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Creating a continuum of care : smart technology in patients with cardiovascular disease

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Creating a continuum of care
Smart technology in patients with cardiovascular disease

Roderick W. Treskes

Colophon

The studies described in this thesis were conducted at the Department of Cardiology of the Leiden University Medical Center, Leiden, The Netherlands

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Creating a continuum of care
Smart technology in patients with cardiovascular disease

Proefschrift

Ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,
volgens het besluit van het College voor Promoties
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Voor mijn ouders

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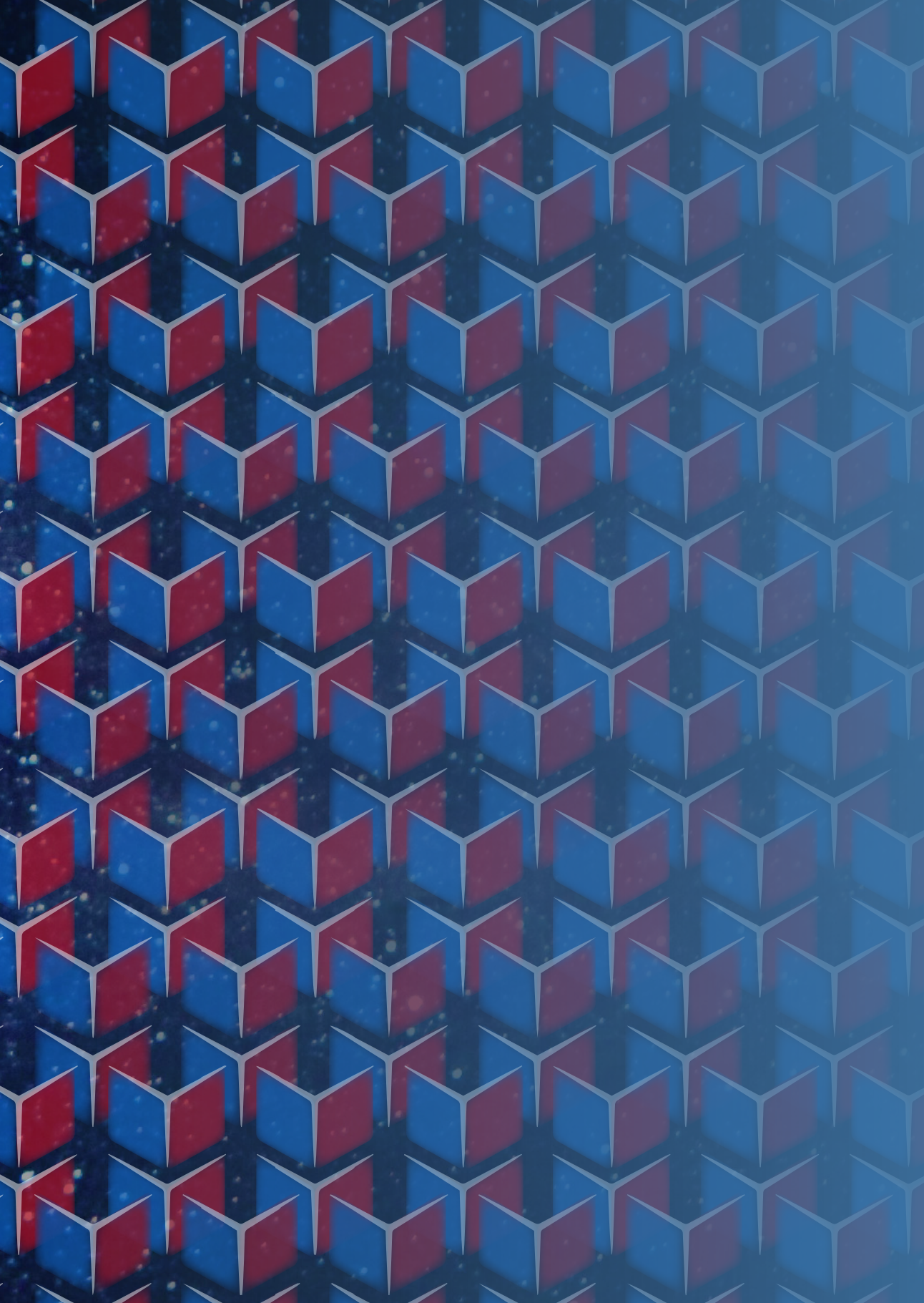


CHAPTER 1

General introduction and outline of the thesis

Setting the scene

Telemedicine has been part of healthcare in Leiden for a long time. The famous Willem Einthoven, Nobel prize laureate in 1924, already transferred his ECGs from his laboratory to the ward via telephone lines.(1) In 1996, ironically, the paper of the Academic Hospital Leiden "Cicero" already showed the hazards of the current health care system (especially the fully packed parking garage) and the solution: the world wide web and the possibility of teleconsultations.(2) After 1996, personal computers, pocket sized agenda's, internet enabled mobile phones and smartphones were consecutively introduced. After the introduction of the iPhone in 2007 and the subsequent inclusion of numerous healthcare apps in the App Store, the potential of e-Health was recognized. First, e-Health has the potential to defrag the current healthcare system. The current healthcare system has become fragmented and patients with chronic conditions often have to switch between multiple doctors, departments and hospitals. As a consequence, information has to be transferred between multiple doctors and no continuous monitoring of patients is currently possible. With e-Health devices, information can be digitally stored and transferred. Furthermore, patients can apply the devices themselves without assistance of staff, enabling more frequent monitoring. Smartphone devices which enable self-measurement of ECG, blood pressure, weight and saturation are already available.(3, 4)

Second, e-Health might help patients with prevention. A recent report of the Centers for Disease Control and Prevention (CDC) showed that approximately 33% of cardiovascular deaths are preventable with lifestyle adjustments.(5) In terms of secondary prevention, regular exercise is as effective as medication in coronary heart disease patients.(6) Mobile apps allow patients to track their lifestyle (body mass index, dietary intake, exercise) and even coach them based on the acquired data. Various apps give hints to exercise more, lose weight or improve dietary intake. It can be expected that these apps will play an important role in primary and secondary prevention of cardiovascular disease in the near future.

Third, mobile apps might help to improve the way patients are informed. Studies have shown that better informed patients (i.e. patients that know cognitively more about the pathophysiology, treatment and prognosis of their disease) have better outcomes.(7) This may be due to various reasons, which include better medication adherence and better lifestyle. Mobile apps can give patients insight in their own data. Furthermore, apps can give information about the pathophysiology of the disease.

Fourth, mostly due to the advantages mentioned above, mobile apps may contribute to higher patient satisfaction.

Fifth, the advantage of mobile health is that it is built on an already existing infrastructure. Data from the Dutch Statistics Bureau (in Dutch: Centraal Bureau voor de Statistiek) show that in 2017, 97.1% of the entire Dutch population had internet and 89% of all Dutch citizens had a smartphone. Of the elderly population (aged 65 years or older), 88.3% had internet access and 62.2% had a smartphone. It is worth noticing that the last percentage was 9.8% in 2012, marking an increase of 535% in five years.(8)

Sixth, mobile health is said to lower costs of healthcare delivery. Costs of healthcare in The Netherlands have increased from 46 billion euros in 2001 up to 96 billion euros in 2016.(9) This amount is expected to increase the upcoming years.(9) Healthcare expenditures are growing faster than the economy, making the system unsustainable for the future. As treatment options are increasing, population size is increasing and life expectancy is increasing, prevalence of cardiovascular disease and subsequent demand for cardiovascular care is estimated to rise in the upcoming 10 years.(10) Mobile health might be an important tool to contain costs of care.

However, scientific evidence published in peer reviewed journals for all promises above is mostly lacking. In telemonitoring for heart failure, for example, two major trials were unable to demonstrate a difference in all-cause mortality or hospital readmissions.(11, 12) Also, scientific evidence for cost-reductions is rare. Although studies have shown that e-Health is cost-effective, most studies show an increase in costs (as well as an increase in clinical effectiveness), but do not show a cost reduction.(13)

Lastly, there is the issue of data safety. There have been examples of apps claimed to measure blood pressure or prevent pregnancy. The blood pressure apps claimed to measure blood pressure with the smartphone camera only. Kumar et al.(14) reviewed the 107 most downloaded apps after searching for “hypertension” in the Apple App Store and Google Play Store. Of all apps, 6.5% claimed to be able to measure blood pressure. None of these apps were validated.(14) Another recent example (though not in cardiovascular disease) is the Natural Cycles app, which claims to predict fertility in women by daily temperature measurements.(15) Nevertheless, 37 women visited a hospital in Sweden for abortion because they became pregnant despite using the app.(16)

In practice, so far, development and implementation of mobile health is mostly money driven. Over the past five years, the number of start-ups in smart technology has grown exponentially, as well as the investment in these start-ups. In 2012, total size of the mHealth market was 6.7 billion US dollars. In 2018, this market is projected to 33.6 billion (an increase of 401%).(17) This has resulted in an exponential increase in apps, smartphone compatible wearables and platforms that collect and represent these data. Of course, these investments have to pay off and therefore it has been suggested that these healthcare technologies might increase supplier induced demand, thereby increasing volumes and costs.

Furthermore, big technology companies (e.g. Apple, Google and Microsoft) are investing in healthcare. They have all resources to become big players in healthcare. They have the money (all companies net incomes are estimated to be 48 billion, 16 billion and 21 billion US dollars in respectively) and the data.(18-20) Apple has launched the Apple Health App, which tracks sensitive health information (such as BMI, temperature and physical activity) and is now launching a service that allows iPhone users to view their electronic medical record on their smartphone.(21) Microsoft has started a similar project, "HealthVault",(22) which allows users to store their medical records on Microsoft owned servers (the cloud). These companies, and especially Google, have the knowledge to transform these data into clinical meaningful information. Google, famously, was able to predict flu epidemics based on search data.(23)

In order for cardiologists to be in the lead in an era where computers are integrated in healthcare delivery, it is important to generate scientific evidence on the effects of e-Health in healthcare delivery.

Defining e-Health

The first step might be to be conclusive on the definition. One of the interesting aspects of e-Health, is the confusion about its definition.(24-30) Searching various dictionaries, it was found that the Oxford Dictionary(24), the Dutch "Van Dale dictionary"(25), Dorland's Medical Dictionary(26) and Stedham's Medical Dictionary(27) do not provide a definition of e-Health. The Dutch medical dictionary "Pinkhof Geneeskundig Woordenboek" defines e-Health as "the use of information and communication technology, especially internet technology and ICT appliance to support health care".(28)
Furthermore, searching the literature in Pubmed using the search term "("ehealth"[ti] OR "e-health"[ti] OR "electronic health"[ti]) AND ("definition"[ti] OR "define"[ti] OR "definitions"[ti])", two eligible reviews were found. The first one by Oh and colleagues, published in 2005, encompasses a thorough search of various scientific

databases including MEDLINE and Web of Science, as well as a search of Google Scholar and Google. A total of 51 unique definitions were found and discussed.(29) In 2012, Showell and al. reviewed the literature for publications about the definition of e-Health. No other eligible articles than Oh et al. were found.(30)

Even when picking one definition of e-Health, the term remains an umbrella term. When following the definition of the RVZ, e-Health can vary from a physician e-mailing his patient to an implantable chip that transfers live blood glucose levels. Therefore, the RVZ subdivides e-Health into: general information, wellness, monitoring of vital signs, establish a diagnosis, therapeutic advices, communication or a combination of the previous.(31) In this thesis, e-Health is predominantly seen as monitoring of vital signs. This is often referred to as telemonitoring.

General outline of the thesis

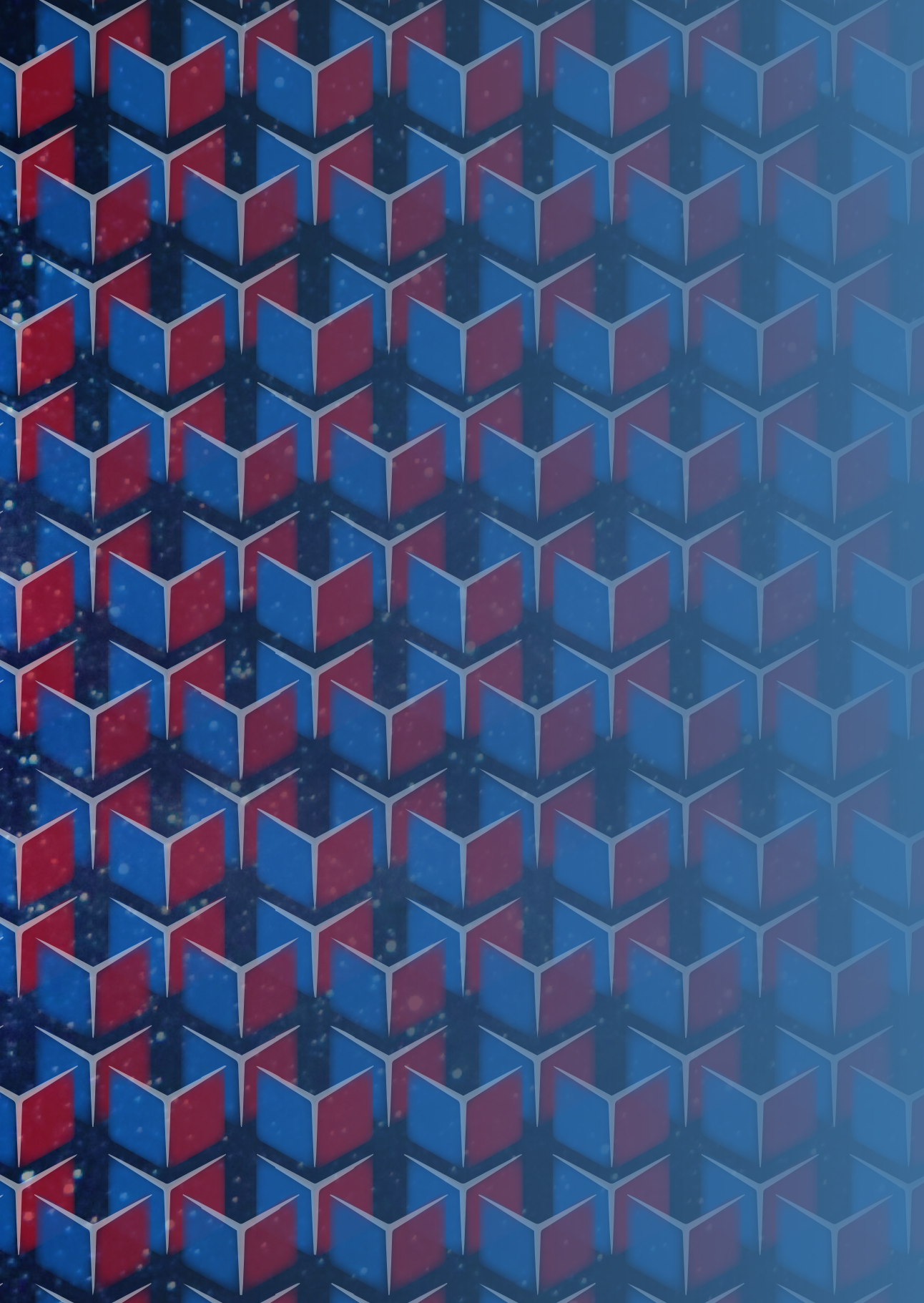
It is the purpose of this thesis to investigate if telemonitoring in patients with cardiovascular disease can improve clinical and cost-effectiveness.

In **chapter 2**, an overview is given of different telemonitoring strategies that are available for patients with cardiovascular disease. In **chapter 3**, it is discussed how data derived from these telemonitoring devices need to be integrated into the electronic medical record in such a way that clinicians are not hampered by information overload. In **chapter 4**, a randomized controlled trial investigating the clinical-, and cost-effectiveness telemonitoring intervention in post myocardial infarction patients is discussed. In **chapter 5**, an RCT investigating the diagnostic detection rate of a mobile ECG device in patients with cryptogenic stroke is presented. The diagnostic accuracy of the blood pressure monitors used in the trial described in chapter 4 are discussed in **chapter 6**, comparing four smartphone compatible blood pressure monitors with an oscillometric device and the gold standard. In **chapter 7**, an overview of tools that are used to improve medication adherence are summarized. A possibility of detection of acute ischemia using serial ECG analysis is proposed in **chapter 8**. In **chapter 9**, a new telemonitoring strategy in patients with congenital heart disease, based on healthcare consumption data, is proposed. **Chapter 10** describes a new method of detecting central sleep apnea in heart failure patients using overnight oximetry. In **chapter 11**, conclusions of the different chapters are summarized.

References

1. Einthoven W. Le telecardiogramme. Arch Int de Physiol. 1906;4:132-64.
2. Dam Pv. Pluis: internet 1996 (cited 2018 February 10th).
3. AliveCor (cited 2018 January 11th). Available from: www.alivecor.com.
4. Nokia Health 2018 (cited 2018 January 31th). Available from: https://health.nokia.com/nl/en/.
5. Preventable Deaths from Heart Disease & Stroke 2013 (cited 2018 February 10th). Available from: https://www.cdc.gov/vitalsigns/heartdisease-stroke/index.html.
6. Naci H, Ioannidis JP. Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study. Bmj. 2013;347:f5577.
7. Greene J, Hibbard J. Why does patient activation matter? An examination of the relationships between patient activation and health-related outcomes. J Gen Intern Med. 2012;27(5):520-6.
8. Bureau DS. Internet: access, use and facilities 2017 (cited 2018 February 10th). Available from: http://statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=83429NED&D1=0,2-5&D2=0,3-6&D3=0&D4=a&HDR=T&STB=G1,G2,G3&VW=T.
9. Healthcare expenditures rise with 1.8 percent in 2016 (in Dutch: zorguitgaven stijgen in 2016 met 1,8 procent) 2016 (cited 2018 February 10th). Available from: https://www.cbs.nl/nl-nl/nieuws/2017/20/zorguitgaven-stijgen-in-2016-met-1-8-procent.
10. Narang A, Sinha SS, Rajagopalan B, Ijioma NN, Jayaram N, Kithcart AP, et al. The Supply and Demand of the Cardiovascular Workforce: Striking the Right Balance. Journal of the American College of Cardiology. 2016;68(15):1680-9.
11. Chaudhry SI, Mattera JA, Curtis JP, Spertus JA, Herrin J, Lin Z, et al. Telemonitoring in patients with heart failure. N Engl J Med. 2010;363(24):2301-9.
12. Koehler F, Winkler S, Schieber M, Sechtem U, Stangl K, Bohm M, et al. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: the telemedical interventional monitoring in heart failure study. Circulation. 2011;123(17):1873-80.
13. de la Torre-Diez I, Lopez-Coronado M, Vaca C, Aguado JS, de Castro C. Cost-utility and cost-effectiveness studies of telemedicine, electronic, and mobile health systems in the literature: a systematic review. Telemedicine journal and e-health : the official journal of the American Telemedicine Association. 2015;21(2):81-5.
14. Kumar N, Khunger M, Gupta A, Garg N. A content analysis of smartphone-based applications for hypertension management. Journal of the American Society of Hypertension : JASH. 2015;9(2):130-6.
15. Natural Cycles 2017 (cited 2018 February 10th). Available from: https://www.naturalcycles.com/en.
16. Wong J. Birth control app reported to Swedish officials after 37 unwanted pregnancies 2018 (cited 2018 February 10th). Available from: https://www.theguardian.com/technology/2018/jan/17/birth-control-app-natural-cycle-pregnancies.

17. mHealth (mobile health) industry market size projection from 2012 to 2020 (in billion U.S. dollars) 2018 (cited 2018 February 10th). Available from: https://www.statista.com/statistics/295771/mhealth-global-market-size/.
18. Apple's net income in the company's fiscal years from 2005 to 2017 (in billion U.S. dollars) 2017 (cited 2018 February 10th). Available from: https://www.statista.com/statistics/267728/apples-net-income-since-2005/.
19. Google's net income from 2001 to 2015 (in million U.S. dollars) 2017 (cited 2018 February 11th). Available from: https://www.statista.com/statistics/266472/googles-net-income/.
20. Microsoft's net income from 2002 to 2017 (in billion U.S. dollars) 2018 (cited 2018 February 11th). Available from: https://www.statista.com/statistics/267808/net-income-of-microsoft-since-2002/.
21. Farr C. Apple will let you keep your medical records on your iPhone 2018 (cited 2018 February 11th). Available from: https://www.cnbc.com/2018/01/24/apple-coo-williams-says-new-health-record-beta-is-right-thing-to-do.html.
22. HealthVault 2018 (cited 2018 February 11th). Available from: https://international.healthvault.com/nl/nl.
23. Ginsberg J, Mohebbi MH, Patel RS, Brammer L, Smolinski MS, Brilliant L. Detecting influenza epidemics using search engine query data. Nature. 2009;457(7232):1012-4.
24. Oxford Dictionary of English. Oxford University Press: Oxford, United Kingdom; 2010.
25. Boon CD, Geeraerts D. Van Dale Groot Woordenboek van de Nederlandse taal. Van Dale Lexicografie: Utrecht, The Netherlands; Antwerpen, Belgium; 2005.
26. Block A, Border W, Bruce B, Christopher K, Drake R, Jangid A, et al. Dorland's Medical Dictionary. Saunders: Philadelphia, Pennsylvania, United States of America; 2011.
27. Stegman J, Branger E, Piper T, Palmer Y, Filardo T, Dirckx J, et al. Stedman's Medical Dictionary. Lippincott Williams & Wilkins: Baltimore, Maryland, United States of America; 2006.
28. Everdingen Jv, Eerenbeemt Avd. Pinkhof Geneeskundig Woordenboek. Bohn, Stafleu en Van Loghum: Houten, The Netherlands; 2012.
29. Oh H, Rizo C, Enkin M, Jadad A. What is eHealth?: a systematic review of published definitions. World Hosp Health Serv. 2005;41(1):32-40.
30. Showell C, Nohr C. How should we define eHealth, and does the definition matter? Stud Health Technol Inform. 2012;180:881-4.
31. Rijen Av, Lint Md, Ottes L. Inzicht in e-health Den Haag2002 (updated 2002; cited 2018 January 24th). Available from: http://www.rvz.net/uploads/docs/Achtergrondstudie_-_E-health_in_zicht.pdf.
32. mHealth: new horizons for health through mobile technologies 2011 (updated 2011; cited 2018 January 24th). Available from: http://www.who.int/goe/publications/goe_mhealth_web.pdf.
33. Meurs P, Blerck-Woerdman Av, Groot W, Kremer J, Mackenbach J, Smit M, et al. Consumenten e-Health Den Haag2015 (cited 2018 January 24th). Available from: https://www.raadrvs.nl/uploads/docs/Advies_Consumenten_eHealth.pdf.



Chapter 2

Mobile health in cardiology: a review of currently available medical apps and equipment for remote monitoring

R.W. Treskes, E.T. van der Velde, R. Barendse, N. Bruining

Expert Rev Med Devices. 2016 Sep;13(9):823-30.

Abstract

Introduction

Recent developments in ICDs and smartphone technology have increased the possibilities for remote monitoring. It is the purpose of this review to give an overview of these new possibilities.

Areas covered

Remote monitoring in ICD allows for early detection of lead fractures and remote follow-up of patients. Possible limitations are the lack of standardization and the possible unsafety of the data stored on the ICD. Secondly, remote monitoring of health parameters using smartphone compatible wearables and smartphone medical apps is addressed. Possible limitations include the fact that the majority of smartphone apps are unregulated by the regulatory authorities and privacy issues such as selling of app-generated data to third parties. Lastly, clinical studies with smartphone apps are discussed.

Expert commentary

New technologies in ICDs and smartphones have the potential to be used for remote monitoring. However, unreliability of smartphone technology, inadequate legislation and lack of reimbursement impede implementation.

Introduction

In the Netherlands, highly-specialized care is centralized in a number of University Medical Centers and other large hospitals.(1) If a patient needs high-specialized care, he is referred from a local hospital to one of these specialized centers.(1, 2) After treatment, a patient is referred back to the local hospital.(3) In this structure, involving more than one treating physician and relatively large distances, adequate data exchange, doctor-doctor communication tools, doctor-patient communication tools and remote vital sign monitoring, could enhance safety, efficiency and patient satisfaction of care.(4)

The introduction of the iPhone, allowing users to use the Internet on their telephone, marked the beginning of massive adaptation of smartphone usage.(5) The iPhone, as well as independently released Android phones, allowed users to build and use health and fitness applications. Concordant with the adaptation of smartphones, smartphone compatible devices that can measure various health parameters such as heart rate (HR), blood pressure (BP) and weight have been introduced on the consumer market.(6, 7) These devices are small, handheld, relatively cheap, do not necessitate the assistance of healthcare staff and allow for automatic transferring of generated data, making them suitable for remote monitoring (RM).(8) These trends have increased the interest in mobile health.(Figure 1)

However, these new possibilities are also subject of several constraints, such as data validity, data safety and patient's privacy.(8, 9) It is therefore the purpose of this review to give an overview of the current possibilities and constraints of new technologies for RM in cardiology.

RM of implanted devices

The implementation of the results of large randomized trials showing the effectiveness of implantable cardioverter-defibrillators (ICDs) in clinical practice has led to an exponential rise in the number of implanted ICDs.(10, 11)(Figure 2) The growing number of ICD recipients has resulted in a rapidly increasing workload with respect to the follow-up of these patients.(12)(Figure 3)

Remote follow-up of implanted pacemakers or ICDs can offer a solution to the problem of overcrowded outpatient clinics, and will bring considerable convenience to the patients since they will have to visit to the outpatient clinic less frequently.(12) The clinical and health economics impact of RM however is still under discussion.(13) An RM system makes it possible to alternatively schedule a remote follow-up between in-clinic follow-up.(14) Furthermore, RM may allow early detection of ICD or lead failures without requiring any patient intervention.(12) Furthermore, RM enables early detection of arrhythmias such as atrial fibrillation or confirm either appropriate or inappropriate shock delivery while the patient is still at home.(12)

RM of ICDs can also aid in early detection of technical problems, including device problems such as battery depletion, but also lead problems such as fracture.(15) For instance, the major defibrillator lead problems experienced with Medtronic's Sprint Fidelis lead have proven to be more predictable using RM; in an observatory study which was part of the effectiveness and cost of ICD follow-up schedule with telecardiology (ECOST) trial, involving 40 patients with an ICD who were home monitored, it was shown that RM allowed the early and reliable detection of lead fractures, without a notification by a patient.(15-17)

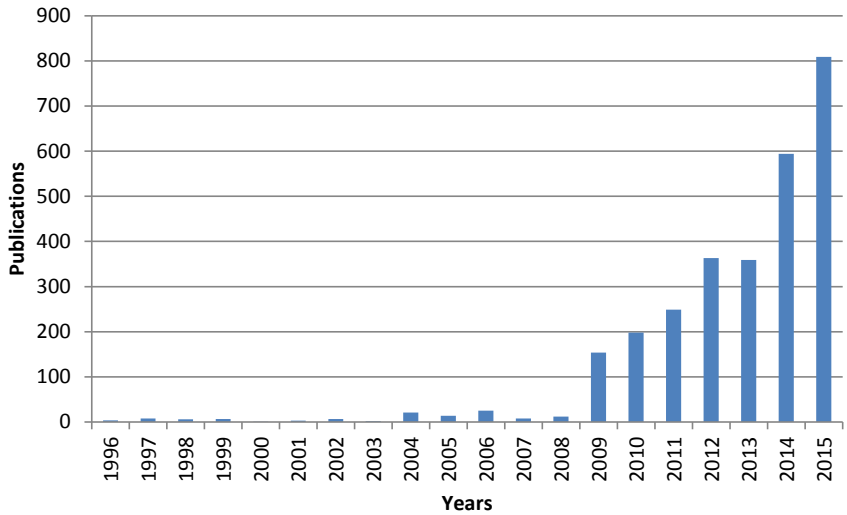


Figure 1. PubMed hits for "mHealth" or "m-Health".

Remote follow-up versus continuous RM

A recent consensus document has proposed terms to standardize the description of the different functions of remote patient management in patients with implanted devices.(18) Remote follow-up involves scheduled automatic device interrogation, which replaces in-office visits for assessing device function; RM involves automatic unscheduled transmission of event alerts; finally patient-initiated interrogations are non-scheduled follow-ups initiated by the patient as a result of a real or perceived clinical event.(19)

Effect of RM on outcomes

Until recently, large randomized trials of RM of patients with ICDs and heart failure (HF) showed no significant difference in mortality.(20, 21) However, a study by Inglis et al.(22) in 2011 has shown that RM appears to have a substantial impact on reducing mortality. This Cochrane Review article included 25 peer-reviewed articles with 11 articles describing randomized controlled trials (RCTs) about telemonitoring

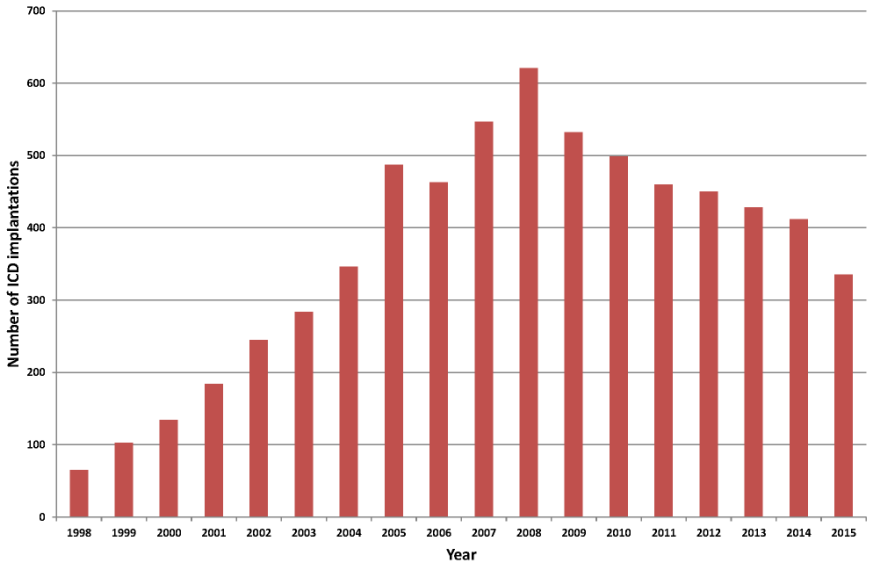


Figure 2. Number of ICD implantations in the Leiden University Medical Center.

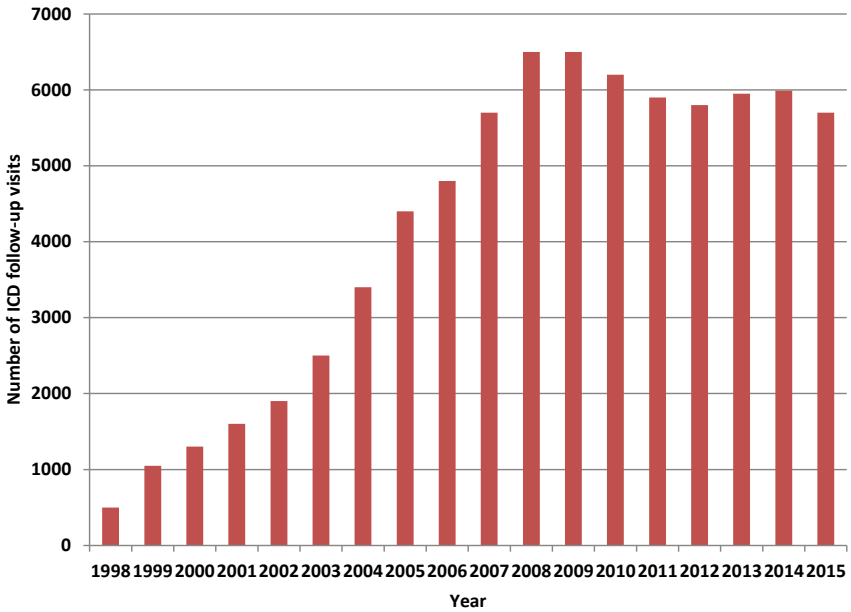


Figure 3. Number of ICD follow-up visits in the Leiden University Medical Center.

(11 articles and 2710 participants) with two analyzing both interventions. In these articles, participants were randomized to either telemonitoring or usual care. All-cause mortality was calculated. The review showed that telemonitoring reduced all-cause mortality (risk ratio (RR): 0.66, *P*<.001). Telemonitoring also reduced hospitalizations (RR 0.79, *P*=.008).(22) Furthermore, in an important recent study by Hindricks et al.,(23) where 664 patients with mild-to-moderately symptomatic chronic HF and a recent dual-chamber ICD or Cardiac Resynchronization Therapy Device implant were randomly assigned to either automatic daily implant-based monitoring in addition to usual care, or usual care alone, the authors showed that after 12 months of follow-up, there was a significantly lower mortality in the RM group (10 vs. 27 deaths, 12 months hazard ratio 0.36, 95% confidence interval 0.17-0.74). They conclude that automatic, daily, implant-based telemonitoring of rhythm and technical parameters had a significantly beneficial effect on the composite clinical score and all-cause mortality.(23)

In a recent study by Klersy et al.,(24) the authors have investigated the effect of RM of implanted cardiac devices on healthcare utilization. In a systemic review and meta-analysis of 11 randomized clinical trials on RM in a total of 5702 patients with heart failure, RM was compared to standard care. The authors conclude that RM is associated with a marked reduction in planned hospital visits and overall costs, without compromising survival or markedly increasing unplanned hospitals visits.(24)

Privacy and security of ICDs

In a December 2012 episode of the popular fictional television series Homeland, the vice president of the United States was assassinated when a terrorist organization wirelessly hacked the implanted pacemaker and induced a tachycardia resulting in a myocardial infarction.(25) Although this scenario may seem far-fetched, there has been a recent demonstration of networked medical device vulnerability: in order to test the vulnerability of security breaches by hackers accessing devices with wireless capability, a group of researchers at the University of Washington, Seattle, WA, USA performed laboratory tests on a Medtronic Maximo DR ICD (Medtronic, Minneapolis, MN, USA). After having partially reversed the ICD's communication protocol, they performed several software radio-based attacks that were able to retrieve encrypted personal patient data, as well as change device settings (including commanded shocks).(26) Therefore, security and privacy of implantable medical devices remain important issues that need more research.(27)

Integration of RM into clinical practice

All of the major manufacturers have developed proprietary methods for data transfer from a patient's device to the healthcare professional.(28) Although there

are some operational differences between manufacturers, the general flow of information is similar with all systems.(28) At regular intervals (depending on the setup of the specific RM system) the implanted device will connect to a receiving system at the patient's home, and then send data on the status of the device and of the patient to the central database system, operated by the device company. The physician can log into a secure website and check the data from the remote follow-up for each patient.(12, 28) However, so far, it has not been possible to integrate the data from RM system into the local electronic health record (EHR) system, which potentially may create patient safety issues. In other words data are stored on different systems and may not be accessible for all healthcare providers.(12) This may potentially result in patient safety issues as it may be difficult to keep track of all information available and information which may be only accessible for certain doctors or technicians. Ideally all information should be available in the EHR system. (12, 28)

Need for standardized data exchange

Since all vendors have developed proprietary solutions for collecting and storing the data from the implanted devices, there is a strong need to be able to import data from the RM database system and to integrate the data into the local EHR in a standardized way.(12) To obtain this goal there is a need for a standard set of observations, communicated in standard messages, such as: therapy settings, events and device self-monitoring. Furthermore, there should be a consistent presentation of data from all devices.(29)

Integrating the Healthcare Enterprise (IHE) Implantable Device Cardiac Observation

To address the requirement of integrating RM data in the local EHR, the IHE Implantable Device Cardiac Observation (IDCO) profile has been developed.(30) IHE is a shared initiative by healthcare professionals and industry to improve the way computer systems in healthcare share information.(31) The IHE IDCO profile defines a standards based transfer of device interrogation information from the interrogation system into the information management system. Features of the IHE IDCO profile are: standard set of observations, communicated in standard messages, consistent presentation of data from all devices, and direct link between interrogating device and local EHR.(32, 33)

Cardiac device outpatient follow-up

The IHE IDCO profile not only brings a solution to the problem of data in the RM database that is not available locally in the Cardiology Information System (CIS). (29) The profile also brings a solution to the following problem: during outpatient

clinic device follow-up, the measurements are performed with the use of a so-called programmer. Such a programmer system can connect wirelessly to the device implanted in the patient, and then extracts the device data (e.g., settings, status, events) from the device. Furthermore, it can also be used to reprogram the settings of the device, if necessary. However, after the measurements are performed, the information needs to be typed in by hand into CIS from a paper report printed on the programmer. The IHE IDCO profile also brings a solution to this problem, by defining standards for this specific data exchange.(31)

Nomenclature

An important part of the IHE IDCO profile is the nomenclature, which is the definition of the variables that are exchanged. Companies that implement the IHE IDCO profile not only need to exchange data in a standard way, but also should make the data available using uniquely defined data definitions.(34)

The Institute of Electrical and Electronics Engineers' (IEEE) Standards Association is defining sets of terminology for 'point-of-care' medical device communication. One of these sets is IEEE 11073-10103 which supports terminology for implantable cardiac devices.(35)

Device vendor involvement and implementation

All large cardiovascular implantable device vendors are involved in the development of the IHE IDCO profile, and in the development of the IEEE 11073-10103 nomenclature standard.(35) All companies have already partially or completely implemented the IHE profile and IEEE standard and have a hardware/software solution available which can be used to communicate with an EHR or data management system.(36)

The implementation from Biotronik (Biotronik SE & Co. KG, Berlin, Germany), Boston Scientific (Marlborough, MA, USA), St Jude Medical (St. Paul, MN, USA) and Sorin (Clamart, France) is freely available, but Medtronic has only implemented the IHE IDCO profile to communicate with their proprietary solution Paceart™. Biotronik, St Jude Medical and Sorin have also already implemented the possibility for the data exchange between a programmer and the EHR. More details also on the implementation have been described previously by Van Der Velde et al.(12)

Remote monitoring with smartphone applications and compatible wearables

ECG devices

There are various devices available for over-the-counter sale that allows their user to make a single lead ECG.(37) These devices are easy-to-use, handheld and do

not require the presence of healthcare professionals. One of these devices is the AliveCor.(6) This device, having the size of a credit card, has two electrodes.(38) Upon placing fingers of one hand against the one electrode and fingers of the other hand against the other electrode the device sends an ultrasound signal. This is picked-up by the smartphone's microphone, filtered and digitalized. Subsequently, a live single lead ECG can be seen on the smartphone screen.(39)
After 30-seconds of measurement, the AliveCor algorithm gives a diagnosis, varying from 'normal', 'possibly abnormal' to 'undetermined'). This algorithm is based on R-R intervals irregularity. In a validation study by Lau et al., it showed a 97% sensitivity and 98% specificity for atrial fibrillation detection.(39) The ECGs are stored on the users smartphone and on AliveCors secured servers (Figure 4).(38)
A patient's account can be linked to a physician's account, allowing the physician to view the ECGs made by the patient. The AliveCor is compatible with Android operating system (OS) and iOS.(38)

BP cuffs

Several smartphone compatible BP cuffs are available for over-the-counter sale. These are all automated oscillometric Bluetooth enabled cuffs, which can be applied without the presence of healthcare staff.(40-42)
Three examples are the iHealth BP5,(40) QardioArm,(41) and Withings Blood pressure monitor.(42) These cuffs are placed around the upper arm of the patient. After automated inflation and deflation, the systolic BP, diastolic BP and heart rate (HR) can be viewed on the smartphone or tablet screen. Results are shown in a device dedicated app. The Qardio and Withings apps are both Android OS and iOS compatible. (41, 42) The iHealth app is only iOS compatible.(40) An advantage of these devices is that data are automatically stored and transferred, saving the patient the time of writing down his measurements and preventing errors in copying the data.

Mobile applications

Adequate measurement of vital signs such as (but not limited to) ECG, BP, HR and weight can be done via smartphone compatible external hardware.(40, 42) There are however apps in the App Store or Play Store that claim to allow the smartphone user to measure heart rate or blood pressure, without the need of external hardware.(43)
These apps rely on photoplethysmography, which is based on the principle that the absorbency of infrared light differs among various types of tissue.(44) The amount of absorbed infrared light determines the amount of infrared light detected by the photodetector. The amount of detected light is determined by the volume of blood crossing the photodetector. Less light is detected when a larger volume of blood is

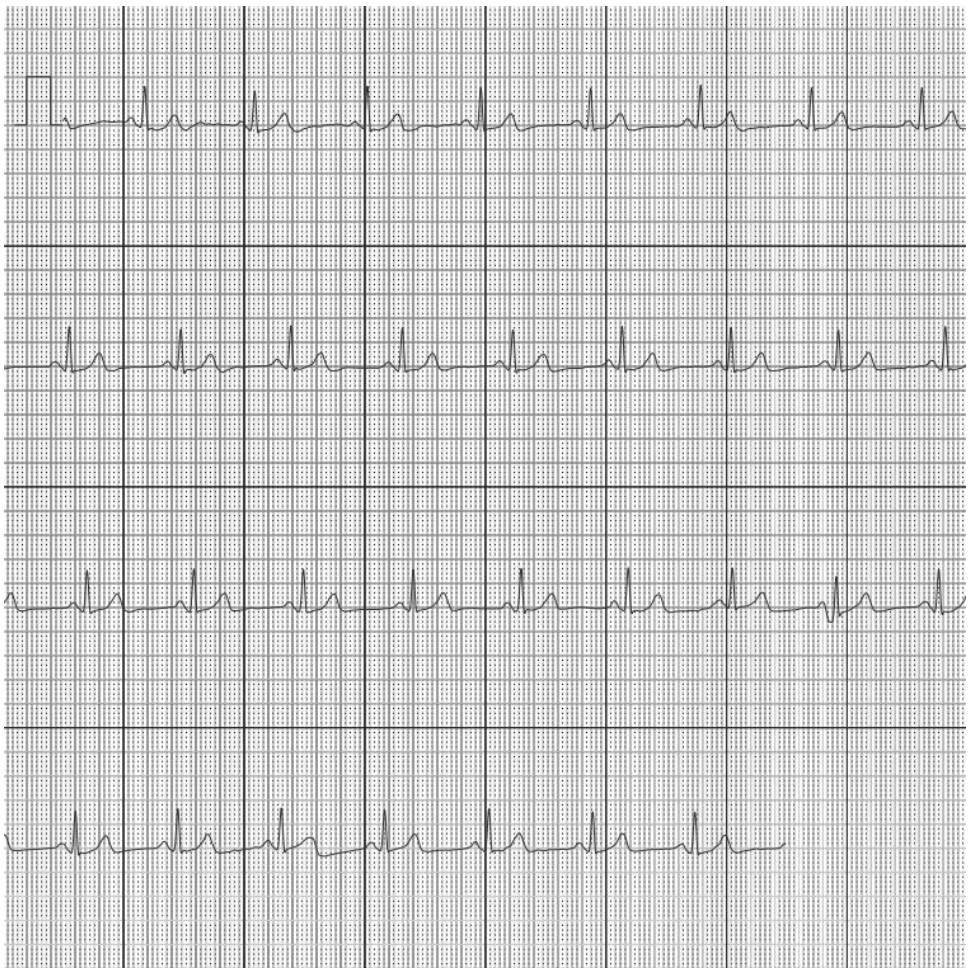


Figure 4. An example of an ECG generated by AliveCor.

crossing the photodetector. Thus, the photodetector is able to detect the pulsatile flow in the arteries.(45, 46) The heart rate can subsequently be calculated by an algorithm.(44)

In these apps, the finger has to be placed in front of the smartphone camera. The flashlight is used to detect volume differences. The heart rate is subsequently calculated by an algorithm in the app.(44) This method has been validated against ECG and oximetry derived HR by Gregoski et al.(44) They investigated 14 healthy subjects. They measured heart rate via an ECG and via the smartphone app simultaneously. All subjects measured their HR during sitting, reading and playing a videogame. The authors compared the HRs and calculated Pearsons correlation coefficients and standard errors of the estimate (SEE). Correlation coefficients of 0.99 were found with an SEE of 0.59 (sitting), 0.94 (reading) and 0.66 (video

game). It was therefore concluded that the app provided reliable HRs.(44) However, the clinical value of these apps may be limited, as these apps are not suitable for continuous heart rate monitoring.

Apps which measure BP are available for download as well. These apps claim to be able to measure BP using only the smartphone's camera.(47) One of these apps is "Quick blood pressure measure and monitor". This app claims to "let you measure your blood pressure using only your iPhone – no cuff required". However, it also claims that it is not a medical device and that the accuracy is still being improved.(47) Furthermore, it is unclear which technique the app is based on. Several articles have described methods for non-invasive continuous BP monitoring, however recognize that these methods are still prone to errors.(48-51)
Measuring BP with only the smartphone might improve healthcare, as it does not require trained healthcare staff and is patient friendly, as it does not require the inflation of a cuff. However, scientific articles which underline the accuracy of these apps are scarce. The reliability of these apps has been questioned in both scientific and non-scientific literature.(52, 53)

Legislation

There are, both in the USA and the European Union (EU), strict regulations for medical devices. A medical device has an intended use, which is the primary purpose for which a medical device is manufactured. All medical devices have to get approval by the US FDA for their intended use before they can be sold and prescribed in the USA or receive a Conformité Européenne-mark before they can be sold and prescribed in the EU.(54, 55)
The FDA and the EU have similar approaches to mobile apps. If a mobile app falls under the definition of medical device, then it needs to be cleared by the certified body (either the FDA in the USA or the European Medical Agency in the EU).
The FDA recognizes that 99% of all health apps are not considered medical devices and are therefore not regulated by the FDA.(54, 55)
According to the EU regulations, mobile apps are considered medical devices if they give a medical diagnosis, if they give a therapeutic advice or if the app is inevitable for the device to function. If an app is considered a medical device, it needs to undergo the same testing and certifying procedures as any other medical device. Selling or prescribing a non CE-marked (EU) or non FDA cleared (USA) app is an offense and can lead to claims for the doctor or manufacturer.(56)
Nevertheless, the fact that a mobile app is not a medical device does not mean that a mobile app is not collecting medical data. Therefore, apart from the regulation, the privacy of patients has to be taken into account when developing, selling or prescribing mobile medical apps.

Privacy and security of mobile apps

An important constraint for implementation of mobile apps in healthcare is privacy and security of the mobile app generated data.(9) Mobile health apps, by definition, generate data about at least part of the user's health. These mobile health generated data are therefore sensitive information and subject of privacy regulations. However, various reports have identified that the majority of mobile apps suffer serious privacy concerns.(57, 58) In a recent article, 79 health apps were evaluated for data safety principles. The results show that the majority did not encrypt data sent over the Internet. A total of 20% did not have a privacy policy.(57) The privacy statements made by mHealth apps have been reviewed by Sunyaev et al.(58) Of 600 commonly used apps only 30.5% had privacy policies. The average reading grade level of these privacy policies was found to be 16 (2.9 standard deviation), which corresponds to college-level literacy. This may inhibit the public's understanding of the privacy risks of mobile applications.(58)

A major concern in collection of data by third parties is the selling of data to third parties. A recent study by Zang et al.(59) investigated the 110 most downloaded free apps. They investigated if the data were transferred to a third-party domain (i.e. a domain that did not primary belong to the application) and categorized that information to identify transmission of sensitive data, personal identifiable data, behaviour data and location data. It found that of the 10 most downloaded health and fitness apps, 9 apps transmitted personal identifiable data to a third party domain.(59)

This selling can even be used for ethically justifiable purposes: Strava, an application that uses global positioning system to track speed and distance during a work-out, sells data to city planners, which use it to decide where new bike paths can be built.(60)

However, there are also purposes which might require further evaluation by privacy and security experts. One concern is that the person's employer or health insurance company will buy the data. Health insurance companies might raise health insurance premiums based on data generated by activity trackers.(61) Recently, the self-insured company British Patrol gave 14000 employees a Fitbit Zip (Fitbit Inc., San Francisco, CA, USA). If an employee walked more than one million steps, he received points that could lower their insurance premiums.(61) Concerns about the usage of data generated by wearables might inhibit adaptation of mobile health apps in clinical practice.(62)

Many mHealth apps target a global community, which makes the manufacturers having to deal with security and privacy laws worldwide. Martinez Pérez et al.(63) reviewed the standards and certifications about security and privacy in North America and the European countries. They state that "In practice, these laws are

too open and too old, and need to be revised and reformulated taking into account the current technologies, industries and healthcare fields, focusing especially on mHealth and the mobile apps industry, which is continuously expanding."(63) Mamlin et al.(64) also point out that the laws, in the United States, need to be updated to match the current methods for recording and transmitting data.(64) Privacy and security issues need to be addressed adequately because otherwise it may adversely affect the trust in mHealth.(65), However, there is no one-size-fits-all approach to security and privacy.(66) mHealth technology should be tailored to deal with the heterogeneous types of information, comfort, skills and concerns of the end users.(67)

Clinical value

Hypertension, lack of physical activity, obesity and smoking are well established risk factors for coronary artery disease (CAD).(68) A combination of these risk factors exponentially raises the chance for the development of CAD.(69) Both medication and lifestyle interventions have been proven to lower BP, lower body mass index and improve lipid profile. In certain clinical studies, lifestyle interventions have been proven to be non-inferior to medication or even stenting.(70, 71) Nevertheless, as the European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice note, changing lifestyle is very difficult.(68) Successful lifestyle interventions often require feedback and training provided by trained healthcare workers and is therefore expensive and small scaled.(68) mHealth can potentially bring training programs to patients on a large scale.

A recent review by Piette et al.(72) identified studies that involved mHealth in weight management, physical activity or smoking cessation. They found that there were numerous trials positively correlating a mHealth intervention and lower BP, lower BMI, higher physical activity and more smoking cessation.(72)

An example of a randomized clinical trial (RCT) with a lower BP is described by Margolis et al.(73) In this RCT, 450 patients were randomized to either home BP measurements (intervention group) or usual care (control group). In the intervention group, patients measured their BP six times a week and sent the data to their pharmacist. The control group received usual care, meaning regular visits to the general practitioner. The results showed that the percentage of patients with controlled BP in the intervention group at twelve months was significantly higher than in the control group. This study is of considerable interest, as it indicates that increasing the frequency of monitoring and subsequent treatment adjustments might improve quality of care.(73)

Burke et al.(74) published a scientific statement on mHealth in cardiology. They reviewed clinical studies in which mobile phones were used to address one or more of the American Heart Association's Life's Simple 7 program health indicators:

healthy weight, enough physical activity, quitting smoking blood glucose and BP control as well as lipids to target levels. For each category, an RCT describing a significant difference between intervention and control groups was found, although several RCTs not finding a significant difference were included as well.(74) Several constraints were applicable to almost every category: whatever tracking device was used, a BP monitor, an ECG apparatus or an activity tracker, it did not stand alone. Concordant coaching, either by SMS, Interactive Voice Recording (IVR), a website or face-to-face, was obligatory in almost all trials in order for the intervention to be clinically effective. The major drawback of this approach is that a mHealth intervention with interactive coaching has seldom been proven to be cost-effective, which inhibits its implementation in healthcare.(72, 74)

Another limitation for clinical implementation is the difficulty to act evidence-based. The methods of all randomized controlled trials differ significantly, making it difficult to extrapolate an evidence-based working method from the literature. Furthermore, there are a lot of so-called “pilot studies” or “feasibility studies”, studies which are typically characterized by a non-randomized design and small sample size.

The final limitation is that in a RCT, one app or mobile technology intervention is studied. Often, this one app is targeting one risk factor for CAD.(74) However, patients at risk for CAD often have more than one risk factor for CAD.(69) So far, very few randomized controlled trials have addressed an intervention in which several apps were applied to the patient at the same time. It can be hypothesized that, given the previously described difficulties to adhere to one app and concordant doctor-patient interaction,(74) adhering to several apps addressing several cardiovascular risk factors will lower the overall clinical effectiveness of the intervention.

Another important question that still needs to be answered in the scientific literature is the long term effect of mHealth lifestyle interventions. Very few studies have studied the effect of a mHealth intervention after coaching is quitted.

Therefore, more research needs to be done in which several apps are applied at the same time. Furthermore, the methods of mHealth intervention need to be standardized for comparison purposes. Lastly, long term effects need to be carefully monitored.

Expert commentary

Mobile health and RM is still in its disruptive phase. The basic tools for remote medicine (i.e. remote diagnosis, remote treatment and remote communication) have been available for less than ten years.(5) Currently, there are a couple of factors essentially inhibiting this new way of delivering care: first, the quality of the available mobile technology is often not sufficient for medical practice. This is the case with most mobile applications for vital sign monitoring. Secondly, the

legislation is still based on traditional medicine. Partly caused by the insufficient quality described above, current policy makers are hesitating to change legislation and allow remote medicine. Thirdly, there is a lack of reimbursement which inhibits active participation in implementation by healthcare professionals. Finally, the long term effects of remote medicine, especially remote coaching, have not been scientifically assessed. Traditionally, legislation and reimbursement regulations are only changed if an intervention has been proven scientifically clinically and cost-effective. As heterogeneity of currently available RCTs and lack of long term evidence inhibit unambiguously scientific conclusions, we expect that remote medicine cannot be fully implemented on a short notice.

Five-year view

We expect that remote medicine, despite the mentioned constraints, will change the way healthcare is delivered. Currently available outpatient clinics, wards and generally ways to deliver healthcare require too much human and financial resources to be sustainable in the future, especially with the ageing population. In five years, there will be more wearables available to measure vital signs. These wearables will be more accurate. Overall, technological constraints will be easily overcome.

With the adjusted legislation, remote medicine will be available to those who prefer to be diagnosed and treated remotely. It is however difficult to expect that remote medicine will be fully implemented in the upcoming five years, especially since medicine is traditionally a slow moving field, keeping in mind that serious legal changes have to be made to speed up the implementation of remote medicine.

Key issues

1. Mobile technology has accelerated remote medicine possibilities.
2. RM has the ability to decrease outpatient clinic visits and improve quality of care. The RM of ICD patients serves as example.
3. A key issue for mobile health to succeed is the integrating of various mobile technology information systems. Therefore, standardization will be a great topic in the nearby future.
4. Mobile access to cardiovascular images, enabling a rapid diagnosis, is still limitedly used since the obliged quality cannot be delivered on mobile phones so far.
5. Mobile apps have the potential to help patient manage their own cardiovascular risk factors, such as blood pressure, weight and activity.
6. The beneficial short term effects of RM have been demonstrated in the literature.

7. Limited literature exists however on the long term effects of mobile apps in RM and lifestyle interventions.
8. The heterogeneity of randomized clinical trials makes it difficult to draw unambiguous conclusions and to practice evidence based medicine.

References

1. NFU, “Erkende Expertisecentra Zeldzame Aandoeningen,” Available via: http://www.nfu.nl/img/pdf/Erkende_expertisecentra_zeldzame_aandoeningen_TOTAAL_FINAL_05-06-2015.pdf, 2015. Retrieved on: 09-05-2016.
2. NFU, “Minister erkent expertisecentra zeldzame aandoeningen,” Available via: http://www.nfu.nl/actueel/minister-erkent-expertisecentra-zeldzame-aandoeningen, 2015. Retrieved on: 09-05-2016.
3. NFU, “Betere samenwerking rond de patiënt met zeldzame aandoening,” Available via: http://www.nfu.nl/actueel/betere-samenwerking-rond-de-patient-met-zeldzame-aandoening, 2016. Retrieved on 11-07-2016.
4. R. W. Treskes, E. T. Van Der Velde, D. E. Atsma, and M. J. Schalij, “Redesigning healthcare: The 2.4 billion euro question? : Connecting smart technology to improve outcome of patients,” Neth Heart J, Apr 6 2016.
5. Statista, “Global Apple iPhone sales from 3rd quarter 2007 to 1st quarter 2016 (in million units),” Retrieved 10-03-2016.
6. AliveCor, Available via: http://www.alivecor.com/, Retrieved on: 26-03-2016.
7. Withings, Available via: http://www.withings.com/eu/en/. Retrieved on: 26-03-2016.
8. P. A. Clark, K. Capuzzi, and J. Harrison, “Telemedicine: medical, legal and ethical perspectives,” Med. Sci. Monit, vol. 16, pp. RA261-RA272, 12/2010 2010.
9. J. G. Anderson, “Social, ethical and legal barriers to e-health,” Int J Med Inform, vol. 76, pp. 480-3, May-Jun 2007.
10. S. G. Priori, C. Blomstrom-Lundqvist, A. Mazzanti, N. Blom, M. Borggrefe, J. Camm, et al., “2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC),” Eur Heart J, vol. 36, pp. 2793-867, Nov 1 2015.
11. I. Goldenberg, J. Gillespie, A. J. Moss, W. J. Hall, H. Klein, S. McNitt, et al., “Long-term benefit of primary prevention with an implantable cardioverter-defibrillator: an extended 8-year follow-up study of the Multicenter Automatic Defibrillator Implantation Trial II,” Circulation, vol. 122, pp. 1265-71, Sep 28 2010.
12. E. T. Van der Velde, D. E. Atsma, H. Foeken, T. A. Witteman, and W. H. Hoekstra, “Remote monitoring of patients with implanted devices: data exchange and integration,” Eur J Prev Cardiol, vol. 20, pp. 8-12, Jun 2013.
13. N. Parthiban, A. Esterman, R. Mahajan, D. J. Twomey, R. K. Pathak, D. H. Lau, et al., “Remote Monitoring of Implantable Cardioverter-Defibrillators: A Systematic Review and Meta-Analysis of Clinical Outcomes,” J Am Coll Cardiol, vol. 65, pp. 2591-600, Jun 23 2015.
14. N. Varma, A. E. Epstein, A. Irimpen, R. Schweikert, and C. Love, “Efficacy and safety of automatic remote monitoring for implantable cardioverter-defibrillator follow-up: the Lumos-T Safely

Reduces Routine Office Device Follow-up (TRUST) trial," Circulation, vol. 122, pp. 325-32, Jul 27 2010.

15. C. J. Borleffs, L. van Erven, R. J. van Bommel, E. T. van der Velde, E. E. van der Wall, J. J. Bax, et al., "Risk of failure of transvenous implantable cardioverter-defibrillator leads," Circ Arrhythm Electrophysiol, vol. 2, pp. 411-6, Aug 2009.
16. L. Guedon-Moreau, P. Chevalier, C. Marquie, C. Kouakam, D. Klug, D. Lacroix, et al., "Contributions of remote monitoring to the follow-up of implantable cardioverter-defibrillator leads under advisory," Eur Heart J, vol. 31, pp. 2246-52, Sep 2010.
17. L. Guedon-Moreau, D. Lacroix, N. Sadoul, J. Clementy, C. Kouakam, J. S. Hermida, et al., "A randomized study of remote follow-up of implantable cardioverter defibrillators: safety and efficacy report of the ECOST trial," Eur Heart J, vol. 34, pp. 605-14, Feb 2013.
18. S. Dubner, A. Auricchio, J. S. Steinberg, P. Vardas, P. Stone, J. Brugada, et al., "ISHNE/EHRA expert consensus on remote monitoring of cardiovascular implantable electronic devices (CIEDs)," Europace, vol. 14, pp. 278-93, Feb 2012.
19. H. Burri, "Remote follow-up and continuous remote monitoring, distinguished," Europace, vol. 15 Suppl 1, pp. i14-i16, Jun 2013.
20. S. I. Chaudhry, J. A. Mattera, J. P. Curtis, J. A. Spertus, J. Herrin, Z. Lin, et al., "Telemonitoring in patients with heart failure," N Engl J Med, vol. 363, pp. 2301-9, Dec 9 2010.
    ***Interesting as it describes a high quality RCT in HF patients.**
21. A. S. Desai, "Home monitoring heart failure care does not improve patient outcomes: looking beyond telephone-based disease management," Circulation, vol. 125, pp. 828-36, Feb 14 2012.
22. S. C. Inglis, R. A. Clark, F. A. McAlister, S. Stewart, and J. G. Cleland, "Which components of heart failure programmes are effective? A systematic review and meta-analysis of the outcomes of structured telephone support or telemonitoring as the primary component of chronic heart failure management in 8323 patients: Abridged Cochrane Review," Eur J Heart Fail, vol. 13, pp. 1028-40, Sep 2011.
23. G. Hindricks, M. Taborsky, M. Glikson, U. Heinrich, B. Schumacher, A. Katz, et al., "Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial," Lancet, vol. 384, pp. 583-590, 8/16/2014.
24. C. Klersy, G. Boriani, A. De Silvestri, G. H. Mairesse, F. Braunschweig, V. Scotti, et al., "Effect of telemonitoring of cardiac implantable electronic devices on healthcare utilization: a meta-analysis of randomized controlled trials in patients with heart failure," Eur J Heart Fail, vol. 18, pp. 195-204, Feb 2016.
25. "Homeland, Season 2, Episode 10 "Broken Hearts"," Available via: http://www.sho.com/sho/homeland/season/2/episode/10#/index, Retrieved: 10-05-2016.
26. H.-B. T. Halperin D, Ransford B, Clark SS, Defend B, Morgan W, Fu K, Kohno T, Maisel WH, "Pacemakers and Implantable Cardiac Defibrillators: Software Radio Attacks and Zero-Power Defenses," Proceedings of the 2008 IEEE Symposium on Security and Privacy, pp. 129-42, 2008.

27. T. H.-B. D Halperin, K Fu, T Kohno, WH Maisel, “Security and privacy for implantable medical devices,” IEEE Pervasive Computing, vol. 7, p. Available via: https://spqr.eecs.umich.edu/papers/b1kohFINAL2.pdf, 2008.
28. H. Burri and D. Senouf, “Remote monitoring and follow-up of pacemakers and implantable cardioverter defibrillators,” Europace, vol. 11, pp. 701-9, Jun 2009.
29. Integrating the Health Enterprise, “PCD Implantable Device Cardiac Observation.,” Available via: http://wiki.ihe.net/index.php/PCD_Implantable_Device_Cardiac_Observation, 2015. Retrieved on: 11-07-2016.
30. Integrating the Health Enterprise, “IHE Cardiology,” Available via: http://www.ihe.net/Cardiology/, Retrieved on: 10-03-2016.
31. Integrating the Health Enterprise, “Main page: Integrating the Healthcare Enterprise,” Available via: http://wiki.ihe.net/index.php?title=Main_Page, Retrieved on: 10-03-2016.
32. H. Heidbuchel, “Telemonitoring of implantable cardiac devices: hurdles towards personalised medicine,” Heart, vol. 97, pp. 931-9, Jun 2011.
33. D. Slotwiner, N. Varma, J. G. Akar, G. Annas, M. Beardsall, R. I. Fogel, et al., “HRS Expert Consensus Statement on remote interrogation and monitoring for cardiovascular implantable electronic devices,” Heart Rhythm, vol. 12, pp. e69-100, Jul 2015.
34. C. C. de Cock, J. Elders, N. M. van Hemel, K. van den Broek, L. van Erven, B. de Mol, et al., “Remote monitoring and follow-up of cardiovascular implantable electronic devices in the Netherlands : An expert consensus report of the Netherlands Society of Cardiology,” Neth Heart J, vol. 20, pp. 53-65, Feb 2012.
35. IEEE Standards Association, “11073-10103-2012-health informatics--point of care medical device communication Part 10103: Nomenclature,” Available via: https://standards.ieee.org/findstds/standard/11073-10103-2012.html, 2012. Retrieved: 10-03-2016.
36. M. Kasparick, S. Schlichting, F. Golatowski, and D. Timmermann, “New IEEE 11073 Standards for interoperable, networked Point-of-Care Medical Devices,” Conf Proc IEEE Eng Med Biol Soc, vol. 2015, pp. 1721-4, Aug 2015.
37. J. Grier, “Comparison and review of portable, handheld, 1-lead/channel ECG/EKG recorders,” Available via: https://www.ndsu.edu/pubweb/~grier/Comparison-handheld-ECG-EKG.html, Retrieved: 09-05-2016.
38. AliveCor, Available at: www.alivecor.com, Retrieved on: 12-01-2016.
39. J. K. Lau, N. Lowres, L. Neubeck, D. B. Brieger, R. W. Sy, C. D. Galloway, et al., “iPhone ECG application for community screening to detect silent atrial fibrillation: a novel technology to prevent stroke,” Int. J. Cardiol, vol. 165, pp. 193-194, 4/30/2013.
40. iHealth, “iHealth Wireless Blood Pressure Monitor,” Available via: https://ihealthlabs.com/blood-pressure-monitors/wireless-blood-pressure-monitor/, Retrieved on: 09-05-2016.
41. Qardio, “QardioArm,” Available via: https://www.getqardio.com/qardioarm-blood-pressure-monitor-iphone-android/, Retrieved on: 09-05-2016.
42. Withings, “Wireless Blood Pressure Monitor,” Available via: https://www.withings.com/eu/en/products/blood-pressure-monitor?, Retrieved on: 09-05-2016.

43. I. Cardiio, “Cardiio - Heart Rate Monitor,” Available via: https://itunes.apple.com/us/app/cardiio-heart-rate-monitor/id542891434?mt=8, Retrieved on: 09-05-2016.
44. M. J. Gregoski, M. Mueller, A. Vertegel, A. Shaporev, B. B. Jackson, R. M. Frenzel, et al., “Development and validation of a smartphone heart rate acquisition application for health promotion and wellness telehealth applications,” Int J Telemed Appl, vol. 2012, p. 696324, 2012.
45. A. Reisner, P. A. Shaltis, D. McCombie, and H. H. Asada, “Utility of the photoplethysmogram in circulatory monitoring,” Anesthesiology, vol. 108, pp. 950-8, May 2008.
46. Millikan, “The Oximeter, an Instrument for Measuring Continuously the Oxygen Saturation of Arterial Blood in Man,” Review of Scientific Instruments, vol. 13, 1942.
47. J. Ren, “Quick Blood Pressure Measure and Monitor,” Available via: https://itunes.apple.com/nl/app/quick-blood-pressure-measure/id890706381?mt=8, Retrieved: 09-05-2016.
48. G. M. Janelle and N. Gravenstein, “An accuracy evaluation of the T-Line Tensymeter (continuous noninvasive blood pressure management device) versus conventional invasive radial artery monitoring in surgical patients,” Anesth Analg, vol. 102, pp. 484-90, Feb 2006.
49. A. V. Challoner and C. A. Ramsay, “A photoelectric plethysmograph for the measurement of cutaneous blood flow,” Phys Med Biol, vol. 19, pp. 317-28, May 1974.
50. J. C. Ruiz-Rodriguez, A. Ruiz-Sanmartin, V. Ribas, J. Caballero, A. Garcia-Roche, J. Riera, et al., “Innovative continuous non-invasive cuffless blood pressure monitoring based on photoplethysmography technology,” Intensive Care Med, vol. 39, pp. 1618-25, Sep 2013.
51. M. Nitzan, Y. Adar, E. Hoffman, E. Shalom, S. Engelberg, I. Z. Ben-Dov, et al., “Comparison of systolic blood pressure values obtained by photoplethysmography and by Korotkoff sounds,” Sensors (Basel), vol. 13, pp. 14797-812, 2013.
52. I. Husain, “Top 10 downloaded iPhone health app can cause significant patient harm,” Available via: http://www.imedicalapps.com/2014/07/iphone-health-app-patient-harm/#, 2014. Retrieved on: 20-02-2016.
53. N. Bruining, E. Caiani, C. Chronaki, P. Guzik, and d. van, V, “Acquisition and analysis of cardiovascular signals on smartphones: potential, pitfalls and perspectives: by the Task Force of the e-Cardiology Working Group of European Society of Cardiology,” Eur. J. Prev. Cardiol, vol. 21, pp. 4-13, 11/2014.
***This document gives insight in the perspective of the e-Cardiology Working Group of the European Society of Cardiology**
54. United States Food and Drug Administration, “Mobile Medical Applications: Guidance for Industry and Food and Drug Administration Staff,” February 9, 2015.
55. European Union, “Green paper on mobile health (“mHealth”),” Available via: https://ec.europa.eu/digital-single-market/en/news/green-paper-mobile-health-mhealth, 2014.
****Very interesting as it describes e-Health as seen by the European Union.**
56. V. E. Meulen S van der, “Dutch DPA finds fitness app violates data protection law,” eHealth Law & Policy, December 2015.
57. K. Huckvale, J. T. Prieto, M. Tilney, P. J. Benghozi, and J. Car, “Unaddressed privacy risks in accredited health and wellness apps: a cross-sectional systematic assessment,” BMC Med, vol. 13, p. 214, 2015.

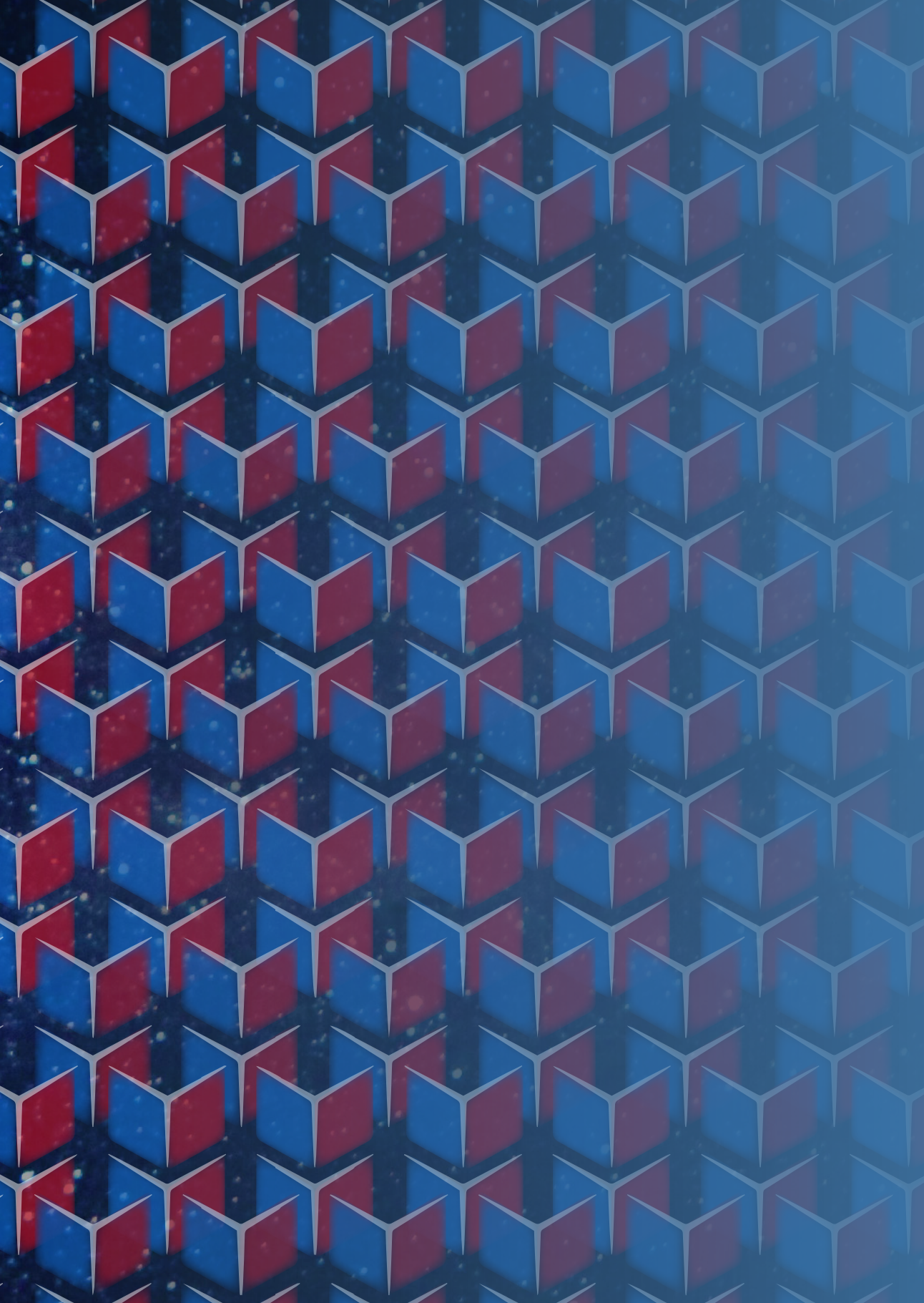
58. A. Sunyaev, T. Dehling, P. L. Taylor, and K. D. Mandl, “Availability and quality of mobile health app privacy policies,” J Am Med Inform Assoc, vol. 22, pp. e28-33, Apr 2015.
59. D. K. Zang J, Graves J, Lisker P, Sweeney L, “Who knows what about me? A survey behind the scenes personal data sharing to third parties by mobile apps,” JOTS Technology Science, 2015. Retrieved on: 20-02-2016.
60. Klosowski, “Lots of Health Apps are selling your data. Here’s why,” 2014. Retrieved 20-03-2016.
61. P. Olson, “Wearable Tech Is Plugging Into Health Insurance,” Available via: http://www.forbes.com/sites/parmyolson/2014/06/19/wearable-tech-health-insurance/#3bdf8b7d5ba1, 2014. Retrieved on: 10-05-2016.
62. D. B. J Cusano, A Starrs, E Viale, M Halverson, R Malhotra, “Digital insurance era: stretch your boundaries. ,” Available via: https://www.accenture.com/us-en/insight-technology-vision-insurance-2015, 2015.
63. B. Martinez-Perez, I. de la Torre-Diez, and M. Lopez-Coronado, “Privacy and security in mobile health apps: a review and recommendations,” J Med Syst, vol. 39, p. 181, Jan 2015.
64. B. W. Mamlin and W. M. Tierney, “The Promise of Information and Communication Technology in Healthcare: Extracting Value From the Chaos,” Am J Med Sci, vol. 351, pp. 59-68, Jan 2016.
65. T. M. Hale and J. C. Kvedar, “Privacy and Security Concerns in Telehealth,” Virtual Mentor, vol. 16, pp. 981-5, 2014.
66. M. M. Baig, H. GholamHosseini, and M. J. Connolly, “Mobile healthcare applications: system design review, critical issues and challenges,” Australas Phys Eng Sci Med, vol. 38, pp. 23-38, Mar 2015.
67. A. A. Atienza, C. Zarcadoolas, W. Vaughon, P. Hughes, V. Patel, W. Y. Chou, et al., “Consumer Attitudes and Perceptions on mHealth Privacy and Security: Findings From a Mixed-Methods Study,” J Health Commun, vol. 20, pp. 673-9, 2015.
68. J. Perk, B. G. De, H. Gohlke, I. Graham, Z. Reiner, M. Verschuren, et al., “European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts),” Eur. Heart J, vol. 33, pp. 1635-1701, 7/2012.
69. M. K. Aktas, V. Ozduran, C. E. Pothier, R. Lang, and M. S. Lauer, “Global risk scores and exercise testing for predicting all-cause mortality in a preventive medicine program,” Jama, vol. 292, pp. 1462-8, Sep 22 2004.
70. H. Naci and J. P. Ioannidis, “Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study,” Br J Sports Med, vol. 49, pp. 1414-22, Nov 2015.
71. R. Hambrecht, C. Walther, S. Mobius-Winkler, S. Gielen, A. Linke, K. Conradi, et al., “Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial,” Circulation, vol. 109, pp. 1371-8, Mar 23 2004.
72. J. D. Piette, J. List, G. K. Rana, W. Townsend, D. Striplin, and M. Heisler, “Mobile Health Devices as Tools for Worldwide Cardiovascular Risk Reduction and Disease Management,” Circulation, vol. 132, pp. 2012-27, Nov 24 2015.

**This review gives an excellent overview of e-Health studies that have been done already.

73. K. L. Margolis, S. E. Asche, A. R. Bergdall, S. P. Dehmer, S. E. Groen, H. M. Kadrmas, et al., "Effect of home blood pressure telemonitoring and pharmacist management on blood pressure control: a cluster randomized clinical trial," JAMA, vol. 310, pp. 46-56, 7/3/2013.

**This paper is interesting as it describes a successful telemonitoring intervention.

74. L. E. Burke, J. Ma, K. M. Azar, G. G. Bennett, E. D. Peterson, Y. Zheng, et al., "Current Science on Consumer Use of Mobile Health for Cardiovascular Disease Prevention: A Scientific Statement From the American Heart Association," Circulation, 8/13/2015.



Chapter 3

Redesigning Healthcare: The 2.4 billion euro question? Connecting smart technology to improve outcome of patients

R.W. Treskes, E.T. Van Der Velde, D.E. Atsma, M.J. Schalij

Neth Heart J. 2016 Jul;24(7-8):441-6.

Abstract

Although it has been possible to transfer electrocardiograms via a phone line for more than 100 years, use of internet-based patient monitoring and communication systems in daily care is uncommon. Despite the introduction of numerous health-monitoring devices, and despite most patients having internet access, the implementation of individualised healthcare services is still limited. On the other hand, hospitals have invested heavily in massive information systems offering limited value for money and connectivity. However, the consumer market for personal healthcare devices is developing rapidly and with the current healthcare-related investments by tech companies it can be expected that the way healthcare is provided will change dramatically. Although a variety of initiatives under the banner of 'e-Health' are deployed, most are characterised by either industry-driven developments without proven clinical effectiveness or individual initiatives lacking the embedding within the traditional organisations. However, the introduction of numerous smart devices and internet-based technologies facilitates the fundamental redesign of healthcare based on the principle of achieving the best possible care for the individual patient at the lowest possible cost.

Conclusion

The way healthcare is delivered will change, but to what degree healthcare professionals together with patients will be able to redesign healthcare in a structured manner is still a question.

Introduction

Approximately 110 years ago, Willem Einthoven was the first person to use telemedicine by sending clinically obtained ECGs by telephone to his laboratory located outside the hospital, because his ECG machine was not allowed on the wards.(1) It took another 80 years, however, to invent and distribute the personal computer (PC, introduced 1981). This event marked the beginning of the widespread use of PCs.(2) In 1991, the 'World Wide Web' or internet was introduced, thereby allowing computers to exchange digital information, and within 5 years companies in different sectors started offering services via internet.(3) By 2013, 97% of the Dutch population had internet access and online banking and online shopping were used by 83% and 82%, respectively, of this group.(4) Furthermore, in the Netherlands 90-98% of all inhabitants can use fourth-generation mobile networks (allowing mobile access to fast internet) and 85-95% of the land area is covered by the two dominant mobile providers.

Computers have also revolutionised healthcare. Laboratory results, diagnostic images and patient records became available online in most hospitals and it became possible to exchange data between healthcare providers. General practitioners (GP) also use PCs to record patient data, and currently 98% of Dutch GPs are storing information in electronic health records.

The current hospital information systems (HIS), however, still have major limitations. Systems are expensive, complex, and connectivity of most systems is limited. Furthermore, commercially developed/used applications such as video-consultation systems, telediagnosis and teletreatment systems are only used by a small number of healthcare providers. The possibilities to extract data out of these applications into the HIS are still limited.(5) With respect to the costs of the commercially available HIS, it is remarkable that hospitals are still willing to invest enormous amounts of money and human resources in generic mainstream systems, offering limited value on investment whereas it can be expected that in the near future information will be stored in the cloud and networked distributed applications will provide optimal support for treating individual patients. A simple calculation of costs returns an astonishing 2.4 billion euros spent by approximately 80 Dutch hospitals to introduce a basic HIS.(6) Maintenance and regular updates of these complex systems are consuming even more money and require large numbers of staff. Money not spent on direct care and presumably to be written off in the near future, as will be discussed.

In the meantime, the consumer market for personal health-monitoring devices and systems is developing rapidly. At present, patients frequently provide their doctors with data obtained using these devices. Although in line with the wish to provide patients with tools to monitor their health, it is not possible to incorporate data

obtained with these devices into the HIS to obtain a comprehensive and patient-specific dataset. However, with the current healthcare-related investments by companies such as Google, Apple, Microsoft, Samsung and Philips it can be expected that the way healthcare is provided will change in the near future. Patients, used to 24/7 services provided by airlines, banks and travel agencies, will demand similar individualised healthcare services. Living in an era in which one can book a flight to a place anywhere in the world at any time, patients will no longer accept waiting weeks for an appointment with a doctor and not getting feedback within a few hours in case of questions. Although a variety of initiatives are currently deployed, most are characterised by either industry-driven developments without proven clinical effectiveness or individual initiatives lacking the embedding within the traditional organisations. Furthermore, most of these initiatives, under the trendy banner of 'e-Health', lack any fundamental thought about the way healthcare should develop. Additionally, the entity e-Health is ill defined and may vary from simple email-based patient-physician conversations to complex diagnostic systems continuously monitoring the health of patients. Last but not least, e-Health is of no value if it is not part of a larger, preconceived plan to improve healthcare. In other words, it is more a question of fundamentally redesigning healthcare with the help/aid of new technologies than of the introduction of healthcare-related gadgets per se without defining how to improve the quality of the provided care.
In this paper we will try to outline the future of healthcare by discussing a patient's journey.

Patient's journey

Let's assume a 30-year-old male patient with no relevant medical history except for a positive family history of cardiovascular disease. The patient is overweight and not performing any physical exercise. Without intervention, this patient is at increased risk of developing cardiovascular disease before the age of 60. The patient visits his GP because of some minor illness.
So how to start? First we have to inform the patient about his risk profile, involve him in a training program and educate him. To achieve this, we activate his personal healthcare record (PHCR) and provide him with educational materials. The patient will buy an activity tracker connected to a secure cloud, giving him feedback about his accomplishments in comparison with age-matched peers. Data from the activity tracker will be stored in the PHCR. Furthermore, the patient will receive advice on how to proceed. Every year he visits his GP who can retrieve data from the PCHR and provide feedback to the patient. So far so good.
At the age of 40, the patient develops diabetes. His GP consults the internal medicine specialist and gives the patient personal diabetes advice. Furthermore, the patient

receives a Bluetooth glucose meter. Data from this meter are sent to PCHR and monitored by the GP.
Despite all efforts, the patient has a myocardial infarction at age 49. He activates the emergency service who connects to his PCHR to evaluate history, current medication and known allergies. Upon arrival, the ambulance crew establishes the diagnosis at his home, and transfers him to the nearest percutaneous coronary intervention (PCI) centre. After the PCI procedure, the patient is treated according to the guidelines, provided with Bluetooth devices enabling him to send data about his heart rhythm, blood pressure and weight to his PCHR and is soon seen at the video consultation clinic. In the next year, regular outpatient consultations are alternated with video consultations and after one year he is referred to the GP who has secure access to all relevant data from the cardiology record. During the following years, the GP electronically asks for advice from the cardiology clinic on a regular basis and the patient is doing fine.
Is this a futuristic impression or just regular care waiting to be implemented? All the different devices and the necessary technical infrastructure are already available; however, borders between different healthcare segments are preventing a widespread implementation.
For this to become reality, training of healthcare providers should change, patients have to be involved in redesigning the system and reimbursement systems should be able to finance healthcare chains rather than individual actors. Furthermore, instead of focussing on too-big-to-fail HIS all efforts should be focused on developing dedicated applications connected to each other to allow the best individualised care at the lowest possible costs.

e-Health

As stated above, e-Health is not very well defined.(7,8) The Dutch Board of Public Health (Raad voor Volksgezondheid, RVZ) defines e-Health as 'the use of new information and communication technologies, especially internet technology, to support and improve health and healthcare'.(9) The World Health Organisation (WHO) on the other hand defines e-Health as 'the transfer of health resources and healthcare by electronic means'.(10) This difference is significant, as the RVZ's definition indicates a supportive approach to e-Health, whereas the WHO's definition indicates a more substituting approach. E-health, irrespective of the definition used, remains a broad term. To clarify this we propose to subdivide e-Health into separate entities as shown in Table 1.

Impact of e-Health implementation

There are numerous examples of e-Health-related studies in the literature. The problem in comparing them is that, although two studies can both be e-Health-

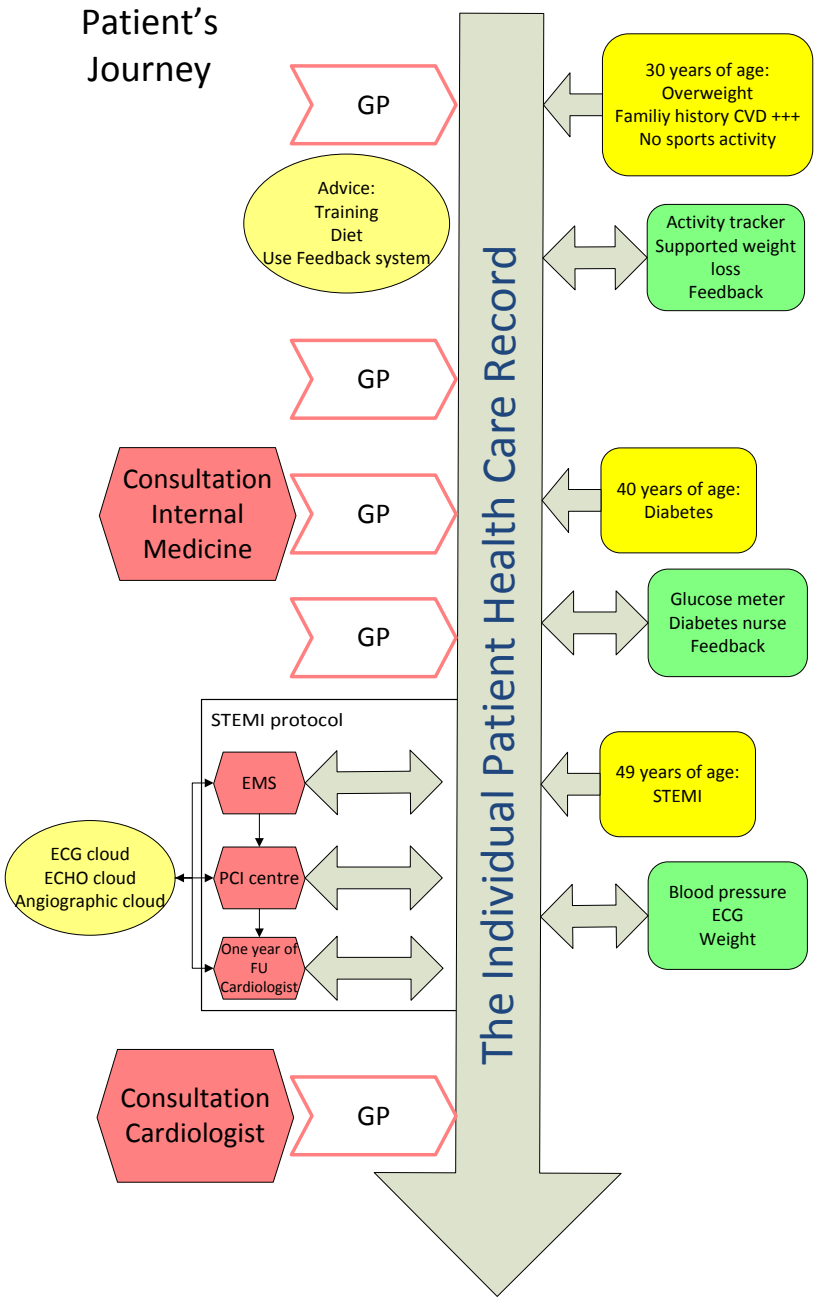


Figure 1. Patient's journey.

Table 1. Different entities of e-Health

E-public health	Encompasses all actions taken using information technology to improve and protect health on a society level
E-support	Encompasses logistical actions needed in healthcare, such as patient access to their own patient files/medical records
E-care	Supports the interview, physical examination, treatment and follow-up using electronic devices
Telemonitoring	The process in which patient parameters are measured remotely. Various devices measuring for instance blood pressure, electrical activity of myocardial cells, oxygen saturation and patients weight are used in clinical practice(17)
Teletreatment	The process in which patients are treated from a remote distance(17)
Teleconsultation	The process in which doctors are consulted from a remote location, using video or email technology, by either colleagues or patients(17)
Telediagnosis	The determination of the nature of a disease at a site remote from the patients on the basis of telehealth methods of transmitted data(17)

Table 2. Reimbursement

What is reimbursed?	**Problems with reimbursement?**
Screen-to-screen contacts	Teleconsultations from a general practitioner to a medical specialist are not reimbursed (currently, only teledermatology is reimbursed)
Telemonitoring (after negotiation with healthcare insurance companies)	Reimbursement is not in proportion to the time an e-Health intervention takes
Telemonitoring and screen-to-screen contacts (STSC) in which the patient is contacted using video-telephony, can be reimbursed	Reimbursed only if a STSC is both a substitute for a face-to-face outpatient clinic visit and if this STSC is a follow-up visit of a previous face-to-face outpatient clinic visit

related, the methods used can differ substantially. Diseases subject to numerous e-Health research projects are arterial hypertension, diabetes and heart failure (HF). Several studies have demonstrated positive effects of telemedicine on outcome of both arterial hypertension and diabetes patients.(11)

The results of telemedicine on the outcome of HF patients are, however, conflicting. Telemonitoring studies using implantable cardioverter-defibrillators (ICDs) demonstrated that remote monitoring of the ICD in HF patients enhances life expectancy and reduces the number of related clinical

Table 3. Mindset of involved stakeholders

Medical staff	1. Are overwhelmed by information from electronic health records and devices 2. Experience a lack of reimbursement for e-Health 3. Have concerns about the quality of the data generated by e-Health and m-Health devices
IT specialists	Are not well enough instructed on what health information doctors need at what time
Patients	1. Do not always understand what is written down in their electronic health record, because of what is often referred to as 'doctors language' 2. Sometimes lack proper experience with information technology, especially smartphone technology
Managers	Have concerns about the logistics of control of the data
Nursing staff	Are afraid that they will be overwhelmed with data

events.(12) The value of phone support systems on the other hand remains debatable. One systematic review found that phone support systems reduced hospitalisation and all-cause mortality in HF patients.(13) However, a large clinical trial comprising 826 HF patients randomised to a phone-based telemonitoring system, and 827 HF patients randomised to regular care found no differences in all-cause mortality or hospital readmission rates. Moreover, there were no differences in the number of patients readmitted for HF, the number of days in hospital or number of hospitalisations.(14)

Where to go from here?

With the introduction of all kinds of smart devices and internet-based technologies, it is possible to redesign healthcare. What do we need? First of all, define the needs of the individual patients, so involve them in the design process. Secondly, introduce dedicated applications to provide both patients and healthcare providers with the optimal information needed at the correct time and place. These applications should be connected to the patient data stored safely in cloud-based systems. Data stored in these systems should be available for registration purposes, to get reimbursement and to benchmark healthcare systems.

The leading principle as stated by Porter in 2012 should be: 'achieving high value for patients must become the overarching goal of healthcare delivery, with value defined as the health outcomes achieved per dollar spent'.(15)

The present generic HIS lack all the criteria defined above. Firstly, initial costs (30-60 million euro per hospital) and costs to keep systems up-to-date are extreme. Secondly, due to the top-down generic design principles it is difficult to fulfil all the

wishes from the different healthcare providers for all scenarios encountered and most systems are full of compromises. Furthermore, due to the obsession of all the parties involved (insurance companies, financing departments, inspectorates, ministry of health, scientific societies) to register, store and report an ever-growing dataset that can be accessed always and everywhere, the design of currently used HIS may lead to the so-called information completeness paradox. In managerial cultures, completeness of data is thought to be a kind of holy grail helping to be in control. However the overload of accumulated data with no particular hierarchy in a patient file may, especially in critical situations, prevent the healthcare professional from taking the correct decisions.(16) Furthermore the current systems are, despite some initiatives, not really informative for the patients themselves.

Therefore, in order to regain control it should be realised that information systems in themselves add no value, but that the value comes from how information is handled. So how to start? By adopting a leading design principle based on the SET (Safe, Effective and Transparent) principles. How to translate this into practice? It is envisioned that a patient has his own patient records stored in the cloud. This virtual record starts at birth and continues to build up during life. In this virtual record all healthcare-related events are stored. Every healthcare provider involved works with a dedicated application which can be obtained from a Medical Application Store (MAS). The MAS contains specific certified applications in which information is gathered and stored in the patient virtual healthcare record. Each stakeholder in the medical field has his own application: cardiology, pulmonology, pharmacy, general practitioners, nursing staff, etc. If a patient is admitted to the department of a relevant stakeholder, that stakeholder activates his or her application and stores the information. In the example (Fig. 2), the paediatrician switches on the paediatrics application at age 5. At the very same time, the information is automatically translated into lay terms, making it understandable for patients. This information is visible in a patient-specific analogue of the application, obtained by the patient from the Patients Application Store (PAS). Each application in the MAS, has an equivalent in the PAS. The PAS contains patient specific information, which encompasses a lay description of the data gathered in the MAS (and made available in the patient cloud), as well as both general and specific information, such as instruction videos and the anatomy and physiology of a relevant organ. The MAS furthermore contains a separate folder in which the physician can write notes which will not be copied to the PAS. The content of MAS and PAS is defined by relevant stakeholders, including medical specialists, patient organisations and educational specialists. Applications should be based on open source software. Furthermore, connectivity and data exchange should be easy. As suggested in Fig. 2, content, design, and certification are brought together in the so-called 3-P application design studio (Patient, Professionals and Public). Following this software structure, the

information will be to-the-point to the physician, understandable to the patient and transparent to the public. Structured storage of information enables easier data extraction for quality assessment purposes.(18)

e-Health implementation

Despite the potential advantages of redesigning healthcare as discussed in the previous section several problems may hamper the rapid and widespread implementation of e-Health. First, instead of reimbursing individual healthcare providers, thereby creating artificial borders between the different sectors, it will be necessary to reimburse healthcare systems. Currently, however, several financial constraints for e-Health implementation are repeatedly reported and summarised in Table 2. Second, it is important to recognise possible hesitations by the involved stakeholders as summarised in Table 3. Third, it is important that data safety is ensured and monitored by an independent inspectorate. Furthermore it is vital that patients are able to refuse the exchange of their data between healthcare providers and that access rights are well described.

It will be important to address these barriers in redesigning healthcare and to stimulate all involved. In other words, change the mindset!

Conclusions

The question is not if the way we provide healthcare will change, but to what extent healthcare professionals together with patients will be able to fundamentally redesign healthcare in a structured manner. This process should start with defining the needs of patients based on the principle of best achievable care at the lowest possible costs.

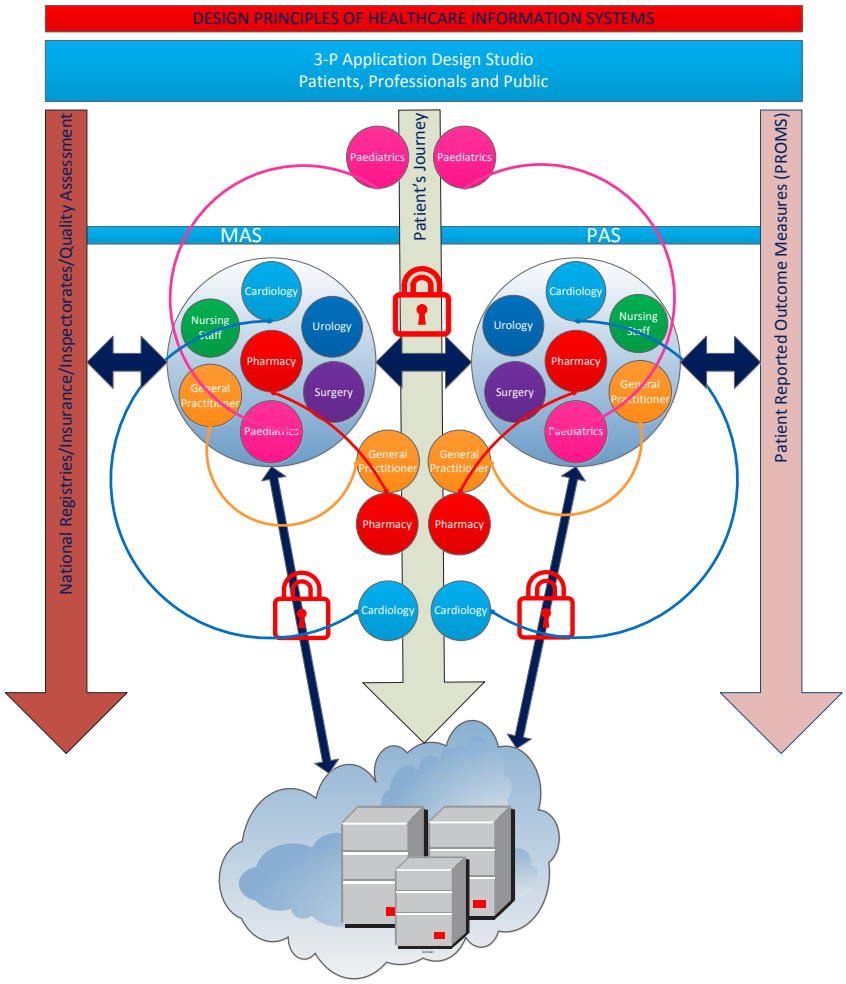
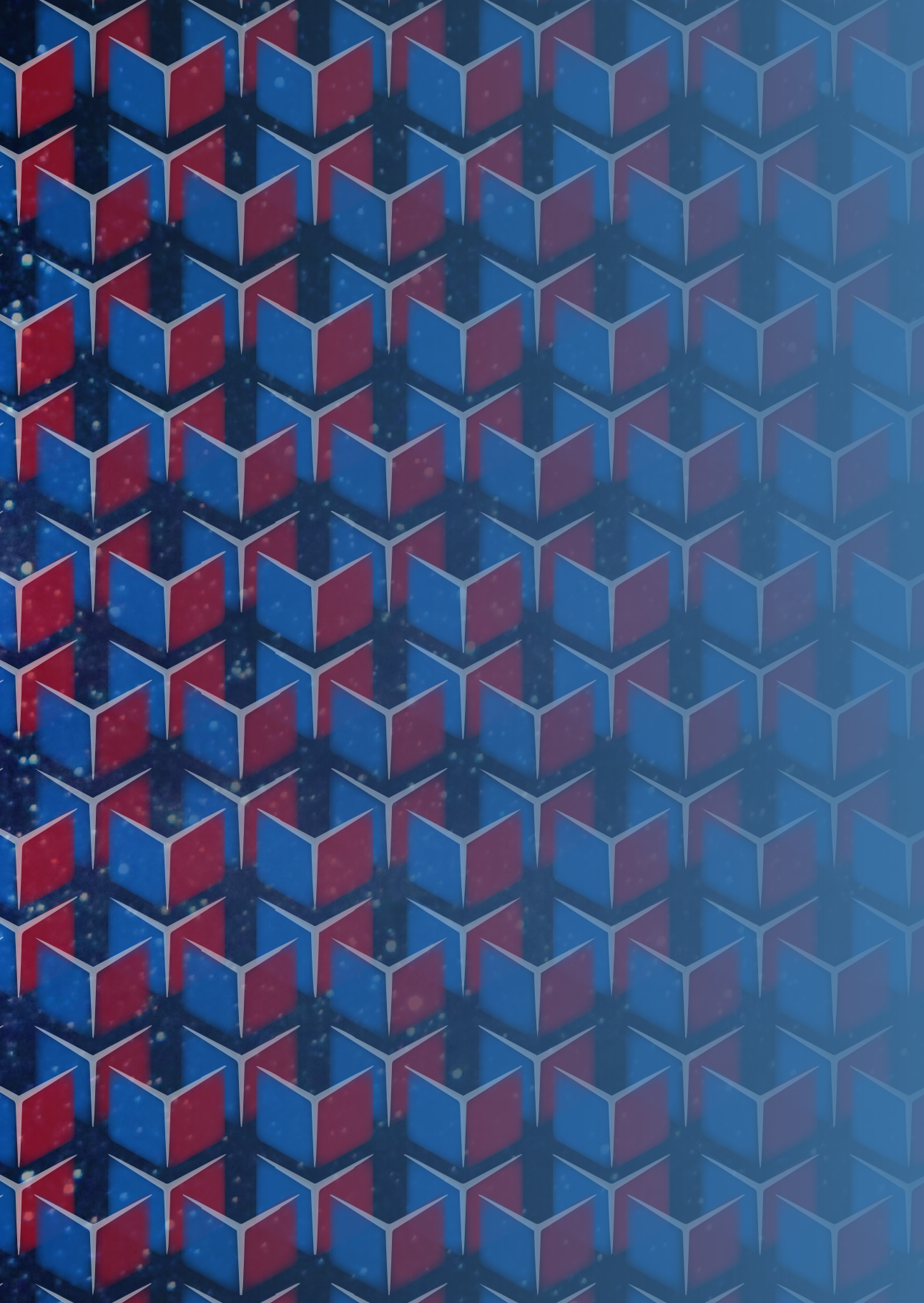


Figure 2. Design principles of healthcare information systems.

References

1. Einthoven W. Le telecardiogramme. Arch Int de Physiol. 1906;4:132-64.
2. eTForecasts. Worldwide PC market. 2015. Available via: http://www.etforecasts.com/ products/ES_pcww1203.html.
3. Wikipedia. Online shopping. 2015. Available via: https://en.wikipedia.org/ wiki/Online_shopping.
4. Centraal Bureau voor de Statistiek. ICT gebruik van personen naar persoonskenmerken. 2014. Available via: http://statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=71098ned&D1=33,55-59,92-113,119,124-133&D2=0&D3=0,l&HDR=G2,G1&STB=T&VW=T.
5. Krijgsman J, Peeters J, Burghouts A, et al. Op naar meerwaarde! eHealth-monitor 2014. Nictiz 2014. Available via: http://www.nictiz.nl/page/eHealth/eHealth-monitor.
6. Dutch Hospital Data. Kengetallen Nederlandse Ziekenhuizen 2012. 2013. Available via: https://www.nvz-ziekenhuizen.nl/_library/13152/Kengetallen%20Nederlandse%20Ziekenhuizen%202012.pdf.
7. Oh H, Rizo C, Enkin M, Jadad A. What is eHealth?: a systematic review of published definitions. World Hosp Health Serv. 2005;41:32-40.
8. Showell C, Nohr C. How should we define eHealth, and does the definition matter? Stud Health Technol Inform. 2012;180:881-4.
9. Rijen AJG van, Lint MW de, Ottes L. Inzicht in e-health. 2002. Available via: http://www.rvz.net/uploads/docs/Achtergrondstudie_-_E-health_in_zicht.pdf.
10. World Health Organization. mHealth: new horizons for health through mobile technologies. 2011. Available via: http://www.who.int/goe/publications/goe_mhealth_web.pdf.
11. Zhai YK, Zhu WJ, Cai YL, Sun DX, Zhao J. Clinical- and cost-effectiveness of telemedicine in type 2 diabetes mellitus: a systematic review and meta-analysis. Medicine (Baltimore). 2014;93:e312.
12. Hindricks G, Taborsky M, Glikson M, et al. Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial. Lancet. 2014;384:583-90.
13. Clark RA, Inglis SC, McAlister FA, Cleland JG, Stewart S. Telemonitoring or structured telephone support programmes for patients with chronic heart failure: systematic review and meta-analysis. BMJ. 2007;334:942.
14. Chaudhry SI, Mattera JA, Curtis JP, et al. Telemonitoring in patients with heart failure. N Engl J Med. 2010;363:2301-9.
15. Porter ME. What is value in healthcare? N Engl J Med. 2010;363:2477-81.
16. Singh H, Spitzmueller C, Petersen NJ, Sawhney MK, Sittig DF. Information overload and missed test results in electronic health record-based settings. JAMA Intern Med. 2013; 22;173:702-4.
17. Block AW, Border WZ, Bruce BB, et al. Dorland's Medical Dictionary. Philadelphia: Saunders; 2011.
18. Eindhoven DC, Wierda E, de Bruijne MC, et al. The year of transparency: measuring quality of cardiac care. Neth Heart J. 2015;23:457-65.



CHAPTER 4

The Box: using smart technology to improve outcome of myocardial infarction patients. Rationale and design of a randomized-controlled trial

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JMIR Res Protoc. 2017 Sep 22;6(9):e186.

Abstract

Background
Recent evidence suggests that frequent monitoring using smartphone compatible wearables might improve clinical effectiveness and patient satisfaction of care.

Objective
The aim of this study is to investigate the clinical effectiveness and patient satisfaction of a smart technology intervention in patients admitted with a ST elevation myocardial infarction (STEMI) or non ST acute coronary syndrome (NST-ACS).

Methods
In this single center, open, randomized controlled trial (RCT) patients who suffered from STEMI or NST-ACS are 1:1 randomized to an intervention group or control group. Both groups are followed up to 1 year after the index event. The intervention group will take daily measurements with a smartphone compatible electrocardiogram device, BP monitor, weight scale and activity tracker. Furthermore, two out of four outpatient clinic visits are replaced by e-visits (1 and 6 months after index event). The control group will receive regular care, consisting of four outpatient clinic visits (1, 3, 6 and 12 months after index event). All patients will be asked to fill in validated questionnaires about patients satisfaction, quality of life, propensity of medication adherence and physical activity.

Results
Primary outcome of this trial is percentage of patients with controlled blood pressure. Secondary outcomes include patient satisfaction, healthcare utilization, major adverse cardiac events, medication adherence, physical activity, quality of life and percentage of patients in which a sustained arrhythmia is detected.

Conclusion
Smart technology could potentially improve care in post-myocardial infarction patients. This trial will investigate whether usage of smart technology can improve clinical-, and cost-effectiveness of care.

Trial registration
NCT02976376 (clinicaltrials.gov)

Introduction

Current European Society of Cardiology guidelines on secondary prevention in patients with sustained ST-segment elevation myocardial infarction (STEMI) or acute coronary syndrome without persistent ST-segment elevation (NST-ACS) recommend tight blood pressure (BP) control, weight control and adequate physical activity after discharge from the hospital, as well as regular electrocardiograms (ECGs).(1, 2) In current practice, the first year after their initial hospitalization these patients regularly visit the outpatient clinic, where the patient is interviewed, weighed, an ECG is made, BP is measured, lifestyle advices are given and pharmaceutical treatment is evaluated.(3)

In this situation, patients must be physically present at the outpatient clinic.(3) This might pose a burden to the patient, especially in remote areas.(4) Furthermore, it necessitates trained healthcare staff, increasing the workload.

Recent advances in information and communication technology have enabled remote monitoring of vital signs and remote doctor-patient contacts (together part of the broad concept “telemedicine”).(5-9) In recent years, a number of smartphone compatible wearables have received a CE-mark and Food and Drug Administration (FDA) clearance and are available for over-the-counter sale in the European Union and the United States.(10) Some of these smartphone compatible wearables allow for the measurement of (depending on the type of wearable) the number of steps taken per day, BP, weight and the recording of an ECG. The devices are easy-to-use and do not require the assistance of trained healthcare staff. Results of measurements are communicated with smartphone applications (app) tailored to the specific device. Data is uploaded via internet to servers of the manufacturer of the device.(10, 11)

Recent research in various patient populations suggests that telemedicine might improve clinical effectiveness and patient satisfaction of care.(12, 13) Remote and more frequent monitoring with subsequent therapy changes has been shown to improve clinical outcome of patients with uncontrolled hypertension(12) (achieving 18.4% more patients with controlled blood pressure) and with type II diabetes mellitus (a 0.37% reduction in HbA1c, which was statistically significant).(13) Furthermore, remote video contact moments, in which the doctor-patient communicate via a video connection, are potentially time saving for patients.(14, 15) One study found that office visits required an average 50 minutes of a patient’s time, while e-visits only required 22 minutes on average.(15)

We therefore hypothesize that telemedicine improves clinical effectiveness and patient satisfaction of care in the follow-up of STEMI and NST-ACS patients. Thus, the aim of this study is to investigate the clinical effectiveness and patient satisfaction of a smart technology intervention in patients after being admitted with

an STEMI or NST-ACS. In this paper, the rationale and design of this open, single center Randomized Controlled Trial (RCT) are presented.

Methods

Study design (design, randomization and follow-up)

"The Box" is a single-center, open, randomized-controlled trial. It is a parallel group study. The study is conducted at the LUMC, a tertiary care hospital in Leiden, The Netherlands. The trial is registered under clinical trial number NCT02976376 (www.clinicaltrials.gov) and NL56453.058.16(www.toetsingonline.nl). After inclusion, patients are 1:1 randomized to either "The Box" (intervention group) or to regular follow-up (control group). Block randomization per 10 participants is performed. Randomization is stratified per primary diagnosis (STEMI or NST-ACS) and per age (≤50, 51-60, 61-70, 71-80 and >80). A website (www.randomizer.org) is used to generate randomization lists.

Patient population

Patients who are admitted to the cardiology department of the Leiden University Medical Center (LUMC) with STEMI(1) or NST-ACS(2) are eligible for participation. Patients with a STEMI or NST-ACS who match the in-, and exclusion criteria are approached for participation in the protocol within 24 hours after primary percutaneous coronary intervention (PCI). The maximum time between primary PCI and study inclusion is 96 hours. All in-, and exclusion criteria are listed in Table 1.

Regular follow-up

Since 2004, the department has a dedicated care track for patients with STEMI or NST-ACS. Details about this protocol have been described previously by Liem et al.(3) Summarizing, patients with signs and symptoms which are possibly related to myocardial infarction are referred to a percutaneous coronary intervention (PCI) center. Upon arrival, they are immediately transferred to the catheterization department, where primary PCI of the culprit lesion is performed. Before discharge, patients are given written and oral information on the importance of medication adherence and lifestyle advices in accordance with the European Guidelines on cardiovascular disease prevention in clinical practice.(16)

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Patient is admitted with acute myocardial infarction
Patient is able to communicate in English or Dutch at B1 level
Exclusion criteria
Body Mass Index > 35 ($kg \cdot m^{-2}$)
Included in another randomized controlled trial
Does not have wireless internet access at home
Less than 18 years old
Considered an incapacitated adult (this decision is left to the discretion of the responsible cardiologist)
Pregnant
Unwilling to sign the informed consent form

After approximately 48-hours, patients are discharged from the hospital. The standard follow-up during the first year after discharge includes four outpatient clinic visits:

1. Approximately 1 month after STEMI or NST-ACS. This includes a BP measurement, a 10-second, 12-lead ECG, laboratory testing (including kidney function, renal function and lipid spectrum) and an interview with a doctor or nurse practitioner.
2. Approximately 3 months after STEMI or NST-ACS. This includes a BP measurement, a 10-second, 12-lead ECG, stress echo, a 24-hour Holter ECG and an interview with a doctor or nurse practitioner.
3. Approximately 6 months after STEMI or NST-ACS. This includes a BP measurement, a 10-second, 12-lead ECG, 24-hour Holter ECG, laboratory testing (including kidney function, renal function and lipid spectrum), a transthoracic echocardiogram (TTE) and an interview with a doctor or nurse practitioner.
4. Approximately 12 months after STEMI or NST-ACS. This includes a BP measurement, a 10-second, 12-lead ECG, laboratory testing (including kidney function, renal function and lipid spectrum), a TTE and an interview with a doctor or nurse practitioner.

Patients who are randomized to regular follow-up receive the same care as patients who do not participate in the study. A flowchart of regular follow-up is given in Figure 1.

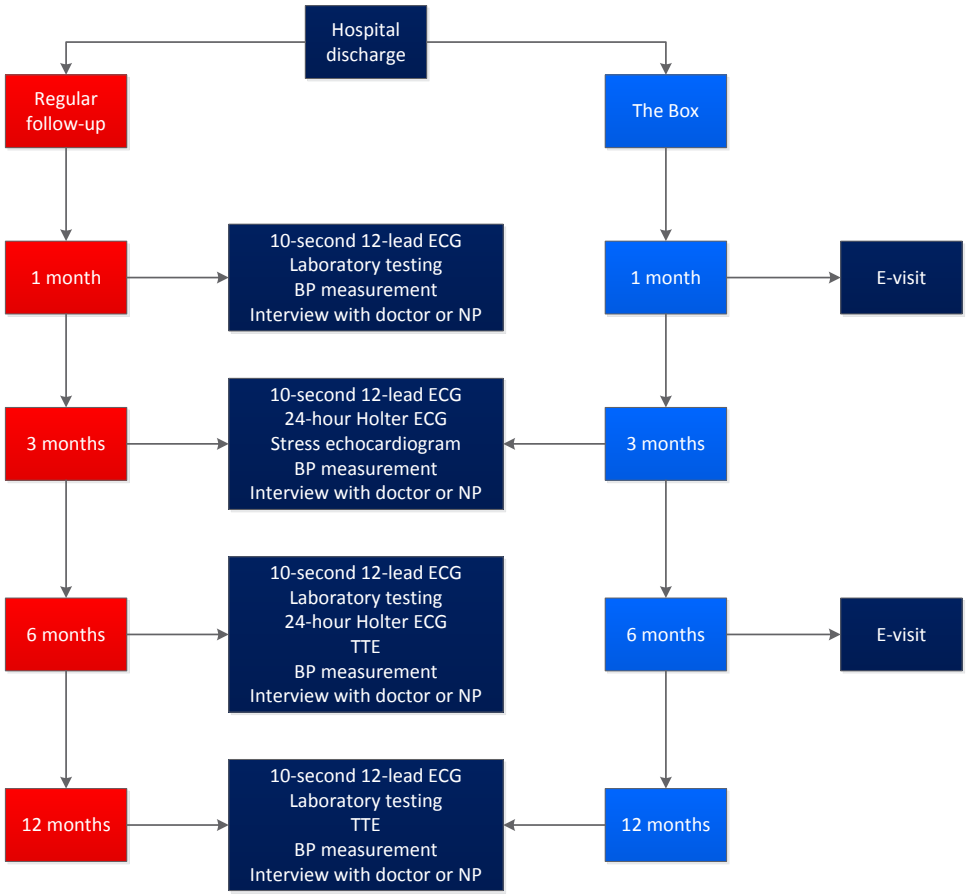


Figure 1. MISSION, follow-up of patients who suffered from STEMI or NST-ACS. BP: blood pressure; ECG: electrocardiogram; NP: nurse practitioner; TTE: transthoracic echocardiogram.

The Box

When randomized to The Box (Figure 2), patients receive a box containing a weight scale, BP monitor, activity tracker and ECG wearable. Patients receive The Box before discharge. They are given the same written and oral information on the importance of medication adherence and lifestyle advices in accordance with the European Guidelines on cardiovascular disease prevention in clinical practice as the control group.(16) The necessary apps are downloaded on the patient's smartphone; necessary accounts are created and the installation of the devices are carried out by a healthcare professional dedicated to the project. Afterwards, patients are given oral instructions on the usage of the devices. They are instructed to measure BP in a sitting position after five minutes of resting. The device should be applied to the left upper arm. Patients are instructed to rest their left under arm

Figure 2. The Box.

on a table. Furthermore, a manual explaining the usage of the below described wearables is handed over with The Box. Also, instruction videos are available on YouTube. Patients who do not own a smartphone or tablet with iOS or Android OS but are willing to participate and randomized to The Box receive a smartphone. Patients are instructed to use their own wireless internet access (e.g. home WiFi network). No mobile data network plan is provided with the smartphone.

Patients are instructed to record a single lead ECG, measure BP and weight daily, preferably at the same moment of the day. Furthermore, they are asked to record a single lead ECG in case of any symptoms of possible cardiac origin (as interpreted by the patient). Lastly, patients are instructed to wear their activity tracker during day to track the daily number of steps and at night to track the duration and quality of sleep. Patients are told that measurements are checked on a daily basis and that they are contacted in case of predefined data irregularities. Patients are explicitly told that they cannot rely on the devices of The Box in emergency situations.

In addition to daily measurements, the 1st and 3rd of the 4 standard outpatient clinic visits are replaced by an e-visit, in which the patient is communicating with the doctor or nurse practitioner via a secured video connection. The content of the interview is comparable to the content of a regular outpatient clinic visit. The same doctors and nurse practitioners are doing the regular outpatient clinic visits and the digital outpatient clinic visits. In the intervention group, the 10-second 12-lead ECG and the laboratory testing one month after the index event is not performed.

Moreover, the 10-second 12-lead ECG, the 24-hour Holter ECG, laboratory testing and the TTE 6 months after the index event is not performed (Figure 1).

Devices

All devices used for this study are non-invasive, battery powered, smartphone compatible devices. They have a CE-mark, are approved by the United States Food and Drug Administration (FDA) and are allowed for over-the-counter sale in the European Union (EU) and the United States of America (USA). The installation and usage of the device is so intuitive that no medical staff needs to assist when the devices are used by the patient.

The usage of the devices requires a smartphone or tablet with Android Operating System (OS) (Google, Mountain View, California, USA) or iOS (Apple Computers, Cupertino, CA, USA). The devices communicate with a dedicated mobile application (app) on the smartphone or tablet, which can be downloaded from the App Store (iOS) or Play Store (Android). The data from the measurements are stored on the smartphone or tablet and uploaded to the app manufacturer's servers (the cloud), which are located in Europe. For synchronization with the cloud, an internet connection (e.g. WiFi, 3G or 4G) is required. Measurements can be done while the smartphone or tablet is offline. In this case, the results of the measurements are stored on the smartphone or tablet, and uploaded to the server when the smartphone is online again.

ECG device

The ECG device (AliveCor, AliveCor Inc., San Francisco, CA, USA) contains two electrodes. The device communicates with the AliveCor app. The ECG device allows the user to record a 30-seconds single lead ECG. To record an ECG, the patient must position two or three fingers of the right hand to one electrode and two or three fingers of the left hand to the other electrode. The device is to be held within approximately 1 to 30 centimetres of the smartphone. An ultrasound signal is sent from the ECG device to the smartphone. This signal is then converted to a live single lead ECG that subsequently is shown on the smartphone screen.(7, 10)

After 30 seconds, an automated algorithm in the app calculates the R-R intervals and formulates a diagnosis, varying from "normal", "possible atrial fibrillation" to "undetermined", on the screen.(10) Then, the patient has the ability to add notes, and is requested to report any symptoms if present before saving the ECG.

Blood pressure monitor

The blood pressure (BP) monitor (Withings S.A., Issy les Moulineaux, France) is a smartphone compatible, battery operated oscillometric blood pressure cuff. It

allows the user to measure systolic BP, diastolic BP and heart rate. The device is applied around the left or right upper arm (depending on the patient's prevalence). Upon pushing the button on the cuff, a connection with the smartphone is made via Bluetooth. The inflation and deflation of the cuff is automated and can be initiated via the dedicated Withings Health Mate app (for iOS and Android) on the smartphone. The average duration of a measurement is approximately 20 seconds. After inflation and deflation, the systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) is shown on the smartphone screen.

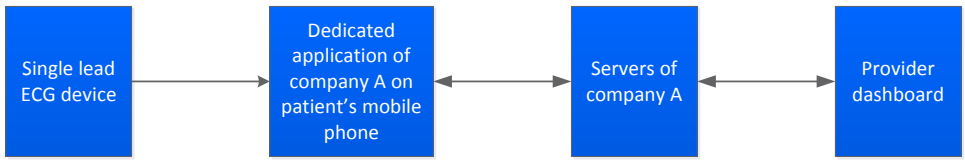


Figure 3. Data integration of single lead ECGs. Legend: company A is the ECG manufacturer. ECG: electrocardiogram.

The weight scale

The weight scale (Withings S.A., Issy les Moulineaux, France) allows the patient to track weight, fat percentage, heart rate and ambient CO_2 parts per million. To measure all four parameters, the patient must stand on the weight scale. While standing on the weight scale, the patient has to select his own account. The results are shown on a screen on the weight scale, and are automatically uploaded via internet to the Withings server.

Activity tracker

The activity tracker (Pulse Ox, Withings S.A., Issy les Moulineaux, France) allows the patient to track the number of steps taken per day. It furthermore allows the patient to track duration and quality of sleep. It has the size of a thumb and can be attached to the wrist or belt. Steps are automatically tracked. The measurement results are sent via Bluetooth to a dedicated smartphone app, compatible with iOS and Android OS.

Storage of the ECGs

Single lead ECGs, made by the single lead ECG device are stored in the cloud. The system offers patients the ability to connect their personal account with a physician's account. The physician then can review the ECGs made by patients linked to his account, including the diagnosis given by the app's algorithm and the symptoms reported by the patient. The automated diagnosis algorithm has a reported sensitivity of 97% and a specificity of 98% for the detection of atrial

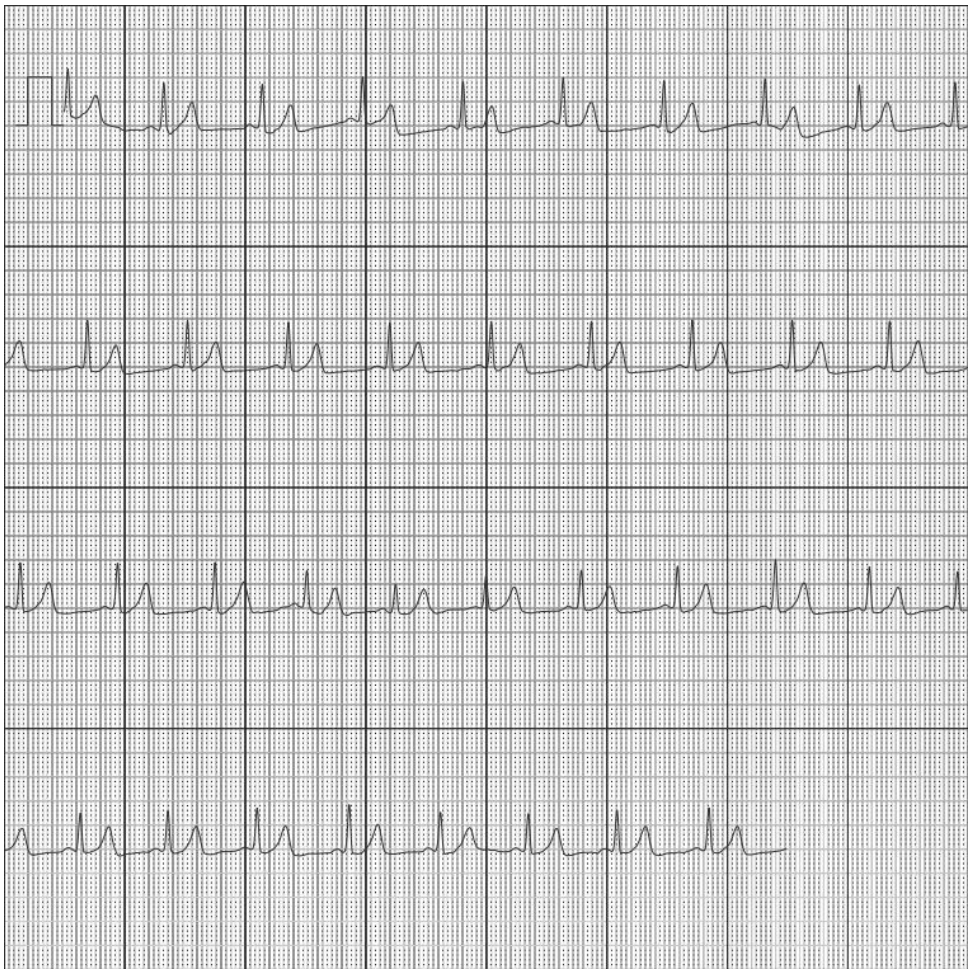


Figure 4. A PDF generated by the ECG device, showing sinus rhythm.

fibrillation.(7) ECGs which are classified by AliveCor as “possible atrial fibrillation” and “undetermined” are subsequently checked by a project dedicated healthcare professional in our department. A patient is contacted if a previously undiagnosed arrhythmia is seen or if a patient repeatedly reported symptoms. A flowchart of the storage of the ECGs is shown in Figure 3. An example of a PDF ECG showing sinus rhythm generated by the ECG device is shown in Figure 4. An example of a PDF ECG showing atrial fibrillation generated by the ECG device is shown in Figure 5.

Data integration in electronic medical record (EMR)

The measurement results from the weight scale, blood pressure monitor and activity tracker are stored on the manufacturer’s server (Withings S.A., Issy les Moulineaux, France). Data are extracted from the Withings server and integrated

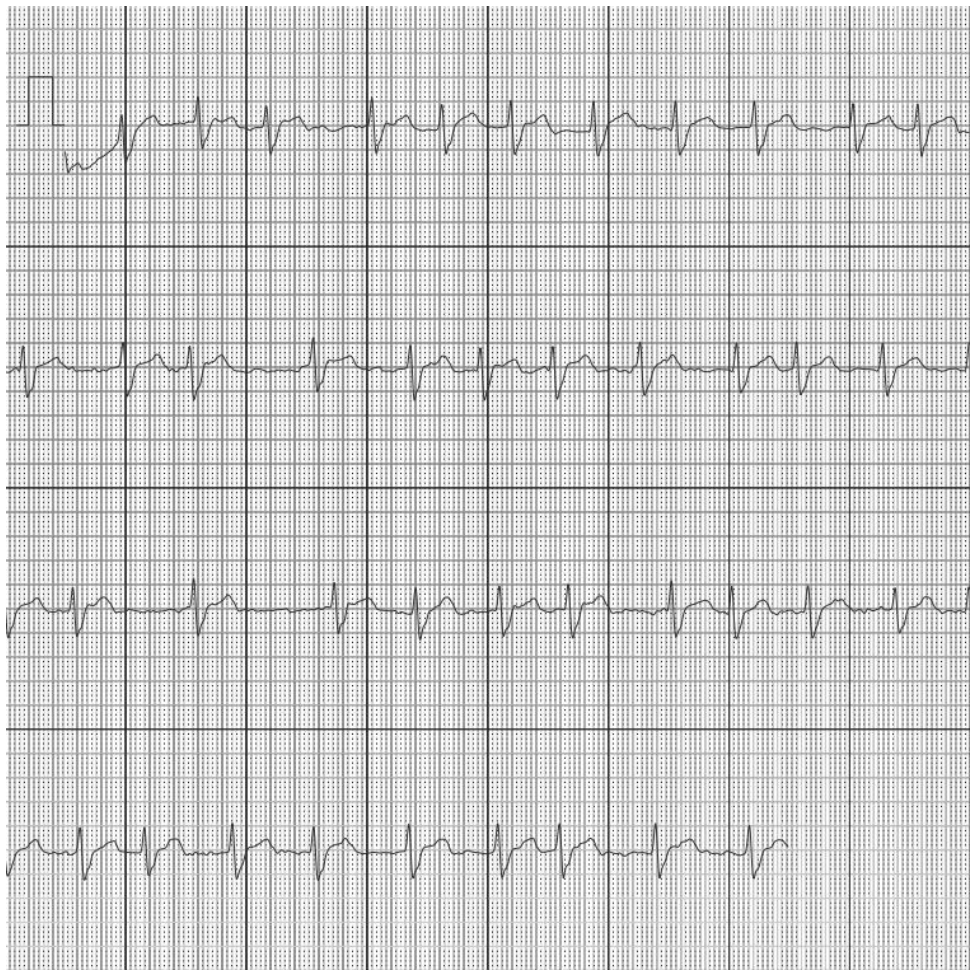


Figure 5. A PDF, generated by the ECG device, showing atrial fibrillation.

in the department's dedicated electronic medical record (EPD-Vision, Department of Cardiology, Leiden University Medical Center, The Netherlands). An automated algorithm searches for predefined irregularities in the data (Table 2). Data can subsequently be displayed in graphic format to facilitate trend analysis. A flowchart of the storage of blood pressure, weight and activity data is given in Figure 6. In case of bugs in this system, a software developer who works at the Department of Cardiology will fix the bug.

Reasons to contact patients

Data are checked daily by a healthcare professional dedicated to the project. When pre-specified irregularities are seen in the data, a patient is contacted within 48 hours by e-mail or phone. These data irregularities are standardized and shown in Table 2.

Table 2. Warnings by the dedicated system

Blood pressure monitor
If a patient has not sent BP for more than 7 consecutive days
If the heart rate is >100 beats per minute
If the systolic BP is >139
If the diastolic BP is > 89
If the systolic BP is 10 mmHg higher than last measurement
If the diastolic BP is 5 mmHg higher than last measurement
If the systolic BP is 10 mmHg higher than 7 measurements before
If the diastolic BP is 5 mmHg higher than 7 measurements before
If the systolic BP is 10 mmHg lower than last measurement
If the diastolic BP is 5 mmHg lower than last measurement
If the systolic BP is 10 mmHg lower than 7 measurements before
If the diastolic BP is 5 mmHg lower than 7 measurements before
Weight scale
If a patient has not sent measurements for more than 7 consecutive days
If the weight is more than 2 kilograms (kg) higher than last measurement
If the weight is more than 3 kilograms (kg) higher than 7 measurements before
If the weight is more than 2 kilograms (kg) lower than last measurement
If the weight is more than 3 kilograms (kg) lower than 7 measurements before
Activity tracker
If a patient has not sent measurements for more than 7 consecutive days

Reasons to adjust therapeutic regimen

Reviewed data are discussed by the data reviewer with the patient's treating physician or nurse practitioner. There are several reasons to contact the patient.

BP monitor: warnings generated by the system on the basis of BP measurements is reviewed by a project dedicated healthcare professional. The reason to change medication is left to the discretion of the treating physician.

Single lead ECG: in case of newly diagnosed arrhythmias lasting at least 30 seconds (atrial fibrillation, atrial flutter, nodal or ventricular escape rhythms, ventricular tachycardias) or at least 4 newly diagnosed asymptomatic premature ventricular contractions (PVC), a 24-Hour Holter ECG is performed. Patients noting chest pain or shortness of breath as symptoms are contacted for an interview by telephone. The decision to change medication or to refer the patient for invasive therapy is left to the discretion of the treating physician.

Weight: weight will not be a primary reason to change therapeutic regimen. Patients can be given lifestyle advices, depending on their height, weight and estimated fat percentage. This is only done at scheduled outpatient clinic visits.

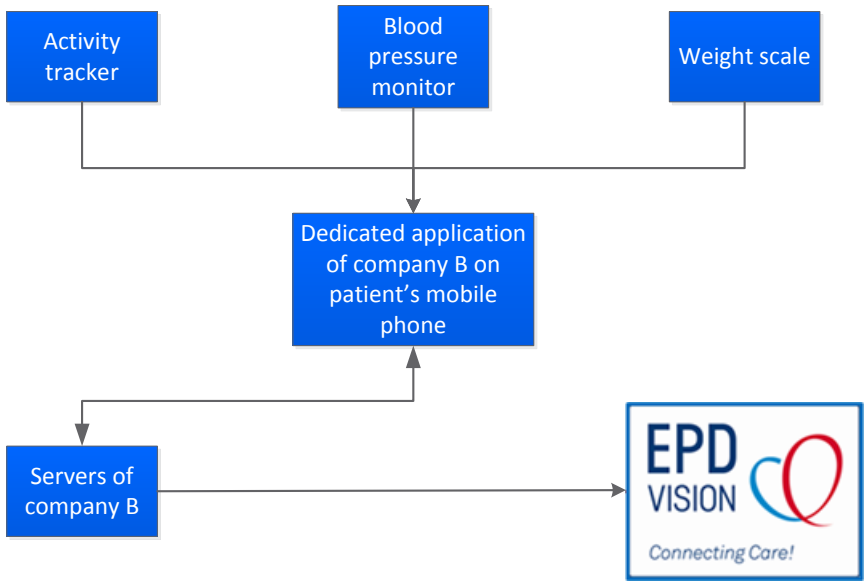


Figure 6. Data integration of the activity tracker, weight scale and BP monitor in the department's Cardiology Information System "EPD-Vision"
Legend: company B is the manufacturer of the activity tracker, blood pressure monitor and weight scale.

Activity: activity tracking data is not a primary reason to change therapeutic regimen. Patients can be advised to exercise more or less, depending on the data. This is only done at scheduled outpatient clinic visits.

Non-adherence

If a patient has not sent measurements from any of his four devices for 21 consecutive days, he is considered non-adherent. A standardized e-mail is sent to the patient, telling that measurements have not been received and that he is urged to contact the hospital in case of any technical difficulties. If no answer is received within 21 days or no measurements are seen within 21 days, the patient is called by telephone. Any technical difficulties or objections by the patient are assessed and solved if possible. If the patient, after this phone call, starts sending measurements, he is considered adherent again. This patient is sent a standardized e-mail in case he becomes non-adherent again. If the patient does not start sending measurements, he is not approached again by e-mail or by telephone to try to affect his non-adherence. However, this patient is not excluded from the trial. This patient is still followed-up according to The Box protocol.

If patients notify the hospital that they want to have regular outpatient clinic visits, they are followed-up according to the regular follow-up protocol.

Questionnaires

All patients, both intervention and control patients, will be asked to fill-in a SF-36 questionnaire,(17) a patient satisfaction questionnaire,(18) a medication adherence questionnaire and an iPAQ questionnaire (to assess the patient's level of physical activity).(19) These questionnaires will be used within one month after myocardial infarction, six months after myocardial infarction and twelve months after myocardial infarction.

Privacy of study participants

To anonymize the data, patients receive an e-mail address consisting of a study code, which they can use to create their Withings and AliveCor accounts. The corresponding names are kept in a separate, password protected database.

Ethical conduct

The study is approved by the Hospital's Medical Ethics Committee (P16.070). It is conducted in accordance to the principles of the Declaration of Helsinki (version 10, October 2013) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO) and Good Clinical Practice. Written offline informed consent will be obtained from all participants. The devices used in this study and described above are approved by our Hospital's Instrumentation Department. All devices are CE marked and are available for sale in the European Union. All devices have been bought by our department for this study. No manufacturer has a role in the study design, data collection, statistical analysis or writing of the manuscript. No financial support is received for this study from any device manufacturer. All devices are provided to study participants who are randomized to The Box group free of charge.

Study withdrawal

Patients who are randomized from The Box group can be withdrawn from the study if they are either non-adherent (as discussed above) or if they themselves wish to withdraw from the study.
Patients who withdraw from regular follow-up are considered lost to follow-up.

Results

Study outcomes

The primary outcome of this study is the percentage of patients with normalized blood pressure (defined as systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg), as measured at the 12-months outpatient clinic visit.

Secondary outcomes of this study are:

1. The percentage of patients with controlled BP (defined as systolic BP <140 mmHg and diastolic BP <90 mmHg), as measured at the 3-month outpatient clinic visit
2. Patient satisfaction, as assessed by patient satisfaction questionnaire(17)
3. Healthcare utilization, defined as an outpatient clinic visit, emergency care visit or admission for any reason. This will be measured via questionnaires and verified by EMR data
4. Major Adverse Cardiac Events (MACE)
   a. Death of any cause
   b. Cardiac death
   c. Recurrent STEMI
   d. Recurrent NST-ACS
   e. Revascularization
   f. Hospitalization for heart failure
   g. TIA
   h. Ischaemic stroke
5. Propensity of medication adherence, measured by the Morisky MMAS-8 scale(20)
6. Physical activity, as measured by the iPAQ questionnaire(19)
7. Quality of life, measured by the SF-36 questionnaire(18)
8. Percentage of patients in which a previously unknown sustained arrhythmia (≥30 seconds) is detected
9. Cost-effectiveness, expressed as the incremental cost-effectiveness ratio

Economic analysis

To assess cost-effectiveness of the intervention, costs per quality adjusted life year (QALY) will be calculated. The analysis is performed from a societal perspective with a time horizon of one year. Patients receive a healthcare resource use questionnaire at 6-months and 12-months. In this questionnaire, a patient is asked to fill in his total healthcare utilization such as outpatient clinic visits, emergency visits and admissions for any reason and visits to the general practitioner. All outpatient clinic visits, emergency visits and admissions for any reason reported in the questionnaire are verified by EMR data. In the same questionnaire, the patient is asked to fill in total medication use. All health care and medication use are multiplied with standard cost prices to calculate costs.(21) To calculate indirect costs, patients are asked to note absence from paid work and unpaid work as well. Productivity costs are calculated using the friction cost method. Absence is again multiplied against standard cost prices.(21) QALYs are calculated from utility scores from the SF-36 questionnaire, which is administered at baseline, 1 month, 6 months and

12 months.(18, 22) Finally costs and QALYs in both groups are compared. It is our hypothesis that societal costs are lower in the intervention group.

Statistical analysis

A power calculation was done using R (R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.r-project.org). It is based on a comparison of two proportions of patients with controlled blood pressure (defined as a SBP of 139 mmHg or less and a DBP of 89 mmHg or less). We hypothesize that in the "The Box" group 95% of the patients achieves a controlled BP, while in the control group, 75% achieves a controlled BP.(23) For this calculation, an alpha of 0.05, a beta of 0.20 and a margin of 0.07 were chosen, yielding a sample size of 200 patients.

Data are analysed according to the intention-to-treat principle. Causes of missing data are tabulated (Supplement A). The percentage of missing data is expected to be low. Therefore, complete case analysis is done. Analysis is based on the missing-at-random assumption. If the percentage of missing values exceeds 7%, multiple imputation is applied in analysis of the data.

After finishing the study (defined as the last patient's last visit), the proportion of patients with controlled blood pressure will be compared with a Chi-Squared Test. Logistic regression might be done if serious imbalances of baseline variables exist to correct for potential confounding variables.

Percentages of patients with controlled BP at three months (secondary outcome 1) and percentages of patients in which a previously unknown sustained arrhythmia is detected will also be compared with a Chi-Squared Test.

Scores of questionnaires (patient satisfaction questionnaire, Morisky MMAS-8 scale, iPAQ questionnaire and SF-36 questionnaire) and healthcare utilization will be compared using an independent t-test. Major Adverse Cardiac Events (MACE) will only be reported. As the study is underpowered, no statistics will be done on MACE. The numbers will be hypothesis generating.

Discussion

In this paper, we presented the rationale and design of single-center, open, randomized-controlled trial. With this trial, we will evaluate the clinical effectiveness of a smart technology intervention in patients with STEMI and NST-ACS.

Clinical effectiveness

It is expected that with daily monitoring of ECG, blood pressure, weight and steps, data will allow for early detection of high blood pressure and the development of arrhythmias. For this study, percentage of patients with controlled BP at 12 months is chosen as primary outcome. Controlled blood pressure is associated with lower

risk of death, recurrent PCI and stroke in patients who suffered from ACS. Therefore, the European guidelines recommend tight BP control via medication and lifestyle advices.
Percentages of 1-year mortality after STEMI or NST-ACS vary, but have been reported to be under 10%.(24) With a sample size of 200, it is expected that this study is underpowered to detect a significant difference in mortality between the intervention group and control group. It is emphasized that it is not the primary objective of this study to demonstrate a difference in mortality. This study is intended to investigate if regular monitoring of clinical parameters including blood pressure can lead to better control of those parameters, therefore being more guideline compliant.

Patient compliance
All devices used in the intervention group are designed for the consumer market. Patients receive assistance with installation of the devices. After measurements, data is automatically transferred to the hospital. It is expected that this helps accurate and timely transmission, which might enhance patient compliance. To test this hypothesis, all reminders sent to patients for not having measured their data are monitored. “No-shows” at digital outpatient clinic visits as well as at the physical outpatient clinic visits are monitored as well. It is hypothesized that there is no significant difference in the percentage of “no-shows” between the digital outpatient clinic visits and the physical outpatient clinic visit.

Patient satisfaction
During the study, patient satisfaction is monitored via a validated questionnaire. (17) In this study, by design, patients in the intervention group monitor ECG, blood pressure and weight more intensively. This increased frequency of monitoring has potential clinical benefits, such as having early detection of high blood pressure or arrhythmias, as well as allowing patients to see and interpret their own data. This might enhance patient satisfaction of care. On the other hand, daily monitoring might pose a burden to the patient, both physically, as patients have to take time to perform the measurements, as well as mentally, as they might associate monitoring with their illness.

Healthcare utilization
A concern of smart technology interventions is the fear that patients, given their non-medical background and their perceived inability to interpreted medical data correctly, increase the number of contact points with hospitals, leading to more outpatient clinic visits and emergency department visits and therefore to a higher burden on both patients and healthcare staff, without improvement of clinical

outcomes. Scientific evidence describing the relation between increased monitoring frequency and healthcare utilization is however scarce. Patients participating in this study receive clear instructions about the usage of the devices, as well as the reasons for the hospital to contact the patients. It is therefore expected that healthcare utilization is not higher in the intervention group.

Generalizability

Patients with a STEMI or NST-ACS who match the in-, and exclusion criteria are eligible for participation. Patients who do not own a smartphone are not excluded from the RCT, but patients who do not have internet access at home are excluded. This might affect generalizability. However, as 97% of the Dutch population has internet access,(25) it is expected that this exclusion criterion affects generalizability only slightly. The fact that a smartphone is used for remote monitoring might affect generalizability as well. Previous literature has indicated that smartphone literacy decreases with age. Furthermore, patients who do own a smartphone might refuse as well, for various reasons.(26) Thirdly, it is known that patients who participate in RCTs have different demographics than patients who do not.(27) It is therefore expected that generalizability is affected. However, it is emphasized that this might be partly due to the involvement of smartphone technology and partly inherent to the RCT study design in general. As patients are given a smartphone in case they do not own one and technical support is provided, generalizability issues are kept to a minimum.

Conclusion

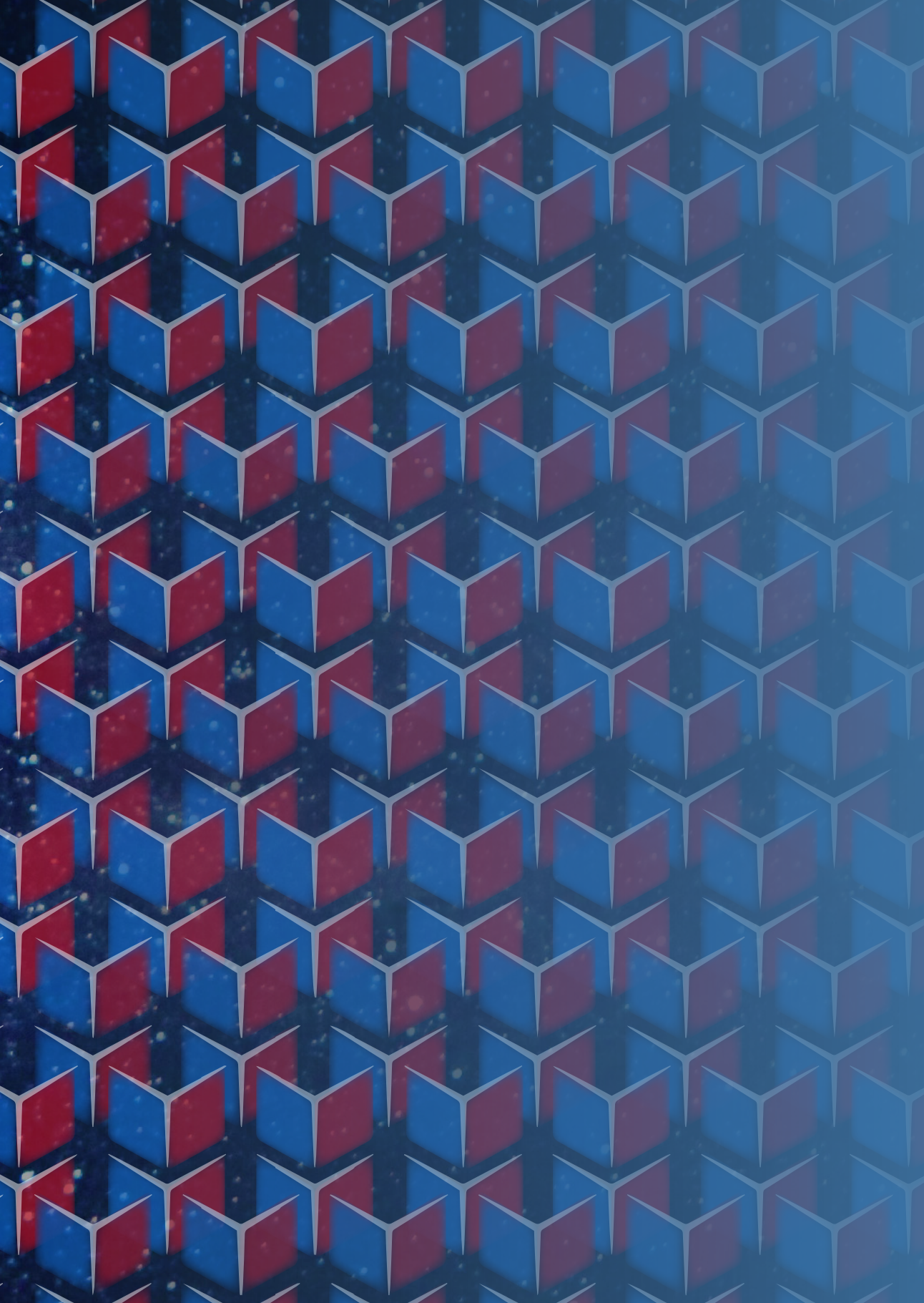
In summary, the rationale and design of a randomized controlled trial is presented that investigates whether a smart technology intervention can increase clinical effectiveness and patient satisfaction in the follow-up of STEMI or NST-ACS patients.

References

1. Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33(20):2569-619. PMID: 22922416.
2. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(3):267-315. PMID: 26320110.
3. Liem SS, van der Hoeven BL, Oemrawsingh PV, Bax JJ, van der Bom JG, Bosch J, et al. MISSION!: optimization of acute and chronic care for patients with acute myocardial infarction. Am Heart J. 2007;153(1):14-1. PMID: 17174628.
4. Williams EM, Ortiz K, Zhang J, Zhou J, Kamen D. The systemic lupus erythematosus travel burden survey: baseline data among a South Carolina cohort. BMC research notes. 2016;9:246. PMID: 27129386.
5. Treskes RW, Van Der Velde ET, Atsma DE, Schalij MJ. Redesigning healthcare: The 2.4 billion euro question? : Connecting smart technology to improve outcome of patients. Neth Heart J. 2016. PMID: 27052894.
6. Topouchian J, Agnoletti D, Blacher J, Youssef A, Chahine MN, Ibanez I, et al. Validation of four devices: Omron M6 Comfort, Omron HEM-7420, Withings BP-800, and Polygreen KP-7670 for home blood pressure measurement according to the European Society of Hypertension International Protocol. Vasc Health Risk Manag. 2014;10:33-44. PMID: 24476688.
7. Lau JK, Lowres N, Neubeck L, Brieger DB, Sy RW, Galloway CD, et al. iPhone ECG application for community screening to detect silent atrial fibrillation: a novel technology to prevent stroke. Int J Cardiol. 2013;165(1):193-4. PMID: 23465249.
8. Frias J, Virdi N, Raja P, Kim Y, Savage G, Osterberg L. Effectiveness of Digital Medicines to Improve Clinical Outcomes in Patients with Uncontrolled Hypertension and Type 2 Diabetes: Prospective, Open-Label, Cluster-Randomized Pilot Clinical Trial. Journal of medical Internet research. 2017;19(7):e246. PMID: 28698169.
9. Storm V, Dorenkamper J, Reinwand DA, Wienert J, De Vries H, Lippke S. Effectiveness of a Web-Based Computer-Tailored Multiple-Lifestyle Intervention for People Interested in Reducing their Cardiovascular Risk: A Randomized Controlled Trial. Journal of medical Internet research. 2016;18(4):e78. PMID: 27068880.
10. Kardia. 2017. www.alivecor.com. Archived at: http://www.webcitation.org/6rvDdV82S.
11. Nokia Health. 2017. https://health.nokia.com/nl/en/. Archived at: http://www.webcitation.org/6rv9MsKXU.
12. Margolis KL, Asche SE, Bergdall AR, Dehmer SP, Groen SE, Kadrmas HM, et al. Effect of home blood pressure telemonitoring and pharmacist management on blood pressure control: a cluster randomized clinical trial. JAMA. 2013;310(1):46-56. PMID: 23821088.

13. Zhai YK, Zhu WJ, Cai YL, Sun DX, Zhao J. Clinical- and cost-effectiveness of telemedicine in type 2 diabetes mellitus: a systematic review and meta-analysis. Medicine (Baltimore). 2014;93(28):e312. PMID: 25526482.
14. Viers BR, Lightner DJ, Rivera ME, Tollefson MK, Boorjian SA, Karnes RJ, et al. Efficiency, satisfaction, and costs for remote video visits following radical prostatectomy: a randomized controlled trial. Eur Urol. 2015;68(4):729-35. PMID: 25900782.
15. Watson AJ, Bergman H, Williams CM, Kvedar JC. A randomized trial to evaluate the efficacy online follow-up visits in the management of acne. Arch Dermatol. 2010;146(4):406-11.
16. Perk J, De BG, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012;33(13):1635-701. PMID: 22555213.
17. Ware JE, Jr., Snyder MK, Wright WR, Davies AR. Defining and measuring patient satisfaction with medical care. Eval Program Plann. 1983;6(3-4):247-63. PMID: 10267253.
18. Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ. 1992;305(6846):160-4. PMID: 1285753.
19. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003;35(8):1381-95. PMID: 12900694.
20. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens (Greenwich). 2008;10(5):348-54. PMID: 18453793.
21. Tan SS, Bouwmans CA, Rutten FF, Hakkaart-van Roijen L. Update of the Dutch Manual for Costing in Economic Evaluations. Int J Technol Assess Health Care. 2012;28(2):152-8. PMID: 22559757.
22. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ. 2002;21(2):271-92. PMID: 11939242.
23. Bangalore S, Qin J, Sloan S, Murphy SA, Cannon CP. What is the optimal blood pressure in patients after acute coronary syndromes?: Relationship of blood pressure and cardiovascular events in the PRavastatin OR atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE IT-TIMI) 22 trial. Circulation. 2010;122(21):2142-51. PMID: 21060068.
24. Puymirat E, Riant E, Aissoui N, Soria A, Ducrocq G, Coste P, et al. beta blockers and mortality after myocardial infarction in patients without heart failure: multicentre prospective cohort study. BMJ. 2016;354:i4801. PMID: 27650822.
25. ICT gebruik van personen naar persoonskenmerken, 2005-2013. 2017. Den Haag. http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=71098NED&D1=33-34,78-91&D2=0&D3=a&HDR=G1,T&STB=G2&VW=T. Archived at: http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=71098NED&D1=33-34,78-91&D2=0&D3=a&HDR=G1,T&STB=G2&VW=T.

26. Anglada-Martinez H, Rovira-Illamola M, Martin-Conde M, Sotoca-Momblona JM, Codina-Jane C. mHealth intervention to improve medication management in chronically ill patients: analysis of the recruitment process. Postgrad Med. 2016;128(4):427-31. PMID: 27007065.
27. Dhruva SS, Redberg RF. Variations between clinical trial participants and Medicare beneficiaries in evidence used for Medicare national coverage decisions. Arch Intern Med. 2008;168(2):136-40. PMID: 18227358.



CHAPTER 5

Mobile phones in cryptogenic strOke patients Bringing sIngle Lead ECGs for Atrial Fibrillation detection (MOBILE-AF): design and rationale

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Abstract

Background

Recently published randomized clinical trials indicate that prolonged ECG monitoring might enhance detection of paroxysmal atrial fibrillation (AF) in cryptogenic stroke or TIA patients. A device that might be suitable for prolonged ECG monitoring is a smartphone compatible ECG device (Kardia Mobile, Alivecor, San Francisco, CA) that allows the patient to record a single lead ECG without the presence of trained healthcare staff. The MOBILE-AF trial will investigate the effectiveness of the ECG device for AF detection in patients with cryptogenic stroke or TIA. In this paper, the rationale and design of the MOBILE-AF trial is presented.

Methods

For this international multicentre trial, 200 patients with cryptogenic stroke or TIA will be randomized. 100 patients will receive the ECG device and will be asked to record their ECG twice daily during a period of one year. 100 patients will receive a 7-Day Holter monitor.

Discussion

The primary outcome of this study is the percentage of patients in which AF is detected in the first year after the index ischaemic stroke or TIA. Secondary outcomes include markers for AF prediction, oral anticoagulation therapy changes, as well as incidence of recurrent stroke and major bleedings. First results can be expected mid-2019.

Trial registration

Number NCT02507986 in ClinicalTrials.gov. Registered in July 2015.

Background

In approximately 30% of all patients with ischaemic stroke or transient ischaemic attack (TIA), no cause can be determined after standard evaluation. These strokes and TIAs are referred to as cryptogenic.(1) One of the known risk-factors for ischaemic stroke is atrial fibrillation (AF).(2) Current guidelines state that oral anticoagulation therapy (OAC) should be prescribed in case AF of any duration above 30 seconds is detected after ischaemic stroke/TIA on a 12-lead ECG or lasting at least 30 seconds(3) on a 24-hour Holter monitor.(3, 4) However, as AF is often asymptomatic and paroxysmal,(5) the detection of AF with the currently advised standard work-up using a 24-hour Holter recording is low.(6, 7)

Consequently, recently published research indicates that AF episodes may be missed using this standard evaluation. In the CRYSTAL-AF(6) and EMBRACE trials,(7) it was demonstrated that prolonged ECG monitoring yielded significantly higher percentages of detected AF in patients with cryptogenic stroke or TIA.(6, 7)

It has been discussed that it is uncertain if subclinical AF, especially short episodes, require anticoagulation in patients with cryptogenic stroke.(8) Several trials (NCT02313909, NCT02427126 and NCT02239120) started to randomize patients with cryptogenic stroke between non-vitamin K oral anticoagulants (NOACs) and aspirin. Pending the results of these trials, the diagnosis of AF after cryptogenic stroke remains to have therapeutic consequences.(3) The diagnostic method therefore remains important.

In the CRYSTAL-AF trial, an implantable cardiac monitor (ICM) showed significantly higher detection rates of AF after 6-months follow-up in patients with cryptogenic stroke. However, placement of an ICM is costly and has some limitations, as it brings in the risk of pocket infection.(6)

In the EMBRACE trial, a 30-day event-triggered loop recorder showed significantly higher rates of AF after 90-days of follow-up. However, the device was moderately tolerated as 60% of all participants completed the full month of wearing the device.(7)

In the past five years, smartphone-connected ECG devices have been developed. One of these devices is the Kardia Mobile (Alivecor, Inc., San Francisco, CA, USA). This a handheld ECG device that transmits and stores a single lead ECG on a smartphone. It is cleared by the United States Food And Drug Administration (FDA) and has received a European Union CE mark for the detection of AF.(9) The device is easy-to-use, non-invasive, electrically safe and can be used on demand. It does not bring in the risk of pocket-infection, does not have to be worn on the body and is cheaper than an ICM.(10, 11) It furthermore does not, in contrast with an ICM, necessitate trained healthcare staff or a dedicated hospital room to hand the device to the patient.(11, 12) Therefore, the Kardia Mobile may be a more feasible alternative for prolonged ECG monitoring in cryptogenic stroke patients. However,

the clinical effectiveness of the Kardia Mobile in detecting AF in cryptogenic stroke patients has not been investigated before.

Therefore, the Mobile phones in cryptogenic strOke patients Bringing sIngle Lead ECGs to detect Atrial Fibrillation (MOBILE AF) trial is designed to investigate the effectiveness of the Kardia Mobile device for AF detection in patients with cryptogenic stroke or TIA and to compare this with the effectiveness of regular follow-up for AF detection.

In this paper the design and rationale of the study are presented.

Methods

Patient population

For this study, patients with cryptogenic stroke or TIA that have been treated at one of the participating centers (see list Appendix A) will be asked to participate. Ischaemic stroke will be defined as an episode of neurological dysfunction caused by focal brain or retinal ischaemia with recent (hours to days) infarction on cerebral imaging.(13) TIA is defined as a transient episode of neurologic dysfunction lasting less than one hour caused by focal brain or retinal ischaemia without recent infarction on cerebral imaging.(14)
A stroke or TIA is defined as cryptogenic if no cause can be determined after standard work-up, consisting of at least:

1. Computed Tomography (CT) of the brain
2. Computed Tomography Angiography (CTA) of head and neck arteries or Echo Doppler of the carotid arteries
3. Transthoracic echocardiography followed by transoesophageal echocardiography when indicated
4. 12-lead 10-second electrocardiography
5. 24-hour ECG monitoring
6. Laboratory tests
    a. Complete blood count
    b. Prothrombin time
    c. Partial thromboplastin time
    d. Serum electrolytes
    e. C-reactive protein
    f. Hepatic and renal chemical analysis
    g. Erythrocyte sedimentation rate

If a stroke or TIA is considered to be cryptogenic, a patient will be evaluated with the described in-, and exclusion criteria. These criteria are listed in Table 1. Generally, adult patients who suffer from a cryptogenic stroke or TIA who are willing to sign informed consent, and are in possession of a smartphone with Android OS or iOS can participate. A maximum duration of six months between diagnosis of the index event and study inclusion is allowed.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Admitted to the stroke unit of participating centres with an ischaemic stroke or TIA
Exclusion criteria
Known aetiology of TIA or ischaemic stroke
TIA or stroke caused by spinal ischaemia
TIA is only present with non-localising symptoms(25)
Uncertainty about the diagnosis of TIA because of unclear clinical symptoms
Myocardial infarction <1 month before stroke
Coronary Artery Bypass Grafting <1 month before stroke
Surgery indicated valvular heart disease
Documented history of AF or atrial flutter
Left ventricular aneurysm on echocardiography
Intracardiac Thrombus on echocardiography
Renal dysfunction (creatinine clearance <30 mL/min/1.73m2)
Patient is not able or willing to sign the informed consent form
Patient is <18 years of age
Patient is considered an incapacitated adult
Patient is not in possession of a smartphone or tablet with Android Operating (OS) System or iOS and is unwilling to arrange one

The Kardia Mobile

The Kardia Mobile device is a handheld smartphone compatible device which contains two electrodes. The Kardia Mobile device is battery powered and electrically safe. The Kardia Mobile device communicates with the Kardia Mobile app, which can be downloaded on smartphones running Android OS or iOS. The device records a 30 sec ECG from the fingers of both hands. A single lead ECG is instantly shown on the smartphone screen. The recording of an ECG does not require the presence of healthcare staff.

An automated algorithm on the Kardia Mobile app checks the ECG for R-R wave irregularity. It delivers a diagnosis citing either “no abnormalities detected”, “possible atrial fibrillation” or “this ECG could not be interpreted”. This is a validated, FDA approved algorithm with a 97% sensitivity and 98% specificity for AF detection.(10)

After the diagnosis, the Kardia Mobile app offers the possibility to take notes. Patients are explicitly asked to take notes of their symptoms, if present, at the time of the recording.
If the diagnosis “possible atrial fibrillation” or “this ECG could not be interpreted” is delivered, the ECG is assessed for the presence of AF on the same or next working day by a PhD student with ample training and experience at the Holter department, who is not blinded to patient data. In case of any uncertainty about the diagnosis, the ECG is evaluated by an experienced cardiologist/electrophysiologist, who is blinded to the patient data. The ECG is saved in a secured cloud environment. ECGs in PDF can be automatically send to and checked by the study supervisors after patients’ consent. An example of such a PDF showing sinus rhythm is presented in Figure 1. An example of such a PDF showing atrial fibrillation is presented in Figure 2.

The Kardia mobile can be discontinued on patient’s request. In case of non-adherence (defined as not having sent a single lead ECG for two consecutive days), patients will first receive a standardized e-mail asking if there are any technical problems. If patients do not send ECGs for another two consecutive days, patients will receive a phone call asking for the reason. Technical issues will be addressed immediately. In case of loss of the Kardia device, a new device will be provided free-of-charge. If patients wish to discontinue their recordings, they will be considered lost to follow-up.

7-Day Holter monitor
For this study, H3+ recorders (Mortara Instrument, Milwaukee, WI, USA) are deployed. All Holter recorders are battery powered and electrically safe. The Holter recorders have a CE mark. The H3+ recorder records three ECG channels continuously. A total of 5 electrodes are applied to the patient’s chest and abdomen. ECG data will be downloaded and analysed using the H-Scribe Holter Analysis System (Mortara Instrument, Milwaukee, WI, USA). This software package analyses the ECG for R-R wave irregularities and automatically detects possible abnormalities such as premature atrial contractions, premature ventricular contractions, supraventricular arrhythmias and ventricular arrhythmias. All Holters are checked by a PhD-Student (who is not blinded to patient data) with ample training and experience at the Holter department, supervised by an experienced senior observer, who is blinded to the patient data. The 7-Day Holter monitor can be discontinued on patient’s request or in case of serious allergic reactions to the patches.

Figure 1. An electrocardiogram (ECG) recorded by the AliveCor device showing sinus rhythm.

Study design, randomization and follow-up

The Mobile phones in cryptogenic strOke patients Bringing sIngle Lead ECGs for Atrial Fibrillation detection trial (MOBILE-AF) is an international multicentre (a list of the six participating centres can be found in Appendix A) randomized open clinical trial, registered under clinical trial numbers NCT02507986 (www.clinicaltrials.gov) and NL54103.058.15 (www.toetsingonline.nl), in accordance with the SPIRIT guidelines (in Appendix B). A flow-chart of the study design is given in Figure 3. It randomizes patients, after inclusion, to follow-up with either the Kardia Mobile (intervention group) or the 7-Day Holter monitor (control group). Block randomization will be performed. Randomization will be stratified per centre and per diagnosis (TIA or

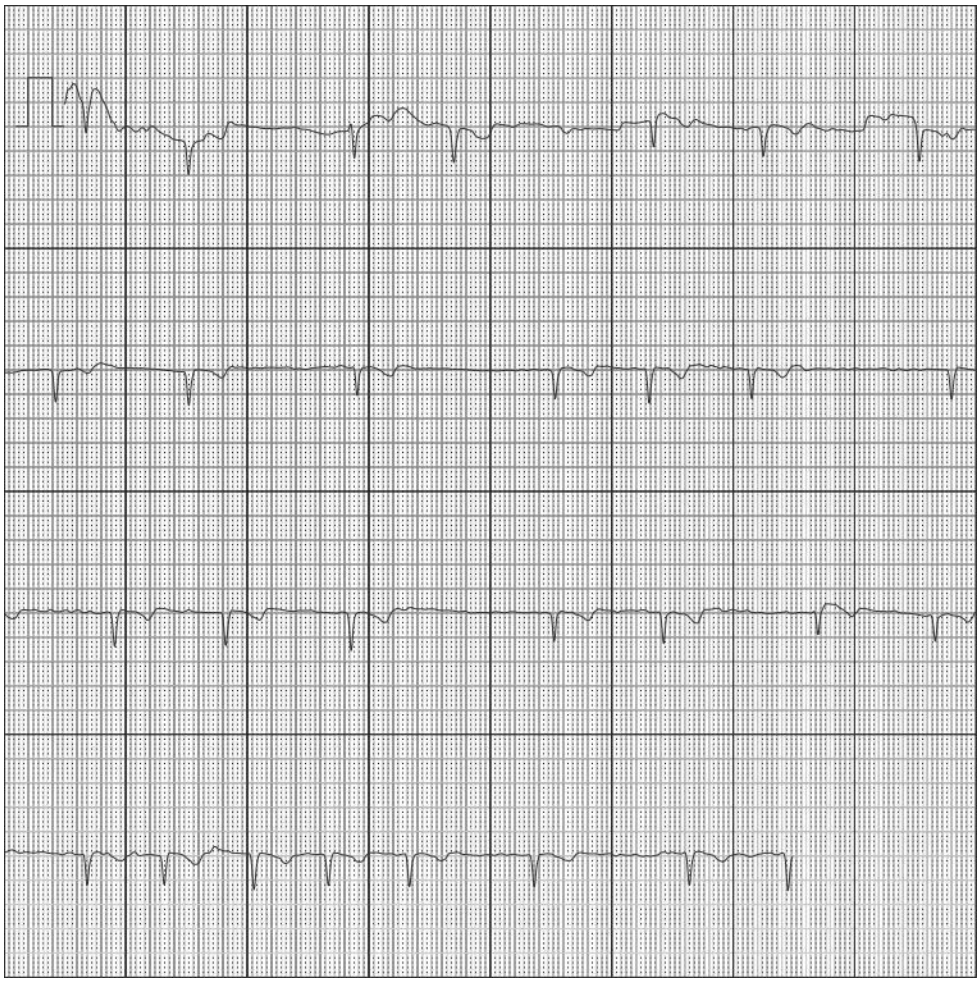


Figure 2. An electrocardiogram (ECG) recorded by the AliveCor device showing atrial fibrillation.

ischaemic stroke). The allocation sequence will be generated using a website (www.randomizer.org) and stored in an Excel (Microsoft, Redmond, Washington, United States of America). The document is only accessible for a PhD-student who is not otherwise involved in the trial. Patients will be approached and randomized by a project dedicated PhD-Student. This PhD-Student will not have access to the allocation sequence.

When randomized to the intervention group, patients will receive the Kardia Mobile device. Patients will receive this device immediately after randomization. Patients will be instructed by a dedicated PhD-Student about the usage of the Kardia Mobile,

including downloading the app, setting up an account and recording an ECG with the Kardia Mobile device.
Patients are requested to record an ECG at least twice daily, with the two measurements separated by at least 6 hours. Furthermore, patients are urged to record an ECG in case of any symptoms of possible cardiac origin, as judged by the patient.

When randomized to the control group, patients' heart rhythm will be recorded for 7 consecutive days (24 hours per day), using the 7-Day Holter monitor. This will be done directly after randomization. After 7 days, patients are referred to regular follow-up after ischaemic stroke or TIA. Regular follow-up usually consists of a referral to the general practitioner who will see patients only in case of symptoms. However, patients might also be followed-up at the site of referral, in which case a patient might have one more scheduled visit to the cardiologist. This is left to the discretion of the treating cardiologist.

In case AF is detected, the recording is sent to the treating cardiologist. The treatment options, including the decision to change anticoagulation treatment, will be left to the discretion of the treating cardiologist.
Patients will continue to participate in the trial, even though AF is documented. Each ECG that shows AF will be sent to the treating cardiologist of the patient.
All patients will continue to receive regular follow-up after cryptogenic stroke or TIA. All study actions are additional to regular follow-up. For both groups at 12 months, a phone call will be scheduled including a standardized interview (Appendix B). If a patient has been admitted to another hospital than the participating centre, the patient and hospital will be asked to share all relevant health information.

Study outcomes
The primary outcome of this study is the percentage of patients in which AF is detected in the first year after the index ischaemic stroke or TIA. The primary outcome will be assessed by two cardiologists who will be blinded to patient data. Both will be working independent from each other. Any disagreements will be solved by consensus. AF is defined as a rhythm with completely irregular RR intervals and no distinct P-waves on the surface ECG.(15)

Secondary outcomes are
1. Pro-BNP levels in all patients within 24 hours after cryptogenic stroke
2. Percentages of atrial ectopy detected on the 24-hour Holter monitor
3. Left atrial diameter and volume on 2D-echocardiography

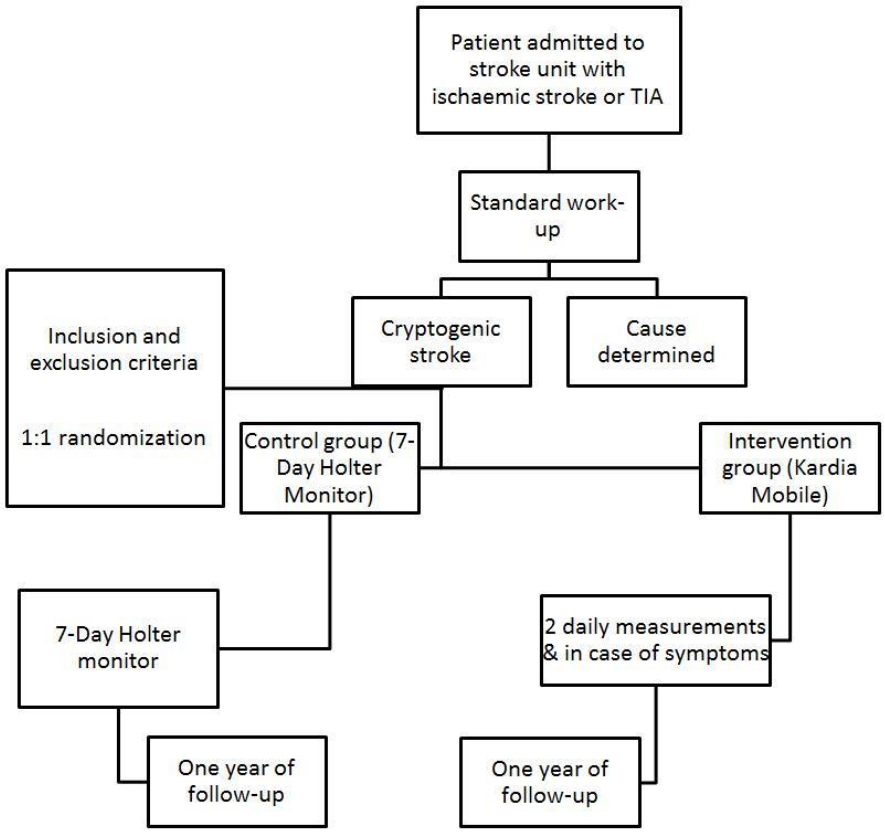


Figure 3. Flowchart of study design

4. Percentage of patients on oral anticoagulation therapy at the beginning and at the end of the study.
5. The incidence of recurrent ischaemic stroke or TIA. Ischaemic stroke will be defined as an episode of neurological dysfunction caused by focal brain or retinal ischaemia with recent infarction on cerebral imaging.(13) TIA is defined as a transient episode of neurologic dysfunction lasting less than one hour caused by focal brain or retinal ischaemia without recent infarction on cerebral imaging.(14) All recurrent ischaemic strokes and TIAs will be evaluated by two neurologists based on information noted in the electronic health records, working independently of each other. Any disagreements will be solved by consensus.
6. Major bleeding (defined as: any bleeding that needs medical treatment or hospital admission/prolongation of admission)
7. Number of single lead ECGs taken per patient, as a measure of compliance

8. Number of Holter studies (either 24-hours, 48-hours or 7-day) done after randomization in both groups (in which the 7-day Holter monitor that is done as part of the trial protocol is not included)
9. Time (in days) between randomization and detection of first AF episode.

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		Close-out
TIMEPOINT**	0	0	1 week	1 year	1 year
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
7-Day Holter monitor			x		x
ECG device (Kardia Mobile)			X	X	x
ASSESSMENTS:					
Prior stroke, prior TIA, primary diagnosis, gender, hypertension, diabetes, smoking status, alcohol, previous bleeding, drug abuse, abnormal liver function, abnormal renal function	X	X			
AF, recurrent stroke, major bleeding, Pro-BNP, atrial ectopy on Holter, change in therapeutic regimen			x	x	X

Figure 4. Standard protocol items: recommendations for interventional trials (SPIRIT) Figure: schedule of enrolment, interventions and assessments.

Statistical analysis

The power calculation was done in PASS (Hintze J. (2008). PASS 2008. NCSS, LLC. Kaysville, Utah, CO. www.ncss.com) and is based on a comparison of two proportions of patients with diagnosed AF in a two by two table with a chi-squared statistic or odds ratio calculated. The underlying assumption is that in 2.0% of the 7-Day Holter monitor group AF will occur. This proportion is assumed to be 12.4% in the Kardia

Mobile group. These percentages are based on the results of the CRYSTAL-AF trial. (6) A sample size of 200 patients was calculated with an alfa level of 0.05 and a power of 0.85. Patients will be 1:1 randomized.
Data will be analysed according to the intention-to-treat principle. After completion of the inclusion of study patients, the proportion of patients with AF will be compared with a Chi-squared test or rate ratio (RR). Causes of missing data will be tabulated. Because of the expected low percentage of missing data, complete case analysis will be done. Analysis will be based on the missing-at-random assumption. In case of serious imbalances of baseline variables after randomization, additional Poisson regression might follow with correction for potential confounding variables at baseline.

Ethical conduct

The study will be conducted according to the principles of the Declaration of Helsinki (version 10, October 2013) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO) and Good Clinical Practice. Potential study subjects will be approached by a project dedicated PhD-Student who is not involved in their treatment. Written informed consent will be obtained from all study participants before randomization. For this study, no data monitoring committee is installed, because both devices are battery powered an electrically safe. They do not bring risks to patients safety. The absence of a DMC is approved by the hospital's MEC. All devices used bear a CE mark and are approved by the United States Food and Drug Administration (FDA). No manufacturer of any devices used in this study is involved in study design, data collection, data analysis, data interpretation or writing of the report. No financial support or any other form of support is received for this study from any manufacturer. If the protocol changes as such that it affects participants who are already participating in the trial, they will be notified by telephone or e-mail by a project dedicated PhD-Student. It is our intention to publish the results of the trial in a peer-reviewed scientific journal.

Data safety

Data Collection Forms, Case Report Forms, Informed Consent Forms and all other study documentation containing subject information will be stored under locked conditions when not in use. Computers and all storage devices containing study data will be password-protected. Data stored on the computer will use an numeric code to identify the subject. Personal information will be kept in a password protected, separate document. Access to data is restricted to study personnel and when required the MEC or the Healthcare Inspectorate as required by Dutch law. No personnel of any manufacturer of any device involved in the study will have access to the study data.

Timeline

The sample size is 200 patients. Our trial started on July 29th, 2016. Our proposed end date is July 1st, 2019. Currently, 6 hospitals are referring patients for the trial. Each center has an estimated sixty patients per year that are eligible for this study. In case of slow recruitment (less than eighty patients in one year), more hospitals will be approached to refer patients for participation in the trial. This will be communicated via clinicaltrials.gov. A final list of centers that referred patients for the trial will be published when the final results of the trial are available.

Discussion

The MOBILE-AF trial is an international multicentre randomized clinical trial that evaluates the efficacy of the Kardia Mobile device in the detection of AF in cryptogenic stroke and TIA patients. To our knowledge, this is the first and only clinical trial that uses the Kardia Mobile for this indication. The Kardia Mobile is a validated device that is non-invasive and easy-to-use. Because of its negligible burden on the patient, its low cost and the fact that it can be used by patients on demand, without the presence of trained health care staff, to our opinion it has potential to improve the yield and cost-effectiveness of AF detection in this population.

Subclinical AF after cryptogenic stroke and subsequent risk of recurrent stroke

Currently, there is scientific uncertainty about the causal relationship between subclinical paroxysmal AF following cryptogenic stroke and the subsequent risk of recurrent stroke.(8, 16-19) In contrast, clinical AF has been a long known independent risk factor for ischaemic stroke.(2) More recent trials in patients without prior ischaemic stroke and implanted pacemakers or ICDs demonstrated that also subclinical paroxysmal AF increased ischaemic stroke risk.(20, 21) One of these trials, the ASSERT trial, found a 2.5 fold increased risk in patients who experienced episodes of subclinical AF lasting more than six minutes. This risk tended to increase in patients who experienced longer or more frequent episodes of subclinical paroxysmal AF. However, the authors noted that the study was underpowered to draw conclusions about this particular question.(20)

Detecting subclinical AF after cryptogenic stroke

In the CRYSTAL-AF trial, 12.4% of paroxysmal AF was found after 12 months in patients wearing an ICM. Of these episodes, 79% were asymptomatic. The median value of maximum duration of an AF episode was 11.2 hours. A total of 61% of all AF episodes was longer than 6 hours.(6) In the EMBRACE trial no data on AF symptoms are given. Of the 284 patients randomized to the 30-day ECG monitoring, 56 (19.7%) had AF of any duration. A total of 44 patients (15.5%) had at least one

episode which lasted longer than 30 seconds. A total of 28 patients (9.9%) had at least one episode which lasted longer than 2.5 minutes.(7)
The Kardia Mobile produces a PDF in which 30 seconds of measurement are shown. Therefore, the duration of an paroxysmal AF episode cannot be adequately determined by the Kardia Mobile. However, we consider it likely that a 30-second recording of AF on the Kardia Mobile will be part of a longer during episode of AF. In comparison, in the CRYSTAL-AF trial 61% of patients with detected AF had episodes which lasted longer than 6 hours.(6) As we expect that most patients will perform a Kardia Mobile measurement twice daily, the chances that the Kardia Mobile will detect sporadically occurring AF episodes lasting only several minutes are low.

Prevention of recurrent stroke

Determining the percentage of anticoagulants users, the percentage of recurrent strokes and the percentages of major bleedings are secondary objectives of the MOBILE-AF trial. At the end of the CRYSTAL-AF TRIAL, 10.1% in the ICM group and 4.6% of all control group patients used OAC. Recurrent stroke occurred in 5.2% in the ICM group and 8.6% in the control group. These results may indicate that OAC in patients with subclinical AF indeed lowers the risk of recurrent stroke. However, no data were shown about the relationship between duration or frequency of AF episodes and recurrent stroke. Furthermore, the study was underpowered to draw conclusions about this specific relation.(6) It therefore remains unclear whether subclinical AF in cryptogenic stroke is of clinical importance. For this reason, we leave the decision to start OAC to the discretion of the patient's treating cardiologist. We will however carefully monitor percentages of patients in which OAC was described, as well as the main effect (stroke recurrence) and side effect (major bleedings) and therefore included these in our secondary objectives.

Prediction of AF occurrence

There are a number of publications available about prediction of the occurrence of mainly paroxysmal AF after cryptogenic stroke or TIA. One is a paper by Rodriguez-Yanez et al., who evaluated 372 patients with cryptogenic stroke. Pro-BNP levels were determined within 24 hours of stroke onset. Patients were followed-up for 2 years for the development of AF. The authors concluded that a pro-BNP≥360 pg/mL had a negative predictive value of 98.6%. Overall, 5.6% of all stroke patients was found to have AF.(22) This is a relatively low percentage, compared with the CRYSTAL-AF (12.4% after one year) and EMBRACE (16.2% after 90-days).(6, 7) This might be explained by the frequency of monitoring: follow-up was done by taking elective 12-lead 10-seconds ECGs. No continuous monitoring was applied.(22) Therefore, as our trial involves more frequent ECG monitoring, we would like to corroborate that a pro-BNP≥360 pg/mL has indeed a high negative predictive value.

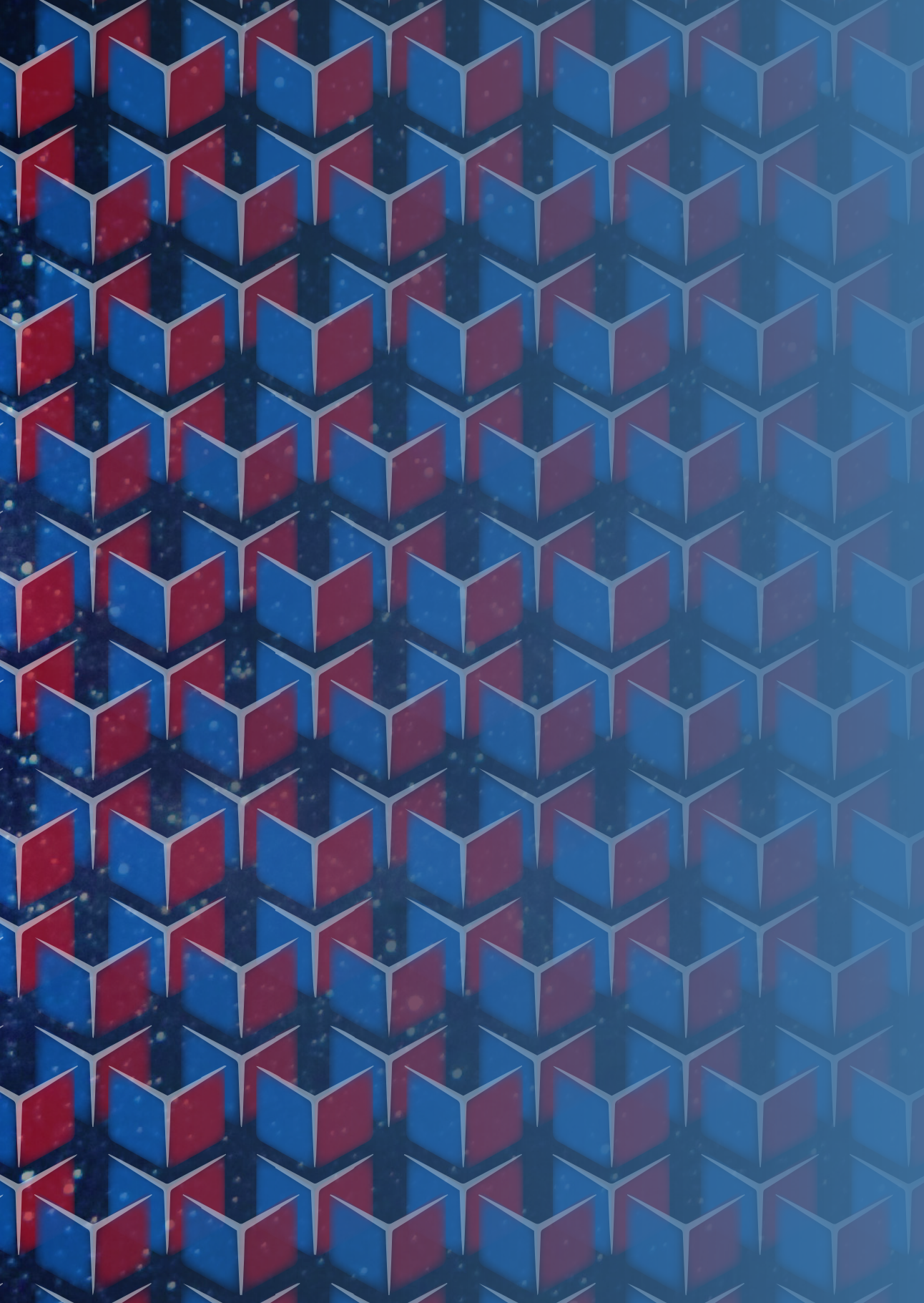
A second is a paper by Gladstone et al., who evaluated 237 patients with cryptogenic stroke or TIA. They assessed the amount of atrial premature beats (ABP) on the 24-hour Holter monitoring which was part of the standard work-up of cryptogenic stroke. They found that the amount of ABPs was strongly and independently associated with the development of subclinical AF within 90 days after cryptogenic stroke.(23) We would like to also confirm these findings in our population.
A third is a paper by Tsang et al.(24), who investigated the relationship between left atrial diameter and volume and the development of AF. They found that an increase in left atrial volume was independently associated with the development of AF. Although this study was not performed in patients who had experienced a cryptogenic stroke, we believe this might also be true for our population. We therefore would like to verify the study's findings in our population.(24)
To our knowledge, these three predictors have not been combined into a prediction score yet. We would like to combine the three predictors and develop a prediction score for the occurrence of paroxysmal AF after cryptogenic stroke or TIA, in order to individualize monitoring strategies for these patients.

Summarizing, we present a study that is designed to investigate the effectiveness of the Kardia Mobile to detect AF in patients with cryptogenic stroke. The Kardia Mobile is a device with serious potential to improve clinical and cost-effectiveness. The first results can be expected end 2018.

References

1. H. P. Adams, Jr., B. H. Bendixen, L. J. Kappelle, J. Biller, B. B. Love, D. L. Gordon, et al., "Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment," Stroke, vol. 24, pp. 35-41, 1/1993.
2. P. A. Wolf, R. D. Abbott, and W. B. Kannel, "Atrial fibrillation as an independent risk factor for stroke: the Framingham Study," Stroke, vol. 22, pp. 983-988, 8/1991.
3. P. Kirchhof, S. Benussi, D. Kotecha, A. Ahlsson, D. Atar, B. Casadei, et al., "2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS," Eur Heart J, vol. 37, pp. 2893-2962, Oct 07 2016.
4. "Guidelines for management of ischaemic stroke and transient ischaemic attack 2008," Cerebrovasc. Dis, vol. 25, pp. 457-507, 2008.
5. J. W. Keach, S. M. Bradley, M. P. Turakhia, and T. M. Maddox, "Early detection of occult atrial fibrillation and stroke prevention," Heart, vol. 101, pp. 1097-1102, 7/2015.
6. T. Sanna, H. C. Diener, R. S. Passman, L. Di, V, R. A. Bernstein, C. A. Morillo, et al., "Cryptogenic stroke and underlying atrial fibrillation," N. Engl. J. Med, vol. 370, pp. 2478-2486, 6/26/2014.
7. D. J. Gladstone, M. Spring, P. Dorian, V. Panzov, K. E. Thorpe, J. Hall, et al., "Atrial fibrillation in patients with cryptogenic stroke," N. Engl. J. Med, vol. 370, pp. 2467-2477, 6/26/2014.
8. B. Silver, "Cryptogenic stroke and atrial fibrillation," N. Engl. J. Med, vol. 371, p. 1259, 9/25/2014.
9. "K140933 - Food and Drug Administration," vol. Available via: http://www.accessdata.fda.gov/cdrh_docs/pdf14/k140933.pdf, ed, 2014. Retrieved on: 15-05-2016.
10. J. K. Lau, N. Lowres, L. Neubeck, D. B. Brieger, R. W. Sy, C. D. Galloway, et al., "iPhone ECG application for community screening to detect silent atrial fibrillation: a novel technology to prevent stroke," Int. J. Cardiol, vol. 165, pp. 193-194, 4/30/2013.
11. ed, Kardia. 2017. www.alivecor.com. Archived at: http://www.webcitation.org/6rvDdV82S.
12. T. A. Kanters, C. Wolff, D. Boyson, C. Kouakam, T. Dinh, L. Hakkaart, et al., "Cost comparison of two implantable cardiac monitors in two different settings: Reveal XT in a catheterization laboratory vs. Reveal LINQ in a procedure room," Europace, vol. 18, pp. 919-24, Jun 2016.
13. R. L. Sacco, S. E. Kasner, J. P. Broderick, L. R. Caplan, J. J. Connors, A. Culebras, et al., "An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association," Stroke, vol. 44, pp. 2064-2089, 7/2013.
14. J. D. Easton, J. L. Saver, G. W. Albers, M. J. Alberts, S. Chaturvedi, E. Feldmann, et al., "Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists," Stroke, vol. 40, pp. 2276-93, Jun 2009.
15. A. J. Camm, P. Kirchhof, G. Y. Lip, U. Schotten, I. Savelieva, S. Ernst, 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, vol. 12, pp. 1360-1420, 10/2010.

16. S. D. Malnick, M. Somin, and S. Goland, “Cryptogenic stroke and atrial fibrillation,” N. Engl. J. Med, vol. 371, pp. 1259-1260, 9/25/2014.
17. D. J. Gladstone, M. Sharma, and J. D. Spence, “Cryptogenic stroke and atrial fibrillation,” N. Engl. J. Med, vol. 371, p. 1260, 9/25/2014.
18. T. Sanna, H. C. Diener, and R. S. Passman, “Cryptogenic stroke and atrial fibrillation,” N. Engl. J. Med, vol. 371, p. 1261, 9/25/2014.
19. H. Kamel, “Heart-rhythm monitoring for evaluation of cryptogenic stroke,” N. Engl. J. Med, vol. 370, pp. 2532-2533, 6/26/2014.
20. J. S. Healey, S. J. Connolly, M. R. Gold, C. W. Israel, I. C. Van Gelder, A. Capucci, et al., “Subclinical atrial fibrillation and the risk of stroke,” N. Engl. J. Med, vol. 366, pp. 120-129, 1/12/2012.
21. T. V. Glotzer, E. G. Daoud, D. G. Wyse, D. E. Singer, M. D. Ezekowitz, C. Hilker, et al., “The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study,” Circ. Arrhythm. Electrophysiol, vol. 2, pp. 474-480, 10/2009.
22. M. Rodriguez-Yanez, S. Arias-Rivas, M. Santamaria-Cadavid, T. Sobrino, J. Castillo, and M. Blanco, “High pro-BNP levels predict the occurrence of atrial fibrillation after cryptogenic stroke,” Neurology, vol. 81, pp. 444-447, 7/30/2013.
23. D. J. Gladstone, P. Dorian, M. Spring, V. Panzov, M. Mamdani, J. S. Healey, et al., “Atrial premature beats predict atrial fibrillation in cryptogenic stroke: results from the EMBRACE trial,” Stroke, vol. 46, pp. 936-941, 4/2015.
24. T. S. Tsang, M. E. Barnes, K. R. Bailey, C. L. Leibson, S. C. Montgomery, Y. Takemoto, et al., “Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women,” Mayo Clin. Proc, vol. 76, pp. 467-475, 5/2001.
25. M. J. Bos, M. J. van Rijn, J. C. Witteman, A. Hofman, P. J. Koudstaal, and M. M. Breteler, “Incidence and prognosis of transient neurological attacks,” Jama, vol. 298, pp. 2877-85, Dec 26 2007.



CHAPTER 6

Comparison of the diagnostic accuracy of four smartphone compatible blood pressure monitors in post-myocardial infarction patients

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Abstract

Introduction

Smartphone compatible blood pressure (BP) devices may be a good alternative to enable self-measurement of BP by patients. Furthermore, automatic transferral of data to the hospital allows for remote monitoring. To our knowledge, no study has compared four of these smartphone compatible BP devices.

Methods

Patients who were followed-up for acute myocardial infarction were asked to participate during their outpatient clinic visit. After 5 minutes of rest, six BP devices were applied. The order was randomized. Four devices were smartphone compatible. One device was an automated oscillometric device. One device was a handheld aneroid sphygmomanometer (reference device). All measurements were compared using a linear mixed model.

Results

A total of 43 patients (62.7±11.3 years, 79% male) were included. Compared to the reference device, four BP monitors yielded a significant higher mean systolic BP and four monitors yielded a significant higher diastolic BP. One device yielded a non-significant lower mean systolic BP and one device yielded a non-significant higher mean diastolic BP. Except for one BP device, all mean differences were smaller than 5 mmHg.

Conclusion

In this study, average inter device variability was shown to be statistically significant, however four devices remained within the predefined range of 5 mmHg for both systolic and diastolic BPs.

Introduction

Blood pressure (BP) measurement is inevitable in BP control, which is considered a cornerstone in the primary and secondary prevention of cardiovascular disease.(1) BP measurement is classically done by a trained healthcare professional using a mercury sphygmomanometer and a stethoscope to generate and auscultate the Korotkoff sounds.(2) Although this method is considered the gold standard, it has some disadvantages: first, involvement of a physician brings in the so-called "white coat hypertension" phenomenon, in which the BP significantly rises in the presence of a physician.(3) Due to this phenomenon, the office BP measurement could inadequately represent the patient's BP.(3) Second, patients often have to come to the outpatient clinic, making the measurement time consuming and a burden to the patient. Lastly, due to the necessity of the presence of a healthcare professional and an outpatient clinic, it is costs more than home BP measurement.(4)

An alternative to outpatient clinic BP measurement is home BP measurement, in which patients use an automated device to measure their BP at home without the presence of trained healthcare staff. Home BP measurement has advantages, as patients do not have to go to the outpatient clinic and it bypasses the white coat hypertension phenomenon.(5) For these reasons, the European Hypertension Society guidelines stress the importance of the use of home BP measurement, noting that using home BP measuring, cardiovascular morbidity and mortality can be predicted significantly better than with office measurements.(5)

Furthermore, it was recently demonstrated that home BP monitoring with antihypertensive treatment adjustments by pharmacists even improved BP control compared to usual care.(6)

Over the past few years, smartphone compatible oscillometric BP monitors have been approved for over-the-counter sale in the European Union.(7-9) These BP monitors can be applied by the patient without the presence of trained healthcare professionals. Furthermore, the storage of data in the Cloud allows for easy and automatic transferral to healthcare professionals.(7-9) Thus, these smartphone compatible BP monitors could be used for more frequent measurements, without the presence or assistance of a trained healthcare professional and the necessity of an outpatient clinic. These features make these smartphone compatible BP monitors suitable for telemedicine. So far, most studies have focused on the validation of one smartphone compatible device in healthy volunteers.(10-13) To our knowledge, no study has yet compared the performances of these four smartphone compatible monitors in a population with a doctor-confirmed cardiovascular disease. Therefore, the aim of this study is to compare the intra- and inter device variability of four smartphone compatible BP monitors with an aneroid sphygmomanometer and an automated, non-smartphone compatible, oscillometric monitor in a population with recent acute myocardial infarction (AMI).

Methods

Patient population

Patients with recent (<1 year) AMI visiting the outpatient clinic as part of the follow-up of their AMI were approached to participate in the study. Patients were excluded if they had had a documented history of an irregular heart rhythm (e.g. atrial fibrillation, atrial flutter, Mobitz II or grade III atrioventricular-block). Furthermore, patients were excluded if they were considered an incapacitated adult, if they were pregnant or if they were unwilling to sign the informed consent form. Patients who did not own a smartphone were not excluded for this study.

BP monitors

Details on the methods of this study and the BP monitors used have previously been described in a conference paper.(14) For this study, six BP monitors were used. The Welch Allyn 767 (Welch Allyn, Skaneateles Falls, NY), the Omron M7 (Omron, Kyoto, Japan), the Withings Wireless Blood Pressure Monitor (Withings, Issy-les-Moulineaux, France), iHealth BP5 (iHealth Lab, Inc., Mountain View, CA), QardioArm (Qardio Inc., San Francisco, CA) and the iHealth BP7 (iHealth Lab, Inc., Mountain View, CA). All devices bear a CE mark and are approved by the Food and Drug Administration (FDA). The Withings Wireless Blood Pressure Monitor, QardioArm, iHealth BP5 and iHealth BP7 are all automated oscillometric devices that are smartphone compatible. These four BP monitors communicate with the smartphone via Bluetooth. Inflation and deflation is automated and started by a command from the smartphone. Results of measurements are sent to the device's dedicated smartphone application (app). The Withings Wireless Blood Pressure Monitor, the QardioArm and the iHealth BP5 are placed around the bare upper arm of the patient. The iHealth BP7 is placed around the bare wrist of the patient. The Omron M7 is an automated oscillometric device. It is placed around the bare upper arm of the patient. Inflation and deflation are automated and started by pushing a button on the device. The Omron M7 is not smartphone compatible.

The Welch Allyn 767 is a handheld aneroid sphygmomanometer. It is placed around the bare upper arm of the patient. The Welch Allyn 767 has to be applied by a trained physician. The device has to be pumped up until the pressure is 10 mmHg higher than the systolic BP of the patients. While deflating, a trained physician needs to auscultate the Korotkoff sounds at the elbow joint. Upon hearing the first Korotkoff sounds, the systolic BP can be determined. When the Korotkoff sounds disappear, the diastolic BP can be determined.(15)

Study procedures

Patients were taken to a separate, quiet room. They were asked to sit down and relax for at least five minutes. During these five minutes, the order of applying the devices was randomized. For randomization, a website (www.randomizer.org) was used. After five minutes of rest, the devices were, one-by-one, applied to the patient. To assure that the devices were applied according to the device manufacturer's instruction manual, a project dedicated healthcare professional applied the device. The arm of patient's preference was used. All devices were applied to the same arm of the patient. Patients were not allowed to talk or drink during the measurements.

The Omron M7, the Withings Wireless Blood Pressure Monitor, the iHealth BP5, the QardioArm and the iHealth BP7 were applied by one of the investigators (RWT). The Welch Allyn 767 was applied by an independent trained physician (DCE), who was blinded to the outcomes of the other measurements. The patient was blinded to all results of all measurements. After the last device last measurement, results of all measurements were discussed with the patient. After a device was applied, it was inflated and deflated three times consecutively, generating three systolic BPs and three diastolic BPs. The average of these three systolic BP measurements was taken as systolic and the average of these three diastolic BP measurements was taken as diastolic BP.

Statistical analysis

IBM SPSS Statistics for Windows, version 23(Armonk, NY: IBM Corp) was used for statistical analysis. Continuous variables were presented as mean±standard deviation or as medians with interquartile range. The analyses were based on the repeated measures design with correlated BPs within patients. Linear mixed models were applied to accommodate this design to compare mean BPs and the variation (variances) of measurements among devices. A *P*-Value of less than 0.05 was considered statistically significant. The variances of the measurements within devices were compared within linear mixed models by likelihood ratio tests comparing models with equal variances versus models with unequal variances within an appropriate chi-square distribution.

Sample size calculation

The power calculation was done in PASS (Hintze J. PASS 2008. NCSS, LLC. Kaysville, Utah, CO. www.ncss.com) and was based on paired t-tests of smartphone device measurements against the measurements of the standard device, assuming a clinically relevant difference of 5 mmHg, a standard deviation of the measurements of 11.4 and a within patient Pearson's correlation of 0.8. The calculated sample size was 43 patients.

Ethical conduct

This study was done in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. The study was approved by the local Research and Ethical Board. All study participants provided written informed consent before participation. All devices for this study were bought from the manufacturers. No manufacturer had a role in the study design, conduction of the study, data analysis or the decision to submit the manuscript for publication.

Results

Study population

A total of 43 study participants (79% male) were included in the study. Mean age was 62.7±11.3 (range 39.5 - 81.6). Median BMI was 26.6 (IQ 24.2 - 29.3). The mean systolic BP (as measured by the Welch Allyn 767) was 119±14 (minimum-maximum range 97 - 160). The mean diastolic BP was 71±8 (minimum-maximum range 50-90). All measurements yielded 258 systolic BPs and 258 diastolic BPs (Figure 1).

Comparison of means

The average systolic BP measured by Welch Allyn was 118.9. The average systolic BP was +0.25 (95% CI (-2.9 2.4), *P*=.856) as measured by Omron, was +5.0 (95% CI (2.3 7.7), *P*<.001) as measured by iHealth BP5, was +7.1 (95% CI (4.4 9.7), *P*<.001) as measured by iHealth BP7, was +4.1 (95% CI (1.3 6.8), *P*=.004) as measured by Qardio and was +3.2 (95% CI (0.5 5.9), *P*=.022) as measured by Withings. These results are summarized in Table 1.

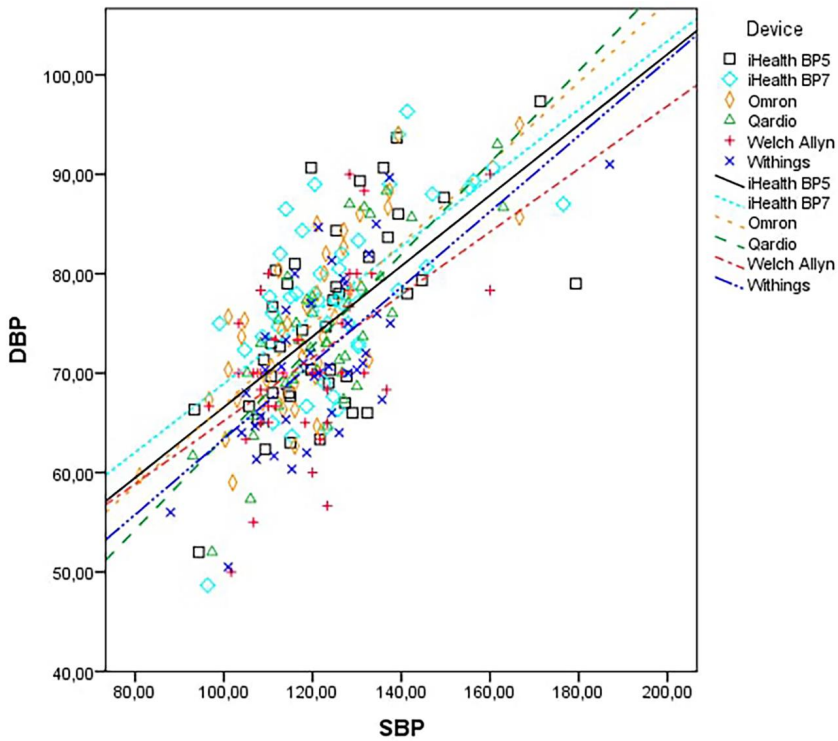


Figure 1. Scatterplot of the 258 measurements by iHealth BP5, iHealth BP7 , Omron M7, Qardio, Welch Allyn and Withings. The x-axis displays the systolic blood pressure (SBP). The y-axis displays the diastolic blood pressure (DBP). The lines displayed are the regression lines per device.

Table 1. Results of systolic BP measurements of all oscillometric devices, compared with the Welch Allyn

Device	Mean systolic BP	Difference with Welch Allyn	95% confidence interval	P-value
Omron	118.6	-0.25	(-2.9 2.4)	*P*=.856
iHealth BP5	124.0	+5.0	(2.3 7.7)	*P*<.001
iHealth BP7	126.0	+7.1	(4.4 9.7)	*P*<.001
Qardio	123.0	+4.1	(1.3 6.8)	*P*=.004
Withings	122.1	+3.2	(0.5 5.9)	*P*=.022

The average diastolic BP measured by Welch Allyn was 71.2. The average diastolic BP was +3.2 (95% CI (1.7 4.5), *P*<.001) as measured by Omron, was +3.9 (95% CI (2.5 5.3), *P*<.001) as measured by iHealth BP5, was +6.7 (95% CI (5.3 8.1), *P*<.001) as measured by iHealth BP7, was +2.9 (95% CI (1.5 4.4), *P*<.001) as measured by Qardio and was +0.7 (95% CI (-0.7 2.2), *P*=.324) as measured by Withings. These results are summarized in Table 2.

Table 2. Results of diastolic BP measurements of all oscillometric devices, compared with the Welch Allyn

	Mean diastolic BP	Difference with Welch Allyn	95% confidence interval	P-value
Omron	74.4	+3.2	(1.7 4.5)	*P*<.001
iHealth BP5	75.1	+3.9	(2.5 5.3)	*P*<.001
iHealth BP7	77.9	+6.7	(5.3 8.1)	*P*<.001
Qardio	74.1	+2.9	(1.5 4.4)	*P*<.001
Withings	71.9	+0.7	(-0.7 2.2)	*P*=.324

Comparison of means of smartphone compatible monitors

The average systolic BP measured by Withings was 122.1. Differences with iHealth BP5 and Qardio were not significant (*P*=.193 and *P*=.547 respectively), while the difference with iHealth BP7 was significant (*P*=.006). These results are summarized in Table 3.

Table 3. Results of systolic BP measurements of smartphone compatible monitors, compared with the Withings Wireless Blood Pressure Monitor

	Mean systolic BP	Difference with Withings	95% confidence interval	P-value
iHealth BP5	124.0	+1.9	(-0.9 4.5)	*P*=.193
iHealth BP7	126.0	+3.9	(1.1 6.6)	*P*=.006
Qardio	123.0	+0.9	(-1.9 3.6)	*P*=.547

The average diastolic BP measured by Withings was 71.9. Differences with iHealth BP5, iHealth BP7 and Qardio were all statistically significant (*P*<.001, *P*<.001 and *P*=.003 respectively). These results are summarized in Table 4.

Table 4. Results of diastolic BP measurements of smartphone compatible monitors, compared with the Withings Wireless Blood Pressure Monitor

	Mean diastolic BP	Difference with Withings	95% confidence interval	P-value
iHealth BP5	124.0	+3.2	(1.7 4.6)	*P*<.001
iHealth BP7	126.0	+3.9	(4.5 7.4)	*P*<.001
Qardio	123.0	+0.9	(0.7 3.7)	*P*=.003

Measurement variability of the devices, systolic BP

The statistical model assuming equal variances of the systolic BPs among devices was tested against the alternative model of unequal variances by comparing the respective -2(log-likelihoods) within the appropriate linear mixed model. The difference of 10.603 was smaller than the critical value of 11.070 of a chi-square(d.f.=5)-distribution and therefore not significant.

Measurement variability of the devices, diastolic BP

For diastolic blood pressures the difference of 23.048 of the two -2(log-likelihoods) was larger than the critical value of 11.070 of a chi-square(d.f.=5)-distribution and therefore was significant.

Discussion

In the current study, inter-, and intra device variability of four smartphone compatible blood pressure monitors were compared with a handheld sphygmomanometer, a non-smartphone compatible oscillometric device and with each other. These monitors may be suitable for home monitoring, as their usage does not require assistance of trained healthcare staff and measurement results can be transferred automatically.

The results demonstrate that, compared with the conventional handheld sphygmomanometer and a non-smartphone compatible oscillometric device, compatible BP monitors tend to yield higher systolic and diastolic BPs. These differences were all statistically significant, except for the diastolic BP by the Withings Wireless Blood Pressure Monitor. However, these differences were also within the predefined range of 5 mmHg, except for the iHealth BP7. Intra-device variability was non-significant for systolic BP, but was significant for diastolic BP.

Validation studies of the devices used in the study have been published previously.(10-13) These studies were all done in accordance with the European Society of Hypertension protocol, in which a device is compared with a mercury sphygmomanometer following a standardized protocol.(16) These studies show a higher mean systolic and diastolic BP for the Omron M7,(10) but a lower mean systolic and diastolic BP for Withings Wireless Blood Pressure Monitor,(13) the iHealth BP5(12) and the iHealth BP7.(11) This is in contrast with the results of this study, in which these devices yielded a higher mean systolic and diastolic BPs. This might be explained by the fact that in this study an overweight population was studied. Oscillometric devices tend to be more inaccurate in patients with a higher BMI.(17)

To our knowledge, studies comparing more than one oscillometric BP monitor with the gold standard have not been performed previously. Studies validating more than one oscillometric device do exist,(13, 18) however, all these studies describe several independently executed validation studies. These studies do not describe the validation of more than one oscillometric device in the same study population.

The fact that smartphone compatible BP monitors tend to yield higher BPs, makes them less suitable for on-spot measurements during outpatient clinic visits. However, the fact that these overestimates are within the 5 mmHg range, and the intra-device consistency of the systolic BP measurements, makes them suitable for home monitoring. With daily measurements, more measurement results

can be generated and the physician can adjust therapeutic regimen on a trend instead on an on-spot measurement. It is hypothesized that these monitors give a reliable average systolic and diastolic BP based on daily measurements and the possibility of a wrong therapeutic regimen change (defined as a physician changing the medication while the patient's BP has not changed) is small. It has already been shown that more frequent home monitoring of BP and changing therapeutic regimen when necessary improves BP control.(6)

There are, however, possibilities for further research. First, the results of this study need to be corroborated in a home situation, preferably with the patients using the devices themselves and without the assistance of trained healthcare staff. Second, the reliability of the BP monitors has to be investigated in the long term. In a hospital setting, BP monitors are calibrated approximately every two years.(19) However, as long term comparison results are lacking, it remains unknown whether this calibration time-frame can be applied to oscillometric devices which are used in a home setting as well.(19) Lastly, our study was conducted in adults with known cardiovascular disease. The results need to be corroborated in other populations, such as children and pregnant women.

Some limitations of our study design need to be mentioned. First of all, this study is meant to compare the four smartphone compatible blood pressure measurements. It is not the primary purpose of this study to validate the devices. All devices have been validated previously.(10-13) Therefore, the results should only be used for comparison purposes. Secondly, although the BP range of our population was quite wide, it need to be mentioned that measurements were done in a specific population. All patients were followed-up for myocardial infarction, and were therefore on antihypertensive drugs. Thirdly, no patients with (a history of) irregular heart rhythms were included in our study. All patients had regular sinus rhythm when they participated in the study. This means that the comparison made in our study cannot be extrapolated to patients who do have irregular heart rhythms. Lastly, our patients were tested in an outpatient clinic of a tertiary care center. A researcher was present during all measurements. Although patients applied the devices themselves, patients were corrected in case of any mistakes in applying the devices.

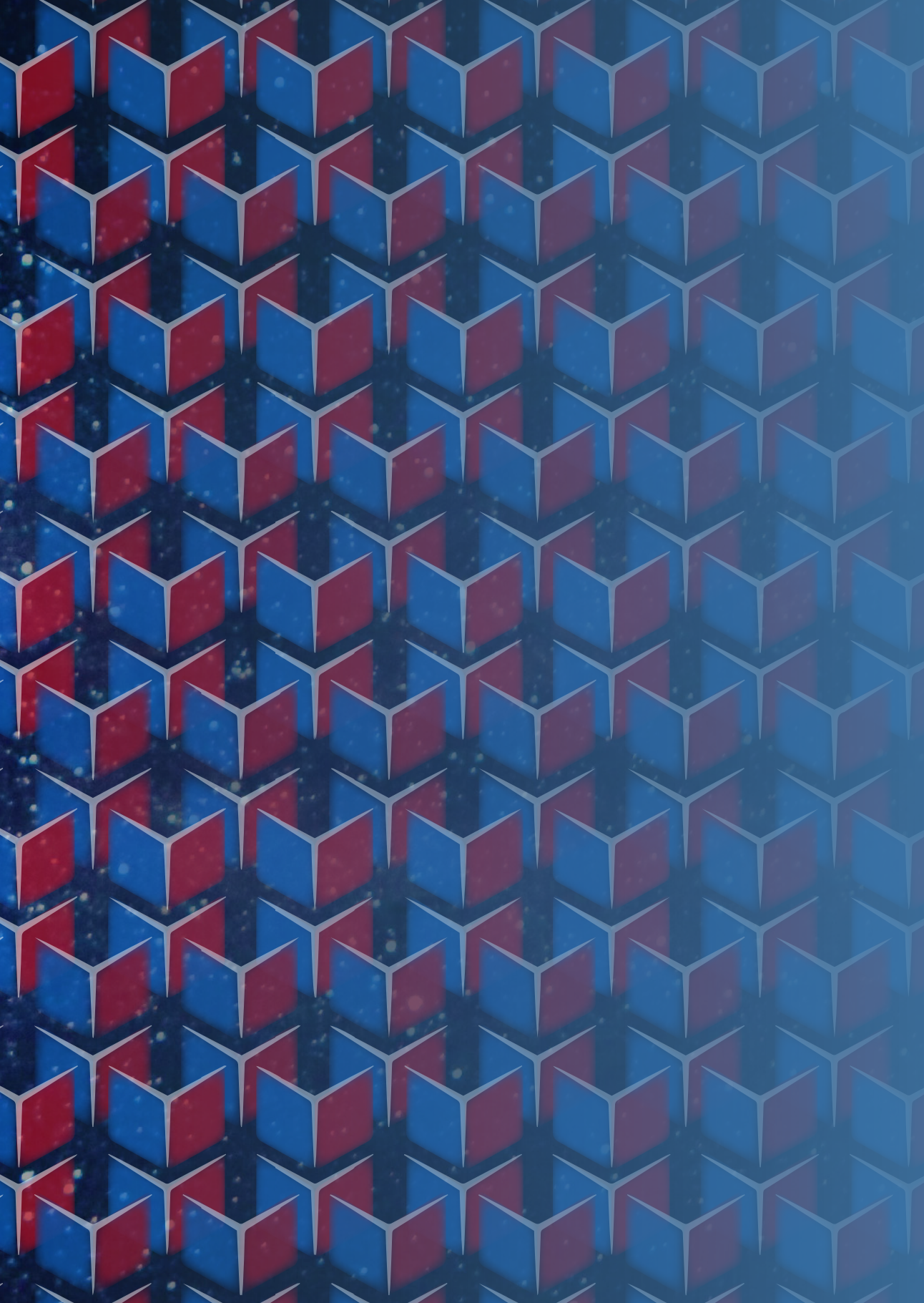
Conclusion

In conclusion, we present a study comparing four validated smartphone compatible BP monitors. Average inter device variability was shown to be statistically significant, however within the predefined range of 5 mmHg for both systolic and diastolic BPs. Furthermore, devices showed comparable consistency for systolic BP, but less so for diastolic BP.

References

1. J. Perk, B. G. De, H. Gohlke, I. Graham, Z. Reiner, M. Verschuren, et al., "European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts)," Eur. Heart J, vol. 33, pp. 1635-1701, 7/2012.
2. T. G. Pickering, J. E. Hall, L. J. Appel, B. E. Falkner, J. Graves, M. N. Hill, et al., "Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research," Circulation, vol. 111, pp. 697-716, 2/8/2005.
3. G. Mancia, G. Bertinieri, G. Grassi, G. Parati, G. Pomidossi, A. Ferrari, et al., "Effects of blood-pressure measurement by the doctor on patient's blood pressure and heart rate," Lancet, vol. 2, pp. 695-698, 9/24/1983.
4. A. Arrieta, J. R. Woods, N. Qiao, and S. J. Jay, "Cost-benefit analysis of home blood pressure monitoring in hypertension diagnosis and treatment: an insurer perspective," Hypertension, vol. 64, pp. 891-6, Oct 2014.
5. G. Mancia, R. Fagard, K. Narkiewicz, J. Redon, A. Zanchetti, M. Bohm, et al., "2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)," Eur. Heart J, vol. 34, pp. 2159-2219, 7/2013.
6. K. L. Margolis, S. E. Asche, A. R. Bergdall, S. P. Dehmer, S. E. Groen, H. M. Kadrmas, et al., "Effect of home blood pressure telemonitoring and pharmacist management on blood pressure control: a cluster randomized clinical trial," JAMA, vol. 310, pp. 46-56, 7/3/2013.
7. iHealth, "iHealth Wireless Blood Pressure Monitor," Available via: https://ihealthlabs.com/blood-pressure-monitors/wireless-blood-pressure-monitor/, Retrieved: 09-05-2016.
8. Withings. Wireless Blood Pressure Monitor. Available: https://www.withings.com/eu/en/products/blood-pressure-monitor.
9. Qardio, "QardioArm," Available via: https://www.getqardio.com/qardioarm-blood-pressure-monitor-iphone-android/, Retrieved: 09-05-2016.
10. A. Coleman, S. Steel, P. Freeman, A. de Greeff, and A. Shennan, "Validation of the Omron M7 (HEM-780-E) oscillometric blood pressure monitoring device according to the British Hypertension Society protocol," Blood Press Monit, vol. 13, pp. 49-54, Feb 2008.
11. Q. Wang, H. Zhao, W. Chen, N. Li, and Y. Wan, "Validation of the iHealth BP7 wrist blood pressure monitor, for self-measurement, according to the European Society of Hypertension International Protocol revision 2010," Blood Press Monit, vol. 19, pp. 54-7, Feb 2014.
12. F. Shang, Y. Zhu, Z. Zhu, L. Liu, and Y. Wan, "Validation of the iHealth BP5 wireless upper arm blood pressure monitor for self-measurement according to the European Society of Hypertension International Protocol revision 2010," Blood Press Monit, vol. 18, pp. 278-81, Oct 2013.

13. J. Topouchian, D. Agnoletti, J. Blacher, A. Youssef, M. N. Chahine, I. Ibanez, et al., “Validation of four devices: Omron M6 Comfort, Omron HEM-7420, Withings BP-800, and Polygreen KP-7670 for home blood pressure measurement according to the European Society of Hypertension International Protocol,” Vasc Health Risk Manag, vol. 10, pp. 33-44, 2014.
14. RW Treskes, ET van der Velde, DC Eindhoven, and MJ Schalij, “Comparison of Four Smartphone Compatible Blood Pressure Monitors,” Computing in Cardiology, vol. 42, pp. 637-640, 2015.
15. N. Korotkoff, “On methods of studying blood pressure [in Russian]. ,” Bull Imperial Mil Med Acad., vol. 11, pp. 365-367, 1905.
16. E. O’Brien, T. Pickering, R. Asmar, M. Myers, G. Parati, J. Staessen, et al., “Working Group on Blood Pressure Monitoring of the European Society of Hypertension International Protocol for validation of blood pressure measuring devices in adults,” Blood Press Monit, vol. 7, pp. 3-17, Feb 2002.
17. M. H. Maxwell, A. U. Waks, P. C. Schroth, M. Karam, and L. P. Dornfeld, “Error in blood-pressure measurement due to incorrect cuff size in obese patients,” Lancet, vol. 2, pp. 33-6, Jul 03 1982.
18. S. N. Wong, R. Y. Tz Sung, and L. C. Leung, “Validation of three oscillometric blood pressure devices against auscultatory mercury sphygmomanometer in children,” Blood Press Monit, vol. 11, pp. 281-91, Oct 2006.
19. N. Bruining, E. Caiani, C. Chronaki, P. Guzik, and d. van, V, “Acquisition and analysis of cardiovascular signals on smartphones: potential, pitfalls and perspectives: by the Task Force of the e-Cardiology Working Group of European Society of Cardiology,” Eur. J. Prev. Cardiol, vol. 21, pp. 4-13, 11/2014.



CHAPTER 7

Implementation of smart technology to improve medication adherence in patients with cardiovascular disease: is it effective?

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Expert Rev Med Devices. 2018 Feb;15(2):119-126.

Abstract

Introduction

Medication adherence is of key importance in the treatment of cardiovascular disease. Studies consistently show that a substantial proportion of patients is non-adherent.

Areas covered

For this review, telemedicine solutions that can potentially improve medication adherence in patients with cardiovascular disease were reviewed. A total of 475 PubMed papers were reviewed, of which 74 were assessed.

Expert commentary

Papers showed that evidence regarding telemedicine solutions is mostly conflictive. Simple SMS reminders might work for patients who do not take their medication because of forgetfulness. Educational interventions and coaching interventions, primarily delivered by telephone or via a web-based platform can be effective tools to enhance medication adherence. Finally, it should be noted that current developments in software engineering may dramatically change the way non-adherence is addressed in the nearby future.

Introduction

Over the past decades, advantages in pharmacological treatment have dramatically improved the prognosis of patients with cardiovascular disease (CVD). Multiple randomized controlled trials (RCTs) have shown a significant decrease in mortality in patients after acute myocardial infarction using beta-blockers,(1) angiotensin converting enzyme (ACE) inhibitors(2) and statins(3) on a daily basis. Also in patients with heart failure, the introduction of numerous drugs has improved prognosis significantly.(4, 5) In patients with atrial fibrillation, new oral anticoagulants have decreased the risk of developing stroke.(6, 7) A recent trial showed that new oral anticoagulants may also decrease the risk of developing acute myocardial infarction in patients with stable coronary artery disease.(8) Moreover, cholesterol lowering medication has significantly lowered the risk of recurrent adverse cardiovascular events.(9-14) However, for treatment to be successful, patients have to adhere to their daily intake of medication.(15) However, several publications have shown that this is often not the case and compliance rates are in general low and partly depend on the medication taken.(16-19) Low adherence to intake of medication is associated with higher mortality rates than if patients do adhere to prescribed daily intake schemes. However, causality could not be confirmed, as this was a retrospective study. The authors acknowledge that patients who take medication consistently are different from patients that do not in other risk factors for mortality..(20)

Ever since the introduction of the iPhone in 2007, it has been recognized as a potential tool to improve healthcare delivery and improve outcomes.(21-24)Smart technology solutions have been developed and investigated for the improvement of medication adherence in various patient populations.(22) These solutions are characterized by using technology, predominantly smartphones, tablets, and/or computers, to remotely monitor and/or coach patients to be more adherent.(25) Advantages of using these systems are the relatively low costs of these systems, the use of existing infrastructure (such as smartphones), and the ease of use.(26) It is the primary purpose of this paper to discuss telemedicine interventions that have been investigated in an experimental design with the goal to improve medication adherence in patients with CVD who take medication orally for more than 180 days consecutively. This period of days was chosen to enhance the chance that patients were taking medication chronically.

Methods

Article selection and categorizing

A search strategy was developed by an experienced librarian (JS). The search strategy was developed using patients-interventions-comparison-outcomes (PICOs). The patient population was defined as patients that had a CVD or and were, as a consequence of their CVD, taking medication orally for 180 consecutive days or more. The intervention was defined as any remote intervention targeting medication adherence. This could be compared to either regular follow-up, a non-digital intervention or another digital intervention. The outcome of the trial had to be medication adherence, either measured by a questionnaire (e.g. Morisky MMAS-8) or by pharmacy claim data. For this strategy, only articles describing the results of a randomized controlled trial (RCT) were included in the paper selection that served as the basis for this review. The complete search strategy is presented in Appendix A. For this paper, a PubMed search was carried out. Of the resulting papers, titles and abstracts were screened by one of the investigators (RT) and papers not matching the inclusion criteria, or matched the exclusion criteria were excluded. These inclusion and exclusion criteria are given in Table 1. Briefly, papers that did not describe a RCT, only described the rationale and design of a RCT, articles not written in English, articles not including medication adherence as primary or secondary outcome, or articles not specifically designed to address medication adherence were excluded. In case of doubt, the full text was evaluated and after reading of the full text, it was decided whether the paper could be included. After the selection, articles were divided into sub-categories, based on the technology the intervention was delivered with (Table 2). These categories were: mobile applications, short message service (SMS), smart pill boxes, web-based interventions (e-learning) and telephone calls (Figure 1). Per category, a qualitative overview of the existing literature is given in the results section.

For this review, mobile applications were defined as an intervention delivered by an application on a mobile phone with iOS or Android OS as operating system. SMS interventions were defined as any intervention that used SMS to deliver content to the patient. Smart pill boxes were defined as boxes for medication, that are equipped with a timer, alarm clock or are Bluetooth enabled and that register whether the medication box has been opened or not. Web-based interventions were defined as any content that was delivered to the patient via a web-browser or data delivered from the patient to the hospital via a web-browser. Finally, telephone interventions were defined as coaching, reminders to take medication or education delivered via the telephone. Papers were classified in one of the categories by one of the authors (RT).

Table 1. Inclusion and exclusion criteria

Inclusion criteria
All papers that were shown in PubMed as result of the search strategy given in Appendix A.
Exclusion criteria
The study does not describe a randomized-controlled trial
Medication adherence is not listed among the primary or secondary outcomes in the method section
The solution described does not involve one of the following items: a computer, smartphone, tablet or internet
The study is not concerned with patients taking medication orally
Paper is not written in English and no English translation is available
Survey papers

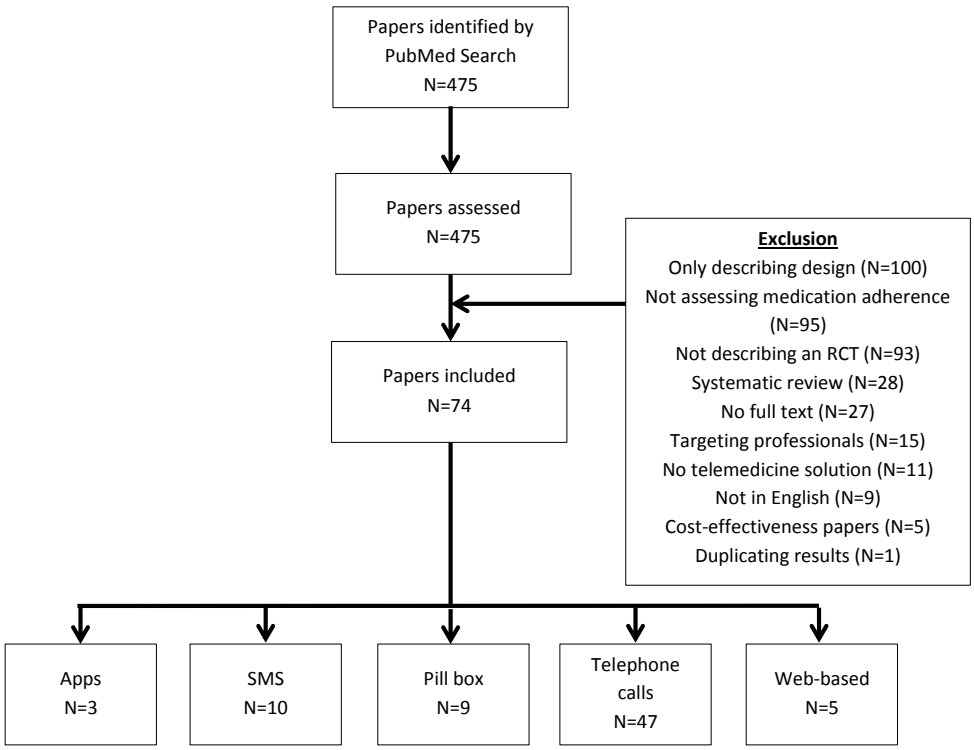


Figure 1. Flow of the inclusion and classification of the papers.

Table 2. Summary of the results per technology

Mobile apps	Mobile apps with educational content might enhance medication adherence. Artificial intelligence is a promising technology.
Smart pill boxes	Evidence regarding the use of smart pill boxes is conflictive. More research needs to be done to pin-point which interventions using smart pill boxes result in better medication adherence
Short message service	Short message services seems a good technology for simple medication reminders
Telephone calls	Telephone calls are effective if they are made by a human being. Automated phone calls show little improvement. Interactive voice recording might be a promising technology.
Web-based interventions	Web-based tools are relatively cheap and therefore an interesting technology. E-Learnings might be beneficial because patients are better informed.

Results

Paper selection

The search strategy, executed on September, 15th, 2017, yielded 475 hits in PubMed. Of these 475 papers, 401 were not further assessed for this study. Reasons for exclusion were: only describing the rationale and design of an RCT (100/401), RCTs not being primarily concerned with medication adherence (95/401), not describing an RCT at all (93/401), papers describing a systematic review (28/401), papers of which no full text could be retrieved (27/401) or narrative review (17/401), targeting healthcare professionals (15/401), not describing an telemedicine solution to improve medication adherence (11/401), papers not in English (9/401), papers describing a cost-effectiveness analysis (5/401) and papers that described results from a previously published RCT ("salami slicing", 1/401).

Papers that were included predominantly described phone interventions (47/74). Other interventions that were described were SMS based (10/74), smart pill boxes (9/74), web-based interventions (5/74) or mobile apps (3/74).

Mobile app

The number of mobile apps has sky-rocketed after the initiation of commercial sales of the iPhone in 2007.(27) Currently, there are over 150,000 health apps available for download in the different App Stores.(28) Some of them address medication adherence and have been tested in RCTs. In a multicenter study by Johnston et al.(29) 174 ticagrelor-treated MI patients were randomized to either an interactive

patient support tool (app) or control. The smartphone app gave patients the possibility to log their medication intake. A reminder SMS was send in case a patient forgot to take his medication. Furthermore, patients received educational messages about the benefits of ticagrelor after MI. At 6 months, larger patient-registered drug adherence was found in the active compared to the control group (non-adherence percentages (based on self-reported medication intake): 16.6% vs 22.8%, *P*=0.025).(29)

Another clue that mobile apps with educational purposes might work is found in a pilot study by Guo et al.(30) 113 patients in the treatment group received the "mAF" (mobile app atrial fibrillation) app, versus 96 patients in the control group (usual care). The app educated patients about their condition and the importance of drug intake. Furthermore, patients could record vital signs with their app. Primary outcome was drug adherence measured with the Pharmacy Quality Alliance adherence (a questionnaire for patients to fill in). Scores were 0 (indicating low risk of non-adherence) in the intervention group and 4 in the control group (indicating moderate risk of non-adherence). Drug adherence was therefore significantly better in the group of patients using the app.(30)

A very promising technology using mobile technology is described in a small study by Labovitz et al.(31) They randomized patients with ischemic stroke, who received anticoagulant therapy, to an Artificial Intelligence (AI) platform group (n=15) or control group (n=13). The AI platform recognized the patient via the smartphone camera with face recognition. Subsequently, the actual ingestion of medication could be recognized and confirmed. The interesting part of using this technology is that it can confirm the actual ingestion of the pill. If an ingestion was not registered, the app gave an automated reminder. Patients randomized to the treatment group received mobile devices with the AI app to provide medication reminders and dosing instructions. Medication adherence based on measured plasma levels was 100% in treatment group and only 50% in control group.(31)

Smart pill boxes

Smart pill boxes, also called "electronic medication-packaging devices"(32) are devices meant for packaging of medication, that are equipped with a timer, alarm clock or are Bluetooth enabled and that register whether the medication box has been opened or not. A criticism of these smart pill boxes is that opening of the box does not confirm the actual ingestion of the pill. There are several RCTs that have investigated the effectiveness of these smart pill boxes. Evidence regarding the effect on medication adherence is however conflicting. Three RCTs have found no statistically significant difference in medication adherence. In a study in 1509 post ACS patients randomized in a 2:1 fashion to electronic pill bottles and social support (N=1003) or to usual care (N=506), medication adherence (based on pharmacy claim

data) was found not statistically different between the two groups. Furthermore, no statistically significant differences were found between study arms in time to first hospitalization for vascular events or death, or other outcomes.(33) Choudry et al.(32) performed a 4-arm 4- block-randomized clinical trial in 53.480 enrolees, patients who were using 1-3 different drugs daily. Patients were randomized to receive a pill bottle with toggles, digital timer cap or a standard pill box, or no device (= control). No statistically significant difference was found in medication adherence (based on pharmacy claim data) between control and any of the treatment groups. One of the conclusion of the authors was that devices may have been more effective if coupled with interventions to ensure consistent use. In a multicenter RCT, Kooy et al.(34) studied medication adherence (based on pharmacy claim data) in 3 patient groups on lipid-lowering medication (statin): smart pill box with reminder system with counselling, smart pill box with reminder system alone, and control (no smart pill box). Results: proportions of adherent patients in both smart pill box groups (69.2% / 72.4%) were not statistically higher than in the control group (64.8%).(34) Two other trials suggest that electronic pill bottles might be beneficial: in one RCT, 150 patients with either hypercholesterolaemia, hypertension or DM were randomized to medication blisters, capable of tracking dosage and timing of medication intake or regular care. There was a statistically significant difference (P=0.04) in intake of Metformin, but no significant difference was found for the other drugs.(35) One trial that showed a significant difference was performed by McKenney et al.(36). The study population consisted of 70 patients, randomly divided in 2 groups (phase 1), and then in 4 groups (phase 2). In phase 1, patients received medication either in vials with time-cap, or standard cap. In phase 2 the four groups were: A (control): standard vial; B: vials with timepiece cap; C: same as B, but this group also received tools to record BP at outpatient clinic visit; D: same as B, but with home BP measurements. In phase 1, the patients in the intervention group had significantly better adherence and significant reduction in systolic (SBP) and diastolic blood pressure (DBP). In phase 2, patients were even higher significant compliance in groups C and D, compared to control. However, there were no further improvements in SBP and DBP.(36)

Short message service

Short message service (SMS) was developed in the 1980s. It was designed to send small size message over the mobile telephone system. The first SMS was sent in 1992.(37) After the commercial implementation of SMS, RCTs investigating its application for medication adherence were published. The RCTs use the same technology, but vary in the way they implement SMS.(38-40) Several RCTs used a SMS intervention in which they sent a SMS on a fixed time with a fixed text. The SMS was a general reminder to the patient to take his medication. Multiple trials demonstrated a

positive effect on medication adherence using this intervention. Of the 10 trials in our study, 9 (38-45) show an increase in medication adherence, while 1 (46) shows no difference in medication adherence. However, these trials all assess short term outcomes. This is problematic, because the effect of simple reminders might decrease over time as messages might become boring and repetitive to patients.(38) Moreover, the intervention only addresses one barrier to adequate medication adherence, namely the patient purely forgetting to take their prescribed medication. Interestingly, one trial did compare a more sophisticated way of implementing SMS with simple reminders. The "Mobile Phone Text Messages to Support Treatment Adherence in Adults With High Blood Pressure (StAR)"(45) trial randomized 1372 patients with hypertension in a 1:1:1 ratio to either interactive SMS, information-only SMS or usual care. The information-only group received general reminders to take medication, whereas the interactive SMS group was able to SMS back to the research team, call the research team and ask specific medication-related questions. Primary outcome was change in systolic BP after 12 months. The SMS-information-only group was superior to usual care (ΔSBP -2.2 mmHg). Interestingly, there was no difference between the interactive SMS group and the SMS-information only group. Although these were the results of only one RCT, they might indicate that SMS is in general unfit to serve as an interactive way of communicating and that other technologies, most notably telephone and web-based interventions are necessary to fully benefit from a two way communication.(45)

Telephone calls

Telephone calls have been subject for RCTs since the 1980s. Although the technology is straightforward and easy to use, the RCTs conducted with this technology show significant inter-study variability regarding patient population, implementation of the technology and outcome assessment. Phone calls can vary from simple, automated reminders to the patient to take their medication to coaching programs via telephone. In various trials, coaching or educating interventions via telephone have been investigated.(47-50) In these RCTs, patients were randomized between a telephone based intervention or control. The telephone based intervention consisted of a nurse calling patients to either coach or educate patients. Coaching patients generally consisted of taking medication according to prescription or addressing barriers to adequate medication intake. Education generally consisted of the nurse educating the patients about the condition they were given medication for and the importance of adequately taking the medication. RCTs generally show an increase in medication adherence in the intervention group compared to the control group. Coaching, especially motivational interviewing, has been proven to improve medication adherence in various patient populations.(51) The disadvantage of a nurse-led intervention is that it is labour intensive and relatively costly.(26)

Another, less labour-intensive way is automated phone calls, in which the call is initiated by a computer system. The voice can either be a computer voice or a human voice that is recorded previously. The important difference between automated phone calls and calls by healthcare professionals is the lack of interaction in the former. One RCT has compared the effectiveness of automated and in-person phone calls.(52) This trial randomized patients who used a certain commercial pharmacy chain to pick up their prescriptions. Patients of which a prescription was received but not purchased within 8 days were randomized. The control group received no intervention, whereas the intervention group first received two automated phone calls and then one in-person phone call. The RCT found no difference in adherence from the automated phone calls, but found a significant and positive difference in the in-person phone calls group.(52) This RCT provides evidence that human interaction in telephone interventions may be more effective than automated, computer initiated phone calls.

An interesting technology that, at least partly, overcomes the drawbacks of automated phone calls is interactive voice recognition (IVR). In this technology, the receiver of a call can interact with the computer via speech recognition or input on the keypad. In the RCT study by Vollmer et al.,(53) 21.752 patients who had prescriptions for ACE inhibitors or statins were randomized to usual care or IVR.(53) The RCT demonstrated that IVR significantly increased adherence to prescribed medications.

An interesting intervention is the combination of self-measurement and coaching by telephone. In an RCT by Bosworth et al.,(48) 636 patients with hypertension were randomized to either usual care, home BP-measurement, a tailored behavioural self-management intervention or a combination of home BP-measurement and a tailored behavioural self-management intervention. The self-management intervention consisted of nurse led education in the risks of hypertension, side effects of medication and the importance of taking medication. Home BP-measurement consisted of measuring and transferring BP 3 times weekly. Interestingly, BP was significantly better controlled in the intervention groups (an average 3.9 mmHg lower blood pressure in the intervention group compared to the control group), but self-reported medication adherence was not.(48) The authors argue that a behavioural intervention might only be interesting if patients can measure the parameter of interest themselves. The combination of self-management and telephone follow-up is therefore an interesting concept and requires further research.

Web-based interventions

Web-based interventions have become increasingly popular in scientific literature, mostly because of the high penetration rate of PCs and Internet. In high-income countries, the average penetration rate of computers is around 85%.(54) Web-

based interventions use mostly low-cost technology and, once developed, can be implemented in large numbers of patients simultaneously.(26) Web-based interventions furthermore have the advantage to induce active participation in patients taking medications for longer periods of time. One such an example is the introduction of e-Learning in patient groups. The advantage of using e-Learning is the ability to educate patients about the medications they are taking and the reasons they are taking it for. As such, patients become better educated and are therefore more likely to take their prescribed medications.(55) An extended version of e-Learning may be the usage of a web-based counselling program. The advantage of a counselling program is that it can coach the patient on top of educating him. A RCT by Keyserling et al.(56) in 385 patients with a high risk of coronary heart disease (Framingham Risk Score ≥ 10%) demonstrated that this is an effective way in reducing cardiovascular risk. The RCT randomized patients to either live counselling or web-based counselling. The trial showed a reduction of 1.5% in Framingham Risk Score in de web-based counselling group and a 2.3% reduction in the live counselling group. However, it was calculated in the trial that the live counselling was almost twice as expensive as the web-based counselling ($207 vs $110 respectively).(56) Therefore, e-Learning programs might be effective and low-cost ways of improving medication adherence. Findings should be corroborated in other patient populations.

Other web-based interventions in study show however less positive results. A RCT by Martin et al.(57) investigated the use of a cyber-nurse in 434 low income patients. The Cyber Nurse (a recorded female voice) gave general health information and told patients to take their medication. This trial found that 51% of the patients in the intervention group were adherent, while 49% of the patients in the control group were adherent. The authors note that the population in this RCT was a medically underserved patient population with low income and low socioeconomic status.(57) They acknowledge that their intervention addressed the issue of patients forgetting to take their medication, but that in a low income, low socioeconomic status patient population financial barriers and social influence might be more important causes of the relatively low adherence rates.

Discussion

This paper gives an insight into the existing literature of different technologies used to improve medication adherence that have been investigated in an RCT. Several non-RTC's studies presented promising technologies, however, in general, evidence comes from RCTs with relatively small sample sizes.

Non-adherence to medication is a major problem. It is associated with higher mortality and morbidity rates. There are various reasons for patients to be non-adherent. A systematic review by Kardas et al.(58) searched 51 systematic reviews to identify determinants of non-adherence. They found 771 determinants of

non-adherence, of which 47 were determinants of persistence. These factors were categorized in socio-economic determinants, healthcare team related determinants, condition related determinants, therapy related determinants and patient related determinants. Most interventions however only target a couple of these 771 determinants and most interventions assume patients forget to take the medication.(58)

The authors identified five commonly used technologies to deliver telemedicine interventions for medication adherence. Some remarks have to be made: first, some technologies exist longer than other technologies. Telephones, for example, have been investigated in RCTs for over three decades, while mobile apps have been investigated for 7 years only. This might explain while only three papers were found that described a mobile app for medication adherence, while there were 47 papers describing telephone apps.

The authors would like to argue that the suitability of the technology depends on the determinant of medication adherence that is being addressed with the technology. RCTs using SMS as technology show that for simple medication reminders this might be a suitable technology. However, RCTs that use SMS for educational purposes show no difference in medication adherence. Education and coaching have been proven as an effective method to increase medication adherence. Evidence from our literature search predominantly points to web-based technologies as a cost-effective tool, most importantly because it is not labour intensive.(26)

It has to be noted that, as of this moment, software is improving fast. Artificial intelligence and machine learning are very likely to bring new possibilities in this field of research. Therefore, as pointed out in our five-year view, it might very well be the case that all the techniques in this review will be obsolete within five years.

Limitations

This paper is a narrative review on telemedicine strategies to improve medication adherence in patients with cardiovascular disease. The “narrative” aspect of the review makes it subject to certain limitations. First, although some aspects of a systematic review were incorporated in the design of this review, this paper does not describe a systematic review. This means that the results section above might be biased. The selection of papers might be biased because only one investigator selected them. The explanation of the various techniques and their effectiveness might be biased, because not all papers could be included in the qualitative analysis. Furthermore, no formal risk of bias analysis was done. Therefore, results could not be weighed against data quality. Finally, inherent to describing the existing literature, there was no assessment nor correction for meta biases such as publication bias. It could very well be that, as in most other scientific fields, papers with a positive

effect are more likely to be published. The authors would however like to emphasize that it was not the purpose of this paper to describe a systematic review.

Expert commentary

Non-adherence to medication intake according to prescription is a complex problem with various causes. Most technologies focus on simply reminding the patient that he has to take his medication. Evidence regarding this approach is conflictive. It is the authors' opinion that generally, these approaches do not take into account the complexity of the problem and the fact that a substantial number of patients is non-adherent for other reasons than simply forgetting to take their medication. Therefore, we believe that further research should not focus on simple reminders.
Approaches that have, in our opinion, huge potential are educational interventions and artificial intelligence. Educational interventions are a good way to activate patients. It has been proven that involved patients (i.e. patients who are willing and able to manage their own health) are at lower risk of being obese, smoke or having a high haemoglobin A1c.(59) Most educational interventions show a significant increase in medication adherence. Web-based interventions seem to favour other technologies, since they are mostly less expensive.(26)

Phone calls can be an effective way of delivering educational interventions. However, with the rise of video-conferencing systems such as Skype (Microsoft, Redmond, Washington, United States of America), it can be expected that these software systems will take over phone calls. The authors recommend an RCT comparing the effect of the same intervention in an intervention group in which the intervention is delivered by video-conferencing, while in the control group, the intervention is delivered via phone calls.

The benefit of the intervention described by Labovitz et al.(31) is that it actually confirms the ingestion of the pill. Furthermore, it can be seen as the first step in artificial intelligence, i.e. the development of interaction between human and computer. The app in this study recognizes the ingestion of a pill and gives feedback to its user. Further improvements in artificial intelligence could have the computer coach and educate the patient based on input received via voice recognition, simulating actual human interaction. Second of all, computers capable of analysing big data could become increasingly important. As discussed above, pharmacy claim data accurately reflects (non-)adherence. If personal health characteristics can be combined with these databases, non-adherence might be predicted. That way, patients which are likely to be non-adherent could be identified. Interventions addressing non-adherence can be tailored to these patients, thereby enabling personalized medicine.(24) Currently, limited voice recognition is possible.

Smartphones are able to recognize clear spoken short instructions. Coaching via smartphones and the internet is also possible. As demonstrated in this review, e-learnings are already available. However, a major barrier to implementing this is the very limited interaction that is possible between computers and humans. In order for computer based coaching to succeed (and not to become boring and repetitive), computers need to "humanize". However, the technology at this moment is not advanced enough for clinical implementation.

Five-year view

Currently available digital solutions to improve medication adherence are based on available software and technologies. However, in the next five years, software will for certain become more advanced and machine learning and artificial intelligence will be usable in everyday practice. The first important change that will have an impact in the way medication non-adherence is addressed is that in five years computers will be able to simulate human interactions adequately. They will most likely be able to read face expressions and react in an appropriate manner. This means that educational interventions can be delivered in an interactive way. Furthermore, new interventions will focus on multiple determinants of medication adherence instead of one per intervention. Advances in software will enable programmers to develop the software in such a way. Machine learning ("the ability of a computer to learn without being explicitly programmed"(60)) will enable another important component: individualization of the way the intervention is delivered. It will take approximately another five years before software is sophisticated enough to allow for individualization. Therefore, it can be expected that in the next five years the development in digital solutions to address non-adherence will be limited. As software becomes available that is sophisticated enough to replace humans, it can be expected that the way non-adherence is addressed will change radically. These developments may personalize the way patients are addressed, taking socio-economic status, cultural preferences and personal characteristics into account.

Key issues

- Medication adherence is of paramount importance in treatment and prevention of cardiovascular disease.
- Educational interventions, delivered via internet or smartphone are effective.
- SMS might be a suitable technology for simple, automated reminders.
- The evidence for the use of smart pill boxes is conflictive.
- Developments in artificial intelligence may dramatically alter the way medication non-adherence is addressed.

References

1. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33:2569-619.
2. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. Lancet. 1995;345:669-85.
3. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366:1267-78.
4. MacIntyre K, Capewell S, Stewart S, et al. Evidence of improving prognosis in heart failure: trends in case fatality in 66 547 patients hospitalized between 1986 and 1995. Circulation. 2000;102:1126-31.
5. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37:2129-200.
6. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med. 2003;349:1019-26.
7. Lopez-Lopez JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. Bmj. 2017;359:j5058.
8. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med. 2017;377:1319-30.
9. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383-9.
10. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333:1301-7.
11. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med. 1996;335:1001-9.
12. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998;339:1349-57.
13. Serruys PW, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. Jama. 2002;287:3215-22.
14. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360:7-22.
15. Perk J, De BG, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other

Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012;33:1635-701.

16. Bosworth HB, Powers BJ, Olsen MK, et al. Home Blood Pressure Management and Improved Blood Pressure Control Results From a Randomized Controlled Trial. Archives of Internal Medicine. 2011;171:1173-80.
17. Ho PM, Magid DJ, Shetterly SM, et al. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. Am Heart J. 2008;155:772-9.
18. Piazza G, Karipineni N, Goldberg HS, et al. Underutilization of Anticoagulation for Stroke Prevention in Atrial Fibrillation. J Am Coll Cardiol. 2016;67:2444-6.
19. Reilly PA, Lehr T, Haertter S, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). J Am Coll Cardiol. 2014;63:321-8.
20. Simpson SH, Eurich DT, Majumdar SR, et al. A meta-analysis of the association between adherence to drug therapy and mortality. Bmj. 2006;333:15.
21. Treskes RW, Van Der Velde ET, Atsma DE, et al. Redesigning healthcare: The 2.4 billion euro question? : Connecting smart technology to improve outcome of patients. Neth Heart J. 2016.
22. Treskes RW, van der Velde ET, Barendse R, et al. Mobile health in cardiology: a review of currently available medical apps and equipment for remote monitoring. Expert Rev Med Devices. 2016;13:823-30.
23. Cowie MR, Bax J, Bruining N, et al. e-Health: a position statement of the European Society of Cardiology. Eur Heart J. 2016;37:63-6.
    ***Interesting, as it gives insight in how the European Society of Cardiology sees e-Health.**
24. Kirchhof P, Sipido KR, Cowie MR, et al. The continuum of personalized cardiovascular medicine: a position paper of the European Society of Cardiology. Eur Heart J. 2014;35:3250-7.
25. Checchi KD, Huybrechts KF, Avorn J, et al. Electronic medication packaging devices and medication adherence: a systematic review. Jama. 2014;312:1237-47.
26. Griffiths F, Lindenmeyer A, Powell J, et al. Why are health care interventions delivered over the internet? A systematic review of the published literature. J Med Internet Res. 2006;8:e10.
27. Number of available apps in the Apple App Store from July 2008 to January 2017 2017 (cited 2017 October 30th). Available via: https://www.statista.com/statistics/263795/number-of-available-apps-in-the-apple-app-store/)..
28. New report finds more than 165,000 mobile health apps now available, takes close look at characteristics & use 2017 (cited 2017 October 30th). Available via: https://www.imedicalapps.com/2015/09/ims-health-apps-report/)..
29. Johnston N, Bodegard J, Jerstrom S, et al. Effects of interactive patient smartphone support app on drug adherence and lifestyle changes in myocardial infarction patients: A randomized study. Am Heart J. 2016;178:85-94.
30. Guo Y, Chen Y, Lane DA, et al. Mobile Health Technology for Atrial Fibrillation Management Integrating Decision Support, Education, and Patient Involvement: mAF App Trial. Am J Med. 2017

31. Labovitz DL, Shafner L, Reyes GM, et al. Using Artificial Intelligence to Reduce the Risk of Nonadherence in Patients on Anticoagulation Therapy. Stroke. 2017;48:1416-9.
****Very interesting, as it describes an artificial intelligence applications for medication adherence.**
32. Choudhry NK, Krumme AA, Ercole PM, et al. Effect of Reminder Devices on Medication Adherence: The REMIND Randomized Clinical Trial. JAMA Intern Med. 2017;177:624-31.
33. Volpp KG, Troxel AB, Mehta SJ, et al. Effect of Electronic Reminders, Financial Incentives, and Social Support on Outcomes After Myocardial Infarction: The HeartStrong Randomized Clinical Trial. JAMA Intern Med. 2017;177:1093-101.
34. Kooy MJ, van Wijk BL, Heerdink ER, et al. Does the use of an electronic reminder device with or without counseling improve adherence to lipid-lowering treatment? The results of a randomized controlled trial. Front Pharmacol. 2013;4:69.
35. Brath H, Morak J, Kastenbauer T, et al. Mobile health (mHealth) based medication adherence measurement - a pilot trial using electronic blisters in diabetes patients. Br J Clin Pharmacol. 2013;76 Suppl 1:47-55.
36. McKenney JM, Munroe WP, Wright JT, Jr. Impact of an electronic medication compliance aid on long-term blood pressure control. J Clin Pharmacol. 1992;32:277-83.
37. SMS 2017 (cited 2017 October 18th). Available via: https://en.wikipedia.org/wiki/SMS).
38. Kamal AK, Shaikh Q, Pasha O, et al. A randomized controlled behavioral intervention trial to improve medication adherence in adult stroke patients with prescription tailored Short Messaging Service (SMS)-SMS4Stroke study. BMC Neurol. 2015;15:212.
39. Maslakpak MH, Safaie M. A Comparison between The Effectiveness of Short Message Service and Reminder Cards Regarding Medication Adherence in Patients with Hypertension: A Randomized Controlled Clinical Trial. Int J Community Based Nurs Midwifery. 2016;4:209-18.
40. Akhu-Zaheya LM, Shiyab WY. The effect of short message system (SMS) reminder on adherence to a healthy diet, medication, and cessation of smoking among adult patients with cardiovascular diseases. Int J Med Inform. 2017;98:65-75.
41. Fang R, Li X. Electronic messaging support service programs improve adherence to lipid-lowering therapy among outpatients with coronary artery disease: an exploratory randomised control study. J Clin Nurs. 2016;25:664-71.
42. Quilici J, Fugon L, Beguin S, et al. Effect of motivational mobile phone short message service on aspirin adherence after coronary stenting for acute coronary syndrome. Int J Cardiol. 2013;168:568-9.
43. Khonsari S, Subramanian P, Chinna K, et al. Effect of a reminder system using an automated short message service on medication adherence following acute coronary syndrome. Eur J Cardiovasc Nurs. 2015;14:170-9.
44. Wald DS, Bestwick JP, Raiman L, et al. Randomised trial of text messaging on adherence to cardiovascular preventive treatment (INTERACT trial). PLoS One. 2014;9:e114268.

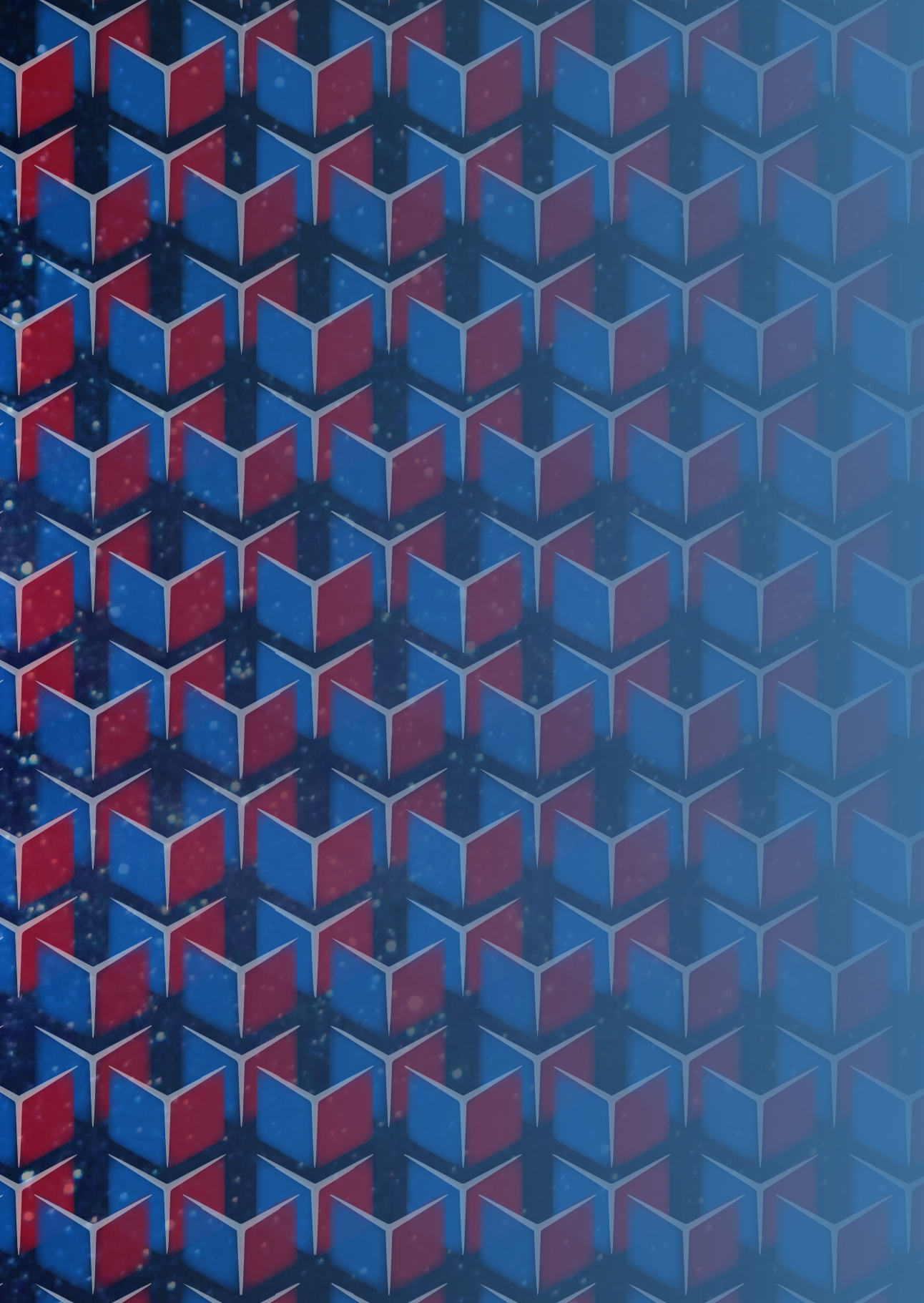
45. Bobrow K, Farmer AJ, Springer D, et al. Mobile Phone Text Messages to Support Treatment Adherence in Adults With High Blood Pressure (SMS-Text Adherence Support (StAR)): A Single-Blind, Randomized Trial. Circulation. 2016;133:592-600.
46. Park LG, Howie-Esquivel J, Whooley MA, et al. Psychosocial factors and medication adherence among patients with coronary heart disease: A text messaging intervention. Eur J Cardiovasc Nurs. 2015;14:264-73.
47. Huber D, Henriksson R, Jakobsson S, et al. Nurse-led telephone-based follow-up of secondary prevention after acute coronary syndrome: One-year results from the randomized controlled NAILED-ACS trial. PLoS One. 2017;12:e0183963.
48. Bosworth HB, Olsen MK, Grubber JM, et al. Two self-management interventions to improve hypertension control: a randomized trial. Ann Intern Med. 2009;151:687-95.
49. Yu M, Chair SY, Chan CW, et al. A health education booklet and telephone follow-ups can improve medication adherence, health-related quality of life, and psychological status of patients with heart failure. Heart Lung. 2015;44:400-7.
50. Hedegaard U, Kjeldsen LJ, Pottegard A, et al. Improving Medication Adherence in Patients with Hypertension: A Randomized Trial. Am J Med. 2015;128:1351-61.
51. Salvo MC, Cannon-Breland ML. Motivational interviewing for medication adherence. J Am Pharm Assoc (2003). 2015;55:e354-61; quiz e62-3.
52. Fischer MA, Choudhry NK, Bykov K, et al. Pharmacy-based interventions to reduce primary medication nonadherence to cardiovascular medications. Med Care. 2014;52:1050-4.
53. Vollmer WM, Owen-Smith AA, Tom JO, et al. Improving adherence to cardiovascular disease medications with information technology. Am J Manag Care. 2014;20:SP502-SP10.
54. Percentage of households with personal computers in 2014 2014 (cited 2017 October 18th). Available via: https://www.statista.com/statistics/551760/worldwide-selected-countries-personal-computers-as-percentage-households/).
55. Lussier MT, Richard C, Glaser E, et al. The impact of a primary care e-communication intervention on the participation of chronic disease patients who had not reached guideline suggested treatment goals. Patient Educ Couns. 2016;99:530-41.
56. Keyserling TC, Sheridan SL, Draeger LB, et al. A comparison of live counseling with a web-based lifestyle and medication intervention to reduce coronary heart disease risk: a randomized clinical trial. JAMA Intern Med. 2014;174:1144-57.
***Interesting trial that compares live counseling with web counseling, which is an important step in moving to telemedicine.**
57. Martin MY, Kim YI, Kratt P, et al. Medication adherence among rural, low-income hypertensive adults: a randomized trial of a multimedia community-based intervention. Am J Health Promot. 2011;25:372-8.
58. Kardas P, Lewek P, Matyjaszczyk M. Determinants of patient adherence: a review of systematic reviews. Front Pharmacol. 2013;4:91.
****Gives an overview of all reasons for patients to be non-adherent and therefore gives insight in the complexity of the problem.**

59. Greene J, Hibbard J. Why does patient activation matter? An examination of the relationships between patient activation and health-related outcomes. J Gen Intern Med. 2012;27:520-6.
60. Wikipedia. Machine learning 2017 (cited 2017 October 18th). Available via: https://en.wikipedia.org/wiki/Machine_learning).

Appendix A, search strategy

((“digital”(tw) OR “online”(tw) OR digital*(tw) OR mobile*(tw) OR “webbased”(tw) OR “web-based”(tw) OR “remote”(tw) OR “ehealth”(tw) OR “e-health”(tw) OR “mhealth”(tw) OR “m-health”(tw) OR “telehealth”(tw) OR electronic communication*(tw) OR “Internet”(mesh) OR “internet”(tw) OR “Telemedicine”(mesh) OR telemed*(tw) OR “Reminder Systems”(mesh) OR “Reminder Systems”(tw) OR “Reminder System”(tw) OR “Reminder Device”(tw) OR “Reminder Devices”(tw) OR “reminder messages”(tw) OR “reminder message”(tw) OR “Telephone”(mesh) OR telephon*(tw) OR “phone”(tw) OR “phones”(tw) OR “Cell Phones”(tw) OR “Smartphone”(tw) OR “Text Messaging”(tw) OR “Cell Phone”(tw) OR “Smartphones”(tw) OR iphon*(tw) OR “Text Messaging”(tw) OR text messag*(tw) OR “texting”(tw) OR “Electronic Mail”(mesh) OR “Electronic Mail”(tw) OR e-mail*(tw) OR email*(tw) OR “Telecommunications”(mesh) OR “app”(tw) OR “apps”(tw) OR webapp*(tw) OR “SMS”(tw) OR “mass communication”(tw) OR “blogging”(tw) OR “blog”(tw) OR “weblog”(tw) OR “social media”(tw) OR twitter*(tw) OR facebook*(tw) OR webcast*(tw) OR “Webcasts as Topic”(Mesh)) AND (“medication taking”(tw) OR “drug taking”(tw) OR “Medication Adherence”(Mesh) OR “medication adherence”(tw) OR “Medication Nonadherence”(tw) OR “Medication Noncompliance”(tw) OR “Medication Non-Adherence”(tw) OR “Medication Non Adherence”(tw) OR “Medication Persistence”(tw) OR “Medication Compliance”(tw) OR “Medication Non-Compliance”(tw) OR “Medication Non Compliance”(tw) OR (“administration and dosage”(subheading) AND “Patient Compliance”(mesh)) OR ((“medication”(tw) OR “medications”(tw) OR “drug”(tw) OR “drugs”(tw)) AND (“adherence”(tw) OR “compliance”(tw) OR “taking”(ti)))) AND (“Cardiovascular Diseases”(Mesh) OR cardiovascular*(tw) OR cardiac(tw) OR “coronary”(tw) OR “Myocardial Infarction”(Mesh) OR “Myocardial Infarction”(tw) OR infarct*(tw) OR “Heart Attack”(tw) OR “Acute Coronary Syndrome”(mesh) OR “Angina Pectoris”(mesh) OR “Acute Coronary Syndrome”(tw) OR “Angina Pectoris”(tw) OR “Angina”(tw) OR “Heart Valve Diseases”(mesh) OR “Heart Valve Diseases”(tw) OR “Aortic Valve Insufficiency”(tw) OR “Aortic Valve Stenosis”(tw) OR “Subvalvular Aortic Stenosis”(tw) OR “Supravalvular Aortic Stenosis”(tw) OR “Heart Valve Prolapse”(tw) OR “Aortic Valve Prolapse”(tw) OR “Mitral Valve Prolapse”(tw) OR “Tricuspid Valve Prolapse”(tw) OR “Mitral Valve Insufficiency”(tw) OR “Mitral Valve Stenosis”(tw) OR “Pulmonary Atresia”(tw) OR “Pulmonary Valve Insufficiency”(tw) OR “Pulmonary Valve Stenosis”(tw) OR “LEOPARD Syndrome”(tw) OR “Pulmonary Subvalvular Stenosis”(tw) OR “Tricuspid Atresia”(tw) OR “Tricuspid Valve Insufficiency”(tw) OR “Tricuspid Valve Stenosis”(tw) OR “Atrial Fibrillation”(Mesh) OR “Atrial Fibrillation”(tw) OR “Atrium Fibrillation”(tw) OR “Heart Failure”(Mesh) OR “Heart Failure”(tw) OR “Hypertension”(mesh) OR “hypertension”(tw) OR hypertens*(tw)

OR “blood pressure”(tw)) AND (“Randomized Controlled Trial”(Publication Type) OR “Randomized Controlled Trials as Topic”(Mesh) OR random*(tw) OR “Placebos”(mesh) OR placebo*(tw) OR “Double-Blind Method”(Mesh) OR double blind*(tw)))



CHAPTER 8

Performance of ST and ventricular gradient difference vectors in electrocardiographic detection of acute myocardial ischemia

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J Electrocardiol. 2015 Jul-Aug;48(4):498-504.

Abstract

Introduction

Serial analysis could improve ECG diagnosis of myocardial ischemia caused by acute coronary occlusion.

Methods

We analysed ECG pairs of 84 cases and 398 controls. In case-patients, who underwent elective percutaneous coronary intervention, ischemic ECGs during balloon occlusion were compared with preceding non-ischemic ECGs. In control-patients, two elective non-ischemic ECGs were compared. In each ECG, the ST vector at the J point and the ventricular gradient (VG) vector was computed, after which difference vectors ΔST and ΔVG were computed within patients. Finally, receiver operating characteristic analysis was done.

Results

Areas under the curve were 0.906 (P<0.001; CI 0.862-0.949; SE 0.022) for ΔST and 0.880 (P<0.001; CI 0.833-0.926; SE 0.024) for ΔVG. Sensitivity and specificity of conventional ST-elevation myocardial infarction (STEMI) criteria were 70.2% and 89.1%, respectively. At matched serial analysis specificity and STEMI specificity, serial analysis sensitivity was 78.6% for ΔST and 71.4% for ΔVG (not significantly different from STEMI sensitivity). At matched serial analysis sensitivity and STEMI sensitivity, serial analysis specificity was 96.5% for ΔST and 89.3% for ΔVG; ΔST and STEMI specificities differed significantly (P<0.001).

Conclusion

Detection of acute myocardial ischemia by serial ECG analysis of ST and VG vectors has equal or even superior performance than the STEMI criteria. This concept should be further evaluated in triage ECGs of patients suspected from having acute myocardial ischemia.

Introduction

Myocardial infarction (MI) is typically caused by acute coronary occlusion (ACO), and its clinical outcome is primarily dependent upon the time elapsed between diagnosis and reperfusion therapy.(1) Best practice requires that the patient receives a standard 12-lead electrocardiogram (ECG) by emergency personnel, because "ST segment deviation" that meets guideline specified "STEMI criteria" is currently accepted for ACO diagnosis.(2) Although STEMI literally means "ST elevation", the deviation of the ST segment from the TP-segment baseline is a quantitative spatial difference, and therefore it may appear as either "elevation" or "depression" in individual ECG leads. (3) The criteria for the ST segment depression termed "STEMI equivalent" have been included in recent guidelines for diagnosis of ACO.(2)

The diagnosis of ACO should have high sensitivity, because a false negative diagnosis causes delayed access to acute reperfusion therapy, and consequently a potentially increased size of the infarcted area.(1) Also, this diagnosis should have high specificity, because of the high cost of activation of the acute coronary intervention laboratory.(4) However, clinical application of the STEMI criteria for optimal triage of an individual patient to acute reperfusion therapy is currently challenged by both their limited sensitivity and specificity. The ST segment deviation of ACO may be insufficient to reach the STEMI criteria threshold, especially in women,(5) whereas many other acute and chronic conditions can also cause these changes.(4) Also, pre-existing non-zero ST amplitudes are confounders for STEMI classification. Serial ECG analysis by comparison of the acute ECG with the individual's previous non-ischemic ECG could potentially facilitate a higher accuracy for the diagnosis of ACO, and is favoured by the guidelines.(6)

Serial analysis aims to detect changes instead of momentary values. This is a potential solution for ECGs of patients who have ST deviations in their baseline ECG. In the situation of acute ischemia due to ACO, the momentary ST deviations are then the result of the acute ischemic changes plus the pre-existing ST deviations. Differential analysis by serial comparison of the acute ECG and a previous ECG without acute ischemia that serves as a reference could help to reveal the ischemic component of the ST deviation. Because of that, the detection thresholds for the changes can be lower than the detection thresholds for momentary values.

A previous study has shown that serial ECG analysis can potentially improve the sensitivity of acute ischemia detection.(7) This study included 84 clinically stable patients undergoing elective PCI with an ECG recorded hours before elective PCI (baseline ECG), and an ECG recorded during balloon inflation (occlusion ECG). Vectorcardiographic ST vectors were calculated in the baseline and occlusion ECGs

and then used to determine the ST difference vector. Depending on the threshold value for the difference vector magnitude, the sensitivity of differential ischemia detection outperformed consideration of the ST segment deviation during balloon occlusion alone with the conventional threshold of 100 µV. Also, serial analysis of the ventricular gradient (the spatial integrals of the heart vector over the QT interval) yielded better sensitivity than STEMI criteria.(7)

However, in the previous study, only patients with an ACO were studied. All patients were therefore true positives. Detection thresholds were suggested on the basis of earlier studies,(8) which concluded that ST vector differences of 50 µV could possibly be used when serial analysis was available. However, detection thresholds are always a compromise between sensitivity and specificity. Because a control group was lacking in the previous study, this compromise could not be determined.(7) It is therefore the purpose of this study to find the compromise between sensitivity and specificity of serial ECG vector analysis for acute myocardial ischemia detection, and to determine the concurrent ST and VG difference vector thresholds. The current study also serves also as a pilot study for later real-world investigations in triage ECGs of patients suspected from ACO.

Methods

Study group, controls

To determine specificity, a group of patients was selected who had no myocardial ischemia during their ECG recordings, thereby serving as controls. The ECGs of these patients were retrospectively selected from the Leiden University Medical Center ECG database, founded in 1986 and now comprising more than 800,000 standard 10-second 12-lead resting ECGs. Only elective ECGs made in the outpatient clinic were selected, ECGs made in the emergency department or during hospital admission were not included. Further requirements were an acceptable technical quality of the ECG and presence of regular sinus rhythm. ECGs with arrhythmias or with paced beats were excluded.

A computer algorithm searched the database for patients who had two suitable ECGs that were made 1-2 years apart in time. To ascertain clinical stability, such ECG pairs were only selected 1) if there was no other ECG made within a 1-year period immediately preceding the first ECG of the pair, 2) if there was no ECG made within the time interval formed by the selected ECG pair, and 3) if there was no mentioning in the patient file of any clinical event in the year before the first ECG of the selected pair or within the time interval formed by the selected ECG pair.

All selected ECGs were analysed by the Leiden ECG Analysis and Decomposition Software (LEADS)(9), described in more detail in the ECG analysis section below.

Main cardiologic diagnoses were noted and were divided in categories that are listed in Table 1 in the Results section. A total of 398 control patients were included.

Study group, cases

To determine sensitivity, the results from a previous study by Ter Haar et al.(7) were used. Details about this study population and the inclusion and exclusion criteria have been previously described.(7)(10) Briefly, the database consists of patients who underwent elective PCI with long balloon inflation times and therefore had a completely occluded coronary artery during several minutes (cases). This database is called the STAFF database and was created from 1995 till 1996, before stenting became available.(11) Each patient had two long ECGs made. One ECG was made prior to PCI when the patient was in stable condition ("baseline ECG"). The other ECG was made during balloon inflation ("occlusion-ECG") when the patient had a completely occluded culprit artery. For each patient, a stable, representative 10s ECG was selected in the baseline ECG, and a 10s ECG was selected after 3 minutes of balloon occlusion. A pair of control and occlusion ECGs could be obtained in 84 patients in the STAFF database.

ECG analysis

General

All analyzed ECGs were interpreted by the Glasgow ECG Analysis Program,(12) and categorized into abnormal or normal with respect to P wave, AV conduction, frontal QRS axis, QRS duration, QT interval, QRS amplitude, ST segment and T wave.

Serial comparison of the ST segment and ventricular gradient vectors

The ECGs of the 398 patients in control population and of the 84 patients in the cases population were analyzed by the Leiden ECG Analysis and Decomposition Software (LEADS) program. This MATLAB program takes the following steps in analysing ECGs:

1. A 3-lead vectorcardiogram (VCG) is synthesized out of a 12-lead electrocardiogram (ECG) using the Kors matrix(13).
2. Ectopic beats or beats of bad technical quality are automatically and/or manually rejected.
3. An averaged beat is computed.
4. The QRS onset, J-point and T-wave offset are automatically determined. The QRS onset is automatically determined by the first detectable deflection of the heart vector from the PQ-segment baseline. The J point is automatically localized at the instant where the heart vector between the QRS complex and the T wave reaches its minimum value. The offset of the T wave is localized in the vector

magnitude signal as the time instant where the tangent to the point with the steepest slope of the descending limb of the T wave intersects the baseline.

5. The automatically determined QRST onset, J point and T wave offset time instants were then manually verified by two observers (RWT and CAS) and when necessary corrected (e.g., in case of notches and slurs at the J point, or in case of a low-amplitude or odd-shaped T wave. Nearly always, small corrections were made in the J point localization, as we adopted the Minnesota procedure (14) for this study. LEADS facilitates a very accurate manual adjustment of the J point by offering the analyst a cross-hair cursor adjustment procedure in an enlarged view of the superimposed 12 ECG leads.
6. LEADS computes magnitude, azimuth and elevation of ST vectors in the average beat. Furthermore, it computes the QRST integral vector, which equals, by definition, the ventricular gradient vector (VG). The computation of the VG out of a vectorcardiogram is illustrated in Figures 1 and 2.

After ST and VG had been determined in both the first and the second ECG of each ECG pair, the ST and VG difference vectors, ΔST and ΔVG, were calculated.

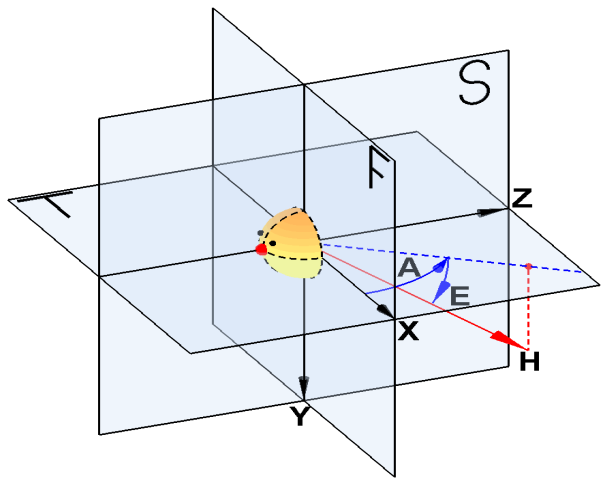


Figure 1. Graphical representation of vectorcardiographic conventions, from Man et al(16), with permission. F=frontal plane. S=sagital plane. T=transversal plane. X=vectorcardiographic x-axis, Y=vectorcardiographic y-axis, Z=vectorcardiographic z-axis. A=azimuth. E=elevation. H=heartvector. The directions of the x-, y-, and z-axes (the x-axis pointing leftwards, the y-axispointing downward and the z-axis pointing backward) are according to the AHA standard(1). An arbitrary heart vector, H (drawn in red) is chosen as an example. The angle between the x-axis and the projection of the heart vector in the transversal plane (blue dotted line) is the azimuth. The angle between the blue dotted line and the heart vector is the elevation.(16)

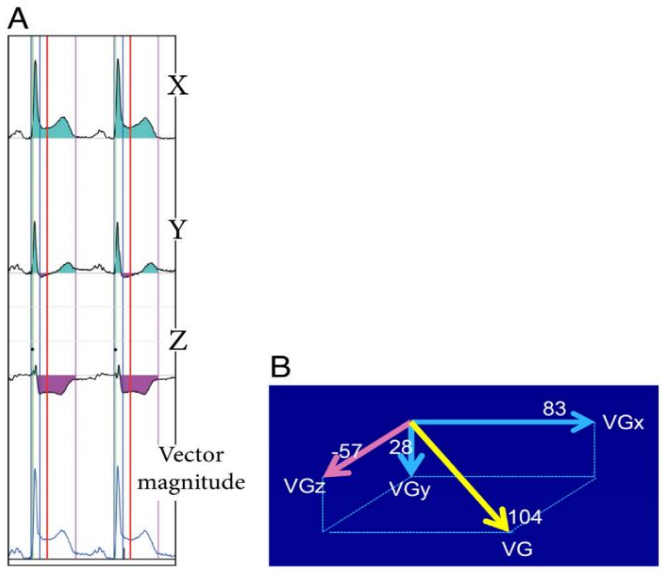


Figure 2. Illustration of the computation of the ventricular gradient, from Ter Haar et al., with permission(7). X=x-axis of the vectorcardiogram. Y=y-axis. Z=z-axis. Panel A depicts a vectorcardiogram, synthesized from a 12-lead 10-seconds ECG during balloon inflation, in which the patient had a completely occluded culprit artery. This vectorcardiogram consists of a x-axis, a y-axis and a z-axis. The time markers indicate onset QRS, the J points, J point + 60 milliseconds and end of the T wave. In this vectorcardiogram, the area under the curve from onset QRS to the end of the T wave is measured. Positive amplitudes in the area contribute positive to the area and negative amplitudes contribute negatively to the area. In this figure, the net areas under the curve in lead X and lead Y are positive and the net area under the curve in lead Z is negative. Panel B shows the x-, y- and z-components of the VG vector. Vector components VGx and VGy point in the same direction as the corresponding lead axes of the vectorcardiogram, because of the positive net areas under the curve. Vector component VGz points in opposite direction of the corresponding lead axis of the vectorcardiogram, because of the negative net area under the curve. Vectorial summation of the three vector components VGx, VGy and VGz yields the resultant VG vector(7).

STEMI criteria

STEMI criteria were applied to the second ECGs of the 398 controls, and to the 84 cases in the STAFF database. An ECG was classified as STEMI when two contiguous leads showed ST elevation of >=0.1 mV, except for leads V2 and V3, which had to show elevation of >=0.2 mV to be classified as STEMI, or when lead V2 and V3 showed ST depression of >=0.05 mV (STEMI equivalent).(2)

STEMI sensitivity was computed as the fraction of the occlusion ECGs that met the STEMI criteria. STEMI specificity was computed as 1 minus the fraction of non-ischemic ECGs that met the STEMI criteria.

ROC analysis

The ΔST and ΔVG values measured in the total study population consisting of 398 controls and 84 cases were used to construct two receiver operating characteristics (ROCs) for the detection of ischemic changes between the two ECGs of each patient. To construct the ΔST ROC, ECGs were classified as ischemic when ΔST was larger than the threshold that was varied along the ROC. To construct the ΔVG ROC, ECGs were classified as ischemic when ΔVG was larger than the threshold that was varied along the ROC. After the ROCs were constructed, ROC analysis was done by computing the area under the curve (AUC) and by computing the statistical significance of the difference between the AUC and 0.5 (random performance).

Comparison of the ΔST and ΔVG ROCs and the STEMI classification performance.

Finally we compared the performance of the ischemia classification by either ΔST or ΔVG with the STEMI analysis. To compare the ΔST and ΔVG sensitivities with the STEMI sensitivity, we computed the sensitivities in the ΔST and ΔVG ROCs at the STEMI specificity. To compare the ΔST and ΔVG specificities with the STEMI specificity, we computed the specificities in the ΔST and ΔVG ROCs at the STEMI sensitivity.

Statistical analysis

We used SPSS (IMB Corp. Released 2014. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) to perform a Receiver Operating Analysis. “Acute Ischemia” was set as state variable, while ΔST and ΔVG were set as “test variable”. MedCalc (MedCalc Software, Ostend, Belgium) was used to test if the two ROC curves were statistically different. Finally, SPSS was used to calculate if the sensitivity and specificity of the STEMI criteria and the ΔST differed significantly, using a McNemar’s test.

Results

A number of 398 clinically stable patients were studied as controls. The average age of these patients was 57 years, with a 16.6 standard deviation; 64% was male. Mean BMI was 26.4 kg·m^2, which means that a slightly overweight population was studied (Table 1).

Table 1. Patient characteristics of the controls

	N	%
N	398	
Age (years)	57±16.6	
Sex (male/female)	254/144	64/36
BMI (kg·m^{-2})	26.4±4.1	

All controls had at least one clinical diagnosis. Systemic hypertension was most prevalent, affecting 28.4% of the population. Second and third most prevalent were valvular heart disease and arrhythmias, present in 26.9% and 26.4% of the population respectively. The prevalences of all noted diagnoses are shown in Table 2.

Table 2. Prevalence of main diagnoses in the controls. The sum of the diagnoses exceeds the number of patients in the controls, because more than one diagnosis can apply to a single patient. N=number of patients

Diagnosis	N	%
Systemic Hypertension	113	28.4
Valvular Heart Disease	107	26.9
Arrhythmia	105	26.4
Myocardial infarction	81	20.4
Conduction disorders	65	16.3
Stable angina	64	16.1
Non-ischemic cardiomyopathy	63	15.8
M. Marfan	56	14.1
Diabetes mellitus	54	13.6
Non-cardiac diagnoses	24	6.0
Heart failure	11	2.8
Pulmonary hypertension	7	1.8

According to the Glasgow ECG interpretation program, 445/796 (55.9%) of the ECGs were classified as abnormal or borderline abnormal; 20.4% of all ECGs were classified as having an abnormal ST segment. An overview of ECG abnormalities is given in Table 3.

Table 3. Major categories of ECG abnormalities in the 796 ECGs of the 398 controls, according to the Glasgow ECG interpretation program. N=number of patients

Category of ECG abnormality	N	%
Sinus tachycardia or sinus bradycardia	239	30.0
Abnormal P wave	66	8.3
Abnormal AV conduction	107	13.4
Abnormal frontal QRS axis	157	19.7
Prolonged QRS duration	168	21.1
High QRS amplitude	47	5.9
Abnormal ST segment	162	20.4
Abnormal T wave	223	28.0
Long QT	19	2.4
Abnormal or borderline abnormal ECG	445	55.9

A number of 84 patients was studied as cases. The average age of all cases was 60 years, with a 11 standard deviation; 64% of all patients was male.

The area under the curve (AUC) of the ΔST ROC was 0.906 (*P*<0.001; CI 0.862-0.949; SE 0.022). The AUC for the ΔVG ROC was 0.880 (*P*<0.001; CI 0.833-0.926; SE 0.024). The ROC curves were shown not to be statistically significant (ΔAUC 0.0263, 95% CI -0.0114 to 0.0640, *P*=0.1712). The ROCs are both shown in Figure 3.

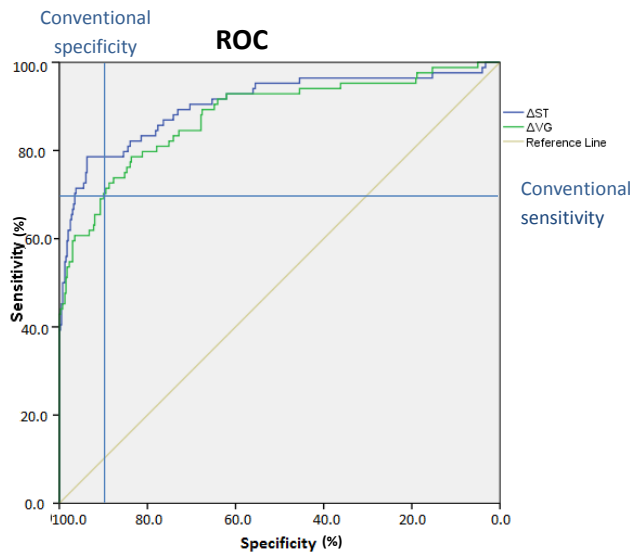


Figure 3. ROCs derived from DST (blue) and from DVG (green). The horizontal and vertical lines indicate the sensitivity and the specificity of the STEMI criteria, respectively.

Sensitivity and specificity of the conventional ST-elevation myocardial infarction (STEMI) criteria was 70.2% and 89.1%, respectively.

When matching serial analysis specificity with STEMI specificity, serial analysis sensitivity was 78.6% for ΔST and 71.4% for ΔVG, the ΔST and STEMI sensitivities did not differ significantly (*P*=0.143, McNemar's test). At matched specificity, the ischemia detection thresholds of ΔST and of ΔVG were 57.5 µV and 25.8 mV·ms, respectively.

When matching serial analysis sensitivity with STEMI sensitivity, serial analysis specificity was 96.5% for ΔST and 89.3% for ΔVG, the ΔST and STEMI specificities differed significantly (*P*<0.001, by a McNemar's test). At matched STEMI sensitivity, the ischemia detection thresholds of ΔST and of ΔVG were 77.7 µV and 26.1 mV·ms, respectively.

The results are given in Tables 4 and 5. A scatterplot of ΔST and corresponding ΔVG of all patients (both cases and controls) is given in Figure 4.

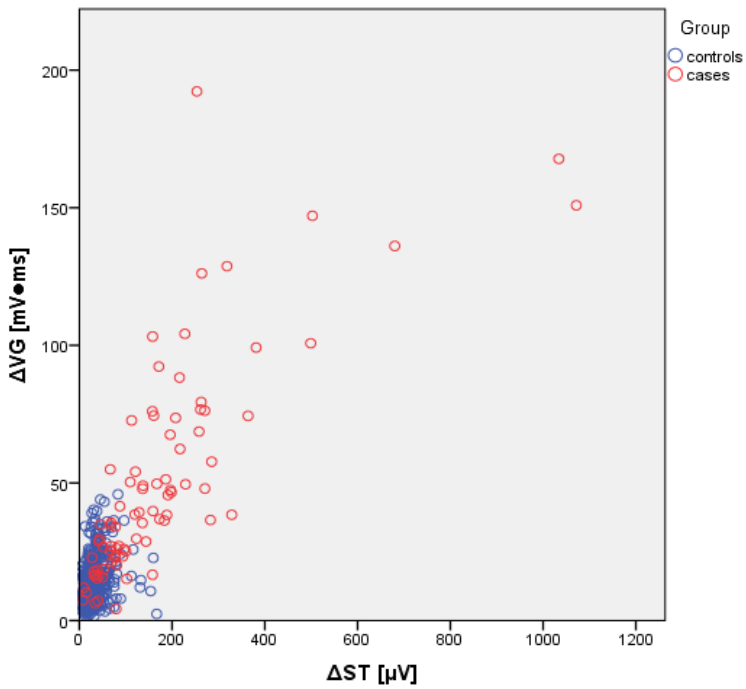


Figure 4. Scatterplot of the ΔST and corresponding ΔVG of both cases (red) and controls (blue).

Table 4. Comparison of the sensitivity of the STEMI criteria and of ΔST and ΔVG ischemia detection when specificity of ΔST and ΔVG ischemia detection is matched with STEMI specificity (89.1%). The corresponding ΔST and ΔVG thresholds are in the third column. There were no statistically significant differences between ΔST and ΔVG sensitivity and STEMI sensitivity

	Sensitivity (%)	Threshold, derived from ROC
STEMI criteria	70.2	
ΔST	78.6	57.5 µV
ΔVG	71.4	25.8 mV·ms

Table 5. Specificity of the STEMI criteria and specificity of ΔST and ΔVG ischemia detection when sensitivity of ΔST and ΔVG ischemia detection is matched with STEMI sensitivity (70.2%). The corresponding ΔST and ΔVG thresholds are in the third column

	Sensitivity (%)	Threshold, derived from ROC
STEMI criteria	89.1	
ΔST	96.5*	77.7 µV
ΔVG	89.3	26.1 mV·ms

*ΔST specificity differed significantly from STEMI specificity (P<.001).

Discussion

The results of our study showed that serial analysis of ST vectors yielded a significantly higher specificity than the STEMI criteria, while there was no significant difference in sensitivity between serial analysis of ST vectors and STEMI criteria, in spite of the fact that the difference in sensitivity, 8.4% (serial: 78.6%; STEMI: 70.2%) was larger than the difference in specificity, 7.4% (serial: 96.5%; STEMI: 89.1%). Obviously, this was caused by the difference between the control group and case group sizes (398 and 84 patients, respectively). A larger group of case patients would likely have yielded a significantly better sensitivity as well. We feel that potential diagnostic improvements in both sensitivity and specificity in the order of magnitude of 8% are clinically relevant, and that further research should follow in order to demonstrate that such improvements can be attained in the “real world” (here: the setting of patients with acute chest pain suspected of having acute coronary syndrome). Admittedly, our current study groups are insufficiently representative.

The practical use of this type of difference analysis requires not only an additional, previous, ECG, but also computerized analysis. Although the difference in ST, ΔST, seems intuitive, it cannot be eyeballed from the 12-lead ECG because of the complexity of the computation of the heart vector. The ventricular gradient is even more complicated as this involves integration (area under the QRST curve). Technical artefacts can hamper this computerized analysis. However, if about 30% to 40% of the beats are of good technical quality, the computer program can make

an adequate calculation of the ΔST and ΔVG vectors by only including these good quality beats.

The ventricular gradient did not really perform better than the STEMI criteria, but we should realize that the ventricular gradient is independent of conduction,(15) and that it is expected to work equally well in patients who have either pre-existent or acute conduction disturbances. In that case, the STEMI criteria cannot be applied, and also the ΔST vector cannot be computed, because the J point is lacking. In those situations the ventricular gradient could be an alternative. Due to the composition of the current study group we have not been able to test this hypothesis, but the data generated by our study prompt for a study in patients with conduction disturbances to assess the potential of the ventricular gradient for ischemia detection.

Several limitations of our study need to be mentioned. One limitation of serial ECG analysis is that it requires a previously made, non-acute resting ECG. Patients that are admitted to the hospital with symptoms of myocardial infarction but without a reference ECG cannot be triaged using this method. However, patients with myocardial infarction often do have a history of stable angina, for which they are followed up by their physician at least once a year including a reference ECG. Many patients will therefore have a previously made non-ischemic resting ECG. In addition, due to increasing technical possibilities it is likely that patients will in the nearby future be able to collect a resting ECG by themselves, which can be collected in a digital patient file, thereby providing a reference ECG for serial ECG analysis. Secondly, all patients in the non-ischemic population were clinically stable. Patients with other acute causes of ST elevation and chest pain (e.g. pericarditis and myocarditis) were not included in the study. Such conditions could lead to false positive detection of acute ischemia, although it must be realized that ST elevation in many ECG leads gives a relatively small ST vector, due to the cancellation effect. Thirdly, all patients in the ischemic population had a completely occluded artery due to balloon inflation. However, balloon inflation is a too static simulation of ACO, that is caused by a thrombus or a vasospasm. Thrombi can resolve partly or completely, while vasospasms can be temporarily. Therefore, in the prehospital phase, it depends on what time exactly the acute ECG is taken whether it will detect acute ischemia. Because of these limitations, the sensitivity and the specificity shown in the ROC might be too optimistic. Further research in the prehospital phase to corroborate the diagnostic performance of ΔST and ΔVG to detect myocardial ischemia is therefore needed, in which special attention is paid to confounders of ST elevation, for example early repolarization pattern, pericarditis and left ventricular hypertrophy.

Summarizing, we studied differential ECG analysis in ECG pairs of cases and controls, all second ECGs of the case patients were made under conditions of acute coronary occlusion. These data facilitated a comparison of conventional STEMI ischemia diagnosis and acute myocardial ischemia diagnosis by serial comparison. We found that serial comparison had similar (for ΔVG) or better (for ΔST) performance than STEMI ischemia diagnosis. These results suggest that serial ECG analysis for acute myocardial ischemia detection is feasible, but this should be confirmed in realistic patient cohorts in the setting of spontaneous acute coronary occlusion. Our study was done with the perspective to be able to deal with situations in which STEMI analysis is hampered, either by nonzero baseline ST deviations, or by absence of a J point, which completely disables ST analysis for ischemia detection. In that case, differential ECG analysis using the ventricular gradient would be a potential solution. These specific patient groups should explicitly be dealt with in future research. Our study was done as an initial feasibility study for serial ECG analysis for acute myocardial ischemia detection, and its positive outcome favours further exploration of this concept.

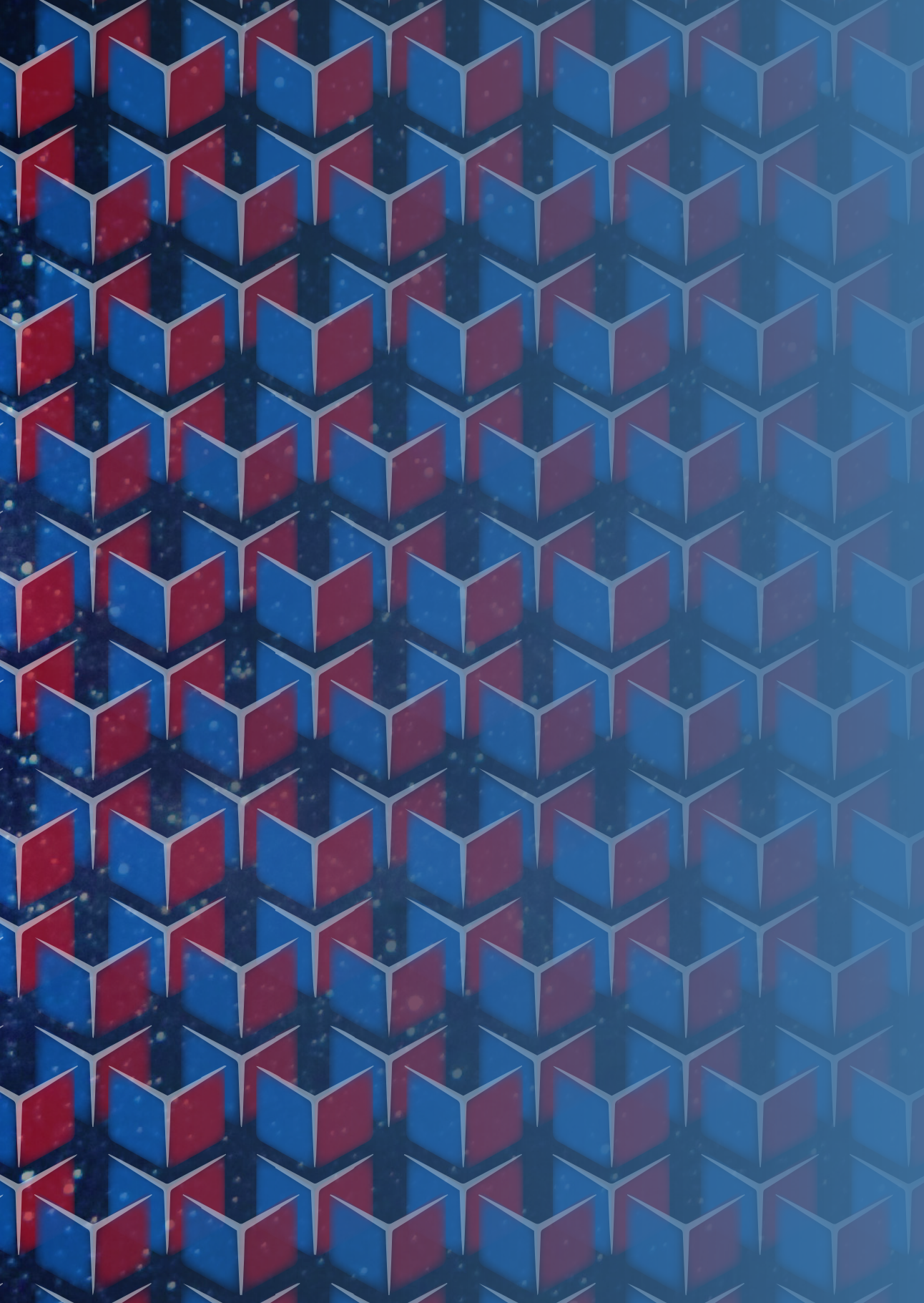
Conclusion

ROC analysis of the performance of both ΔST and ΔVG and comparison with the performance of conventional STEMI ischemia diagnosis suggests that serial ECG analysis of ST and VG vectors to detect acute myocardial ischemia is feasible and has either equal or even superior performance than the conventional method. This concept should be further evaluated in triage ECGs of patients suspected from having acute myocardial ischemia. Specifically, serial ECG analysis for ischemia detection should be studied in patients with conditions that hamper conventional STEMI diagnosis (patients with pre-existing nonzero ST deviations, and patients in whom during ischemia no J point can be determined).

References

1. Armstrong PW, Wagner G, Goodman SG, Van de Werf F, Granger C, Wallentin L, et al. ST segment resolution in ASSENT 3: insights into the role of three different treatment strategies for acute myocardial infarction. Eur Heart J 2003;24:1515-22.
2. Wagner GS, Macfarlane P, Wellens H, Josephson M, Gorgels A, Mirvis DM, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part VI: acute ischemia/infarction: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. Circulation 2009;119:e262-70.
3. Martin TN, Groenning BA, Murray HM, Steedman T, Foster JE, Elliot AT, et al. ST-segment deviation analysis of the admission 12-lead electrocardiogram as an aid to early diagnosis of acute myocardial infarction with a cardiac magnetic resonance imaging gold standard. J Am Coll Cardiol 2007;50:1021-8.
4. Jayroe JB, Spodick DH, Nikus K, Madias J, Fiol M, De Luna AB, et al. Differentiating ST elevation myocardial infarction and nonischemic causes of ST elevation by analyzing the presenting electrocardiogram. Am J Cardiol 2009;103:301-6.
5. Maynard C, Selker HP, Beshansky JR, Griffith JL, Schmid CH, Califf RM, et al. The exclusion of women from clinical trials of thrombolytic therapy: implications for developing the thrombolytic predictive instrument database. Med Decis Making 1995;15:38-43.
6. Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569-619.
7. ter Haar CC, Maan AC, Warren SG, Ringborn M, Horacek BM, Schalij MJ, et al. Difference vectors to describe dynamics of the ST segment and the ventricular gradient in acute ischemia. J Electrocardiol 2013;46:302-11.
8. Jensen SM, Johansson G, Osterman G, Reiz S, and Naslund U. On-line computerized vectorcardiography monitoring of myocardial ischemia during coronary angioplasty: comparison with 12-lead electrocardiography. Coron Artery Dis 1994;5:507-14.
9. Draisma HH, Swenne CA, van de Vooren H, Maan AC, Hooft van Huysduynen B, van der Wall EE, et al. LEADS: An interactive research oriented ECG/VCG analysis system. Computing in Cardiology 2005;32:515-8. Online available at http://cinc.org/archives/2005/pdf/0515.pdf.
10. Ter Haar CC, Maan AC, Schalij MJ, and Swenne CA. Directionality and proportionality of the ST and ventricular gradient difference vectors during acute ischemia. J Electrocardiol 2014;47:500-4.
11. Warren SG and Wagner GS. The STAFF studies of the first 5 minutes of percutaneous coronary angioplasty balloon occlusion in man. J Electrocardiol 2014;47:402-7.
12. Macfarlane PW, Devine B, Latif S, McLaughlin S, Shoat DB, and Watts MP. Methodology of ECG interpretation in the Glasgow program. Methods Inf Med 1990;29:354-61.

13. Kors JA, van HG, Sittig AC, and van Bemmel JH. Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. Eur Heart J 1990;11:1083-92.
14. Prineas R, Crow R, and Blackburn H. The Minnesota Code Manual of Electrocardiograhic Findings. John Wright-PSG, Inc. Littleton, MA; 1982.
15. Burger HC. A theoretical elucidation of the notion ventricular gradient. Am Heart J 1957;53:240-6.
16. Man S, Rahmattulla C, Maan AC, van der Putten NH, Dijk WA, van Zwet EW, et al. Acute coronary syndrome with a totally occluded culprit artery: relation of the ST injury vector with ST-elevation and non-ST elevation ECGs. J Electrocardiol 2014;47:183-90.



CHAPTER 9

Adults with congenital heart disease: ready for mobile health?

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Submitted

Abstract

Purpose

Mobile health (mHealth) could improve outcome and reduce emergency care utilization of grown-up patients with congenital heart disease (GUCH). Inappropriate use of mHealth, however, can lead to data overload for professionals and unnecessary measurements for patients, increasing burden for both. We aimed to determine the clinical characteristics of patients with high emergency care utilization and to test whether these patients were willing to start using mHealth.

Methods

Clinical characteristics and emergency care utilization of consecutive GUCH patients who visited one of the two participating cardiologists at the outpatient clinic of the Academic Medical Center in Amsterdam were studied retrospectively. All patients were approached to fill in an mHealth questionnaire. A frequency of three or more emergency visits in 5 years was defined as high emergency care utilization.

Results

In total, 202 consecutive GUCH patients who visited one of the two participating cardiologists were studied. Median age was 41 years, 47% were male, and 51% were symptomatic. In the past five years, 134 emergency visits were identified. Of all patients, 8% had high emergency care utilization. High emergency care utilization was associated with patients being symptomatic, using anti-arrhythmic drug therapy or diuretics. In total, 75% of all patients with high emergency care utilization were willing to start using mHealth.

Conclusion

GUCH patients who are symptomatic, those on anti-arrhythmic drug therapy and those on diuretics are suitable candidates to enroll in future mHealth initiatives because of both high care utilization and high motivation to start using mHealth.

Introduction

Congenital heart disease (CHD) is one of the most common birth defects.(1-3) During the past decades, life expectancy of children born with a CHD has increased dramatically. At present, 95% of children with CHD reach adulthood.(1) However, many of the grown-ups with congenital heart disease (GUCH) are chronically affected by residual sequelae leading to unpredictable arrhythmias, heart failure and a reduced quality of life.(4-8) In general, GUCH patients have a high utilization of emergency resources, with emergency care utilization increasing as age progresses.(4) As the population of GUCH patients is increasing in number and age, total emergency care utilization of this population is expected to increase.(9)

Mobile health (mHealth) is the provision of medical care by mobile technologies capable of delivering health information, monitoring clinical signs and enabling direct care and patient education.(10) Using mobile technology, vital signs can be collected and sent immediately to a treating cardiologist. E-visits enable immediate and remote contact between doctor and patient.(11) Therefore, potential benefits of mHealth include rapid delivery of round-the-clock care, enhance daily monitoring and hence timely response and more convenience for patients and improve access for patients.(12) In order to improve outcome and reduce emergency care utilization careful selection of patients that are most likely to benefit from an mHealth intervention is warranted. If used in an inappropriate patient population, mHealth can lead to data overload for healthcare professionals and unnecessary measurements for patients, increasing burden for both.(13) Patients with a high emergency care utilization and high motivation to start using mHealth are suitable candidates to initiate new mHealth initiatives on. It is therefore the primary objective of this study to determine the clinical characteristics of GUCH patients with high emergency care utilization. It is the secondary objective to combine these findings with the results of an mHealth questionnaire, to test whether GUCH patients with high emergency care utilization are willing to start using mHealth.

Methods

Population and data collection

For this study, two cardiologists specialized in GUCH (BB & BM) approached consecutive patients who had an appointment at the outpatient clinic with them to fill in an mHealth questionnaire. These patients visited the outpatient clinic at the Academic Medical Center in Amsterdam between April 2016 and September 2016. Clinical characteristics and emergency care utilization of these GUCH patients were studied retrospectively. Clinical characteristics that were noted were: severity of the CHD (in accordance with the Bethesda conference) (14), history of cardiac surgery, history of pacemaker or implantable cardioverter defibrillator (ICD) implantation

and the use of diuretics or any antiarrhythmic drug therapy. In case of antiarrhythmic drug therapy, the indication was noted as well. Beta-blockers were considered an antiarrhythmic drug therapy if the drug was initiated or the dose was altered for symptoms of palpitations or treatment for arrhythmia control. Cardiac related symptoms were expressed by the New York Heart Association (NYHA) Functional Class. GUCH patients with a NYHA class II or higher were considered symptomatic. Emergency care utilization was defined as visits to the Emergency Room, Cardiac Care Unit or unplanned outpatient clinic visits. Outpatient clinic visits were counted if they included a visit to a cardiologist, cardiologist in training, heart failure nurse or dedicated CHD nurse at the department of Cardiology of the Academic Medical Center. An outpatient clinic visit was characterized as "unplanned", if the electronic medical record (EMR) explicitly stated that the patient was seen in case of symptoms. Interventions that were noted following an emergency care visit were any type of open-heart surgery, aneurysm surgery, pacemaker or ICD implantation or replacement, diagnostic catheterizations, electrical cardioversions (ECV), catheter based interventions and bronchoscopy in case of hemoptysis. We defined high care utilization as a score of three or more emergency visits between June 1st, 2011 and December 31st, 2016.
All patients were approached to fill in an mHealth questionnaire on paper. Details of the questionnaire have been described previously.(15) Exclusion criteria for participating in this questionnaire were being mentally impaired (by physician's discretion), illiterate in Dutch or being younger than 18 years of age.

Ethical Approval
For the collecting of medical data of all the participating GUCH patients, permission was granted by the Ethics Committee (reference number W16_057). For the questionnaire survey no approval from the Institutions' Ethics Committee was required under Dutch law, since it was not burdensome for patients.

Data management and statistics
SPSS 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) was used for statistical analysis. To identify GUCH patients who would most likely benefit from mHealth, determinants were set off against an emergency care utilization of three or more emergency visits and/or interventions in the past five years. Variables were compared with a chi-squared test. A P-Value $\leq$ 0.05 was considered statistically significant.

Results

Population characteristics

In total 202 consecutive patients who visited the outpatient clinic and had an appointment with one of the two participating cardiologists (BB & BM) at the Academic Medical Center in Amsterdam between April 2016 and September 2016 were studied. Median age was 41 years (interquartile range 32 – 50, range 18 – 78 years), 47% was male and 51% was symptomatic. Of all patients, 19% had mild CHD, 61% moderate CHD and 20% severe CHD. A total of 83% had a history of cardiac surgery and 8% had a pacemaker or ICD implanted. A percentage of 31% used antiarrhythmic drug therapy and 9% used diuretics (Table 1). Only 5% were in NYHA class IV. All patients filled in the mHealth questionnaire.

Table 1. Comparison of high and low care utilization

	All patients N=202	**Low care utilization N=186 (92%)**	**High care utilization N=16 (8%)**	**p**
Median Age, years	41 (18-78)	40 (18-78)	42 (23-77)	
Male, %	47	46	43	.816
Congenital heart disease				
Mild, *%*	19	19	25	.548
Moderate, *%*	61	62	50	.352
Severe, *%*	20	19	25	.548
New York Heart Association Class				
Class I, *%*	49	51	13	<.001
Class ≥II, *%*	51	49	87	<.001
Event history				
Cardiac surgery, *%*	83	83	75	.363
PM/ICD implantation, *%*	8	8	19	.121
Medication				
Diuretics, *%*	9	7	44	<.001
Anti-arrhythmic, *%*	31	27	69	.001
mHealth				
Smartphone utilization (%)	93	94	87	.369
Ready to use mHealth (%)	71	70	75	.70

Emergency visits

In the past five years, 202 patients accounted for 134 emergency visits. Of all 202 patients, 59 (29%) had one or more emergency visits. Of all 202 patients, 16 (8%)

had high care utilization, compared to 186 (92%) with low care utilization. No significant differences in gender, history of cardiac surgery or severity of CHD were found between patients with high and low care utilization. Significant differences were found in NYHA class (87% vs 49%, *P*<.001), use of diuretics (44% vs 7%, *P*<.001) and use of antiarrhythmic drug therapy (69% vs 27%, *P*=.001) (Table 1).
Table 2 and Figure 1 show all symptoms patients presented themselves with, consequent diagnoses made, and treatment administered. Most patients presented themselves with either palpitations (41%) or chest pain (24%). In 46% of all cases, no diagnosis of cardiac nature was found. In 37% of all cases, a patient was diagnosed with an arrhythmia (Figure 1).

Table 2. Information on emergency visits

2A symptoms	**N (%)**
Palpitations	55 (41%)
Chest pain	32 (24%)
Fever	16 (12%)
Fatigue	13 (10%)
Shortness of breath	7 (5%)
Hemoptysis	6 (4%)
Neurological symptoms	5 (4%)
2B diagnoses	**N (%)**
No diagnosis of cardiac nature	62 (46%)
Arrhythmia	50 (37%)
Endocarditis	6 (5%)
Pulmonary hypertension	6 (5%)
Stroke	5 (4%)
Valvular heart disease	3 (2%)
Heart Failure	2 (1%)
2C therapeutic regimen consequences	**N (%)**
No changes in therapeutic regimen	59 (44%)
Medication changes	52 (39%)
Electrocardioversion	29 (21%)
Interventions	4 (3%)
Planned interventions	3 (2%)

Emergency visits resulted in a variety of different actions. In 44% of all cases therapeutic regimen was not changed. Drug therapy was changed in 52 (39%) cases. In 8 (15%) out of 55 cases of palpitations, therapeutic regimen was not changed. Therapeutic regimen changes included 16 (29%) cases of ECV, 13 (24%)

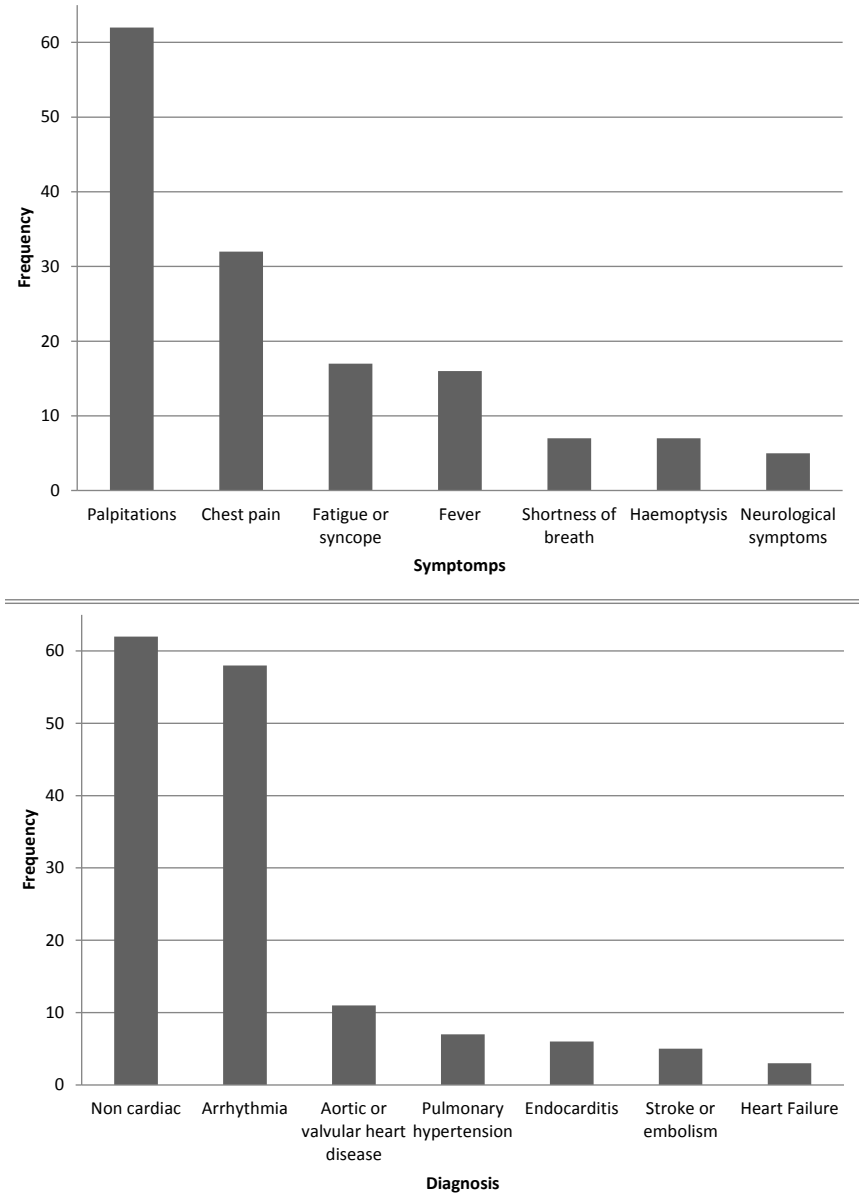


Figure 1. Frequency emergency care visit reasons and subsequent diagnoses.
Legend: red: frequency of symptoms. Blue: frequency of diagnoses

cases of adjusting antiarrhythmic drug therapy after ECV, 7 (13%) cases of adjusting antiarrhythmic drug therapy only, 10 (18%) cases of initiating antiarrhythmic drug therapy and 1 (2%) case of radiofrequency ablation. The 32 cases of chest pain resulted in no action in 29 cases (91%). Therapeutic regimen changes included 3 (9%) cases of initiating antibiotic treatment for the suspicion of endocarditis.

Patient motivation to start using mHealth amongst patients with high emergency care utilization

In total, 16 GUCH patients had high care utilization. Median age was 46 years, 56% was female and 87% was symptomatic. Of all 202 GUCH patients, 25% had a mild CHD, 50% a moderate and 25% a severe CHD. Antiarrhythmic drug therapy was used by 69% of patients and diuretics were used by 44% of patients.

Of all patients with high care utilization, 87% were in possession of a smartphone and 18% claimed to use mHealth already. Of all patients, 44% wanted information about their disease, while 44% wanted lifestyle advices via mobile technology. A total of 56% were willing to fill in vital signs on their smartphone, 56% were willing to fill in symptoms on their smartphone, 62% wanted advice in case of aberrant vitals, 62% wanted advice in case of symptoms of possible cardiac origin and 75% were willing to start using mHealth.

In contrast, in the low care utilization group, 131 (70%) patients were willing to start using mHealth (Figure 2).

Discussion

To our knowledge this is the first study to determine suitability of candidates to enroll in new mHealth initiatives in GUCH patients. In our study, we identified symptomatic patients who are on diuretics or antiarrhythmic drug therapy to be more likely to visit the emergency room. These patients might benefit from mHealth, as emergency visits could be prevented via mHealth. In patients with few emergency visits, mHealth is less likely to be beneficial as it is a priori less likely to prevent an emergency visit. Therefore, our study could help to avoid initiation of mHealth with the goal to decrease emergency care utilization in an inappropriate patient population and could prevent unnecessary measurements for patients. Furthermore therapeutic regimen was not changed in 44% of all emergency visits. These visits might also be reducible via mHealth.

Emergency care utilization

In this study, 29% of all participating GUCH patients had an emergency visit in the past five years. This was lower than the study of Mackie et al.(16) and Verheugt et al.(17), who reported that 68% and 50% of their study population had an emergency visit, respectively. Definitions of emergency care utilization between Mackie et

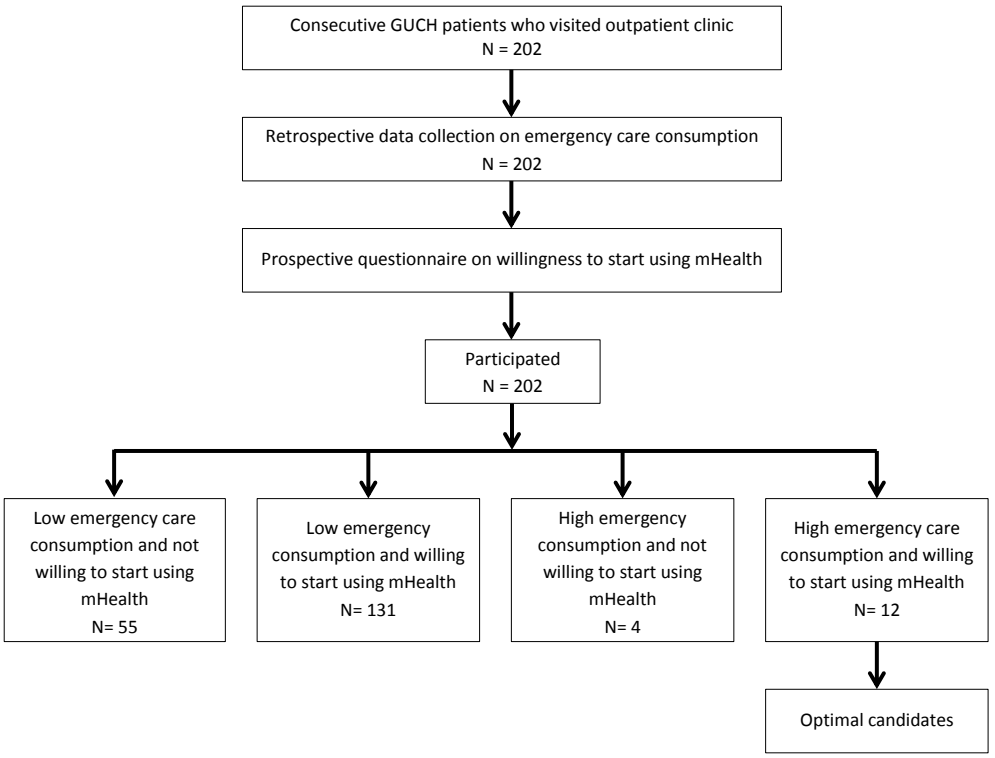


Figure 2. Flow-chart of patient selection.

al., Verheugt et al. and our study were comparable. It is therefore hypothesized that this difference is due to the fact that for this study, only emergency visits at the Academic Medical Center were analyzed. The Academic Medical Center is a tertiary hospital, treating patients from a large geographic region. In emergency cases, these patients are more likely to visit a local hospital close by their homes. These emergency visits are not counted in this study. Therefore, the frequency of emergency visits could be higher in our study population. In our study most patients presented with palpitations and chest pain. Arrhythmias were the most common final diagnosis. Only by one percent of patients heart failure was diagnosed, which was lower than in studies by Cedars et al (18) and Negishi et al.(19) There are several explanations: first, patients might have been admitted to other hospitals. Second, in this study, diagnoses were classified according to primary diagnosis. Some patients with arrhythmias visited with heart failure symptoms, but were diagnosed in the "arrhythmia category". Third, two nurse practitioners specialized in heart failure had optimized treatment at the outpatient clinic, which could potentially have led to a reduction of deteriorations in heart function. Finally, in our study population,

31% had been hospitalized in the past five years. This was in line with the study of Mackie et al.(16) and Moons et al.(20)

Selecting GUCH patients for mobile health

Our study showed that the majority of patients were willing to use mHealth applications. Several validated technologies that allow for remote ECG monitoring and automatic transmission are already available (21) and easy to use. For selecting the best candidate for possible future mHealth initiatives inclusion criteria should be: GUCH patients, experiencing frequent palpitations and/or chest pain, able to operate a smartphone and having high care utilization. Furthermore, having severe CHD, using diuretics and/or antiarrhythmic drug therapy, having an implant or experiencing symptoms can be taken into account in selecting the GUCH patients. Gender and age should not be a discrimination factor. Issues regarding privacy will need to be addressed, since this new technology will be sensitive for breach of privacy. Lastly, mHealth literacy is an important predictor of success of an mHealth intervention.(22) Therefore, acceptability should be taken into account when initiating mHealth initiatives in this group.

Limitations

This study was limited by the fact that data collection was done in a single tertiary medical center, which could potentially affect generalizability. No data from other hospitals were incorporated in this study. Therefore, data on healthcare utilization presented in this study might be an underestimation, as GUCH patients that participated could have been admitted to other hospitals. Lastly, 16 patients in our study had a high emergency care utilization. This sample size is relatively small and the percentages derived from this sample size should therefore be cautiously interpreted.

Planned healthcare utilization

This study was primarily concerned with the role of mHealth to decrease emergency care utilization. It might however be possible that frequent measurements of vital signs and remote doctor-patient contact will decrease the need for planned in-office visits as well. Moreover, mHealth could also contribute to the improvement of patient satisfaction and patient health engagement.(23) This should be measured in future mHealth initiatives as well.

Conclusion

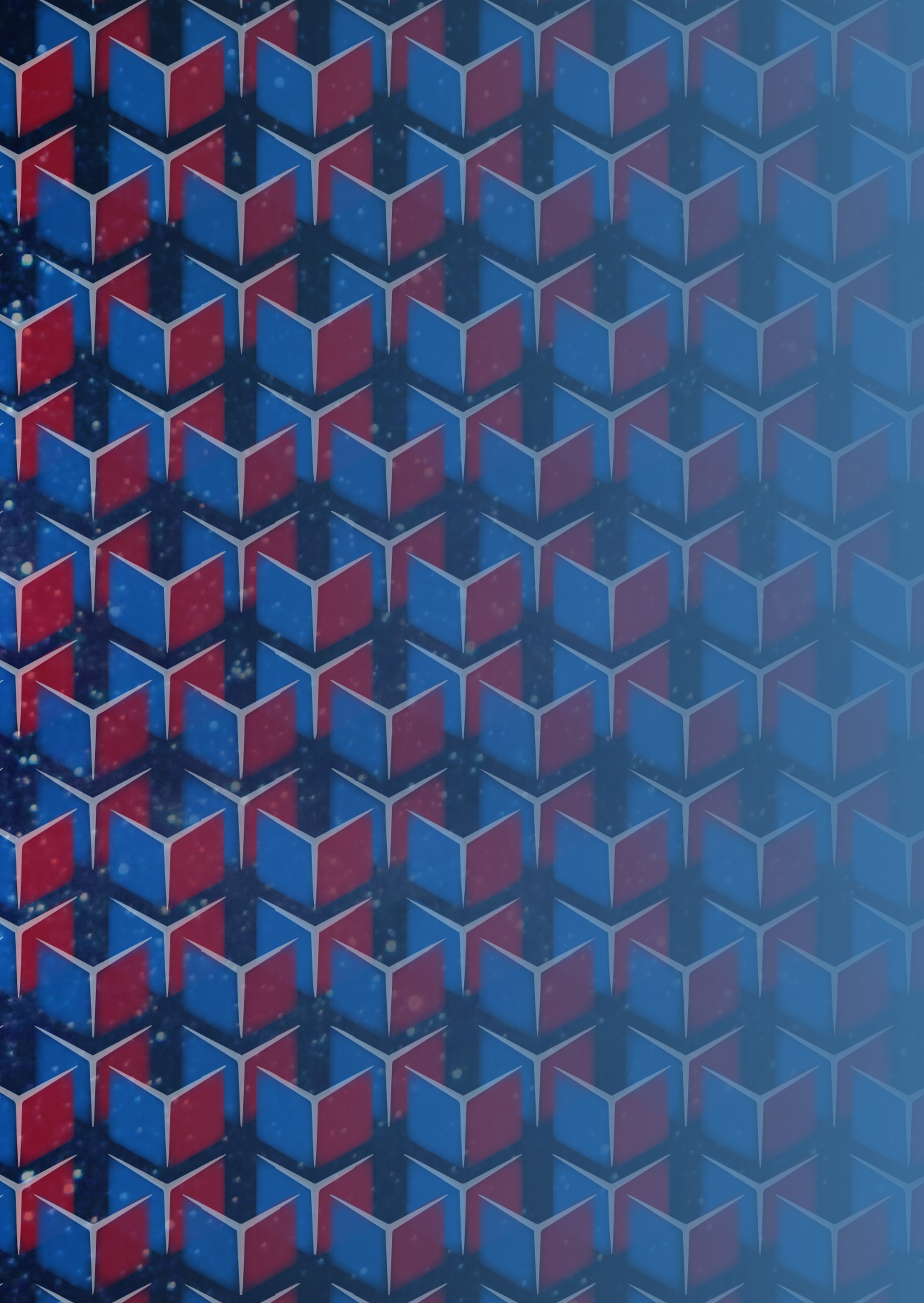
GUCH patients who are symptomatic, those on anti-arrhythmic drug therapy and those on diuretics are optimal candidates to enroll in new mHealth initiatives because of both a high care utilization and high motivation. Our study contributes to

appropriate patient selection for mHealth initiatives that aim to prevent emergency care utilization, thereby contributing to an efficient use of mHealth.

References

1. Tennant PW, Pearce MS, Bythell M, Rankin J. 20-year survival of children born with congenital anomalies: a population-based study. Lancet. 2010;375(9715):649-56.
2. Canfield MA, Honein MA, Yuskiv N, et al. National estimates and race/ethnic-specific variation of selected birth defects in the United States, 1999-2001. Birth Defects Res A Clin Mol Teratol. 2006;76(11):747-56.
3. Bird TM, Hobbs CA, Cleves MA, Tilford JM, Robbins JM. National rates of birth defects among hospitalized newborns. Birth Defects Res A Clin Mol Teratol. 2006;76(11):762-9.
4. Baumgartner H, Bonhoeffer P, De Groot NM, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J. 2010;31(23):2915-57.
5. Koyak Z, Kroon B, de Groot JR, et al. Efficacy of antiarrhythmic drugs in adults with congenital heart disease and supraventricular tachycardias. Am J Cardiol. 2013;112(9):1461-7.
6. Schuuring MJ, van Gulik EC, Koolbergen DR, et al. Determinants of clinical right ventricular failure after congenital heart surgery in adults. J Cardiothorac Vasc Anesth. 2013;27(4):723-7.
7. Zomer AC, Vaartjes I, van der Velde ET, et al. Heart failure admissions in adults with congenital heart disease; risk factors and prognosis. Int J Cardiol. 2013;168(3):2487-93.
8. Schuuring MJ, van Riel AC, Vis JC, et al. New predictors of mortality in adults with congenital heart disease and pulmonary hypertension: Midterm outcome of a prospective study. Int J Cardiol. 2015;181:270-6.
9. Tutarel O, Kempny A, Alonso-Gonzalez R, et al. Congenital heart disease beyond the age of 60: emergence of a new population with high resource utilization, high morbidity, and high mortality. Eur Heart J. 2014;35(11):725-32.
10. Cowie MR, Bax J, Bruining N, et al. e-Health: a position statement of the European Society of Cardiology. Eur Heart J. 2016;37(1):63-6.
11. Treskes RW, van der Velde ET, Barendse R, Bruining N. Mobile health in cardiology: a review of currently available medical apps and equipment for remote monitoring. Expert Rev Med Devices. 2016;13(9):823-30.
12. Dorsey ER, Topol EJ. State of Telehealth. N Engl J Med. 2016;375(2):154-61.
13. Clark PA, Capuzzi K, Harrison J. Telemedicine: medical, legal and ethical perspectives. Med Sci Monit. 2010;16(12):RA261-RA72.
14. Warnes CA, Liberthson R, Danielson GK, et al. Task force 1: the changing profile of congenital heart disease in adult life. J Am Coll Cardiol. 2001;37(5):1170-5.
15. Schuuring MJ, Backx AP, Zwart R, et al. Mobile health in adults with congenital heart disease: current use and future needs. Neth Heart J. 2016.
16. Mackie AS, Pilote L, Ionescu-Ittu R, Rahme E, Marelli AJ. Health care resource utilization in adults with congenital heart disease. Am J Cardiol. 2007;99(6):839-43.
17. Verheugt CL, Uiterwaal CS, van der Velde ET, et al. The emerging burden of hospital admissions of adults with congenital heart disease. Heart. 2010;96(11):872-8.
18. Cedars AM, Burns S, Novak EL, Amin AP. Predictors of Rehospitalization Among Adults With Congenital Heart Disease Are Lesion Specific. Circ Cardiovasc Qual Outcomes. 2016.

19. Negishi J, Ohuchi H, Yasuda K, Miyazaki A, Norifumi N, Yamada O. Unscheduled hospitalization in adults with congenital heart disease. Korean Circ J. 2015;45(1):59-66.
20. Moons P, Siebens K, De Geest S, Abraham I, Budts W, Gewillig M. A pilot study of expenditures on, and utilization of resources in, health care in adults with congenital heart disease. Cardiol Young. 2001;11(3):301-13.
21. Al-Zaiti SS, Shusterman V, Carey MG. Novel technical solutions for wireless ECG transmission & analysis in the age of the internet cloud. J Electrocardiol. 2013;46(6):540-5.
22. Gordon NP, Hornbrook MC. Differences in Access to and Preferences for Using Patient Portals and Other eHealth Technologies Based on Race, Ethnicity, and Age: A Database and Survey Study of Seniors in a Large Health Plan. J Med Internet Res. 2016;18(3):e50.
23. De Rosis S, Barsanti S. Patient satisfaction, e-health and the evolution of the patient-general practitioner relationship: Evidence from an Italian survey. Health Policy. 2016;120(11):1279-92.



CHAPTER 10

Mobile health application to screen for central sleep apnea in patients with stable heart failure

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Submitted

Abstract

Background

Polysomnography (PSG) is the gold standard for detection of central sleep apnea (CSA) in stable heart failure (HF) patients. PSG is however costly, time consuming and a burden to the patient and therefore unsuitable as screening method. An E-Health application to measure overnight oximetry may be an acceptable screening alternative.

Objective

The purpose of this study is therefore to assess if overnight pulse oximetry using a smartphone compatible oximeter can be used to detect CSA in a stable HF population.

Methods

A total of 26 patients with stable HF underwent one night of both a polygraph (PG) and overnight saturation by a smartphone compatible oximeter. Primary endpoint was the agreement between oxygen desaturation index (ODI) above or below 15 of the smartphone compatible oximeter and the diagnosis of the PG.

Results

Median age was 66.4 (62-71) years and 92% was male. Body mass index was 27.1 (24.4-30.8) $kg \cdot m^{-2}$. Seven patients had CSA and 6 patients had obstructive sleep apnea. Of the 7 (.32) patients with CSA that were included in the analysis, 3 (.13) had an ODI≥15. The other 4 (.18) had an ODI<15. Of all patients without CSA, 8 (.36) had an ODI<15. A McNemar's test yielded a P-Value of .549.

Conclusions

Oxygen desaturation, when measured by this E-Health application, is a weak predictor of CSA in stable HF patients.

Introduction

Central sleep apnoea (CSA) is characterized by sleep disordered breathing associated with diminished or absent respiratory effort. It is often accompanied by symptoms of tiredness, excessive daytime sleepiness and frequent nocturnal awakenings.(1, 2) CSA and Cheyne-Stokes respiratory breathing are common in congestive heart failure (CHF) patients, with a reported prevalence of 30- 50%.(3) Moreover, CSA in chronic heart failure is associated with increased mortality and reduced left ventricular function.(4) In addition, treatment of CSA with continuous positive airway pressure (CPAP) in chronic heart failure has shown to improve left ventricular function in patients who are responders to treatment.(5)

Currently, polysomnography (PSG) is the gold standard for the diagnosis of CSA. However, PSG is a burden to the patient as it disrupts sleep. Furthermore, it is time consuming for technicians to evaluate, as one PSG examination takes 2 hours to fully evaluate. In addition, the polygraph (PG) is an easier way of evaluating sleep disordered breathing as compared to full PSG, but still disrupts normal sleep for a patient with an already reduced quality of life. Other screening methods to reduce the number of P(S)Gs may therefore be preferred.

Developing new screening methods, including E-Health applications, questionnaires and wireless overnight pulse oximetry for patients with CHF might optimize the number of patients screened for CSA. Furthermore, it may be more patient friendly in a group of patients with an already diminished quality of life.

One possible screening method is the use of E-Health applications (apps). Recent developments in the E-Health industry resulted in a variety of E-Health apps which claim that they can detect sleep disordered breathing. Most of these applications are however not clinically validated. One example of an app that (according to the manufacturer) gives accurate saturation measurements is the iSpO2 app (Masimo Corporation, Irvine, California, United States of America).(6, 7) This app allows its user, by using the app and an oximeter, to record saturation, heart rate and pulse index. Digital storage of the data allows for rapid transmission and analysis, minimizing the involvement of technicians. Previous studies have suggested that overnight oximetry can be used to detect obstructive sleep apnea (OSA) in various patient populations. However, overnight oximetry has not been evaluated as screening method in patients with stable heart failure. This study is therefore performed to evaluate the possible use of overnight pulse oximetry can identify patients with CSA in a CHF population using a validated mHealth app.

Methods

Patient population

Patients with stable heart failure, who visited the outpatient clinic of the department of Cardiology of the Leiden University Medical Center, were eligible for study participation if they met all inclusion and exclusion criteria. Inclusion and exclusion criteria are listed in Table 1. Briefly, patients who had stable heart failure, according to ESC guidelines,(8) had no history of OSA or CSA, had no history of ischaemic or haemorrhagic stroke and who had a life-expectancy of more than 12 weeks (by physician's discretion) were eligible.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Chronic heart failure, according to ESC guidelines(1)
Aged ≥18 years
Exclusion criteria
History of obstructive sleep apnea syndrome
History of central sleep apnea syndrome
History of ischaemic stroke
History of haemorrhagic stroke
History of chronic obstructive pulmonary disease
Evidence of fluid retention at the time of study inclusion
History of surgery under general anaesthesia ≤3 months before study inclusion
Intravenous injection of diuretics ≤1 month before study inclusion
Unwilling to sign the informed consent form
Life-expectancy ≤12 weeks, by physician's discretion
History of left-ventricular assist device implantation
Use of oxygen on a daily basis
Pregnancy

Study design and conductance

The study was a single cohort non-randomized open prospective trial. Patients with stable heart failure were asked to participate by a treating cardiologist at a regularly scheduled HF outpatient clinic visit. Patients received information from a project-dedicated healthcare professional. If patients were willing to participate, they visited the department of pulmonology within 1.5 months. At day one, a project-dedicated healthcare professional with ample training applied the PG. Furthermore, the patient was given a smartphone and smartphone compatible oximeter. Patients received oral and written instructions on the use of the smartphone and smartphone compatible oximeter. Patients were instructed to attach the smartphone compatible

oximeter contralateral to the hand where the PG attached. During the first night, patients slept with both the PG and the smartphone compatible oximeter attached. After one night, patients returned the PG to the hospital. The second, third and fourth night, patients slept with only the smartphone compatible oximeter attached. After the fourth night, patients returned the smartphone compatible oximeter to the hospital. A flowchart of these events is given in Figure 1.

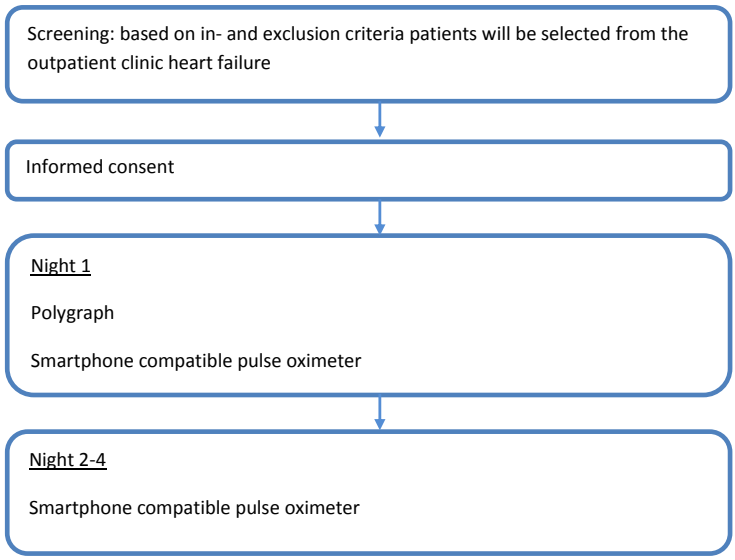


Figure 1. Flow chart of patient selection.

Devices

The PG equipment (Cidelec, Angers, France) consisted of a nasal cannula, a suprasternal sensor, thoracic and abdominal gauges, a finger pulse oximeter, a light sensor, body position and an activity sensor. The pulse oximeter has a sampling rate of 8 Hertz (Hz). Both the smartphone (iPhone 5s, Apple, Cupertino, California, United States of America) and the smartphone compatible pulse oximeter (Masimo, Irvine, California, United States of America) were provided by the hospital for the duration of study participation. The smartphone compatible pulse oximeter is worn at the fingertip and is connected with the smartphone via a wire. The pulse oximeter has a sampling rate of 1 sample/second.

Devices used in this study were battery powered and electrically safe and approved by the Hospital's Instrumentation Department.

Data analysis

CSA and OSA were diagnosed with the results of the PG, in accordance to the America Association of Sleep Medicine guidelines.(9) A patient was diagnosed with sleep apnea if the PG showed an apnea-hypopnea index (AHI) of ≥15 per hour. Sleep apnea was subsequently classified as CSA or OSA. A patient was diagnosed with CSA if of all apnea and hypopnea events, ≥50% were classified as "central". A patient was diagnosed with OSA if <50% of all apnea and hypopnea events were classified as "central". Definitions for apnea and hypopnea events and their subdivision in central or obstructive were derived from the "AASM manual for the scoring of sleep and associated events".(9) The oxygen desaturation index (ODI) was defined as the average number of dips in saturation per hour. A cut-off value of 15 was chosen for the ODI. A dip was defined as a ≥3% decrease in saturation which lasted ≥10 seconds from the baseline saturation. The baseline saturation was determined in the hospital right after the PG was attached to the patient. The PGs were reviewed by a senior pulmonary physician with ample training who was blinded to the results of the oximeter compatible application.

The oximeter compatible application (Masimo) generates a CSV file, which was imported into a dedicated Matlab script (The MathWorks, Natick, Massachusetts, United States) and average SpO2, lowest SpO2, total percentage of time spend with a saturation <90% and the ODI were calculated. The ODI was again defined as the average number of dips in saturation per hour. A dip was defined as a ≥3% decrease in saturation which lasted ≥10 seconds from the average saturation over the 11th minute of measurement.(9) The smartphone compatible oximeter data were analysed by a project dedicated professional with ample training who was blinded to the results of the PG.

End points

The primary endpoint is the agreement between ODI of the smartphone compatible oximeter and the diagnosis of the PG, expressed as four numbers (the number of patients who have both CSA, as diagnosed by PG, and >=15 dips/hour on the smartphone compatible oximeter, the number of patients who have CSA and <=15 dips/hour, the number of patients who do not have CSA and >= 15 dips/hour, the number of patients who do not have CSA and <= 15 dips/hour), depicted in a 2 x 2 table.

Secondary endpoints include:

1. The percentage of detected sleep apnea (either of obstructive or central aetiology) in the study population by the PG
2. The percentage of detected CSA in the study population by the PG
3. The agreement between the ODI, measured by the PG, and sleep apnea (either obstructive or central aetiology) in the study population
4. The agreement between the ODI, measured by the PG, for CSA in the study population
5. Median difference in ODI, lowest saturation and average saturation between the PG and mobile pulse oximeter
6. The sensitivity and specificity of pulse oximetry to detect CSA by saturation dips > 15/h
7. The percentage of patients able to use the e-health device as instructed

Statistical analysis

R (R foundation for statistical computing, Vienna, Austria) was used to perform a power calculation for a McNemar's test. A alpha level of .05 was chosen and a beta level of 0.20. Based on unpublished research by our study group, we estimated the ratio of p01/p10 (p01 being the false positives and p10 being the false negatives) to be 12 and the sum of p10 and p01 to be 0.39. This yielded a sample size of 26 patients.

SPSS 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) was used for statistical analysis. Continuous variables are expressed as median with interquartile range (IQR) from the 25th to the 75th percentile.

Significance of the primary endpoint was calculated using a McNemar's test. A *P*-Value≤.05 was considered statistically significant. A Blant-Altman was drafted to assess the short term reproducibility of the ODI. On the x-axis, ODI of the first night is depicted. On the y-axis, the difference in ODI between the first and second night is depicted.

Results

Patient population

A total of 26 patients were included in the study. Median age was 66.4 (62-71) years and 92% was male. Body mass index was 27.1 (24.4-30.8) kg·m^{-2}. All patients had NYHA class I (15.4%) or NYHA class II (84.6%), 61.5% had an ischemic cardiomyopathy. Median left ventricular ejection fraction was 34% (24-45), median ProBNP was 748 (244.6-1479) ng/L and median neck circumference was 41 (38-44) cm. Population characteristics are summarized in Table 2.

Table 2. Baseline characteristics

N	26
Age, years	66.4 (62.2-70.6)
Male gender (%)	24 (92.3%)
Body Mass Index, $kg \cdot m^{-2}$	27.1 (24.4-30.8)
NYHA class (%)	
I	4 (15.4%)
II	22 (84.6%)
Ischemic Cardiomyopathy (%)	16 (61.5%)
LVEF, %	34 (23.5-45)
ProBNP (%)	748 (244.6-1479)
Neck circumference, cm	41 (35-49)

Polygraph

A total of 26 PGs were issued. One PG was of insufficient diagnostic quality and one PG was too short to establish a diagnosis. Both patients were not willing to undergo a second PG. Of the 24 patients that had a PG of diagnostic quality, 14 (58%) had sleep apnea (of either aetiology). A total of 8 (33%) were diagnosed with CSA and 6 (25%) were diagnosed with OSA (secondary endpoint number 1 and number 2). In 10 (41%) cases no sleep apnea was detected. Median sleep duration was 6.5 (IQR: 5.4-7.4) hours. Median AHI was 17 (IQR: 6.5-27.8). Median ODI was 16 (IQR: 5.5-28). Median number of hypopneas per night was 62 (IQR: 30.8-79.8). Median number of dips was 92.5 (IQR: 33.3-156).

Overnight oximetry

All 26 participants transferred at least one CSV file containing the overnight saturation measured by the smartphone compatible pulse oximeter. Of the 4 patients who did not transfer a CSV file of their first night (the night they also underwent the PG), 2 patients could not be diagnosed due to a PG of insufficient quality (as described above). The other 2 patients forgot to attach the smartphone compatible pulse oximeter in their first night. Therefore, 22 patients were included in the analysis of the primary endpoint and secondary endpoint number 3, 4, 5 and 6 (Figure 2). Of the 26 patients who participated, 13 (50%) were able to transfer CSV files of four consecutive nights. A total of 9 (35%) patients transferred CSV files of 3 nights, 1 (4%) transferred CSV files of 2 nights and 3 (12%) transferred CSV files of only 1 night.

Of all files transferred, median saturation was 95.7 (IQR: 94.5-96.7). Median lowest saturation was 87 (82-90). Median ODI was 10.1 (2.9-20.3). Total dips were 75.5 (21-144.8) and total sleep was 8.1 (6.7-9.4) hours.

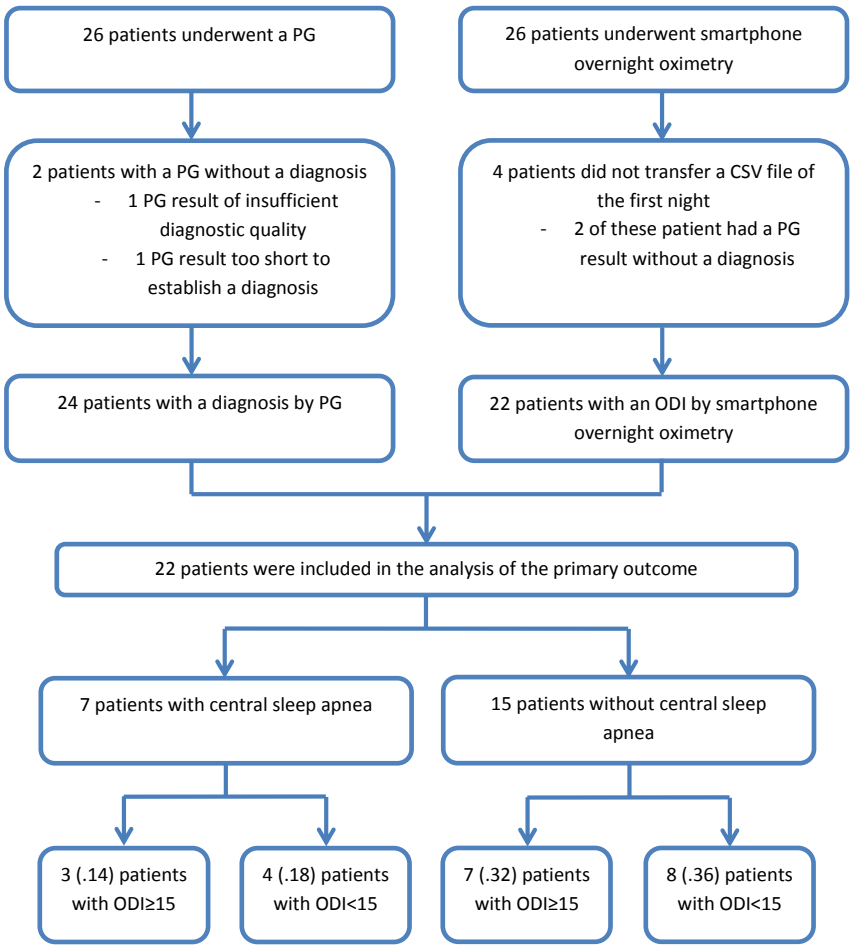


Figure 2. Flowchart of the results of the primary outcome.

Primary endpoint

Of the 7 (.32) patients with CSA that were included in the analysis, 3 (.13) had an ODI≥15. The other 4 (.18) patients had an ODI<15. Of all 15 patients without CSA that were included in the analysis, 8 (.36) had an ODI<15. These data are given in Table 3. A McNemar's test yielded a P-Value of .549.

Table 3. Number (proportions) of patients with central sleep apnea (yes/no) and an ODI of ≥15 or <15 (as measured by the smartphone compatible oximeter)

	Central sleep apnea (+)	Central sleep apnea (-)	Total
ODI mobile pulse oximeter≥15	3 (.14)	7 (.32)	10 (.45)
ODI mobile pulse oximeter<15	4 (.18)	8 (.36)	12 (.55)
Total	7 (.32)	15 (.68)	22 (1)

Secondary endpoints

Of all 13 patients with sleep apnea, 6 had an ODI≥15, measured by Masimo. Of all 9 patients without sleep apnea, 5 had an ODI<15. These data are given in Table 4A.

Table 4A. Number of patients with sleep apnea (yes/no) and an ODI of ≥15 or <15 (as measured by the smartphone compatible pulse oximeter)

	Sleep apnea (+)	Sleep apnea (-)	Total
ODI smartphone compatible oximeter≥15	6 (.27)	4 (.18)	10 (.45)
ODI smartphone compatible oximeter<15	7 (.32)	5 (.23)	12 (.55)
Total	13 (.59)	9 (.41)	22 (1)

Of all 7 patients with CSA, 6 had an ODI (measured by the PG) ≥15. Of all patients without CSA, 9 had an ODI<15. These data are given in Table 4B.

Table 4B. Number of patients with central sleep apnea (yes/no) and an ODI of ≥15 or <15 (as measured by the PG)

	Central sleep apnea (+)	Central sleep apnea (-)	Total
ODI PG≥15	6 (.27)	6 (.27)	12 (.55)
ODI PG<15	1 (.05)	9 (.41)	10 (.45)
Total	7 (.32)	15 (.68)	22 (1)

Of all 13 patients with sleep apnea (of either aetiology), 12 had a ODI≥15 (measured by the PG). Of all 9 patients without sleep apnea, 9 had an ODI<15. These data are given in Table 4C.

Table 4C. Number of patients with sleep apnea (yes/no) and an ODI of ≥15 or <15 (as measured by the PG)

	Sleep apnea (+)	Sleep apnea (-)	Total
ODI PG≥15	12 (.55)	0 (0)	12 ()
ODI PG<15	1 (.05)	9 (.41)	10 ()
Total	13 (.59)	9 (.41)	22 (1)

The sensitivity of the ODI for the detection of CSA is therefore 43%. The specificity of the ODI for CSA is 53%. The positive predictive value is 30%. The negative predictive value is 67%.

A Blant-Altman is provided in Figure 3 to show the short term reproducibility of the ODI in participating patients.

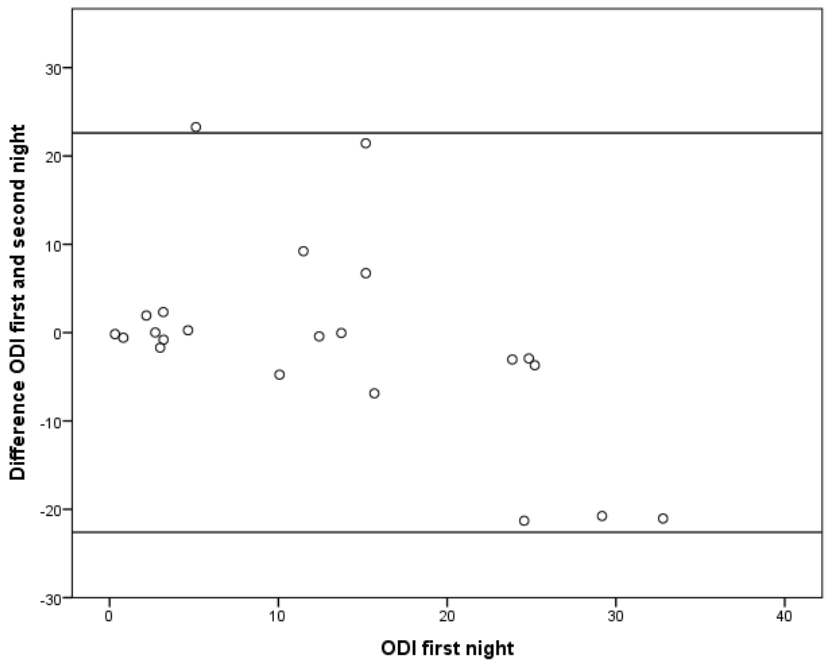


Figure 3. Bland-Altman of the ODI of the first night (x-axis) and the difference in ODI between the first and second night (y-axis).

Difference between the PG and mobile pulse oximeter

The median difference in ODI was 2.1 higher measured with the PG (IQR: -4.3,14.3). The smartphone compatible oximeter yielded a median saturation which was 3.1 (IQR: 2.6-4.1) percentage points higher than the saturation measured by the PG. There was no difference in the median lowest saturation measured by both devices (both 83%).

Discussion

This study investigated the use of a smartphone compatible oximeter to measure the ODI for the detection of CSA in stable HF patients. Oxygen desaturation, when measured by an e-Health device, appeared to be a weak predictor of CSA in stable HF patients. Also in this elderly group of patients correct use of this e-health device was only achieved by 50% of patients. On the other hand, ODI when measured by a validated device might be a good predictor of sleep apnea of any aetiology in stable HF patients. It was found that 58% of participating patients had sleep apnea. Of all patients, 33% had CSA and 25% had OSA. These percentages are lower than the prevalence found by Oldenburg et al.(10) In a screening study of 700 patients, they showed that 70% had sleep apnea, with 40% having CSA and 30% having OSA. This difference may be explained (at least partly) by the relatively small sample size, but possibly also by differences in severity of heart failure in these patients.

In our study, a median number of dips of 92.5 was found. This was significantly higher than in a study by Davies et al. in 12 heart failure patients, who described four dips per patient per night. We expect that this difference is largely due to the difference in definition of a “dip”. Davies et al. defined a dip as “a fall of >4% in oxygen saturation from a stable baseline that lasted >30 seconds”, while in the current study a dip was defined as a ≥3% decrease lasting 10 seconds. This was necessary in order to define dips equally between the PG software and our smartphone compatible oximeter.

ODI as a potential screening tool for CSA

This study showed that the ODI, measured by either the PG or smartphone compatible oximeter, correlates poorly with the diagnosis of CSA. The McNemar’s test yielded a non-significant P-Value of .549. There was however a good correlation between the ODI measured by the PG and the diagnosis of sleep apnea (of either aetiology). It is acknowledged that the study was not powered on this outcome. Furthermore, it is acknowledged that hypopneas in PGs are scored based on desaturation events. Therefore, the diagnosis of sleep apnea is partially dependent on the ODI. However, the strong outcome of 0 false positives and 1 false negatives indicate that the ODI might indeed be a good screening method. This should be investigated in further research.

Implications for clinical practice

Our study found that in 58% of patients with stable HF, any form of sleep apnea (either of central or obstructive aetiology) was found. Both OSA and CSA are associated with higher mortality and lower quality of life in patients with stable HF.(4) Therefore, early diagnosis is of paramount importance. However, screening for OSA or CSA is not recommended by current guidelines, but with such a high

prevalence, routine screening of patients should be considered. But perhaps screening should not focus on the distinction between OSA and CSA, as both have clinical implications.(8). And since ODI has shown to correlate well with sleep apnea of any aetiology, research easy to perform overnight oximetry e-health devices to screen for sleep apnea in patients with stable HF still seems necessary.

e-Health utilization in a heart failure population

In this study, patients were asked to attach, record and e-mail the overnight saturations themselves. Instructions about the use of the mobile phone, the Masimo patch and the e-mailing of the CSV files were given after the PG was attached to the patient. However, of all patients, 13 were unable to transfer four CSV files. These results should be seen as hypothesis generating, but do indicate that when conducting a study in an older and vulnerable population, the e-Health system should be tailored to the patient population. Furthermore, time spend in patient education of the e-Health system should not be underestimated.

Differences in saturation measured by the PG and by the mobile pulse oximeter

Our results showed some significant differences in predictive value of the ODI for both sleep apnea of any aetiology and CSA, median ODI and median average saturation between the PG and the smartphone compatible pulse oximeter. There are several explanations for this phenomenon: first of all, the smartphone compatible oximeter used in this study has not been validated for saturation measurement during sleep. Therefore, motion during sleep and movements of the fingers might result in different results than the oximeter of the PG, which has been designed specifically for overnight saturation measurement. Secondly, patients attached the smartphone compatible oximeter themselves at home. Although instructions were given in the hospital, it is uncertain whether patients attached the device in the proper way. Improper placement usually gives no signal and therefore no saturation in the CSV file. However, slight improper placement might result in improper values in the CSV file.

Limitations

This study has experienced some limitations that have affected its results. Unfortunately, in two patients, it was not possible to get a diagnosis from the PG. These two patients were not willing to undergo a second PG. However, given the numbers of the primary endpoint and a relatively high P-Value of .549, it is unlikely that three extra patients would have changed the data significantly. Furthermore, some patients could not deal with the smartphone technology given, despite ample instructions. As a consequence, 13 patients were unable to record their overnight saturation for 4 consecutive nights. Lastly, we did not do PGs in healthy volunteers.

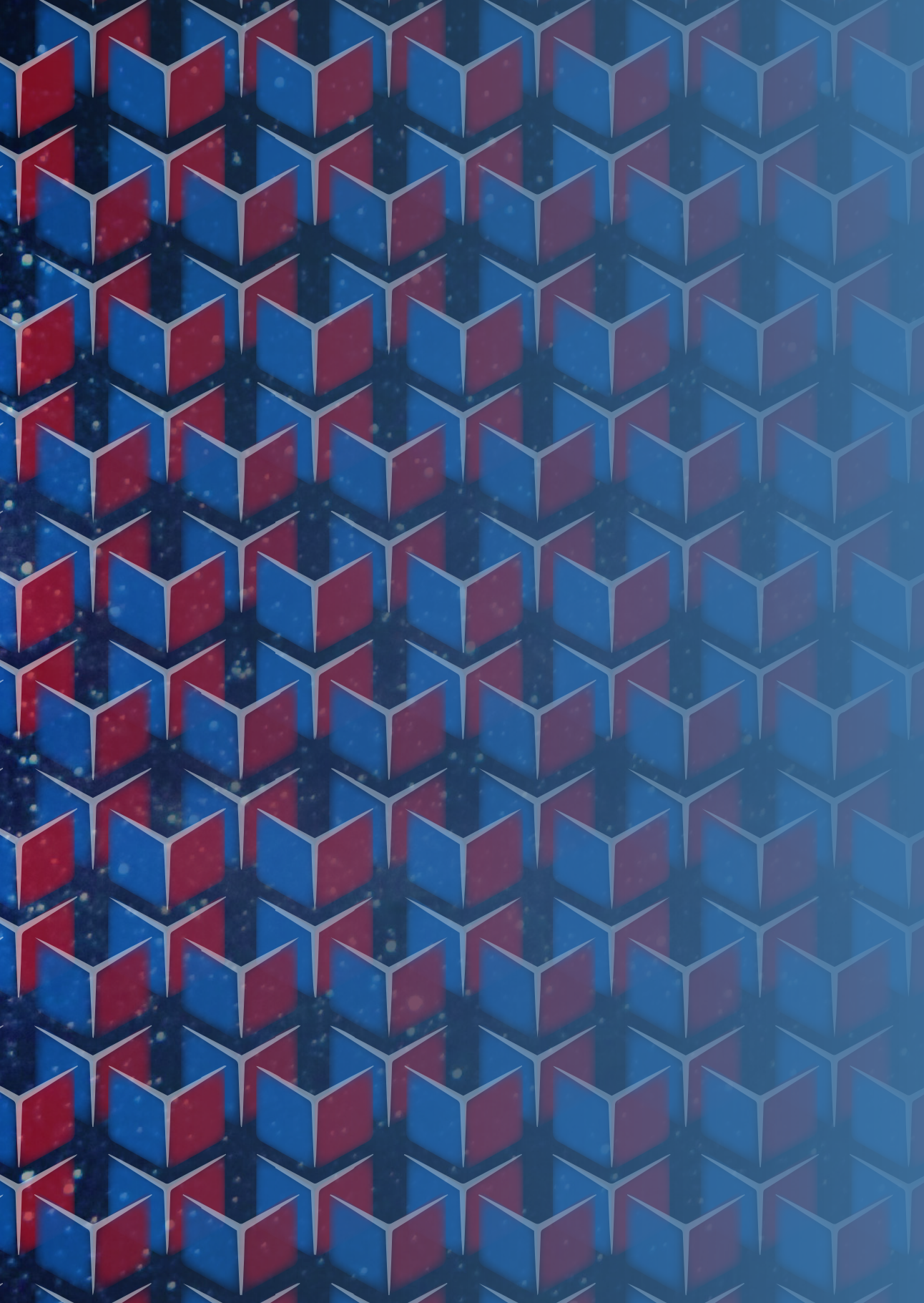
Therefore, the prevalence of oxygen desaturation in a healthy population (matched by age and sex) is not known.

Conclusion

Oxygen desaturation, when measured by this e-Health device, is a weak predictor of CSA in stable HF patients. The ODI, when measured by a validated device, might be a good predictor of sleep apnea of any aetiology in stable HF patients. This study also corroborated the high prevalence of sleep apnea in stable HF patients. Therefore, more research in screening for sleep apnea detection in stable HF patients is warranted, which might be possible by using validated overnight oximetry, but must be easy to perform in this kind of elderly patient group.

References

1. Block A, Border W, Bruce B, Christopher K, Drake R, Jangid A, et al. Dorland's Medical Dictionary. Saunders: Philadelphia, Pennsylvania, United States of America; 2011.
2. Aurora RN, Chowdhuri S, Ramar K, Bista SR, Casey KR, Lamm CI, et al. The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. Sleep. 2012;35(1):17-40.
3. Costanzo MR, Khayat R, Ponikowski P, Augostini R, Stellbrink C, Mianulli M, et al. Mechanisms and clinical consequences of untreated central sleep apnea in heart failure. J Am Coll Cardiol. 2015;65(1):72-84.
4. Javaheri S, Shukla R, Zeigler H, Wexler L. Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. J Am Coll Cardiol. 2007;49(20):2028-34.
5. Arzt M, Floras JS, Logan AG, Kimoff RJ, Series F, Morrison D, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). Circulation. 2007;115(25):3173-80.
6. iSpO2 Rx Pulse Oximeter 2014 (cited 2018 January 18th). Available from: http://www.masimo.com/siteassets/uk2/images/ispo2/lab8048a_sell_sheet_ispo2rx_british.pdf.
7. Huizing MJ, Villamor-Martinez E, Chavagne IA, Vanagt WY, Spaanderman MAE, Villamor E. Reliability and Validity of a Smartphone-Paired Pulse Oximeter for Screening of Critical Congenital Heart Defects in Newborns. Neonatology. 2017;112(4):324-9.
8. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European heart journal. 2016;37(27):2129-200.
9. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2012;8(5):597-619.
10. Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. European journal of heart failure. 2007;9(3):251-7.



CHAPTER 11

Summary and conclusions

The aim of this thesis was to investigate the use of smart technology in patients with cardiovascular disease. This thesis focuses on the various applications of telemonitoring. It does not only concentrate on clinical effectiveness, but also on patient satisfaction and cost-effectiveness. As e-Health is a relatively new concept, there is not much data available. The research described in this thesis is therefore mostly exploratory.

In the general introduction, **chapter 1,** it is explained that e-Health and smart technology are two poorly defined concepts. For the purpose of this thesis, two definitions are given to indicate the scope of this thesis. Furthermore, the scope of telemedicine is explained and an outline of the thesis is given.

Chapter 2 elaborates on the introduction and gives an overview of already existing technologies. Telemonitoring of implantable cardioverter defibrillators (ICDs) and telemonitoring with smart technology is described. Telemonitoring of ICDs in heart failure patients has been shown to decrease all-cause mortality and hospitalizations. Furthermore, lead fractures were sooner recognized. Lastly, total healthcare consumption was shown to decrease. There are however some safety concerns regarding the data of the ICD. In laboratory circumstances, a group from the University of Washington was able to hack an ICD and to adjust its settings. The data safety of the ICD should therefore be followed with concern. The second part of this review focused on the usage of smart technology. In contrast with ICDs, the clinical benefit of smart technology for telemonitoring has not been demonstrated. There are various applications available to measure ECG, blood pressure, weight and steps. However, these applications are poorly regulated, partly because they are often not considered to be medical devices. Research has shown that multiple apps lack a privacy policy, sell collected data to third parties and do not use encryption to protect data. In order for smart technology to succeed, these concerns need immediate attention.

The role of electronic medical records (EMRs) in the patient's journey is discussed in **chapter 3**. Current existing commonly used EMR systems suffer from a couple of shortcomings: first, they are very expensive. A cost calculation returned an astonishing €2.2 billion spending on EMRs in The Netherlands in 2016 alone. Second, these systems are very generic, which inhibits the input of accurate specialty specific information. Instead, the information should be made in the specific MAS-PAS system. This system is tailored to a patient's journey. Every specialty has its own, tailored, EMR. In case a patient is referred to a certain specialty, the EMR of that specialty (MAS) is opened. Simultaneously, a patient's part is opened (PAS). In

this part, all medical terms are represented as lay terms. In such a way, the patient is better informed and therefore empowered.

The rationale and design of a randomized controlled trial (RCT) in which smart technology is used in the follow-up of acute myocardial infarction (AMI) is described in **chapter 4.** Guidelines recommend a series of pharmaceutical and life style interventions to lower risk of major adverse cardiac events such as revascularization, recurrent AMI, stroke and cardiovascular mortality. Smart technology may be a low cost and clinically effective tool to help patients measure their own vital signs. By sending these data to the hospital, both doctor and patient have more insight in the patient's health. By better informing patients and doctors, shared decision making can be improved. This RCT includes patients that have been admitted for AMI (either with or without ST elevation) at the Cardiology Department of the Leiden University Medical Center. These patients are 1:1 randomized between The Box and regular follow-up. In regular follow-up, patients are followed up with four outpatient clinic visits and no monitoring in between. In The Box group, two outpatient clinic visits are replaced by an e-visit. Furthermore, patients use smart technology to send a single lead electrocardiogram (ECG), their blood pressure, their weight scale and their step count every day. These data are checked by a project dedicated PhD student. In case of possible abnormalities, the patient is contacted and therapeutic regimen can be adjusted if necessary. The sample size of this RCT is 200.

Chapter 5 gives the rationale and design of the MOBILE-AF trial. This RCT includes patients who have been admitted with cryptogenic stroke or TIA. Previous research showed that in approximately 30% of all stroke patients, no aetiology can be determined. These strokes are called cryptogenic. In approximately 1-2% of these patients, atrial fibrillation (AF) is found in the work-up, currently consisting of a 12-lead ECG and a 24-hour Holter monitor. Recent research of prolonged AF monitoring indicated that the AF burden may in fact be higher in this patient population. In the CRYSTAL-AF trial, in 12.4% of patients with prolonged monitoring, AF was detected. However, the device used in this trial is relatively expensive and brings in the risk of pocket infection. Therefore, there is a need for a less expensive and less invasive alternative. One device that is a good alternative may be the AliveCor. This device enables the patient to record a single lead ECG on their smartphone for 30-seconds. Via internet, this single lead ECG is sent to the hospital. In this trial, patients are randomized in a 1:1 fashion to either the single lead ECG device (intervention group) or to a 7-day Holter monitor (control group). When randomized to the intervention group, patients record a single lead ECG 2 times a day for one year. When randomized to the control group, patients wear one additional Holter

monitor for 7 days consecutively. Primary endpoint is the percentage of patients in which AF is detected after one year. The sample size of this RCT is 200.

In **chapter 6**, a study that compares four smartphone compatible blood pressure (BP) monitors is described. Several smartphone compatible BP monitors are validated and available for over-the-counter sale. So far, no study compared these four BP monitors. Therefore, in this study, 43 patients underwent 6 consecutive measurements with four smartphone compatible BP monitors, one oscillometric device and one handheld sphygmomanometer. Primary outcome was the difference in systolic BP between the handheld sphygmomanometer and the other 5 devices. All devices differed significantly, but were well within the accepted range of 5 mmHg, except for one monitor. This chapter showed that smartphone compatible BP monitors are generally well within the accepted range of 5 mmHg and can therefore be used for serial measurements.

In **chapter 7** tools that are used to improve medication adherence in patients with cardiovascular disease are summarized in a narrative review. Medication adherence is of crucial importance in the treatment of cardiovascular disease. Previous research has shown that cardiovascular mortality is significantly higher in patients who are non-adherent. It is the purpose of this review to give an overview of various technologies that are available to address medication adherence. PubMed was searched. The 74 articles that were included were divided into one of the following categories: mobile apps, smart pill boxes, short message service (SMS), telephone calls or web-based interventions. SMS was shown to be a good choice for short, simple reminders. Web-based interventions were shown to be effective for educational purposes. Moreover, their low cost makes them an appealing choice in addressing non-adherence. The evidence for smart pill boxes in the literature is limited and further research is needed there.

Chapter 8 focuses on the clinical value of serial ECG analysis to detect acute ischemia in patients with chest pain. So far, serial ECG analysis has been difficult to implement in practice, because it requires a baseline ECG of every patient. However, with smart technology, this might be possible in the nearby future. In this chapter, the sensitivity and specificity of serial analysis of the ST-segment and ventricular gradient was investigated. To determine sensitivity, a cohort of 84 patients with long balloon inflation times during elective percutaneous coronary intervention (PCI) was used. To determine specificity, a cohort of 398 clinically stable patients without acute myocardial ischemia was used. A ROC curve was drawn. Using a specificity of 89.1% (current STEMI specificity), STEMI criteria showed a sensitivity of 70.2%, ΔST showed a sensitivity of 78.6% and ΔVG showed a sensitivity of 71.4%. The

article therefore concluded that serial ECG analysis of ST-segments can significantly improve diagnosis of acute myocardial ischemia.

To select patients for future e-Health studies, clinical characteristics and emergency care utilization in grown-ups with congenital heart disease (GUCH) with proven interest in e-Health are described in **chapter 9**. Consecutive patients who visited the outpatient clinic were given an e-Health questionnaire. Afterwards, their clinical characteristics and number of visits to the emergency care department were noted. A frequency of three or more visits in 5 years was defined as high care utilization. Of all patients, 8% had a high emergency care utilization. These were predominantly symptomatic patients on anti-arrhythmic therapy or diuretics. In total, 75% of these patients were willing to start using e-Health.

Finally, **chapter 10** describes a screening study in stable heart failure (HF) patients. Previous research in large cohorts has shown that central sleep apnea (CSA) is prevalent (30-50%) in stable HF patients. CSA is associated with higher cardiovascular mortality in this population. Currently, CSA is diagnosed by a polygraph (PG). However, a PG is a burden to the patient and time consuming to analyse. It is therefore unsuitable as screenings method. There is a need for a more patient friendly alternative that is less time consuming. One alternative might be overnight oximetry using a smartphone compatible app. The results of overnight oximetry are sent to the hospital and can be analysed by a MATLAB algorithm. It was the purpose of this study to investigate if overnight oximetry could predict CSA in stable HF patients. A total of 26 patients underwent a PG and overnight oximetry simultaneously in one night. The oxygen desaturation index (the number of dips per hour) was compared to the result of the PG. Results confirmed that sleep apnea is prevalent in stable HF patients (33% CSA, 58% sleep apnea of any aetiology). The ODI, measured by the app, was a weak predictor of both CSA and sleep apnea. However, the ODI, when measured by the PG, was a strong predictor of CSA. This chapter indicates that more research is necessary to make screening in stable HF patients possible.

Conclusions and future perspectives

E-Health is a relatively new concept in the medical field. In theory, e-Health could improve clinical effectiveness, improve patient satisfaction, lower costs of healthcare. Very importantly, it could contribute to the delivery of healthcare in areas where doctors are scarce (remote areas and low-income countries). However, so far, scientific evidence for e-Health is limited.

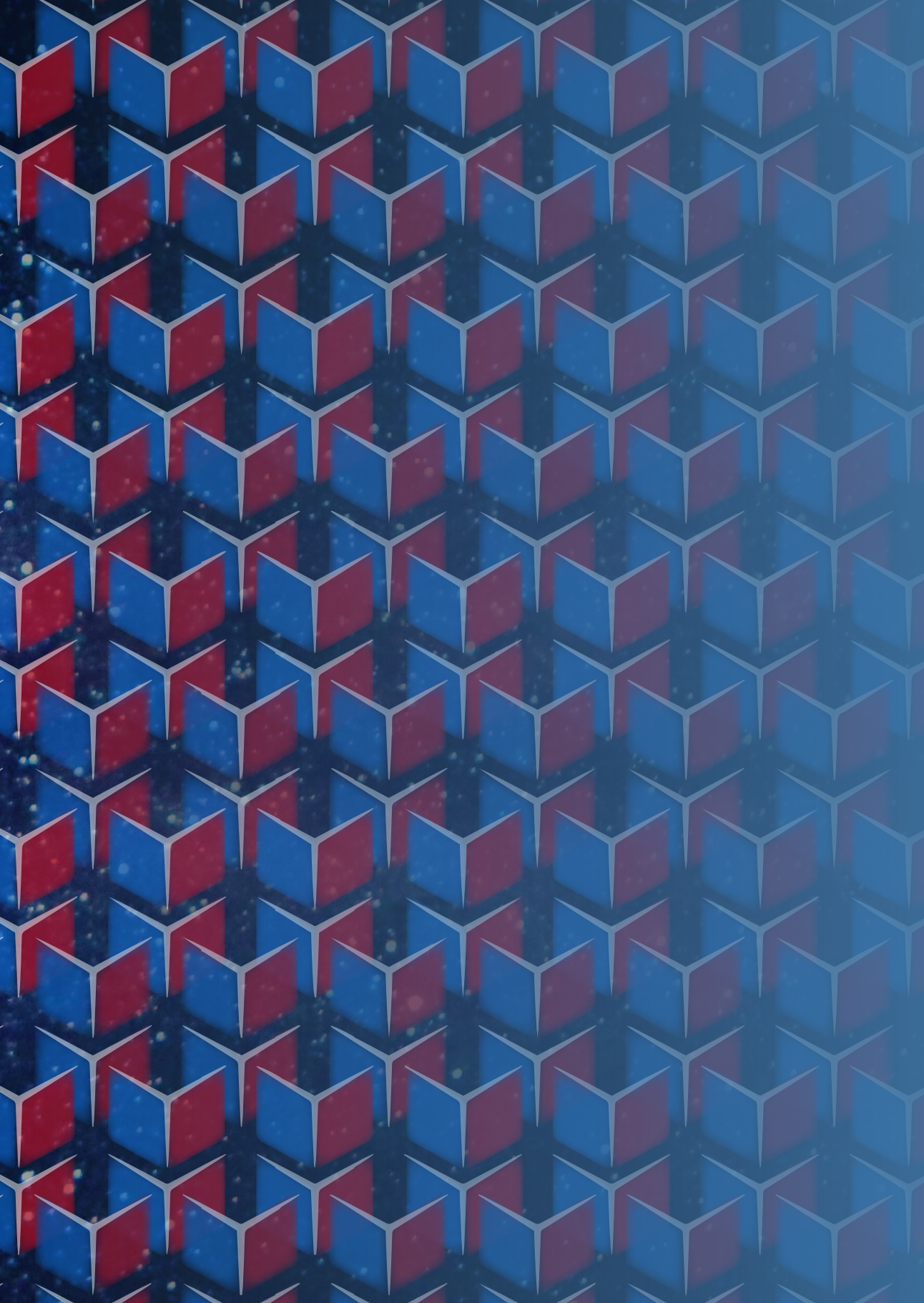
In this thesis, the rationale and design for two randomized controlled trials were described. The Box investigates the use of smart technology in patients who are followed-up after acute myocardial infarction (AMI). The last patient was included on November 9th, 2017. Therefore, final results will be available in November 2018. It is the hypothesis of the authors that patient satisfaction will increase. It is furthermore expected that by actively involving patients in their own rehabilitation, adherence to therapeutic regimen will improve.

The other trial of which the rationale and design is described is the MOBILE-AF trial. It is the hypothesis of the authors that the AliveCor will be a more effective and more patient friendly alternative to the Holter monitor. It is acknowledged that the AliveCor has not been compared with the Reveal LINQ. However, the Reveal LINQ is not recommended as standard by clinical guidelines. In case it becomes so, the Reveal LINQ could be compared to the AliveCor in a future trial. The authors also acknowledge that cumulative evidence contradicts the causal relationship between AF and cryptogenic stroke. The ATTICUS trial, in which patients are randomized to a NOAC or regular treatment, regardless of AF detection, is recognized by the authors and its results are followed with caution.

One might argue that the future of e-Health is even more interesting than its past or present.
The invention of the iPhone has hugely influenced the field of e-Health and was indispensable in generating the field of mobile health. In the past 10 years, mobile technology has been rapidly adopted. Mobile phones have become faster, percentage of the Dutch population that uses internet has increased and companies have started to use social media as an important way of communicating with their customers. In the upcoming years, it is expected that existing technologies (smartphones, internet) will be improved. Secondly, it is expected that new ICT (such as the internet of things and block chain) will have a major influence on e-Health.
The implementation of these technologies will also be one of the challenges of implementing e-Health. There is a huge discrepancy between the implementation time in information and communication technology (ICT) and the implementation time in medicine. Technologies in ICT that were invented 5 years ago are generally considered old. In medicine, it takes on average more than 10 years to bring a drug to the market. This is mostly because of the rigorous evidence that needs to be generated for a drug to be approved. Therefore, the authors believe that future research should not depend on a single technology. Instead, research should focus on a clinical problem for which a smartphone compatible technology changes the way that problem is approached. That way, the results of a trial will still be valid if the technology is further improved.

Another challenge that needs to be addressed is the digital literacy of the current population with cardiovascular disease. In chapter 9, it was shown that 50% of all patients was not able to perform (a very simple) task on the smartphone. This is a very specific form of non-adherence that should be addressed if smart technology becomes part of clinical practice. First, e-Health innovations should be made simple. Second, it should be taken into account that most e-Health applications will be used by an elderly population. Therefore, concordant visual and audial adjustments (larger buttons, louder instructions) should be made in the applications.

E-Health is a promising concept that may improve the way healthcare is delivered. In 15 years, the current state of e-Health could be known as the first stone of the bridge that was built to connect home and healthcare.



CHAPTER 12

Samenvatting en conclusies

Het doel van dit proefschrift was om het gebruik van smart technology bij patiënten met hart-, en vaatziekten te onderzoeken. Dit proefschrift concentreert zich op de verschillende gebruiksmogelijkheden van telemonitoring. Het concentreert zich niet alleen op klinische effectiviteit, maar ook op patiënttevredenheid en kosteneffectiviteit. Doordat e-Health een relatief nieuw begrip is, was er niet veel data beschikbaar. Het onderzoek in dit proefschrift beschreven is daarom vooral ontdekkend van aard.

In de algemene introductie, **hoofdstuk 1,** wordt uitgelegd dat e-Health en smart technology twee slecht gedefinieerde begrippen zijn. Voor dit proefschrift worden twee definities gegeven om een indicatie te geven van de strekking van dit proefschrift. Tevens wordt de strekking van telegeneeskunde uitgelegd en wordt een schets van dit proefschrift gegeven.

Hoofdstuk 2 borduurt voort op de introductie en geeft een overzicht van reeds bestaande technologieën. Telemonitoring van implanteerbare cardioverter defibrillatoren (ICDs) en telemonitoring met smart technology worden beschreven. Het is aangetoond dat telemonitoring met ICDS in patiënten met hartfalen de mortaliteit verlaagt en ziekenhuisopnamen vermindert. Tevens werden draadbreuken eerder herkend. Tot slot is aangetoond dat het algehele zorggebruik minder was. Er zijn echter wat zorgen over de data veiligheid van de ICD. In laboratorium omstandigheden bleek een onderzoeksgroep van de Universiteit van Washington in staat om een ICD te hacken en haar instellingen aan te passen. De dataveiligheid van de ICD moet daarom nauwlettend in de gaten worden gehouden. Het tweede gedeelte van deze review concentreerde zich op het gebruik van smart technology. In tegenstelling tot ICDs, is de klinische meerwaarde van smart technology van telemonitoring nog niet aangetoond. Er zijn verschillende applicaties beschikbaar om ECG, bloeddruk, gewicht en stappen te meten. Echter, deze applicaties zijn minder goed gereguleerd, gedeeltelijk doordat ze vaak niet als medische apparatuur worden gezien. Onderzoek heeft uitgewezen dat veel apps geen privacy policy hebben, eigenaren van apps de verzamelde data verkopen aan derden en dat apps geen encryptie gebruiken om data te beveiligen. Om smart technology te laten slagen, is het belangrijk dat deze bedenkingen onmiddellijke aandacht krijgen.

De rol van elektronische patiëntendossiers (EPDs) in de Patient's Journey wordt besproken in **hoofdstuk 3**. De momenteel bestaande veelgebruikte EPDs hebben een paar tekortkomingen: ten eerste zijn ze zeer duur. Een kostenberekening liet zien dat per jaar ongeveer 2.2 miljard euro wordt uitgegeven aan EPDs in Nederland in 2016. Ten tweede zijn de systemen zeer generiek, waardoor accurate, specialistische

informatie niet goed opgeslagen kan worden. In plaats daarvan zou de informatie ingevoerd moeten worden in het MAS-PAS systeem. Dit systeem is aangepast aan de Patient's Journey. Elk specialisme heeft haar eigen, op maat gemaakte EPD. Als een patiënt wordt verwezen naar een bepaald specialisme, wordt het EPD van dit specialisme (MAS) geopend. Tegelijkertijd wordt een patiëntgedeelte geopend (PAS). In dit gedeelte worden alle medische termen weergegeven in leken termen. Op deze manier is een patiënt beter geïnformeerd en daarom "empowered".

De motivering en het ontwerp van een gerandomiseerde gecontroleerde studie (RCT) waarin smart technology wordt gebruikt in de follow-up van patiënten met een acuut hartinfarct (AHI) wordt beschreven in **hoofdstuk 4**. Richtlijnen bevelen een aantal farmaceutische en levensstijl interventies aan om het risico op belangrijke ongunstige cardiale gebeurtenissen zoals revascularisatie, een terugkerend AHI, een herseninfarct of cardiovasculaire sterfte te verlagen. Smart technology kan een goedkoop en klinische effectief hulpmiddel zijn om patiënten te helpen hun eigen vitale parameters te laten meten. Als deze data naar het ziekenhuis wordt verstuurd, kunnen zowel dokter en patiënt meer inzicht krijgen in de gezondheid van de patiënt. Als artsen en patiënten beter geïnformeerd zijn, kan dit gedeelte beslisvorming verbeteren. Deze RCT includeert patiënten die zijn opgenomen met een AHI (zowel met als zonder ST elevatie) op de afdeling cardiologie van het Leids Universitair Medisch Centrum. Deze patiënten worden 1:1 gerandomiseerd tussen The Box en reguliere controle. Bij reguliere controle worden patiënten gevolgd met vier polibezoeken zonder telemonitoring tussendoor. In The Box groep worden twee polibezoeken vervangen door een digitaal bezoek. Tevens gebruiken patiënten slimme technologie om een één-afleiding elektrocardiogram (ECG), een bloeddruk, een gewicht en het aantal stappen dagelijks door te sturen. Deze data worden nagekeken door een PhD Student. Als er mogelijke afwijkingen worden gezien, wordt er contact opgenomen met de patiënt en wordt de therapie aangepast als dit nodig is. De steekproefgrootte van deze RCT is 200.

Hoofdstuk 5 geeft de motivering en het ontwerp van het MOBILE-AF onderzoek. Deze RCT includeert patiënten die opgenomen zijn geweest voor een cryptogeen herseninfarct of TIA. Eerder onderzoek liet zien dat in ongeveer 30% van alle herseninfarct patiënten geen oorzaak kon worden aangetoond. Deze herseninfarcten worden cryptogeen genoemd. Bij ongeveer 1-2% van deze patiënten wordt atriumfibrilleren gevonden in de evaluatie, momenteel bestaande uit een 12-afleidingen ECG en een 24-uurs Holter. Recent onderzoek met langer AF monitoring liet zien dat de incidentie van AF hoger kan zijn in deze populatie. In het CRYSTAL-AF onderzoek werd in 12.4% van de patiënten met langere AF monitoring AF aangetoond. Echter, het apparaat dat gebruikt werd in dit onderzoek

is relatief duur en geeft een risico op pocket infectie. Daarom is er behoefte aan een goedkoper en minder invasief alternatief. Een apparaat dat een goed alternatief kan zijn, is de AliveCor. Met dit apparaat kunnen patiënten een één-afleiding ECG maken op hun smartphone gedurende 30 seconden. Via internet kan dit één-afleiding ECG doorgestuurd worden naar het ziekenhuis. In dit onderzoek worden patiënten 1:1 gerandomiseerd naar dit één-afleiding apparaat (interventiegroep) of naar een 7-daagse Holter (controle groep). Als patiënten naar de interventiegroep gerandomiseerd zijn, nemen zij twee keer per dag, gedurende een jaar, een één-afleiding ECG op. Als patiënten naar de controlegroep gerandomiseerd zijn, dragen ze één extra 7-daagse Holter monitor. Het primaire eindpunt is het percentage van patiënten waarin AF is gedetecteerd na één jaar. De steekproefgrootte van deze RCT is 200.

In **hoofdstuk 6** wordt een studie beschreven die een vergelijking tussen vier smartphone compatibele bloeddrukmeters beschrijft. Verschillende smartphone compatibele bloeddrukmeters zijn gevalideerd en zijn beschikbaar voor over-the-counter verkoop. Tot dusver heeft nog geen studie deze vier bloeddrukmeters vergeleken. Daarom ondergingen in deze studie 43 patiënten 6 opeenvolgende metingen met vier smartphone compatibele bloeddrukmeters, één oscillometrisch apparaat en één sfygmomanometer. De primaire uitkomst was het verschil in systolische bloeddruk tussen de sfygmomanometer en de andere vijf apparaten. Alle apparaten verschilden significant, maar waren binnen het geaccepteerde verschil van 5 mmHg, behalve één meter. Dit hoofdstuk liet zien dat smartphone compatibele bloeddrukmeters binnen het geaccepteerde verschil van 5 mmHg vielen en daarom gebruikt kunnen worden voor seriële analyse.

In **hoofdstuk 7** worden hulpmiddelen, die worden gebruikt om medicatietrouw bij patiënten met cardiovasculaire ziekten te verhogen, samengevat. Medicatietrouw is van cruciaal belang bij het behandelen van cardiovasculaire ziekten. Eerder onderzoek heeft uitgewezen dat cardiovasculaire sterfte significant hoger is bij patiënten die medicatie ontrouw zijn. Het is het doel van deze review om een overzicht te geven van de verschillende technologieën die beschikbaar zijn voor het verhogen van medicatietrouw. Hiervoor werd PubMed doorzocht. De 74 artikelen die werden geïncludeerd werden onderverdeeld in één van de volgende categorieën: mobiele applicaties, smart pill boxes, short message service, telefoongesprekken of interventies via het World Wide Web. SMS bleek goed voor korte, simpele herinneringen. Interventies via het World Wide Web bleken effectief voor educatieve doeleinden. Verder maakte vooral de lage kosten hen een aantrekkelijke keuze bij het verhelpen van medicatie ontrouw. Het bewijs voor smart pill boxes in de literatuur is beperkt en verder onderzoek is daarvoor nodig.

Hoofdstuk 8 focust zich op de klinische waarde van seriële ECG analyse om acute ischemie te detecteren bij patiënten met pijn op de borst. Tot dusver is het moeilijk geweest om seriële ECG analyse in de praktijk te implementeren, omdat daar een baseline ECG van elke patiënt voor nodig is. Echter, met smart technology zou dit mogelijk kunnen zijn in de nabije toekomst. In dit hoofdstuk wordt de sensitiviteit en specificiteit van seriële analyse van het ST-segment en de ventriculaire gradiënt onderzocht. Om sensitiviteit te bepalen, werd een cohort van 84 patiënten met lange ballon opblaastijden tijdens een electieve percutane coronaire interventie gebruikt. Om specificiteit te bepalen, werd een cohort van 398 klinisch stabiele patiënten zonder acute ischemie gebruikt. Een ROC curve werd getekend. Bij een specificiteit van 89.1% (de specificiteit van de huidige STEMI criteria), lieten de STEMI criteria een specificiteit van 70.2%, DST een sensitiviteit van 78.6% en DVG een sensitiviteit van 71.4% zien. In het hoofdstuk werd geconcludeerd dat seriële ECG analyse van ST-segmenten de diagnose van acute ischemie significant kan verbeteren.

Om patiënten te selecteren voor toekomstige e-Health studies, worden de klinische karakteristieken en spoedeisende hulp gebruik van volwassenen met congenitale hartziekten met een bewezen interesse in e-Health beschreven in **hoofdstuk 9**. Opeenvolgende patiënten die de polikliniek bezochten kregen een e-Health vragenlijst. Daarna werden hun klinische karakteristieken en aantal bezoeken aan de spoedeisende hulp genoteerd. Een frequentie van drie of meer bezoeken binnen vijf jaar werd gezien als hoog spoedeisende hulp gebruik. Van alle patiënten had 8% een hoog spoedeisende hulp gebruik. Dit waren voornamelijk symptomatische patiënten die antiarrhythmica of diuretica gebruikten. In totaal wilde 75% van deze patiënten e-Health gaan gebruiken.

Tot slot beschrijft **hoofdstuk 10** een screening studie bij patiënten met stabiel hartfalen (HF). Eerder onderzoek in grote cohorten heeft laten zien dat centraal slaapapneu (CSA) prevalent is (30-50%) bij patiënten met stabiel hartfalen. CSA is geassocieerd met een hogere cardiovasculaire mortaliteit in deze populatie. Op dit moment wordt CSA gediagnosticeerd met een polygraaf (PG). Echter, een PG is een belasting voor de patiënt en tijdrovend om te analyseren. Het is daarom ongeschikt als screening methode. Er is daarom behoefte aan een patiëntvriendelijkere methode die minder tijd kost. Nachtelijke saturatiemetingen kunnen een alternatief zijn waarbij een smartphone compatibele app wordt gebruikt. De resultaten van de nachtelijke saturatiemetingen worden naar het ziekenhuis gestuurd en kunnen worden geanalyseerd door een MATLAB algoritme. Het was het doel van deze studie om te onderzoeken of nachtelijke saturatiemetingen CSA konden voorspellen bij patiënten met stabiel HF. In totaal ondergingen 26 patiënten een PG en nachtelijke saturatiemetingen tegelijkertijd in één nacht. De zuurstof desaturatie index (het

aantal dips per uur) werd vergeleken met het resultaat van de PG. De resultaten bevestigden dat slaapapneu prevalent is bij patiënten met stabiel hartfalen (33% CSA, 58% slaapapneu van elke etiologie). De ODI, gemeten door de app, was een zwakke voorspeller van zowel CSA als slaapapneu. Echter, de ODI, gemeten door de PG, was een sterke voorspeller van CSA. Dit hoofdstuk duidt erop dat meer onderzoek nodig is om screening bij patiënten met stabiel HF mogelijk te maken.

Conclusies en toekomstperspectieven

E-Health is een relatief nieuw concept in de geneeskunde. In theorie zou e-Health klinische effectiviteit en patiënttevredenheid kunnen verbeteren tegen lagere kosten. Het zou tevens kunnen bijdragen aan het leveren van gezondheidszorg in gebieden waar dokters schaars zijn (afgelegen gebieden en lage-inkomens landen). Echter, tot dusver is het wetenschappelijk bewijs voor deze claims beperkt.

In dit proefschrift werd de motivering en het ontwerp van twee gerandomiseerde studies beschreven. The Box onderzoekt het gebruik van smart technology bij patiënten die gevolgd worden voor een acuut hartinfarct (AHI). De laatste patiënt werd geïncludeerd op 9 november 2017. De resultaten zijn daarom beschikbaar in november 2018. Het is de hypothese van de auteurs dat de patiënttevredenheid omhoog gaat. Tevens wordt verwacht dat door patiënten actief te betrekken bij hun eigen herstel, zij de behandeladviezen strikter zullen naleven.

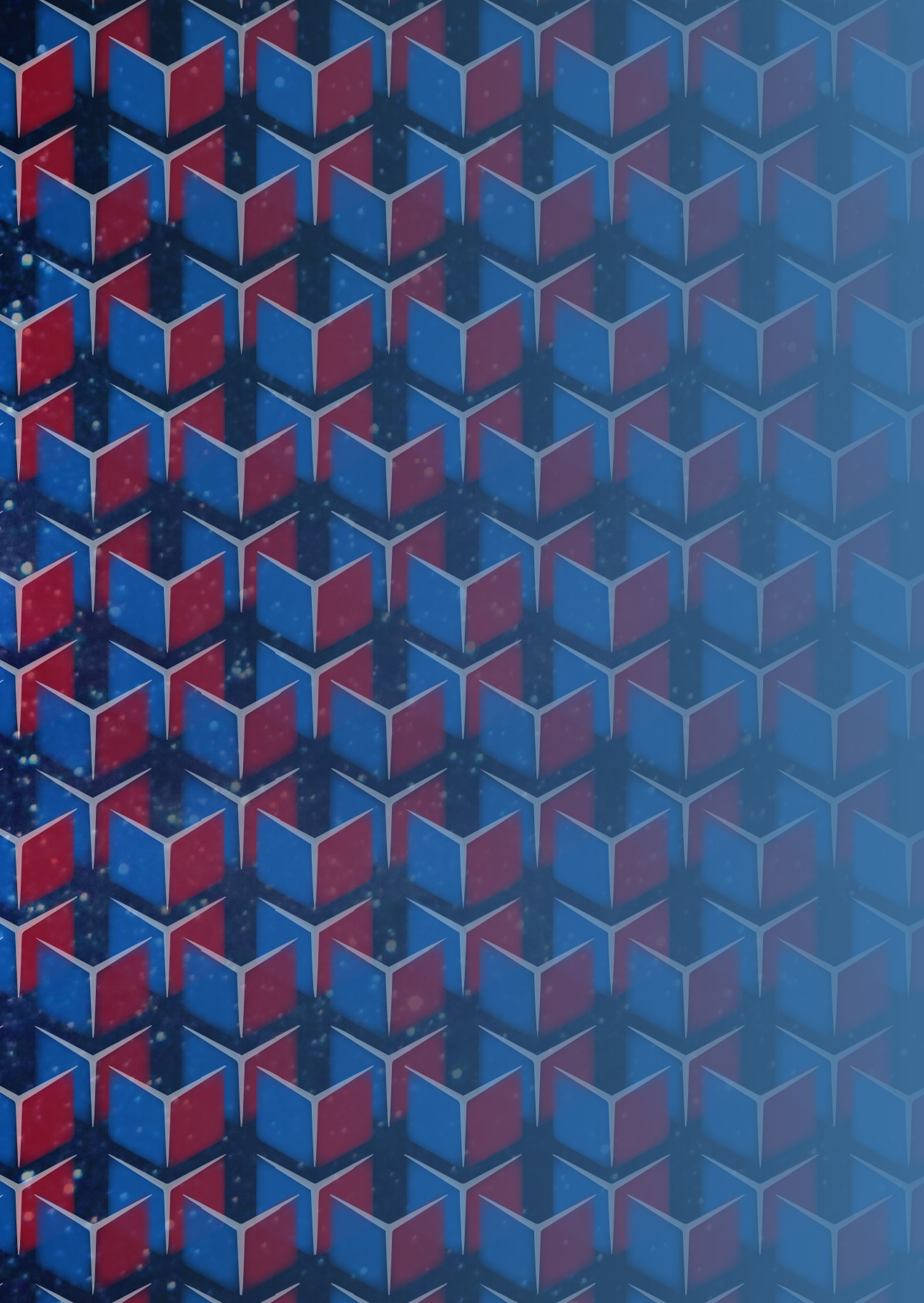
Het andere onderzoek waarvan de motivering en het ontwerp werden beschreven is de MOBILE-AF trial. Het is de hypothese dat de AliveCor een effectiever en patiëntvriendelijker alternatief is voor de Holter. Het wordt erkend dat de AliveCor niet vergeleken is met de Reveal LINQ. Echter, de Reveal LINQ is op dit moment niet de standaard volgens de richtlijnen. Als het dat wel wordt, kan de Reveal LINQ vergeleken worden met de AliveCor in een toekomstig onderzoek. De auteurs erkennen ook dat steeds meer bewijs de causale relatie tussen AF en een herseninfarct tegenspreekt. De ATTICUS trial, waarin patiënten worden gerandomiseerd tussen een NOAC of een reguliere behandeling, ongeacht de detectie van AF, wordt erkend door de auteurs en de resultaten worden nauwlettend in de gaten gehouden.

Men zou kunnen beargumenteren dat de toekomst van e-Health misschien wel interessanter is dan haar verleden of het heden. De presentatie van de iPhone heeft een grote invloed gehad op e-Health en was onmisbaar bij het creëren van mobile health. In de laatste tien jaar is mobiele technologie onderdeel van het alledaagse leven geworden. Mobiele telefoons zijn sneller geworden, het percentage van de Nederlanders dat internet gebruikt is toegenomen en bedrijven zijn sociale media gaan gebruiken als een belangrijk kanaal om met hun klanten te communiceren. In de

komende jaren is de verwachting dat deze bestaande technologieën (smartphone, internet) worden verbeterd. Daarnaast is de verwachting dat nieuwe ICT (zoals het Internet of Things en Blockchain) een grote invloed hebben op e-Health. Het implementeren van deze technologieën zal dan ook een grote uitdaging worden bij het implementeren van e-Health. Er is een groot verschil in de tijd die het duurt om nieuwe ICT te implementeren en de tijd die het duurt om medische technologie te implementeren. Technologieën in de ICT die vijf jaar geleden zijn uitgevonden worden over het algemeen als oud gezien. In de geneeskunde duurt het echter gemiddeld meer dan 10 jaar om een nieuw medicijn naar de markt te brengen. Dit komt voornamelijk door het bewijs dat gegenereerd moet worden voordat een medicijn goedgekeurd wordt. De auteurs geloven daarom dat onderzoek zich niet moet concentreren op één technologie. In plaats daarvan moet onderzoek zich concentreren op een klinisch probleem waarbij een smartphone compatibele technologie de manier waarop het probleem benaderd wordt, verandert. Op die manier blijven de resultaten van een onderzoek valide als de technologie veranderd wordt.

Een andere uitdaging die aangesproken moet worden is de digitale geletterdheid van de huidige populatie met cardiovasculaire ziekten. In hoofdstuk 9 werd aangetoond dat 50% van alle patiënten niet in staat was een simpele handeling op de smartphone uit te voeren. Dit is een hele specifieke vorm van therapieontrouw die aangesproken moet worden als smart technology onderdeel wordt van de klinische praktijk. Ten eerste moeten e-Health innovaties simpel worden gemaakt. Ten tweede moet rekening gehouden worden met dat de meeste e-Health applicaties zullen worden gebruikt door ouderen. Daarom moeten overeenkomende audiovisuele aanpassingen (grotere knoppen, luidere instructies) worden gedaan in de applicaties.

E-Health is een veelbelovend concept dat de manier waarop gezondheidszorg geleverd wordt kan verbeteren. Over 15 jaar zou de huidige status van e-Health bekend kunnen staan als de eerste steen van de brug die gebouwd werd om huis en gezondheidszorg te verbinden.



List of abbreviations
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Dankwoord
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List of abbreviations

ABP	atrial premature beat
ACE	angiotensin converting enzyme
ACO	acute coronary occlusion
AF	atrial fibrillation
AMI	acute myocardial infarction
AUC	area under the curve
OS	operating system
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CIS	cardiology information system
CDC	Center for Disease Control and Prevention
CE	Conformité Européenne
CT	computed tomography
CTA	computed tomography angiography
GUCH	grown-up with congenital heart disease
CHD	congenital heart disease
CPAP	continuous positive airway pressure
CSA	central sleep apnea
CVD	cardiovascular disease
DBP	diastolic blood pressure
ECG	electrocardiogram
ECV	electrical cardioversions
ECOST	Effectiveness and Costs of ICD follow-up schedule with telecardiology
EU	European Union
EMR	electronic medical record
FDA	Food and Drug Administration
GP	general practitioner
HbA1c	hemoglobin A1c
HF	heart failure
HR	heart rate
HIS	hospital information system
ICM	implantable cardiac monitor
ICD	implantable cardioverter-defibrillator
ICT	information and communication technology
IDCO	implantable device cardiac observation
IEEE	The Institute of Electrical and Electronics Engineers
IHE	Integrating the Healthcare Enterprise

IVR	interactive voice recording
LEADS	Leiden ECG Analysis and Decomposition Software
LUMC	Leiden University Medical Center
MACE	major adverse cardiac events
MAS	medical application store
mHealth	mobile health
MI	myocardial infarction
MOBILE-AF	Mobile phones in cryptogenic Stroke patients Bringing sIngle Lead ECGs for Atrial Fibrillation
NOAC	non-vitamin K oral anticoagulant
NP	nurse practitioner
NST-ACS	non ST acute coronary syndrome
OAC	oral anticoagulation therapy
ODI	oxygen desaturation index
OSA	obstructive sleep apnea
PAS	patients application store
PC	personal computer
PCI	percutaneous coronary intervention
PG	polygraph
PHCR	personal healthcare record
PICOs	patients-interventions-comparison-outcomes
PSG	polysomnography
PVC	premature ventricular contractions
QALY	quality adjusted life year
RCT	randomized clinical trial
RM	remote monitoring
RR	risk ratio
SBP	systolic blood pressure
SEE	standard errors of the estimate
SET	safe, effective and transparent
SMS	short message service
StAR	Mobile Phone Text Messages to Support Treatment Adherence in Adults With High Blood Pressure
STEMI	ST elevation myocardial infarction
STSC	screen-to-screen contacts
TIA	transient ischaemic attack
TTE	transthoracic echocardiogram
USA	United States of America
VCG	vectorcardiogram
VG	ventricular gradient

WHO	World Health Organization

Dutch abbreviations

AHI	acuut hartinfarct
EPD	elektronisch patiëntendossier
RVZ	Raad voor Volksgezondheid en Zorg

List of publications

Treskes RW, Van der Velde ET, Schoones JW, Schalij MJ. Implementation of smart technology to improve medication adherence in patients with cardiovascular disease: is it effective? Expert Rev Med Devices. 2018 Feb;15(2):119-126.

Treskes RW, van Winden LA, van Keulen N, Atsma DE, van der Velde ET, van den Akker-van Marle E, Mertens B, Schalij MJ. Using Smart Technology to Improve Outcomes in Myocardial Infarction Patients: Rationale and Design of a Protocol for a Randomized Controlled Trial, The Box. JMIR Res Protoc. 2017 Sep 22;6(9):e186.

Treskes RW, Gielen W, Wermer MJ, Grauss RW, van Alem AP, Dehnavi RA, Kirchhof CJ, van der Velde ET, Maan AC, Wolterbeek R, Overbeek OM, Schalij MJ, Trines SA. Mobile phones in cryptogenic strOke patients Bringing sIngle Lead ECGs for Atrial Fibrillation detection (MOBILE-AF): study protocol for a randomised controlled trial. Trials. 2017 Aug 29;18(1):402.

Treskes RW, Wolterbeek R, van der Velde ET, Eindhoven DC, Schalij MJ. Comparison of the diagnostic accuracy of four smartphone-compatible blood pressure monitors in post-myocardial infarction patients. J Telemed Telecare. 2017 Jan 1:1357633X17704092.

Treskes RW, van der Velde ET, Barendse R, Bruining N. Mobile health in cardiology: a review of currently available medical apps and equipment for remote monitoring. Expert Rev Med Devices. 2016 Sep;13(9):823-30.

Treskes RW, Van Der Velde ET, Atsma DE, Schalij MJ. Redesigning healthcare: The 2.4 billion euro question? : Connecting smart technology to improve outcome of patients. Neth Heart J. 2016 Jul;24(7-8):441-6. doi: 10.1007/s12471-016-0834-6. Review.

Couperus LE, Vliegen HW, Henkens IR, Maan AC, **Treskes RW**, de Vries JK, Schouffoer AA, Swenne CA, Schalij MJ, Scherptong RW. Electrocardiographic detection of pulmonary hypertension in patients with systemic sclerosis using the ventricular gradient. J Electrocardiol. 2016 Jan-Feb;49(1):60-8.

De Jongh MC, Ter Haar CC, Man S, **Treskes RW**, Maan AC, Schalij MJ, Swenne CA. Intra-individual ECG changes over 25 years: How long can elective ECGs be used as reference for acute ischemia detection? J Electrocardiol. 2015 Jul-Aug;48(4):490-7.

Treskes RW, Ter Haar CC, Man S, De Jongh MC, Maan AC, Wolterbeek R, Schalij MJ, Wagner GS, Swenne CA. Performance of ST and ventricular gradient difference vectors in electrocardiographic detection of acute myocardial ischemia. J Electrocardiol. 2015 Jul-Aug;48(4):498-504.

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Curriculum Vitae

Roderick Willem Treskes werd geboren op 28 september 1993 te Alkmaar. In 2011 haalde hij zijn gymnasiumdiploma aan het Murmelliusgymnasium te Alkmaar. Van 2011 tot en met 2014 studeerde hij geneeskunde aan de Universiteit Leiden, alwaar hij in 2014 zijn bachelordiploma behaalde. Zijn studie combineerde hij met het Honours College, waarvoor hij in 2014 zijn honoursdiploma behaalde. Tijdens zijn bachelor werkte hij als Holteranalist en gaf hij onderwijs in de pathofysiologie van cardiovasculaire ziektebeelden. In 2015 begon hij aan zijn promotieonderzoek op de afdeling Cardiologie van het Leids Universitair Medisch Centrum onder leiding van professor doctor Martin-Jan Schalij, met als onderwerp de inzet van smarttechnologie bij patiënten met hart- en vaatziekten. De resultaten van dit onderzoek staan in dit proefschrift beschreven. Zijn promotie combineerde hij met een master gezondheidseconomie aan de London School of Economics and Political Science. In januari 2018 hervatte hij zijn studie geneeskunde, die hij combineert met een voortzetting van het in dit proefschrift beschreven onderzoek, waarna hij zal starten met de opleiding tot cardioloog vanuit het Leids Universitair Medisch Centrum (opleider: professor doctor M.J. Schalij).