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

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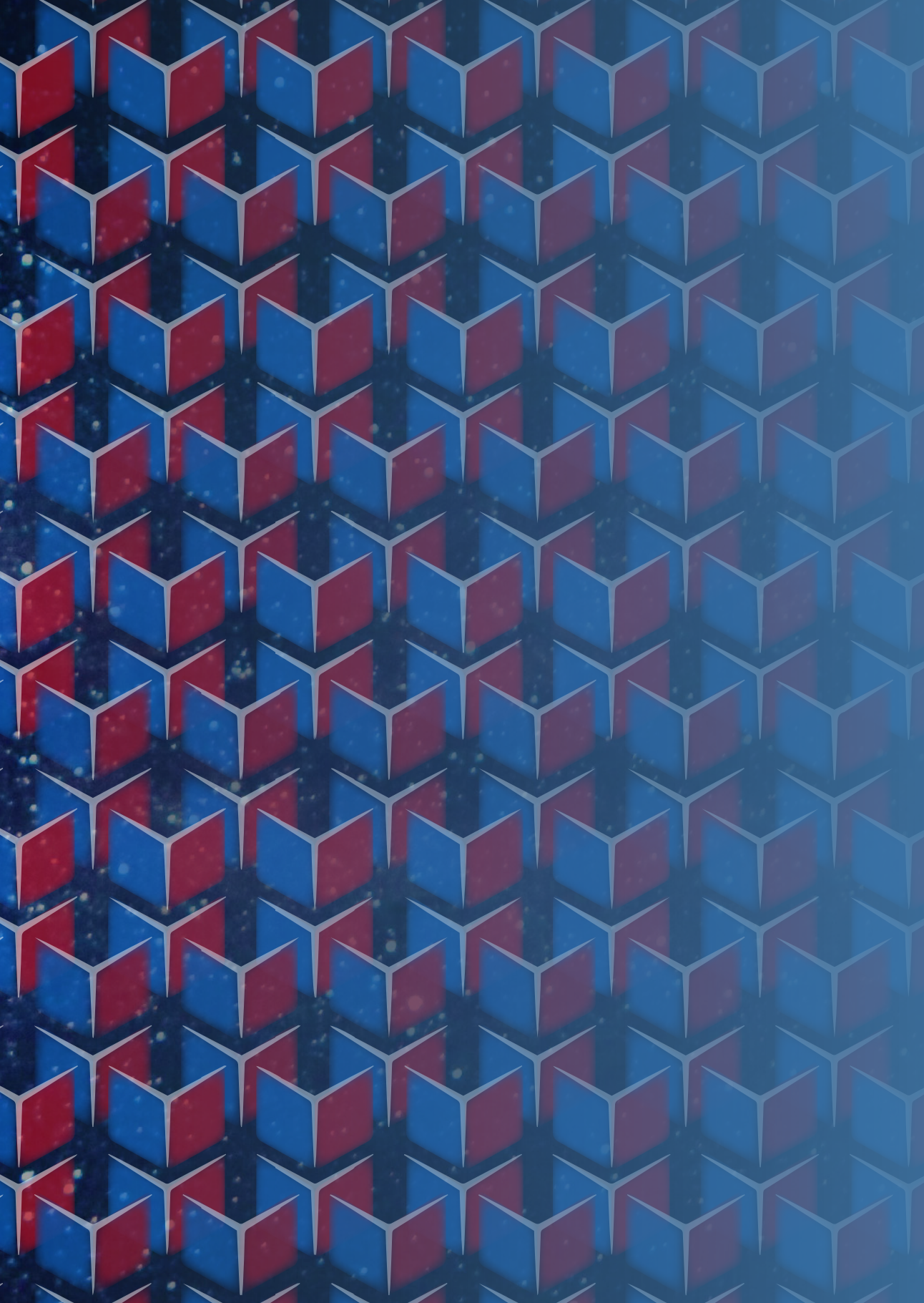


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Chapter 2

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

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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)

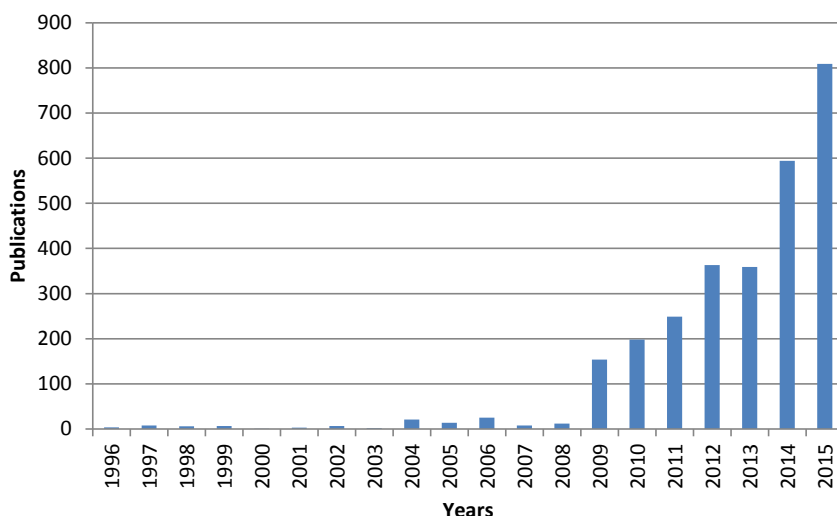


Figure 1. PubMed hits for “mHealth” or “m-Health”.

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

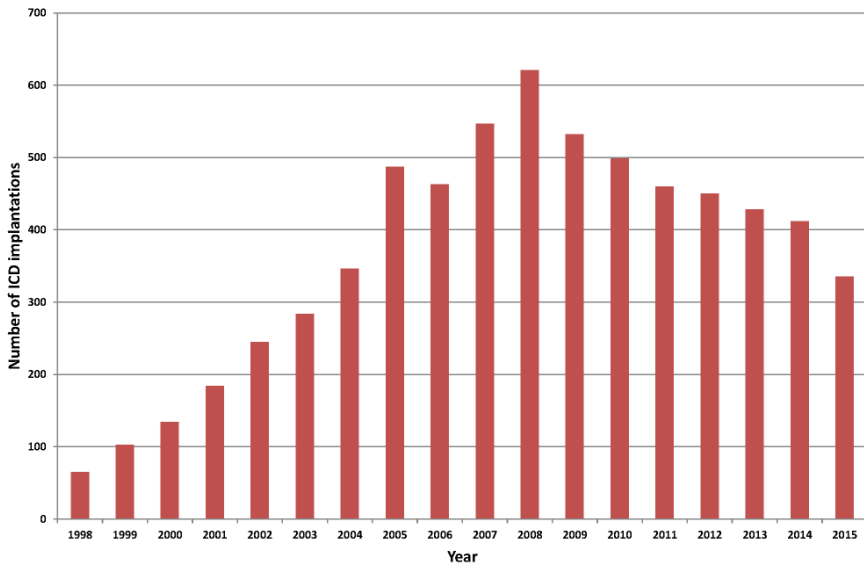


Figure 2. Number of ICD implantations in the Leiden University Medical Center.

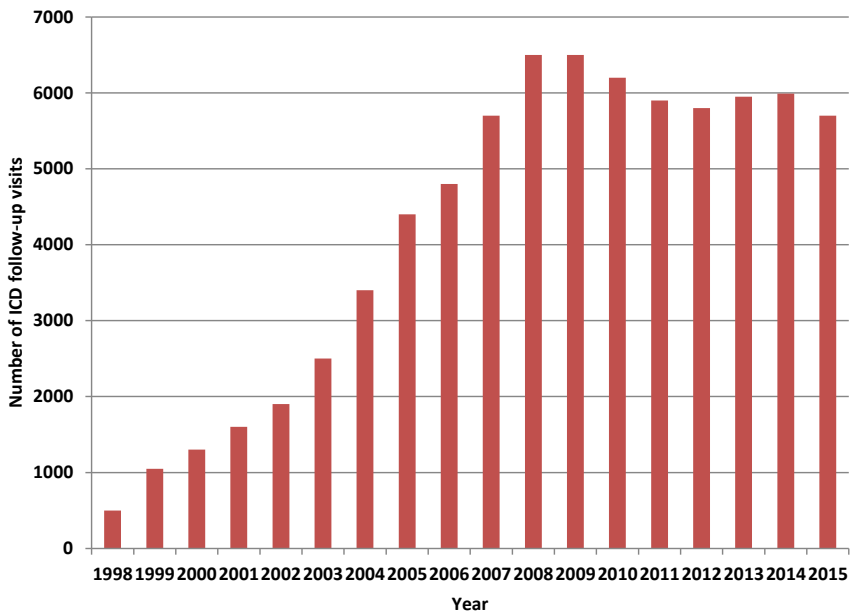


Figure 3. Number of ICD follow-up visits in the Leiden University Medical Center.

(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

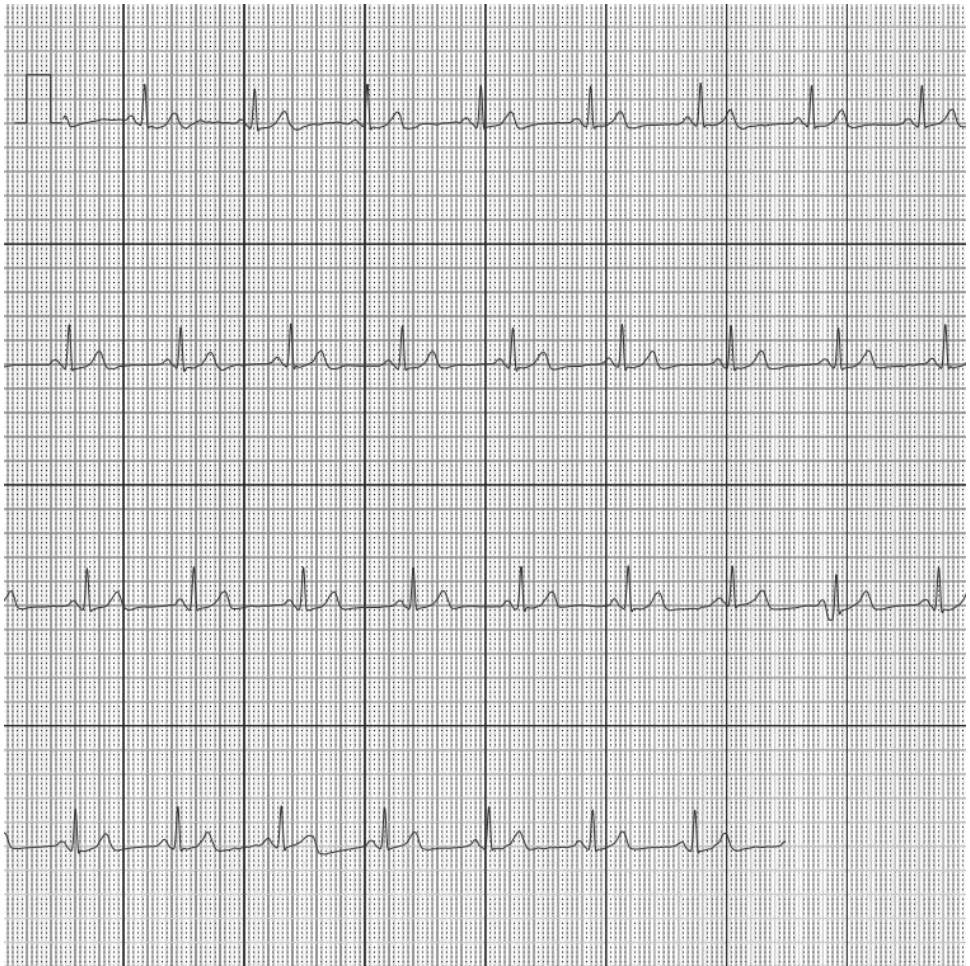


Figure 4. An example of an ECG generated by AliveCor.

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 quit.

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.

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