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 highly prevalent among the elderly. While AF often remains asymptomatic and therefore untreated, it can lead to serious complications. Stroke prevention guidelines recommend opportunistic screening for heart rhythm irregularities in people aged 65 and older. Pulse palpation has a high sensitivity but a lower specificity. A novel smartphone application, FibriCheck (Qompium, Hasselt, Belgium), was recently introduced as an alternative screening method. This app uses the technique of photoplethysmography (PPG) to detect AF. This study was designed to investigate the diagnostic accuracy of the FibriCheck app for the detection of AF.

Methods
A phase II diagnostic accuracy study in a convenience sample of 242 subjects recruited in primary care. The majority of the participants were patients with a known history of AF (n = 160). A PPG measurement was obtained while patients held their index finger on the smartphone camera during one minute. A synchronized single-lead ECG was taken on the chest. Poor signal quality measurements were excluded by a software filter. Both traces were interpreted by the FibriCheck AF algorithm. First, the results of the FibriCheck algorithm were compared with 12-lead electrocardiographic recordings. Secondly, beat-to-beat comparison was done between the PPG and the single-lead ECG measurements.

Results
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) were 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. Beat-to-beat analysis of the synchronized PPG and single-lead ECG traces showed a small difference in performance (99% uniform diagnoses), due to the different measurement method.

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. The PPG measurement method nearly matched single-lead ECG performance. These findings make the app 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.
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, Switzerland)\(^16\), 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, FibiCheck (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 FibiCheck 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 was 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%, and a confidence interval of 4%. In order to include sufficient patients with AF ($n =$), 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 heparins, 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$_2$DS$_2$-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 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)\textsuperscript{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) and could be manually activated by the investigator. The module was wirelessly connected to the FibriCheck-app on the smartphone. The single-lead ECG trace was visible on the screen during measurement (Attachments – figure 3-4). 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\textsuperscript{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 (Figure 1). 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.

**Figure 1 – Synchronized single-lead ECG and PPG signal**
Left: a patient with normal sinus rhythm. Right: a patient with atrial fibrillation (AF). The arrows indicate the RR-interval between two consecutive heart beats.

**Results**

**Study population**
A total of 242 subjects participated in this study (Figure 2- Flowchart of study participants). Five subjects were excluded because their data were not saved properly, due to a technical error. Table 1 shows the characteristics of the patients according to the presence of AF. Of the remaining 237 participants, 122 (51%) were women. The mean age of the participants was 78 ± 8 years (range: 65 – 95). The two cardiologists agreed on the presence of AF in 225 subjects. The ECG’s of 12 participants (5.1%) were evaluated by a third cardiologist. In all, 111 (47%) subjects were in AF at the moment of the study. One participant (0.4%) was newly diagnosed with AF. In the AF population, the median clinical frailty score was 4 (IQR: 3 - 5). The median CHA2DS2-VASc-score of the AF population was 5 (IQR: 4 – 6) and all had ≥ 2. In this group, 11 patients (10%) received a platelet aggregation inhibitor and 102 (92%) received anticoagulation therapy. Of those in sinus rhythm (n = 126), the median CHA2DS2-VASc-score was 4 (IQR: 3 - 5) and nearly all (98%) had ≥ 2. In this group the median Framingham risk score was 8 (IQR: 6 – 10), matching with a predicted 10-year risk to develop AF of ≥ 16%. In total, 40 patients (17%) 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). 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.

PPG analysis versus 12-lead ECG
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.

Figure 2 – Flowchart of study participants

Single-lead ECG analysis versus 12-lead ECG
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 = 237)

<table>
<thead>
<tr>
<th></th>
<th>All (n = 237)</th>
<th>AF present (n = 111)</th>
<th>AF absent (n = 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>78 ± 8</td>
<td>80 ± 8</td>
<td>76 ± 8</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>115 (48.5)</td>
<td>58 (52.3)</td>
<td>57 (45.2)</td>
</tr>
<tr>
<td><strong>Risk scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Frailty score, median (IQR)</td>
<td>4 (2 - 4)</td>
<td>4 (3 - 5)</td>
<td>3 (2 - 4)</td>
</tr>
<tr>
<td>CHA2DS2-VASc-score, median (IQR)</td>
<td>4 (3 - 6)</td>
<td>5 (4 - 6)</td>
<td>4 (3 - 5)</td>
</tr>
<tr>
<td>CHA2DS2-VASc-score ≥ 2, n (%)</td>
<td>234 (98.7)</td>
<td>111 (100)</td>
<td>123 (97.6)</td>
</tr>
<tr>
<td>Framingham risk score, median (IQR)</td>
<td>-</td>
<td>-</td>
<td>8 (6 - 10)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of AF in medical records, n (%)</td>
<td>160 (67.5)</td>
<td>110 (99.1)</td>
<td>50 (39.7)</td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>26.1 ± 4.7</td>
<td>25.8 ± 4.3</td>
<td>26.3 ± 5.0</td>
</tr>
<tr>
<td>Diabetes mellitus type II, n (%)</td>
<td>47 (19.8)</td>
<td>28 (25.2)</td>
<td>19 (15.1)</td>
</tr>
<tr>
<td>Vascular disease, n (%)</td>
<td>98 (41.4)</td>
<td>54 (48.6)</td>
<td>44 (34.9)</td>
</tr>
<tr>
<td>TE, TIA or CVA, n (%)</td>
<td>51 (21.5)</td>
<td>33 (29.7)</td>
<td>18 (14.3)</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>74 (31.2)</td>
<td>49 (44.1)</td>
<td>25 (19.8)</td>
</tr>
<tr>
<td>Cardiac murmur, n (%)</td>
<td>58 (24.5)</td>
<td>39 (35.1)</td>
<td>19 (15.1)</td>
</tr>
<tr>
<td>Pacemaker, n (%)</td>
<td>23 (9.7)</td>
<td>14 (12.6)</td>
<td>9 (7.1)</td>
</tr>
<tr>
<td>Pacemaker rhythm, n (%)</td>
<td>18 (7.6)</td>
<td>10 (9.0)</td>
<td>8 (6.3)</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>198 (83.5)</td>
<td>102 (91.9)</td>
<td>96 (76.2)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg), mean ± SD</td>
<td>129 ± 16</td>
<td>129 ± 17</td>
<td>130 ± 15</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg), mean ± SD</td>
<td>74 ± 9</td>
<td>75 ± 10</td>
<td>74 ± 8</td>
</tr>
<tr>
<td>Heart rate at rest (bpm), mean ± SD</td>
<td>78 ± 19</td>
<td>83 ± 19</td>
<td>72 ± 17</td>
</tr>
<tr>
<td><strong>Antihypertensives</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>86 (36.3)</td>
<td>57 (51.4)</td>
<td>29 (23.0)</td>
</tr>
<tr>
<td>Beta-blockers, n (%)</td>
<td>134 (56.5)</td>
<td>76 (68.5)</td>
<td>58 (46.0)</td>
</tr>
<tr>
<td>Calcium channel blockers, n (%)</td>
<td>51 (21.5)</td>
<td>24 (21.6)</td>
<td>27 (21.4)</td>
</tr>
<tr>
<td>ACE inhibitors, n (%)</td>
<td>64 (27.0)</td>
<td>38 (34.2)</td>
<td>26 (20.6)</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonists, n (%)</td>
<td>42 (17.7)</td>
<td>21 (18.9)</td>
<td>21 (16.7)</td>
</tr>
<tr>
<td>Centrally acting agents, n (%)</td>
<td>2 (0.8)</td>
<td>2 (1.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Anti-thrombotic treatment</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No anti-aggregantia or anticoagulantia, n (%)</td>
<td>59 (24.9)</td>
<td>3 (2.7)</td>
<td>56 (44.4)</td>
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<tr>
<td>Platelet aggregation inhibitors, n (%)</td>
<td>49 (20.7)</td>
<td>11 (9.9)</td>
<td>38 (30.2)</td>
</tr>
<tr>
<td>Anticoagulantia, n (%)</td>
<td>139 (58.6)</td>
<td>102 (91.9)</td>
<td>37 (29.4)</td>
</tr>
<tr>
<td>Vitamin K antagonists, n (%)</td>
<td>55 (23.2)</td>
<td>43 (38.7)</td>
<td>12 (9.5)</td>
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<tr>
<td>New oral anticoagulants, n (%)</td>
<td>80 (33.8)</td>
<td>56 (50.5)</td>
<td>24 (19.0)</td>
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<tr>
<td>Low-molecular-weight heparins, n (%)</td>
<td>4 (1.7)</td>
<td>3 (2.7)</td>
<td>1 (0.8)</td>
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<tr>
<td><strong>Smartphone usage</strong></td>
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<tr>
<td>Smartphone ownership, n (%)</td>
<td>40 (16.9)</td>
<td>11 (9.9)</td>
<td>29 (23)</td>
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<tr>
<td>Maturity handling smartphone, median (IQR)</td>
<td>4 (2 - 4)</td>
<td>4 (3 - 4)</td>
<td>3 (2 - 4)</td>
</tr>
</tbody>
</table>

SD: standard deviation; IQR: inter-quartile range; TIA: transient ischemic attack; CVA: cerebrovascular accident; mmHg: millimeters of mercury; bpm: beats per minute

PPG analysis versus single-lead ECG

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. 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.

<table>
<thead>
<tr>
<th></th>
<th>Atrial fibrillation present</th>
<th>Atrial fibrillation absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPG positive result</td>
<td>90</td>
<td>12</td>
<td>102</td>
</tr>
<tr>
<td>PPG negative result</td>
<td>2</td>
<td>86</td>
<td>88</td>
</tr>
<tr>
<td>Total</td>
<td>92</td>
<td>98</td>
<td>190</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
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<th>Atrial fibrillation present</th>
<th>Atrial fibrillation absent</th>
<th>Total</th>
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<tbody>
<tr>
<td>1-lead positive result</td>
<td>96</td>
<td>11</td>
<td>107</td>
</tr>
<tr>
<td>1-lead negative result</td>
<td>2</td>
<td>100</td>
<td>102</td>
</tr>
<tr>
<td>Total</td>
<td>98</td>
<td>111</td>
<td>209</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
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<th>Atrial fibrillation present</th>
<th>Atrial fibrillation absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPG positive result</td>
<td>97</td>
<td>2</td>
<td>99</td>
</tr>
<tr>
<td>PPG negative result</td>
<td>0</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>Total</td>
<td>97</td>
<td>86</td>
<td>183</td>
</tr>
</tbody>
</table>

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 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. found a sensitivity of 94% and a specificity of 99% in cardiology clinic patients. Desteghe et al. 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, cheap and practical measurement method without the need for special infrastructure or 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 workload 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. However, in our study population, 17% owned a smartphone, which is lower than the value of 27% reported in a recent Austrian and American 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 these 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 FibiCheck 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. PPG measurement nearly matched single-lead ECG performance. These findings make the app 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
Acknowledgements

I sincerely thank dr. Bert Vaes, my supervisor, for his guidance and encouragement in carrying out this thesis in family medicine. I also thank my colleague, dr. Ruth Van Haelst, for the cooperation and the many hours of PPG and ECG measurements. I also wish to express my gratitude to Pr. dr. Lars Grieten and the Qompium team, who rendered their help during the period of my project work. The completion of this undertaking could not have been possible without the participation and assistance of so many people whose names may not all be enumerated. I would like to mention the colleagues and secretaries of GP centers Van ‘t Sestich, UGP, Keizersberg, Lipsius, Bleyenbergh and in particular Brugberg and Tweewaters in Leuven. The contributions are sincerely appreciated and gratefully acknowledged. In addition, I would like to thank my colleagues dr. David Borst, dr. Wendy Demuynck and dr. Charlotte Thysen, for the cooperation and wonderful work in the feasibility study prior to the current validation study. Finally, my heartfelt thanks go to my girlfriend, nearest friends and family for their empathic and inspiring support.
Figure 1
Anatomical location of the ECG module on the chest and left index finger 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: home screen. Once the external 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.
Dutch Abstract

Inleiding
Voorkamerfibrillatie (VKF) is een frequente aandoening bij ouderen en kan tot ernstige complicaties leiden. Door de grote fractie asymptomatische VKF-patiënten, krijgen velen niet de gepaste behandeling. Richtlijnen rond CVA-preventie adviseren opportunistische screening bij 65-plussers. Polspalpatie heeft een hoge sensitiviteit maar een lagere specificiteit. Recent werd een nieuwe smartphone-applicatie ontwikkeld, FibriCheck (Qompium, Hasselt, Belgium), als alternatieve methode voor VKF-screening. Deze app kan via fotopletysmografie (PPG) VKF opsporen. Deze studie werd opgezet om de diagnostische accuraatheid van de FibriCheck app voor VKF te onderzoeken.

Methode

Resultaten
De kwaliteitsaperture van de app classatte 29 PPG’s en 10 single-lead tracés als onvoldoende betrouwbaarite. Voor de PPG-meettechniek en de interpretatie door het FibriCheck-algoritme werd een sensitiviteit van 98% (95% CI 92 - 100), een specificiteit van 88% (95% CI 80 - 94) en een accuraathed 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 accuraathed van 94% (95% CI 91 - 97) gevonden. De 11 vals positieve resultaten werden verklaard door atriale (n = 10) en ventriculaire (n = 1) extrasystolen. Bij beat-to-beat vergelijking van de PPG- en single-lead ECG tracés, werd een klein verschil in accuraathed gevonden (99% uniforme diagnoses), overeenkomstig het verschil in meetmethode.

Besluit
De FibriCheck is een toegankelijke standalone smartphone applicatie die goede resultaten neerzette in een eerstelijns convenience sample. PPG benaderde als meetmethode de resultaten van single-lead ECG. De eerste versie van de app scoorde een hoge accuraathed 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 master thesis you can use this mail as approval by the ethics committee.

Met vriendelijke groeten
An Stockmans

Application

Biomedische Wetenschappen
Ethische begeleiding masterproeven

Validatie van een nieuwe smartphone-applicatie (Cardimon) ter diagnostiek van VVK in de huisartsengeneeskunde

Studenten:
Christophe Mortelmans (christophe.mortelmans@student.kuleuven.be)
Bert Vaes (bert.vaes@med.kuleuven.be - Acad. Centr. voor Huisartsgeneeskunde)
Promotor:
Bert Vaes (bert.vaes@med.kuleuven.be - Acad. Centr. voor Huisartsgeneeskunde)
Huisartsenopleiding:
Master in de huisartsengeneeskunde (Leuven o.a.)
Ze zijn onderdeel van een groter project waarvoor reeds goedkeuring van de Ethische commissie werd behaald.

Aanvullende informatie:

- De app kreeg een update. Met de eerste resultaten van de haalbaarheidss Studie gingen de ontwikkelaars verder aan de slag. Dit met als hoofdrol een afname van het aantal vals positieve (minimale onderzoek røde schermen met een normale ECG totgevoegd).
- Inzake risico voor de patiënt veranderd en niets.

Bijkomende gegevens:

Achtergrond:

Voortsnellerbril is een frequent probleem bij oudere. Een deel van de patienten (12-30%) naasten in de bron) heeft geen last van symptomen en is zich niet bewust van dit fenomeen.

Klachten en andere symptomen die vaak worden onthouden bij het gebruik van de app zijn:

- De app bereidt de patiënt voor op de diagnose. Zowel bij de patient als bij de eenheid van de app zijn deze symptomen kenmerkend voor de diagnose.

Methodologie:

Met de goedkeuring van promotor Bert Vaes zal de verantwoordelijke huisartsel een project in de huisartsengeneeskunde. De medische beroepsgroepen van de VVK in de huisartsengeneeskunde. De verantwoordelijkheid van de huisarts leeft ook in de behandelkliniek van de patiënt. De patiënt mag niet worden bekend met het gebruik van de app door de huisarts. De patiënt mag niet worden bekend met het gebruik van de app door de huisarts. De patiënt mag niet worden bekend met het gebruik van de app door de huisarts. De patiënt mag niet worden bekend met het gebruik van de app door de huisarts.
Biomedische Wetenschappen
Ethische begeleiding masterproeven

De vragen tot screening kan komen van de arts of de patiënt. Voor de patiënt zijn voorbeelden: stress, angsten, droomtrauma, CRN, etc. De patiënt kan wordt gestimuleerd door de studie en vragen worden naar best voortgeven aan de hand.

Bij matiging in een definitieve begeleiding wordt vervolgens een informeel-concept ondernomen. Indien de patiënt niet vierde deel van het meting kan op dat moment niet plaatsvinden, zal de arts de reden daarvoor noteren op een formulier tenminste een idee te verwezen naar de reden waarom de patiënt niet vierde deel van de studie en vragen wordt naar best voortgeven aan de hand.

Na de bespreking en voorafgaand aan de starten met de app wordt de patiënt door de onderzoeker in een schriftelijke vorm gegeven. De patiënt krijgt een mededeling over de studie en vragen wordt naar best voortgeven aan de hand.

De apotheker van de Cardiomi de patiënt wordt opgelet op de iPhone 6S en voorgaande gegevens (e-mail of de naam van de patiënt) worden ingevuld. Elke meting wordt gestart en vervolgens op een volgorde en volgorde van een code van dubbel NLD o.v.b. de naam van de patiënt en code (NLD: nieuwste code NLD)

De gegevens van de app zijn slechts beschikbaar op het scherm en worden alleen gebruikt voor de onderzoeker met therapeutische milt van de patiënt.

Indien bij de app niet voldoende gegevens of de bevonden reeds behaalden werden met antwoord voor de vragen wordt gestart, de patiënt krijgt een mededeling over de studie en vragen wordt naar best voortgeven aan de hand.

Deze gevorderde onderzoeker moet ook de hulp van de patiënt en de studie van de patiënt voorbereiden. Hij of zij kan een arts of verpleegkundige zijn. De patiënt neemt een geestelijke zitting over de iPhone naar een of meer met medisch materiaal, de tekst van de app wordt het scherm en de studie en vragen wordt naar best voortgeven aan de hand.

Indien tijdens de meting de app niet correct kan worden gegeven, de patiënt doet een nieuwe taak en geniet van de studie en vragen wordt naar best voortgeven aan de hand.

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Voor de app in de studie worden ongeveer een week later de gevorderde onderzoeker moet ook de hulp van de patiënt en de studie van de patiënt voorbereiden. Hij of zij kan een arts of verpleegkundige zijn. De patiënt neemt een geestelijke zitting over de iPhone naar een of meer medische gegevens, de tekst van de app wordt het scherm en de studie en vragen wordt naar best voortgeven aan de hand.

De patiënt wordt gevraagd of hij/zij in de studie en vragen wordt naar best voortgeven aan de hand. Indien dit niet gebeurt, de patiënt doet een nieuwe taak en geniet van de studie en vragen wordt naar best voortgeven aan de hand.

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De gegevens die de app op de smartphone worden gegeven, de patiënt doet een nieuwe taak en geniet van de studie en vragen wordt naar best voortgeven aan de hand. Indien dit niet gebeurt, de patiënt doet een nieuwe taak en geniet van de studie en vragen wordt naar best voortgeven aan de hand.