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Maastricht University

Faculteit Geneeskunde en Levenswetenschappen
School voor Levenswetenschappen

master in de biomedische wetenschappen

Masterthesis

Photoplethysmography: A possible new approach for the early detection of atrial fibrillation in cryptogenic stroke patients

Kübra Dönmez

Scriptie ingediend tot het behalen van de graad van master in de biomedische wetenschappen, afstudeerrichting klinische biomedische wetenschappen

PROMOTOR :

Prof. Dr. Pieter VANDERVOORT

BEGELEIDER :

Mevrouw Femke WOUTERS

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Photoplethysmography: A possible new approach for the early detection of atrial fibrillation in cryptogenic stroke patients

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*Running title: *The use of mHealth for AF detection in CS patients*

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Keywords: Cryptogenic stroke, Atrial Fibrillation, Insertable Cardiac Monitor, Mobile Health, Long-term heart rhythm monitoring

ABSTRACT

BACKGROUND – Approximately 1.1 million Europeans suffer from a stroke yearly, with ischemic stroke accounting for 80-85%. Furthermore, 25% of these strokes are from undetermined etiology (i.e. cryptogenic). A major risk factor is undetected atrial fibrillation (AF). Therefore, long-term heart rhythm monitoring is needed. This study investigated if a photoplethysmography-based mobile health application (FibriCheck®) has a similar AF detection rate compared to the insertable cardiac monitor.

METHODS – Cryptogenic stroke and TIA patients were recruited and randomized in the smartphone (n=64) and smartwatch (n=57) group. They were asked to use the FibriCheck® application for six months.

RESULTS - FibriCheck® and ICM detected AF in 14.1% and 8.2% of the patients within six months (p=0.27), respectively. There was no significant difference in AF burden and duration between FibriCheck® and ICM (p=0.29). The FibriCheck® results showed a significant difference in insufficient signal quality between the smartwatch and smartphone group (p<0.001). The compliance and motivation in the smartphone group and the total number of measurements taken by the smartwatch decreased significantly over time (p<0.001, p<0.001, and p=0.014, respectively).

CONCLUSION - FibriCheck® had a similar AF detection rate compared to ICM. However, the FibriCheck® measurements decreased over time, and some were of insufficient signal quality. A similar AF burden and duration between FibriCheck® and ICM could be due to the small number of patients with AF. In conclusion, these results indicate that FibriCheck® could be used as an addition to ICM, but a larger sample size is needed to confirm this.

INTRODUCTION

Ischemic stroke and transient ischemic attack

Stroke is the second leading cause of mortality and disability in Europe, with ± 1.1 million stroke patients yearly [1, 2]. By 2025, due to the ageing population, it is also expected that 1.5 million Europeans will experience a stroke annually [2]. Furthermore, according to the Belgium Stroke Council, there are 25,000 stroke patients in Belgium each year [3].

The two main types of stroke can be classified as either ischemic or hemorrhagic [4, 5]. However, ischemic stroke is the most common type in 80–85% of all stroke patients [2, 4, 6, 7]. It is caused by a disturbance in blood

flow to specific brain parts, resulting in an oxygen shortage and subsequent cerebral infarction [4, 5]. An ischemic stroke has different clinical symptoms, depending on the affected area in the brain by the obstruction of the arteries [8]. In particular, speech disturbance and paralysis on one side of the body are the most typical symptoms [9]. In addition, to recognize the early signs of an ischemic stroke, the American Heart and Stroke Association (AHA/ASA) has developed the FAST system [6, 8]. FAST stands for face (facial droop), arm (numbness or weakness in the arm), speech (difficulties while speaking or understanding speech), and time of onset [6, 8]. If any of these symptoms are present, emergency services or the hospital should be contacted immediately [6].

There are some risk factors for developing an ischemic stroke. The non-modifiable risk factors include advanced age, gender (higher risk in women), ethnicity (higher risk in Africans), family history of stroke, and genetics (hypercoagulable disorders, sickle cell anemia, etc.). On the other hand, some modifiable risk factors are hypertension, diabetes mellitus, smoking, obesity, hyperlipidemia and heavy alcohol usage [7, 8, 10, 11]. Patients with one of these predefined risk factors have a higher risk of developing an ischemic stroke over time [7, 11]. Moreover, patients can also suffer from a transient ischemic attack (TIA), which has similar risk factors as an ischemic stroke [5, 10]. A transient ischemic attack has the same origin as an ischemic stroke but is defined as a "mini-stroke". This is because TIA patients have no permanent brain damage (i.e. cerebral infarction), and the symptoms disappear within 24 hours [5, 12]. Both ischemic stroke and TIA patients have a high risk of recurrence. Furthermore, TIA patients have an increased risk of developing an ischemic stroke [5, 10, 12]. Therefore, it is crucial to determine the cause of ischemic stroke and TIA to prevent recurrence.

The prognosis and outcomes of the patients are influenced by the etiology of ischemic stroke [13]. Thus, understanding the etiology of ischemic stroke is important for effective management, treatment, and secondary prevention. Therefore, the Trial Org 10172 in Acute Stroke Treatment (TOAST) classification is used to determine the etiology of ischemic stroke [13]. According to the TOAST classification, there are five subtypes of ischemic stroke, namely: (I) large-artery atherosclerosis (25%), (II) small-vessel disease (i.e. lacunar infarcts) (25%), (III) stroke of undetermined etiology (i.e. cryptogenic) (25%), (IV) cardiogenic embolism (20%), and (V) stroke of other determined etiology (i.e. patent foramen ovale (PFO), coagulation disorders, etc.) (5%) [4, 5, 13-15]. Therefore, a timely diagnosis is critical for receiving the appropriate treatment. First, the physician performs a physical examination, during which the vital and laboratory parameters are also checked. Afterwards, brain imaging (Computed Tomography (CT) or Magnetic Resonance Imaging (MRI)) will be performed, looking at the presence and location of the infarct zone and/or any intracerebral hemorrhage [5]. Moreover, the following clinical investigations are also performed during the hospital stay: CT angiography or MR angiography, transthoracic (TTE) or- transoesophageal echocardiography (TEE), laboratory tests, blood pressure and- 24h electrocardiography monitoring [5, 15, 16]. A proper diagnosis and treatment can be determined based on the findings of these diagnostic examinations. This will lead to a better prognosis and prevention of recurrent stroke in these patients.

Atrial fibrillation in cryptogenic stroke

In approximately one-third of all ischemic stroke and TIA patients, the cause remains unknown at hospital discharge [16-18]. As mentioned earlier, these patients are classified as cryptogenic [16]. However, more than 30% of ischemic strokes (including TIAs) are caused by atrial fibrillation (AF) [19]. It is the most prevalent heart rhythm disorder in Europe and is often the cause of ischemic stroke [12].

In AF, there is disrupted electrical activity in the atria, which leads to an irregular heart rhythm [20]. This causes an abnormal blood flow through the heart, which ultimately can lead to blood clot formation (i.e. thrombus) in the left atrium. These blood clots can move through the bloodstream to the brain and occlude a cerebral artery (i.e. cardioembolic stroke) [12, 20]. Ischemic stroke due to AF is often more serious (e.g. fatal) because it leads to higher disability (e.g. permanent impairment), and it increases the risk for recurrence [21, 22]. Consequently, these patients mostly have a worse prognosis with more extended hospital stays. This also increases the hospital burden and costs [22].

There are some risk factors for AF, such as advanced age, hypertension, congenital heart

disease, diabetes mellitus, hyperthyroidism, obesity, and heavy alcohol consumption [20, 23]. These risk factors are similar to those of an ischemic stroke. Patients with AF can have symptoms such as palpitations, dizziness, chest pain, and dyspnea [20, 24]. However, AF is mostly asymptomatic and paroxysmal [17, 19, 25]. As a result, AF often remains undetected during short-term heart rhythm monitoring [17, 25, 26]. Nowadays, there are several methods for detecting AF, such as periodic electrocardiography (ECG) and Holter monitoring (e.g. 24h or seven-day) [27]. However, the 12-lead and- 24h ECG monitoring is the standard of care for detecting AF in the hospital [28].

The European Stroke Organization (ESO) recommends long-term ECG monitoring in cryptogenic stroke and TIA patients to detect asymptomatic and paroxysmal AF [28, 29]. Previous studies have also shown that prolonged heart rhythm monitoring increases AF detection rate compared to short-term heart rhythm monitoring [21, 30]. Thus, long-term heart rhythm monitoring is crucial because early detection of AF will lead to secondary prevention of a recurrent stroke [26]. The latter is essential, as a recurrent stroke or TIA results in prolonged recovery, poorer outcomes, extended hospital stays, and increased risk of death [31].

The initial therapy given after cryptogenic stroke and TIA is antiplatelets (e.g. aspirin, clopidogrel, etc.), which reduces the risk of a recurrent stroke [5, 31, 32]. However, when AF is detected in these patients, oral anticoagulants (OAC) is recommended [5, 27]. This is because anticoagulants (e.g. edoxaban, warfarin, etc.) reduce the risk of a recurrent stroke by 39% compared to antiplatelet therapy [33-35]. According to current guidelines, AF should last for 30 seconds to start OAC therapy in cryptogenic stroke and TIA patients [17].

Insertable cardiac monitor

Insertable cardiac monitors (ICMs) are currently the gold standard in long-term heart rhythm monitoring for the early detection of AF in cryptogenic stroke and TIA patients [36]. These devices (based on ECG) are small, implanted subcutaneously, and can measure the heart rhythm continuously for approximately three years [29, 37]. The sensitivity of ICMs in detecting AF ranges from 96% to 100%, while the specificity ranges from 67% to 86%. Furthermore, the AF burden can be determined from the results of the ICM [38]. *Sanna et al.* compared the use of ICM with the conventional (ECG monitoring in hospital) follow-up in patients with cryptogenic stroke. The results showed that ICM had detected 12.4% AF after 12 months, compared to 2.0% for the standard of care [21, 30, 39]. Moreover, early AF detection has also led to increased use of anticoagulants in the ICM group for the secondary prevention of a recurrent stroke [39]. Other studies also demonstrated a higher AF detection rate with ICM compared to external cardiac monitors (i.e. 12-lead ECG, Holter monitoring, and telemetry) [40, 41]. Detection of AF with ICM and the initiation of anticoagulants were also associated with a decreased risk of recurrence in cryptogenic stroke and TIA patients [41].

Despite these advantages of ICM compared to the standard of care, there are also several disadvantages. First, the implantation of an ICM is an invasive and expensive procedure, leading to the underutilization of this device [17, 29]. Secondly, it also requires a lot of effort from nurses to be alert and to check the ICM data thoroughly. Besides this, complications can occur, such as pain or infection on the implant site, device dysfunction causing false signals or signal loss, and a scar on the implant site [42]. Furthermore, there can be a long waitlist for a seven-day Holter or ICM implantation in hospitals. Patients may experience AF during this intermediate period after hospital discharge, which physicians could miss. Therefore, new alternatives or additions (e.g. less invasive) to ICMs are needed for the follow-up of cryptogenic stroke and TIA patients. This may fill the gap in the follow-up period, and patients will have multiple options for AF detection in the future.

Mobile Health applications for AF detection

Mobile technology is emerging in healthcare, with mobile health (mHealth) applications for smartphones and smartwatches becoming increasingly popular [17, 43]. This has ensured that various smartphone and smartwatch applications have been developed to detect AF [17, 43, 44]. These new applications have the potential to be used as a non-invasive, less expensive, and more accessible alternative for the long-term follow-up of cryptogenic stroke and TIA patients [17]. Currently, several mHealth technologies are available for detecting AF, such as ECG-based applications and

photoplethysmography (PPG) -based applications [44, 45].

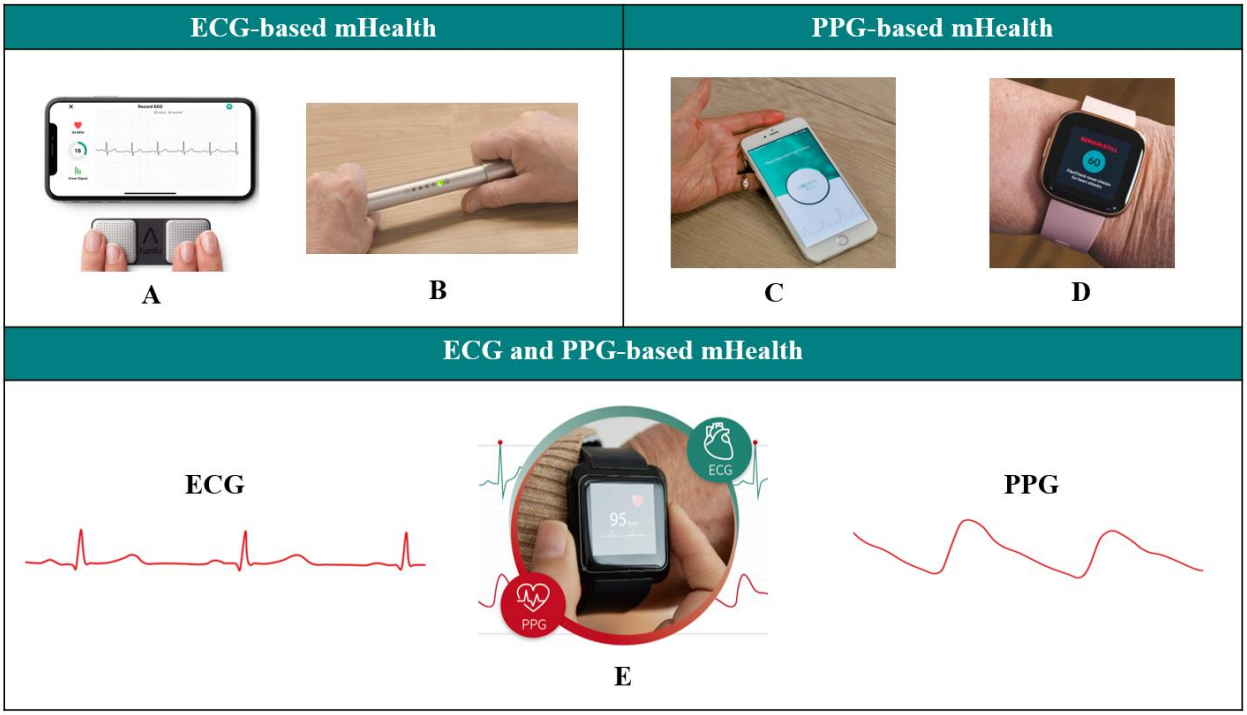


Figure 1. Overview of the various mHealth applications for the detection of atrial fibrillation. A) Alivecor KardiaMobile, B) MyDiagnostick, C) FibriCheck®, D) Fitbit® (with the FibriCheck® app), E) Smartwatch with ECG and PPG-based technology [46]. *ECG, electrocardiography; PPG, photoplethysmography; mHealth, mobile health*

The different mHealth applications are shown in **Figure 1**. An example is the handheld ECG-based application AliveCor Inc. (San Francisco, CA, USA) with the ECG plate KardiaMobile, which has a sensitivity and specificity of 95.3% and 97.5%, respectively. This handheld device is connected to the smartphone and can measure the heart rhythm by a single- or 6-lead ECG. The user should put their fingers on both sides of the device for 30 seconds to register the heart rhythm [43, 44]. MyDiagnostick (Maastricht, Netherlands) is another handheld single-lead ECG-based device that can be used to detect AF. This device consists of a stick on which patients must hold a metal plate for 60 seconds with both hands on the left and right side [43, 44, 47]. According to the findings of *Tieleman et al.*, MyDiagnostick has a sensitivity and a specificity of 100% and 95.9% for the detection of AF, respectively [44, 48]. Examples of PPG-based smartphone applications are FibriCheck® (Qompium, Hasselt, Belgium) and Preventicus® Heartbeats (Preventicus GmbH, Jena, Germany) [17, 44]. Photoplethysmography technology is based on an optical technique [17, 43, 49]. This means that it detects changes in blood volume (with every heartbeat) in the skin capillaries through light absorption [44, 47]. By putting the fingertip on the smartphone's camera (with the flash), the amount of reflected light can be measured.

Consequently, the heart rhythm can be determined (based on the RR intervals) with every heartbeat [44, 47, 50], see **Figure 2** [51]. Another example of PPG-based applications for detecting AF is smartwatches (e.g. FibriCheck® on a Fitbit® or Apple Watch) [17, 44].

These smartwatches can measure the heart rhythm semi-continuously by putting a light source/sensor and a camera into the back of the smartwatch [17, 44]. Lastly, there are also smartwatches based on PPG- and ECG technology, produced by several companies (e.g. Apple®, Samsung®, Fitbit®) [17].

ICM versus FibriCheck®

As mentioned earlier, FibriCheck® is an FDA-approved and CE-marked smartphone app that uses PPG technology (in smartphones or smartwatches) to measure the heart rhythm [29]. *Proesmans et al.* previously demonstrated the high sensitivity (96%) and specificity (97%) of the FibriCheck® app for the detection of AF using smartphones compared to single-lead

ECG, which had a sensitivity of 95% and a specificity of 97% [50].

always accept. Therefore, new approaches are needed for the long-term follow-up of

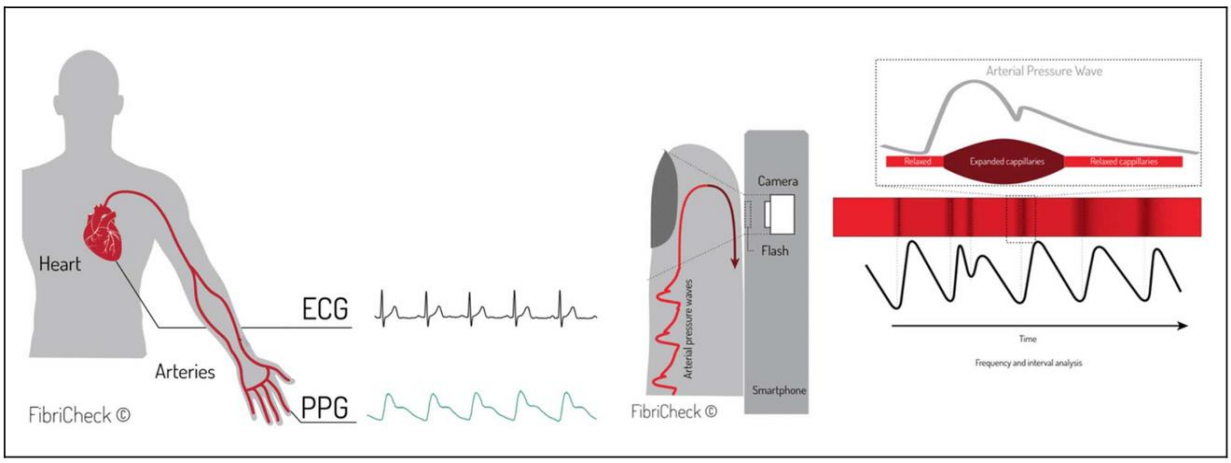


Figure 2. Photoplethysmography (PPG) principle by a smartphone (FibriCheck®). The difference between ECG and PPG is shown on the left. The PPG technology using a smartphone camera and flash to measure the heart rhythm is presented on the right [51].

Compared to ICMs, FibriCheck® is non-invasive, inexpensive, and can be used by patients at any time when needed [29]. Another difference is the AF detection limit between ICM and FibriCheck®. FibriCheck® has an AF detection limit of 30 seconds since a measurement takes 60 seconds, whereas ICM has an AF detection limit of 2 minutes [29]. However, it is still unknown how long an AF episode should take to form a blood clot (i.e. thrombus) [22]. Furthermore, there is no evidence that patients with paroxysmal AF lasting less than 30 seconds should not receive OAC therapy [12]. Additionally, according to the ESC guidelines, the diagnosis of clinical AF is only confirmed by an ECG, with AF lasting at least 30 seconds [52]. Moreover, mHealth applications can be challenging to use in an elderly patient population. Therefore, FibriCheck® needs more validation to be used for diagnosing AF in cryptogenic stroke and TIA patients.

Study aim

If the origin of a cryptogenic stroke and TIA is unknown, the proper treatment cannot be given. Nowadays, undetected AF is an important issue in cryptogenic stroke and TIA patients because it can lead to a recurrent stroke. Therefore, long-term heart rhythm monitoring is crucial for the detection of AF in these patients. Currently, these patients are scheduled for an ICM implantation if a seven-day Holter does not detect AF. However, this is an invasive and expensive procedure, which patients do not cryptogenic stroke and TIA patients. In this study, we want to investigate if PPG-based mHealth has an equivalent AF detection rate compared to ICM in cryptogenic stroke and TIA patients. Because to our knowledge, there are no previous studies that compared ICM with PPG-based mHealth for the early detection of AF in these patients. Therefore, we hypothesize that PPG-based mHealth applications are non-inferior to ICM in the early detection of AF and could be an addition to the follow-up of cryptogenic stroke and TIA patients. Finally, we believe that the results of this paper will lead to new insights for the long-term follow-up of these patients.

METHODS

Study design

The REMOTE study is a prospective, multicentric, interventional, randomized trial in which cryptogenic stroke and TIA patients are recruited in Ziekenhuis Oost-Limburg and Jessa Hospital. The use of PPG-based mHealth (FibriCheck®) in smartphones and smartwatches was compared to the ICM in cryptogenic stroke and TIA patients. These patients had to use the FibriCheck® application for six months, starting on the day of the ICM implantation. They were randomly assigned in a 1:1 ratio to the smartphone or smartwatch group. The study was performed double-blinded, which means that both the patients and physicians were blinded for the FibriCheck® results during the study period. The results of the ICM were collected for 12 months in each patient.

Table 1: Overview of the in- and exclusion criteria of the REMOTE study.

Inclusion criteria	Exclusion criteria
Diagnosis of cryptogenic ischemic stroke or TIA	History of AF or atrial flutter
Age ≥ 18 years	Life expectancy < one year
The patient or his/her legal representative is willing to sign the informed consent form	Not qualified for ICM insertion
	Indication or contraindication for permanent OAC use at recruitment
	Untreated hyperthyroidism
	MI or coronary artery bypass grafting less than a month before the onset of the stroke
	Presence of PFO and an indication to start OAC according to the European Stroke Organization guidelines
	Not able to understand the Dutch language
	Patient or partner is not in possession of a smartphone
	Inclusion in another clinical trial that will influence the goals of this study

TIA, transient ischemic attack; AF, atrial fibrillation; ICM, insertable cardiac monitor; OAC, oral anticoagulant; MI, myocardial infarction; PFO, patent foramen ovale.

Study objectives

The primary aim of this study was to determine whether PPG-based mHealth using FibriCheck® has an equivalent AF detection rate compared to ICM in cryptogenic stroke and TIA patients. The secondary objective was to determine the AF burden and duration with FibriCheck® compared to ICM in these patients. Additionally, the AF detection rate between smartphones and smartwatches was also investigated. The compliance and motivation of these patients were also examined. Furthermore, the vision on mHealth and the user experience were assessed. Lastly, the feeling of safety was examined between FibriCheck® and ICM after six months.

Study population

This paper collected data of cryptogenic stroke and TIA patients that received an ICM in Ziekenhuis Oost-Limburg and the Jessa Hospital between September 2020 and April 2023. The in- and exclusion criteria are shown in **Table 1**.

Study set-up

Firstly, cryptogenic stroke patients received a seven-day Holter (i.e. Rooti). During this procedure, the patients were informed about the study by the co-investigators. A few weeks later, the results of the Rooti were discussed by the cardiologist. In case of no AF episodes, the patients were scheduled for an ICM implantation. On the day of the ICM implantation, the study was again explained to the patients. They were included in the study when they agreed and signed the informed consent. Afterwards, patients were randomly assigned to the smartphone or smartwatch group. Subsequently, FibriCheck® was installed on their smartphone. If the patient was assigned to the smartwatch group, a Fitbit® versa 2 was installed (with the FibriCheck® app) and given to the study participant.

Patients in the smartphone group were asked to perform two measurements per day and in case of symptoms (e.g. palpitations, dyspnoea, and others) with the FibriCheck® app for six months. During the measurement, they had to put their fingertip on the camera flash of their smartphone for 60 seconds. Subsequently, the heart rhythm was registered and sent to the FibriCheck® dashboard. The patients in the smartwatch group had to wear the smartwatch constantly during the study period (six months), except while charging. The Versa 2 automatically performed one-minute semi-continuous measurements with the FibriCheck® app every nine minutes. Previously, the FibriCheck® app measured the heart rhythm every three minutes. On the day of the inclusion, the patients also had to complete a questionnaire about their vision on mHealth **Supplementary Table 1**. At the end of the study, patients were again requested to fill in the same questionnaire with additional questionnaires about their user experience (**Supplementary Table 2**) [53] and feeling of safety (**Supplementary Table 3**).

The results of FibriCheck® were available to the researchers on the FibriCheck® dashboard. A red label on the dashboard represented a possible AF, while a green label

meant a sinus rhythm. Furthermore, an orange label indicated other arrhythmias, and a blue one represented insufficient signal quality. The participants received a notification from the study team when they did not performed the measurements for more than two days or when too many blue measurements were taken with the smartphone. If the problem was not resolved, they were called for further instructions. After the follow-up period of six months of using FibriCheck®, a report was made with a summary of all results, which was uploaded in the electronic medical record (HIX, Healthcare information eXchange; KWS, klinisch workstation) of the patients.

The ICM results were checked by a remote monitoring team of the hospital, which was the standard of care. The patients were contacted in case of irregularities or an AF detection, and a treatment plan was started. Thus, the ICM results were not blinded for the patient and cardiologist. At specific time points, patients had a consultation with the cardiologist to check the ICM. After the six-month follow-up period, the participants were contacted and asked to complete the remaining questionnaires. Patients in the smartwatch group were also required to return the Fitbit® to the study team. After 12 months, the ICM data were collected from the device dashboards (Medtronic, Ireland; Biotronik, Germany; St. Jude abbot, United States). At the end of the study, the FibriCheck® and ICM results were compared. The study period for each patient is shown in **Supplementary Figure 1**.

Data collection

All data were collected from HIX, KWS, and device dashboards. These data were pseudonymized before data storage and analysis. The patients received a study number, and the collected data were stored in an Electronic Case Report Form (Castor EDC, The Netherlands). General demographical data were collected, such as birth year, sex, height, weight, and body mass index (BMI). The medical history was also collected, which included smoking history, different comorbidities related to stroke (i.e. arterial hypertension, diabetes mellitus, hypercholesterolemia, dyslipidemia, congestive heart failure, chronic kidney disease, patent foramen ovale, etc.), date of stroke/TIA onset, and history of stroke/TIA. Moreover, stroke-related scores were gathered: Modified Ranking Scale (MRS) (0-6), National Institutes of Health Stroke Scale (NIHSS) (0-42), CHA_2DS_2VASc (0-9), and Alberta Stroke Program Early CT score (ASPECTS). In-hospital examinations (MRI scan, CT scan, laboratory results, etc.) were also obtained and stored in Castor. Furthermore, the medications administered during hospitalization and after hospital discharge (at four weeks, six months, and one year) were collected.

Data about the AF detection were collected from the device dashboards of FibriCheck® and ICM. This included the date and duration of the AF episodes. Additionally, the presence of other arrhythmias was stored in Castor. The AF burden for each patient was calculated by the number of hours in AF divided by the study period time (i.e. 4320 hours or less if the patient was still being monitored). The compliance was assessed by dividing the total number of measurements taken by the total number of expected or recommended measurements (i.e. two measurements per day for six months or 180 days) [17]. The patient's motivation was assessed by the number of days with at least two measurements per day divided by the number of days on which the FibriCheck® app was to be used (i.e. six months or 180 days or less if the patient was still being monitored) [17]. The data of the questionnaires were collected on a paper version, and the answers were stored in Castor. The user experience questionnaire consisted of 26 questions with a 7-point Likert scale, whereby each item consisted of two terms with opposite interpretations (e.g. conservative/innovative). The terms were randomly arranged for each item, so half of the items started with a positive term and the other half with a negative term. The most negative response was represented by -3, a neutral response by 0, and the most positive response by +3 [54]. Finally, the answers to the feeling of safety questionnaire were also based on this scoring system.

Statistical analysis

Statistical analysis was carried out using SPSS 28.0 (version 15). The Shapiro-Wilk was used to test the normality. Depending on the normality, continuous data were expressed as mean ± SD or median (IQR 1 – IQR 3). Categorical variables were presented as numbers (n) and percentages (%). Continuous data of the FibriCheck®-app and ICM were analyzed with a paired t-test or Wilcoxon signed-rank test, when appropriate. The McNemar test was performed for the

categorical variables. Significant differences between the smartphone and smartwatch group were checked by the unpaired t-test. In case of non-normally distributed data, the Mann-Whitney U test was used. The categorical variables were analyzed using the Pearson Chi-square test or Fisher exact test, when appropriate. For the comparison of the compliance, motivation and the number of measurements performed over time, a Friedman test and *post-hoc* Sign test with Bonferroni correction was performed. Finally, a p-value < 0.05 was considered significant.

Ethical approval

The protocol of this study was in accordance with the Declaration of Helsinki and the medical ethics committee of Ziekenhuis Oost-Limburg, Jessa Hospital, and Hasselt University had approved it. The study was started in September 2020 and will be completed around February 2025. Finally, the study was also registered at ClinicalTrials.gov (NCT05006105) [17].

RESULTS

Study population and patient characteristics

The study population comprised 136 cryptogenic stroke/TIA patients, of which 102 were from Ziekenhuis Oost-Limburg and 34 from the Jessa Hospital. However, six individuals didn't receive an ICM and were excluded before randomization. After randomization, 70 participants were assigned to the smartphone group and 60 patients to the smartwatch group. In total, there were nine drop-outs during the study period. The following reasons were given in the smartphone group: a) deleted the FibriCheck® account (n=1), b) perceived the measurements as a burden (n=4), and c) couldn't install FibriCheck® at home (n=1). The participants in the other group dropped out because a) the ICM was replaced with a pacemaker (n=1), b) perceived the measurements as a burden (n=1), and c) had an allergic reaction to the wristband (n=1).

Finally, 64 smartphone and 57 smartwatch participants were statistically analyzed (see **Figure 3**). The patient characteristics of the study population are shown in **Table 2**. Male participants and cryptogenic stroke patients predominated in the study. Most participants had no history of stroke or TIA and showed no symptoms according to the Modified Ranking Scale (MRS). The most common comorbidities were arterial hypertension and hypercholesterolemia. Overall, no statistically significant differences were found between the smartphone and smartwatch group. Lastly, the median time between stroke event and ICM implantation was 85 (51.5 – 123.5) days.

Atrial fibrillation detection between ICM and FibriCheck®

During the first six months, the ICM and FibriCheck® algorithms detected AF in 23 (27.0%) and 20 (23.5%) patients, respectively. After annotation by a medical caregiver, the ICM detected AF only in 7 (8.2%) patients. When only considering AF episodes without reported insufficient data quality, FibriCheck® detected AF in 12 (14.1%) patients, 3 (25.0%) of whom used a smartphone, and 9 (75.0%) were in the smartwatch group. No significant differences in first AF detection were found during the study period between FibriCheck® and ICM (p=0.27). The ICM detected AF for the first time in another 4 (4.7%) patients after six months, resulting in a 12-month AF detection yield of 12.9%. However, the ICM detected false-positive AF episodes in 18 (21.2%) patients within 12 months. These false AF episodes were reported in the electronic medical records as sinus arrhythmia, atrial/ventricular/ supraventricular extrasystoles, or atrial flutter. Nevertheless, oral anticoagulant (OAC) was started in one of these patients due to recurrent TIAs. Moreover, in some cases, FibriCheck® detected AF with reduced signal quality, while the ICM confirmed it as a sinus rhythm. In summary, no AF was found in 74 (87.1%) patients based on ICM, while 73 (85.9%) patients didn't have AF based on FibriCheck®. However, one year after ICM insertion, the ICM detected AF in 11 (12.0%) patients, and there were false-positive measurements in 18 (21.2%) patients. As mentioned earlier, after six months, FibriCheck® detected AF in 12 (14.1%) patients, while there was no AF in the other 73 (85.9%) patients. In summary, the AF findings are presented in **Table 3**. The sensitivity and specificity of FibriCheck® compared to ICMs in detecting AF were 36.4% and 89.2%, respectively.

Initiation of oral anticoagulants and successful telemonitoring in cryptogenic stroke and TIA patients

Oral anticoagulants was started in 11 patients with AF detected on ICM within one-year.

However, AF was annotated as an extrasystole/premature beat in one patient. Moreover, we could not collect further data from one drop-out patient with AF.

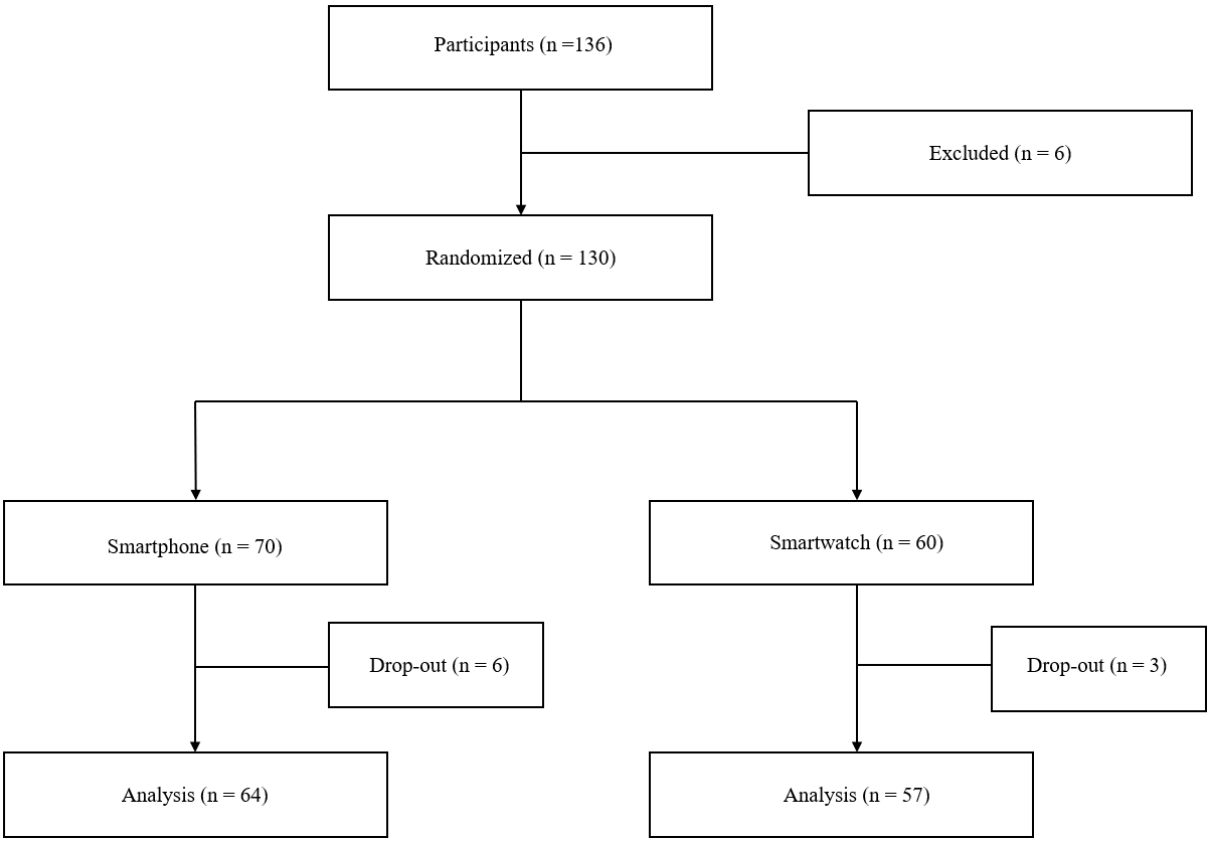


Figure 3. Flowchart of the patient recruitment and randomization.

Furthermore, FibriCheck® also detected AF in 5 of these 10 AF patients. The mean time between AF detection and OAC start was 83.5 ± 69.6 days for ICM and 110.3 ± 110.0 days for FibriCheck®. No significant difference was found between these two (p=0.53). Telemonitoring was successful in 81.8% of these patients. Remarkably, OAC was started in two patients the day after AF was detected on ICM. In one of these patients, Asaflow (80 mg/day) was replaced by Lixiana (60 mg/day). In the other patient, Clopidogrel (75 mg/day) was replaced by Lixiana (60 mg/day). Remarkably, multiple AF episodes (i.e. 22 episodes) were detected with FibriCheck® in one patient during the study period, while we noticed that the ICM telemonitoring was ineffective at that moment. This result was eventually reviewed with the cardiologist. The patient was also informed by telephone of the FibriCheck® findings. Consequently, the cardiologist decided to replace Clopidogrel (75 mg/day) with Lixiana (60 mg/day), because the brain lesions were probably a result of the intermittent AF.

Overall, telemonitoring with ICM was successful in 74.4% of the patients within six months, while this was 67.6% after six months. There was no significant difference between the smartphone and smartwatch group in case of successful telemonitoring during and after the study period (p=0.52, p=0.95, respectively). The median time between ICM implantation and AF detection with ICM (n=7) and FibriCheck® (n=4) was 3.0 (1.0 – 64.0) days and 7.0 (2.25 – 96.5) days, respectively. No statistically significant difference was found (p=0.11).

AF burden and duration

The median AF burden was 0.006% (0.007 – 0.024%) with ICM (n=7), while this was 0.18% (0.01 – 2.92%) for FibriCheck® (n=12). The median AF duration was 0.16 h (0.03 – 0.49 h) with ICM (n=7), while this was 5.06 h (0.48 – 126.3 h) for FibriCheck® (n=12). The AF burden and duration between the two cardiac monitoring methods showed no significant differences (p=0.29, p=0.29, respectively). In addition, the median AF burden of ICM (n=11)

Table 2. Patient characteristics.

Characteristics	Smartphone (n= 64)	Smartwatch (n= 57)	P-value
Age (in years)	63.0 (57.3 – 71.8)	66.0 (58.0 – 71.5)	0.52
Sex			0.93
Male	42 (65.6%)	37 (64.9%)	
Female	22 (34.4%)	20 (35.1%)	
BMI (in kg/m^2)	26.8 (24.0 – 29.3)	27.2 (24.1 – 29.4)	0,51
Diagnosis			0.74
Stroke	51 (79.7%)	44 (77.2%)	
TIA	13 (20.3%)	13 (22.8 %)	
History			
Stroke	10 (15.6%)	8 (14.0%)	0.81
TIA	4 (6.3%)	5 (8.8%)	0.60
No history of stroke or TIA	51 (79.7%)	45 (78.9%)	0.92
Modified Ranking Scale (MRS)			0.52
No symptoms	43 (81.1%)	42 (79.2%)	
No significant disability	7 (13.2%)	9 (17.0%)	
Slight disability	3 (5.7%)	1 (1.9%)	
Moderate disability	0 (0%)	1 (1.9%)	
NIHSS score	1.0 (0 – 3.0)	1.0 (0 – 3.0)	0.95
CHA_2DS_2VASc score	4.0 (3.0 – 5.0)	4.0 (3.0 – 5.0)	0.86
Smoking			0.72
Current	17 (26.6%)	14 (24.6%)	
Former	17 (26.6%)	19 (33.3%)	
No	30 (46.9%)	24 (42.1%)	
Comorbidities			
Arterial hypertension	41 (64.1%)	36 (63.2%)	0.92
Diabetes Mellitus	7 (10.9%)	10 (17.5%)	0.29
Hypercholesterolemia	40 (62.5%)	36 (63.2%)	0.94
Family history of CVDs	16 (25.0%)	19 (33.3%)	0.31
Peripheral artery disease	4 (6.3%)	5 (8.8%)	0.60
Myocardial infarction	3 (4.7%)	6 (10.5%)	0.22
Atherosclerosis	9 (14.1%)	12 (21.1%)	0.31
PFO	14 (21.9%)	14 (24.6%)	0.73
Coronary artery disease	7 (10.9%)	7 (12.3%)	0.82
No comorbidities	6 (9.4%)	6 (10.5%)	0.83
Days between stroke and ICM implantation	91.0 (65.8 – 126.5)	101.5 (71.8 – 134.5)	0.27

BMI, body mass index (in kg/m^2); TIA, transient ischemic attack; NIHSS, score on National Institutes of Health Stroke Scale ranges from 0 to 42: higher score means more severe neurological defects; CHA_2DS_2VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and gender category (female) ranges from 0 to 9: a higher score means an increased risk of stroke; ICM, insertable cardiac monitor; CVDs, cardiovascular diseases; PFO, patent foramen ovale. * Statistical analysis were performed using the Mann-Whitney U test and the Chi-squared test. * $p<0.05$.

over 12 months was 0.006% (0.001 – 0.06%). Telemonitoring was only successful in 12 (63.2%) of these AF patients, while it failed in the other 5 (26.3%) patients. The last 2 (10.5%) patients were still under observation.

Insertable cardiac monitor recordings

As mentioned earlier, three types of ICMs were implanted during the study. The Medtronic was placed in 70 (82.4%) patients, while the Biotronik and St. Jude were implanted in 13 (15.3%) and 2 (2.4%) patients, respectively.

The ICM continuously measured the heart rhythm, whereby other cardiac arrhythmias could also be detected during the study. Ventricular tachycardia was detected in 17.4% of the patients, of which 58.8% were approved, and 41.2% were disapproved. Additionally, a pause was detected in 14.0% of the patients. In total, nine pauses (69.3%) were confirmed. Furthermore, bradycardia was found in five

Table 3. Overview of the AF findings with FibriCheck® (within 6 months) and ICM (within 12 months).

		FibriCheck®	
		AF	No AF
ICM	AF	4 (4.7%)	7 (8.2%)
	No AF	8 (9.4%)	66 (77.7%)

ICM, insertable cardiac monitor; AF, atrial fibrillation.

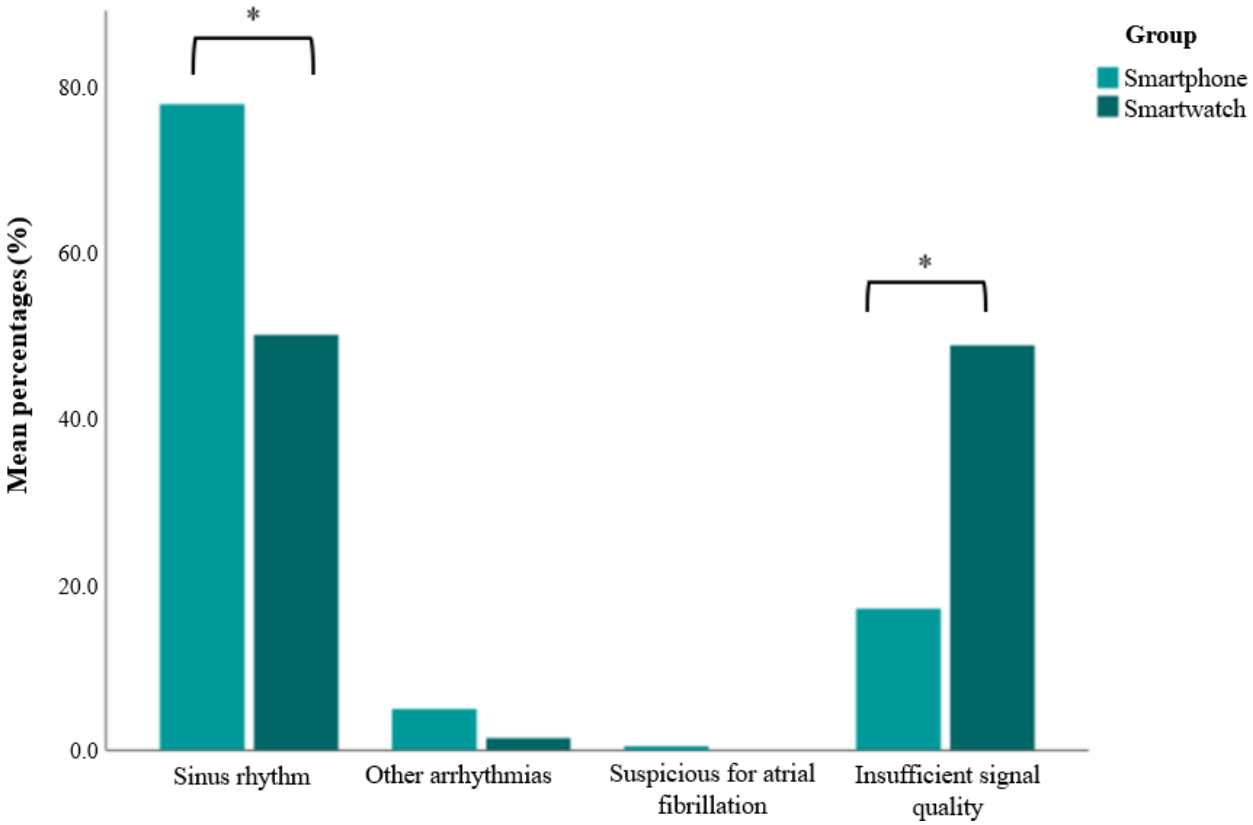


Figure 4. Overview of the FibriCheck® recordings. The mean percentages (%) are plotted in function of the different FibriCheck® recordings. The light green bar presents the recordings of the smartphone group, while the dark green bar represents the smartwatch group. Statistical analysis was performed using the Mann-Whitney U test. * $p<0.05$.

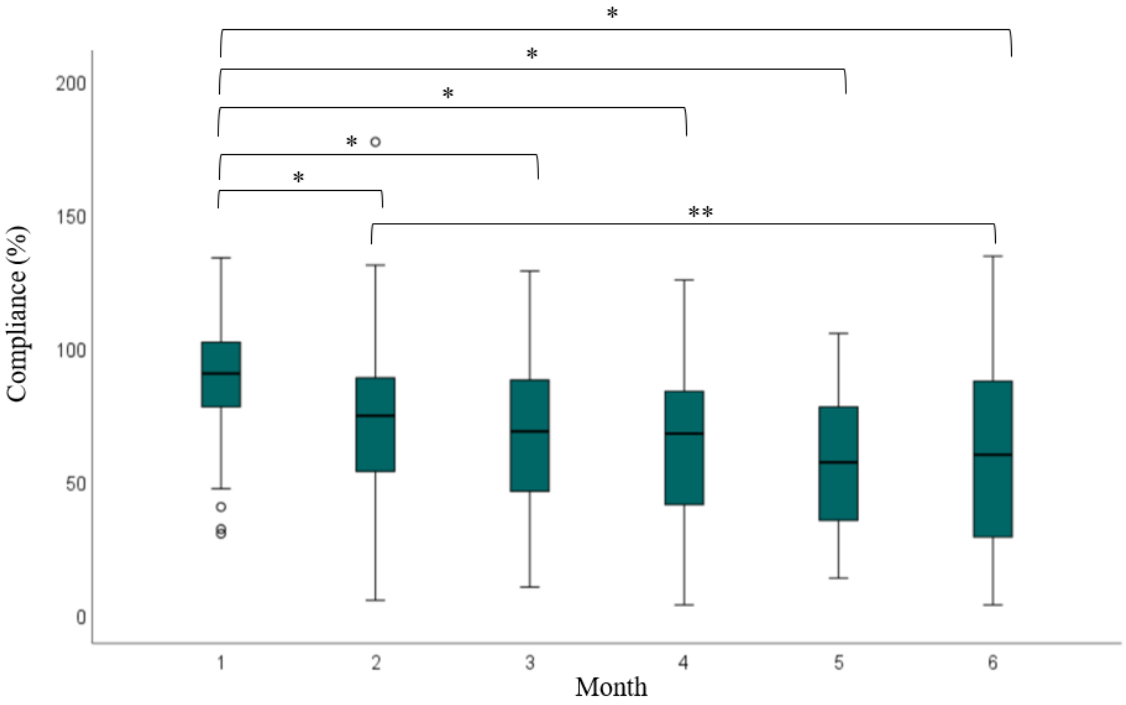
patients within six months. After six months, ventricular tachycardia was confirmed in 10 patients (58.8%). A pause was confirmed in seven patients (53.9%), while bradycardia was only found in 2 patients (1.7%). Interestingly, the ICM was repositioned in one study participant due to dysfunction.

FibriCheck® recordings

Figure 4 presents the results of FibriCheck® recordings between the smartphone and smartwatch group. There were four labels (sinus rhythm, other arrhythmias (extrasystole, tachycardia, etc.), suspicious for AF, and insufficient signal quality), and for each label, the mean percentage (%) was calculated for both groups.

The mean percentage of sinus rhythm was significantly higher in the smartphone group than in the smartwatch group ($p<0.001$). There was no significant differences between the groups in detecting other cardiac arrhythmias and possible AF ($p=0.59$, $p=0.09$, respectively). The insufficient signal quality was significantly higher in the smartwatch group than the smartphone group ($p<0.001$).

A)



B)

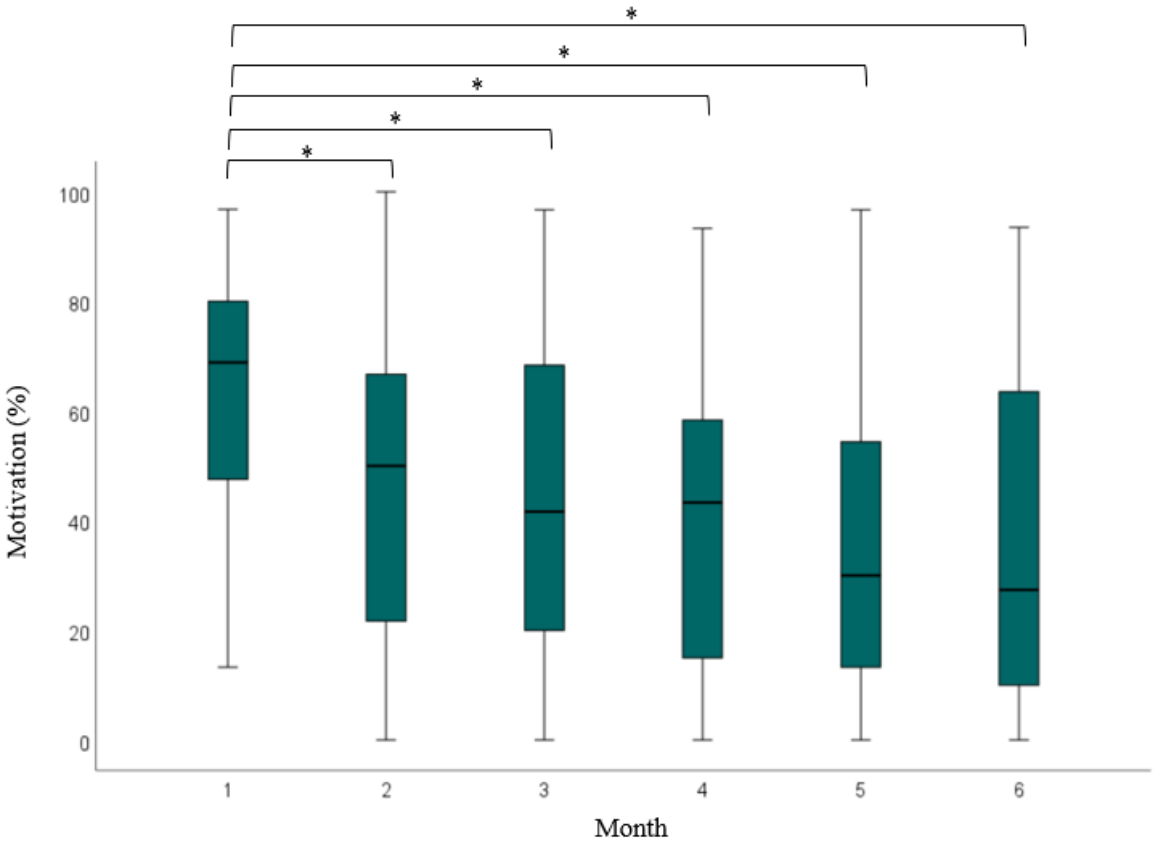


Figure 5. Overview of the compliance (A) and motivation (B) in the smartphone group over the six-month follow-up period. Statistical analyses were performed using the Friedman test, followed by a *post-hoc* Sign test with Bonferroni correction. ** p<0.001, ** p=0.002*

Compliance, motivation and number of measurements with mHealth

First of all, drop-out patients (n=9) were not included in the analyses of the compliance, motivation, and the number of measurements. The median time between ICM implantation and drop-out date was 47 (36.5 – 110.5) days.

The compliance and motivation were assessed in the smartphone group (n=44), as shown in **Figure 5 (A, B)**. Both compliance and motivation had a significance level of $p<0.003$ after Bonferroni correction, and a significant decrease was noticed after the first month ($p<0.001$). However, compliance was also significantly decreased between the second and sixth month ($p=0.002$).

The number of measurements in the smartwatch group was also evaluated (see **Figure 6**). Overall, the number of measurements decreased significantly over time ($p=0.014$). Moreover, a slight decrease in the number of measurements was observed after the first month. After this decline, there was a similar trend in the other months. The median number of measurements with the smartwatch was 13,382.5 (5482,8 – 22,260.8).

Half of these patients used the Fitbit®, while the other half were in the smartphone group. Participants were contacted who had issues with the FibriCheck® and Fitbit® applications. These problems were mainly related to insufficient Bluetooth or Wi-Fi connection, or participants logged out of the app, changed the FibriCheck® clockface, had synchronization problems, or deleted the study account or application accidentally. In total, 25 (29.4%) patients needed assistance in person, 53 (62.4%) patients were helped with instructions by telephone, and 8 (9.5%) patients by e-mail. 11 (12.9%) participants completed the study without any assistance.

Vision on mHealth, user experience and feeling of safety

Before the study, only 81.8% of the patients knew that mHealth applications existed, while this was 96.1% after the study. There was no clear difference between the types of applications used before and after the study. The answers to the vision on mHealth questionnaire also showed that patients prefer to use mHealth applications certified by mHealthBelgium,

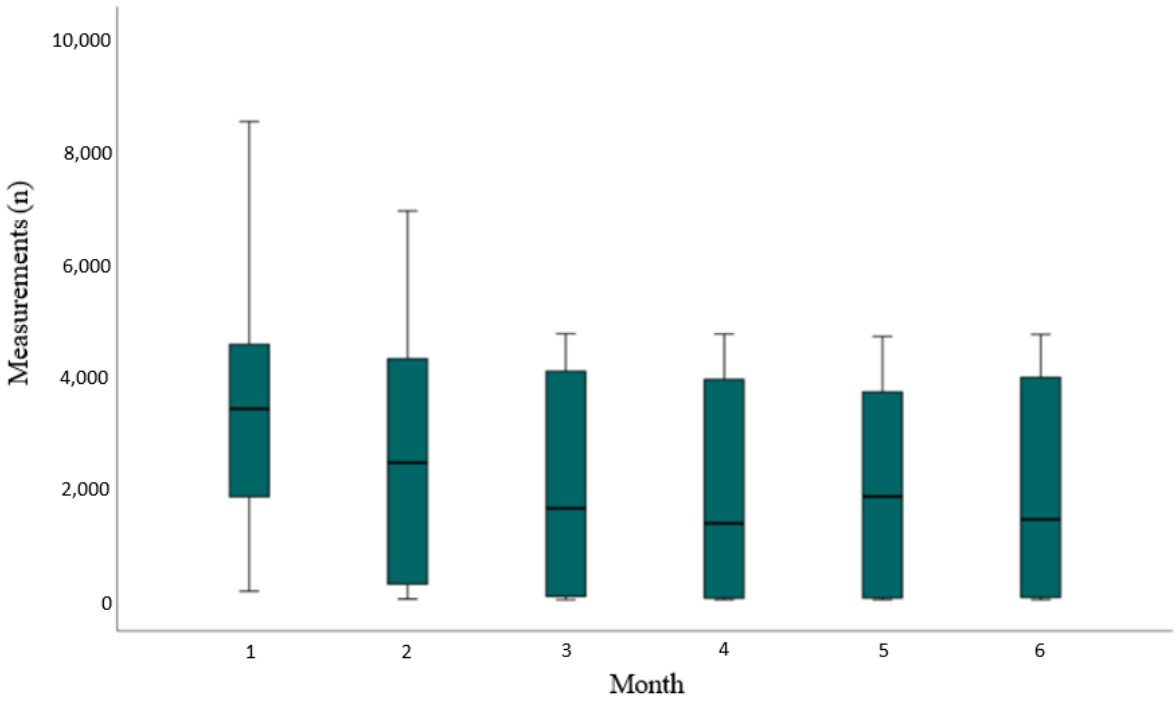


Figure 6. Overview of the number of measurements per month in the smartwatch group. Theoretically, 4800 measurements were expected with the Fitbit® per month. Statistical analyses were performed using the Friedman test, followed by a *post-hoc* Sign test with Bonferroni correction.

FibriCheck® notifications

During the study period, 74 (87.1%) participants received at least one FibriCheck® notification. which is a government organization (see **Supplementary Table 4**.).

The user experience of FibriCheck® was assessed by the validated User Experience Questionnaire (UEQ). This questionnaire analysed the user experience according to six categories: attractiveness, perspicuity, efficiency, dependability, stimulation, and novelty. The answers of 11 patients in the smartphone group and five patients in the smartwatch group were not included in the analysis due to inconsistencies. **Supplementary Figure 2 (A)** shows the results of this questionnaire based on the mean score in each category. There was a significant difference in perspicuity between the smartphone and smartwatch group (p=0.0025). There was no significant difference between the smartphone and smartwatch group in the other categories.

The feeling of safety questionnaire was based on the same scoring system **Supplementary Figure 2 (B)**. This questionnaire analysed the safety feeling of patients between FibriCheck® and ICM. There were three categories (safety, securely, and reliability), and no significant difference was found between the two cardiac monitoring methods. The mean score for all categories was always above two. Thus, patients had a similar positive feeling with FibriCheck® and ICM.

DISCUSSION

REMOTE study

The aim of the REMOTE study was to compare the use of the mHealth application FibriCheck® with ICM in the early detection of AF in cryptogenic stroke and TIA patients. We investigated whether FibriCheck® and ICM have a similar AF detection rate in these patients. The obtained results gave us more insight into the use of mHealth (i.e. FibriCheck®). In this way, we could possibly offer patients non-invasive alternatives for long-term cardiac monitoring in the future.

Atrial fibrillation detection between ICM and FibriCheck®

The ICM detected AF in 8.2% of the patients within six months. Furthermore, AF was detected with ICM in 12.9% of the patients over 12 months. These findings were comparable with the CRYSTAL-AF study, in which ICM detected AF in 8.9% of the patients within six months and 12.4% within 12 months [39]. On the other hand, FibriCheck® detected AF in 14.1% of the patients. Remarkably, the smartwatch group detected more AF episodes with FibriCheck® than the smartphone group. Atrial fibrillation episodes were possibly missed in the smartphone group because the heart rhythm was only measured 2x60 seconds per day (spot-check measurements) with the phone, while the smartwatch performed semi-continuous measurements every nine minutes. Consequently, this indicates the importance of continuous heart rhythm monitoring in detecting paroxysmal AF. No statistically significant difference was found in AF detection between the two cardiac monitoring methods (i.e. ICM versus FibriCheck®). Additionally, the ICM detected four AF episodes after six months. This was also the case in other studies, where AF was still detected with ICM after six months [39, 55]. However, it was less detected than during the first six months. This could be due to unsuccessful telemonitoring and no cardiology consultation. As a result, AF episodes may be missed during the study period, as the ICM is usually read out during a consultation. Moreover, AF can be detected during an emergency admission to the hospital, which was the case in one of our participants. Therefore, FibriCheck® is useful in such situations and might be used as an additional tool.

The median time between stroke and ICM implantation was longer in our study compared to other studies [39, 41]. However, AF was detected quickly after ICM insertion. This could be due to the small sample size. Furthermore, we can conclude that ICM should be implanted soon after a stroke. Nowadays, there are very long waiting lists for ICMs. Thus, FibriCheck® plays a crucial role in this intermediate period.

Insertable cardiac monitor recordings

Most of our participants (82.4%) received the ICM of Medtronic®, with an AF algorithm based on an AF detection limit of two minutes. A previous study showed that Medtronic® had a sensitivity of 96.1% in patients with known AF [38, 56]. However, false-positive AF episodes were found in 21.2% of the patients within 12 months. There are several reasons for false positive AF episodes, for example, oversensing, noise, premature ventricular contractions, signal drop out, and sinus arrhythmia [38, 57, 58]. False positive AF episodes could also be a precursor to a “real’ AF episode. Dysfunction of ICM was also found in one patient during the study. This caused frequent oversensing with artefacts. Consequently, the ICM was again replaced. All of these situations require nurses or

cardiologists to review episodes multiple times. FibriCheck® could be used here as an additional checkpoint and reduce the workload of healthcare professionals [17]. The Medtronic also has a limited memory. When the storage capacity is exceeded, old measurements are deleted to store new AF episodes [39]. In this case, AF episodes could be missed. Therefore, cardiology consultations are essential during the follow-up period of cryptogenic stroke and TIA patients. However, this creates an additional hospital burden.

Initiation of oral anticoagulants in cryptogenic stroke and TIA patients

Oral anticoagulants was started in all patients with AF. The mean time between AF detection and OAC start seemed higher for FibriCheck® than ICM. This is because the FibriCheck® results are reported in the electronic medical report after the follow-up period, while successful telemonitoring with ICM ensures faster decision-making. On the other hand, unsuccessful telemonitoring also caused a delayed OAC start. Therefore, successful telemonitoring is very important for a proper treatment plan. Furthermore, FibriCheck® could also be used outside the study. An advantage of this is that patients are immediately informed if AF is detected, while the ICM results are not available to patients. For this reason, FibriCheck® could be used as an additional tool for the early detection of AF in cryptogenic stroke and TIA patients. From our results, we can also observe the crucial role of FibriCheck®. Surprisingly, the cardiologist decided to start OAC in one patient with many AF episodes detected with FibriCheck®. There is still a debate in the literature about when OAC should be started. However, an AF episode with a minimum duration of 30 seconds is considered enough to start OAC [12]. A limitation is that PPG cannot diagnose AF. An ECG recording is required to confirm AF and to start OAC usage [12, 29]. Remarkably, one patient in our study experienced an AF episode of 10 seconds. The episode was detected with ICM, and OAC was started by the cardiologist.

AF burden and duration

There was a clear trend in AF burden and duration between FibriCheck® (n=12) and ICM (n=7). The AF burden and duration of FibriCheck® seemed higher than ICM. This is mainly caused by the small sample size, resulting in a limited number of AF episodes, but also the unsuccessful telemonitoring with ICM. Furthermore, an estimate was made based on the number of measurements taken with FibriCheck®. Multiple measurements before and after an AF detection will yield a more accurate estimate of AF duration. However, this was not the case in the smartphone group because they were requested to take two measurements per day. If they were not blinded to the FibriCheck® results, a possible AF detection would lead to additional measurements. Moreover, AF episodes can last for a long time. Patients can experience an AF episode of 1h to 24h [56]. Thus, spot-check measurements may not be enough to determine the duration of the AF episode. So, multiple measurements with FibriCheck® are needed to accurately estimate the AF duration. This was not always the case in our study groups, resulting in an overestimation of the AF duration and burden.

FibriCheck® recordings

In total, there were four labels for the FibriCheck® recordings. The smartphone group had more measurements with a sinus rhythm, while the smartwatch group had more data with insufficient signal quality. There are several possible explanations for these results. First of all, the participants in the smartphone group were aware when they performed a measurement. These participants were warned to remain still during the recording so the heart rhythm could be measured accurately [17]. This was not the case in the smartwatch group. The automatic semi-continuous measurements were performed while the participants went about their daily activities (i.e. walking). Thus, the smartwatch was more sensitive to movements, possibly leading to motion artefacts [17, 29, 59]. Another possible explanation is that the watch group did not always wear the Fitbit® (e.g. while charging, showering, etc.). Therefore, it was also crucial for the watch group to wear the Fitbit® at night because then the body movements are reduced (see **Supplementary Figure 3**). The insufficient signal quality in the smartphone group could be due to patients with multiple phone cameras. The distance between the flash and the camera is usually large, which can cause patients to mistake where to put their fingertip. Moreover, when the distance between the finger and the camera becomes too great, the fingertip is less lighted by the flash.

There was no significant difference between both groups in detecting other arrhythmias and AF, possibly due to the small sample size and limited patients with AF. However, the smartphone group seemed to have more episodes of other arrhythmias. This is probably due to the additional measurements in the smartphone group when they experienced symptoms [17]. The low sensitivity of FibriCheck® (36.4%) in our study may be due to the elderly population. There is a reduced blood supply to the peripheral tissues in these patients. As a result, they often have cold fingers, which affects the quality of the PPG signal, resulting in a low sensitivity [60].

Compliance, motivation and number of measurements with mHealth

The compliance and motivation in the smartphone group decreased significantly over time. This means that participants didn't always perform two measurements per day during the different months. This could be due to the blinding of the FibriCheck® results. Blinding was essential to obtain reliable results. However, this reduced the motivation of the patients to perform the measurements. The participants also claimed that if the results were not blinded, they would be more motivated to perform the measurements. According to some participants, the study period was also long, reducing their motivation. Another reason for the reduced number of measurements is that patients sometimes develop memory problems or dementia after a stroke [2, 17, 61]. However, they were reminded with notifications to perform the measurements. Only 11 patients completed the study without notifications. This indicates the importance of constant follow-up by a caregiver. Additionally, more patients in the smartphone group quickly dropped out of the study. The main reason was that they found the measurements as a burden, which is also seen in the decreased compliance and motivation. This was not the case in the smartwatch group.

The compliance and motivation couldn't be calculated in the smartwatch group. Instead, the total number of semi-continuous measurements per month was examined. The results showed an overall significant difference. However, according to the *post-hoc* Sign test, there were no specific significant differences between the different months. A reason for this is that the participants didn't have to carry out measurements themselves. They only had to wear the Fitbit® and charge when needed. However, the number of measurements slightly decreased compared to the first month. This is probably due to the switch from the automatic measurements. The heart rhythm of the first included patients in the smartwatch group was measured every three minutes. This created a large amount of dataset (i.e. many measurements), which led to errors. As a result, the FibriCheck® team decided to switch to automatic measurements every nine minutes. Theoretically, we expected a total of 28,800 automatic measurements with the Fitbit® watch. Although, it was impossible to reach this number because the patients could not wear the watch constantly (e.g. when it was charging). Moreover, patients usually had synchronization or Bluetooth problems, so the measurements were not always forwarded. The Fitbit® watch also had limited storage capacity, which caused for data loss. This was avoided as much as possible by sending notifications or giving instructions by telephone to the patients. Ischemic stroke patients are also often elderly [62]. These patients are usually not used to mobile technology and need more assistance. This can also be observed in the user experience questionnaire. Participants had a significant difference in perspicuity. Patients also usually have privacy concerns when mHealth applications are recommended [63]. This older population should receive enough education about mHealth technology so that we can include more patients in the future. This will ultimately ensure a larger sample size and more reliable results.

Study limitations

The REMOTE study has some limitations, notably related to the small sample size and technical issues. First of all, the distribution of the patients in the study groups was not equal because of the limited amount of smartwatches. However, the study is still ongoing. Thus, the number of participants may change in the meantime. Some participants also didn't complete the six-month study period, resulting in insufficient data. Some AF episodes probably had not yet occurred. As mentioned earlier, the patient's motivation and compliance decreased over time, and some patients had difficulty performing the measurements. All of this resulted in additional data loss.

CONCLUSION

This study identified the use of PPG-based mHealth in the early detection of AF in cryptogenic stroke and TIA patients compared to ICM. Our analysis showed that FibriCheck® had a similar AF detection rate compared to ICM. However, the FibriCheck® measurements decreased over time, and some were of insufficient signal quality. On the other hand, the ICM resulted in many false-positive results, and telemonitoring was not effective in all patients. In some cases, AF was detected by FibriCheck® and not by ICM and vice versa. A similar AF burden and duration between FibriCheck® and ICM was observed. However, this could be due to the limited number of patients with AF thus far. The compliance and motivation of the patients were crucial to get accurate results in the smartphone group. In conclusion, these results indicate that FibriCheck® could be used as an addition to ICM, but a larger sample size and further analysis is needed to confirm this.

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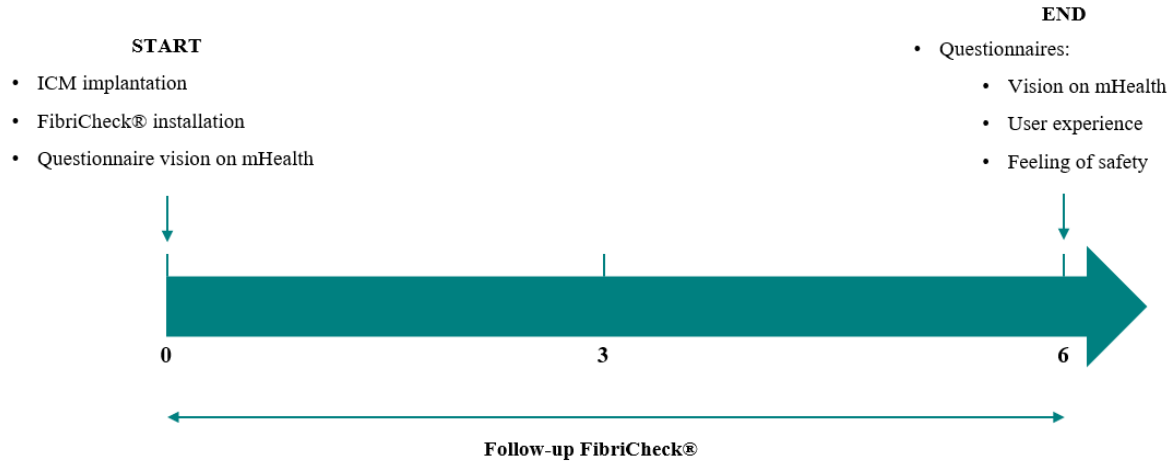
SUPPLEMENTARY INFORMATION

Supplementary Figure 1. Timeline of the study period.



ICM, insertable cardiac monitor; mHealth, mobile Health.

Supplementary Table 1. Questionnaire vision on mHealth.

Patient study ID: Date: Timing questionnaire: ☐ Before use mHealth (1 month after discharge) ☐ After use mHealth (after 6 months of using FibriCheck®)	
1. Are you aware of the availability of health apps (applications) for smartphones?	☐ Yes ☐ No
2. What type of applications do you download?	☐ Games ☐ Educational ☐ Books ☐ News ☐ Social ☐ Health and lifestyle ☐ Economic ☐ Other:
3. What kind of app do you download when you download an health app?	☐ BMI/alcohol units ☐ Smoking cessation ☐ Diet and nutrition ☐ Fitness (e.g. pedometer) ☐ Relaxation ☐ None ☐ Other:
4. Check the box that best describes what you think. 1. I would use a health application that is **not** supported by a recognized health instance such as mHealthBELGIUM.	☐ Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree
2. I would use a health application that is supported by a recognized health instance such as mHealthBELGIUM.	☐ Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree

Supplementary Table 2. mHealth user experience questionnaire.

Patient study ID:					**Date:**				
		1	**2**	**3**	**4**	**5**	**6**	**7**	
1.	Annoying	☐	☐	☐	☐	☐	☐	☐	Enjoyable
2.	Not understandable	☐	☐	☐	☐	☐	☐	☐	Understandable
3.	Creative	☐	☐	☐	☐	☐	☐	☐	Dull
4.	Easy to learn	☐	☐	☐	☐	☐	☐	☐	Difficult to learn
5.	Valuable	☐	☐	☐	☐	☐	☐	☐	Inferior
6.	Boring	☐	☐	☐	☐	☐	☐	☐	Exciting
7.	Not interesting	☐	☐	☐	☐	☐	☐	☐	Interesting
8.	Unpredictable	☐	☐	☐	☐	☐	☐	☐	Predictable
9.	Fast	☐	☐	☐	☐	☐	☐	☐	Slow
10.	Inventive	☐	☐	☐	☐	☐	☐	☐	Conventional
11.	Obstructive	☐	☐	☐	☐	☐	☐	☐	Supportive
12.	Good	☐	☐	☐	☐	☐	☐	☐	Bad
13.	Complicated	☐	☐	☐	☐	☐	☐	☐	Easy
14.	Unlikable	☐	☐	☐	☐	☐	☐	☐	Pleasing
15.	Usual	☐	☐	☐	☐	☐	☐	☐	Leading edge
16.	Unpleasant	☐	☐	☐	☐	☐	☐	☐	Pleasant
17.	Secure	☐	☐	☐	☐	☐	☐	☐	Not secure
18.	Motivating	☐	☐	☐	☐	☐	☐	☐	Demotivating
19.	Meets expectations	☐	☐	☐	☐	☐	☐	☐	Does not meet expectations
20.	Inefficient	☐	☐	☐	☐	☐	☐	☐	Efficient
21.	Clear	☐	☐	☐	☐	☐	☐	☐	Confusing
22.	Impractical	☐	☐	☐	☐	☐	☐	☐	Practical
23.	Organized	☐	☐	☐	☐	☐	☐	☐	Cluttered
24.	Attractive	☐	☐	☐	☐	☐	☐	☐	Unattractive
25.	Friendly	☐	☐	☐	☐	☐	☐	☐	Unfriendly
26.	Conservative	☐	☐	☐	☐	☐	☐	☐	Innovative
		1	**2**	**3**	**4**	**5**	**6**	**7**	

Supplementary Table 3. Feeling of safety questionnaire.

Patient study ID: Date:

How did you feel when using the smartphone application FibriCheck® to detect cardiac arrhythmias?

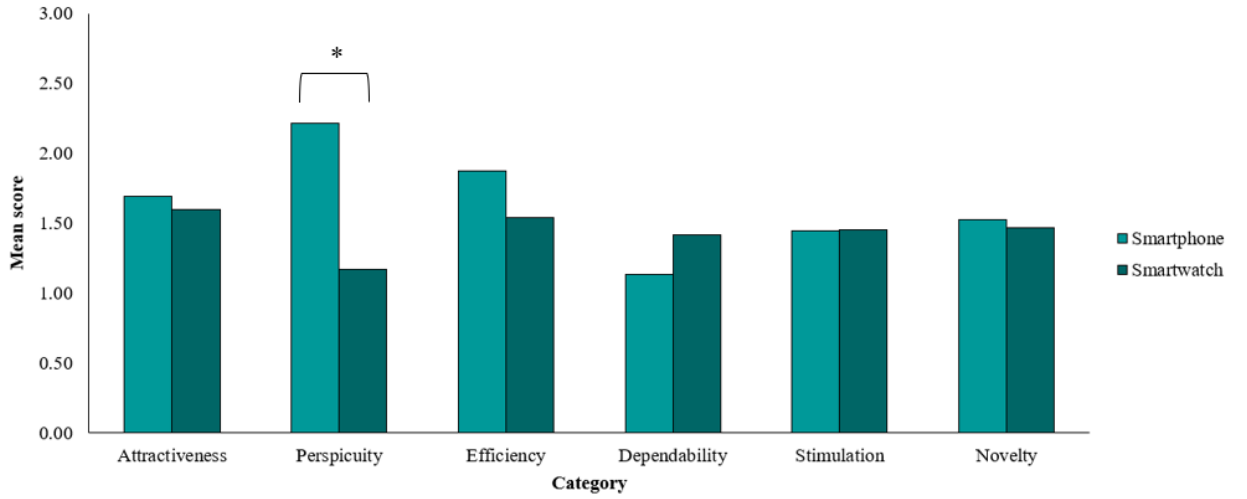
Mobile Health (FibriCheck® application)								
	1	**2**	**3**	**4**	**5**	**6**	**7**	
Secure	☐	☐	☐	☐	☐	☐	☐	Not secure
At ease	☐	☐	☐	☐	☐	☐	☐	Worried
Reliable	☐	☐	☐	☐	☐	☐	☐	Unreliable

How did you feel about the device implanted in your chest that detects cardiac arrhythmias?

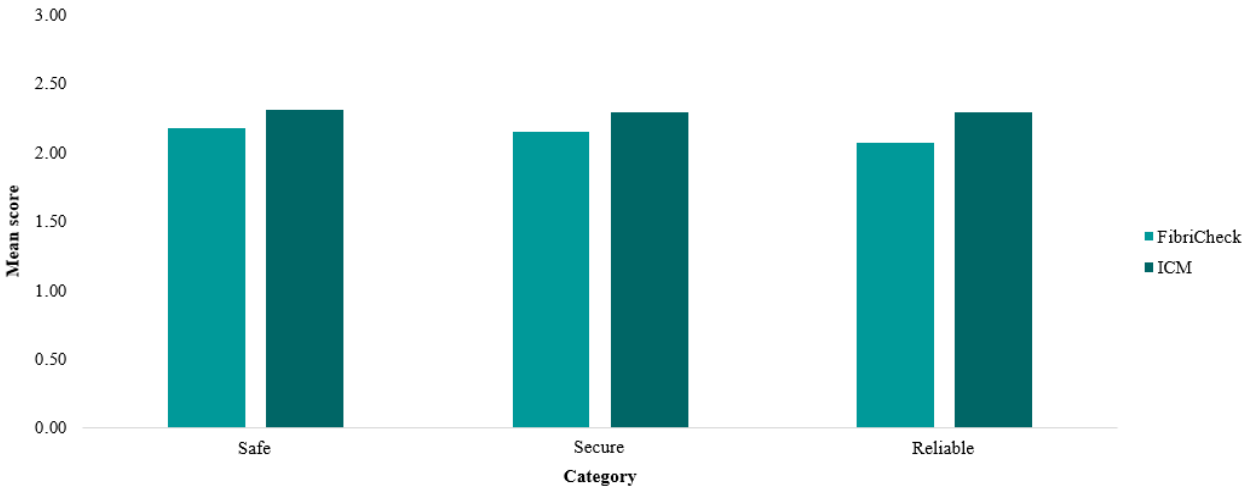
ICM (insertable cardiac monitor)								
	1	**2**	**3**	**4**	**5**	**6**	**7**	
Secure	☐	☐	☐	☐	☐	☐	☐	Not secure
At ease	☐	☐	☐	☐	☐	☐	☐	Worried
Reliable	☐	☐	☐	☐	☐	☐	☐	Unreliable

Supplementary Figure 2. The mean score of the answers to the questionnaires of user experience (A) and feeling of safety (B).

A)



B)



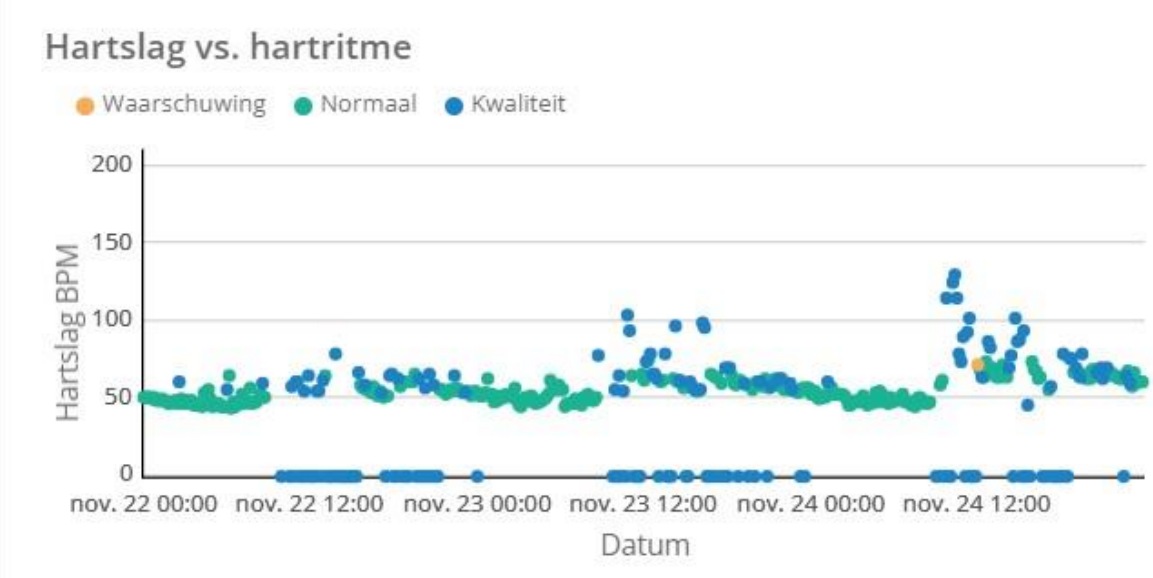
*The light and dark green bars (A) represent the smartphone/FibriCheck® and smartwatch/ICM group, respectively. *p=0.0025*

ICM, insertable cardiac monitor.

Supplementary Table 4. Overview of the answers on the vision on mHealth questionnaire.

	Before	After
☐ Yes	81.8%	96.1%
☐ No	18.2%	3.9%
☐ Games	31.9%	18.5%
☐ Educational	22.4%	20.2%
☐ Books	4.3%	8.4%
☐ News	64.7%	42.0%
☐ Social	79.3%	48.7%
☐ Health and lifestyle	44.8%	28.6%
☐ Economic	64.7%	44.5%
☐ Other: heritage, weather, physiotherapist related, cycling route..	3.4%	1.7%
☐ BMI/alcohol units	5.0%	6.6%
☐ Smoking cessation	1.7%	1.7%
☐ Diet and nutrition	5.8%	5.8%
☐ Fitness (e.g. pedometer)	43.8%	29.8%
☐ Relaxation	3.3%	4.1%
☐ None	53.7%	28.1%
☐ Other: blood pressure- and temperature monitor, orthopedic app.	1.7%	0.8%
☐ Strongly agree	0.8%	0%
☐ Agree	17.4%	6.6%
☐ Neutral	44.6%	33.9%
☐ Disagree	14.0%	11.6%
☐ Strongly disagree	23.1%	10.7%
☐ Strongly agree	37.2%	28.1%
☐ Agree	28.1%	19.8%
☐ Neutral	30.6%	13.2%
☐ Disagree	1.7%	0.8%
☐ Strongly disagree	2.5%	0.8%

Supplementary Figure 3. An example of measurements at night (green) and during the day (blue).



The heart rate is shown on the y-axis, and the date and hour of the measurement on the x-axis. The green, orange, and blue labels represents the heart rhythm.