

Executive Summary

2020/2021 ISHNE/ HRS/ EHRA/ APHRS Collaborative Statement on mHealth in Arrhythmia Management: Digital Medical Tools for Heart Rhythm Professionals

From the International Society for Holter and Noninvasive Electrocardiology/ Heart Rhythm Society/ European Heart Rhythm Association/ Asia-Pacific Heart Rhythm Society

Niraj Varma (ISHNE Chair)
Iwona Cygankiewicz (ISHNE Vice-Chair)
Mintu P. Turakhia (HRS Vice-Chair)
Hein Heidbuchel (EHRA Vice-Chair)
Yufeng Hu (APHRS Vice-Chair)

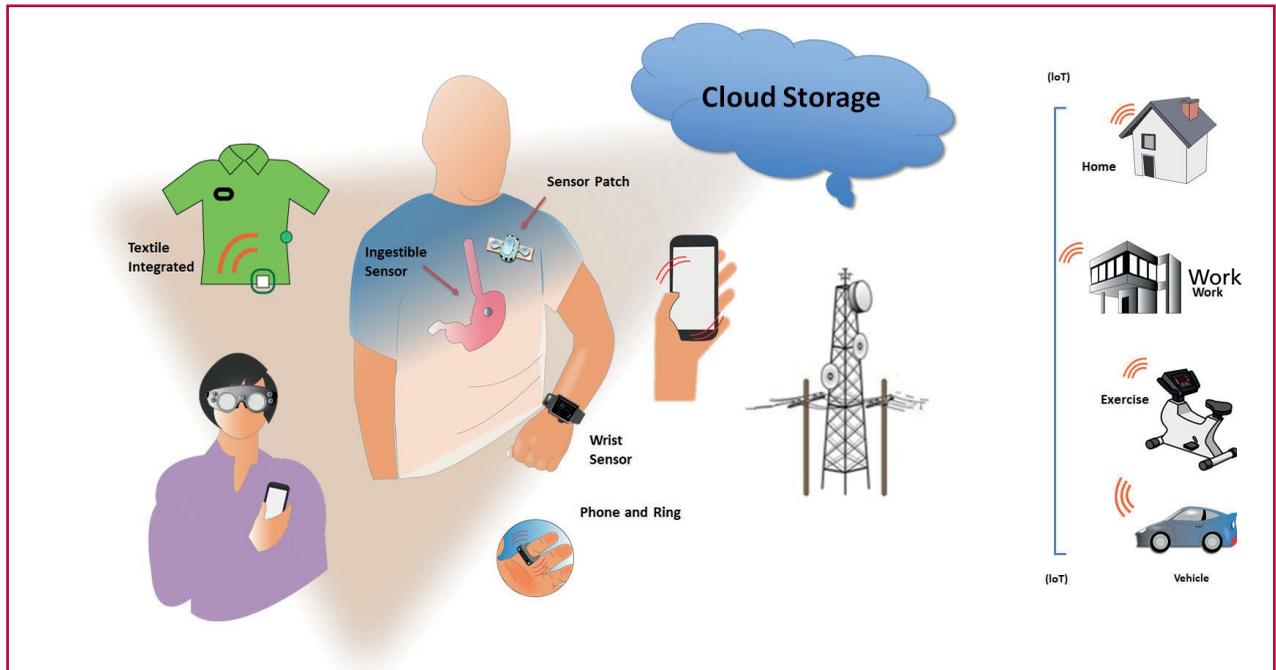
Cleveland Clinic, Cleveland, OH;
Medical University of Lodz, Poland;
Stanford University, Palo Alto, CA,
University Hospital, Antwerp, Belgium;
Taipei Veterans General Hospital, Taipei, Taiwan

Authors (in alphabetical order):

| | |
|------------------------|--|
| Lin Yee Chen | University of Minnesota, Minneapolis, MN |
| Jean- Philippe Couderc | University of Rochester, Rochester, NY |
| Edmond Cronin | Temple University, Philadelphia, PA |
| Jerry Estep | Cleveland Clinic, Cleveland, OH |
| Lars Grieten | Hasselt University |
| Deirdre A. Lane | University of Liverpool, Liverpool, United Kingdom |
| Reena Mehra | Cleveland Clinic, Cleveland, OH |
| Alex Page | University of Rochester, Rochester, NY |
| Rod Passman | Northwestern University Feinberg School of Medicine, Chicago, IL |
| Jonathan P. Piccini | Duke University, NC |
| Ewa Piotrowicz | National Institute of Cardiology, Warsaw |
| Ryszard Piotrowicz | National Institute of Cardiology, Warsaw |
| Pyotr G Platonov | Lund University, Lund, Sweden |
| Antonio Luiz Ribeiro | Universidade Federal de Minas Gerais, Belo Horizonte, Brazil |
| Robert E. Rich | Cleveland Clinic, Cleveland, OH |
| Andrea M. Russo | Cooper University Hospital, Camden, NJ |
| David Slotwiner | Cornell University, New York, NY |
| Jonathan S. Steinberg | University of Rochester, Rochester, NY |
| Emma Svennberg | Karolinska University Hospital, Stockholm, Sweden |

This publication has been translated by Revista Argentina de Cardiologia led by Sergio Dubner, MD with permission. This translated version shall neither replace nor supersede the English-language version, which remains the official version. Authors and collaborating societies shall not be responsible for any errors, discrepancies, or misinterpretations arising from this translation. Translations may not include any addenda or errata to the document. Please check the English-language version for any updates to the document (<https://doi.org/10.1111/anec.12795>).

1. Introduction
 - 1.1 Document scope and rationale
2. mHealth technologies
 - 2.1. Ambulatory ECG monitoring
 - 2.2. New mHealth based modalities for arrhythmia monitoring
 - 2.2.1 ECG based
 - 2.2.1.1. Handheld devices
 - 2.2.1.2. Wearable patches
 - 2.2.1.3. Biotextiles
 - 2.2.1.4. Smartphone and smartwatch-based devices
 - 2.2.2. Non-ECG based
 - 2.2.2.1. Photoplethysmography
 - 2.2.2.2. Oscillometry
 - 2.2.2.3. Mechanocardiography
 - 2.2.2.4. Contactless video plethysmography
 - 2.2.2.5. Smart speakers
3. mHealth applications for arrhythmias
 - 3.1. Atrial fibrillation
 - 3.1.1. Undiagnosed atrial fibrillation identification
 - 3.1.2. Targeted identification in high risk individuals
 - 3.1.3. Diagnostics in people with established atrial fibrillation
 - 3.1.4. Atrial fibrillation therapy
 - 3.2. Sudden cardiac death
4. Comorbidities
 - 4.1. Ischemic heart disease
 - 4.2. Heart failure
 - 4.2.1. Mobile technologies for managing heart failure
 - 4.2.2. Hybrid telerehabilitation in heart failure patients
 - 4.3. Diabetes
 - 4.4. Hypertension
 - 4.5. Disorders including sleep apnea
 - 4.6. Lifestyle
 - 4.6.1. Physical activity
 - 4.6.2. Diet
5. Patient self-management – integrated chronic care
 - 5.1. Patient engagement
 - 5.2. Behavioral modification
 - 5.3. Patients as part of a community
 - 5.4. Maintaining patient engagement
 - 5.5. Digital divide
6. Clinical trials
7. Operational challenges
 - 7.1. Health care system- eHealth monitoring and hospital ecosystem
 - 7.2. Cybersecurity guidance for mHealth devices
 - 7.2.1. Hacking strategies and methods in mHealth technologies
 - 7.2.2. Recommendations to the manufacturer
 - 7.2.3. Recommendations to clinicians and administrator
 - 7.2.4. Recommendations to patients
 - 7.3. Reimbursement
 - 7.4. Regulatory landscape for mHealth devices
8. Predictive analytics
9. Future directions



mHealth tools for the individual. Sensors can be embedded in a variety of wearables. (IoT: internet of things- connects from any location to hospital or cloud; See Table 1)

Abbreviations

| | | | |
|--------------|---------------------------------------|--------------|--|
| AI | artificial intelligence | HR | heart rate |
| ACC | American College of Cardiology | HRS | Heart Rhythm Society |
| ACS | acute coronary syndrome | ICD | implantable cardioverter defibrillator |
| AED | automated external defibrillator | ILR | implantable loop recorder |
| AF | atrial fibrillation | ISHNE | International Society for Holter and Noninvasive Electrocardiology |
| AHA | American Heart Association | JITAI | Just in time adaptive intervention |
| AHRE | atrial high rate episodes | MCT | Mobile cardiac telemetry |
| APHRS | Asia-Pacific Heart Rhythm Society | OAC | oral anticoagulants |
| BP | blood pressure | PACs | premature atrial complexes |
| CIED | cardiac implantable electronic device | PDAs | personal digital assistants |
| CPR | cardiopulmonary resuscitation | PPG | photoplethysmography |
| CRT | cardiac resynchronization therapy | PVCs | premature ventricular complexes |
| EHRA | European Heart Rhythm Association | RCT | randomized clinical trials |
| EMR | electronic medical records | RM | remote monitoring |
| ESUS | embolic stroke of unknown source | SCA | sudden cardiac arrest |
| FDA | Food and Drugs Administration | TADA | Technology Assisted Dietary Assessment |
| GPS | global positioning signal | VT | ventricular tachycardia |
| HCP | health care professionals | | |
| HF | heart failure | | |

1. INTRODUCTION

1.1. Document Scope and Rationale

Digital health is an umbrella term to describe the use of digital information, data, and communication technologies to collect, share, and analyze health information in order to improve patient health, education and health-care delivery (<https://www.fcc.gov/general/five-questions-you-can-ask-your-doctor-about-digital-health#ab>) (Turakhia 2016). This concept encompasses telehealth, electronic health records, implantable device monitoring, wearable sensor data, analytics and artificial intelligence, behavioral health, and personalized medicine. Among these, mobile health –or “mHealth” is a component of digital health, defined by the World Health Organization as “medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices” (https://apps.who.int/gb/ebwha/pdf_files/WHA71/A71_20-en.pdf?ua=1). Utilization of these devices has proliferated among health-conscious consumers in recent years, and is likely to continue rapid expansion and integration in more formalized medical settings.

mHealth flows intuitively to health professionals in the field of arrhythmia management from experience gained through remote monitoring of cardiovascular implantable electronic devices (CIEDs), such as pacemakers and implantable cardioverter defibrillators (ICDs) (Varma 2010). A wealth of data garnered from many studies over the last 10-15 years have confirmed the benefits of remote technology-assisted follow-up, and established it as standard of care (Varma 2013, Slotwiner 2019). However, results of remote monitoring (RM) of CIEDs may not be immediately generalizable to mHealth. For instance, the former is restricted to those with cardiac disease (largely arrhythmias and heart failure (HF)) i.e. a group already defined as patients. The care pathways for CIED remote monitoring are also well defined, with billing and reimbursement in place in the United States and many other parts of the world. In comparison mHealth differs: it is widely available in the form of consumer products that penetrate most sectors of society, including individuals without formal medical diagnoses; it may be applied to a wider group of medical conditions; data can be self-monitored rather than assessed by health care professionals; and reimbursement models are not mature. Indeed, some heart rhythm tracking capabilities may be indirectly acquired in products purchased for different goals, and then subsequently used. Conversely, in the medical space, applications are largely not prescribed by health care professionals (HCPs), often lack validation for disease management use cases, and care pathways remain varied or poorly defined. Nevertheless, if properly implemented, the intersection of these two communities opens up a broad spectrum of opportunities, extending from population screening and surveillance for undiagnosed disease to longitudinal disease management, and importantly, engaging patients in their own cycle of care, allowing much health care to be asynchronous and virtualized. Its value and degree of integration will depend on different healthcare systems in different countries.

mHealth has value only if the acquired information leads to decisions that improve outcome. This requires a clear path of information flow and actionability. Moreover, all stakeholders need to be aware of the logistical chain, so that everyone knows what to expect and to define clear responsibilities (possibly including device vendors). Similarly, actions taken based on the monitored information should be transparent to all stakeholders. For example, for a patient who records and transmits an irregular heart rhythm via a wearable device, a designated decision process should be followed to confirm whether the rhythm is atrial fibrillation (AF) or not, whether confirmation by another diagnostic test is required, how that is arranged, and finally what therapy should be implemented and in what reasonable timeframe? Clearly, there are risks of increasing cost from medical testing and provoking anxiety in consumers – who by virtue of seeking a medical verification become patients. Again, CIED experience sets a precedent. Studies that have shown improved outcome with telemonitoring succeeded when integrated into a clear logistical framework for a specific use case of disease management (e.g. IN-TIME for remote monitoring in CRT patients, CARDIOMEMS) (Abraham 2011, Hindricks 2014, Varma 2013). Replicating this with mHealth creates challenges for healthcare providers and goes far beyond the technological capabilities of the monitoring and transmission equipment. Implementation will require defined aims and fundamental changes to existing workflows and responsibilities. Such changes are always difficult. Apart from the organizational issues required to achieve such changes, reimbursement may drive or hinder such changes in the workplace. Awareness of these factors has been heightened by the SARS-Cov-2 pandemic, during which telemedicine solutions have been advocated to reduce patient contact with health care providers yet continue health care delivery (Varma 2020).

In view of the rapid technological development and popularity of wearable and other mobile devices, and the need for analysis and planning of the mHealth infrastructure, ISHNE (International Society of Holter and Non-invasive Electrocardiology), HRS (Heart Rhythm Society), EHRA (European Heart Rhythm Association), and APHRS (Asia Pacific Heart Rhythm Association), recognized the need for this consensus statement. The aim of this document is to define state-of-the-art mHealth technologies and their application in arrhythmia management and explore future directions for clinical application. As such, the scope of the document encom-

passes discussion of the different mHealth technologies currently available or in development; the acquisition of health-related data; the applications of such data, including disease identification and management, clinical trials, the patient perspective, and the issues that must be addressed in the future to permit useful application of mHealth technologies. Additionally, discussion is extended to mHealth facilitation of those comorbidities increasingly recognized to influence arrhythmia management (e.g. obesity and sleep apnea) which are becoming the responsibility of heart rhythm professionals (Chung 2020).

2. MHEALTH TECHNOLOGIES

Dedicated applications and sensors, within or adjunctive to mobile communication devices enable users to monitor, collect and share physiologic and health data. Their applications range from diagnostic, decision support, disease management, evaluation of medication adherence, and for educational and clinical research purposes (Figure 1).

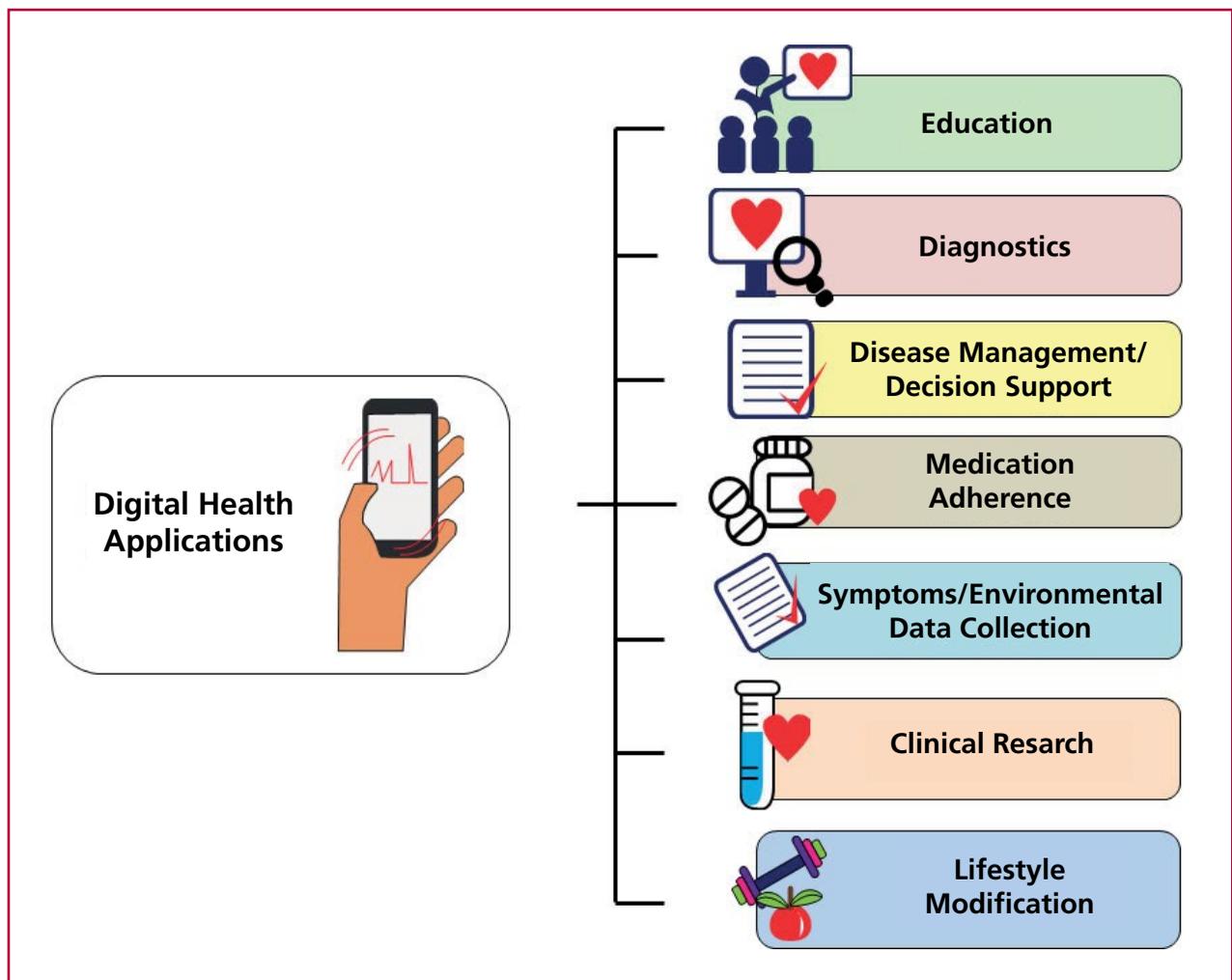


Fig. 1. Application of digital health technologies in arrhythmias. (Many of these sectors are interconnected).

Table 1. mHealth based modalities for arrhythmia monitoring

| ECG-based devices | Signal acquisition and visualization | ECG duration | Signal storage and transmission | Indications/ Populations tested | Advantages | Limitations |
|--------------------------|---|---|---|---|--|---|
| ECG-based devices | | | | | | |
| Hand-held | External sensors; Single or multilead ECG on demand; Display in-screen ECG or screen of PC/laptop/ smartphone, after transmission or real-time ECG analysis available | Intermittent Recording: 10 sec to 2 minutes | Built-in memory Bluetooth WiFi | Palpitations AF screening | Easy to use Low cost | Short ECG duration |
| Wearable patches | Built-in electrodes Patch attached to the skin | Continuous recording- Up to 14 days | Built-in memory with post-hoc analysis, or Bluetooth transmission with real-time analysis in selected devices | Low risk patients with palpitations and syncope; AF screening | Continuous longer term ECG recording; Built-in alarm button High patients' compliance; Patients can affix at home Water-resistant | Single-channel ECG Skin irritation |
| Biotextiles | Electrodes/sensors embedded into biotextile- vests, belts Single or multi-channel | Continuous recording up to 30 days | Built-in memory Real time Bluetooth transmission | Low risk patients with palpitations and syncope AF screening | Continuous long-term recording; Built-in alarm button; High patients' acceptance and adherence; Multiparameter evaluation; Can be used as monitoring and treating device (WCD) | Limited availability Movement artifacts |

| ECG-based devices | Signal acquisition and visualization | ECG duration | Signal storage and transmission | Indications/ Populations tested | Advantages | Limitations |
|----------------------------|--|--|---|--|---|---|
| Smartphone-based | External sensors attached to mobile phone Single / multilead ECG Real time ECG on smartphone's screen or PC/ laptop after transmission | Intermittent recording up to 30 sec Patient- activated | Built-in memory Real time or post-hoc transmission | Low risk patients with palpitations AF screening | Widely available Long-life possibility of intermittent recording | Intermittent recording |
| Smartwatch-based | Built-in sensors | Intermittent recording Patient activated | Built-in memory Real time or post-hoc transmission | Low risk patients with palpitations AF screening | Widely available Long-life possibility of intermittent recording | Intermittent recording Single- channel |
| Non-ECG-based | | | | | | |
| Photoplethysmography (PPG) | HR from changes in reflectance of the tissue blood volume of a skin surface | Intermittent patient activated in smartphones Continuous measurement of heart rate in smartwatches and wristbands | Built-in memory Real-time or post-hoc transmission | Low risk patients with palpitations AF screening Heart rate measurement during physical activity | Widely available | Irregular heart-presumed AF |
| Oscillometry | Blood pressure monitors with heart rate measurement | Intermittent recording during BP measurement | Built-in memory Post-hoc transmission | Heart rate assessment Opportunistic AF screening | Widely available | Irregular heart-presumed AF |
| Video-recording | Camera from smartphones, TVs | Patient activated; Continuous recording in prespecified timeframe | Real-time or post hoc transmission | Low risk patients with palpitations AF screening Undiagnosed falls | Can use existing cameras from household goods | Irregular heart-presumed AF Limited availability |

AF- atrial fibrillation, BP- blood pressure, HR- heart rate, WCD- Wearable cardioverter defibrillator

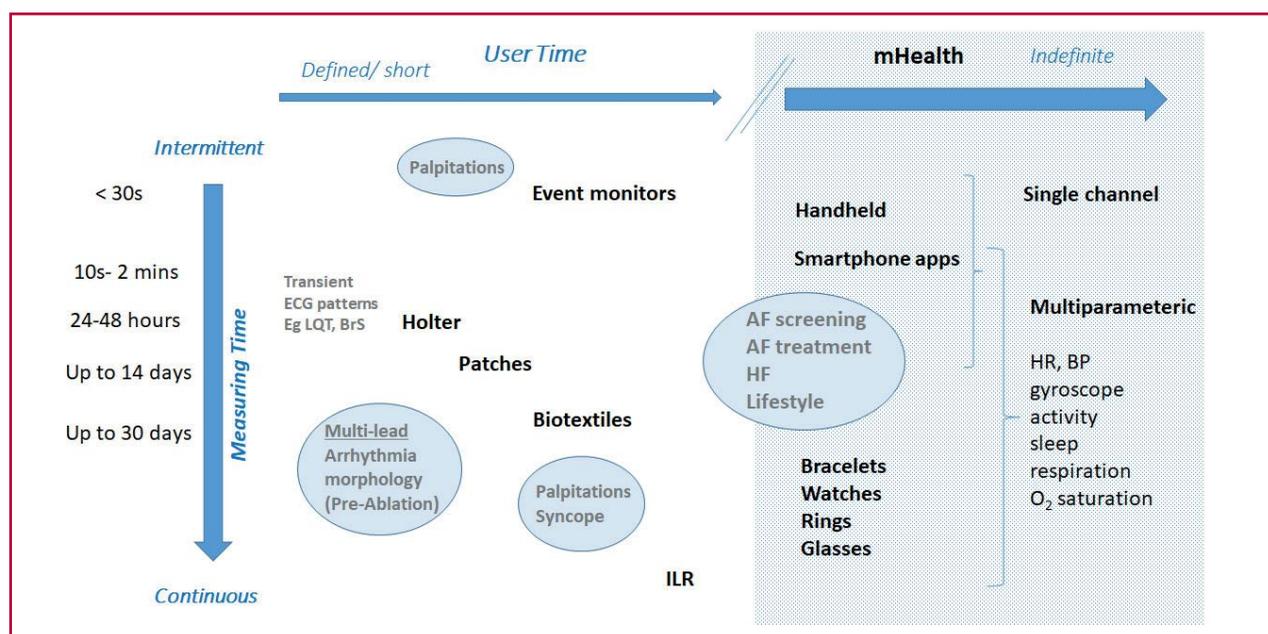
Applications to arrhythmias

- Diagnostic
 - evaluate patients with symptoms suggestive of arrhythmias
 - assess patients' response to both pharmacological and invasive treatment of arrhythmias
- Screening
 - increasing emphasis on AF

2.1. Ambulatory ECG monitoring

This is the cornerstone diagnostic method and the choice of technique and time frame depend on whether symptoms (e.g. palpitations, syncope) are present and how often they occur (Figure 2). In the current era, AF management has received most emphasis.

- Conventional ambulatory ECG devices with “continuous” or “intermittent” recording abilities (e.g. Holter, Mobile Cardiac Telemetry (MCT)) increase the diagnostic yield for suspected arrhythmias but limitations, patient discomfort and inconvenience remain important implementation barriers (Steinberg, 2017).
- Implantable loop recorders (ILRs) continuously monitor cardiac rhythm, but only record an ECG shortly before and after activation by either the patient or by an automated algorithm. Several approved ILR devices are available (Musat 2018, Sakhil 2019, Tomson 2015) and several studies have been performed to evaluate the diagnostic accuracy of these devices (Ciconte 2017, Hindricks 2010, Mittal 2016, Nolker 2016, Sanders 2016). Since ILRs are invasive and costly, some functions may shift to mHealth.



Traditional wearable monitors are used for defined, short periods of time. Advantages are continuous monitoring, and ability to use multiple leads which may be important for arrhythmia differentiation. AF- atrial fibrillation, BP- blood pressure, BrS- Brugada pattern HF- heart failure, HR- heart rate, ILR- implantable loop recorder, LQT- long QT

Fig. 2. mHealth devices for arrhythmia monitoring according to indications

2.2. New mHealth based modalities for arrhythmia monitoring

These can be divided into those using:

- ECG tracings (single or multilead, in intermittent or continuous format, of various durations)
- Non-ECG technologies such as pulse photoplethysmography (PPG)

Validation of their notified data (or underlying algorithms) and mechanisms for professional review (as established for CIEDs and MCTs) are scant, if at all (See Section 7). This is open to risks of not detecting significant events and/or overtreatment - eg false positive episodes of AF - if not confirmed by expert physicians.

2.2.1. ECG-based

Among these, handheld and patch systems have undergone the most extensive validation.

2.2.1.1. Handheld devices

Several standalone handheld devices operate without additional hardware. The devices can store ECG tracings (short, 30 sec to 1 minute, single or multilead) which can be uploaded to a computer for review and are usually available for physicians via web-based platforms. Studies across diverse populations have documented the diagnostic accuracy of handheld devices in detection of AF by short-term rhythm monitoring (Desteghe 2017, Doliwa 2009, Hendriks 2014, Kaasenbrood 2016, Poulsen 2017, Svennberg 2017, Tavernier 2018, Tieleman 2014, Vaes 2014) (Table 2)

2.2.1.2. Wearable Patches

Commercially available patches can be worn up to 14 days (Barrett 2014, Turakhia 2013). Unlike adhesive electrodes for lead-based systems, the water-resistant patches are not removed during the monitoring period leading to greater wear time, more analyzable data, and no lead reversal errors. After the monitoring period, the device is returned to the manufacturer for data extraction, analysis by a proprietary algorithm, and further secondary analysis of potential arrhythmias by medical technicians. A diagnostic report is sent to the treating physician. As the patch has no external leads, it is perceived to be more comfortable to wear compared to conventional Holter monitors, with 94% of the patients preferring the patch over the Holter (Barrett 2014). Newer patch-based systems add near- real-time analytics and by transmitting data continuously to the cloud. This may facilitate more rapid data collection and diagnosis. Multiparametric monitoring may be enabled with a patch worn for up to 3 months (Stehlik 2020).

2.2.1.3. Biotextiles

Textile-based systems for ECG monitoring were initially designed to ensure patients' comfort during daily activities and address the needs of active patients. These vests and elastic bands adapt easily to patients' movements that is particularly important for those performing physical activities. These biomedical devices capture the electrocardiographic signal via electrodes integrated into the garment that enables non-invasive acquisition of ECG signal up to 30 days. Single/multi lead selection (up to full 12-leads) and event activation are available (Eliot 2019, Eysenck 2019, Fabregat 2014, Feito 2019, Pagola 2018) . The wearable cardioverter-defibrillator transmits 2-channel ECG data to an online patient management database allowing for remote monitoring of high-risk patients. Recent incorporation of heart sound evaluation that may predict HF decompensation will be tested in a prospective trial (HEARIT-Reg trial ClinicalTrials.gov Identifier: NCT03203629).

2.2.1.4. Smartphone and smartwatch-based devices

More recently, non-wearable solutions coupled to the smartphone have emerged. These devices (e.g.see Table 2 and Varma 2020) allow the user to perform a "spot check" single-lead ECG strip, usually of up to 30 seconds or longer by placing a finger of each hand on the two electrodes, usually located on the phone case or external card (Figure 3). The tracings can be reviewed on the smartphone, electronically stored or transmitted for review by the user's provider if desired. These have been directed largely to AF.

Sensitivity and specificity depend on the software, the population studied and the prevalence of AF in the population. There is also an accessory band for a smartwatch to allow ECG recording. Recently, a new 6-lead case has been developed, allowing for 30 second recording of all 6 limb leads by touching each of the three electrodes. The QT interval may be derived from this (<https://cardiacrhythmnews.com/kardiamobile-6l-can-be-used-to-measure-qt-duration-in-covid-19-patients/>) (Chung 2015, Garabelli 2016) but can be underestimated (Koltowski 2019).

• **Limitations**

- o Single lead devices. Noise-free tracing may be more difficult for older patients or those with physical limitations (tremor, stroke, etc).
- o Although the interpretation algorithms typically have received regulatory oversight, these algorithms can frequently misclassify rhythms (Bumgarner 2018). For example, the Apple Watch is unable to assess the ECG for AF if the heart rate is above 150 or below 50 bpm(https://www.apple.com/healthcare/docs/site/Apple_Watch_Arrhythmia_Detection.pdf) and is cleared by the Food and Drug Administration only for use in persons without a diagnosis of AF (Figure 4) (<https://support.apple.com/en-us/HT208931>, accessed January 2, 2020).(See Section 6: Clinical trials) .
- o For consumer watches, ECG diagnosis is considered a pre-diagnostic pending medical verification and not designed to be acted on without clinician review.
- o ECG classification of other arrhythmias (PVCs, PACs, VT) is currently unavailable

Table 2. Exemplary validation studies for various m-Health technologies

| | Device | Author | n | Setting | Comparator | Sensitivity (%) | Sensitivity (%) | Requires ECG confirmation |
|-----------------------|--------------------------------|-----------------|------------|------------------------------------|---|--|---|---------------------------|
| | Pulse palpation | Cooke, 2006 | 2385 | meta-analysis | 12-lead ECG | 94 | 72 | + |
| Handheld devices | Zenicor | Doliwa, 2009 | 100 | Outpatient cardiology clinic | 12-lead ECG interpreted by cardiologist | 96 | 92 | |
| | MyDiagnostick | Tieleman, 2014 | 192 | Outpatient cardiology clinic | 12-lead ECG interpreted by cardiologist | 100 | 96 | |
| | Omron HCG-801 | Kearley, 2014 | 999 | Primary care practices | 12-lead ECG interpreted by cardiologist | 94.4 | 94.6 | |
| | Merlin ECG event recorders | Kearley, 2014 | 999 | Primary care practices | 12-lead ECG interpreted by cardiologist | 93.9 | 90.1 | |
| Smartphone ECG device | AliveCor Kardia Mobile | Lau, 2013 | 204 | Recruited patients | 12-lead ECG interpreted by cardiologist | 98 | 97 | |
| Smartphone device-PPG | CardioRhythm iPhone | Chan, 2016 | 1013 | Primary care clinic | Single lead AliveCor ECG | 93 | 98 | + |
| | PULSE-SMART App | McManus, 2016 | 219 | Patients under-going cardioversion | 12-lead ECG or 3-channel telemetry | 97 | 94 | + |
| | FibriCheck App | Proesmans, 2019 | 223 112 | Primary care practices | 12-lead ECG | 95 | 97 | + |
| Smartwatch ECG | KardiaBand automated algorithm | Bumgarner, 2018 | 405 | Patients undergoing cardioversion | 12-lead ECG | 93 | 84 | |
| Blood pressure device | Microlife | Wiesel, 2009 | | Cardiology outpatients | 12-lead ECG | 95, 97 for one or 3 measurements, respectively | 86, 89 for one, or 3 measurements, respectively | + |

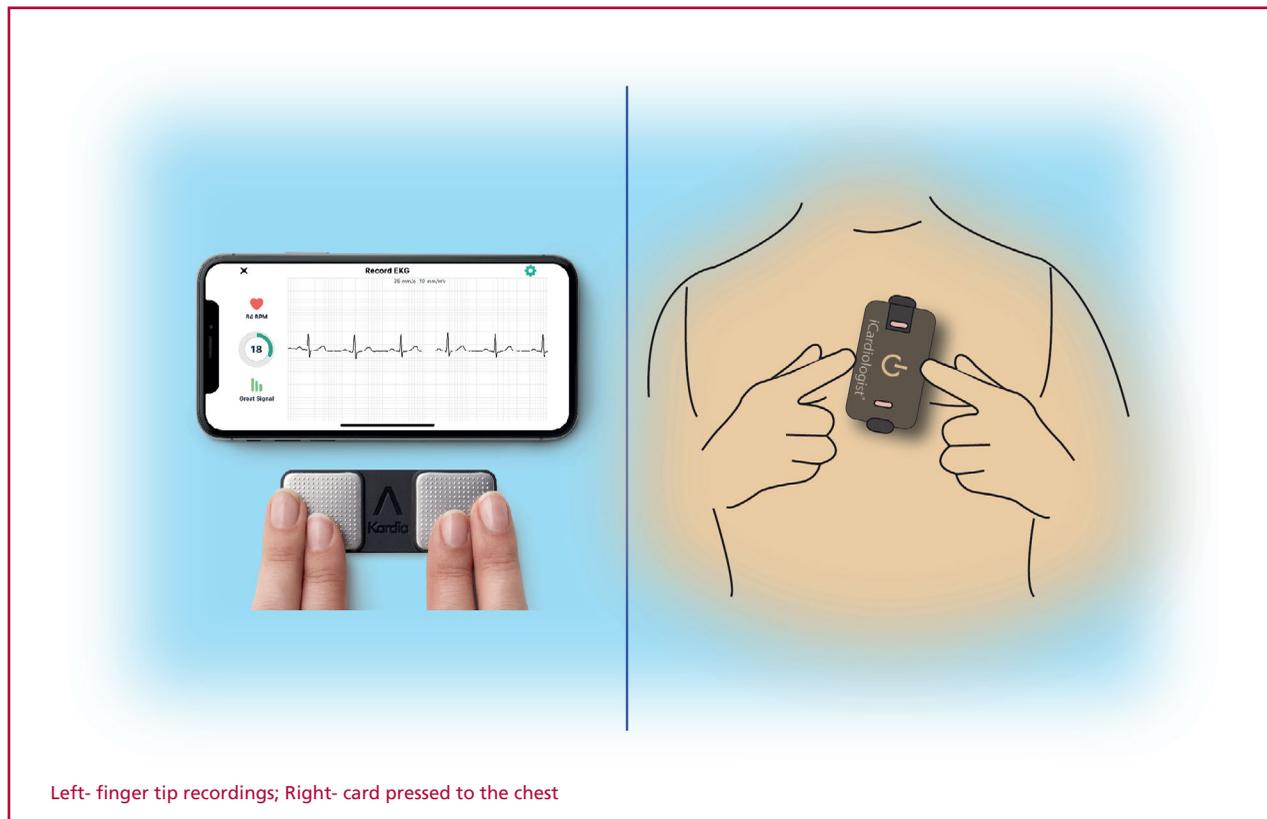


Fig. 3. ECG iPhone mobile applications

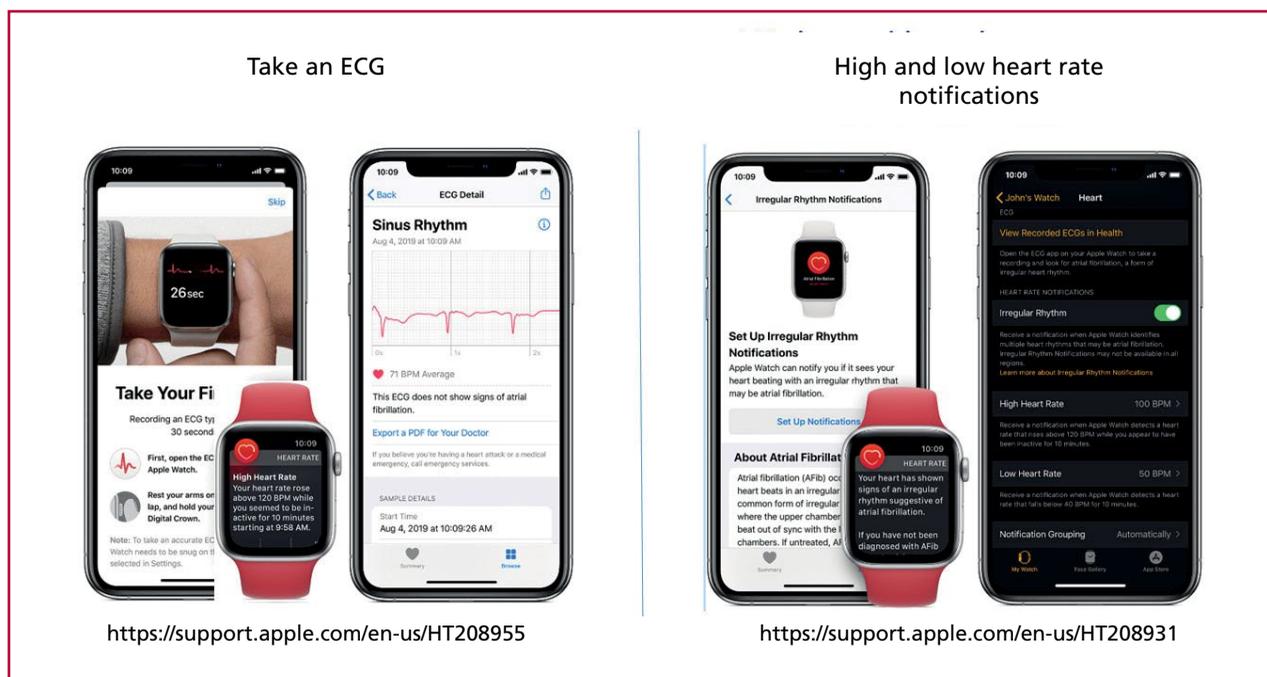


Fig. 4. Apple Watch

2.2.2. Non ECG-based

2.2.2.1. Photoplethysmography

The photoplethysmography (PPG) technologies allow for the detection of arrhythmias using hardware already present on most consumer devices (smartwatches and fitness bands) through a downloadable application. Using a light source and a photodetector, the pulse waveform can be measured by detecting changes in the light intensity (Conroy 2017, McManus 2013). An automated algorithm can subsequently analyze the generated pulse waveform to detect AF.

- **Applications**

This technology has been applied for use with smartphones using the phone's camera to measure a fingertip pulse waveform (Choi 2017, McManus 2013, McManus 2016, Proesmans 2019). The smartphone based PPG applications have been utilized in at-risk population to detect AF and as a screening tool in the general population (Verbrugge 2019). (See Section 6: Clinical Trials).

The PPG technology has also been incorporated in smartwatches to measure heart rate and rhythm (Dorr 2019, Guo 2019). Some have developed prototypes of a band that includes a single channel ECG, multi-wavelength PPG and tri-axial accelerometry recording simultaneously at 128 Hz (Nemati 2016) and others use a deep neural network based on PPG sensors to detect AF (<https://www.mobihealthnews.com/content/study-apple-watch-paired-deep-neural-network-detects-atrial-fibrillation-97-percent-accuracy> ; <https://mrhythmstudy.org>).

2.2.2.2. Oscillometry

The automatic oscillometric BP monitors derive from the heart rhythm regularity algorithmically (Chen 2017). Automated BP monitors have been used for opportunistic AF detection. Such capability could be added to continuous BP recording devices (Kario 2016). Several studies addressed the diagnostic accuracy (Chan 2017, Chen 2017, Gandolfo 2015, Kearley 2014, Marazzi 2012, Stergiou 2009, Wiesel 2009, Wiesel 2014) and the feasibility of this device as a screening tool (Chan 2017, Omboni 2016, Wiesel 2017).

The following have undergone preliminary study.

2.2.2.3. Mechanocardiography

Mechanocardiography uses accelerometers and gyroscopes to sense the mechanical activity of the heart. A smartwatch (Sony Experia) was placed on the chest in supine patients to detect micro movements of the chest. Possibly, carrying this device in a pocket may have utility but is likely to be confounded by movement (e.g. walking) artefacts. (Uakkola 2018)

2.2.2.4. Contactless video plethysmography

Non-contact video monitoring of respiration and heart rate have been developed less than 15 years ago (Couderc 2015, Takano 2007, Verkruyse 2008). It is a monitoring technique extracting the photoplethysmographic-like signals from a standard digital RGB video recording of the human skin and specifically of an individual's face. The videoplethysmographic signal describes the absorption peak of ambient light by the hemoglobin from the facial skin (Dautov 2018, Tsouri 2015). By using mobile devices with cameras, the deployment of the technology is easy and scalable since it does not require the use and distribution of any physical devices (Yan 2020). One requirement for these technologies is steady focus: thus moving subjects present a challenge. It is important to avoid recording, sending or communicating any video of the patient thus protecting privacy and dignity. Issues regarding privacy, confidentiality, and legal and ethical obligation to treat are crucial factors to be considered when these technologies are deployed at larger scale (Turakhia 2019).

2.2.2.5. Smart speakers

Identification of abnormal heart rate patterns may be made possible by converting smart speakers into a sonar device with emission of in-audible frequencies sound waves and receiving them to detect motion. These are not in consumer domain but potentially have wide scalability (Chan 2019, Wang 2019).

3. MHEALTH APPLICATIONS FOR ARRHYTHMIAS

Typically, most patients with palpitations and dizziness are evaluated using the various technologies reviewed in section 2.1 (Steinberg 2017). Smart devices may be useful in pediatric patients (Gropler 2018)

3.1. Atrial fibrillation

New digital health and sensor technologies have the potential for early identification of AF. These may be directed to several broad groups: for screening the general population or managing the already diagnosed, for fol-

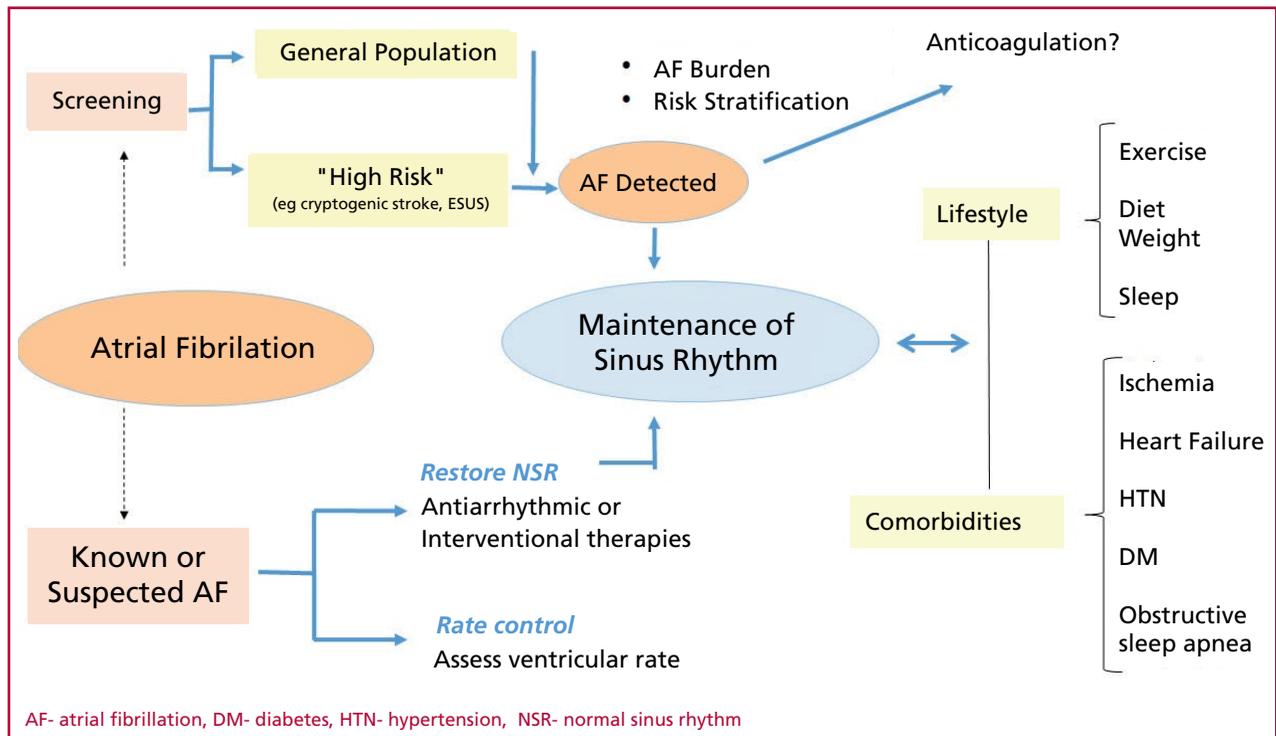


Fig. 5. mHealth and AF. Applications include screening for AF in general or high risk populations, managing comorbidities and lifestyles important for prevention and control, as well as managing treatment of known AF.

lowing responses to treatment, and increasingly to managing comorbidities and lifestyle modification (section 4) (Figure 5).

3.1.1. Undiagnosed AF Identification

Many m-Health technologies to detect AF are readily available directly to those without defined disease and are not deployed as individual or public health interventions. Rather, consumers who possess these technologies, such as smartwatches or smartphone-connected ECG recorders, opt into the use of these technologies. Therefore, consumer-driven AF identification is not the same as healthcare-initiated AF screening. AF identification by these devices requires confirmation, since these AF screening tools have variable specificity (Table 2), raising the potential of a high false positive rate in a low prevalence population, and risks of unnecessary treatment. There have been almost 500 studies assessing accuracy of mHealth devices for AF detection, as described in recent systematic reviews (Giebel 2019, Lowres, 2019, O'Sullivan 2020). Two large-scale screening trials were reported recently (See Section 6).

No large outcome trial of screen detected AF and hard endpoints of stroke and death has been conducted as yet. Although an incidental diagnosis of AF seems to be associated with increased risk of stroke and protection by OAC therapy (Freedman 2016; Martinez 2014 Tsivgoulis 2019), clinical trials to determine any benefit for opportunistically detected AF have not yet been completed but are underway (Gudmundsdottir 2019, Steinhubl 2018, Svennberg 2015, Heartline study www.heartline.com). This effort addresses the concern that AF detected by screening may identify inherently lower risk patients so that efficacy of anticoagulation (and its risk/benefit ratio) requires recalibration. The European and American guidelines do recommend opportunistic screening for early identification of undiagnosed AF in patients aged ≥ 65 years (Freedman 2017, January 2019, Kirchhof 2016). On the other hand the U.S. Preventive Services Task Force has presently given an "insufficient" recommendation for systematic screening for AF with electrocardiograms (Jonas 2018).

3.1.2. Targeted identification in high-risk individuals

Cryptogenic stroke/TIA

Up to 1/3 of ischemic strokes are attributed to AF mediated embolism to the brain (Hannon 2010). Hence, prolonged monitoring for AF post-stroke has been recommended in recent guidelines (January 2019, Kirchhof 2016, Schnabel 2019). The results of AF detection have been heterogeneous (Kishore 2014; Sanna 2014, Zung-

sontiporn 2018). A meta-analysis showed that a step-wise approach to AF detection in post-stroke patients led to AF detection in 23.7 % of patients (Sposato 2015) while a combined analysis of two randomized and two observational studies showed a 55% reduction in recurrent stroke following prolonged cardiac monitoring (Tsvigoulis 2019). However, the optimal AF duration threshold for initiating anticoagulation is currently unknown.

The risk of undiagnosed AF and other sources of thrombi has been considered high in embolic strokes of unknown source (ESUS), prompting studies that evaluated whether empiric NOAC therapy is more effective than antiplatelet therapy without a requirement of AF detection. Two of these studies, NAVIGATE ESUS (Hart 2018) and RESPECT-ESUS (Diener 2018) have not shown a reduction in recurrent stroke in patients receiving NOACs. A third study is ongoing, including patients with suggested atrial myopathy (enlarged atria, increased levels of NT-proBNP or enlarged P waves) (Kamel 2019).

Other high-risk individuals

mHealth ECG recorders can facilitate frequent brief (e.g. 30 seconds) recordings over prolonged periods of time by the very ubiquity of devices. These devices are particularly well suited to capture intermittent or nonpersistent arrhythmias (Charitos 2012, Yano 2016). AF burden, increasingly recognized as a powerful independent predictor of stroke (Chen 2018), though accurately measured by implanted devices (Varma 2005), cannot be readily calculated from intermittent ECG data.

Formal screening with mHealth ECG recordings has yielded meaningful incidences of newly diagnosed AF, statistically greater than if diagnosis relied only on the office ECG (Table 3). The yield generally is enhanced by the presence of risk factors, such as older age and higher CHA2DS2-VASc scores. Lowres et al in a patient level meta-analysis found that new AF detection rate increased progressively with age from 0.34% for <60 years to 2.73% ≥85 years. Importantly, the number of subjects needed to screen to discover AF meeting indications for anticoagulation was 1089 for subjects <60 years but 83 ≥65 years.

3.1.3. Diagnostics in people with established AF

mHealth has important implications for the care of those already diagnosed with AF. While several studies succeeded in establishing the sensitivity and specificity of novel devices for the detection of AF, no study to date has yet evaluated the utility of an mHealth intervention in affecting clinical outcomes. The iPhone Helping Evaluate Atrial Fibrillation Rhythm through Technology study (iHEART) is a single center, prospective, randomized controlled trial and the Heartline study seek to accomplish this goal (Caceres 2019, Hickey 2016, <https://www.heartline.com>).

3.1.4. Atrial fibrillation therapy

AF Burden

Current guidelines for anticoagulation are based principally on the presence of risk factors and a diagnosis of clinical AF, regardless of AF duration, symptomatology or burden (January 2019). However, there is increasing recognition that AF burden matters; eg. paroxysmal events have less thrombo-embolic risk than persistent AF (Chen 2018). AF burden can be characterized as %/time monitored, longest duration, and density. CIED-retrieved data provide an insight into natural history and associated sequelae (Healey 2012, Kaplan 2019, Van Gelder 2017, Varma 2005). This led to oral anticoagulation intervention trials to determine the ability to reduce stroke on the basis of AF duration (Lopes 2017, Martin 2015). These suggest that a threshold exists below which the risk of thromboembolic stroke is low and risk-benefit ratio may not justify chronic administration of oral anticoagulants. Device-detected, “sub-clinical” atrial high-rate episodes (AHRE) lasting 6 minutes to 24 hours are associated with increased stroke risk, but the absolute risk is considerably lower than expected based on risk factors alone (Glutzer 2003, Healey 2012, van Gelder 2017). Whether these require anticoagulation in high-risk individuals is the subject of ongoing studies (Kirchhof 2017, Lopes 2017, van Gelder 2017). AF detection using digital health tools offer further insights in patients without indication for implantable devices and extends AF screening to younger patients without cardiovascular disease and low thrombo-embolic potential. Those with high AF burden (defined by ≥ 11.4%; mean duration 11.7 hours) detected on a 14-day patch monitor had an increased thromboembolic event rate compared to those with lower AF burdens (Go 2018). There remains significant treatment variation in use of OAC, especially for device-detected AF (Perino 2019). This may be due to a large clinical uncertainty regarding the optimal cutpoint, even though observational data indicate that OAC is associated with a decreased risk of stroke for episodes > 24 hours and possibly for episodes of 6-24 hours (Perino 2019). Currently, there are no prospectively- validated cutpoints or risk models that incorporate AF burden into decision making for stroke prevention therapies.

- **Key knowledge gap** Identify characteristics (duration, episode number/ density) and risk factors that justify anticoagulation for mHealth detected AF.

Table 3. Selected screening studies for atrial fibrillation using newer technologies

| | Device | Author, year | Setting | Comparator | n | Mean age | Duration of monitoring | New AF detection (%) |
|-----------------------------|---|--|--|---|---------|----------|---|--------------------------------|
| Handheld ECG device | Zenico SL | Berge, 2018 | Norway systematic | Age 63-5_ CHADS-VaSC \geq 2 (M) or \geq 3 (F) | 1510 | 63.9 | 10 sec Twice daily for 2 weeks | 0.9% |
| | Zenico SL | Svennberg, 2015 | Sweden systematic | Age 75/76 | 7173 | 75 | 10 sec Twice daily for 2 weeks | 3.0% |
| | Zenico SL | Engdahl, 2013 | Sweden systematic | Age 75/76 + CHADS2 risk score \geq 2 | 403 | 75 | 10 sec Twice daily for 2 weeks | 7.4% |
| | Zenico SL | Kemp Gudmundsdottir, 2020 | Sweden systematic | Age 75/76+ NTproBNP \geq 125ng/l | 3766 | 75 | 10 sec Twice daily for 2 weeks | 4.4% |
| | Zenico SL | Doliwa, 2012 | Sweden Post-discharge | Recent ischemic stroke/TIA and no prior AF | 249 | 72.3 | 10 sec 30 days | 4.8% |
| | My Diagnostick | Tieleman, 2014 | Netherlands | Influenza vaccination | 676 | 74 | 1 min | 1.6% |
| | My Diagnostick | Kaasenbrood 2020 | Netherlands Primary care Opportunistic | Age>65 | 919 | | 1 min | 1.43% |
| | My Diagnostick SL | Tavernier, 2018 | Belgium Geriatric ward | Geriatric | 252 | 84 | Daily 1 min during hospitalization (median 5) | 13% |
| ECG Patch | ZioPatch iRhythm | Turakhia, 2015 (STUDY-AF) | US | Males, age \geq 65 and \geq risk factors | 75 | 69 | Two weeks continuous | 5.3% |
| | ZioPatch iRhythm | Steinhubl, 2018 | US National health plan members | Age \geq 75 or M>55/ F>65+risk factors | 2659 | 72.4 | Continuous 4 weeks | 2.4% |
| | Zio XT Patch | Roney, 2019 ARIC study | US Community surveillance study | No prior AF | 386 | 79 | Continuous 2-4 weeks | 2.5% (2 weeks) 4% (4 weeks) |
| | Zio Patch | Heckbert, 2018 Multi-Ethnic Study of Atherosclerosis | US Community surveillance study | No prior AF | 804 | 75 | Continuous 2-4 weeks | 4% (AFB/ AFL) |
| Smartphone ECG based | AliveCor Kardia Mobile SL | Lowres, 2014 (SEARCH-AF) | Australia Pharmacy Opportunistic | Age \geq 65 | 1000 | 76 | 30 sec | 1.5% |
| | AliveCor Kardia Mobile SL | Chan, 2016 | Hong Kong Outpatient clinic | Age \geq 65 or HTA/diabetes | 1013 | 68.4 | 30 sec | 0.5% |
| | AliveCor KardiaMobile SL | Halcox, 2017 (REHEARSE AF) | UK Randomized trial | Age \geq 65 +CHA2DS2-VASc \geq 2 | 1001 | 72.6 | 30 sec Twice weekly for 1 year | 3.8% |
| Smartphone device PPG based | CardioMobile app | Chan, 2016 | Hong Kong Outpatient | Age \geq 65 or HTA | 1013 | 68.4 | 30 sec | 0.5% |
| | Huawei wristband (Honor Band 4) or Huawei Watch | Guo, 2019 | General population across China | Age > 18 years | 187,912 | 35 years | \geq 14 days | 0.23% |
| Smartwatch | Apple smartwatch, iPhone app | Perez, 2019 | General population across USA | Age > 22 years | 419,297 | 41 years | Median 117 days | 0.52% irregular heart rhythm |

Rhythm and Rate control

While we await data on OAC treatment for mHealth detected AF, the finding of the arrhythmia should initiate mHealth monitoring of NSR retention, QT intervals (important for those on some anti-arrhythmic drugs (Garebelli 2016) and discussion of cardiovascular risk factor modification and lifestyle changes, since AF coexists with comorbidities that may influence its occurrence and natural history (See Section 4). In rate control strategy The European Society of Cardiology recommends lenient resting heart rate targets (<100-110) whereas the ACC/AHA/HRS guidelines recommend a target rate of <80 bpm. mHealth technologies can be used to assess ventricular rates during AF over long time periods and evaluate the effects of rate-control therapies (January 2019, Kirchoff 2016).

3.2. Sudden cardiac death (See also section 4.1 Ischemia)

Ventricular arrhythmias

Detection of symptomatic ventricular tachycardia (VT) has been reported using the AliveCor cardiac monitor (AliveCor, San Francisco, USA) and SmartWatch (Ringwald 2019, Waks 2015). PVCs may challenge to PPG-based systems, as many PVCs are non-perfusing (Billet 2019).

Syncope

Prolonged ambulatory monitoring using medical-grade devices has been the mainstay of cardiac rhythm diagnosis during episodes of syncope (Steinberg 2017). A randomized controlled trial of AliveCor versus usual care in participants presenting with palpitations or pre-syncope showed a faster and increased rate of detection of symptomatic arrhythmias in the intervention group, suggesting that at least in pre-syncope, patient-activated rhythm detection using a commercially available mHealth device is productive (Reed, 2019). There is a significant overlap between transient loss of consciousness and mechanical falls due to orthostatic intolerance, neurologic or orthopedic problems (Davis 2010, Heinrich 2010). Mobile applications that combine analysis of heart rate monitoring together with fall detection, GPS positioning, video recording with display of patients' surroundings, and the capability to send alerts either triggered by patients in case of symptoms or automatically in case of detected falls, may be useful.

Cardiac arrest

It is possible that mHealth devices may be able to predict cardiac arrest. Once cardiac arrest occurs, rapid identification is essential to trigger a response by emergency responders. Wearable devices that combine physiologic monitoring, GPS, and a method of communication with emergency services such as cellular service are well positioned to provide almost instantaneous alert as well as location information (Kwon 2019, Praveen 2019). mHealth devices may be able to identify pulse and agonal breathing. The ubiquity of mobile phones in society leads to more rapid notification of emergency services, and the possibility of a dispatcher gathering information from a bystander at the patient's side and delivering instructions on care, such as CPR. This was associated with improved outcomes for a variety of emergencies (Wu 2012). Notification of lay first responders in the vicinity of a cardiac arrest is also feasible with current technology (Ringh 2015). Whether a trained or novice bystander responds, mobile devices may be further useful to provide voice (or video) instructions from a dispatcher or from the device itself. Studies of pre-recorded audio, live video, and animation-based instruction have shown improvements in some aspects of CPR delivery and AED use, although technology continues to evolve (Bolle 2009, Choa 2008, Merchant 2010, You 2008). One limitation is that as such apps are unregulated, many do not convey current basic life support algorithms and may have poor usability (Kalz 2014). Mobile devices have also the potential to assist with the retrieval and use of AEDs (Hatakeyama 2018, Neves Briard 2019, Sakai 2011). An emerging approach is the dispatch of an AED via a drone to the location of the cardiac arrest, which is expected to reduce time-to-defibrillation, especially in rural areas (Boutilier 2017, Claesson, 2017). The complete chain from activation of citizen responders was tested in the Hearrunner trial (Andelius 2020).

4. COMORBIDITIES

Comorbidity management may directly affect arrhythmia recurrence and outcome (Chung 2020, January 2019). (Figure 5). mHealth has significant potential for facilitating these interventions (Figure 6). Key determinants to successful uptake of decision support apps will be their user-friendliness and complexity and the delivery of electronic communications and feedback to the patient. Tele-monitoring nested in a more complex intervention, including additional support, as face-to-face counselling, telecounseling, education, behavioural management, medication management and adherence contracts, promises sustainable benefit.

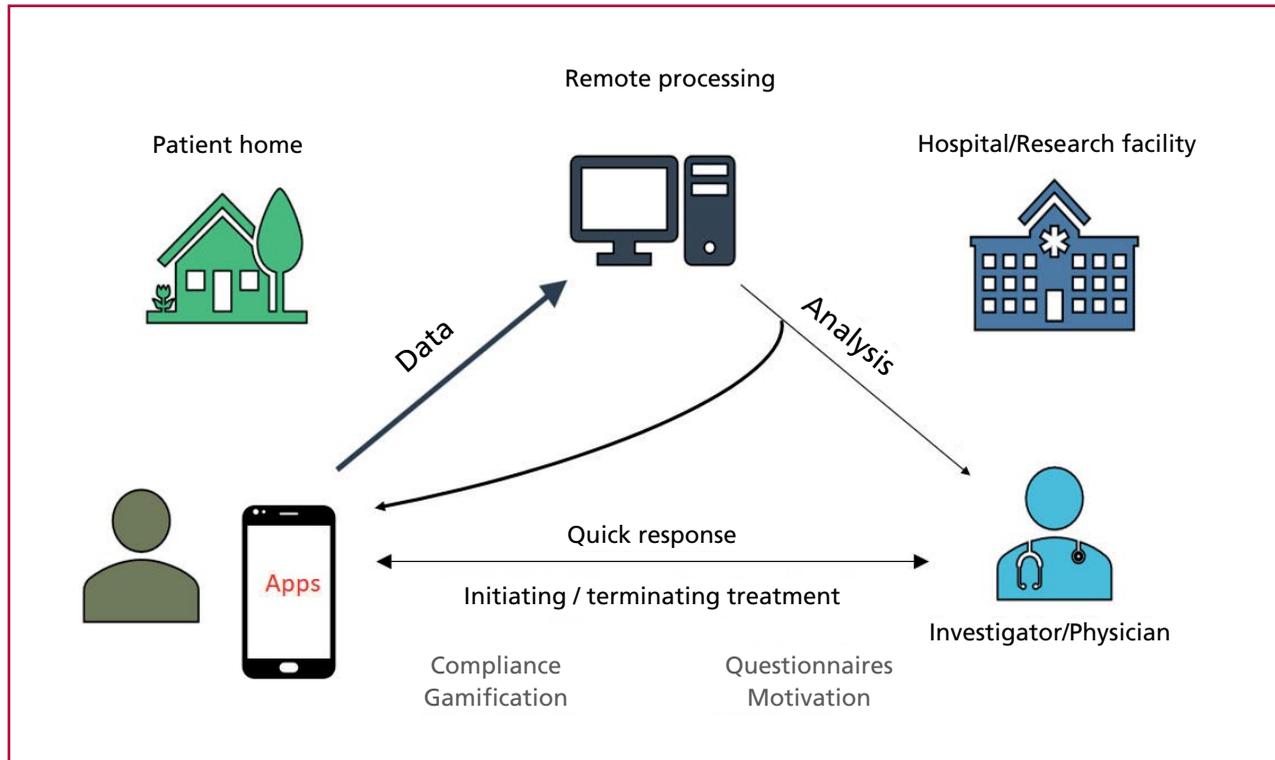


Fig. 6. Digital applications can integrate patient relayed information of sensor and clinical information with automatic remote analysis and/or clinic adjudication for treatment adjustments, but also permit patients to receive education and treatment

4.1. Ischemic heart disease

Early management (eg primary angioplasty) of acute ischemic syndromes may reduce infarct territory and ventricular arrhythmias. AF after myocardial infarction worsens prognosis (Pizzetti 2011). From the home setting, mHealth may improve symptom recognition and earlier presentation, ie “symptom-to-door time” (Moser 2006). Three lead ECG tracings (as well as derived augmented limb leads) can be recorded with commercially available smart-watches (Avila, 2019). An emerging technology (www.heartbeam.com) uses a credit card sized device pressed against the user's chest (Figure 3) to relay 3D vector derivation of ECG signals for cloud-based analysis. In the field, ECG transmission by emergency responders to hospitals reduced door-to-balloon time and peak troponin (Clemmensen 2010, Sanchez-Ross M 2011).

Post-hospital care may be facilitated by mobile technologies regarding medication adherence, follow-up procedures and future appointments (Chow 2015, Horwitz LI 2013, Unal 2018, Ziaieian B 2013). Sensors measuring heart rate, respiration rate, and exercise parameters may permit home based cardiac rehabilitation and overcome traditional limitations of availability, cost, and convenience (Zwisler 2016). (Varnfield 2014). (See also Hybrid telerehabilitation in HF patients Section 4.2.2.).

4.2. Heart Failure

4.2.1. Mobile Technologies for Managing Heart Failure

Sensors that detect respiratory rate and pattern by detecting movement of the chest wall via pressure, microphone (sounds), stretch, or accelerometry, (as well as traditional heart rate (ECG), blood pressure (BP) and weight) may have applications in HF. Preliminary results using a disposable multisensor chest patch in the LINK-HF study were encouraging (Stehlik 2020), detecting precursors of hospitalization for HF exacerbation with 76% to 88% sensitivity and 85% specificity, one week before clinical manifestations. Exercise training is recommended for all stable HF patients (Piepoli 2011, Ponikowski 2016). Home-based telerehabilitation is associated with high adherence, improved physical capacity (Piotrowicz 2015) and psychological status (Piotrowicz 2016) and was more effective than usual care in improving peak VO₂, 6-minute walk distance and QoL in a randomized, trial (Piotrowicz 2019, Piotrowicz 2019).

4.3. Diabetes

Diabetes mellitus and metabolic syndrome are strong risk factors for the development of morbidity and mortality associated with a range of cardiovascular diseases. mHealth modalities self-management were recommended recently by ESC guidelines on diabetes and cardiovascular diseases (Cosentino 2019). Glycemic control may reduce AF development and recurrence (Chao 2012, Chang 2014, Gu 2011, Otake 2009). Efficacy for improving glycemic control in randomized controlled trials has shown mixed results (Agarwal 2019, Fleming 2020, Pal 2014, Quinn 2011, Whaley 2019).

4.4. Hypertension

Hypertension, because of its high prevalence, provides the highest attributable risk for the development of AF (Huxley 2011). BP telemonitoring might be more effective than usual care in achieving target BP (Bosworth 2011, Kim 2015, McManus 2010). A meta-analysis showed that, compared with usual care, BP tele-monitoring improved office systolic BP and diastolic BP by 3.99 mm Hg (95% confidence interval (CI): 5.06–2.93; $P < 0.001$) and 1.99 mm Hg (95% CI: –2.60 to –1.39; $P < 0.001$), respectively (Duan 2017).

4.5. Disorders Including Sleep Apnea (See also Heart Failure Section 4.2.1)

Sleep disorders are widely prevalent and contribute to cardiovascular risk and arrhythmias, especially AF (Daghlal 2019, Hirshkowitz 2015, Mehra 2006, May 2016, May 2017, Institute of Medicine Report: Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem), (Institute of Medicine (US) Committee on Sleep Medicine and Research//www.ncbi.nlm.nih.gov/books/NBK19961. Treating sleep apnea may reduce AF burden (Qureshi 2015, Youssef 2018).

Consumer technology preinstalled on many smartphones directed to sleep medicine measure total sleep time accurately, but not more detailed parameters such as sleep efficiency and different sleep stages (Mantua, 2016). Wearable devices may detect sleep apnea with good accuracy compared to gold-standard polysomnography (Selvaraj 2014) and transform the approach to sleep disorder screening, diagnosis and treatment. Sleep irregularity diagnosed by 7 day wrist actigraphy was linked to risk of cardiovascular events (Huang 2020).

4.6. Lifestyle (See Figure 5)

4.6.1 Physical activity

Fitness represents an enormous market for mobile technologies, and a significant opportunity to improve the health of a wide range of mHealth consumers. Many of these recreational apps monitor daily physical activity and support a healthy lifestyle by counting the number of steps daily, on-line training, and motivation coaching (McConnell 2018).

- Cardiorespiratory fitness has an inverse relationship to AF burden (Faselis 2015).
- Improvement in exercise capacity of 2 METs in overweight individuals may double freedom from AF (Pathak 2015)

Endurance athletes may have increased AF risk (Abdulla 2009, Anderson 2013). Mobile devices can be used as a self-monitoring tool for managing (Aroganam 2019, Li 2016, Peake 2018, Peart 2019, Seshadri 2019) performance and level of training but can also provide valuable information regarding heart rhythm irregularity suggestive of arrhythmias- which should trigger formal cardiological evaluation.

4.6.2. Diet

Weight loss combined with risk factor modification is a Class 1 (B-R) recommendation in the treatment of AF (January 2019). A >10% weight reduction/ target BMI <27 kg/m² reduces AF burden (Pathak 2015). Compliance with this recommendation is poor; the reasons include among others, inability to track food intake (Abed 2013, Donnellan 2019, Pathak 2015). There are currently many consumer-oriented mobile-phone based applications (apps) designed for tracking food intake but require multiple steps ; eg the user types in the food consumed and then scrolls through the search results to match with the program's food and nutrient database. Next, after finding a matching food type, the user must estimate and enter an amount. These apps require significant user input and time burden along with high possibility of error (Griffiths 2018).Despite their profusion, high-quality evidence for efficacy is lacking (Dounavi 2019).

5. PATIENT SELF-MANAGEMENT - INTEGRATED CHRONIC CARE

5.1. Patient engagement

Structured management programs including intensive patient education may improve outcomes (Angaran 2015, Coorey 2018, Gandhi 2017, Hendriks 2012; Park- 2016, Phaeffli 2016, Slotwiner- 2019, USPTF 2014). mHealth may reach more patients more effectively through ease of access and wider dissemination. mHealth

may facilitate information sharing and interaction between patients and health care professionals (HCPs) without the need for an elaborate infrastructure, overcoming traditional barriers of cost, time, distance, embarrassment/stigma, marginalised groups, health inequities, etc (Chow 2016, Walsh 2014). (Figure 6). HCPs may use apps to guide explanations of the condition and treatment options, utilising videos, avatars, and individualised risk scores, enabling greater patient understanding and encouraging a two-way exchange of information to achieve a concordant decision about treatment. This may encourage active participation and appropriate self-management (eg for AF, hypertension, glucose) to improve key outcomes (Hagglund 2015, Varnfield 2014). mHealth permits information and apps to be tailored appropriately for language, literacy levels (including 'text to speech' technology) and cultural differences to promote engagement (Coorey 2018, Neubeck 2017, Redfern 2016).

The model requires data presentation that is intelligible in lay terms and that patients assume responsibility and accountability for tracking conditions effectively and taking corrective measures. The mobile atrial fibrillation (mAFA) app, incorporating decision support, education and patient engagement, significantly improved AF patients' knowledge, medication adherence, quality of life and satisfaction to anticoagulation compared to usual care (Guo 2017). Notably, demands of self-management may be excessive for even well intentioned patients required to be facile with setting up their own medical monitoring device, assessing frequency of download, interpreting and acting on data when required, and troubleshooting. These are not trivial challenges.

5.2. Behavioral modification

Individual health status has been found to be a strong independent predictor of mortality and cardiovascular events (Rumsfeld 2013). mHealth may catalyze positive behavioral change using support with text messaging (Chow 2015) or mobile applications to remind patients of medication doses and times, as well as medical appointments (although synchronization with healthcare providers and/or EMR is generally lacking). The "Just-in-time adaptive intervention" (JITAI) premise is to provide the appropriate type and amount of support to an individual at the correct time, with the ability to adjust depending on the person's current internal and situational factors (Nahum-Shani 2018). mHealth technology is an ideal platform to facilitate JITAIs by providing 'real-time' personalised information, which can be utilized to inform the intervention delivered. JITAIs have been widely employed for health promotion and to support behaviour change but evidence of their efficacy is limited (Gustafson 2014, Patrick 2009, Riley 2008). Timing is integral to the perception of benefit, as is receptivity to accept and use the support (Nahum-Shani 2015). Bespoke, multi-faceted mHealth tools, with motivational messages and incorporating gamification are most engaging (Coorey 2018, Gandhi 2017, Park 2016, Pfaelli 2016).

Incorporation of gamification strategies (e.g., rewards, prizes, avatars, performance feedback, leader-boards, competitions, and social connection) into mHealth promotes patient engagement and sustains healthy behaviours (Blondon, Cugelman 2013, Edwards 2016, Johnson 2016, Sardi 2017). However, a recent systematic review demonstrated that only 4% (64/1680) of English-language 'top-rated' health apps incorporated ≥ 1 gaming feature (Edwards 2016). There is limited hypothesis-generated data for these mHealth interventions, and their efficacy in this context is as yet unmeasured. Self-regulatory behaviour change techniques, such as feedback and monitoring (including self-monitoring), comparison of behaviour, rewards, incentives and threats, and social support are the most common behaviour change techniques employed in gamification apps and are frequently utilised in successful non-gaming apps targeting health promotion and secondary prevention (Conroy 2014, , Direito 2014, Edwards 2016). Engaging with apps involving gamification can also improve emotional well-being through feelings of accomplishment and social connectivity (Johnson 2016).

5.3. Patients as part of a community

Incorporation of a patient as part of a wider community may offer benefits. Social networking is widely used for health (Fox 2011). On-line communities enable individuals to 'meet', share their experiences, discuss treatment, and receive and provide support from peers, patient organisations, or HCPs (Fox 2011, Swan 2009, Swan 2012). Whilst crowdsourcing via the internet and social networks allows collective sharing and exchange of information from a large number of people, the integrity and accuracy of such information remains largely unvetted and as such may be unreliable (Besaleva & Weaver).

5.4. Maintaining Patient Engagement

Sustaining healthy behaviours and minimising intervention fatigue is paramount to long-term maintenance. Although mHealth may help to maintain motivation, available data demonstrates significant attrition with mHealth interventions targeting risk factors and chronic conditions, even when people report liking the intervention and have purchased it (Chaudhry 2010, Flores Mateo 2015, Fukuoka 2015, Morgan 2017, Owen 2015, Simblett 2018, Whitehead 2016, web-Endevaour, Perez 2019).

A representative patient's experience is described below:

"A few years ago (2017) a friend told me about a new app that he had installed on his iPhone that would allow him to measure his heart rate through a fingertip pulse. Having an irregular heartbeat, under control through medication, I was very interested to try the new app. I thought it would provide me the opportunity to know more about myself, specifically how my heart operated under stress and at different times of day, before, during and after physical exertion of a variety of my favorite sports and pastimes like tennis, golf, biking and fly fishing.

At first, I was quite satisfied with the rudimentary calculations. Then I noticed during my international business travels that the device was often down during US nighttime hours during which time I thought the 'hosts' were making repairs or improvements. I also noticed that there were several radically incorrect readings especially during early morning hours. It simply wasn't performing up to the standards of more traditional monitoring devices. I found as well that the host's increasing attempt to up-sell to premium packages and other online health management tools became quite burdensome.

Before long, I felt almost addicted to the device and ultimately quit on it altogether. In retrospect, I believe that if I had had a proper introduction to the device by a trained medical specialist, I might have had a different expectation of this online tool, how to use it and how to interpret its data output."

Understanding the basis for health-protective behaviour is vital (Dunton 2018). Cost, service connectivity, and credibility of information sources are important factors. However, patient engagement may be jeopardised by worries about privacy and personal data security (Burke 2015, Chow 2016, Kumar 2013, Steinhubl 2015). Continued clinic support may be necessary, but level and duration will likely depend on condition monitored and goals for treatment. Reduction in compulsory routine in-clinic evaluations and reliance on continuous remote monitoring improved retention to long-term follow up of patients with CIEDs (Varma 2014). In one heart failure trial, gain was related to the period of remote instruction. Whether this indicates that efficacy of the active program had peaked and stabilized or that it needed to be sustained is unclear (Varma 2020). Ideally, a training program should be finite in time but its effects durable.

5.5. Digital Divide

Although mHealth promises transformation of health care, it can potentially exacerbate disparities in health care along sociodemographic lines. Older people are perceived to engage less with mHealth. However the lack of familiarity with the technology and access to mobile devices, rather than lack of engagement per se, remain the principal barriers (Coorey 2018, Gallagher 2017, Tarakji 2018, Pew 2017, Neubeck 2015). There is also disparity across the educational spectrum, with smartphone usage in 57% of the population with less than high school education and 91% of the population who graduated from college, and income, with smartphone usage in 67% of the population with income annual \leq \$30,000 and 93% of the population with income \geq \$75,000 (PR.C Mobile 2018).

There is heterogeneity of mHealth availability among different countries (Varma 2020) regulatory or marketing rules, or simply unaffordable to either individuals or differing health care systems. While leveraging and incorporating smartphone-based technology into workflow and processes, a strategy is needed in parallel to ensure that those without access will continue to receive appropriate high quality care (Bhavnani 2017).

6. CLINICAL TRIALS

Traditionally, clinical trials testing drugs and devices for arrhythmias utilized time-to-event outcomes and analyses, such as first recurrence of AF after a blanking period (Piccini, 2017). Patients randomized to the control and intervention would be monitored intermittently, either with ambulatory devices and/or in-clinic visit. Such monitoring had limited sensitivity for recurrent arrhythmias, including symptomatic and asymptomatic episodes. Furthermore, time-to-first event may not accurately capture reductions in arrhythmia burden, which have also been shown to be beneficial in recent randomized trials (Andrade 2019). While CIEDs (pacemakers, defibrillators, ILRs) can be leveraged for continuous monitoring (Varma 2005), these studies do not generalize to broader CIED-free populations.

Most free-standing handheld ECG monitors, some with automated AF detection (Table 1) do not have cellular or networking capability and therefore generally cannot transmit data or findings in real time. This is where smart- or mobile-connected arrhythmia and pulse detection technologies have significant promise. These may enhance detection and measurement of clinical outcomes while also allowing for remote or virtual data collection without the need for site-based study visits. Examples include remote rhythm assessment with single or multilead ECGs from smartphone or smartwatch-based technologies and automatic ascertainment of hospitalizations using smartphone-based geofencing (Nguyen 2017). These operational enhancements, in turn, can improve participant satisfaction, reduce cost, improve study efficiency, and facilitate or expand enrollment. An example is the ongoing Health eHeart study, a site-free cardiovascular research study that leverages self-reported data, data from wearable sensors, electronic health records, and other importable "big data" to enable rapid-cycle, low-cost interventional and observational cardiovascular research (<https://www.health-eheartstudy.org/>).

Screening

Two recent large scale studies highlight the potential advantages of mHealth for AF screening and treatment. The Apple Heart Study was a highly pragmatic, single-arm investigational device exemption study designed to test the performance and safety of a PPG-based irregular rhythm detection algorithm on the Apple Watch for identification of AF (Perez 2019, Turakhia 2019). The study was a siteless “bring your own device” study, such that participants needed their own compatible smartphone and watch to enroll online. All study procedures, including eligibility verification, onboarding, enrollment, and data collection, were performed via the study app, which could be downloaded from the app store. If a participant received an irregular pulse notification, then subsequent study visits were done via video conferencing to study physicians directly with the app. The study enrolled over 419,000 participants without pre-existing AF in just an eight-month period, in large part due to the pragmatic, virtual design and easy accessibility (Figure 4). The algorithm was found to have a positive predictive value of simultaneous ECG-confirmed AF of 0.84 (Perez 2019). Only 0.5% of the enrolled population received any irregular pulse notification, but 3.2% of those age ≥ 65 years received notifications. However, only 153/450 (34%) patients had AF detected by a subsequent single ECG patches after the irregular rhythm notification was received. This may reflect the paroxysmal nature of early-stage AF rather than explicit false positives. Because the study only administered ECG patch monitoring to those with irregular rhythm notification rather than the entire cohort or to negative controls, the negative predictive value was not estimated. It should be noticed that the Apple Heart Study was in a population without diagnosed AF; test performance and diagnostic yield could be considerably different in a population with known AF, and this software is not approved for use for AF surveillance in established AF.

The Huawei Heart Study was similar, using smart device-based (Huawei fitness band or smartwatch) PPG technology (Guo 2019). The algorithm had been validated with over 29 485 PPG signals before commencement of the trial.) More than 246,000 people downloaded the PPG screening app, of which about 187,000 individuals monitored their pulse rhythm for 7 months. AF was found in 0.23% (slightly lower than Apple Heart, possibly due to a younger and healthier enrolled cohort). Validation was achieved in 87% (PPV $> 90\%$) compared to 34% in Apple Heart. The results indicated that this was a feasible frequent continuous monitoring approach for the screening and early detection of AF in a large population. Moreover, data enabled management decisions eg almost 80% high risk patients were anticoagulated. Subsequent enrollment into the mAFA II trial showed significantly reduced risk of rehospitalization and clinical adverse events (Guo 2020). These trial results encourage incorporation of such technology effectively into the AF management pathways at multiple levels ie screening and detection of AF, as well as early interventions to reduce stroke and other AF-related complications.

Another large scale virtual study to identify episodes of irregular heart rhythm suggestive of AF was announced by Fitbit in May 2020 (HRS 2020 7 May 2020).

Point of Care

The next step beyond parameterizing safety could be to actionably guide therapy at the point of care (Figure 6). For example, patients could obtain ECGs before and after taking “pill-in-the-pocket” antiarrhythmic drug therapy such as flecainide to confirm AF, ensure no QRS widening, and confirm restoration of sinus rhythm. A similar approach has been proposed for rhythm-guided use of direct oral anticoagulants in lower-risk AF patients with infrequent episodes either spontaneously or as the result of a rhythm control intervention including drugs and ablation; a randomized trial is in development (Passman 2016). The use of smartwatch-guided rate control as a treatment strategy could also be tested, as this may provide a more personalized approach rather than prior randomized trials of lenient versus strict rate control that used population level rather than personalized heart rate treatment thresholds (Van Gelder 2010).

Potential limitations are several. These include access (See 5.4.2 Digital Divide). mHealth-based evaluation of clinical endpoints may be confounded if adherence is low, particularly if there are no secondary means of endpoint assessments (Guo 2017). Virtual designs may be more susceptible to the loss of participant engagement. For example, if monitoring is completely reliant upon mobile health technology and there are no traditional measures or in-person visits to assess arrhythmia, then significant missing data due to low-adherence may become a major limitation that could imperil the validity and generalizability of the findings. For example, among the 2,161 of the 419,297 that received an irregular pulse notification in the Apple Heart Study, only 945 completed a subsequent protocolled first study visit. Of these 658 ambulatory ECG patches shipped, there were only 450 with returned and analyzable data (Perez 2019). Development of effective strategies to increase retention and maintain high engagement remains an unmet need and is an area ripe for more research.

Adoption and reimbursement rest on demonstration of improved outcomes. More specifically, the clinical and prognostic impact of new outcome measures based on mobile health technologies may not be clear and require fresh calibration. This is important for AF. For example, how do changes in AF burden compare to reductions in time to symptomatic sustained AF? Should AF identified on near-continuous smartwatch monitoring be considered equivalent to AF diagnosed at hospitalization or in clinic? There is a growing body of literature

that the “dose” of AF burden matters for a variety of important clinical endpoints, including stroke, HF, and death (See Section 3.1.3) (Chen 2018, Glotzer 2009, Kaplan 2019, Piccini 2019, Wong 2018). Does pill in the pocket DOAC treatment of PAF adequately cover the risk of stroke? Some measures remain less well studied, like the occurrence of irregularity with a wearable pulse-based monitor system, particularly without ECG confirmation. Since these mHealth prediagnostic or diagnostic tools may then be directly tied to initiation or termination of treatment, rigorous evaluation of clinical safety and efficacy will be required, and in some cases, warrant a combined drug-device regulatory approval.

7. OPERATIONAL CHALLENGES

7.1. Health Care System – Ehealth Monitoring and Hospital Ecosystem

Transmission

A fundamental but as yet unresolved challenge of incorporating mHealth into clinical practice is the channel of data communication between patient and provider. This may differ depending upon whether the data is physician-facing (eg for CIEDs) or patient-facing (consumer digital health products eg the Apple Watch (Apple Inc., Cupertino, Ca).

Interoperability • Lack of organized infrastructure to receive incoming data

Assimilating the data obtained from digital health tools, whether implantable or wearable, is proving to be one of the greatest clinical challenges. Clinicians feel increasingly burdened as both the volume of data as well as the sources of data increase. It requires a consensus from the clinical community regarding definitions of the terminology and agreement on what data are necessary. It requires a coalition of clinicians, engineers, regulatory agencies as well as regulatory and/or financial incentives for vendors for resolution.

Interoperability • Lack of organized infrastructure to transmit data and instructions

There is interest in mHealth to support patients with text messaging (Chow 2015) or mobile applications to remind patients of medication doses and times or medical appointments.

7.2. Cybersecurity Guidance for mHealth Devices

Interconnection of medical devices and clinical data promises facilitation of clinical care but also creates opportunities for intrusions by maleficent actors (i.e. hackers) (PHI) (Jalali 2019, Kruse 2017). Healthcare facilities and medical device companies present attractive targets because a number of attack strategies can yield large financial rewards:

- 1) Ransomware. A hospital's systems can be locked out (e.g. data may be encrypted) until the attacker is paid (Mansfield, 2016, Network security 2016)
- 2) Theft and sale of patient data (i.e. PHI).
- 3) Company attack. A hacker may identify flaws in a system or device, short the company's stock, then make the flaws public. Scenarios where a cyber attack results in the deaths of individuals or groups, but to date no such attack is known to have occurred in the real world.

7.2.1 Hacking strategies and methods in mHealth technologies

Often times, attackers will not directly compromise the system that they are after; they will instead start by compromising a weaker link. The process of chaining exploits to work through a system is called pivoting. Each pivot or “hop” enables new privileges that bring the hacker closer to desired goals.

The easiest thing to exploit is often a person with phishing campaigns. A compromised email account can be used to reset passwords for other services, and to distribute more realistic phishing messages.

7.2.2. Recommendations to the manufacturer

It is not possible to create systems that cannot be hacked. However, systems/devices should be designed to fail gracefully in conjunction with a plan. This enables rapid correction in the event of intrusion.

These communications could be made more secure but less usable (e.g. requiring wires), or less secure but more usable (e.g. using Bluetooth).

7.2.3. Recommendations to clinicians and administrators

The organization should be designed with security in layers (also called defense in depth), where each system is protected with more than one layer of security. Hence a breach in one layer will not necessarily result in total compromise.

Regulatory frameworks around cybersecurity are changing rapidly (Voelker 2018). The FDA (as well as other regulatory agencies worldwide) now includes security as a part of device safety/efficacy checks, and we en-

courage readers to report security issues to manufacturers and the government (e.g. through FDA Medwatch) (Shuren 2018).

7.2.4. Recommendations to patients

Clear advice to patients concerning cybersecurity should be followed by a formal patient informed consent.

7.3. Reimbursement

Reimbursement is a powerful driver of adoption of new clinical pathways and typically instituted once an intervention has been proven scientifically valid and cost-effective (Treskes 2016). This process has only just started in mHealth and may be more complex to measure given the wide scope of telemedicine.

- *Reduced costs*
mHealth may help individuals adhere to health recommendations, empower active participation in lifestyle changes to modify cardiovascular risk profile, and promote adherence to medical therapy (Feldman 2018).
- *Increased costs*
Conversely, there are costs associated with administering mHealth programs. Healthcare providers will be required to spend time reviewing and interpreting potentially voluminous results. This requires financial compensation in order to maintain a viable practice.
- *Remote monitoring of implanted devices*
Remote-monitoring reimbursement (eg US, Germany, France, UK) is implemented in a discrete way following the protocols of randomized trials like TRUST or IN-TIME (Varma 2010, Hindricks 2014) with billing after demonstration of a remote contact, with a maximum number per year. Responsibilities for reimbursement may extend beyond traditional parties in health care, and drive novel pathways. Mobile device companies are clearly interested in reimbursement issues, evidenced by contact between Apple health executives and insurance companies (Bruining 2014).

7.4. Regulatory Landscape for mHealth Devices

The pace of changes and improvement of digital technology is furiously fast. With the release and spread of the 5G cellular technology, this growth will probably be strengthened, and new frontiers around data streaming and associated analytics will be crossed. In the U.S., mHealth technologies are primarily led by private organizations operating under constraints linked to financial incentives (CMS reimbursement guidelines), patient privacy (Health Insurance Portability and Accountability Act), and patient safety (Food and Drug Administration, FDA).

8. PREDICTIVE ANALYTICS

Artificial Intelligence (AI) is a broad term that describes any computational programs that normally require human intelligence such as image perception, pattern classifications, inference, or prediction (www.oed.com; Kagiya, 2019). The potential synergy between AI and mHealth may enable solutions to improve patient outcomes and increase efficiency with reduced costs in healthcare (Davenport 2019; Marcolino 2018). Smartphone apps and wearable devices generate a huge amount of data that exceed the human capacity of integration and interpretation (Steinhilbl 2015). This knowledge may be directed to treat an individual, or understand populations. For instance, 6 billion nights of surrogate sleep data reflecting global sleep deprivation may potentially inform public health initiatives (<https://aasm.org/fitbit-scientists-reveal-results-analysis-6-billion-nights-sleep-data>). Mobile health with internet connection enables cloud based predictive analytics from individual level information (Bumgarner 2018, Nascimento 2018, Ribeiro 2019).

Cardiology has been an early area of investigation in AI due to the abundance of data well suited for classification and prediction (Seetharam 2019). Neural networks have been tested, trained, and successfully validated to be at least as accurate, if not more, than physicians in diagnosis or classification of 12-lead ECGs and recognition of arrhythmias in rhythm strips and ambulatory ECG recordings, and even identify left ventricular dysfunction (Attia 2019, Hannun 2019, Ribeiro 2019, Smith 2019). These methods have the potential for a point-of-use diagnosis of a wearable sensor or consumer device and without delays of requiring clinical confirmation, although rigorous safety assessments of unsupervised use will be necessary. More recently, AI methods have also been applied to prediction, not just classification, for example, using 12-lead ECG to predict risk of AF from a sinus rhythm ECG (Attia 2019).

In mHealth applications, AI has been embedded in smartwatch and smartphone-connected ECG for semi-automated diagnosis of arrhythmias (Bumgarner 2018, Halcox 2017). These serve as pre-diagnostics rather than supplanting a physician interpretation. In HF, a cloud-based analytics platform used a general machine learning method of similarity-based modeling which models the behavior of complex systems (eg, aircraft engines) to create a predictive algorithm for HF decompensation, using data streamed from a chest patch sensor.

Limitations exist. Studies on AI are still scarce and validation generally lacking. Most algorithms work with the "black box" principle, without allowing the user to know the reasons why a diagnosis or recommendation was generated, which can be a problem, especially if the algorithms were designed for a different environment than the one that the current patient is inserted (Ribeiro 2019). Issues regarding cost-effectiveness, implementation, ethics, privacy, and safety are still unsolved. Thus, high-quality evidence that supports the adoption is not available at this time.

Table 4. Randomized Trials with Neutral Results Based on External-Device Remote Patient Monitoring (RPM)

| Study Name | Sample Size | Study Design and Tested Modality | Potential Explanation for Lack of Benefit |
|--|-----------------------|--|--|
| TIM-HF (Koehler Circulation 2011) | N = 710 (355 on RPM) | Randomized trial of a Bluetooth-enabled device designed to follow 3-lead electrocardiography, blood pressure and weight | Participants had stable HF, so it may be that remote monitoring is not as effective in lower-risk patients |
| Tele-HF (Chaudhry N Engl J Med 2010) | N= 1653 (826 on RPM) | Telephone-based interactive voice response system with a higher risk population than in the TIM-HF study | Patient adherence was poor, with <55% of the study subjects using the device 3 days per week by the end of the study. Interestingly, a smaller previous trial had shown benefit; this difference in results implies that how a technology is implemented might determine benefit |
| BEAT-HF (Ong JAMA Intern Med 2016) | N = 1437 (715 on RPM) | Health-coaching telephone calls with monitoring of weight, blood pressure, heart rate, and symptoms in a high-risk population with 50% rehospitalization rate | Non-adherence was the primary limitation, with only 61% of patients more than half-adherent in the first 30 days |
| Mayo Clinic Study (Takahashi Arch Intern Med 2012) | N = 205 (102 on RPM) | Telemonitoring in a primary care (PC) panel (various health conditions and not only HF) in the top 10% of Elder Risk Assessment Index managed with biometrics (BP, HR, weight, pulse oximetry, etc) plus daily symptom assessment. Video conference capability was present | Abnormal telehealth data were directed to PC providers. It is unclear what action this drove. It might have caused the PC provider to direct the patient to an emergency department or a hospital. Could increased symptom surveillance actually increase health care utilization? |
| TEHAF (Boyne Eur J Heart Fail 2012) | N = 382 (197 on RPM) | Electronic device to assess symptoms and educate patients with HF. Abnormal symptoms directed to a monitoring nurse. Device tailored itself to patient's knowledge | Excellent adherence with use of the device. Planned and unplanned face-to-face HF nurse visits were higher in the control group. Event rates for both groups were lower than expected. Primary limitation appeared to be the excellent outcomes in the control group. |
| LINK-HF (Stehlik, Circ HF 2020) | N=100 | Disposable multisensor chest patch for 3 months linked via smartphone to cloud analytics. Apply machine learning algorithm. | Pilot study, compliance eroded. However, this detected precursors of hospitalization for HF exacerbation with 76% to 88% sensitivity and 85% specificity. |

9. FUTURE DIRECTIONS

mHealth is disruptive at multiple levels of health care but requires significant investment in validation, demonstration of clinical utility and value. Stakeholders, each with independent concerns and constraints, (Table 5) lack consensus or coordination with design, use cases, and implementation (Figure 7). Thus formal recommendations for integration of mHealth into clinical practice cannot be made at this time. This is exemplified by the US Preventative Services Task Forces statement that "evidence is insufficient to initiate therapy for AF

Table 5. Conditions, Stakeholders and Expectations

| | Applications/ Conditions | Opportunities | Challenges to resolve |
|--------------------------|--|---|---|
| Bio-signals monitored | Diverse | Multi-parametric trending Contactless screening | Lack of validation Transmission frequency Ethics |
| Target condition | Arrhythmias Treatment Follow up Rehabilitation Lifestyle modification Chronic disease | Screening Prevention Facilitate management | Lack of outcome data |
| Users | Healthy consumers | Increase use by patients | Managing the “worried well” |
| Patient Expectations | Confidence Engagement Education | Data access Real-time treatment Self-management | Data access Driven by popular press Excessive focus on data without clinical context Digital divide Lack of internet access |
| Physician Expectations | Versatility | Validation Improve patient outcome Reduce in-clinic visits Real-time patient treatment Predictive Analytics Precision Medicine | Absence of FDA approval Lack of outcome data Establish transmission frequency Define clinical actionability Manage false-positives Standardize data flow Manage data overload Inter-operability with EMR Mechanism for feedback to patients for treatment decisions; Assurance of patient adherence Physician or Manufacturer? Reimbursement Legal responsibility |
| Hospital | Improve efficiencies Improve access | Predictive analytics Interoperability Cybersecurity Reimbursement | Lack of outcome data Value impact Legal responsibility |
| Technology/ Manufacturer | Direct to Consumer Sales | Patient care Community care | Learn treatment pathways Partner with clinic Legal responsibility Predictive analytics |
| Payor | Reduce costs Improve outcome | Cost-benefit analysis | |

detected by mHealth” - despite the fact that AF has been an early use case with strong patient and clinician interest (Curry 2018). Thus mHealth devices are currently non-prescription devices marketed directly to consumers to track data without enabling interventions.

Some of the steps needed to standardize mHealth applications are outlined below.

1. Validation

- Promote standards and create tools for the comparative assessment of functionality, relative to a medical use device.

Results from different devices applied to the same condition may not match: for example, the diagnosis of AF by ECG or PPG based systems are made very differently. This has significant implications for medical decisions.

2. Identify clinical care pathways

• Screening

- o Assess value according to the population addressed
- o Establish a uniform set of criteria for clinical actionability (Slotwiner 2019)

Screening should be medically directed and not driven by commercial interests. AF detected with mHealth technologies (“healthy consumers”) may not have the same implications as for cohorts with clinically diagnosed AF. Data from low risk populations has higher risk of false positives, generating additional tests and overtreatment with resultant clinical risk to patient costs to the payor. Unless directed to higher risk populations, AF screening using mHealth technologies may fail similarly to many medical screening programs throughout history.

Key knowledge gaps

• Disease management

- o Identify characteristics (duration, episode number/ density) and risk factors that justify anticoagulation for mHealth detected AF.
- o Identify conditions and schedules for home-based therapeutic strategies that may reduce dependency on clinic evaluations (as shown for CIEDs)
- o Identify signals that predict decompensation and design pre-emptive interventions
- o Assess efficacy of therapies

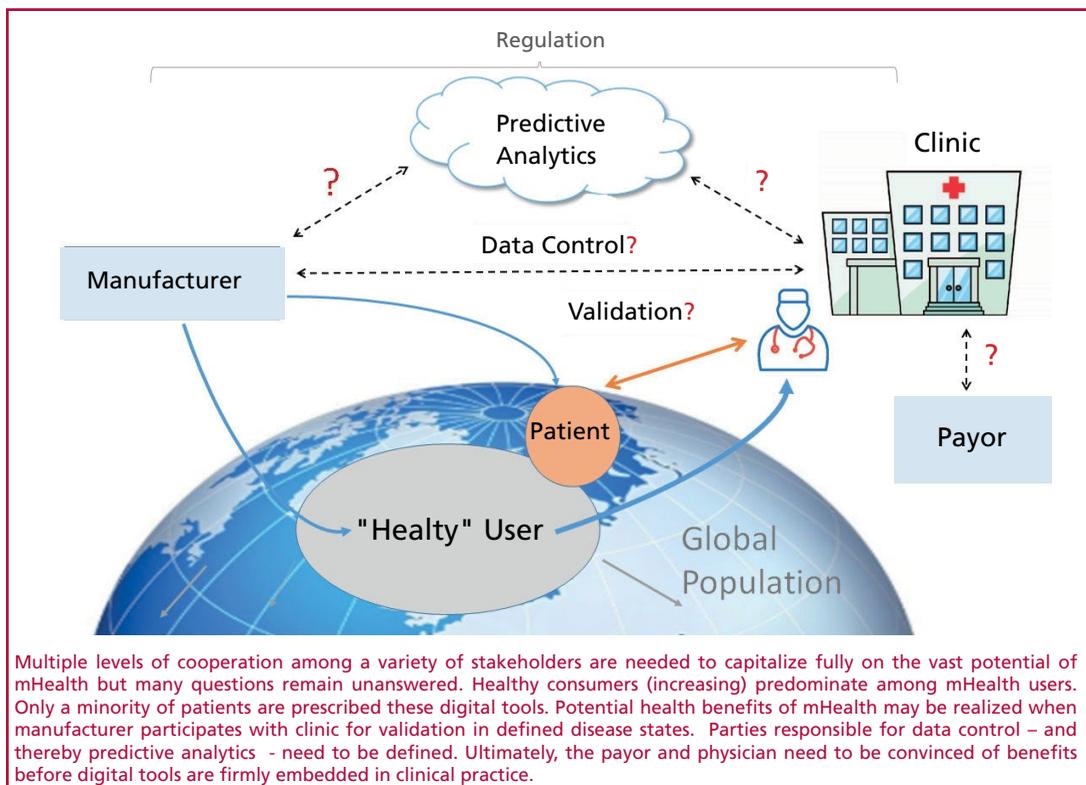


Fig. 7. Connectivity- and Questions

- **Outcomes**

Evidence for benefit of mHealth directed

- o arrhythmia treatment
- o management of modulating factors (eg comorbidities, lifestyle modifications)

3. Implementation

- **Cost effectiveness**

Impact on health care system and reimbursement

Impact on costs to patient or consumer

- **Public health and Professional society initiatives**

Education, awareness

Bring together stakeholders

Guidelines

4. Patient Self management

- Education on which data are clinically actionable in individual's clinical context and Tailor monitoring schedule accordingly (Pluymaekers 2020).
- Safety

5. Manufacturer

mHealth introduces the manufacturer as a party with significant responsibilities. A direct to-consumer health-care delivery bypasses both the clinician, health care system, and insurer, without addressing the needs of health professionals – who remain responsible for clinical decision making on acquired data.

6. Assign responsibilities

- Identify parties (manufacturer, hospital, third party) responsible for cybersecurity, data protection and liability for mis-diagnosis or missed diagnosis
- Ethical and societal issues with multiple screening (Yan 2019, Turakhia 2020).

7. Health Care Delivery

Interconnectedness between individual applications and with existing health care architectures may reshape the current environment.

Concluding Remarks

Few of the mHealth technologies described are universally approved and/or affordable. The WHO envisioned that increasing the capacity to implement and scale up cost-effective innovative digital health could play a major role in towards achieving universal health coverage and ensuring access to quality health services, at the same time recognizing barriers similar to those discussed here. Some of these can be resolved rapidly, as seen in response to the recent SARS-Cov-2 global pandemic which forced a need for contactless monitoring and thereby adoption of digital tools (DHSS, FDA, Varma 2020). Regulatory bodies were responsive, approving technologies, relaxing rules confining use of telehealth services within borders and to certain patient populations, and creating a reimbursement structure, illustrating that appropriate solutions can be created when necessary.

Demonstration of the clinical utility of mHealth has the potential to revolutionize how populations interact with health services, worldwide.