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Maastricht University

# Faculteit Geneeskunde en Levenswetenschappen
## *School voor Levenswetenschappen*
master in de biomedische wetenschappen

***Masterthesis***

***Identifying pitfalls and opportunities of atrial fibrillation detection by the implantable cardiac monitor and mobile health in cryptogenic stroke patients***

**Bo Daelman**

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

**2021**
**2022**

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# Identifying pitfalls and opportunities of atrial fibrillation detection by the implantable cardiac monitor and mobile health in cryptogenic stroke patients

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*Running title: *Cardiac monitoring in cryptogenic stroke patients*

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**Keywords:** cryptogenic stroke, atrial fibrillation, implantable cardiac monitor, loop recorder, mobile health, FibriCheck, cardiac rhythm monitoring

## ABSTRACT

**BACKGROUND – Approximately one-third of the strokes are classified as cryptogenic due to their unknown etiology. A possible cause is atrial fibrillation (AF). Therefore, long-term cardiac monitoring by the invasive and expensive implantable cardiac monitor (ICM) is advocated. However, smartphone and smartwatch applications have emerged as reliable non-invasive and inexpensive alternatives to detect AF. This study examines if the photoplethysmography-based FibriCheck application has a similar AF detection yield compared to the ICM in cryptogenic stroke and transient ischemic attack (TIA) patients.**

**METHODS – Cryptogenic stroke and TIA patients (n=64) received an ICM to enable AF detection. Additionally, they were randomized into a smartphone (n=36) or smartwatch (n=28) group for the six-month FibriCheck use.**

**RESULTS – There was no significant difference in AF detection between the ICM and FibriCheck (n=4, n=9, respectively, $p$=0.180). Furthermore, AF detection was not significantly different between the smartphone and smartwatch users (n=4, n=5, respectively, $p$=0.446). However, the smartwatch group had significantly more recordings with insufficient signal quality ($p$=0.002). Motivation and compliance of FibriCheck usage were calculated for the smartphone group and decreased significantly over time ($p$=0.002, $p\leq$0.001). The number of smartwatch measurements also reduced significantly ($p\leq$0.001). The user experience and sense of safety were comparable between the cardiac monitoring devices.**

**CONCLUSION – The insufficient signal quality and decreasing number of FibriCheck recordings over time are considerable limitations. However, FibriCheck and the ICM have a similar AF detection rate in cryptogenic stroke and TIA patients. Therefore, FibriCheck could have an added value in their follow-up, but further research is needed.**

## INTRODUCTION

*Ischemic stroke and etiology*

Ischemic stroke, a blockage of the blood flow to the brain, is the second leading cause of death in Europe and a major reason for disability (1-3). A stroke is characterized by (I) sudden numbness or weakness of the face, arm, or leg, especially on one side of the body, (II) sudden confusion, trouble speaking or understanding speech, (III) sudden difficulty seeing in one or both eyes (i.e., loss or blurring of vision), (IV) sudden trouble walking, dizziness, loss of balance or coordination and (V) a sudden severe headache with unknown cause. The main symptoms are represented in the FAST test. This stands for Face (face drop on one side), Arms (not being able to lift both arms due to weakness or numbness), Speech (slurred speech or trouble understanding), and Time which emphasizes the importance of immediately contacting the hospital

when symptoms are present (4). In general, over one in seven women and one in ten men die from this disorder each year (1-3). There are approximately 19,000 stroke cases per year in Belgium, or 52 a day (5, 6). Furthermore, stroke prevalence increases with advanced age and black race. Additional risk factors are hypertension, cardiovascular disorders, dyslipidemia, diabetes mellitus, physical inactivity, obesity and smoking (7, 8). In 7-20% of the stroke patients, a second stroke occurs within a year, causing even higher mortality, functional dependency and healthcare cost (9). Therefore, it is important to determine the underlying cause of the stroke.

The etiology of ischemic stroke affects prognosis, outcome, and management which can help prevent recurrence. A system for categorizing subtypes of ischemic stroke mainly based on etiology has been developed for the Trial of Org 10172 in Acute Stroke Treatment (TOAST). The TOAST classification system includes five subtypes of ischemic stroke: (I) large-artery atherosclerosis, (II) cardio-embolism, (III) small-vessel occlusion (i.e., lacunar), (IV) stroke of other determined etiology, and (V) stroke of undetermined etiology (i.e., cryptogenic) (10). Diagnosis is based on clinical features and collected data from brain imaging (CT/MRI), cardiac imaging (echocardiography, transthoracic echocardiograms (TTE) or transesophageal echocardiograms (TEE)), duplex imaging of the carotid arteries and laboratory results (10). Determining the cause of the stroke has a major influence on the treatment choice. Therefore, a correct and rapid diagnosis is important to prevent recurrence.

*Cryptogenic stroke and its relation to atrial fibrillation*

The origin of ischemic stroke remains unexplained in one-third of the cases. These strokes are classified as cryptogenic (2, 11). A transient ischemic attack (TIA), a temporary disruption in the blood supply to the brain, could be a warning sign for a future ischemic stroke. Consequently, it is essential to determine the underlying cause of the TIA or cryptogenic stroke to prevent the occurrence of a future stroke (11, 12). Several possible mechanisms can cause a cryptogenic stroke or TIA, one of these is atrial fibrillation (AF) (1, 2). This cardiac arrhythmia is associated with a five-fold increased risk for embolism and stroke, and is responsible for at least 17% of all ischemic strokes (11). Furthermore, mortality, severity, functional dependency and stroke recurrence are worse in patients with AF strokes compared to non-AF strokes (13). Thereby, AF strokes entail a higher healthcare cost and burden (13). Risk factors for AF development are similar to those of an ischemic stroke, namely hypertension, advanced age, diabetes mellitus, coronary heart disease, lipid metabolism disorders and smoking (14). Nonetheless, the role of AF as a cause of stroke remains underestimated. This is possibly due to it often not being continuously present (paroxysmal AF) and its potential asymptomatic character. Consequently, it may remain undetected during the short-term cardiac monitoring in the hospital (11). Therefore, the European Society of Cardiology (ESC) advocates for long-term heart rate and heart rhythm control in patients with a cryptogenic stroke or TIA (15). This could contribute to the detection of AF as the origin of the stroke and may cause important therapeutic changes that can help prevent a secondary stroke (11). Usually, ischemic stroke patients will receive antiplatelet therapy to prevent recurrence. However, oral anticoagulant (OAC) treatment is initiated when AF is diagnosed due to its superiority over antiplatelet drugs for recurrence prevention in this population (11, 16).

The standard of care cardiac rhythm examinations for stroke patients currently comprises an in-hospital electrocardiogram (ECG), followed by cardiac monitoring for at least 24 hours for AF detection (17, 18). It is known that there is a clear relation between monitoring duration and the likelihood of diagnosing AF. Therefore, prolonged cardiac monitoring is advocated (15, 19). Examples of such long-term monitoring devices are a seven-day holter (non-invasive) and an implantable cardiac monitor (ICM). The latter will be inserted subcutaneously (invasive) (11, 19).

*The implantable cardiac monitor*

The ICM is a small leadless device that continuously monitors the heart rhythm for up to three years. Furthermore, it contains an AF detection algorithm that enables it to reliably estimate the incidence and duration of AF episodes (AF burden). Thereby, it provides an opportunity to investigate the incidence of AF in patients with a cryptogenic stroke or TIA by performing long-term

cardiac monitoring highly sensitive for AF (11, 19). The sinus and AF rhythm both have a unique R-R interval pattern. The ICM's AF detection algorithm uses irregularities and incoherencies of these R-R intervals to identify patterns in the ventricular conduction (19). The R-R intervals are analyzed within a two-minute period of time. If a specific pattern of uncorrelated irregularity is found during these two minutes, this is classified as AF (19, 20). A study by Hindricks et al. concluded a sensitivity and specificity of 96% and 85% for AF detection with an ICM. Additionally, the specificity is further improved by a manual review of the recorded measurements (19, 20).

The CRYSTAL AF study by Sanna et al. compared the ICM for long-term monitoring with the conventional follow-up, consisting of assessment with an ECG (control group), in 441 stroke patients (2). They concluded that cardiac monitoring for 36 months with the ICM could result in AF detection in up to 30% of the cryptogenic stroke patients, compared to 3% in the control group. Furthermore, there was not only a significantly higher rate of AF detection, but also a greater initiation of OAC usage to treat AF and a reduction in stroke recurrence (2). This indicates the importance of long-term monitoring in cryptogenic stroke patients. In part thanks to these findings, there has been an increase in ICM usage. However, there is still an underutilization. This could be caused by the invasiveness and the high cost related to the device. Furthermore, the ICM could cause complications like infection (18, 21). Another disadvantage is the long waiting time between the seven-day holter monitoring and the ICM placement. It is possible that during this period of time, AF episodes can occur and subsequently will be missed. Overall, in addition to the ICM, there is a high need for an effective, less invasive and more affordable long-term detection method.

*Mobile health (mHealth)*

The use of mobile devices such as smartphones, tablet computers and smartwatches, and accompanying applications (apps) has continuously grown over the past years (22). Thereby, the emerging field of mobile health (mHealth) may play an important role in healthcare transformation. Mobile health is a general term for using a mobile network in the practice of medicine and public health. It includes mobile devices such as smartphones and smartwatches to monitor, educate and deliver health information (23). A major advantage is its ability to reach a big audience anywhere and at any moment (24). In 2017, there were 165,000 mHealth applications available, demonstrating the potential of mHealth to enhance individual and public medical care (23). Therefore, mHealth could provide a less invasive and more affordable long-term monitoring strategy to detect AF.

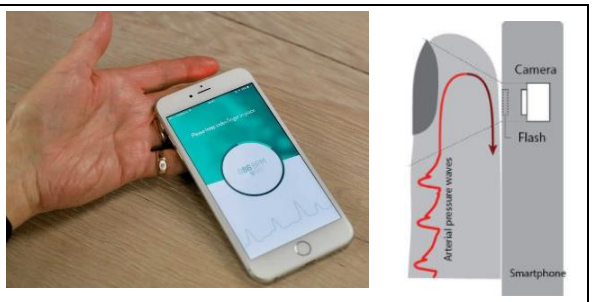


**Figure 1 – Photoplethysmography (PPG) principle**. Left, the smartphone application. Right, the PPG principle (25).

*Examples of mHealth devices for heart rhythm measurement*

There are already several mHealth devices and applications on the market that allow a heart rate recording and the possible detection of AF (26, 27). A well-known example is the Apple Watch (Apple Inc.®, Cupertino, California, United States). The Apple Heart Study used the Apple Watch Series 1 to 3 and a proprietary algorithm to detect an irregular pulse and indicate arrhythmia based on the photoplethysmography (PPG) principle (28). This is done by illuminating the skin (e.g., by the camera on a phone) and measuring the amount of reflected light to determine the blood volume pulse variation (Figure 1). In this way, the heartbeat is recorded and the rhythm can be determined based on the intervals between heartbeats (29). They concluded that 34% of the individuals with an arrhythmia notification were later found to have AF. In participants notified of an irregular pulse, the positive predictive value was 84% (28, 30). In contrast, the Apple Watch Series 4 uses the PPG and single-lead ECG (iECG) principle to detect the heart rate (31). The iECG is performed by two electrodes: one built into a "digital crown" (a button on the side of the smartwatch) and one at the back of the device. The user places the watch on his wrist and subsequently

places his fingers of the other hand on the digital crown. Next, the recordings are analyzed by an algorithm (32). The rhythm analysis is reported after 30 seconds of recording and is best done at rest. Its findings are classified as sinus rhythm, AF, or inconclusive (31). The ECG application has received FDA clearance and has a sensitivity of 96% and specificity of 97% for AF detection. However, it is expected that during everyday use, the number of unreadable or unclassified measurements will increase, which may change the performance of the ECG app (31). The KardiaMobile and KardiaMobile 6L (AliveCor®, Mountain View, California, United States) are other wearable devices recording ECG tracings. KardiaMobile uses a single-lead ECG with FDA clearance to detect AF, bradycardia, tachycardia and a normal heart rate. The KardiaMobile 6L can also distinguish between these heart rates. Additionally, it performs a six-lead (6L) ECG, which is more detailed and provides more information (26, 33). Compared to the earlier discussed Apple smartwatches, the KardiaMobile (6L) uses electrodes on a small plate (26). These electrodes can be incorporated within a smartphone case. Several studies with the KardiaMobile single-lead ECG were performed, showing a sensitivity varying between 67% and 100% and a specificity between 94% and > 98%. (31, 34-36). Besides applications based on ECG measurements, several companies focus on heart rate monitoring based only on PPG. One of them is Huawei, which performed a study to investigate the effectiveness of AF screening using the PPG technology on a wristband (Honor Band 4) or wristwatch (Huawei Watch GT and Honor Watch) (Huawei Technologies Co., Ltd., Shenzhen, China) (37). They used a specific Huawei PPG algorithm and concluded a 92% positive predictive value for the PPG signals (37). Another example of a company specializing in PPG measurements for heart rate analysis is Preventicus ® (Jena, Germany) (38). Their Heartbeats app algorithm analyzes PPG signals recorded by a standard smartphone camera and discriminates between sinus rhythm and absolute arrhythmia consistent with AF. When five minutes of PPG heart rhythm analysis was performed, the algorithm detected AF with a sensitivity of 92% and specificity of 99.6%. On the other hand, when the analysis time was reduced to one minute, sensitivity and specificity were reduced to 90% and 99%, respectively. However, when considering the number of files not suitable for analysis due to poor quality, the one-minute analysis classified AF correctly in 89% of the cases, compared to 61% for a five-minute analysis (38). The Preventicus Heartbeats app can nowadays also be used on a smartwatch (Gear Fit 2, Samsung) (39). Finally, Fitbit ® (San Francisco, California, United States) recently developed its own PPG-

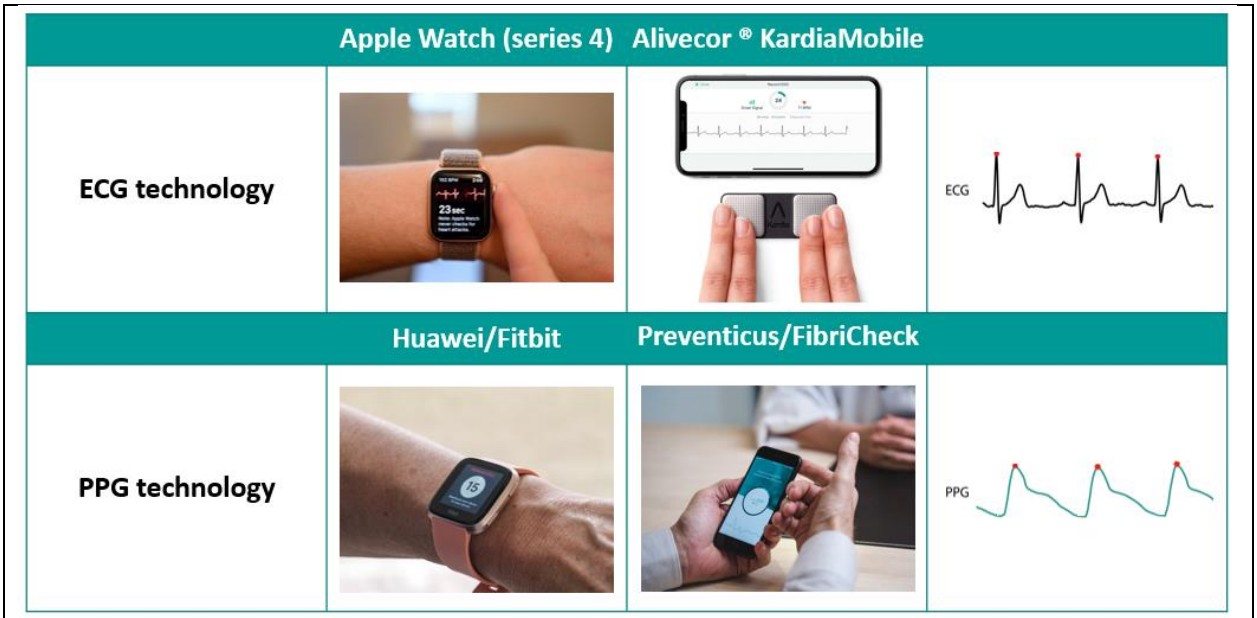


**Figure 2 – Overview of different mobile health devices for atrial fibrillation detection on the market.**

based software algorithm for AF detection (40). Furthermore, Fitbit collaborates with FibriCheck (Qompium, Hasselt, Belgium) to provide customers with an application to measure their heart rate and detect arrhythmias. In this study, we will focus on the use of the FibriCheck app to detect AF in cryptogenic stroke and TIA patients. Figure 2 shows an overview of different mHealth devices for AF detection.

*FibriCheck usage for heart rhythm detection*

FibriCheck uses the PPG technique to monitor the heartbeat and heart rhythm (29). Due to its non-invasive character, simplicity and cost-benefit ratio, it is a popular method to monitor the heart rhythm of a patient (41). Proesmans et al. compared the use of FibriCheck on a smartphone with a single-lead ECG. They concluded that the FibriCheck AF algorithm could accurately detect AF with a sensitivity and specificity of respectively 96% and 97% compared to 95% and 97% for the single-lead ECG. (29). Additionally, another study by Proesmans et al. compared AF detection by FibriCheck with a 12-lead ECG in 63 cryptogenic stroke patients. They observed a need for prolonged cardiac monitoring to prevent a secondary stroke and concluded that FibriCheck could be a cost-effective method for long-term cardiac monitoring (42).

*ICM compared to FibriCheck*

A big difference between the ICM and FibriCheck is the minimum duration of AF to be detected. The ICM annotates true AF if the episode is ≥ two minutes long (20, 43). However, a FibriCheck measurement lasts one minute. Consequently, the threshold for AF detection with FibriCheck is placed on at least 30 seconds. It is still unknown how long an episode needs to last to develop a blood clot. A study by Tran et al. examined if physicians are likely to use short runs of AF to diagnose arrhythmia (44). However, they focused on using a 12-lead ECG or ambulatory monitoring, not the ICM or mHealth. They concluded that 36% accepted a single run of < 30 seconds on ambulatory monitoring. Furthermore, stroke physicians were twice as likely to accept < 30 seconds of arrhythmia to diagnose AF. Only 6% of the physicians demanded more than two minutes as a diagnostic threshold (44). Based on these findings, physicians are open to accepting a short run for the AF diagnosis instead of the imposed two minutes. Another major difference is the use of ECG by ICM compared to PPG by FibriCheck. The latter is a relatively new technique that still needs to be validated extensively. A recent study concluded that 62% of health care practitioners had recommended patient use of a digital device for AF detection. However, only 27% of the physicians reported that they were (very) likely to diagnose AF from a 30-second PPG recording compared to 72% for a similar-duration ECG measurement. This reflects their opinion that PPG-based technology has a lower AF detection accuracy than an ECG. Hopefully, thorough PPG validation will counteract this belief (45).

*Summary and aim*

In conclusion, long-term cardiac monitoring in cryptogenic stroke and TIA patients is essential to improve AF detection and potentially improve the prevention of a second stroke. Nowadays, this is done by the invasive and expensive ICM. Consequently, there is a high need for a less-invasive and more affordable detection method. A possible solution would be using smartphones and smartwatches with the FibriCheck application (mHealth). However, FibriCheck has not yet been compared to the long-term cardiac monitoring device, ICM. Therefore, this study examines if FibriCheck has a similar AF detection rate compared to the ICM in cryptogenic stroke and TIA patients. It is hypothesized that FibriCheck (mHealth) has a similar detection rate and therefore has an added value in AF detection in these stroke patients. Additionally, FibriCheck adherence (e.g., motivation and compliance), user experience and sense of safety will be examined as secondary endpoints.

## METHODS

*Study design*

The study was a prospective, monocentric, interventional, randomized trial performed at the Ziekenhuis Oost-Limburg in Genk. The overall aim was to compare AF detection between PPG-based mHealth (FibriCheck app on smartphones and smartwatches) and the ICM in cryptogenic stroke and TIA patients. The patients used the FibriCheck app for six months, starting on the day of ICM implantation. They were randomized in a 1:1 manner between the smartphone and smartwatch

group. The results from the mHealth monitoring were blinded for the patient and the physician. The ICM results were collected for 12 months.

The primary objective was to compare the AF detection rate between the ICM and FibriCheck based on AF detection, duration and frequency of AF episodes (AF burden), and time to first AF detection.

The first secondary outcome measure was the difference in AF detection between the smartphone and smartwatch group. Furthermore, they were compared based on user experience. Finally, the difference in sense of safety between the ICM and FibriCheck was analyzed after six months.

The study protocol was in accordance with the Declaration of Helsinki and was approved by the ethical committees of Ziekenhuis Oost-Limburg (Genk, Belgium) and Hasselt University (Hasselt, Belgium) (19/0093U). The study was registered at ClinicalTrials.gov (NCT05006105).

*Study population*

The study population consisted of cryptogenic ischemic stroke and TIA patients at the Ziekenhuis Oost-Limburg in Genk who received an ICM implantation. They were included from October 2020 to April 2022. The inclusion and exclusion criteria are listed in Table 1.

*Study procedure*

All eligible patients were approached during their hospitalization and were informed about the study's aim and procedure. A couple of weeks later, the patients received a seven-day holter (Rooti) during which they were informed once more. When the Rooti findings showed no AF, they qualified for an ICM. After discussing the Rooti results, the cardiologist reminded them of their possible study participation. If they qualified for an ICM and agreed to participate, the informed consent was signed on the day of implantation. At this moment, the patient was randomized into the smartphone or smartwatch group. Furthermore, FibriCheck was installed and explained. Study participants in the smartphone group were asked to perform two

**Table 1 – Overview of the inclusion and exclusion criteria.**

| Inclusion criteria | Exclusion criteria |
|---|---|
| Diagnosis of cryptogenic ischemic stroke or TIA | History of AF or atrial flutter |
| 18 years old or older | Not qualified for ICM implantation |
| The patient or its legal representative is willing to sign informed consent | Life expectancy of less than one year |
| | (Contra)indication for permanent OAC treatment |
| | Untreated hyperthyroidism |
| | Myocardial infarction or coronary bypass grafting less than one month before stroke onset |
| | Presence of a PFO which is/was an indication to start OAC according to the European Stroke Organization guidelines |
| | Inclusion in another clinical trial that will affect the objectives of this study |
| | Not being able to understand Dutch |
| | The patient or partner does not have a smartphone |

TIA, transient ischemic attack; AF, atrial fibrillation; ICM, implantable cardiac monitor; OAC, oral anticoagulation; PFO, patent foramen ovale.

measurements a day and more if they experienced symptoms. Patients in the smartwatch group received a Fitbit Versa 2 with the FibriCheck application for six months. They were asked to continuously wear the smartwatch, which automatically performed semi-continuous measurements of one minute every nine minutes. Previously this was done every three minutes. Next, the participants were also requested to fill out a questionnaire about their vision on mHealth. After hospital discharge, FibriCheck measurements were monitored via the dashboard. The labels were allocated by the FibriCheck algorithm and were checked by a physician in case of irregularity. A standardized reminder was sent when the patient did not perform measurements for two days. After six months, a report with the FibriCheck findings was uploaded to their electronic medical record. The ICM telemonitoring was conducted according to the usual care, which comprises revision of detected irregularities by a dedicated nurse. If anomalies were confirmed, the cardiologist was contacted and therapy adjustments were made. Approximately six months after implantation, the patients had a cardiology appointment during which the ICM was checked. At this moment, the remaining questionnaires about their vision on mHealth, user experience [46] and sense of safety were filled out. If applicable, the smartwatch was returned. One year after implantation, the ICM data was once more collected from the device's dashboard.

*Data collection*

All the participants were given a study number and all data was encoded in the electronic case report form (Castor EDC, The Netherlands). The collected demographic variables were the year of birth, gender, height, weight and body mass index (BMI). Information about comorbidities and cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, smoking, and hypercholesterolemia was compiled. Furthermore, data related to the stroke/TIA was gathered: date of occurrence, history of stroke/TIA, stroke-related scores such as the Modified Ranking Scale (MRS), National Institutes of Health Stroke Scale (NIHSS), $CHA_2DS_2$-VASC, Alberta Stroke Program Early CT Score (ASPECTS) and the conclusions of the hospital examinations. Additionally, all relevant medication administered during hospitalization, after one month, six months and one year were listed. Information about AF detection, date of the first detection, duration of the episode and the presence of other arrhythmias detected with FibriCheck and the ICM was collected from the device dashboards (Qompium, Biotronik and Medtronic). Furthermore, the motivation and compliance of FibriCheck usage were assessed. The motivation was calculated as the number of days with at least two daily spot-checks divided by the number of days on which the application should be used. The compliance was calculated as the total number of spot-checks performed divided by the total number of recommended spot-checks (47). The questionnaires about vision on mHealth, sense of safety and user experience were filled out. The latter contains 26 items consisting of a pair of terms with opposite meanings (e.g., efficient/inefficient etc.). Half of the items start with the positive term, the others with the negative term (in randomized order). The items are rated on a 7-point Likert scale and are scaled from -3 (fully agree with negative term) to +3 (fully agree with positive term) (48). The sense of safety questionnaire informs about how the safety, securely and reliability of both monitoring methods were experienced. These scores were also based on a 7-point Likert scale, and were changed to range from -3 to +3. Lastly, any additional information needed to answer the in- and exclusion criteria was collected.

*Statistical analysis*

Normality and homogeneity were checked by the Shapiro-Wilk and Levene's test. The other assumptions were also assessed. Nominal and ordinal data were examined with the Fisher's exact or Chi square test. Data of mHealth and the ICM were compared with a paired t-test. The smartphone and smartwatch group were compared by an unpaired t-test. When normality was not proven, a non-parametric equivalence was used. Changes over time were examined by a Friedman test and post hoc Sign test with Bonferroni correction. Data were considered significant at $p < 0.05$ and are presented as mean ± standard deviation (SD), median and interquartile range (IQR), absolute numbers (n) and percentages (%). All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) 28.0 (IBM ® SPSS ® Inc., Chicago, Illinois, United States).

**RESULTS**

*Study population*

The study population consisted of 76 patients (Figure 3). However, after inclusion six patients were not eligible for an ICM, and were therefore excluded. The remaining 70 patients were randomized into a smartphone (n = 39) and smartwatch group (n = 31). Additionally, six patients were drop-out because they experienced the measurements as a burden (n = 3), deleted the FibriCheck account (n = 1), had an allergic reaction to the wristband (n = 1) or needed to switch from an ICM to a pacemaker (n = 1). In general, 36 patients with the smartphone application and 28 patients provided with a smartwatch were analyzed. The demographics of these patients (n = 64) are shown in Table 2. There were no significant differences in the characteristics between the smartphone and smartwatch group.

*Cardiac monitoring with mobile health*

The participants in the smartphone group performed 10,552 measurements in total. In the smartwatch group, 196,797 recordings were performed. The mean number of recordings was 278 for participants in the smartphone group and 7,029 for smartwatch users. The recordings were labeled as sinus rhythm, low signal quality, other arrhythmias (e.g., bradycardia, tachycardia, extrasystoles etc.) or suspected atrial fibrillation (Table 3). The percentage of sinus rhythm was significantly higher in the smartphone group compared to the smartwatch group ($p = 0.010$). On the other hand, the percentage of low-quality measurements was higher in the smartwatch group ($p = 0.002$). The presence of low-quality recordings was also compared with age, gender, number of smartphone cameras and smartphone brand. However, no significant differences were observed (Supplementary Table 1).

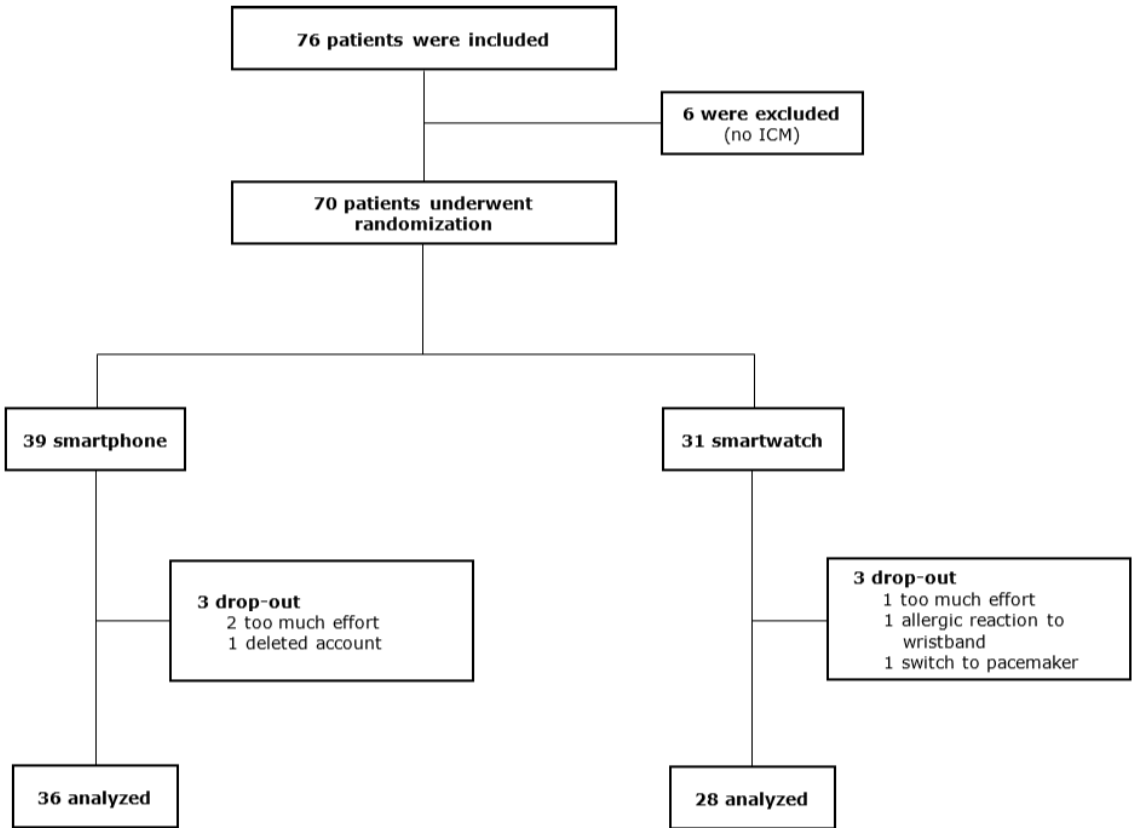


**Figure 3 – Enrollment and randomization of the study participants.** ICM, implantable cardiac monitor.

**Table 2** – **Demographic characteristics.**

| Characteristic | Smartphone group (n = 36) | Smartwatch group (n = 28) | P-value |
|---|---|---|---|
| Age, years | 62.4 ± 12.5 | 62.6 ± 8.9 | 0.203 |
| **Gender, n (%)** | | | 0.705 |
| Male | 26 (72.2%) | 19 (67.9%) | |
| Female | 10 (27.8%) | 9 (32.1%) | |
| BMI, kg/m² | 27.1 (24.1 – 35.2) | 28.4 (24.3 – 31.5) | 0.486 |
| **Diagnosis, n (%)** | | | 0.528 |
| Stroke | 27 (75.0%) | 19 (67.9%) | |
| TIA | 9 (25.0%) | 9 (32.1%) | |
| PFO, n (%) | 10 (27.8%) | 5 (17.9%) | 0.353 |
| Hypertension, n (%) | 25 (69.4%) | 19 (67.9%) | 0.892 |
| Diabetes, n (%) | 4 (11.1%) | 4 (14.3%) | 0.703 |
| Hypercholesterolemia, n (%) | 23 (63.9%) | 16 (57.1%) | 0.583 |
| **Smoking, n (%)** | | | 0.094 |
| Current | 14 (38.9%) | 4 (14.3%) | |
| Former | 9 (25.0%) | 10 (35.7%) | |
| No | 13 (36.1%) | 14 (50.0%) | |

BMI, body mass index; TIA, transient ischemic attack; PFO, patent foramen ovale. Statisics were performed using the Unpaired t-test, Mann-Whitney U test, Chi square test and Fisher's exact test.

**Table 3** – **Labeling of photoplethysmography–based FibriCheck recordings**.

| Label | Smartphone group (n = 10,552) | Smartwatch group (n = 196,797) | P-value |
|---|---|---|---|
| Sinus rhythm, n (%) | 7,992 (75.7%) | 95,295 (48.4%) | **0.010** |
| Low signal quality, n (%) | 1,994 (18.9%) | 99,396 (50.5%) | **0.002** |
| Other arrhythmias, n (%) | 540 (5.1%) | 2,027 (1.0%) | 0.500 |
| Atrial fibrillation, n (%) | 26 (0.3%) | 79 (0.0%) | 0.613 |

Statistics were performed using a Mann-Withney U test.

The detection of possible atrial fibrillation and other arrhythmias was similar between both groups ($p$ = 0.613 and $p$ = 0.500, respectively). In total, 105 AF episodes were recorded, of which 3 with symptoms (2.9%). The experienced symptoms were being lightheaded (n = 2) and a combination of being lightheaded and experiencing palpitations (n = 1). There were 2,567 recordings labeled as another arrhythmia, of which 28 with symptoms (1.1%) such as confusion, fatigue, lightheaded, palpitations and shortness of breath.

*Mobile health motivation and compliance*

FibriCheck adherence over six months was examined for the smartphone group (Figure 4). The drop-out patients were included in this analysis.

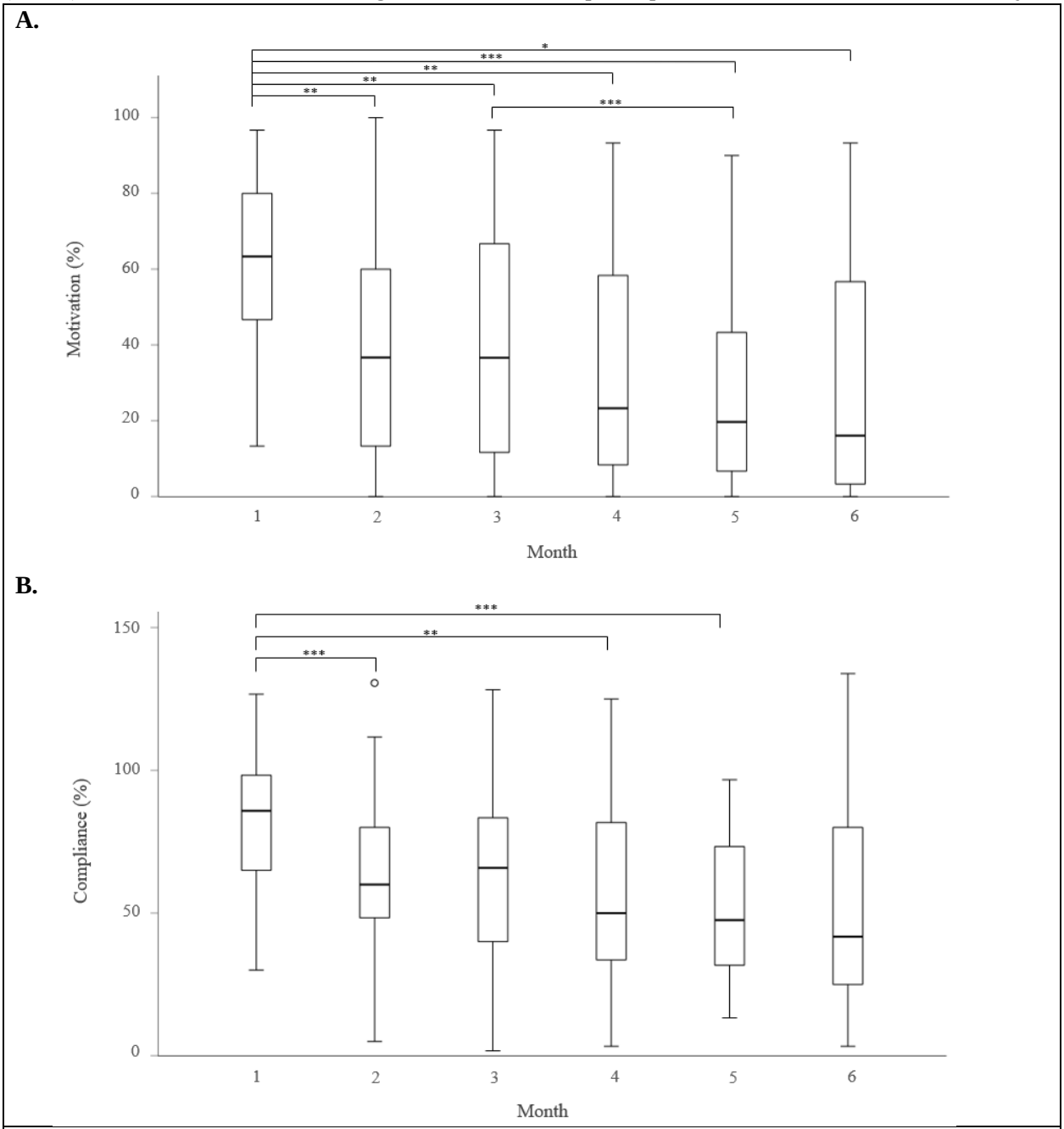


**Figure 4 – FibriCheck adherence of the smartphone group. (A)** Motivation of using the PPG-based FibriCheck application on a smartphone for six months. **(B)** Compliance of using the PPG-based FibriCheck application on a smartphone for six months. Statistics were performed using the Friedman test, post-hoc Sign test and Bonferroni correction. * *p = 0.002*, ** *p = 0.001*, *** *p < 0.001*

However, not all patients finished FibriCheck usage at the time of analysis. The number of analyzed patients for month one to six are respectively, n = 34, n = 33, n = 32, n = 31, n = 26, n = 25. Post hoc analysis was performed by the Sign test with Bonferroni correction ($p < 0.003$). After one month, the motivation significantly decreased (Figure 4A). Furthermore, there was a significant decrease in motivation between the third and fifth month of FibriCheck usage ($p < 0.001$). As indicated in Figure 4B, the compliance decreased significantly after month one compared with months two, four and five (respectively, $p < 0.001$, $p = 0.001$ and $p < 0.001$). Additionally, the compliance and motivation were compared between age, gender, number of used apps before and after FibriCheck and the number of apps downloaded after finishing FibriCheck usage. No significant differences were

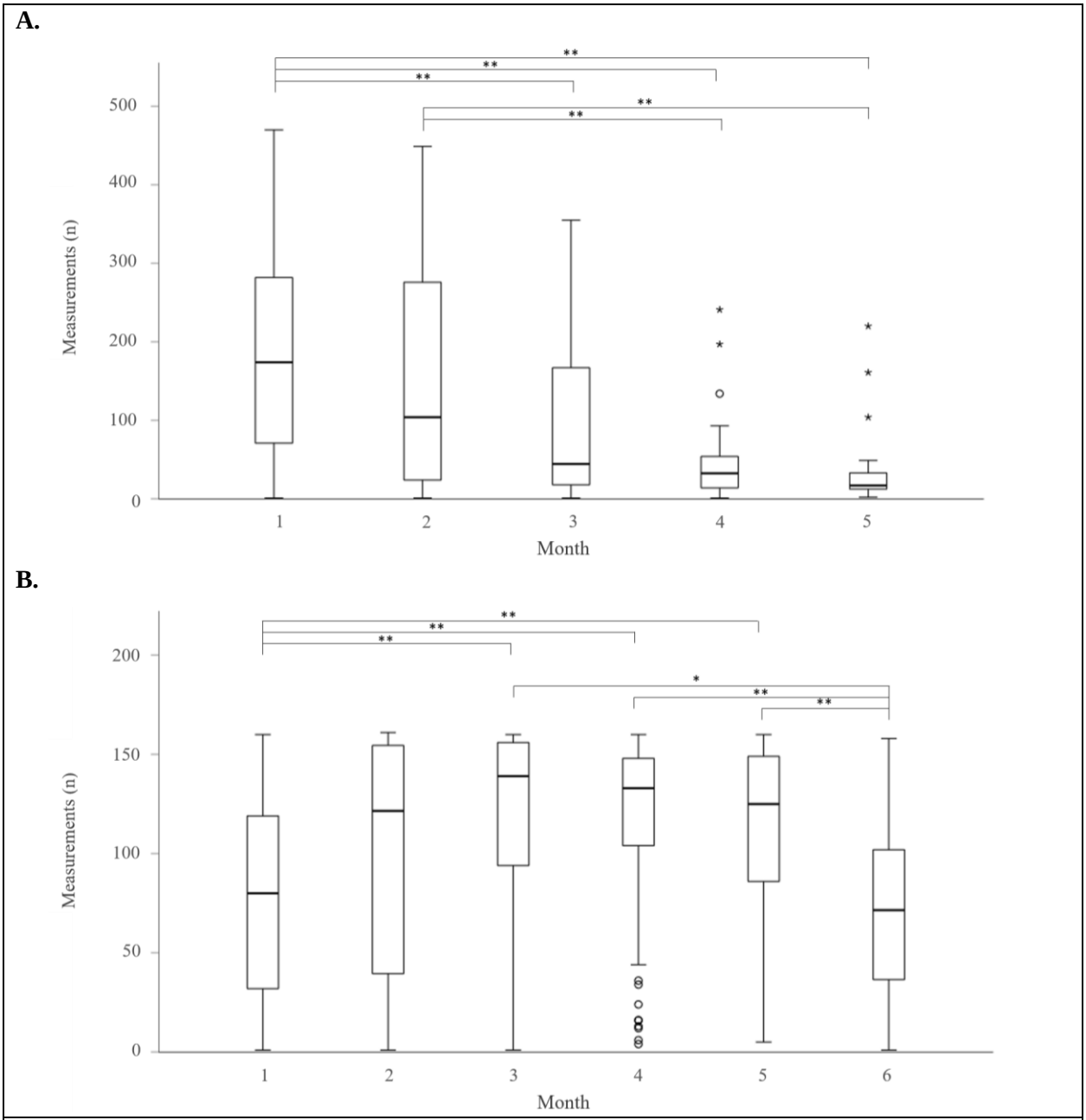


**Figure 5 – FibriCheck adherence of the smartwatch group. (A)** Median number of recordings performed per day by the smartwatch every three minutes over time. **(B)** Median number of recordings performed per day by the smartwatch every nine minutes over time. Statistics were performed by the Friedman test, post-hoc Sign test and Bonferroni correction. * $p = 0.001$ ** $p < 0.001$

observed (Supplementary Table 2). The smartwatch group was compared based on the number of measurements performed per day over time (Figure 5). In total, 22 patients started in the three-minute measuring schedule. The number of patients analyzed for month one to five are respectively, n = 22, n = 16, n = 9, n = 4 and n = 2. Post hoc analysis was performed by the Sign test with Bonferroni correction ($p < 0.005$). There was a significant decrease in the number of performed recordings a day between month one and month three, four and five and between month two and month four and five ($p < 0.001$) (Figure 5A). Due to the change to semi-continuous measurements every nine minutes, not all patients finished or started the six-month FibriCheck use within the three-minute schedule. Overall, fourteen patients used the nine-minute schedule. Respectively n = 9, n = 4, n = 7, n = 6, n = 5 and n = 6 patients were analyzed for month one to six. After Bonferroni correction, the p-value was set to $p < 0.003$. There was a significant increase in the number of performed measurements between month one and month three, four and five ($p < 0.001$). On the other hand, the number of measurements decreased significantly between month three and month six ($p = 0.001$), between month four and month six ($p < 0.001$) and between month five and six ($p < 0.001$) (Figure 5B).

*Cardiac monitoring with the ICM*

In this study, cardiac monitors of the Medtronic (n = 52) and Biotronik (n = 12) brands were implanted. First, all ICM data was labeled by the ICM algorithm. If there were any irregularities, a dedicated nurse revised them, which resulted in approved and disapproved recordings. In general, 558 AF episodes were detected by the ICM. However, after revision, only eight of them were approved. One of these was recorded by a Biotronik device and the Medtronic detected the remaining seven. When comparing the Biotronik and Medtronic measurements, significantly more disapproved episodes were recorded by the Biotronik ($p < 0.001$) (Table 4).

*AF detection comparison between ICM and mobile health*

An overview of the approved AF incidence detected by the ICM and FibriCheck (smartphone and smartwatch) is presented in Table 5. The ICM identified approved AF in four (10.0%) patients. FibriCheck, on the other hand, detected the presence of AF in 9 out of 40 patients (22.5%) who finished the six-month app usage. Four of these patients performed measurements with the smartphone. The other five were included in the smartwatch group. There was no significant difference in the number of patients with AF detection between the ICM and FibriCheck or between the smartphone and smartwatch group ($p = 0.180$ and $p = 0.446$, respectively).

In two patients, AF was detected by both the ICM and FibriCheck. In the first patient, included in the smartphone group, both methods detected AF 51 days after the stroke and the episode lasted 28 hours and 22 minutes. As a consequence, the patient started Edoxaban 60 mg. Three months after AF detection, an ablation was performed. In the second patient, the smartwatch recorded an AF episode with 19.0% reduced signal quality 53 days after the stroke. On the other hand, the ICM detected AF 167

**Table 4** – **Atrial fibrillation detection with the insertable cardiac monitor.**

| Label | Total | Approved | Disapproved | P-value |
|---|---|---|---|---|
| Total AF detected | 558 | 8 | 550 | |
| **Device** | | | | **< 0.001** |
| Biotronik (n = 12) | 412 | 1 | 411 | |
| Medtronic (n = 52) | 146 | 7 | 139 | |

AF, atrial fibrillation. Statiscs were performed using the Fisher's exact test.

**Table 5 – AF incidence detected by the implantable cardiac monitor and FibriCheck after six-month use.**

| | AF incidence | P-value |
|---|---|---|
| **Device** | | 0.180 |
| ICM (n = 40) | 4 (10.0%) | |
| FibriCheck (n = 40) | 9 (22.5%) | |
| **FibriCheck** | | 0.446 |
| Smartphone (n = 25) | 4 (16.0%) | |
| Smartwatch (n = 17) | 5 (29.4%) | |

ICM, implantable cardiac monitor. Statistics were performed using the McNemar test and Fisher's exact test.

days post-stroke. The episode lasted 122 seconds and the use of Apixaban 5 mg (two times a day) was initiated.

The remaining two patients in which the ICM detected AF were included in the smartphone group. The detection occurred 121 and 184 days after the stroke. Both patients started OAC, respectively Lixiana 60 mg and Xarelto 20 mg. In the first patient there was no FibriCheck recording performed on the day of AF detection. The second patient performed a recording 30 minutes after the ICM detected a two-minute AF episode. The FibriCheck recording consisted of 43.0% low signal quality and detected sinus rhythm.

Lastly, FibriCheck alone recorded possible AF in seven patients. Three of them were included in the smartphone group and four in the smartwatch group. All recordings had a reduced quality. The time until first detection varied from 63 to 267 days after the stroke (n = 2) or TIA (n = 5). None of them started anticoagulation therapy.

*User experience and sense of safety*

The user experience of FibriCheck on a smartwatch and smartphone was compared by the validated User Experience Questionnaire (UEQ). This questionnaire consists of 26 questions grouped into six different categories (attractiveness, perspicuity, efficiency, dependability, stimulation and novelty). Figure 6A shows the mean score of the six categories. There was no significant difference between the smartphone and smartwatch group. The sense of safety was compared between FibriCheck and the ICM. No significant difference between the cardiac monitoring methods based on the mean safety, securely and reliability score was observed (Figure 6B). Overall, the patients have a similar sense of safety with the ICM and FibriCheck.

## DISCUSSION

The overall aim of this study was to compare the usability of AF detection between PPG-based mHealth (FibriCheck app on smartphone and smartwatch) and the ICM in cryptogenic stroke and TIA patients.

*Cardiac monitoring with the ICM*

The ICM diagnosed AF in four patients (10.0%), two of whom also had an AF registration by FibriCheck. All of them started the use of OAC in compliance with the treatment guidelines. This study established a similar detection rate compared with the CRYSTAL AF study, in which 8.9% of the patients with an ICM had an AF detection after six months (2).

In total, 8 of the 558 AF episodes registered with the gold standard ICM were approved. Consequently, 98.6% of the AF episodes were false-positive (FP). Several studies examined the diagnostic yield and accuracy of the Medtronic ICM in cryptogenic stroke patients. First, a study by Chorin et al. concluded that at least 84.0% of the

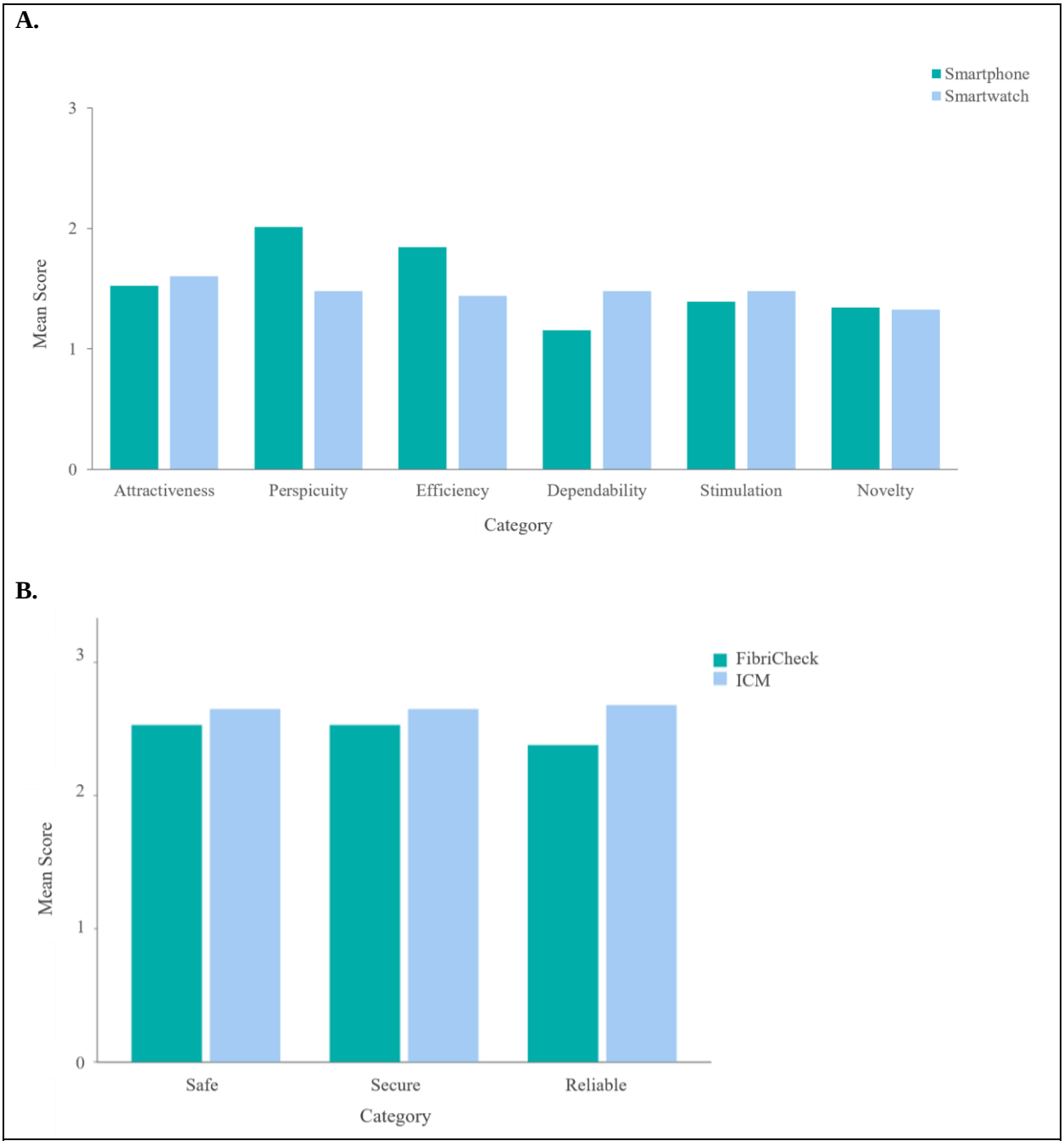


**Figure 6 – User experience and sense of safety. (A)** User experience of FibriCheck compared between the smartphone (green) and smartwatch (blue). **(B)** Sense of safety compared between FibriCheck (green) and ICM (blue). A score of three is the best possible/completely agree, a score of zero is neutral and a score of minus three is the worst/completely disagree. Statistics were performed by the (A) Unpaired t-test and (B) Paired t-test.

AF alerts were FP (49). Additionally, a study by Afzal et al. observed 86.0% FP detections in cryptogenic stroke patients. This was significantly higher compared to the 45.6% and 71.4% in patients who received an ICM for atrial fibrillation or a syncope. Approximately 71.0% of the detected AF episodes observed in the scheduled downloads were FP, and 100.0% of the FP alert transmissions were based on AF detection (50). Lastly, the multicentric cohort study by O'Shea et al. resulted in a general FP detection of 59.8%, and 74.2% of the AF alerts were allocated as FP (51). The FP AF detection rate by the Medtronic was higher in our study (95.2%) compared to the previously discussed research. The significantly higher FP detection with the Biotronik device compared to the Medtronic, was remarkable and can indicate the presence of a too sensitive algorithm or an inadequate Biotronik diagnostic yield. Comprehensive comparison with other studies regarding the FP Biotronik detection was not possible due to the limited amount of performed studies. One study found misclassification in 43.3% of the patients, but no definite percentage of false AF detection was given. Unlike our research, they concluded that the FP detection was low (52).

The high amount of erroneous labeling by the ICM algorithm causes a significant workload of episode revision. Consequently, if there are too many irregularities, it is possible that not all of them are checked. This may result in incorrect or unnecessary therapy initiation (47, 50). Therefore, limiting FPs is essential. They could be caused by ventricular and atrial ectopy, oversensing, noise, implant position, implant technique and algorithm performance (50, 53). A possible solution would be the development of more sophisticated algorithms. Furthermore, custom programming based on the implantation indication and patient characteristics may cause FP reduction (50, 53, 54).

*AF detection comparison between ICM and mobile health*

FibriCheck recorded AF in nine patients, four of them used the smartphone and five were included in the smartwatch group. On the other hand, the ICM diagnosed AF in only four patients, of which FibriCheck also detected two. Consequently, there were two patients without a FibriCheck AF observation. One of them did not perform a recording on the day of ICM registration. The other one had executed a sinus rhythm measurement 30 minutes after the ICM detected a two-minute AF episode. This indicates the importance of continuous monitoring especially in the case of short AF episodes.

There was no significant difference in the number of patients with AF detection between FibriCheck and the ICM or between the smartphone and smartwatch group. However, only a small number of patients were analyzed because not all of them finished the six-month monitoring at the moment of analysis due to the ongoing nature of the trial. As a consequence, the total number of AF detections could still increase further. Remarkably, almost double of the patients in the smartwatch group (29.4%) had an AF detection compared to those in the smartphone group (16.0%). This could be due to the semi-continuous measurements performed by the smartwatch. Thereby, it approximates the continuous monitoring of the ICM and could have an added value compared to the smartphone spot-check recordings.

*Cardiac monitoring with mobile health*

There were significantly more sinus rhythm recordings and less insufficient signal quality labeling in the smartphone compared to the smartwatch group. The insufficient quality measurements could replace the sinus rhythm recordings, causing an increase in sinus rhythm labeling in the smartphone compared with the smartwatch users. Interestingly, approximately half of the recordings performed by the smartwatch group were labeled as low signal quality which can be caused by the high sensitivity to motion fraction, since the patients are unaware when a recording is performed. This emphasizes the importance of wearing the smartwatch at night, allowing fewer movement artifacts. Additionally, the smartwatch performs more recordings, increasing the chances of low signal quality measurements. On the other hand, the smartphone recordings are actively performed, resulting in a higher likelihood of the patient remaining still (47). However, a trend was seen between the number of smartphone cameras and the percentage of low signal quality recordings. The emergence of smartphones with more cameras may thus interfere with the quality of FibriCheck measurements. However, this could be prevented by a better education on how to perform the

recordings. For example, the latest FibriCheck update first shows whether the finger is placed on the (proper) camera by turning on the lens, and then the measurement is started. This increases the chances of correctly performing the recordings and could contribute to a lower amount of insufficient signal quality.

*Mobile health motivation and compliance*

Information about the long-term compliance and motivation of the FibriCheck usage by cryptogenic stroke and TIA patients is still limited. Our study examined the adherence of the smartphone users. However, the motivation and compliance could not be calculated for the smartwatch group, making it hard to compare both groups. The motivation and compliance of the smartphone group decreased significantly over time. Remarkable, the minimum motivation was 0.0% during all months, except the first. This indicates that some patients did not once perform the recommended two measurements a day in months two to six. In conclusion, the patients became less motivated and compliant over time. This could be caused by the blinding of the results during the six-month follow-up. If these were unblinded, a possible AF recording could encourage the patient to perform more measurements.

To gain insight into the adherence of the smartwatch group, the number of measurements performed daily for six months was compared. In this study, two different measuring schedules were used. First, recordings were executed every three minutes. However, due to several problems caused by data overload, the algorithm was adapted to record a measurement every nine minutes.

The number of recordings performed every three minutes decreased significantly over time. In theory, 480 recordings a day are expected. However, the smartwatch needs to be charged daily due to the intense algorithm, making it impossible to reach this number. Furthermore, the maximum number of performed recordings over time was not consistent, indicating the presence of other problems. First, technical issues such as an inactive schedule prevented the recordings from being made. Moreover, problems in the Bluetooth connection resulted in a decrease in data sent to the dashboard, and because only a limited number of recordings could be saved on the watch, this may have led to data loss. During the six-month monitoring, an attempt was made to solve the problems. Unfortunately, this was not always successful, resulting in the adaptation of the measurement schedule.

In the nine-minute schedule, the maximum number of executed measurements was almost constant, implying the presence of fewer issues. First, an increase in the performed recordings was observed, but after month three this declined. An explanation could be that the technical problems were solved during the first months, but after a couple of months, these issues reoccurred and remained present. The experienced problems were an inactive measuring schedule, issues with the Bluetooth connection, or a spontaneous log-out of the FibriCheck account.

In addition to the technical issues, a reduction in measurements could also be due to the user. Cryptogenic stroke and TIA patients can experience memory dysfunction, resulting in forgetting to perform the recordings. However, they received daily reminders to perform recordings, wear the smartwatch or synchronize the watch (47). Furthermore, digital health literacy also influences patient engagement and adherence (55). Digital health literate patients have the necessary knowledge to use a smartphone-based app (e.g., FibriCheck) or other mobile devices (e.g., smartwatch). Furthermore, they understand how the collected data or information could benefit their health management. Consequently, it is important that the patient's digital health literacy is assessed and the individual needs are checked before implementing mHealth. This will improve patient engagement and adherence to digital health technology (55).

The considerable decrease in measurements over time could affect the sensitivity of the smartphone and smartwatch (47). The smartphone is already expected to be less effective in AF detection because of the limited number of performed measurements. When only two recordings are executed each day, this enhances the chances of missing short episodes. This was the case in the patient where the ICM detected an AF episode of two minutes, but the FibriCheck recording 30 minutes later observed sinus rhythm. Similarly, if fewer smartwatch recordings are performed, the detection of short-lived episodes,

present in paroxysmal AF, can be compromised. However, there is no consensus on the threshold determining which AF episode duration is clinically relevant (2, 56). A recent study confirmed an association between AF and stroke when using a threshold of 5.5 hours, and there was a significantly increased stroke risk with a duration of 23 hours or more. Thereby, two measurements each day with a smartphone or smartwatch can detect clinically relevant AF (47, 57). However, the previously mentioned patient started oral anticoagulation based on a two-minute AF episode. This indicates the lack of a standardized threshold which needs to be reached before treatment will be initiated.

*Study limitations*

Despite the importance of this research, there are several study limitations. First, the number of patients included in the smartphone and smartwatch group was not evenly distributed due to technical issues with the watch. Next, since the study is still ongoing not all patients have already finished the six-month FibriCheck usage, resulting in a limited amount of data. Thereby, it is possible that not all AF episodes have already occurred. Third, the blinding of the mHealth results for the patient and physician decreased the motivation and compliance significantly. However, this was necessary to ensure that all clinical decisions were solely based on the ICM recordings, as recommended in the guidelines. Additionally, FibriCheck cannot diagnose AF, hence the need for an extra ECG to confirm these findings. Another limitation is the possibility that short episodes were missed with FibriCheck. This could be due to problems with the watch's automatic measuring schedule or the limited number of smartphone spot-checks. However, there is no consensus on which AF episode duration is clinically relevant. Thereby, the possible missed short episodes may even be irrelevant (47). Lastly, the examined cryptogenic stroke and TIA patients may have experienced memory dysfunction, making them more prone to forget the FibriCheck usage. On the other hand, it is mostly an older population, thus, smartphones and smartwatches may not even be implemented. Additionally, even when they own these devices, not all patients are sufficiently digital health literate to operate them.

## CONCLUSION

This paper indicates the pitfalls and opportunities of AF detection in cryptogenic stroke and TIA patients using mHealth on smartphones and smartwatches, and the ICM. Our study observed no significant difference in AF detection between the different cardiac monitoring methods. However, only a limited number of patients was analyzed, emphasizing the need for future research. Moreover, even the state-of-the-art ICM yielded many false AF registrations. Therefore, FibriCheck and ICM findings both still need confirmation by a trained nurse or physician, increasing the workload. Furthermore, besides technical issues, digital health literacy, memory dysfunction and blinding of the results also contribute to the reduction in FibriCheck adherence. These are important observations that need to be taken into account in future research or in the implementation of mHealth.

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**SUPPLEMENTARY INFORMATION**

**Supplementary Table 1** – **Percentage of low-quality measurements.**

| | Insufficient quality measurements (%) | P-value |
|---|---|---|
| **Age** | | 0.406 |
| > 65 years (n = 22) | 41.6 (12.7 – 60.5) | |
| ≤ 65 years (n = 20) | 25.8 (6.3 – 55.0) | |
| **Gender** | | 0.571 |
| Male (n = 28) | 32.3 (6.3 – 60.3) | |
| Female (n = 14) | 41.0 (15.2 – 54.3) | |
| **Number of cameras** | | 0.157 |
| One (n = 8) | 4.5 (0.9 – 47.0) | |
| Two or more (n = 17) | 14.7 (6.5 – 45.0) | |
| **Smartphone brand** | | 0.366 |
| Apple (n = 10) | 9.5 (6.4 – 60.2) | |
| Huawei (n = 2) | 58.0 (44.4 - …) | |
| Motorola (n = 1) | 42.5 | |
| OnePlus (n = 1) | 14.7 | |
| Samsung (n = 9) | 5.1 (0.4 – 22.2) | |
| Vestel (n = 1) | 6.7 | |
| Xiaomi (n = 1) | 3.6 | |

Statistics were performed using the Mann-Whitney U test and Kruskal Wallis test.

**Supplementary Table 2 – Motivation and compliance of the smartphone group compared between age, gender and number of used smartphone applications.**

| | Motivation (%) | P-value | Compliance (%) | P-value |
|---|---|---|---|---|
| **Age** | | 0.813 | | 0.699 |
| > 65 years (n = 12) | 38.0 ± 25.9 | | 59.5 ± 31.6 | |
| ≤ 65 years (n = 15) | 35.7 ± 24.5 | | 55.2 ± 24.9 | |
| **Gender** | | 0.376 | | 0.653 |
| Male (n = 21) | 39.8 (16.3 – 61.5) | | 58.0 ± 30.7 | |
| Female (n = 6) | 23.2 (17.6 – 34.8) | | 54.1 ± 13.4 | |
| **Number of apps before FC** | | 0.366 | | 0.347 |
| No apps (n = 2) | 26.0 ± 30.5 | | 45.8 ± 40.8 | |
| 1-2 apps (n = 9) | 46.1 ± 27.6 | | 68.0 ± 28.4 | |
| 3 or more apps (n = 16) | 32.8 ± 22.4 | | 52.4 ± 25.8 | |
| **Number of apps after FC** | | 0.813 | | 0.740 |
| No apps (n = 1) | 47.5 | | 74.6 | |
| 1-2 apps (n = 6) | 40.2 ± 30.5 | | 61.0 ± 28.0 | |
| 3 or more apps (n = 14) | 43.2 ± 22.9 | | 65.2 ± 24.6 | |
| **Downloaded apps after FC** | | 0.468 | | 0.340 |
| Deleted apps (n = 2) | 25.2 ± 25.4 | | 41.7 (21.5 - ….) | |
| No new apps (n = 11) | 47.5 ± 25.5 | | 74.6 (45.9 – 87.6) | |
| 1-2 new apps (n = 8) | 40.0 ± 22.2 | | 56.1 (47.5 – 75.8) | |

FC, FibriCheck. Statistics were performed using the Unpaired t-test, Mann-Whitney U test, One way ANOVA and Kruskal Wallis test.