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Thijs Vandenbergk

DOCTORAL DISSERTATION

Connectivity matrix
of mobile health:
Pieces of the digital puzzle

Promoter: Prof. Dr. Irena Grooten

Co-promoters: Prof. Dr. Valerie Storms

Promoter: Prof. dr. Lars Grieten | Hasselt University

Co-promoter: dr. Valerie Storms | Hasselt University

Jury members: Prof. dr. Ivo Lambrichts (Chair) | Hasselt University

Prof. Dr. Pieter Vandervoort | Hasselt University

Prof. dr. Marcel Ameloot | Hasselt University

Prof. dr. ir. Ronald Thoelen | Hasselt University

Prof. dr. Bart Van den Bosch | KU Leuven

Roger Lemmens | IMEC

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In God we trust, all others must bring data.

~ W. Edwards Deming ~

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LIST OF ABBREVIATIONS

Admin	Administrator
AES	Advanced Encryption Standard
ABP	Arterial Blood Pressure
AF	Atrial Fibrillation
AMI	Acute Myocardial Infarction
ANOVA	Analysis of Variance
BPM	Beats Per Minute
CAD	Coronary Artery Disease
CI	Confidence Interval
CR	Cardiac Rehabilitation
CVA	Cerebrovascular Accidents
CVD	Cardiovascular Disease
DCC	Direct Current Cardioversion
DEQ	Depressive Experiences Questionnaire
DHARMA	Digital Health Research Platform Mobile Health
EAPC	European Association of Preventive Cardiology
ECG	Electrocardiography
ECR	Experiences in Closed Relationships
ESC	European Society of Cardiology
FDA	Food and Drug Administration
GAD	Generalized Anxiety Disorder
GP	General Practitioner
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart Rate
HRV	Heart Rate Variability
IQR	Interquartile Range
LED	Light-Emitting Diode
LLA	Lower Limit of Agreement
MAR	Missing At Random
MPS	Multidimensional Perfectionism Scale
NPV	Negative Predictive Value
NRMSE	Normalized Root Mean Square Error
PC	Personal Computer
PCS	Pain Catastrophizing Scale

PHP	Hypertext Preprocessor
PHQ	Patient Health Questionnaire
PIH	Pregnancy-Induced Hypertension
PPG	Photoplethysmography
PPI	Peak-to-Peak Interval
PPV	Positive Predictive Value
PREMOM	Pregnancy Remote Monitoring
RBG	Red, Green, and Blue
RM	Remote Monitoring
RMSE	Root Mean Square Error
RRI	R-R Intervals
SD	Standard Deviation
UC	Usual Care
ULA	Upper Limit of Agreement
WAMP	Windows, Apache, MySQL and PHP

GENERAL INTRODUCTION

GENERAL INTRODUCTION

According to the World Health Organization (WHO), approximately 56.9 million people died from any kind of disease in 2016. Chronic diseases such as ischemic heart disease, chronic obstructive pulmonary disease, cancer, and diabetes mellitus were by far the leading causes of these deaths [1]. WHO attributes up to 60% of deaths to chronic conditions and foresees that this proportion will exceed 73% by 2020 [2]. Moreover, these chronic conditions are seldom curable and require life-long care, so routine check-ups and unexpected hospitalizations are common for this patient population, contributing to immense healthcare costs and the diminution of patients' quality of life [3, 4]. The permanent and continuous need for disease management, also outside the hospital, has prompted the development of telehealth and telemedicine solutions [2].

'Telemedicine' refers to the delivery of healthcare services by healthcare professionals from a distance, using information and communication technologies to exchange clinically relevant information required for the diagnosis, treatment, and prevention of disease and injuries, for research and evaluation, and for the continuing education of healthcare providers, all in the interests of advancing the health of individuals and their communities [5]. 'Telehealth', in contrast, includes a broader variety of clinical and nonclinical remote healthcare services, often provided by nurses, such as patient education, help with medication adherence ('telepharmacy'), and troubleshooting health issues [6]. A graphical representation of the relation between Telehealth, Telemedicine and mobile health is shown in Figure 1.

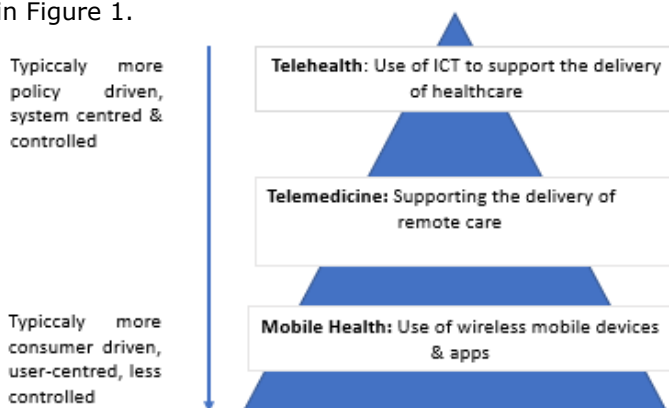


Figure 1: Overlapping concepts of Telehealth, Telemedicine and Mobile Health

Mobile health is a specific part of Telehealth and describes the use of mobile communication devices, such as wireless patient monitoring devices, smartphones, personal digital assistants, and tablet computers to provide health services. Mobile applications (apps) and, in some instances, companion mobile devices and sensors are the enablers of mobile health and the drivers of these systems [7]. The patient can monitor his/her condition from the home environment and via remote monitoring, allowing clinicians to remotely follow-up vital parameters and to intervene when necessary [8]. This provides an additional informational dimension to standard clinical care, which is mainly driven by in-office spot checks and limited ambulatory tests. A clinical remote program, for example a cardiac rehabilitation (CR) program, often combines telehealth and telemedicine components. In its most comprehensive format, CR includes remote monitoring (e.g. physical activity, vital signs, therapy adherence, ...), telecoaching (coaching from a distance by email, SMS, and telephone), social interaction, and e-learning. The use of an educational platform for patients is a relatively new concept. It is known from the literature that the education of patients via a video platform results in better patient outcomes, better risk factor management and more awareness of their disease condition [9-11]. However, The specific role and value of e-learning in telerehabilitation for cardiac patients were hardly assessed [9,10].

Mobile health is a booming industry following the trend of the smartphone which has become increasingly integrated into the lives of the global population. An increase of almost 1 billion smartphone users occurred between 2014 (1.57 billion) and 2017 (2.32 billion), and this number is expected to rise to 2.87 billion users in 2020 [12]. Today, more than 318,000 health-related apps for smartphones are available at online app stores, most of them developed for Android and/or iOS platforms [13]. The recent introduction of the smartphone to healthcare systems could be advantageous because safe, reliable and clinically effective mobile health apps are able to improve patient health [14]. Consequently, the current revolution in mobile health technology may transform the traditional healthcare organization into a more efficient and sustainable way of working [15, 16]. This will not only benefit patients, but also healthcare organizations and the society as a whole. Using mobile health apps with regular data uploads will allow patients to reduce the number of ambulatory consultations [17].

Mobile apps can also be used as an interface between the patient and clinician, as a channel for communication. Clinicians can immediately intervene when a patient's health is deteriorating because some apps are equipped with an alert system, thus preventing the development of more severe complications [18, 19]. Moreover, patients who receive feedback are more aware of their disease status and show better adherence to therapy [20]. It is also possible to connect mobile health apps to portable devices or sensors [21]. Recently, smartphones began to be used for medical purposes to measure numerous vital parameters, such as heart rate (HR) and body temperature [22]. However, it is noticed that this increase in downloading of health-related apps by costumers is no longer continued because many healthcare apps have not been validated [23].

According to European regulations, an app is considered a medical device when it records and registers data for further medical purposes, such as the diagnosis, monitoring, or treatment of a medical condition. This includes medical apps that are used to collect data for clinical trials. These apps must comply with the regulatory requirements for medical devices set out in the European Medical Device Directive (93/42/EEC) and require a CE mark before they can be sold in the European Union [24, 25]. In the US, such a device requires presales approval from the Food and Drug Administration (FDA). In addition to CE regulations, FDA requires clinical effectiveness studies of the medical devices. Recently, the FDA introduced the software Precertification (Pre-Cert) Pilot Program. This program will inform manufacturers about the development of a regulatory model to assess the safety and effectiveness of software technologies without inhibiting patient access to these technologies. The first version of the Pre-Cert 1.0 program will be available for pilot testing in 2019 [26].

However, CE or FDA certification are required for manufacturers wishing to sell their products, reimbursement approval will still be needed for each individual country [27]. In Belgium, there were several initiatives initiated in 2017-2018 by the minister of social affairs and public health Maggy de Block, to explore the clinical implementation of medical smartphone apps and the implications on the level of financing, legislation and liability, and health care organization. The results and conclusions out of these projects were consolidated and a reimbursement validation pyramid was developed.

This pyramid will be implemented in 2019 and shows the reimbursement criteria for mobile health tools. These criteria are: CE-certification and compliant with the General Data Protection Regulation (GDPR), interoperability with eHealth services, evidence-based and cost-effective.

Consumers' demand for clinically validated and reliable health apps and sensors clearly outpace the research required to understand their benefits, risks, and impacts on health outcomes. In fact, researchers and developers must still investigate, develop and assess the complete spectrum of mobile health technologies, to create safe, scalable, and effective applications. To that end, powerful frameworks and tools that support the development and validation of multidisciplinary mobile health applications are required [28]. These validation frameworks must address app content quality, usability, the need to match apps to consumers' general and health literacy levels, device connectivity standards (for apps that connect to instruments such as glucometers, blood pressure monitors, etc.), app security, and user privacy [29]. Future research is needed to investigate and describe necessary elements in validating and comparing medical apps versus standard technology.

The increasing availability of reliable and validated health apps & connected wearable devices will lead to the digitization of health & healthcare delivery information and will generate an exponential growth of health-related and lifestyle data [30]. Large and high-quality annotated datasets may be used to develop smart algorithms based on artificial intelligence techniques in order to extract the clinically important information and predict disease worsening. Data aggregation by connection of different data sources (e.g. patient-generated data based on apps and wearables at home, electronic patient records in the hospital, data collected by paramedics, etc.) is essential for research and development of predictive algorithms. Those algorithms will provide decision support to care professionals and semi-automated feedback to patients, necessary to efficiently manage large patient populations.

Despite the substantial technological advances that have been made in developing novel sensory systems and the efforts in the field of certified medical applications, there has been limited investment at the infrastructural level to connect, aggregate and handle the amount of information that is generated. Limited tools are available to handle these huge amounts of data, especially those generated by health care applications [31]. With the rapid increase in novel tools and technologies, data connectivity and aggregation have become a cornerstone in finding workable solutions to manage these patients in clinical practice and scientific research in digital health [32]. The commercial remote monitoring technology market is fragmented. This makes it difficult to combine different data sources because the many different manufacturers and technology providers have each developed their own data platforms to capture the data from their associated sensors and communicate them using a stand-alone software solution or web application. This makes data aggregation impossible when sensors from different technology vendors are used. Clinical practice and academic research based on remote monitoring are limited by these closed manufacturer-owned platforms. Therefore, a generic and open digital research platform for remote monitoring is required to allow academic and clinical research on the topic of remote monitoring to be undertaken. This platform must be able to tackle the issues of third-party device integration and the collection of various data feeds from patient populations.

When data from medical devices or apps are captured in a platform, access can be given to both the healthcare practitioner and the patient. Doctors and nurses can interpret the data to make a diagnosis or modify the current patient treatment, and data can also be transformed into information, recommendations, and education for the patient. Proper patient education is very important. Patients who have a clear understanding of their after-hospital care instructions are 30% less likely to be readmitted or to visit an emergency department than patients who lack this information [33]. It is estimated that 40%–80% of the medical information provided by healthcare workers during in-office consultations is forgotten instantly [34]. Future research is needed to investigate the use of (digital) patient education in a patient population.

An issue that raises important questions in telemedicine is the rather low adherence rate to remote monitoring, especially during long-term monitoring [35-38]. 'Adherence' is defined as the extent to which the patient's behavior is consistent with the prescription of drugs and the guidelines for a healthy lifestyle [39]. The methods used to measure treatment adherence are either direct or indirect. Direct methods include directly observed therapies and the measurement of drug, metabolite, or biological marker levels in the blood. Indirect methods of determining adherence include patient questionnaires, diaries or self-reports, pill counts, recording the rate of prescription refills, and the assessment of patient's clinical physiological markers [40, 41]. To increase the adherence rates of patients and ensure the successful implementation of new mobile health programs, it is essential to investigate the experiences and perceptions of the patients during and after the remote monitoring program. Also, the role of patients' psychosocial characteristics (severity of depression or anxiety, cognitive factors, attachment styles, and personality traits) needs to be explored in their adherence to remote monitoring.

RESEARCH OBJECTIVES

This PhD thesis focuses on four main research objectives to explore essential components of mobile health services. A schematic overview of the different objectives of this PhD thesis, is given in Figure 2.

Objective 1 – Validation: Investigate the use of a medical app for atrial fibrillation detection at home by clinical validation and evaluation of a new smartphone based technology.

Objective 2 – Monitoring: Development of a vendor-independent mobile health research platform to facilitate clinical mHealth research.

Objective 3 – Education: Explore the usage of an e-learning platform for patients in the domain of cardiac rehabilitation.

Objective 4 – Motivation: Investigate the influence of patient characteristics on adherence rate and the perceptions of remote monitoring in the domain of high-risk pregnancies.

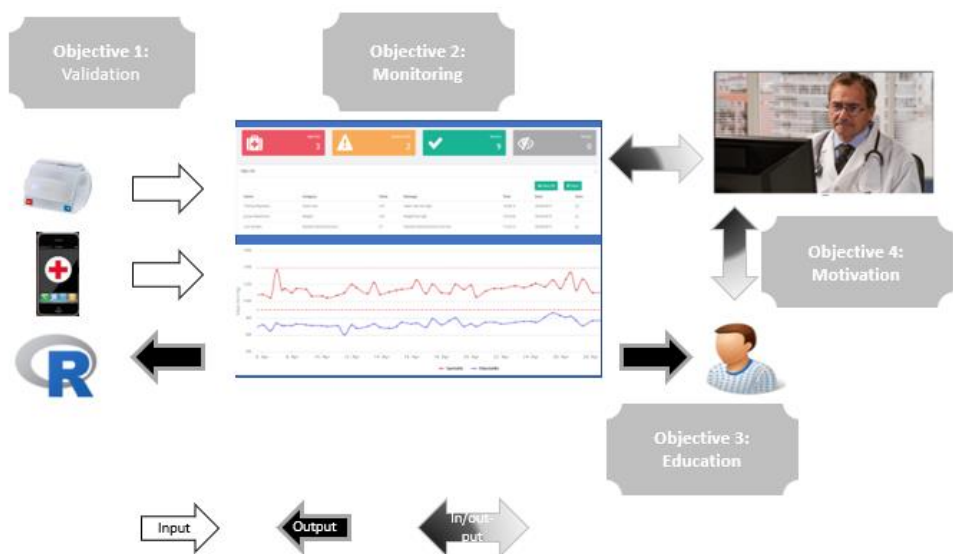


Figure 2: Schematic overview of the different objectives in this thesis

Each objective was covered by the following research chapters:

Objective 1: Heart-rate monitors (Chapter 1) and smartphone photoplethysmography (PPG) signals (Chapter 2) were investigated and clinically validated to explore the use of a PPG signal for heart rate and heart rhythm analysis. Based on these results, a follow-up random controlled trial (RCT) was performed to assess the feasibility, added value, and effectiveness of the FibriCheck application for the follow-up and detection of AF after a direct current cardioversion (Chapter 3).

Objective 2: The development and implementation of a vendor-independent mobile health research platform to monitor, aggregate and analyze vital parameters and their context of patients in different medical domains (Chapter 4).

Objective 3: An RCT was performed to investigate the proportion of patients who enter a digital e-learning platform and whether sociodemographic and medical factors influence cardiac-based e-learning usage (Chapter 5).

Objective 4: Relationship between patient characteristics and adherence rates to remote monitoring were determined in the light of high-risk pregnancies (Chapter 6). The perceptions of nurses, doctors and patients about the use of remote monitoring devices and services were investigated during a study on remote monitoring for women at high risk of pre-eclampsia (Chapter 7).

PART I – VALIDATION:

INVESTIGATE THE USE OF A MEDICAL APP FOR ATRIAL
FIBRILLATION DETECTION AT HOME BY CLINICAL VALIDATION
AND EVALUATION OF A NEW SMARTPHONE BASED TECHNOLOGY

CHAPTER 1

Clinical Validation of Heart Rate Apps: Mixed-Methods Evaluation Study

Vandenberk T, Stans J, Mortelmans C, Van Haelst R, Van Schelvergem G, Pelckmans C, Smeets CJ, Lanssens D, De Cannière H, Storms V, Thijs IM, Vaes B, Vandervoort PM.

JMIR Mhealth Uhealth. 2017 Mar 9;5(3):e25

ABSTRACT

Background: Photoplethysmography (PPG) is a proven way to measure heart rate (HR). This technology is already available in smartphones, which allows measuring HR only by using the smartphone. Given the widespread availability of smartphones, this creates a scalable way to enable mobile HR monitoring. An essential precondition is that these technologies are as reliable and accurate as the current clinical (gold) standards. At this moment, there is no consensus on a gold standard method for the validation of HR apps. This results in different validation processes that do not always reflect the veracious outcome of comparison.

Objective: The aim of this paper was to investigate and describe the necessary elements in validating and comparing HR apps versus standard technology.

Methods: The FibriCheck (Qompium) app was used in two separate prospective nonrandomized studies. In the first study, the HR of the FibriCheck app was consecutively compared with 2 different Food and Drug Administration (FDA)-cleared HR devices: the Nonin oximeter and the AliveCor Mobile ECG. In the second study, a next step in validation was performed by comparing the beat-to-beat intervals of the FibriCheck app to a synchronized ECG recording.

Results: In the first study, the HR (BPM, beats per minute) of 88 random subjects consecutively measured with the 3 devices showed a correlation coefficient of .834 between FibriCheck and Nonin, .88 between FibriCheck and AliveCor, and .897 between Nonin and AliveCor. A single way analysis of variance (ANOVA; $P=.61$) was executed to test the hypothesis that there were no significant differences between the HRs as measured by the 3 devices. In the second study, 20,298 (ms) R-R intervals (RRI)–peak-to-peak intervals (PPI) from 229 subjects were analyzed. This resulted in a positive correlation ($rs=.993$, root mean square deviation [RMSE]=23.04 ms, and normalized root mean square error [NRMSE]=0.012) between the PPI from FibriCheck and the RRI from the wearable ECG. There was no significant difference ($P=.92$) between these intervals.

Conclusion: Our findings suggest that the most suitable method for the validation of an HR app is a simultaneous measurement of the HR by the smartphone app and an ECG system, compared on the basis of beat-to-beat analysis. This approach could lead to more correct assessments of the accuracy of HR apps.

INTRODUCTION

The rapid evolution of technology has brought highly sophisticated electronic devices such as smartphones in our daily lives. The market for these devices is growing at a rapid pace. Globally, there are about 2.6 billion smartphone subscriptions, and by 2020, this number is projected to reach 6.1 billion [42]. Smartphones with multimedia capabilities open new possibilities for app development and service delivery [43]. Recently, smartphones have started to be used for medical purposes to measure numerous vital parameters such as heart rate (HR) and body temperature. This enables the use of a smartphone as a wireless HR monitor [22]. HR is nowadays measured by nurses who have congested schedules and therefore limited time to measure the HR of patients. HR-sensing devices may be a solution for this problem and can be useful in extending the reach of vital signs monitoring in- and outside hospitals, which is typically limited by constraints on human resources [44]. Nowadays, the use of wireless monitors for assessment of HR is a common component of health and fitness programs. Unlike HR apps on smartphones, these HR monitors require a telemetric strap to be worn around the thoracic region or arm to ensure electrocardiography (ECG)-derived HR [45].

The heart is an electromechanical pump with a rhythmic pumping cycle, in which the electrical activity of the heart can be represented in the electrocardiogram by a *P*-, *QRS*-, and *T*-wave. For HR and rhythm analysis, the ECG still remains the gold standard. The contraction of the heart propagates a blood pressure pulse wave through the arterial system that travels to the peripheries. A typical arterial blood pressure waveform comprises a systolic upstroke representing the ventricular ejection. After the systolic contraction, the aortic valve closes, which results in a sudden drop in pressure called the dichroic notch [46]. When the pulse pressure wave is passed, these arteries relax and eject the excessive blood they accumulated, allowing them to return to their initial state. When the areas with dense capillary beds are studied (ie, fingertips, toes, and earlobes), it is possible to observe this pooling of blood by using optical technologies. This technique is also known as the photoplethysmography (PPG) principle. The relationship between ECG, arterial blood pressure (ABP), and PPG is visualized in Figure 1.

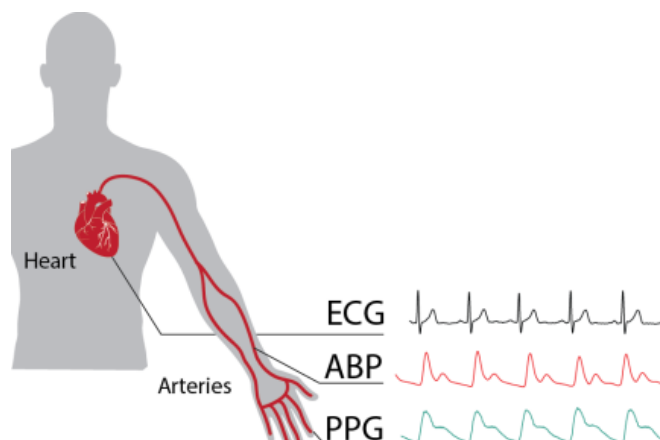


Figure 1: Visualized relation between ECG, ABP and PPG

PPG is already used in the clinic to measure oxygen saturation and pulse rate [47]. Additionally, it can also be used to estimate cardiac output [48]. PPG used as signal to measure HR is described as the pulse signal. As such, PPG can be used to measure HR without the need for an ECG device. Furthermore, the HR derived from the PPG signal can be used in a series of calculations to determine the heart rate variability (HRV) [49].

PPG is easy to set up, convenient, simple, and economically efficient. It uses a probe that contains a light source and a photodetector to detect the blood volume pulse. The amount of backscattered light corresponds with the variation in blood volume [50]. Hertzman [51] were the first to find a relationship between the intensity of backscattered light and blood volume in 1938. Traditional PPG systems typically use a narrow wavelength light source (i.e., light-emitting diodes [LEDs] with certain colors such as infrared, red, or green) and a specific photodetector to detect PPG signals through the skin. Interestingly, the smartphone camera in combination with the LED flashlight is able to detect these small variations in skin color caused by the blood flow (Figure 2). The camera uses wide-bandwidth pixel-enabling color detection in the red, green, and blue range (RGB-color).

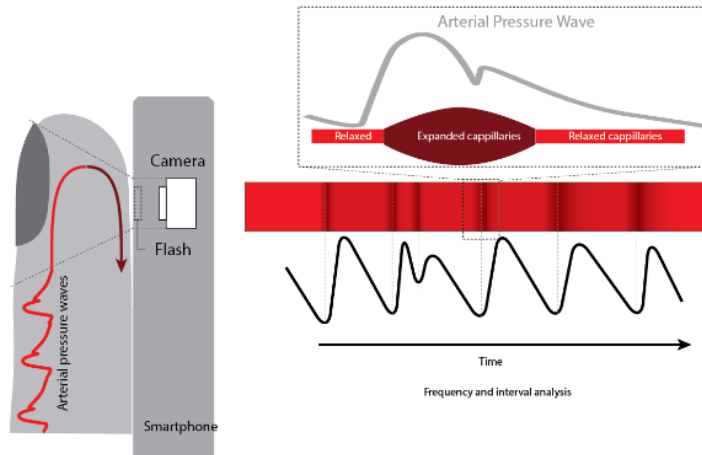


Figure 2: PPG principle by smartphone

In 2010, Jonathan and Leahy presented a case study which concluded that HR could indeed be measured through PPG by using a smartphone. This case experiment was confirmed by Gregoski et al in 2011 [45, 52]. Currently, numerous smartphone apps exist that measure HR. However, the validity of these apps has not always been confirmed [53]. At this moment, there is no consensus on a gold standard method for the validation of a HR app based on a PPG signal. This results in different validation processes that not always reflect the veracious outcome of comparison. Validation can be done in two ways: (1) by comparing the HR [44, 54] or (2) by comparing the ECG- derived R-R intervals (RRI) [55, 56] and the PPG-derived peak-to-peak intervals (PPI) [57] as shown in Figure 3. The goal of this paper was to explore which of the two validation approaches is more suited and to investigate and describe the necessary elements in validating and comparing HR apps versus standard technology.

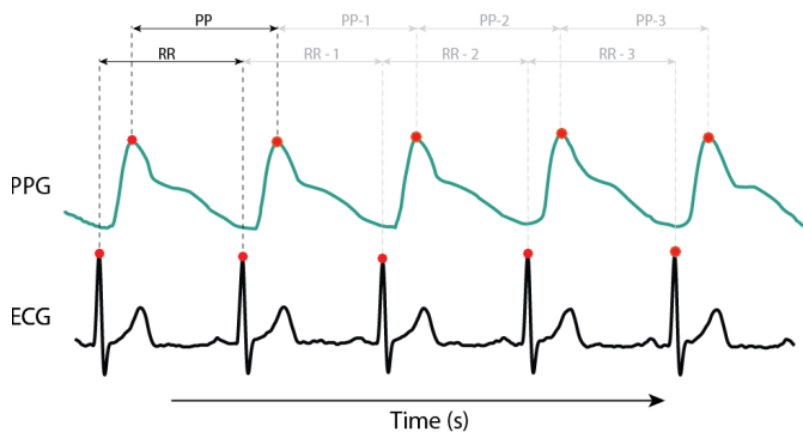


Figure 3: Beat-to-beat analysis from RR- and PP-intervals

METHODS

To investigate the correct method that should be used to clinically validate smartphone apps that measure HR, the smartphone app FibriCheck (Qompium, Hasselt, Belgium) was used as test case. For this purpose, two separate, independent, prospective nonrandomized studies were performed. In the first study, the HR as measured by FibriCheck was compared with the HR measured by 2 sequentially used Food and Drug Administration (FDA)-cleared HR-measuring devices. In the second study, the beat-to-beat (RRI/PPI) accuracy of the FibriCheck app was compared with a raw single-lead ECG that was recorded in a synchronized way. For this, a validated and wearable ECG recorder [58] (Imec Holst Centre,) was used. Both studies comply with the Declaration of Helsinki. The study protocol was approved by the local committee on human research, and all participants provided written informed consent.

Study 1: FibriCheck Compared With FDA-Approved HR Devices

Only 2 FDA-cleared HR measurement devices were used, that is, Nonin oximeter (Nonin Medical, Plymouth, USA) and AliveCor (AliveCor Inc., California, USA). These 2 devices, which employ different measurement methods, were used to validate a novel smartphone app that measured the participant's HR based on the PPG principle. Nonin uses the transmission PPG method as a stand-alone device, whereas AliveCor uses the ECG as a method measured with a smartphone. The participant's HR was measured 3 times with each measuring device according to the protocol of Terbizan et al [59]. Both FibriCheck and AliveCor were installed on an iPhone 5 (Apple Inc). Participants were recruited in the tertiary care center Ziekenhuis Oost-Limburg (ZOL, Genk, Belgium) in 2015. Inclusion criteria were 18 years or older and able to provide the Dutch written informed consent. Exclusion criteria were failure to obtain valid data with any device or failure to correctly follow the protocol.

A normalization period of 10 min before the first measurement was used to obtain a resting HR. For standardization, all measurements were performed in the same order, that is, FibriCheck app, Nonin oximeter, and AliveCor. The FibriCheck app measures the HR for 10 s by placing the index finger over the rear camera and LED while holding the smartphone in the other hand (Figure 4, left).

Nonin and AliveCor measurements were performed according to the manufacturers' guidelines.



Figure 4: Graphical representation of how measurements are performed using the different devices. Left, FibriCheck application; Middle, Nonin oximeter; Right, AliveCor.

Figure 5 represents a graphical overview of the step-by-step approach of measurement in study 1. In case of the FibriCheck app, the shown HR result value in beats per minute (BPM) was used, whereas for both the Nonin oximeter and AliveCor app, the minimum and maximum HR during a 10s measurement were averaged. Subsequently, all results of HRs measured by the different devices were statistically compared with each other.

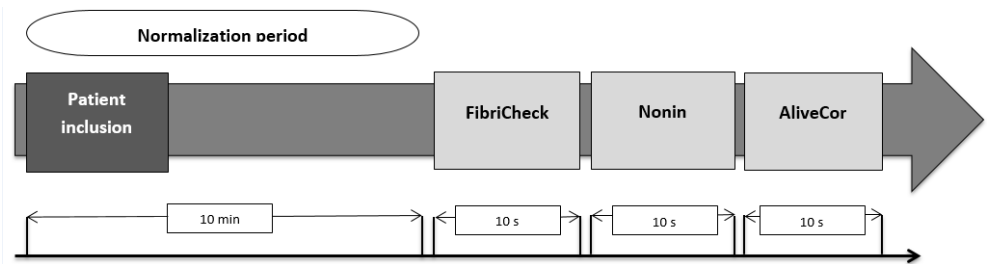


Figure 5: Graphical overview measurement-process study 1

The Shapiro-Wilk test was performed to test for normality. Different tests were performed to analyze the results. First, a Pearson correlation test of each possible pair of methods was performed to assess correlation. Second, the agreement between methods was assessed by the construction of Bland-Altman plots of the same pairs. Finally, a paired student t test and single-way analysis of variance (ANOVA) test were executed to see whether there was a significant difference between the HR as measured by the different methods. Statistical analysis and generation of Bland-Altman plots were performed by using R statistical software (version 3.2.2).

Study 2: FibriCheck Beat-to-Beat Accuracy Compared with Wearable ECG in Broad Dynamic Range

The beat-to-beat accuracy of the FibriCheck app was verified by comparing it with a wearable ECG patch. To do so, the FibriCheck smartphone app was used and installed on an iPhone 5S. This app also enables synchronization of the PPG signal, with a simultaneously measured ECG signal of a single-lead wearable ECG patch. This wearable device was attached to the upper left corner of the patient's chest with 2 disposable electrodes (Figure 6). This enables comparing the raw data of the 2 devices (i.e., FibriCheck and wearable ECG) and measurement principles (i.e., PPG and ECG). Inclusion criteria were 18 years or older and able to provide the Dutch written informed consent.

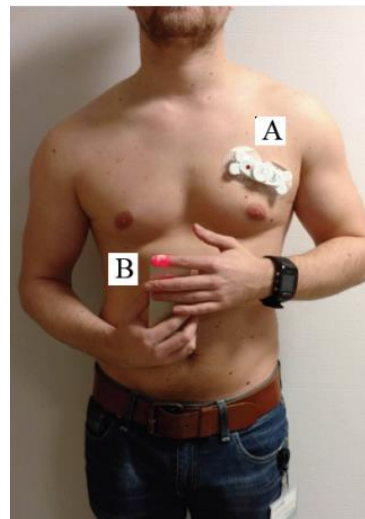


Figure 6: Measurement setup for simultaneous PPG and ECG recording. A wearable ECG sensor to measure one lead ECG data; B, FibriCheck application to measure PPG data.

Patients with an active pacemaker rhythm were excluded. Patients were either included by a general practitioner (GP) or by a researcher in ZOL between November 2015 and March 2016.

The GP enrolled male and female patients over the age of 65 years, with or without a history or diagnosis of atrial fibrillation (AF). The researcher included subjects who were diagnosed with AF by a 12-lead ECG system and healthy subjects who underwent a sports session. The study population is heterogeneous since it contains patients with a regular or irregular heart rhythm as well as low and high HRs.

Subjects, included by the GP, were measured in a sitting position and asked to perform three consecutive measurements of 60 s. AF patients, included by the researcher, were measured 3 to 6 times in a lying or sitting position. The sports session involved 5 min cycling at a high pace on a stationary exercise bike to reach a maximum HR. Two measurements before and after the exercise were done.

The FibrCheck app converts 60 Hz video data to raw signals, which were processed with Matlab (Math-Works) to derive the corresponding PPG signal. Time synchronization between ECG and PPG was automatically done by the FibrCheck app. Subsequently, peak detection of the ECG signal and the preconditioned PPG signal was performed by blinded and manual annotation of the identified peaks using Matlab. Finally, it was possible to extract the interpeak distance. An example of the automatic synchronization is shown in Figure 7.

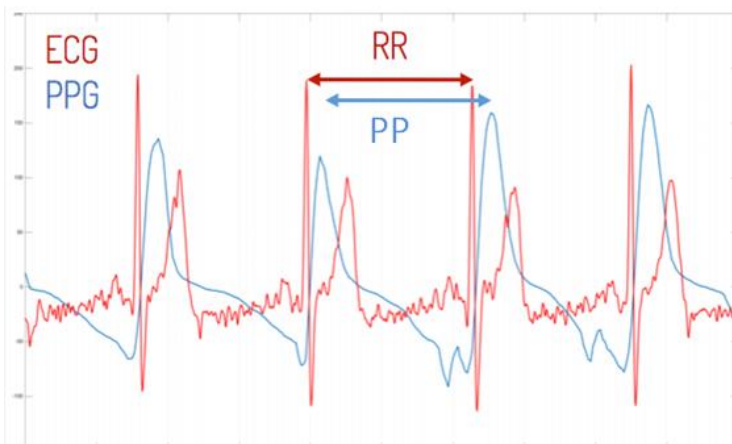


Figure 7: Synchronisation of ECG and PPG signal

The Kolmogorov-Smirnov test was performed to test for normality. The not normally distributed data are expressed as a median and interquartile range (IQR). A two-sided Wilcoxon signed-rank test was performed to compare two continuous variables for the not-normally distributed data. Correlation between the two continuous variables was calculated by a Spearman correlation test. All analyses were two-sided, and the level of significance was set at a value of .05. Root mean square error (RMSE) and normalized root mean square error (NRMSE) were performed to evaluate the range of errors between predicted and observed values. Data analyses were performed with R statistical software (version 3.2.2). Graphical presentations, such as correlations plots, Bland-Altman plot, and Kernel density plots, were made in RStudio version 0.99.486 (RStudio Inc).

RESULTS

Study 1: FibriCheck Compared With FDA-Approved HR Devices

In total, 91 persons were included in the study. A total of 3 persons were excluded from analysis because of failure to obtain valid data with 1 or more devices. This resulted in a final study population of 88 subjects. Table 1 shows the characteristics of these patients. Data are expressed as mean (standard deviation [SD]).

Table 1. Characteristics of patients in study 1.

Variable	Men (n=50)	Women (n=38)	All
Age in years, mean (SD)	49 (18)	45 (18)	47 (18)
Height, mean (SD)	177 (8)	166 (5)	172 (9)
Weight, mean (SD)	82 (14)	67 (7)	75 (14)

Table 2 gives an overview of the measured HRs. The average HR is 69 BPM for the Nonin, 71 BPM for the FibriCheck app, and 69 BPM for the AliveCor. Data are expressed as mean (SD).

The HR measurements as acquired by the three different methods were compared for assessing the ability of the FibriCheck app to correctly measure subjects’ HR. First, two-sided Pearson correlation tests were performed to evaluate the correlation between each possible pair of devices. Second, a paired student *t* test was performed. Thereafter, the RMSE and NRMSE were calculated (Table 3).

Table 2. Heart rates from Nonin, FibriCheck, and AliveCor.

Measuring device	Heart rate, mean (SD ^a)
Nonin, bpm ^b	69 (12)
FibriCheck, bpm	71 (13)
AliveCor, bpm	69 (12)

^aSD: standard deviation.

^bBPM: beats per minute.

Table 3. Correlation coefficients, statistical significance, root mean square error, and normalized root mean square error for each pair of devices.

Pair of devices	Correlation coefficient (<i>r</i>)	Statistical significance (two-tailed)	Root mean square error (beats per minute)	Normalized root mean square error (beats per minute)
FibriCheck–Nonin	.834	<i>P</i> =.36	7.40	0.11
FibriCheck–AliveCor	.88	<i>P</i> =.45	6.26	0.09
Nonin–AliveCor	.897	<i>P</i> =.87	5.46	0.08

Finally, an ANOVA test was performed to evaluate whether there was a significant difference between the results of the HR measurements of the different devices. The results indicate no significant difference (*P*=.61) between the HRs measured by the 3 different devices.

Results show high correlations without significant differences for all device pairs. However, since correlation does not necessarily imply agreement, Bland-Altman plots were constructed to evaluate agreement between each pair of devices (Figure 8).

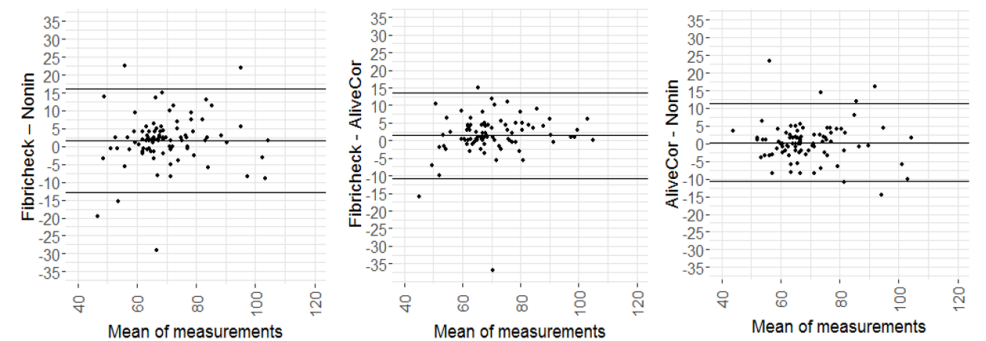


Figure 8: Bland-Altman plots for each device pair. The mean difference (bias), 1.96 (lower limit of agreement, LLA) and +1.96 standard deviations (upper limit of agreement, ULA) are plotted as full lines.

The mean bias ranged from 0.29 bpm (Nonin–AliveCor) to 1.42 bpm (FibriCheck–AliveCor) and 1.72 bpm (FibriCheck–Nonin). Some measurements were not situated between the lower limit of agreement (LLA) and the upper limit of agreement (ULA).

Study 2: FibriCheck Beat-to-Beat Accuracy Compared with Wearable ECG in Broad Dynamic Range

A total of 247 subjects were measured with the FibriCheck app in the presence of a GP (n=238) or a researcher in ZOL (n=19). The researcher included both healthy subjects (n=12) and patients who were diagnosed with AF by a 12-lead ECG system (n=7). Around 18 patients from the total study population, all included by the GP, had a pacemaker and were all excluded. Therefore, the final study population included 229 subjects. Table 4 shows the characteristics of these patients.

Table 4. Characteristics of patients in study 2.

Variable	Men (n=105)	Women (n=120)	All ^a
Age in years, mean (SD ^b)	74 (14)	76 (14)	75 (14)
Height in centimeters, mean (SD)	174 (8)	161 (7)	166 (14)
Weight in kilograms, mean (SD)	80 (14)	68 (14)	73 (15)
Diabetic, n (%)	20 (19)	24 (20)	44 (20)
Atrial fibrillation, n (%)	50 (48)	48 (40)	98 (44)
Systolic blood pressure in mm Hg, mean (SD)	129 (14)	131 (20)	130 (17) ^c
Diastolic blood pressure in mm Hg, mean (SD)	74 (8)	74 (11)	74 (10) ^c
CHA ₂ DS ₂ -VASc ^d score, mean (SD)	3.6 (1.8)	4.6 (1.9)	4.1 (1.9)

^aDemographics of 4 patients were reported as missing data.

^bSD: standard deviation.

^cSystolic and diastolic blood pressure were not included for patients who underwent the sport session.

^dCHA₂DS₂-VASc calculates the stroke risk for patients with atrial fibrillation.

Table 5 provides the study results. In total, 237 measurements (PPG-ECG pairs) were performed, which resulted in a 20,298 beat-to-beat analysis. An average interval of 758 (RRI) and 758 (PPI) was observed.

Table 5. Overview study results.

Variable	ECG ^a	PPG ^b
Number of Intervals	20,298	20,298
Average interval (ms)	758.4 (351.6)	758.2 (333.3)
Minimum value (ms)	312.5	316.7
Maximum value (ms)	2223.0	2233.0

^aECG: electrocardiography.

^bPPG: photoplethysmography.

The Wilcoxon signed-rank test showed no significant difference between ECG and PPG ($P=.92$). To calculate the correlation and difference between the ECG and PPG measurement, the Spearman rank-order correlation, RMSE, and NRMSE were calculated. A correlation of $rs=.993$ was found, with $RMSE=23.04$ ms and $NRMSE=0.012$ ms.

Additionally, a Bland-Altman plot was made, showing the differences between the beat-to-beat intervals of the PPG-ECG pairs in function of the means. The error distribution and the distribution of the mean duration of the intervals of the PPG-ECG pairs are visualized by kernel density plots (Figure 9). The mean bias is 0.26 (23.045) with a 95% CI from -45.82 to 46.35 . The CI ($\mu \pm 1.96\sigma$) is visualized by the horizontal lines.

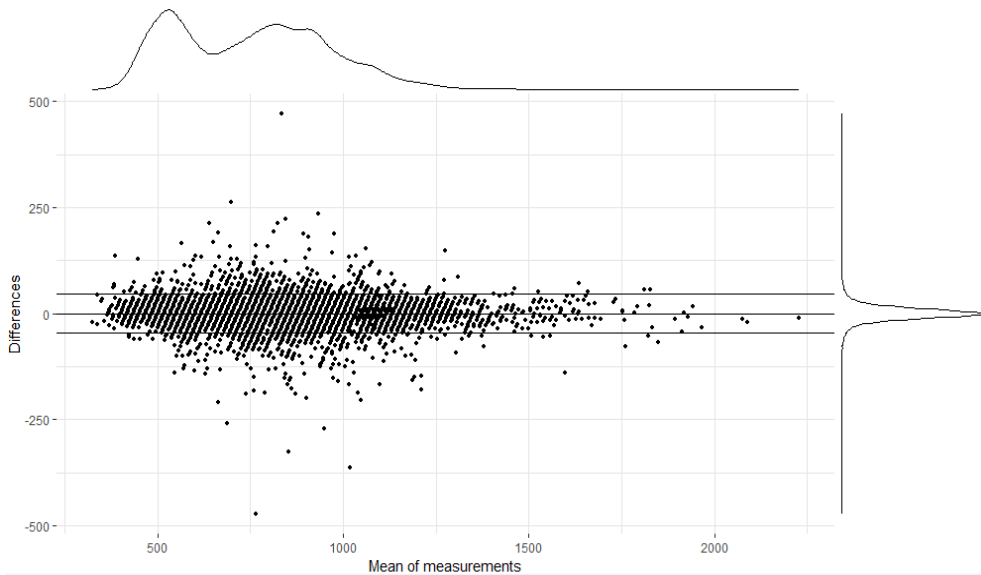


Figure 9: Bland-Altman plot comparing the reference RRI (ECG) to the PPI (PPG)

An in-depth analysis was performed to investigate differences within the study results. This detailed analysis was based on two categories: low versus high HR and regular versus irregular intervals.

On the basis of the definition by Laskowski of a resting HR [60] a distinction was made between a resting HR (40-100 BPM) and high HR (100-170 BPM). Figure 10 visualizes and Table 6 describes the study results for this distinction.

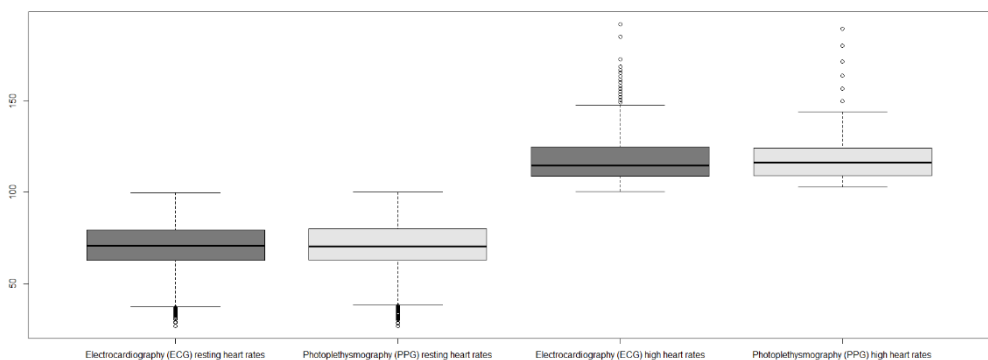


Figure 10: Overview heart rates divided in resting and high heart rates

Table 6. Summary of intervals divided in low, high, and overall heart rate.

Variable	Interval 40-100 heart rate		Interval 100-170 heart rate	
	ECG ^a	PPG ^b	ECG	PPG
Number of intervals	13,913	13,913	6385	6385
Average interval (ms)	869.5 (203.2)	868.9 (200)	516.4 (70.3)	516.9 (66.6)
Minimum value (ms)	601.6	483.3	312.5	316.7
Maximum value (ms)	2223.0	2223.0	597.7	1000

^aECG: electrocardiography.

^bPPG: photoplethysmography.

No significant difference was observed between both techniques within the interval 40-100 ($P=.76$) or interval 100-170 ($P=.69$). Correlation of interval 40-100 between ECG and PPG was strong ($rs=.985$; RMSE=25.32 ms and NRMSE=0.014). Interval 100-170 was also strongly correlated ($rs=.956$; RMSE=17.06 ms and NRMSE=0.025). The correlation between both techniques is plotted in Figure 11.

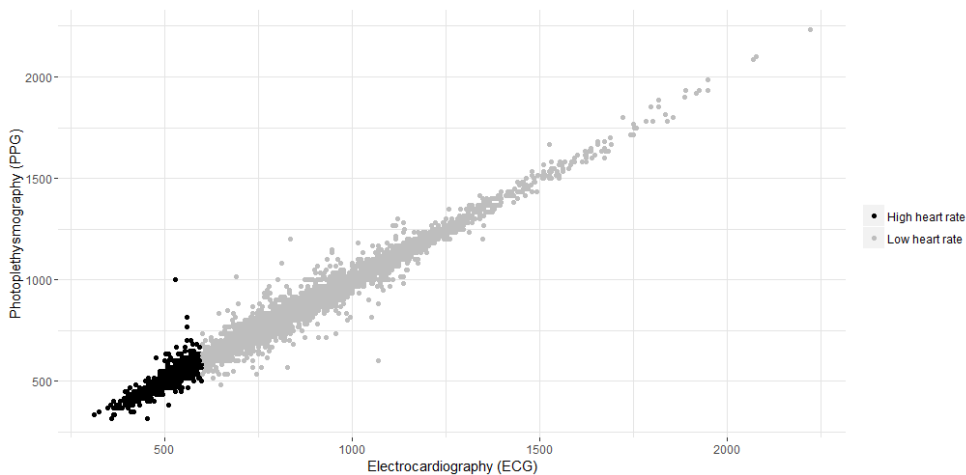


Figure 11: Correlation of intervals for both techniques (i.e. ECG and PPG) in ms. Grey, high heart rates; Black, low heart rates.

A last step in analysis was performed by investigating the differences between regular and irregular intervals. Figure 12 visualizes the measurements divided into irregular and regular intervals.

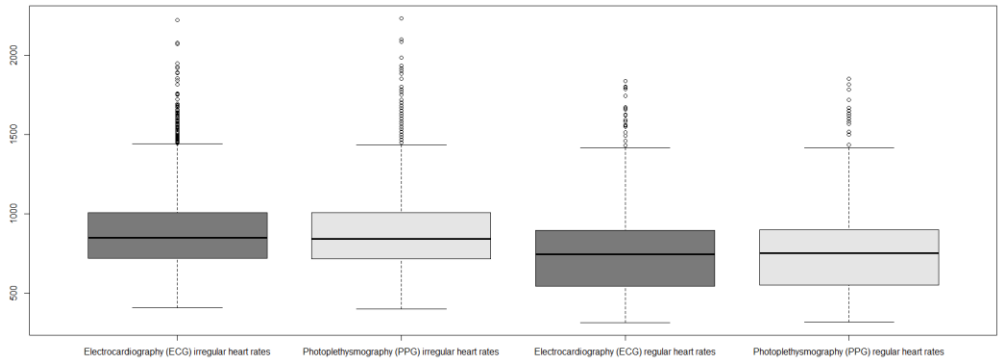


Figure 12: Overview of beat-to-beat intervals divided in irregular and regular beats

Table 7 describes the study results for this category. A total of 2648 intervals were obtained from patients with AF versus 17649 from patients with regular heart rhythms.

Table 7. Summary of intervals divided into regular and irregular beat-to-beats.

Variable	Regular		Irregular	
	ECG ^a	PPG ^b	ECG	PPG
Number of intervals	17,649	17,649	2648	2648
Average interval (ms)	738.9 (204.8)	738.6 (205.3)	888.5 (241.4)	888 (241)
Minimum value (ms)	312.5	316.6	406.3	400
Maximum value (ms)	1835.9	1850	2222.6	2233.3

^aECG: electrocardiography.

^bPPG: photoplethysmography.

No significant difference was observed between both techniques within group regular HR ($P=.9204$) or group AF ($P=.9252$). Correlation for group regular between ECG and PPG was strong ($rs=.994$; RMSE=20.49 ms and NRMSE=0.013). Group irregular was also strongly correlated ($rs=.9832$; RMSE=37.62 ms and NRMSE=0.021). The correlation between both techniques is plotted in Figure 13.

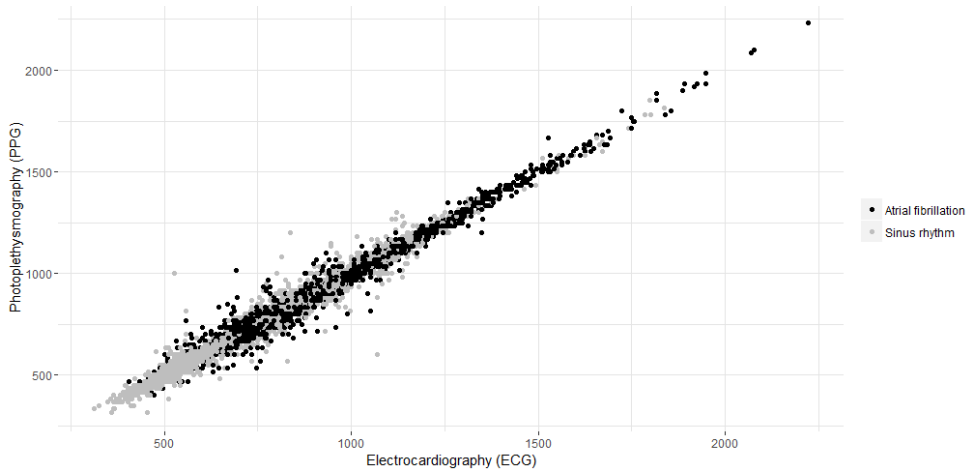


Figure 13: Correlation of intervals for both techniques (i.e. ECG and PPG) in ms. Grey, irregular intervals; Black, regular intervals.

DISCUSSION

Principal Findings

We sought to determine an approach to validate an HR-measuring app. For this experiment, we set up two different studies for determining the correct approach to answer the research question. The results were interpreted on the criterion validity (demonstrated by statistical test for a high correlation between new tool and the existing standard) and construct validity (refers to the systematic change in results when the input variable is under varying conditions) as described by Franko [61].

Study 1, FibriCheck compared with FDA approved HR devices, compared 3 tools for measuring HRs in a large sample of volunteers. The tools (Nonin and AliveCor) are approved by the FDA and are already used in clinical practice. The third one is the FibriCheck app. The results of the study, for criterion validity, show a correlation coefficient of .834 between FibriCheck and Nonin, .88 between FibriCheck and AliveCor, and .897 between Nonin and AliveCor. A single way ANOVA, $P=.61$ was executed to construct validity indicating that there is no significant difference between the HRs as measured by the 3 devices.

Study 2, FibriCheck beat-to-beat accuracy compared with wearable ECG, compared the RRI-PPI intervals at the same moment from the FibriCheck app in relation to the data of a wearable ECG. The results of the study show a positive correlation of .993 between RRIs and PPIs. This result supports the validity criteria. For construct validity, no significant difference ($P=.92$) was shown between the intervals from FibriCheck and the intervals from the wearable ECG.

Terbizan et al [59] suggested a minimum correlation of .9 for heart monitors to be clinically reliable. On the basis of the measured results in study 1, no pair of devices complies with this correlation. Terbizan et al suggest to interpret the device as “not reliable.” This is contradictory because both AliveCor and Nonin have an FDA approval. Bland-Altman plots showed some outliers between the devices. In this study, outliers need to be included in the dataset because of the legitimate character of the observation.

A “not reliable” correlation could have multiple causes. For example, there are device-related (eg, different hardware) causes that could influence the signal of the measurement. Furthermore, algorithms converting the PPG signal into HR measurements differ between manufacturers, including in the way they cope with nonperfect measurements. Therefore, when the captured PPG signal is incomplete, for example, because of vibrations or movement by the finger, resulting HR measurements can differ between HR apps and monitors, even when the raw data are identical.

These differing results can be assessed by running the algorithms on a reference database such as the MIT-BIH arrhythmia database for ECG records [62].

In addition, it is important to consider device specifications when evaluating an HR app on the smartphone. The app therefore needs to be validated on a smartphone with minimal device requirements. Smartphones with lower system specifications than required could result in “not reliable” results of the app. It is important for the manufacturer of that HR app to ensure the minimal hardware requirements of hardware. This creates the obligation for manufacturers to evaluate apps on multiple smartphones.

Besides possible hardware and algorithm explanations, there could be time-related causes (eg, measurement on different time) that could result in physiological changes causing a change in HR. This could be eliminated by doing synchronous measurements with these devices.

Another explanation could be that taking average of the minimum and maximum HR during a 10-s interval is not the optimal procedure to obtain a reading from these devices. The FibriCheck app gives a single result after a 10-s measurement, whereas the Nonin oximeter gives a continuous reading and the AliveCor a minimum and maximum HR result after 10 s. To address this mismatch, the average of the minimum and maximum HR of a 10-s reading was used in case of the Nonin oximeter and AliveCor.

Further research should be conducted to investigate whether there is a stronger correlation between Nonin and AliveCor than the current results suggest; some suggestions are given below. Related to the possible time- and analytics-related causes of this result, the next step in validation was performed. Experiment 2 for the beat-to-beat detection between the FibriCheck and an ECG device was set up.

Study 2 shows a positive correlation result of .993, an RMSE of 23.04 ms, and an NRMS of 0.012 for the intervals of the FibriCheck app and ECG device. This means that both methods are almost identical. This result suggests that the FibriCheck app could be used as a clinically validated app for measuring HR. The protocol of study 2 confirms the research question of an approach to validate an HR-measuring smartphone app.

Study Limitations

Although the results of this study are encouraging, there are a number of limitations to the study that could be taken into account for further research. First of all, the sample comprised both healthy and unhealthy volunteers who were recruited in a hospital setting and in general practice. However, this means that the sample may not be representative of the general population outside the hospital and general practice that could benefit from the smartphone app.

Measurements of the PPG signal could result in multiple limitations. For example, people with small or calloused fingertips may not be suitable for the detection of a PPG signal measured by the smartphone app. They will have inaccurate HR measurements because of problems with light absorption, on which the PPG principle is based. Additionally, patients with poor blood circulation can also show bad signals. Besides physical factors, environmental factors should also be taken into account. For example, ambient temperature has an influence on the blood circulation in the fingertips.

Study 1 coped with some specific limitations based on the study protocol. Due to the need to use both hands for the AliveCor and FibriCheck app, HRs from the 3 different devices were measured sequentially, leading to time intervals of about 30 s to 1 min between the different measurements. This could cause small changes in HR because of small physiological changes. Another limitation of nonsimultaneous HR measurement could be a learning effect for using a mobile HR app. This learning effect could result in a (small) decrease in HR.

There were a number of measurements that fell outside the LLA and ULA. These deviations could be caused by several factors compromising an optimal reading. For example, it could be possible that pressing too hard on the smartphone's camera impairs the possibility of a good PPG measurement. For the Nonin oximeter, an incorrect positioning of the device on the finger could hamper a correct reading. Further research could assess whether incorrect usage of these devices can cause deviant HR readings and how to optimally instruct people to avoid these errors.

Conclusions

Smartphones with multimedia capabilities open new possibilities for app development and service delivery [43]. In the last decades, smartphone apps that measure different vital parameters, such as HR, were developed. At this time, apps that measure the HR of a subject can be installed on a variety of smartphones [50]. However, the validity of these apps has not always been confirmed. This paper describes an approach for the clinical validation of an HR app. The current findings suggest that the most suitable method for the validation of an HR app is a simultaneous measurement of the HR by the smartphone app and an ECG system and comparing the obtained intervals. This approach could lead to almost exact accuracy in the clinical setting. Further studies are needed to evaluate the accuracy outside the hospital and in daily life of subjects.

CHAPTER 2

Diagnosing Atrial Fibrillation based on the qualitative
analysis of a smartphone derived PPG waveform

Vandenberk T, Pelckmans C, Mortelmans C, Van Haelst R, Proesmans
T, Storms V, Thijs I, Vaes B, Vandervoort P & Grieten L

*** Submitted at Journal of Atrial Fibrillation ***

ABSTRACT

Background: Atrial Fibrillation (AF) is the most common cardiac arrhythmia in clinical practice with a prevalence of 1-2% and is gaining interest as the arrhythmia is becoming more prevalent in our society. Difficulties in the detection of AF arise as the clinical presentation is often non-specific or asymptomatic, emphasizing the need to implement screening programs. Studies show that opportunistic screening is more likely to be cost-effective than systematic population screening. Therefore, international guidelines recommend opportunistic screening in every patient aged 65 years and older. To identify AF at an early stage with a minimum of costs, new innovative technologies based on either pulse irregularity or rhythm analysis of a PPG or ECG trace, are becoming available. The objective of this paper was to determine the diagnostic accuracy to identify AF based on the visual interpretation of a smartphone-derived PPG signal versus single-lead ECG and the gold standard 12-lead ECG.

Methods: Visualized traces of PPG, simultaneously recorded single-lead ECG and subsequently recorded 12-lead ECG measurements were selected for diagnosis by two independent cardiologists. Sensitivity, specificity, and positive and negative predictive values were calculated to determine the diagnostic accuracy of the PPG traces compared to the single-lead and 12-lead ECG traces.

Results: Both studies, PPG versus single lead ECG and PPG versus 12-lead ECG, showed similar results. When insufficient data measurements were classified as 'normal', McNemar's chi squared test showed a significant difference between the PPG versus single-lead ECG and PPG versus 12-lead ECG measurements. After eliminating inferior quality measurements (indicated by application or at least one cardiologist), further data-analysis was done. Accuracy increased to 97.1% for reviewer 1 and 94.6% for reviewer 2 in the PPG versus single-lead ECG study and to 98.6% for reviewer 1 and 96.1% for reviewer 2 in the PPG versus 12-lead ECG study. No significant differences were found between PPG interpretation and ECG interpretation.

Conclusion: Interpretation of a PPG signal showed a high diagnostic accuracy for detection of AF, although a significant difference was observed compared to both single-lead and 12-lead ECG interpretation. The sensitivity and specificity increased after data-analysis of solely high-quality measurements, and the difference in interpretation of PPG and single-lead/12-lead ECG became non-significant.

Keywords: Atrial Fibrillation; electrocardiography; photoplethysmography; smartphone; diagnostic accuracy; visual interpretation

INTRODUCTION

Atrial Fibrillation (AF) is the most common cardiac arrhythmia in clinical practice and is gaining interest as the arrhythmia is becoming more prevalent in our society. Worldwide, 33.5 million people are affected with AF [63]. One in four middle-aged Europeans will eventually develop AF during their lifetime. The prevalence of AF increases with age from 2% at 65 years to nearly 9% at older ages. The incidence of AF is also predicted to double over the next 20 years, with expectations of 120 000 to 215 000 new cases per year by 2030 in Europe alone [64]. The presence of AF can lead to serious complications. Both paroxysmal and permanent AF double mortality and triple the chance of developing congestive heart failure. Furthermore, AF is associated with a five-fold increased risk of stroke and thromboembolic events [65]. Over 20% of all cerebrovascular accidents (CVA) are directly related to AF. Although primary preventive therapy for AF patients is readily available, difficulties arise as the clinical presentation of AF is often non-specific or asymptomatic. Of all patients who suffer with 'silent AF', 30% has no symptoms. Indeed, in almost half of the patients with an AF-related stroke, the arrhythmia has been found to be asymptomatic, undiagnosed and therefore untreated [66]. Furthermore, studies on ischemic stroke demonstrate that AF is frequently only diagnosed during or after an event [67]. Current guidelines of the European Society of Cardiology (ESC) therefore recommend opportunistic screening in every patient aged 65 years and older by pulse palpation and, if irregular, 12-lead ECG [68]. The 12-lead ECG remains the gold standard in clinical practice to diagnose AF, however, because of its time-consuming nature it is not regularly performed in primary care settings [69]. Furthermore, as AF episodes can be brief and infrequent, the reliance on a single spot-check will most likely result in a missed diagnosis [70]. Since this screening methodology is bound to a physical location, only patients presenting at clinical office have the potential to be screened. Although systematic screening programs targeting the general population have the potential to increase the diagnostic yield [71], the cost of population screening based on 12-lead ECG cannot be underestimated. Studies show that opportunistic screening is more likely to be cost-effective than systematic population screening [72].

New promising tools, based on either pulse irregularity or rhythm analysis of an ECG trace, can change the cost-benefit equation in favour of a more systematic approach of screening for AF in the community [73].

New single-lead ECG technologies are developed: implantable loop recorders, blood pressure monitors, smartphone devices, handheld single-lead ECG recorders and ECG patches [74]. Handheld ECG recorders receive increasing interest for opportunistic screening, as they are easy to use, portable, cost-effective and often rely on immediate algorithm-based interpretation [74]. Multiple screening and performance studies used handheld (single-lead) ECG devices, like MyDiagnostic, Omron Heart Scan, AliveCor and Zenicor.

In-out hospital settings, such devices have shown high sensitivity and good specificity (90.0-99.1%) [75, 76]. The advantage of a smartphone based application like Kardiamobile (AliveCor Inc., California, USA), which records a single-lead ECG trace using a smartphone cover, is the widespread use of smartphones. Globally, there are about 3.1 billion smartphone subscriptions, and by 2020, this number is projected to reach 6.1 billion [42].

Also, a new generation of technology based on the optical sensing technique photoplethysmography (PPG) has been developed [77]. Smartphone-based PPG applications have the tremendous advantage that no additional hardware is required to analyse the heart rhythm. PPG is based on the principle that, when illuminated, blood absorbs more light than the surrounding tissue. In addition, variations in blood volume due to the cardiac cycle affect the absorption and reflectance of light. Interestingly, by placing the finger on the camera of a modern smartphone, a PPG waveform is acquired by capturing pulsatile changes in light intensity reflected from a finger illuminated by the smartphone flash (Figure 1).

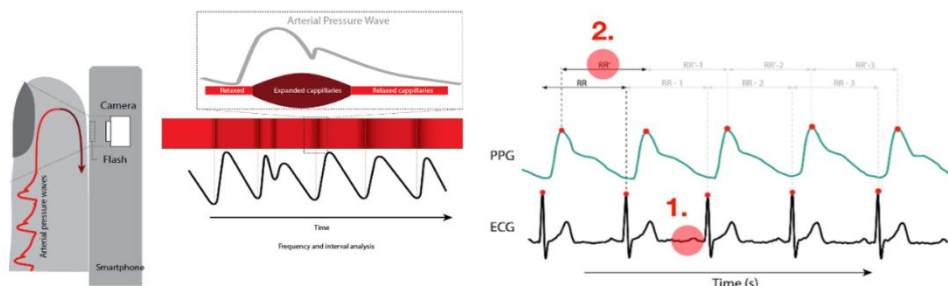


Figure 1: The principle of photoplethysmography (a) and the synergies and differences between ECG and PPG signals (b)

The intensity changes are correlated with the sequence of the cardiac cycle and enable the detection of the pulse rate and, more importantly, the pulse rhythm. The diagnosis of atrial fibrillation is made on two criteria according to the guidelines: 1) the absence of P-waves on an ECG trace and (2) an irregularity of the RR intervals. Since PPG is a volumetric measurement, it is only possible to monitor the ventricular activity that generates a cardiac output. The correlation of patterns between simultaneously recorded ECG and smartphone PPG signals was reported in a previous study [78]. Although the PPG signal provides a quantifiable metric towards cardiac rhythm assessment, no studies are available assessing the possibility to interpret a raw PPG waveform to diagnose AF. The potential to diagnose AF based on a visual interpretation of the PPG signal needs to be investigated as a first step towards the development of an algorithm for AF diagnosis. In this regard, the objective of this paper was to test the hypothesis that AF can be diagnosed by visual interpretation of a raw PPG waveform compared to the single-lead ECG and 12-lead ECG gold standard.

METHODS

Study design and study participants

This study was set up to investigate the diagnostic performance of the visual interpretation of a PPG waveform. The study complies with the Declaration of Helsinki and was approved by the ethical review board of the Medical Faculty of the KU Leuven, Belgium (no MP 05256) and the ethical board of Hospital East-Limburg (no 14/090U). All study subjects provided written informed consent before participation. Patients were either included by a general practitioner (GP), or by a researcher in the hospital (Ziekenhuis Oost-Limburg, Genk) between November 2015 and March 2016. In total, 134 patients over the age of 65 years, with or without a history or diagnosis of atrial fibrillation (AF), were included. Patients were asked to perform three consecutive measurements with a PPG recording smartphone application, while simultaneously recording a single-lead ECG trace. These measurements were subsequently followed by a 12-lead ECG. With the app, installed on an iPhone 5S, the heart rhythm was measured for 60 seconds by placing the index finger over the rear camera and LED while holding the smartphone in the other hand. A validated and wearable ECG recorder (Imec Holst Centre) was used for the single-lead ECG measurements [58].

Reference test

Next, a 12-lead ECG was recorded and immediately printed. The used (digital) ECG-devices were: CardiMax FCP-7101 (Fukuda Denshi, Tokyo, Japan), CP 50 (Welch Allyn, New York, USA), Universal ECG (QRS Diagnostic, Plymouth MN, USA) and ECG-1150 (Nihon Kohden Corporation, Tokyo, Japan). The ECGs were reviewed for the presence of AF (Minnesota code 8-3-1) by two independent cardiologists blinded for the PPG recordings. In case of inconsistent results, a third cardiologist revised the ECG to obtain a consensus.

Index test

After performing the PPG measurements, the 60 Hz video data measured by the app were converted to raw signals. These raw signals were processed with Matlab (The MathWorks, Inc., Massachusetts, USA) to derive the corresponding waveforms (Figure 2).

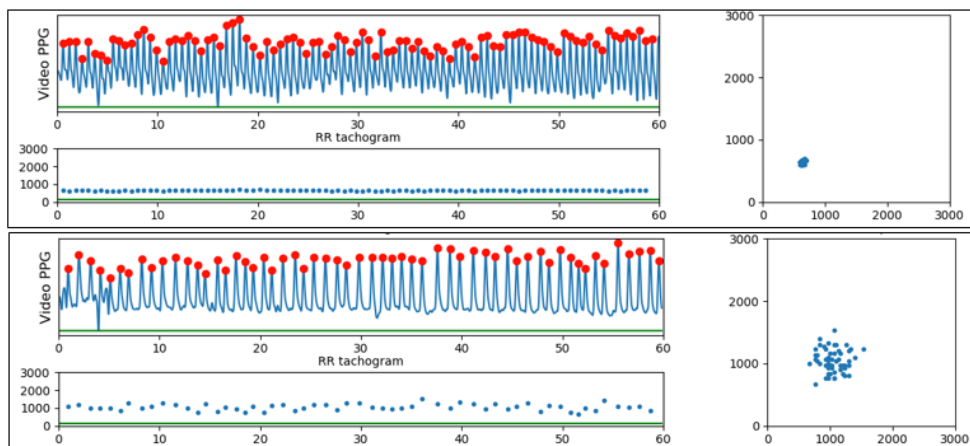


Figure 2: Graphical representation of visualised raw PPG waveform signals, RR-tachogram and Poincaré plot. (a) A normal sinus rhythm and (b) atrial fibrillation

RR-tachogram and poincaré plots were created for both the PPG and 1-lead ECG measurement to provide additional information. These plots show the distance between the detected peaks (RR interval) and the duration of each RR-interval (RR n) in function of its preceding RR-interval (RR $n-1$), respectively. All PPG and single-lead ECG traces were randomly presented for visual review to two independent cardiologists unfamiliar with PPG and blinded for the 12-lead ECG results.

To interpret the results, the analysis was done based on three review rounds. In the first review, all measurements were involved in the analysis, including measurements of insufficient signal quality. The application provided an insufficient signal quality indicator[79]. Recordings indicated as bad quality were excluded for the second review. In the last review, all measurement of inferior quality, indicated by at least one cardiologist, were excluded. In both first and second analysis, data analysis was performed with insufficient quality measurements as 'normal' and with insufficient quality measurements categorized as 'AF'.

Data analysis

Each PPG and ECG file was labelled as 'sinus rhythm', 'atrial fibrillation' or 'inferior quality'. The results based on visual revision of the PPG-traces were compared with the results of the corresponding single-lead and 12-lead ECG traces. In case of inconsistent single-lead diagnoses from the reviewers, the result of the 12-lead ECG measurements was taken as reference. Sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) were determined for each cardiologist to assess the accuracy of the index test. The McNemar test was performed to determine differences on a dichotomous dependent variable between the single-lead/12-lead ECG and PPG measurements. Cohen's kappa coefficients were calculated to determine the inter-observer agreement (precision). Cramér's V test was executed to calculate the association between two categorical (nominal) variables. All analyses were two-sided, and the level of significance was set at a value of .05. Data analyses were performed with R statistical software (version 3.2.2).

RESULTS

Study 1: PPG versus 12-lead ECG

In total, 133 patients who fulfilled the inclusion criteria participated in the study (Table 1). Overall mean age was 78 ± 8 years, 47% was male. AF was present in 69 patients (51.1%) with a mean CHA₂DS₂-VASc score of 4.5 ± 1.8 . Three patients (4.5%) had a pacemaker.

A total of 317 PPG-ECG pairs were recorded. Between the first and second analysis, a total of 17 pairs (5.4%) were removed, and an extra 21 pairs (7%) were removed between the second and third analysis. Overview of the number of PPG-ECG files per step in the analysis process can be found in supplementary tables.

Table 1. Characteristics of patients

Variable	Men (n=64)	Women (n=68)	All ^a
Age in years, mean (SD ^b)	77 (8)	80 (8)	79 (8)
Height in centimetres, mean (SD)	173 (8)	166 (21)	167 (17)
Weight in kilograms, mean (SD)	79 (13)	67 (16)	73 (16)
Diabetic, n (%)	12 (19)	19 (28)	31 (22)
Atrial fibrillation, n (%)	36 (56)	33 (49)	69 (51)
Systolic blood pressure in mm Hg, mean (SD)	130 (12)	135 (21)	133 (18)
Diastolic blood pressure in mm Hg, mean (SD)	75 (7)	74 (12)	74 (10)
CHA ₂ DS ₂ -VASc score ^c , mean (SD)	4.0 (1.7)	5.0 (1.7)	4.5 (1.8)
Pacemaker, n (%)	1 (2)	2 (3)	3 (4)

^aDemographics of 3 patients were reported as missing data.

^bSD: standard deviation.

^cCHA₂DS₂-VASc calculates the stroke risk for patients with atrial fibrillation

Analysis 1: all data included

A total of 317 PPG-ECG pairs were involved in the first analysis. Cardiologist 1 indicated 21 measurements as inferior quality. Of these, 6 were labelled by the 12-lead ECG results as sinus rhythm, and 15 as AF. Cardiologist 2 indicated 36 insufficient quality measurements, 10 were labelled as sinus rhythm, and 26 as AF. When categorizing these measurements as 'normal', a sensitivity of 88.3% (95% CI 82.5-92.7%) and a specificity of 95.6% (95% CI 92.2-98.9%) for reviewer 1 were found, compared to a sensitivity of 78.9% (95% CI 72.1-84.8%) and a specificity of 95.6% (95% CI 91.3-98.5%) for reviewer 2. The diagnosis of reviewer 1 resulted in an accuracy rate of 92.1% (95% CI 88.6%-94.8%), in comparison with an accuracy rate of 86.8% (95% CI 82.5%-90.3%) for reviewer 2.

Using the same approach, but classifying the insufficient quality measurements as 'AF', a sensitivity of 97.1% (95% CI 93.3-99.0%) for reviewer 1, and 94.2% (95% CI 89.5%-97.2%) for reviewer 2 were found. Diagnosis of review 1 resulted in a specificity rate of 93.8% (95% CI 89.2-96.9%), in comparison with 89.0% (95% CI 82.8%-93.6%) for reviewer 2. Reviewer 1 scored an accuracy rate of 95.4% (95% CI 92.6%-97.4%), compared to 91.8% (95% CI 88.2%-94.6%) for reviewer 2. The individual diagnostic accuracy of the PPG interpretation for both reviewer 1 and 2 can be found in supplementary tables.

Analysis 2: Exclusion of insufficient measurements indicated by the algorithm

After removing 17 measurements of insufficient quality, indicated by the algorithm, 300 ECG-PPG pairs remained in the analysis. When categorizing insufficient quality as 'normal' sensitivity increased to 93.8% (95% CI 88.9-97.0%) for reviewer 1 and to 83.9% (95% CI 77.2%-89.2%) for reviewer 2. Specificity for reviewer 1 raised to 97.1% (95% CI 92.8-99.2%), compared to 95.7% (95% CI 90.8%-98.4%) for reviewer 2. The accuracy rate for reviewer 1 was 95.3% (95% CI 92.3-97.4%), while reviewer 2 achieved an accuracy rate of 89.3% (95% CI 85.3-92.6%). By categorizing the insufficient quality measurements as 'AF', sensitivity of review 1 resulted in 96.9% (95% CI 92.9-99.0%), compared to 93.8% (95% CI 88.9-97.0%) for review 2.

Specificity rates were 96.4% (95% CI 91.8-98.8%) for reviewer 1 and 93.5% (95% CI 88.1-97.0%) for reviewer 2. The diagnosis of reviewer 1 resulted in an accuracy rate of 96.7% (95% CI 94.0-98.4%), while reviewer 2 achieved a result of 93.7% (95% CI 90.3-96.2%).

Analysis 3:

After deleting the insufficient measurements indicated by the algorithm, the reviewers indicated an additional 21 PPG measurements as insufficient quality. Together with the removed data in analysis 2, this resulted in 279 good quality measurements. Sensitivity and specificity for reviewer 1 increased to 97.2% (95% CI 93.0-99.3%) and 97.0% (95% CI 92.6-99.2%). Reviewer 2 achieved a similar raise in sensitivity 93.1% (95% CI 87.6-96.6%) and specificity 96.3% (95% CI 91.6-98.8%). Accuracy rates climbed to 97.1% (95% CI 94.4-98.8%) for reviewer 1, and 94.6% (95% CI 91.3%-96.7%) for reviewer 2.

Statistical analysis

McNemar's chi-squared showed a significant difference when categorizing insufficient quality as normal ($P = 0.005$) or as AF ($P < .001$) between the interpretation of the PPG and ECG signals after the first analysis. When insufficient quality data was categorized as normal, Cramers V test showed an association of 0.85 and 0.75 for reviewer 1 and 2, respectively. Insufficient quality categorized as AF resulted in an association of 0.9 for reviewer 1 and 0.84 for reviewer 2. A Cohen's kappa of 0.92 was observed between the two reviewers.

In the second analysis, no significant differences for reviewer 1 were observed. When insufficient data was categorized as normal, a significant difference ($P < .001$) was observed for reviewer 2 related to no significant difference when the data was categorized as 'AF'. Cramers V test for reviewer 1 showed an association of 0.91 compared to 0.79 for reviewer 2 when insufficient data was categorized as normal, and an association of 0.93 for reviewer 1 and 0.87 for reviewer 2 when insufficient data was categorized as 'AF'. Similar to analysis 1, a Cohen's kappa of 0.92 was observed between the two reviewers. In the third analysis, no significant differences between the PPG and ECG pairs were found for the reviewers. The Cramers V test showed an association of 0.94 for reviewer 1 and 0.89 for reviewer 2. A Cohen's kappa coefficient of 0.95 was observed between the two reviewers.

Study 2: PPG versus single-lead ECG

In total, 134 patients who fulfilled the inclusion criteria were included in the study. Table 2 shows the characteristics of these patients. Overall mean age was 78 ± 8 years, 47% was male. AF was present in 70 patients (51.9%) with a mean CHA₂DS₂-VASc score of 4.5 ± 1.8 . Ten patients (7.4%) had a pacemaker.

Table 2. Characteristics of patients

Variable	Men (n=64)	Women (n=68)	All ^a
Age in years, mean (SD ^b)	77 (8)	80 (8)	79 (8)
Height in centimetres, mean (SD)	173 (8)	161 (7)	167 (10)
Weight in kilograms, mean (SD)	79 (13)	67 (16)	73 (16)
Diabetic, n (%)	12 (19)	19 (28)	31 (24)
Atrial fibrillation, n (%)	36 (56)	34 (50)	70 (53)
Systolic blood pressure in mm Hg, mean (SD)	130 (12)	135 (22)	133 (18)
Diastolic blood pressure in mm Hg, mean (SD)	75 (7)	74 (13)	74 (10)
CHA ₂ DS ₂ -VASc score ^c , mean (SD)	4.0 (1.7)	4.9 (1.7)	4.5 (1.78)
Pacemaker, n (%)	5 (8)	5 (7)	10 (8)

^aDemographics of 3 patients were reported as missing data.

^bSD: standard deviation.

^cCHA₂DS₂-VASc calculates the stroke risk for patients with atrial fibrillation

A total of 322 paired measurements were selected for review. 176 corresponding single-lead ECG measurements were identified as AF and 146 as sinus rhythm. 11 (3 sinus and 8 AF) single-lead ECG measurements were inconsistent diagnosed between the two reviewers. Between the first and the second analysis a total of 21 pairs (6.52%) were removed. 26 pairs (8.64%) were removed between second and third analysis. Overview of the number of PPG-ECG files per step in the analysis process can be found in supplementary tables.

Analysis 1: all data included

Cardiologist 1 indicated 21 measurements as inferior quality. Of these, 6 were labelled by the 1-lead ECG results as sinus rhythm, and 15 as AF. Cardiologist 2 indicated 38 insufficient quality measurements, 11 were labelled as sinus rhythm, and 27 as AF. When categorizing these measurements as 'normal', a sensitivity of 89.0% (95% CI 83.4-93.3%) and a specificity of 99.3% (95% CI 96.2-99.9%) for reviewer 1 were found, compared to a sensitivity of 79.3% (95% CI 72.5-85.1%) and a specificity of 98.6% (95% CI 95.2-99.8%) for reviewer 2. The diagnosis of reviewer 1 resulted in an accuracy rate of 93.7% (95% CI 90.4%-96.1%), in comparison with an accuracy rate of 88.1% (95% CI 84.1%-91.5%) for reviewer 2.

Using the same approach, but classifying the insufficient quality measurements as 'AF', a sensitivity of 97.7% (95% CI 94.3-99.4%) for reviewer 1, and 94.8% (95% CI 90.4-97.6%) for reviewer 2 were found. Diagnosis of review 1 resulted in a specificity rate of 95.1% (95% CI 90.2-98.0%), in comparison with 91.1% (95% CI 85.3-95.2) for reviewer 2. Reviewer 1 scored an accuracy rate of 96.5% (95% CI 93.9-98.3), compared to 93.1% (95% CI 89.8-95.6) for reviewer 2. The individual diagnostic accuracy of the PPG interpretation for both reviewer 1 and 2 can be found in supplementary tables.

Analysis 2: Exclusion of insufficient measurements indicated by the algorithm

After removing 21 measurements of insufficient quality, indicated by the algorithm, 301 ECG-PPG pairs remained in the analysis. When categorizing insufficient quality as 'normal' sensitivity increased to 94.4% (95% CI 89.7-97.4) for reviewer 1 and to 84.5% (95% CI 77.9-89.7) for reviewer 2. Specificity for reviewer 1 raised to 100% (95% CI 97.3-100) compared to 98.6% (95% CI 94.9-99.8) for reviewer 2. The accuracy rate for reviewer 1 was 97.0% (95% CI 94.3-98.6), while reviewer 2 achieved an accuracy rate of 91.0% (95% CI 87.1-94.0). By categorizing the insufficient quality measurements as 'AF', sensitivity of review 1 resulted in 97.6% (95% CI 93.8-99.3), compared to 94.4% (95% CI 89.7-97.4) for review 2. Specificity rates were 98.5% (95% CI 94.8-99.8) for reviewer 1 and 95.7% (95% CI 90.8-98.4) for reviewer 2.

The diagnosis of reviewer 1 resulted in an accuracy rate of 98.0% (95% CI 95.7-99.3), while reviewer 2 achieved a result of 95.0% (95% CI 91.9-97.2).

Analysis 3: Exclusion of all insufficient measurements

After deleting the insufficient measurements indicated by the algorithm, the reviewers indicated an additional 26 PPG measurements as insufficient quality. Together with the removed data in analysis 2, this resulted in 275 good quality measurements. Sensitivity and specificity for reviewer 1 increased to 97.5% (95% CI 93.7-99.3) and 100% (95% CI 97.3-100). Reviewer 2 achieved a similar raise in sensitivity 93.8% (95% CI 88.5-97.1) and specificity 98.5% (95% CI 94.7-99.8). Accuracy rates climbed to 98.6% (95% CI 96.5-99.6) for reviewer 1, and 96.1% (95% CI 93.1-98.0) for reviewer 2.

Statistical analysis

McNemar's chi-squared showed a significant difference when categorizing insufficient quality as normal ($P < .001$) or as AF ($P < .001$) between the interpretation of the PPG and ECG signals after the first analysis. When insufficient quality data was categorized as normal, Cramers V test showed an association of 0.88 and 0.78 for reviewer 1 and 2, respectively. Insufficient quality categorized as AF resulted in an association of 0.93 for reviewer 1 and 0.86 for reviewer 2. A Cohen's kappa of 0.84 was observed between the two reviewers.

In the second analysis, significant differences for reviewer 1 ($P = 0.01$) and for reviewer 2 ($P < .001$) were observed when insufficient data was categorized as 'normal'. When insufficient data were categorized as 'AF', no significant differences for the two reviewers were found, Cramers V test for reviewer 1 showed an association of 0.94 compared to 0.83 for reviewer 2 when insufficient data was categorized as normal, and an association of 0.96 for reviewer 1 and 0.9 for reviewer 2 when insufficient data was categorized as 'AF'. Similar to analysis 1, a Cohen's kappa of 0.85 was observed between the two reviewers.

In the third analysis, no significant differences between the PPG and ECG pairs were found for the reviewers. The Cramers V test showed an association of 0.97 for reviewer 1 and 0.92 for reviewer 2. A Cohen's kappa coefficient of 0.95 was observed between the two reviewers.

Table 3: Diagnostic accuracy of PPG analysis 1 compared to the single-lead ECG and 12-lead ECG

	Sensitivity	Specificity	PPV	NPV	Positive likelihood ratio	Negative likelihood ratio	Accuracy
Insufficient quality categorized as 'normal'							
PPG Reviewer 1: 12-lead ECG	88.3% (CI: 82.5-92.7)	96.6% (CI 92.2-98.9)	96.8% (CI 92.7-98.6)	87.6% (CI 82.4-91.4)	25.8 (CI 10.9-61.1)	0.12 (CI 0.1-0.2)	92.1% (CI 88.6-94.8)
PPG Reviewer 2 12-lead ECG	79.0% (CI 72.1-84.8)	95.9% (CI 91.3-98.5)	95.7% (CI 91.1-98.0)	79.6% (CI 74.4-83.9)	19.2 (CI 8.7-42.2)	0.22 (CI 0.2-0.3)	86.8% (CI 82.5-90.3)
PPG Reviewer 1: 1-lead ECG	89.0% (CI 83.4-93.3)	99.3% (CI 96.2-99.9)	99.4% (CI 95.6-99.9)	88.2% (CI 83.0-92.0)	127.3 (CI 18.04-898.2)	0.11 (CI 0.1-0.2)	93.7% (CI 90.4-96.1)
PPG Reviewer 2: 1-lead ECG	79.3% (CI 72.5-85.1)	98.6% (CI 95.2-99.8)	98.6% (CI 94.6-99.6)	80.00% (CI 74.9-84.3)	57.9 (CI 14.6-229.8)	0.21 (CI 0.2-0.3)	88.1% (CI 84.1-91.5)
Insufficient quality categorized as 'AF'							
PPG Reviewer 1: 12-lead ECG	97.1% (CI 93.3-99.1)	93.8% (CI 89.2-96.9)	93.8% (CI 89.5-96.4)	97.1% (CI 93.3-98.8)	15.6 (CI 8.8-27.7)	0.03 (CI 0.0-0.1)	95.4% (CI 92.6-97.4)
PPG Reviewer 2 12-lead ECG	94.2% (CI 89.5-97.2)	89.0% (CI 82.8-93.6)	91.0% (CI 86.4-94.1)	92.7% (CI 87.6-96.0)	8.6 (CI 5.4-13.7)	0.07 (CI 0.0-0.1)	91.8% (CI 88.2-94.6)
PPG Reviewer 1: 1-lead ECG	97.7% (CI 94.3-99.4)	95.1% (CI 90.2-98.0)	96.1% (CI 92.2-98.1)	97.2% (CI 92.8-98.9)	20.0 (CI 9.7-41.1)	0.02 (CI 0.0-0.1)	96.5% (CI 93.9-98.3)
PPG Reviewer 2: 1-lead ECG	94.8% (CI 90.4-97.6)	91.1% (CI 85.3-95.2)	92.7% (CI 88.3-95.6)	93.7% (CI 88.6-96.6)	10.7 (CI 6.3-17.9)	0.06 (CI 0.0-0.1)	93.1% (CI 89.8-95.7)

Table 4: Diagnostic accuracy of PPG analysis 2 compared to the single-lead ECG and 12-lead ECG.

	Sensitivity	Specificity	PPV	NPV	Positive likelihood ratio	Negative likelihood ratio	Accuracy
Insufficient quality categorized as 'normal'							
PPG Reviewer 1: 12-lead ECG	93.8% (CI 88.9-97.0)	97.1% (CI 92.8-99.2)	97.4% (CI 93.4-99.0)	93.1% (CI 88.1-96.1)	32.6 (CI 12.4-85.7)	0.06 (CI 0.0-0.1)	95.3% (CI 92.3-97.4)
PPG Reviewer 2 12-lead ECG	83.9% (CI 77.3-89.2)	95.7% (CI 90.8-98.4)	95.7% (CI 91.1-98.0)	83.7% (CI 78.2-87.9)	19.4 (CI 8.9-42.6)	0.17 (CI 0.1-0.2)	89.3% (CI 85.3-92.6)
PPG Reviewer 1: 1-lead ECG	94.4% (CI 89.7-97.4)	100% (CI 97.3-100)	100%	93.8% (CI 88.9-96.6)		0.06 (CI 0.0-0.1)	97.0% (CI 94.3-98.6)
PPG Reviewer 2: 1-lead ECG	84.5% (CI 77.9-89.7)	98.6% (CI 94.9-99.8)	98.6% (CI 94.5-99.6)	84.5% (CI 79.1-88.6)	58.3 (CI 14.7-231.1)	0.16 (CI 0.1-0.2)	91.0% (CI 87.1-94.0)
Insufficient quality categorized as 'AF'							
PPG Reviewer 1: 12-lead ECG	96.9% (CI 92.9-99.0)	96.4% (CI 91.8-98.8)	96.9% (CI 93.0-98.7)	96.4% (CI 91.9-98.5)	26.9 (CI 11.4-63.7)	0.03 (CI 0.0-0.1)	96.7% (CI 94.0-98.4)
PPG Reviewer 2 12-lead ECG	93.8% (CI 88.9-97.0)	93.5% (CI 88.1-97.0)	94.4% (CI 89.9-96.9)	92.9% (CI 87.7-96.0)	14.5 (CI 7.7-27.3)	0.07 (CI 0.0-0.1)	93.7% (CI 90.3-96.1)
PPG Reviewer 1: 1-lead ECG	97.6% (CI 93.8-99.3)	98.5% (CI 94.8-99.8)	98.7% (CI 95.3-99.7)	97.1% (CI 92.7-99.0)	66.3 (CI 16.8-262.6)	0.02 (CI 0.0-0.1)	98.0% (CI 95.7-99.3)
PPG Reviewer 2: 1-lead ECG	94.4% (CI 89.7-97.4)	95.7% (CI 90.8-98.4)	96.2% (CI 92.1-98.2)	93.6% (CI 88.6-96.5)	21.7 (CI 9.9-47.5)	0.06 (CI 0.0-0.1)	95.0% (CI 91.9-97.2)

Table 5: Diagnostic accuracy of PPG analysis 3 compared to the single-lead ECG and 12-lead ECG.

	Sensitivity	Specificity	PPV	NPV	Positive likelihood ratio	Negative likelihood ratio	Accuracy
PPG Reviewer 1: 12-lead ECG	97.2% (CI 93.0-99.3)	97.0% (CI 92.6-99.2)	97.2% (CI 93.0-98.9)	97.0% (CI 92.6-98.9)	32.8 (CI 12.5-86.2)	0.03 (CI 0.0-0.1)	97.1% (CI 94.4-98.8)
PPG Reviewer 2 12-lead ECG	93.1% (CI 87.6-96.6)	96.3% (CI 91.6-98.8)	96.4% (CI 91.9-98.5)	92.9% (CI 87.7-96.0)	25.1 (CI 10.6-59.5)	0.07 (CI 0.0-0.1)	94.6% (CI 91.3-96.7)
PPG Reviewer 1: 1-lead ECG	97.5% (CI 93.7-99.3)	100% (CI 97.3-100)	100%	97.1% (CI 92.7-98.9)		0.03 (CI 0.0-0.1)	98.6% (CI 96.5-99.6)
PPG Reviewer 2: 1-lead ECG	93.8% (CI 88.5-97.1)	98.5% (CI 94.7-99.8)	98.6% (CI 94.50-99.6)	93.6% (CI 88.6-96.5)	62.8 (CI 15.9-284.8)	0.06 (CI 0.0-0.1)	96.1% (CI 93.1-98.0)

Table 6. Overview significance and association data study 1

	ANALYSIS 1				ANALYSIS 2				ANALYSIS 3	
	Insufficient quality categorized as 'normal'		Insufficient quality categorized as 'AF'		Insufficient quality categorized as 'normal'		Insufficient quality categorized as 'AF'			
	PPG review 1	PPG review 2	PPG review 1	PPG review 2	PPG review 1	PPG review 2	PPG review 1	PPG review 2	PPG review 1	PPG review 2
STUDY 1: PPG VERSUS 12-LEAD ECG										
MCNEMAR'S CHI-SQUARED	0.01*	0.00*	0.21	0.33	0.18	0.00*	1.00	1.00	1.00	0.30
CRAMERS V	0.85	0.75	0.90	0.84	0.91	0.80	0.93	0.87	0.94	0.89
STUDY 2: PPG VERSUS SINGLE-LEAD ECG										
MCNEMAR'S CHI-SQUARED	0.00*	0.00*	0.55	0.52	0.01*	0.00*	0.68	0.61	0.13	0.07
CRAMERS V	0.88	0.78	0.93	0.86	0.94	0.83	0.96	0.90	0.97	0.92

* = significant at $p < .05$

DISCUSSION

In this study, the possibility to diagnose AF based on the visual interpretation of a PPG waveform, captured with a smartphone camera, was evaluated. To determine the accuracy, a single-lead ECG and 12-lead ECG as gold standard were used. Previous work already demonstrated the possibility to differentiate between AF and sinus rhythm based on a PPG-deriving smartphone application using an algorithm [69]. The study was executed on a small cohort of patients, with one specific type of smartphone (iPhone 4S). To our knowledge, this is the first study that evaluated the raw smartphone-derived PPG signals compared to 12-lead ECG, without the use of digital algorithms.

Study 1: PPG versus 12-lead ECG

For this experiment, 317 samples of PPG versus 12-lead ECG measurements were compared. The results of this study indicate a very high accuracy for diagnosing AF based on a raw PPG waveform when good quality ECG and PPG traces were used. Sensitivity and specificity improved when PPG waveforms of inferior quality were excluded. The PPG-smartphone application gave an inferior quality indication for 17 measurements. The accuracy increased further when all inferior quality measurement, indicated by the reviewers and the algorithm, were removed. The algorithmic quality indicator was more selective in identifying bad quality measurements compared to the reviewers. This indicates that more advanced digital techniques (for example an algorithm) are less sensitive for the quality of a PPG trace for diagnosis, compared to the cardiologists.

The results of this study correspond with the reported accuracy of 96% sensitivity and 93% specificity reported for many ECG algorithms [80]. A PPV of 97.2% for reviewer 1 and 96.4% for reviewer 2, and a NPV of 97.04% for reviewer 1 and 92.86% for reviewer 2 corresponds with the reported 92.2% PPV and 92.0 % NPV for smartphone based AF detection with an algorithm [74].

The significance of the test was evaluated by the McNemar's chi-squared. In the first and second analysis of the data, a significant difference was observed between interpretation of the PPG and ECG measurements. After deleting the inferior quality waveforms, indicated by the reviewers, the difference became non-significant. This result again indicates the need of a quality filter when processing the data.

The inter-observer kappa coefficient rose from 0.92 in the first analysis to 0.95 in the third. For all three analyses, this result corresponds to the Kappa range 0.81-0.99 indicating an almost perfect agreement. This concludes that there was no significant difference between the evaluations of the two reviewers.

The last evaluation of the study was done by the Chi-Square Test of Independence by the Cramers V test, measuring the correlation between nominal variables. When insufficient quality was categorized as 'normal' a moderate value for both reviewer 1 as reviewer 2 were obtained. As stated above, the most insufficient data measurements were AF diagnosed. After deleting insufficient measurements, a strong correlation for both reviewers were achieved. These results confirm the need of a quality filter to achieve the highest correlation between PPG and 12-lead ECG.

Study 2: PPG versus single-lead ECG

For this experiment, 322 samples of PPG versus single-lead ECG data were compared. The results of this study are comparable to the results of the PPG versus 12-lead ECG study. Similar, sensitivity and specificity improved significantly when PPG waveforms of inferior quality were excluded. Identical, results of this study indicate very high accuracy for diagnosing AF based on a raw PPG waveform when good quality one-lead ECG and PPG traces were used. A PPV of 100% for reviewer 1 and 98.6% for reviewer 2, and a NPV of 97.1% for reviewer 1 and 93.6% for reviewer 2 corresponds with the reported sensitivity (94.0-100%) and specificity (90.0-99.1) out-hospital ECG devices like MyDiagnostic, Omron Heart scan and AliveCor [75, 76]. The significance of the results was evaluated by the McNemar's chi-squared. A significant difference was observed in analysis 1 when insufficient data was categorized as 'normal'. This indicates that a further analysis was needed to receive compatible results for PPG analysis.

After deleting the insufficient data, no significant differences were found. This strengthens the need for quality analysis on a PPG waveform. The inter-observer kappa coefficient and Cramer's V also improved remarkably between analysis 1 and 3.

The results of the two studies shows multiple similarities. Based on the sensitivity, specificity, PPV and NPV reported in the two studies, we observed that eliminating inferior quality measurements had the greatest positive impact on sensitivity and NPV. This was caused by the high percentage of AF measurements that were indicated as insufficient quality. In the first analysis of the PPG versus 12-lead study, 71.4% of insufficient quality measurements for reviewer 1 and 72.2% of insufficient quality measurements for reviewer 2 were labelled as AF. The insufficient quality % of AF measurement in the PPG versus single-lead study was 71.4% for reviewer 1 and 72.2% for reviewer 2 in the first analysis. In the second analysis, this percentage climbed to 83.3% for reviewer 1 and 84.2% for reviewer 2 in the first study compared to 71.43% for reviewer 1 and 80% for reviewer 2 in the second study. As both sensitivity and NPV are calculated by 'false negative' results in the denominator, we can conclude that inferior measurements have the most influence on false negative results. Based on these results, we conclude that a crucial step of reviewing a PPG waveform is the evaluation of the quality of the data. Quality filters can help to increase the accuracy of the PPG waveform review.

In contradiction to the obtained high Cohen's kappa, a remarkable difference in analysis 1 and 2 for sensitivity rates was observed between the 2 reviewers in both studies when insufficient data was categorized as 'normal'. In addition to more false positive diagnosis of reviewer 2 compared to reviewer 1, reviewer 2 also indicated more measurements as insufficient quality. Because limited education about diagnosing AF based on a PPG waveform was provided, it is possible that reviewer 2 needed more training in this topic.

Although the results of this study are encouraging, there are several limitations that should be considered for further research. First, the sample comprised both healthy and unhealthy volunteers who were recruited in a hospital setting and in general practice. However, this means that this sample may not be representative and extrapolation to other patient populations and to the general population is uncertain.

Second, the visualized traces of measurements were randomly selected and included. Next to sinus rhythm and AF, other types of arrhythmias, like (supra) ventricular ectopic beats and atrial flutter were involved. This could have hampered the diagnosis of AF or sinus rhythm. Third, a single-lead ECG measurement in comparison to a 12-lead ECG has the limitation that atrial activity, depicted by P-waves, is less prominent in Lead 1. Prior studies have shown that atrial flutter is difficult to diagnose on a single-lead ECG trace [75]. Fourth, measurements of the PPG signal can be prone to multiple limitations. For example, people with small or calloused fingertips may not be able to successfully perform a PPG measurement with the smartphone app. They will have inaccurate HR measurements because of problems with light absorption and reflection, on which the PPG principle is based. Additionally, patients with poor blood circulation are more likely to perform measurements of insufficient quality. Fifth, PPG signals are also more vulnerable to motion artefacts compared to ECG signals [81]. Last limitation of this study is the sequential way of performing the PPG and 12-lead ECG measurements. Due to the paroxysmal nature of AF, it could be possible that the status (regular or irregular) of the heart rhythm changed between two consecutive measurements.

One of the greatest advantages of a smartphone PPG application is that no additional hardware is required to record the heart rhythm, resulting in a low barrier to use. Together with the frequent use of smartphone devices, this offers the potential for the implementation of mass screening projects. The results of this study emphasize the need to develop dedicated algorithms for AF diagnosis based on a PPG signal for a broad range of smartphone types. Future research is needed to determine the diagnostic quality of such algorithms. A next step in validation of the PPG signal can be performed by organising a self-monitoring study to identify AF in a home setting.

Conclusion

New promising tools to detect AF are available. In contrast to other one-lead ECG screening tools, PPG-based smartphone applications have the tremendous advantage that no additional hardware is required to analyse the heart rhythm. The use of such an application for AF diagnosis resulted in a relatively high accuracy, although a significant difference was observed compared to single-lead and 12-lead ECG. Data-analysis of solely high-quality measurements resulted in increased sensitivity and specificity rates, and the results between PPG and single-lead/12-lead ECG became non-significant. This stresses the importance to focus on algorithms that improve the quality or detect impaired quality issues related to the signal. Although further research is required, this study demonstrates the potential to detect and diagnose AF in patients using a PPG based applications for AF detection.

SUPPLEMENTARY DATA

Overview of the number of PPG-ECG files per step in the analysis process

	Study 1: PPG versus 12-lead ECG			Study 2: PPG versus single-lead ECG		
	Sinus rhythm	Atrial Fibrillation	Total	Sinus rhythm	Atrial Fibrillation	Total
Analysis 1	146 (46.1%)	171 (53.9%)	317	146 (45.3%)	176 (54.7%)	322
Analysis 2	139 (46.3%)	161 (53.7%)	300	138 (45.9%)	163 (54.2%)	301
Analysis 3	135 (48.4%)	144 (51.6%)	279	131 (47.6%)	144 (52.4%)	275

Note: Analysis 1: all measurements. Analysis 2: exclusion of bad signal indicated by app. Analysis 3: exclusion of inferior quality indicated by one or both cardiologists

Diagnostic accuracy of the PPG interpretation by reviewer 1 in analysis 1.

Insufficient quality categorized as 'normal'

	PPG positive	PPG negative
12-lead ECG positive (n = 171)	151	20
12-lead ECG negative (n = 146)	5	141
1-lead ECG positive (n = 174)	154	19
1-lead ECG negative (n = 146)	1	142

Insufficient quality categorized as 'atrial fibrillation'

	PPG positive	PPG negative
12-lead ECG positive (n = 171)	166	5
12-lead ECG negative (n = 146)	11	135
1-lead ECG positive (n = 174)	171	4
1-lead ECG negative (n = 146)	7	136

PPG: photoplethysmography, ECG: electrocardiography

Diagnostic accuracy of the PPG interpretation by reviewer 2 in analysis 1.

Insufficient quality categorized as 'normal'		
	PPG positive	PPG negative
12-lead ECG positive (n = 171)	135	36
12-lead ECG negative (n = 146)	6	140
1-lead ECG positive (n = 174)	138	36
1-lead ECG negative (n = 146)	2	144
Insufficient quality categorized as 'atrial fibrillation'		
	PPG positive	PPG negative
12-lead ECG positive (n = 171)	161	10
12-lead ECG negative (n = 146)	16	130
1-lead ECG positive (n = 174)	165	9
1-lead ECG negative (n = 146)	13	133

PPG: photoplethysmography, ECG: electrocardiography

Diagnostic accuracy of the PPG interpretation by reviewer 1 in analysis 2.

Insufficient quality categorized as 'normal'		
	PPG positive	PPG negative
12-lead ECG positive (n = 161)	151	10
12-lead ECG negative (n = 139)	4	135
1-lead ECG positive (n = 161)	152	9
1-lead ECG negative (n = 136)	0	136
Insufficient quality categorized as 'atrial fibrillation'		
	PPG positive	PPG negative
12-lead ECG positive (n = 161)	156	5
12-lead ECG negative (n = 139)	5	134
1-lead ECG positive (n = 163)	159	4
1-lead ECG negative (n = 136)	2	134

PPG: photoplethysmography, ECG: electrocardiography

Diagnostic accuracy of the PPG interpretation by reviewer 2 in analysis 2.

Insufficient quality categorized as 'normal'		
	PPG positive	PPG negative
12-lead ECG positive (n = 161)	135	26
12-lead ECG negative (n = 139)	6	133
1-lead ECG positive (n = 161)	136	25
1-lead ECG negative (n = 138)	2	136
Insufficient quality categorized as 'atrial fibrillation'		
	PPG positive	PPG negative
12-lead ECG positive (n = 161)	151	10
12-lead ECG negative (n = 139)	9	130
1-lead ECG positive (n = 161)	152	9
12-lead ECG negative (n = 138)	6	132

PPG: photoplethysmography, ECG: electrocardiography

Diagnostic accuracy of the PPG interpretation by reviewer 1 in analysis 3.

	PPG positive	PPG negative
12-lead ECG positive (n = 144)	140	4
12-lead ECG negative (n = 135)	4	131
1-lead ECG positive (n = 158)	154	4
1-lead ECG negative (n = 134)	0	134

PPG: photoplethysmography, ECG: electrocardiography

Diagnostic accuracy of the PPG interpretation by reviewer 2 in analysis 3.

	PPG positive	PPG negative
12-lead ECG positive (n = 144)	134	10
12-lead ECG negative (n = 135)	5	130
1-lead ECG positive (n = 145)	136	9
1-lead ECG negative (n = 132)	0	132

PPG: photoplethysmography, ECG: electrocardiography

CHAPTER 3

Smartphone application for instant detection of recurring
atrial fibrillation: a randomized controlled trial

Vandenberk T*, Desteghe L*, D'Onofrio V, Kluts K, Proesmans T,
Smeets C, Lanssens D, De Canniere H, Storms V, Thijs I, Dendale P,
Heidbuchel H, Vandervoort P & Grieten L

* Equally contributed

*** In press at Acta Cardiologica ***

ABSTRACT

Background: Current usual care (UC) for patients admitted with atrial fibrillation focuses on symptom relief by reconvertng the irregular heart rhythm to sinus rhythm. This often occurs by means of a direct current cardioversion (DCC). A new electrocardiogram (ECG) recording is taken during a follow-up consultation within six weeks, since a recurrence ratio of up to 67% can be expected. By using a smartphone with a custom-made application (FibriCheck®), long-term monitoring becomes available which can create an increase in patient empowerment. The smartphone camera and flash can be used to detect and analyse the cardiac pulse rate and rhythm by measuring the PPG signal in the fingertip

Objective: Assessing the feasibility, added value, and effectiveness of the FibriCheck smartphone application for the follow-up and detection of AF after DCC.

Methods: In this RCT trial, patients who were successfully treated with a DCC were recruited between January 2016 and June 2016. Patients were randomized to a control group (UC) or remote monitoring group who had to measure their heart rhythm two times a day. All patients received a follow-up appointment after as part of their standard post-DCC care path during which a confirmative ECG was taken.

Results: 35 patients were included in the study, 15 (43%) in the TM-group and 20 (57%) in the UC-group. Six (40%) patients in the TM-group compared to 4 (40%) in the control group had a confirmed recurrence of AF during the study period. These were detected after an average of 6 ($\pm$ 2.7) days. All recurrences were confirmed by 12-lead ECG. 18% of the smartphone measurements indicated AF, and only 5% of the measurements had bad signal quality issues.

Conclusions: The use of a smartphone application in a post-AF treatment setting is feasible and enables faster detection of AF recurrence compared to usual care.

Keywords: mHealth; atrial fibrillation; mass screening

INTRODUCTION

Atrial Fibrillation (AF) is the most common heart rhythm disorder with a prevalence of 1 to 2% of the world population [82-86]. This number is expected to increase further during the following years due to population ageing and a rising number of conditions predisposing to AF [86, 87]. AF is associated with increased morbidity and mortality, mainly related to stroke and heart failure [88-90]. This, in turn, will lead to an increased hospitalization rate and imposes a significant economic burden on the healthcare system [91, 92]. Therefore, management of these patients is becoming more and more important.

Two out of three patients with AF experience AF-related symptoms, which impact their quality of life [93-95]. Besides the initiation of oral anticoagulation therapy when indicated to prevent thromboembolic events, current standard care for patients with AF focuses on relieving symptoms by reconvert the irregular heart rhythm to normal sinus rhythm [68]. Restoring and maintaining the heart rhythm can be performed in different ways: by means of medication, via a direct current cardioversion (DCC) or an ablation procedure [68].

During a DCC, patients are hospitalized for a couple of hours and an electrical shock is delivered transthoracic to reconvert AF to sinus rhythm. Usual care after a DCC includes a follow-up consultation visit with the cardiologist after about six weeks to record a new electrocardiogram (ECG) to evaluate the outcome. A recurrence rate of up to 67% is common in AF patients depending on the duration of the period, patients' profile, and medication use [96, 97].

Nevertheless, in an early stage of the disease, AF has a capricious character. As the arrhythmia may not always be present, the detection of AF is often difficult. Today, ambulatory visits are the standard manner to diagnose and follow-up a patient.

New remote monitoring tools to monitor heart rate and rhythm became available: implantable loop recorders, Holter monitors, single lead ECG patches, or handheld ECG cases that can be coupled to a smartphone [98-100]. However, these are often cumbersome, expensive and require additional hardware. Smartphone use is increasing worldwide, also in the elderly. This offers a great opportunity for remote follow-up of certain medical conditions, such as AF, in future healthcare [101]. Photoplethysmography (PPG) is a technique that has been digitalized and reused over the last years to measure vital parameters like heart rhythm.

By using a smartphone camera, the cardiac pulse rate and rhythm can be measured by capturing the PPG signal in the fingertip [102]. PPG can be measured using a smartphone without the need for additional add-ons. FibriCheck® (Qompium, Belgium) is a certified medical application that enables heart rhythm monitoring based on PPG, and that can accurately distinguish AF from sinus rhythm. The ability to diagnose AF or sinus rhythm based on an algorithm has already been evaluated in previous research [69, 103].

The correlation of patterns between simultaneously recorded ECG and FibriCheck PPG signals was also reported in a previous study [104]. Moreover, this smartphone application also allows for remote monitoring to facilitate AF detection and follow-up. FibriCheck is connected to an online platform allowing for real-time review of measurements. The aim of this study was to assess the feasibility, added value, and effectiveness of the FibriCheck smartphone application for the follow-up and detection of AF after a DCC.

METHODS

Study design and patient recruitment

A prospective, multicenter randomized controlled trial was performed to investigate the advantage of providing post-DCC patients with a smartphone application to detect AF. The study complies with the declaration of Helsinki. The study protocol was approved by the local ethical committee in each center and all participants provided written informed consent. Participants in whom AF was confirmed by a cardiologist, subsequently successfully treated with DCC and older than 18 years were recruited in the tertiary care centers Hospital East Limburg (ZOL, Genk Belgium) and Jessa Hospital (Hasselt, Belgium) between January 2016 and June 2016. Exclusion criteria were: physically not able to perform measurements with the FibriCheck app, pacemaker-dependent heart rhythm or perniois. Included study patients were block randomized by sealed envelopes to usual care or to a remote monitoring group.

Measurements and follow-up

All included patients, both in the UC group and in the TM group, received a follow-up appointment with their cardiologist about 6 weeks after their DCC as part of the standard care path. A confirmative ECG was taken during this visit. During the baseline visit, clinical and demographical variables were obtained from patients' medical records.

Included patients randomized to the remote monitoring group received an iPhone 5S (Apple Inc, USA) with FibriCheck installed. They also received adequate education from the study team on how to perform proper measurements with the application. Those patients were asked to measure their heart rhythm with the FibriCheck app twice a day (i.e. morning and evening), and additionally when AF related symptoms such as heart palpitations, shortness of breath and weakness were noticed. All recordings were automatically uploaded to an online dashboard for daily follow-up. Each recorded signal was transferred and visualized on an online platform in an unprocessed (raw data waveform) and processed way. This allowed the visual review of the measurement. A trained biomedical student reviewed the received measurements.

If AF was detected, an event report was made and the cardiologist was contacted to confirm the diagnosis and decide on follow-up needs (Figure 1).

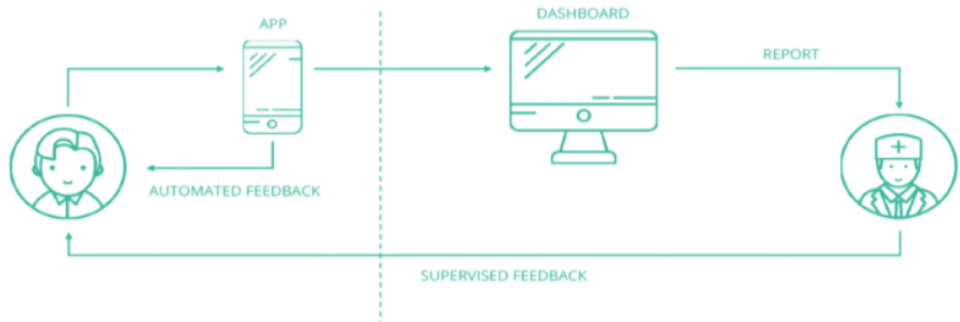


Figure 1: Loop system to evaluate the measurements with the FibrCheck smartphone application.

The primary endpoint of this study was the detection of AF-recurrence after DCC compared to UC. Secondary endpoints included: total heart rhythm measurements, compliance during the study period and signal quality of the measurements. Confirmation of AF and time until a follow-up appointment were documented for both the intervention and control group.

The FibrCheck application

The FibrCheck application was used in this study as a tool to measure heart rate and rhythm, based on the PPG signal. The FibrCheck app measures the heart rhythm for 60 seconds by placing the index finger over the rear camera and LED while holding the smartphone in the other hand (Figure 2).



Figure 2: Use of the FibrCheck application to measure heart rate. The smartphone is held steadily in the right hand, while placing the left index finger on the camera and LED light source.

Light from the smartphone's LED is sent into the fingertip and in this way, blood volume changes, caused by the vascular pulse wave propagating through the finger can be detected by the camera. More specifically, the reflected light correlates with the blood volume that makes a wave-like motion during each heartbeat. A PPG wave of a heartbeat consists of a systolic and a diastolic wave. The systolic wave of the PPG signal correlates with the R peak of the ECG. Therefore, the PPG peaks can be used to measure heart rate and variabilities in heart rhythm. Patients were asked not to move or talk during the measurements to improve signal quality. At the start of a measurement, the LED light is activated and, when a good signal is detected, the PPG-waveform is captured during 60 seconds. After the measurement, patients could indicate possible symptoms that they experienced during the measurement.

After processing the PPG-waveforms, the algorithms labelled each measurement as regular rhythm, irregular rhythm, possible irregular rhythm or insufficient quality. Furthermore, an RR-interval plot and a Poincaré plot were generated for each measurement (Figure 3).

These plots show the distance between the detected peaks (RR interval) and the duration of each RR-interval (RR_n) in function of it preceding RR-interval (RR_{n-1}), respectively. Dispersion in both plots indicates the possible presence of an arrhythmia.

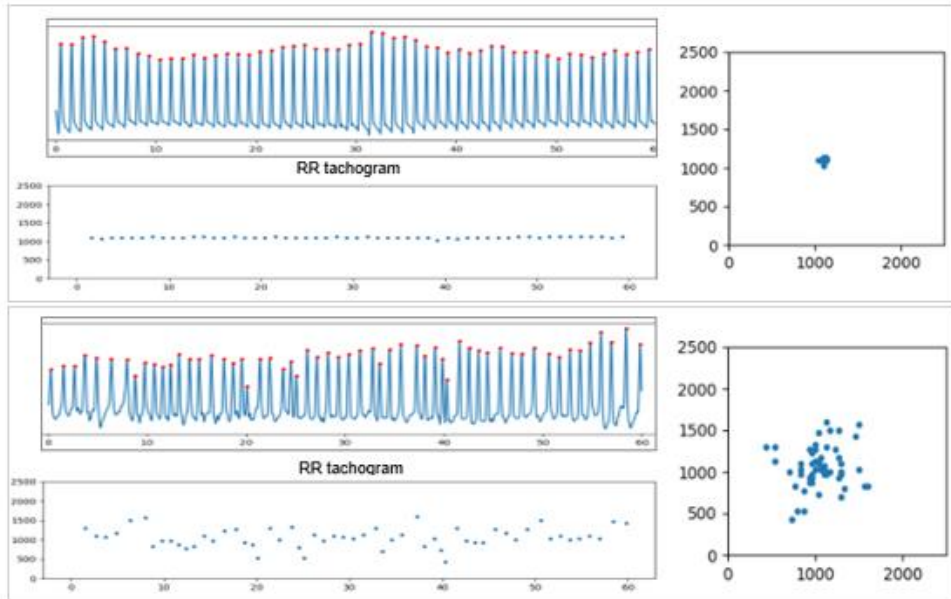


Figure 3: Graphical representation of visualised raw PPG waveform signals, RR-tachogram and Poincaré plot. (a) A normal sinus rhythm and (b) atrial fibrillation. PPG, photoplethysmogram.

Statistical methods

The Shapiro-Wilk test was performed to test for normality. Normally distributed data are expressed as average $\pm$ standard deviation (SD), while non-normally distributed data are displayed as a median and interquartile range (IQR). A student t-test (normal distribution) and Mann-Whitney U test (non-normal distribution) were performed to compare both groups. This analysis was two-sided and the level of significance was set at 0.05. Data analysis was performed with R statistical software Version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient demographics

A total of 35 patients were included in the study, 15 (43%) in the remote monitoring and 20 (57%) in the usual care control group. A local researcher in every hospital included patients in the interventional as well as the control group in a randomized manner. Baseline population characteristics are shown in Table 1.

Table 1. Baseline population characteristics.

Variable	Intervention group (n=15)	Control group (n=20)	All (n=35)	Statistical significance (2-tailed), P value
Age in years, mean (SD ^a)	64 (±7)	69 (±8)	67 (±8)	0.07
Height in centimetres, mean (SD)	171 (±12)	174 (±13)	173 (±13)	0.53
Weight in kilograms, mean (SD)	94 (±18)	86 (±17)	89 (±18)	0.18
CHA ₂ DS ₂ -VASc ^b score	2 (0-2)	2 (2-3)	2 (1-2)	0.045

^a SD: standard deviation.

^b The CHA₂DS₂-VASc score calculates the stroke risk for patients with atrial fibrillation.

Follow-up of the patients

In the remote monitoring group, six patients had a detected recurrence of AF in the time period between DCC and the planned follow-up visit at 6 weeks. On average, recurrence was detected 6.3 (± 2.7) days after DCC. The earliest recurrence was detected after two days, while the latest on day nine. All indicated recurrences by the smartphone application were confirmed by the 6-week ECG.

In the control group, 4 patients were diagnosed with AF based on the 12-lead ECG taken during the follow-up consultation. Detection and confirmation of AF in the control group patients occurred after 46.5 (± 11.2) days during their consultation visit. Based on the day of detection, a significant difference ($P < .001$) was observed between the remote monitoring group and the control group.

Initially, a follow-up appointment for the intervention group was planned 35.4 days (32.8 days for recurrence and 37.1 days for non-recurrence) after DCC compared to 35.7 days (46.5 days for recurrence and 32.9 days for non-recurrence) for the control group. However, actual follow-up visits for recurrence patients from the intervention group occurred after 28 (± 6.3) days, 4 days earlier than planned. During the follow-up consultation for the intervention group patients, all recurrences diagnosed by the 6-week ECG were already indicated by the FibriCheck smartphone application. Patients in the intervention group without recurrent AF had a consultation after 37.1 days. Figure 4 gives a graphical overview of the detection and appoint day for all study patients.

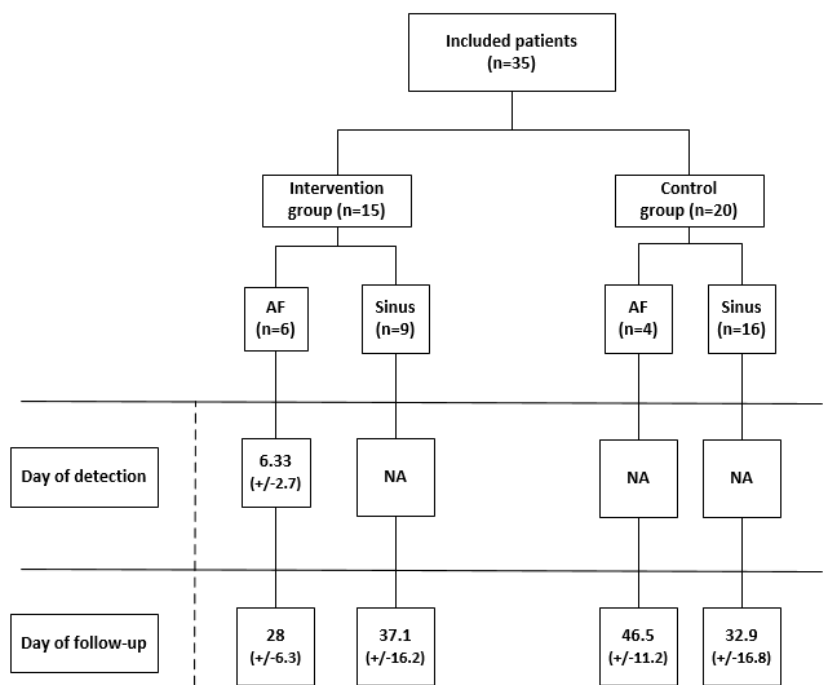


Figure 4: study overview day of detection and AF follow-up appointment

Remote monitoring characteristics

A total of 15 patients were remotely monitored by taking twice-daily measurements of their heart rhythm between the DCC and the follow-up appointment. In total, 898 measurements were received during the study period, with an average of 60 measurements per patient. On average, patients measured their heart rhythm between one or two times per day (1.9 ± 0.4). In total, 52 measurements were missing based on the requested twice-daily frequency. This led to a compliance rate of 94.5%. During 31.6 days of follow-up, 166 (18.5%) heart rhythms suspicious of AF, 651 (72.5%) sinus rhythms, 40 (4.5%) irregular rhythms, and 41 (4.6%) insufficient quality measurements were collected.

DISCUSSION

This study showed that patients who underwent a DCC and who were provided with a smartphone application to detect AF results in a faster detection of AF recurrence compared to usual care.

On average, detection of recurrence took place at day 6 after DCC in the intervention group, with the earliest detection already after 2 days. In the control group, the detection of AF occurred after 46 days. This means that by using the smartphone application, recurrence of AF can be detected 7 times faster compared to current standard practice. In current practice, patients do not have information about asymptomatic paroxysmal AF episodes since patients only get a single spot-check during their in-hospital follow-up visit.

Atrial fibrillation is a progressive disorder and over time many patients will develop more sustained forms of the arrhythmia. Early detection of the arrhythmia is required to set up the correct treatment plan in order to decrease morbidity and mortality rates. Moreover, early detection and management of AF can also improve the response to rhythm control therapy, keeping the patient longer in the normal sinus rhythm [105]. Prior similar research in the field of screening tools to monitor AF-recurrence post cardioversion remains sparse up until today. Fetsch T, et al. investigated the efficacy and safety of two anti-arrhythmic drugs in preventing the recurrence of AF after DCC. 1882 patients (mean age: 63 ± 9 years, 66% male) were provided with an event recorder (Tele-ECG) and had to record and transmit via telephone at least one ECG per day during follow-up. A total of 191,103 Tele-ECG's were recorded and transmitted during 266 days. 95% of all AF recurrences were detected in the daily Tele-ECG [106]. The study of Weijis et al. included 50 patients (mean age 68 ± 9 years, 68% male) who were successfully cardioverted for persistent AF. Heart rhythm was monitored during 4 weeks using the MyDiagnostick. On the second day after cardioversion, there were 3 patients with a recurrence of persistent AF. 15 other patients were followed over the next 6 days; and 3 more patients having an AF recurrence during week 2 and 3 [107].

Due to the faster detection of AF-recurrence in the intervention group, the day of follow-up dropped to 28 days for the recurrence AF-patients in the intervention group.

On average, patients with recurrence received a follow-up appointment 4 days earlier than initially planned. Since the recurrence was discovered on average at day 6, improvements could be made to shorten the time between the detection of AF and the follow-up appointment. Due to the variable character in AF recurrences, the management of arranging an instant follow-up appointment was not always possible. Moreover, most patients were treated with oral anticoagulation therapy decreasing the risk for stroke, which could be another explanation for why scheduling an immediate follow-up appointment was not always required.

At this point in time, a follow-up visit about 6 weeks after a DCC for each patient is still standard care. However, by making use of a smartphone application for monitoring heart rhythm, standard care could evolve to a more personalized follow-up schedule allowing patients with an early recurrence to receive an early consultation. The follow-up appointment of patients without a recurrence could even be cancelled or postponed. This would relieve the economic burden of AF on the current healthcare system. Using the FibriCheck application can also reassure patients knowing that their heart rhythm will be remotely followed-up at the hospital. If a heart arrhythmia is detected, physicians will be able to intervene fast, when needed.

A high compliance rate of 94.5% was achieved, resulting in 898 measurements. This high compliance rate reflects the ease of use of the smartphone application since the study was performed in a technophobic user group. Only 5% of the measurements indicates a bad signal quality, which is low since PPG signals are more vulnerable to motion artefacts compared to ECG signals [81].

Study limitations

Although the results of this study are encouraging, there are several limitations to the study that should be considered for further research. First, a rather small sample of patients was recruited in a hospital setting. This means that this sample may not be representative and that extrapolation to other patient populations and to the general population is uncertain.

Second, using the application still provides short snapshots of the heart rhythm of only one minute each time.

Third, most of the warning measurements were caused by other types of arrhythmias, like (supra)ventricular ectopic beats and atrial flutter. These other types of heart arrhythmias are confusing for diagnosing AF or sinus rhythm, however the possibility to detect other arrhythmias could be interesting for the cardiologist. Further algorithm development is needed to lower the 4.57% insufficient quality measurements. Fourth, no data about symptomatic or asymptomatic AF-episodes were taken into account. As current care focuses on relieving AF symptoms, this data can be useful in the daily practice of AF management.

Finally, measurements of the PPG signal can be prone to multiple limitations. For example, people with small or calloused fingertips may not be able to successfully perform a PPG measurement with the smartphone application. They will have inaccurate heart rhythm measurements because of problems with light absorption and reflection, on which the PPG principle is based. Additionally, patients with a poor blood circulation are more likely to perform measurements of insufficient quality. However, this limitation had a small effect on the study based on the 5% bad quality measurements.

Future directions

The current study proved the added value of the FibriCheck smartphone application in terms of detecting the recurrence of AF in a post-DCC setting. Future research should focus on determining the accuracy and added value in other populations and settings like patients who underwent catheter ablation or elderly.

A smartphone application can also be used as a systematic screening tool for AF in patients with an expected high prevalence of AF (e.g. after cryptogenic stroke, elderly with different cardiovascular comorbidities). The algorithm of the FibriCheck application could be applied in a smartwatch allowing for semi-continuous heart rhythm measurements. Furthermore, it would be interesting to study the cost-effectiveness of implementing these new tools into daily practice. One should keep in mind that a 12-lead ECG measurement remains the gold standard for the diagnosis of AF [68, 98].

Conclusions

The use of the FibriCheck smartphone application in a post-AF intervention setting is feasible and enables faster detection of AF recurrence. The usability of the application was good, which is reflected by a high patient compliance. The FibriCheck smartphone application is therefore a useful tool to monitor and manage patients treated for AF after DCC.

PART II – MONITORING:

DEVELOPMENT OF A VENDOR-INDEPENDENT MOBILE HEALTH
RESEARCH PLATFORM TO FACILITATE CLINICAL
MHEALTH RESEARCH

CHAPTER 4

Vendor-independent mobile health monitoring platform:
A research platform for digital health studies

Vandenberk T, Storms V, Lanssens D, De Canniere H, Smeets C,
Thijs I, Batool T, Vanrompay Y, Vandervoort P & Grieten L

*** In press at JMIR***

ABSTRACT

Background: Medical smartphone applications and mobile health devices are rapidly entering mainstream use owing to the rising number of smartphone users. Consequently, a large amount of consumer-generated data is being collected. Based on technological advances in innovative sensory systems, data connectivity and aggregation have become cornerstones in developing workable solutions for remote-monitoring systems in clinical practice. However, few systems are currently available to handle such data, especially for clinical use.

Objective: The aim of this project was to develop and implement the Digital Health Research Platform for Mobile Health (DHARMA), which combines data saved in different formats from a variety of sources into a single integrated digital platform suitable for mobile remote-monitoring projects.

Methods: DHARMA comprises a smartphone application, a web-based platform, and custom middleware, and has been developed to collect, store, process and visualize data from different vendor-specific sensors. The middleware is a component-based system with independent building blocks for user authentication, study and patient administration, data handling, questionnaire management, patient files, and reporting.

Results: A prototype version of the research platform has been tested and deployed in multiple clinical studies. In this paper, we used the platform for the follow-up of pregnant women at risk of developing pre-eclampsia. The patients' blood pressure, weight, and activity were semi-automatically captured at home using different devices. DHARMA automatically collected and stored data from each source, and enabled data processing for the end users in terms of study-specific parameters, thresholds, and visualization.

Conclusions: The increasing use of mobile health applications and connected medical devices is leading to a large amount of data for collection. There has been limited investment into handling and aggregating data from different sources for use in academic and clinical research focusing on remote monitoring projects.

In this project, we created a modular mobile health research platform to collect and integrate data from a variety of third-party devices in several patient populations. The functionality of the platform was demonstrated in a real-life setting among women with high-risk pregnancies.

Keywords: research platform, remote monitoring, mobile health, mobile health devices

INTRODUCTION

The increasing penetration of smartphones into consumer markets, as well as the growth in connected devices for healthcare, sport and wellness is leading to a dramatic increase in consumer-generated data [30]. Smartphones are becoming increasingly integrated into the global population. The number of smartphone users increased by nearly one billion people between 2014 (1.57 billion) and 2017 (2.32 billion), with an expected further increase to 2.87 billion users by 2020 [108]. There are currently more than 259,000 health-related smartphone applications (apps) available in online app stores; most of these apps were developed for Android and/or iOS [21]. The same technologies and concepts can also be applied to support healthcare. Remote monitoring of patients' vital signs and behaviors in their home environment could play an essential role in achieving a sustainable and high-quality healthcare system [109, 110] and reduce healthcare costs [8, 21, 110] by offering near-continuous patient follow-up, better data management strategies, and better treatment adherence. Some examples of chronic diseases that could benefit from this type of platform include diabetes, heart failure, and cardiac arrhythmias [111-113]. The information obtained by remote monitoring provides an additional dimension to that possible with standard clinical care, which is undertaken mainly by spot-checks in the clinic. Continuous real-time patient tracking and processing of various parameters will influence the way healthcare practitioners deal with prevention, diagnostics, and disease management.

It is already possible to connect mobile health apps to a wide range of portable devices or sensors [18], such as those used to measure physiological parameters (e.g., blood pressure, blood glucose, weight, and activity) [114]. An electrocardiogram (ECG) can be recorded via an app connected to a wearable ECG device [115]. In addition to the advantages for patients, doctors will also benefit from mobile health tools. Mobile apps can be used as an interface between the patient and clinician via a communication channel [18, 19], which could act as a substitute for some ambulatory visits [116]. Because they enable patients to be monitored in their home environment, mobile health tools could prevent some hospitalizations or shorten the hospital stay [8, 21], and have positive effects on medical outcomes, healthcare expenditure [8] and quality of life.

These benefits would be due partly because the patient stays in their familiar environment, and partly because continuous monitoring gives the opportunity for immediate intervention if needed [18].

Remote monitoring patients at home requires a data communication system between the patient and the healthcare professional. Typically, the patient is equipped at home with a set of sensors that measure vital signs as well as a smartphone app that collects data on such as behavior, symptoms, and location. These data are collected on a cloud-based server that is accessed by the healthcare professional. Options for decision support and that provide semi-automatic feedback to patients are necessary to manage large patient populations.

Despite the significant technological advances in developing novel sensory systems and state-of-the-art devices, there has been limited investment in developing the infrastructure that is required to connect and handle the amount of information that these devices generate. In particular, there are limited tools available to handle this health information in terms of clinical applications [31]. With the rapid increase in novel tools and technologies, data connectivity and aggregation have become cornerstones in developing workable solutions to manage patients in clinical practice and to support scientific research into the provision of digital-based health [32]. However, the commercial remote-monitoring technology market is highly fragmented because each vendor has developed their own data platform for recording data from their associated sensors and to communicate these using stand-alone software solutions or web apps. Accordingly, it is impossible to aggregate data obtained from the sensors developed by different vendors. Clinical practice and academic research that rely on remote monitoring are limited by these closed, manufacturer-owned platforms. Therefore, a generic and open digital research platform for remote monitoring is needed to allow academic and clinical research into remote monitoring. The platform is required to overcome the problems of third-party device integration and the collection of various data feeds from patient populations.

In this paper, we discuss the development of a generic and open digital research platform for remote monitoring that can be used to perform academic and clinical research into remote monitoring. This digital platform overcomes the problems of third-party device integration and the collection of various data feeds from patient populations. The collected data can be analyzed using the platform and presented visually to the caregiver. We demonstrate the functionality of the platform in a real-life setting, among women with high-risk pregnancies.

METHODS

The concept and design of our modular DHARMA platform were focused primarily on clinical usability. Accordingly, healthcare professionals (doctors and nurses) participated in each stage of its conceptualization and development, from design and prototyping through to implementation and user trials. The app consists of a web-based user interface and a JAVA-hypertext preprocessor (PHP) backend. The platform is set up on a cloud server. The front- and back-ends are coded in various languages. The front-end is built in PHP with a combination of bootstrap and Laravel frameworks. The back-end is built on a combination of PHP and object-oriented programming language (JAVA) to ensure cross-platform compatibility. The server runs on Windows, Apache, MySQL, and PHP (WAMP) platforms. Due to the highly valuable content of the database system, the database is backed up daily and archived.

Technical architecture and data security

The platform was built as plug-able component-based middleware. As mentioned by Piwek et al. [117], data security and patient privacy are essential to the adoption of digital smartphone research methods. A centralized data structure and shared research platform for multiple projects, as proposed in this work, eliminates the need to develop individual data security solutions for individual studies [118]. Given the use of highly sensitive data, the Health Insurance Portability and Accountability Act (HIPAA), especially the technical regulations, were used to achieve the highest possible level of security. We also followed the Privacy by Design principle of the General Data Protection Regulation (GDPR). Strict security protocols are in place to ensure data safety, including several firewalls and SSL certificates embedded in the cloud-hosting infrastructure, virtual server, and database. OpenVPN is implemented to ensure a safe connection between the personal computer (PC) and the server. The database is encrypted by Cipher Block Chaining in combination with Advanced Encryption Standard (AES). User authentication for access to the platform is handled by a user login, protected by Google's (Mountain View, California, USA) reCAPTCHA technique. All false login attempts are logged in the database, revealing unwanted access attempts and allowing us to create IP exclusion rules. Communication between the database and the platform is encrypted by the AES-Rijndael algorithm.

All data exchange with external databases is performed using the handshake principle, based on a standardized OAuth verification/authentication procedure.

Components

The concept of components was introduced to manage different studies on a single platform. Each study consists of at least one or multiple components (e.g. data handling and questionnaires), which can be activated by a study leader.

1. Study and patient administration

Every clinical study is divided into multiple levels, starting with the hospital acting as the lead partner of the clinical study (level 1; e.g. Hospital East-Limburg, Genk, Belgium). The next level is the medical domain (level 2; e.g. gynecology) and the third level is the study itself (level 3; e.g. PREMOM). This multi-level approach allows us to implement user rights and develop alert thresholds on each level of the project. Currently, three user profiles are defined: patient, study leader and administrator (admin). After completing the registration process, two possible methods are provided. First, the admin can appoint a user as a study leader, and then a study leader can assign the user as a patient for inclusion in a specific study. This hierarchical model allows study leaders to independently create and follow-up patients.

2. Data handling

The goal of DHARMA is aggregation and visualization of multiple vital parameters that are collected by using medical devices and apps from different vendors without the need to consult the vendor-specific platforms. The remote-monitoring platform can receive information directly or collect data by connecting to other databases. If new values are uploaded by a user, DHARMA receives a notification and automatically launches the technical process needed to aggregate and store the data in its own database. Duplication of these data enables secure storage and accessibility for analysis and alert-generation. Figure 1 is a graphic representation of the data flow in DHARMA.

Because the sensors record diverse types of data, ranging from discrete values to longitudinal values collected throughout the day, a metamodel was designed to handle and store data from each sensor.

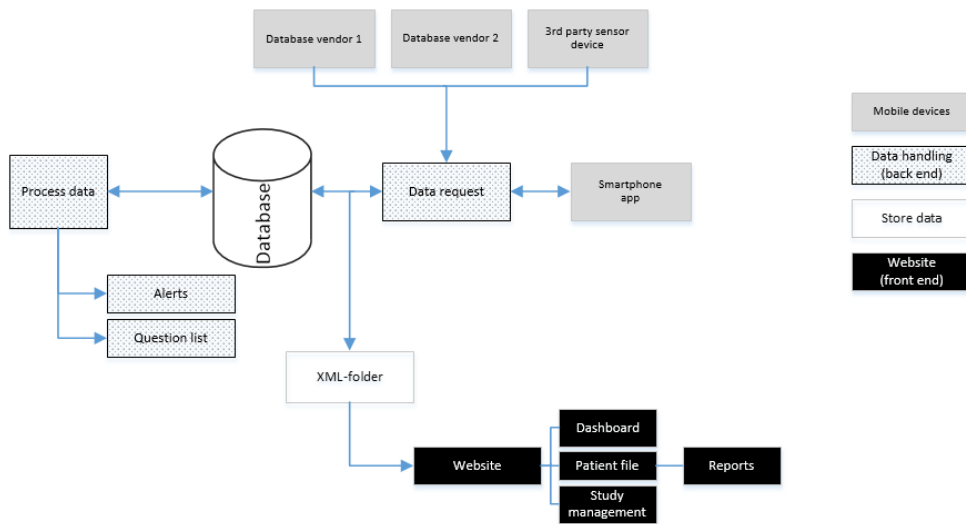


Figure 1. Overview of the data flow of the DHARMA platform.

To handle large amounts of data, such as intraday (minute-by-minute) results from an activity tracker, data are compressed into a tailored XML file that is stored in a folder structure on the server.

To generate an efficient data collection workflow, an alert engine was developed that can interpret and handle medical and technical alerts. Medical alerts are based on the collected data and detect a value outside specified thresholds. The thresholds are specified for each study project (level 3) and can dynamically support longitudinal changes and more complex interpretations. However, the configuration of patient-level alerts can be set to individual ranges based on clinical guidelines. Based on the clinical input, the alerts are categorized as normal, medium, or high priority. Technical alerts are defined by messages containing information about missed data transmissions. This triage system could help organize the clinical call center activities.

3. Question management

The 'question management' component was implemented to receive additional, context-related information from patients via questionnaires. Context information could help researchers to interpret (different) vital parameters [119]. Web-based questionnaires and app-based questionnaires can be developed and linked to DHARMA. For web-based questionnaires, the URL for the questionnaire is sent to the patient's e-mail address, and the patient can log in to the platform to answer the questionnaire. We developed the DHARMA smartphone app for app-based questionnaires. This app was built in the cross-platform Xamarin language to enable a solution compatible with both Android and iOS. The user interface was developed with Xamarin Forms. A secured oauth2 API connection between the platform and the app was developed to handle data flow. A local smartphone SQLite database is used to save and answer questionnaires offline. The app was integrated with Firebase Cloud Messaging to notify patients when a questionnaire is delivered to the smartphone app. Questionnaires can be sent automatically via email or via the smartphone app by the Laravel task scheduler. This script consists of the questionnaire ID, study project name, and date and time stamps. Questionnaires can be developed by the study leaders or admins, and consist out of individual questions. Each question has an identical ID and can be used in multiple questionnaires. Questions can be written as open, multiple choice, yes/no, or scale.

4. Patient file

A patient file component was created to arrange the information into individual patient records. Each record consists of four main tabs: medical information, statistics, questionnaires, and follow-up. The medical information tab allows the study leader and the clinician to view study-specific patient parameters or comorbidities. Study parameters include the study-specific information needed to interpret the vital parameters. The statistics tab displays a graphical overview of each vital parameter. The questions tab provides an overview of the questionnaires that were sent to and completed by the patient. The follow-up tab allows caregivers to send text messages among multiple disciplines. Each patient contact is logged in this tab.

5. Reports

A report component was created to provide a comprehensive digital overview of the patient's status. The overview can be printed or downloaded and e-mailed to the patient's doctor or caregiver. Lava Charts (Google Chart API) was used to visualize the patient's data in charts and graphs.

RESULTS

The remote-monitoring study platform was built between February 2015 and July 2018. The custom-made remote-monitoring platform was deployed to monitor patients outside the hospital in several projects, including multiple sclerosis, low back pain, and osteoporosis studies in which the patients’ activity data (number of steps and intensity) were tracked.

Overview of platform data

Table 1 provides an overview of the main study projects in which DHARMA was tested, together with the numbers of patients and the vital parameters. Each vital parameter displays the number of individual measurements that were uploaded during the study.

Table 1. Remote study projects included in DHARMA

Study	Sample size	Blood pressure	Weight	Activity data
PREMOM	604	95835	9430	35520
MS	36	0	14	1544
Low back pain	33	12	110	2191
Osteoporosis	13	25	857	1603

The main project in which DHARMA was tested was the PREMOM (pregnancy remote monitoring) study [120-122]. Briefly, this prospective cohort study enrolled pregnant women at high risk of developing pre-eclampsia. Patients were provided with a commercial activity tracker, wireless blood-pressure monitor, and a smart-body scale analyzer from iHealth (Mountain View, California, USA) or Withings (Issy-les-Moulineux, France). The participating women were asked to measure their blood pressure twice daily, their weight once daily, and to wear an activity tracker for 24 hours/day. All of the information recorded by the devices was sent wirelessly to the smartphone, which then transmitted the data to the online platform for aggregation. The sensors collected up to 12 different signals as functions of time, enabling multi-parametric longitudinal research. A midwife reviewed all incoming remote-monitoring data via the dashboard.

The alert engine discriminated between normal and alarm signals for the following: systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or weight gain >1 kg/day. Alarm events were sent to the obstetrician in order to discuss possible interventions.

Dashboard and visualization

Besides collecting and handling different sources of information, one of the main objectives of the platform is to provide the researcher/clinician with efficient visualization of all patient data. If the data triggered a specific alert, the dashboard prioritized the alerts based on the predefined thresholds and displayed them to the person responsible for reviewing the data. This enables the platform to triage patient alerts and facilitate patient handling and follow-up. Figure 2 shows an overview of the dashboard.

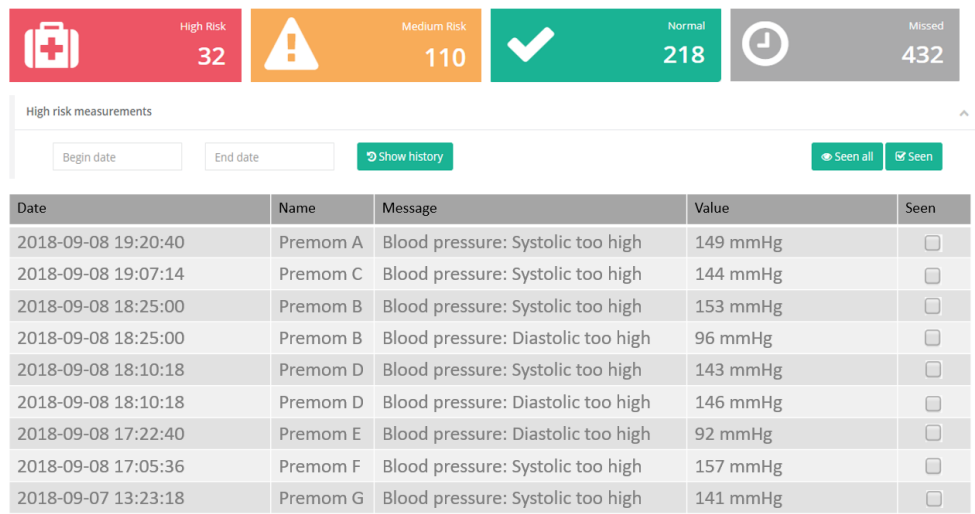


Figure 2. Screenshot of the alerts presented to the study leader and the clinician after logging into the dashboard. Data were triaged based on predetermined thresholds into normal, medium, or high risk

Patient file

The patient records bundle the individual patient’s information into a single file. The received parameters are individually plotted as functions of time to identify specific trends that could trigger an alert by crossing specified thresholds. In the patient shown in Figure 3, systolic blood pressure showed a trend towards crossing the pre-defined thresholds (140 mmHg for systolic blood pressure and 90 mmHg for systolic blood pressure), triggering a high-risk alert. Based on these results, the patient was admitted to hospital where early symptoms of pre-eclampsia were identified and appropriate treatment was started.

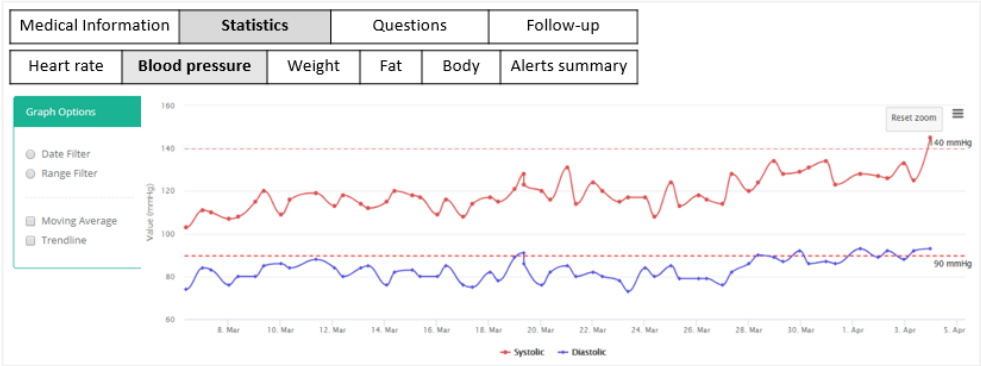


Figure 3: Overview graph of a patient’s blood pressure displaying both the systolic and diastolic blood pressure, with the predefined alert thresholds indicated with dashed lines.

Data structure and data handling: activity data

The challenges of working with different types of data include how to handle, analyze, and store the data appropriately and transparently. In the normal workflow, only the summarized values of larger datasets are used because granular detail is not required for daily patient management. However, if required, the data are available for online data processing or can be exported for offline scientific research, such as the development of novel algorithms or data-processing techniques. Figure 4 shows the averaged step count over a period of 12 weeks. Granular, minute-by-minute data are also shown for a single day in Figure 5.

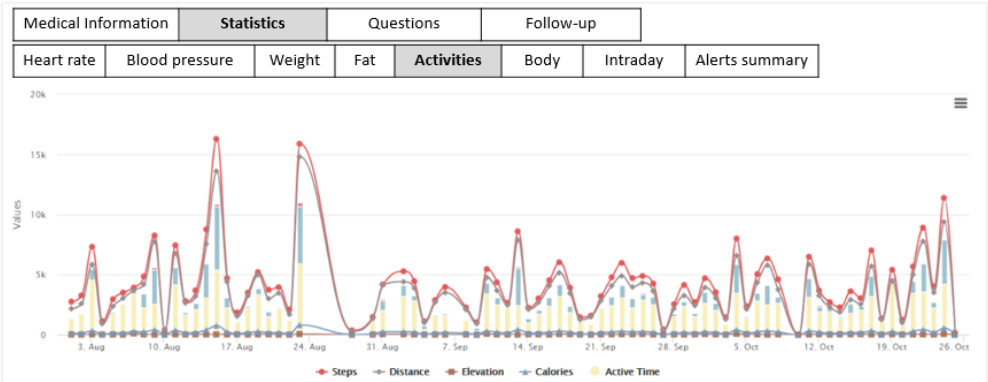


Figure 4: An example of longitudinal activity data for a period of about 2 months.

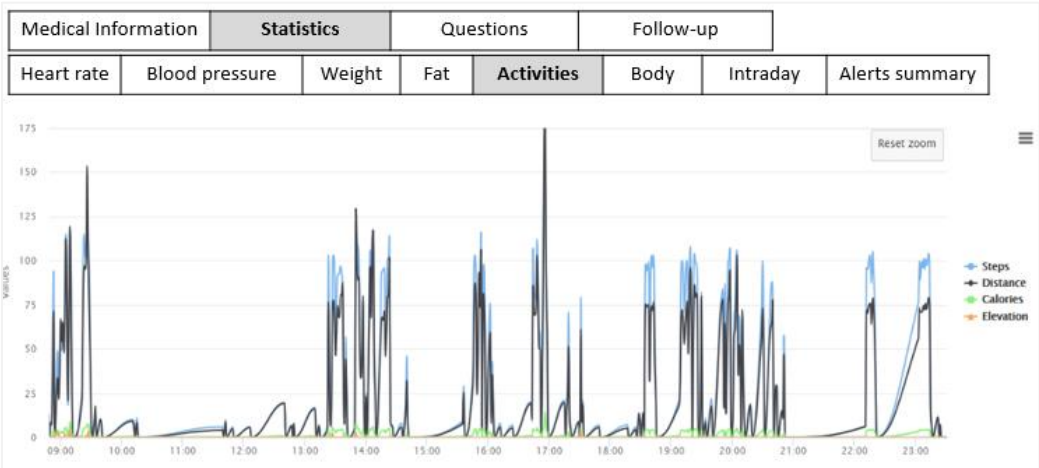


Figure 5. Granular example of the activity level per minute for a period of about 15 hours.

DISCUSSION

Principal considerations

The current paper outlines the development of a digital health research platform for remote monitoring. By combining advanced wearable sensors with smartphone technologies for remote monitoring, it is possible to monitor the health of patients in their home environment, an approach that may reduce the number of healthcare visits. Remote monitoring requires multiple hardware and infrastructure tools. Each vendor provides dedicated infrastructure and data review platforms specific to their own devices. Accordingly, data aggregation is impossible when collating data from medical devices and tools from different manufacturers, creating a barrier to clinical practice and academic research. This fragmentation is also very inconvenient for the user. Therefore a 'one size fits all' solution (i.e. one platform for all devices) is highly desirable [123].

A health monitoring system can only provide its greatest usability if it can be fully integrated into the user's and the physician's daily workflow. The goal of our project is to integrate the data streams from multiple medical device vendors and allow healthcare practitioners to efficiently evaluate a patient's health status. This will improve efficiencies in cost and time. In addition, the platform was designed to enable rapid and cost-effective scalability.

Privacy is a fundamental right in the public healthcare domain, especially following to the recently implemented General Data Protection Regulations. Healthcare practitioners and patients are becoming increasingly aware of this important aspect. Confidential handling and storage of private patient data has also become a critical aspect of study design. Therefore, all private personal data in our platform is de-identified and every unique identifying number, characteristic or name is removed. Moreover, all participants need to provide signed, written informed consent.

Comparison with prior work

The development of a centralized visualization platform has been described in earlier reports; e.g., for monitoring of arrhythmias [124], non-motor symptoms of Parkinson's disease [125], and pressure ulcers [126]. However, most of these studies monitored a specific disease, and thus the platforms have limited applicability to studies of other diseases. In the study of Zens et al. [118], the authors developed a modular smartphone application that could be used in different medical studies without the need for advanced programming skills. Another example of an open-source framework is Apple's ResearchKit (Apple Inc, USA). However, the initial studies revealed that technical programming skills, like Object C or Swift, are needed to develop a functional app [127-129]. Another limitation is that ResearchKit only supports iOS devices.

Other platforms, including ResearchStack and ResearchDroid, have been developed for use in research projects. ResearchStack is a functional software development kit with a framework comparable to that of ResearchKit, for developing research apps for Android devices [130]. ResearchDroid is an Android library developed to automate survey forms and the information-building process [131]. Appbakery integrates ResearchKit and ResearchDroid, enabling researchers to create apps without requiring programming skills [132]. More recently, Google's Open Data Kit allows researchers to set up a study simply, with a scalable app. Patient data can be exported to a CSV file or viewed in the Google Cloud platform [133]. As examples of PC-based software, PsychoPy [134] and Labview (National Instruments) enable users to create individual software solutions with a graphical user interface in a process that does not require programming skills. The platform most similar to DHARMA was developed by Validic, and can provide continuous access to personal health data obtained by over 350 in-home medical devices and wearables. Companies like Philips and IBM also provide health platforms for remote monitoring. Although these commercially available platforms could have worked for the PREMOM research project, there were three main reasons why we chose to develop our own platform. First, due to the limited budget and the need for a vendor-independent research platform, we created our own solution that had the minimum number of components and required minimum development.

Second, the platform needs to be flexible and customizable for use with new study (invalidated) thresholds. Third, we used integrated components and functions, which could differ from the development roadmap for commercial platforms.

Opportunities and future improvements

Although DHARMA provides exciting opportunities to improve remote-monitoring services, it is not free from limitations. First, the data recorded by the medical devices are initially sent to the vendor's dedicated database. This means that the vendor (e.g. iHealth or Withings) also owns the patient's data. An iHealth/Withings study profile without the patient's personal data was created in the PREMOM study to de-identify the patients who were included in the follow-up program. This approach could be improved by creating a third-party app that connects directly to the medical devices; however, not all vendors allow direct access to their medical device via an open API. This process would bypass data transfer to an external company. A second limitation is the applicability of remote-monitoring projects among technophobic individuals and people with limited cognition or ability to express consent, such as neonates, elderly, and sedated patients in an intensive care unit (ICU) [135]. Related to this limitation, some people may not comply with manual entry of daily information, especially in long-term monitoring settings [38]. Automated 'invisible' wearables, such as smartwatches or smart clothing, could help address non-compliance issues. Finally, it is difficult to keep pace with the rapidly evolving smartphone and wearable sensor technologies.

Our platform was initially developed using PHP version 5.6.18, whereas the latest version is 7.4 at the time of writing. An advantage of DHARMA is its flexible architecture, which enables rapid integration of new smartphone and wearable sensor technologies as they become available. Currently, participants in DHARMA remote-monitoring projects need to provide written informed consent in order to be enrolled in each study, as previously reported by Eysenbach et al. [136]. Zens et al. [118] described an alternative approach that uses an eligibility module to check the inclusion criteria and an integrated electronic informed consent component to obtain consent via a customized app. In the future, a similar component could be integrated into the DHARMA mobile smartphone app.

Another step to improve the platform will involve embracing the definitions of standard information models and IT communication standards such as HL7 FHIR, together with clinical terminologies, such as SNOMED CT, to ensure interoperability with hospital electronic medical record (EMR) systems [137]. Our platform can be seamlessly integrated into a patient's daily life, but introducing it into a physician's standard workflow may require integration with existing EMR systems.

Conclusion

Smartphone health apps and medical devices collect large amounts of vendor-specific data. There are currently very few tools to collate and handle the data generated by multiple medical devices. We developed a component-based digital research platform to integrate the data in different formats from different sensors into a single integrated system. The platform performed well in a healthcare setting in real-time circumstances for the follow-up of pregnant women at risk of developing pre-eclampsia. The next stage in its development will involve integrating the platform with existing EMR systems to create a closed-loop information system.

Scientists or companies willing to contribute to this project are welcome to contact the authors.

PART III – EDUCATION:

EXPLORE THE USAGE OF AN E-LEARNING PLATFORM FOR
PATIENTS IN THE DOMAIN OF CARDIAC REHABILITATION

CHAPTER 5

Telerehabilitation for cardiac patients: a multicenter randomized, controlled trial investigating the usage of a post-discharge e-learning platform

Vandenberk T, Frederix I, Geurden A, Janssen L, Orolé S, Degryse L, Smeets S, Bielen J, Puts S, Dendale M, Scherrenberg M, Govaerts M, Thijs I, Storms V, Vandervoort P, Grieten L & Dendale P.

*** Submitted at JMIR***

ABSTRACT

Background: Cardiac rehabilitation is recommended by the European Society of Cardiology (ESC) after the initial coronary event for patients with acute coronary syndrome. However, attendance to CR programs and especially maintenance programs after out-patient CR are less than 50%. A possible approach to increase adherence and attendance to maintenance CR programs is telerehabilitation. In its most comprehensive format, telerehabilitation includes telemonitoring (i.e. remote monitoring), tele coaching (i.e. coaching from a distance by email/SMS/telephone), social interaction, and e-learning. The specific role and value of e-learning in telerehabilitation for CAD patients were hardly assessed.

Objective: The objective of this study was to create a platform with information and educational videos presented by doctors, nurses, physiotherapists and other care actors. The aim of this study is to investigate the proportion of patients who enter an e-learning platform and whether sociodemographic and medical factors influence cardiac-based e-learning usage.

Methods: Patients diagnosed with a coronary artery disease were included in a multi-center randomized controlled trial (N = 985). All patients obtained conventional cardiac care, while 508 patients received in addition to standard care a one-month access to an e-learning platform with tailored educational information. This information consisted out of 20 main video units, all with content relevant in secondary prevention for ischemic heart disease. All platform data such as the number of log-ins per patient, total time on the platform, type and number of videos viewed, were logged.

Results: 508 patients (83% male; aged 63±10 years) were included in the intervention group of this study while 264 (52%) participants entered the platform. Median of platform consultation was 2 [1-3] during the one-month period and patients spent 22.50 [5.22-49.56] min watching 7.5 [3-14] video units. Both multiple as single logistic regression showed that in-center CR participation ($P=.01$) and educational attainment ($P=.02$) significantly affect the chance that a patient entered the e-learning platform. Furthermore, a significant influence of age ($P=.05$) was found on time spent watching videos.

Conclusion: The results indicate the interest in the use of an e-learning platform for providing additional medical specific information about coronary diseases. However, there are substantial differences in usage among patients.

Keywords: eHealth, e-learning, Cardiac telerehabilitation

INTRODUCTION

In Europe, 45% of all deaths each year are caused by cardiovascular disease (CVD) of which 1.8 million deaths are caused by coronary heart disease (CHD). Of all deaths per year, 14% died of coronary artery disease (CAD) before the age of 65 and 17% before the age of 75. Of the people aged 45 or above, 7.3% died within 30 days following admission to hospital for Acute Myocardial Infarction (AMI), and 9.3% died after ischemic stroke [138, 139]. These numbers demonstrate that many people are affected by CVD and CAD, and that secondary prevention is needed. One way to prevent recurrence of CAD (secondary prevention) is by participation in a cardiac rehabilitation (CR) program since they have shown to have benefits for patients with CHD [140, 141]. A CR program is a multi-factorial intervention with supervised physical exercise, risk factor modification, nutritional counseling, patient education and psychosocial management as core components [142]. Secondary prevention by means of CR is recommended by the European Society of Cardiology after the initial coronary event for patients with acute coronary syndrome, patients undergoing reperfusion and patients with stable coronary disease [143]. CR often starts immediately after major CHD events and last for 12 weeks. Although CR is proven effective for patients with CHD, attendance to CR programs and especially maintenance programs after out-patient CR are less than 50% [144]. This could be related to the strength of the physician's referral, being female, being older, having a lower educational status, having a poor functional capacity, and distance to the rehabilitation center and availability of transportation [145, 146]. A possible approach to increase adherence and attendance to maintenance programs and a healthy lifestyle is telerehabilitation which can reduce the barriers of distance to the rehabilitation center and the availability of transportation [147]. In its most comprehensive format, telerehabilitation includes telemonitoring (i.e. remote monitoring), tele coaching (i.e. coaching from a distance by email/SMS/telephone), social interaction, and e-learning. The specific role and value of e-learning in telerehabilitation for CAD patients were hardly assessed [9,10]. The use of an educational platform for patients is a relatively new concept. It is known from the literature that the education of patients via a video platform results in better patient outcomes, better risk factor management and more awareness of their disease condition [9-11].

Proper patient education seems highly relevant. Patients who have a clear understanding of their after-hospital care instructions are 30% less likely to be readmitted or to visit the emergency department than patients who lack this information [11]. However, it is estimated that 40-80% of the medical information provided by health-care workers is forgotten instantly [34]. The best way to achieve this goal is by e-learning videos that are short, use both visual and auditory elements, and contain patient experiences and/or correct medical information [148, 149].

However, more research is needed to conclude the usage of e-learning in a patient population. The primary endpoint of the study was the proportion of patients who watched videos on the e-learning platform. The secondary endpoint was the influences of the sociodemographic and medical characteristics on the platform in log and usage.

METHODS

Study design and patient population

The eEduHeart 1 was a multi-center, prospective, randomized study. It was conducted in Jessa hospital and hospital Oost-Limburg between November 2015 and February 2018. The study protocol of the study was approved by the ethical committee of the leading hospital, Jessa hospital (reference No. 15.82/cardio15.11). A detailed description of the full study protocol has been published previously [150].

This Pilot Trial included patients suffering from CAD for which they were treated conservatively, with a percutaneous coronary intervention or with coronary artery bypass grafting; and were randomized by sealed envelopes in a control or intervention group. Patients were recruited at the rehabilitation center or at medium care by the researchers. To reduce barriers to using the website, a printed manual was given and patients were encouraged to contact the project team in case of problems or questions. They were excluded from the study if they did not have access to a computer with internet, could not fully understand the E-learning packages due to having dementia or cognitive impairment, if they were unable to speak Dutch (foreign patients), or if they had advanced visual and/or auditory impairments. Patients were also excluded if they were already participating in another e-learning trial during the Pilot Trial study period, or if they refused to provide a signed informed consent. The sociodemographic variables that were analyzed comprised age, gender (male, female), vocational status (employed, unemployed, retired), educational attainment (primary education, secondary education, higher education, university) and whether the subject participated or was participating in an in-center CR program or not. Medical variables that were analyzed comprised of smoking, type of cardiac pathology, treatment of IHD, diabetes mellitus, arterial hypertension, hyperlipidemia, family history of IDH, artery disease and ejection fraction. This study complies with the Declaration of Helsinki, and a written informed consent was obtained from all participants.

The intervention group received access to an online e-learning platform in addition to standard care. Patients had one-month unlimited access to the website starting from the first login.

The platform contained 20 video unit topics focusing on secondary prevention for coronary diseases as described by the European Association of Preventive Cardiology (EAPC) [151].

Each topic contained two types of videos. Type I videos had medics and paramedics that highlighted the etiology, pathophysiology and treatment of CAD; the associated comorbidities and the ways to prevent recurrence. Type II videos had patients sharing their stories from their own experience about their illness and their rehabilitation afterward.

Statistical analysis

Data management and statistical analysis were performed using SAS software (version 9.4). All analyses were two-sided, and the level of significance was set at a value of .05. The unknown sociodemographic and medical variables consisting of missing data ad random (MAR). This problem was handled by performing multiple imputations. Single and multiple logistic regression were performed to assess the proportion of patients that watched videos on the platform. Linear and multiple regression were performed to determine which sociodemographic and medical characteristics had a significant influence on the usage of the e-learning platform. The logarithm of the usage time was used as a dependent variable to establish normally distributed data. The uptake rate and adherence were assessed using the number of logins, time spent on the platform (contact time), time spent watching the videos (dry time), number of videos watched, and time spent watching an individual video for each patient. These data were tested for normal distribution with the Shapiro Wilk test. Non-normally distributed data was presented using the median [IQR] instead of the mean[SD].

RESULTS

In total, 985 patients who fulfilled the inclusion criteria participated in the study. 508 patients were assigned to the intervention group.

Patient demographics

In total, 508 participants were entered the intervention group. Patients were average 63 (± 10) years old. 421 (83%) of these patients were men. Of these participants, 264 (52%) logged into the website. Table 1 gives an overview of the patient demographics from all participants in the intervention group and the patient characteristics of the participants who entered the platform at least once.

Table 1. Overview demographics

	Intervention group (n = 508)	Platform entrance (n = 263)
Continuous variable, mean (SD)		
Age	63(± 10)	62 (± 9)
Categorical variables, n (%)		
Gender		
Male	421 (83%)	219 (83%)
Female	87 (17%)	45 (17%)
CR participation		
Yes:	315 (62%)	180 (68%)
No:	53 (10%)	17 (6%)
Unknown	140 (28%)	67 (25%)
Educational status		
Primary education	51 (10%)	26 (10%)
Secondary education	237 (47%)	118 (45%)
Higher education	89 (18%)	61 (23%)
University	35 (7%)	20 (8%)
Unknown	96 (19%)	39 (15%)
Vocational status		
Employed	137 (27%)	73 (28%)
Unemployed	42 (8%)	27 (10%)
Retired	235 (46%)	125 (48%)
Unknown	94 (19%)	39 (15%)

Platform statistics

In total, 264 patients entered the platform with a median platform consultation of 2 [1-3]. Almost half of the patients (47%) logged only 1 time into the platform. Figure 1 shows this percentage of patients related to their total numbers of login.

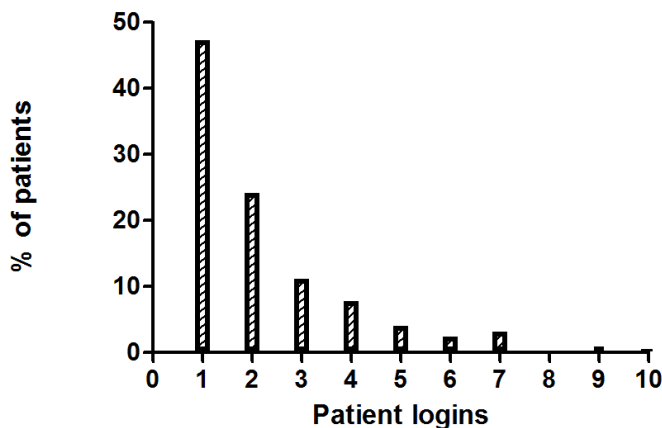


Figure 1: The percentage of patients related to their total numbers of login

Of those subjects that logged in on the platform, the median of the 'total in-log time' was 27.17 min (Q1 = 8.57 min, Q3 = 49.56 min) while participants viewed in total 7.5 (3-14) videos. An overall significant ($P < .001$) correlation ($R = 0.54$) between the number of logins and total contact time was found. The median time of the time spent watching videos was 22.50 minutes (Q1= 5.22 min, Q3= 49.56 min). The patients who logged in once, spent the lowest time to watch videos in total, while the patient which logged in ten times had the highest median time (Figure 2).

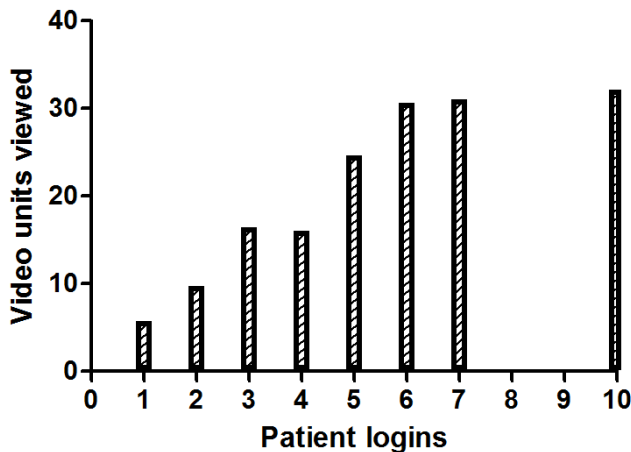


Figure 2: Watched videos per number of logins

There was a significant ($P < .001$) small relationship ($R = 0.51$) between the total time watching videos and the number of logins. Overall platform usage statistics can be found in table 2.

Table 2. Platform usage patient demographics

		Platform consul- tation	Platform duration time	Videos duration time	Video units watched
Gender					
	Male	2 [1 - 3]	26.5 [8.5 - 59.4]	22.2 [5.5 - 49.5]	7 [3 - 14]
	Female	2 [1 - 2]	33.2 [9.2 - 66.5]	25.4 [6.3 - 49.4]	8 [3 - 14]
CR					
	Yes	2 [1 - 3]	29.2 [8.5 - 60.5]	23.5 [6.1 - 49.2]	8 [3 - 14]
	No	1 [1 - 2]	11.3 [5.1 - 24.4]	8.1 [1.5 - 22.4]	3 [2 - 7]
Education					
	Primary	2 [1 - 3]	25.5 [10.0-45.6]	14.7 [7.0 - 35.1]	6.5 [2.3-9.8]
	Secondary	2 [1 - 3]	26.9 [10.2-67.3]	23.1 [7.2- 51.7]	7 [4 - 15]
	Higher	2 [1 - 2]	29.8 [7.9-60.6]	23.8 [5.8 - 50.7]	11 [3 - 14]
	University	1.5 [1 - 4]	38.5 [11.9- 116.7]	29.2 [10.7 - 88.6]	9 [4.8- 23.3]
Work					
	Employed	2 [1-2.75]	25.6 [8.1- 67.3]	23.1 [5.3 - 51.7]	9 [3 - 15.5]
	Un- employed	2 [1 - 2]	23.5 [9.4 - 45.4]	15.8 [7.6 - 28.8]	6 [2.5 - 9.5]
	Senior	2 [1 - 4]	32.2 [10.7-61.7]	25.5 [7.2 - 51.1]	8 [4 - 15]

20 videos of different content could be watched on the e-learning platform after logging in. The most watched videos on the e-learning platform were: physical activity with was viewed by 61% of participants, Risk factors for a myocardial infarct (57%), Medication and adverse events (57%), Healthy diet (51%) and Driving a car (48%). The least watched movies on the e-learning platform were 'The experience of a myocardial infarct' (27%), 'Tele-rehabilitation' (25%), 'Can others understand my disorder' (25%) and 'Being a caregiver; tips for a family member' (24%).

Patient characteristics

The influences of the sociodemographic and medical characteristics on the platform in log and usage were determined by logistic and multiple regression. Both single logistic regression as multiple logistic regression showed that educational attainment ($P = .03$) and participation in an in-center CR program ($P = .01$) significantly influences the chance that a patient enters the e-learning platform. Multiple linear regression showed that age significant (negatively) influenced the time spent on watching videos. Table 3 describes for each sociodemographic and medical group the p-values for platform login and platform usage.

Table 3. Regression models of the influence of sociodemographic and medical factors on e-learning platform usage

Sociodemographic and medical factors	Log in platform		Platform usage	
	p-value ^a (single variable)	p-value ^b (all variables)	p-value ^c (single variable)	p-value ^d (all variables)
Gender	.97	.89	.80	.49
Vocational status	.38	.17	.40	.12
Educational attainment	.03	.02	.93	.94
Participation in an in-center CR program	.01	.01	.21	.31
Age	.70	.53	.39	.049
Smoking	.63	.61	.88	.69
Type of cardiac pathology	.96	.96	.71	.60
Treatment of IHD	.70	.85	.44	.44
Diabetes mellitus	.08	.15	.77	.93
Arterial hypertension	.88	.80	.52	.69
Hyperlipidemia	.49	.999	.89	.72
Familial Hx	.77	.93	.44	.52
Peripheral artery disease	.26	.31	.44	.33
EF	.69	.37	.79	.57

^a p-value of the covariate of the single logistic regression model with the proportion of patients who watched videos as the dependent variable and only one sociodemographic or medical factor included as a covariate
^b p-value of each covariate of the multiple logistic regression model with the proportion of patients who watched videos as the dependent variable and all sociodemographic and medical factors included as covariates
^c p-value of the covariate of the single linear regression model with the logarithm of the usage time as the dependent variable and only one sociodemographic or medical factor included as a covariate
^d p-value of each covariate of the multiple linear regression model with the logarithm of the usage time as the dependent variable and all sociodemographic and medical factors included as covariates

Gender: Male, Female
Vocational status: Employed, Unemployed, Retired
Educational attainment: Primary education, secondary education, higher education, university
Participation in an in-center CR program: Yes, No
Smoking: Non-smoking, Prior smoking, Current smoker
Type of cardiac pathology: STEMI, NSTEMI, UA, SA
Treatment of IHD: CABG, PCI, Medical R
Diabetes mellitus: No, Yes
Arterial hypertension: No, Yes
Hyperlipidemia: No, Yes
Familial History CAD: No, Yes
Peripheral artery disease: No, Yes
Ejection Fraction: >50%, 35-50%, < 35%

DISCUSSION

The aim of this study was to examine the proportions of patients who watched videos on the e-learning platform and the influences of the sociodemographic and medical characteristics on the platform in log and usage. The results of this study showed that the majority of the participants entered the e-learning platform. The chance that a patient logged into the platform was influenced by in-center CR participation and educational attainment, while age (negatively) affected the time spent watching videos.

Of the intervention group, 48% chose to not log in on the platform and to use it. This number is approximately in line with the study of van Os-Medendorp et al. and with the study of Schweier et al., where respectively 42% and 54% of the intervention group did not log in on the platform [12, 152]. A likely reason for this is that the study population was not that familiar with modern technology like the use of the internet on a computer or smartphone. The usage of an e-learning platform requires a face-to-face explanation of the platform in older patients to reduce the barrier of computer skills [16]. Other studies have found that human support is important in engaging user with online interventions [153, 154], because it is known that high attrition rates in eHealth interventions are not uncommon [155, 156]. Technical difficulties, like the loading time of a video, also could be a reason for this observation. It is known that when the website has a loading time of more than 2 seconds, the patients will stop and drop out [157, 158]. 52.74% of the patients in the intervention group who used the platform, logged in multiple times. This could be explained by the fact that these patients were intrinsically motivated to learn about their disease through the platform and that they had experienced advantages of the videos [158].

The findings of this study showed a significant influence of CR participation, education attainment and age on platform entering and usage. Other studies already reported the relation between educational attainment and age on web-based programs. Individuals were less likely to attend e-health projects if they had lower educational attainment [159]. In contrast to this study, the study of Kelders et al. showed that older people were more motivated to use a web-based intervention program for healthy dietary and physical activity.

This result is supported by the study of Brouwer et al. [160] that investigated the characteristics of visitors to an Internet-delivered computer-tailored lifestyle intervention. However, the patients of the studies of Kelder et al. (mean age: 41.5 ± 11 years) and Brouwers et al. (the oldest categorical group was > 50) were younger than the patients in this study. It is possible that middle-aged patients are more likely to use e-health programs, but elderly lack computer skills to use these programs.

The total contact time of the e-learning platform in this study was 27.17 minutes (Q1=8.57, Q3=49.56). This duration is similar to the study of Santer et al., where patients spent 34 minutes (Q1= 20, Q3= 50) on the website [161]. The video about 'physical activity' had the highest time spent watching in total. A possible reason for this could be that the patients did not understand the beneficial relationship between exercise and CAD and, consequently, that they are very interested in this. Furthermore, the video about 'physical activity' was placed on top of the platform list, which might be another explanation why this video was popular.

The study contained a few limitations. First, mostly older men were included. It remains a challenge whether these obtained results are also applicable for women. Secondly, the reason why patients did not log in on the website was not questioned, which seems interesting for future research. This could be questioned by using a survey. Besides these limitations, the study also had positive aspects. This randomized controlled study design was multi-centric and contained a large IHD patient population. The study indicates that an internet-based E-learning platform was well used by the CAD patient population since more than half the patients of the intervention group (52%) used the platform. In the future, it is also advisable to collect data of the patients that do not want to participate in the study since this can be useful to check for bias [162].

To conclude, this eEduHeart 1 study indicates that the majority of the patients are interested in additional CVD information when a web-based e-learning platform is provided. However, attention is required for a small group of patients who did not attend CR neither the information session. These study findings also have a clinical and health policy impact. They provide an indication for using e-learning strategies in daily clinical practice.

This has the potential to increase the number of the target group (i.e. IHD) patients that receive the educational content, but also to improve the quality of educational content delivery. Future research should investigate whether a web-based, e-learning platform is more effective to improve pathology-specific knowledge in CAD patients than traditional in-person educational lectures alone. Also, research needs to be done whether e-learning is an effective educational tool in other cardiac patient populations (e.g. heart failure patients, atrial fibrillation patients). In addition, further research is highly required to assess whether improved patient education and knowledge also translate into improved hard, objective, clinical outcomes.

PART IV – MOTIVATION:

INVESTIGATE THE INFLUENCE OF PATIENT CHARACTERISTICS ON
ADHERENCE RATE AND THE PERCEPTIONS OF REMOTE
MONITORING IN THE DOMAIN OF HIGH-RISK PREGNANCIES

CHAPTER 6

Relationship between adherence to remote monitoring and patient characteristics in women with pregnancy-induced hypertension

Vandenberk T*, Lanssen D*, Storms V, Thijs I, Bamelis L, Grieten L, Gyselaers W, Tang E & Luyten P.

* Equally contributed

*** In press at JMIR***

ABSTRACT

Background: Pregnancy-induced hypertension (PIH) is associated with high levels of morbidity and mortality in mothers, fetuses, and newborns. New technologies, such as remote monitoring (RM), were introduced in 2015 into the care of patients at risk of PIH in Ziekenhuis Oost-Limburg (Genk, Belgium) to improve both maternal and neonatal outcomes. In developing new strategies for obstetric care in pregnant women, including RM, it is important to understand the psychosocial characteristics associated with adherence to RM in order to optimize care. Therefore, the aim of this study was to explore the role of patients' psychosocial characteristics (severity of depression or anxiety, cognitive factors, attachment styles, and personality traits) in their adherence to RM.

Material and methods: Questionnaires were sent by email to 108 mothers the day after they entered an RM program for pregnant women at risk of PIH. The Generalized Anxiety Disorder Assessment (GAD-7) and Patient Health Questionnaire-9 (PHQ-9) were used to assess anxiety and the severity of depression, respectively; an adaptation of the Pain Catastrophizing Scale (PCS) was used to assess cognitive factors; and attachment and personality were measured with the Experiences in Close Relationships-Revised Scale (ECR-R), and the Depressive Experiences Questionnaire (DEQ-A) and the Multidimensional Perfectionism Scale (MPS), respectively.

Results: The moderate adherence group showed significantly higher levels of anxiety and depression, negative cognitions and insecure attachment styles, especially compared with the over-adherence group. The low adherence group scored significantly higher than the other groups on other-oriented perfectionism. There were no significant differences between the good and over-adherence groups. Single linear regression showed that the answers on the PHQ-9 and ECR-E questionnaires were significantly related to the adherence rate.

Conclusion: This study demonstrates the relationships between adherence to RM and patient characteristics in women at risk of PIH. Alertness towards the group of women who show less than optimal adherence is essential. These findings call for further research on the management of PIH and the importance of individual tailoring of RM in this patient group.

INTRODUCTION

Pregnancy-induced hypertension (PIH), which is a complication in 6%–10% of pregnancies, is defined as a systolic blood pressure (BP) > 140 mmHg and diastolic BP > 90 mmHg. PIH refers to one of four conditions: (a) pre-existing hypertension, (b) gestational hypertension, (c) pre-eclampsia, and (d) unclassifiable hypertension [163]. It is a major cause of maternal, fetal, and neonatal morbidity and mortality [163, 164]. The assessment of women with pregnancies complicated by PIH includes clinical follow-up, serological investigations, and fetal ultrasound. The type and frequency of follow-up depends on the kind and severity of the hypertensive disorder [163]. The goal of treatment is to prevent significant cerebrovascular and cardiovascular events in the mother, without compromising fetal well-being [165].

New techniques to support these strategies have recently been developed, including remote monitoring (RM), which can be broadly defined as the use of telecommunication technologies to facilitate the transmission of medical information and services between healthcare providers and patients [166]. RM is a relatively new approach (dating back to the early 1990s) that facilitates patient management at home [167]. As part of the Hasselt University and Limburg Clinical Research Program (LCRP), Ziekenhuis Oost-Limburg (ZOL, Genk, Belgium), a large hospital in the east of Belgium, added RM to the prenatal care of women with PIH. All women diagnosed with PIH who delivered at the outpatient prenatal clinic of ZOL were included. Women received RM on demand of the responsible obstetrician before admission or after discharge from the prenatal ward. The criteria to initiate RM were PIH at gestational age > 12 weeks where an intensive follow-up until delivery was desirable. Women without a mobile phone, a gestational age less than 12 weeks, a fetus with congenital malformations, and women who refused informed consent were excluded and received conventional care. Women consenting for RM were asked to perform two blood pressure measurements a day with the iHealth Blood Pressure Monitor (iHealth Feel), fill in once a week their weight on the app, and to wear continuously an iHealth activity tracker (iHealth Wave) (iHealth, Paris, France). The data from the monitor devices were transmitted to a Web-based dashboard developed by the Mobile Health Unit of the University of Hasselt and the Future Health Department of ZOL.

Predetermined alarm signals were set; one midwife performed remote follow-up of all transformed data at the dashboard. Alarm events were communicated with the obstetrician in charge to discuss management options before contacting and instructing patients at home. Therapeutic interventions were according to local management.

Our first results were promising, suggesting that the addition of RM to the prenatal care protocol for women at risk of gestational hypertensive disease reduces prenatal hospitalization (until the moment of delivery), inductions, and pre-eclampsia compared with the levels in women who receive conventional care. Furthermore, is it likely that women monitored with RM will enter labor spontaneously and will be more likely to be diagnosed with gestational hypertension rather than pre-eclampsia than women treated with conventional care [168]. RM has also been effective in the follow-up of pregnant women with issues such as problematic blood pressure and bodyweight [169, 170]. However, adherence to RM is an important concern. Several studies have reported low rates of adherence to RM [35-37]. 'Adherence' refers to the extent to which a patient follows a pre-specified treatment regimen or protocol [39]. The methods used to measure treatment adherence are either direct or indirect. Direct methods include observation and the assessment of metabolites or biological markers in the blood. Indirect methods include self-report questionnaires, pill counts, rate of prescription refilling, and the clinical assessment of patients' physiological markers [40, 41].

In developing new strategies (including RM) to optimize the obstetric care of pregnant women, it is important to investigate the patients' characteristics, as these will potentially affect their adherence to RM. The peripartum period has long been known to be associated with increased levels of stress and anxiety, related to the transition to parenthood and parental tasks and concerns associated with this transition [171]. However, when PIH is present, it potentially increases the already elevated levels of stress and anxiety associated with this normative and normally adaptive heightened 'maternal preoccupation' in the perinatal period [172, 173].

In this context, cognitive factors, such as catastrophizing or rumination, and insecure attachment styles and personality factors, such as perfectionism and dependency, have been associated with problems in negotiating the challenges of parenthood, which are expressed as increased levels of anxiety and depression [174-176]. Mothers with a tendency to catastrophize, for instance, might be excessively worried about PIH, and might therefore show either poor adherence to RM because they wish to avoid potentially threatening information; or alternatively, they might engage excessively in RM, and RM might become an obsession for them. Individuals with avoidant attachment styles and high levels of self-critical perfectionism might show a similar pattern of avoidance or over-adherence, whereas those with anxious attachment and/or dependent personality traits might become overly compliant with RM. Poor medical outcomes and higher mortality rates in individuals with attachment avoidance and self-critical perfectionism have been associated with a tendency to deny health problems and compulsive autonomy (the belief that one must be able to manage one's problems on one's own) [177].

In contrast, individuals with high levels of attachment anxiety and dependency traits typically seek help readily, typically leading to better health outcomes (e.g., earlier detection of cancer), but also with excessive use of medical care [178-180]. Regarding perfectionism, different dimensions have been discerned [181]: self-oriented perfectionism refers to having high personal standards and the need to constantly live up to these high standards, while other-oriented perfectionism refers to expecting perfection and high performance from others; finally, socially prescribed perfectionism refers to a constant striving to live up to others' high standards and expectations. Individuals with high levels of self-oriented or socially prescribed perfectionism might show excessive adherence to RM, whereas individuals with increased levels of other-oriented perfectionism might show low adherence due to a skeptical attitude towards others and the RM program in particular.

To the best of our knowledge, no research to date has examined the relationships between adherence to RM and patient characteristics. Therefore, the primary endpoint of this study was to explore the roles of depression and anxiety, cognitive factors, and attachment and personality traits in relation to adherence to RM.

Based on the findings discussed above, we expected that anxiety and depression, and cognitive factors, such as rumination and catastrophizing, would be increased in low and excessively adherent mothers. Similarly, we expected high levels of attachment avoidance and self-critical perfectionism to be associated with low or over-adherence. Furthermore, we hypothesized high levels of attachment anxiety and dependent personality features to be related to over-adherence. Finally, we expected high levels of self-oriented or socially prescribed perfectionism to be associated with over-adherence, whereas high levels of other-oriented perfectionism were hypothesized to be related to low adherence. The secondary endpoint of the study was the relation between the individual questionnaire and the adherence rate.

METHODS

This study is part of the Pregnancy Remote Monitoring (PREMOM) study, an observational study involving eight hospitals in Limburg (Belgium), undertaken to optimize gestational outcomes in pregnancies complicated with PIH. The PREMOM protocol and main results have been reported elsewhere [168, 182, 183]. Briefly, women consenting to RM underwent obstetric surveillance with a wireless blood pressure monitor and an activity tracker. They were asked to make one blood pressure measurement in the morning and one in the evening, to enter one weight measurement weekly, and to wear the activity tracker 24 h a day until delivery or hospital admission. When alarm signals were detected (systolic BP > 140 mmHg, diastolic BP > 90 mmHg, or weight gain > 1 kg/day) by the responsible midwife, the obstetrician-in-charge was contacted to discuss the management options before the patient was contacted at home. The types of interventions were: (a) expectant management; (b) ambulatory blood sampling and 24 h urine collection at home; (c) adjustment of antihypertensive therapy and/or physical activity; (d) admission to the prenatal ward; or (e) induction of labor. The therapeutic interventions were based on local management strategies.

Pregnant women were given information about the study at the start of their RM program. All the women provided written informed consent to participate in the study. The Ziekenhuis Oost-Limburg Medical Ethics Committee approved the study. The characteristics of the participants were collected at inclusion in the PREMOM program. Demographic and obstetric information was collected at recruitment and after delivery, from the hospital administration and/or billing records. All participants received an email containing a SurveyMonkey link. After logging in, the participants were asked to complete six questionnaires (see subsection Questionnaires).

Participants

One hundred twenty-four mothers from the PREMOM study were invited to participate in the present study. Seven (5.65%) of them declined participation because of lack of interest. Of the remaining 117 pregnant women, seven (5.98%) were hospitalized in the prenatal ward with complications before they could complete the questionnaires.

In total, 110 pregnant women (88.71%) completed the questionnaires, two of whom were excluded from the final analysis because their data were invalid due to failure to fill out the questionnaires correctly.

Questionnaires

The Generalized Anxiety Disorder Assessment (GAD-7) scale was used to assess anxiety. It consists of seven items to be rated on a 4-point Likert scale ranging from 0 to 3. The Patient Health Questionnaire-9 (PHQ-9) was used to measure the severity of depression.

This questionnaire consists of nine items to be rated on a 4-point Likert scale ranging from 0 to 3. The Pain Catastrophizing Scale (PCS) assesses painful experiences and indicators of negative thoughts. It consists of 13 items to be scored on a balanced 5-point Likert scale ranging from 1 to 5. This questionnaire was adapted by the research team to include pregnancy-related questions. Anxious and avoidant attachment styles were measured by the 36 items from the Experiences in Close Relationships-Revised Scale (ECR-R), to be rated on a 7-point Likert scale ranging from 1 to 7. The Depressive Experiences Questionnaire (DEQ-A) was used to assess self-criticism and dependency, consisting of 20 items to be scored on a 7-point Likert scale ranging from 1 to 7. Finally, the Multidimensional Perfectionism Scale (MPS) measures self-oriented, other-oriented, and socially prescribed dimensions of perfectionism, using 45 items to be rated on a balanced 7-point Likert scale ranging from 1 to 7. For all six questionnaires, higher scores indicate higher levels of anxiety, depression, cognitive, attachment, or personality traits of interest.

Adherence

Patients' adherence to their scheduled daily measurements was determined by tracking the total number of scheduled events and then counting the actual number of measurements made. This from the moment of inclusion, until 90 days later. A total of 180 measurements was expected: 90 days x 2 measurements/a day. The adherence rate was calculated as follows: number of measurements made/180 potential measurements × 100%. This ratio provides a robust measure of adherence.

With this formula, adherence ranges between 0% (in case the patient did not make any measurement during her pregnancy) to over 100% (in case the pregnant woman performed more than two blood pressure measurements a day). The study population of pregnant women was divided into four study groups: (a) those with an adherence rate of < 30% (low adherence); (b) those with an adherence rate of 30%–80% (moderate adherence); (c) those with an adherence rate of 80%–100% (good adherence); and (d) those with an adherence rate of > 100% (over- adherence).

Statistical analysis

Data were analyzed with the R (version 3.2.2) statistical software. The Shapiro–Wilk test was used to assess whether the data were normally distributed. Nonparametric tests were used when the normality assumption was violated. Non-normally distributed data are expressed as medians and interquartile ranges (IQRs). ANOVA was used to test within-group comparisons. An independent *t* test (parametric) and/or the Mann–Whitney *U* test (nonparametric) was used for between-group comparisons. Single linear regression was performed to determine which questionnaire had a significant relation with the adherence rate. P-values < 0.05 were considered statistically significant.

RESULTS

Participant demographic and obstetric characteristics

In total, 108 participants completed the questionnaires. The patient demographic and obstetric characteristics are presented in Table 1. In the total sample, the median adherence was 89.4% (IQR: 54.7–103.3); the median age was 30 years (IQR: 28–33); the median pre-pregnancy weight was 76 kg (IQR: 66–91); the mean height was 167 cm ($SD = 7$); the median body mass index (BMI) was 27 kg/m² (IQR: 24–32); and 38% of the women were primiparous. There were no significant differences in any of these demographic or obstetric characteristics among the four adherence groups (see Table 1).

Table 1. Characteristics of the study participants

	Low adherence range: (0.0–27.8)	Moderate adherence range: (36.1– 78.3)	Good adherence range: (81.7– 100.0)	Over- adherence range: (100.6 – 156.1)	P- value
Number of participants	12	32	31	33	
Adherence (%), median [IQR]	9.2 (0.0-18.6)	56.4 (47.2- 71.4)	90.4 (88.3- 97.5)	107.2 (103.9- 116.1)	
Age (years), median [IQR]	31 [29-34]	30 [28-36]	30 [28-32]	30 [28-33]	.77
Pre-pregnancy weight (kg), median [IQR]	76 [64-88]	78 [68-90]	72 [67-87]	82 [65-95]	.37
Height (cm), <i>M (SD)</i>	170 ± 4	166 ± 6	168 ± 8	166 ± 7	.89
BMI (kg/m ²), median [IQR]	28 [22-32]	28 [24-31]	26 [24-30]	29 [24-34]	.36
Primigravida, <i>n (%)</i>	7 (58)	8 (25)	7 (23)	19 (58)	.15

Relationships between patient characteristics, questionnaire and adherence to RM

As expected, the results showed that several patient characteristics were associated with adherence, particularly in the groups with lower levels of adherence, although unexpected findings also emerged (see Table 2). Specifically, participants in the moderate adherence group were characterized by the highest levels of anxiety and depression, particularly compared with the over-adherence group, although these differences were quite modest. However, the moderate adherence group showed significantly elevated levels of rumination, magnification, and helplessness (cognitive factors) and elevated levels of both attachment anxiety and avoidance compared with the good and over-adherence groups. There were no significant differences between the good and over-adherence groups.

Contrary to expectation, self-criticism and dependency were not associated with adherence. Other-oriented perfectionism was the only patient personality trait that distinguished the low adherence group from the other three groups, suggesting that this group of patients was characterized by high levels of criticism towards others, and particularly towards others who failed to meet their expectations.

Single linear regression showed that the PHQ-9 ($P = .01$) and ECR-R ($P = .01$) questionnaires were significantly related to the adherence rate. Table 2 describes for each questionnaire and adherence group the median[IQR] or mean($\pm$ SD) and p-values.

Table 2. Answers questionnaires related to adherence groups. Data are expressed as median[IQR] or mean($\pm$ SD)

	Adherence groups				p						
	Low adherence	Moderate adherence	Good adherence	Over adherence	1-2	1-3	1-4	2-3	2-4	3-4	Linear regression ^a
Anxiety and depression											
GAD-7	4.0 [2.8-6.8]	6.0 [3.0- 8.3]	6.0 [2.0-8.0]	4.0 [2.0-6.0]	.40	.62	.61	.55	.00*	.14	.13
PHQ-9	3.5 [2.8-8.0]	5.0 [2.8-8.3]	4.0 [2.0-7.0]	3.0 [2.0-5.0]	.78	.62	.21	.27	.03*	.29	.01*
Cognitive factors											
PCS											
rumination	4.5 [1.0-7.5]	7.0 [4.0-12.0]	5.0 [2.0-9.5]	4.0 [2.0-8.0]	.07	.50	.97	.07	.01*	.32	.14
magnification	3.0 [2.0-6.0]	6.0 [3.0-8.0]	4.0 [2.5-7.0]	4.0 [3.0-5.0]	.07	.48	.77	.20	.03*	.62	.23
helplessness	5.0 [2.8-8.0]	7.5 [5.5-12.3]	6.0 [3.0-12.0]	5.0 [3.0-8.0]	.07	.49	.79	.19	.02*	.47	.12

Attachment and personality											
ECR-R											
avoidance	2.6	2.8	2.6	2.3	.98	.37	.19	.22	.049*	.56	.01*
anxiety	2.8	3.0	2.8	2.7	.66	.66	.32	.17	.042*	.31	.01*
DEQ-A											
dependency	36.0 ±7.8	34.5±10.0	32.0±7.6	33.4±6.2	.60	.14	.32	.27	.63	.40	.08
self-criticism	27.0 [24.0- 29.8]	28.0 [23.0-30.3]	26.0 [21.0- 29.0]	25.0 [23.0- 27.0]	.80	.38	.47	.45	.69	.79	.14
MPS											
self-oriented perfectionism	71.0 ±11.4	56.8±17.6	65.7±15.8	62.6±17.0	.00*	.24	.07	.04	.18	.45	.81
other oriented perfectionism	57.1±3.9	45.5±10.6	50.1±8.6	48.1±8.7	.00*	.00*	.00*	.06	.28	.35	.09
Socially prescribed perfectionism	50.0 ±11.4	46.4±8.9	47.6±12.3	47.1±12.2	.34	.54	.46	.68	.81	.87	.45

Note: 1, group with less than 30% adherence; 2, group with 30%–80% adherence; 3, group with 80%–100% adherence; 4, group with more than 100% adherence;

^a p-value of the covariate of the single linear regression model with the compliance rate as the dependent variable and only one specific questionnaire included as a covariate

*significant at $P < 0.05$

DISCUSSION

Principal results

We investigated the relationships between patient characteristics questionnaires of pregnant women at risk of PIH and their adherence rates in an RM program. To our knowledge, this is the first study to investigate the potential role of patient characteristics questionnaires in adherence to an RM program for pregnant women at risk of PIH. Three interesting sets of findings emerged.

First, as expected, women exhibiting moderate adherence showed higher scores for negative psychosocial traits. Specifically, the moderately adherent group was notably characterized by high levels of both attachment avoidance and anxiety, as well as tendencies to ruminate, feel helpless, and magnify problems. It seems these women may have shown suboptimal adherence to the program because they worried highly and ruminated upon potential negative outcomes. As a result, they may want to avoid any potential confrontation with threatening information. If this assumption is correct, this has important implications for the future implementation of RM, because the early identification of these women may increase their adherence and thus prevent negative outcomes.

Second, although women in the low adherence group (< 30% adherence) seemed to have similar psychosocial characteristics to the women who showed good and over-adherence, they were distinguished by markedly elevated levels of other-oriented perfectionism. This suggests that these women display poor adherence because they are very critical of others, perhaps including the health-care staff proposing and initiating RM. Because other-oriented perfectionism has been associated with an extremely judgmental attitude towards others [181], these women may be 'difficult to reach', particularly with an intervention that involves very little personal contact between the patient and the healthcare provider. Therefore, when RM is implemented, it may be crucial to screen for these traits and to develop a preferably brief and cost-effective intervention to address these issues in such women.

Third, in marked contrast to our expectations, there were no significant differences between the good and over-adherence groups. We expected traits such as high levels of self-criticism and rumination to be associated with very high levels of adherence, reflecting a maladaptive preoccupation with RM, leading to excessive healthcare behaviors. However, none of these traits distinguished this group of mothers from those with good adherence. Therefore, what we initially thought would reflect 'high' adherence' (i.e., measuring blood pressure more than the requested two times a day) might reflect the normal 'maternal preoccupation' with the health of their baby that characterizes mothers in the peripartum period [184].

This maternal preoccupation is thought to reflect a biological and psychological preparedness to give birth, which from an evolutionary perspective, is adaptive. Therefore, these findings warn against interpreting the seemingly over-adherence of mothers to RM as problematic. Of course, there may be a group of mothers for whom this normative preoccupation becomes a maladaptive preoccupation, but further research is required to investigate this.

Last, the findings of this study showed a significant relation between the PHQ-9 and ECR-R questionnaire and the adherence rate.

Strengths and limitations

Our study is the first to demonstrate relationships between patient psychosocial characteristics and adherence rates in an RM program. Our results should contribute to an increased use of RM in obstetric care, as encouraged by the European Communities in the eHealth Action Plan. An awareness of the influence of patient characteristics on adherence rates can be useful in selecting particular pregnant women for an RM program. Although the results of this study are encouraging, a number of limitations must be taken into account in future research. First, the generalizability of the results may be affected by the single-center design of the study. Second, the results of the study relied on self-reported data. To include diagnoses in questionnaires, for example GAD-7, clinical diagnostic interviews would be required. Furthermore, the difficulty in assessing depression prenatally is that several symptoms of depression, such as fatigue, appetite change, and sleep problems, are also associated with pregnancy.

During clinical diagnostic interviews, a study-specific guide can be used to determine whether the study participants perceive their symptoms to be pregnancy-related [185, 186]. Third, the questionnaires were completed on a single moment basis. It is possible that exceptional events influenced the women's responses to the questionnaires.

The overall adherence rate in this study (mean, 79.56%; median, 89.44%) corresponds to reported rates of 70.40% and 90.00% adherence to blood pressure measurements [187, 188]. As reported by many studies, the adherence rate usually decreases steadily over time. This reduction was more evident in the first weeks or months after the start of RM [188, 189]. Participants' nonadherence to the manual entry of daily information, especially in long-term monitoring programs, is also a problem [38].

Recommendations for further research

Multiple trajectories and predictors of health-related quality of life (HRQOL) have been determined in women during pregnancy. For instance, young maternal age, low education, financial dissatisfaction, unplanned pregnancy, pregnancy-related symptoms, depression, and domestic violence may be associated with low HRQOL [190]. Future studies should investigate the influence of these variables on adherence rates to RM. The results of the low adherence group may indicate that these mothers underreport distress because of a critical and hostile attitude towards RM. Future research is required to investigate this issue. The study of Biaggi et al. [191] demonstrated that depression rates tend to increase with each trimester, and that anxiety and pain interference also increases significantly over time during the third trimester [192, 193]. Future research should confirm the results of this study in other longitudinal periods of pregnancy. Maternal anxiety during pregnancy is associated with several adverse outcomes, including spontaneous abortion, increased cesarean section, pre-eclampsia, placental abruption, preterm labor, low birth weight, smaller head circumference, and lower mental development scores in infants [194, 195]. Future research should investigate the relationships between several adverse outcomes of pregnancy and adherence rates.

Conclusion

The peripartum period has long been known to be associated with increased levels of stress and anxiety, which can be exacerbated by PIH and negatively influence adherence rates. This study shows that anxiety, depression, and negative cognitive and attachment styles, but also other-oriented perfectionism, are characteristic of women with less than optimal adherence. Because the results of the low adherence group threaten both the wellbeing and the follow-up of the patient, further research is required to determine possible strategies to improve the management of PIH.

CHAPTER 7

The Perceptions of Midwives, Obstetricians and recently delivered Mothers to Remote Monitoring for Prenatal Care

Lanssens D*, **Vandenberk T***, Lodewijckx J, Peeters T, Storms V,
Thijs IM, Grieten L & Gyselaers W.

* Equally contributed

*** In press at JMIR***

ABSTRACT

Background: The Pregnancy Remote Monitoring (PREMOM) study enrolled pregnant women at increased risk of developing hypertensive disorders of pregnancy (HDP) and investigated the effect of remote monitoring (RM) additional to their prenatal follow-up. In this study, we will investigate the perceptions and experiences of mothers, midwives, and obstetricians who participated in the PREMOM study.

Methods: Specific questionnaires for the mothers, midwives and obstetricians were developed, handling five domains: (1) prior knowledge and experience of RM; (2) reactions to abnormal values; (3) privacy; (4) quality and patient safety; and (5) financial aspects. The caregivers were also questioned about which issues they consider important when implementing RM. A five-point Likert scale was used to provide objective scores.

Results: Ninety-one participants completed the questionnaires. The mothers, midwives, and obstetricians reported positive experiences and perceptions of RM, although most of them had no or little prior experience with this technology. They support a further roll-out of RM in Belgium. Nearly three-quarters of the mothers (34/47, 72%) did not report any problems with taking the measurements at the required times. Almost half of the mothers (19/47, 40%) wanted to be contacted within 3–12 hours after abnormal measurement values, preferably by telephone.

Conclusions: Although the majority of midwives and obstetricians had no or very little experience with RM before enrolling in the PREMOM study, they reported, based on their one year experience, that RM is an important component in the follow-up of high-risk pregnancies and would recommend it to their colleagues and pregnant patients.

INTRODUCTION

Due to demographic changes and rapid improvements in medical technology, the healthcare sector is confronted with major challenges and great opportunities. The care and follow-up of a pregnant woman and (unborn) baby is an important element in healthcare. Due to the changing lifestyles of pregnant women, the number of high-risk pregnancies is elevated over the last few decades [196-198]. Therefore, there is a need to increase the efficiency of follow-up for these pregnancies without loss of quality of care. Telemedicine represents an opportunity for the follow-up of high-risk pregnancies.

Defined as the use of information and communication technologies for supporting health and health-related activities [199], telemedicine is not simply an addition to conventional care, but rather is implemented in current private and public healthcare approaches. Remote monitoring (RM) represents a type of telemedicine that has a broad definition. It is useful for conducting medical practice from a distance and has been used in a wide variety of electronic healthcare applications [200]. RM can be performed either by live monitoring of vital parameters, or asynchronously, whereby data obtained in the patient's home environment are sent to the caregiver [199]. Examples of chronic diseases, which could benefit from RM, are (among others) diabetes, heart failure, and cardiac arrhythmias [112, 113, 201]. The Pregnancy Remote Monitoring (PREMOM) study, which started in January 2015 in a tertiary center Ziekenhuis Oost-Limburg (Genk, Belgium), involved RM of pregnant women at high risk of hypertensive disorders of pregnancy (HDP). The PREMOM study design, data collection method and first promising results are described in detail elsewhere [120, 121]. Briefly, the PREMOM study was performed in the outpatient clinic of a 2nd level prenatal center where pregnant women with HDP received RM or conventional care (CC). Women in the RM group received obstetric surveillance using a BP monitor, an activity tracker and a weight scale. They were asked to measure blood pressure twice a day, measure their weight once a week, and to wear an activity tracker during the 24 hours/day. These data were automatically sent by Wi-Fi or Bluetooth to an online platform which was developed by the Mobile Health Unit (UHasselt), and a midwife reviewed the parameters every workday.

The activity data were tracked to investigate the influence of the daily activity (e.g. total amount of steps/day) on the development of HDP. Predetermined thresholds (systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg or weight gain > 1 kg/day) were configured and resulted in automatically generated alarm signals.

The midwife discussed the alarm events with the obstetrician in charge to discuss the appropriate medical treatment. The midwife contacted the patients to give additional instructions about possible medical interventions like altered medication schemes. These therapeutic interventions were according to local management. Because no research has been done to investigate the perceptions or expectations of a prenatal RM follow-up program, we performed a quantitative survey on recently delivered women and caregivers (which are both the obstetricians and the midwives). Here, we describe the main outcomes, which cover the following domains: 'prior knowledge and experience of RM', 'reactions to abnormal values', 'privacy', 'quality and patient safety' and 'financial aspects'. Caregivers were also asked about important aspects to consider when implementing RM.

METHODS

Questionnaires

Three questionnaires were designed by the research group of the Mobile Health Unit (University of Hasselt, Hasselt, Belgium). The questionnaires were designed for women who were followed-up with RM during their last pregnancy, the midwives working at the Ziekenhuis Oost-Limburg (Genk, Belgium) (ZOL) who are involved in the use of RM, and the consulting obstetricians working at several hospitals in Limburg. The questionnaires assessed five items to elucidate the perceptions and experiences of the participants in PREMOM towards RM, and were based on the six building blocks established by the Mobile Health working group of VOKA Health Community (Brussels, Belgium): (1) protection of data, privacy, and the use of big data; (2) national/international regulations and responsibility; (3) quality, accessibility, and patient safety; (4) technology and interoperability; (5) financial aspects and business models; and (6) supportive policy frameworks in telemedicine. The results of the descriptive PREMOM questionnaires on the domains 'prior knowledge and experience of RM', 'reactions to abnormal values', 'privacy', 'quality and patient safety', and 'financial aspects', which are important to caregivers for further implementation of RM, are discussed in this manuscript. The questionnaires were drafted in April 2016 using Survey Monkey (Survey Monkey, 2016), and could be completed online. All questions were assessed using five-point Likert scales to obtain objective scores (Appendix I - III).

Participants

The questionnaires were sent in April 2016 to the women, midwives and obstetricians who participated in the PREMOM study in 2015. Student midwives and doctors in training were excluded from the present study.

Data collection

The study participants received an e-mail from the research team with a link to the online survey. E-mail reminders were sent to all participants at 9 and 23 days after the first invitation.

Analysis

Mean scores and ranks were assessed for each question using descriptive analytical methods. The number of participants included in the analyses of individual questions was different from the total number of analyzed questionnaires because some mothers, midwives, and obstetricians did not complete all of the questions. At least half of the questionnaire had to be completed before the questionnaire was included in the analysis. Statistical analysis was performed with Statistical Package for Social Sciences release 24.0 (IBM SPSS Inc).

Ethical considerations

A generic link to maintain anonymity was sent to the participants to fill in the survey. A bulk e-mail was sent with the subjects' e-mail addresses included as a BCC to ensure there were no recognizable personal elements in the e-mail.

The e-mail was addressed with 'Dear Madam', or 'Dear Colleague', to remove the personal salutation to participate in this study. In addition, no personal ID of the participants was asked or electronically reported when completing the questionnaires. Unique IP addresses prevented duplicate responses to the questionnaires. The Medical Ethics Committee of Ziekenhuis Oost-Limburg approved this study (nr. 14/078U).

RESULTS

The study population consisted out of 158 people: 92 mothers (58 %), 52 midwives (33%), and 14 obstetricians (9%). The total number of involved pregnant women in the PREMOM study $n = 119$, so 77% (92/119) of the participants were contacted after their delivery. The missing 27 women didn't answer their phone, didn't have an e-mail address or there was a language barrier. One obstetrician was excluded from final analyses because less than 50% of the questionnaire was completed. Therefore, the total response rate was 58%. An overview of the questions to the midwives, obstetricians and recently delivered mothers, and their answers, are submitted in Appendix 1. The demographics of the participants are listed in Table 1.

Table 1: Characteristics of participants

Characteristics of women who have involved with RM during their last pregnancy (n = 47)	Response categories	Results	
		N	%
Age	< 20 year	0	0
	20 – 25 years	5	11
	26 – 30 years	16	34
	31 – 35 years	21	45
	36 – 40 years	4	9
	> 40 year	1	2
Primigravity	Primipara	21	45
	Multipara	26	55
History of hypertensive disorders of pregnancy	Yes	17	36
	No	10	21
	N/A	20	43
Level of education	Lower secondary school	4	9
	Higher secondary school	12	26
	High school	20	43
	University	11	23
Characteristics of the midwives (n = 35)	Response categories	Results	
		N	%
Age	20 – 25 years	3	9
	26 – 30 years	8	23
	31 – 35 years	7	20
	36 – 40 years	3	9
	> 40 year	14	40
Years of experience	< 5 year	4	11
	5 – 15 years	15	43
	16 – 25 years	8	23
	> 25 year	8	23
Main activity on nurse unit	Delivery unit	11	31
	Maternity	8	23
	Maternal Intensive Care	10	29
	Prenatal visits	6	17
Characteristics of the obstetricians (n = 9)	Response categories	Results	
		N	%
Years of experience	< 5 year	1	11
	5 – 15 years	6	67
	16 – 25 years	0	0
	> 25 year	2	22
Main activity on their specialism	Delivery unit	4	44
	Obstetrician	4	44
	Oncology	1	11
RM = remote monitoring; N/A = not applicable			

Prior knowledge and experience of RM

The first part of the questionnaire examined the midwife's and obstetrician's prior knowledge or experience of RM. Overall, 29/35 midwives (83%) and 7/9 (78%) obstetricians reported little or no experience of RM (Figure 1).

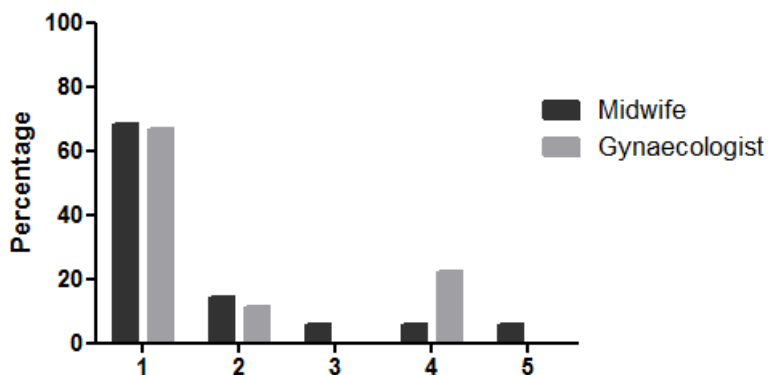


Figure 1: Summary of responses from the midwives and obstetricians on the question 'Please indicate with a score from 1 (strongly disagree) to 5 (strongly agree): I had already experience with RM before this study.'

The midwives were also asked about their experience of RM as a threat to their daily work. The majority (29/35, 83%) of midwives did not perceive RM as a threat to their work.

Timing and method of communication in case of an event

Nearly three-quarters (34/47, 72%) of the participating mothers reported that they had no problems with performing the measurements at the requested times. Of the 7 mothers (15%) who reported difficulties with the recommended measurements, 4 (57%) were 36–40 years old, 2 (29%) between 26–30 years and 1 (14%) between 31–35 years.

Participants were also asked about the acceptable time limit for being contacted by their caregiver in case of an unexpected event. Of 47 women who completed the questionnaire, 13 (28%) preferred to be contacted within 3 hours of the event, 19 (40%) agreed to be contacted between 3–12 hours, and 15 (32%) complied with being contacted > 12 hours after the event (Figure 2).

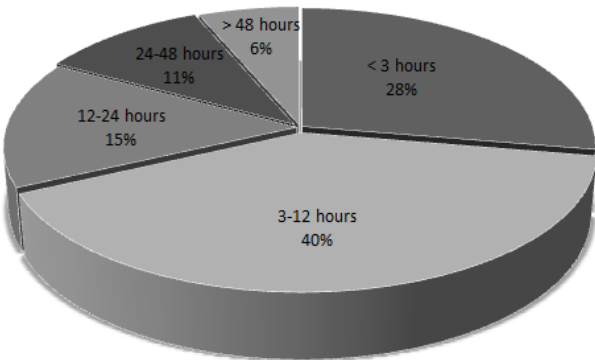


Figure 2: Summary of responses to the question ‘Within how much time do you want to be contacted about events?’

Interestingly, 4/5 mothers (80%) aged < 25 years asked to be contacted within 3 hours of an event. The participants were also asked how to be contacted following an event. The participants’ first preference was to be contacted by telephone (weighted average 4.55/5), second preference was during a prenatal consultation (weighted average 3.94/5) and the third preference was contacted by using text messages (weighted average 3.17/5). Finally, we asked the participants who should contact the women in case of an event. The mothers and midwives stated that the obstetrician should be the first to contact the pregnant woman after an abnormal event. However, the obstetricians reported that their representing researcher should be the first caregiver to contact the pregnant woman in case of an event.

Privacy

The mothers were asked if they felt that regularly sharing their health data was a threat to their privacy. Most (41/47, 87%) of the mothers reported that they did not have any negative concerns about privacy. Three mothers (aged 36-40 years) reported sharing health data as a threat to their privacy.

Quality and patient safety

The mothers were asked about the importance of RM in the follow-up of their pregnancy. Most (42/47, 89 %) of the mothers had a positive response to this question. Meanwhile, 28/35 (80%) midwives reported that RM provided added value to pregnant women and 27/35 (77%) midwives felt that RM improved the care for high risk pregnancies . This percentage is slightly higher than that of obstetricians; 6/9 (67%) of whom felt that RM provided added value to their patients (Figure 3).

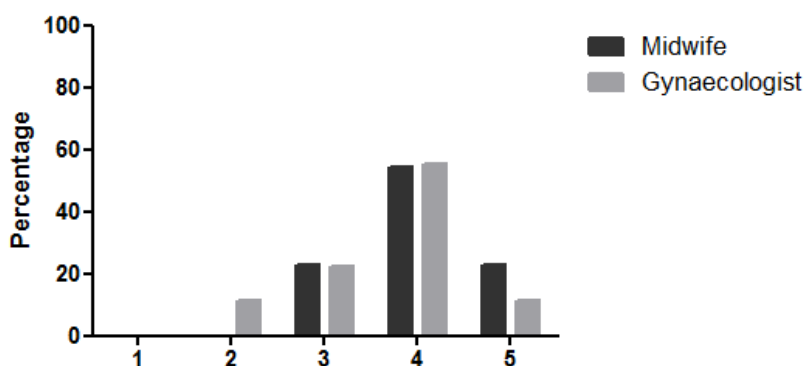


Figure 3: Summary of responses from the midwives and obstetricians to the question "Do you believe that RM improves the care for pregnant women with an increased risk of gestational complications? Please indicate with a score from 1 (strongly disagree) to 5 (strongly agree).

Moreover, 8/9 (89%) obstetricians responded, based on their experience of the PREMOM study, that the pregnant women did not request additional prenatal consultations for the purpose of viewing their own vital parameters. Finally, 39/47 (83%) mothers reported that RM gave them a feeling of safety.

Financial aspect

An important element in new healthcare practices is their financial cost. Therefore, the relative and absolute costs of each component in telemonitoring programs need to be evaluated. All three groups of participants reported that the cost of RM should be as low as possible, and about half of the mothers expected RM to be for free, so no personal contribution by the patient (25/47, 53%). It is also important to obtain information on any potential payer of RM. The mothers expected the hospital to be the main payer, followed by health insurance (company), whereas midwives and obstetricians felt that the pregnant women should also personally contribute to the cost of RM.

Further implementation of RM

The midwives and obstetricians were asked about important factors to support the implementation of RM into daily practice. Most of the midwives (31/35, 89%) felt that it is important to receive additional training on “the information that must be given to pregnant women about HDP and the added value of RM for this disease”. Obstetricians (7/9, 78%) considered this 11% less necessary compared to the midwives. The obstetricians (8/9, 89%) felt that training on the technical handling of the devices (e.g. installation and common problems) was the most important factor. About three-quarters of midwives (27/35, 77%) had the same response to this question. In terms of the final evaluation of the project, the obstetricians were asked whether they would recommend RM to pregnant women and their colleagues. Overall, 6/9 (67%) obstetricians supported this service and would recommend it to their patients while 7/9 (78%) obstetricians would recommend RM to their colleagues. Finally, 6/9 (67%) obstetricians recommended that this follow-up should be expanded to all pregnant women in Belgium who are at increased risk of HDP.

DISCUSSION

Principal findings

RM is a relatively new field in the obstetrical research. Earlier studies of TM which included cervical dilatation/preterm labor as the main outcome, demonstrated that transmitting uterine activity by telecommunication resulted in significantly prolonged pregnancy survivals [202, 203]. Articles of TM for GDM demonstrated lower levels of frustration and concerns about their diabetes, and a better acceptance of their diabetic condition [204], elated feelings of self-efficacy [205] and a reduction in (unscheduled) face-to-face visits [206, 207] in the TM group compared with the control group. On top, a cost reduction [208, 209] and elevated feelings of maternal satisfaction [205, 210, 211] were obtained when TM was used in obstetrical care. The newborns had a higher gestational age at delivery [209] and were less likely to have a low birth weight [202, 209] or to be admitted to the Neonatal Intensive Care Unit (NICU) [202, 209] when the TM group was compared with a control group. Fetuses with abnormal versus normal fetal heart rate at home monitoring were more likely to have an earlier gestational age [212]. Recent studies about RM in women at risk for HDP demonstrated that those women did have less inductions, more spontaneous labors, and less maternal and neonatal hospitalizations when compared with conventional care [120, 121]. Also, a cost-effective effect for the healthcare system was shown on women at risk for HDP who received RM [122]. To our knowledge, this is the first quantitative survey of an RM program for prenatal care. The results show that the majority of midwives and obstetricians had no or very little experience of RM before they participated in the PREMOM study. After taking part in the PREMOM study and the survey, the midwives reported that RM is not a threat to their daily work. The majority of mothers who were supervised by RM during their last pregnancy did not experience any problems with taking the required measurements at the specified times. Most of the mothers thought that it is acceptable to be contacted within 3–12 hours after an abnormal value, and they preferred to be contacted by telephone. The study of Giardina et al. showed the duality of feedback after an (abnormal) test. Nearly two-thirds of clinicians agreed that patients should receive direct feedback after a normal test.

However, the majority of physicians expressed concerns about direct notification of clinically abnormal test results based on patient's anxiety, confusion, lack of expertise to interpret the results, seeking of unreliable information to understand the results, and concerns that the patient would seek care without consulting their provider. The results of the study showed that doctors would be comfortable with a time interval of 24-48h for contacting a patient after an abnormal test result [213].

'Privacy' is a critical aspect of healthcare and RM [214]. The mothers did not have concerns about sharing their health data with their obstetrician. As mentioned by Piwek et al. [117] data security and patients' privacy are essential elements for the adoption of digital smartphone research methods. Some risk-averse participants might be unwilling to share their clinical data with a commercial partner. However, none of the participants reported any privacy breaches using RM during this study.

The quality of care experienced by pregnant women with (increased risk of) HDP was enhanced by RM, as reported by the surveyed mothers and caregivers, and supported by the results of the prior pilot study [168]. Mothers who were involved in the project reported that RM gave them a feeling of security throughout their pregnancy. Previous research concluded that pregnant women with gestational diabetes mellitus had an increased sense of self-regulation when they used RM to send their blood glucose levels to their midwives [205, 215]. Meanwhile, other research showed that pregnant women had heightened feelings of maternal satisfaction when using RM as additional care with their labor induction [216, 217].

The mothers, midwives, and obstetricians included in this study reported that RM is an important aspect of the follow-up of (high risk) pregnancies. An issue that raises important questions in telemedicine is the rather low adherence rate to remote monitoring, especially during long-term monitoring [35-38]. Measuring blood pressure, body weight, and activity every day is a prerequisite to ensure adequate monitoring of pregnant women although this may appear burdensome to many pregnant women. However, the mothers surveyed in this study did not experience this obstacle. The obstetricians stated that they would recommend RM to colleagues and other pregnant women. Most of the obstetricians proposed extending RM to all women with high-risk pregnancies in Belgium.

The obstetricians and midwives also reported that all users need additional training to support the implementation of RM. Earlier research already mentioned the challenging in terms of training these obstetricians and midwives in the collection and interpretation of results, as well as incorporation of the remote patient data into routine clinical practice [218].

Strengths and limitations of the study

Despite the increased implementation of RM in healthcare, its use is still limited in obstetrics. To our knowledge, this was the first study to investigate the perceptions of obstetricians, midwives, and recently delivered mothers to the use of RM for preterm follow-up of pregnancies at risk for HDP. Another strength of this study is that it included stakeholders involved in the use of RM, including caregivers and actual users. The questionnaires also allowed the participants to explain their responses to each question, allowing us to obtain supplementary information. Furthermore, the participants could complete the questionnaire anonymously. Finally, a relatively high percentage of participants in the PREMOM study completed the questionnaires.

Although the results of this study are encouraging, there are several limitations that should be considered for future research. First, because the questionnaire was completed anonymously, it was not possible to contact the individual participants to request additional information. Second, the questionnaire was digital and completed in an uncontrolled condition, so it is unclear whether the participants were exposed to external influences when they completed the questionnaire. Additionally, the three groups in this study had small sample sizes, which could affect external validity. Third, this study is performed in a local hospital with can reduce the generalization of the results. Finally, the study included obstetricians who worked at several hospitals in Limburg, but the midwives and mothers were enrolled only from a single center (Ziekenhuis Oost-Limburg).

Recommendations for further research

Both the mothers and the midwives felt that the obstetrician should be responsible for contacting the patient after an abnormal event, while the obstetricians suggested that their reporting researcher is responsible for this task.

This may relate to the organization of prenatal care in Belgium, where midwives nearly act as obstetric nurses instead of independent midwives and the prenatal care for pregnant women mostly is performed by an obstetrician, nevertheless if a pregnant woman has a high or a low-risk pregnancy. It is remarkable that none of these three groups felt that this could be a task of the patient's midwife, although the researcher in this study is certified as a midwife. Still, the allocation of RM – coordination to the responsibilities of the midwives seem logic, as they act as an intermediary between the pregnant woman and the obstetrician. Clearly, further research is needed to understand the factors underlying this opinion and how it could be changed. Additionally, both the mothers as the healthcare workers stated that RM should be offered for free or they want to pay as less as possible for the RM services. Although a cost-effectiveness study is executed and it has proven that RM makes a cost saving possible for the healthcare system [122], a willingness to pay study is not performed yet. This study would have an additional value to set a price for the RM services when the healthcare society or the hospital asks for it.

Further, although 66% of the obstetricians would recommend RM to their patients and 77% to their colleagues, the obstetricians who would not recommend it did not give any reason for this. A following qualitative questionnaire which investigates the underlying reasons for this should be helpful the further implement RM in the standard prenatal care for women at risk for HDP.

Interestingly, the mothers preferred to be contacted between 3 and 12 hours after an abnormal clinical measurement. This implicates that the clinical data should be monitored 24/7 in order to evaluate and interpret the vital parameters of pregnant women, and permit an intervention if necessary. Therefore, we recommend developing a system of care aimed at providing these services. As been shown in our previous studies, the prenatal ward will be less burdened by women with HDP due to our RM prenatal follow-up [121, 168]. Finally, although the mothers with abnormal events were invited to additional prenatal consultations to assess the fetal and maternal well-being, none of the patients or the participating obstetricians believed that this was needed and as such was no treat for overloading the healthcare system.

These findings may contradict the statement that the medicalization of childbirth has gone too far and too many medical interventions are performed in pregnancies, which has arisen from a variety of sources [219-224].

Conclusions

Although most midwives and obstetricians had no or very little experience with RM before they participated in the PREMOM study, they felt that it is an important aspect of the follow-up of pregnancies at risk for HDP. Most of the mothers who were supervised by RM during their last pregnancy thought that it was acceptable to be contacted within 3–12 hours after an abnormal value, and they preferred to be contacted by telephone. The majority of women had no concerns about regularly sharing their clinical data with their obstetrician, and they reported that RM gave them a feeling of security throughout their pregnancy. To our knowledge, this is the first quantitative survey of mothers, midwives, and obstetricians involved in an RM program in prenatal care. Further studies are needed to understand the underlying opinions of mothers, midwives, and obstetricians to RM. Based on our findings, we propose developing a care system with 24/7 surveillance by RM for mothers at high risk of HDP.

GENERAL DISCUSSION

GENERAL DISCUSSION

The aim of this doctoral thesis was to investigate essential components of remote monitoring. First, a smartphone application using the PPG signal for detection of heart rhythm disorders was clinically validated. Second, a vendor-independent research platform for remote monitoring was built. Third, the use of the digital online e-learning platform was investigated. Finally, the patient characteristics that affected the adherence rates and perceptions of remote monitoring were determined.

PART I – VALIDATION: INVESTIGATE THE USE OF A MEDICAL APP FOR ATRIAL FIBRILLATION DETECTION AT HOME BY CLINICAL VALIDATION AND EVALUATION OF A NEW SMARTPHONE BASED TECHNOLOGY

The first objective of this thesis was to examine the validation methodology of new remote monitoring tools for heart rate and heart rhythm. Start-ups and companies of new medical monitoring devices have difficulties to scale up their development and to introduce new, sophisticated clinical products onto the market because there is a lack of standardization and detailed descriptions of validation methodologies. Currently, numerous smartphone apps exist that measure HR. However, the validity of these apps has not always been confirmed [50]. There is currently no consensus on a gold standard method for the validation of an HR application based on a PPG signal.

In Chapter 1, two validation methods are analyzed: 1) by comparing the HR between different electrocardiography (ECG) and PPG devices; and 2) by comparing ECG-derived RR intervals (RRI) and PPG-derived peak-to-peak (PPI) intervals. In the first study, FibrCheck (Qompium) was compared with two FDA-approved HR devices, Nonin and AliveCor. FibrCheck is a smartphone application that measures heart rate and heart rhythm based on PPG analysis. Nonin used the transmission PPG methods as a stand-alone device, whereas AliveCor uses the one-lead ECG as a method measured with a smartphone. One-way analysis of variance (ANOVA) showed no significant difference between the HRs measured with the three devices. However, the minimum correlation of 0.9 for heart monitors, suggested by Terbizan et al., was not reached between all the devices [59]. The second study showed a positive correlation of 0.99 for the intervals measured with the FibrCheck app and the ECG device.

This result suggests that the PPG signal measured by the FibriCheck application can be used as a clinically validated method for measuring HR. The findings of this chapter suggest that the best suitable method for the validation of an HR app is the simultaneous measurement of HR with the smartphone app and an ECG system, and a comparison of the intervals obtained.

Based on the almost exact agreement between the RRI and PPI intervals, a qualitative analysis of the smartphone-derived PPG waveform was performed (Chapter 2).

The diagnosis of atrial fibrillation (AF) based on a visual interpretation of the PPG signal was compared with the results of the single-lead ECG and 12-lead ECG gold standard method as a first step towards the development of an algorithm for AF diagnosis. The interpretation of the PPG signal showed high diagnostic accuracy in the detection of AF. However, a significant difference was observed between both 12-lead ECG versus PPG and single lead ECG versus PPG interpretations. The sensitivity and specificity increased for both studies when only high-quality measurements were analyzed. Implementing a quality assessment for the PPG measurements made by the application will increase the accuracy as the differences in the interpretation of PPG and single-lead/12-lead ECG became insignificant.

In the last chapter addressing this objective (Chapter 3), the feasibility, added value, and effectiveness of the FibriCheck smartphone app were assessed in the management of AF after DCC. An RCT study was set up to compare the detection of AF-recurrence after DCC. The results showed that relapse of AF was detected earlier in patients who were followed with the app compared to patients in standard care. Currently, in standard care, patients have no information about asymptomatic paroxysmal AF episodes because they only undergo a single spot-check during their in-hospital follow-up visit. By using a smartphone app to monitor heart rhythm, standard care could evolve into a more personalized follow-up schedule that allows patients with early recurrence to receive an early re-evaluation of treatment strategy.

PART II – MONITORING: DEVELOPMENT OF A VENDOR-INDEPENDENT MOBILE HEALTH RESEARCH PLATFORM TO FACILITATE CLINICAL MHEALTH RESEARCH

In the next part of this thesis, a vendor-independent mobile health research platform was built (Chapter 4). Limited tools are available to handle the huge amounts of data generated by health-related smartphone apps and mobile health devices, especially for clinical use and research purposes. A component-based platform was developed with the following independent building blocks: study and patient administration, data handling, questionnaire management, a patient file, and reports. A smartphone application was built to receive additional (context) information by using questionnaires. Manual questionnaires could be sent from the platform by selecting the appropriate questionnaire and patients who had to fill in this questionnaire. Questionnaires could also be sent automatically based on a fixed moment in time or when abnormal parameters were observed. Exceeding pre-set limit values could automatically trigger the sending of a questionnaire to the patient. A prototype version of the mobile health research platform has been developed, tested, and implemented in multiple clinical studies. One of the use cases was the remote follow-up of pregnant women at risk of developing pre-eclampsia.

A next step in the improvement of the platform is the definition of a common information model, using IT-communication standards, such as HL7 FHIR, and clinical terminologies, such as SNOMED CT, to ensure its interoperability with the electronic medical record (EMR). The platform can be integrated seamlessly into the physician's standard workflow, although integration with existing EMR systems is desirable.

Furthermore, the robustness of the platform needs to be investigated and validated to ensure the ability of the platform to continue to operate correctly across the wide range of operational conditions, and fails outside the range [225].

PART III – EDUCATION: EXPLORE THE USAGE OF AN E-LEARNING PLATFORM FOR PATIENTS IN THE DOMAIN OF CARDIAC REHABILITATION

Besides capturing data from medical devices or apps, a platform can also be used to educate patients, in a process called 'e-learning'. Chapter 5 reports the use of an e-learning platform for patients with coronary heart disease.

An internet-based e-learning platform specifically developed for the coronary artery disease (CAD) patient population was used by half (52%) of the patients in the intervention group. Participation in in-center CR, education, and age influenced the use of cardiac-based e-learning among coronary heart disease patients. It became clear that attention should be paid to the group of patients (48%) who did not use the e-learning platform, however they agreed to participate in the study. High dropouts and reduction of long-term usage rates in eHealth interventions are an often cited problem in trials on web-based interventions [155, 160, 226]. Further research should investigate whether a web-based e-learning platform is more effective in improving the pathology-specific knowledge of CAD patients than traditional in-person educational lectures alone.

PART IV – MOTIVATION: INVESTIGATE THE INFLUENCE OF PATIENT CHARACTERISTICS ON ADHERENCE RATE AND THE PERCEPTIONS OF REMOTE MONITORING IN THE DOMAIN OF HIGH-RISK PREGNANCIES

Related to chapter 5, following a prespecified treatment regimen or protocol, defined as 'adherence', is an essential concern in remote monitoring. Several studies have reported low rates of adherence to remote monitoring [227-229]. Low adherence rates can refer to two different processes: 1) losing participants to follow-up (dropout attrition) and 2) non-usage of the e-health service (non-usage attrition) [156]. In developing new strategies for remote monitoring, it is crucial to investigate the patient characteristics that are associated with adherence to these protocols, in order to optimize care. In chapter 6, the role of patients' psychosocial characteristics (severity of depression or anxiety, cognitive factors, attachment styles, and personality traits) in their adherence to remote monitoring were investigated. Pregnant women used the mobile devices connected to the DHARMA platform as described in chapter 4.

The study shows that both fear and depression and cognitive factors such as other-oriented perfectionism are more prevalent in women with lower adherence. These factors threaten both the well-being of patients that display low adherence to remote monitoring and their follow-up by medical professionals. Answers on the PHQ-9 and ECR-R questionnaires were significantly related to the adherence rate.

Compared to the adherence rate of the study in pregnant women, the adherence of the RCT study for the detection of AF-recurrence after DCC was remarkable better. A possible explanation can be the (recent history for) presence of symptoms of the disease. While patients from the RCT study underwent a DCC for AF-related symptoms, the manifestation of GHD related symptoms often occurs later in the pregnancy period.

Further research is required to determine the causality relation between personality characteristics, disease symptoms and rates of compliance with remote monitoring and possible approaches to improve adherence for patients. However, the study in pregnant women shows clearly that a multidisciplinary team is required to guide a pregnant woman at risk of Gestational Hypertensive Disorders (GHD) through the remote monitoring process.

In the last chapter of this thesis, the perceptions of patients and healthcare providers involved in the Premom remote monitoring program were assessed. In particular, midwives, obstetricians, and women who recently given birth were asked about their experiences and preferences in a remote monitoring program. Although most of the midwives and gynecologists involved had no or minimal experience of remote monitoring before the project, after working with this program for 1 year, they considered remote monitoring an important factor in the follow-up of high-risk pregnancies. Both midwife as gynecologist would recommend it to pregnant women and their colleague caregivers, and they proposed extending remote monitoring to all women with high-risk pregnancies. However, additional training on the technical aspects of remote monitoring (devices, software platform, etc.) is required. Most of the mothers were also satisfied with the remote monitoring prenatal follow-up. They reported a feeling of security throughout their pregnancy and were not concerned about sharing their health data with the caregiver. The majority of mothers wanted to be contacted within 3–12 hours after performing a measurement with an abnormal result, preferably by phone. These results imply the need for a care center to undertake 24/7 surveillance of the vital parameters of these patients.

FUTURE PERSPECTIVES

This doctoral thesis has increased the knowledge and tools available for the use of remote monitoring in the medical context. However, many critical elements remain to be explored.

In this thesis, we emphasized the importance of clinical testing of new technologies and mobile health services to guarantee patient safety and high-quality data. We validated the smartphone-based PPG signal as a tool for detecting AF compared to the one-lead ECG and 12-lead ECG gold standard. Every provider of medical technology or software must undergo extensive clinical trials to be compliant with the highest international standards of the American (FDA) and/or European (CE) regulatory bodies before they may enter the American or European market. To reduce the time-to-market for these companies, further research is needed to determine the appropriate validation method for each mobile health process, signal and technique. Also, future work is needed to provide reference databases with high qualitative & annotated data to entrepreneurs for supporting the development of artificial intelligence without the need for time-consuming data collection. A nice example is the MIT-BIH Arrhythmia Database with labeled ECG records [62].

To facilitate remote monitoring of patients in a clinical setting and to perform research on the effectiveness and cost-efficiency of mobile health services, we developed a digital mobile health research platform. This platform is a digital sandbox to facilitate rapid prototype development at low cost and to facilitate research. As the complexity of remote monitoring increases (from discrete data to more continuous data streams), future research needs to investigate how those platforms will deal with the following elements:

- Context information to interpret the data of measured parameters

Different types of context information can be distinguished like: measurable medical context (i.e. temperature, HR, blood pressure), non-measure context (i.e. dizziness, vomit, headache), risk factors (i.e. smoking, alcohol), physical activity (i.e. walking, running, sleeping) and environment context (i.e. temperature, light exposure, sound). Information about these context factors can give additional insight about the reason for an abnormal measurement of a vital parameter.

Research is needed to better understand the effect of the variability in context on collecting time-intensive data in real-world settings.

- Synchronizing the different data streams from multiple devices

As been shown in this thesis, the best approach to validate an HR app is by a simultaneous measurement on the RH by the smartphone app and an ECG system, compared on the basis of a beat-to-beat analysis. A major challenge in using multi-modal, distributed sensor systems is to maintain a temporal synchronization between individually recorded data streams with different frequencies. Future research is needed to determine data processing algorithms to simplify validation, combination and interpretation of multi-sensor data streams.

- Patient communication and feedback

Earlier research showed that patients communication and feedback process can increase usage, adoption, and the value of apps used to encourage self-management and collaborative care. Further research is needed to determine a communication and feedback system that can be implemented and used across multiple remote monitoring projects. The system needs to adaptive, flexible and tailored to individual patient-specific needs.

The success of long term use and implementation of eHealth interventions, remote monitoring and mobile health is strongly related to individual perspectives and motivations of patients. It is clear that providing a digital system or tool is insufficient to ensure a high adherence rate. Individual motivations must be understood and management pathways established to guarantee the participation of every patient. Related to the WHO's five dimensions of adherence (health system factors, social and economic factors, therapy-related factors, condition-related factors and patient-related factors) [230], further research is needed to determine the corresponding associations between long-term therapies and e-health projects to determine solutions to increase the adherence rate. Advantages and disadvantages of monitoring tools for patients with specific characteristics in heterogenous patient populations need to be determined.

Last, when telehealth and remote monitoring tools become more mainstream in the follow-up of patients, reimbursement for (effective and cost-efficient) validated tools is required to ensure new developments and incentives for doctors' prescriptions. The development of new types of medical devices will be restricted if reimbursement by governments and insurance companies is uncertain. A shift to value-based reimbursement will also affect to whom the devices are marketed and sold, and how the new buyers value the products.

KEY MESSAGES

Below are the final key messages of this thesis. This provides an overview of our work, which involved four years of research.

**Part I
Validation** The most suitable method for the validation of a smartphone based HR application is the simultaneous measurement of HR by the smartphone app and an ECG system, compared on the basis of beat-to-beat analysis.

Diagnosing AF based on a raw smartphone-based PPG waveform, results in a high sensitivity and specificity between a PPG signal and both single-lead and 12-lead ECG interpretations. When such a PPG based smartphone application was delivered to patients, an earlier relapse of AF was detected compared to patients in standard care.

**Part II
Monitoring** A vendor-independent mobile health research platform was built that tackles the third-party device integration and the collection of various data feeds from patient populations.

**Part III
Education** The usage of an e-learning platform for coronary artery disease was influenced by in-center CR participation, educational attainment and age.

**Part IV
Motivation** Fear, depression and cognitive factors such as other-oriented perfectionism are related to woman with lower adherence rate in the RM of pregnant women at risk of GHD. Mothers, midwives and gynecologist evaluated this RM project as an important factor in the follow-up of (high-risk) pregnancies.

SUMMARY|SAMENVATTING

SUMMARY

Mobile health is defined as services supported by mobile communication devices, such as wireless patient monitoring devices, smartphones, personal digital assistants, and tablet computers. Mobile smartphone applications (apps) and, in some instances, companion mobile devices and sensors are the enablers of mobile health and the drivers of the systems. Via remote monitoring the patient can monitor his condition from his home environment enabling the clinicians to remotely follow-up vital parameters and having the possibility to intervene when necessary.

Novel insights into crucial mobile health elements were found during this thesis. A validation framework for smartphone-based heart rate monitoring was developed based on the beat-to-beat analysis. It became clear that atrial fibrillation can be diagnosed based on the smartphone PPG signal with almost exact sensitivity and specificity compared to the gold 12-lead ECG standard. This makes it possible to screen, detect and diagnose atrial fibrillation without the need for additional hardware. The same FibriCheck smartphone application was used in an RCT study, where patients with the smartphone application had a faster detection of relapse compared to patients without a smartphone application. A digital vendor-independent mobile health research platform was built to solve the issues about third-party device integration, and the collection of various data feeds from patient populations. This platform was used to follow-up patients with multiple sclerosis, low back pain, osteoporosis and pregnant women at risk for pregnancy-induced hypertension. The next step in the development will be the integration with existing EMR systems to create a closed-loop information system.

When telehealth tools, such as e-learning, are provided to patients suffering from coronary heart diseases, the majority of participants entered the platform. However, attention is required to the substantial number of patients who did not use the provided system. In-center cardiac rehabilitation, education attainment and age are factors which influenced the platform usage. Another important aspect that influences the use of and adherence to remote monitoring tools is the character of the patient. This thesis showed that both fear and depression, cognitive factors as other-oriented perfectionism are related to women with low adherence to remote monitoring in a project of women for risk of IDH.

Participants and caregivers from the same study considered RM as an important aspect of the prenatal follow-up of women at risk for GHD and would recommend it to their colleagues and other women at risk for GHD.

The future of mobile health tools looks promising; however, attention needs to be given to validation processes for medical smartphone applications, reimbursement for mobile health technology and integration of platform with existing electronic patient software in hospitals. This doctoral thesis increased the knowledge and insight in the complex structure of the digital mobile health puzzle.

SAMENVATTING

Mobiele gezondheidszorg verwijst naar het opvolgen van de patiëntenstatus met behulp van digitale toepassingen, zoals mobiele medische toestellen, smartphones en tablets. Door middel van remote monitoring wordt het mogelijk om een patiënt zijn/haar medische status in de thuisomgeving te blijven opvolgen vanuit het ziekenhuis of huisartsenkabinet. Hierdoor wordt een snellere detectie van achteruitgang, diagnose of aanpassing van behandeling mogelijk.

In deze thesis werden nieuwe essentiële inzichten rond mobiele gezondheidszorg bekomen. Een methodiek voor het valideren van een smartphone-applicatie voor het meten van de hartslag werd ontwikkeld, gebaseerd op de beat-to-beat analyse. Deze thesis toont aan dat voorkamerfibrillatie (VKF) gediagnostiseerd kan worden op basis van een smartphone met led en camera met bijna dezelfde sensitiviteit en specificiteit als het hedendaags gebruikte 12-lead ECG signaal. Dit maakt het mogelijk om VKF te screenen, detecteren en diagnosticeren met behulp van een smartphone, waardoor extra hardware overbodig wordt. Dezelfde FibriCheck smartphone applicatie werd gebruikt in een multicentrische RCT-studie, waarbij terugval van voorkamerfibrillatie sneller werd vastgesteld en gevalideerd bij patiënten met de smartphone-app in vergelijking met patiënten zonder app.

Het centrale thema van dit doctoraat was de ontwikkeling van een digitaal onderzoeksplatform voor remote monitoring. Dit platform is onafhankelijk van leverancier, product of patiëntenpopulatie, waardoor gegevens van verschillende toestellen en toepassingen in één database kunnen worden opgeslagen. Dit platform werd gebruikt om patiënten op te volgen rond de volgende aandoeningen: multiple sclerose, lage rugpijn, osteoporose en zwangere vrouwen met een risico op zwangerschapsvergiftiging. De volgende stap in de ontwikkeling van dit platform, is de integratie met het elektronische patiëntendossier om een volledig gesloten informatieketen te verkrijgen.

In een e-learningstudie bij patiënten met coronaire aandoeningen werd aangetoond dat de meerderheid van patiënten deze telegeneeskundetoepassing gebruiken als dit hen wordt aangeboden. Desondanks dient er aandacht geschonken te worden aan een relevant percentage van patiënten die deze toepassingen niet gebruiken.

Het gebruik van deze toepassingen werd in deze e-learning studie beïnvloed door leeftijd, opleidingsniveau en de aanwezigheid in cardiorevalidatie. Psychosociale problemen en persoonlijkheidskenmerken zijn een bijkomend belangrijk aspect in het adequaat gebruik van remote monitoring tools. Dit proefschrift toont een relatie aan tussen angst, depressie en perfectionisme enerzijds en het adequaat gebruik van remote monitoringstoestellen anderzijds bij een studie van zwangere vrouwen met een risico op zwangerschapsvergiftiging. Zwangere vrouwen, vroedvrouwen en gynaecologen uit deze studie beschouwen remote monitoring als een belangrijk onderdeel van de opvolging van zwangere vrouwen met risico op zwangerschapsvergiftiging.

De toekomst van mobiele gezondheidszorgtoepassingen ziet er veelbelovend uit. Er zal wel rekening gehouden moeten worden met het valideren van medische smartphone applicaties, terugbetaling voor mobiele gezondheidszorgtoepassingen en de integratie van toepassingen en platforms in het elektronische patientendossier. Deze doctoraatsthesis heeft alvast kennis en inzicht bijgebracht in de complexe structuur van de digitale gezondheidszorgpuzzel.

REFERENCES

1. WHO. *The top 10 causes of death*. 2018; Available from: <http://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death>.
2. [A.U.]. *Second Global Survey on eHealth (Global Observatory for eHealth): mHealth: New horizons for health through mobile technologies* 2011 [cited 2017 20-01]; Available from: http://www.who.int/goe/publications/goe_mhealth_web.pdf
3. Megari, K., *Quality of Life in Chronic Disease Patients*. Health Psychol Res, 2013. **1**(3): p. e27.
4. Reed, M., *Reducing Out-of-Pocket Costs to Coordinate Prescription Medication Benefit Design with Chronic Disease Outreach and Clinical Care*. J Gen Intern Med., 2017. **32**(382): p. 1-2.
5. WHO, *A health telematics policy in support of WHO's Health-For-All strategy for global health development: report of the WHO group consultation on health telematics*. 11-16 December, Geneva, 1997. World Health Organization, 1998.
6. Nelson, R., *Telemedicine and Telehealth: The Potential to Improve Rural Access to Care*. Am J Nurs, 2017. **117**(6): p. 17-18.
7. Weinstein, R.S., et al., *Telemedicine, telehealth, and mobile health applications that work: opportunities and barriers*. Am J Med, 2014. **127**(3): p. 183-7.
8. Hamine S, G.-G.E., Faulx D, Green BB, Ginsburg AS, *Impact of mHealth Chronic Disease Management on Treatment Adherence and Patient Outcomes: A Systematic Review*. J Med Internet Res, 2015. **17**(2)(e52).
9. Denny, M.C., et al., *Video-based educational intervention associated with improved stroke literacy, self-efficacy, and patient satisfaction*. PLoS One, 2017. **12**(3): p. e0171952.
10. Albert, N.M., R. Buchsbaum, and J. Li, *Randomized study of the effect of video education on heart failure healthcare utilization, symptoms, and self-care behaviors*. Patient Educ Couns, 2007. **69**(1-3): p. 129-39.
11. Klein-Fedyshin, M., et al., *Collaborating to enhance patient education and recovery*. J Med Libr Assoc, 2005. **93**(4): p. 440-5.
12. van Os-Medendorp, H., et al., *Usage and users of online self-management programs for adult patients with atopic dermatitis and food allergy: an explorative study*. JMIR Res Protoc, 2015. **4**(2): p. e57.
13. State, L., <https://liquid-state.com/digital-health-app-trends-2018/>. 2018.
14. Steinhubl, S.R., E.D. Muse, and E.J. Topol, *The emerging field of mobile health*. Sci Transl Med, 2015. **7**(283): p. 283rv3.
15. Ben-Zeev, D., et al., *Strategies for mHealth research: lessons from 3 mobile intervention studies*. Adm Policy Ment Health, 2015. **42**(2): p. 157-67.

16. Bashi, N., C. Windsor, and C. Douglas, *Evaluating a Web-Based Self-Management Intervention in Heart Failure Patients: A Pilot Study*. JMIR Res Protoc, 2016. **5**(2): p. e116.
17. Househ, M., E. Borycki, and A. Kushniruk, *Empowering patients through social media: the benefits and challenges*. Health Informatics J, 2014. **20**(1): p. 50-8.
18. Kruse, C.S., M. Mileski, and J. Moreno, *Mobile health solutions for the aging population: A systematic narrative analysis*. J Telemed Telecare, 2017. **23**(4): p. 439-451.
19. Zhang, Y., et al., *Remote Mobile Health Monitoring System Based on Smart Phone and Browser/Server Structure*. J Healthc Eng, 2015. **6**(4): p. 717-37.
20. Gondek, D., et al., *Feedback from Outcome Measures and Treatment Effectiveness, Treatment Efficiency, and Collaborative Practice: A Systematic Review*. Adm Policy Ment Health, 2016. **43**(3): p. 325-43.
21. Research2guidance, *mHealth Economics 2016 – Current Status and Trends of the mHealth App Market*. 2016.
22. Kumar, S., et al., *Mobile health technology evaluation: the mHealth evidence workshop*. Am J Prev Med, 2013. **45**(2): p. 228-36.
23. Wesley, K.M. and P.J. Fizur, *A review of mobile applications to help adolescent and young adult cancer patients*. Adolesc Health Med Ther, 2015. **6**: p. 141-8.
24. Van den Akker, H., *Medical apps under the new European MDR, in Factory*. 2017.
25. Sorenson, C. and M. Drummond, *Improving Medical Device Regulation: The United States and Europe in Perspective*. The Milbank Quarterly, 2014. **92**(1): p. 114-150.
26. FDA. *Digital Health Software Precertification (Pre-Cert) Program*. 2018; Available from: <https://www.fda.gov/medicaldevices/digitalhealth/digitalhealthprecertprogram/>.
27. Mishra, S., *FDA, CE mark or something else?—Thinking fast and slow*. Indian Heart Journal, 2017. **69**(1): p. 1-5.
28. Banos, O., et al., *Design, implementation and validation of a novel open framework for agile development of mobile health applications*. Biomed Eng Online, 2015. **14** **Suppl 2**: p. S6.
29. Boulos, M.N., et al., *Mobile medical and health apps: state of the art, concerns, regulatory control and certification*. Online J Public Health Inform, 2014. **5**(3): p. 229.
30. Boulos, M.N.K., et al., *How smartphones are changing the face of mobile and participatory healthcare: an overview, with example from eCAALYX*. BioMedical Engineering OnLine, 2011. **10**: p. 24-24.

31. Yoo, S., et al., *Realization of Real-Time Clinical Data Integration Using Advanced Database Technology*. AMIA Annual Symposium Proceedings, 2003. **2003**: p. 738-742.
32. Stead, W.W., et al., *Integration and beyond: linking information from disparate sources and into workflow*. J Am Med Inform Assoc, 2000. **7**(2): p. 135-45.
33. Davis, S.A., et al., *Patient adoption of an internet based diabetes medication tool to improve adherence: A pilot study*. Patient Educ Couns, 2017. **100**(1): p. 174-178.
34. Kessels, R.P.C., *Patients' memory for medical information*. Journal of the Royal Society of Medicine, 2003. **96**(5): p. 219-222.
35. Toogood PA, A.M., Spear JA, Cook SM, Cook DJ, Taunton MJ, *The monitoring of activity at home after total hip arthroplasty*. Bone Joint J, 2016. **98-B**(11): p. 4.
36. Law LM, E.N., Wason JM., *Use of an embedded, micro-randomised trial to investigate non-compliance in telehealth interventions*. Clin Trials., 2016. **13**(4): p. 7.
37. Lynga Patrik, F.B., Langius-Eklöf Ann & Bohm Katarina, *Perceptions of transmission of body weight and telemonitoring in patients with heart failure?* Int J Qualitative Stud Health Well-being, 2013. **8**: p. 7.
38. Jonassaint, C.R., et al., *Usability and Feasibility of an mHealth Intervention for Monitoring and Managing Pain Symptoms in Sickle Cell Disease: The Sickle Cell Disease Mobile Application to Record Symptoms via Technology (SMART)*. Hemoglobin, 2015. **39**(3): p. 162-8.
39. Souza, W.K., et al., *Self measurement of blood pressure for control of blood pressure levels and adherence to treatment*. Arq Bras Cardiol, 2012. **98**(2): p. 167-74.
40. Osterberg, L. and T. Blaschke, *Adherence to medication*. N Engl J Med, 2005. **353**(5): p. 487-97.
41. Erdine, S. and E. Arslan, *Monitoring treatment adherence in hypertension*. Curr Hypertens Rep, 2013. **15**(4): p. 269-72.
42. Lunden, I. *Smartphone Users Globally By 2020, Overtaking Basic Fixed Phone Subscriptions*. 2015; Available from: <https://techcrunch.com/2015/06/02/6-1b-smartphone-users-globally-by-2020-overtaking-basic-fixed-phone-subscriptions/>.
43. Pelegris, P., et al., *A novel method to detect heart beat rate using a mobile phone*. Conf Proc IEEE Eng Med Biol Soc, 2010. **2010**: p. 5488-91.
44. Kroll, R.R., J.G. Boyd, and D.M. Maslove, *Accuracy of a Wrist-Worn Wearable Device for Monitoring Heart Rates in Hospital Inpatients: A Prospective Observational Study*. J Med Internet Res, 2016. **18**(9): p. e253.

45. Gregoski, M.J., et al., *Development and validation of a smartphone heart rate acquisition application for health promotion and wellness telehealth applications*. Int J Telemed Appl, 2012. **2012**: p. 696324.
46. Politi, M.T., et al., *The dicrotic notch analyzed by a numerical model*. Comput Biol Med, 2016. **72**: p. 54-64.
47. Friberg, L., et al., *Population screening of 75- and 76-year-old men and women for silent atrial fibrillation (STROKESTOP)*. Europace, 2013. **15**(1): p. 135-40.
48. Couetil, J.P., *[Studies of mitral valve insufficiency and indications for surgery]*. Soins Chir, 1987(74): p. 5-8.
49. Pinheiro, N., et al. *Can PPG be used for HRV analysis?* in 2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). 2016.
50. Elgendi, M., *On the analysis of fingertip photoplethysmogram signals*. Curr Cardiol Rev, 2012. **8**(1): p. 14-25.
51. Hertzman, A., *The blood supply of various skin areas as estimated by the photoelectric plethysmograph*. Amer J Physiol, 1938. **1924**(329): p. 40.
52. Jonathan, E. and M. Leahy, *Investigating a smartphone imaging unit for photoplethysmography*. Physiol Meas, 2010. **31**(11): p. N79-83.
53. Ho, C.L., et al., *Smartphone applications (apps) for heart rate measurement in children: comparison with electrocardiography monitor*. Pediatr Cardiol, 2014. **35**(4): p. 726-31.
54. Jo, E., et al., *Validation of Biofeedback Wearables for Photoplethysmographic Heart Rate Tracking*. J Sports Sci Med, 2016. **15**(3): p. 540-547.
55. Giles, D., N. Draper, and W. Neil, *Validity of the Polar V800 heart rate monitor to measure RR intervals at rest*. Eur J Appl Physiol, 2016. **116**(3): p. 563-71.
56. Gamelin, F.X., S. Berthoin, and L. Bosquet, *Validity of the polar S810 heart rate monitor to measure R-R intervals at rest*. Med Sci Sports Exerc, 2006. **38**(5): p. 887-93.
57. Selvaraj, N., et al., *Assessment of heart rate variability derived from fingertip photoplethysmography as compared to electrocardiography*. J Med Eng Technol, 2008. **32**(6): p. 479-84.
58. Torfs, T., et al., *Clinical validation of a low-power and wearable ECG patch for long term full-disclosure monitoring*. J Electrocardiol, 2014. **47**(6): p. 881-9.
59. Terbizan, D.J., B.A. Dolezal, and C. Albano, *Validity of Seven Commercially Available Heart Rate Monitors*. Measurement in Physical Education and Exercise Science, 2002. **6**(4): p. 243-247.

60. Laskowski, E. *What's a normal resting heart rate?* 2016; Available from: <http://www.mayoclinic.org/healthy-lifestyle/fitness/expert-answers/heart-rate/faq-20057979>.
61. Franko, *validate an app: how to design your study and get published*. Journal MTM, 2012: p. 1:2:1--4.
62. Moody, G.B. and R.G. Mark, *The impact of the MIT-BIH arrhythmia database*. IEEE Eng Med Biol Mag, 2001. **20**(3): p. 45-50.
63. Chugh, S.S., et al., *Global burden of atrial fibrillation in developed and developing nations*. Glob Heart, 2014. **9**(1): p. 113-9.
64. Kotecha, D. and J.P. Piccini, *Atrial fibrillation in heart failure: what should we do?* Eur Heart J, 2015. **36**(46): p. 3250-7.
65. Camm, A.J., et al., *Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)*. Europace, 2010. **12**(10): p. 1360-420.
66. Lowres, N., et al., *Screening to identify unknown atrial fibrillation. A systematic review*. Thromb Haemost, 2013. **110**(2): p. 213-22.
67. Kishore, A., et al., *Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis*. Stroke, 2014. **45**(2): p. 520-6.
68. Kirchhof, P., et al., *2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS*. Eur Heart J, 2016. **37**(38): p. 2893-2962.
69. Chan, P.H., et al., *Diagnostic Performance of a Smartphone-Based Photoplethysmographic Application for Atrial Fibrillation Screening in a Primary Care Setting*. J Am Heart Assoc, 2016. **5**(7).
70. Puskas, J.D., et al., *"Spot" ECGs Underestimate Atrial Fibrillation Recurrence After Surgical Ablation*. Innovations (Phila), 2008. **3**(1): p. 7-11.
71. Svennberg, E., et al., *Mass Screening for Untreated Atrial Fibrillation: The STROKESTOP Study*. Circulation, 2015. **131**(25): p. 2176-84.
72. Welton, N.J., et al., *Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis*. Health Technol Assess, 2017. **21**(29): p. 1-236.
73. Jacobs, M.S., et al., *Cost-effectiveness of screening for atrial fibrillation in primary care with a handheld, single-lead electrocardiogram device in the Netherlands*. Europace, 2018. **20**(1): p. 12-18.
74. Rozen, G., et al., *Diagnostic Accuracy of a Novel Mobile Phone Application for the Detection and Monitoring of Atrial Fibrillation*. Am J Cardiol, 2018.
75. Doliwa, P.S., V. Frykman, and M. Rosenqvist, *Short-term ECG for out of hospital detection of silent atrial fibrillation episodes*. Scand Cardiovasc J, 2009. **43**(3): p. 163-8.

76. Haberman, Z.C., et al., *Wireless Smartphone ECG Enables Large-Scale Screening in Diverse Populations*. J Cardiovasc Electrophysiol, 2015. **26**(5): p. 520-6.
77. Burri, H., *Screening for Atrial Fibrillation Using Smartphones and Smartwatches*. Vol. 04. 2018. 11.
78. Vandenberg, T., et al., *Clinical Validation of Heart Rate Apps: Mixed-Methods Evaluation Study*. JMIR Mhealth Uhealth, 2017. **5**(8): p. e129.
79. Mortelmans, C., et al., *Smartphone-based use of the photoplethysmography technique to detect atrial fibrillation in primary care: a diagnostic accuracy study of the FibriCheck application (Preprint)*. 2018.
80. Nemati, S., et al., *Monitoring and detecting atrial fibrillation using wearable technology*. Conf Proc IEEE Eng Med Biol Soc, 2016. **2016**: p. 3394-3397.
81. Tang, S.C., et al., *Identification of Atrial Fibrillation by Quantitative Analyses of Fingertip Photoplethysmogram*. Sci Rep, 2017. **7**: p. 45644.
82. Chugh, S.S., et al., *Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study*. Circulation, 2014. **129**(8): p. 837-47.
83. Lloyd-Jones, D.M., et al., *Lifetime risk for development of atrial fibrillation: the Framingham Heart Study*. Circulation, 2004. **110**(9): p. 1042-6.
84. Go, A.S., et al., *Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study*. Jama, 2001. **285**(18): p. 2370-5.
85. Heeringa, J., et al., *Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study*. Eur Heart J, 2006. **27**(8): p. 949-53.
86. Colilla, S., et al., *Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population*. Am J Cardiol, 2013. **112**(8): p. 1142-7.
87. Schnabel, R.B., et al., *50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study*. Lancet, 2015. **386**(9989): p. 154-62.
88. Benjamin, E.J., et al., *Impact of atrial fibrillation on the risk of death: the Framingham Heart Study*. Circulation, 1998. **98**(10): p. 946-52.
89. Stewart, S., et al., *A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study*. Am J Med, 2002. **113**(5): p. 359-64.
90. Andersson, T., et al., *All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995-2008: a Swedish nationwide long-term case-control study*. Eur Heart J, 2013. **34**(14): p. 1061-7.
91. Stewart, S., et al., *Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK*. Heart, 2004. **90**(3): p. 286-92.

92. Kim, M.H., et al., *Estimation of total incremental health care costs in patients with atrial fibrillation in the United States*. Circ Cardiovasc Qual Outcomes, 2011. **4**(3): p. 313-20.
93. Thrall, G., et al., *Quality of life in patients with atrial fibrillation: a systematic review*. Am J Med, 2006. **119**(5): p. 448 e1-19.
94. Dorian, P., et al., *The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy*. J Am Coll Cardiol, 2000. **36**(4): p. 1303-9.
95. Steg, P.G., et al., *Symptoms, functional status and quality of life in patients with controlled and uncontrolled atrial fibrillation: data from the RealiseAF cross-sectional international registry*. Heart, 2012. **98**(3): p. 195-201.
96. Frick, M., et al., *Factors predicting success rate and recurrence of atrial fibrillation after first electrical cardioversion in patients with persistent atrial fibrillation*. Clin Cardiol, 2001. **24**(3): p. 238-44.
97. Fetsch, T., et al., *Prevention of atrial fibrillation after cardioversion: results of the PAFAC trial*. European Heart Journal, 2004. **25**(16): p. 1385-1394.
98. Mairesse, G.H., et al., *Screening for atrial fibrillation: a European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLAECE)*. Europace, 2017. **19**(10): p. 1589-1623.
99. Turakhia, M.P., et al., *Rationale and design of a large-scale, app-based study to identify cardiac arrhythmias using a smartwatch: The Apple Heart Study*. Am Heart J, 2018.
100. Singh, N., et al., *Clinical Implications of Technological Advances in Screening for Atrial Fibrillation*. Prog Cardiovasc Dis, 2018. **60**(4-5): p. 550-559.
101. Pipitprapat, W., et al., *The validation of smartphone applications for heart rate measurement*. Ann Med, 2018: p. 1-7.
102. Brasier, N., et al., *Detection of atrial fibrillation with a smartphone camera: first prospective, international, two-centre, clinical validation study (DETECT AF PRO)*. Europace, 2018.
103. Lee, J., et al., *Atrial fibrillation detection using a smart phone*. Conf Proc IEEE Eng Med Biol Soc, 2012. **2012**: p. 1177-80.
104. Vandenberg, T., et al., *Clinical Validation of Heart Rate Apps: Mixed-Methods Evaluation Study*. JMIR Mhealth Uhealth, 2017. **5**(8): p. e129.
105. Kirchhof, P., et al., *2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS*. Eur Heart J, 2016. **37**(38): p. 2893-2962.
106. Fetsch, T., et al., *Prevention of atrial fibrillation after cardioversion: results of the PAFAC trial*. Eur Heart J, 2004. **25**(16): p. 1385-94.

107. Weijs, B., et al., *Cardioversion of persistent atrial fibrillation is associated with a 24-hour relapse gap: Observations from prolonged postcardioversion rhythm monitoring*. Clin Cardiol, 2018. **41**(3): p. 366-371.
108. Statista. *Number of smartphone users worldwide from 2014 to 2020 (in billions)*. 2018; Available from: <https://www.statista.com/statistics/330695/number-of-smartphone-users-worldwide/>.
109. Lee, J.H., *Future of the Smartphone for Patients and Healthcare Providers*. Healthc Inform Res, 2016. **22**(1): p. 1-2.
110. Baig, M.M., H. GholamHosseini, and M.J. Connolly, *Mobile healthcare applications: system design review, critical issues and challenges*. Australas Phys Eng Sci Med, 2015. **38**(1): p. 23-38.
111. Association, A.D., *Diagnosis and classification of diabetes mellitus*. Diabetes Care, 2009. **32 Suppl 1**: p. S62-7.
112. Ramani, G.V., P.A. Uber, and M.R. Mehra, *Chronic heart failure: contemporary diagnosis and management*. Mayo Clin Proc, 2010. **85**(2): p. 180-95.
113. Levy, S., *Atrial fibrillation, the arrhythmia of the elderly, causes and associated conditions*. Anadolu Kardiyol Derg, 2002. **2**(1): p. 55-60.
114. Vashist, S.K., E.M. Schneider, and J.H. Luong, *Commercial Smartphone-Based Devices and Smart Applications for Personalized Healthcare Monitoring and Management*. Diagnostics (Basel), 2014. **4**(3): p. 104-28.
115. Brucal, S.G., et al., *Portable electrocardiogram device using Android smartphone*. Conf Proc IEEE Eng Med Biol Soc, 2016. **2016**: p. 509-512.
116. Steinhubl, S.R., E.D. Muse, and E.J. Topol, *Can mobile health technologies transform health care? Jama*, 2013. **310**(22): p. 2395-6.
117. Piwek, L. and D.A. Ellis, *Can Programming Frameworks Bring Smartphones into the Mainstream of Psychological Science? Front Psychol*, 2016. **7**: p. 1252.
118. Zens, M., et al., *Development of a Modular Research Platform to Create Medical Observational Studies for Mobile Devices*. JMIR Res Protoc, 2017. **6**(5): p. e99.
119. Koohpayehzadeh, J., et al., *Validity and reliability of activities coaching context questionnaire*. Medical Journal of the Islamic Republic of Iran, 2014. **28**: p. 41-41.
120. Lanssens, D., et al., *Remote Monitoring of Hypertension Diseases in Pregnancy: A Pilot Study*. JMIR Mhealth Uhealth, 2017. **5**(3): p. e25.
121. Lanssens, D., et al., *The impact of a remote monitoring program on the prenatal follow-up of women with gestational hypertensive disorders*. Eur J Obstet Gynecol Reprod Biol, 2018. **223**: p. 72-78.

122. Lanssens, D., et al., *Prenatal Remote Monitoring of Women With Gestational Hypertensive Diseases: Cost Analysis*. J Med Internet Res, 2018. **20**(3): p. e102.
123. Weiss, J.P., et al., *Towards Designing a Secure Exchange Platform for Diabetes Monitoring and Therapy*. Stud Health Technol Inform, 2018. **248**: p. 239-246.
124. Raj, S. and K.C. Ray, *A Personalized Arrhythmia Monitoring Platform*. Sci Rep, 2018. **8**(1): p. 11395.
125. Cancela, J., et al., *Monitoring of motor and non-motor symptoms of Parkinson's disease through a mHealth platform*. Conf Proc IEEE Eng Med Biol Soc, 2016. **2016**: p. 663-666.
126. Rodrigues, J.J., et al., *Mobile health platform for pressure ulcer monitoring with electronic health record integration*. Health Informatics J, 2013. **19**(4): p. 300-11.
127. Webster, D.E., et al., *The Mole Mapper Study, mobile phone skin imaging and melanoma risk data collected using ResearchKit*. Sci Data, 2017. **4**: p. 170005.
128. Zens, M., et al., *"Back on Track": A Mobile App Observational Study Using Apple's ResearchKit Framework*. JMIR Mhealth Uhealth, 2017. **5**(2): p. e23.
129. Chan, Y.Y., et al., *The Asthma Mobile Health Study, a large-scale clinical observational study using ResearchKit*. Nat Biotechnol, 2017. **35**(4): p. 354-362.
130. Estrin D, C.M., Lakin N *An SDK for building research study apps on Android*. 2017.
131. Suhail, M., *ResearchDroid: An Android Forms and Consent Library*. 2016.
132. X, T. *Appbakery - Mobilize Research*. 2015; Available from: <http://trialx.com/appbakery/>.
133. Sharif, B., et al., *Developing a digital data collection platform to measure the prevalence of sepsis in Wales*. J Am Med Inform Assoc, 2016. **23**(6): p. 1185-1189.
134. Peirce, J.W., *PsychoPy—Psychophysics software in Python*. Journal of Neuroscience Methods, 2007. **162**(1-2): p. 8-13.
135. Yang, G., et al., *IoT-based Remote Pain Monitoring System: from Device to Cloud Platform*. IEEE Journal of Biomedical and Health Informatics, 2018: p. 1-1.
136. Eysenbach, G. and J. Wyatt, *Using the Internet for surveys and health research*. J Med Internet Res, 2002. **4**(2): p. E13.
137. Benson, T., *Using SNOMED and HL7 Together*. 2010. p. 217-225.
138. Townsend, N., et al., *Cardiovascular disease in Europe: epidemiological update 2016*. Eur Heart J, 2016. **37**(42): p. 3232-3245.
139. Wilkins, E., et al., *European cardiovascular disease statistics 2017*. European Heart Network: Brussels, Belgium, 2017.

140. Lavie, C.J. and R.V. Milani, *Cardiac rehabilitation and exercise training in secondary coronary heart disease prevention*. Prog Cardiovasc Dis, 2011. **53**(6): p. 397-403.
141. Lavie, C.J., et al., *Exercise training and cardiac rehabilitation in primary and secondary prevention of coronary heart disease*. Mayo Clin Proc, 2009. **84**(4): p. 373-83.
142. McMahon, S.R., P.A. Ades, and P.D. Thompson, *The role of cardiac rehabilitation in patients with heart disease*. Trends Cardiovasc Med, 2017. **27**(6): p. 420-425.
143. Giannuzzi, P., et al., *Secondary prevention through cardiac rehabilitation: position paper of the Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology*. Eur Heart J, 2003. **24**(13): p. 1273-8.
144. Kotseva, K., et al., *EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries*. Eur J Prev Cardiol, 2016. **23**(6): p. 636-48.
145. Daly, J., et al., *Barriers to participation in and adherence to cardiac rehabilitation programs: a critical literature review*. Prog Cardiovasc Nurs, 2002. **17**(1): p. 8-17.
146. Ruano-Ravina, A., et al., *Participation and adherence to cardiac rehabilitation programs. A systematic review*. International Journal of Cardiology. **223**: p. 436-443.
147. Frederix, I., et al., *A review of telerehabilitation for cardiac patients*. J Telemed Telecare, 2015. **21**(1): p. 45-53.
148. Frentsos, J.M., *Use of Videos as Supplemental Education Tools Across the Cancer Trajectory*. Clin J Oncol Nurs, 2015. **19**(6): p. E126-30.
149. Clerici, C.A., et al., *Videos on rhabdomyosarcoma on YouTube: an example of the availability of information on pediatric tumors on the web*. J Pediatr Hematol Oncol, 2012. **34**(8): p. e329-31.
150. Frederix, I., et al., *eEduHeart I: A Multicenter, Randomized, Controlled Trial Investigating the Effectiveness of a Cardiac Web-Based eLearning Platform - Rationale and Study Design*. Cardiology, 2017. **136**(3): p. 157-163.
151. Piepoli, M.F., et al., *Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: a policy statement from the cardiac rehabilitation section of the European Association for Cardiovascular Prevention & Rehabilitation. Endorsed by the Committee for Practice Guidelines of the European Society of Cardiology*. Eur J Prev Cardiol, 2014. **21**(6): p. 664-81.

152. Schweier, R., et al., *A web-based peer-modeling intervention aimed at lifestyle changes in patients with coronary heart disease and chronic back pain: sequential controlled trial*. J Med Internet Res, 2014. **16**(7): p. e177.
153. Kelders, S.M., et al., *Persuasive system design does matter: a systematic review of adherence to web-based interventions*. J Med Internet Res, 2012. **14**(6): p. e152.
154. Tonkin-Crine, S., et al., *Exploring patients' views of a cognitive behavioral therapy-based website for the self-management of irritable bowel syndrome symptoms*. J Med Internet Res, 2013. **15**(9): p. e190.
155. Rosser, B.A., et al., *Technologically-assisted behaviour change: a systematic review of studies of novel technologies for the management of chronic illness*. J Telemed Telecare, 2009. **15**(7): p. 327-38.
156. Eysenbach, G., *The law of attrition*. J Med Internet Res, 2005. **7**(1): p. e11.
157. Krishnan, S.S. and R.K. Sitaraman, *Video Stream Quality Impacts Viewer Behavior: Inferring Causality Using Quasi-Experimental Designs*. IEEE/ACM Transactions on Networking, 2013. **21**(6): p. 2001-2014.
158. Walthouwer, M.J., et al., *Use and Effectiveness of a Video- and Text-Driven Web-Based Computer-Tailored Intervention: Randomized Controlled Trial*. J Med Internet Res, 2015. **17**(9): p. e222.
159. Wall, M. and L. Teeland, *Non-participants in a preventive health examination for cardiovascular disease: characteristics, reasons for non-participation, and willingness to participate in the future*. Scand J Prim Health Care, 2004. **22**(4): p. 248-51.
160. Brouwer, W., et al., *Characteristics of visitors and revisitors to an Internet-delivered computer-tailored lifestyle intervention implemented for use by the general public*. Health Educ Res, 2010. **25**(4): p. 585-95.
161. Santer, M., et al., *Supporting self-care for families of children with eczema with a Web-based intervention plus health care professional support: pilot randomized controlled trial*. J Med Internet Res, 2014. **16**(3): p. e70.
162. Ross, S.E., et al., *Providing a web-based online medical record with electronic communication capabilities to patients with congestive heart failure: randomized trial*. J Med Internet Res, 2004. **6**(2): p. e12.
163. Evangelia Kintiraki, S.P., George Kotronis, Dimitrios G. Goulis, & Vasilios Kotsis, *Pregnancy-induced hypertension*. Hormones, 2015. **14**(2): p. 12.
164. Hermida, D.E.A.R.C., *Ambulatory Blood Pressure Monitoring for the Early Identification of Hypertension in Pregnancy*. Chronobiology International 2012. **30**(1 - 2): p. 26.
165. Garovic, A.G.K.V.D., *The Management of Hypertension in Pregnancy*. Adv Chronic Kidney Dis., 2013. **20**(3): p. 10.
166. Emelda NO, W.P., & Magann E, *Telemedicine in Obstetrics*. CLIN OBSTET GYNECOL, 2013. **56**(3): p. 12.

167. Cruz J, B.D., & Marques A, *A Home Telemonitoring in COPD: a Systematic Review of Methodologies and Patients' Adherence*. . INT J MED INFORM, 2014. **83**(14).
168. Lanssens, D., Vandenberk, T., Smeets, C.J., De Cannière, H., Molenberghs, G., Van Moerbeke, A., van den Hoogen, A., Roibjns, T., Vonck, S., Staelens, A., Storms, V., Thijs, IM., Grieten, L., & Gyselaers, W., *Remote Monitoring of Hypertension Diseases in Pregnancy: a Pilot Study*. JMIR Mhealth Uhealth, 2017. **5**(3): p. 10.
169. Ganapathy R, G.A., Castleman JS., *Remote monitoring of blood pressure to reduce the risk of preeclampsia related complications with an innovative use of mobile technology*. Pregnancy Hypertens., 2016. **6**(4): p. 12.
170. Rhoads, S.J., et al., *Exploring Implementation of m-Health Monitoring in Postpartum Women with Hypertension*. Telemed J E Health, 2017.
171. Slade A, C.L., Sadler LS & Miller M., *The psychology and psychopathology of pregnancy: Reorganization and transformation*. The psychology and psychopathology of pregnancy: Reorganization and transformation, ed. H.o.i.m. health. Vol. 3. 2009, New York: Guilford Press. 17.
172. KD, B., *Stress, symptoms, self-monitoring confidence, well-being, and social support in the progression of preeclampsia/gestational hypertension*. Journal of Obstetric, Gynecologic & Neonatal Nursing,, 2007. **36**(5): p. 10.
173. Leeners, B., et al., *Psychosocial distress associated with treatment of hypertensive diseases in pregnancy*. Psychosomatics, 2008. **49**(5): p. 413-9.
174. Karsnitz, D.B. and S. Ward, *Spectrum of anxiety disorders: diagnosis and pharmacologic treatment*. J Midwifery Womens Health, 2011. **56**(3): p. 266-81.
175. Weisberg, R.B. and J.A. Paquette, *Screening and treatment of anxiety disorders in pregnant and lactating women*. Womens Health Issues, 2002. **12**(1): p. 32-6.
176. Sutter-Dallay, A.L., et al., *Women with anxiety disorders during pregnancy are at increased risk of intense postnatal depressive symptoms: a prospective survey of the MATQUID cohort*. Eur Psychiatry, 2004. **19**(8): p. 459-63.
177. Mikulincer, M. and P.R. Shaver, *Attachment, group-related processes, and psychotherapy*. Int J Group Psychother, 2007. **57**(2): p. 233-45.
178. Bornstein, R.F. and M.A. Languirand, *Healthy dependency: Leaning on others without losing yourself*. Healthy dependency: Leaning on others without losing yourself. 2003, New York, NY, US: Newmarket Press. 270-270.
179. Ciechanowski, P., et al., *The relationship of attachment style to depression, catastrophizing and health care utilization in patients with chronic pain*. Pain, 2003. **104**(3): p. 627-37.

180. Ciechanowski, P.S., et al., *Attachment theory: a model for health care utilization and somatization*. Psychosom Med, 2002. **64**(4): p. 660-7.
181. Hewitt, P.L., et al., *The Multidimensional Perfectionism Scale: Reliability, validity, and psychometric properties in psychiatric samples*. Psychological Assessment: A Journal of Consulting and Clinical Psychology, 1991. **3**(3): p. 464-468.
182. Lanssens, D., et al., *The impact of a remote monitoring program on the prenatal follow-up of women with gestational hypertensive disorders*. J Med Internet Res, 2018. **223**: p. 72-78.
183. Lanssens D, V.T., Smeets C, De Cannière H, Vonck S, Claessens J, Heyrman Y, Vandijck D, Storms V, Thijs I, Grieten L, Gyselaers W., *Cost- analysis of prenatal remote monitoring of women with gestational hypertensive diseases*. 2018.
184. Mayes, L.C. and J.F. Leckman, *Parental representations and subclinical changes in postpartum mood*. Infant Ment Health J, 2007. **28**(3): p. 281-295.
185. Sidebottom, A.C., et al., *Validation of the Patient Health Questionnaire (PHQ)-9 for prenatal depression screening*. Arch Womens Ment Health, 2012. **15**(5): p. 367-74.
186. Yonkers, K.A., et al., *Typical somatic symptoms of pregnancy and their impact on a diagnosis of major depressive disorder*. Gen Hosp Psychiatry, 2009. **31**(4): p. 327-33.
187. Port, K., K. Palm, and M. Viigimaa, *Daily usage and efficiency of remote home monitoring in hypertensive patients over a one-year period*. J Telemed Telecare, 2005. **11 Suppl 1**: p. 34-6.
188. Celler, B., et al., *Patient Adherence to Scheduled Vital Sign Measurements During Home Telemonitoring: Analysis of the Intervention Arm in a Before and After Trial*. JMIR Med Inform, 2018. **6**(2): p. e15.
189. Maeder, A., et al., *Patient Compliance in Home-Based Self-Care Telehealth Projects*. J Telemed Telecare, 2015. **21**(8): p. 439-42.
190. Bai, G., et al., *Trajectories and predictors of women's health-related quality of life during pregnancy: A large longitudinal cohort study*. PLoS One, 2018. **13**(4): p. e0194999.
191. Biaggi, A., et al., *Identifying the women at risk of antenatal anxiety and depression: A systematic review*. J Affect Disord, 2016. **191**: p. 62-77.
192. Ballard, C.G., et al., *Prevalence of postnatal psychiatric morbidity in mothers and fathers*. Br J Psychiatry, 1994. **164**(6): p. 782-8.
193. Simpson, W., et al., *Comparative efficacy of the generalized anxiety disorder 7-item scale and the Edinburgh Postnatal Depression Scale as screening tools for generalized anxiety disorder in pregnancy and the postpartum period*. Can J Psychiatry, 2014. **59**(8): p. 434-40.

194. Austin, M.P., *Antenatal screening and early intervention for "perinatal" distress, depression and anxiety: where to from here?* Arch Womens Ment Health, 2004. **7**(1): p. 1-6.
195. Zhong, Q.Y., et al., *Diagnostic Validity of the Generalized Anxiety Disorder - 7 (GAD-7) among Pregnant Women*. PLoS One, 2015. **10**(4): p. e0125096.
196. Forno, E., et al., *Maternal obesity in pregnancy, gestational weight gain, and risk of childhood asthma*. Pediatrics, 2014. **134**(2): p. e535-46.
197. Nerenberg, K., S.S. Daskalopoulou, and K. Dasgupta, *Gestational diabetes and hypertensive disorders of pregnancy as vascular risk signals: an overview and grading of the evidence*. Can J Cardiol, 2014. **30**(7): p. 765-73.
198. Whitworth, M. and T. Dowswell, *Routine pre-pregnancy health promotion for improving pregnancy outcomes*. Cochrane Database Syst Rev, 2009(4): p. CD007536.
199. Saner, H. and E. van der Velde, *eHealth in cardiovascular medicine: A clinical update*. Eur J Prev Cardiol, 2016. **23**(2 suppl): p. 5-12.
200. COCIR, *COCIR Telemedicine Toolkit for a better Deployment and Use of Telehealth*. 2011. p. p37.
201. American Diabetes, A., *Diagnosis and classification of diabetes mellitus*. Diabetes Care, 2009. **32 Suppl 1**: p. S62-7.
202. Corwin MJ, M.S., Sunderij SG, Gall S, How H, Patel V, & Gray M., *Multicenter randomized clinical trial of home uterine activity monitoring: Pregnancy outcomes for all women randomized*. AM J OBSTET GYNECOL, 1996. **175**(5): p. 5.
203. Wapner, J.R., Cotton, D.B., Artal, R., Librizzi, R.J., & Ross, M.G., *A randomized multicenter trial assessing a home uterine activity monitoring device used in the absence of daily nursing contact*. Am J Obstet Gynecol, 1995. **172**(8): p. 1026.
204. Dalfrà, M.G., A. Nicolucci, and A. Lapolla, *The effect of telemedicine on outcome and quality of life in pregnant women with diabetes*. J Telemed Telecare, 2009. **15**(5): p. 238-42.
205. Homko, C.J., et al., *Use of an internet-based telemedicine system to manage underserved women with gestational diabetes mellitus*. Diabetes Technol Ther, 2007. **9**(3): p. 297-306.
206. Perez-Ferre, N., et al., *A Telemedicine system based on Internet and short message service as a new approach in the follow-up of patients with gestational diabetes*. Diabetes Res Clin Pract, 2010. **87**(2): p. e15-7.
207. Pérez-Ferre N, G.M., Fernandez D, Velasco V, Runkle I, de la Cruz MJ, Rojas-Marcos PR, del Valle L, & Calle-Pascual AL, *The Outcomes of Gestational Diabetes Mellitus after a Telecare Approach Are Not Inferior to Traditional Outpatient Clinic Visits*. International Journal of Endocrinology, 2010. **2010**: p. 6.

208. Buysse, H., De Moor, G., Van Maele, G., Baert, E., Thienpont, G., Temmerman, M., *Cost-effectiveness of telemonitoring for high-risk pregnant women*. International Journal of Medical Informatics, 2008. **77**: p. 7.
209. Morrison J, B.N., Jacques D, Coleman S K & Tanziano GJ, *Telemedicine: Cost-effective Management of High Risk Pregnancy*. MANAG CARE, 2001. **10**(11): p. 8.
210. Rauf, Z., O'Brien, E., Stampalija, T., Illioniu, F.P., Lavender, T., & Alfirevic, Z., *Home Labour Induction with Retrievable Prostaglandin Pessary and Continuous Telemetric Trans-Abdominal Fetal ECG Monitoring*. PLoS One, 2011. **6**(11): p. 5.
211. O'Brien, E., Rauf, Z., Alfirevic, Z., Lavender, T., *Women's experiences of outpatient induction of labour with remote continuous monitoring*. Midwifery, 2013. **29**: p. 7.
212. Kuleva, M., Salomon, L.J., Benoist, G., Ville, Y., & Dumez, Y., *The Value of Daily Fetal Heart Rate Home Monitoring in Addition to Serial Ultrasound Examinations in Pregnancies Complicated by Fetal Gastroschisis*. Prenatal Diagnosis, 2012. **32**: p. 8.
213. Giardina, T.D., et al., *Releasing test results directly to patients: A multisite survey of physician perspectives*. Patient Educ Couns, 2015. **98**(6): p. 788-96.
214. Beirlaen P., B.B., Bruynseraede C., De Maesschalck L., De Maeyer C., De Raedt W., Dehouck J., Delameilleure M., Denie T., Dock, P., Lambrechts, M., Mattheus R., Meyvis W., Pype P., Ravellingen J., Roelandts H., Smolders R., Staelraeve S., Valckenaerts P., Van Asch K., Van Emelen J., Van Garsse S., Van Herck P., Van Hove D., Van Parijs J., van Vooren P., Vancayzeele, S., Vanden Wijngaerts M., Verhenneman, G., & Willems P, *Mhealth as Key to Quality and Affordability of Care*. Whitepaper Voka Health Community mobile Health, 2015: p. P44.
215. Perez-Ferre, N., et al., *The outcomes of gestational diabetes mellitus after a telecare approach are not inferior to traditional outpatient clinic visits*. Int J Endocrinol, 2010. **2010**: p. 386941.
216. O'Brien, E., et al., *Women's experiences of outpatient induction of labour with remote continuous monitoring*. Midwifery, 2013. **29**(4): p. 325-31.
217. Rauf, Z., et al., *Home labour induction with retrievable prostaglandin pessary and continuous telemetric trans-abdominal fetal ECG monitoring*. PLoS One, 2011. **6**(11): p. e28129.
218. Davis, M.M., et al., *A systematic review of clinician and staff views on the acceptability of incorporating remote monitoring technology into primary care*. Telemed J E Health, 2014. **20**(5): p. 428-38.

219. Christiaens, W., S. Van De Velde, and P. Bracke, *Pregnant women's fear of childbirth in midwife- and obstetrician-led care in Belgium and the Netherlands: test of the medicalization hypothesis*. *Women Health*, 2011. **51**(3): p. 220-39.
220. Johanson, R., M. Newburn, and A. Macfarlane, *Has the medicalisation of childbirth gone too far?* *Bmj*, 2002. **324**(7342): p. 892-5.
221. Kuo, S.C., *[A gender perspective on medicalized childbirth]*. *Hu Li Za Zhi*, 2015. **62**(1): p. 10-5.
222. Parry, D.C., *"We wanted a birth experience, not a medical experience": exploring Canadian women's use of midwifery*. *Health Care Women Int*, 2008. **29**(8): p. 784-806.
223. Sedigh Mobarakabadi, S., K. Mirzaei Najmabadi, and M. Ghazi Tabatabaie, *Ambivalence towards childbirth in a medicalized context: a qualitative inquiry among Iranian mothers*. *Iran Red Crescent Med J*, 2015. **17**(3): p. e24262.
224. Shaw, J.C., *The medicalization of birth and midwifery as resistance*. *Health Care Women Int*, 2013. **34**(6): p. 522-36.
225. Cámara, J., et al., *Robustness-Driven Resilience Evaluation of Self-Adaptive Software Systems*. *IEEE Transactions on Dependable and Secure Computing*, 2017. **14**(1): p. 50-64.
226. Wangberg, S.C., T.S. Bergmo, and J.-A.K. Johnsen, *Adherence in Internet-based interventions*. *Patient preference and adherence*, 2008. **2**: p. 57-65.
227. Toogood, P.A., et al., *The monitoring of activity at home after total hip arthroplasty*. *Bone Joint J*, 2016. **98-b**(11): p. 1450-1454.
228. Law, L.M., N. Edirisinghe, and J.M. Wason, *Use of an embedded, micro-randomised trial to investigate non-compliance in telehealth interventions*. *Clin Trials*, 2016. **13**(4): p. 417-24.
229. Lynga, P., et al., *Perceptions of transmission of body weight and telemonitoring in patients with heart failure?* *Int J Qual Stud Health Well-being*, 2013. **8**: p. 21524.
230. WHO, *Adherence to long-term therapies; evidence for action* 2003.

CURRICULUM VITAE

Vandenberk Thijs

Date of birth: 20 August 1988 (Lommel Belgium)

Nationality: Belgian

Address: Sparrenlaan 23
3270 Scherpenheuvel

E-mail thijsvandenberk@hotmail.com

Education

2010 – 2012	Master in Management and policy in health care	KULeuven
2007 – 2010	Professional Bachelor of Nutrition and Dietetics	Plantijnhogeschool Antwerpen

Professional experience

01/2019 –	Project Manager EPD	Heilig Hart Mol
02/2015 – 03/2019	PhD research	Hasselt University
06/2014 – 02/2015	Medical software Consultant	E-trinity CTG
04/2013 – 06/2014	Implementation Consultant	Xperthis, Heverlee
12/2012 – 04/2013	Software Consultant	ChipSoft Niel/Amsterdam

SCIENTIFIC ACHIEVEMENTS

PAPERS PUBLISHED IN INTERNATIONAL PEER-REVIEWED JOURNALS

Langsens D, **Vandenberk T**, Smeets CJ, De Cannière H, Vonck S, Claessens J, Heyrman Y, Vandijck D, Storms V, Thijs IM, Grieten L, Gyselaers W. *Prenatal Remote Monitoring of Women with Gestational Hypertensive Diseases: Cost Analysis*. J Med Internet Res. 2018; 20(3): e102."

Smeets CJ, Vranken J, Van der Auwera J, Verbrugge FH, Mullens W, Dupont M, Grieten L, De Cannière H, Langsens D, **Vandenberk T**, Storms V, Thijs IM, Vandervoort PM. *Bioimpedance Alerts from Cardiovascular Implantable Electronic Devices: Observational Study of Diagnostic Relevance and Clinical Outcomes*. J Med Internet Res. 2017; 19(11): e393."

Langsens D, **Vandenberk T**, Thijs IM, Grieten L, Gyselaers W. *Effectiveness of Telemonitoring in Obstetrics: Scoping review*. J Med Internet Res. 2017; 19(9): e327. "

Vandenberk T, Stans J, Mortelmans C, van Haelst R, Van Schelvergem G, Pelckmans C, Smeets CJ, Langsens D, De Cannière H, Storms V, Thijs IM, Vaes B, Vandervoort PM. *Clinical Validation of Heart Rate Apps: Mixed-Methods Evaluation Study*. JMIR Mhealth Uhealth. 2017; 5(8): e129."

Langsens D, **Vandenberk T**, Smeets CJ, De Cannière H, Molenberghs G, Van Moerbeke A, van den Hoogen A, Robijns T, Vonck S, Staelens A, Storms V, Thijs IM, Grieten L, Gyselaers W. *Remote Monitoring of Hypertension Diseases in Pregnancy: A Pilot Study*. JMIR Mhealth Uhealth. 2017; 5(3): e25."

Smeets CJP, Verbrugge FH, Vranken J, Van der Auwera J, Mullens W, Dupont M, Grieten L, De Cannière H, Langsens D, **Vandenberk T**, Storms V, Thijs IM, Vandervoort P. *Protocol - driven remote monitoring of cardiac resynchronization therapy as part of a heart failure disease management strategy*. Acta Cardiol. 2017: 1 – 10."

Grieten L, **Vandenberk T**, Nuyens D. 'Smart' solutions for paroxysmal atrial fibrillation? *Europace*. 2017 Jul 1;19(7):1108. doi: 10.1093/europace/euw164.

Frederix I, **Vandenberk T**, Janssen L, Geurden A, Vandervoort P, Dendale P. *eEduHeart I: A Multicenter, Randomized, Controlled Trial Investigating the Effectiveness of a Cardiac Web-Based eLearning Platform - Rationale and Study Design*. *Cardiology*. 2017;136(3):157-163. doi: 10.1159/000448393. Epub 2016 Sep 23."

Laanssens D, Vonck S, **Vandenberk T**, Schraepen C, Storms V, Thijs IM, Grieten L, Gyselaers W. *A prenatal remote monitoring program in pregnancies complicated with gestational hypertensive disorders: what are the contributors to the cost savings?* *Telemed J E Health*. 2018 Oct 30. doi: 10.1089/tmj.2018.0147

PAPERS IN REVIEW IN INTERNATIONAL PEER-REVIEWED JOURNALS

Laanssens D*, **Vandenberk T***, Lodewijckx J, Peeters T, Thijs IM, Grieten L, Gyselaers W.

*The perception of midwives, gynecologists and recently delivered women to remote monitoring for prenatal care. *Shared first authorship.*

de Cannière H, Smeets CJ, Lee S, Squillace G, Groenendaal W, Grieten L, Laanssens D, **Vandenberk T**, Storms V, Thijs IM, Vandervoort PM. *Optimal electrode configuration for a wearable bioimpedance-based respiration monitoring device.*

Vandenberk T, Pelckmans C, Mortelmans C, Van Haelst R, Proesmans T, Storms V, Thijs I, Vaes B, Vandervoort P, Grieten L. *Diagnosing Atrial Fibrillation based on the qualitative analysis of a smartphone derived PPG waveform.*

Vandenberk T, Storms V, Laanssens D, De Canniere H, Smeets C, Thijs I, Batool T, Vanrompay Y, Vandervoort P, Grieten L. *Vendor-independent mobile health monitoring platform: A research platform for digital health studies.*

Vandenberk T, Frederix I, Geurden A, Janssen L, Orolé S, Degryse L, Smeets S, Bielen J, Puts S, Dendale M, Scherrenberg M, Govaerts M, Thijs I, Storms V, Vandervoort P, Grieten L, Dendale P. *Telerehabilitation for cardiac patients: a multicenter randomized, controlled trial investigating the usage of a post-discharge e-learning platform*

Vandenberk T*, Lanssen D*, Storms V, Thijs I, Bamelis L, Grieten L, Gyselaers W, Tang E, Luyten P. *Relationship between adherence to remote monitoring and patient characteristics in women with pregnancy-induced hypertension.*
*Shared first authorship

Vandenberk T*, Desteghe L*, D'Onofrio V, Kluts K, Proesmans T, Smeets C, Lanssens D, De Canniere H, Storms V, Thijs I, Dendale P, Heidbuchel H, Vandervoort P, Grieten L. *Smartphone application for instant detection of recurring atrial fibrillation: a randomized controlled trial.* *Shared first authorship

OTHER PUBLICATIONS

Lanssens D, **Vandenberk T**, Lodewijckx J, Peeters T, Thijs iM, Grieten L, Gyselaers W. *De perceptie van pas bevallen moeders, vroedvrouwen en gynaecologen over een prenatale opvolging aangevuld met telemonitoring.* Tijdschrift voor Vroedvrouwen. 2017; 23(1): 19-28.

ABSTRACTS AT (INTER)NATIONAL CONFERENCES

Lanssens D, **Vandenberk T**, Lodewijckx J, Peeters T, Grieten L, Gyselaers W. 'Telemonitoring bij zwangeren met GHD'. VBOV Trefdag. Location: Ghent, Belgium. Date: 20 October, 2016."

Lanssens D, **Vandenberk T**, Lodewijckx T, Peeters T, Grieten L, Gyselaers W. 'The perception of an implemented remote monitoring follow-up program by patients, midwives and obstetricians' Third European Congress on eCardiology and eHealth. Location: Berlin, Germany. Date: 26 – 28 October 2016."

Smeets CJ, Verbrugge FH, Vranken J, Van der Auwera J, Mullens W, Dupont M, Grieten L, De Cannière H, Lanssens D, **Vandenberk T**, Storms V, Thijs IM, Vandervoort P. *Remote disease monitoring of cardiac resynchronization therapy patients* (Poster, 3rd European Congress on eCardiology and eHealth, Berlin, Germany)

Smeets CJ, Verbrugge FH, Vranken J, Van der Auwera J, Mullens W, Dupont M, Grieten L, De Cannière H, Lanssens D, **Vandenberk T**, Storms V, Thijs IM, Vandervoort P. *Bioimpedance algorithms in implantable electronic cardiac devices: relevant diagnostics or waste of time?* (Poster, ACC.17:66th Annual Scientific Session & Expo, Washington, USA).

Vandenberk T, V. D'Onofrio, J. Van der Auwera, I. Thijs, V. Storms, P. Vandervoort, L. Grieten. *Smartphone application for detection of recurrent Atrial Fibrillation*. (Poster, 3rd European Congress on eCardiology and eHealth, Berlin, Germany)

Lanssens D, **Vandenberk T**, Lodewijckx J, Peeters T, Grieten L, Gyselaers W. *The perception of an implemented Remote Monitoring Follow-up Program by Patients, Midwives and Obstetricians*. (Poster, 3rd European Congress on eCardiology and eHealth, Berlin, Germany)

Vandenberk T, Reekmans J, Habex S, Reyskens T, Pelssers M, Geusens N, Lanssens D, Vandervoort P, Storms V, Grieten L. *Vendor-independent mobile health monitoring platform: A research platform for digital health studies*. (Biomedica 2015)

ORAL PRESENTATIONS

Vandenberk T, Van Schelvergem J, Pelckmans C, Thijs I, Storms V, Vaes B, Vandervoort P. *PPG versus single lead ECG for the diagnosis of Atrial Fibrillation*. (4th European Congress on eCardio & eHealth)

Vandenberk T, Frederix I, Janssen L, Geurden A, Storms V, Vandervoort P, Grieten L, Dendale P. *Do Coronary Artery Disease Patients Use an E-Learning Platform when Provided*. (Med-e-Tel, Luxembourg)

AWARDS

2017	Young Investigator Award	European Society of Cardiology
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