Validation of a new smartphone application ("FibriCheck") for the diagnosis of atrial fibrillation in primary care

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Abstract

Background

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. While its prevalence increases with age, AF often remains asymptomatic and therefore untreated. The presence of AF can lead to serious complications, of which stroke is the most important. In order to lower medical costs and improve quality of life, early detection and prevention are necessary. European guidelines recommend opportunistic screening in people aged 65 and older. Pulse palpation, the most commonly used method for AF screening, has a high sensitivity but a lower specificity. Alternative screening methods often require external hardware. Recently, a new smartphone application for AF detection, *FibriCheck*, has been developed. This app only uses the flashlight and camera of a smartphone to detect AF, through the technique of photoplethysmography (PPG).

Methods

General practice patients aged 65 and older and preferably with a history of AF, were invited. Participants with active pacemakers were excluded. Three different ways of measurement for AF detection were used in this study. At the same time of a PPG measurement (holding left index finger on the camera during one minute), a synchronized single-lead ECG (external module on the chest) was taken. Both traces were interpreted by the FibriCheck AF algorithm after poor signal quality measurements were excluded by a software filter. First, the results of the FibriCheck algorithm were compared with the cardiologists' 12-lead ECG protocol to calculate diagnostic accuracy. Secondly, beat-to-beat comparison was done between the PPG and the single-lead ECG measurements.

Results

A total of 242 subjects participated in this study. The signal quality filter of the application defined 29 PPG's and 10 single-lead traces as poor and unreliable signal quality. For the PPG measurement and interpretation by the FibriCheck app a sensitivity of 98% (95% CI 92 - 100), a specificity of 88% (95% CI 80 - 94) and an accuracy of 93% (95% CI 89 - 96) was obtained. False positive results were caused by atrial (n = 7) or ventricular (n = 1) extrasystoles and by failure of the quality filter of the application in recognizing a poor and unreliable signal (n = 4). For the single-lead ECG interpretation by the FibriCheck app a sensitivity of 98% (95% CI 93 - 100), a specificity of 90% (95% CI 83 - 95) and an accuracy of 94% (95% CI 91 - 97) was found. The 11 false positive results were due to atrial (n = 10) and ventricular (n = 1) extrasystoles.

Discussion

The FibriCheck algorithm has a good capacity to rule out AF. False positive results were mainly due to the presence of extrasystoles and low signal quality. Considering the PPG accuracy is approximating the value for the single-lead ECG measurement method, these results can be called promising for the Fibricheck application. Because the same AF algorithm was used and simultaneous beat-to-beat analysis was carried out, the small difference in performance solely lies in the method of signal measurement.

Conclusion

The FibriCheck is an accessible standalone smartphone application that showed promising results for AF detection in a primary care convenience sample. The first version of the app scored a high accuracy and sensitivity and a moderate to high specificity. This makes it a possible candidate to implement in future screening or case-finding programs for AF. Yet, further research is needed to determine the place of the FibriCheck in such a strategy.

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Background

Affecting more than 8.8 million adults in the European Union, atrial fibrillation (AF) is currently the most common sustained cardiac arrhythmia[1]. The prevalence of AF is about 2.2% and increases with age: rising to 6.4% in people aged 60 and older to over 8% in a population aged 80 and older[1,2]. The prevalence of AF is estimated to at least double by 2050[3,4]. The presence of AF can lead to serious complications. Both paroxysmal and permanent AF double mortality and triple the chance of developing congestive heart failure[5]. Atrial fibrillation also increases the risk of stroke with a factor five[6,7]. Over 20% of all cerebrovascular accidents (CVA) are directly attributable to AF[3,4]. In almost half of the patients with an AF-related stroke, arrhythmia has been found to be asymptomatic, undiagnosed and therefore untreated[4,7-8]. An effective antithrombotic therapy reduces the risk of stroke with 60%[9]. In order to lower medical costs and improve quality of life, early detection and prevention are necessary[10-12].

In a large systematic review[4], 30 screening programs were compared. Systematic and opportunistic screening both identified 1.4% of unknown AF in the screened population aged 65 and older. Although European guidelines[3] recommend opportunistic screening in people aged 65 and older, the awareness is still low among general practitioners. Pulse palpation currently remains the most commonly used method for screening. This method has a high sensitivity (91-100%) but a lower specificity (70-77%)[13-14]. Therefore, a 12-lead electrocardiography (ECG) is still recommended in case of pulse irregularity[3].

The development of new screening methods for AF has been a hot topic over the last few years. These devices or software can assist the physician in the diagnosis and follow-up of AF. For example: a three-lead ECG taken with an automated external defibrillator (AED)[15], the *Watch BP* blood pressure monitor (Microlife WatchBP AG, Widnau, Switserland)[16], the *MyDiagostick* (Applied Biomedical Systems BV, Maastricht, Netherlands)[14] and the *Omron Heart scan* (OMRON Healthcare Europe BV, Hoofddorp, Netherlands)[17]. Despite this evolution, few of these new devices were actually implemented in Belgian primary care.

In addition to new devices, multiple smartphone applications were developed in order to facilitate screening for AF. Worldwide, it is estimated that 19 million people currently use mobile health devices and the number is increasing[18]. Of the people aged 65 and older in Europe, 27% owned a smartphone in 2014[19]. Moreover, it is mainly due to seniors that smartphone penetration on the European market is still growing[20]. This increase offers great opportunities for AF screening through smartphone applications. An example of such a smartphone app is the *AliveCor* (AliveCor, San Francisco, U.S.A.)[21], producing a single-lead ECG in one minute. A limitation of this app is that –like the previous devices– extra hardware (i.e. a special cover with ECG-electrodes) is needed. In order to facilitate screening, easy-to-use apps are needed, which do not require external material.

Recently, a new smartphone application for AF detection, *FibriCheck* (Qompium, Hasselt, Belgium), has been developed. In order to identify heart rhythm irregularities, this app only uses the flashlight and camera which are often present on a smartphone. Therefore, this study was designed to investigate the diagnostic accuracy of the Fibricheck app in a convenience sample of patients aged 65 and older in general practice.

Methods

Study Population

Multiple GP centers (n = 17) were asked to join in this project. The investigators performed a search in the electronic medical file of each practice, in order to make a list of all people

aged 65 and older with a history of AF. A convenience sample of patients with a history of (paroxysmal or permanent) AF were invited by phone and during consultation. In addition, patients without cardiac arrhythmia were asked to participate.

A sample size[22] of 200 subjects was needed. This calculation was based on a probability of finding a false positive result of 5% or less ($\alpha = 0.05$), an estimated prevalence of AF of 50% in the study population, an expected sensitivity and specificity of 95% (following the results of the previous study in controlled setting) and a confidence interval of 4%. In order to include sufficient patients with AF (n = 100), patients with a known history of AF were invited to participate.

The participating patients were invited to the cabinet of their own GP or were visited at home. The inclusion and measurement period took place from October 2015 until March 2016. All patients gave informed consent. The study was approved by the ethical review board of the Medical Faculty of the KU Leuven, Belgium (no MP 05256).

First, a number of data to describe the study population was noted by the investigators (CM, RV): age, sex, presence of obesity (BMI>30) and heart failure, systolic and diastolic blood pressure and cardiac murmur on auscultation. The intake of antihypertensive medication and anticoagulants (low-molecular-weight heparines, vitamin-K-inhibitors and NOAC's) or platelet aggregation inhibitors was registered. Based on clinical examination and data from the electronic medical file, the different components of the CHA_2DS_2-VASc-score[23-24] were listed. Furthermore, a calculation of the Framingham risk score[25] took place. When unable to determine the date of onset of cardiac murmur and heart failure, these conditions were considered as newly diagnosed at the moment of the study. The dependency of the patients was scaled from one to nine with the Canadian clinical frailty index[26-27].

Atrial fibrillation measurements

After the basic clinical examination and questioning, three different ways of measurement for the diagnosis of AF were used in this study. A photoplethysmography (PPG) signal (FibriCheck app) and a single-lead ECG (external patch) were obtained simultaneously, prior to a 12-lead ECG. All exams were performed by one of the investigators, blinded for the results of the Fibricheck app. Both the PPG and single-lead traces were assessed by the FibriCheck AF algorithm. In this study, the app was installed and used on an iPhone 5S (Apple, Cupertino, USA).

PPG

FibriCheck (Qompium, Hasselt, Belgium) is a new smartphone application that measures the rhythm of the heart through the technique of photoplethysmography (PPG). The software calculates the blood volume pulse variation in the local arterioles, depending on the amount of reflected light on the camera. This way, each heartbeat is recorded and the rhythm is determined based on the RR-interval.

First, patients were asked to adopt the standard position (Attachments – figure 1): sitting on a chair, the arms resting on the table, holding the smartphone in vertical position with their right hand. Next, patients were invited to cover the flashlight and the camera on the back of the smartphone horizontally with their left index finger. In case of good contact, the screen turned red and the physician started the measurement manually. The index phalange was lighted for one minute. A countdown clock was visible on the screen. People were asked not to speak nor move during the measurement. Three consecutive measurements were performed. If the finger was removed from the camera, an extra (fourth) measurement was carried out.

The FibriCheck application was configured in a data-recording mode with only raw data collection. The investigator checked if the colour of the screen remained red, to ensure good contact. The maturity of handling a smartphone was scored on a scale from one to four (1: Very good handling of smartphone, knows how to hold it and how it works; 2: Has knowledge of the smartphone and only requires minor input on how to perform the handlings; 3: Has knowledge of the smartphone but needs a lot of input on how to perform the handlings; 4: Has never held a smartphone or has many issues in holding it correctly and performing the handlings). The quality of the measurement was scaled by the investigator from one to four (1: Good measurement in steady position; 2: Slight movement/some talk during measurement; 3: Moderate movement/frequent talking during measurement; 4: Finger was removed from camera during measurement).

The FibriCheck app disposes of a software filter to score the quality of the PPG signal (0: poor signal, unreliable result; 1: good signal, reliable result). The PPG signal quality judgement of the filter was based on the ability to detect and differentiate heart beats. If heart beat detection was compromised with noise, or if heart beats were absent, these measurements were filtered out as bad quality and the results were not included in the analysis. If more than one measurement was defined as a good signal, opportunistic selection took place, based on the quality of the PPG trace. Following beat detection and quality judgement, the PPG data were interpreted by the AF algorithm of the application for diagnosis.

Single-lead ECG

At the same time of the PPG measurement, a synchronized single-lead ECG was taken and interpreted by the FibriCheck AF algorithm. An external module (Imec, Heverlee, Belgium)[28] was used, validated for single-lead ECG registration. The module was attached with a patch on the left side of the patient's chest (Attachments – figure 2):, above the heart (zone rib 2 – rib 3). The module could be manually activated by the investigator and was wirelessly connected to the FibriCheck-app on the smartphone. The one-lead ECG trace, visible on the screen (Attachments – figure 3-4): was assessed by the investigator from one to four (1: No QRS visible; 2: Slight QRS visible; 3: QRS visible; 4: QRS and P-wave visible). All measurement data were saved anonymously on the smartphone and then transferred to a secured online data platform. Raw data were analyzed offline afterwards. The raw single-lead signal quality was also scored by the filter software of the FibriCheck app (0: poor signal, unreliable result; 1: good signal, reliable result). QRS-complexes were detected using the Pan-Tompkins method[29]. Poor quality measurements were excluded from further analysis and opportunistic selection took place, based on the quality of the remaining ECG traces. Next, the reliable measurements were evaluated by the FibriCheck AF algorithm based on RR-interval variability analysis.

Reference standard

A 12-lead ECG was taken by the same investigator and immediately printed. The used digital ECG-devices were: CardiMax FCP-7101 (Fukuda Denshi, Tokyo, Japan), CP 50 (Welch Allyn, New York, USA), Universal ECG (QRS Diagnostic, Plymouth MN, USA) and ECG-1150 (Nihon Kohden Corporation, Tokyo, Japan). The ECG's were protocolled for the presence of AF (Minnesota code 8-3-1) by two independent and double-blinded cardiologists. In case of inconsistent results, these ECG's were protocolled by a third cardiologist. Patients wearing a pacemaker were excluded if the pacemaker was configured in active pacing mode.

Statistical analysis

First, the resulting diagnosis of the new FibriCheck app based on the measurement and interpretation of the PPG signal was compared with the 12-lead ECG, the reference

standard. Secondly, the interpretation of the single-lead ECG traces by the FibriCheck AF algorithm was compared with the reference standard. Finally, the results of the PPG analysis were set against the results of the single-lead ECG diagnosis. Since the latter two measurements were carried out simultaneously, this method offered the opportunity of beat-to-beat comparison (Attachments – figure 5):. In case of inconsistencies between both results, further analysis was done to reveal the underlying reason (e.g. poor signal quality missed by the filter software). Sensitivity and specificity and their 95% confidence interval were calculated using 2x2 tables (MedCalc°, Mariakerke, Belgium). The positive and negative predictive values were then estimated based on an expected prevalence of AF of 6% in the population aged 65 or older.

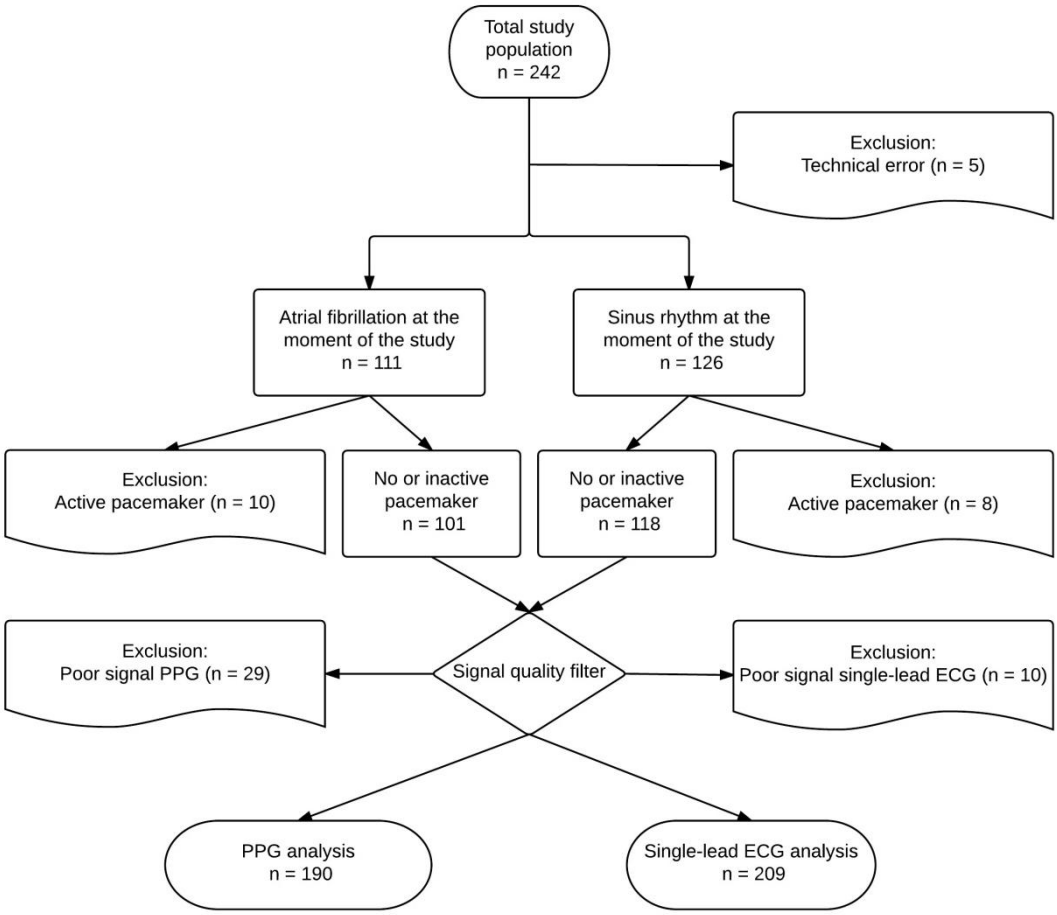
Results

Study population

A total of 242 subjects participated in this study (Flowchart - figure 1). Five subjects were excluded because their data were not saved properly, due to a technical error. At the moment of the study, the 12-lead ECG showed atrial fibrillation to be present in 111 participants (47%).

Of the 23 patients wearing a pacemaker, 18 were excluded because they were in active pacing mode during the measurements. The signal quality filter of the application defined 29 PPG's and 10 single-lead traces as poor and unreliable signal quality. These data were therefore excluded. Further PPG and single-lead analysis were continued with 190 and 209 subjects respectively.

Figure 1: Flowchart of study participants



PPG analysis versus ECG

Study population

Of the remaining 190 participants, 109 (57%) were women. The mean age of the participants was 77 ± 8 years (range: 65 – 95). The two cardiologists agreed on the presence of AF in 183 subjects. The ECG of 7 participants (3.7%) was evaluated by a third cardiologist. In all, 92 subjects (48%) were in AF at the moment of the study. One subject (1.5%) was newly diagnosed with AF.

Table 1 shows the characteristics of the patients according to the presence of AF. In the AF population, the median clinical frailty score was 4 (IQR: 3 - 5). The median CHA_2DS_2-VASc-score of the AF population was 5 (IQR: 4 – 6) and all had ≥ 2. In this group 8 patients (8.7%) received a platelet aggregation inhibitor and 84 (91%) received anticoagulation therapy. Of those in sinus rhythm (n = 98), the median CHA_2DS_2-VASc-score was 4 (IQR: 3 - 5) and nearly all (99%) had ≥ 2. In this group the median Framingham risk score was 8 (IQR: 6 – 9), matching with a predicted 10-year risk of AF ≥ 16%. In total, 34 patients (18%) had a smartphone of their own. The median score of maturity handling a smartphone was 4 (IQR: 2 – 4). This finding was less prominent in the non-AF group. This subpopulation scored a median of 3 (IQR: 2-4).

PPG results

Based on the PPG measurements, the Fibricheck application showed an AF positive result in 102 subjects and a negative result in 88 participants. The PPG results matched the diagnosis of the cardiologists 176 times (97%). Of the 14 inconsistent results, 12 were found to be false positive and 2 were false negative. The false positive results were caused by atrial (n = 7) or ventricular (n = 1) extrasystoles and by failure of the quality filter of the application in recognizing a poor and unreliable signal (n = 4). The false negative results followed wrong peak detection (n = 1) and misinterpretation of an atrial flutter (n = 1). On the basis of these results a sensitivity of the PPG measurement and interpretation of the FibriCheck app of 98% (95% CI 92 - 100), a specificity of 88% (95% CI 80 - 94) and an accuracy of 93% (95% CI 89 - 96) was obtained (Table 2).
In this study population, the positive predictive value was 88% (95% CI 80 – 94) and the negative predictive value 98% (95% CI 92 - 98). Based on an expected prevalence of 6% in the general population aged 65 or older, a positive predictive value of 34% (95% CI 27 - 42) and a negative predictive value of 99.9% (95% CI 99 - 100) were estimated.

Single-lead ECG analysis versus ECG

Study population

The quality of the single-lead-ECG signal was scored as good and reliable in 209 patients.
The ECG of 7 (3.3%) participants was also evaluated by a third cardiologist. A total of 136 participants had a known history of AF (65%). At the moment of the study 98 (47%) subjects were in AF. One subject was newly diagnosed with AF (1.4%).

Single-lead ECG results

The obtained single-lead ECG trace was interpreted by the FibriCheck app as AF positive in 107 subjects and as sinus rhythm in 102 subjects. The results of the single-lead protocol matched with the evaluation of the cardiologists in 196 participants (94%) (Table 3). The 11 false positive results were due to atrial (n = 10) and ventricular (n = 1) extrasystoles. The 2 false negative results were caused by wrong QRS-peak detection (n = 1) and misinterpretation of an atrial flutter (n = 1). On the basis of these results a sensitivity for the

single-lead ECG interpretation of the FibriCheck app of 98% (95% CI 93 - 100), a specificity of 90% (95% CI 83 - 95) and an accuracy of 94% (95% CI 91 - 97) was obtained.

In this study population, the positive predictive value was 90% (95% CI 82 - 95) and the negative predictive value 98% (95% CI 93 - 100). Based on an expected AF prevalence of 6% in the general population aged 65 or older, a positive predictive value of 39% (95% CI 31 - 47) and a negative predictive value of 99.9% (95% CI 99 - 100) were estimated.

Table 1: Characteristics of the PPG study population (n = 190)

	All (n = 190)	AF present (n = 92)	AF absent (n = 98)
Age, mean ± SD	77 ± 8	79 ± 8	76 ± 8
Male gender, n (%)	81 (42.6)	45 (48.9%)	36 (36.7%)
Risk scores			
Clinical Frailty score, median (IQR)	3 (2 - 4)	4 (3 - 5)	3 (2 - 4)
CHA_2DS_2-VASc-score, median (IQR)	4 (3 - 6)	5 (4 - 6)	4 (3 - 5)
CHA_2DS_2-VASc-score ≥ 2, n (%)	189 (99.5)	92 (100)	97 (99.0)
Framingham risk score, median (IQR)	-	-	8 (6 - 9)
Comorbidities			
History of AF in medical records, n (%)	122 (64.2)	91 (98.9)	31 (31.6)
BMI, mean ± SD	26.2 ± 4.8	26.0 ± 4.4	26.4 ± 5.1
Diabetes mellitus type II, n (%)	41 (21.6)	25 (27.2)	16 (16.3)
Vascular disease, n (%)	70 (36.8)	41 (44.6)	29 (29.6)
TE, TIA or CVA, n (%)	43 (22.6)	30 (32.6)	13 (13.3)
Congestive heart failure, n (%)	55 (28.9)	37 (40.2)	18 (18.4)
Cardiac murmur, n (%)	46 (24.2)	34 (37.0)	12 (12.2)
Inactive pacemaker, n (%)	5 (2.6)	4 (4.3)	1 (1.0)
Arterial hypertension, n (%)	159 (83.7%)	84 (91.3)	75 (76.5)
Systolic blood pressure, mean ± SD	130 ± 16	130 ± 16	130 ± 17
Diastolic blood pressure, mean ± SD	74 ± 9	75 ± 11	73 ± 8
Heart rate at rest, mean ± SD	76 ± 18	83 ± 19	71 ± 14
Antihypertensives			
Diuretics, n (%)	70 (36.8)	47 (51.1)	23 (23.5)
Beta-blockers, n (%)	113 (59.5)	66 (71.7)	47 (48.0)
Calcium channel blockers, n (%)	40 (21.1)	21 (22.8)	19 (19.4)
ACE inhibitors, n (%)	44 (23.2)	26 (28.3)	18 (18.4)
Angiotensin II receptor antagonists, n (%)	36 (18.9)	19 (20.7)	17 (17.3)
Centrally acting agents, n (%)	2 (1.1)	2 (2.2)	0 (0.0)
Anti-thrombotic treatment			
No anti-aggregantia or anticoagulantia, n (%)	45 (23.7)	0 (0.0)	65 (66.3)
Platelet aggregation inhibitors, n (%)	39 (20.5)	8 (8.7)	11 (11.2)
Anticoagulantia, n (%)	106 (55.8)	84 (91.3)	22 (22.4)
Vitamin K antagonists, n (%)	46 (24.2)	39 (42.4)	7 (7.1)
New oral anticoagulants, n (%)	58 (30.5)	43 (46.7)	15 (15.3)
Smartphone usage			
Smartphone ownership, n (%)	34 (17.9)	11 (17.9)	23 (23.5)
Maturity handling smartphone, median (IQR)	4 (2 - 4)	4 (3 - 4)	3 (2 - 4)

SD: standard deviation; IQR: inter-quartile range;
TIA: transient ischaemic attack; CVA: cerebrovascular accident

PPG versus single-lead ECG analysis

Study Population

In 183 subjects, both the quality of the PPG and the single-lead ECG trace was scored as good and reliable. At the moment of measurement, 97 (53%) of the participants were in AF based on the FibriCheck interpretation of the single-lead ECG.

PPG versus single-lead ECG results

The PPG results matched the output of the single-lead protocol 181 times (99%) (Table 4). If the FibriCheck interpretation of the single-lead trace would be considered as reference standard, the PPG measurement and diagnosis of the FibriCheck app would result in a sensitivity of 100% (95% CI 94 - 100), a specificity of 98% (95% CI 92 - 100) and an accuracy of 99% (95% CI 97 - 100).

In this study population the positive predictive value was 98% (95% CI 93 - 100) and the negative predictive value 100% (95% CI 94 - 100). Based on an expected prevalence of 6% in the general population aged 65 or older a positive predictive value of 73% (95% CI 62 - 82) and a negative predictive value of 100% (95% CI 99 - 100) were estimated.

Table 2: 2x2 table to calculate the diagnostic accuracy of the PPG-measurements: measurement and interpretation by the FibriCheck application.

	Atrial fibrillation present	**Atrial fibrillation absent**	Total
PPG positive result	90	12	102
PPG negative result	2	86	88
Total	92	98	190

Table 3: 2x2 table to calculate the diagnostic accuracy of the single-lead ECG's: interpretation by the FibriCheck application.

	Atrial fibrillation present	**Atrial fibrillation absent**	Total
1-lead positive result	96	11	107
1-lead negative result	2	100	102
Total	98	111	209

Table 4: 2x2 table to calculate the diagnostic accuracy of the PPG-results set against the single-lead ECG interpretation as reference standard

	Atrial fibrillation present	**Atrial fibrillation absent**	Total
PPG positive result	97	2	99
PPG negative result	0	84	84
Total	97	86	183

Discussion

Summary of the most important results

In this study of a convenience sample in primary care, a new smartphone application and its ability to detect AF, based on two different measurement methods, was evaluated. The FibriCheck algorithm was able to accurately diagnose AF based on the obtained single-lead ECG with a high sensitivity and specificity. The application scored an equally high sensitivity, but a slightly lower specificity when measuring and interpreting the PPG signal. The high sensitivity of the application reflects the good capacity of the algorithm to rule out AF. False positive results were mainly due to the presence of extrasystoles and low signal quality that remained undetected by the filter. Considering the PPG accuracy is approximating the value

for the validated single-lead ECG measurement method, these results can be called promising for the Fibricheck application. Because the same AF algorithm was used and simultaneous beat-to-beat analysis was carried out, the small difference in performance solely lies in the method of signal measurement.

Findings in context of previous research

The results for the FibriCheck are comparable to the diagnostic accuracy found for other screening methods and devices. A recent systematic review and meta-analysis[30] investigating the accuracy of different methods for detecting an irregular pulse and suspected atrial fibrillation, found the greatest accuracy for blood pressure monitors and non-12-lead ECG's. The modified sphygmomanometers had a pooled sensitivity of 98% and specificity of 92%. Non-12-lead ECGs scored a sensitivity of 91% and a specificity of 95%. However, when focusing on the primary care setting, a lower specificity of 89% was obtained. In the meta-analysis smartphone applications also scored a very good accuracy with a sensitivity of 97% and a specificity of 95%. However, the authors state that these findings need to be interpreted with caution since multiple algorithms were used and only three small studies were included. Recent literature indeed shows divergent accuracy values for new smartphone applications. For the AliveCor for example, Haberman et al.[31] found a sensitivity of 94% and a specificity of 99% in cardiology clinic patients. Desteghe et al.[32] found lower values in hospitalized patients with a sensitivity ranging 55-79% and a specificity between 97.5-97.9%. It is important to point out the heterogeneity in population between conducted studies: most subjects participated during hospitalization and the AF prevalence differed significantly. This makes it harder to compare these data with our findings that were obtained in primary care, which is the target setting of AF screening. Pulse palpation, the current leading AF screening method, achieved a comparable sensitivity of 92% in the meta-analysis. However, the specificity value of 82% was only moderate, reflecting more false positive results than previous methods.

(Dis)Advantages

A novel smartphone application for AF detection was investigated in this diagnostic study and compared with a single-lead and 12-lead ECG. The main advantages of the app are that it is a quick, reasonably priced and practical measurement method without the need for special infrastructure nor any external hardware. There are no necessary wires or electrodes. The patient does not require any experience or medical education in order to use the app. As a result, the work load is minimal for the physician, who can remotely review the transferred data. This enables optimal patient follow-up in a less time-consuming way. Furthermore, an important extra asset is the high accessibility of smartphone applications, given the documented steep increase of smartphone usage in the elderly[19-20,33]. However, in our study population, 18% owned a smartphone, which is lower than the value of 27% reported in a recent Austrian[19] and American[33] senior survey.

A disadvantage was the number of false positive results, due to atrial or ventricular extrasystoles, a known AF screening issue using RR-interval variability analysis. Secondly, a number of –mostly PPG– measurements were excluded, because of poor signal quality. We had the impression that this noise in signal was in part caused by bad contact due to the loss of concentration or the influence of tremor, though this numbers were not registered. It is a limitation not seen in, for example, modified blood pressure monitors or the MyDiagnostick. Tremors during measurement could have been caused by white-coat induced stress or limited maturity handling a smartphone. It is likely that in future generations this lack of familiarity will partially fade. A personal learning-curve could also improve longitudinal screening potential. Additionally, the software filter was not always able to detect poor signal quality as such, which had a negative influence on the specificity.

Implementation in daily practice

Early detection of (asymptomatic) AF reduces the medical and financial burden of stroke. It is expected that both AF prevalence and smartphone usage in senior populations will continue to rise. Based on these findings and our evaluation of the first version of the FibriCheck application, a great opportunity lies in AF screening through PPG measurement in primary care. General practitioners can play an important role in coordinating screening and case-finding in high-risk patients, implementing smartphone apps in their clinical practice. Furthermore, this mobile technology also allows screening for paroxysmal AF and follow-up of treated patients after resynchronization.

Future research

After this phase II diagnostic study, future research is needed to investigate the effect of implementing the FibriCheck in daily practice by using a cluster randomized trial. The place of the FibriCheck in possible future screening or case-finding programs for AF therefore remains to be determined. Moreover, the measurement method and AF algorithm will be further improved in order to optimize diagnostic accuracy. Goals are a reduction of bad PPG signal quality and a differentiation between AF and extrasystoles by the algorithm. Evaluation of future versions of the AF algorithm can be done based on our collected PPG and single-lead data.

Strengths and limitations of the study

This is the first study investigating the diagnostic accuracy of the FibriCheck smartphone application in a real world primary care population. Simultaneous measurement of PPG and single-lead ECG traces offered the opportunity of beat-to-beat comparison of the two measurement methods. Therefore, false positive results could be further explored afterwards. The single-lead chest ECG could also be used for external interpretation. For example ectopic beats could be identified more easily and distinguished from noise.

However, a few limitations should be noted. First, different digital ECG devices were used as the reference standard instead of one standardized device. Second, even if we tried to keep it short, there was always a gap of several minutes between PPG measurement and the 12-lead ECG. Heart rhythm (e.g. extrasystoles or paroxysmal AF) might have changed in that time period. Third, patients used the smartphone under observation of an investigator. The yield of high-quality PPG recordings may be lower when the recording is not supervised (e.g. home setting). Fourth, when the date of onset of cardiac murmur or heart failure remained unknown, the study date was chosen to calculate the Framingham risk score. This might have provoked an underestimation of the score and therefore the 10-year risk to develop AF. Fifth, to calculate the PPV and NPV in a population over 65 years old, we assumed an AF prevalence of 6%. However, due to the heterogeneity between conducted studies, various values were found for AF prevalence in literature. Furthermore, studying a convenience sample, extrapolation of these results to the general primary care population aged 65 and older should be made with caution.

Conclusion

The FibriCheck is an accessible standalone smartphone application that showed promising results for AF detection in a primary care convenience sample. The first version of the app scored a high accuracy and sensitivity and a moderate to high specificity. This makes it a possible candidate to implement in future screening or case-finding programs for AF. Yet, further research is needed to determine the place of the FibriCheck in such a strategy.

Abbreviations

AF: Atrial fibrillation
CI: Confidence interval
CVA: Cerebrovascular accident
ECG: Electrocardiogram
IQR: Inter-quartile range
PPG: Photoplethysmography
SD: Standard deviation
TIA: Transient ischaemic attack

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Attachements

Figures



Figure 1 - *anatomical location of the ECG module on the chest and left index covering the flashlight and camera of the smartphone.*



Figure 2 - *External single-lead ECG module of the FibriCheck app with two self-adhesive electrodes.*

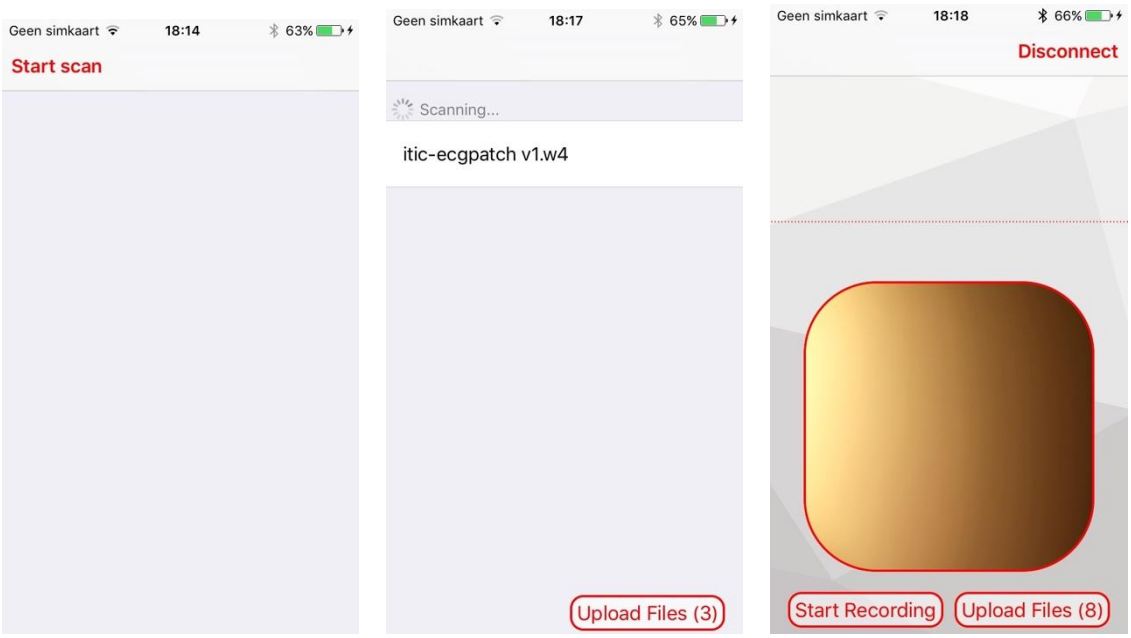


Figure 3 - *Left: homescreen. Once the extern module is turned on, the physician selects "Start scan".*
Middle: If the module was found by the sensor, it will be displayed in the list and can be activated.
Right: Once activated, the camera turns on and this screen is displayed. The phone is handed to the patient. In case of a good position of the left index, the screen will turn red and the measurement can be started by pushing the "Start Recording" button.

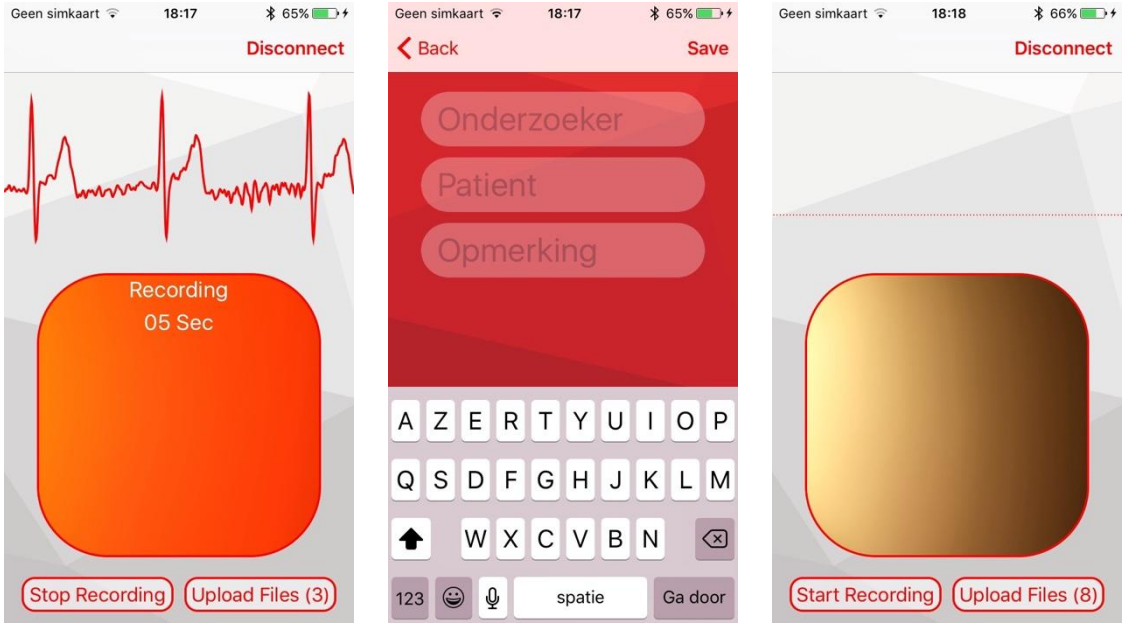


Figure 4 *- Left: the single-lead ECG trace and clock during measurement. Middle: after one minute of measurement the data can be saved on the smartphone. Right: The data can now be uploaded to the secured online platform.*

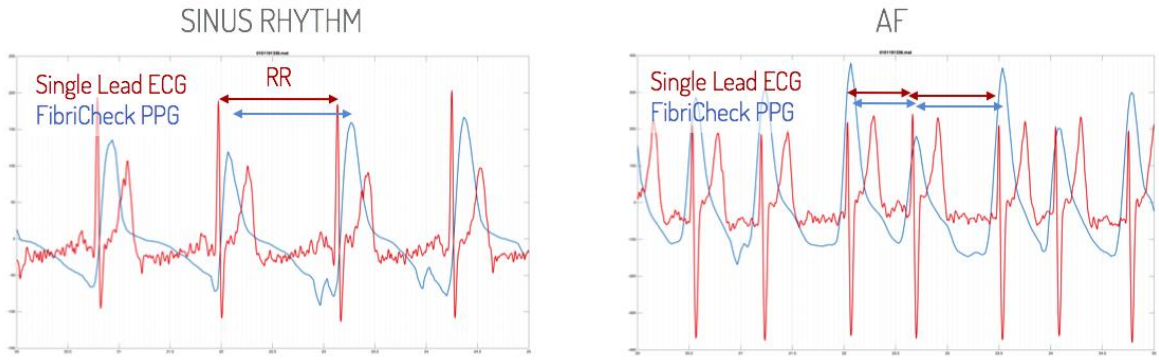


Figure 5 – *Left: a synchronized ECG and PPG signal for a patient with normal sinus rhythm. Right: a synchronized recording for a patient with atrial fibrillation. The arrows indicate the RR-interval between two consecutive heart beats.*

Dutch Abstract

Inleiding

Voorkamerfibrillatie (VKF) is de meest frequente hartritmestoornis na extrasystolen. De prevalentie stijgt fors met de leeftijd. Door de grote fractie asymptomatische (paroxysmale) VKF-patiënten, krijgen velen niet de gepaste behandeling. VKF kan ernstige complicaties veroorzaken, waaronder een beroerte. Teneinde het medische kostenplaatje onder controle te houden en levenskwaliteit te bevorderen, zijn vroege opsporing en behandeling belangrijk. Europese richtlijnen adviseren opportunistische screening bij 65-plussers. Polspalpatie, momenteel de meest courrante screeningsmethode voor VKF, heeft een hoge sensitiviteit maar een lagere specificiteit. Alternatieve methodes vereisen vaak extra meetmateriaal. Recent werd een nieuwe smartphone-applicatie ontwikkeld, *FibriCheck*. Deze app kan via fotopletysmografie (PPG) VKF opsporen wanneer de patiënt de wijsvinger gedurende één minuut op de smarphone camera houdt.

Methode

Eerstelijnspatiënten boven 65 jaar, hoofdzakelijk met een VKF-voorgeschiedenis, werden uitgenodigd. Deelnemers met een actieve pacemaker werden geëxcludeerd. Mogelijke VKF werd in deze studie op drie manieren opgespoord. Op hetzelfde ogenblik als de PPG-meting werd een gesynchroniseerd single-lead ECG genomen op de borstkas. Na de exclusie van signalen van slechte kwaliteit door de softwarefilter, werden beide tracés geïnterpreteerd door hetzelfde VKF-algoritme van FibriCheck. De resultaten van beide meettechnieken werden vergeleken met het specialistisch 12-lead ECG-protocol. Nadien werden PPG- en single-lead-ECG-uitkomsten ook onderling vergeleken via beat-to-beat-analyse.

Resultaten

In totaal werden de metingen uitgevoerd bij 242 deelnemers. De kwaliteitsfilter van de app klasseerde 29 PPG's en 10 single-lead tracés als onvoldoende betrouwbare metingen. Voor de PPG-meettechniek en de interpretatie door het FibriCheck-algortime werd een sensitiviteit van 98% (95% CI 92 - 100), een specificiteit van 88% (95% CI 80 - 94) en een accuraatheid van 93% (95% CI 89 - 96) gevonden. Vals positieven werden veroorzaak door atriale (n = 7) of ventriculaire (n = 1) extrasystolen en door slechte metingskwaliteit die niet opgemerkt werd door de filter (n = 4). Voor de single-lead ECG interpretatie werd een sensitiviteit van 98% (95% CI 93 - 100), een specificiteit van 90% (95% CI 83 - 95) en een accuraatheid van 94% (95% CI 91 - 97) gevonden. De 11 vals positieve resultaten werden verklaard door atriale (n = 10) en ventriculaire (n = 1) extrasystolen.

Discussie

Het FibriCheck-algoritme slaagt er goed in om VKF uit te sluiten. Vals positieve resultaten zag men vooral bij voorkomen van extrasystolen en metingen van lage kwaliteit. Daar de accuraatheid van de PPG-meetmethode deze voor single-lead ECG benadert, kunnen deze resultaten veelbelovend worden genoemd voor de FibriCheck app. Vermits hetzelfde VKF-algoritme werd toegepast op beide tracés en 'beat-to-beat-analyse' werd uitgevoerd, wordt het (kleine) verschil in prestatie verklaard door de verschillende meetmethode.

Besluit

De FibriCheck is een toegankelijke standalone smartphone applicatie die goede resultaten neerzette in een eerstelijns convenience sample. De eerste versie van de app scoorde een hoge accuraatheid en sensitiviteit en een matig tot hoge specificiteit. Dit creëert mogelijkheden naar implementatie in toekomstige screening- of case-finding-programma's voor VKF. Verder onderzoek is echter nodig om de plaats van de FibriCheck in zo'n strategie te bepalen.

Ethical committee

Approval

Van: An Stockmans <an.stockmans@icho.be>
Verzonden: woensdag 8 april 2015 11:20
Aan: Bert Vaes
CC: Christophe Mortelmans
Onderwerp: Betreft uw aanvraag Ethische begeleiding masterproeven

Betreft uw aanvraag Ethische begeleiding masterproeven

Beste student
Dear student

Uw aanvraag werd aanvaard door de ethische commissie van het UZ Leuven. Dit wil zeggen dat de ethische commissie van oordeel is dat uw studie volgens de gangbare ethische normen wordt uitgevoerd.
Indien u van plan bent uw masterproef te publiceren kan u deze mail als bewijs van goedkeuring door een ethische commissie aan het betreffende tijdschrift doorgeven.

Your application was accepted by the Ethics Committee of the University Hospitals Leuven. This means that the Ethics Committee acknowledges that your study is carried out according to the prevailing ethical standards.
If you plan to publish your masterthesis you can use this mail as approval by the ethics committee.
Met vriendelijke groeten
An Stockmans

Application

KU LEUVEN **Biomedische Wetenschappen**

Ethische begeleiding masterproeven

mp05256	Validatie van een nieuwe smartphone-applicatie ('Cardimoni') ter diagnose van VKF in de huisartsgeneeskunde

Student(en):
Christophe Mortelmans (christophe.mortelmans@student.kuleuven.be)
Promotor:
Bert Vaes (Bert.Vaes@med.kuleuven.be - u0087897 - Acad. Centr. voor Huisartsgeneeskunde)
Hoofdonderzoeker:

Faculteit:
Geneeskunde
Opleiding:
Master in de huisartsgeneeskunde (Leuven e.a.)
Het onderzoek is:
multicentrisch
De opdrachtgever is:
academisch (universiteit,...)

Het onderzoek is:
Het onderzoek is onderdeel van een groter project waarvoor reeds goedkeuring van de Ethische commissie werd bekomen.
CTC s-nummer:
S03244

Het onderzoek is een aanvulling of bevat nieuwe elementen.
Aanvulling of nieuwe elementen

Deze studie bouwt verder op de haalbaarheidsstudie die momenteel loopt (i.s.m. vier studenten 4e master huisartsgeneeskunde, KU Leuven) en waarvoor reeds toestemming van de ethische commissie werd bekomen.

Aanvullingen zijn:

- De eerste haalbaarheidsstudie liep t.e.m. 5/2015 en is een samenwerking tussen haio en vier studenten 4e master huisartsgeneeskunde. De metingen voor de huidige studie zullen plaatsvinden tussen 6/2015 en 2/2016 en alleen onder leiding van de haio en zijn promotor.

- De supervisie van het onderzoek met de app (vinger op de cameralens leggen) kan ook gebeuren door een geëduceerd verpleegkundige. In de vorige aanvraag werden alleen artsen en student-onderzoekers vermeld.

- Behalve screening op consultatie bij de huisarts, wordt hier ook vermelding gemaakt van screening bij patiënten op huisbezoek (thuis of in het rusthuis).

- De app kreeg een update. Met de eerste resultaten van de haalbaarheidsstudie gingen de ontwikkelaars verder aan de slag. Dit met als hoofddoel een afname van het aantal vals positieven (minder onterecht rode schermen met een onnodig ECG tot gevolg).

- Inzake risico voor de patiënt verandert er niets.

Bijkomende gegevens:

Achtergrond:

Voorkamerfibrillatie is een frequent probleem bij ouderen. Een deel van de patiënten (12-30% naargelang de bron) heeft geen last van symptomen en is zich niet bewust van de ritmestoornis. Aanwezigheid van VKF leidt tot een sterk verhoogd risico op complicaties, waaronder een CVA. Vroege opsporing en diagnose van VKF is dus belangrijk voor de patiënt. Tegelijk zien we in de medische sector een steeds groter aantal elektronische applicaties opduiken die de arts kunnen bijstaan in het diagnosticeren of opvolgen van een bepaalde aandoening.

Vraagstelling:

In dit manama-onderzoek wordt de nieuwe 'app' *Cardimoni* onder de loep genomen. Deze applicatie werd recent ontwikkeld om hartritmestoornissen te kunnen opsporen via de smartphone. De vraagt stelt zich of deze app een meerwaarde kan zijn voor de huisartsgeneeskunde en op welke manier ze kan geïntegreerd worden in de eerste lijn.

Methodologie:

Met de goedkeuring van promotor Bert Vaes zal de verantwoordelijke haio meerdere huisartspraktijken in Vlaanderen met informatie over dit project aanschrijven (achtergrond, vraagstelling, methode, diagram van het protocol, verloop van een consultatie en info-poster). Huisartsen die akkoord gaan met het te volgen protocol zullen worden ingeschakeld om de applicatie in de eerste lijn te testen. De screening loopt in de periode juni '15 – februari '16. Tijdens het onderzoek zal er overleg plaatsvinden met het team van Dr. Wilfried Mullens en Dr. Lars Grieten (UHasselt) evenals met het ZOL die respectievelijk instonden voor de ontwikkeling van de applicatie en eerste validatie ervan (op afdeling cardiologie). Het doel is te komen tot een paper met een besluit over het mogelijk gebruik van de app door de huisarts. Deze studie bouwt verder op de haalbaarheidsstudie die momenteel loopt (i.s.m. vier studenten 4e master huisartsgeneeskunde, KU Leuven) en waarvoor reeds toestemming van de ethische commissie werd bekomen.

In de studie zal door de gemobiliseerde onderzoekers opportunistisch gescreend worden naar voorkamerfibrillatie. Alle wilsbekwame patiënten van 65 jaar of ouder, zowel mannen als vrouwen, zullen worden gevraagd om deel te nemen aan de studie. Het kan gaan om mensen die zich aanmelden op de raadpleging in de praktijk dan wel om patiënten die worden gezien op huisbezoek thuis of in het rusthuis. Om de bereikte populatie te vergroten kan daarnaast ook actief op zoek gegaan worden naar deelnemers: patiënten die o.b.v. hun medisch dossier in aanmerking komen, kunnen telefonisch worden gecontacteerd door de behandelende arts. Zo de patiënt interesse toont, kan een contactmoment worden afgesproken.

De vraag tot screening kan komen van de arts of de patiënt. Voor de patiënten werden verduidelijkende info-brochures en posters verzorgd die zullen worden gedistribueerd via de onderzoekers (wachtzaal, artsenkabinet, CRA rusthuis, etc.). De patiënt wordt geïnformeerd over de studie en vragen worden naar best vermogen beantwoord.

Bij mondelinge instemming tot deelname wordt vervolgens een informed consent ondertekend. Indien de patiënt niet wenst deel te nemen of de meting kan op dat moment niet plaatsvinden, zal de arts de reden daarvoor noteren op een formulier teneinde een idee te vormen over de drempels die voor patiënten belangrijk zijn en belissen over al dan niet deelname. Het staat de patiënt echter vrij geen reden op te geven. De patiënt zal van een weigering tot deelname of een eventuele voortijdige beëindiging van dit onderzoek geen nadelige gevolgen ondervinden.

Na de toestemming en voorafgaand aan de meting met de app wordt door de onderzoeker een aantal gegevens over de patiënt op een formulier genoteerd: de leeftijd, het geslacht, het aanwezig zijn van obesitas (BMI>30) en de op dat moment gemeten systolische bloeddruk (> of < 160mmHg). Op basis van gegevens uit het medisch dossier, verkregen info vanwege de huisarts of de actuele klinische toestand worden ook genoteerd: de aanwezigheid van medicamenteuse behandeling voor arteriële hypertensie, een cardiaal geruis, hartfalen en eerdere symptomen (palpitaties, (pre)syncopes, vermoeidheid).

De applicatie 'Cardimoni' wordt opgestart op een iPhone 5S en voorgaande gegevens (exclusief de naam van de patiënt) worden ingevoerd. Elke meting wordt voorzien van een volgnummer en voorafgegaan door een code van drie letters o.b.v. de naam van de onderzoeker: V(oornaam)A(chternaa)M-000 (bv.CMS001). De naam van de patiënt is slechts beschikbaar op het schriftelijke formulier en alleen bedoeld voor de onderzoeker met therapeutische relatie met de patiënt.

Patiënten bij wie VKF eerder al werd vastgesteld en die bovendien reeds behandeld worden met anticoagulantia worden geëxcludeerd. Zo VKF bekend is maar nog geen anticoagulatietherapie werd opgestart, wordt de meting wel uitgevoerd.

De superviserende onderzoeker moet op de hoogte zijn van de studie en de te volgen procedure. Hij of zij kan een arts of verpleegkundige zijn. De patiënt neemt een gestandaardiseerde zithouding aan: de iPhone neemt men vast met de rechterhand, de linker wijsvinger legt men horizontaal op de camera op de achterzijde van de iPhone (niet actief drukken) en men laat de handen rusten op de bovenbenen. Extensies of hoesjes voor de smartphone zijn niet toegelaten en er wordt steeds met eenzelfde type iPhone (5S) gewerkt. De patiënt wordt vooraf goed ingelicht over de duur van het onderzoek (1 minuut) en de aan te nemen houding. Hij of zij wordt ook verzocht niet te praten noch te bewegen tijdens de duur van de meting. Mits de patiënt aangeeft alles te begrijpen, wordt de meting gestart. De onderzoeker meldt wanneer het onderzoek is afgelopen.

Bij aanvang van de meting start de cameraflitser van de iPhone op. Via photoplethysmografie (PPG) analyseert de applicatie het hartritme o.b.v. de pulsaties in de lokale arteriolen.

Indien tijdens de meting de opgegeven procedure niet correct kan worden volgehouden (bv. de patiënt begint te praten of te bewegen; hij/zij slaagt er niet in de vinger op de camera te houden of heeft zeer koude handen; foutmelding door het toestel) wordt de meting afgebroken. De

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patiënt wordt opnieuw geëduceerd en er volgt een tweede poging. Deze tweede meting krijgt de letter 'a' toegevoegd aan de naam (bv.CMS001a). Zo de tweede poging faalt, wordt de patiënt geëxcludeerd uit de studie en wordt de reden tot moeizame meting genoteerd.

Na het succesvol doorlopen van de procedure geeft de applicatie de hartfrequentie weer evenals een kleurcode. In het geval van een groen scherm (normaal sinusaal ritme) wordt de patiënt gerustgesteld. Een rood scherm suggereert een onregelmatig hartritme (bv. VKF). In dat geval wordt tijdens dezelfde consultatie aanvullend een 12-lead-ECG genomen ter bevestiging en specifiëring van het afwijkende hartritme. Voor een eventueel extra onderzoek t.g.v. deelname (met name het ECG) zal geen meerkost worden aangerekend voor de patiënt. Het ECG wordt uitgeprint en voorzien van de lettercode overeenkomstig de meting (bv. CMS001). Op de print worden geen namen noch persoonlijke aantekeningen gemaakt. Op het overzichtsformulier wordt door de onderzoeker aangeduid dat een ECG werd afgenomen met een korte interpretatie of beschrijving (bv. 'VKF'). De originele protocols worden bijgehouden en zullen achteraf door een geblindeerde cardioloog worden gecontroleerd.

Indien volgend op het ECG verdere behandeling en opvolging nodig blijkt, zal deze gebeuren door de behandelende arts van de patiënt.

Wanneer de app een rood scherm weergeeft bij een patiënt die thuis of in het rusthuis wordt gescreend, wordt bij voorkeur gebruikt gemaakt van een daar aanwezig (of draagbaar) 12-lead-ECG-toestel. Het type toestel wordt steeds genoteerd. Indien dit niet voorhanden is, wordt de patiënt gevraagd zich binnen de zeven dagen aan te melden voor een ECG. De tijd tussen het ECG en screening wordt in dat geval genoteerd.

De gegevens die de applicatie opslaat op de smartphone worden draadloos doorgezonden naar het beveiligd online platform van Cardimoni waar de PPG-metingen verder worden geanalyseerd en gespecifieerd. Ter evaluatie zullen de verzamelde gegevens later worden vergeleken met de beoordeling door een geblindeerde cardioloog.

De ontwikkelaars van de applicatie werken o.b.v. de eerste conclusies van de momenteel lopende haalbaarheidsstudie aan een verbetering van de app met oog op de volgende grotere studie die hierboven besproken werd. Werkpunten zijn o.a.: de meting pas laten starten zodra de applicatie bevestigt dat er goed contact is tussen wijsvinger en camera; verlagen van het aantal vals positieven (vermijden van onnodige ECG's volgend op een onterecht rood scherm, bv. bij fysiologische extrasystolen).