70±11 (IC) 69±12 (UC)	47.3% 48% (IC) 46% (UC)	100%	12 months	Change in the proportion of patients treated with OAC Reduction in stroke risk	• Change in proportion of patients on OAC: from 68% to 80% (IC) from 64% to 67% (UC) • Absolute difference in the change between groups was 9.1% (95% CI 3.8-14.4); OR of change in the use of OAC between groups was 3.28 (95% CI 1.67-6.44; adjusted p value=0.0002). • Kaplan-Meier estimates showed a reduction in the stroke in the IC vs. UC (HR 0.48, 95% CI 0.23-0.99; log-rank p value=0·0434).

Study	Country	Design	Intervention	No. of patients	Age (years)	Females	%of AF patients	Study duration	Outcomes measured	Results
Peleg et al (208)	Italy	Prospecti ve single arm	Remote patient-management system - AF education - patient health record - symptom tracking - lifestyle tracking - CDSS - medication adherence - heart rate/rhythm monitoring - blood pressure monitoring	10	N/D	N/D	100%	127.2 ±68.6 day s	Patient compliance to ECG and blood pressure measurement Patient QoL (EuroQoL and AFEQT) Clinician / patient compliance to DSS recommendations Patient satisfaction (Likert scale) Clinician satisfaction (Likert scale)	• Patient compliance to ECG and blood pressure measurement was 0.65±0.28 and 0.75±1.33, respectively • The proportion of AF episodes in patient-initiated measurements was higher than that found in system-initiated requests (p=0.01) • Patient QoL: increased from 77.6 ± 0.23 to 78.4 ± 0.23; 50% patients improved, 18% remained, 37.5% deteriorated (EuroQoL, utility coefficient), from 67.5 ± 18.6 to 80.1 ± 13.0; 62.5% patients improved, 12.5% remained, 25% deteriorated (EuroQoL, analogue score) from 73.0 ± 14.9 to 67.8 ± 11.1; 25% patients improved, 12.5% remained, 62.5% deteriorated AFEQT, (overall score), from 72.3±18.7 to 71.9±21.7; 37.5% patients improved, 37.5% remained; 25% deteriorated (AFEQT, treatment satisfaction) • Clinician compliance to DSS recommendations (0.3) • Patient compliance to DSS recommendations (>0.9) • Patient satisfaction: system increased patient's confidence (in 50% of patients), made ability to adapt to context (86%), improved patients' peace of mind during travel (88%), improved their interaction with clinicians (>50%); was recommend to others (100%), was intended to use it in the future (89%); not complicated patients' lives (33%) • Clinician satisfaction: system helped to identify priorities and increases patient safety (in 100% of clinicians), made it easier to manage patients (100%)

AF, atrial fibrillation; AFDST, Atrial fibrillation Decision Support tool; AFEQT, Atrial Fibrillation Effect on Quality of life; AFSDM, Atrial fibrillation shared decision-making tool; AI, artificial intelligence; CDS, clinical decision support; CDS-AF, Clinical Decision Support for Atrial Fibrillation; CDSS, computerized decision support system; DARTS, Decision Analysis in Routine Treatment Study; ECG, electrocardiogram; IC, intervention care; INR, international Normalized Ratio; MMAS-8, Morisky 8-item Medication Adherence Scale; N/OAC, oral anticoagulant; PAM, Patient Activation Measure; RCT, randomized controlled trial; UC, usual care.

Table S8. Excluded studies and reason for exclusion.

Author, year, reference	Reason for exclusion
Lau 2013 (209)	Wrong intervention (development optimized algorithm for AF detection)
Lee 2013 (210)	Wrong intervention (development new AF detection technology)
McManus 2013 (211)	Wrong intervention (development new AF detection technology)
Shrivastav 2014 (212)	Wrong intervention (not focused only on AF population)
Chung 2015 (213)	Wrong intervention (development new QTc interval detection technology)
Marcolino 2015 (214)	Wrong intervention (description of teleservice collecting 12-lead ECG)
Nguyen 2015 (215)	Wrong intervention (not focused only on AF population)
Weidemann 2016 (216)	Wrong intervention (not focused only on AF population)
Coppetti 2017 (217)	Wrong intervention (not focused only on AF population)
Chong 2018 (218)	Wrong intervention (development new AF detection technology)
Lahdenoja 2018 (219)	Wrong intervention (development new AF detection technology)
Nguyen 2018 (220)	Wrong intervention (development new AF detection technology)
Baca-Motes 2019 (221)	Wrong intervention (methods for recruitment potential research participants)
Marinucci 2020 (222)	Wrong intervention (development new AF detection technology)
Luo 2021 (223)	Wrong intervention (development new AF detection technology)

AF, atrial fibrillation; ECG, electrocardiogram.

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CHAPTER 6

Long-term intermittent versus short continuous heart rhythm monitoring for the detection of atrial fibrillation recurrences after catheter ablation

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Abstract

Background: The utility of long-term intermittent heart rhythm monitoring after atrial fibrillation (AF) ablation remains unclear. Therefore, we compared the efficacy and usability of long-term intermittent (AliveCor Kardia® (ACK)) versus short continuous (Holter) heart rhythm monitoring for the detection of AF recurrences after AF ablation and evaluated ACK accuracy to detect AF.

Methods: Patients were provided with Holter (for ≥24 h) simultaneously with an ACK (4 weeks) used three times a day and in case of symptoms. The primary endpoint was the difference in proportion of patients diagnosed with recurrent AF by ACK as compared to Holter monitoring. Secondary endpoints were the usability (System Usability Scale and a four-item questionnaire) of ACK and Holter monitoring; and the accuracy of the ACK algorithm for AF detection.

Results: Out of 126 post-ablation patients, 115 (91.3%; 35 females, median age 64.0 [58.0-68.0] years) transmitted overall 7838 ACK ECG recordings. ACK and Holter monitoring detected 29 (25.2%) and 17 (14.8%) patients with AF recurrences, respectively ($p < 0.001$). More than 2 weeks of ACK monitoring did not have additional diagnostic yield for detection of AF recurrences. Patients graded ACK higher than Holter monitoring and found ACK more convenient in daily usage than Holter ($p < 0.001$). Sensitivity and specificity of ACK for AF detection were 95.3% and 97.5%, respectively.

Conclusions: Long-term intermittent monitoring by ACK more effectively detects AF recurrences after AF ablation and has a higher patients' usability than short continuous Holter monitoring. ACK showed a high accuracy to detect AF.

Keywords: AliveCor; Atrial fibrillation; Holter; Telemonitoring; e-health; m-health.

Introduction

Catheter ablation is a recommended treatment option in patients with symptomatic atrial fibrillation (AF). [1] Heart rhythm monitoring in the post-ablation period is essential for several reasons: 1) it is of clinical importance to determine whether complaints of palpitations result from recurrent AF (symptom-rhythm correlation), 2) arrhythmia monitoring can influence decision making in asymptomatic AF patients and 3) arrhythmia monitoring is an important component at assessing the outcomes of catheter ablation, clinically and in trials. [2] The diagnosis of post-ablation AF recurrences is commonly based on scheduled or symptom-initiated short-term continuous electrocardiogram (ECG) monitoring tools, such as Holter monitoring or event recorders. [1] However, these short continuous heart rhythm monitoring approaches may miss arrhythmia episodes following AF catheter ablation, particularly if they are asymptomatic. [3] More intensive monitoring is related to a better detection of both symptomatic and asymptomatic AF after catheter ablation. [3] An implantable loop recorder is the gold standard for long-term continuous monitoring, but this technology has several inherent limitations like invasiveness, local complications at the implantation site and high costs. External recordings such as handheld rhythm monitoring devices connected to smartphone applications have been developed to overcome these limitations. [2] Although Food and Drug Administration (FDA)/Conformitè Europëenne (CE)-approved external ECG monitoring devices have been validated for the detection of AF, [4] the utility for heart rhythm monitoring after AF ablation remains unclear.

In this prospective observational study, we compared the effectiveness and usability of a long-term intermittent heart rhythm monitoring approach using a single-lead ECG monitor (AliveCor Kardia® (ACK)) with a short continuous heart rhythm monitoring approach using Holter for the detection of AF recurrences after AF ablation. Additionally, we evaluated ACK accuracy for AF detection.

Methods

Study population

Patients (≥18 years) who underwent paroxysmal AF ablation from May 2017 to October 2019 in the Maastricht University Medical Centre, The Netherlands, were included in this study. Individuals were excluded if they had no smartphone and were not able to operate the ACK system after instructions. Additionally, just a limited number of ACK devices was available, which was a limiting factor in inclusion of patients.

Study design

This prospective observational cohort study complies with the Declaration of Helsinki and was approved by the Institutional Review Board at the Medical Centre (Committee reference number: NL 174232). All patients provided written informed consent.

Study procedures

As a standard of post-AF ablation follow-up care, [1] outpatient clinic visits including Holter monitoring (minimum 24 h) at three, six and 12 months follow-up were performed. At one of these time points patients were provided with an ACK (AliveCor Inc., Mountain View, CA) simultaneously with Holter and instructed to use the ACK monitor to record 30-s ECG recordings three times daily and in case of symptoms for a period of 4 weeks. Patients were instructed to record an ECG by placing two (index and middle) fingers of each hand on the electrodes of the ACK device. If an ECG recording could not be obtained, different finger positions were allowed.

Primary and secondary endpoints

The primary endpoint was the difference in proportion of patients with AF recurrences detected by long-term intermittent heart rhythm monitoring using ACK compared to short continuous heart rhythm monitoring using Holter. Secondary endpoints included 1) the usability and user-friendliness of both long-term intermittent heart rhythm monitoring by ACK and short continuous heart rhythm monitoring by Holter, 2) the correlation between clinical/demographic variables and long-term intermittent heart rhythm recordings transmission with ACK (total days used, total number of sent ECG recordings and mean number of ECG recordings sent per day) and 3) the sensitivity and specificity of the ACK algorithm for AF detection.

Data collection

Baseline clinical characteristics (demographics, medical history and therapy prior ablation) were retrieved from patients' medical records. We collected the study Holter ECG recordings at three, six or 12 months follow-up. The ACK ECG recordings were sent separately via email to the research team and stored in the hospital electronic database. Data on usability and user-friendliness of both ACK and Holter monitoring were obtained from a 10-item questionnaire (System Usability Scale) [5] and an additional four-item researcher-designed questionnaire (Fig. A1; supplementary material online).

ECG analysis

The ECG recordings were interpreted by the ACK algorithm as follows: 1) normal, 2) possible AF, 3) unreadable and 4) unclassified. An “unreadable” message implies that there was too much interference during this recording. This could be electrical or sound interference. “Unclassified” means that the algorithm could not classify the ECG as normal or AF and interference was not detected. An example of an unclassified tracing is when heart rate exceeds 100 beats per minute (tachycardia), or abnormality of P-wave (PAC) or QRS complex (PVC) is observed. All ACK ECG recordings were analysed by two researchers experienced in ECG evaluation (A.N.L.H. and M.G) separately and in case of doubt, by a third researcher (N.A.H.A.P) to provide a definite diagnosis. Their diagnosis was considered as the gold standard to assess the sensitivity and specificity of the ACK algorithm. The researchers were asked to rate the ACK ECG recordings as either adequate or inadequate in terms of AF recognition and to make a diagnosis of ECG recordings as 1) sinus rhythm, with or without premature atrial contractions (PAC) and/or premature ventricular contractions (PVC), 2) AF (defined as a minimum of 30 s of AF), 3) other arrhythmias (including atrial flutter or a regular supraventricular tachycardia) or 4) unreadable. Unreadable ACK ECG recordings were defined as having too much interference (more than 50% of a single 30-s record).

Questionnaire analysis

Patients were asked to fulfil a short 10-item questionnaire (System Usability Scale) [5] to evaluate the usability for both ACK and Holter monitoring with an additional four-item researcher-designed questionnaire with statements pointed from one to five.

1. I find the Holter monitoring easy[1], neutral[3]or difficult in daily usage (5 points).

2. I find the ACK monitoring easy[1], neutral[3]or difficult in daily usage (5 points).

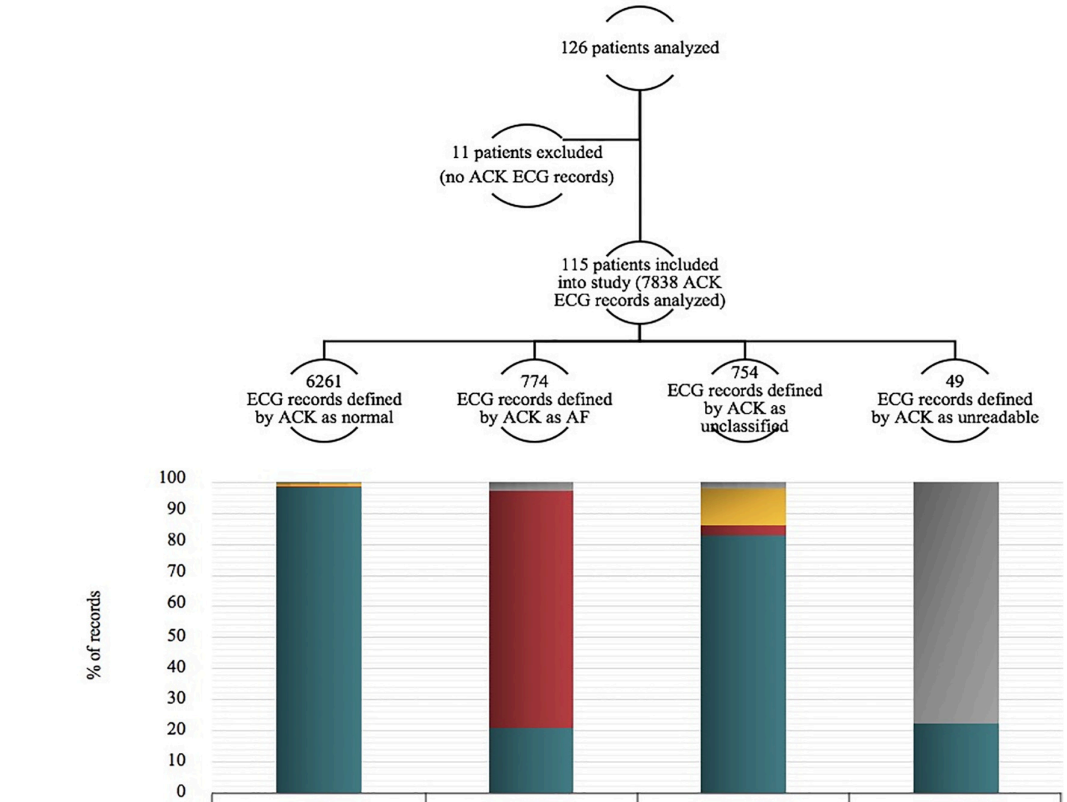
3. More convenient in daily usage was the Holter monitoring[1], irrelevant[3], ACK monitoring (5 points).

4. I would recommend the Holter monitoring[1], irrelevant[3], ACK monitoring (5 points) for heart rhythm monitoring.

System Usability Scale (SUS) scores were converted into grades from A, which indicates superior performance, to F (for failing performance). The ranges of particular grades were as follows: A (78.9–100%), B (72.6–78.8%), C (62.7–72.5%), D (51.7–62.6%) and F (0–51.6%). The grade C was divided into C1 (62.7–67.9%) and C2 (68.0–72.5%). Devices scoring below the average SUS score of 68.0% are considered to cause a problem with usability. [5]

Statistical analysis

All continuous variables were tested for normality with the Shapiro-Wilk test. Variables with normal distribution were expressed as mean ± standard deviation (SD). Nonparametric variables were expressed as median [interquartile range (IQR)] and categorical variables as counts (n) with percentages (%). Fisher's exact test was used to compare categorical variables. Differences in continuous parameters were compared using independent-samples t-test and non-parametric Mann-Whitney U test as applicable. To assess correlations with clinical/demographic variables and usage of ACK, Spearman's correlation was calculated. Statistical significance was assumed at a 5% level. For database management and statistical analysis, we used IBM SPSS Version 25 (IBM Corporation, Somers, NY, USA).



	SR	AF	unclassified	unreadable
unreadable	0.2%	2.6%	2.8%	77.6%
other arrhythmias	1.2%	0.1%	11.9%	0%
AF	0.1%	76.5%	3.2%	0%
SR	98.5%	20.8%	82.9%	22.4%

Figure 1. Study flow-chart and classification of the ECG records by AliveCor Kardia® and researchers.
AF, atrial fibrillation; SR, sinus rhythm; ACK, AliveCor Kardia®; ECG, electrocardiogram.

Results

Out of 126 post-AF ablation patients, 115 (91.3%) patients (35 females, median age 64.0 [58.0–68.0] years) transmitted their ACK recordings and were included in this analysis. A study flow-chart is presented in Fig. 1 and clinical characteristics of the study group in Table 1. The monitoring strategies (Holter and ACK) were evaluated at 3 months follow-up in 74 patients (64.3%), at 6 months follow-up in 16 patients (13.9%), and at 12 months follow-up in 25 patients (21.7%).

Primary endpoint

The primary endpoint, the proportion of patients with recurrent AF detected by long-term intermittent heart rhythm monitoring using ACK and short continuous heart rhythm monitoring using Holter was 29 (25.2%) and 17 (14.8%), respectively ($p < 0.001$) as shown in Fig. 2. During the 3-, 6- and 12-month follow-up visits 12 patients (16.2%), 1 (6.3%), and 4 (16.0%) with recurrent AF were detected by Holter ECG, and 20 patients (27.0%), 2 (12.5%), and 7 (28.0%) with recurrent AF were detected by ACK, respectively. Fig. 3 (panel A) presents analyses of patients with recurrent AF detected by Holter monitoring and long-term intermittent heart rhythm monitoring using ACK and number of ECG recordings. In 17 patients AF recurrence was detected by both ACK and Holter. In 12 patients AF recurrence was detected by ACK, but not by Holter ECG. There was no patient, in whom AF recurrence was detected by Holter ECG only and missed by ACK. The two monitoring approaches detected AF recurrences during the same monitoring period in 12 patients (red cells) and during different monitoring periods in five patients (blue cells). In those patients marked with only green cells, recurrent AF was detected solely by long-term intermittent heart rhythm monitoring with ACK. Noteworthy, in two patients (#5 and #7) short continuous heart rhythm monitoring by Holter was initiated and removed before first use of long-term intermittent heart rhythm monitoring by ACK, therefore we could not evaluate both monitoring approaches at the same time (bolded cells). Fig. 3 (panel B) presents long-term intermittent heart rhythm monitoring time by ACK needed to detect all patients with recurrent AF. In 16 [13.9%] patients AF was detected within 24 h by long-term intermittent heart rhythm monitoring using ACK. All patients with AF recurrences were detected within 14-days of long-term intermittent heart rhythm monitoring with ACK.

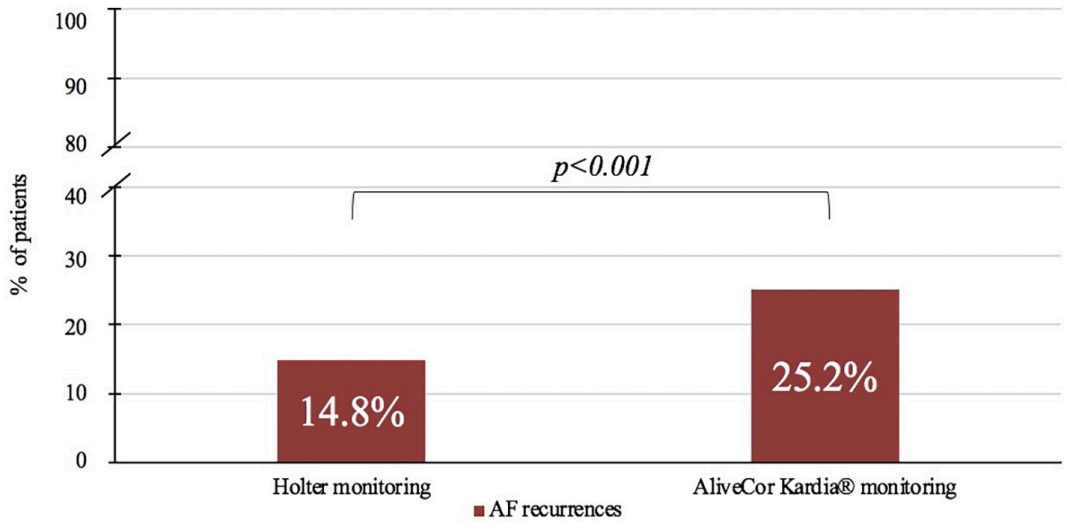


Figure 2. Proportion of patients diagnosed with atrial fibrillation recurrences by AliveCor Kardia® vs Holter monitoring approach.
AF, atrial fibrillation.

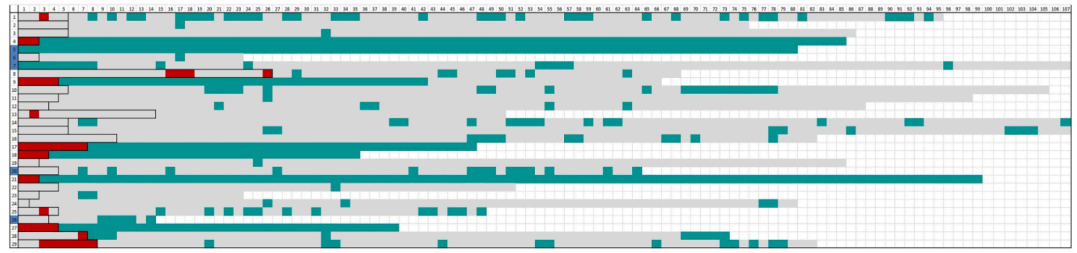
Table 1. Clinical characteristics of included patients.

Study group (n = 115)	
Demographics	
Age (years) median [IQR]	64.0 [58.0–68.0]
Female	35 (30.4%)
Body mass index (kg/m2) median [IQR]	27.1 [24.8–30.9]; n = *114*
Cardiovascular diseases	
Myocardial infarction	10 (8.7%)
PCI	12 (10.4%)
CABG	2 (1.7%)
Peripheral vascular disease	4 (3.5%)
Diabetes mellitus	11 (9.6%)
Hypertension	57 (49.6%)
Congestive heart failure	12 (10.4%)
Obesity (body mass index ≥30 kg/m2)	33 (28.7%); n = *114*
Hypercholesterolemia	19 (16.5%)
Stroke/TIA/pulmonary embolism	12 (10.4%)
History of AF ablation	19 (16.5%)
History of AFL ablation	10 (8.7%)
Device therapy (PM/CRT/ICD)	3 (2.6%)
Non-cardiovascular diseases	
Thyroid disease (hypo/hyperthyroidism)	7 (6.1%)
OSAS	7 (6.1%)
COPD	6 (5.2%)
Thromboembolic risk	
$CHA_2DS_2VASc = 0$	21 (18.3%)
$CHA_2DS_2VASc = 1$	28 (24.3%)
$CHA_2DS_2VASc \geq 2$	66 (57.4%)
Medications	
Oral anticoagulants	98 (85.2%)
Acenocoumarol	9 (7.8%)
Apixaban	19 16.5%)
Dabigatran	15 (13.0%)
Rivaroxaban	46 (40.0%)

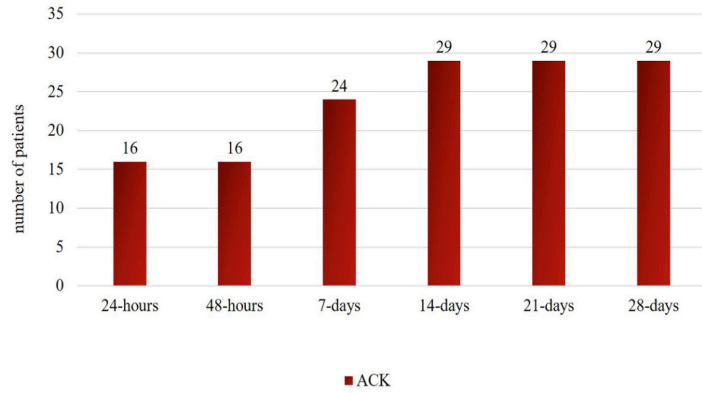
	Study group (n = 115)
Medications	
Edoxaban	9 (7.8%)
Antiplatelet drugs	5 (4.3%)
ASA	3 (2.6%)
Clopidogrel	2 (1.7%)
Beta-blockers	52 (45.2%)
Antiarrhythmic drugs	70 (60.9%)
Diuretics	22 (19.1%)
Dihydropyridine-CCB	11 (9.6%)
Non-dihydropyridine- CCB	7 (6.1%)
ACEI	27 (23.5%)
ARB	28 (24.3%)
MRA	4 (3.5%)
Digoxin	7 (6.1%)
Ablation procedure	
PVI	109 (94.8%)
PVI with cavotricuspid isthmus	4 (3.5%)
Hybrid	2 (1.7%)
Holter monitoring duration	
24 h	103 (89.6%)
48 h	4 (3.5%)
7 days	8 (7.0%)

Number provided after the semicolon indicates the total number of patients available for that variable. Values depicted as number of patients (n) with percentages unless indicated otherwise.

ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; AFL, atrial flutter; ASA, acetylsalicylic acid; bpm, beat per minute; CABG, coronary artery bypass surgery; CCB, calcium channel blockers; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; IQR, interquartile range; MRA, mineralocorticoid receptor antagonists; ms, milliseconds; OSAS, obstructive sleep apnea syndrome; PCI, percutaneous coronary intervention; PM, pacemaker; PVI, pulmonary vein isolation; TIA, transient ischemic attack.



(a)



(b)

Figure 3. Analysis of the 29 patients with recurrent atrial fibrillation detected by AliveCor Kardia® and Holter monitoring.

Panel A. Patients and their electrocardiogram recordings (from 1 to 107) with recurrent atrial fibrillation (AF) detected solely by AliveCor Kardia® (ACK) (green cells) and without detected AF (grey cells). In 17 patients AF recurrence was detected by both ACK and Holter. In 12 patients AF recurrence was detected by ACK, but not by Holter ECG. There was no patient, in whom AF recurrence was detected by Holter ECG only and missed by ACK. Red (n = 12) and blue (n = 5) cells indicate AF recurrences detected by ACK and Holter in the same and different monitoring periods, respectively. Cells with bolded frames mean period of Holter monitoring. White cells indicate no recordings. Patients numbered #7, #14 and #15 had more than 107 recordings (112, 111 and 117, respectively). Presented number of 107 recordings was chosen based on number of last recording with detected AF. Panel B. ACK monitoring time needed to detect AF in patients.

During follow-up, the long-term intermittent heart rhythm monitoring approach by ACK detected 20 (69.0%) patients with paroxysmal AF recurrence as well as 9 (31.0%) with persistent AF recurrence. ACK and Holter monitoring had equal diagnostic yield in detection of persistent AF as Holter ECG detected AF recurrence in 8 out of these 9 patients with persistent AF. The reason why persistent AF was not detected in one patient was that the Holter was attached before ACK use.

Usability and user-friendliness

Out of 115 patients, 61 (53.0%) completed the SUS questionnaires for both the long-term intermittent heart rhythm monitoring approach by ACK and short continuous heart rhythm monitoring approach by Holter and 72 (62.6%) completed the four-item questionnaire. Overall, 49 (80.4%) patients scored long-term intermittent heart rhythm monitoring by ACK and 36 (59.1%) patients scored short continuous heart rhythm monitoring by Holter as more than the average SUS score of 68.0% (p = 0.203). Patients graded long-term heart rhythm monitoring by ACK higher (A grade in 40 [65.6%]) as compared to short continuous heart rhythm monitoring by Holter (A grade in 27 [44.3%], p = 0.006). The detailed grade information is presented in Fig. 4 (panel A). Patients

found ACK in the long-term intermittent heart rhythm monitoring approach more convenient in daily usage in comparison to Holter in the short continuous heart rhythm monitoring approach (59 [79.8%] vs 5 [6.8%], p < 0.001) and would recommend the long-term intermittent heart rhythm approach using ACK over the short continuous heart rhythm approach using Holter for arrhythmia monitoring (53 [73.7%] vs 6 [8.4%], p < 0.001) (Fig. 4, panel B).

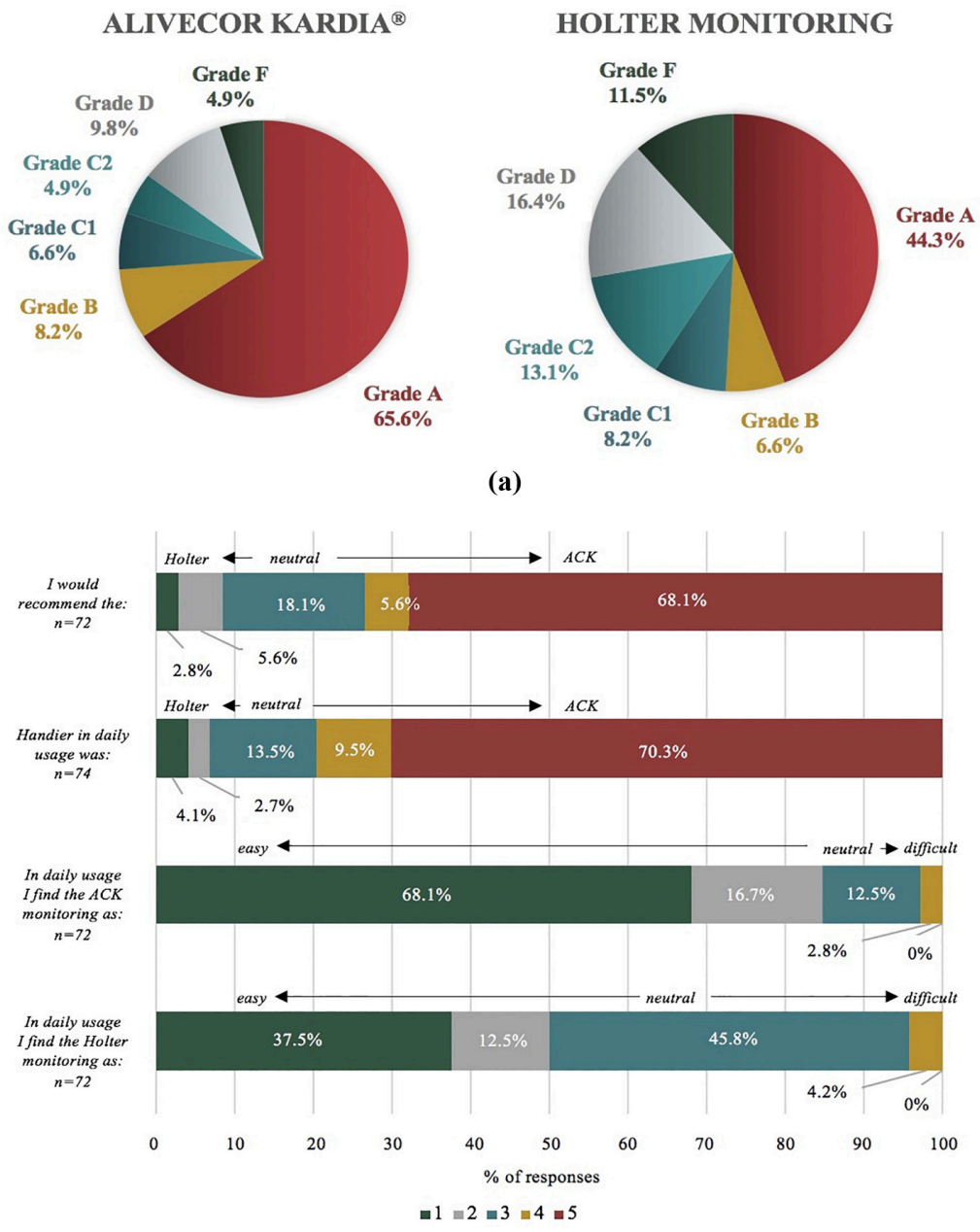


Figure 4. The usability of both AliveCor Kardia® and Holter monitoring.
Panel A. Results from System Usability Scale. Panel B. Results from 4-item researcher-designed questionnaire. ACK, AliveCor Kardia®.

AliveCor Kardia® transmissions

During the study period 7838 ECG recordings were received. The median ACK usage time in the long-term intermittent heart rhythm monitoring approach was 28.0 [21.0–32.0] days, and mean number of recordings was 68 ± 28 per patient (Table 2). Most patients with AF recurrences (>50%) sent more than 61 ECG recordings and used ACK for more than 21 days. Of the 19 (16.5%) patients who transmitted less than twice a day on average, only three (10.3%) had documented AF recurrences. There were no significant differences in number of days of ACK usage or number of ECGs taken between patients with or without recurrent AF in the long-term intermittent heart rhythm monitoring approach. However, patients with recurrent AF performed more ECG recordings a day than those without AF recurrences (median 2.9 [2.6–3.5] vs 2.7 [2.3–2.9], p = 0.003). A significant relationship was found between female sex, older age and thyroid disease and number of ECGs taken per day in the long-term intermittent heart rhythm monitoring approach (Table A1; supplementary material online).

Table 2. AliveCor Kardia® usage statistics.

Variable	Study group (n = 115)			*p*-Value
	All patients	Patients without AF recurrences (n = 86)	Patients with AF recurrences (n = 29)	
Days from enrollment to last tracing				
Median [IQR]	28.0 [21.0–32.0]	28 [20.8–32.3]	28 [19.0–32.0]	0.689
≥41	6 (5.2%)	5 (5.8%)	1 (3.4%)	1.000
31–40	34 (29.6%)	25 (29.1%)	9 (31.0%)	0.819
21–30	47 (40.9%)	35 (40.7%)	12 (41.4%)	1.000
11–20	21(18.3%)	16 (18.6%)	5 (17.2%)	1.000
0–10	7 (6.1%)	5 (5.8%)	2 (6.9%)	1.000
Total tracings sent				
Mean ± SD	68.2 ± 28.2	67.0 ± 28.3	71.7 ± 28.1	0.430
≥101	12 (10.4%)	8 (9.3%)	4 (13.8%)	0.494
81–100	29 (25.2%)	20 (23.3%)	9 (31.0%)	0.461
61–80	32 (27.8%)	25 (29.1%)	7 (24.1%)	0.811
41–60	25 (21.7%)	21 (24.4%)	4 (13.8%)	0.302
21–40	9 (7.8%)	5 (5.8%)	4 (13.8%)	0.227
0–20	8 (7.0%)	7 (8.1%)	1 (3.4%)	0.677
Number of tracings sent per day				
Median [IQR]	2.7 [2.3–3.0]	2.7 [2.3–2.9]	2.9 [2.6–3.5]	0.003
>3	22 (19.1%)	10 (11.6%)	12 (41.4%)	0.002
2–3	74 (64.3%)	60 (69.8%)	14 (48.3%)	0.045
<2	19 (16.5%)	16 (18.6%)	3 (10.3%)	0.394

Values depicted as number of patients (n) with percentages unless indicated otherwise.
AF, atrial fibrillation; SD, standard deviation; IQR, interquartile range.

ECG classification

The ACK algorithm categorized 6261 (79.9%) ECGs as normal rhythm, 774 (9.9%) as possible AF, 754 (9.6%) as unclassified and 49 (0.6%) as unreadable. When the ECG was classified as normal rhythm by the ACK algorithm, the research team agreed in 98.5% (92.0% without ectopy, 6.5% with ectopy). When AF was detected by the ACK algorithm, the researchers' assessment confirmed AF in 76.5% of cases. From the ECGs that were classified by the ACK algorithm as unclassifiable, the researchers' team was able to provide a diagnosis in 98.0% of cases. Even in the category unreadable, 22.4% of the ECGs could be interpreted by the research team as sinus rhythm. Classification of the ECGs by the ACK algorithm and researchers are presented in Fig. 1 and Table 3. Moreover, in Fig. A2 (supplementary material online) a reclassification of recordings assessed by the ACK algorithm as AF and unclassified is presented.

Table 3. Interpretation of the electrocardiograms by the AliveCor Kardia® algorithm (bold) and subsequent interpretation by the researcher (normal).

Normal rhythm (ACK)	**6261 (79.9%)**
Atrial fibrillation	5 (0.1%)
Sinus rhythm	6167 (98.5%)
Without ectopy	5762 (92.0%)
With PAC	306 (4.9%)
With PVC	92 (1.5%)
With PAC and PVC	9 (0.1%)
Other arrhythmias	72 (1.2%)
Unreadable	15 (0.2%)
Possible atrial fibrillation (ACK)	**774 (9.9%)**
Atrial fibrillation	592 (76.5%)
Sinus rhythm	161 (20.8%)
Without ectopy	74 (9.6%)
With PAC	84 (10.9%)
With PVC	1 (0.1%)
With PAC and PVC	2 (0.3%)
Other arrhythmias	1 (0.1%)
Unreadable	20 (2.6%)
Unclassified (ACK)	**754 (9.6%)**
Atrial fibrillation	24 (3.2%)
Sinus rhythm	625 (82.9%)
Without ectopy	407 (54.0%)
With PAC	171 (22.7%)
With PVC	38 (5.0%)
With PAC and PVC	9 (1.2%)
Other arrhythmias	90 (11.9%)
Unreadable	15 (2.0%)
Unreadable (ACK)	**49 (0.6%)**
Atrial fibrillation	0 (0%)
Sinus rhythm	11 (22.4%)
Without ectopy	10 (22.4%)
With PAC	1 (2.0%)
With PVC	0 (0%)
With PAC and PVC	0 (0%)
Other arrhythmias	0 (0%)
Unreadable	38 (77.6%)

Values depicted as number of patients (n) with percentages.
ACK, AliveCor Kardia®; PAC, premature atrial contractions; PVC, premature ventricular contractions.

Sensitivity and specificity

Using the assessment of the research team as reference standard, the ACK diagnostic algorithm displayed a sensitivity of 95.3%, specificity of 97.5%, positive predictive value of 76.5% and negative predictive value of 99.6% for AF detection. For normal sinus rhythm these percentages were 88.6%, 89.2%, 98.5% and 49.5%, respectively (Fig. A3; supplementary material online). The majority of false-positive ACK ECGs were associated with low-voltage p-waves and atrial ectopy.

Discussion

To our best knowledge, the present study is the first prospective direct comparison of a long-term intermittent heart rhythm monitoring with short continuous heart rhythm monitoring approach concerning the detection of AF recurrences after AF ablation in a large number of post-AF ablation patients. We demonstrated, that 4 weeks of long-term intermittent heart rhythm monitoring by ACK identified more patients with AF-recurrences after AF ablation than short continuous heart rhythm monitoring by Holter. Patients' usability for ACK in the long-term intermittent heart rhythm monitoring approach was higher than for Holter in the short continuous heart rhythm monitoring approach. ACK showed a high accuracy for detection of AF.

The identification of patients with recurrent AF after AF ablation depends on the heart rhythm monitoring strategy in the follow-up period. We demonstrated that a long-term intermittent heart rhythm monitoring approach using ACK resulted in the identification of more patients with AF recurrence compared to a short continuous heart rhythm monitoring approach using Holter. Interestingly, more than 14 days of long-term intermittent heart rhythm monitoring did not increase the detection rate of recurrent AF, suggesting that 14 days may represent a sufficient monitoring time for intermittent heart rhythm follow-up using ACK after AF ablation.

The detection of AF recurrences after AF ablation is of particular interest in clinical and research settings to monitor the effectiveness and success rate of the intervention. There are numerous clinical risk factors associated with recurrent AF after AF ablation, [6,7] which deserve an optimal management, particularly if AF recurrence occurs. [8] Long-term intermittent heart rhythm monitoring by wearables such as ACK also involves patients in their own AF management process, and patient involvement, empowerment and self-management are important components of integrated care approaches recommended in current AF guidelines. [1] By this means, patients are empowered to monitor their vital parameters and self-manage their condition. Moreover, since patients decide on the number and timing of measurements, information about symptom-rhythm correlation is provided and this increases awareness, which makes patients better prepared for their consultations with physicians. Additionally, this approach is critically dependent on the willingness and adherence of the AF patients to perform the measurements. The time-period of 4 weeks and the straightforward, simple and short measurement procedure (maximum 1 min) of this approach appears easy to incorporate in daily routine for patients. Although patients were instructed to record ECGs three times daily, there was a large range in usage with some patients transmitting one recording and some transmitting more than 100 during the 4 weeks window. Possible reasons for lack of use include the following: patients may not have felt the need to continue to record ECGs because lack of symptoms, a long sequence of sinus rhythm recordings or AF, as they might have already known they had persistent AF; patients may have found it burdensome to take ECG measurements every day; and/or patients may have forgotten to take measurements. Interestingly, we observed a strong correlation between female sex, older age, thyroid disease and increased number of ECG recordings taken per day. This suggests that age is not a limitation for innovative solutions such as m-health tools for patients with AF. [9,10]

As demonstrated in previous studies, the diagnostic accuracy of long-term intermittent heart rhythm monitoring by single-lead handheld ECG devices in the detection of AF recurrences after AF ablation is comparable or even better than the traditional short continuous heart rhythm monitoring methods (transtelephonic and Holter monitoring). [4] Long-term continuous heart rhythm monitoring with an implanted device is likely to detect more episodes of paroxysmal AF than long-term intermittent heart rhythm ECG readings, [3] however, implanted devices are relatively expensive, require a minor surgical procedure and need health care professional monitoring. In contrast, long-term intermittent heart rhythm monitoring with single-lead handheld ECG devices including ACK has been assessed and validated in several studies to be both a cheap and appropriate option for AF detection. [4] Based on the meta-analysis by Wong et al., sensitivity and specificity of handheld ECG devices varied from 54.5% to 100% and from 61.9% to 100%, respectively. In our study, the sensitivity and specificity of ACK for AF detection were 95.3% and 97.5%, respectively. Nevertheless, the observed 23.5% false positive rate of ACK indicates that visual review of ACK recordings by experts in ECG evaluation is recommended in detection of AF recurrences. Besides single-lead handheld ECG devices, also other types of handheld long-term intermittent heart rhythm monitoring are able to detect AF recurrences. Wide accessibility and low cost of photoplethysmography-based devices might be optional for identification of AF recurrences after AF ablation, as in this setting AF detection, but not AF diagnosis is needed. [11] These devices are interesting tools for remote heart rate and rhythm monitoring of patients who have already been diagnosed with AF.

For implementation of the long-term intermittent heart rhythm monitoring approach by a one-lead mobile ECG device like the ACK in an existing regular healthcare setting, a dedicated m-Health infrastructure is required. An example is the TeleCheck-AF approach, which incorporates an on-demand m-Health infrastructure based on a mobile application using photoplethysmography technology to allow remote heart rate and rhythm monitoring through teleconsultation. [9,10,12,13] Components of the TeleCheck-AF approach could be used to allow effective implementation of the long-term intermittent heart rhythm monitoring approach in post-AF ablation clinics.

Limitations of the study

Our study comprised several limitations. Firstly, the ACK records only lead I, which can make it difficult to distinguish atrial flutter from sinus rhythm or a regular supraventricular tachycardia, therefore we included all aforementioned arrhythmias in one group “tachycardia”. Secondly, ACK recordings last only 30 s. If there was an arrhythmia like AF only at the beginning or at the end of the registration, we could not be certain how long this episode actually lasted which could lead to an underestimation of true AF recurrence rates. Thirdly, there may be selection bias, as we included only those patients who were willing to use the ACK system. Therefore, there should be caution in generalizing our findings to all patients with AF, as results may differ in other patient populations. Fourthly, we excluded 11 patients from the study as no recordings were received from them. Usability problems are supposed to be the main reason for this lack of transmitted ACK recordings and therefore patients' usability in our study might be overestimated. Fifthly, according to the current recommendations for the minimum follow-up screening after AF ablation described in the “2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation” [2], a 24-h Holter ECG was performed in the majority (89.6%) of the participating patients in our study. Possibly, expanding the duration of Holter ECG from one to seven days could result in an increased AF detection rate, which requires further prospective testing in future studies. However, extension of Holter ECG monitoring duration likely results in increased inconvenience for patients. Also, the diagnostic yield of routine scheduled recordings compared to symptom-guided ACK measurements requires further study. Finally, in the present study the reference for analysis of the ACK recordings was the researchers' interpretation. In a study by Bumgarner et al., the reported sensitivity and specificity of ACK for AF detection were 93% an 97%, respectively, when comparing the ACK classification to interpretation by a cardiologist. However, specificity dropped to 84% when comparing the ACK classification to simultaneous 12-lead ECG, [14] therefore our specificity of the ACK might also be an overestimation.

Conclusions

In this study, 4 weeks of long-term intermittent heart rhythm monitoring by ACK identified more patients with AF recurrences after AF ablation than short continuous heart rhythm monitoring by Holter ECG. ACK in the long-term intermittent heart rhythm monitoring approach displayed a high diagnostic accuracy, while having a higher patients' usability as compared to Holter in the short continuous heart rhythm monitoring approach. Long-term intermittent heart rhythm monitoring by handheld devices may provide a promising tool for rhythm follow-up after AF ablation procedures.

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Supplementary material

Table S1. Spearman's correlation between clinical/ demographic variables and AliveCor Kardia® usage within:

A) group of all patients

Variables	Total days used	Total number of ECG recordings	Mean ECG recordings per day
Age	-0.101	0.075	0.234*
Female gender	0.039	0.139	0.218*
Body mass index	-0.035	-0.084	-0.032
Myocardial infarction	-0.135	-0.092	0.055
PCI	-0.195*	-0.155	0.014
CABG	-0.009	0.015	0.096
Peripheral vascular disease	0.113	0.032	-0.06
Diabetes mellitus	-0.016	0.091	0.18
Hypertension	0.013	0.008	0.002
Congestive heart failure	0.002	0.028	-0.014
Obesity	0.027	-0.013	0.08
Hypercholesterolemia	-0.042	0.074	0.16
Stroke/TIA/pulmonary embolism	0.017	0.01	0.017
$CHA_2DS_2VAS_C$ score	-0.027	0.057	0.18
History of AF ablation	-0.118	-0.03	0.15
History of AFL ablation	0.015	-0.005	-0.082
Device therapy	0.046	0.091	0.153
Thyroid disease (hypo/hyperthyroidism)	-0.053	0.068	0.224*
COPD	-0.013	-0.024	-0.084
OSAS	0.002	-0.119	-0.118

** Correlation is significant at the 0.05 level (2-tailed); the corresponding Spearman's correlation value is |rs| = 0.183*

B) group of patients without atrial fibrillation recurrences

Variables	Total days used	Total number of ECG recordings	Mean ECG recordings per day
Age	-0.044	0.052	0.207
Female gender	0.14	0.192	0.217*
Body mass index	-0.054	-0.098	0.087
Myocardial infarction	-0.178	-0.163	0.01
PCI	-0.225*	-0.213*	-0.046
CABG	-0.016	0.02	0.153
Peripheral vascular disease	0.088	-0.047	-0.158
Diabetes mellitus	-0.012	0.122	0.251*
Hypertension	-0.015	-0.092	-0.072
Congestive heart failure	0.025	0.118	0.053
Obesity	0.053	0.043	0.227*
Hypercholesterolemia	-0.068	0.027	0.137
Stroke/TIA/pulmonary embolism	0.036	0.074	0.001
$CHA_2DS_2VAS_C$ score	0.046	0.097	0.187
History of AF ablation	-0.063	0.037	0.185
History of AFL ablation	0.004	-0.074	-0.149
Device therapy	0.049	0.11	0.227
Thyroid disease (hypo/hyperthyroidism)	0.092	0.201	0.161
COPD	-0.038	-0.058	-0.107
OSAS	-0.071	-0.171	-0.056

** Correlation is significant at the 0.05 level (2-tailed); the corresponding Spearman's correlation value is |rs| = 0.212*

C) group of patients with atrial fibrillation recurrences

Variables	Total days used	Total number of ECG recordings	Mean ECG recordings per day
Age	-0.248	0.088	0.153
Female gender	-0.263	-0.028	0.357
Body mass index	0.057	-0.084	-0.412
Myocardial infarction	-0.014	0.135	0.082
PCI	-0.114	0.024	0.006
CABG	NA	NA	NA
Peripheral vascular disease	0.181	0.316	0.193
Diabetes mellitus	-0.033	0.065	0.049
Hypertension	0.12	0.328	-0.067
Congestive heart failure	-0.041	-0.168	-0.215
Obesity	-0.042	-0.171	-0.301
Hypercholesterolemia	0.029	0.159	0.048
Stroke/TIA/pulmonary embolism	-0.03	-0.155	0.084
$CHA_2DS_2VAS_C$ score	-0.201	-0.014	0.107
History of AF ablation	-0.353	-0.257	0.156
History of AFL ablation	0.041	0.203	0.114
Device therapy	NA	NA	NA
Thyroid disease (hypo/hyperthyroidism)	-0.332	-0.196	0.299
COPD	0.079	0.102	-0.034
OSAS	0.283	0.102	-0.238

** Correlation is significant at the 0.05 level (2-tailed); the corresponding Spearman's correlation value is |rs| = 0.368.*
ECG, electrocardiogram; AF, atrial fibrillation; AFL, atrial flutter; CABG, coronary artery bypass surgery; COPD, chronic obstructive pulmonary disease; NA, non-applicable; OSAS, obstructive sleep apnea syndrome; PCI, percutaneous coronary intervention; TIA, transient ischemic attack

Study number: ….

Questionnaire part 1: AliveCor heart monitor

System Usability Scale*

© Digital Equipment Corporation, 1986(1).

	Strongly disagree				Strongly agree
1. I think that I would like to use the AliveCor frequently.	1	2	3	4	5
2. I found the AliveCor unnecessarily complex.	1	2	3	4	5
3. I thought the AliveCor was easy to use.	1	2	3	4	5
4. I think that I would need the support of a technical person to be able to use the AliveCor.	1	2	3	4	5
5. I found the various functions of the AliveCor were well integrated.	1	2	3	4	5
6. I thought there was too much inconsistency in the AliveCor.	1	2	3	4	5
7. I would imagine that most people would learn to use the AliveCor very quickly.	1	2	3	4	5
8. I found the AliveCor very cumbersome to use.	1	2	3	4	5
9. I felt very confident using the AliveCor.	1	2	3	4	5
10. I needed to learn a lot of things before I could get going with the AliveCor.	1	2	3	4	5

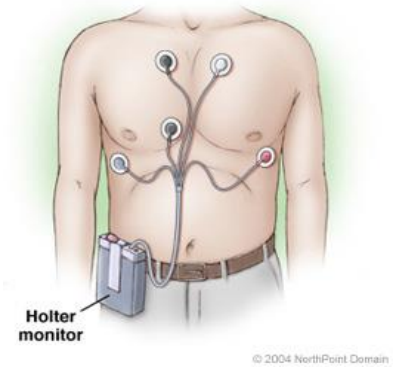
1.Brooke J. "SUS: a "quick and dirty" usability scale". . Usability Evaluation in Industry London:Taylor and Francis. 1996

Figure S1. System Usability Scale and four-item researcher-designed questionnaire.

Study number: ….

Questionnaire part 2: Holter

System Usability Scale*



	Strongly disagree				Strongly agree
1. I think that I would like to use the Holter frequently.	1	2	3	4	5
2. I found the Holter unnecessarily complex.	1	2	3	4	5
3. I thought the Holter was easy to use.	1	2	3	4	5
4. I think that I would need the support of a technical person to be able to use the Holter.	1	2	3	4	5
5. I found the various functions of the Holter were well integrated.	1	2	3	4	5
6. I thought there was too much inconsistency in the Holter.	1	2	3	4	5
7. I would imagine that most people would learn to use the Holter very quickly.	1	2	3	4	5
8. I found the Holter very cumbersome to use.	1	2	3	4	5
9. I felt very confident using the Holter.	1	2	3	4	5
10. I needed to learn a lot of things before I could get going with the Holter.	1	2	3	4	5

1.Brooke J. "SUS: a "quick and dirty" usability scale". . Usability Evaluation in Industry London:Taylor and Francis. 1996.

Figure S1 (continuation). System Usability Scale and four-item researcher-designed questionnaire.

Study number: ….

Questionnaire part 3

	Easy		Neutral		Difficult
1. I find the Holter monitoring:	1	2	3	4	5

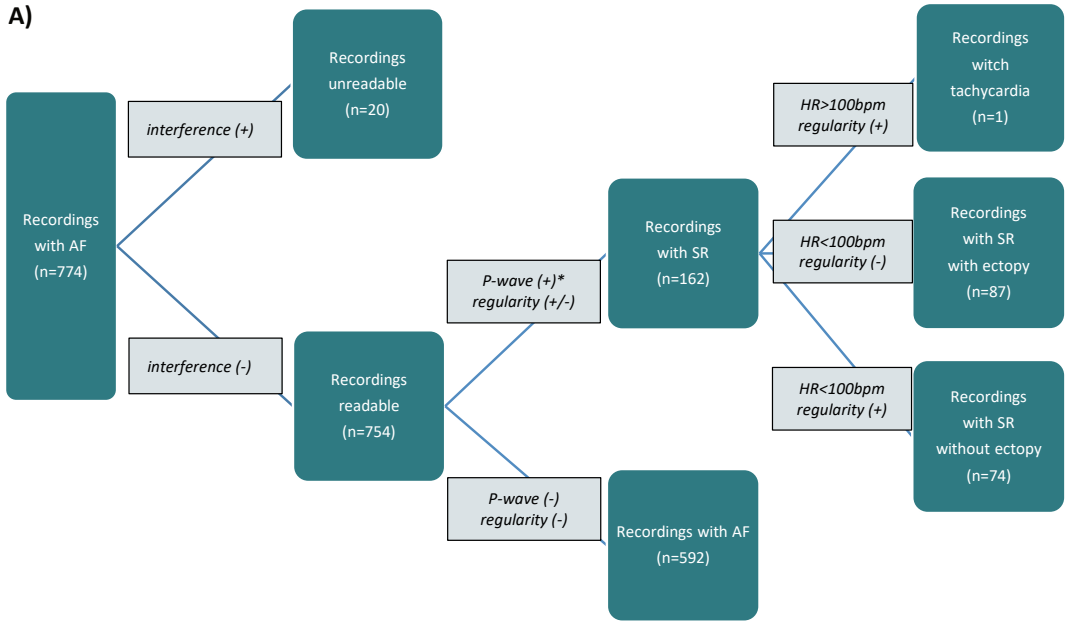
	Easy		Neutral		Difficult
2. I find the AliveCor monitoring:	1	2	3	4	5

	Holter		Neutral		AliveCor
3. More convenient in daily usage was the:	1	2	3	4	5

	Holter		Neutral		AliveCor
4. I would recommend the:	1	2	3	4	5

Figure S1 (continuation). System Usability Scale and four-item researcher-designed questionnaire.

A)



B)

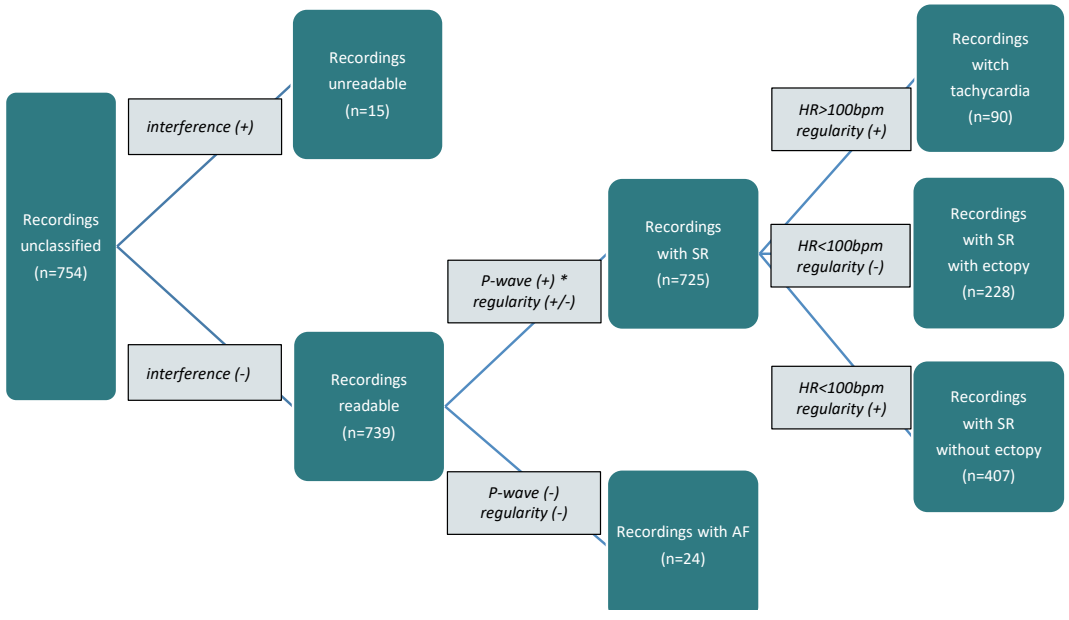


Figure S2. Researcher reclassification of recordings classified as atrial fibrillation (A) and unclassified (B) by AliveCor Kardia® algorithm.
**or P-wave invisible (due to low amplitude/ motion artifacts)*
AF, atrial fibrillation; SR, sinus rhythm; HR, heart rate

A)

AF

		Researcher: Positive	Researcher: Negative	
ACK algorithm	Positive	592	182	PPV 76.5%
	Negative	29	7035	NPV 99.6%
		Sensitivity 95.3%	Specificity 97.5%	Accuracy 97.3%

B)

SR

		Researcher: Positive	Researcher: Negative	
ACK algorithm	Positive	6167	94	PPV 98.5%
	Negative	797	780	NPV 49.5%
		Sensitivity 88.6%	Specificity 89.2%	Accuracy 88.6%

Figure S3. Two by two matrices of atrial fibrillation (A) and sinus rhythm (B).
AF, atrial fibrillation; SR, sinus rhythm; ACK, AliveCor Kardia®; NPV, negative predictive value; PPV, positive predictive value

CHAPTER 7

Accuracy of continuous photoplethysmography-based 1-minute mean heart rate assessment during atrial fibrillation

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**contributed equally*

Europace. 2023 Mar 30;25(3):835-844.

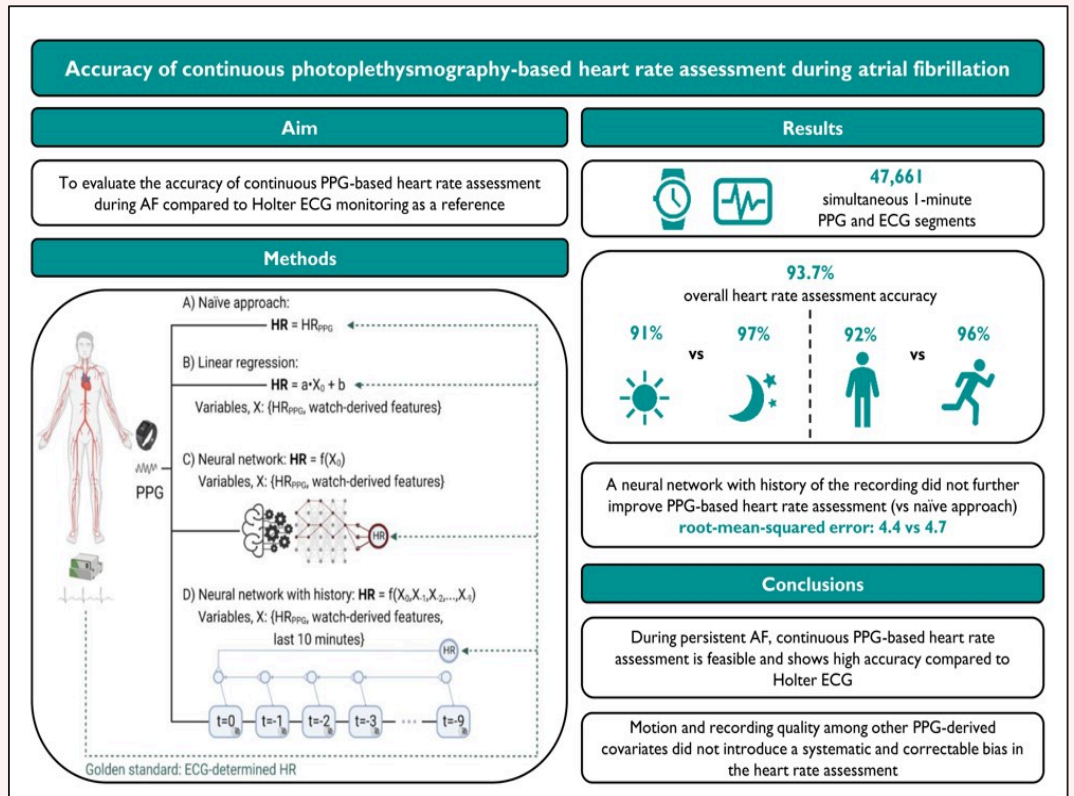
Abstract

Aims: Although mobile health tools using photoplethysmography (PPG) technology have been validated for the detection of atrial fibrillation (AF), their utility for heart rate assessment during AF remains unclear. Therefore, we aimed to evaluate the accuracy of continuous PPG-based 1 min mean heart rate assessment during AF.

Methods and results: Persistent AF patients were provided with Holter electrocardiography (ECG) (for ≥24 h) simultaneously with a PPG-equipped smartwatch. Both the PPG-based smartwatch and Holter ECG automatically and continuously monitored patients' heart rate/rhythm. ECG and PPG recordings were synchronized and divided into 1 min segments, from which a PPG-based and an ECG-based average heart rate estimation were extracted. In total, 47 661 simultaneous ECG and PPG 1 min heart rate segments were analysed in 50 patients (34% women, age 73 ± 8 years). The agreement between ECG-determined and PPG-determined 1 min mean heart rate was high [root mean squared error (RMSE): 4.7 bpm]. The 1 min mean heart rate estimated using PPG was accurate within ±10% in 93.7% of the corresponding ECG-derived 1 min mean heart rate segments. PPG-based 1 min mean heart rate estimation was more often accurate during night-time (97%) than day-time (91%, P < 0.001) and during low levels (96%) compared to high levels of motion (92%, P < 0.001). A neural network with a 10 min history of the recording did not further improve the PPG-based 1 min mean heart rate assessment [RMSE: 4.4 (95% confidence interval: 3.5-5.2 bpm)]. Only chronic heart failure was associated with a lower agreement between ECG-derived and PPG-derived 1 min mean heart rates (P = 0.040).

Conclusion: During persistent AF, continuous PPG-based 1 min mean heart rate assessment is feasible in 60% of the analysed period and shows high accuracy compared with Holter ECG for heart rates <110 bpm.

Keywords: 1 min mean heart rate assessment; Electrocardiography; Mobile health; Persistent atrial fibrillation; Photoplethysmography.



Graphic abstract.

Introduction

According to current European Society of Cardiology (ESC) guidelines, rate control is an integral part of atrial fibrillation (AF) management (1) in order to improve AF-related symptoms (2). To date, lenient rate control (resting heart rate target <110 bpm) is recommended, unless a patient is highly symptomatic and requires stricter rate control (1, 3). To determine the adequacy of rate control, heart rate assessment based on scheduled or symptom-initiated electrocardiogram (ECG) monitoring tools, such as a 10-second resting ECG, Holter ECG or event recorders, is recommended (4). However, these heart rate monitoring tools can be costly and often cumbersome for patients in daily use. Therefore, mobile health (mHealth) solutions have been developed to overcome these limitations (5-8). Within the TeleCheck-AF project (9), a remote pathway consisting of photoplethysmography (PPG)-based heart rate/rhythm monitoring and teleconsultation has been created and introduced permanently to standard of care for comprehensive AF management. Although mHealth tools using PPG technology have been validated for the detection of AF , it is unclear whether mHealth tools can accurately determine the heart rate during AF (10).

In this prospective observational study, we aimed to 1) evaluate the accuracy of continuous PPG-based 1-minute mean heart rate assessment during AF compared to Holter ECG monitoring as a reference and 2) establish predictors for accurate PPG-based 1-minute mean heart rate assessment in patients with persistent AF.

Methods

Study population

From October 2020 to July 2021, consecutive patients (≥18 years) with persistent AF scheduled for Holter monitoring (of minimum 24 hours) in the Maastricht University Medical Centre+ (MUMC+), Maastricht, The Netherlands, were included. Individuals with implantable pacemakers were excluded.

Study design

This prospective observational cohort study was performed in compliance with the Declaration of Helsinki and approved by the Institutional Review Board at the MUMC+ (Committee reference number: NL 174232). All patients provided written informed consent.

Study procedures

Outpatient clinic visits included Holter monitoring (minimum 24 hours duration) (SEER Light monitor, GE Healthcare, Milwaukee, WI, USA) as a part of standard care. The Holter monitor provided three channels of diagnostic-quality ECG and its sampling rate was 128 samples per second. At this time point, patients were provided a PPG-equipped smartwatch (Samsung Galaxy Watch3, Samsung, Suwon, South Korea). The smartwatch software was Food and Drug Administration (FDA)-approved and Conformité Européenne (CE)-marked with 25 Hz sampling rate. The manufacturer claim about the minimum heart rate that can be accurately measured using PPG was 20 bpm. There is no claim about the maximum heart rate that can be accurately measured. Patients were instructed to wear the smartwatch during the period of the Holter monitoring. Both the PPG-equipped smartwatch and Holter automatically and continuously monitored patients' heart rate and rhythm around the clock. All activities of daily living were allowed without any specific restrictions.

Data collection and data analysis

The continuous recordings of ECG and PPG were aligned using time stamps and divided into separate 1-minute segments. The PPG signals were preprocessed to remove noise and facilitate heartbeat detection. This process included interpolation at 30Hz, a Moving Average Filter, and a Savitzky-Golay filter, taking the derivative and normalizing the signal. Every channel of the raw PPG signal was preprocessed accordingly. The deep neural network of FibriCheck intrinsically calculated and extracted features from the pre-processed PPG signal and calculated the average 1-minute heart rate based on these features. The covariates included 1) heart rate variability, 2) a PPG signal quality metric, 3) a motion index and 4) a variation in motion index. Heart rate variability was quantified as the root mean square of successive differences (RMSSD) of detected heart beats. To categorize the PPG recordings into sufficient or insufficient quality to detect and differentiate heartbeats (quality metric), raw signals were analysed by a recurrent neural network algorithm of FibriCheck as described elsewhere (11). This deep neural network determined automatically the quality of the signal and annotated the signal accordingly. The network was trained to identify segments of insufficient signal quality based on the amount of noise. Just heart beats within the sufficient signal quality segment of the 1-minute PPG recording were used to compute the heart rate. The heart rate (beats per minute) was computed as 60 (seconds per minute), divided by the average of at least 20 beat-to-beat intervals (in seconds). The complete PPG recording was classified as insufficient quality when less than 20 heartbeats with sufficient quality were detected; for those PPG recordings with insufficient quality, PPG-based 1-minute mean heart rate could not be assessed by the FibriCheck algorithm. Examples of PPG-based 1-minute mean heart rate segments with insufficient and sufficient quality were presented in Supplementary Figure S1. Motion was defined as the average magnitude of the accelerometer vector during the measurement. The accelerometer acquired 50 Hz signals. The motion index was determined for each measurement and recordings were classified based on quartiles (G1, G2, G3 or G4) after excluding recordings with insufficient quality. Variation in motion index was defined as the standard deviation (SD) of the motion (vector) over the entire measurement.

Holter recordings and annotations were exported from the MARS ambulatory Holter ECG analysis system (GE Healthcare, Milwaukee, WI, USA) and reviewed by a certified Holter ECG technician. The ECG-derived 1-minute mean heart rate served as the golden standard. Simultaneous PPG and ECG 1-minute segments with insufficient quality for analysis were excluded.

Statistical analyses

The segments were categorized based on ECG-based 1-minute mean heart rate into three rate control ranges: ≤80 bpm, 80-110 bpm and insufficient rate control >110 bpm (3). We defined an accurate PPG-based assessment of the 1-minute mean heart rate as one that deviated less than ±10% from the corresponding ECG-derived 1-minute mean heart rate. To evaluate the effect of time of recording on the accuracy of PPG-based 1-minute mean heart rate assessment, we split the data into day-time (predominantly active and/or awake period between 8 am and 10 pm) and night-time (predominantly rest and/or sleeping period between 12 am and 6 am). Because people go to bed and get out of bed at different times, we excluded segments recorded between 10 pm and 12 am and between 6 am and 8 am, respectively, from the day-time/night-time analysis. To investigate the effect of motion on the accuracy of 1-minute mean heart rate assessment, we categorized the 1-minute segments into four groups (G1-4) using the motion index. G1 was defined as minimum to lower quartile (≤9.85 m/s^2), G2 as lower quartile to median (9.86-9.92 m/s^2), G3 as median to upper quartile (9.93-10.04 m/s^2), and G4 as upper quartile to maximum (≥10.05 m/s^2; G4).

All continuous variables were tested for normality with the Shapiro-Wilk test. Variables with a normal distribution were presented as mean ± SD. Non-normal variables were expressed as median [interquartile range (IQR)] and categorical variables as numbers (n) with percentages (%). For the comparison of categorical data, the Fisher's exact tests were used. Differences in continuous parameters were compared using independent-samples t-tests and non-parametric Mann-Whitney U tests, as appropriate. The agreement between PPG-based 1-minute mean heart rate estimation and ECG-derived 1-minute mean heart rate during AF was assessed using a Bland-Altman analysis. We used the root-mean-squared error (RMSE) to quantify the disagreement. The RMSE is particularly sensitive to outliers (i.e. clinically relevant mistakes) and was defined as follows: $RMSE = \sqrt{\frac{1}{N}\sum_N (HR_{PPG} - HR_{ECG})^2}$.

We took four approaches for PPG-based 1-minute mean heart rate estimation (Figure 1). The naïve approach (A) amounted to taking the PPG-based estimate at face value. To adjust for a possible systematic bias or trend, we employed a linear regression model (B). Because some biases may work in a non-linear way (e.g. only at higher heart rates or only at high levels of noise), we employed a simple neural network (C) to correct any such biases. This model C had two hidden layers with each ten neurons. Sudden changes in PPG-based heart rate might conceivably be an incorrect measurement due to movement or noise, and thus we constructed an advanced neural network (D) which was supplied with data from up to nine previous minutes along with data from the segment under analysis. The duration of recording history was arbitrarily chosen to give a proper baseline. The model D was designed with memory using blocks of long short-term memory (LSTM) (12). The network consisted of two parallel processing paths with each four LSTM blocks with five units each, followed by a fully-connected layer with eight neurons. The two paths were concatenated at the fully-connected level and connected to one final output neuron.

Models B-D were fitted and tested using 5-fold cross-validation to make the approaches comparable. Model A required no fitting of parameters, making cross-validation obsolete for this model. A P-value ≤ 0.05 was considered statistically significant. We used IBM SPSS Version 28 (IBM Corporation, Somers, New York, USA) for database management and statistical analysis, and models were fitted using Tensorflow v. 2.8 in Python v. 3.8.

Results

We included 50 consecutive patients with persistent AF (34% women, age 73±8 years) in the present study and divided those in patients with a high (≥95%) or low (<95%) agreement rate between PPG-based 1-minute mean heart rate assessment and ECG-derived 1-minute mean heart rate assessment (Table 1). Many (70%) had hypertension, and 26% had chronic heart failure. Most patients (88%) had an increased thromboembolic risk (CHA_2DS_2-VASc score ≥2 in men or ≥3 in women), and 96% were anticoagulated. The duration of the Holter recording was 24 hours in 45 patients (90%) and 48 hours in 5 patients (10%).

PPG-based and ECG-based 1-minute mean heart rate assessment

The recordings from the 50 patients amounted to 79,443 minutes of simultaneous ECG- and PPG recording, of which 47,661 1-minute segments (60%) passed the inclusion criteria. A total of 31,782 (40%) simultaneous PPG and ECG segments with insufficient quality for analysis were excluded. Ninety segments were excluded for ECG quality insufficiency, 24,006 segments for PPG-based insufficient quality and 7,686 segments for both ECG and PPG quality insufficiency. Based on ECG analysis, 30,968 segments (65%) showed a 1-minute mean heart rate ≤80 bpm of which 299 segments (1%) ≤40 bpm, 15,239 segments (32%) showed a 1-minute mean heart rate between 80 and 110 bpm, and 1,454 segments (3%) showed a 1-minute mean heart rate of >110 bpm.

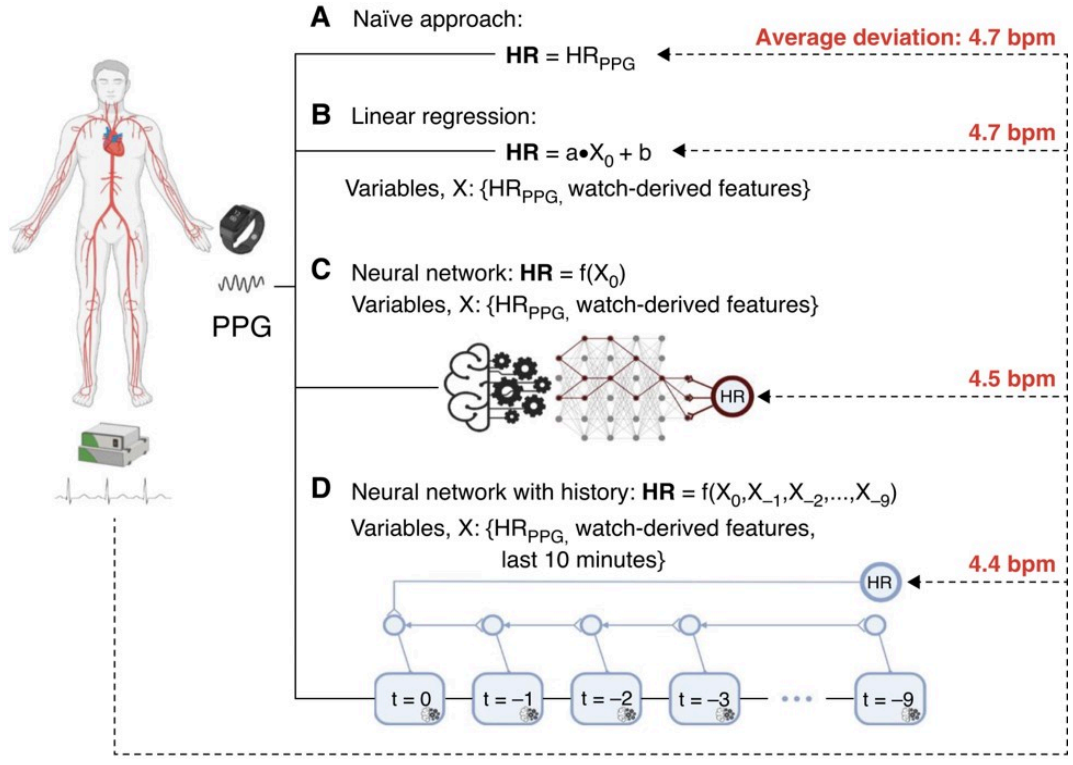


Figure 1. Four approaches to the 1 min mean heart rate estimation using PPG.

The naïve approach (A) using the PPG-derived 1 min mean heart rate at face value demonstrates a low deviation from the ECG-determined 1 min mean heart rate. The linear regression (B) incorporates the watch-derived features of heart rate variability, motion, motion variability, and PPG signal quality, and demonstrates no significant systematic bias. The simple neural network (C) allows non-linear corrections for covariates, and the advanced neural network (D) has access to the nine preceding minutes of recording, in addition to the segment under analysis. The neural networks make insignificantly better predictions of the true 1 min mean heart rate than the raw PPG predictions, suggesting little to no systematic bias from heart rate variability, movement, and PPG signal quality on the PPG-based 1 min mean heart rate assessment. ECG, electrocardiography; HR, heart rate; PPG, photoplethysmography.

Across all simultaneous ECG and PPG recordings with sufficient quality, the mean, minimum and maximum for ECG-derived 1-minute mean heart rates were 75±16 bpm, 30 bpm and 157 bpm, respectively and for PPG-based 1-minute mean heart rates 74±16 bpm, 31 bpm and 167 bpm, respectively. Included covariates had a median of 0.26 (0.20-0.32) ms for RMSSD, 0.03 (0.00-0.22) for PPG signal quality, 9.90 (9.84-9.98) m/s^2 for motion index and 0.05 (0.04-0.28) m/s^2 for motion index variation. Substituting the PPG-based 1-minute mean heart rate for the ECG-derived 1-minute mean heart rate was associated with an RMSE of 4.7 bpm and the Bland-Altman lower and upper limit boundary (defined as ±1.96 SD) were -8.4 bpm and 9.9 bpm, respectively (Figure 2, A). The linear regression, which would correct any systematic bias in the PPG-based 1-minute mean heart rate estimation was associated with an error of 4.7 bpm and the limits of agreement were -9.2 to 9.5 bpm [95% CI: 3.9 – 5.5], indicating that no systematic bias was found (Figure 2, B). The simple neural network, designed to correct any non-linear bias, was associated with an error of 4.5 bpm and the limits of agreement were -9.0 to 9.2 bpm [95% CI: 3.6 – 5.5], which was also not significantly better than the naïve approach (Figure 2, C). We found no evidence of outliers in the

Table 1. Clinical characteristics of included patients, divided in two groups according to agreement rate between PPG and ECG heart rate.

Variable	Study group (n=50)	Low agreement rate (n=15)	High agreement rate (n=35)	*P*-value
Demographics				
Age (years) – median (IQR)	75 (68-79)	75 (62-82)	75 (69-78)	0.840
Female sex	17 (34%)	3 (20%)	14 (40%)	0.171
BMI (kg/m^2) – median (IQR)	27.6 (24.7-31.9)	27.5 (24.7-29.4)	27.8 (24.6-32.1)	0.582
AF				
First-detected AF	5 (10%)	1 (7%)	4 (11%)	1.000
Previous CV (electrical and/or pharmacological)*	20/45 (44%)	5/14 (36%)	15/31 (48%)	0.428
Ablation therapy for AF*	4/45 (9%)	1/14 (7%)	3/31 (10%)	1.000
Cardiovascular diseases				
Myocardial infarction	9 (18%)	5 (33%)	4 (11%)	0.106
PCI/PTCA	6 (12%)	3 (20%)	3 (9%)	0.348
CABG	4 (8%)	1 (7%)	3 (9%)	1.000
Peripheral vascular disease	2 (4%)	0 (0%)	2 (6%)	1.000
Diabetes mellitus	7 (14%)	1 (7%)	6 (17%)	0.659
Hypertension	35 (70%)	9 (60%)	26 (74%)	0.333
Chronic heart failure	13 (26%)	7 (47%)	6 (17%)	0.040
Obesity (BMI $\geq$30kg/m2)	15 (30%)	2 (13%)	13 (37%)	0.176
Stroke/TIA/pulmonary embolism	11 (22%)	3 (20%)	8 (23%)	1.000
Thromboembolic risk				
CHA_2DS_2-VASc score = 0 (if male), = 1 (if women)	2 (4%)	1 (7%)	1 (3%)	0.514
CHA_2DS_2-VASc score ≥2 (if male), ≥3 (if women)	44 (88%)	12 (80%)	32 (91%)	0.348
Medication				
Oral anticoagulants	48 (96%)	15 (100%)	33 (94%)	1.000
Antiplatelet drugs	3 (6%)	1 (7%)	2 (6%)	1.000
Beta-blockers	39 (78%)	11 (73%)	28 (80%)	0.713
Antiarrhythmic drugs	4 (8%)	2 (13%)	2 (6%)	0.574
Diuretics	20 (40%)	7 (47%)	13 (37%)	0.529
CCB	13 (26%)	4 (27%)	9 (26%)	1.000
ACEI	15 (30%)	5 (33%)	10 (29%)	0.747
ARB	16 (32%)	7 (47%)	9 (26%)	0.191
MRA	4 (8%)	1 (7%)	3 (9%)	1.000
Digoxin	11 (22%)	6 (40%)	5 (14%)	0.070

*Values are depicted as the number of patients (n) with percentages unless indicated otherwise. * Results after excluding patients with first-detected AF.*
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass surgery; CCB, calcium channel blockers; CRT, cardiac resynchronization therapy; CV, cardioversion; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; MRA, mineralocorticoid receptor antagonists; PCI, percutaneous coronary intervention; PM, pacemaker; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischemic attack

PPG-based 1-minute mean heart rate assessments that could be corrected with use of a sliding window of ten minutes (error: 4.4 bpm and limits of agreement: -8.4 to 9.1 bpm [95% CI: 3.5 – 5.2], Figure 2, D). The PPG-based 1-minute mean heart rate estimates were accurate within ±10% in 93.7% of the 1-minute segments (95% CI: 93.5-94.0%). Deviations >±10% were seen among all 50 patients; with a median number of PPG-based 1-minute mean heart rate estimates with deviations >±10% per patient of 26 (16-46). Accuracy declined with increased 1-minute mean heart rate. Of the segments with a 1-minute mean heart rate ≤80 bpm (65%), PPG-based 1-minute mean heart rate assessment deviated less than ±10% from the corresponding ECG-derived 1-minute mean heart rate in 95%. For segments with a ECG-derived 1-minute mean heart rate 80-110 bpm (32%), accuracy was 93%. Of the segments with a 1-minute mean heart rate >110 bpm (3%), PPG-based 1-minute mean heart rate assessment deviated less than ±10% from the corresponding ECG-derived 1-minute mean heart rate in 75% (Figure 3). Even for very low 1-minute mean heart rates (≤40 bpm) (1%), accuracy remained high at 92%.

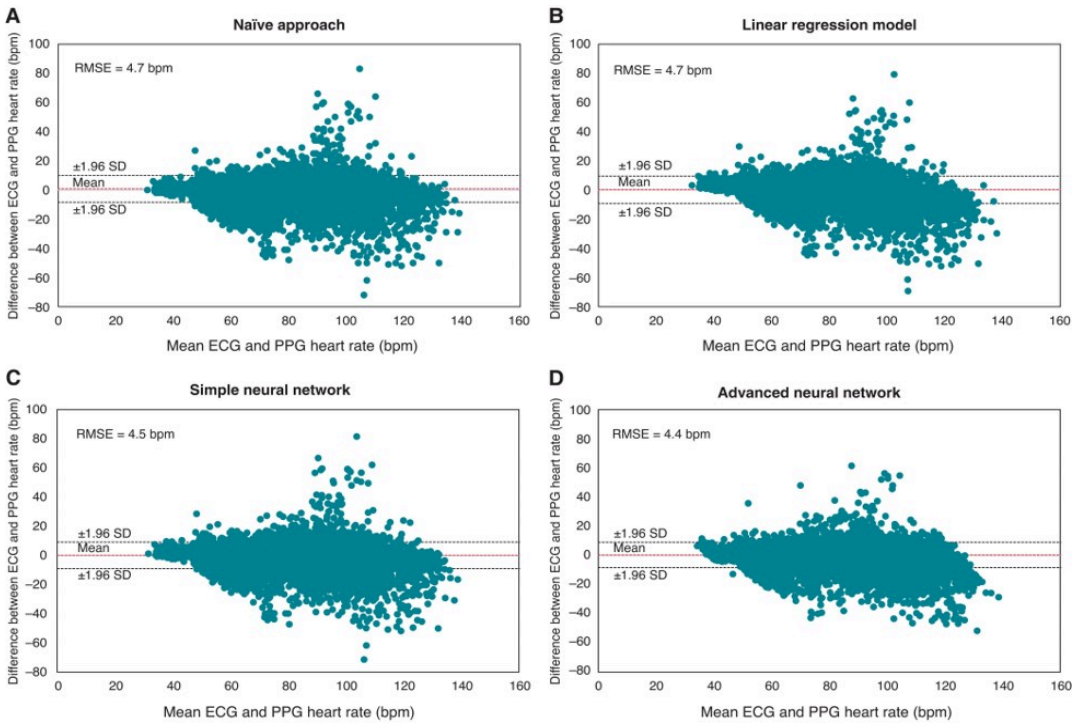


Figure 2. Agreement between the ECG-derived and PPG-based 1 min mean heart rate.
Bland–Altman plots for the four approaches (see Figure and the text for a description of the methods). ECG, electrocardiography; PPG, photopletysmography; RMSE, root mean squared error; SD, standard deviation.

1-minute mean heart rate assessment during activity and during night-time

Out of the 47,661 PPG 1-minute mean heart rate fragments, 38,529 (81%) were available for day-time/night-time analysis and 9,132 (19%) segments were excluded as they were recorded between 10 pm and 12 am and between 6 am and 8 am. A total of 22,176 simultaneous recordings (58%) were performed during day-time and 16,353 (42%) during night-time (Table 2). PPG-based 1-minute mean heart rate assessment was more accurate during night-time compared to during day-time (15,811 (97%) vs 20,162 (91%), *P*<0.001) (Table 3). Correspondingly, categorizing recordings into the correct heart rate group (≤80, 80-110, >110 bpm, i.e. a rough assessment) was more successful

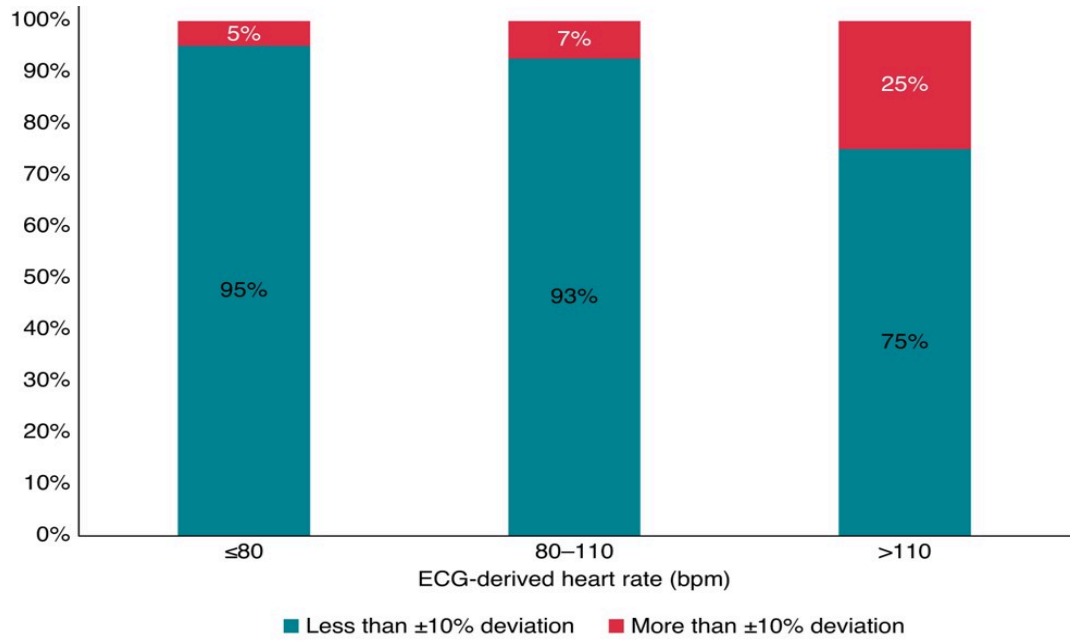


Figure 3. Percentage of PPG-based 1 min mean heart rate assessments that are accurate to within ±10%. *ECG, electrocardiography; PPG, photoplethysmography.*

Motion data was available for all 47,661 1-minute segments. A total of 14,796 simultaneous recordings (31%) were categorized in the motion quartile G1, 14,321 (30%) in G2, 11,758 (25%) in G3 and 6,786 (14%) in G4 (Table 4). The accuracy of the PPG-based 1-minute mean heart rate assessment was higher during lower motion levels compared to the higher motion levels (G1: 14,149 [96%] vs G2: 13,458 [94%] vs G3: 10,806 [92%] vs G4 6,268 [92%], *P*<0.001) (Table 3). Categorizing recordings into the right heart rate group (≤80 bpm vs 80-110 bpm vs >110 bpm) was more accurate at lower compared to higher motion levels (G1: 14,337 [97%] vs G2: 13,422 [94%] vs G3: 10,821 [92%] vs G4: 6,134 [90%], respectively, *P*<0.001) (Table 4).

Table 2. PPG-based 1-minute mean heart rate and ECG-derived 1-minute mean heart rate fragments during day-time and night-time.

		PPG-based 1-minute mean heart rate					
		Day			Night		
		≤80 bpm	80 – 110 bpm	>110 bpm	≤80 bpm	80 – 110 bpm	>110 bpm
ECG-derived 1-minute mean heart rate	≤80 bpm	10,720 (93.5%)	722 (6.3%)	23 (0.2%)	13,422 (99.1%)	120 (0.9%)	1 (0.0%)
	80 – 110 bpm	836 (8.8%)	8,593 (90.4%)	77 (0.8%)	256 (9.2%)	2,514 (90.6%)	5 (0.2%)
	>110 bpm	9 (0.7 %)	451 (37.4%)	745 (61.8%)	0	15 (43%)	20 (57%)

The green boxes represent the accurately assessed PPG-based 1-minute mean heart rate fragments and the red boxes represent the inaccurately assessed PPG-based 1-minute mean heart rate fragments when using ECG-derived 1-minute mean heart rate as reference.
Abbreviations: ECG, electrocardiography; PPG, photoplethysmography

Table 3. PPG-based 1-minute mean heart rate and ECG-derived 1-minute mean heart rate fragments per motion-based quartile.

		Low motion (G1)			Low-medium motion (G2)		
PPG-based 1-minute mean heart rate		**≤80 bpm**	**80 – 110 bpm**	**>110 bpm**	**≤80 bpm**	**80 – 110 bpm**	**>110 bpm**
ECG-derived 1-minute mean heart rate	**≤80 bpm**	11,537 (36%)	180 (1%)	7 (0.02%)	9,539 (30%)	294 (1%)	11 (0.03%)
	80 – 110 bpm	227 (2%)	2,733 (19%)	6 (0.04%)	450 (3%)	3,688 (26%)	18 (0.13%)
	>110 bpm	0	39 (3%)	67 (5%)	2 (0.15%)	124 (9%)	195 (15%)

		Medium-high motion (G3)			High motion (G4)		
PPG-based 1-minute mean heart rate		**≤80 bpm**	**80 – 110 bpm**	**>110 bpm**	**≤80 bpm**	**80 – 110 bpm**	**>110 bpm**
ECG-derived 1-minute mean heart rate	**≤80 bpm**	6,796 (21%)	347 (1%)	3 (0.01%)	3,079 (10%)	202 (1%)	5 (0.02%)
	80 – 110 bpm	383 (3%)	3,784 (26%)	36 (0.25%)	238 (2%)	2,757 (19%)	35 (0.24%)
	>110 bpm	4 (0.31%)	164 (13%)	241 (18%)	3 (0.23%)	169 (13%)	298 (23%)

PPG 1-minute mean heart rate fragments were split into motion index-based groups (G). G1 is defined as minimum to lower quartile (≤9.85 m/s²), G2 as lower quartile to median (9.86-9.92 m/s²), G3 as median to higher quartile (9.93-10.04 m/s²), and G4 as higher quartile to maximum (≥10.05 m/s²). The green boxes represent the accurately assessed PPG-based 1-minute mean heart rate fragments and the red boxes represent the inaccurately assessed PPG-based 1-minute mean heart rate fragments when using ECG-derived 1-minute mean heart rate as reference.
Abbreviations: ECG, electrocardiography; PPG, photoplethysmography

Table 4. PPG-based 1-minute mean heart rate estimation when considering day-time/night-time and motion levels.

PPG-based 1-minute mean heart rate estimation when considering the following 1-minute recordings:	**RMSE**	**Bland-Altman Lower – Upper limit boundary**
Day-time	6.0	-10.7 – 12.8
Night-time	2.8	-5.0 – 5.9
Low motion (G1)	3.5	-6.4 – 7.5
Low-medium motion (G2)	4.5	-8.2 – 9.5
Medium-high motion (G3)	5.4	-9.7 – 11.5
High motion (G4)	5.6	-9.8 – 12.0

Abbreviations: PPG, photoplethysmography; RMSE, root-mean-squared error

Clinical predictors of poor PPG-predictions

On average, 953±259 1-minute segments were available per patient. Mean 1-minute mean heart rate per patient was 74±13 bpm based on ECG and 73±13 bpm based on PPG. Substituting the mean PPG-based 1-minute mean heart rate for the mean ECG-derived 1-minute mean heart rate per patient was associated with an RMSE of 2.2 bpm and the Bland-Altman lower and upper limit boundary (defined as ±1.96 SD) were -3.6 bpm and 5.1 bpm, respectively (Figure 4, A). ECG-derived and PPG-based maximum 1-minute mean heart rate per patient was 110±18 bpm and 115±16 bpm, respectively. Substituting the PPG-based maximum 1-minute mean heart rate for the ECG-derived maximum 1-minute mean heart rate per patient was associated with an RMSE of 18.2 bpm and the Bland-Altman lower and upper limit boundary (defined as ±1.96 SD) were -40.6 bpm and 30.9 bpm, respectively (Figure 4, B). ECG-derived and PPG-based minimum 1-minute mean heart rate per patient were 58±11 bpm and 56±10 bpm, respectively. Substituting the PPG-based minimum 1-minute mean heart rate for the ECG-derived minimum 1-minute mean heart rate per patient was associated with an RMSE of 4.7 bpm and the Bland-Altman lower and upper limit boundary (defined as ±1.96 SD) were -6.9 bpm and 11.4 bpm, respectively (Figure 4, C). The proportion of recording time per patient with a ECG-derived 1-minute mean heart rate ≤110 bpm was 98±7% and with a PPG-based 1-minute mean heart rate ≤110 bpm was 98±6%. 2,980 (6.3%) PPG recordings deviated more and 44,681 (93.7%) PPG recordings deviated less than ±10% from the corresponding ECG-derived 1-minute mean heart rate. The mean and median proportion of inaccurate measurements (deviation more than ±10%) per patient were 6.5%±11.4 and 2.9% (1.7-6.6), respectively. Most patients had a good agreement between PPG-based 1-minute mean heart rate assessment and ECG-derived 1-minute mean heart rate assessment, but 15 patients (30%) had an agreement rate <95%. Detailed characteristics of the patients with low and high agreement rates are presented in Table 1. Only chronic heart failure was more common in the group with a low agreement rate (7 [47%] vs 6 [17%], *P*=0.040).

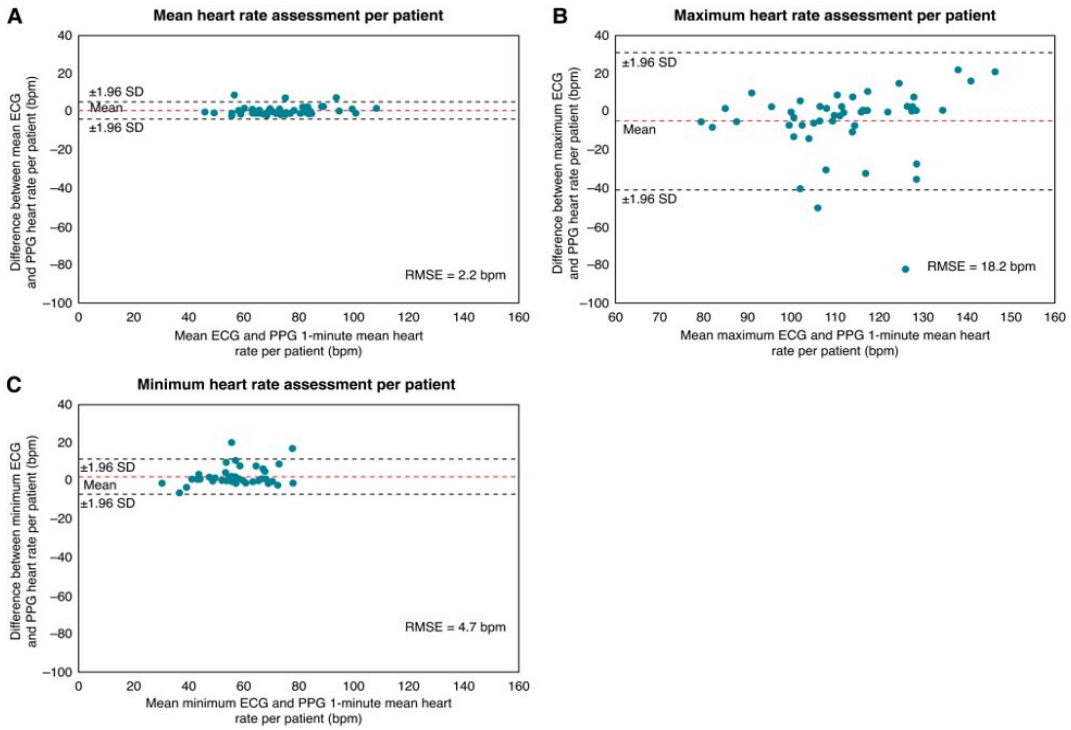


Figure 4. Agreement between the mean, maximum, and minimum ECG-derived and PPG-based 1 min mean heart rates per patient.
ECG, electrocardiography; PPG, photoplethysmography; RMSE, root mean squared error; SD, standard deviation.

Discussion

The utility and limitations of PPG technology to assess heart rate during AF has been addressed and discussed in previous studies (13-15). This study is the first to evaluate the accuracy of continuous PPG-based 1-minute mean heart rate monitoring in patients with persistent AF. The main findings of our study are as follows. First, PPG technology is suitable to accurately assess 1-minute mean heart rate during AF without a clinically significant bias compared to Holter ECG monitoring as reference. Second, the accuracy of PPG-based 1-minute mean heart rate assessment was better during night- than day-time and during lower compared to higher motion levels. Third, a neural network with access to PPG-derived 1-minute mean heart rate and additional covariates did not augment the already high validity of 1-minute mean heart rate assessment. Finally, the agreement rate between PPG-based 1-minute mean heart rate and ECG-derived 1-minute mean heart rate was lower in patients with a clinical history of chronic heart failure.

We found a strong agreement between 1-minute mean heart rate during AF assessed by PPG technology with simultaneous ECG recordings, which supports the use of PPG-based 1-minute mean heart rate monitoring as a feasible strategy for rate control management in AF patients. The current ESC guidelines recommend a lenient rate control strategy with a resting heart rate below 110 bpm (1, 3) and identifying periods with too fast (tachyarrhythmia) or too slow (bradyarrhythmia) ventricular responses during AF is important to maintain optimal exercise tolerance and reduce the risk of heart failure (tachycardiomyopathy) (16). Theoretically, underestimation of fast heart rates during AF can occur due to so-called pulse deficit (17). The high beat-to-beat variability in AF may result in variable diastolic filling of the ventricular system and consequently in reduced amplitudes of the PPG peaks

due to changes in the perfusion of the microvasculature. This may impair signal recognition and heart rate computation in the PPG waveforms, what makes the estimation of heart rate from peripheral pulse more challenging, especially at higher heart rates (13, 18). In our study, 3% of 1-minute ECG fragments showed a mean heart rate above 110 bpm, and in 75% of those cases, the PPG-based 1-minute mean heart rate assessment deviated less than ±10% from the corresponding ECG-derived 1-minute mean heart rate. Furthermore, only 1% of 1-minute ECG fragments showed a 1-minute mean heart rate ≤40 bpm, and in 92% of those cases, the PPG-based 1-minute mean heart rate assessment deviated less than ±10% from the corresponding ECG-derived 1-minute mean heart rate. Thus, PPG-based 1-minute mean heart rate estimation seems feasible to guide lenient rate control during AF. However, in some cases, PPG may underestimate true faster 1-minute mean heart rates >110 bpm during AF. The best way how to deal with this problem clinically remains uncertain. Whether novel PPG algorithms incorporating additional PPG waveform features identifying possible pulse loss and consequent underestimation of heart rate or additional ECG recordings represent the best solution remains to be determined. Additionally, it is important to note, that despite a good performance of PPG to assess slow 1-minute mean heart rates during AF, the mechanism of heart rates ≤40 bpm (e.g. AV block or sinus arrest) cannot be assessed based on PPG-recordings (14).

Despite being overall effective in assessing 1-minute mean heart rate, our results showed that the accuracy of 1-minute mean heart rate assessment by PPG technology may be limited by some factors impacting the recording quality. Patient movement has been shown previously to lead to motion artefacts in PPG signals, which negatively impacts the proportion of insufficient quality PPG recording fragments (19). In our analysis, we confirmed this finding and showed that after exclusion of insufficient quality fragments, motion did still affect the accuracy of PPG-based 1-minute mean heart rate estimation. We also observed that PPG-based 1-minute mean heart rate assessment during night-time was more accurate than during day-time. Factors such as a lower degree of respiratory arrhythmia and the absence of various heart rate stimuli during night may partially explain this finding (20). Therefore, periods of low physical activity and the night-time provide an excellent time window for PPG-based 1-minute mean heart rate assessment during AF. As suggested in previous studies, further integration of accelerometer information in the PPG sensor could provide a means of quantifying the displacement of the sensor during use and may help to correct for possible movement artefacts in PPG signals (21). Despite the high validity of 1-minute mean heart rate assessment using the crude PPG measurements, we sought to further improve accuracy with the use of artificial intelligence. PPG signals are well-suited data for machine learning approaches and have been used primarily in deep neural networks to detect AF (22, 23). Although we saw a trend towards more accurate 1-minute mean heart rate estimations when motion index and recording quality among other covariates were supplied to a deep learning model, we saw no significant improvement. Importantly, all inputs were post-processed data (e.g. the PPG-derived heart rate of a 60-second segment) and it is possible that application of deep learning to the waveforms derived from the raw PPG signal may yield higher accuracy and diminish the lack of beat recognition due to the pulse deficit problem (17, 24). A 9-minute history did not lead to a significantly more accurate 1-minute mean heart rate prediction despite the trend to improvement. We speculate that outliers/extreme errors, which the history might help identify, are uncommon or may have already been excluded due to poor recording quality. These findings indicate that crude mHealth PPG-based 1-minute mean heart rate assessment, which is feasible and robust, does not require further artificial intelligence augmentation.

Furthermore, patients with a high agreement rate between PPG-based 1-minute mean heart rate and ECG-derived 1-minute mean heart rate less frequently had chronic heart failure compared to those with a low agreement rate. The exact reason remains unclear, but factors such as arterial stiffness and progressed atherosclerosis have been shown to impact the shape and timing of the PPG pulse wave

(25), which may contribute to the observed low agreement rate between ECG-derived and PPG-based heart rate in patients with chronic heart failure. Whether chronic heart failure should stop us using PPG technology for the assessment of heart rate during AF warrants further prospective evaluation. Furthermore, although we found no association between chronic heart failure and covariates such as the use of beta-blockers, ECG-derived 1-minute mean heart rate as well as the level of motion (Supplementary Table S1), we cannot exclude the influence of these covariates in patients with chronic heart failure on the accuracy of PPG-based 1-minute mean heart rate assessment due to the small size of the study group.

Limitations

Our study has several limitations. First, although we had a large number of combined PPG and ECG recording segments available to evaluate the accuracy of PPG-based 1-minute mean heart rate estimation, the number of recruited patients was limited which may have impaired the identification of predictors for accurate 1-minute mean heart rate assessment during AF. Second, we included only persistent AF patients and it remains unclear whether the findings can be generalized to all patients with AF. Data recorded during sinus rhythm and during the transition of the heart rhythm (from AF to sinus rhythm or vice versa) would be needed to evaluate how PPG-based 1-minute mean heart rate assessment performs in paroxysmal AF. Third, we examined the accuracy of PPG-based 1-minute mean heart rate assessment during 24 hours of monitoring, but further long-term follow-up recordings are needed to evaluate the performance during longer recordings. Fourth, due to the combined use of one specific software algorithm and one specific smartwatch device the results cannot be generalized to other vendors and models without validation. Fifth, 40% of the 1-minute segments did not pass the inclusion criteria for sufficient quality, which might have impacted the results. However, we showed that PPG-based 1-minute mean heart rate assessment gives feasible heart rate estimations to guide lenient rate control despite a high number of missing 1-minute PPG recordings. Sixth, the number of ECG-derived 1-minute mean heart rate fragments >110 bpm was limited. Therefore, the capability of PPG-based 1-minute mean heart rate estimation at higher rates remains uncertain. Despite that, in 75% of the 1,454 cases with a 1-minute mean heart rate >110 bpm, the PPG-based 1-minute mean heart rate assessment deviated less than ±10% from the corresponding ECG-derived 1-minute mean heart rate. Seventh, the Bland-Altman analysis only defined the interval of agreement between ECG-derived and PPG-based 1-minute mean heart rate assessment, it does not say whether those limits are acceptable or not as this depends on clinical necessity. Finally, we assessed mean heart rate computed over 1-minute segments instead of beat-to-beat heart rate for the determination of PPG-based heart rate.

Conclusions

Continuous PPG-based 1-minute mean heart rate assessment during AF seems feasible to guide lenient rate control and shows good accuracy compared to Holter ECG as a reference. Future studies need to be performed to evaluate how to integrate PPG-derived heart rate information into clinical decision-making processes to guide rate control in patients with AF. Motion and recording quality among other PPG-derived covariates did not introduce a systematic and correctable bias in the 1-minute mean heart rate assessment. Chronic heart failure was associated with a lower accuracy of PPG-based 1-minute mean heart rate assessment.

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Supplementary material

Table S1. Covariates for accurate PPG-based heart rate assessment per patient based on chronic heart failure.

Variable	Chronic heart failure		
	No (n=37)	**Yes (n=13)**	***P*-value**
Beta- blockers – n (%)	28 (76%)	11 (85%)	0.704
ECG-derived heart rate (bpm) – median (IQR)	73 (64-82)	78 (63-83)	0.536
Level of motion (m/s^2) – median (IQR)	9.90 (9.87-9.94)	9.90 (9.87-9.92)	0.870

Abbreviations: bpm, beats per minute; IQR, interquartile range; PPG, photoplethysmography

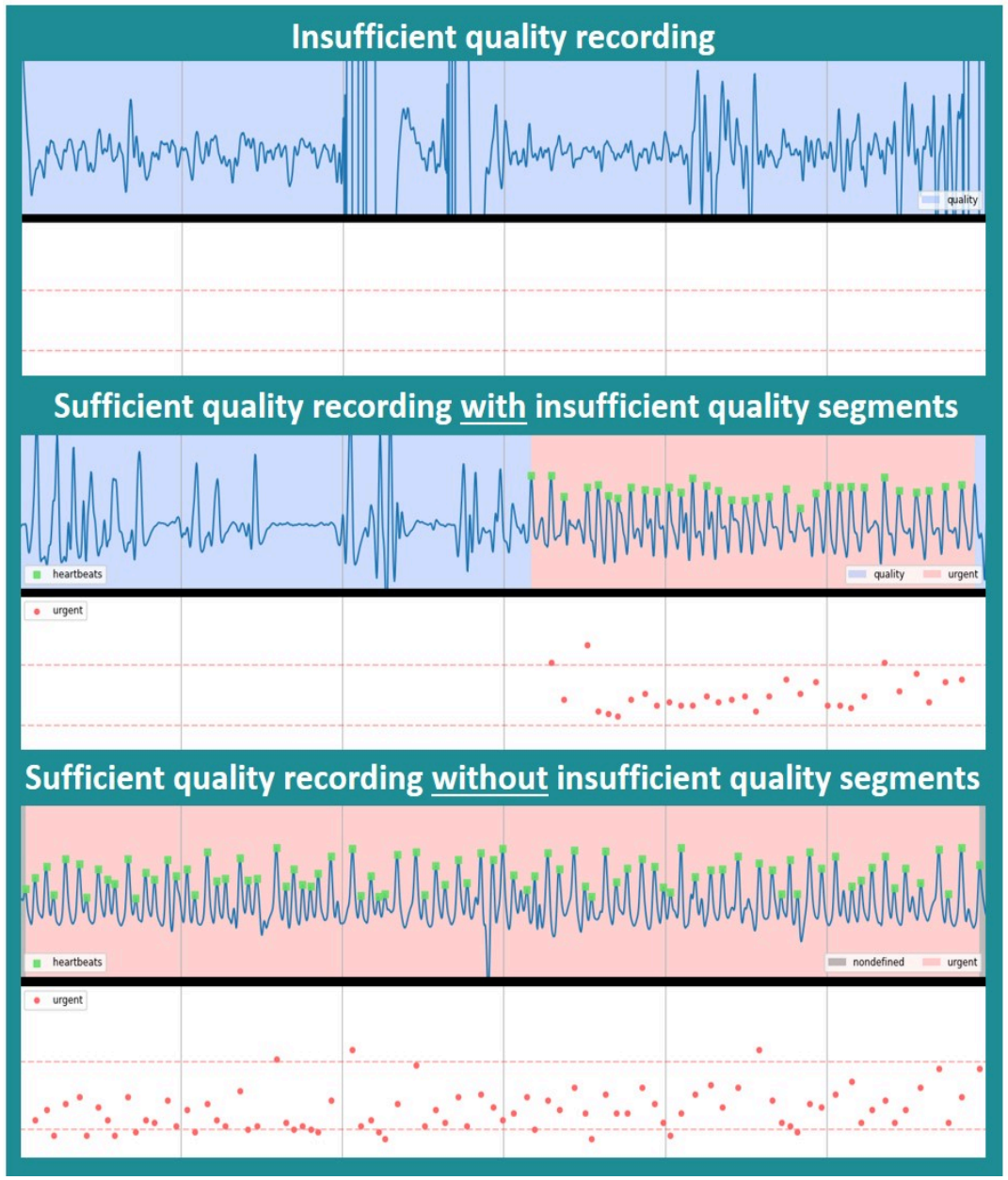

Figure S1. Examples of 1-minute PPG-based heart rate recordings with (in)sufficient quality.
The upper example represents a PPG-based heart rate recording with insufficient quality (less than 20 heart beats with sufficient quality were detected). Such recording was excluded from analysis in its entirety. The middle example represents a PPG-based heart rate recording with sufficient quality (20 or more heart beats with sufficient quality were detected) but with several insufficient quality segments included. Only the sufficient quality segments of this recording were included in analysis. The lower example represents a PPG-based heart rate recording with sufficient quality (all detected heart beats were of sufficient quality). Such recording was included in analysis in its entirety. Red dots indicate heart beats with sufficient quality accurately detected by the algorithm.
Abbreviations: PPG, photoplethysmography

PART III

Implementation and results of mobile health in atrial fibrillation detection and management

CHAPTER 8

Implementation of an on-demand app-based heart rate and rhythm monitoring infrastructure for the management of atrial fibrillation through teleconsultation: TeleCheck-AF

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Europace. 2021 Mar 8;23(3):345-352.

Abstract

During the coronavirus 2019 (COVID-19) pandemic, outpatient visits in the atrial fibrillation (AF) clinic of the Maastricht University Medical Centre (MUMC+) were transferred into teleconsultations. The aim was to develop an on-demand app-based heart rate and rhythm monitoring infrastructure to allow appropriate management of AF through teleconsultation. In line with the fundamental aspects of integrated care, including actively involving patients in the care process and providing comprehensive care by a multidisciplinary team, we implemented a mobile health (mHealth) intervention to support teleconsultations with AF patients: TeleCheck-AF. The TeleCheck-AF approach guarantees the continuity of comprehensive AF management and supports integrated care through teleconsultation during COVID-19. It incorporates three important components: (i) a structured teleconsultation ('Tele'), (ii) a CE-marked app-based on-demand heart rate and rhythm monitoring infrastructure ('Check'), and (iii) comprehensive AF management ('AF'). In this article, we describe the components and implementation of the TeleCheck-AF approach in an integrated and specialized AF-clinic through teleconsultation. The TeleCheck-AF approach is currently implemented in numerous European centres during COVID-19.

Keywords: Atrial fibrillation; Integrated care; Mobile app; Teleconsultation; Telehealth; mHealth.

Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia and associated with morbidity such as heart failure and an increased risk of thromboembolic complications, and mortality.1 Patients with AF are considered vulnerable and monitoring of vital parameters, particularly heart rhythm and rate, is important and recommended to guide treatment decisions and prevent AF-related morbidity, such as tachy-cardiomyopathy.2

During the coronavirus 2019 (COVID-19) pandemic, social distancing was implemented as part of the strategy to prevent extensive spread of the virus and consequently keeping the number of cases at a manageable level for the medical system (flattening the curve). Despite these preventive interventions, as of 3 June 2020, 6 348 900 confirmed cases of severe acute respiratory syndrome virus 2 (SARS-CoV-2) infections causing COVID-19 have been reported globally, including 380 810 deaths.3 Among these, a significant proportion of affected individuals appears to suffer from concomitant cardiovascular conditions.4 Medical centres responded by keeping vulnerable multi-morbid patients with chronic conditions out of the hospital and elective cases as well as outpatient appointments were cancelled or performed as teleconsultations, where possible.

Early during the COVID-19 pandemic, the AF outpatient clinic (AF-clinic) of the Maastricht University Medical Centre (MUMC+) was restructured to maintain the management of vulnerable multimorbid AF patients out of the hospital to prevent worsening of the condition as well as to prevent AF-related hospitalizations. Traditional face-to-face outpatient consultations in AF-clinics were transferred into teleconsultations. The downside of this was that teleconsultations were conducted without any information about heart rhythm or rate of the patients, which resulted in discomfort and uncertainty of the physician and patient. While symptoms could be assessed by detailed history taking, the presence of AF, and even more important, the ventricular rate during AF in patients with persistent AF prone to develop tachy-cardiomyopathy was not known. Adoption of medication was mainly based on physician's instinct and subjective patient-reported symptoms rather than on objective measures, and hindered a safe and individualized treatment approach, which is one of the goals of integrated AF-clinics.

In line with the fundamental aspects of integrated care, such as actively involving patients in the care process and providing comprehensive care by a multidisciplinary team, we implemented a mobile health (mHealth) intervention to support teleconsultations with AF patients: TeleCheck-AF. In this article, we describe the components and implementation of the TeleCheck-AF approach in an integrated and specialized AF-clinic through teleconsultation during COVID-19.

The TeleCheck-AF approach

The TeleCheck-AF approach guarantees the continuity of comprehensive AF management and supports integrated care through teleconsultation during COVID-19. It incorporates three important components: (i) a structured teleconsultation ('Tele'), (ii) an app-based on-demand heart rate and rhythm monitoring infrastructure ('Check'), and (iii) comprehensive AF management ('AF') (Figure 1).

Teleconsultation

Teleconsultation allows healthcare professionals to conduct remote patient consultations and

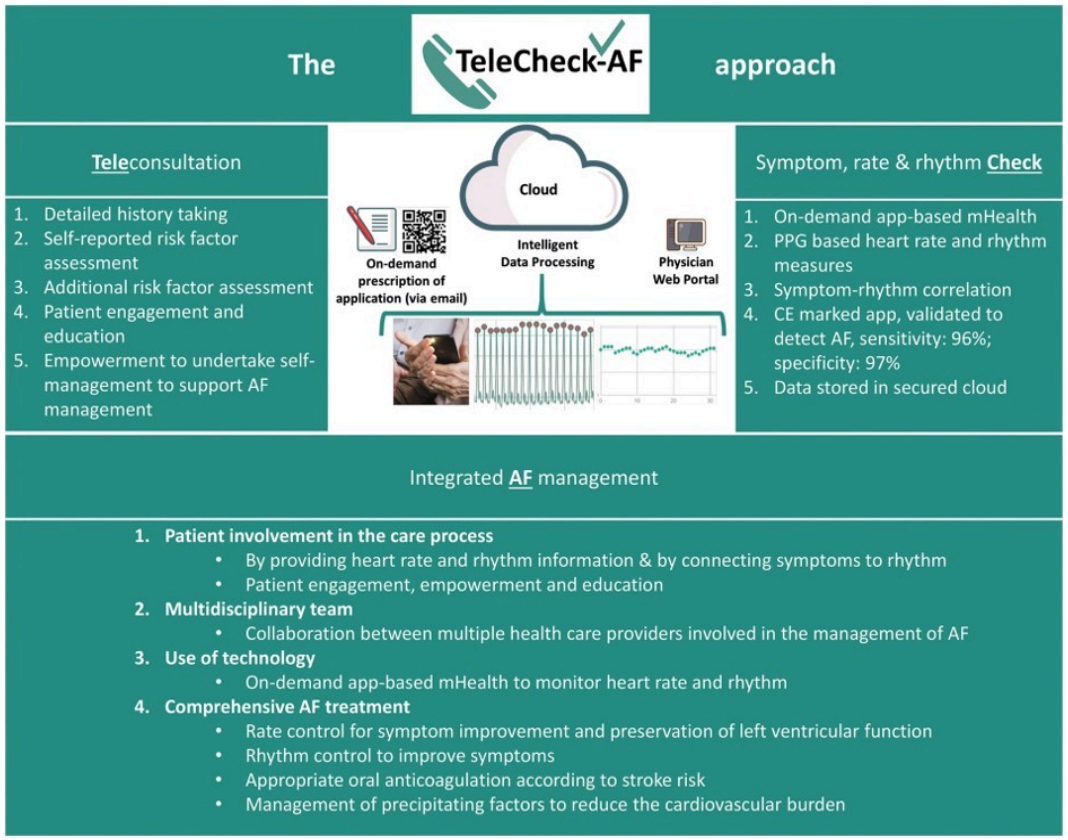

Figure 1. The TeleCheck-AF approach consist of three important components.
A structured teleconsultation ('Tele'), an app-based on-demand heart rate and rhythm monitoring infrastructure ('Check'), and a comprehensive atrial fibrillation management ('AF').

communication between physicians.5 It can be organized by a telephone conversation as well as by videoconferencing or videotelephony. Cardiologists/electrophysiologists as well as specialized AF nurses can be involved in teleconsultation and all contribute to patient education and ultimately in shared decision-making processes. According to current AF guidelines,2 patient characteristics, comorbidities and AF risk factors should be assessed, and as such structured history taking is an important part of the teleconsultation. Although new teleconsultation solutions can produce remote situations that are relatively similar to face-to-face interactions, a standardized assessment of heart rate and rhythm remains challenging. In TeleCheck-AF, we introduce an on-demand app-based heart rate and rhythm monitoring infrastructure for the integration of remote documentation and guidance of AF management through teleconsultation.

On-demand app-based symptom, heart rate, and rhythm check

Remote heart rate and rhythm assessment in TeleCheck-AF is ensured by an on-demand monitoring infrastructure, which is based on a mobile phone app (FibriCheck®) using photo-plethysmography (PPG) technology through the built-in camera. This app is CE marked, connected to a secured and certified cloud and validated (sensitivity: 96%; specificity: 97%) to detect AF via PPG signals and to provide rate measures during sinus rhythm and AF.6,7 Patients are instructed to use this app three times every day and in case of symptoms to provide a semi-

continuous longitudinal information about heart rate, rhythm and symptoms. The simultaneous assessment of heart rhythm and symptoms in the app allows assessment of symptom-rhythm correlation. The goal is to provide heart rate and rhythm information to allow a better assessment of the disease state of the patient and to support in treatment decisions during the teleconsultation. On-demand, the app can be activated for a limited predefined time period by a QR-code, which acts as a mHealth-prescription. Once the app is activated by the QR-code, all PPG recordings are instantly submitted to a secured cloud which is accessible by the treating physician and can be used during the teleconsultation. In this TeleCheck-AF approach, we propose activation of the app for 7 days. However, dependent on the clinical question and the physician preference, the use of the app can be adapted and controlled by providing respective QR-codes. The app regularly reminds the patients by pop-up messages to assess heart rate and rhythm which supports adherence and provides suggestions on how to improve recording quality in case of failed measurements. Additionally, the app provides educational information about AF, its complications and treatment.

Atrial fibrillation management

The management of AF consists of four main domains: (i) rate control for symptom management and preservation of left ventricular function, (ii) rhythm control to improve symptoms, (iii) prescribing appropriate oral anticoagulation according to stroke risk to prevent thromboembolic complications, and (iv) management of precipitating factors (i.e. underlying cardiovascular conditions and modifiable risk factors) to reduce the cardiovascular burden.2 Given the multifaceted character of AF management and limitations due to fragmentation of care, novel models of care delivery have been identified to improve efficiency and co-ordination of care, whilst improving clinical and patient outcomes. Integrated care is such an approach that is based on the principles of the Chronic Care Model8 and aims to provide care which is in line with the patient's needs, preferences and values and is based on the best available evidence. The concept of integrated care for AF management consists of four fundamental and indispensable aspects, including:

Patient involvement in the care process: Following a patient-centred approach, it is important to actively involve patients and their caregivers in the care delivery, which includes involvement in decision-making as well as undertaking self-management activities to support the treatment.9 Engagement is an important vehicle to build trust between patient and care provider and for the patient to understand their fundamental role in the care team.

Multidisciplinary team: A multidisciplinary team is often involved to appropriately manage this complex condition. The infrastructure of such collaborative practice model should be built in an AF-clinic and requires collaboration and communication between multiple specialists that can be involved in the management of AF. Moreover, integration of specialized hospital care and primary health care is crucial to warrant continuous delivery of care and structured follow-up in the appropriate setting, with important roles for nurses and allied health professionals in terms of patient education and co-ordination of care.9

Use of technology: The use of smart technology is helpful for health care professionals (e.g. decision support technology, telemonitoring or mHealth) as well as for patients (e.g. disease-specific educational applications, monitoring technology).10,11 These applications aim to encourage integrated AF management whether it is by supporting decision-making in the treatment team or empowering patients to monitor their vital parameters and self-manage their condition.

Comprehensive treatment and access to all treatment options: The management of AF should cover all domains of AF treatment as described before, however, the composition and content of these domains will differ per individual patient and the availability of resources.

These fundamental aspects of integrated care are the basic infrastructure of integrated, specialized AF-clinics. In our institution, the AF-clinic was developed a decade ago and has demonstrated clinical value,12–14 and international guidelines have adopted this approach, which is recommended as the Gold Standard management approach for AF.2 The TeleCheck-AF approach underlines the multifaceted character of AF management. The mHealth intervention puts the patient 'in charge of their own care', by asking them to prove vital data in order to determine the best possible treatment. Engagement with the patient and providing clear instructions is key, which commences before the teleconference. Within the teleconsultation, dedicated AF treatment—based on the data provided by the patient—will be provided as part of a comprehensive AF management approach provided by a multidisciplinary team.

Implementation of TeleCheck-AF in an integrated atrial fibrillation care approach

Who is eligible?

Heart rate and rhythm assessment in the TeleCheck-AF approach is based on PPG measures by an app. As diagnosis of AF still requires a documentation of an AF episode by electro-cardiogram, 2TeleCheck-AF is mainly appealing for the remote management of patients with previously documented AF. We identified several clinical scenarios in which TeleCheck-AF could support AF management through teleconsultations during the COVID-19 pandemic. First, for the assessment of heart rate and rhythm in patients scheduled for an outpatient clinic visit. Second, to guide rate control in patients who report with symptomatic (haemodynamically stable) recurrent AF episodes to the general practitioner, outpatient clinic, or emergency department. Third, since no Holter recordings are available during COVID-19, the approach can be used to assess rate and rhythm after ablation for AF and fourth, to up-titrate beta-blockers in patients with heart failure. In addition to assessment of heart rate and rhythm, the app also provides information on symptom-rhythm correlation by simultaneously assessing symptoms.

TeleCheck-AF patient instruction

Instruction and education of patients are key factors for successful implementation of the remote on-demand heart rate and rhythm monitoring for the management of AF patients. A case co-ordinator (e.g. a secretary or nurse) has an important role in clearly instructing the patient about why, how and when to use the app.

Why

The case co-ordinator explains that due to COVID-19 pandemic all face-to-face consultations are transferred to teleconsultations and that an electrocardiogram (ECG) cannot be performed to assess heart rate and rhythm. Therefore, an mHealth-prescription to use the FibriCheck® app is provided.

How

The case co-ordinator provides instruction which includes an installation manual together with the activation QR-code which is sent to the patient by e-mail (Figure 2). The case co-ordinator evaluates after 24 h in the cloud if patients were able to activate the app and to perform measurements (Figure 3). In case patients need further support, the case co-ordinator or the helpdesk of FibriCheck® can be contacted.

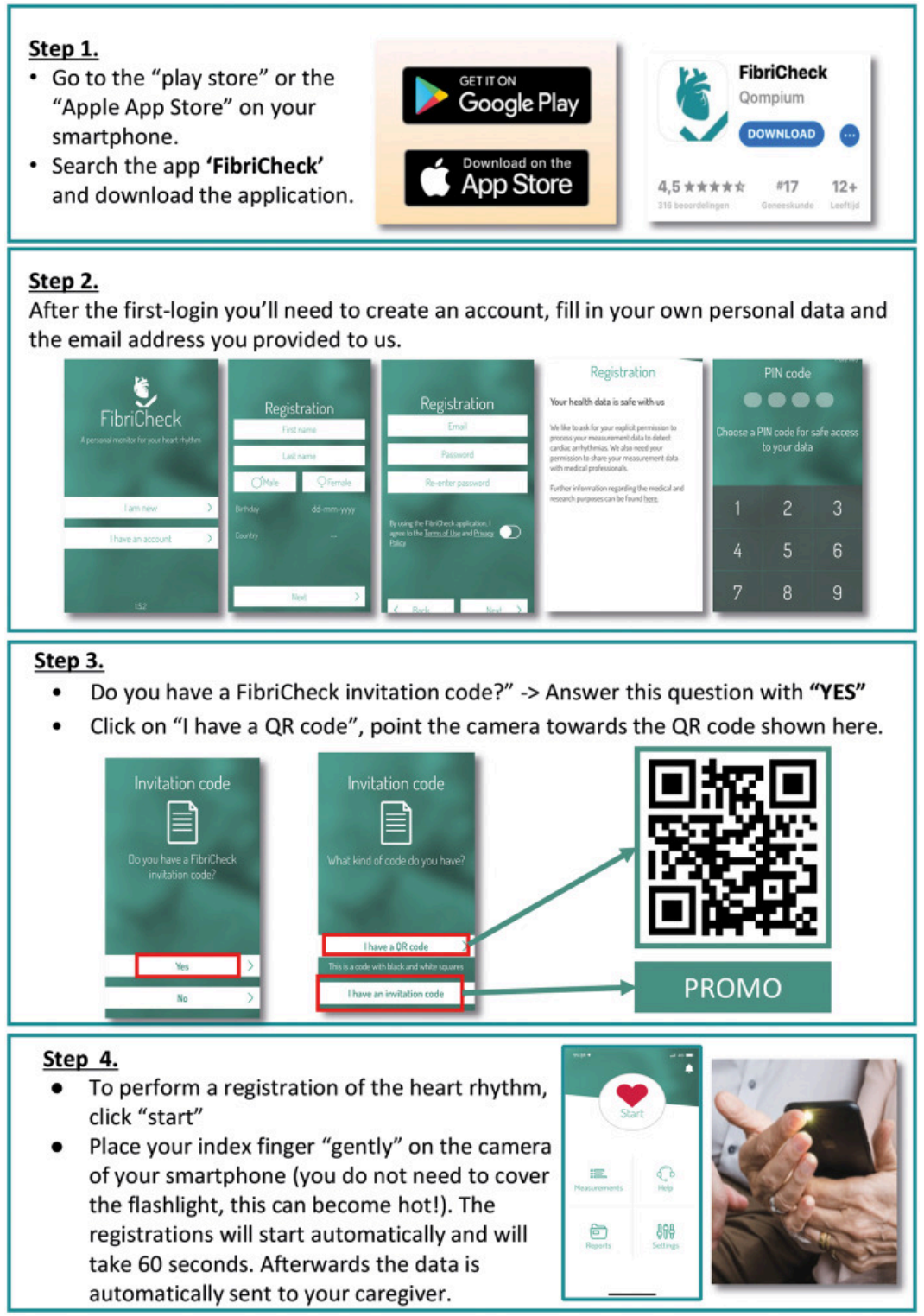

Figure 2. Installation manual including the QR-code for activation.
This manual provides a step by step approach to download the app and how to perform a measurement.

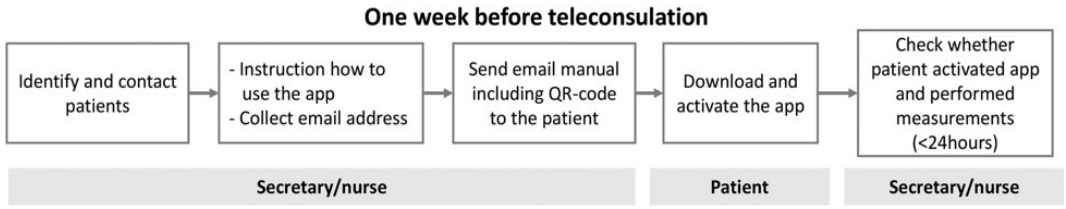

Figure 3. Organization of the care pathway, preparation phase.
One week before the teleconsultation, the physician identifies eligible patients. Subsequent, the secretary or nurse contacts the patient and explains that the face-to-face consultations is transferred to teleconsultation due to the COVID-19 pandemic. An e-mail including the manual and QR-code is sent to the patient; after 24 h the secretary/nurse check whether the patient activated the app.

When

The provided patient manual instructs the patient to perform three measurements a day and in case of symptoms for a period of 7 days before the teleconsultation. In addition, patients are asked to assess their body weight and blood pressure, if possible, on a daily basis and provide the measurements during the teleconsultation.

Adherence

The on-demand mHealth approach is critically dependent on the willingness and adherence of the AF patients to perform the measurements. Besides education and engaging patients in their own AF management several features implemented in the app improve the adherence in TeleCheck-AF. On a daily basis, an automatic pop-up message is sent to the patients as reminder to perform heart rate and rhythm measurements. Additionally, the time-period of 'only' 7 days and the straightforward, simple and short measurement procedure (maximum 2 min) makes this approach very acceptable for patients.

Implementation of heart rate and rhythm information into teleconsultation After 7 days, the QR-code expires, and the data collection stops. In the cloud, an automatic report is generated containing a summary of all measurements including heart rate, rhythm and symptoms. Additionally, all healthcare professionals have access to the raw PPG traces of their patients via the cloud. Before the planned teleconsultation, the physician logs into the cloud and can easily assess heart rate, rhythm and symptoms recorded by the patients during the week before which can be used to guide AF-management during the teleconsultation (Figure 4). If needed, patients are asked to repeat the measurements for one more week to check if medication changes for rate and rhythm control were effective or not. For this, they receive a new QR-code which then can be activated and a follow-up teleconsultation will be planned. Structured and comprehensive risk assessment and management is an important part of TeleCheck-AF during the teleconsultation. Based on self-reported body weight and blood pressure, obesity and hypertension can be managed, and general lifestyle changes recommended (Table 1).

In addition to healthcare professionals, also the app facilitates education by providing information on AF, risk factors, lifestyle, heart failure, and stroke risk (Figure 5). Furthermore, education about the importance of lifestyle and risk factor management as well as treatment adherence is provided by online information material (e.g. www.getsmartaboutafib.net).

Discussion

In recent online statements on the European Society of Cardiology website as well as in consensus papers on the guidance for the management of AF patients during the COVID-19 pandemic from

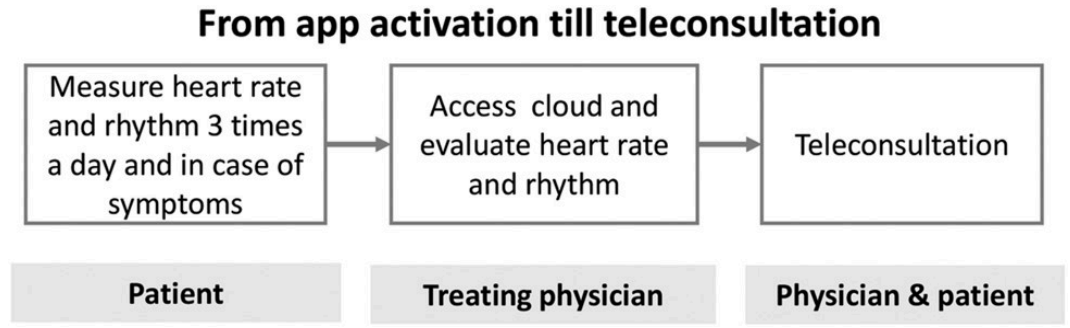

Figure 4. Organization of the care pathway.
During 1 week before the teleconsultation, patients are asked to measure three times a day and in case of symptoms. Before the teleconsultation, the treating physician logs into the cloud to evaluate the measurement.

Table 1. Structured teleconsultation.

Structured teleconsultation
1. Remote assessment of heart rate and rhythm
2. Detailed history taking
3. Stroke risk assessment (CHA_2DS_2-VASC score)
4. Self-reported risk factor assessment
• Hypertension
• Obesity
5. Additional risk factor assessment
• Glucose, kidney function, hypercholesterolaemia, and thyroid function if needed in collaboration with general practitioner
• Education and lifestyle advise
• AF management: adaptation of rate control, anticoagulation treatment

the Heart Rhythm Society, American College of Cardiology, and American Heart Association,15 the use of telemedicine and mHealth solutions for remote patient care are recommended. However, a universal solution to allow wide and fast implementation of mHealth infrastructures is not provided. Herein, we describe our TeleCheck-AF approach incorporating a remote on-demand app-based heart rate and rhythm monitoring infrastructure and a comprehensive AF management approach through teleconsultation.

TeleCheck-AF includes fundamental components of a comprehensive integrated care approach (Figure 1). The patient is actively involved in the treatment trajectory by monitoring heart rate and rhythm information, as well as blood pressure and weight measures. Education about AF

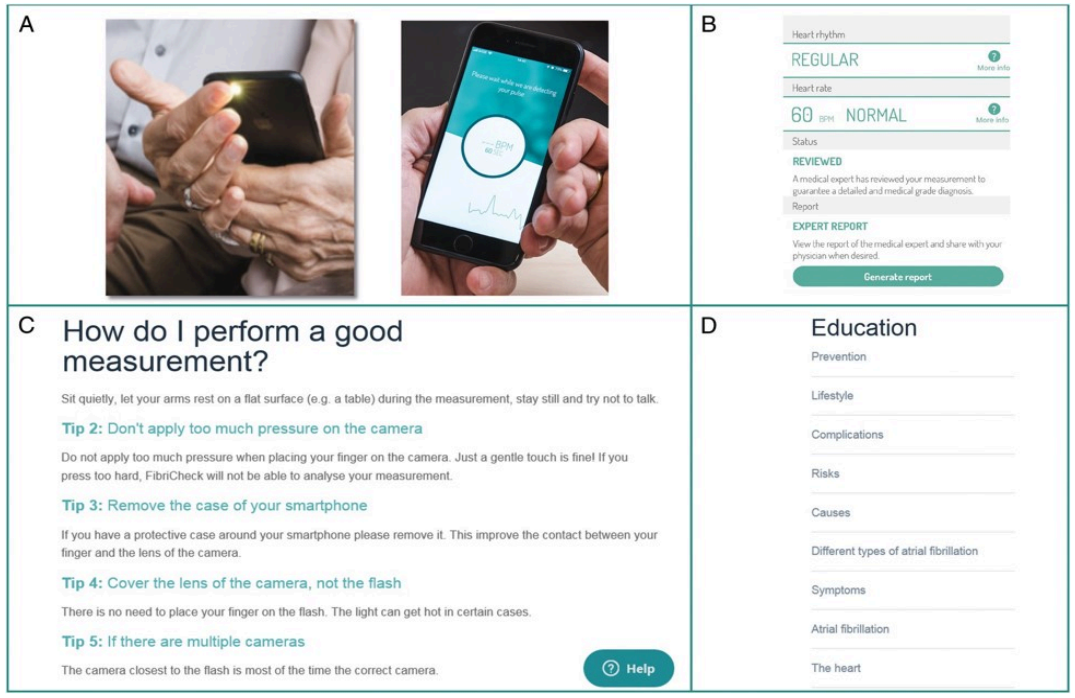

Figure 5. Usage of the FibriCheck.
(A) An example of performing a measurement is shown. (B) A report after a measurement is shown. (C) Instructions to improve the quality of a measurement is shown. (D) Summarizes the topics of the education provided by the FibriCheck app.

management and the importance of lifestyle and risk factor management is provided by a multidisciplinary team during teleconsultations. Also, there is a focus on empowering patients to self-manage these conditions which includes treatment adherence. Moreover, the app provides push notifications with information about their condition and the importance of adhering to the treatment regimen. This supports self-management and ensures a regular data collection. The app is a true example of mHealth impacting both the patient (i.e. patient involvement by active role to provide data on rate and rhythm and reminding to adhere to the treatment regimen), as well as the health care professional (i.e. validated insights in rate and rhythm). During COVID-19, the accessibility to elective interventions and procedures such as electrical cardioversion as well as elective invasive interventions such as AF ablation is limited.16 Nevertheless, remote adaptation of rate and rhythm medication guided by the on-demand monitoring infrastructure together with a comprehensive risk factor management, which has been shown to maintain sinus rhythm and reduce the need of AF ablation,15 are elemental parts of TeleCheck-AF and helps managing AF patients during the COVID-19 pandemic.

The on-demand mHealth application for a limited predefined time period of 7 days prior the scheduled teleconsultation within the TeleCheck-AF approach is novel and differs from previous settings where mHealth is typically used for a longer rhythm monitoring period or provide decision support, risk assessment and patient education according to existing guidelines.7,17,18 The goal in TeleCheck-AF is to make heart rate and rhythm information available, to allow a better assessment of the disease state of the patient and to support in treatment decisions through teleconsultation. The limited validity, regulated by a QR code, avoids unnecessary data-load. Additionally, maintenance costs associated with long term use of apps do not occur with an on-demand approach, which makes this TeleCheck-AF approach available for low costs.

An app-based approach has several advantages over device-based or wearable-based approaches during the COVID-19 pandemic. No hardware is required which has several hygienic and logistical advantages. The heart rate and rhythm monitoring infrastructure in TeleCheck-AF is a complete stand-alone unit, does not require any installation of software on a computer and can be combined in a flexible way with teleconsultation via telephone conversation, videoconferencing, or videotelephony. A potential disadvantage is, that an ECG cannot be provided; however, the FibriCheck app algorithm is able to validly inform about the presence of AF and current heart rate.6

The broad accessibility of the mobile phone app used in TeleCheck-AF allows a fast implementation of the herein described mHealth infrastructure during the COVID-19 pandemic. Currently, MUMC+ makes the TeleCheck-AF infrastructure available in numerous large European centres focused on AF management within the TeleCheck-AF project. The TeleCheck-AF project was initiated on the 04 April 2020. The motto is: 'Let's keep our AF patients out of the hospital during COVID-19!'. The goal is to maintain and secure AF care during COVID-19 and we are currently inviting other European centres to participate in this project.19 For more information visit our website: www.telecheck-af.com and follow #TeleCheckAF on Twitter.

Perspectives and challenges

In the TeleCheck-AF project, we aim to show that the TeleCheck-AF approach can be easily implemented and used in different European centres during the COVID-19 pandemic. Besides other factors, the lack of uniform European-wide legislation for teleprescription of drugs, digital health and reimbursement models have largely prevented the widespread use and broad clinical implementation of digital health services.20 Hopefully, the challenges of COVID-19 may help speed up the discussions with health insurances, hospitals and industry partners are required to allow broader clinical implementation of this infrastructure in the future.20 Whether TeleCheck-AF represents a streamlined and cost-effective monitoring system after the COVID-19 pandemic should be evaluated. For this further study is warranted to test for efficacy, safety and durability of this approach.

Conclusion

Herein, we describe a new mHealth approach facilitating AF management through teleconsultation. The TeleCheck-AF approach incorporates a structured teleconsultation, CE marked app-based on-demand heart rate and rhythm monitoring and integrated specialized AF management, and it can be easily implemented in European centres during COVID-19.

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5. Mold F, Hendy J, Lai YL, de Lusignan S. Electronic consultation in primary care between providers and patients: systematic review. JMIR Med Inform 2019;7: e13042. Figure 5 Usage of the FibriCheck. (A) An example of performing a measurement is shown. (B) A report after a measurement is shown. (C) Instructions to improve the quality of a measurement is shown. (D) Summarizes the topics of the education provided by the FibriCheck app. On-demand app-based heart rate and rhythm monitoring infrastructure 7
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CHAPTER 9

Coordination of a remote mHealth infrastructure for atrial fibrillation management during COVID-19 and beyond: TeleCheck-AF

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Abstract

During the coronavirus 2019 (COVID-19) pandemic, outpatient visits for patients with atrial fibrillation (AF), were converted into teleconsultations. As a response to this, a novel mobile health (mHealth) intervention was developed to support these teleconsultations with AF patients: TeleCheck-AF. This approach incorporates three fundamental components: 1) “Tele”: A structured teleconsultation. 2) “Check”: An app-based on-demand heart rate and rhythm monitoring infrastructure. 3) “AF”: comprehensive AF management.

This report highlights the significant importance of coordination of the TeleCheck-AF approach at multiple levels and underlines the importance of streamlining care processes provided by a multidisciplinary team, using an mHealth intervention, during the COVID-19 pandemic. Moreover, this report reflects on how the TeleCheck-AF approach has contributed to strengthening the health system in maintaining management of this prevalent sustained cardiac arrhythmia, whilst keeping patients out of hospital, during the pandemic and beyond.

Background

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia, associated with increased morbidity such as heart failure, thromboembolic complications, and mortality. Management of AF is a multifaceted process that goes beyond the treatment of the arrhythmia alone. In addition to controlling the arrhythmia (heart rate and rhythm control), assessment of stroke risk and the administration of appropriate anticoagulation to prevent strokes, the management of concomitant risk factors represents an important component of AF treatment as it can reduce AF symptom burden and may reverse the type and natural progression of AF.1 A multidisciplinary team approach involving cardiologists, electrophysiologists, nurses, allied health professionals as well as primary care physicians, amongst others, should be in place, following a patient-centred approach which places the patient in a central role in decision-making. Integrated care has been identified as a suitable approach to implement comprehensive AF care within specialised AF outpatient clinics through face-to-face contacts.2,3 Significant improvements in the quality of care delivery4 as well as in patient outcomes have been demonstrated when applying such specialized AF-Clinics in clinical practice.5–8

During the coronavirus 2019 (COVID-19) pandemic, traditional face-to-face consultations in AF outpatient clinics were constrainedly converted into teleconsultations. At the Maastricht University Medical Centre+ (MUMC+), Maastricht, the Netherlands, we developed a mobile health (mHealth) infrastructure to support teleconsultations with AF patients to guarantee the continuity of comprehensive AF management through teleconsultations during COVID-19: The TeleCheck-AF approach.9,10 In this article, we explain the coordination of the TeleCheck-AF approach and the implementation of this mHealth intervention in European centres.

TeleCheck-AF

TeleCheck-AF incorporates three important components (Figure 1): 1) a structured teleconsultation, which allows health care professionals to conduct remote patient consultations (‘Tele’), 2) an app-based on-demand heart rate and rhythm monitoring infrastructure based on a CE-marked mobile phone app: www.fibricheck.com (‘Check’) and 3) comprehensive AF management (‘AF’) consisting of four main domains: i) rate control for symptom management and preservation of left ventricular function, ii) rhythm control to improve symptoms, iii) prescribing appropriate oral anticoagulation according to stroke risk to prevent thromboembolic complications, and iv) management of precipitating factors (i.e. underlying cardiovascular conditions and modifiable risk factors) to reduce the cardiovascular burden.11 The TeleCheck-AF approach is an on-demand mHealth intervention which is provided to patients for seven days prior to a scheduled teleconsultation. Patients are instructed to measure heart rate and rhythm and symptoms, three times a day and in case of symptoms using the FibriCheck® app. This app is based on photoplethysmography (PPG) technology using the built-in camera on the smartphone, allowing semi-continuously heart rate and rhythm monitoring of AF patients prior to the teleconsultation. This on-demand mHealth approach provides vital parameters and enables physicians to use heart rate and rhythm data for the decision-making process related to treatment and management AF patients.

Care coordination

Coordination of AF care

Integrated care has been identified to manage patients with chronic conditions. The integrated care approach to manage AF, has been defined fusing four indispensable key elements to provide efficient

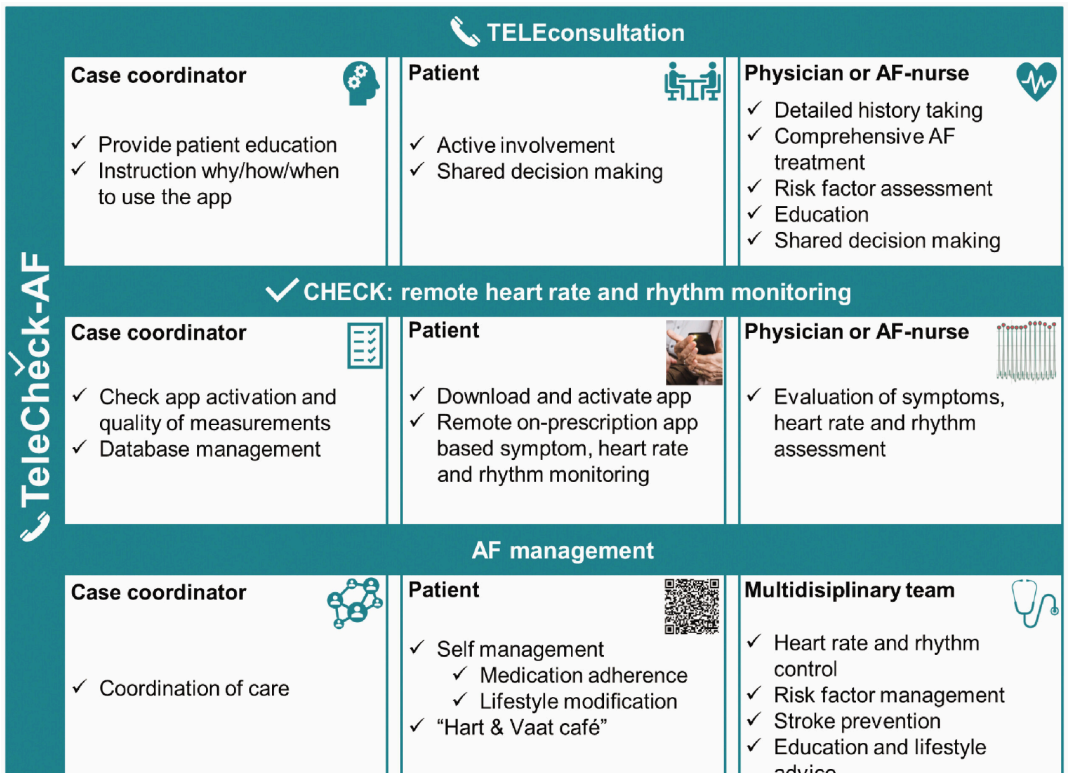


Figure 1. Multi-level care coordination within the TeleCheck-AF approach.

in their care (including patient education and instruction, and empowering patients to self-manage their condition), 2) a multidisciplinary team approach, 3) the use of technology to support integrated care, and 4) a comprehensive AF treatment approach.1 This systematic approach was defined as a 'coordinated patient-centred approach by interdisciplinary specialists to improve outcomes'.12 Given the multifaceted character of AF treatment; involvement of the patient, their carers as well as multiple specialists; and potentially multiple institutions, coordination is crucial.13 Specifically, this relates to multiple stages of coordination: 1) coordination of care that is required to be provided, including the specialists involved as well as the organization of a structured follow-up, 2) coordination of patients' self-management and adherence to treatment regimen, and 3) coordination of the dissemination of the mHealth infrastructure.

Coordination of TeleCheck-AF and the role of a case coordinator

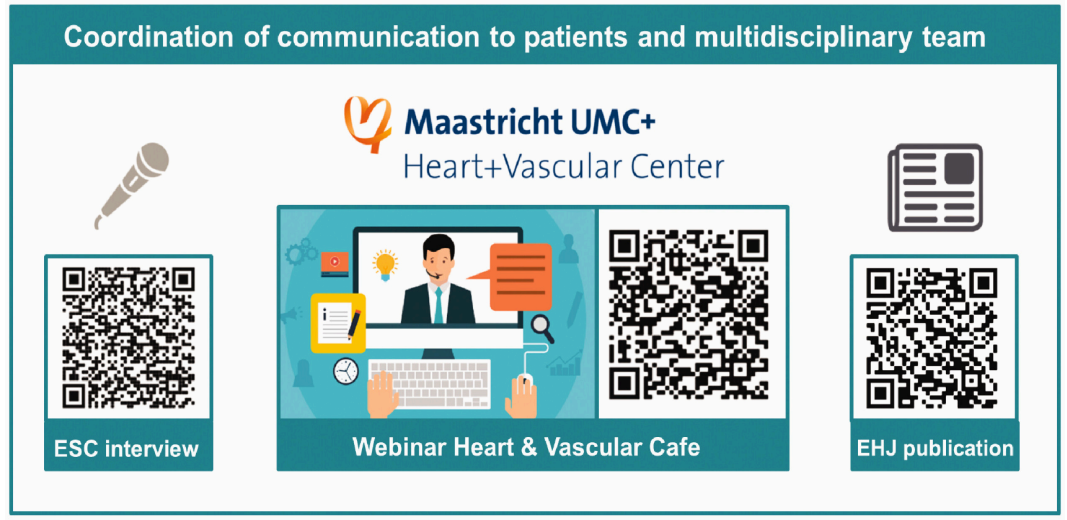
A case coordinator has a key role in the coordination of the TeleCheck-AF process. This role can be performed by admin staff or health care professionals. The case coordinator's role is crucial during the first (telephone) contact with the patient in which the TeleCheck-AF approach is initiated, and the patient is provided with clear education and instruction about the use of the heart rate and rhythm monitoring application.9,10 The case coordinator facilitates the first telephone contact with patients to explain that due to the COVID-19 pandemic all traditional face-to-face consultations are converted into teleconsultations and standard 12-lead electrocardiogram (ECG) examination will be replaced by the mHealth application (FibriCheck®) for heart rate and rhythm analysis. Additionally, the case coordinator provides clear instructions to patients how and when to use the app and sends a manual by e-mail. Twenty-four hours after the initiation call, the case coordinator evaluates whether patients were able to activate the app and to

perform measurements. The case coordinator would then re-contact the patient as well as if recordings were of insufficient quality, to provide patients with additional instructions. The number of individuals aged 65 and above owning a smartphone is currently increasing.14 However, technological knowledge limitations may underlie slower adoption of new technology. Therefore, it is crucial to provide clear instruction to all patients involved. The case coordinator can also be contacted by the patients for further support or questions.

Coordination of patients' self-management

TeleCheck-AF calls upon the responsibility of patients: this means that coordination of performing measures lies mainly with the patients themselves. Patients' adherence and willingness to participate and perform the measures as prescribed is essential for the collection of measurements. In fact, a short intervention for only seven days may increase commitment and prevent mHealth fatigue. Clear education and empowerment by the case coordinator on the importance of the proper use of the mHealth prescription seems to be effective for most patients. In addition, the user-friendliness, daily notifications provided by the app, and the support of carers may increase adherence as well. The use of the mHealth intervention stimulates patients to take an active role in their self-management of AF. Moreover, patient experiences have been very positive, and some patients even register comments, or try to seek out situations in which they normally experience symptoms. They are eager to discuss these results with their physician and thereby take on a more active role during consultation. This provides an excellent opportunity for shared decision making, as the patients may feel more involved in their own care. The vast majority of patients indicates during teleconsultation that they would like to use the mHealth prescription for a longer period of time, since they find it comforting to be able to check their heart rhythm in case of symptoms.

An online webinar for patients and those interested, was organized to provide in-depth information about the TeleCheck-AF approach, but also to answer questions of attendees.15 This ''Hart&Vaat Café'' (Heart&Vascular Cafe) is normally hosted in a local café, where patients can get together to meet fellow patients. However, due to the COVID-19 pandemic the Café was organized online, which was the first time in the 10 year existence of this local initiative (Figure 2).



ESC = European Society of Cardiology, EHJ = European Heart Journal

Figure 2. Coordination of communication to patients and multidisciplinary team.

Coordination of infrastructures

One of the challenges to effectively implement the TeleCheck-AF approach in standard clinical care is the development and coordination of the mHealth infrastructure. Embedding the app in patient care requires a safe, reliable, patient-friendly, easy and non-time consuming to use infrastructure. Within TeleCheck-AF the mHealth infrastructure consists of the three important components ("Tele", "Check", "AF"). Standard operating procedure documents were developed to implement and standardize this approach for dissemination to other centres.11 Experiences and feedback from patients and health care professionals were used to optimize the infrastructure and the coordination. Another important element for embedding this mHealth approach in clinical practices is the accessibility of the recordings by other healthcare professionals. For this, a connection with the patients' Electronic Health Record (EHR), enabling automatic transmission of the recordings from the secured cloud to the EHR, is crucial and developments are currently guided by the Healthcare Innovation Lab of the Maastricht University Medical Centre+.

Implementation and initiation of TeleCheck-AF throughout hospitals in Europe

Currently, the TeleCheck-AF approach is implemented in 36 clinical centres throughout 12 European countries and this number is still growing. To allow this rapid expansion, we used social media (#TeleCheck-AF on Twitter and LinkedIn) to distribute information and experiences related to the project which stimulated and encouraged other centres to participate. The European Society of Cardiology featured TeleCheck-AF on its website.16 We were invited for radio and television interviews and organized a video-conference to on-board new centres to explain how to use and set-up the TeleCheck-AF approach. The role of the initiating centre (MUMC+) is not only to familiarize the centres with TeleCheck-AF, but also to coordinate the project via weekly newsletters to provide updates to the participating centres and included patients, solve technical problems related to the mobile application, raise funds for project development and collect project information from various social media platforms to strengthen credibility.

Discussion

The TeleCheck-AF mHealth infrastructure has been developed to remotely assess information on heart rate and rhythm in patients with AF, to support teleconsultations during the COVID-19 pandemic. The approach has been rapidly embedded in the clinical setting and has been well adopted by patients and health care professionals. In fact, the TeleCeck-AF approach has been integrated in a way that it will remain even after the COVID-19 restrictions. However, it is crucial to evaluate the mHealth infrastructure and determine further utilization in the clinical pathway for arrhythmia patients.17 The approach has potential to improve patient outcomes, increase access to health care providers whilst reducing health care utilization (i.e. outpatient visits and presentations to the emergency department) and decrease the burden on the health care system and cost. Despite these advantages, areas for improvement have been identified that should be considered in refining the TeleCheck-AF approach as part of the standard AF care.

Reimbursement is a barrier to more widespread adoption of mHealth in general. During the COVID-19 pandemic, technology and companies provided temporary support. Nevertheless, such support has limits and without a coherent funding system to cover such services, the application will be limited to those patients who may be willing to pay out-of-pocket for telemedicine solutions. In collaboration with the Healthcare Innovation Lab, Maastricht University Medical Centre+, discussions with government and health care insurers are ongoing to secure funding for the approach. Privacy and security of patient data is legitimate since patients may not exactly know who will be responding to and sharing their personal medical information. Reliable security and privacy legislation should be in place, and a robust privacy and security plan with identification of the data controller company (FibriCheck®) is essential. This should be communicated with patients and may increase patient confidence and reassurance.

As technology is advancing quickly, alternative media, e.g. short messages instead of email contact, may extend the communication between the case coordinator and the patient. In addition to just solving app-related technical problems and providing support, the coordinator's role could be extended into coordination of the care process by means of collecting and assessing risk factors and provide additional material for lifestyle advices and disease self-management. This would ensure patient empowerment through engagement and providing personalised care.

After the COVID-19 pandemic, teleconsultations supported by the TeleCheck-AF approach could be provided as an alternative to traditional face-to-face visits in the outpatient department. Depending on patient preferences, the optimal strategy for each individual patient should be discussed between health care professional and patient and then selected in a shared decision making process.18

The availability of new mHealth technologies and infrastructures such as the TeleCheck-AF approach may help to improve the quality of care, to increase access to the most optimal treatment tailored to the individual patient and to overcome equity issues related to demographics and socioeconomic status. More research is needed to develop and validate novel care pathways incorporating existing mHealth tools. One of the main requirements of future mHealth applications will be a flexible cloud infrastructure around it. This will allow the adaptation of the mHealth infrastructure to support the optimal care pathway instead of adapting the care pathways around an inflexible mHealth tool and infrastructure. Additionally, the mHealth end users, e.g. physicians and patients, should be involved from the early stages in the development and finetuning of future technologies. The TeleCheck-AF approach was initially developed in an AF outpatient clinic by close collaboration of a multidisciplinary team, including physicians and specialised AF-nurses together with secretaries who served as case coordinators. Along the track further development and refinement was undertaken based on valuable feedback from physicians, nurses, secretaries and patients, demonstrating the importance of a multidisciplinary approach. TeleCheck-AF represents an example of an on-demand health monitoring which can be tailored to the patient's needs, values and preferences, and as such contributed significantly to the strengthening of AF services in responding to COVID-19.

Although the TeleCheck-AF approach is specifically designed for the management of AF, it has potential to be extended to comprehensive management of other conditions. As an example, it may be helpful to assess heart rate control in the treatment of heart failure. Moreover, the on-demand mHealth approach may serve as a basic principle which can be translated and tailored to the requirements of chronic conditions in which it is conceivable that the fundamental aspects of the approach will remain.

Conclusion

The TeleCheck-AF approach has been developed in the heat of the COVID-19 pandemic and was a significant source of support and reassurance for both patients and health care providers. Coordination appeared to be a key concept, intertwined with numerous aspects of the mHealth infrastructure: from empowering patients to self-manage the on-demand application, to implementation of the approach in clinical centres, aiming to strengthening the health system response to COVID-19. Nevertheless, despite the modes of care delivery, coordination of care will remain crucial to provide care that is responsive to individual patient values and preferences and aligns with evidence-based recommendations.

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CHAPTER 10

Patient motivation and adherence to an on-demand app-based heart rate and rhythm monitoring for atrial fibrillation management: data from the TeleCheck-AF project

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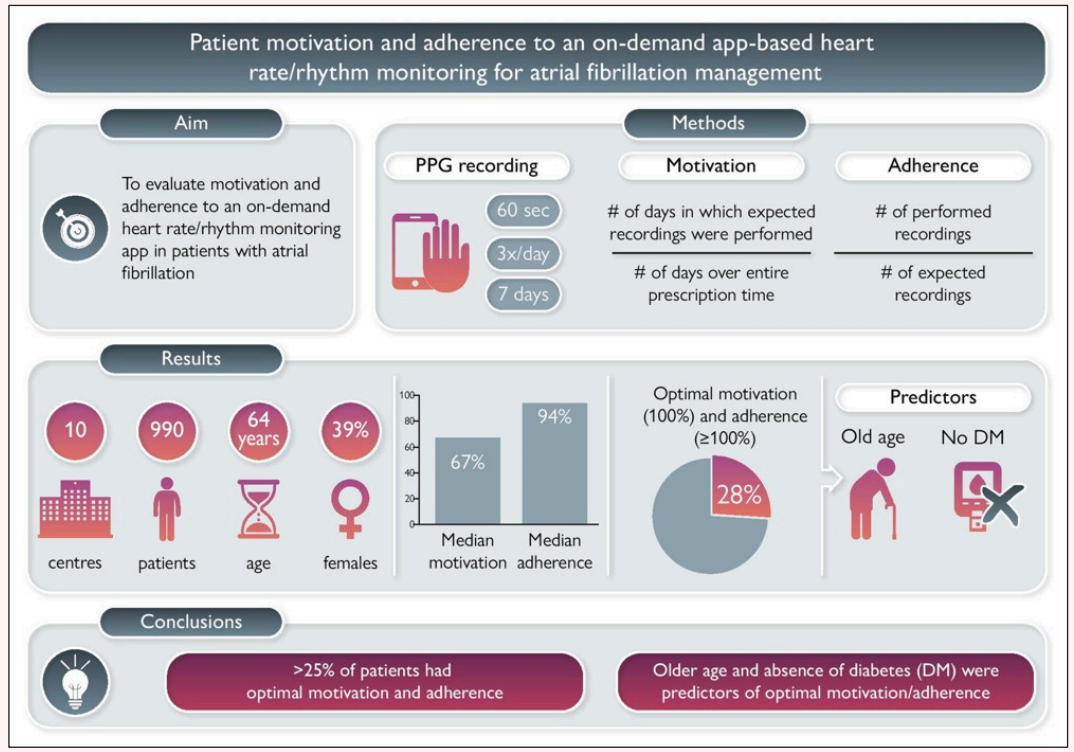
Abstract

Aims: The aim of this TeleCheck-AF sub-analysis was to evaluate motivation and adherence to on-demand heart rate/rhythm monitoring app in patients with atrial fibrillation (AF).

Methods and results: Patients were instructed to perform 60 s app-based heart rate/rhythm recordings 3 times daily and in case of symptoms for 7 consecutive days prior to teleconsultation. Motivation was defined as number of days in which the expected number of measurements (≥3/day) were performed per number of days over the entire prescription period. Adherence was defined as number of performed measurements per number of expected measurements over the entire prescription period. Data from 990 consecutive patients with diagnosed AF [median age 64 (57-71) years, 39% female] from 10 centres were analyzed. Patients with both optimal motivation (100%) and adherence (≥100%) constituted 28% of the study population and had a lower percentage of recordings in sinus rhythm [90 (53-100%) vs. 100 (64-100%), P < 0.001] compared with others. Older age and absence of diabetes were predictors of both optimal motivation and adherence [odds ratio (OR) 1.02, 95% coincidence interval (95% CI): 1.01-1.04, P < 0.001 and OR: 0.49, 95% CI: 0.28-0.86, P = 0.013, respectively]. Patients with 100% motivation also had ≥100% adherence. Independent predictors for optimal adherence alone were older age (OR: 1.02, 95% CI: 1.00-1.04, P = 0.014), female sex (OR: 1.70, 95% CI: 1.29-2.23, P < 0.001), previous AF ablation (OR: 1.35, 95% CI: 1.03-1.07, P = 0.028).

Conclusion: In the TeleCheck-AF project, more than one-fourth of patients had optimal motivation and adherence to app-based heart rate/rhythm monitoring. Older age and absence of diabetes were predictors of optimal motivation/adherence.

Keywords: Atrial fibrillation; Mobile health; Photoplethysmography; Risk factors; Thromboembolic risk.



Graphic abstract.

Introduction

The number of mobile health (mHealth) applications dedicated to heart rate and rhythm monitoring in patients with atrial fibrillation (AF) is constantly increasing with growing numbers of devices and/or applications with Conformité Européenne (CE) and/or Food and Drug Administration approval.1,2 Despite high accuracy to detect AF, the efficacy of these mHealth applications is critically determined by the ability and willingness of the patient to use them. The World Health Organization (WHO) has stated that increasing patient adherence to interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments.3 Therefore, the evaluation of patient motivation and adherence to mHealth applications in real-life scenarios and understanding their predictors is important to further improve their usability in contributing to the delivery of patient care.

During the coronavirus disease 2019 (COVID-19) pandemic, a novel mHealth approach consisting of the on-demand use of a photoplethysmography (PPG)-based mobile app for remote heart rate and rhythm monitoring supported a scheduled teleconsultation and the integration into comprehensive AF management was communicated and set up within the TeleCheck-AF project.4 Multiple centres participated in the TeleCheck-AF project, and all centres provided standardized patient education and material to their patients, which was specifically developed to optimize patient involvement and engagement during the remote care delivery.5 The educational material was designed based on the experience of the coordinating centre [Maastricht University Medical Centre+ (MUMC +)] during the implementation of this mHealth infrastructure in the healthcare system.6,7 Systematically assessed patient experience and feedback collected within AF-dedicated outpatient clinics were continuously incorporated to further refine the TeleCheck-AF approach. Project members also frequently organized workshops that brought patients and healthcare providers in contact with scientists to exchange insights of the TeleCheck-AF infrastructure. A large number of patients were enrolled in the TeleCheck-AF project and recent surveys showed positive patient and centre experiences.6 The majority (>80%) of patients reported ease of use and installation of the mHealth app and more than 80% of the centres reported no problems during the implementation of the TeleCheck-AF approach in the healthcare system.6 However, patient motivation and adherence to this mHealth approach and their predictors has not been investigated previously.

The aim of this sub-analysis of the real-world mHealth project TeleCheck-AF was to evaluate patient motivation and adherence to an on-demand mobile app-based heart rate and rhythm monitoring application.

Methods

TeleCheck-AF

Details on the TeleCheck-AF project have been reported elsewhere.4 Briefly, TeleCheck-AF is an mHealth infrastructure developed to provide ongoing management and comprehensive care to patients with AF during the COVID-19 pandemic lockdown within cardiology centres in Europe. The TeleCheck-AF infrastructure consists of a structured teleconsultation ('Tele'), on-demand app-based heart rate, rhythm, and symptom monitoring ('Check') and its integration into comprehensive AF management ('AF'). The retrospective data collection from the participating TeleCheck-AF centres was conducted in accordance with the Declaration of Helsinki8 and was approved by the local ethics committees.

Patient population

From April 2020 to July 2021, patients aged ≥ 18 years, scheduled for teleconsultation in participating European cardiology centres were offered to participate within the TeleCheck-AF project. Participating patients were eligible if they had a smartphone and were willing to use the on-demand heart rate and rhythm monitoring mobile application. Among all 41 centres, the 10 centres that included the highest number of patients (≥25) were invited to participate in the retrospective data collection: (i) MUMC+, Maastricht, the Netherlands; (ii) Radboud University Medical Center, Nijmegen, the Netherlands; (iii) Rijnstate Hospital, Arnhem, the Netherlands; (iv) Hannover Heart Rhythm Center, Hannover, Germany; (v) University Hospital Cologne, Cologne, Germany; (vi) Medical University of Graz, Graz, Austria; (vii) Ziekenhuis Oost-Limburg, Leuven, Belgium; (viii) Liverpool Heart and Chest Hospital, Liverpool, United Kingdom; (ix) Department of Cardiology, King George Hospital, Ilford, United Kingdom; (x) Medical University of Warsaw, Warsaw, Poland.

Definitions

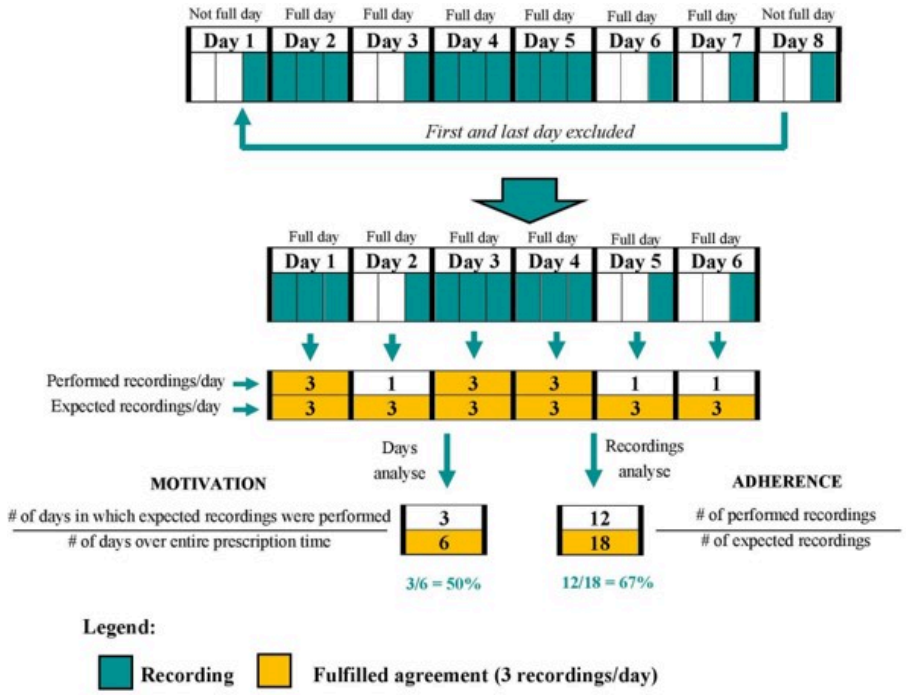
In the healthcare sector, motivation can be defined as an 'individual's degree of willingness to exert and maintain an effort towards organizational goals'.9 Medication adherence is defined by the WHO as 'the degree to which the person's behaviour corresponds with the agreed recommendations from a healthcare provider'.3

In the current analysis, the first and last day of the prescription were removed, as these were non-complete days (first day was the day of receiving the QR code and the last day was the day of the teleconsultation). Therefore, motivation and adherence were calculated for 6 consecutive full days. Motivation was defined as the number of days in which the expected number of measurements (at least 3 daily) were performed per number of days over the entire prescription period. Adherence was defined as the number of measurements per number of expected measurements (at least 3 daily) over the entire prescription period. In case of multiple prescriptions, the initial prescription was used in the analyses. The detail scheme of analysis is provided in Figure 1 with examples of motivation and adherence calculations. Based on Figure 1, patients can have only motivation of 0% (without day of 3 or more recordings during 6 full monitoring days), 17% (1 day of 3 or more recordings during 6 full monitoring days), 33% (2 days), 50% (3 days), 67% (4 days), 83% (5 days), or 100% (6 days). The same was applicable to adherence, where patients could have 0%, 5.6%, 11%, and so on adherence, given performing 0, 1, 2, and so on recordings per 18 expected recordings.

The patients were divided into 2 groups according to motivation as low-to-moderate (<100%) and optimal (100%) groups, and adherence as low-to-moderate (<100%) and optimal (≥100%) groups. The low-to-moderate motivation group was further divided into 2 numerically similar halves of patients: a low (motivation of 0, 17, or 33%) and a moderate (motivation of 50, 67, or 83%) groups. The low-to-moderate adherence group was further divided in 2 into numerically similar halves of patients: a low (adherence of 0, 5.6, 11, 17, 22, 28, 33, 39, 44, 50, 56, 61, or 67%) and moderate (adherence of 72, 78, 83, 89, or 94%) groups. The PPG recordings were interpreted by the FibriCheck® algorithm (sensitivity: 96%; specificity: 97%10) as sinus rhythm, AF-rhythm and non-regular rhythm that could not be classified as AF (e.g. extrasystoles, bradycardia, or tachycardia).

Patient guidance and instruction

At least 1 week prior to a scheduled teleconsultation appointment, patients were provided with a CE-marked PPG-based mobile phone heart rate and rhythm monitoring application (FibriCheck®, Qompium, Hasselt, Belgium). Patients were instructed to perform 60 s recordings 3 times daily and



Example: Three days with minimum 3 recordings gives a motivation of 3/6= 50%.

# of days in which expected recordings were performed	0	1	2	3	4	5	6
# of days over entire prescription time	18	18	18	18	18	18	18
Motivation, %	0	17	33	50	67	83	100

Example: Twelve recordings during the 6 days gives an adherence of 12/18= 67%.

# of performed recordings	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	≥18
#of expected recordings	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18
Adherence, %	0	5.6	11	17	22	28	33	39	44	50	56	61	67	72	78	83	89	94	≥100

Figure 1. Motivation and adherence analyses.
Patients were prescribed the mobile app for 7 days to monitor their heart rate/rhythm. On the first day, patients received the QR code and on the last day, the teleconsultation was scheduled. Given that the first and last days were non-complete days, motivation and adherence were calculated for 6 full days. In the figure, each day was divided into 3 cells providing the expected 3 recordings per day. Green cells represent the performed recording. Days with performed 3 recordings fulfilled the study agreement and are marked in yellow. Motivation was defined as the number of days in which the expected number of measurements were performed per number of days over the entire prescription period (in this scenario, per 6 days). Adherence was defined as the number of measurements per number of expected measurements over the entire prescription period (in this scenario, per 18 recordings). The examples of motivation and adherence calculations are shown in the figure.

in case of symptoms for 7 consecutive days. To support patient motivation and adherence, several educational and reminding interventions were introduced. Once daily, patients received a notification through the app as a reminder to perform heart rate and rhythm recordings. In addition, patients were instructed by the app how to improve recording quality in case of measurements with insufficient quality and were provided with educational information about AF, its complications, and treatment. For more details, see our previous work.4

Data collection

Baseline patient characteristics (demographics and medical history) were retrieved from patients' electronic case report forms provided to all centres participating in the retrospective analysis.

Statistical analysis

All continuous variables were pre-tested for normal distribution using the Shapiro–Wilk test and were assessed as non-parametric. Continuous variables are therefore presented as median [interquartile range (IQR)]; however, in 'Recordings (per patient)' part of Table 1 assessing the percentage of a particular rhythm, we additionally provided percentages as mean ± standard deviation, given low IQR. Categorical variables are presented as numbers (n) with percentages (%). Differences in continuous parameters were compared using the non-parametric Mann–Whitney U test or Kruskal–Wallis test as applicable. The Bonferroni correction was applied to address the multiple comparison issue. For the comparison of categorical data, the Pearson's $\chi 2$ test was used. To assess predictors of optimal motivation and adherence, multiple logistic regression analysis was performed using a stepwise forward procedure. In this analysis, statistically significant (in univariate analysis) baseline characteristic variables were included. Age was included as continuous variable assessed every 10 units. A two-sided P-value of 0.05 was considered statistically significant. For database management and statistical analysis, we used SAS 14.1 (SAS Institute Inc., Cary, NC, USA).

Results

Available data from 990 patients with diagnosed AF were analyzed. Median age was 64 (57–71) years and 387 (39%) of patients were females (Table 1). Almost one-third (29%; 288/990) of all patients were aged ≥70 years, whereas 32 (3.2%) were aged ≥80 years, The overall median patient motivation and adherence was 67 and 94%, respectively, and its detailed distribution is shown in Figure 2 (in detail in Supplementary material online, Figure S1). Patients were divided into 3 groups regarding their motivation: low (n = 346), moderate (n = 362), and optimal (n = 282), as well as their adherence: low (n = 254), moderate (n = 291), and optimal (n = 445). All patients (n = 282) with optimal motivation had also optimal adherence.

Motivation and adherence

Patients with both optimal motivation and adherence were older compared with the rest of the study population (median age 66 (58–72) vs. 63 (56–70) years, P = 0.001), less frequently had diabetes (5.7% vs. 10%, P = 0.034) and had a lower percentage of recordings in sinus rhythm [90 (53–100%) vs. 100 (64–100%), respectively, P < 0.001] in favour of a larger percentage of recordings in non-regular rhythm [0 (0–14%) vs. 0 (0–1.3%), respectively, P < 0.001]. Less patients with both optimal motivation and adherence had just sinus rhythm (39% vs. 51%, P < 0.001) in the recordings compared with the remaining cohort. Detailed comparison of patients with optimal motivation and adherence with the remaining study population is presented in Table 1.

Table 1. Baseline characteristics of study population according to adherence and motivation.

Variable	All (*n* = 990)	Both optimal motivation (100%) and adherence (≥100%)		*P*-value
		No (*n* = 708)	Yes (*n* = 282)	
Demographics				
Female sex	387/990 (39%)	273/708 (39%)	114/282 (40%)	0.614
Age (years)	64 (57–71)	63 (56–70)	66 (58–72)	0.001
BMI (kg/m2)	27 (25–30); *n* = 926	27 (25–30); *n* = 655	27 (24–30); *n* = 271	0.954
AF				
AF	873/979 (89%)	622/699 (89%)	251/280 (90%)	0.716
First detected AF	64/870 (7.4%)	46/619 (7.4%)	18/251 (7.2%)	1.000
Paroxysmal AF	546/869 (63%)	393/619 (64%)	153/250 (61%)	0.290
Persistent AF	297/869 (34%)	211/619 (34%)	86/250 (34%)	
Permanent AF	26/869 (3.0%)	15/619 (2.4%)	11/250 (4.4%)	
Previous CV	444/938 (47%)	310/669 (46%)	134/269 (50%)	0.289
Ablation therapy for AF	456/950 (48%)	315/679 (46%)	141/271 (52%)	0.131
Cardiovascular diseases				
Vascular disease	143/951 (15%)	99/673 (15%)	44/278 (16%)	0.690
Congestive heart failure	114/990 (12%)	81/708 (11%)	33/282 (12%)	0.912
Device therapy (PM/CRT/ICD)	41/986 (4.2%)	35/704 (5.0%)	6/282 (2.1%)	0.051
Stroke/TIA/pulmonary embolism	91/989 (9.2%)	59/707 (8.4%)	32/282 (11%)	0.145
Hemorrhagic events	8/989 (0.8%)	5/707 (0.7%)	3/282 (1.1%)	0.695
Hypertension	477/989 (48%)	342/707 (48%)	135/282 (48%)	0.888
Diabetes mellitus	87/990 (8.8%)	71/708 (10%)	16/282 (5.7%)	0.034
Smoking (current/former)	298/807 (37%)	219/574 (38%)	79/233 (34%)	0.261
Non-cardiovascular diseases				
Sleep apnoea	72/750 (9.6%)	50/530 (9.4%)	22/220 (10%)	0.787
Chronic obstructive pulmonary disease	48/989 (4.9%)	34/707 (4.8%)	14/282 (5.0%)	0.872
Chronic kidney disease	46/989 (4.7%)	37/707 (5.2%)	9/282 (3.2%)	0.185
Thromboembolic risk				
CHA_2DS_2-VASc	2 (1–3)	2 (1–3)	2 (1–3)	0.107
CHA_2DS_2-VASc score ≥ 2 (if male), ≥3 (if female)	440/943 (47%)	299/667 (45%)	141/276 (51%)	0.085
Medications				
Cardiovascular drugs ≥4	265/988 (27%)	194/706 (29%)	71/282 (25%)	0.475
Cardiovascular drugs ≥3	514/988 (52%)	373/706 (53%)	141/282 (50%)	0.438
Oral anticoagulants	756/986 (77%)	536/704 (76%)	220/282 (78%)	0.560
Antiplatelet drugs	39/986 (4.0%)	30/704 (4.3%)	9/282 (3.2%)	0.588
Beta-blockers	562/986 (57%)	396/704 (56%)	166/282 (59%)	0.477
Antiarrhythmic drugs	335/985 (34%)	247/703 (35%)	88/282 (31%)	0.265
Diuretics	187/986 (19%)	139/704 (20%)	48/282 (17%)	0.369
Dihydropyridine-CCB	105/881 (12%)	79/627 (13%)	26/254 (10%)	0.360

Variable	All (*n* = 990)	Both optimal motivation (100%) and adherence (≥100%)		*P*-value
		No (*n* = 708)	Yes (*n* = 282)	
Non-dihydropyridine-CCB	56/881 (6.4%)	35/627 (5.6%)	21/254 (8.3%)	0.169
RAAS-acting agents	402/986 (41%)	287/704 (41%)	115/282 (41%)	0.931
Digoxin	63/986 (6.4%)	44/704 (6.3%)	19/282 (6.7%)	0.774
Median recordings (per patient)				
Total	17 (12–20)	15 (12–17)	22 (19–27)	<0.001
Symptomatic a	17 (3.8–41%) 26 ± 29%	15 (0–41%) 26 ± 29%	18 (5.3–43%) 27 ± 27%	0.077
AF a	0 (0–10%) 16 ± 34%	0 (0–0%) 15 ± 33%	0 (0–18%) 19 ± 35%	0.003
Sinus rhythm a	100 (64–100%) 75 ± 37%	100 (64–100%) 76 ± 37%	90 (53–100%) 72 ± 36%	<0.001
Non-regular rhythm a	0 (0–7.1%) 7.4 ± 16%	0 (0–1.3%) 6.7 ± 16%	0 (0–14%) 9.3 ± 16%	<0.001
Number of patients with 100% recordings accompanied by:				
Symptoms	49/990 (5.0%)	34/708 (4.8%)	9/282 (3.2%)	0.303
AF	100/990 (10%)	79/708 (11%)	34/282 (12%)	0.660
Sinus rhythm	516/990 (52%)	394/708 (51%)	111/282 (39%)	<0.001

a percentage of quality recordings.

AF, atrial fibrillation; BMI, body mass index; CCB, calcium channel blocker; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; M. pacemaker; RAAS, renin–angiotensin–aldosterone system; TIA, transient ischaemic attack. Data provided after semicolon indicated available data per variable.

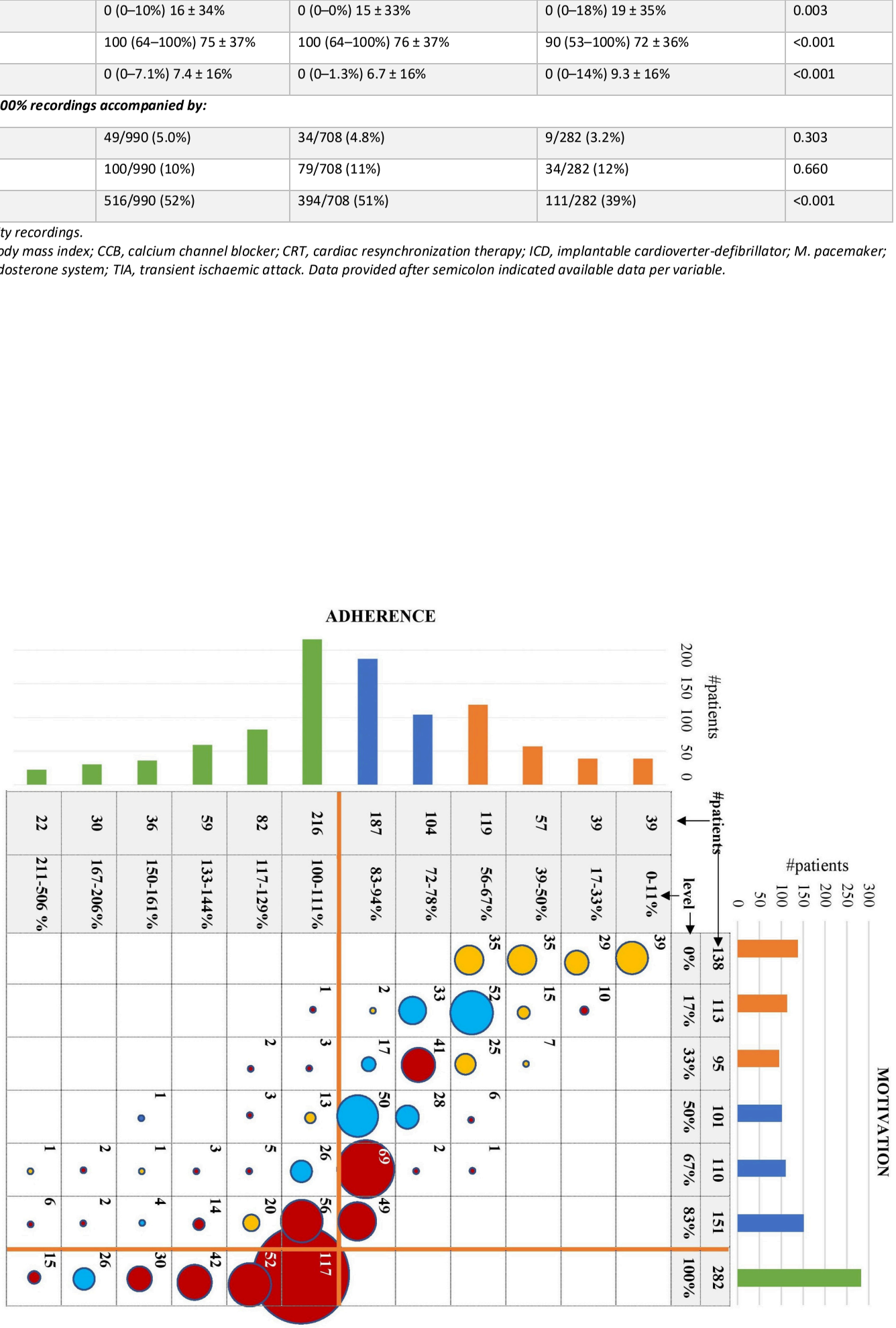


Figure 2. Distribution of patients according to motivation and adherence level.

Orange bars represent low motivation or adherence, blue bars represent moderate motivation or adherence, and green represent mean optimal motivation or adherence. Patients were divided into tertiles based on age groups: aged <59 years, 59–68 years and >68 years. The circles reflect the dominance of patients aged <59 years (yellow), aged 59–68 years (blue), and aged >68 years (red) in each motivation/adherence group. Thick orange lines divide motivation and adherence for optimal and non-optimal values.

Adherence alone

All patients with 100% motivation had in parallel at least 100% adherence. Patients with optimal adherence alone were older than patients with moderate and low adherence [median age 65 (58–71) vs. 64 (56–70) and 62 (55–70) years, respectively, P = 0.009], were more often females (46% vs. 33% and 34%, respectively, P = 0.007), had more often undergone AF ablations (52% vs. 49% and 41%, respectively, P = 0.024), and had higher thromboembolic risk based on CHA2DS2-VASc score [2 (1–3) vs. 2 (1–3) and 1 (1–3), P = 0.023]. Patients with optimal adherence had a higher percentage of recordings with AF [0 (0–18%) vs. 0 (0–0%) and 0 (0–0%), respectively, P < 0.001] and recordings with non-regular rhythm [0 (0–13%) vs. 0 (0–0%) and 0 (0–0%), respectively, P < 0.001) in favour of lower percentage of recordings with sinus rhythm [90 (57–100%) vs. 100 (80–100%) and 100 (54–100%), respectively, P < 0.001]. Interestingly, patients with low adherence more often had only symptomatic recordings or only sinus rhythm recordings (6.8% vs. 3.2%, P = 0.035 and 59% vs. 40%, P < 0.001, respectively) than patients with optimal adherence. Detailed comparison of patients with low, moderate and optimal adherence is presented in Table 2.

Predictors of optimal motivation and adherence

In logistic regression analysis, higher age and absence of diabetes were identified as independent predictors of both optimal motivation and adherence [odds ratio (OR): 1.02, 95% coincidence interval [95% CI]: 1.01–1.04, P < 0.001 and OR, 0.49, 95% CI: 0.28–0.86, P = 0.013, respectively). As the patients with 100% motivation also had ≥100% adherence, independent predictors for optimal adherence alone were age (OR: 1.02, 95% CI: 1.00–1.04, P = 0.014), female sex (OR: 1.70, 95% CI: 1.29–2.23, P < 0.001) and previous AF ablation (OR: 1.35, 95% CI: 1.03–1.70, P = 0.028). The results of the logistic regression are presented in Figure 3.

Age group analysis

As age was an independent predictor of optimal motivation and adherence to the mHealth application, we illustrated this association in Figure 2. First, we collated the motivation (x-axis) and adherence (y-axis) with circles (z-axis) whose size correlated with the number of the patient group in particular percentage of motivation and adherence (also mentioned as numbers). Low motivation or adherence were represented by orange bars, moderate motivation or adherence by blue bars, and optimal motivation or adherence by green bars. Then, we divided patients in tertiles regarding age for groups: aged <59 years (n = 313), 59–68 (n = 348) and >68 (n = 329). The dominance of patients aged <59 years, 59–68 years, and >68 years in a group of particular percentage of motivation and adherence was represented as yellow, blue, and red circles, respectively. The clear increasing in contribution of the oldest group of patients (red circles) and decreasing contribution of the youngest group (yellow circles) of patients along with the increasing motivation and adherence was observed.

Within each age tertile (<59, 59–68, and >68 years), patients were divided for those with and without optimal motivation/adherence as shown in Supplementary material online, Table S1. Figure 4 shows that higher percentage of patients with 100% motivation and at least 100% adherence was observed in the cohort older than 68 years compared with those aged 59–68 and <59 years (34% vs. 29% and 24%, respectively, P = 0.007). Patients with (vs. without) optimal motivation and adherence had higher percentage of recordings with AF [0 (0–18%) vs. 0 (0–0%), P = 0.005] in age group <59 years, and higher percentage of recordings with non-regular rhythm in age group of 59–68 and >68 years [0 (0–15%) vs. 0 (0–0%), P < 0.001 and 0 (0–15%) vs. 0 (0–5.6%), P = 0.011, respectively]. A higher, although non-statistically significant, number of patients with 100% recordings accompanied with symptoms were observed in group with (vs. without) optimal

motivation and adherence in <59 and 59–68 age groups (4.2% vs. 3.7%, P = 0.738 and 6.0% vs. 4.4%, P = 0.584, respectively); however, inverse association was observed in oldest (>68 years) group (0% vs. 6.4%, P = 0.003) as shown in Supplementary material online, Table S1.

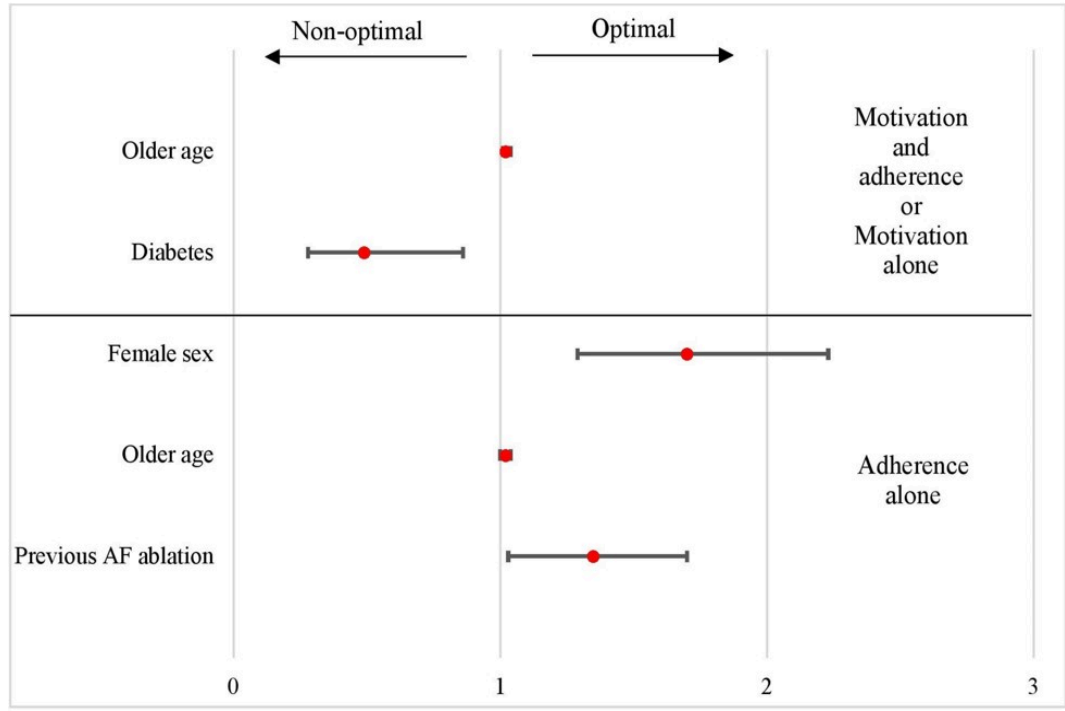


Figure 3. Predictors for both optimal motivation and adherence and optimal adherence alone shown as odd ratio (OR) and 95% coincidence intervals (CIs).
Predictors for both optimal motivation and adherence, and optimal motivation alone are the same and are shown jointly, whereas predictors for optimal adherence alone are shown separately

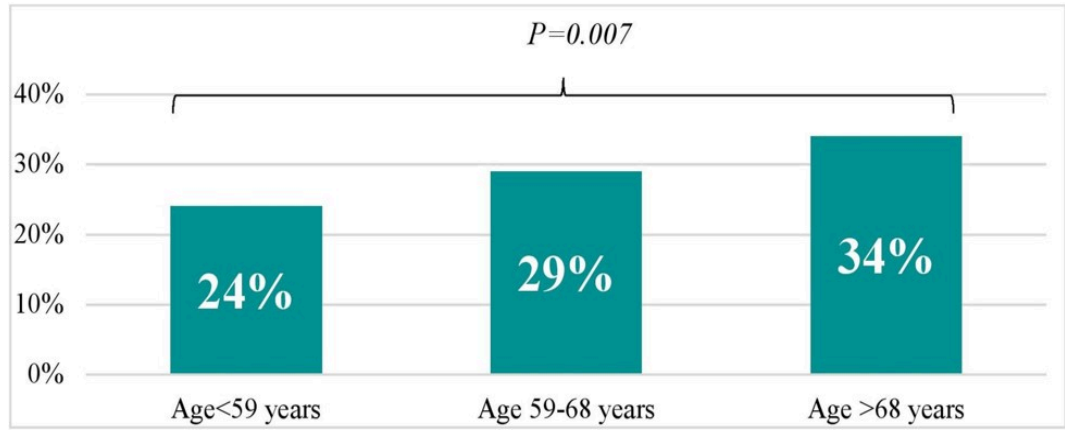


Figure 4. Percent age of patients with both optimal motivation and adherence in the different age groups.
Patients were divided in tertiles based on age groups: aged <59 years, 59–68 years, and >68 years. Columns represent the percentage of both optimal motivation and adherence in each age group. P-value is provided for all group comparisons.

Table 2. Baseline characteristics of study population according to motivation.

Variable	Motivation			*P*-value	Adherence			*P*-value
	Low (0–33%) (*n* = 346)	**Moderate (50–83%) (*n* = 362)**	**Optimal (100%) (*n* = 282)**		**Low (<72%) (*n* = 254)**	**Moderate (72 to <100%) (*n* = 291)**	**Optimal (≥ 100%) (*n* = 445)**	
Demographics								
Female sex	122/346 (35%)	139/362 (42%)	114/282 (40%)	0.184	87/254 (34%)	96/291 (33%)	204/445 (46%)	0.007
Age (years)	62 (55–70)	64 (56–71)	66 (58–72)	0.002	62 (55–70)	64 (56–70)	65 (58–71)	0.009
BMI (kg/m2)	27 (25–30); *n* = 313	27 (24–30); *n* = 342	27 (24–30); *n* = 271	0.905	27 (25–30); *n* = 230	27 (25–29); *n* = 270	27 (24–30); *n* = 426	0.514
AF								
AF	303/343 (88%)	319/356 (90%)	251/280 (90%)	0.827	222/252 (88%)	259/285 (91%)	392/442 (89%)	0.530
First detected AF	25/303 (8.3%)	21/316 (6.7%)	18/251 (7.2%)	0.740	17/222 (7.7%)	18/256 (7.0%)	29/392 (7.4%)	0.966
Paroxysmal AF	189/301 (63%)	204/318 (64%)	153/250 (61%)	0.540	135/221 (61%)	176/258 (68%)	235/390 (60%)	0.287
Persistent AF	106/301 (35%)	105/318 (33%)	86/250 (34%)		80/221 (36%)	76/258 (29%)	141/390 (36%)	
Permanent AF	6/301 (2.0%)	9/318 (2.8%)	11/250 (4.4%)		6/221 (2.7%)	6/258 (2.3%)	14/390 (3.6%)	
Previous CV	152/328 (46%)	158/341 (46%)	134/269 (50%)	0.524	113/243 (47%)	127/278 (46%)	204/417 (49%)	0.849
Ablation therapy for AF	145/332 (44%)	170/347 (49%)	141/271 (52%)	0.112	101/247 (41%)	135/278 (49%)	220/425 (52%)	0.024
Cardiovascular diseases								
Vascular disease	54/320 (17%)	45/353 (13%)	44/278 (16%)	0.297	38/236 (16%)	44/279 (16%)	61/436 (14%)	0.705
Congestive heart failure	39/346 (11%)	42/362 (12%)	33/282 (12%)	0.984	31/254 (12%)	32/291 (11%)	51/445 (11%)	0.906
Device therapy (PM/CRT/ICD)	18/343 (5.3%)	17/361 (4.7%)	6/282 (2.1%)	0.122	16/252 (6.4%)	10/290 (3.5%)	15/444 (3.4%)	0.130
Stroke/TIA/pulmonary embolism	25/345 (7.3%)	34/362 (9.4%)	32/282 (11%)	0.207	15/253 (5.9%)	31/291 (11%)	45/445 (10%)	0.110
Hemorrhagic events	3/345 (0.9%)	2/362 (0.6%)	3/282 (1.1%)	0.763	2/253 (0.8%)	3/291 (1.0%)	3/445 (0.8%)	0.869
Hypertension	167/346 (48%)	175/361 (48%)	135/282 (48%)	0.988	119/254 (47%)	145/291 (50%)	213/444 (48%)	0.778
Diabetes mellitus	29/346 (8.4%)	42/362 (12%)	16/282 (5.7%)	0.029	20/254 (7.9%)	28/291 (9.6%)	39/445 (8.8%)	0.772
Smoking (current/former)	106/268 (40%)	113/306 (37%)	79/233 (34%)	0.426	75/193 (39%)	93/249 (37%)	130/365 (36%)	0.742
Non-cardiovascular diseases								
Obstructive sleep apnea syndrome	27/271 (10%)	23/259 (8.9%)	22/220 (10%)	0.889	19/195 (9.7%)	24/221 (11%)	29/334 (8.7%)	0.693
Chronic obstructive pulmonary disease	22/345 (6.4%)	12/362 (3.3%)	14/282 (5.0%)	0.166	15/253 (5.9%)	11/291 (3.8%)	22/445 (4.9%)	0.505
Chronic kidney disease	18/345 (5.2%)	19/362 (5.3%)	9/282 (3.2%)	0.388	12/253 (4.7%)	18/291 (6.2%)	16/445 (3.6%)	0.263
Thromboembolic risk								
CHA_2DS_2-VASc score	2 (1–3)	2 (1–3)	2 (1–3)	0.091	1 (1–3)	2 (1–3)	2 (1–3)	0.023
CHA_2DS_2-VASc score ≥ 2 (if male), ≥3 (if female)	135/317 (43%)	164/350 (47%)	141/276 (51%)	0.117	95/233 (41%)	130/277 (47%)	215/433 (50%)	0.090
Medications								

Variable	Motivation			*P*-value	Adherence			*P*-value
	Low (0–33%) (*n* = 346)	**Moderate (50–83%) (*n* = 362)**	**Optimal (100%) (*n* = 282)**		**Low (<72%) (*n* = 254)**	**Moderate (72 to <100%) (*n* = 291)**	**Optimal (≥ 100%) (*n* = 445)**	
Cardiovascular drugs ≥4	103/344 (30%)	91/362 (25%)	71/282 (25%)	0.270	78/252 (31%)	73/291 (25%)	114/445 (26%)	0.227
Cardiovascular drugs ≥3	186/344 (54%)	187/362 (52%)	141/282 (50%)	0.589	137/252 (54%)	150/291 (52%)	227/445 (51%)	0.683
Oral anticoagulants	258/343 (75%)	278/361 (77%)	220/282 (78%)	0.701	185/252 (73%)	222/290 (77%)	349/444 (79%)	0.297
Antiplatelet drugs	16/343 (4.7%)	14/361 (3.9%)	9/282 (3.2%)	0.640	10/252 (4.0%)	14/290 (4.8%)	15/444 (3.4%)	0.616
Beta-blockers	203/343 (59%)	193/361 (53%)	166/282 (59%)	0.233	155/252 (62%)	146/290 (50%)	261/444 (59%)	0.355
Antiarrhythmic drugs	119/342 (35%)	128/361 (35%)	88/282 (31%)	0.492	82/251 (34%)	100/290 (34%)	153/444 (34%)	0.874
Diuretics	66/343 (19%)	73/361 (20%)	48/282 (17%)	0.582	50/252 (20%)	53/290 (18%)	84/444 (19%)	0.898
Dihydropyridine-CCB	44/299 (15%)	35/328 (11%)	26/254 (10%)	0.183	31/221 (14%)	33/266 (12%)	41/394 (10%)	0.396
Non-dihydropyridine-CCB	17/299 (5.7%)	18/328 (5.5%)	21/254 (8.3%)	0.333	11/221 (5.0%)	19/266 (7.1%)	26/394 (6.6%)	0.600
RAAS-acting agents	144/342 (42%)	143/362 (40%)	115/282 (41%)	0.831	106/252 (42%)	116/290 (40%)	180/444 (41%)	0.958
Digoxin	19/343 (5.5%)	25/361 (6.9%)	19/282 (6.7%)	0.724	14/252 (5.6%)	19/290 (6.6%)	30/444 (6.8%)	0.816
Recordings (per patient)								
Total	11 (9–13)	17 (16–19)	22 (19–27)	<0.001	11 (8–12)	16 (15–17)	21 (19–25)	<0.001
Symptomatic a	14 (0–35%) 24 ± 29%	18 (5.6–46%) 28 ± 29%	18 (5.3–43%) 27 ± 27%	0.002	14 (0–39%) 25 ± 30%	13 (0–36%) 24 ± 27%	20 (5.3–45%) 29 ± 28%	<0.001
AF a	0 (0–0%) 16 ± 35%	0 (0–9.7%) 15 ± 31%	0 (0–18%) 19 ± 35%	0.005	0 (0–0%) 17 ± 36%	0 (0–0%) 13 ± 31%	0 (0–18%) 18 ± 33%	<0.001
Sinus rhythm a	100 (62–100%) 74 ± 40%	100 (67–100%) 78 ± 34%	90 (53–100%) 72 ± 36%	0.002	100 (54–100%) 73 ± 41%	100 (80–100%) 81 ± 34%	90 (57–100%) 73 ± 35%	<0.001
Non-regular rhythm a	0 (0–0%) 5.7 ± 16%	0 (0–6.7%) 7.5 ± 16%	0 (0–14%) 9.3 ± 16%	<0.001	0 (0–0%) 5.3 ± 16%	0 (0–0%) 6.0 ± 15%	0 (0–13%) 9.6 ± 17%	<0.001
Number of patients with 100% recordings accompanied by:								
Symptoms	20/346 (5.8%)	14/362 (3.9%)	9/282 (3.2%)	0.248	21/306 (6.8%)	8/239 (3.4%)	14/445 (3.2%)	0.035
AF	44/346 (13%)	35/362 (9.7%)	34/282 (12%)	0.415	42/306 (14%)	23/239 (9.6%)	48/445(11%)	0.289
Sinus rhythm	204/346 (59%)	190/362 (52%)	111/282 (39%)	<0.001	182/306 (59%)	145/239 (61%)	178/445 (40%)	<0.001

a percentage of quality recordings.

AF, atrial fibrillation; BMI, body mass index; CCB, calcium channel blocker; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; M. pacemaker; RAAS, renin-angiotensin-aldosterone system; TIA, transient ischaemic attack. Data provided after semicolon indicated available data per variable.

Discussion

This is the first study assessing patient motivation and adherence to on-demand heart rate and rhythm monitoring application for remote AF management supported by teleconsultation in a large real-world mHealth project.

Assessment and explanation of optimal motivation and adherence

The optimal or most appropriate way to assess motivation and adherence to mHealth application remains unclear, and consensus is lacking. In this analysis of the TeleCheck-AF project, we propose a novel way to assess motivation and adherence. Based on our definitions, median motivation and adherence were 67 and 94%, respectively. Twenty-eight percent of patients showed an optimal (100%) motivation and 45% showed an optimal (at least 100%) adherence. Higher adherence than motivation could be explained by the fact that patients performed more than the expected recording (≥3/day) for example to 'compensate' low number of days in which recordings were performed or due to higher percentage of AF (especially in age group >59 years) and non-regular heart rhythm recordings (mainly in those aged ≥59 years), which may have led to uncertainty and triggered additional measurements. Therefore, not just patient education on AF and on how and when to use the application but also on other causes of irregular heart rhythm recordings, such as respiratory sinus arrhythmia and premature contractions, should be discussed with patients in whom mHealth-based heart rate and rhythm monitoring is used.11 Interestingly, in the group with low adherence, a larger proportion of PPG recordings was accompanied by symptoms, compared with the group with optimal adherence. This suggests that patients with low adherence may mainly perform measurements when they experience symptoms, whereas patients with optimal adherence stick to the recommendations to perform 3 recordings per day, which accumulates PPG recordings irrespective of symptoms over time.

Threshold of optimal motivation and adherence

According to a recent WHO report, adherence to long-term therapy for chronic illnesses in developed countries averages 50%.3 However, the WHO report mainly focuses on a long treatment period. In contrast, TeleCheck-AF was designed as a 1-week mHealth intervention only, which may explain the relatively high observed adherence. In the literature, there is no clear agreement on how to stratify patients into 'good' and 'poor' adherence. Some classifications have been proposed to evaluate the adherence to hypertensive drug administration.12 However, the arbitrarily selected thresholds to categorize patients to good and poor adherence (set at 80%) are usually not challenged by sensitivity testing, different interventions or links to outcome and should therefore not be generalized to different clinical scenarios. In the mobile Atrial Fibrillation App (mAFA)-II trial, good management adherence was assessed as monitoring time (at least 14 days) since initial monitoring of at least 70%.13 Although, this cut-off resulted in a high proportion of patients that had good adherence to (70.8%) and persistence of use of (91.7%) the mAFA app, the validity of this cut-off point and detailed definition of 'adherence to treatment' in this study remain unknown. To overcome the limitation of the absence of clear thresholds for 'good' and 'poor' adherence, we mainly reported on patients with optimal adherence and/or motivation in this study.

Most of the available studies concern the impact of mHealth solutions on motivation and adherence to specific behaviour change strategies such as medication use by sending motivational messages/alerts, drug adherence statistics, or remote educational platforms. The actual motivation and adherence to mHealth devices/apps use is sparse, and more research is required in this field.

Predictors of optimal motivation and adherence

In TeleCheck-AF, higher age was identified as an independent predictor for better motivation and adherence. Both the large proportion of older patients enrolled in TeleCheck-AF, as well as the good motivation and adherence to the instructions suggest a good mHealth literacy and acceptance in older patients. Similarly, in a study by Desteghe et al.14, motivation to use an mHealth app, aiming to improve adherence to performing a daily 'healthy' challenge during a 90-day period, was higher in elderly AF patients (mean age of 69 years) than in younger participants of the study. Therefore, increased age of patients should not discourage physicians, nurses, and allied health professionals to provide mHealth applications to their patients.

Another independent predictor for both optimal motivation and adherence was lack of diabetes. In a recent study by Larsen et al.15, although median adherence to daily use of a heart rhythm/rate wrist monitor for 8–12 weeks to reinforce physical activity change strategies in pregnant women with diabetes was 90%, full days of wear (≥600 min) were much more infrequent and median adherence was 50%. Diabetic neuropathy or other diabetes-associated complications may affect the perception of symptoms and therefore reducing the number of symptom-triggered recordings.

In addition, female sex and previous history of AF ablation were identified as independent predictors of optimal adherence. Higher adherence to mHealth treatment in the group of patients who previously underwent AF ablation could be explained by patients' concerns about their own health and willingness to control their health as best and scrupulously as possible. According to previous studies,16 women are more sensitive to threat-related stimuli and experience more negative effects than men. They are more likely to seek medical advice, preventive measures, and remedies. That well-described behavioural difference between men and women could explain higher adherence of female (vs. male) patients to mHealth treatment in our study population.

Assistance in obtaining optimal motivation and adherence

Patient education and information are important and established approaches to ensure and facilitate patient adherence and motivation.17 According to a recent study, age and educational level are crucial domains for successful implementation of telemedicine.18 Within TeleCheck-AF, we developed and published standardized instructions that were followed by all participating centres.4–6,19 Information about strategies to educate and empower patients to self-manage the on-demand mHealth application and the required care co-ordination, including implementation of the approach into clinical practice, were provided to the participating centres.7 However, as this mHealth-based approach was tailored to the individual patient and in centre-/country-specific conditions, it cannot be ruled out that some changes in patient management have been adopted. Moreover, education and involvement of patients and their carers in the care process is a crucial part of integrated care approaches.20 Specialized AF clinics based on the concept of integrated care21 are highly suitable to incorporate educational strategies to empower patients to be involved, use the technology, and thus take ownership of their self-management. The availability of such infrastructure and tailored patient educational strategies has likely contributed critically to the herein described adherence and motivation of enrolled patients. However, it is worth to emphasize that adherence and motivation to treatment should be a part of the long-term management of AF. Globally, AF guidelines advocate a self-management approach that encompasses a range of activities such as tracking symptoms, increasing physical activity, or supporting mental health in an effort to engage patients to take an active role in their own care, which has become even more evident during the COVID-19 lockdown periods.22 Patient self-efficacy is a key enabler of self-management and should be promoted through education, guidance and empowerment.23 Considering that the average AF patient is burdened with numerous

conditions, education should be tailored to the individual patient, provided in a structured approach and by multidisciplinary teams with sufficient knowledge to ensure comprehensive care.24,25

Strengths and limitations

To our knowledge, this analysis of the TeleCheck-AF project provides the first real-world data set on patient adherence and motivation to a standardized mHealth application integrated in remote AF management. Importantly, TeleCheck-AF incorporated an on-demand mHealth application for 7 days only. Longer mHealth-based monitoring has been associated with longitudinally decreasing patient adherence and motivation over time. In addition, there may be selection bias, as it includes only patients who were willing to use the mobile app in this real-life setting, and there should be caution in generalizing these findings to all patients with AF. Further intervention studies comparing the effect of notifications reminding to perform recordings on motivation and adherence level are required. Finally, differences in providing education and information on this mHealth project in particular centre could have influenced the results.

Conclusions

Within the TeleCheck-AF project, the overall adherence to this mHealth application was high, with a mean adherence of 94% and a motivation of 67%. Higher age and absence of diabetes are independent predictors for patient motivation and adherence to instructions to use a PPG-based app on-demand for 7 days supported teleconsultation within the TeleCheck-AF project. Therefore physicians, nurses, and allied health specialists involved in the management and care for patients with AF should not be discouraged to provide a mHealth infrastructure to elderly patients. Other predictors of mHealth adherence in TeleCheck-AF were the female sex and previous AF ablation (adherence).

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Supplementary material

Table S1. Baseline characteristics of study population according to age and adherence/motivation.

Variable	Aged <59 (n=313)		Aged 59-68 (n=348)		Aged >68 (n=329)	
	Both optimal motivation (100%) and adherence (≥100%)		Both optimal motivation (100%) and adherence (≥100%)		Both optimal motivation (100%) and adherence (≥100%)	
	No (n=242)	Yes (n=71)	No (n=248)	Yes (n=100)	No (n=218)	Yes (n=111)
Demographics						
Female sex	76/242 (31%)	25/71 (35%)	101/248 (41%)	34/100 (34%)	96/218 (44%)	55/111 (50%)
Age (years)	52 [45-56] [c]	53 [49-56][b]	63 [61-66] [c]	65 [62-67][b]	73 [71-76] [c]	73 [70-76][b]
BMI (kg/m2)	27 [25-30] [a c]; n=218	29 [25-32][a b] ; n=65	27 [25-30] [c]; n=241	27 [25-29] [b]; n=97	26 [24-29] [c]; n=196	26 [24-29] [b]; n=109
AF						
AF	198/237 (84%) [c]	57/71 (80%) [b]	228/245 (93%) [c]	93/99 (94%) [b]	196/217 (90%) [c]	101/110 (92%) [b]
First detected AF	10/197 (5.1%) [c]	5/57 (8.8%)	18/226 (8.0%) [c]	6/93 (6.5%)	18/196 (9.2%) [c]	7/101 (6.9%)
Paroxysmal AF	126/197 (64%) [c]	40/57 (70%) [b]	155/227 (68%) [c]	57/93 (61%) [b]	112/195 (57%) [c]	56/100 (56%) [b]
Persistent AF	70/197 (36%) [c]	17/57 (30%) [b]	67/227 (30%) [c]	34/93 (37%) [b]	74/195 (38%) [c]	35/100 (35%) [b]
Permanent AF	1/197 (0.5%)	0/57 (0%) [b]	5/227 (2.2%)	2/93 (2.2%) [b]	9/195 (4.6%)	9/100 (9.0%) [b]
Previous CV	111/243 (46%)	25/71 (35%)	108/248 (44%)	53/100 (53%)	91/218 (42%)	56/111 (50%)
Ablation therapy for AF	102/228 (45%)	28/66 (42%)	116/241 (48%)	57/96 (59%)	97/210 (46%)	56/109 (51%)
Cardiovascular diseases						
Vascular disease	13/229 (5.7%) [c]	5/69 (7.3%) [b]	39/235 (17%) [c]	14/98 (14%) [b]	47/209 (22%) [c]	25/111 (23%) [b]
Congestive heart failure	14/242 (5.8%) [c]	7/71 (9.9%)	34/248 (14%) [c]	16/100 (16%)	33/216 (15%) [c]	10/111 (9.0%)

Variable	Aged <59 (n=313)		Aged 59-68 (n=348)		Aged >68 (n=329)	
	Both optimal motivation (100%) and adherence (≥100%)		Both optimal motivation (100%) and adherence (≥100%)		Both optimal motivation (100%) and adherence (≥100%)	
	No (n=242)	Yes (n=71)	No (n=248)	Yes (n=100)	No (n=218)	Yes (n=111)
Device therapy (PM/CRT/ICD)	8/239 (3.4%) [c]	1/71 (1.4%)	9/247 (3.6%) [c]	3/100 (3.0%)	18/218 (8.3%) [a c]	2/111 (1.8%) [a]
Stroke/TIA/pulmonary embolism	11/241 (4.6%) [c]	1/71 (1.4%) [b]	18/248 (7.3%) [c]	11/100 (11%) [b]	30/218 (14%) [c]	20/111 (18%) [b]
Hemorrhagic events	0/241 (0%)	0/71 (0%)	2/248 (0.8%)	2/100 (2.0%)	3/218 (1.4%)	1/111 (0.9%)
Hypertension	74/241 (31%) [c]	23/71 (32%) [b]	132/248 (53%) [c]	45/100 (45%) [b]	136/218 (62%) [c]	67/111 (60%) [b]
Diabetes mellitus	9/242 (3.7%) [c]	4/71(5.6%)	29/248 (12%) [c]	6/100 (6.0%)	33/218(15%) [a c]	6/111 (5.4%) [a]
Smoking (current/former)	61/189 (32%) [c]	15/62 (24%)	98/212 (46%) [c]	33/83 (40%)	60/173 (35%) [c]	31/88 (35%)
Non-cardiovascular diseases						
Sleep apnea	15/185 (8.1%)	3/54 (5.6%)	21/179 (12%)	10/78 (13%)	14/167 (8.4%)	9/88 (10%)
Chronic obstructive pulmonary disease	5/241 (2.1%) [c]	0/71 (0%)	11/248 (4.4%) [c]	7/100 (7.0%)	18/218 (8.3%) [c]	7/111 (6.3%)
Chronic kidney disease	3/241 (1.2%) [c]	1/71 (1.4%)	16/248 (6.1%) [c]	2/100 (2.0%)	19/218 (8.7%) [c]	6/111 (5.4%)
Thromboembolic risk						
CHA_2DS_2-VASc	1 [0-1] [c]	1 [0-1] [b]	2 [1-3] [c]	2 [1-2] [b]	3 [2-4] [c]	3 [2-4] [b]
CHA_2DS_2-VASc score ≥ 2 (if male), ≥3 (if female)	28/226 (12%) [c]	9/69 (13%) [b]	94/234 (40%) [c]	41/96 (43%) [b]	177/207 (86%) [c]	91/111 (82%) [b]

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Variable	Aged <59 (n=313)		Aged 59-68 (n=348)		Aged >68 (n=329)	
	Both optimal motivation (100%) and adherence (≥100%)		Both optimal motivation (100%) and adherence (≥100%)		Both optimal motivation (100%) and adherence (≥100%)	
	No (n=242)	Yes (n=71)	No (n=248)	Yes (n=100)	No (n=218)	Yes (n=111)
Medications						
Cardiovascular drugs ≥4	36/241 (15%) [c]	13/71 (18%)	70/247 (28%) [c]	25/100 (25%)	88/218 (40%) [c]	33/111 (30%)
Cardiovascular drugs ≥3	86/241 (36%) [c]	28/71 (39%)	143/247 (58%) [c]	52/100 (52%)	144/218 (66%) [c]	61/111 (55%)
Oral anticoagulants	141/240 (59%) [c]	40/71 (56%) [b]	196/247 (79%) [c]	80/100 (80%) [b]	199/217 (92%) [c]	100/111 (90%) [b]
Antiplatelet drugs	7/240 (2.9%)	1/71 (1.4%)	13/247 (5.3%)	4/100 (4.0%)	10/217 (4.6%)	4/111 (3.6%)
Beta-blockers	110/240(46%) [a c]	42/71 (59%) [a]	150/247 (61%) [c]	53/100 (53%)	136/217 (63%) [c]	71/111 (64%)
Antiarrhythmic drugs	79/240 (33%)	21/71 (30%)	99/247 (40%)	36/100 (36%)	69/217 (32%)	31/111 (28%)
Diuretics	25/240 (10%) [c]	7/71 (9.9%)	39/247 (16%) [c]	16/100 (16%)	75/217 (35%) [a c]	25/111 (23%) [a]
Dihydropyridine-CCB	18/207 (8.7%) [c]	8/63 (13%)	25/222 (11%) [c]	8/88 (9.1%)	36/198 (18%) [c]	10/103 (9.7%)
Non-dihydropyridine-CCB	6/207 (2.9%)	4/63 (6.4%)	16/222 (7.2%)	6/88 (6.8%)	13/198 (6.6%)	11/103 (11%)
RAAS-acting agents	64/240 (26%) [c]	20/71 (28%) [b]	112/247 (45%) [c]	40/100 (40%) [b]	111/217 (51%) [c]	55/111 (50%) [b]
Digoxin	3/240 (1.3%) [c]	4/71 (5.6%)	18/247 (7.3%) [c]	6/100 (6.0%)	23/217 (11%) [c]	9/111 (8.1%)
Recordings (per patient)						
Total	14 [10-17] [a]	22 [19-26] [a]	15 [12-18] [a]	21 [19-27] [a]	16 [12-17] [a]	22 [19-26] [a]

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Variable	Aged <59 (n=313)		Aged 59-68 (n=348)		Aged >68 (n=329)	
	Both optimal motivation (100%) and adherence (≥100%)		Both optimal motivation (100%) and adherence (≥100%)		Both optimal motivation (100%) and adherence (≥100%)	
	No (n=242)	Yes (n=71)	No (n=248)	Yes (n=100)	No (n=218)	Yes (n=111)
Symptomatic*	18 [0-41%][c] 27±29%	17 [5.3-57%] 32±31%	14 [0-36%][a c] 24±27%	22 [5.6-45%][a] 30±29%	15 [0-44%][c] 28±31%	16 [5.0-37%] 22±22%
AF*	0 [0-0%][a] 8.4+25%	0 [0-18%][a] 15±30%	0 [0-0%] 15+32%	0 [0-21%] 19±35%	0 [0-29%] 24±39%	0 [0-21%] 22±37%
Sinus rhythm*	100 [83-100%][c] 83±32%	96 [68-100%] 76±35%	100[65-100%][a c] 77±37%	89 [58-100%][a] 72±35%	91 [27-100%][c] 67±41%	85 [39-100%] 68±38%
Non-regular rhythm*	0 [0-0%] 5.8±15%	0 [0-10%] 9.0±19%	0 [0-0%][a] 6.9±17%	0 [0-15%][a] 14±8.5%	0 [0-5.6%][a] 7.2±16%	0 [0-15%][a] 10±17%
Number of patients with 100% recordings accompanied by:						
Symptoms	9/242(3.7%)	3/71 (4.2%)	11/248 (4.4%)	6/100 (6.0%)	14/218 (6.4%)[a]	0/111 (0%)[a]
AF	15/242 (6.2%)	6/71 (8.5%)	24/248 (9.6%)	11/100 (11%)	40/218 (18%)	17/111 (15%)
Sinus rhythm	157/242 (65%)	37/71 (52%)	140/248 (56%)[a]	32/100 (32%)[a]	97/218 (45%)	42/111 (38%)

a *statistical significant difference (P value <0.05) between patients with and without both optimal (⩾100%) motivation and adherence within each age group (<59, 59-68 and >68 years)*

b *statistical significant difference (P value <0.05) between patients with both optimal (⩾100%) motivation and adherence aged <59 vs 59-68 vs >68 years*

c *statistical significant difference (P value <0.05) between patients without both optimal (⩾100%) motivation and adherence aged <59 vs 59-68 vs >68 years*

Abbreviations: see Table 1; SR, sinus rhythm

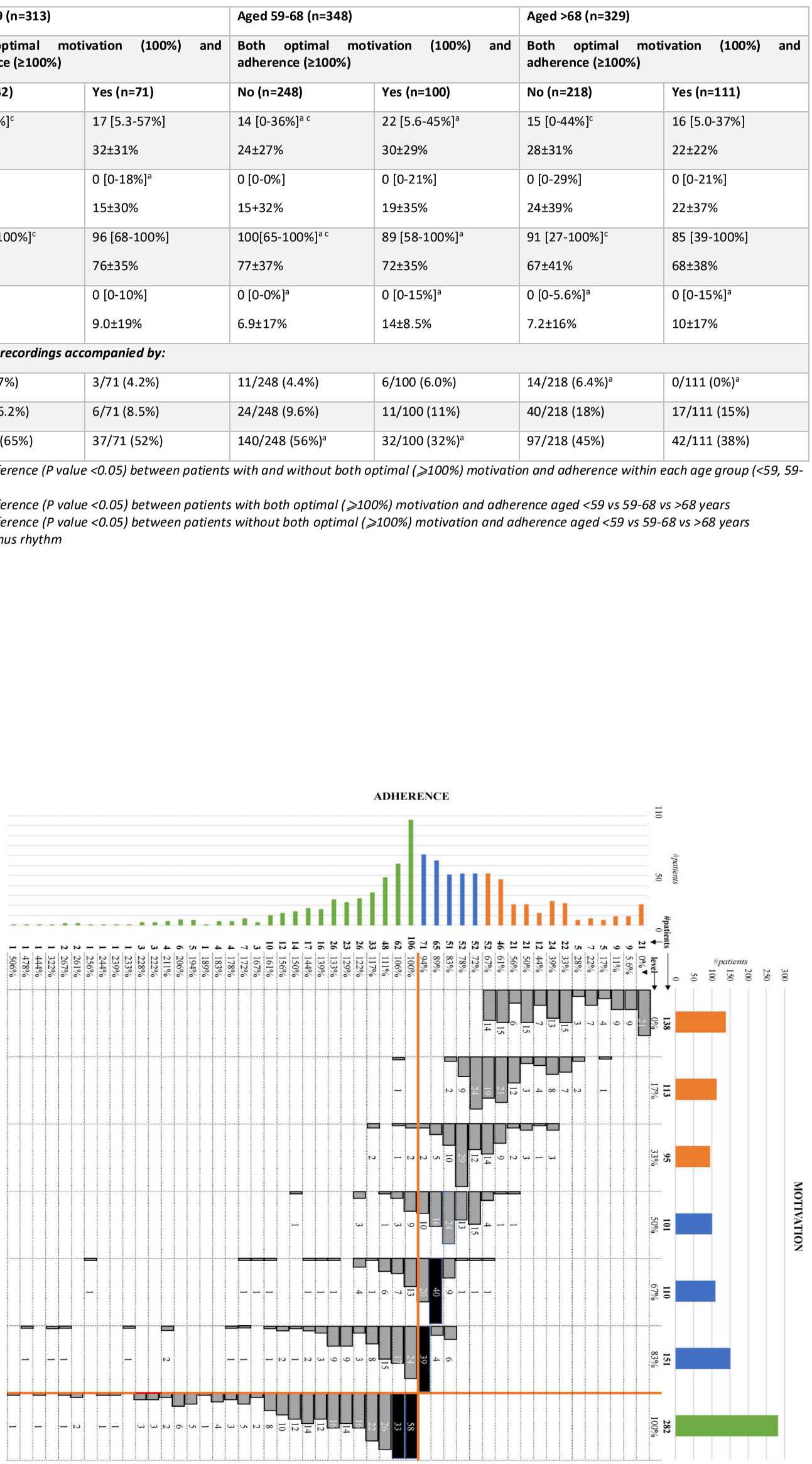

Figure S1. Detailed distribution of patients according to motivation and adherence level.

Orange bars represent low motivation or adherence, blue bars represent moderate motivation or adherence, green bars represent optimal motivation or adherence. Grey bars represent the number of patients in each motivation/adherence group. Black bars represent >30 patients.

CHAPTER 11

Self-Reported Mobile Health-Based Risk Factor and CHA2DS2-VASc-Score Assessment in Patients With Atrial Fibrillation: TeleCheck-AF Results

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Abstract

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 CHA2DS2-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 CHA2DS2-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 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 CHA2DS2-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 CHA2DS2-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 CHA2DS2-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 CHA2DS2-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 CHA2DS2-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 CHA2DS2-VASc-score 0 (male), 1 (female) and EHR-based CHA2DS2-VASc-score ≥ 1 (male), ≥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 CHA2DS2-VASc-score ≥1 (male), ≥2 (female) and EHR-based CHA2DS2-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 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).

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

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

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).

Assessment of Thromboembolic Risk and Anticoagulation

CHA2DS2-VASc-scores were determined based on information derived from the mobile app and by information derived from the EHR. Compared to the CHA2DS2-VASc-score derived from data in the EHR, the mobile app-based assessment of the CHA2DS2-VASc-score identified a lower proportion of patients with a high thromboembolic risk and CHA2DS2-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 CHA2DS2-VASc-score ≥2 (if male) and ≥3 (if female), half (46%) of patients

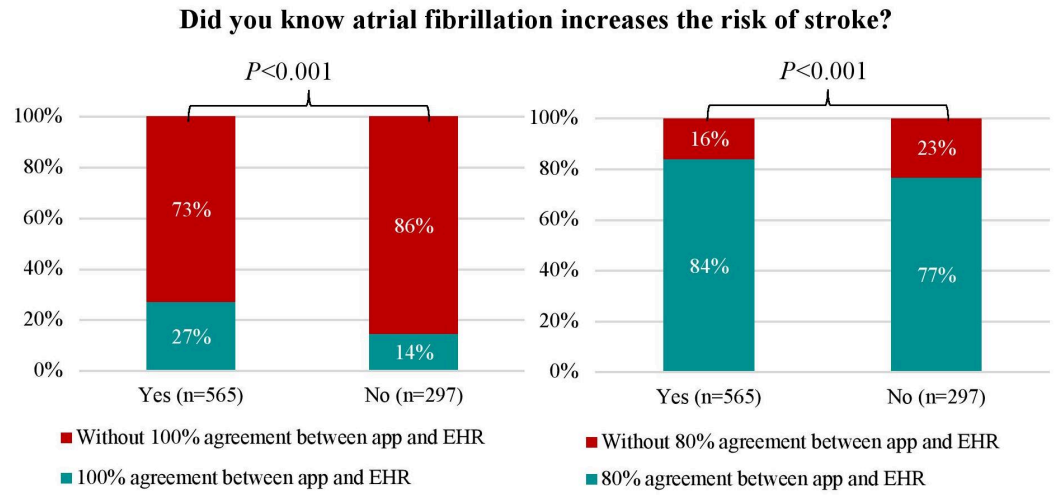

Figure 1. Comparison between patients with and without 100% and ≥80% agreement between electronic health record- and app-based results and patients' knowledge about atrial fibrillation as a risk for stroke.
Abbreviations: see Table 1

with EHR-based CHA2DS2-VASc-score 1 (if male) and 2 (if female) and quarter (26%) of patients with EHR-based CHA2DS2-VASc-score 0 (if male) and 1 (if female) (Figure 3A). Compared to the CHA2DS2-VASc-score derived from data in the EHR, the app-based assessment of the CHA2DS2-VASc-score would have resulted in a different indications for OAC in 6.1% of patients with EHR-based CHA2DS2-VASc-score ≥1 (if male) and ≥2 (if female) and 26% of patients with EHR-based CHA2DS2-VASc-score 0 (if male) and 1 (if female) (Figure 3B). The proportion of patients with a CHA2DS2-VASc-score ≥1 (if male) and ≥2 (if female) based on the mobile app and the EHR was comparable (Supplementary Figure 2).

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 CHA2DS2-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.

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-

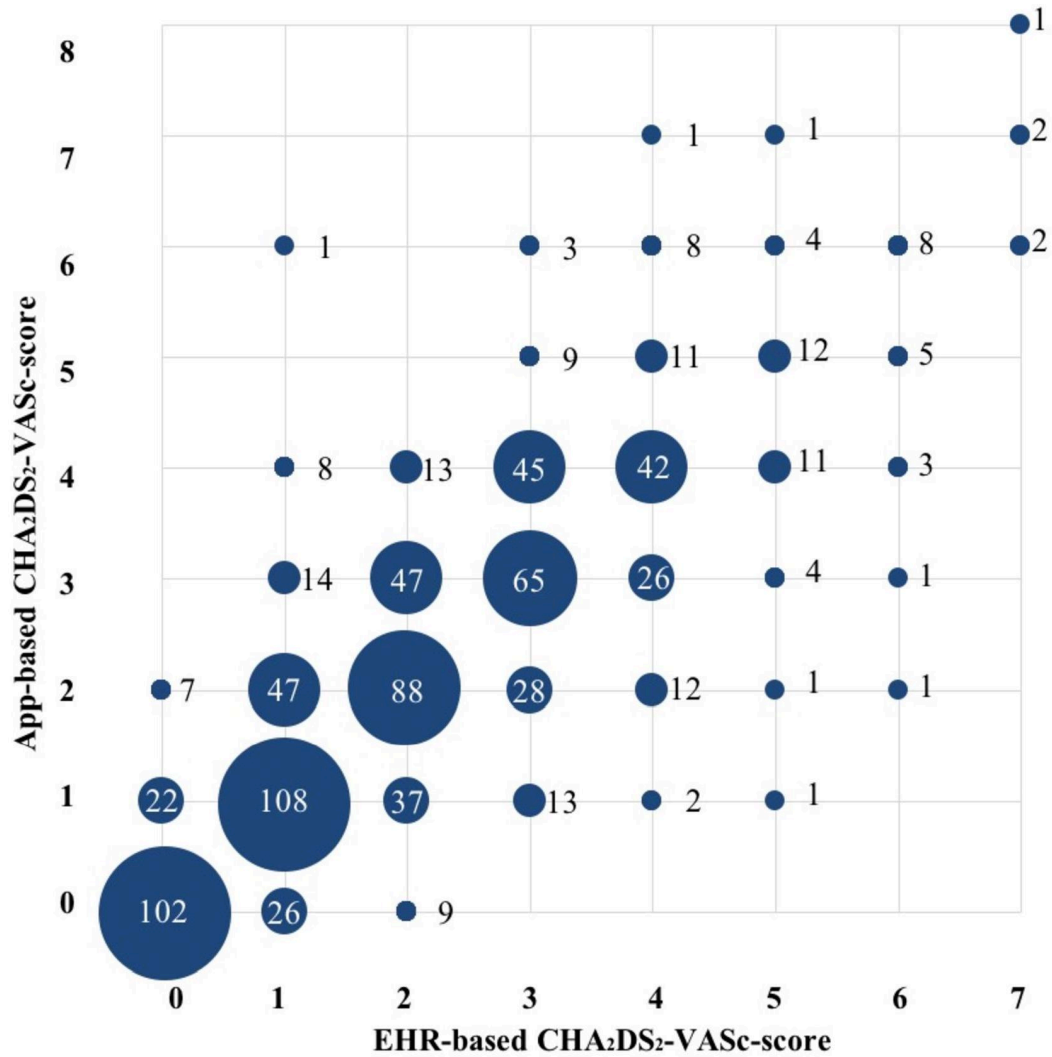

Figure 2. Comparison between electronic health record- and app-based CHA2DS2-VASc score (n = 853).
Size of the circles represent the numbers of patients (also mentioned as numbers).
Abbreviations: see Table 1.

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 CHA2DS2-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,

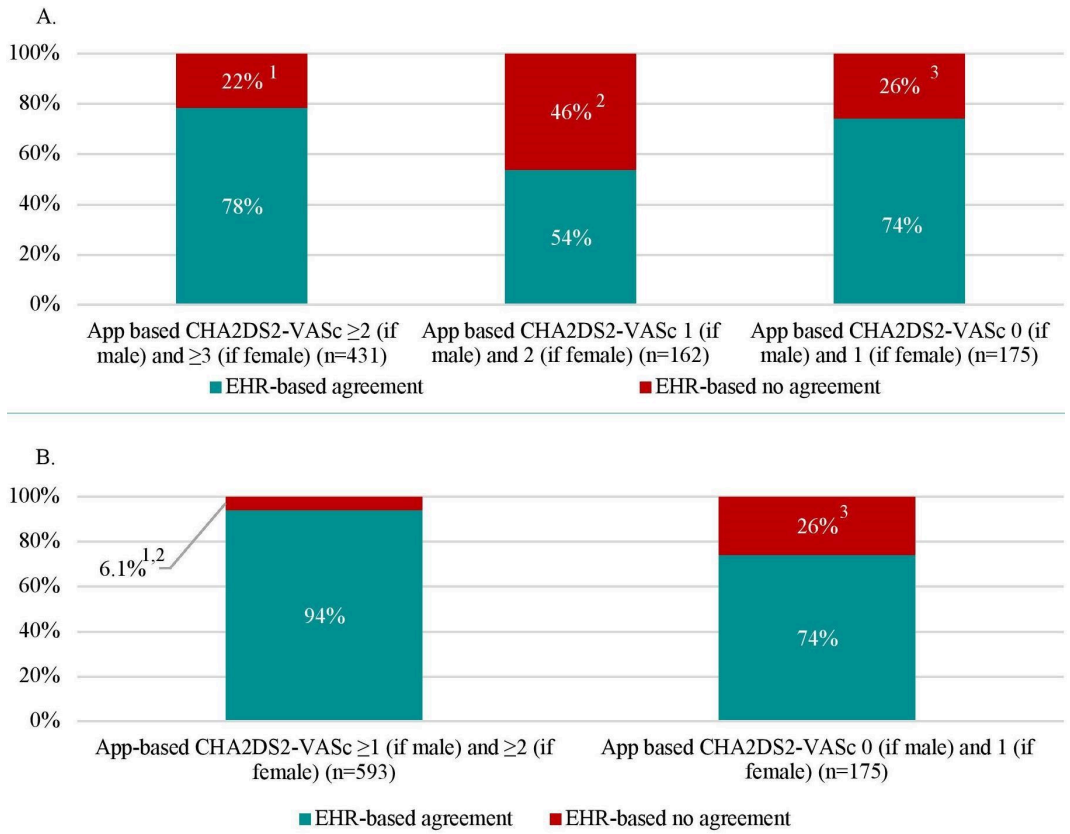

Figure 3. Thromboembolic (CHA2DS2-VASc) score in patients with atrial fibrillation based on electronic health record- and app-based results (n = 768).
(A) represents recommended (App-based CHA2DS2-VASc ≥2 [if male] and ≥3 [if female]), to be considered (App-based CHA2DS2-VASc 1 [if male] and 2 [if female]), and not recommended (App-based CHA2DS2-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 1.1EHR-based CHA2DS2-VASc 0 (if male) and 1 (if female) in 2.8% of patients, CHA2DS2-VASc 1 (if male) and 2 (if female) in 19% of patients. 2EHR-based CHA2DS2-VASc 0 (if male) and 1 (if female) in 15% of patients, CHA2DS2-VASc ≥2 (if male) and ≥3 (if female) in 31% of patients. 3EHR-based CHA2DS2-VASc ≥2 (if male) and ≥3 (if female) in 5.1% of patients, CHA2DS2-VASc 1 (if male) and 2 (if female) in 21% of patients.

"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 CHA2DS2-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 (CHA2DS2-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 CHA2DS2-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 CHA2DS2-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.

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Supplementary material

Table S1. 10-item questionnaire.

App-based question in English	App-based question in Dutch	App-based question in German	App-based question in Polish	EHR-based variable definition
Did you know atrial fibrillation increases the risk of stroke?	Wist je dat voorkamerfibrillatie of boezemfibrillatie het risico op een beroerte verhoogt?	Wussten Sie, dass Vorhofflimmern das Risiko eines Schlaganfalls erhöht?	Czy wiesz, że migotanie przedsionków zwiększa ryzyko udaru?	NA
Do you have a pacemaker?	Heb je een pacemaker?	Haben Sie einen Herzschrittmacher?	Czy masz stymulator serca?	Pacemaker
Were you ever diagnosed with cardiac arrhythmias?	Werden er al eerder hartritmestoornissen bij je vastgesteld?	Wurden bereits Herzrhythmusstörungen bei Ihnen festgestellt?	Czy kiedykolwiek zdiagnozowano u Ciebie arytmie	AF, atrial flutter, ectopic beats (PACs and PVCs) and/or SVT
Are you (or were you before) diagnosed with or treated for atrial fibrillation or AF?	Ben je (of was je voorheen) gediagnosticeerd of behandeld voor voorkamerfibrillatie of VKF?	Sind (oder waren) Sie wegen Vorhofflimmern (VHF) in Behandlung oder wurde diese Diagnose bei Ihnen gestellt?	Czy zdiagnozowano lub leczono migotanie przedsionków?	AF
Are you (or were you before) treated for heart failure or pulmonary edema?	Ben je (of was je voorheen) in behandeling voor hartfalen of longoedeem?	Sind (oder waren) Sie wegen Herzversagen oder eines Lungenödems in Behandlung?	Czy jesteś (lub byłeś wcześniej) leczony z powodu niewydolności serca lub zatorowości płucnej?	PE and/or HFrEF (LVEF ≤ 40%), HFmEF (LVEF 41 – 49%), or HFpEF (LVEF ≥ 50%)
Are you (or were you before) treated for vascular disease in your legs or aorta? Or did you ever suffer from a heart attack?	Ben je (of was je voorheen) in behandeling voor vaatlijden (bv. aderverkalking) in de benen of in de aorta? Of heb je ooit al een hartinfarct gekregen?	Sind (oder waren) Sie wegen Gefäßleiden in den Beinen oder der Aorta in Behandlung? Oder hatten Sie einen Herzinfarkt?	Czy jesteś (lub byłeś wcześniej) leczony z powodu miażdżycy w kończynach dolnych lub aorcie? A może kiedykolwiek miałeś zawał serca?	MI, PCI/PTCA, CABG, peripheral vascular disease
Did you ever suffer from thrombosis or a stroke, with or without serious consequences (CVA or TIA)?	Heb je ooit al een trombose of beroerte gehad, met of zonder nasleep (CVA of TIA)?	Hatten Sie bereits eine Thrombose oder einen Schlaganfall, mit oder ohne Nachwirkungen (CVA oder TIA)?	Czy kiedykolwiek miałeś zakrzepicę, udar mózgu lub przemijający atak niedokrwienny mózgu?	CVA and/or TIA

App-based question in English	App-based question in Dutch	App-based question in German	App-based question in Polish	EHR-based variable definition
Are you (or were you before) treated for hypertension?	Ben je (of was je voorheen) in behandeling voor een te hoge bloeddruk?	Sind (oder waren) Sie wegen Bluthochdruck in Behandlung?	Czy jesteś (lub byłeś wcześniej) leczony na nadciśnienie?	Hypertension and/or hypertensive medication (ACEI, ARB, MRA, CCB, diuretics)
Are you (or were you before) treated for diabetes?	Ben je (of was je voorheen) in behandeling voor diabetes?	Sind (oder waren) Sie wegen Diabetes in Behandlung?	Czy jesteś (lub byłeś wcześniej) leczony na cukrzycę?	DMI, DMII and/or glucose-lowering medication
Do you take anticoagulants?	Neem je een bloedverdunner/anticoagalant?	Nehmen Sie Gerinnungshemmer?	Czy bierzesz antykoagulanty?	NOAC and/or VKA

EHR-based "arrhythmias" variable includes patients who were ever diagnosed with AF, atrial flutter, ectopic beats (PACs and PVCs), and/or supraventricular tachycardia. The EHR-based "heart failure/PE" variable is defined as all patients diagnosed with PE and/or HFrEF (LVEF ≤ 40%), HFmEF (LVEF 41 – 49%), or HFpEF (LVEF ≥ 50%). EHR-based "artery disease" variable incorporates patients who were diagnosed with coronary artery disease (myocardial infarction, PCI/PTCA, or CABG and/or peripheral artery disease. EHR-based "AF" variable includes patients who were ever diagnosed with AF. The EHR-based "TIA/CVA" variable is defined as patients diagnosed with CVA and/or TIA. Patients diagnosed with hypertension and/or treated with hypertensive medication comprise the EHR-based variable "hypertension" and patients diagnosed with DM type 1 or type 2, and/or treated with glucose-lowering medication comprise the EHR-based variable "diabetes". The EHR-based "anticoagulants" variable is defined as patients treated with NOAC and/or VKA.

ACEI, angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; CVA, cerebrovascular accident; DM, diabetes mellitus; EHR, electronic health record; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NOAC, novel oral anticoagulant; PAC, premature atrial contraction; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; PVC, premature ventricular contraction; SVT, supraventricular tachycardia; TIA, transient ischemic attack; VKA, vitamin K antagonist

Table S2. Comparison between patients who had 100% agreement in app-based risk factors and electronic health record-based variables and who had not.

Variable	100% in agreement (n=196)	Not 100% in agreement (n=666)	P-value
Demographics			
Female sex	72 (36.7%)	249 (37.4%)	0.933
Age (years)	63 [56 – 70]	66 [57 – 72]	0.014
BMI (kg/m2)	26.2 [23.8 – 29.0]; *n=186*	27.2 [24.7 – 30.4]; *n=606*	0.002
AF			
AF	186 (94.9%)	598 (89.8%)	0.033
First detected AF	9 (4.8%); *n=186*	64 (10.7%); *n=598*	0.014
Previous cardioversion (electrical and/or pharmaceutical)	80 (40.8%)	301 (45.3%); *n=665*	0.288
Ablation therapy for AF	124 (63.3%)	256 (38.5%); *n=665*	<0.001
Other arrhythmias	76 (45.5%); *n=167*	266 (43.5%); *n=611*	0.661
AF knowledge	153 (78.1%)	412 (61.2%)	<0.001
Cardiovascular diseases			
Coronary artery disease	8 (4.1%)	114 (17%)	<0.001
Peripheral vascular disease	0 (0.0%)	14 (2.1%)	0.049
Diabetes mellitus	9 (4.6%)	74 (11.1%)	0.023
Hypertension	57 (29.1%)	361 (54.2%)	<0.001
Congestive heart failure	14 (7.1%)	102 (15.3%); *n=666*	0.003
Obesity (BMI ≥30kg/m2)	32 (17.2%); *n=186*	160 (26.3%); *n=608*	0.011
Hypercholesterolemia	53 (27.6%); *n=192*	216 (33.0%); *n=655*	0.186

Variable	100% in agreement (n=196)	Not 100% in agreement (n=666)	P-value
Stroke/TIA/pulmonary embolism	14 (7.1%)	72 (10.8%)	0.174
Hemorrhagic events	1 (0.5%)	2 (0.3%)	0.539
Device therapy (PM/CRT/ICD)	3 (1.5%)	38 (5.7%)	0.013
Non-cardiovascular diseases			
Obstructive sleep apnea syndrome	17 (13.8%); *n=123*	58 (12.0%); *n=484*	0.848
Chronic obstructive pulmonary disease	3 (1.5%)	47 (7.1%)	0.003
Chronic kidney disease	5 (2.6%)	34 (5.1%)	0.170
Thromboembolic risk			
CHA_2DS_2-VASc score 0 (if male), 1 (if female)	76 (39.6%); *n=192*	118 (18.2%); *n=649*	<0.001
CHA_2DS_2-VASc score 1 (if male), 2 (if female)	53 (27.6%); *n=192*	164 (25.3%); *n=649*	0.512
CHA_2DS_2-VASc score ≥ 2 (if male), ≥3 (if female)	63 (33%); *n=192*	367 (56.6%); *n=649*	<0.001
Medications			
Oral anticoagulants	141 (71.9%)	562 (84.3%)	<0.001
Antiplatelet drugs	2 (1.0%)	26 (3.9%)	0.063
Beta-blockers	87 (44.4%)	401 (60.2%)	<0.001
Antiarrhythmic drugs	70 (35.7%)	222 (33.3%)	0.546
Diuretics	32 (16.3%)	156 (23.4%)	0.039
Dihydropyridine-CCB	15 (7.7%)	97 (14.6%)	0.011
Non-dihydropyridine-CCB	6 (3.1%)	38 (5.7%)	0.195

Variable	100% in agreement (n=196)	Not 100% in agreement (n=666)	P-value
ACEI	18 (9.2%)	136 (20.4%)	<0.001
ARB	33 (16.8%)	161 (24.2%)	0.032
MRA	6 (3.1%)	35 (5.3%)	0.254
Digoxin	7 (3.6%)	59 (8.9%)	0.014

Number provided after the semicolon indicates the total number of patients available for that variable.
AF, atrial fibrillation; ACEI; angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; PM. pacemaker; TIA, transient ischemic attack

Table S3. Comparison between patients who completed and who did not complete the mobile app-based questionnaire.

Variable	Completed (n=954)	Not completed (n=40)	P-value
Demographics			
Female sex	363 (38.1%)	17 (42.5%)	0.570
Age (years)	65 [57 – 71]	61 [52 – 69]	0.046*
BMI (kg/m2)	27.1 [24.5 – 29.8]; *n=860*	27.4 [24.8 – 31.9]; *n=37*	0.395
AF			
AF	839 (90.2%); *n=930*	33 (84.6%); *n=39*	0.270
First detected AF	75 (9.0%); *n=836*	2 (6.1%); *n=33*	0.761
Previous cardioversion (electrical and/or pharmaceutical)	408 (42.8%); *n=953*	21 (52.5%)	0.255
Ablation therapy for AF	410 (43.0%); *n=953*	12 (30.0%)	0.103
Other arrhythmias	370 (43.8%); *n=844*	15 (42.9%); *n=35*	0.909
AF knowledge	630 (66.1%)	NA	NA
Cardiovascular diseases			
Coronary artery disease	138 (14.7%); *n=936*	4 (10.0%)	0.499
Peripheral vascular disease	16 (1.6%); *n=936*	0 (0.0%)	1.000
Diabetes mellitus	93 (9.9%); *n=936*	6 (15.0%)	0.284
Hypertension	461 (49.3%); *n=935*	24 (60.0%)	0.185
Congestive heart failure	134 (14.3%); *n=936*	7 (17.5%)	0.575
Obesity (BMI ≥30kg/m2)	206 (24.0%); *n=860*	14 (37.8%);*n=37*	0.055
Hypercholesterolemia	300 (32.6%); *n=919*	13 (32.5%)	0.985
Stroke/TIA/pulmonary embolism	91 (9.7%); *n=936*	5 (12.5%)	0.584
Hemorrhagic events	5 (0.5%); *n=937*	0 (0%)	1.000
Device therapy (PM/CRT/ICD)	45 (4.8%); *n=933*	3 (7.5%)	0.442
Non-cardiovascular diseases			
Obstructive sleep apnea syndrome	80 (11.8%); *n=676*	4 (12.9%); *n=31*	0.778
Chronic obstructive pulmonary disease	50 (5.3%); *n=937*	1 (2.5%)	0.717
Chronic kidney disease	46 (4.9%); *n=937*	2 (5.0%)	1.000
Thromboembolic risk			
CHA_2DS_2-VASc score 0 (if male), 1 (if female)	210 (23.0%); *n=912*	13 (33.3%); *n=39*	0.174
CHA_2DS_2-VASc score 1 (if male), 2 (if female)	235 (25.8%); *n=912*	10 (25.6%); *n=39*	1.000
CHA_2DS_2-VASc score ≥ 2 (if male), ≥3 (if female)	467 (51.2%); *n=912*	16 (41.0%); *n=39*	0.253
Medications			
Oral anticoagulants	748 (80.3%); *n=931*	30 (75.0%)	0.407
Antiplatelet drugs	34 (3.7%); *n=931*	2 (5.0%)	0.656
Beta-blockers	535 (57.5%); *n=930*	27 (67.5%)	0.211
Antiarrhythmic drugs	303 (32.6%); *n=930*	16 (40.0%)	0.328
Diuretics	204 (21.9%); *n=930*	10 (25.0%)	0.647

Variable	Completed (n=954)	Not completed (n=40)	P-value
Dihydropyridine-CCB	117 (12.6%); *n=930*	5 (12.5%)	0.988
Non-dihydropyridine-CCB	53 (5.7%); *n=930*	3 (7.5%)	0.498
ACEI	171 (18.4%); *n=930*	9 (22.5%)	0.512
ARB	214 (23.0%); *n=930*	12 (30.0%)	0.306
MRA	49 (5.3%); *n=930*	4 (10.0%)	0.270
Digoxin	72 (7.7%); *n=930*	1 (2.5%)	0.356

Number provided after the semicolon indicates the total number of patients available for that variable.
Abbreviations: see Table S2.

Table S4. Predictors of 100% app-electronic health record agreement.

Table S4. Predictors of 100% app-electronic health record agreement.

Parameter	OR	95% CI	*P*-value
Previous AF ablation therapy	2.40	1.64-3.51	<0.001
AF knowledge	2.30	1.51-3.52	<0.001
Coronary artery disease	0.28	0.13-0.61	<0.001
Hypertension	0.41	0.28-0.61	<0.001
Beta-blocker therapy	0.64	0.44-0.94	0.023

AF, atrial fibrillation; CI, confidence interval; OR, odds ratio

Table S5. Demographics and 10-item questionnaire compared to electronic health record-based results per country.

Variable	Electronic health record-based	App-based	P-value
The Netherlands (n=630)			
Demographics			
Female sex	249 (39.5%)	250 (39.7%)	1.000
Age (years)	67 [59 – 72]	67 [59 – 72]	0.050
Questionnaire parameters			
Did you know atrial fibrillation increases the risk of stroke?	NA	329 (52.3%); *n=629*	NA
Do you have a pacemaker?	14 (2.3%); *n=611*	19 (3.1%); *n=611*	0.063
Were you ever diagnosed with cardiac arrhythmias?	601 (98.7%); *n=609*	524 (86.0%); *n=609*	<0.001
Are you (or were you before) diagnosed with or treated for atrial fibrillation or AF?	557 (91.2%); *n=611*	352 (57.6%); *n=611*	<0.001
Are you (or were you before) treated for heart failure or pulmonary edema?	89 (14.6%); *n=611*	199 (32.6%); *n=611*	<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?	89 (14.5%); *n=613*	77 (12.6%); *n=613*	0.175
Did you ever suffer from thrombosis or a stroke, with or without serious consequences (CVA or TIA)?	68 (11.1%); *n=612*	86 (14.1%); *n=612*	0.015
Are you (or were you before) treated for hypertension?	288 (47.0%); *n=613*	246 (40.1%); *n=613*	<0.001
Are you (or were you before) treated for diabetes?	65 (10.6%); *n=613*	72 (11.7%); *n=613*	0.311
Do you take anticoagulants?	502 (82.2%); *n=611*	505 (82.7%); *n=611*	0.720
Thromboembolic risk			
CHA_2DS_2-VASc score 0 (if male), 1 (if female)	119 (19.7%); *n=603*	122 (20.2%); *n=603*	0.691
CHA_2DS_2-VASc score 1 (if male), 2 (if female)	160 (26.5%); *n=603*	144 (23.9%); *n=603*	0.176
CHA_2DS_2-VASc score ≥ 2 (if male), ≥3 (if female)	324 (53.7%); *n=603*	337 (55.9%); *n=603*	0.205
Germany (n=191)			
Demographics			
Female sex	71 (37.2%)	73 (38.2%)	0.625
Age (years)	65 [53 – 71]; *n=132*	64 [54 – 71]; *n=132*	0.937
Questionnaire parameters			
Did you know atrial fibrillation increases the risk of stroke?	NA	177 (92.7%)	NA
Do you have a pacemaker?	7 (3.7%); *n=190*	12 (6.3%); *n=190*	0.063
Were you ever diagnosed with cardiac arrhythmias?	174 (92.6%); *n=188*	181 (96.3%); *n=188*	0.143
Are you (or were you before) diagnosed with or treated for atrial fibrillation or AF?	156 (83.4%); *n=187*	167 (89.3%); *n=187*	0.013

Variable	Electronic health record-based	App-based	P-value
Are you (or were you before) treated for heart failure or pulmonary edema?	32 (16.8%); *n=190*	13 (6.8%); *n=190*	0.004
Are you (or were you before) treated for vascular disease in your legs or aorta? Or did you ever suffer from a heart attack?	41 (21.6%); *n=190*	37 (19.5%); *n=190*	0.585
Did you ever suffer from thrombosis or a stroke, with or without serious consequences (CVA or TIA)?	12 (6.3%); *n=190*	100 (52.6%); *n=190*	<0.001
Are you (or were you before) treated for hypertension?	105 (55.6%); *n=189*	20 (10.6%); *n=189*	<0.001
Are you (or were you before) treated for diabetes?	19 (10.0%); *n=190*	27 (14.2%); *n=190*	0.268
Do you take anticoagulants?	133 (70.4%); *n=189*	142 (75.1%); *n=189*	0.049
Thromboembolic risk			
CHA_2DS_2-VASc score 0 (if male), 1 (if female)	40 (30.8%); *n=130*	38 (29.2%); *n=130*	0.527
CHA_2DS_2-VASc score 1 (if male), 2 (if female)	21 (16.2%); *n=130*	13 (10.0%); *n=130*	0.088
CHA_2DS_2-VASc score ≥ 2 (if male), ≥3 (if female)	69 (79.8%); *n=130*	79 (60.1%); *n=130*	0.033
Austria (n=79)			
Demographics			
Female sex	24 (30.4%)	27 (34.2%)	0.453
Age (years)	58 [51 – 63]	58 [50 – 64]	0.670

Variable	Electronic health record-based	App-based	P-value
Questionnaire parameters			
Did you know atrial fibrillation increases the risk of stroke?	NA	72 (91.1%)	NA
Do you have a pacemaker?	1 (1.3%); *n=77*	4 (5.2%); *n=77*	0.250
Were you ever diagnosed with cardiac arrhythmias?	76 (98.7%); *n=77*	71 (92.2%); *n=77*	0.125
Are you (or were you before) diagnosed with or treated for atrial fibrillation or AF?	72 (93.5%); *n=77*	72 (93.5%); *n=77*	1.000
Are you (or were you before) treated for heart failure or pulmonary edema?	7 (8.9%)	4 (5.1%)	0.508
Are you (or were you before) treated for vascular disease in your legs or aorta? Or did you ever suffer from a heart attack?	7 (8.9%)	4 (5.1%)	0.375
Did you ever suffer from thrombosis or a stroke, with or without serious consequences (CVA or TIA)?	2 (2.5%)	29 (36.7%)	<0.001
Are you (or were you before) treated for hypertension?	43 (54.4%)	1 (1.3%)	<0.001
Are you (or were you before) treated for diabetes?	4 (5.1%)	8 (10.1%)	0.344
Do you take anticoagulants?	72 (91.1%)	61 (77.2%)	0.027
Thromboembolic risk			
CHA_2DS_2-VASc score 0 (if male), 1 (if female)	23 (60.0%); *n=69*	30 (43.5%); *n=69*	0.090

Variable	Electronic health record-based	App-based	P-value
CHA_2DS_2-VASc score 1 (if male), 2 (if female)	25 (36.2%) *n=69*	12 (17.4%); *n=69*	0.016
CHA_2DS_2-VASc score ≥ 2 (if male), ≥3 (if female)	21 (30.4%); *n=69*	27 (39.1%); *n=69*	0.239
Poland (n=30)			
Demographics			
Female sex	13 (43.3%)	13 (43.3%)	1.000
Age (years)	60 [50 – 68]	60 [50 – 68]	0.317
Questionnaire parameters			
Did you know atrial fibrillation increases the risk of stroke?	NA	28 (93.3%)	NA
Do you have a pacemaker?	1 (3.3%)	1 (3.3%)	1.000
Were you ever diagnosed with cardiac arrhythmias?	30 (100.0%)	30 (100.0%)	1.000
Are you (or were you before) diagnosed with or treated for atrial fibrillation or AF?	30 (100.0%)	29 (96.7%)	1.000
Are you (or were you before) treated for heart failure or pulmonary edema?	2 (6.7%)	6 (20.0%)	0.219
Are you (or were you before) treated for vascular disease in your legs or aorta? Or did you ever suffer from a heart attack?	7 (23.3%)	5 (16.7%)	0.687
Did you ever suffer from thrombosis or a stroke, with or without serious consequences (CVA or TIA)?	0 (0.0%)	20 (66.7%)	<0.001

Variable	Electronic health record-based	App-based	P-value
Are you (or were you before) treated for hypertension?	20 (66.7%)	5 (16.7%)	<0.001
Are you (or were you before) treated for diabetes?	3 (10.0%)	1 (3.3%)	0.625
Do you take anticoagulants?	29 (100.0%); *n=29*	23 (79.3%); *n=29*	0.008
Thromboembolic risk			
CHA_2DS_2-VASc score 0 (if male), 1 (if female)	7 (23.3%)	5 (16.7%)	0.778
CHA_2DS_2-VASc score 1 (if male), 2 (if female)	9 (30.0%)	4 (13.3%)	0.132
CHA_2DS_2-VASc score ≥ 2 (if male), ≥3 (if female)	14 (46.7%)	21 (70.0%)	0.035
United Kingdom (n=24)			
Demographics			
Female sex	6 (25.0%)	6 (25.0%)	1.000
Age (years)	64 [55 – 71]	64 [55 – 71]	0.317
Questionnaire parameters			
Did you know atrial fibrillation increases the risk of stroke?	NA	24 (100%)	NA
Do you have a pacemaker?	1 (4.2%)	2 (8.3%)	1.000
Were you ever diagnosed with cardiac arrhythmias?	24 (100.0%)	22 (91.7%)	0.687

Variable	Electronic health record-based	App-based	P-value
Are you (or were you before) diagnosed with or treated for atrial fibrillation or AF?	23 (95.8%)	24 (100.0%)	1.000
Are you (or were you before) treated for heart failure or pulmonary edema?	4 (16.7%)	2 (8.3%)	0.687
Are you (or were you before) treated for vascular disease in your legs or aorta? Or did you ever suffer from a heart attack?	3 (12.5%)	3 (12.5%)	1.000
Did you ever suffer from thrombosis or a stroke, with or without serious consequences (CVA or TIA)?	1 (4.2%)	7 (29.2%)	0.031
Are you (or were you before) treated for hypertension?	5 (20.8%)	2 (8.3%)	0.453
Are you (or were you before) treated for diabetes?	2 (8.3%)	2 (8.3%)	1.000
Do you take anticoagulants?	12 (52.2%); *n=23*	12 (52.2%); *n=23*	1.000
Thromboembolic risk			
CHA_2DS_2VASc-score 0 (if male), 1 (if female)	8 (38.1%); *n=21*	9 (42.9%); *n=21*	0.564
CHA_2DS_2VASc-score 1 (if male), 2 (if female)	5 (23.9%); *n=21*	3 (14.3%); *n=21*	0.414
CHA_2DS_2VASc-score ≥ 2 (if male), ≥3 (if female)	8 (38.1%); *n=21*	9 (42.9%); *n=21*	0.564

Number provided after the semicolon indicates the total number of patients available for that variable.
Abbreviations: see Table S1.

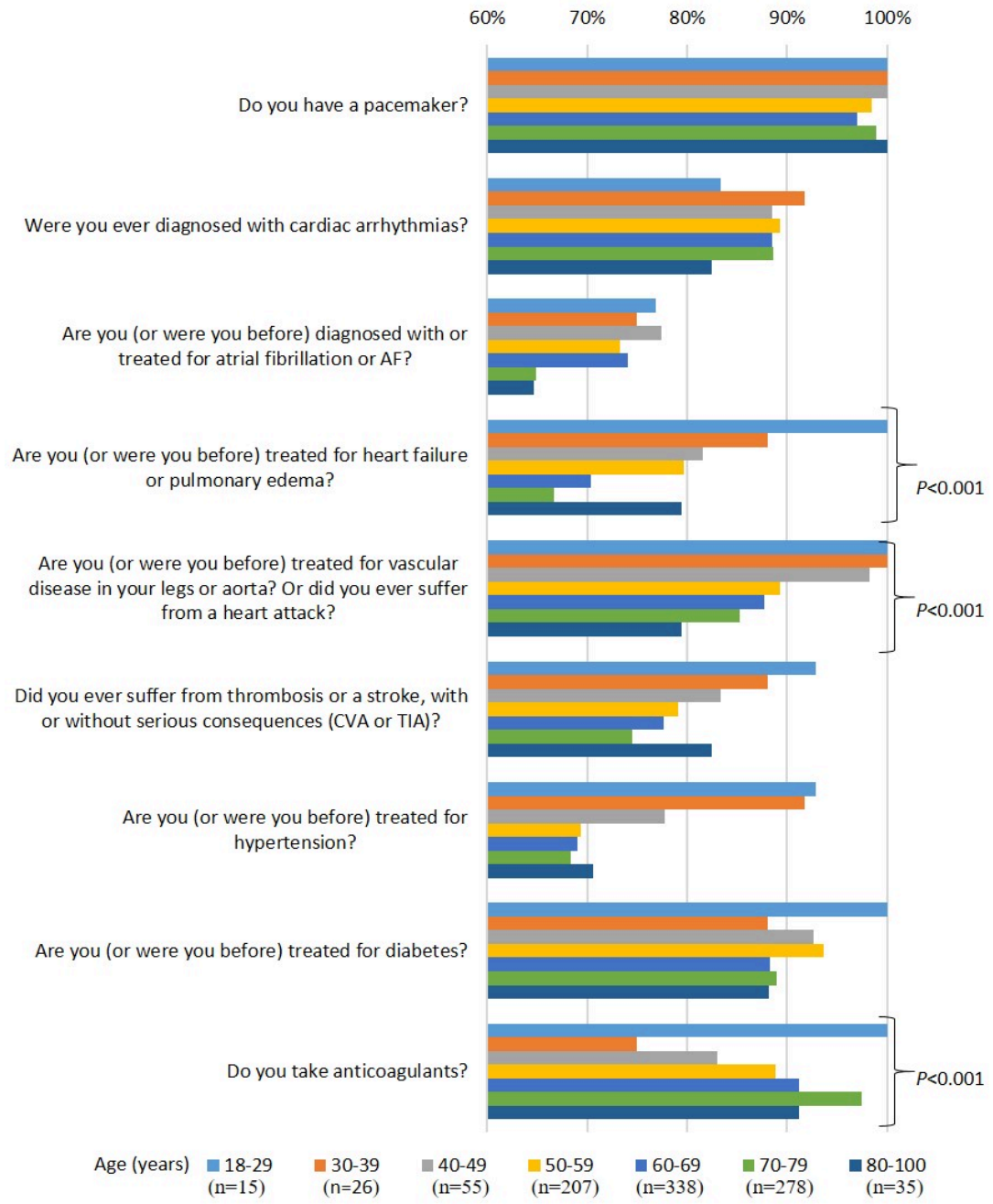

Figure S1. App-based questions in agreement with electronic health records depending on age group. *Abbreviations: see Table S1.*

Figure S2. Accuracy and agreement of app-based vs electronic health record-based choice to oral anticoagulation in patients with atrial fibrillation (n=765[1]).

The accuracy of app-based and EHR-based choice to OAC should be taken with caution, as it's based only on thromboembolic score without consideration renal function, bleeding risk or valvular heart disease.

[1] 3 patients with CHA_2DS_2-VASc ≥2 (if male) and ≥3 (if female), without information on anticoagulation

[2] App-based overtreatment in 13% of patients and undertreatment in 4.3% of patients

[3] EHR-based overtreatment in 11% of patients and undertreatment in 3.5% of patients

[4] EHR-based correct

[5] EHR-based overtreatment in 3.6% of patients and undertreatment in 1.1% of patients

EHR, electronic health record; OAC, oral anticoagulation

App-based_correct: OAC treatment (based on EHR) in patients with CHA_2DS_2-VASc ≥1 (if male) and ≥2 (if female), based on app

EHR-based_correct: OAC treatment (based on EHR) in patients with CHA_2DS_2-VASc ≥1 (if male) and ≥2 (if female), based on HER

App-based_undertreatment: no OAC treatment (based on EHR) in patients with CHA_2DS_2-VASc ≥1 (if male) and ≥2 (if female) based on app

EHR-based_undertreatment: no OAC treatment (based on EHR) in patients with CHA_2DS_2-VASc ≥1 (if male) and ≥2 (if female) based on HER

App-based_overtreatment: OAC treatment (based on EHR) in patients with CHA_2DS_2-VASc 0 (if male) and 1 (if female) based on app

EHR-based_overtreatment: OAC treatment (based on EHR) in patients with CHA_2DS_2-VASc 0 (if male) and 1 (if female) based on EHR

CHAPTER 12

Mobile app-based symptom-rhythm correlation assessment in patients with persistent atrial fibrillation

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Abstract

Background: The assessment of symptom-rhythm correlation (SRC) in patients with persistent atrial fibrillation (AF) is challenging. Therefore, we performed a novel mobile app-based approach to assess SRC in persistent AF.

Methods: Consecutive persistent AF patients planned for electrical cardioversion (ECV) used a mobile app to record a 60-s photoplethysmogram (PPG) and report symptoms once daily and in case of symptoms for four weeks prior and three weeks after ECV. Within each patient, SRC was quantified by the SRC-index defined as the sum of symptomatic AF recordings and asymptomatic non-AF recordings divided by the sum of all recordings.

Results: Of 88 patients (33% women, age 68 ± 9 years) included, 78% reported any symptoms during recordings. The overall SRC-index was 0.61 (0.44-0.79). The study population was divided into SRC-index tertiles: low (<0.47), medium (0.47-0.73) and high (≥0.73). Patients within the low (vs high) SRC-index tertile had more often heart failure and diabetes mellitus (both 24.1% vs 6.9%). Extrasystoles occurred in 19% of all symptomatic non-AF PPG recordings. Within each patient, PPG recordings with the highest (vs lowest) tertile of pulse rates conferred an increased risk for symptomatic AF recordings (odds ratio [OR] 1.26, 95% coincidence interval [CI] 1.04-1.52) and symptomatic non-AF recordings (OR 2.93, 95% CI 2.16-3.97). Pulse variability was not associated with reported symptoms.

Conclusions: In patients with persistent AF, SRC is relatively low. Pulse rate is the main determinant of reported symptoms. Further studies are required to verify whether integrating mobile app-based SRC assessment in current workflows can improve AF management.

Keywords: Atrial fibrillation; Electrical cardioversion; Mobile health; Symptom-rhythm correlation; Telemonitoring.

Introduction

According to current atrial fibrillation (AF) guideline recommendations, AF management should focus on the comprehensive ABC (AF Better Care) pathway incorporating anticoagulation therapy, better symptom management and comprehensive comorbidity treatment [1], [2], [3]. To improve symptom control and quality of life, the identification of AF-related symptoms is important as it guides personalized and joint decision making on either rate- or rhythm control. Particularly in patients with persistent AF (defined as continuously sustained AF beyond seven days, including episodes terminated by cardioversion after ≥7 days [1]) it is difficult to determine the association between patient self-reported symptoms and the underlying heart rhythm (symptom-rhythm correlation [SRC]) [4,5]. Differentiating between symptoms caused by AF (specific AF symptoms) and those caused by other underlying cardiovascular or non-cardiovascular conditions or risk factors (non-specific symptoms in AF) is often challenging, and no standardized strategy to assess SRC in AF patients is available [5]. Previously, we showed that symptom assessment around electrical cardioversion (ECV), once before ECV and once within 1-month follow-up, rarely identifies an SRC in persistent AF patients and often suggests changes in symptom pattern irrespective of changes seen in heart rhythm [6]. Mobile app-based simultaneous symptom and rhythm monitoring may improve SRC assessment but has not been described nor investigated before.

We hereby introduce a novel mobile app-based simultaneous symptom and rhythm monitoring approach to assess SRC in patients with persistent AF, which has been developed within the TeleCheck-AF project [7]. We aimed to 1) evaluate SRC and 2) establish related covariates for SRC in patients with persistent AF.

Methods

Project design

This is a substudy of the TeleCheck-AF project performed at the Maastricht University Medical Centre+ (MUMC+), Maastricht, The Netherlands, focusing on persistent AF patients monitored and managed around planned ECV. The TeleCheck-AF project is described in detail elsewhere [7]. Within this project, a uniform mobile health (mHealth) approach consisting of the on-demand use of a photoplethysmography (PPG)-based mobile app for remote rate and rhythm monitoring was introduced. This approach was set up around specific clinical scenarios and integrated into comprehensive AF management in several centres in Europe [8]. The TeleCheck-AF project was performed in compliance with the Declaration of Helsinki and approved by the Institutional Review Board at the MUMC+ (METC2020–1337).

Study population

From April 2020 to February 2021, consecutive patients (≥18 years) with persistent AF scheduled for ECV in the MUMC+ were included. Individuals were excluded if they did not have a smartphone, could not operate the mobile application system after instructions or had an implanted pacemaker.

Study procedures

Patients were provided with a Conformité Européenne (CE)-marked, on-demand mobile phone application monitoring heart rate and rhythm and symptoms (FibriCheck®, Qompium, Hasselt, Belgium). Access to this PPG-based application was prescribed in the form of a temporary QR code, and a short instruction for heart rate and rhythm measurements was provided. A case coordinator was responsible for sending the code and instructing the patients carefully on how to use the application. Within 24 h of sending the code, the case coordinator also evaluated whether the patients could activate the app and perform the measurements. Once the app was activated by the

QR-code, the PPG recordings and corresponding symptom statuses were instantly synchronized to a secured and certified cloud (www.fibricheck.com), to which the treating physician and research team had access.

Patients were instructed to record a 60-s PPG through their smartphone's built-in camera once daily and additionally when experiencing symptoms for four weeks preceding ECV and three weeks following ECV. After completing a recording, patients were instructed to specify in the mobile app if they experienced any of the following symptoms during the preceding PPG measurement: no symptoms, palpitations, chest pain, dyspnea, confusion, light-headedness, fatigue, and/or others. The app provided the patients with regular reminders to assess their heart rate/rhythm, to actively report the presence/absence of symptoms via pop-up notifications, and with precise instructions on how to improve the quality of measurements in case of insufficient signal quality [7].

Data collection

Baseline clinical characteristics (demographics and medical history) were retrieved from patients' medical records. Heart rhythm status and corresponding symptom status of each PPG-recording were retrieved from the secured and certified cloud. The raw waveforms of the PPG recordings were extracted from the FibriCheck cloud in European Data Format (EDF) format. The remaining data points were exported in comma-separated values (CSV) format.

Data analysis

Symptom-rhythm correlation assessment

Patients could report more than one symptom experienced during the PPG recording. For SRC assessment, the predominant symptom per measurement chosen from the symptoms list was included in the analysis. The chronologic order of the annotated symptoms per recording was used to determine the predominant symptom.

The PPG recordings were interpreted by the FibriCheck® algorithm as follows: 1) regular rhythm, 2) warning, 3) possible AF ('AF-rhythm'), and 4) insufficient quality. 'Regular rhythm' was defined as a recording presenting sinus rhythm. A measurement labelled as 'warning' implied that the algorithm detected some abnormalities that could not be classified as AF (e.g. extrasystoles, bradycardia or tachycardia), and there was no interference. For this study, regular and warning rhythms were further considered as 'non-AF rhythm'. An 'insufficient quality' recording indicated that too much interference was detected to perform a detailed rhythm analysis. The treating physician and research team had access to the raw data of the PPG signals together with the RR-tachogram and Poincaré plot. Additionally, certified technicians reviewed all algorithm analysis-based irregular PPG recordings, and the results were integrated into the secured cloud. This could have further increased the accuracy to detect AF episodes [9].

For this study, only measurements classified as non-AF rhythm (non-AF PPG recordings including regular and warning rhythms) and AF-rhythm (AF PPG recordings) were considered in the SRC assessment. AF recordings with the presence of self-reported symptoms were defined as symptomatic AF PPG recordings, AF recordings without symptoms as asymptomatic AF PPG recordings, non-AF recordings with the presence of symptoms as symptomatic non-AF PPG recordings, and non-AF recordings without self-reported symptoms as asymptomatic non-AF PPG recordings (Fig. 1).

We assessed the SRC by considering the association between self-reported symptoms and rhythm status. The SRC per patient was quantified by the SRC-index, defined as the number of symptomatic AF recordings and asymptomatic non-AF recordings divided by all recordings regardless of symptom status (Fig. 1).

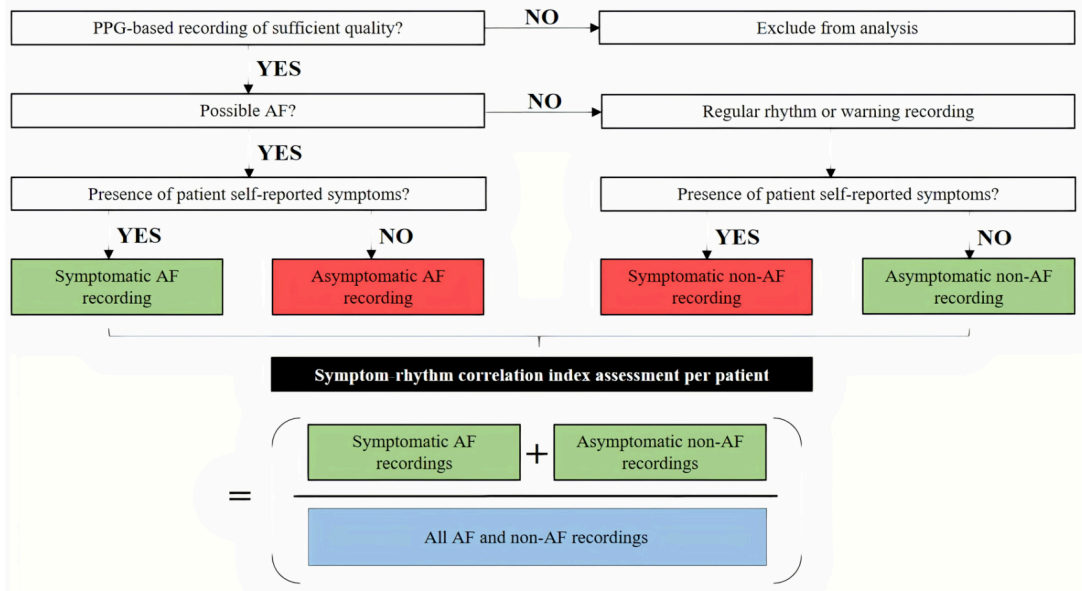

Figure 1. Flow chart symptom-rhythm correlation index assessment.
AF, atrial fibrillation; PPG, photoplethysmography.

Pulse rate variability assessment

60-s PPG recordings were processed in Matlab® (The MathWorks, USA) for pulse rate variability assessment. Baseline wander was removed using a high-pass filter with a cutoff frequency of 0.5 Hz. Motion artifacts were automatically identified using a 10-s sliding window, in which the peaks were detected and assessed for outliers. Segments containing artifacts were rejected from the analysis. From the time series of pulse intervals, we calculated the mean pulse interval, the standard deviation (SD) of pulse intervals, the root-mean-square of successive pulse interval differences (RMSSD) and the standard deviation of successive pulse interval differences (SDSD) as these are the most common parameters used for pulse rate variability assessment [10].

Patient compliance and motivation assessment

Patient compliance and motivation were calculated to assess adherence to the study protocol. Compliance was defined as the number of PPG measurements per number of expected PPG measurements (at least one daily) over the entire study period (from three weeks before ECV until four weeks after ECV). Motivation was defined as the number of days in which the expected number of PPG measurements (at least one daily) were performed per number of days over the entire study period.

Statistical analyses

All continuous variables were tested for normality with the Shapiro-Wilk test. Variables with normal distribution were expressed as mean ± SD. Nonparametric variables were presented as median [interquartile range (IQR)] and categorical variables as numbers (n) with percentages (%). Differences in continuous parameters were compared using one-way ANOVA and nonparametric Kruskal-Wallis test, as applicable. For the comparison of categorical data, the Pearson's chi-squared tests were used. A binary logistic generalized estimating equation was used to develop a model for the dichotomous symptom outcome (odds ratio [OR] for symptomatic PPG recordings and OR for asymptomatic PPG recordings with their 95% confidence interval [95% CI]) using the within-patient

standardized pulse rate and pulse rate variability data in AF and non-AF. Statistical significance was assumed at a 5% level. For database management and statistical analysis, we used IBM SPSS Version 25 (IBM Corporation, Somers, New York, USA).

Results

Data from 88 consecutive persistent AF patients (age 68 ± 9 years, 33.0% women) referred for ECV in the MUMC+ were analysed (Table 1). Of these patients, 11.4% suffered from diabetes mellitus, 48.9% from hypertension and 25.0% from chronic heart failure. The prevalence of obesity (body mass index [BMI] ≥30 kg/m2 was 33.3% and a history of myocardial infarction was present in 11.4%. In 60.2% of patients, thromboembolic risk was increased (CHA2DS2-VASc score ≥ 2 in men or ≥ 3 in women), and all were anticoagulated. Antiarrhythmic drugs were used in 23.9% of patients, 69.3% received beta-blockers, 7.0% non-dihydropyridine calcium channel blockers and 25.0% digoxin. The overall median patient compliance and motivation to use the mobile app-based simultaneous symptom and rhythm monitoring approach were high, with 164% and 92%, respectively.

Rhythm and symptom variability

ECV was performed in 77 patients (87.5%) among all included patients. In 11 patients (12.5%), the scheduled ECV was cancelled as these converted to sinus rhythm spontaneously (of these, nine patients had a paroxysmal AF pattern, and two patients were in stable sinus rhythm throughout the remaining monitoring period). ECV was successful in 74 patients (96.1%) and unsuccessful in three patients (3.9%). Within three weeks after ECV, 48 out of 77 patients (62.3%) had PPG-documented recurrence of AF.

In total, 6359 separate PPG recordings were analysed (mean number of PPG recordings per patient 72 ± 43; mean number of monitoring days per patient 46 ± 7; mean number of recordings per day per patient 1.6 ± 0.91). Of these PPG recordings, 1964 (31%) were symptomatic AF recordings, 1843 (29%) asymptomatic non-AF recordings, 1993 (31%) asymptomatic AF recordings and 559 (9%) symptomatic non-AF recordings. The majority of patients (78%) reported symptoms during their PPG recordings and 22% of patients were completely asymptomatic. Fatigue (30%) was the most common reported symptom, followed by palpitations (17%), chest pain (9%), shortness of breath (8%), other (7%), light-headed (5%) and several (3%). Among all patients with PPG-documented AF (n = 86), 77% reported symptoms and 23% were completely asymptomatic during AF PPG recordings. In AF PPG recordings, fatigue (30%) was the most common reported symptom, followed by palpitations (19%), shortness of breath (8%), other (8%), chest pain (7%), light-headed (2%) and several (2%). Of all patients with PPG-documented non-AF (n = 79), nearly half of patients (48%) reported symptoms and 52% were completely asymptomatic during non-AF PPG recordings. In non-AF PPG recordings, fatigue (16%) was the most common reported symptom, followed by palpitations (10%), light-headed (6%), several (4%), chest pain (4%), shortness of breath (4%) and other (4%). In the 66 patients who reported any symptoms during AF PPG recordings, the mean percentage of symptomatic AF PPG recordings per patient was 56%. In the 40 patients who reported any symptoms during non-AF PPG recordings, the mean percentage of symptomatic non-AF PPG recordings per patient was 43%. There was no difference in patient-reported predominant symptom type during non-AF and AF PPG recordings per patient based on comorbidities, such as chronic heart failure and diabetes mellitus, of which symptoms often overlap with those associated with AF (Supplementary Table S1).

Symptom burden (defined as the proportion of symptomatic PPG recordings per all PPG recordings) was 42% prior to ECV compared to 31% after ECV. Symptomatic AF PPG recordings comprised 59% (n = 66) of all AF PPG recordings preceding ECV and 57% (n = 41) following ECV,

Table 1. Clinical characteristics of included patients, divided in tertiles according to symptom-rhythm correlation index.

Variable	Study group (*n* = 88)	Low [<0.47] SRC-index (*n* = 29)	Moderate [0.47–0.73] SRC-index(*n* = 30)	High [≥0.73] SRC-index (*n* = 29)	*P*-value
Demographics					
Age (years) – mean ± SD	68 ± 9	68 ± 10	68 ± 9	68 ± 7	0.918
Female sex	29 (33.0%)	8 (27.6%)	10 (33.3%)	11 (37.9%)	0.703
BMI (kg/m2) – mean ± SD	28.2 ± 4.7; *n* = 87	27.9 ± 4.7; n = 29	28.8 ± 4.5; n = 30	27.9 ± 4.8; *n* = 28	0.686
AF					
First-detected AF	19 (21.6%)	7 (24.1%)	2 (6.7%)	10 (34.5%)*	0.032
Current AF episode duration >6 months**	53 (91.4%); *n* = 58	17 (85.0%); *n* = 20	24 (96.0%); *n* = 25	12 (92.3%); *n* = 13	0.422
Current AF episode duration >12 months**	45 (77.6%); n = 58	13 (65.0%); n = 20	21 (84.0%); n = 25	11 (84.6%); n = 13	0.249
Previous CV (electrical and/or pharmacological)**	41 (59.4%); *n* = 69	14 (63.6%); *n* = 22	20 (71.4%); n = 28	7 (36.8%); *n* = 19	0.054
Ablation therapy for AF**	17 (24.6%); n = 69	4 (18.2%); n = 22	8 (28.6%); n = 28	5 (26.3%); n = 19	0.685
Cardiovascular diseases					
Myocardial infarction	10 (11.4%)	3 (10.3%)	1 (3.3%)	6 (20.7%)	0.108
PCI/PTCA	9 (10.2%)	2 (6.9%)	2 (6.7%)	5 (17.2%)	0.314
CABG	3 (3.4%)	2 (6.9%)	1 (3.3%)	0 (0.0%)	0.351
Peripheral vascular disease	1 (1.1%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0.376
Diabetes mellitus	10 (11.4%)	7 (24.1%)	1 (3.3%)	2 (6.9%)	0.027

Variable	Study group (*n* = 88)	Low [<0.47] SRC-index (*n* = 29)	Moderate [0.47–0.73] SRC-index(*n* = 30)	High [≥0.73] SRC-index (*n* = 29)	*P*-value
Hypertension	43 (48.9%)	15 (51.7%)	13 (43.3%)	15 (51.7%)	0.757
Chronic heart failure	22 (25.0%)	7 (24.1%)	13 (43.3%)	2 (6.9%)*	0.005
Obesity (BMI ≥30 kg/m2)	29 (33.3%); n = 87	9 (31.0%); n = 29	10 (33.3%); n = 30	10 (35.7%); n = 28	0.932
Stroke/TIA/pulmonary embolism	5 (5.7%)	0 (0.0%)	3 (10.0%)	2 (6.9%)	0.238
Device therapy (PM/CRT/ICD)	5 (5.7%)	0 (0.0%)	2 (6.7%)	3 (10.3%)	0.226
Transthoracic echocardiographic parameters					
LVEF (%) – median (IQR)	52 (45–59); *n* = 77	55 (45–61); *n* = 26	50 (45–55); *n* = 27	52 (43–59); *n* = 24	0.374
Left atrial volume – mean ± SD	96 ± 30; *n* = 76	102 ± 27; n = 25	92 ± 32; n = 28	95 ± 30; *n* = 23	0.448
Valvular heart disease	6 (7.1%); *n* = 84	1 (3.7%); n = 27	3 (10.0%); n = 30	2 (7.4%); n = 27	0.653
Thromboembolic risk					
CHA_2DS_2-VASc score = 0 (if male), = 1 (if women)	14 (15.9%)	5 (17.2%)	5 (16.7%)	4 (13.8%)	0.928
CHA_2DS_2-VASc score = 1 (if male), = 2 (if women)	21 (23.9%)	7 (24.1%)	6 (20.0%)	8 (27.6%)	0.791
CHA_2DS_2-VASc score ≥ 2 (if male), ≥3 (if women)	53 (60.2%)	17 (58.6%)	19 (63.3%)	17 (58.6%)	0.912
Medications					
Oral anticoagulants	88 (100.0%)	29 (100.0%)	30 (100.0%)	29 (100.0%)	NA
Antiplatelet drugs	2 (2.3%)	0 (0.0%)	0 (0.0%)	2 (6.9%)	0.125
Beta-blockers	61 (69.3%)	21 (72.4%)	18 (60.0%)	22 (75.9%)	0.379
Antiarrhythmic drugs	21 (23.9%)	4 (13.8%)	12 (40.0%)	5 (17.2%)	0.037
Diuretics	29 (33.0%)	11 (37.9%)	9 (30.0%)	9 (31.0%)	0.782
Dihydropyridine-CCB	17 (19.8%)	8 (28.6%)	2 (6.9%)	7 (24.1%)	0.093
Non-dihydropyridine-CCB	6 (7.0%)	1 (3.6%)	3 (10.3%)	2 (6.9%)	0.604
ACEI	24 (27.3%)	7 (24.1%)	10 (33.3%)	7 (24.1%)	0.656
ARB	18 (20.5%)	5 (17.2%)	7 (23.3%)	6 (20.7%)	0.845
MRA	2 (2.3%)	0 (0.0%)	1 (3.3%)	1 (3.4%)	0.604
Digoxin	22 (25.0%)	11 (37.9%)	5 (16.7%)	6 (20.7%)	0.136

*The number provided after the semicolon indicates the total number of patients available for that variable. Values are depicted as the number of patients (n) with percentages unless indicated otherwise. * P-value ≤0.05 for comparison between moderate vs high symptom-rhythm correlation. The Bonferroni correction was applied to address the multiple comparison issues.** Results after excluding patients with first-detected AF.*

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass surgery; CCB, calcium channel blockers; CRT, cardiac resynchronization therapy; CV, cardioversion; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LVEF, left ventriuclar ejection fraction; MRA, mineralocorticoid receptor antagonists; NA, not applicable; PCI, percutaneous coronary intervention; PM, pacemaker; PTCA, percutaneous transluminal coronary angioplasty; SD, standard deviation; TIA, transient ischemic attack.

while asymptomatic non-AF PPG recordings made up 82% (n = 73) of all non-AF PPG recordings before ECV and 82% (n = 73) after ECV. Preceding and following ECV, the most common predominant self-reported symptom was fatigue, comprising 38% and 33% of symptom measurements, respectively. About 67% of patients reported ≥2 types of symptoms pre-ECV, and 64% did this post-ECV. Interestingly, intra-individually variable symptom patterns, defined as changes in predominant self-reported symptoms within patients around ECV, were present in 37 patients (42%) (Supplementary Fig. S1).

Symptom-rhythm correlation

The proportion of symptomatic AF PPG recordings for all AF PPG recordings was low (40% [5–83%]), whereas the proportion of asymptomatic non-AF PPG recordings per all non-AF PPG recordings was high (92% [67–100%]). Therefore, mainly driven by a large number of asymptomatic AF PPG recordings, the overall SRC-index was 0.61 (0.44–0.79).

We grouped patients into tertiles using the SRC-index; in low (<0.47), moderate (0.47–0.73) and high (≥0.73) (Table 1). Detailed distribution of patients regarding the SRC-index is provided in Supplementary Fig. S2. Patients in the highest SRC-index tertile more often had first-detected AF (34.5% vs 6.7% of patients in moderate tertile vs 24.1% of patients in low tertile, P = 0.032) and were less often diagnosed with chronic heart failure (6.9% vs 43.3% vs 24.1%, respectively, P = 0.005). Moreover, patients in the low (vs moderate and high) SRC-index tertile were more frequently diagnosed with diabetes mellitus (24.1% vs 3.3% and 6.9%, P = 0.027) and less often received antiarrhythmic drugs (13.8% vs 40.0% and 17.2%, P = 0.037). No statistically significant differences in duration of current AF episode, the use of rate control drugs such as beta-blockers with the highest contribution of metoprolol, as well as in echocardiography-derived cardiac dimensions or functional parameters were observed between the low, moderate and high SRC-index group. Although 24.6% of patients had a previous AF ablation, what could influence the symptom burden as patients with previous AF ablation are more prone to have asymptomatic AF events and therefore have lower SRC-index as compared to patients without previous AF ablation [11], we found no statistically significant difference between the low, moderate and high SRC-index group according to prevalence of previous AF ablation as well as between patients with and without previous AF ablation according to type of recordings (Supplementary Table S2).

SRC in the pre-ECV and post-ECV period were compared. After exclusion of the PPG recordings performed at the day of ECV, the overall SRC-index in the pre-ECV period (n = 3199 recordings) was 0.49 (0.03–0.88), whereas the overall SRC-index in the post-ECV period (n = 2983 recordings) was 0.73 (0.40–0.92). In additional analysis restricted to post-ECV period, we divided patients into tertiles using the post-ECV SRC-index; in low (<0.55), moderate (0.55–0.88) and high (≥0.88) SRC-index (Supplementary Table S3). Within three weeks after ECV, 48 out of 77 patients (62.3%) had PPG-documented recurrence of AF. In patients with AF recurrence, median pulse rate per patient in AF prior and after ECV was 78 bpm (73–85) and 76 bpm (72–83), respectively, P = 0.008. There was no statistically significant difference between the low, moderate and high SRC-index group according to the time to AF recurrence (3 days [2–5]; n = 21 vs 4 days [3−10]; n = 17 vs 1 day [1–8]; n = 9, P = 0.110). Patients in the high SRC-index tertile more often used dihydropyridine calcium channel blockers compared to those in the moderate and low SRC-index tertiles (35.5% vs 10.3% vs 10.7%, respectively, P = 0.018).

Extrasystoles, pulse rate and pulse rate variability as determinants of symptoms

Of all non-AF PPG recordings, 22% were symptomatic. Extrasystoles occurred in 12% of all non-AF PPG recordings. The proportion of all symptomatic non-AF PPG recordings with extrasystoles was 19%, while extrasystoles just occurred in 10% of all asymptomatic non-AF PPG recordings (Fig. 2).

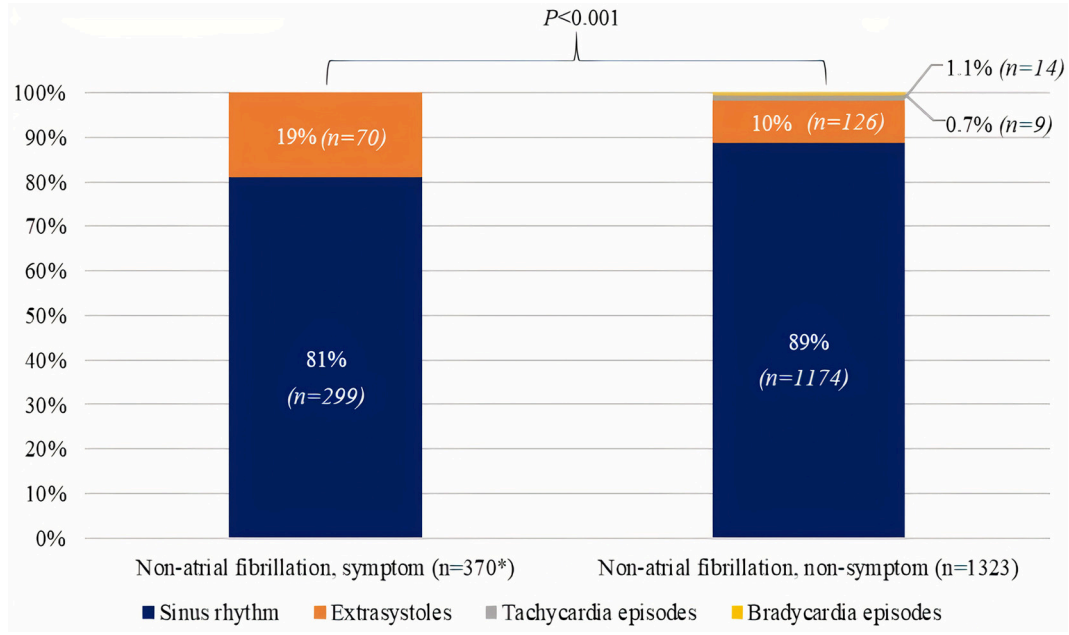

Figure 2. Occurrence of specific rhythms within non-atrial fibrillation recordings depending on the presence and absence of symptoms.
** + 1 recording presenting atrial flutter.*

The proportion of all non-AF PPG recording per patient classified as extrasystoles, bradycardias and tachycardias was 4.7%. There was no statistically significant difference in the proportion of 'warning' recordings in patients with low vs moderate vs high SRC-index (3% [0–7] vs 2% [0–10] vs 2% [0–6], P = 0.784).

The median pulse rate during symptomatic AF PPG recordings was 78 bpm (72–86) with a range of 41–119 bpm and during asymptomatic AF PPG recordings 77 bpm (70–85) with a range of 36–121 bpm. Pulse rate during symptomatic and asymptomatic non-AF PPG recordings ranged between 40 and 109 bpm (median 65 bpm [59–72]) and between 35 and 152 bpm (median 61 bpm [55–67]), respectively (Supplementary Fig. S3). There was a significant increase in the percentage of symptomatic AF and non-AF PPG recordings with increasing pulse rates, but not with increasing pulse rate variabilities (Supplementary Table S4). Especially the percentage of light-headedness and palpitations as self-reported symptom increased with increasing pulse rate in AF, while in non-AF PPG recordings, increasing pulse rate was related to increasing percentage of chest pain, fatigue, light-headedness and palpitations as self-reported symptom (Supplementary Table S5). To exclude the eventual risk of the biases associated with an unequal number of performed recordings per patient, we sub-analysed 20 patients with ≥45 AF PPG recordings (Supplementary Fig. S4). Within each patient, PPG recordings with the highest (vs lowest) tertile of pulse rates conferred an increased risk for symptomatic AF recordings (OR 1.26, 95% CI 1.04–1.52) and symptomatic non-AF recordings (OR 2.93, 95% CI 2.16–3.97) (Fig. 3). Fig. 4 represents the percentage of symptomatic AF and non-AF PPG recordings per pulse rate tertile (low, moderate, high) within a particular patient. An example of recordings showing pulse rate variability based on increasing individual pulse rate (tertiles) is presented in Supplementary Fig. S5. There were no statistically significant differences in mean pulse rate and pulse rate variability between the low, moderate and high SRC-index group (Supplementary Table S6).

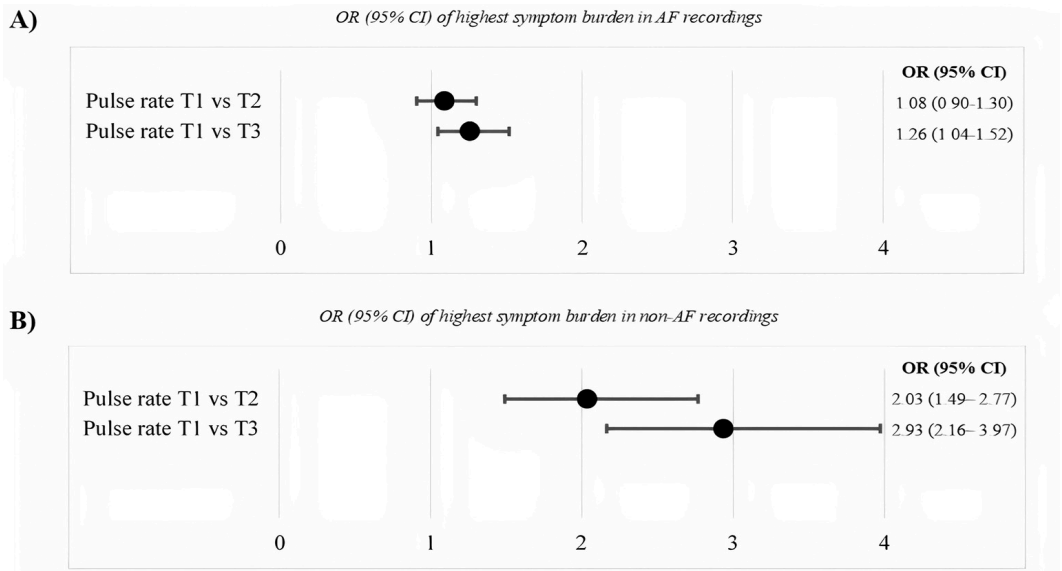

Figure 3. Symptom burden depending on increasing tertiles of pulse rate in symptomatic photoplethysmography recordings both representing atrial fibrillation (Panel A) and non-atrial fibrillation (Panel B). *AF, atrial fibrillation; CI, coincidence interval; OR, odd ratio; T, tertile.*

Discussion

The assessment of SRC in AF patients has been addressed and discussed in previous analyses [6,12], and is frequently used in the clinic to guide AF management decision-making. To the best of our knowledge, the present study is the first to assess SRC in persistent AF patients using a mHealth approach of simultaneous PPG-based heart rhythm/rate monitoring and active interrogation of patient-reported symptoms, which provides a novel approach to systematically assess SRC in persistent AF. Despite the relatively low SRC, the established association of symptom burden with comorbidities and the greater risk of symptoms with higher ventricular response rates are all well recognized features of AF. Most evidence on SRC in AF populations comes from patients in post-ablation period [12]. Semi-continuous longitudinal assessment of symptomatic and asymptomatic AF episodes around ECV adds novel findings in patients with persistent AF. Interestingly, the strategy of how sinus rhythm is restored may impact SRC by differentially influencing the perception of AF after ablation compared to ECV. SRC assessment around ECV by inducing immediate restoration of sinus rhythm allows the evaluation whether symptoms improve or whether symptom burden remains unaffected [13].

The main findings of our study are as follows. First, a low proportion of all rhythm recordings with simultaneous symptom monitoring were in line with an SRC, resulting in an overall low SRC-index (defined as the sum of symptomatic AF recordings and asymptomatic non-AF recordings divided by the sum of all recordings). Second, patients with the lowest degree of SRC-index more frequently suffered from chronic heart failure and diabetes mellitus as compared to those with the highest degree of SRC-index. Third, extrasystoles can explain a minority of symptomatic non-AF PPG recordings. Finally, a higher pulse rate, but not a higher pulse irregularity, was associated with a higher probability of a symptomatic recording during AF and non-AF PPG recordings in persistent AF patients.

Although most patients in our study reported symptoms during AF, a remarkable number of AF PPG recordings during the same persistent AF episode were not associated with self-reported symptoms assessed through active interrogation of patient-reported symptoms. Additionally, in line with previous

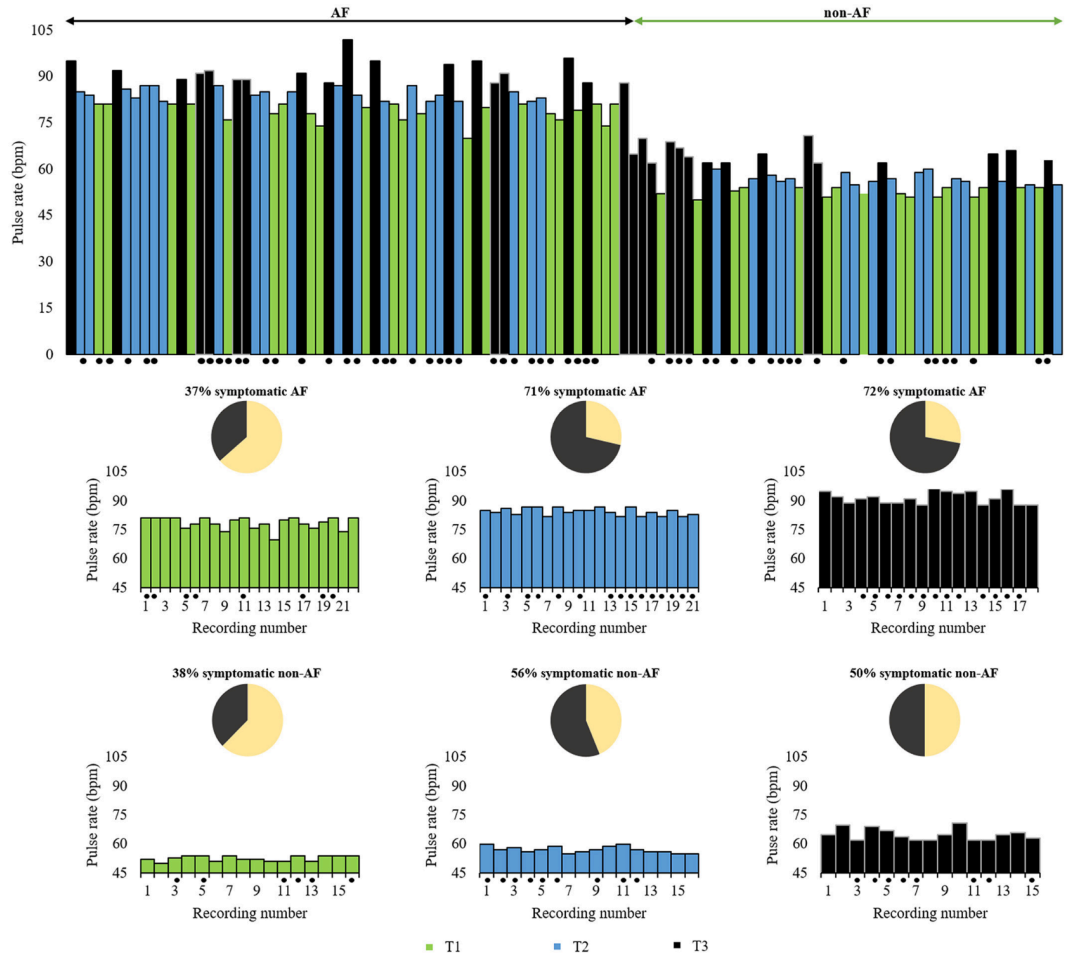

Figure 4. The percentage of symptomatic atrial fibrillation and non-atrial fibrillation photoplethysmography recordings per pulse rate tertile (low, moderate, high) within a particular patient.
Green, blue and black bars indicate individual low, moderate and high tertile of patient's pulse rate, respectively. Black dots below the particular bars indicate symptomatic recordings. Upper panel: Pulse rate during recordings performed by a particular patient. Middle and low panels: Column bars representing individual low, moderate and high tertiles of patient's pulse rate during recordings with atrial fibrillation (middle panel) and non-atrial fibrillation (low panel). Pie graphs above column-graphs represent the percentage of symptomatic recordings in each pulse rate tertile group (low, moderate and high).
AF, atrial fibrillation; bpm, beats per minute; T, tertile. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

observation, patients experienced a wide variety of symptoms during persistent AF episodes, including fatigue, chest pain, palpitations, light-headedness and shortness of breath [4,6], and there was high variability in patient-reported predominant symptoms before and after ECV [6]. Interestingly, fatigue was the most common reported symptom in patients with persistent AF, whereas individuals with paroxysmal AF are more likely to experience palpitations [14]. This heterogeneity in terms of symptom presentation may be explained by high variability in symptom perception [1,5] and affected by several sociodemographic characteristics such as the level of anxiety and depression as well as multiple pathophysiologic mechanisms [14]. Psychological aspect assessment around mHealth use would be an interesting component to improve SRC measurement in the near future. Additionally, concomitant

cardiovascular or non-cardiovascular conditions and risk factors as well as the number of underlying comorbidities may contribute to altered self-reported symptom perception in AF patients [15]. The central role of somatosensory and insula cortices in interoceptive attention endorses their proposed contribution to subjective emotional feeling states arising from representations of bodily responses [16]. Importantly, this variability in symptoms, overall symptom burden and SRC in patients with persistent AF cannot be adequately assessed by spot assessment in outpatient AF clinics [6], and therefore may require approaches of simultaneous rhythm monitoring and active interrogation of patient-reported symptoms as introduced in this study.

The notion that a persistent AF episode is not always symptomatic is interesting. It may depend on the pulse rate and activation of the autonomic nervous system, as these may influence the patient's perception of AF episodes [14]. We thereby show that within each patient, PPG AF recordings with the individually highest pulse rates conferred a 1.26-fold increased risk of being associated with symptoms compared with the individually slowest AF PPG recordings, which is in line with prior work [17]. Interestingly, the extent of pulse irregularity in the PPG signal did not relate to symptoms. This supports the potential role of effective rate control in improved symptom management of persistent AF patients. Although we found no association between symptoms and overmedication (usage of >2 of the following cardiovascular drugs: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antiarrhythmic drugs, beta-blockers, calcium channel blockers, digoxin, diuretics, mineralocorticoid receptor antagonists) or usage of a particular cardiovascular drug (Supplementary Table S7), we cannot exclude the influence of cardiovascular drugs on the occurrence of side effects in the form of symptoms due to the small size of the study group.

Additionally, our data showed that half of the patients were symptomatic during non-AF PPG recordings, which is in line with previous study [18]. A small proportion of all non-AF PPG recordings per patient (4.7%) were classified as extrasystoles, bradycardias and tachycardias which may explain symptoms reported by patients during non-AF PPG recordings. However, there was no statistically significant difference in the proportion of 'warning' recordings in patients with low vs moderate vs high SRC-index. Interestingly, also during non-AF PPG recordings, increased pulse rates were associated with increased symptom burden. An explanation might be the presence of non-specific disease-related symptoms related to other comorbidities and risk factors or anxiety. However, the cause-effect relationship remains unclear.

Related covariates of SRC may identify the patients who could profit the most from heart rhythm control in regard to symptom reduction. The current study found that patients with poor SRC were more often diagnosed with comorbidities, including chronic heart failure and diabetes mellitus, which is in line with previous work [19,20]. Diabetic patients could have problems with AF symptom discrimination regarding frequently occurring neuropathic pain [19]. In contrast, heart failure patients share common symptoms with AF, which makes it difficult to separate symptoms caused by heart failure from those caused by AF [20]. These findings highlight the challenge in symptom management in multi-morbid AF patients and may partly explain the suboptimal improvement in symptoms when solely focussing on rhythm control in patients with persistent AF and comorbidities. Therefore, following current AF-guidelines, an integrated and multidisciplinary care approach focused on comprehensive treatment including optimal and personalized management of underlying conditions and risk factor management may be required to achieve optimal symptom control in persistent AF patients [[1], [2], [3]]. Moreover, the recommended patient-centred focus, as part of an integrated approach, requires active involvement of the patient, which includes education and clear instruction on e.g. the use of mHealth and the reporting of symptoms. However, this requires further investigation.

The low SRC described by this study as well as the notion that many persistent AF patients still perceived symptoms even after restoration of sinus rhythm through ECV indicate that patient self-reported symptoms alone are not an accurate and reliable means of assessing the current rhythm status. This could also explain the relatively low SRC in this analysis and has important implications for several clinical scenarios, including assessing AF patients exclusively during teleconsultations and evaluating AF recurrences and AF burden during follow-up after rhythm control strategy approaches. Implementation of on-demand mHealth approaches, e.g. around teleconsultation (TeleCheck-AF [7]), around ECV (TeleWAS-AF [21]) or for follow-up after AF ablation [22], may provide better heart rhythm monitoring with simultaneous symptom assessment and allow informed decision making and integration of the data into clinical workflows [23].

Despite the fact that most patients were reporting symptoms during AF, a remarkable number of AF PPG recordings were not associated with self-reported symptoms. Nevertheless, the number of patients in whom all AF PPG recordings were asymptomatic was very low. Therefore, instead of categorising patients into symptomatic versus asymptomatic AF patients, we introduced the mobile app-based SRC-index as a continuous variable. Although recent studies suggest that asymptomatic AF patients profit from rhythm control comparable to symptomatic patients [24], the implication of SRC assessment for managing AF patients needs to be investigated in future studies.

Limitations

Our study had several limitations. Firstly, due to the subjective symptom evaluation by AF patients, we could not determine whether symptoms were causally linked to AF or whether they are just associated with AF. Secondly, symptom severity assessment, a primary endpoint of AF management, was not considered. Secondly, symptom severity and quality of life assessment, both important endpoints of AF management [1,25], were not incorporated in the current mobile application used in our study. Patient education on symptom quality and development is required to assess symptom severity better [26]. The best way how to educate and involve patients in the assessment of symptom quality and severity requires further study. Thirdly, there may be selection bias, as only persistent AF patients with symptoms that are severe enough for ECV indication and those willing to use the mobile app were included. Therefore, caution should be taken before generalizing our findings to all patients with AF. Also the number of recruited patients was limited, which may impact the statistical power. Fourthly, as patients were instructed to perform a PPG recording once daily as well as when experiencing symptoms, SRC analysis might be influenced by more symptom positive recordings. Fifthly, the possibility that patients did not perform PPG recordings every time they experienced symptoms might have influenced our SRC findings by less symptom positive recordings. Additionally, as we were not able to completely separate scheduled recordings from patient-initiated recordings, the interpretation of patient-reported symptoms might have be influenced. Finally, the monitoring periods pre- and post-ECV were not equal (four weeks vs three weeks, respectively), and based on this, the number of PPG recordings was skewed towards AF presence which might also have impact on SRC analysis.

Conclusions

In persistent AF patients, simultaneous mobile app-based symptom and rhythm monitoring revealed a relatively low overall SRC, which was mainly driven by a majority of AF recordings which were asymptomatic. Extrasystoles can explain a minority of symptomatic non-AF PPG recordings. Pulse rate, but not pulse variability, is the main determinant of reported symptoms during AF and non-AF PPG recordings. Further studies are required to test whether mobile app-based SRC assessment can be implemented in current workflows and integrated into a personalized symptom and rhythm control AF management approach.

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Supplementary material

Table S1. Predominant symptom type within non-atrial fibrillation and atrial fibrillation recordings per patient based on chronic heart failure and diabetes mellitus.

Predominant symptom type	Chronic heart failure			Diabetes mellitus		
	Yes	No	*P*-value	Yes (n=9)	No (n=70)	*P*-value
Within non-AF recordings per patient (n=79)						
No symptoms	11 (55.0%)	30 (50.8%)	0.748	6 (66.7%)	35 (50.0%)	0.484
Chest pain	2 (10.0%)	1 (1.7%)	0.156	0 (0.0%)	3 (4.3%)	1.000
Fatigue	1 (5.0%)	12 (20.3%)	0.166	1 (11.1%)	12 (17.1%)	1.000
Light-headed	3 (15.0%)	2 (3.4%)	0.100	0 (0.0%)	5 (7.1%)	1.000
Palpitations	1 (5.0%)	7 (11.9%)	0.672	2 (22.2%)	6 (8.6%)	0.225
Shortness of breath	0 (0.0%)	3 (5.1%)	0.567	0 (0.0%)	3 (4.3%)	1.000
Other	0 (0.0%)	3 (5.1%)	0.567	0 (0.0%)	3 (4.3%)	1.000
Several	2 (10.0%)	1 (1.7%)	0.156	0 (0.0%)	3 (4.3%)	1.000
Within AF recordings per patient (n=86)						
No symptoms	6 (27.3%)	14 (21.9%)	0.605	4 (40.0%)	16 (21.1%)	0.232
Chest pain	1 (4.5%)	5 (7.8%)	1.000	1 (10.0%)	5 (6.6%)	0.535
Fatigue	5 (22.7%)	21 (32.8%)	0.374	3 (30.0%)	23 (30.3%)	1.000
Light-headed	1 (4.5%)	1 (1.6%)	0.448	0 (0.0%)	2 (2.6%)	1.000
Palpitations	5 (22.7%)	11 (17.2%)	0.542	2 (20.0%)	14 (18.4%)	1.000
Shortness of breath	2 (9.1%)	5 (7.8%)	1.000	0 (0.0%)	7 (9.2%)	1.000
Other	2 (9.1%)	5 (7.8%)	1.000	0 (0.0%)	7 (9.2%)	1.000
Several	0 (0.0%)	2 (3.1%)	1.000	0 (0.0%)	2 (2.6%)	1.000

Values are depicted as the number of patients (n) with percentages.
AF, atrial fibrillation

Table S2. Type of recording for patients with and without previous atrial fibrillation ablation.

Variable	Without previous AF ablation (n=52)	Previous AF ablation (n=17)	*P*-value
SRC-index	0.54 (0.45-0.77)	0.65 (0.48-0.75)	0.365
AF	32 (22-62)	33 (20-52)	0.856
Unclassified	1(0-5)	1 (0-11)	0.651
Insufficient quality	2 (0-10)	4 (1-14)	0.437
Regular rhythm	17 (4-33)	16 (6-50)	0.411
Symptoms	17 (4-53)	14 (0-48)	0.586
Symptoms AF	11 (3-33)	6 (0-36)	0.605
Symptoms non-AF	1 (0-6)	0 (0-7)	0.506
Symptoms unclassified	0 (0-1)	0 (0-0)	0.348
Symptoms regular rhythm	1 (0-4)	0 (0-6)	0.555
Symptoms insufficient quality	0 (0-2)	0 (0-5)	0.886
No symptoms	36 (22-56)	39 (11-66)	0.856
No symptoms AF	19 (6-30)	14 (0-24)	0.271
No symptoms non-AF	14 (4-26)	13 (4-40)	0.733
No symptoms unclassified	1 (0-2)	1 (0-7)	0.477
No symptoms regular rhythm	13 (3-24)	10 (3-40)	0.933
No symptoms insufficient quality	0 (0-4)	1 (0-8)	0.679

Values are depicted as median with interquartile range.
AF, atrial fibrillation; SRC, symptom-rhythm correlation

Table S3. Clinical characteristics of included patients, divided in tertiles according to symptom-rhythm correlation index, restricted to post-electrical cardioversion recordings.

Variable	Low [<0.55] SRC-index (n=28)	Moderate [0.55 – 0.88] SRC-index (n=29)	High [≥0.88] SRC-index (n=31)	*P*-value
Demographics				
Age (years) – mean±SD	69±10	67±9	68±7	0.535
Female sex	12 (42.9%)	10 (34.5%)	7 (22.6%)	0.249
BMI (kg/m2) – mean±SD	28.6±4.4	28.1±5.3	28.1±4.4; *n=30*	0.883
AF				
First-detected AF	5 (17.9%)	6 (20.7%)	8 (25.8%)	0.752
Current AF episode duration >6 months**	19 (95.0%); n=20	15 (83.3%); n=18	19 (95.0%); n=20	0.342
Current AF episode duration >12 months**	15 (75.0%); n=20	13 (72.2%); n=18	17 (85.0%); n=20	0.604
Previous CV (electrical and/or pharmacological)**	14 (60.9%); *n=23*	13 (56.5%); *n=23*	14 (60.9%); *n=23*	0.942
Ablation therapy for AF**	5 (21.7%); *n=23*	5 (21.7%); *n=23*	7 (30.4%); *n=23*	0.732
Cardiovascular diseases				
Myocardial infarction	2 (7.1%)	4 (13.8%)	4 (12.9%)	0.691
PCI/PTCA	1 (3.6%)	3 (10.3%)	5 (16.1%)	0.283
CABG	2 (7.1%)	1 (3.4%)	0 (0.0%)	0.320
Peripheral vascular disease	0 (0.0%)	1 (3.4%)	0 (0.0%)	0.357
Diabetes mellitus	4 (14.3%)	1 (3.4%)	5 (16.1%)	0.254
Hypertension	12 (42.9%)	14 (48.3%)	17 (54.8%)	0.653
Chronic heart failure	7 (25.0%)	9 (31.0%)	6 (19.4%)	0.580
Obesity (BMI ≥30kg/m2)	10 (35.7%)	9 (31.0%)	10 (33.3%); *n=30*	0.932
Stroke/TIA/pulmonary embolism	1 (3.6%)	1 (3.4%)	3 (9.7%)	0.490
Device therapy (PM/CRT/ICD)	0 (0.0%)	3 (10.3%)	2 (6.5%)	0.235
Transthoracic echocardiographic parameters				
LVEF (%) – median (IQR)	55 (44-60); *n=26*	48 (37-55); *n=25*	55 (47-60); *n=26*	0.277
Left atrial volume – mean±SD	101±28; *n=25*	98±34; n=*26*	88±26; *n=25*	0.263
Valvular heart disease	0 (0.0%); n=27	3 (10.7%); n=28	3 (10.3%); n=29	0.216
Thromboembolic risk				
CHA_2DS_2-VASc score = 0 (if male), = 1 (if women)	5 (17.9%)	6 (20.7%)	3 (9.7%)	0.478
CHA_2DS_2-VASc score = 1 (if male), = 2 (if women)	8 (28.6%)	7 (24.1%)	6 (19.4%)	0.708
CHA_2DS_2-VASc score ≥2 (if male), ≥3 (if women)	15 (53.6%)	16 (55.2%)	22 (71.0%)	0.313
Medications				
Oral anticoagulants	28 (100.0%)	29 (100.0%)	31 (100.0%)	NA
Antiplatelet drugs	0 (0.0%)	1 (3.4%)	1 (3.2%)	0.619
Beta-blockers	17 (60.7%)	22 (75.9%)	22 (71.0%)	0.450
Antiarrhythmic drugs	7 (25.0%)	7 (24.1%)	7 (22.6%)	0.976

Variable	Low [<0.55] SRC-index (n=28)	Moderate [0.55 – 0.88] SRC-index (n=29)	High [≥0.88] SRC-index (n=31)	*P*-value
Diuretics	13 (46.4%)	9 (31.0%)	7 (22.6%)	0.145
Dihydropyridine-CCB	3 (10.7%)	3 (10.3%)	11 (35.5%)	0.018
Non-dihydropyridine-CCB	2 (7.1%)	2 (6.9%)	2 (6.5%)	0.994
ACEI	5 (17.9%)	9 (31.0%)	10 (32.3%)	0.397
ARB	6 (21.4%)	7 (24.1%)	5 (16.1%)	0.735
MRA	0 (0.0%)	2 (6.9%)	0 (0.0%)	0.125
Digoxin	6 (21.4%)	6 (20.7%)	10 (32.3%)	0.509

*The number provided after the semicolon indicates the total number of patients available for that variable. Values are depicted as the number of patients (n) with percentages unless indicated otherwise. ** Results after excluding patients with first-detected AF.*

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass surgery; CCB, calcium channel blockers; CRT, cardiac resynchronization therapy; CV, cardioversion; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LVEF, left ventriuclar ejection fraction; MRA, mineralocorticoid receptor antagonists; NA, not applicable; PCI, percutaneous coronary intervention; PM, pacemaker; PTCA, percutaneous transluminal coronary angioplasty; SD, standard deviation; TIA, transient ischemic attack

Table S4. Percentage of symptomatic atrial fibrillation and non-atrial fibrillation recordings for each recordings-based tertile.

Symptomatic AF PPG recordings				**Symptomatic non-AF PPG recordings**			
T1	**T2**	**T3**	***P*-value**	**T1**	**T2**	**T3**	***P*-value**
Increasing pulse rate tertiles				Increasing pulse rate tertiles			
408 (44.6%)	449 (46.5%)	428 (50.3%)	0.052	76 (12.9%)	133 (23.2%)	161 (30.3%)	<0.001
Increasing SDNN tertiles				Increasing SDNN tertiles			
432 (47.8%)	434 (47.5%)	419 (45.8%)	0.664	131 (23.1%)	107 (18.9%)	132 (23.6%)	0.107
Increasing SDSD tertiles				Increasing SDSD tertiles			
440 (48.7%)	432 (47.3%)	a413 (452%)	0.324	134 (23.6%)	106 (18.8%)	130 (23.2%)	0.092
Increasing RMSSD tertiles				Increasing RMSSD tertiles			
439 (48.6%)	432 (47.3%)	414 (45.3%)	0.371	134 (23.6%)	106 (18.7%)	130 (23.3%)	0.087

Values are depicted as the number of recordings (n) with percentages.

AF, atrial fibrillation; PPG, photoplethysmography; RMSSD, root mean square of successive differences; SDNN, standard deviation of intervals; SDSD, standard deviation of successive differences; T, tertile

Table S5. Percentage of symptomatic atrial fibrillation and non-atrial fibrillation recordings for each recordings-based tertile per symptom type.

Symptomatic AF PPG recordings					**Symptomatic non-AF PPG recordings**			
T1	**T2**	**T3**	***P*-value**		**T1**	**T2**	**T3**	***P*-value**
Increasing pulse rate tertiles					**Increasing pulse rate tertiles**			
Chest pain					Chest pain			
14 (23.3%)	29 (48.3%)	17 (28.3%)	0.088		8 (36.4%)	1 (4.5%)	13 (59.1%)	0.002
Fatigue					Fatigue			
167 (37.6%)	149 (33.6%)	128 (28.8%)	0.584		24 (17.4%)	50 (36.2%)	64 (46.4%)	<0.001
Lightheaded					Lightheaded			
10 (14.3%)	20 (28.6%)	40 (57.1%)	<0.001		10 (20.8%)	6 (12.5%)	32 (66.7%)	<0.001
Palpitations					Palpitations			
106 (26.2%)	153 (37.9%)	145 (35.9%)	0.002		19 (18.8%)	54 (53.5%)	28 (27.7%)	<0.001
Shortness of breath					Shortness of breath			
69 (40.4%)	51 (29.8%)	51 (29.8%)	0.257		12 (26.1%)	16 (34.8%)	18 (39.1%)	0.147
Other					Other			
42 (30.9%)	47 (34.6%)	47 (34.6%)	0.397		3 (20.0%)	6 (40.0%)	6 (40.0%)	0.315

Values are depicted as the number of recordings (n) with percentages.
AF, atrial fibrillation; PPG, photoplethysmography; T, tertile

Table S6. Mean pulse rate and pulse rate variability per patient in overall (*Panel A*), atrial fibrillation recordings (*Panel B*) and non-atrial fibrillation recordings (*Panel C*).

A)

Variable	**Study group (n=88)**	**Low [<0.47] SRC-index (n=29)**	**Moderate [0.47 – 0.73] SRC-index (n=30)**	**High [≥0.73] SRC-index (n=29)**	***P*-value**
Overall					
Pulse rate, beat/min	72.4±9.3	72.3±9.7	73.5±10.0	71.5±8.2	0.729
SDNN, ms	156.9±52.7	165.3±48.0	147.3±49.9	158.4±59.7	0.417
SDSD, ms	213.1±70.3	225.8±64.3	198.9±66.9	215.1±78.8	0.338
RMSSD, ms	211.5±69.7	224.1±63.7	197.4±66.3	213.5±78.1	0.338

B)

Variable	**Study group (n=86)**	**Low [<0.47] SRC-index (n=28)**	**Moderate [0.47 – 0.73] SRC-index (n=30)**	**High [≥0.73] SRC-index (n=28)**	***P*-value**
AF					
Pulse rate, beat/min	79.5±10.7	76.3±10.8	81.0±10.8	79.1±7.4	0.194
SDNN, ms	202.3±46.4	200.8±37.9	197.0±42.8	201.8±52.3	0.910
SDSD, ms	274.5±60.2	273.2±49.1	267.0±55.0	275.0±70.0	0.861
RMSSD, ms	273.6±60.7	271.1±48.4	265.1±54.4	273.0±69.2	0.864

C)

Variable	**Study group (n=79)**	**Low [<0.47] SRC-index (n=25)**	**Moderate [0.47 – 0.73] SRC-index (n=30)**	**High [≥0.73] SRC-index (n=24)**	***P*-value**
Non-AF					
Pulse rate, beat/min	63.3±9.6	64.0±9.6	63.2±9.4	61.8±9.4	0.467
SDNN, ms	76.2±38.9	75.9±43.6	73.0±38.7	80.5±35.1	0.464
SDSD, ms	100.5±50.6	99.9±57.0	92.1±47.7	111.6±46.8	0.184
RMSSD, ms	98.4±50.8	98.8±56.4	88.3±49.2	110.7±45.8	0.133

Values are depicted as mean ± standard deviation.
AF, atrial fibrillation; RMSSD, root mean square of successive differences; SDNN, standard deviation of intervals; SDSD, standard deviation of successive differences; SRC, symptom-rhythm correlation

Table S7. The association between symptoms and cardiovascular medications.

Medication	No symptoms (n=19)	Symptoms (n=69)							*P*-value
		Chest pain (n=8)	Fatigue (n=26)	Light-headed (n=4)	Other (n=6)	Palpitations (n=15)	Shortness of breath (n=7)	Several (n=3)	
Beta-blockers	16 (84.2%)	3 (37.5%)	18 (69.2%)	2 (50.0%)	5 (83.3%)	10 (66.7%)	5 (71.4%)	2 (66.7%)	0.417
Antiarrhythmic drugs	4 (21.1%)	2 (25.0%)	6 (23.1%)	2 (50.0%)	2 (33.3%)	2 (13.3%)	2 (28.6%)	1 (33.3%)	0.881
Digoxin	6 (31.6%)	3 (37.5%)	4 (15.4%)	0 (0.0%)	2 (33.3%)	4 (26.7%)	2 (28.6%)	1 (33.3%)	0.765
Cardiovascular drugs* >2	15 (78.9%)	5 (62.5%)	18 (69.2%)	2 (50.0%)	5 (83.3%)	7 (46.7%)	6 (85.7%)	1 (33.3%)	0.327

Values are depicted as the number of patients (n) with percentages.
**angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antiarrhythmic drugs, betablockers, calcium channel blockers, digoxin, diuretics, mineralocorticoid receptor antagonists*

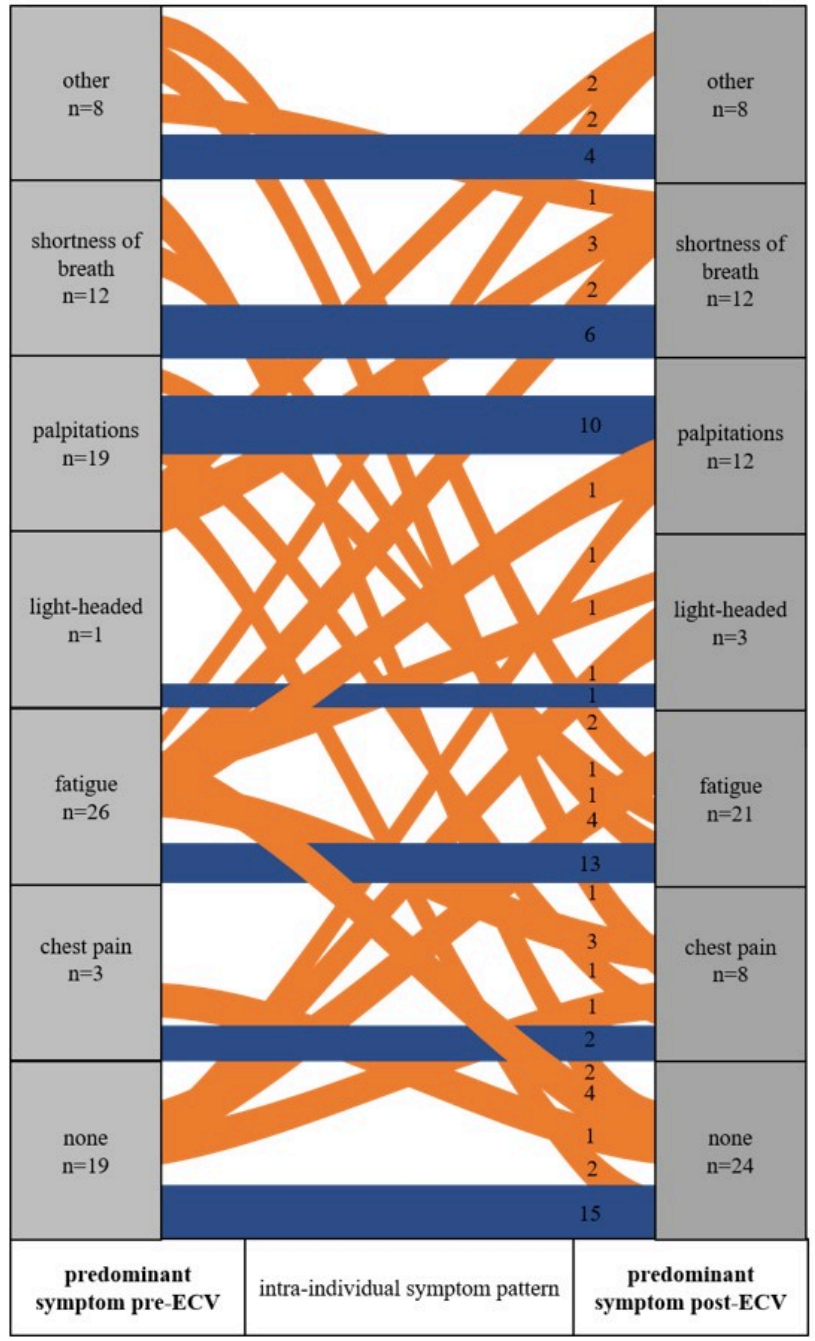

Figure S1. Symptom variability around electrical cardioversion per patient.
The orange lines indicate patients with an intra-individually variable symptom pattern around ECV, defined as changes in predominant self-reported symptoms within patients around ECV. The blue lines indicate patients without changes in predominant self-reported symptoms around ECV.
ECV, electrical cardioversion

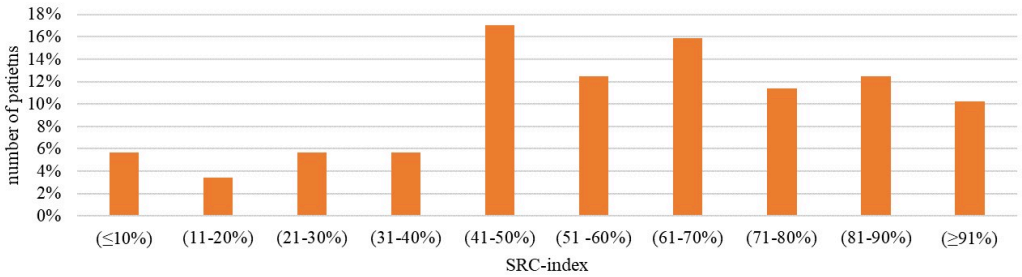

Figure S2. Distribution of symptom-rhythm correlation index.
SRC, symptom-rhythm correlation

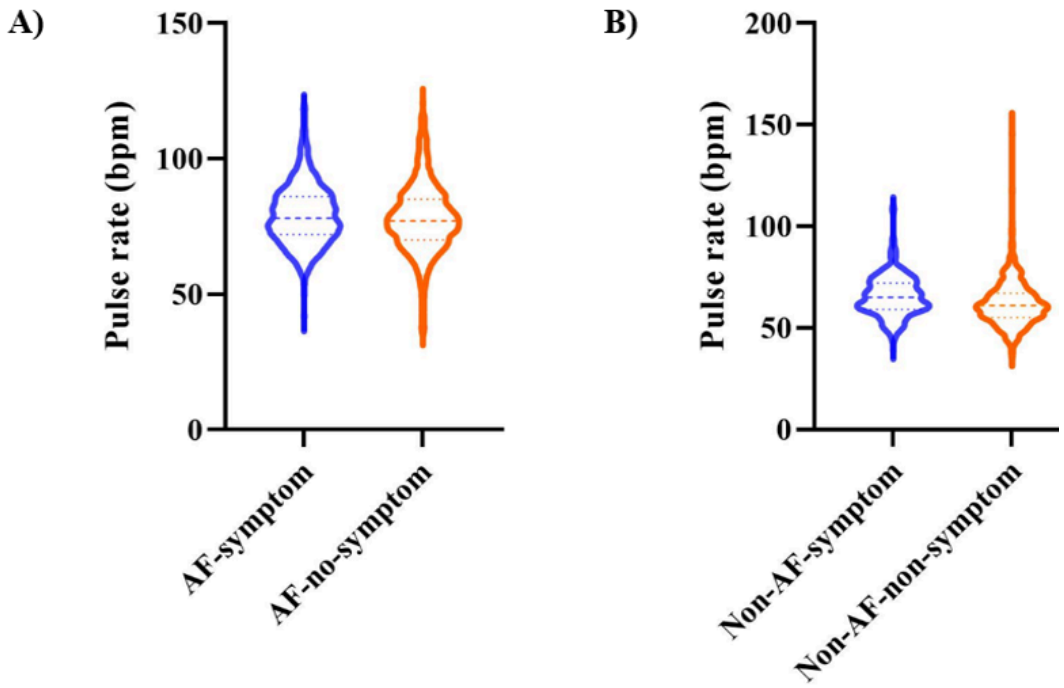

Figure S3. Pulse rate range during atrial fibrillation (*panel A*) and non-atrial fibrillation (*panel B*) for symptomatic versus asymptomatic recordings.
AF, atrial fibrillation

Figure S4. Sub-analysis of patients with 45 or more atrial fibrillation recordings (n=20) in correlation with symptom burden and tertiles (low, moderate and high) of pulse rate variability parameters.
RMSSD, root mean square of successive differences; SDNN, standard deviation of intervals; SDSD, standard deviation of successive differences; T, tertile

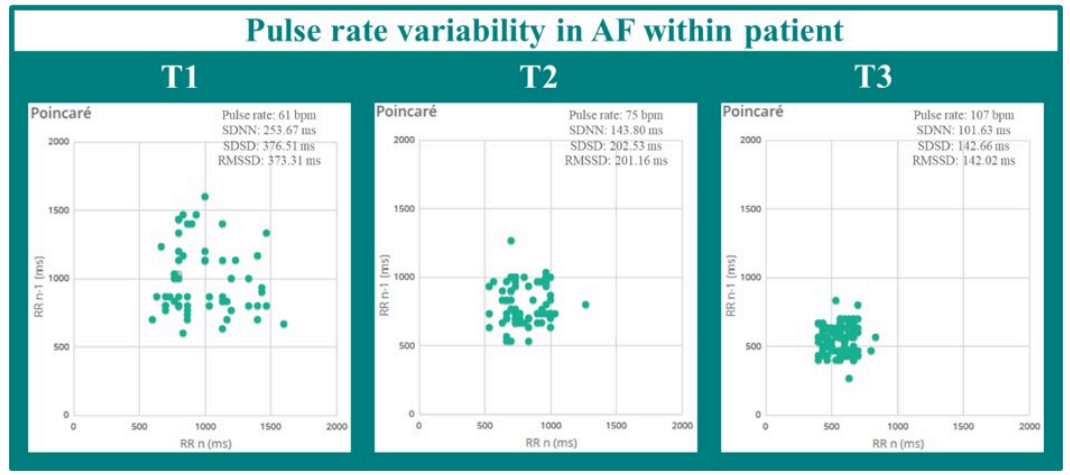

Figure S5. An example of recordings showing pulse rate variability in atrial fibrillation within a patient.
AF, atrial fibrillation; RMSSD, root mean square of successive differences; SDNN, standard deviation of intervals; SDSD, standard deviation of successive differences; T, tertile

CHAPTER 13

General discussion

Traditional (early) atrial fibrillation detection and management

The prevalence of AF has been constantly rising and this increase is projected to continue in the years to come (1). Undiagnosed and undertreated AF contributes to ischaemic stroke, heart failure and coronary artery disease (2). Therefore, the timing of AF detection and restoration of sinus rhythm in AF patients matters. Early diagnosis of AF before it becomes symptomatic can enable early rhythm treatment, which has been shown to reduce mortality, morbidity, and cardiovascular hospitalization in clinical AF (3). Furthermore, AF can occur in association with structural and electrical remodelling processes in the atria (4, 5). A part of this remodelling process can be attributed to AF itself and thus early restoration of sinus rhythm should be effective in reducing AF progression and associated complications (6).

Screening for AF could increase early detection and subsequent treatment of AF (7-10). AF screening can be performed opportunistically or systematically (10-13). Opportunistic screening is performed as a part of clinical contacts for any other reason than screening, for example during a routine GP consultation of during cardiovascular risk factor management. Systematic screening is defined as screening irrespective of medical contacts or need, for example population-based screening programme, in-hospital screening or during vaccination appointments. Screening strategies should be chosen by carefully weighing the risks and benefits of screening (13, 14). Recent meta-analysis showed a higher rate of new AF detection using systematic screening compared to opportunistic screening (15, 16). Nevertheless, the clinical impact and clinical consequences of AF identified and diagnosed in asymptomatic individuals in the context of screening programmes is not fully elucidated and so far show limited or no benefit in the screened populations. Only two randomized controlled trials (RCTs) on clinical outcomes in screening-detected AF patients have been published and showed inconsistent results (17, 18). The STOKESTOP study (18) found a small reduction in the combined endpoint of mortality, stroke and major bleeding and the LOOP study (17) found no significant decline in the combined endpoint of stroke and systemic embolism. Further randomized trials are needed to investigate the long-term clinical outcomes of AF screening programmes.

In newly detected AF patients, structured assessment of stroke risk as well as the assessment of comorbidities and symptoms is crucial to allow early AF management following the ABC holistic pathway (19). Patients with AF may have various symptoms (20-22), but its challenging to differentiate between AF-related symptoms and symptoms in AF (23). To improve symptom control, the identification of AF-related symptoms is important as it may identify patients who profit from rhythm control in regard to reduction in symptom burden. However, standardized strategies to assess the association between symptoms and rhythm status (symptom-rhythm correlation) are currently not available. A possible way to assess symptom-rhythm correlation was evaluated in **Chapter 3**. In this cohort of 81 patients with persistent AF, ECV was used as a diagnostic tool to evaluate symptom-rhythm correlation. We found that spot-check-based symptom-rhythm correlation assessment around rhythm control by ECV, once before ECV and once at the first outpatient AF clinic follow-up visit (within one month after ECV), rarely identifies a symptom-rhythm correlation. Additionally, ECV often suggests changes in symptom pattern. One important limitation of this study was that the predominant self-reported symptoms around ECV were obtained retrospectively from patient medical records and not simultaneously with rhythm information. Therefore, a longitudinal assessment of symptoms during simultaneous rhythm monitoring around ECV could guide this 'diagnostic ECV' better. In further research we evaluated if this strategy could more optimal assess symptom-rhythm correlation in patients with persistent AF (**Chapter 12**). Additional research is warranted to establish the clinical implications of symptom-rhythm correlation assessment for AF management.

Mobile health for (remote) atrial fibrillation detection and management

Monitoring of heart rate and rhythm are important for the management of AF patients and prevention of AF-related morbidity (12). Remote heart rate and rhythm monitoring by means of novel mHealth technologies provides an opportunity to bring the best standard of care and expertise to the patient rather than the patient having to visit an outpatient clinic. Different mHealth tools are available for remote heart rate and rhythm assessment. Therefore, we evaluated the available literature on mHealth solutions in AF detection and management in our systematic review (**Chapter 5**). We observed that differences between mHealth solutions for the detection and management of AF are mainly based on the technology used (ECG vs PPG). Based on the current international AF management guidelines of the ESC, ECG confirmation (even single-lead ECG of 30 seconds or more) is mandated for the diagnosis of AF (12). PPG technology is not sufficient to diagnose AF based on current ESC guidelines. However, there are already some data demonstrating that PPG technology is nearly as accurate as ECG to detect AF (24, 25). The ongoing randomized-controlled Heartline Study (NCT04276441) will additionally investigate whether PPG-based devices could reduce thromboembolic events by early AF detection. Moreover, mHealth solutions with the same technologies may differ based on the method of measurement (handheld vs wearable device), placement on the body, number of leads, and device type, as well as the way of collecting data (intermittent vs continuous, spot vs longitudinal assessment), which could also influence the sensitivity and specificity of AF detection. Therefore, the choice of mHealth solutions for the detection and management of AF should be patient-tailored, considering clinical case, symptom frequency, expected duration of monitoring, local infrastructure and patient's preference (7).

In this thesis, the feasibility of mHealth in two specific clinical AF cases was evaluated (**Chapter 6 & 7**). First, heart rhythm monitoring in the post-ablation period is essential for several reasons: 1) it is of clinical importance to determine whether complaints of palpitations result from recurrent AF (symptom-rhythm correlation), 2) arrhythmia monitoring can influence decision making in asymptomatic AF patients and 3) arrhythmia monitoring is an important component at assessing the outcomes of catheter ablation, clinically and in trials (26). The diagnosis of post-ablation AF recurrences is commonly based on scheduled or symptom-initiated short-term continuous ECG monitoring tools, such as Holter monitoring (12). However, these short continuous heart rhythm monitoring approaches can be costly, cumbersome and may miss arrhythmia episodes following AFcatheter ablation, particularly if they are asymptomatic (27). In our study of 115 patients who underwent paroxysmal AF ablation, we showed that long-term intermittent monitoring using an ECG-based digital device can overcome this limitation and more effectively detects AF recurrences after AF ablation than short continuous Holter ECG monitoring (**Chapter 6**). This is in line with the results of a recent systematic review and meta-analysis showing high accuracy levels for ECG-based digital devices: sensitivity ranged from 54.5% to 100% and specificity from 61.9% to 100% (28). Nevertheless, long-term continuous heart rhythm monitoring with an implanted device is likely to detect more episodes of paroxysmal AF than long-term intermittent heart rhythm ECG readings, but these implanted devices are relatively expensive, require a minor surgical procedure and need health care professional monitoring (27). Second, in patients with AF lenient rate control (resting heart rate target <110 bpm) is recommended, unless a patient is highly symptomatic and requires stricter rate control (12, 29). To determine the adequacy of rate control, heart rate assessment based on scheduled or symptom-initiated ECG monitoring tools, such as a 10-second resting ECG, Holter ECG or event recorders, is recommended (30). However, as mentioned above, these heart rate monitoring tools have several limitations. In our cohort of 50 persistent AF patients, we observed that PPG-based 1-minute mean heart rate estimation during AF seems feasible to guide lenient rate control and shows good accuracy compared to Holter ECG as a reference. However, in some cases, PPG may underestimate true faster 1-minute mean heart rates >110 bpm during AF

(**Chapter 7**). Theoretically, underestimation of fast heart rates during AF can occur due to so-called pulse deficit (7). The high beat-to-beat variability in AF may result in variable diastolic filling of the ventricular system and consequently in reduced amplitudes of the PPG peaks due to changes in the perfusion of the microvasculature. This may impair signal recognition and heart rate computation in the PPG waveforms, what makes the estimation of heart rate from peripheral pulse more challenging, especially at higher heart rate (31, 32). The question remains however, what the best way is how to deal with this problem clinically. Whether novel PPG algorithms incorporating additional PPG waveform features identifying possible pulse loss and consequent underestimation of heart rate or additional ECG recordings represent the best solution remains to be determined. Obviously, further studies are needed to evaluate how to integrate PPG-derived heart rate information into clinical decision-making processes to guide rate control in patients with AF.

The use of mHealth is an important component of integrated care, which has been recognized as a suitable approach to manage AF patients (12). mHealth should support integrated care in terms of actively involving patients in their care process. Patient engagement in their own treatment-decision making can improve therapeutic adherence and patients' satisfaction with the disease management (33). Patient education (via mHealth) is key for engagement in chronic disease management and may optimize communication between patients and health care providers, increase patient involvement in management decisions, and encourage self-management activities (34). It also demonstrates improvements in patient knowledge, behaviour, and quality of life (35, 36). In addition, we showed that in 134 patients planned for AF ablation a mHealth-based virtual reality preprocedural educational video led to better information provision, and procedure-related knowledge, higher satisfaction and less worries regarding the procedure (37). Nevertheless, several barriers need to be overcome to widespread mHealth adaption in healthcare systems. Until now, most mHealth tools are available within a patient-initiated paying-model which, together with the absence of financial support provided by government or private insurances, complicates the clinical implementation and guidance of mHealth use by the treating physician (38). In addition, clinical work-intensive and expensive management of large volumes of data remains a challenge as well, complicating the implementation of mHealth-based results into healthcare system (39). Also, reimbursement is a barrier to more widespread adoption of mHealth in general. Without coherent funding to cover mHealth, the applications will be limited to those patients who may be willing to pay out-of-pocket for telemedicine solutions.

Implementation and results of mobile health in atrial fibrillation detection and management

The COVID-19 pandemic resulted in an acceleration of mHealth use in cardiology clinics (40). Also in Maastricht, all traditional face-to-face consultations in the AF outpatient clinic were constrainedly converted into teleconsultations. We developed a mHealth infrastructure to support teleconsultations with AF patients to guarantee the continuity of comprehensive AF management through teleconsultations during COVID-19: the TeleCheck-AF approach. TeleCheck-AF is a remote on-demand heart rate and rhythm monitoring infrastructure, which is based on a mobile phone app using PPG technology allowing remote heart rate and rhythm monitoring and simultaneously symptom assessment (**Chapter 8-12**). We reported our first results of thirty patients which showed that the low costs, convenience, and broad accessibility of the mHealth solution makes it feasible to implement this novel app-based on-demand heart rate and rhythm monitoring infrastructure to efficiently provide teleconsultations in an AF population (41). Afterwards, the implementation process of the TeleCheck-AF approach in an integrated and specialized AF-clinic through teleconsultation during COVID-19 was described (**Chapter 8 & 9**). Currently, this infrastructure is implemented in 41 European centres. For this PPG-based infrastructure, no hardware is required, which has several hygienic and logistical advantages. Additionally, this on-demand approach was regulated by a prescription to use the app for a limited predefined time period, which avoids

unnecessary data-load. Besides, a potential disadvantage is that no ECG is provided, but the algorithm used by the app can validly inform about the presence of AF (24, 25) and current heart rate (**Chapter 7**). TeleCheck-AF calls upon the responsibility of patients: this means that coordination of performing measures lies mainly with the patients themselves (**Chapter 9**). Patients' adherence and willingness to participate and perform the measures as prescribed is essential for the collection of measurements. In our study of 990 patients from ten TeleCheck-AF centres was confirmed that more than one-fourth of patients had optimal adherence and motivation to the TeleCheck-AF infrastructure consisting of heart rate and rhythm monitoring three times daily for seven consecutive days prior teleconsultation (**Chapter 10**). Clear and tailored patient-education may facilitate patient adherence and motivation (42). However, the lack of standardized reimbursement models for such digital AF care infrastructures was identified as a relevant burden for clinical implementation of TeleCheck-AF. Additionally, in a recent survey conducted by the European Heart Rhythm Association (EHRA), 73.5% of respondents confirmed a lack of standardized reimbursement structured in their country for consultations related to digital devices (43). In order to design novel Dutch reimbursement models to accelerate transformation towards telemedicine-based AF management, the MUMC+ together with Dutch health insurances collected data on changes in healthcare utilization and resulting declarable care products during the implementation of the TeleCheck-AF approach in the MUMC+ AF-Clinic. Our study results indicated that implementation of TeleCheck-AF was associated with a change in health care utilization, which resulted in a downwards shift in declarable care products (44). These results may create the basis for a new reimbursement code for the TeleCheck-AF approach in the Netherlands. Future multicentre, prospective studies with longer follow-up are needed to determine the long-term impact of TeleCheck-AF on healthcare utilisation, safety, efficacy and costs in the care of patients with AF.

To test whether the TeleCheck-AF approach can be implemented in current routine clinical practise, we examined the feasibility of this infrastructure in specific clinical scenarios. The TeleCheck-AF infrastructure may be beneficial for cardiovascular and comorbidity risk optimization to prevent stroke, based on the CHA2DS2-VASc-score. We observed that remote mobile app-based self-reported assessment of AF risk factors and CHA2DS2-VASc-score in 954 AF patients within the TeleCheck-AF project was feasible and it showed 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 CHA2DS2-VASc-score (**Chapter 11**). One important limitation of this study was that the assessment of risk factors was just a spot assessment. 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 (45, 46). Structured app-based longitudinal risk factor assessment requires further research. Furthermore, mobile app-based simultaneous heart rate and rhythm monitoring within the TeleCheck-AF project may also be valuable to assess symptom-rhythm correlation in patients with persistent AF. We tried to observe this symptom-rhythm correlation in a prospective observational cohort of persistent AF patients planned for ECV in the MUMC+ (**Chapter 12**). Longitudinal simultaneous mobile app-based symptom and heart rhythm monitoring revealed a relatively low symptom-rhythm correlation, which was mainly driven by a majority of AF recordings that were asymptomatic. Furthermore, pulse rate was the main determinant of reported symptoms during AF and non-AF PPG recordings. Besides this valuable information on symptom-rhythm correlation, simultaneous mobile app-based symptom and rhythm monitoring also provides insights into pattern of the arrhythmia since also patients with presumed persistent AF may have a self-terminating pattern (unpublished data of the TeleConvert-AF study). Future research is required to verify whether integrating mobile app-based symptom-rhythm correlation assessment in current workflows can improve AF management.

To conclude, the work presented in this thesis gave a comprehensive overview of the current state of art in AF detection and management. mHealth has the extraordinary potential to improve the care of AF and rapidly redefine the framework for its management. Nevertheless, the use of mHealth has also important barriers and challenges. We need further high-quality randomized clinical trials to investigate the effect of mHealth use on clinical outcomes in AF.

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CHAPTER 14

Summary, Samenvatting, Scientific and societal impact, Dankwoord, About the author, List of publications

Summary

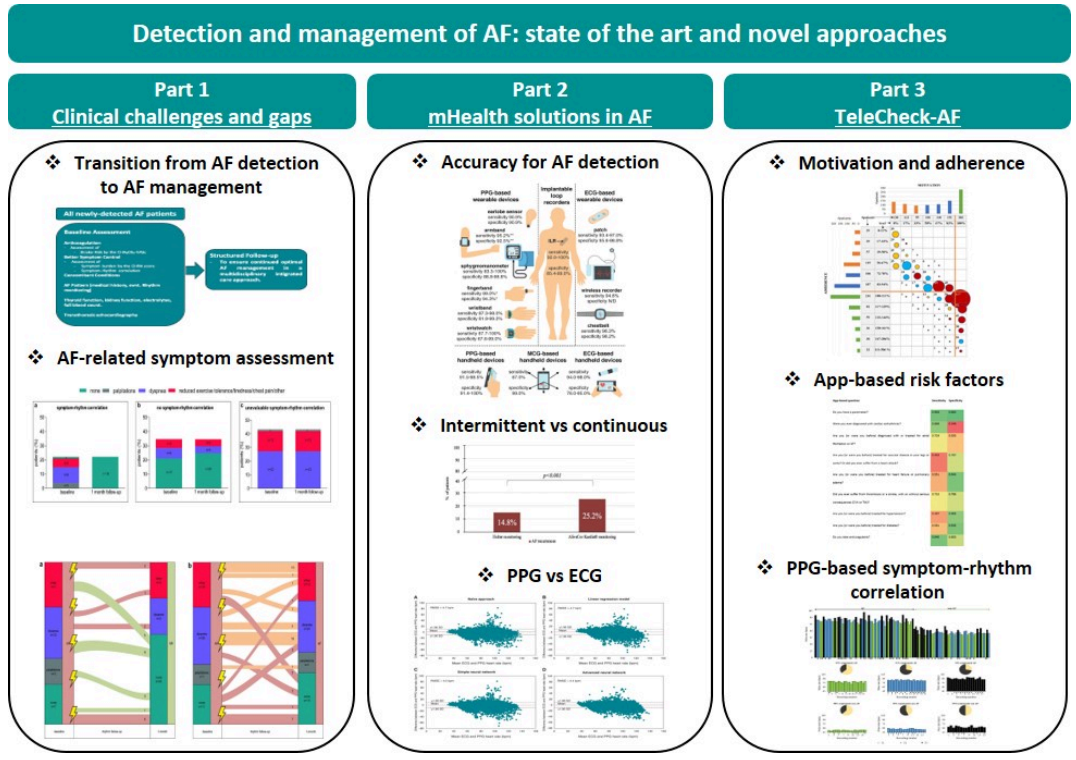
AF is the most prevalent sustained cardiac arrhythmia and associated with morbidity such as heart failure and an increased risk of thromboembolic complications, and mortality, and significantly increases burden to health care. Patients with AF are considered vulnerable and therefore monitoring of heart rate and heart rhythm is important for the management of AF and prevention of AF-related morbidity. Novel mHealth solutions have been introduced to assist in the detection of AF as well as to support remote management of patients with AF. In this thesis, the current state of art in AF detection and management is evaluated and novel AF detection and management approaches are developed and introduced.

Part 1 focuses on the traditional AF detection and management strategies and the associated clinical challenges and gaps of evidence. To improve AF management, the identification of AF-related symptoms is important as it may identify patients who profit from rhythm control in regard to reduction in symptom burden. Since standardized strategies to assess the association between symptoms and rhythm status are currently not available, we evaluated the current clinical strategy to investigate symptom-rhythm correlation in patients with persistent AF. Spot-check assessment of symptom-rhythm correlation around rhythm control by ECV rarely identified a symptom-rhythm correlation and there was high variability in self-reported symptoms before and after ECV in patients with AF recurrence (**Chapter 3**). One important limitation of this study was that the predominantly self-reported symptoms around ECV were obtained retrospectively from patients' medical records and not simultaneously with heart rhythm information. To overcome this limitation, we developed and further investigated a novel mHealth approach to assess symptom-rhythm correlation in patients with persistent AF. Within the TeleCheck-AF project, a more longitudinal mobile app-based assessment of symptoms during simultaneous heart rhythm monitoring around ECV to guide this 'diagnostic ECV' was evaluated and revealed a relatively low overall symptom-rhythm correlation (**Chapter 12**).

Part 2 discusses the importance of available mHealth solutions for remote AF detection and management. Our systematic review showed that the accuracy of mHealth tools differs with respect to the type and technology used, as well as application setting, and study population (**Chapter 5**). Based on this, we studied the utility of long-term intermittent ECG-based heart rhythm monitoring using AliveCor Kardia (ACK) compared to short continuous ECG-based heart rhythm monitoring using Holter for the detection of AF recurrence after AF ablation. Four weeks ACK monitoring more effectively detected AF recurrences than ≥24h Holter monitoring (**Chapter 6**). Additionally, in **Chapter 7** we prospectively investigated the accuracy of continuous mHealth PPG-based heart rate assessment during AF in comparison with continuous Holter ECG monitoring as a reference. Our results suggest that 1 min mean heart rate estimation using PPG is highly accurate.

In part 3, the implementation process and coordination (**Chapter 8 & 9**) as well as the first results of the TeleCheck-AF approach are described. We found that TeleCheck-AF is associated with relatively low costs, convenience, and broad accessibility of the mHealth solution, which makes it feasible to implement this novel app-based on-demand heart rate and rhythm monitoring infrastructure to efficiently provide teleconsultations in an AF population. The results also confirmed that there is high patient's adherence and motivation to perform the prescribed measures (**Chapter 10**) and that the TeleCheck-AF infrastructure seems beneficial for cardiovascular and comorbidity risk optimization to prevent stroke (**Chapter 11**). Further research is required to verify whether integrating the TeleCheck-AF approach in current AF workflows can improve AF management.

To conclude, mHealth has the extraordinary potential to improve the care of AF and rapidly redefine the framework for its management. Nevertheless, the use of mHealth has also important barriers and challenges. Future high-quality randomized clinical trials should investigate how to integrate mHealth-derived heart rhythm and rate information into clinical decision-making processes to guide AF management as well as the effect of mHealth use on clinical outcomes in AF patients.



Summarizing figure. Detection and management of AF: state of art and novel approaches.
AF, atrial fibrillation; ECG, electrocardiography; PPG, photoplethysmography

Samenvatting

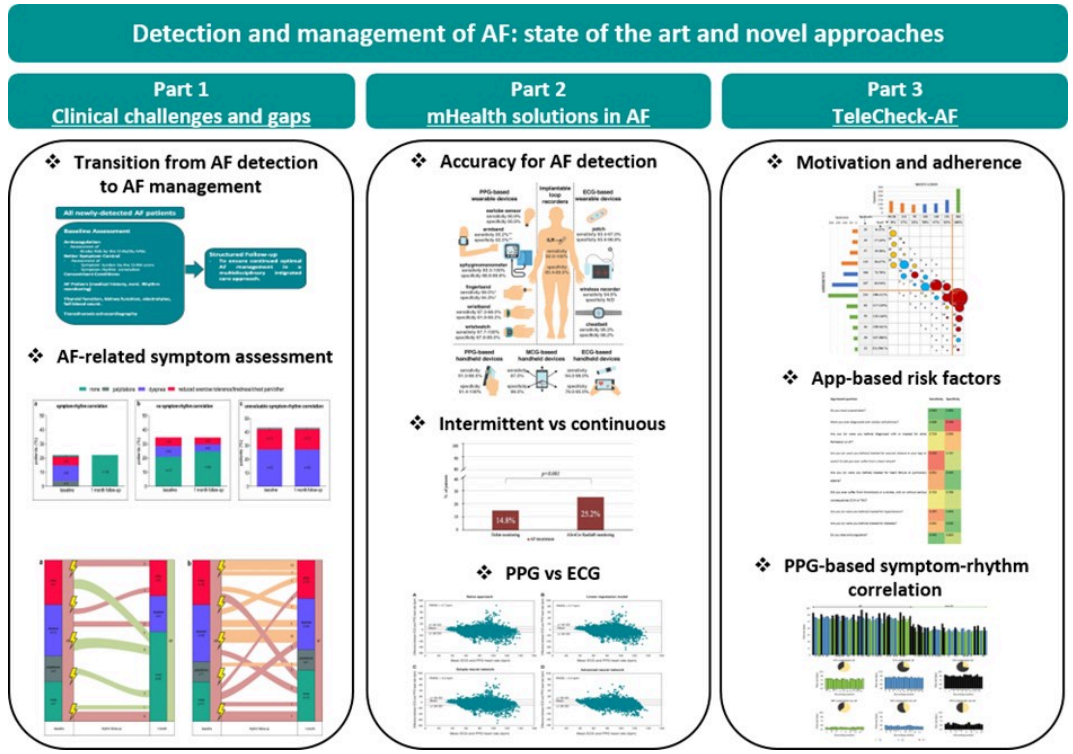
Atriumfibrilleren (AF) is de meest voorkomende aanhoudende hartritmestoornis, is geassocieerd met morbiditeit, zoals hartfalen en een verhoogd risico op trombo-embolische complicaties, en mortaliteit, en verhoogt aanzienlijk de belasting op de gezondheidszorg. Patiënten met AF worden als kwetsbaar beschouwd en daarom is monitoring van hartslag en hartritme belangrijk voor de behandeling van AF en de preventie van AF-gerelateerde morbiditeit. Nieuwe mobile health (mHealth)-oplossingen kunnen worden ingezet om te helpen bij de detectie van AF en om behandeling van patiënten met AF op afstand te ondersteunen. In dit proefschrift wordt de huidige stand van zaken op het gebied van AF detectie en behandeling geëvalueerd en worden nieuwe benaderingen ontwikkeld en geïntroduceerd.

Deel 1 richt zich op de traditionele AF detectie- en behandelingsstrategieën en de bijkomende klinische uitdagingen en hiaten in bewijs. Om AF behandeling te verbeteren, is de identificatie van AF-gerelateerde symptomen belangrijk, dit kan namelijk patiënten identificeren die baat zullen hebben bij ritmecontrole met betrekking tot vermindering van de symptoomlast. Echter is het vaak moeilijk om te achterhalen of iemand symptomen heeft door AF of dat de symptomen veroorzaakt worden door de comorbiditeiten die vaak aanwezig zijn bij patiënten met AF. Momenteel zijn er geen gestandaardiseerde strategieën beschikbaar om de associatie tussen symptomen en hartritmestatus te beoordelen. In onze retrospectieve analyse werden symptomen en hartritme beoordeeld eenmaal vóór elektrische cardioversie (ECV) en eenmaal een maand na ECV. Na een maand had 64% van de patiënten recidief AF. Wat verder opviel is dat deze manier van symptoom en hartritme evaluatie niet vaak resulteerde in een symptoom-ritme correlatie. Daarnaast was er een grote variabiliteit in zelf gerapporteerde symptomen vóór en na ECV bij patiënten met een recidief van AF (**Hoofdstuk 3**). Een belangrijke limitatie van deze studie was dat de zelf gerapporteerde symptomen rondom ECV retrospectief werden verkregen uit de medische dossiers van patiënten en niet gelijktijdig met hartritme-informatie. Om deze limitatie te ondervangen, hebben we een mHealth-gebaseerde aanpak voor symptoom-ritme correlatie beoordeling bij patiënten met AF ontwikkeld en verder onderzocht. Binnen het TeleCheck-AF-project werd een infrastructuur voor longitudinale app-gebaseerde beoordeling van symptomen tijdens gelijktijdige hartritmemonitoring rondom ECV geëvalueerd, en toonde een relatief lage symptoom-ritmecorrelatie bij patiënten met peristent AF rondom ECV (**Hoofdstuk 12**).

Deel 2 bespreekt het belang van beschikbare mHealth-oplossingen voor AF detectie en behandeling op afstand. Ons systematische review liet zien dat de nauwkeurigheid van mHealth hulpmiddelen verschilt met betrekking tot het type en de gebruikte technologie, evenals de setting en de onderzoekspopulatie (**Hoofdstuk 5**). Op basis hiervan hebben we het nut onderzocht van langdurige intermitterende ECG-gebaseerde hartritmemonitoring middels AliveCor Kardia (ACK) in vergelijking met kortdurende continue ECG-gebaseerde hartritmemonitoring middels Holter voor de detectie van AF recidieven na AF ablatie. Vier weken ACK monitoring was effectiever in de detectie van AF recidieven dan ≥24-uurs Holter monitoring (**Hoofdstuk 6**). Daarnaast hebben we in **Hoofdstuk 7** prospectief de nauwkeurigheid van continue mHealth-gebaseerde hartslagmeting tijdens AF middels PPG technologie vergeleken met continue Holter ECG monitoring als referentie. Onze resultaten suggereren dat de gemiddelde hartslagmeting per minuut middels PPG zeer nauwkeurig is.

In deel 3 worden het implementatieproces en de coördinatie (**Hoofdstuk 8 & 9**) als ook de eerste resultaten van de TeleCheck-AF aanpak beschreven. We ondervonden dat de TeleCheck-AF infrastructuur uitvoerbaar is, gemakkelijk in gebruik, breed toegankelijk en laag in kosten. Dit suggereert de haalbaarheid van implementatie van de nieuwe app-gebaseerde hartslag- en hartritmemonitoring infrastructuur met als doel verbeterde AF zorg op afstand. De resultaten bevestigden ook dat patiënten therapietrouw zijn, hun motivatie om de voorgeschreven metingen uit te voeren groot is (**Hoofdstuk 10**) en dat de TeleCheck-AF aanpak gunstig lijkt voor het optimaliseren van het cardiovasculair- en comorbiditeiten-risicoprofiel van AF patiënten om zo beroertes te voorkomen (**Hoofdstuk 11**). Toekomstig onderzoek is nodig om te verifiëren of integratie van de TeleCheck-AF aanpak in de huidige AF zorgpaden kan resulteren in verbeterde AF behandeling.

Concluderend heeft mHealth het buitengewone potentieel om de zorg voor AF te verbeteren en om snel het kader voor de behandeling ervan te herdefiniëren. Toch kent het gebruik van mHealth ook belangrijke barrières en uitdagingen. Toekomstige gerandomiseerde klinische studies moeten uitwijzen hoe mHealth afgeleide hartritme- en hartfrequentie-informatie kan worden geïntegreerd in klinische besluitvormingsprocessen om AF behandeling te begeleiden als ook het effect van mHealth gebruik op klinische uitkomsten bij AF patiënten.



Samenvattend figuur. Detectie en behandeling van AF: stand van zaken en nieuwe benaderingen.
AF, atriumfibrilleren; ECG, elektrocardiografie; PPG, fotoplethysmografie

Scientific and societal impact

AF is the most common sustained arrhythmia in adults worldwide (1). In the Netherlands about 373,700 people are diagnosed with AF (2). As a result of the high prevalence of AF, the clinical and economic impact of the disease is substantial. Nowadays, AF management focuses on the alleviation of patient symptoms, improvement of patient quality of life, and minimization of the morbidity associated with AF (3-5). Monitoring of heart rate and rhythm are important for the management of AF patients and prevention of AF-related morbidity (6). Over the last decades, many mHealth solutions have become available for heart rate and rhythm assessment, but no standardized infrastructure was available for remote heart rate and rhythm monitoring. Therefore, we developed a remote heart rate and rhythm monitoring infrastructure that is based on PPG technology: TeleCheck-AF (**Chapter 8-12**). The TeleCheck-AF approach presents an alternative and/or supplement to traditional face-to-face consultations with a potential to reduce in-office and unnecessary hospital visits, thereby reducing health care burden, and to improve health care in regions of the world where health care providers are only available at large distances. This mHealth infrastructure showed convenience, broad accessibility, and relatively low costs, which makes it feasible to implement this novel app-based on-demand heart rate and rhythm monitoring infrastructure to efficiently provide teleconsultations in an AF population. However, the lack of standardized reimbursement models for such digital AF care infrastructures was identified as a relevant burden for clinical implementation of TeleCheck-AF. In order to design novel Dutch reimbursement models to accelerate transformation towards telemedicine-based AF management, the MUMC+ together with Dutch health insurances collected data on changes in healthcare utilization and resulting DBC care products during the implementation of the TeleCheck-AF approach in the MUMC+ AF clinic. Our study findings indicated that implementation of TeleCheck-AF was associated with a change in health care utilization, which resulted in a downwards shift from medium weight DBC care products to light weight DBC care products for AF management (7). Since the light weight DBC care products do not cover all costs for implementation of the mHealth-based teleconsultation infrastructure, an optional billing code: Facultatieve prestatie “Telecheck atriumfibrilleren TB/REG-21679-01” for mHealth use was created in the Netherlands. The optional billing code does not reimburse the use of mHealth directly but can be used to partly compensate the resulting potential financial gap resulting from a drop in DBC care product due to AF disease managing through the TeleCheck-AF approach. In addition, based on the experiences from TeleCheck-AF, an educational structured stepwise practical guide on PPG signal interpretation was developed (8). TeleCheck-AF results were also presented on several (inter)national conferences and contributed to the EHRA practical guide on the use of digital devices for arrhythmias, from early detection through management and implementation (9). Furthermore, the TeleCheck-AF infrastructure may improve patient education and patient engagement in their own treatment-decision making which can improve therapeutic adherence and patients’ satisfaction with the disease management. The exact scientific and societal impact will be examined in the randomized TeleCheck-AF trial.

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About the author

Astrid Hermans was born on May 27th, 1995, in Kessel, The Netherlands. In 2014, she graduated from secondary school at Het Bouwens in Panningen and started the bachelor Health sciences at Maastricht University (Maastricht). After achieving the BSc degree in 2017, she started the master Biomedical sciences at Radboud University in Nijmegen, where she graduated with distinction (cum laude) in 2019. During her master's, she completed a 8-month research internship at the Physiology department at Radboud University Medical Centre in Nijmegen (under supervision of Prof. dr. Thijssen) and a 7-month research internship at the Cardiology department at Maastricht University Medical Centre in Maastricht (under supervision of Prof. dr. Schotten). After obtaining her MSc degree, she started working as PhD-student in the atrial fibrillation research group of Prof. dr. K. Vernooy, Dr. D. Linz and Prof. dr. U. Schotten at the department of Cardiology of Maastricht University Medical Centre (Maastricht). Her main aim was to evaluate the current state of art in atrial fibrillation detection and management as well as to develop and introduce novel mobile health approaches for the detection and management of atrial fibrillation. Her scientific work was presented at several national and international congresses and is summarized in this thesis. In September 2023, she started as post-doc at the Cardiovascular Research Institute Maastricht in Maastricht.

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1. Pluymaekers NAHA, **Hermans ANL**, Middeldorp ME, Kadhim K, Crijns HJGM, Sanders P, Linz D. Gender differences and daily variation in atrial fibrillation risk factor profiles: Considerations for risk factor management. Int J Cardiol Heart Vasc. 2019 Nov 19;25:100442. doi: 10.1016/j.ijcha.2019.100442. PMID: 31890862; PMCID: PMC6923505.

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Presentations

Aug 2020	Detection of atrial fibrillation recurrences after ablation: long-term intermittent versus short continuous heart rhythm monitoring. Poster presentation, ESC congress – The Digital Experience.
Apr 2021	Electrical cardioversion to assess the association between self-reported symptoms and rhythm status in patients with persistent atrial fibrillation. Poster presentation, EHRA online congress.
Apr 2021	Virtual reality to improve patient information and reduce anxiety towards atrial fibrillation ablation in times of remote patient care (and after). Poster presentation, EHRA online congress.
Aug 2021	Evaluation of the feasibility and accuracy of remote mobile app-based self-reported atrial fibrillation risk factor assessment in patients with atrial fibrillation: TeleCheck-AF results. Poster presentation, ESC congress – The Digital Experience.
Sep 2021	Long-term intermittent versus short continuous heart rhythm monitoring for the detection of atrial fibrillation recurrences after catheter ablation. Invited oral presentation, Heart Rhythm congress – on demand.
Apr 2022	Mobile app-based symptom-rhythm correlation assessment in patients with persistent atrial fibrillation. Moderated poster presentation, EHRA congress, Copenhagen, Denmark.
Apr 2022	Mobile app-based symptom-rhythm correlation assessment in patients with persistent atrial fibrillation. Moderated poster presentation, NVVC Voorjaars-congres, 's-Hertogenbosch, The Netherlands.
Apr 2023	Accuracy of continuous photoplethysmography-based heart rate assessment during atrial fibrillation. Oral presentation, EHRA congress, Barcelona, Spain.
Apr 2023	The European TeleCheck-AF project on remote app-based management of atrial fibrillation: ablation outpatient clinic experience. Oral presentation (e-cardiology award session), EHRA congress, Barcelona, Spain.