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Maastricht University

Faculty of Medicine and Life Sciences
School for Life Sciences
Master of Biomedical Sciences

Masterthesis

First in world implementation of a smartphone application in primary and secondary prevention of stroke

Tine Proesmans

Thesis presented in fulfillment of the requirements for the degree of Master of Biomedical Sciences, specialization Bioelectronics and Nanotechnology

SUPERVISOR :

Prof. dr. Anitha ETHIRAJAN

SUPERVISOR :

Prof. dr. Lars GRIETEN

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ACKNOWLEDGEMENTS

This master thesis marks the end of my master Biomedical Sciences, Bioelectronics and Nanotechnology, at the University of Hasselt. It investigates the capabilities of FibriCheck, a smartphone application that analyses the heart rhythm to detect irregularities. Finishing this research project could not have been possible without the help of many people.

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I hope you will enjoy reading my master thesis!

Tine

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LIST OF ABBREVIATIONS

AF	Atrial fibrillation
CE	Conformité Européenne
CHA_2DS_2-VASc	Congestive heart failure, hypertension, age ≥75, diabetes, stroke, vascular disease, age 65-75, sex category
CHARGE	Cohorts for Heart and Aging Research in Genomic Epidemiology
CI	Confidence interval
ECG	Electrocardiography, electrocardiogram
ESC	European Society of Cardiology
ICER	Incremental cost-effectiveness ratio
iECG	iPhone single-lead ECG
NPV	Negative predictive value
PPG	Photoplethysmography, photoplethysmogram
PPV	Positive predictive value
QALY	Quality adjusted life year
Se	Sensitivity
Sp	Specificity
WTP	Willingness to pay

ABSTRACT

Introduction: With an ageing population globally, the burden of atrial fibrillation (AF) and its complication of stroke continues to rise. Current screening strategies are hampered by large expenses, specialised equipment, time investment, logistics, and medical personnel. Novel screening tools are creating a paradigm shift in current perspective by changing the cost-benefit equation in favour of a more systematic approach of screening. In this work, FibriCheck™, an optical-based smartphone application, is introduced as new screening tool to aid for the detection of AF and prevention of stroke.

Methods: A four-step research process was followed. (I) A community-based systematic screening programme assessed the diagnostic accuracy of the application with respect to single-lead iECG, forming the reference standard. (II) A nine-day completely digital mass screening programme, targeting the general Belgian population, was rolled-out. (III) The diagnostic yield of the application as a long-term monitoring device for primary and secondary stroke prevention in high risk patients was evaluated in a multicentre national study, elucidating the impact on current clinical practice. (IV) A Markov model was used to extrapolate beyond observed study outcomes to calculate the long-term cost-effectiveness of FibriCheck screening in stroke patients.

Results: (I) The application was able to detect previously undiagnosed AF in 0.8% of the general population with 100% sensitivity, 97% specificity and 97% accuracy. All screen-detected AF-patients had an increased stroke risk. (II) 12,328 participants on-boarded the nine-day screening programme within 48 hours. 136 AF-patients were identified, resulting in an overall prevalence of 1.1% in the general Belgian population. 81 AF-cases (60%) were confirmed on ECG following consultation of a medical professional. (III) Prolonged monitoring in high risk patient populations identified AF in 13% of the individuals, including 5% previously undiagnosed. Compared with usual care, 18% of the AF-patients were identified on 12-lead ECG and 10% would have received prolonged monitoring as part of their planned care-path. (IV) The Markov model indicated 26 quality adjusted life years (QALY) and substantial cost savings of €1.189 per QALY gained when implementing the application in a population of 1,000 post-cryptogenic stroke patients.

Conclusion: FibriCheck proved to be an accurate and reliable means to detect AF in unselected and selected populations in a cost-effective way. The time has come to re-evaluate current screening and monitoring strategies and to advocate for widespread systematic screening programmes to detect AF and prevent strokes.

Keywords: atrial fibrillation – stroke – prevention – screening – smartphone – photoplethysmography

INTRODUCTION

ATRIAL FIBRILLATION IS CAUSED BY CARDIAC REMODELLING

The mechanical activity of the heart is controlled by electrical stimuli. Although most hearts beat with a remarkable fidelity and resilience, under certain circumstances the rhythm of the heart can fail. Structural and electrophysiological abnormalities, caused by various pathways and mechanisms, alter the atrial tissue, ultimately resulting in atrial fibrillation (AF). Underlying heart diseases stimulate atrial remodelling and subsequent fibrosis, which is followed by an increase in left atrial pressure, atrial dilatation and changes in wall stress. The resulting anatomical vulnerability causes alterations in the electrical conduction pathway of the atria, resulting in the firing of ectopic beats and a low threshold re-entry circuit. During ectopic firing, the electrical signal does not start in the sinoatrial node, but all over the atrial wall. Re-entry of electrical signals in other electrical circuits, due to the low threshold, results in the sustaining of these ectopic beats. Hence, the electrical signals travel throughout the atria in a fast and irregular way, causing the atria to quiver or fibrillate (1).

Due to a loss of atrial contraction, a suboptimal ventricular rate control, and a variability in ventricular filling, AF is associated with adverse hemodynamic effects resulting in a reduced cardiac output of up to 20%. Although there are different symptoms which can be clearly assigned to these alterations in cardiac output, such as fatigue, palpitations, dyspnea, hypotension, syncope, and heart failure, most patients experience no symptoms, or mild symptoms which can be mistakenly attributed to other causes. An additional consequence of the adverse hemodynamic changes, along with changes in blood composition involving platelets, coagulatory proteins, and inflammatory cytokines, is the prothrombotic state associated with AF. This is reflected by a five-fold greater risk of stroke and thromboembolism in patients with AF. Stroke is one of the most feared complications since AF-related strokes are more often fatal and associated with a 50% increased likelihood of remaining disabled compared with strokes from other causes. Approximately 30% of AF-patients die within one year of a stroke, and up to 30% of survivors are permanently disabled (2).

Thanks to the underlying mechanisms, the natural history of AF involves a gradual worsening over time. Initially, AF-episodes might occur only sporadic and might be asymptomatic, but over time the duration of the episodes lengthens and more frequent and symptomatic attacks can be observed (Figure 1) (3).

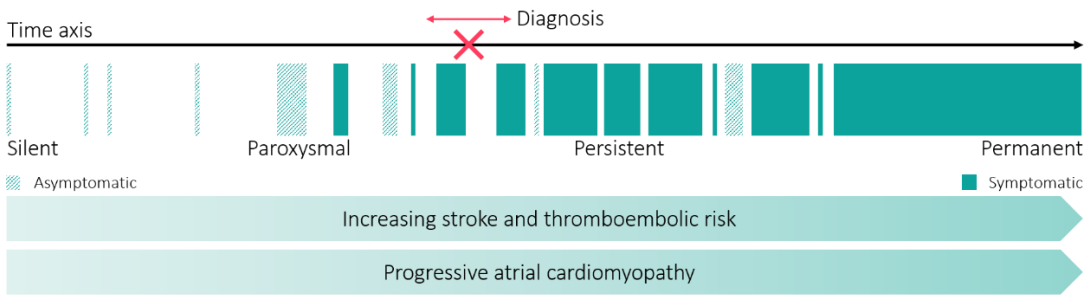


Figure 1. *Example of the evolution of atrial fibrillation over time. The frequency and duration of episodes increase, together with an evolution to a more symptomatic clinical presentation. The first clinical diagnosis of atrial fibrillation may shift along the time axis to occur earlier or later.*

THERAPY TO RESTORE AND PREVENT

Since AF takes place after a process of cardiac remodelling and fibrosis, treatment aiming to minimise this adverse remodelling pathway should be initiated at the earliest opportunity. Depending on the duration of AF-episodes, the clinical presentation, and the presence of comorbidities, management and treatment of AF can be individually set up for each patient. The Task Force for Management of Atrial Fibrillation of the European Society of Cardiology (ESC) provides guidelines supporting medical practitioners with regulations to provide the best treatment for AF-patients considering outcome and risk-benefit ratios. Treatment options for patients with AF consist of either rate or rhythm control, or a combination of both. The goal of rate control is to restore a normal ventricular heart rate by slowing the fast beat down, allowing for proper diastolic filling and coronary perfusion. This can be achieved pharmacologically by using drugs that slow nodal conduction. Although an initial rate control strategy can be beneficial for many patients, rhythm control, directed at converting to and maintaining normal sinus rhythm, should be considered. The standard procedure for rhythm control is by direct current cardioversion in which the patient receives a synchronized electrical shock transthoracic. If the source of the irregular heartbeat can be localised, ablation becomes another option. Here, radiofrequency electrical current is used to apply lesions to isolate the affected part from the remainder of the tissue, thus discontinuing uncontrolled electrical conduction (4).

Although the above treatment options are effective to restore heart rate and rhythm, there is an important rate of relapsed patients that should undergo new treatment. Furthermore, neither strategies are intended to prevent strokes. Thus, along with restoring and maintaining normal sinus rhythm and controlling the ventricular rate, treatment strategies of AF consist of the administration of anticoagulation therapy. This can reduce the risk of stroke by about two-thirds and the risk of mortality by approximately one-quarter, but is associated with an increased risk of bleeding. Individual consideration of the balance of potential benefits (risk reduction in stroke or thromboembolism) versus potential harms (risk increase in major bleeding) is recommended in order to offer anticoagulation therapy to patients who have a favourable risk-benefit profile (5).

SCREENING FOR ATRIAL FIBRILLATION TO AVOID STROKES

Difficulties arise as the clinical presentation of AF is most often non-specific or asymptomatic. This results in a large population that will never seek medical attention, nor receive primary preventive therapy. It is estimated that 25% of patients who have an AF-related stroke are only diagnosed with AF at the time of stroke or shortly thereafter (6). Failure to diagnose AF before the onset of events precludes these patients from any meaningful preventive therapy. Furthermore, besides reducing the risk of thromboembolic events, identifying patients with asymptomatic AF who might benefit from treatment will reduce the frequency and severity of future symptoms and overall mortality (7).

In order to achieve this, many screening programmes and solutions are being examined, as it is now well understood that screening for previously undiagnosed AF is fruitful and associated with the prevention of strokes. Thus, since 2012, the ESC guidelines have recommended opportunistic screening for AF by pulse palpation and 12-lead ECG during clinic visits in every patient aged 65 and older. Another screening strategy is systematic

screening, where an entire population is invited to participate. Systematic screening for AF in adult populations could potentially increase diagnostic rates by identifying people with asymptomatic AF, and those who are symptomatic but remain undiagnosed because of failure to attribute symptoms to the arrhythmia and to seek medical attention. Overall, screening offers an ideal opportunity to not only assess previously undiagnosed AF-patients for suitability of anticoagulation therapy, but also to review patients with known AF for appropriate prescription of anticoagulation and for patients' compliance with taking the prescribed medication (4).

Electrocardiography – The gold standard

Signal explanation

The electrical stimuli controlling the mechanical activity of the heart can be measured on the body surface by a 12-lead ECG. Ten cables placed on predetermined positions on the chest allow for the registration of the direction of depolarization, which causes the heart to contract. The sinoatrial node in the right atrium acts as a pacemaker and spontaneously fires at an average of 70 times per minute at rest, and up to 200 times per minute during rigorous activity. These electrical signals are transmitted to all atrial myocytes, resulting in the coordinated depolarization and contraction of the atria (Figure 2). On an ECG, the atrial depolarization is visualized as a P-wave. The electrical activity of the sinoatrial node is transferred to the atrioventricular node, connecting atria and ventricles. Here, the electrical activity is delayed for about 20 milliseconds, giving the atria time to fill the ventricles with blood. After this delay, the impulse is guided through specialized fibres forming the bundle of His, the bundle branches and the Purkinje fibres, leading to the rapid depolarization of all ventricular myocytes and the coordinated contraction of the ventricles (Figure 2). The depolarization of the ventricles is visualized as the QRS-complex on an ECG. Slow repolarization of the ventricles, represented by the T-wave on an ECG, will lead to cardiac relaxation and the completion of one cardiac cycle (8).

On a normal ECG from a patient in sinus rhythm, the rhythm is regular, which is reflected by a regular distance between R-peaks (RR-interval, one complete cardiac cycle). Moreover, a P-wave can be distinguished and clearly seen. In contrast, on an ECG from a patient with AF, the RR-intervals are irregular and, while electrical activity suggestive of P-waves can be seen in some leads, there are no distinct P-waves. Thus, even when an atrial cycle length (the interval between two atrial activations or the PP-interval) can be defined, it is not regular and often less than 200 milliseconds, which translates to an atrial rate greater than 300 beats per minute (9).

Available ECG-based tools for screening

For the diagnosis of AF, a 12-lead ECG recording is necessary and remains the gold standard in clinical practice today (4). However, given that AF-episodes can be brief and infrequent, the short documentation period of a 12-lead ECG is an important limitation. Recent studies clearly showed that extending the monitoring duration to 24 hours, or even 7 days, significantly increased the AF-detection rate, leading to a four-fold increase in the number of diagnosed cases compared to single time-point measurements (10-14). Extended rhythm monitoring is possible with an external Holter monitor or even continuously using implantable cardiac devices such as pacemakers, cardioverter defibrillators, or subcutaneous cardiac monitors. Although these devices offer an extended monitoring period and continuous rhythm information, issues of cost and inconvenience have motivated the

development of new methods to improve the detection rate. ECG patches combine the features of the present-day Holter with real-time data transmission and analysis. These devices allow for monitoring periods of up to 14 days, a significantly longer monitoring period than a Holter, ultimately resulting in an improvement of clinical accuracy. Although these patch monitors are patient-friendly due to their lack of electrodes and lead wires, the adhesive materials limit the device-on-skin longevity. Single-lead ECG signals can be recorded by electrodes which are embedded in the smartphone casing or integrated into the smartwatch wristband, which then transmits data wirelessly to a smartphone or smartwatch application. These novel tools are more powerful at arrhythmia detection than wearable monitors, but they still rely on additional dedicated hardware (15). Heart rate and heart rhythm measurements have also shown to be possible using a smartphone without any additional substrates. These standalone applications are based on the principle of photoplethysmography (16).

PHOTOPLETHYSMOGRAPHY – AN OLD TECHNIQUE IN NEW TOOLS

SIGNAL EXPLANATION

The mechanical activity of the heart, evoked by electrical stimuli, can be examined by manual pulse palpation. Although this strategy is recommended in every eligible patient visiting clinical practice, this method is not regularly performed and is prone to a low accuracy. Luckily, current technology offers new innovative tools modernizing the analysis of this physiological signal. This modernized signal is captured using the photoplethysmography (PPG) technique (17).

PPG is an optical bio-monitoring technique used to non-invasively measure the blood volume changes occurring in the dermal microvascular tissue bed. The technique is based on the principles that blood absorbs more light than the surrounding tissue, and that variations in blood volume due to the heart action affect the absorption and reflection of light. These two principles can be employed to detect blood flow (16). As an optical technique, PPG requires a light source and a photodetector to detect cardio-vascular pulse waves propagating through the body. The light source illuminates the tissue, and the photodetector senses small variations in reflected light intensity associated with changes in blood volume. Given that the interaction of light with biological tissue can be complex, and can involve scattering, absorption, and reflection, the wavelength of the light source is of great importance. The ideal wavelengths for PPG should have greater absorption for blood compared to other tissue components, as this would allow for accurate monitoring of blood volume changes. It is known that light in the red and infrared (IR) ranges are absorbed by water, while shorter wavelengths are strongly absorbed by melanin. Therefore, red and near IR light are typically utilized as light sources in PPG sensors. However, green-wavelength PPG devices are becoming increasingly popular for their large intensity variations and their low sensitivity to motion artefacts, resulting in a better signal-to-noise ratio (18).

Despite its simple appearance, the waveform measured by PPG is a highly complex signal that contains an abundance of information in its shape, height, and timing. When the heart pumps blood through the body during systole, the amount of blood that reaches the capillaries in the skin surface increases, resulting in more light absorption (Figure 2). The blood then travels back to the heart through the venous network, leading to a decrease of blood volume in the capillaries and less light absorption. So, the larger the blood volume at the measured site,

the more light gets absorbed, the less light is reflected, and the resultant intensity captured by the detector is smaller. During systole, the amount of light reflected is less than during diastole, causing the raw PPG signal to resemble a mirror image of an arterial blood pressure waveform (Figure 2) (17).

The low-cost and simplicity of this optical technology offers significant benefits to healthcare (19). The time period between each peak of the PPG waveform represents the repetition of the cardiac cycle (RR-interval), and can be used to analyse pulse rate and pulse rhythm. Despite the advantages of this stand-alone, simple, and low cost tool, some important drawbacks compared to ECG should be mentioned. The signal quality of PPG is highly sensitive to noise and motion artefacts, affecting diagnostic accuracy. Furthermore, since the PPG technique measures pulse waves propagating through the body, only the ventricular activity can be measured. In contrast to an ECG signal measuring the electrical activity of the heart, contraction of the atria (P-waves) cannot be documented, and rhythm analysis on PPG is solely based on RR-interval regularity (Figure 2) (20).

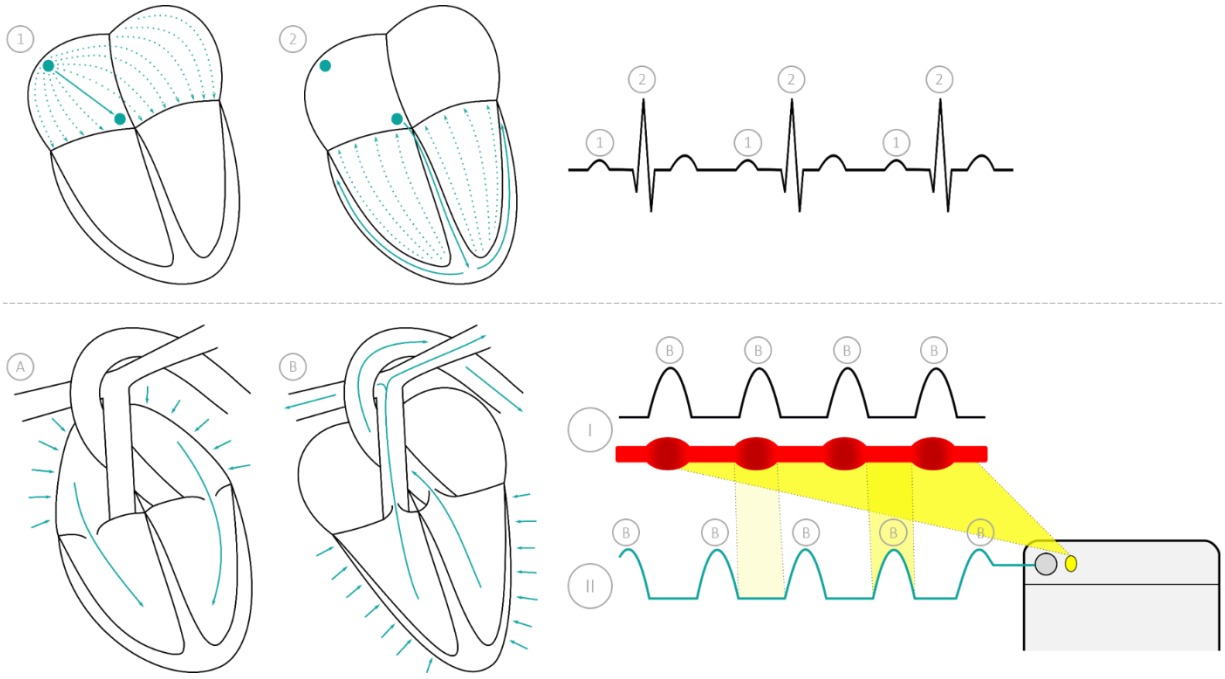


Figure 2. *The electrical activity of the heart is measurable with electrocardiography (upper panel). The mechanical activity, evoked by the electrical stimuli, is measureable with photoplethysmography (lower panel). Atrial depolarization (1), represented by the P-wave on an ECG, causes the atria to contract and fill the ventricles with blood (A). Ventricular depolarization (2), visualised by the QRS-complex on an ECG, causes the ventricles to contract and pump blood through the body (B). This results in a pulse pressure wave traveling from the heart to the extremities (I). Light from the smartphone flash can reach the capillaries and the reflected light is captured by the smartphone camera. The intensity changes of the captured light comprise the PPG waveform (II).*

Available PPG-based tools for screening

Although the measurement of blood volume changes based on the PPG-technique is a centuries-old method, the technique has experienced some modernisation over the past years (21). Traditional pulse oximeters, which are extensively used in clinical practice to monitor the blood saturation of patients, have currently been equipped with algorithms allowing for the analysis of the pulse rhythm. Recently, it has been demonstrated that the PPG waveform can also be acquired and digitalized using the pseudo-white smartphone flash as light source, and the smartphone camera as photodetector. The intensity changes of the captured video frames correlate with the

variations of light absorption by blood and reflection. Smartphones thus have the potential to distinguish AF from sinus rhythm without the need of additional dedicated hardware (22).

A large number of smartphone applications that measure heart rate using the PPG technique are available, but those that process data for rhythm analysis are limited. Screening for AF using smartphone PPG was first reported by Lee and colleagues in 2012 (23). There are a number of commercially available apps to detect AF, but these have never been clinically validated. As with any diagnostic test, validation of accuracy is mandatory, and the method should be subjected to regulatory approval before being used in clinical practice. FibriCheck (Qompium, Hasselt, Belgium) is Conformité Européenne (CE) approved for the detection of AF based on a PPG signal captured by the smartphone camera. AF is diagnosed by an algorithm using artificial intelligence with signal pattern recognition. FibriCheck has been clinically validated in several studies (24), with the most recent study reporting 98% accuracy, 100% sensitivity and 98% specificity when comparing algorithm-based interpretation of the PPG trace to visual interpretation of an ECG trace by cardiologists.

UNMET CLINICAL AND SCIENTIFIC NEEDS

The increased risk of stroke and thromboembolic events, together with other comorbidities associated with AF, cause an immense economic and public health burden which can be substantially reduced by preventing AF-related strokes. Stroke prevention relies firstly on timely diagnosis of AF, and secondly on appropriate anticoagulation treatment. However, as AF is often asymptomatic, many patients are unaware of their condition with the first diagnosis being made only after a stroke or transient ischemic attack (25). The European Society of Cardiology (ESC) therefore recommends that all patients aged 65 and older presenting at clinical practice should be screened by pulse palpation and, if irregular, 12-lead ECG (4). This methodology, known as opportunistic screening, has the potential to detect previously unknown AF in 1.4% of these elderly patients (26). However, because of the time-consuming nature of routine pulse palpation and subsequent ECG recording, this is not regularly performed in primary care settings. As AF-episodes can be brief and infrequent, the reliance on a single spot-check will most likely result in a missed diagnosis. Furthermore, since this screening methodology is bound to a physical location, only patients presenting at the physician's office have the potential to be screened. As a result, an estimated 40% of the AF-patients still remains undiagnosed (27).

This gap in clinical practice can be bridged by implementing systematic screening programmes targeting the general population (28). To date, however, systematic screening is not recommended by current guidelines. The recommendations of these guidelines are based on pooled results of randomized controlled trials evaluating opportunistic screening versus systematic screening. These studies unanimously report that both screening strategies have a comparable diagnostic yield, but that the cost of opportunistic screening was significantly lower than the cost of systematic screening from the perspective of the health service provider. It should however be noted that these studies, forming the evidence base of current guidelines, seem to be limited by conventional screening technologies. A systematic screening programme where all participants undergo a 12-lead ECG recording is not able to increase the diagnostic yield in a cost-effective way. Moreover, despite the clear

relationship between the duration of monitoring and the diagnostic yield, more frequent and prolonged monitoring is not feasible with this strategy (28).

It is suggested that new technologies can offer an answer to these unmet clinical and scientific needs. Novel screening tools based on pulse irregularity are creating a paradigm shift by changing the cost-benefit equation in favour of a more systematic approach of screening for AF in the community (29). In this regard, the FibriCheck application is proposed as a new screening tool to aid for the detection of AF and prevention of strokes. The clinical validation of the PPG signal has already been carried out and indicated a great opportunity for AF-screening through PPG measurements in primary and secondary prevention of stroke. However, a lack of insights into the implementation and performance in real-life populations are hindering the acceptance of FibriCheck as a new screening tool. A stepwise research methodology will address these needs. First, a community-based systematic screening programme will assess the diagnostic accuracy of the application with respect to single-lead ECG, forming the reference standard (Chapter I). After establishing the diagnostic power in a real-life population, a nine-day completely digital mass screening programme will be organised targeting the general Belgian population (Chapter II). The implementation of FibriCheck will also be assessed in a clinical setting. Here, the diagnostic yield of the application as a long-term monitoring tool in primary and secondary prevention will be evaluated in a multicentre national study, elucidating the impact on current clinical practice (Chapter III). After assessing the diagnostic performance, the last remaining question that needs to be addressed is the cost-effectiveness. A Markov model will be used to extrapolate beyond observed study outcomes providing a framework for longer term economic analysis (Chapter IV).

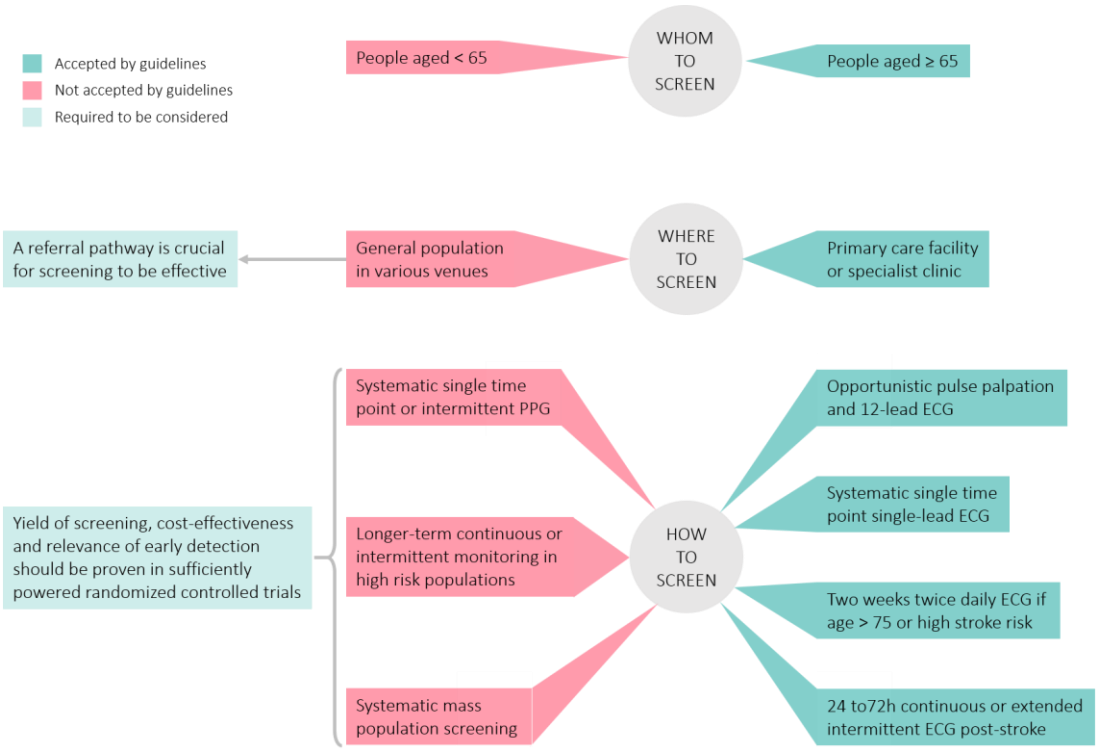


Figure 3. The current state of screening strategies and unmet clinical and scientific needs (29). ECG: electrocardiography, PPG: photoplethysmography.

CHAPTER I: DIAGNOSTIC ACCURACY IN A SYSTEMATIC SCREENING PROGRAMME

It is suggested that new technologies are able to bridge the gap created by the limitations hampering conventional screening tools. Despite the urgency for systematic population screenings and the development of novel screening technologies, only few clinical studies address the implementation of such tools in a real-life population setting. As a result, systematic screening is not yet recommended by current guidelines due to several justified concerns and lack of sufficiently powered evidence to refute these. Is a systematic approach cost-effective? What is the clinical relevance of an increased diagnostic rate and early AF-detection? What is the real-life diagnostic accuracy of these novel screening tools? It is not yet possible to answer all these questions. This study investigates the diagnostic accuracy of FibriCheck in a systematic population screening.

The abstract of this study was submitted to the European Society of Cardiology Congress 2018 in Munich, and was selected for Best Poster Presentation. Submission of this study for publication in *The European Journal of Pacing, Arrhythmias, and Cardiac Electrophysiology* is ongoing.

METHODS

STUDY DESIGN AND STUDY POPULATION

During the Belgian Heart Rhythm Week, 1359 Belgian citizens voluntarily participated in a community based systematic screening programme organized in two clinical centres in the Northern part of Belgium. All citizens aged 18 and above were eligible for participation. For every participant, baseline characteristics and stroke risk parameters to calculate the CHA_2DS_2-VASc score (a validated risk stratification scheme including congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease and sex) were documented. Two consecutive heart rhythm measurements were performed under limited medical supervision. A PPG measurement was obtained using the FibriCheck smartphone application (Qompium NV, Hasselt, Belgium), immediately followed by a single-lead iPhone ECG recording (iECG) using the AliveCor heart monitor (AliveCor Inc., California, USA). The iECG traces were subsequently printed and reviewed by a blinded, independent cardiologist to provide the reference standard. The local Ethics Committee approved this multicentre screening study and written informed consent was obtained from all participants before inclusion. The study protocol complies with the Declaration of Helsinki.

SCREENING PROCEDURE AND SCREENING DEVICES

A PPG waveform was acquired from each participant using an iPhone 5S running the FibriCheck application. The PPG signal was obtained using the smartphone's camera capturing the changes in reflected light from the patient's finger. The PPG waveforms were sampled at 30 Hz, and each waveform was filtered using a bandpass filter to remove baseline wander and high frequency noise. Each PPG recording lasted 60 seconds and was classified automatically by the FibriCheck algorithm, based on RR-interval irregularity, as sinus rhythm, irregular rhythm, possible AF, or insufficient quality.

Subsequently, an iECG recording was obtained from all participants using the AliveCor heart monitor. The trace was acquired for 30 seconds by placing two or more fingers from each hand on the device electrodes. The iECG recordings were transmitted to the iPhone 5S running the AliveCor application, processed to remove noise, and interpreted by an automated algorithm. This was based on the criteria of P-wave absence and RR-interval irregularity to diagnose AF. The iECG traces were also classified as sinus rhythm, irregular rhythm, possible AF, or insufficient quality. Finally, traces with the automated rhythm interpretation redacted were printed. A cardiologist who was blinding for the FibriCheck classifications and the patient's baseline information independently reviewed the printouts to provide a reference diagnosis.

Although both screening tools provided an automated interpretation, participants and researchers were blinded for these results to avoid interference and biasing. In case of irregularities or ambiguity, a 12-lead ECG was used for confirmation.

Data analysis

From the total study population, a general screening population (age > 40 years) was selected for further analysis. The primary objective was to evaluate the diagnostic accuracy of the FibriCheck smartphone application to detect AF against interpretation of an iECG trace by a cardiologist, providing the reference diagnosis. For comparison, the accuracy of the AliveCor automated AF-detection algorithm was also evaluated against the reference standard.

Although the intent of screening for AF is straightforward (either a positive or negative result), both screening tools have a subdivision to categorize heart rhythms in AF, sinus rhythm or other arrhythmias. This extra category provides a clinical challenge on how to interpret screening results and how to evaluate diagnostic accuracy. As both applications are positioned as a screening tool, the most logic consequence for further analysis is to consider an irregular rhythm result the same as possible AF, because a false positive result is preferred over missing a patient due to a false negative result. However, as this approach may be considered as subjective, a dual assessment was made. Interpretation of solely the sinus rhythm category as sinus rhythm, and the other categories as AF, will minimise false negative results and thus maximise sensitivity. By interpreting the possible AF category as AF, and the other categories as sinus rhythm, false positive results are minimised which will lead to a maximum specificity. To avoid biasing, both approaches were applied before and after exclusion of insufficient quality measurements. Diagnostic accuracy testing was performed using 2x2 tables (MedCalc Software, Belgium). Sensitivity, specificity and accuracy are expressed as percentages with their exact Clopper-Pearson confidence intervals (CI).

RESULTS

DESCRIPTIVE POPULATION CHARACTERISTICS

A total of 1359 participants were screened, 1179 were older than 40 years forming the general screening population (GSP) (Figure 4). The mean age of the GSP was 63 ± 11 years and ranged from 40 to 100 years, 41% was male. 9 newly diagnosed AF-cases were identified, resulting in an overall prevalence of 0.8% in the GSP with 0.5% in women and 1.3% in men. This corresponds to a prevalence of 1.6% in the ≥ 65 age group. The average age of the AF-group was 73 ± 4 years and ranged from 67 to 82 years.

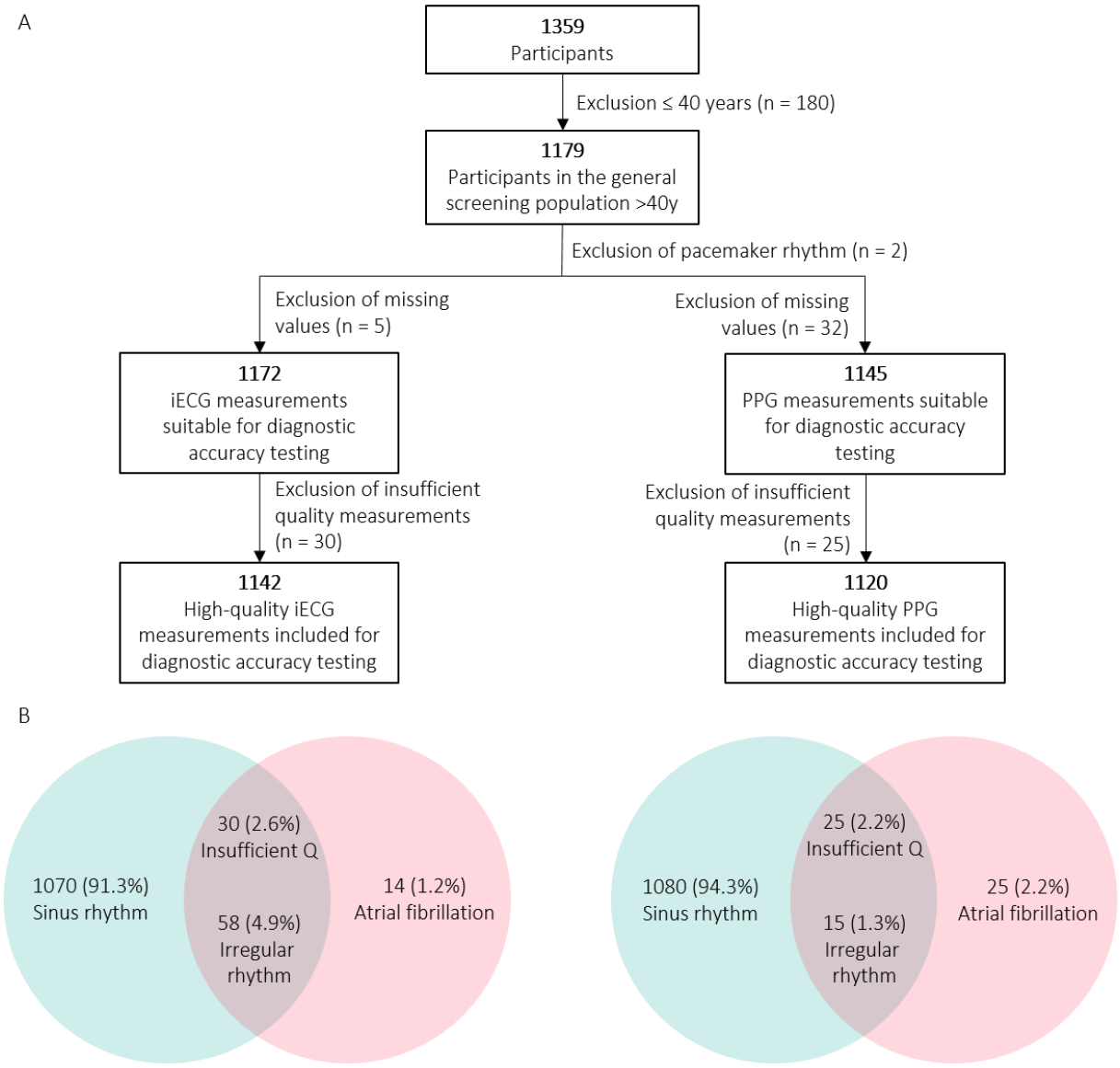


Figure 4. Patient and measurement flowchart (A). The 'insufficient quality' and 'irregular rhythm' categories will be classified under 'sinus rhythm' or 'atrial fibrillation' in a dual assessment to evaluate diagnostic accuracy, before and after exclusion of insufficient quality measurements (B).

Stroke risk parameters were assessed, and the CHA_2DS_2-VASc score was calculated to determine stroke risk in AF-patients (Table 1). 7 participants with a positive AF-screening (77.8%) had a CHA_2DS_2-VASc score of two or more, indicating a high stroke risk. Surprisingly, two AF-patients with a CHA_2DS_2-VASc score of 3 and 4 were not anticoagulated.

Table 1. *Stroke risk parameters and CHA_2DS_2-VASc score for the general screening population (GSP) and the atrial fibrillation group (AF). Percentages were calculated for the number of patients after adjustment of missing values.*

Stroke risk parameters	GSP (n = 1179)	AF (n = 9)
Arterial hypertension	391/1174 (33.3%)	4/9 (44.4%)
Diabetes mellitus	80/1178 (6.8%)	1/9 (11.1%)
Congestive heart failure	26/627 (4.1%)	0/9 (0%)
Previous stroke	37/1172 (3.2%)	0/9 (0%)
Vascular disease	84/1171 (7.2%)	1/9 (11.1%)
Age between 65 and 75 y	391/1179 (33.2%)	3/9 (33.3%)
Age ≥ 75 y	177/1179 (9.2%)	6/9 (66.7%)
CHA_2DS_2-VASc (mean ±SD)	1.8 ± 1.2	2.7 ± 1.2

Diagnostic accuracy

With the AliveCor heart monitor, 1172 iECG traces were obtained and were included for diagnostic accuracy testing. From these measurements, 1070 were identified as sinus rhythm (91.3%), 14 as possible AF (1.2%), 58 as irregular rhythm (4.9%) and 30 as insufficient quality (2.6%). After eliminating these insufficient quality traces, 1142 remaining iECG traces were included in a second diagnostic accuracy analysis. FibriCheck recorded a total of 1145 PPG traces, of which 1080 were identified as sinus rhythm (94%), 25 as possible AF (2.2%), 15 as irregular rhythm (1.3%) and 25 as insufficient quality (2.2%). All these measurements were included for diagnostic accuracy testing. After exclusion of insufficient quality measurements, 1120 high-quality PPG measurements underwent a second accuracy analysis. The accuracy of the algorithmic-based tools with respect to visual rhythm-interpretation, before and after quality adjustment, was assessed. As both the FibriCheck application and the AliveCor heart monitor are positioned as screening tools, and are implemented as such in this study, the focus is put on the approach obtaining maximum sensitivity (Figure 5).

	Before quality adjustment				After quality adjustment			
	Max sensitivity		Max specificity		Max sensitivity		Max specificity	
	PPG	iECG	PPG	iECG	PPG	iECG	PPG	iECG
Total (n)	1145	1172	1145	1172	1120	1142	1120	1142
No AF (n)	1080	1070	1120	1158	1080	1070	1095	1128
AF (n)	65	102	25	14	40	72	25	14
PPV (%)	32.0	22.7	50.9	80.7	44.0	29.6	54.3	82.5
NPV (%)	100	100	99.4	99.7	100	100	99.7	100
Sensitivity (%)	**100**	**100**	75.0	88.9	**100**	**100**	85.7	100
Specificity (%)	**95.0**	**92.0**	98.3	99.5	**97.0**	**94.4**	98.3	99.5
Accuracy (%)	**95.0**	**92.1**	98.2	99.4	**97.1**	**94.4**	98.2	99.5

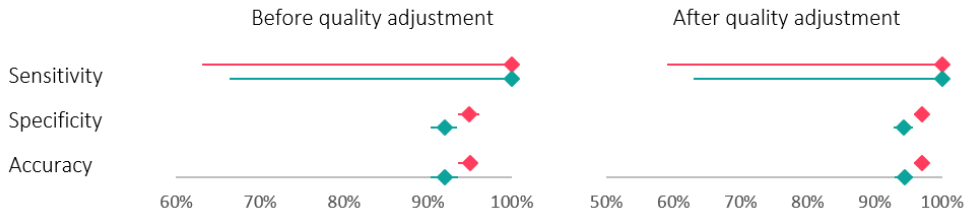


Figure 5. Diagnostic accuracy of algorithmic interpretation of PPG and iECG. The highlighted sensitivity, specificity, and accuracy values are visualised with their 95% confidence intervals. PPG: photoplethysmography, iECG: single-lead iPhone ECG, AF: atrial fibrillation, PPV: positive predictive value, NPV: negative predictive value.

With insufficient quality measurements taken into account, the algorithmic interpretation of PPG-measurements scored 100% (95% CI 63.1-100%) sensitivity, 95.0% (95% CI 93.6-96.2%) specificity and 95.0% (95% CI 93.6-96.2%) accuracy. The algorithmic interpretation of single-lead ECG measurements scored 100% (95% CI 66.4-100%) sensitivity, 92.0% (95% CI 90.3-93.5%) specificity and 92.1% (95% CI 90.4-93.6%) accuracy. After excluding insufficient quality measurements, the diagnostic capabilities of both tools increased. This resulted in a sensitivity of 100% (95% CI 59.0-100%), specificity of 97.0% (95% CI 95.9-98.0%) and accuracy of 97.1% (95% CI 95.9-98.0%) for PPG, and a sensitivity of 100% (95% CI 63.1-100%), specificity of 94.4% (95% CI 92.9-95.6%) and an accuracy of 94.4% (95% CI 92.9-95.7%) for iECG. The sensitivity represents the probability that the screening result will be positive when AF is present (true positive rate), whereas the specificity is the probability that the screening result will be negative when AF is not present (true negative rate). The accuracy gives the overall probability that a patient will be correctly classified. Since the 95% confidence intervals are sensitive to the sample size, and as the sensitivity is calculated using the small number of true positive AF-screenings, a broad interval can be observed.

The positive predictive value is the probability that AF is present when a screening result is positive. Vice versa, the negative predictive value represents the probability that AF is not present when a screening result is negative. In contrast to the sensitivity, specificity, and accuracy, the PPV and NPV are calculated with the detected prevalence taken into account. Since the sample sizes in this population did not reflect the real prevalence of the AF in the general population, the positive and negative predictive values were recalculated following Bayes' theorem, given a prevalence of 2.3% in a population aged 40 and older.

$$PPV = \frac{sensitivity\ x\ prevalence}{sensitivity\ x\ prevalence + (1 - specificity)\ x\ (1 - prevalence)}$$

$$NPV = \frac{specificity\ x\ (1 - prevalence)}{(1 - sensitivity)\ x\ prevalence + specificity\ x\ (1 - prevalence)}$$

It can be expected that, together with the maximum sensitivity, the NPV value will be maximised (100%). The PPV value is consequently lower with this approach, but increases when maximising the specificity.

DISCUSSION

In this study, the diagnostic performance of FibriCheck in a real-life community setting was assessed. The FibriCheck smartphone application was able to detect AF with a high sensitivity (100%) and a high specificity (97%), comparable to the reference single-lead iECG device. Recent studies assessing the diagnostic performance of new tools for community AF-screening reported similar diagnostic capabilities (Table 2). The majority of these studies evaluated the diagnostic power of the same single-lead iECG device, and reported a sensitivity of 71.4 to 98.5%, a specificity of 91.4 to 99.4%, a PPV of 76.9 to 82.3% and an NPV of 97.4 to 99.2% (30-32). An automated blood pressure monitor with an AF-detection algorithm scored 80.6% sensitivity, 98.7% specificity, 42.4% PPV and 99.8% NPV (33). There were two studies available reporting on the diagnostic performance of a PPG-based smartphone application. Compared to cardiologist review of a single-lead iECG trace, this application had a sensitivity of 92.9%, a specificity of 97.7%, a PPV of 53.1% and an NPV of 99.8% (31). Comparison of this application with 12-lead ECG yielded similar results with a slight decrease in specificity and a remarkably increased PPV value (34).

Since the in here described intend of the FibriCheck application is to serve as a screening tool, and not as a substitute for the standard ECG, the focus was put on obtaining maximum sensitivity (100%). In this scenario, missing an AF-patient due to false negative results are undesirable, but a moderate number of false-positive results are acceptable given that screen-detected patients will receive a 12-lead ECG to confirm diagnosis. Biasing an algorithm for enhanced sensitivity is an acceptable measure for algorithmic-based devices when being used in a screening setting (35). Although this approach was also applied in the comparable screening studies, maximum sensitivities and negative predictive values were not reported (Table 2). As a result, screening programmes with these tools risk missing AF-patients due to false negative results. Although a high sensitivity is desirable, there is always a trade-off with lower specificity, which can create much extra work and costs in verifying diagnosis with an ECG.

Since none of the participants included in the FibriCheck screening study had a history of AF, the prevalence of previously undiagnosed AF in this screening programme was 0.8% in the general screening population (aged > 40), and 1.6% in the population aged ≥ 65. Recent community screenings reported a newly diagnosed AF rate ranging from 0.5 to 3% (Table 3) (14, 31, 32, 36-38). Comparison of these results should be made with caution, since the overall prevalence and the prevalence of new AF are highly dependent on the age of the screened population. When comparing the results of the FibriCheck screening with published results, the prevalence should be adjusted for the age of the compared population. There were no studies available reporting on systematic population screenings with PPG-based screening tools.

In order to obtain reliable results on the accuracy of FibriCheck in a real-world population setting, this study was performed under limited medical supervision. Furthermore, participants and researchers were blinded for the algorithmic diagnosis to avoid biasing by any reaction evoked by the result. However, it is possible that the use of the application in a completely unsupervised setting may lead to a higher number of false positive results caused by motion artefacts, reducing the specificity. Devices with automatic diagnostic algorithms require low-noise and high-quality signals for optimal performance. Indeed, when excluding insufficient quality measurements, the diagnostic values for both devices increased. This illustrates the importance and impact of a quality filter on the diagnostic performance. In order to obtain a high-quality PPG trace with the FibriCheck application, proper finger placement and the avoidance of motion artefacts is crucial. This could be difficult for some persons, especially in an elderly population. Individuals with diseases causing tremor, with calloused fingertips, or with an impaired blood flow, are less likely to record high-quality measurements. With an ageing population becoming more and more technically advanced, it is expected that the number of insufficient quality measurements due to unfamiliarity with the technique will decrease. Next to this, the quality of the recorded PPG traces and the consequent diagnostic accuracy is highly dependent on the performance of the algorithm. The development and improvement of a dedicated algorithm will decrease the number of insufficient quality measurements, thereby increasing the diagnostic accuracy. Nevertheless, further research is warranted to assess whether the application can achieve the same level of accuracy in a completely unsupervised setting.

To conclude, FibriCheck was able to detect an important number of unknown AF-patients with a high diagnostic accuracy in a real-life setting. Our results suggest that the high sensitivity and negative predictive value of the FibriCheck smartphone application, together with its low cost and broad accessibility, can make mass population screening for AF highly feasible and effective. The moderate positive predictive value stresses the importance of cardiologist review after a positive screening result.

Table 2. The diagnostic performance of novel atrial fibrillation screening tools in the community, and the diagnostic performance of FibriCheck and AliveCor in this study (green). se: sensitivity, sp: specificity, PPV: positive predictive value, NPV: negative predictive value.

Population	Screening tool	Validation method	Diagnostic accuracy	Study
1,000 participants aged ≥ 65	Single-lead iECG (AliveCor)	Cardiologist review of iECG	98.5% se, 91.4% sp, 79.3% PPV, 97.4% NPV	Lowres, 2014 (30)
1,013 participants aged ≥ 65	Single-lead iECG (AliveCor)	Cardiologist review of iECG	71.4% se, 99.4% sp, 76.9% PPV, 99.2% NPV	Chan, 2016 (31)
10,735 participants aged ≥ 50	Single-lead iECG (AliveCor)	Cardiologist review of iECG	76.8% se, 99.6% sp, 83.2% PPV, 99.4% NPV	Chan, 2017 (32)
1,013 participants aged ≥ 65	Smartphone PPG (Cardiio Rhythm)	Cardiologist review of iECG	92.9% se, 97.7% sp, 53.1% PPV, 99.8% NPV	Chan, 2016 (31)
98 participants aged > 18	Smartphone PPG (Cardiio Rhythm)	12-lead ECG	93.1% se, 90.9% sp, 92.2% PPV, 92.0% NPV	Rozen, 2018 (34)
5,969 participants aged ≥ 65	Automated blood pressure monitor (Microlife WatchBP)	Cardiologist review of iECG	80.6% se, 98.7% sp, 42.4% PPV, 99.8% NPV	Chan, 2017 (33)
1,179 participants aged > 40	Smartphone PPG (FibriCheck)	Cardiologist review of iECG	100% se, 97.0% sp, 44.0% PPV, 100% NPV	Thesis, 2018
1,179 participants aged > 40	Single-lead iECG (AliveCor)	Cardiologist review of iECG	100% se, 94.4% sp, 29.6% PPV, 100% NPV	Thesis, 2018

Table 3. The diagnostic yield of single time-point systematic community screening. For comparison, the age-adjusted prevalence of previously undiagnosed atrial fibrillation detected in the FibriCheck screening (green).

Population	Screening tool	Total AF (n, %)	New AF (n, %)	Reference	New AF (n, %)
5,000 German citizens aged 35-74	12-lead ECG	161 (3.2%)	25 (0.5%)	Schnabel, 2012 (36)	4/1070 (0.4%)
4,890 Irish citizens aged ≥ 50	Three-lead ECG	118 (2.4%)	45 (0.9%)	Frewen, 2013 (37)	9/1040 (0.9%)
7,172 Swedish citizens aged 75 and 76	Single-lead ECG	884 (12.3%)	218 (3%)	Svennberg, 2015 (14)	2/58 (3.4%)
13,122 Chinese citizens aged ≥ 18	Single-lead ECG	239 (1.8%)	101 (0.8%)	Chan, 2016 (39)	9/1359 (0.7%)
65,747 Belgian citizens aged > 40	Single-lead ECG	911 (1.4%)	603 (0.9%)	Proietti, 2016 (38)	9/1179 (0.8%)
10,735 Chinese citizens aged ≥ 50	Single-lead ECG	244 (2.3%)	74 (0.7%)	Chan, 2017 (32)	9/1040 (0.9%)

CHAPTER II: FEASIBILITY AND IMPACT OF A COMPLETELY DIGITAL MASS POPULATION SCREENING

There is an increasing demand for the implementation of population screenings to detect AF and prevent strokes. Up to now, few was known concerning the diagnostic accuracy that novel screening tools can achieve in a community setting. Chapter I evaluated the implementation of FibriCheck in a systematic screening programme and demonstrated the high diagnostic accuracy that was obtained in this real-life setting. These results pave the way for more widespread and less supervised population screenings with FibriCheck as dedicated device. To demonstrate this, a pilot project was set up to evaluate the feasibility and impact of a completely digital population screening using only an existing communication infrastructure and the FibriCheck application. The uptake, compliance and outcome will be evaluated and discussed.

The abstract of this study has been submitted as a late breaking clinical trial to the European Society of Cardiology Congress, review is pending. The abstract is currently being submitted to the American Heart Association Congress 2018 in Chicago. Submission of this study to *The European Heart Journal* and *The New England Journal of Medicine* is ongoing.

METHODS

This study was positioned as a pilot mass community screening to assess the feasibility and impact of screening with the FibriCheck application at scale. A local media campaign was organized covering an article in online and written press available to 92,638 subscribers (Figure 6). The article contained a QR-code giving free access to the application, informed the readers of the screening programme, and created the required awareness on the value of AF-screening.

Figure 6. Article in local newspaper informing on the screening and inviting to participate.

In addition, the article contained instructions on how to install the application and how to participate in the screening programme. Participants were instructed to measure their heart rhythm twice a day and when experiencing symptoms, for a monitoring period of nine consecutive days. After annotating symptoms, the measurement was sent to a secure server for analysis. Each measurement was automatically classified as sinus rhythm, possible AF, irregular rhythm, or insufficient quality. The number of insufficient quality measurements was closely monitored. Participants not able to perform high-quality measurements received notifications in the application guiding them to perform good measurements. Notifications were also used to keep all participants compliant to the screening protocol. Upon termination of the nine-day monitoring period, the accounts were closed and users received a diagnostic end-report containing a general conclusion and an overview of their rhythm traces. Four months after reporting, a follow-up questionnaire was sent to evaluate the impact of the screening programme.

Prior to the account activation in the app, users were informed of and asked to agree with the privacy policy and terms of service, and by this consenting to participate in the project.

Results

The media campaign was available to a community of 92,638 subscribers. Within 48 hours, 12,328 individuals (13% uptake) enrolled in the screening programme and completed the monitoring period of nine consecutive days, demonstrating the feasibility of digital mass screening. This yielded a considerable database containing 120,446 traces of 60-second PPG measurements. The compliance to the recommended measurement protocol of two measurements per day was 70.8%. Rhythm analysis of these measurements resulted in 140,325 (86.6%) regular rhythms, 5,440 (4.4%) irregular rhythms, 640 (0.5%) possible AF-traces and 10,041 (8.3%) measurements of insufficient quality. Overall, 1.3 ± 0.75 attempts were needed to successfully complete a measurement. The amount of measurements of insufficient quality decreased from 22% on the first day to 6% on the last day of the monitoring period. This illustrates a learning curve associated with an increase in familiarity with the technique (Figure 7). In order to further enhance diagnostic quality, all measurements indicated by the algorithm as irregular or possible AF underwent a second analysis through visual verification by medical technicians, under supervision of cardiologists, specialized to analyse PPG-signals.

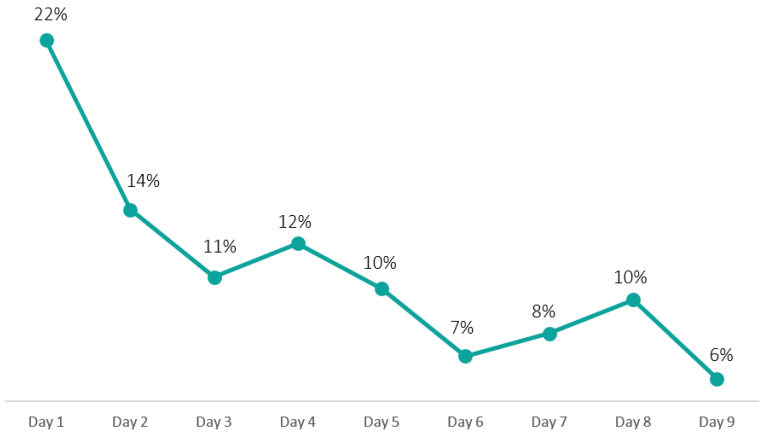
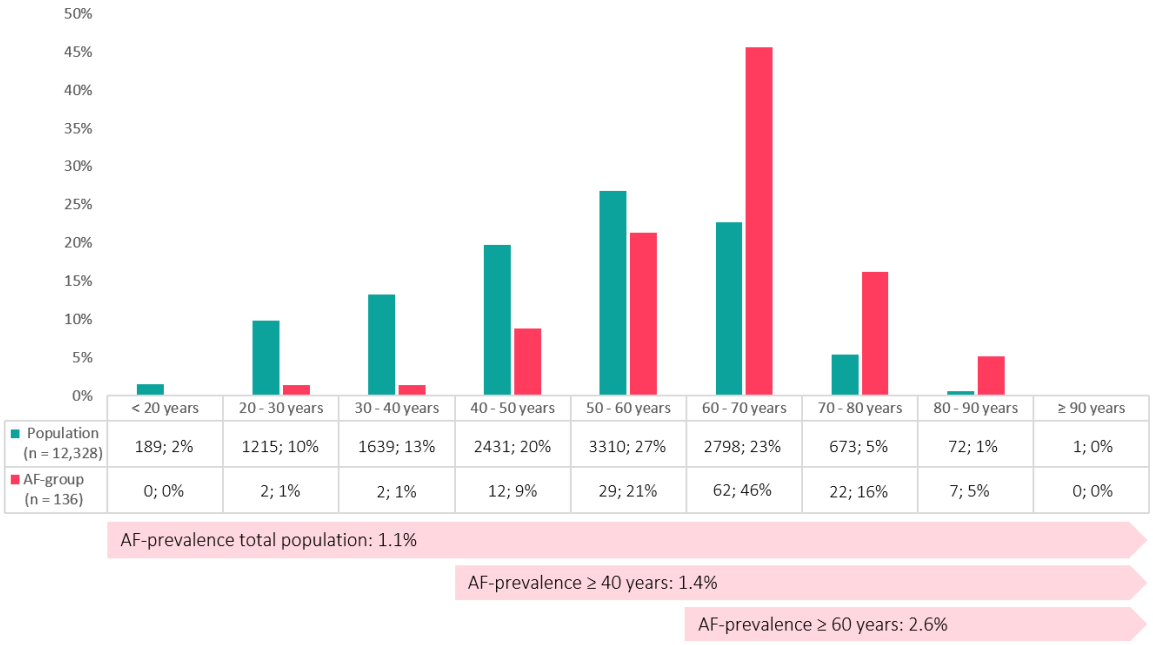


Figure 7. The decrease in insufficient quality measurements illustrates a learning curve.

The average age of the screened population was 49.9 ± 14.3 years (Figure 8), 58% was male. In total, 136 AF-patients were identified in the general population, resulting in an overall AF-prevalence of 1.1%. 75% of these patients did not experience any symptoms. The average age of the AF-group was 62.8 ± 10.9 years, 70% was male.



	< 20 years	20 - 30 years	30 - 40 years	40 - 50 years	50 - 60 years	60 - 70 years	70 - 80 years	80 - 90 years	≥ 90 years
Population (n = 12,328)	189; 2%	1215; 10%	1639; 13%	2431; 20%	3310; 27%	2798; 23%	673; 5%	72; 1%	1; 0%
AF-group (n = 136)	0; 0%	2; 1%	2; 1%	12; 9%	29; 21%	62; 46%	22; 16%	7; 5%	0; 0%

Figure 8. Age distribution of the general population and the AF-group. Overall AF-prevalence and AF-prevalence for the ≥ 40 and ≥ 60 population.

51 of the 136 AF-patients (38%) were detected on first PPG-measurement (Figure 9). The remaining 85 patients (62%) were identified in the course of the monitoring period. 38/136 AF-patients (28%) had persistent AF and were all identified on first measurement. 98/136 patients (72%) had paroxysmal AF, of which 14 were detected on first measurement.

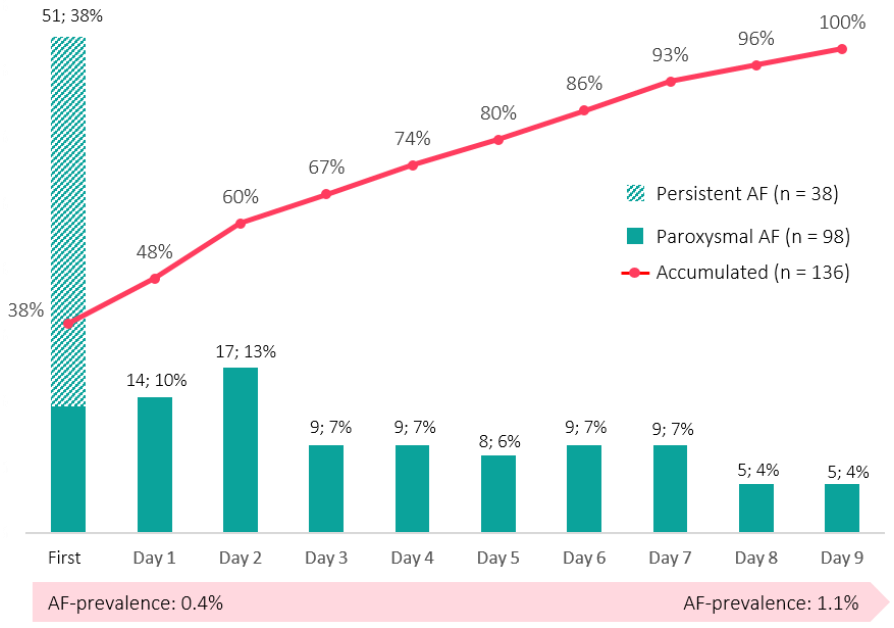


Figure 9. Time to first detection of AF among participants undergoing intermittent PPG recordings. Prolonged monitoring resulted in an almost threefold increased detection.

The participants were informed of the detection of possible AF in their end-report and referred to a medical professional to confirm diagnosis. Four months after reporting, a follow-up questionnaire was sent to the 136 AF-patients to assess the clinical impact and value of the screening programme (Figure 10). 100 patients (73%) consented to fill in the questionnaire. 40% of the subjects were new AF-cases, of which 21/40 (53%) consulted their general practitioner (GP) or cardiologist to confirm diagnosis, and 60% had a known history of AF. This resulted in 81 ECG-confirmed AF-cases (60%) four months after participating in the screening programme. 17/60 (28%) known AF-patients consulted their GP and received an adjustment of their current care strategy, 43/60 (72%) known AF-patients stayed on the same care path. Persistent or permanent AF was confirmed on 12-lead ECG, paroxysmal AF was confirmed on Holter monitor or implantable loop recorder.

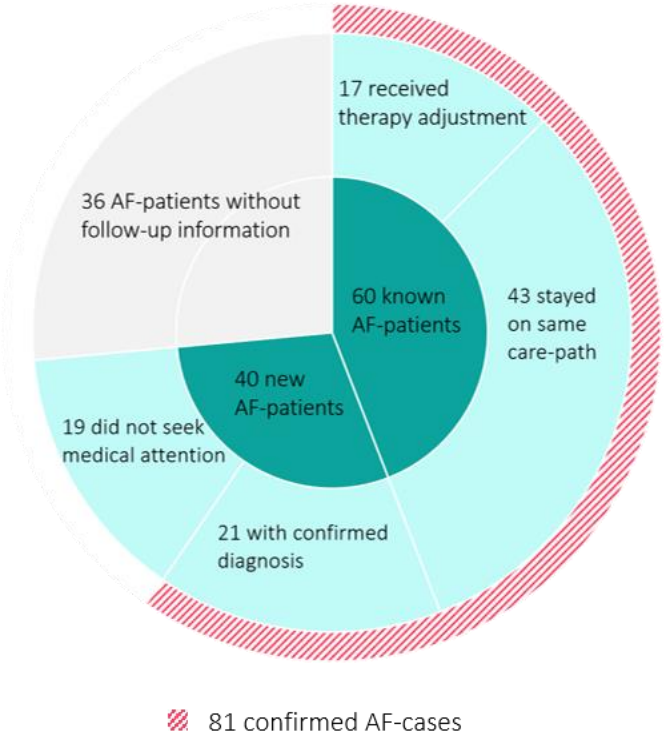


Figure 10. This screening programme resulted in adjustment of therapy for 17 previously diagnosed AF-patients and start of therapy of 21 newly diagnosed AF-patients. 81 AF-cases were confirmed on 12-lead ECG, Holter or implantable loop recorder.

Discussion

Impact and feasibility of the screening programme

This study is commendable for several reasons. It was conducted in an unselected general population and participants performed measurements remotely with no medical supervision. Results obtained with this approach are highly relevant, since this provides real-life population data. The simple screening protocol was acceptable and feasible and resulted in the detection of an important number of undiagnosed AF-patients. Furthermore, it offered an ideal opportunity to evaluate prescription of and adherence to guideline-recommended anticoagulation therapy. This is of great clinical value as the existing widespread anticoagulation under-treatment in patients with

AF further contributes to an unnecessary high stroke incidence (40). Following this screening, 28% of the previously diagnosed AF-patients received an adjustment of their current care strategy.

Since most patients with AF have paroxysmal episodes, a single recording would not suffice and most likely result in a missed diagnosis (29). Indeed, only 14 from the 98 paroxysmal AF-cases (14.3%) in this study were identified on first PPG measurement, in contrast to all 38 persistent AF-cases detected on first measurement. Prolonged monitoring resulted in an almost three-fold increase in the likelihood of a diagnosis of AF being made, from a prevalence of 0.4% on the first measurement to a total prevalence of 1.1% over the nine-day monitoring period. Literature search for comparable studies reporting on longer-term (intermittent) screening in an unselected population did not yield the desired results. To our knowledge, this is the first prolonged systematic screening programme targeting the general population. Up to now, unselected screening across the general population was not feasible, acceptable or cost-effective due to the need of dedicated expensive ECG-based devices and the reliance on existing clinical infrastructure (29).

A few studies investigated longer-term monitoring in selected high risk populations. Engdahl and colleagues (41) reported results of a community screening targeting all individuals aged 75 and 76 years. An initial 12-lead ECG screening detected AF in 1.2% of those screened, compared to 4.7% following two weeks intermittent monitoring. Steinhubl and colleagues (42) provided 1,739 individuals identified with an increased stroke risk with a wearable ECG patch (Zio Patch, San Francisco, USA) for four months, and reported new diagnosis of AF in 5.1%. Halcox and colleagues (43) reported an almost four-fold increase in diagnostic rate, from 1% on a single screening to 3.8% following twice weekly intermittent single-lead iECG recordings over a period of 12 months in 1,001 patients aged ≥ 65 years. Due to the selected high risk populations and the overall longer monitoring durations, these studies all reported significantly higher numbers for AF-prevalence.

The increase in diagnostic yield in the FibriCheck community screening was caused by the detection a large amount of paroxysmal patients that would likely have remained undiagnosed in traditional screening programmes. Although the increase in diagnostic yield is a rewarding result of the screening programme, justified concerns about the relevance of early identification of (asymptomatic) paroxysmal AF and the need of anticoagulation therapy in these patients are surfacing (44). Available evidence suggests that paroxysmal patients experience at least a stroke risk similar to persistent patients (29). This is however based on findings from patients monitored by implantable devices, and it is unclear how this compares with the risk associated with paroxysmal episodes of uncertain frequency and duration detected during a prolonged screening campaign (45). Implementation of this screening protocol, together with a substantiated patient documentation and follow-up, allows for the construction of a database of longitudinally monitored patients that will offer insights in the clinical course of AF and the relationship between AF-burden and stroke risk. Awaiting further studies addressing these uncertainties, the obtained results already underline the importance, clinical value, and feasibility of longer-term intermittent recordings in an unselected general population as a screening strategy.

Evaluation of the uptake

Because our invitation process merely included a single media campaign via a local newspaper, an acceptable participation rate was achieved. Based on the number of participants (12,328) and the latest available numbers on newspaper distribution (92,638 subscribers, including online newspaper readership), an uptake of 13% was calculated. It should however be noted that the distribution of online and written press cannot be tracked and that therefore the uptake of this screening programme cannot be reliably evaluated. A previous community screening in Sweden did perform a comprehensive evaluation of the participation rate of their screening programme (46). They reported that socio-economic factors, education level, disposable income, immigrant backgrounds, and marital status had a significant impact on the participation rate. Higher rates were observed among invitees with a high educational level, invitees with a high to medium income, and married invitees. Furthermore, cultural contexts affecting language barriers and confidence in health systems and society in general may have influenced participation. An important factor to be taken into account is the low public awareness of AF and its debilitating consequences (47). It is widely recognized, and even stated in the ESC guidelines, that education is a prerequisite for informed and involved patients. Furthermore, a sceptical and controversial attitude towards innovative digital technologies may also have influenced participation rates. It can be expected that participation rates will increase by targeted efforts aiming at increasing awareness of the screening benefits and trust in new tools.

The strength of the FibriCheck community screening is the completely digital approach. Where traditional clinical trials are limited in the number of subjects that can be included, this out-of-the-box approach was able to include a considerable number of participants and process a large volume of valuable data without overconsuming healthcare resources. However, the choice of an entirely digital approach may have created a barrier to participate. Participants who did not have access to the internet, did not own a smartphone, or were unable to operate the application were by study design excluded from the screening programme. This presumably included a proportion of individuals at risk. Nonetheless, it is expected that this gap will decrease together with the increasing smartphone ownership among the elderly. With an increasing relevant population owning a smartphone (48), PPG as a software-only solution is the ideal candidate to enable mass population screening.

To conclude, this screening programme, by not relying on existing clinical infrastructure and not being hampered by large expenses, dedicated equipment, time investment, logistics and medical personnel, proved to be remarkably feasible and scalable. The time has come to re-evaluate current recommendations in guidelines and propose consideration of widespread screening for AF. Although this completely digital screening programme has demonstrated its merits, we are eagerly awaiting additional clinical studies as well as economic simulations of cost-effectiveness. Screening for undiagnosed AF in the community, no matter how effective, feasible and scalable, is futile without integrated next steps for follow-up and management (29), especially since the reliance on solely PPG measurements will not suffice as a definitive diagnosis.

CHAPTER III: LONG-TERM MONITORING IN HIGH RISK PATIENTS

Previous studies addressed the diagnostic accuracy of FibriCheck as a screening tool in the general population, and the feasibility of longer-term screening with FibriCheck at scale. These studies targeted an unselected general population with the main objective to identify high risk AF-patients eligible for preventive therapy. Another strategy is to pre-select a population that would benefit from intensified screening. This study addresses the implementation of FibriCheck in high risk patient populations as a solution for primary and secondary stroke prevention, and evaluates the added value to current clinical practice.

The abstract of this study was submitted to the European Society of Cardiology Congress and selected for oral presentation. Submission for the American Heart Association Congress in ongoing.

METHODS

STUDY DESIGN

The primary objective of this multicentre national study was to evaluate if FibriCheck allows for an early detection of AF in comparison to conventional approaches used in today's clinical practice. It is hypothesized that the use of FibriCheck would enable a faster detection of new or recurrent AF compared to usual case finding in clinical practice. Since the FibriCheck application was implemented on top of current clinical practice, the number of AF-patients identified with FibriCheck versus the number of patients identified during their originally planned usual care path could be quantified. Because it can be expected that the use of FibriCheck would result in a reduction of follow-up consultations, the secondary objective was a quantification and calculation of the cost-effectiveness of FibriCheck in high risk patients (Chapter IV).

Eight clinical centres located in the Northern part of Belgium participated in this study. High risk patients in primary and secondary prevention, where the detection of AF will lead to a therapeutic intervention, were included. Patients that previously had an intervention to control their heart rhythm were also included. Here, FibriCheck was used to monitor the heart rhythm in a home environment in order to timely react to post-interventional AF-recurrence. The protocol was approved by the Ethics Committees of all participating centres and written informed consent was obtained from all patients before participation.

MONITORING PROCEDURE

The participating centres included patients in one of the following groups: (I) patients without structural heart disease, (II) patients with structural heart disease, (III) patients with high-risk parameters for AF development, (IV) post-cryptogenic stroke patients, (V) post-cardioversion and (VI) post-ablation patients. Non-native Dutch and pacemaker rhythm were exclusion criteria, together with conditions compromising the ability to measure with the FibriCheck application, low adherence to the provided protocol, and no self-care ability. Inclusion criteria were group-specific (Figure 11).

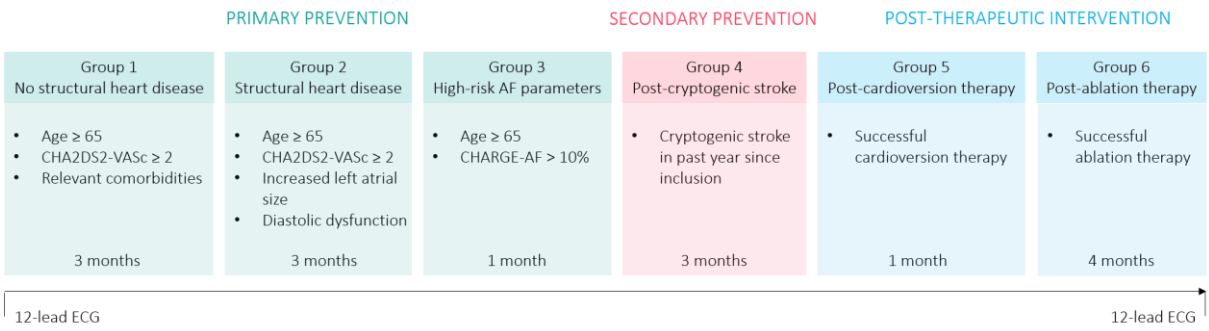


Figure 11. *Patient groups, their inclusion criteria and monitoring period. The CHARGE-AF risk score included age, race, height, weight, systolic and diastolic blood pressure, use of hypertensives, diabetes, heart failure, and history of premature myocardial infarction. The CHA_2DS_2-VASc score included congestive heart failure, hypertension, diabetes mellitus, stroke, vascular disease, age, and sex. At the beginning of the monitoring period and at study closure, the participants received a 12-lead ECG.*

Demographic and baseline data were collected using a questionnaire at time of inclusion. To determine the impact of FibriCheck on current clinical practice, the initially planned care path was documented. This resulted in a study design where the patient itself would be its own control. A baseline 12-lead ECG measurement was performed. Depending on the group, the patients monitored their heart rhythm for a period of one to four months by measuring twice daily with the FibriCheck app and additionally when experiencing symptoms (Figure 11). All measurements were reviewed and evaluated by the treating physician or the FibriCheck remote monitoring centre. At study closure, again a 12-lead ECG measurement was performed.

The prevalence of new and recurrent AF was assessed. The CHA_2DS_2-VASc score was calculated and the number of patients on anticoagulation therapy was documented. A comparison was made between the detection yield of FibriCheck and the detection yield of conventional strategies in clinical practice. A follow-up study performed a health-economic analysis to determine the cost-effectiveness of FibriCheck monitoring in post-cryptogenic stroke patients (Chapter IV).

Results

This study demonstrated the on-boarding of a large group of patients. The majority of patients were categorized in groups for patients with structural heart disease (I), patients with high-risk parameters for AF development (III) and post-ablation patients (VI). A total of 460 patients were included in this multi-centre study, 168 (37%) were female (Figure 12). The average age of this population was 66 ± 12 years. The average CHA_2DS_2-VASc sore was 2.2 ± 2.5 and 97 (21%) patients were anticoagulated. A total of 47,667 measurements were performed from which 81% was normal and 2% was indicative for AF. Only a fraction of 7% insufficient quality measurements were recorded, typically first measurements after which the development of a learning curve could be observed. Only 34% of the measurements were labelled with symptoms. A 91% compliance in successfully completing two measurements per day was observed.

61 AF-patients were identified, resulting in an overall AF-prevalence of 13%. Because of the high rate of relapse associated with therapeutic interventions, the highest prevalence was observed in post-cardioversion and post-ablation patients, 38% and 21% respectively. The lowest prevalence was detected in patients with high risk parameters for AF development and post-cryptogenic stroke patients. Overall, 25 participants (5%) were first

diagnosed during this study. As expected, these participants were mainly detected in the primary prevention group. The average age of the AF-group was 66 ± 11 years. The average CHA_2DS_2-VASc score was 2.4 ± 1.6 and 15 AF-patients (25%) were anticoagulated. Since a previous stroke is an important risk factor when calculating the CHA_2DS_2-VASc score, the average score for post-cryptogenic stroke patients was the highest.

		PRIMARY PREVENTION			SECONDARY PREVENTION	POST-THERAPEUTIC INTERVENTION		
		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	**Total**
	General population							
	Patients (n, %)	20 (4%)	89 (19%)	174 (38%)	63 (14%)	34 (7%)	80 (17%)	**460 (100%)**
	Female (n, %)	13 (65%)	34 (38%)	73 (42%)	20 (32%)	8 (24%)	20 (25%)	**168 (37%)**
	Age (m ± SD)	63 ± 15	66 ± 11	73 ± 12	63 ± 10	64 ± 10	58 ± 11	**66 ± 12**
	CHADSVASC (m ± SD)	1.7 ± 1.3	2.2 ± 1.4	2.2 ± 1.5	2.3 ± 1.6	2.1 ± 1.4	2.1 ± 1.5	**2.2 ± 1.5**
	Anticoagulation (n, %)	4 (20%)	12 (13%)	35 (20%)	18 (29%)	11 (32%)	17 (21%)	**97 (21%)**
	AF-group							
	AF (n, %)	2 (10%)	9 (10%)	16 (9%)	4 (6%)	13 (38%)	17 (21%)	**61 (13%)**
	Newly detected (n, %)	2 (10%)	6 (7%)	11 (6%)	3 (5%)	1 (3%)	2 (3%)	**25 (5%)**
	Age (m ± SD)	69 ± 6	67 ± 9	69 ± 14	73 ± 9	66 ± 11	62 ± 8	**66 ± 11**
	CHADSVASC (m ± SD)	0.5 ± 0.7	2.7 ± 1.8	3 ± 1.6	3.3 ± 1.7	2.2 ± 1.6	2 ± 1.5	**2.4 ± 1.6**
	Anticoagulation (n, %)	1(50%)	1 (11%)	3 (19%)	1(25%)	6 (46%)	3 (18%)	**15 (25%)**
	12-lead ECG[1] (n, %)	0	0	3 (19%)	0	5 (48%)	3 (18%)	**11 (18%)**
CONTROL	**Usual care**							
	12-lead ECG[2] (n, %)	1 (50%)	8 (89%)	4 (25%)	2 (50%)	12 (92%)	10 (59%)	**37 (61%)**
	Holter[2] (n, %)	0	0	0	0	0	6 (35%)	**6 (10%)**

Figure 12. Overview. (I) patients without structural heart disease, (II) patients with structural heart disease, (III) patients with high risk parameters for AF development, (IV) post-cryptogenic stroke patients, (V) post-cardioversion patients, and (VI) post-ablation patients. Results of 12-lead ECG measurement performed at study closure.[1] Patients for which regular 12-lead ECG measurements and Holter monitors are planned according to the documented usual care plan.[2]

11 of the 61 AF-patients identified with FibriCheck (18%) were also identified based on the 12-lead ECG measurement taken at study closure. When questioning the physicians concerning the planned usual care path, it appeared that 37 of the 61 AF-patients (61%) would have received 12-lead ECG monitoring during follow-up consultations. 6/61 (10%) AF-patients would have received 24-hour Holter monitoring. Patients with structural heart disease, post-cardioversion patients and post-ablation patients had the greatest chance of being frequently monitored during follow-up consultations.

DISCUSSION

This study demonstrates the on-boarding and long-term monitoring of 460 patients from either primary or secondary prevention, or post-interventional therapy. As expected from the selected high risk population, an overall high AF-prevalence was reported. This study assessed whether prolonged monitoring in relevant patient groups was superior to conventional follow-up for the detection of new or recurrent AF.

PRIMARY PREVENTION

Patients from the primary prevention group were selected based on high-risk parameters including an increased age, increased CHARGE-AF score, increased CHA_2DS_2-VASc score and presence of relevant comorbidities. The overall AF-prevalence ranged from 9 to 10% detected over a period of one to three months. The prevalence of previously undiagnosed AF ranged from 6 to 10%. The high overall prevalence and the prevalence of new AF indicated that these parameters allowed for the identification of at-risk patients who would benefit from intensified screening.

Age is the simplest variable that can aid targeted screening. With each decade of advancing age, AF-prevalence roughly doubles (49). This has led to the development of current clinical guidelines recommending opportunistic screening in every patient of at least 65 years (4, 26). The CHARGE-AF score was developed to predict the five-year risk for AF development based on age, race, length, weight, systolic and diastolic blood pressure, hypertension, diabetes, heart failure and myocardial infarction. Although this has been clinically validated in several studies including more than 95,000 individuals, there were no studies available using an increased CHARGE-AF score to select patients for targeted screening (50-53). On the other hand, although not developed and validated for this purpose, the CHA_2DS_2-VASc score has been increasingly used for AF-risk prediction (54). The criteria of at least two CHA_2DS_2-VASc risk factors, together with an increasing age, has been used in previous studies to select a high risk patient group (Table 4). These studies reported an overall prevalence ranging from 4.7% to 12.3% (14, 41, 45, 55, 56). The prevalence was highly dependent on the type of monitoring device, duration of the monitoring period and the age of the population. Two-week intermittent single-lead ECG recordings was the most frequently applied strategy to detect AF in high risk populations. One study used 30-month intermittent monitoring using an automated blood pressure device with an AF-detection algorithm (56). No studies were available on intermittent PPG monitoring.

Since structural heart disease and AF are linked by similar risk factors, share a common pathophysiology, and can cause and exacerbate each other (57), patient selection based on relevant comorbidities is another strategy to target screening. Structural heart diseases are associated with diastolic dysfunction and an increased left atrial volume. This causes structural and electrical remodelling and culminates in the development of AF (57). Both the Framingham Heart Study (58) and the Cardiovascular Health Study (59) showed that an enlarged left atrium was significantly associated with AF-incidence, and reported that a 30% increased left atrial volume was associated with a 43% greater risk of AF development (58, 59). These cardiac conditions that predispose to the development of AF generally confer an adverse prognosis due to an increased stroke risk, thus justifying intensified screening.

Although these underlying cardiac conditions are well known risk factors, no studies were available specifically targeting these patients for prolonged screening programmes.

Secondary prevention

In this study, 63 post-stroke patients were included and monitored with FibriCheck for three months. An overall AF-prevalence of 6% was found. None of these patients were detected on 12-lead ECG taken at study closure. Two AF-patients would have received regular 12-lead ECG checks and none of the AF-patients would have received 24-hour Holter monitoring as part of their planned usual care path. Previous studies on prolonged cardiac monitoring in stroke patients reported an AF-prevalence of 5.3 to 16.1% following a monitoring duration of one to six months (Table 5). These studies relied on either external intermittent monitoring or continuous monitoring with an implantable cardiac device. These and our results demonstrate that prolonged monitoring in post-stroke is superior to conventional methods used in terms of AF-detection yield.

Current guidelines recommend 24- to 72-hour ECG monitoring to rule out AF in patients with an ischemic stroke (60). If the cause remains uncertain after routine evaluation, which is the case in 20 to 40% of the patients, the stroke is classified as 'cryptogenic' and patients are treated with antiplatelet therapy for secondary stroke prevention. However, antiplatelet therapy is known to be only minimally effective in the presence of AF. Given the high risk of stroke recurrence in patients who experienced an AF-related stroke, strategies to improve the detection of underlying AF are of great clinical importance (61). Since traditional ECG monitoring is not sufficiently sensitive for the detection of paroxysmal AF, it is likely that AF is being routinely underdiagnosed and undertreated with the current approach (62). An increased detection of AF, as proven possible with the FibriCheck application, allows for a greater number of patients to benefit from anticoagulation therapy, and for the best possible reduction of recurrent stroke and the associated morbidity and mortality.

Post-cardioversion therapy

Cardioversion is successful in 75 to 95% of the patients, but AF-recurrence is common, especially during the first two weeks. 40 to 60% of the cardioverted patients relapses into AF within three months and around 60 to 80% within one year subsequent to the procedure (63). The Finnish Cardio Version study, the largest study reporting on post-cardioversion outcomes, identified a significant risk of thromboembolism, particularly in patients without post-procedure anticoagulation (64). Preventive therapy in post-cardioversion patients is currently based on symptomatic recurrences on the one hand, and available information about AF-pattern on the other hand. However, with conventional methods, the information about AF-recurrence and pattern is limited. Prolonged or continuous rhythm information allows for an evaluation of the efficacy of the interventional therapy which would enable faster and evidence-supported clinical decision making.

This study included 34 post-cardioversion patients for one-month monitoring with the FibriCheck application. AF was found in 13 patients (38%), of which 12 would have received regular ECG spot checks as part of their planned care path. Despite the known risk for thromboembolism, an important anticoagulation under-treatment was observed in this population. Only two studies evaluating the use of screening tools to monitor AF-recurrence post-

cardioversion were identified (Table 6). These studies relied on intermittent ECG monitoring and reported recurrent AF in 42% of the cardioverted patients after four weeks, and in up to 67% after 226 days (65, 66).

Post-ablation therapy

Because electrical triggers from the pulmonary veins initiate paroxysmal AF, restoration of sinus rhythm is achieved through isolation of pulmonary veins and additional ablation in the posterior left atrial wall. Post-procedural complications include recurrent AF and stroke, with the highest risk during the first week (67). Therefore, anticoagulation therapy should be prescribed to all patients for at least eight weeks following ablation. Early arrhythmia recurrence is not uncommon up to three months post-ablation and occurs in 43 to 59% of the patients. Although these early recurrences are transient and do not represent treatment failure *per se*, it is widely recognized as a risk factor for longer-term recurrence (67). Early recurrence may be caused by an inflammatory response or the recovery of pulmonary vein conduction, and late recurrence is more likely to result from the emergence of new foci and mechanisms of AF development, together with the recovery of conduction of previously ablated sites. It is suggested that the time of recurrence, and thus the time of detection, affects the probability of maintaining sinus rhythm following additional interventions. Early restoration of sinus rhythm is likely to prevent progressive atrial electrical remodelling and to facilitate long-term maintenance of sinus rhythm (68). Indeed, there is evidence that early treatment with cardioversion after ablation improves long-term outcomes. Restoration of sinus rhythm was reported in 50% post-ablation patients who underwent cardioversion within thirty days after recurrence. If cardioversion was postponed for more than thirty days, all patients would require a second ablation procedure. To date, a better understanding in the correlation between early and long-term recurrence is hindered by an inability to continuously monitor these patients. Prolonged monitoring allows for timely intervention and, in addition, data from longitudinally monitored patients can offer more insights in rhythm outcome and progression of recurrent AF.

This study monitored 80 post-ablation patients with FibriCheck for a duration of four months and detected AF in 21%. Klemm and colleagues reported the same AF-prevalence after six-month monitoring of 80 post-ablation patients with intermittent single-lead ECG recordings using a handheld device (Table 7) (69). Continuous follow-up with implantable cardiac devices for a duration of 12-months detected AF-recurrence in 41% of the subjects (70). In contrast, 7-day Holter monitoring 12 months post-ablation detected recurrent AF in 26% of the monitored patients (71).

Limitations

Despite the clinical relevance of the presented results, a few important limitations should be discussed. There are a few discrepancies between the inclusion criteria and the population characteristics of the patient groups. This study was conducted with minimal supervision of a research team, and patient inclusion did not always strictly comply with the predefined criteria. Furthermore, the patient groups were not evenly represented and were monitored for different durations. A comparison of outcomes of different groups should therefore be made with caution.

Prolonged monitoring in similar at-risk patient groups has already been evaluated in previous studies and yielded promising results. However, this had little effect on clinical practice since these studies were not sufficiently powered due to the lack of a control group. Although this was partially mitigated in this study by implementing a protocol where each patient would be its own control, this is not a standard procedure and is prone to biased reporting. We are eagerly awaiting sufficiently powered controlled randomized trials to confirm whether extended monitoring would improve AF detection and treatment rates compared to current clinical practice.

STRENGTHS

The discussed limitations stress the need for sufficiently powered clinical trials to evaluate hard outcomes. However, some strengths should not go unnoticed. All relevant comparable studies evaluated shorter- and longer-term, intermittent or continuous, monitoring with ECG devices. This study presents the first preliminary results from prolonged PPG-monitoring in different high risk populations. Although similar results were achieved compared to ECG studies, some advantages of PPG over ECG are worth mentioning. Extended monitoring with currently available ECG-based event recorders is likely to miss a fraction of paroxysmal AF-episodes. The external leads of these devices cause patient discomfort, which results in a poor patient compliance that may decline rapidly upon increasing the monitoring durations. Implantable cardiac monitors provide long-term continuous rhythm information, but are expensive and require invasive surgery. Novel, non-invasive handheld ECG devices are becoming available, but require the purchase of dedicated hardware, thereby limiting its use in some populations.

All results point in one direction: 'the longer you look, the more you find'. Where long-term ECG monitoring is hampered by a decreased compliance and increased cost, long-term PPG monitoring proved to be highly feasible. It can be conclude that FibriCheck is a promising candidate for prolonged cardiac monitoring in selected populations. Irrespective of the risk factors, this is of high clinical value and superior over conventional strategies used in current clinical practice. Further research is needed to evaluate whether pre-selection based on any criteria allows for effective screening in a target population and prevention of first or recurrent stroke.

Table 4. Prolonged cardiac monitoring in high risk patients selected based on increased aged and additional stroke risk factors. For continuous monitoring devices, AF was defined as an episode of missing P-waves and irregular RR-intervals of a period of at least 30 seconds, as defined by the ESC Task Force (72).

Study design	Prevalence	Study
1-month intermittent monitoring with automated blood pressure monitor in 139 patients aged ≥ 65 with additional CHA_2DS_2-VASc risk factors.	11.5% (1.4% new AF)	Wiesel, 2013 (56)
2-week intermittent single-lead ECG recordings in 848 patients aged 75 and 76 with at least two additional CHA_2DS_2-VASc risk factors.	4.7%	Engdahl, 2013 (41)
2-week continuous monitoring with wearable single-lead ECG patch in 75 patients aged ≥ 55 with at least two additional CHA_2DS_2-VASc risk factors.	5.3%	Turakhia, 2015 (45)
2-week intermittent single-lead ECG recordings in 7,173 patients aged 75 and 76.	12.3% (3.0% new AF)	Svennberg, 2015 (14)
2-week intermittent single-lead ECG recordings in 1,510 patients aged ≥ 65 and with at least two additional CHA_2DS_2-VASc risk factors.	7.6% (0.9% new AF)	Berge, 2017 (55)
3-month intermittent PPG recordings in 20 patients with an average age of 63, at least one additional CHA_2DS_2-VASc risk factor and relevant comorbidities.	10% new AF	Thesis, 2018
3-month intermittent PPG recordings in 89 patients with an average age of 66, at least one additional CHA_2DS_2-VASc risk factor, increased left atrial size or diastolic dysfunction.	10% (7% new AF)	Thesis, 2018
1-month intermittent PPG recordings in 174 patients with an average age of 73 and an increased 5-year risk for AF-development according to the CHARGE-AF score.	9% (6% new AF)	Thesis, 2018

Table 5. *Prolonged screening in stroke patients.*

Study design	Prevalence	Study
21-day intermittent three-lead ECG recordings with handheld device in 56 patients aged ≥ 18 experiencing a cryptogenic stroke within the last three months.	5.3%	Tayal, 2008 (73)
1-month intermittent ECG recordings with patient-activated patch in 98 post-stroke patients following a negative 24h Holter.	9%	Gaillard, 2010 (74)
1-month intermittent single-lead ECG recordings with handheld device in 156 patients six months post-cryptogenic stroke.	5.4%	Miller, 2013 (75)
1-month monitoring with event-triggered recording belt around the chest in 572 patients aged ≥ 55 six months post-cryptogenic stroke. Conventional 24h Holter monitoring in the control group resulted in 3.2% AF detection.	16.1%	EMBRACE, 2014 (76)
6-month monitoring of 221 patients with implantable cardiac device within 90 days after the index event. Conventional 24h Holter monitoring in the control group detect AF in 1.4%.	8.9%	CRYSTAL-AF, 2014 (77)
3-month intermittent PPG recordings in 63 post-stroke patients with an average age of 63	6%	Thesis, 2018

Table 6. *Prolonged monitoring post-cardioversion therapy.*

Study design	Prevalence	Study
Intermittent recordings with handheld single-lead ECG device over an average monitoring period of 266 days in 848 cardioverted patients aged 18 to 80.	67%	Fetsch, 2004 (65)
4-week intermittent recordings with handheld single-lead ECG device after successful electrical cardioversion in 50 patients, average age 68. Patients were included one hour after cardioversion.	42%	Weijs, 2018 (66)
Intermittent PPG recordings for 1 month in 34 cardioverted patients with an average age of 64.	38%	Thesis, 2018

Table 7. *Prolonged monitoring post-ablation therapy.*

Study design	Prevalence	Study
24-hour and 7-day Holter monitoring 12 months post-ablation in 100 patients. Conventional 24 Holter detected an AF-recurrence of 12%.	26%	Kottkamp, 2004 (71)
6-month intermittent recordings with handheld single-lead ECG device in 80 ablated patients.	21%	Klemm, 2006 (69)
12-month follow-up with implantable cardiac monitoring in 129 post-ablation patients.	41%	Pokushalov, 2011 (70)
4-month intermittent PPG recordings in 80 ablated patients with an average age of 58.	21%	Thesis, 2018

CHAPTER IV: HEALTH ECONOMIC ASSESSMENT OF LONG-TERM MONITORING IN STROKE PATIENTS

The previous study demonstrated the clinical value of prolonged rhythm monitoring with FibriCheck in high risk patient populations. One important question remains to be answered before considering to integrate such strategy in existing health care systems: is AF-screening a cost-effective use of scarce healthcare resources? A sequel study used a Markov model to estimate the cost-effective of FibriCheck monitoring in post-cryptogenic stroke patients. A Markov model allows for the extrapolation beyond observed study outcomes to perform longer-term economic analyses.

The abstract of this study is currently being submitted to the American Heart Association Congress.

METHODS

In the previous study (Chapter III), 63 post-cryptogenic stroke patients monitored their heart rhythm for three months using the FibriCheck application. At time of inclusion and study end, a 12-lead ECG was taken. The planned usual care-path of the participating patients was documented. In addition to the previously described study design, the cost-effectiveness of FibriCheck monitoring in this patient group was evaluated using a Markov model (Figure 13). The model simulated the health status of 1,000 patients, aged 65 and older, over a period of 35 years. Rates of AF-detection and anticoagulation therapy from this study and published literature, together with epidemiological data from Belgium, were used to predict lifetime costs, effectiveness and benefits of anticoagulation therapy. The alternatives being investigated were opportunistic screening, usual care (i.e. regular case finding) and FibriCheck screening.

Patients entered the Markov model in the 'post-stroke' health state (Figure 13). The monitoring strategy (i.e. opportunistic monitoring, FibriCheck monitoring or regular case finding) determined the odds of detecting AF. Detection of AF and patients' treatment status determined the clinical event rates (ischemic stroke, intracranial haemorrhage, minor or major bleeding, and mortality). Patients' quality of life declined after a clinical event. As patients moved through different states in the model, they accrued direct healthcare costs, life-years and quality adjusted life-years (QALYs). The risk of ischemic stroke and intracranial haemorrhage increased with age. The model was limited to one event per person. The incremental cost-effectiveness ratio, which is the ratio of the estimated difference between the costs of different screening strategies and the estimated difference between the outcomes of these strategies in terms of QALYs, was calculated. Because the model inputs are based on assumptions, albeit derived from relevant recent literature and previous study results, this unintentionally included a degree of uncertainty. A sensitivity analysis was designed to estimate if and how this uncertainty may impact the precision of the outcome estimates.

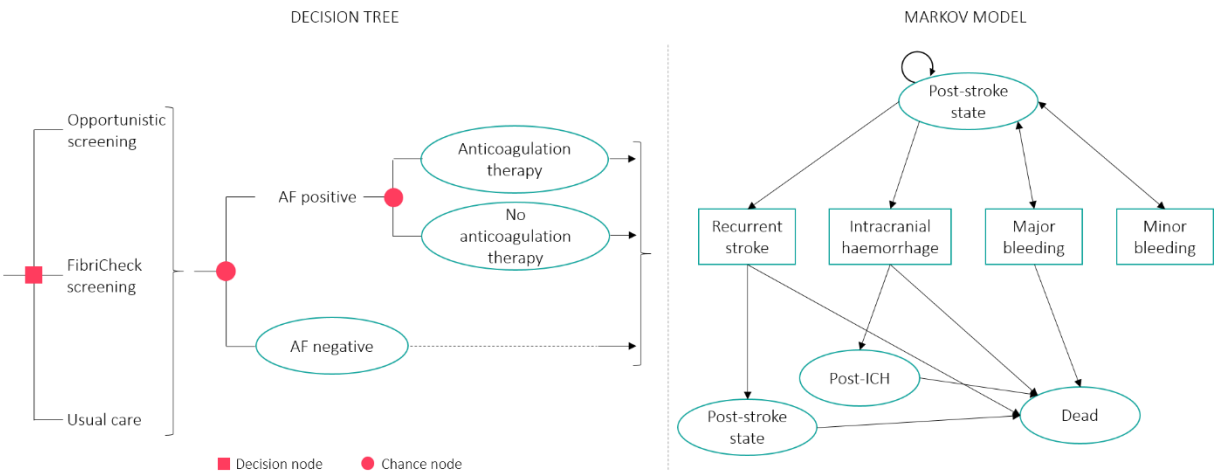


Figure 13. Structure of the decision analytic Markov model. The first part is a decision tree that represents the screening problem. The second part is a Markov model where patient's costs and health states are simulated for a time horizon of 35 years. Ellipses represent the health states and squares the events.

Results

There are two distinct components to a health-economic assessment: a within-trial analysis and a longer term model-based analysis. The post-cryptogenic stroke patients from the previous study (Chapter III) were selected to evaluate the cost-effectiveness of prolonged FibriCheck monitoring. In this group, 4/63 patients were identified with AF, resulting in a prevalence of 6%. None of these cases were detected with 12-lead ECG and only one AF-patient would have received Holter monitoring as part of the planned care-path.

The Markov model indicated that both opportunistic screening and usual care were inferior to FibriCheck screening in terms of cost-effectiveness due to lower case findings and higher costs. Comparing FibriCheck monitoring with conventional follow-up for patients post-cryptogenic stroke, the implementation of FibriCheck in a population of 1,000 patients resulted in 26 QALYs and an incremental cost-effectiveness ratio (ICER) of *minus* €1,189 per QALY gained. The sensitivity analysis did not alter these results.

Discussion

Previously published studies demonstrated that prolonged ECG monitoring in post-stroke patients was superior in terms of AF-detection rate, and likely to be cost-effective compared to conventional follow-up recommended by guidelines and used in clinical practice today. To our knowledge, this is the first study evaluating prolonged cardiac monitoring using a PPG-based smartphone application as secondary stroke prevention strategy. With an ICER of *minus* €1,189 per QALY gained, prolonged FibriCheck monitoring is not only cost-effective, but also cost-saving compared to conventional follow-up strategies. An approach is considered cost-effective when the costs are below the societal 'willingness to pay' for a QALY (78). This is a threshold defined by the World Health Organization based on multiples of a country's *per-capita* gross domestic product, thus dependent on the country and healthcare system. These thresholds are used by policy-makers when deciding which health interventions are good value for money and worth funding. Data on cost-effectiveness are warranted to inform clinical practice and health policy decisions about the optimal monitoring strategies for secondary stroke prevention. Awaiting randomized

controlled trials with hard endpoints able to determine the real-life cost-effectiveness, simulation with a Markov model is an acceptable and widely used method.

Searching literature for comparable studies yielded two studies evaluating the cost-effectiveness of prolonged screening in post-stroke patients (Table 8) (79, 80). Two studies on cost-effectiveness of prolonged screening in other at-risk populations were also included (81, 82), together with cost-effectiveness studies evaluating systematic and opportunistic screening with no screening in the general population (i.e. usual care, regular case finding) (30, 83-86). It can be observed that there is a lot of variation between these results, and although some approaches may seem to consume significantly more healthcare resources than others, all approaches were identified to be cost-effective based on the presented ICER per QALY gained and the willingness-to-pay of the corresponding health system. This is the first health economic assessment of long-term intermittent PPG monitoring that reported not only to be cost effective, but also to be cost-saving. Although a comparison of the included studies is not straightforward since they are dependent on the country's specific willingness-to-pay threshold to be cost-effective, it is clear that the results of FibriCheck are outstanding.

Table 8. Overview of recent health economic analyses using Markov models to evaluate prolonged ECG screening in stroke patients (first panel), prolonged ECG screening in the general population (second panel), and opportunistic and systematic community ECG screening (third panel); all compared to conventional approaches in routine practice. ICER: incremental cost ratio, WTP: willingness to pay.

Study design	Result	Reference
Four-month intermittent PPG monitoring in 1,000 stroke patients over a time horizon of 35 years.	4-month PPG monitoring proved to be cost-saving with an ICER of minus €1,189 per QALY gained. WTP Belgium: €30,000 per QALY gained.	Thesis, 2018
30-day intermittent single-lead ECG recordings and 24-hour continuous Holter monitoring versus conventional follow-up in 1,000 75-year-old stroke patients over a time horizon of 20 years.	The ICERs of conventional care, Holter monitoring and intermittent ECG recordings were €624, €661 and €616 per QALY gained, respectively.	Levin, 2015 (79)
7, 14 and 30 days ECG monitoring versus conventional 24-hour ECG in cryptogenic stroke patients aged ≥ 55 years.	30-day ECG monitoring proved to be cost-effective with an ICER of €2,000 per QALY gained.	Yong, 2016 (80)
Two weeks intermittent single-lead ECG recording (Zenicor-EKG, Sweden) in 13,000 75- and 76-year-old individuals.	Two-week Intermittent ECG monitoring had an ICER of €4,313 per QALY gained.	Aronsson, 2015 (81)
14-day extended screening with handheld ECG and one-time screening with 12-lead ECG versus routine practice in 1,000 75-year-old individuals.	Both screening approaches were superior to routine practice with ICERs of US$47,949 (€45,379) and US$58,728 (€55,580) per QALY gained, respectively. WTP USA: $50,000 per QALY gained.	Wygant, 2018 (82)
ECG-based systematic (n = 5000) and opportunistic screening (n = 5000) compared with routine practice in patients ≥ 65 years from fifty primary care centres in the UK over a time horizon of 12 months.	Opportunistic screening was the most cost-effective with an ICER of £337 (€494) per QALY gained. WTP UK: £20,000 to £30,000 per QALY gained.	Hobbs, 2005 (84)
Single screening with iPhone ECG (iECG, AliveCor Heart monitor) of 1,000 participants aged ≥ 65 in 10 pharmacies in Sydney, Australia.	The ICER of iECG screening in the community was AU$5,988 (€3,142) per QALY gained. WTP Australia: AU$69,900 par QALY gained.	Lowres, 2014 (30)
Opportunistic pulse palpation with confirmatory 12-lead ECG in patients aged ≥ 65 in primary care in Ireland over a time horizon of 25 years.	Opportunistic screening was cost-effective with an ICER of €20,271 per QALY gained.	Moran, 2015 (85)
Single screening with handheld single-lead ECG (MyDiagnostick) in patients aged ≥ 65 attending the seasonal influenza vaccination in the Netherlands.	Handheld single-lead ECG screening had an ICER of €764 per QALY gained. WTP The Netherlands: €80,000 per QALY gained.	Jacobs, 2018 (86)

CONCLUSION AND FUTURE PERSPECTIVES

In Chapter I, FibriCheck proved to be able to detect AF with a high diagnostic accuracy in a real-life setting. Up until now, diagnostic accuracy studies were performed in selected populations and controlled settings. Although further study is warranted to determine whether the application will achieve the same accuracy in a completely unsupervised setting, these results suggest that, together with its low cost and high accessibility, FibriCheck can make mass population screening for AF highly feasible. This was demonstrated in Chapter II. Where conventional long-term screening was only beneficial in selected high risk patients, a completely digital approach allows for screening in an unselected general population. By not relying on existing clinical infrastructure nor being hampered by large expenses, dedicated equipment, time investment, logistics and medical personnel, 12,328 participants effortlessly on-boarded for a nine-day screening programme. 136 AF-patients (1.1%) were identified in the general population, of which 60% was confirmed on ECG following consultation of a medical professional.

Current clinical guidelines acknowledge the need of prolonged cardiac monitoring in high risk individuals to prevent first or recurrent stroke. However, official recommendations cannot be made yet since conventional monitoring tools fail to prove feasibility, acceptability, and cost-effectiveness. Where long-term ECG monitoring is hampered by a decreased compliance and increased cost, long-term PPG monitoring demonstrated to be highly feasible and to be a promising candidate for prolonged cardiac monitoring in selected at-risk populations (Chapter III). The last remaining question concerning cost-effectiveness of prolonged PPG-monitoring was answered in Chapter IV, where FibriCheck not only proved to be cost-effective, but also to be cost-*saving* compared to strategies in current clinical practice.

The in here presented results are of great clinical value for healthcare policy makers and clinicians. Although it was already widely recognized that conventional tools and strategies are not able to improve AF-detection for better stroke prevention, recommendation of new tools and strategies in guidelines is hindered due to the lack of clinical evidence. In order to make a real impact on clinical practice, sufficiently powered randomized controlled trials are necessary. Awaiting further studies, this thesis highlights the capabilities of FibriCheck in primary and secondary prevention of AF-induced strokes.

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First in world implementation of a smartphone application in primary and secondary prevention of stroke

Richting: **Master of Biomedical Sciences-Bioelectronics and Nanotechnology**
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