

What is the value of digital tools for cardiovascular patients?

A comprehensive review of evidence for effectiveness and cost-effectiveness for prevention and management

July 2020

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The review was funded by the European Heart Network



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Aim

The potential of digital health in the prevention and management of cardiovascular disease is increasingly recognised. The aim of this paper is to provide an overview of the current evidence and remaining gaps of digital health tools for cardiovascular patients. For that purpose, the research team reviewed the most important digital health trials from 2000 until the end of 2019.

Executive summary

The number of people with cardiovascular disease is increasing yearly. This leads to continuously increasing workload and costs and hence pressure on healthcare systems in Europe. At the same time, new technologies such as wearables, biosensors, smartphone applications and artificial intelligence are being developed in a fast pace. In the last decade, there is an increased interest in applying these new technologies to advance cardiovascular diagnosis and care with the aim to improve patient outcomes and to reduce the economic pressure on many healthcare systems in Europe.

The use of technology in medicine is called digital health. Digital health is often divided in two main components, namely mHealth and telemedicine. mHealth comprises the use of smartphones, tablets and wearable technologies for health services. Telemedicine on the other hand can be defined as the delivery of remote care.

Digital health has the potential of improving primary prevention of cardiovascular disease by increasing patient empowerment and remote follow-up with smartphone applications, text messaging and internet-based interventions. This report looks at the potential of digital health for the following modifiable risk factors: arterial hypertension, diabetes mellitus (type 2 diabetes), smoking, overweight and obesity, and a sedentary lifestyle.

Key findings in the role of digital health in arterial hypertension:

- Current evidence suggests that telemonitoring could be effective in reducing blood pressure, but more research is needed to confirm the added value of telemonitoring to self-monitoring.
- More research is also required to confirm the cost-effectiveness of this intervention.
- Smartphone applications have much potential in remote monitoring and improving hypertensive patients' medication adherence. However, there is not yet enough evidence to confirm the effectiveness of mHealth applications in hypertension management.

Key findings in the role of digital health in diabetes mellitus (type 2 diabetes):

- Telemonitoring of blood glucose in type 2 diabetes patients seems to improve control of glycaemia, health-related quality of life and HbA1C. More trials are needed to support the implementation of telemonitoring.
- The use of text messaging and smartphone applications could also play a role in the chronic management of type 2 diabetes. Text messaging could increase therapy adherence and improve lifestyle choices. More research and larger trials will be indispensable to confirm the cost-effectiveness in comparison with standard care and telemonitoring.
- Several trials demonstrate that smartphone application can reduce HbA1C. This suggests that smartphone applications will play a role in type 2 diabetes management in the future. More research is needed to confirm this.

Key findings in the role of digital health in smoking cessation:

- Internet-based smoking cessation programmes present very contradictory results. A recent meta-analysis of 2019 suggests that internet-based smoking cessation interventions increased the odds of cessation by 29% in the short term and by 19% in the long term. However, more evidence is needed to implement internet-based intervention in regular care.
- Evidence shows that text messaging is an effective intervention to improve cessation rates and that it could be a standard element of smoking cessation interventions.
- Smartphone applications could be effective; however only four trials on such interventions were published between 2015 and the end of 2019. More evidence is needed.

Key findings in the role of digital health for weight loss:

- Internet-based weight loss interventions have positive effects on diet choices, physical activity and weight.
- Smartphone applications can help to achieve a moderate short-term weight loss. More research is needed to demonstrate long-term results and to assess the cost-effectiveness of these interventions.
- The effectiveness of text-messaging interventions for weight loss remains debatable. Two meta-analyses demonstrated a small effect of text-messaging interventions in short-term weight loss. However, lack of long-term results indicate that further studies

are required. Research is also needed on the cost-effectiveness of text-messaging interventions.

Key findings in the role of digital health for improving physical activity:

- Pedometer- or activity tracker-based interventions are associated with reduced sedentary time among adults in the short term. Larger and longer trials are still needed to evaluate long-term effects and cost-effectiveness of these interventions.
- Smartphone applications for increasing physical activity have positive effects, however the effects are small. More research and larger trials are needed to confirm the long-term maintenance of higher physical activity.
- Text messaging can lead to increased physical activity.
- The effect of online social networks, gamification and incentives has been investigated in multiple small trials. Most of these interventions show modest improvement of physical activity.

Furthermore, digital health has also proved to be effective to deliver remote cardiac rehabilitation in patients with ischemic heart disease. Our key findings regarding telerehabilitation are the following:

- Home-based exercise training or telerehabilitation for ischaemic heart disease patients is an effective way to deliver exercise training in patients who cannot attend centre-based cardiac rehabilitation.
- Home-based exercise training or telerehabilitation for ischaemic heart disease patients is an effective way to deliver exercise training as an add-on to centre-based cardiac rehabilitation to increase long-term effects of cardiac rehabilitation.
- Several trials suggest that telerehabilitation, whether standalone or as add-on, is cost-effective. However, larger studies in different healthcare systems, as well as more cost-effectiveness research are needed.

Review of evidence on digital health for secondary prevention of ischaemic heart disease identified that:

- Lifestyle management of ischaemic heart disease with the help of digital health tools is an effective way to optimise risk factor profiles of patients.

- Telephone counselling, text messaging and smartphone applications are effective, while Internet-based interventions have failed to prove effectiveness up to now.
- Smartphone applications have the potential to provide very accessible pocket-size interventions.

Telemonitoring of heart failure patients is already well studied but some controversy regarding its effectiveness remain. Similarly, most studies show positive effects on exercise capacity and quality of life (QoL) in telerehabilitation of heart failure. However, there is uncertainty with respect to long term outcomes. The key points regarding telemonitoring in heart failure patients are the following:

- Many trials have demonstrated the effectiveness of telemonitoring in reducing rehospitalisation and in improving heart failure patients' quality of life.
- Meta-analyses of these trials demonstrate significant improvement in outcomes from telemonitoring interventions, especially in the short term. However, some large multi-centre trials have failed to demonstrate effectiveness of telemonitoring.
- New randomised multicentre studies are needed to identify which telemonitoring interventions are effective.

The key points regarding telephone follow-up in heart failure patients are the following:

- Telephone counselling can be effective in reducing hospital admission for heart failure but seems most effective in improving patients' health knowledge and self-care skills.
- Cost-effectiveness of a structured telephone counselling approach remains questionable.

The key points regarding smartphone applications and text messaging interventions for heart failure patients are the following:

- There is not yet very strong evidence for the use of smartphones in improving heart failure patients' self-management with long-term outcomes.
- Most trials have very small sample sizes and short follow-up periods.
- The potential of smartphone use in long-term management of heart failure may be considerable. But it needs to be demonstrated through long-term randomised multi-centre trials.

The key points regarding telerehabilitation in heart failure patients are the following:

- There is still a debate whether telerehabilitation is effective in reducing rehospitalisation and mortality in heart failure patients.
- More research in home-based exercise training in heart failure is needed to investigate the long-term effects.

The key points regarding home-hospitalisation in heart failure patients are the following:

- Home-hospitalisation supported by IT technology could potentially reduce the need for hospital beds and improve heart failure patients' outcomes and quality of life.
- Home-hospitalisation research is still in its infancy, awaiting strong proof from randomised controlled trials.
- The necessary technology and organisation can, nevertheless, already be used to help in safely discharging heart failure patients earlier.

Digital health provides many opportunities in the field of cardiac arrhythmia. Smartphones, smartwatches, and bio patches are exciting new technologies for ambulatory monitoring and screening of atrial fibrillation. Nonetheless, more research is still required to confirm the cost-effectiveness of these interventions. Specifically:

- Smartwatches, handheld devices and bio patches show some promising results for long-term monitoring and mass screening; however, more research is needed to confirm their accuracy and cost-effectiveness.
- More research is also needed to investigate the role and implementation of digital health monitoring in current workflows and care pathways.

Key findings regarding prehospital emergency ECG include:

- Prehospital ECGs can be transmitted through telemedicine devices, telephone, smartphones etc.
- Multiple studies demonstrated that prehospital ECG is associated with lower door-to-balloon time and increased survival.

Review of evidence in digital health for anticoagulation treatment in atrial suggest that:

- Digital health technology can increase patients' adherence to treatment.

- No good cost-effectiveness studies are available, but it may be expected that these low-cost interventions will prove to be cost saving.

Multiple trials have reported the effectiveness and cost-effectiveness of remote monitoring of cardiovascular implantable electronic devices (CIEDs) by reducing rehospitalisation, mortality and healthcare costs in combination with high patient and health professional satisfaction. Specifically,

- Most trials and meta-analyses demonstrate that remote monitoring of CIEDs is effective in reducing rehospitalisation, mortality and healthcare costs.
- The use of intrathoracic impedance monitoring with CIEDs, an early warning of impending decompensation in heart failure patients, needs further investigation.
- Patient-reported health status and ICD acceptance did not differ between patients on remote monitoring and patients receiving usual care.
- Studies demonstrate high satisfaction with remote monitoring.
- Patients with a preference for remote monitoring were more likely to be higher educated and in employment.

The key points regarding use of wireless implantable hemodynamic monitoring systems are the following:

- The CHAMPION trial demonstrates a large reduction in hospitalisation after six months follow-up for patients with severe heart failure.
- More research is needed to consistently implement implantable hemodynamic monitors in standard care, but most trials show promising results.

The key points regarding remote monitoring of CIEDs for detection of cardiac arrhythmias are the following:

- Arrhythmias detected by remote monitoring are predictive of adverse events.
- Device-detected atrial fibrillation is associated with an increased risk of ischaemic stroke.
- Changing the OAC administration based on arrhythmia detection by CIED is feasible.

The key points regarding implantable loop recorders are the following:

- Implantable loop recorders are effective in the diagnosis of unexplained syncope.

- Implantable loop recorders can play an important role in the diagnosis of paroxysmal atrial fibrillation and life-threatening arrhythmias.

Artificial intelligence could potentially play a big role in electrocardiography (ECG) diagnosis, cardiovascular imaging and risk prediction models.

Co-creation of digital health tools with all relevant stakeholders, including patients and health professionals, is key to overcome common barriers such as lack of personal motivation, low digital literacy, lack of interoperability and increased workload. Furthermore, integration of the electronic medical records is important not to overwhelm physicians with digital health tools and data.

There are already many digital health trials in cardiology. Unfortunately, most of these trials are performed in one centre with a small sample size. Hence more studies are desirable to investigate the long term effects of digital health interventions and the cost-effectiveness thereof.

List of abbreviations

ACS: Acute Coronary syndrome

AF/AFIB: Atrial Fibrillation

AUC: Area under the Curve

BP: Blood pressure

CABG: Coronary artery bypass grafting

CAD: Coronary artery disease

CIED: Cardiovascular implantable electronic devices

CR: Cardiac rehabilitation

CRT: Cardiac resynchronisation therapy

CVD: Cardiovascular disease

EC: Exercise capacity

ECG: Electrocardiography

EMR: Electronic medical record

EU: European Union

FDA: Food and Drug administration

GDPR: General Data Protection Regulation

GPS: Global positioning system

HbA1C: Glycated haemoglobin

HF: Heart failure

HFmrEF: HF mid-range ejection fraction

HFpEF: HF with preserved ejection fraction

HFrfEF: Heart failure with reduced ejection

ICBT: Internet delivered Cognitive behavioural therapy

ICD: Implantable cardioverter-defibrillator

ICT: Information and communications technology

IHD: Ischemic heart disease

ILR: Implantable loop recorder

INR: International Normalized Ratio

IVRS: Interactive voice response system

MI: Myocardial infarction

MRI: Magnetic resonance imaging

NHS: National Health Service

OAC: Oral anticoagulation

PCI: Percutaneous coronary intervention

PPG: Photoplethysmography

QoL: Quality of life

RCT: Randomized Controlled trial

RM: Remote monitoring

SMS: Short messaging service

SPECT: Single-photon emission computed tomography

STEMI: ST-elevation myocardial infarction

T2DM: Type 2 diabetes mellitus

VKA: Vitamin K antagonist

Methodology of search

The literature search was performed following the principles of a systematic review. The initial searches were performed in June 2019 and continuously updated until early December 2019. The MEDLINE and EMBASE database were utilised for the search. All MESH terms belonging to ‘heart diseases’, ‘cardiovascular disease’ or ‘digital health’ were reviewed. All published articles from 2000 until the end of December 2019 were included. The main inclusion criteria were articles in English and studies performed in humans. Abstract, conference papers and systematic reviews were excluded. All references (titles plus abstracts) were evaluated by one expert. In addition, the references of recent meta-analyses and the references of all systematic reviews were assessed to ensure completeness of the review. Furthermore, the references were checked for all included papers in the review (snowballing) to complete the list. No quality assessment was applied for the annexes was used to give a full overview of published trials in digital health. Articles were selected for this review text on the basis of study design, sample size and endpoints with preference for multicentre RCTs, studies with large sample size and studies reporting long term clinical outcomes.

Introduction

Cardiovascular disease (CVD) includes all heart and circulatory diseases. CVD has many forms and includes:

- Ischaemic heart disease (IHD), also known as coronary artery disease (CAD). This is caused by atherosclerosis in which fatty plaque deposits cause the coronary artery walls to narrow, resulting in reduced blood flow to the heart. This is the primary cause of heart attacks.
- Chronic stable angina, which is chest pain that occurs when the heart is working hard (stress, exercise) and needs more oxygen. This is often induced by physical exertion and indicates a damaged heart function or narrowing of the coronary arteries.
- Peripheral artery disease in which narrowed arteries reduce blood flow to the limbs, common in diabetics and smokers. This is a major cause of lower-limb amputations.
- Heart rhythm disturbances. Sudden cardiac death is often the first and final appearance of other underlying CVDs and, consequently, is a permanent concern for most patients with CVD. Atrial fibrillation (AF or AFIB) is the most prevalent arrhythmia with irregular heart rate symptoms that may cause stroke, heart failure, palpitations, fatigue, and shortness of breath.
- Heart failure (HF), which occurs when damage to the heart muscle is severe enough to prevent it from functioning properly; rates of morbidity and mortality from severe HF are higher than many cancers. In particular, regular rehospitalisation of HF patients creates a personal and socio-economic burden.
- Valvular heart disease, of which aortic stenosis and mitral valve insufficiency are most common.
- Congenital and inherited heart conditions, often resulting in reduced quality of life (QoL) and increased risk of sudden death.
- A stroke is a medical condition in which poor blood flow to the brain results in cell death. There are two main types of stroke: ischemic, due to lack of blood flow, and haemorrhagic, due to bleeding. Digital health for stroke prevention or management is not in the scope of this review paper.

The prevalence of cardiovascular disease increases yearly (1). More than 85 and 49 million people with CVD are living in Europe and the EU, respectively. In 2015, there were just

under 11.3 million new cases of CVD in Europe and 6.1 million in the EU (1). Cardiovascular disease such as HF, AF, and ischaemic cardiomyopathies make up a large portion of the chronic disease burden, carrying an important socio-economic impact (2). CVD is estimated to cost the EU economy €210 billion a year. This amount comprises around 53% (€111 billion) in healthcare costs, 26% (€54 billion) in productivity losses, and 21% (€45 billion) in informal care of people with CVD (1). The cost presents a challenge for the current healthcare budgets in Europe (3). There is an increased need for the care and monitoring of elderly people living at home and of people with chronic diseases (3). The shortage of qualified staff to care for patients with chronic diseases stimulates the search for innovation in healthcare systems (4). The recent technological revolution has created an opportunity to redesign and improve the quality of our current healthcare (5).

Digital health is most frequently defined as the use of information and communication technologies to treat patients, conduct research, educate patients and healthcare professionals, monitor acute but mostly chronic diseases, and to monitor and compare the national public CVD status with other countries (6).

Digital health consists of two main components, namely, mHealth and telemedicine. mHealth can be further divided into the use of a smartphone, tablet, or wearable technology for health services (3). Examples of mHealth interventions are smartphone applications and Internet-based programmes for self-management and lifestyle monitoring. Telemedicine can be defined as the delivery of remote care. It can be divided into two components: telerehabilitation and telemonitoring (3).

Digital health has high potential (6) in facilitating a modern delivery of sustainable and efficient healthcare. Moreover, it can enable a high quality of personalised care and optimal patient satisfaction.

The key to exploiting the clear potential of digital health in delivering safe, effective, sustainable, and satisfactory care will be streamlining the implementation process. One problem that many digital health solutions have had up to now is that these interventions have been mainly technology-driven. Co-creation of innovative applications with health professionals and patients will be essential for the future of digital health. The lack of interoperability with other digital tools, electronic medical records (EMRs), and

reimbursement issues are additional hurdles in the large-scale implementation of digital health in healthcare (5).

The following topics will be discussed in this report:

- Digital health in primary prevention of cardiovascular disease
- Digital health in secondary prevention of ischaemic heart disease
- Digital health in heart failure management
- Home-hospitalisation for heart failure
- Digital health in cardiac arrhythmia diagnosis and management
- Digital health for cardiovascular implantable devices
- Big data and artificial intelligence in cardiology
- Considerations for implementing digital health

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Chapter 1: Digital Health in primary prevention

Digital health can play an important role in primary prevention. Internet-based tools and smartphone applications can be used for screening, lifestyle monitoring, self-management, adherence to pharmacotherapy, education, and psychological support (1). An advantage of digital health is the potential to transform prevention into more patient-centred care with content that is customised to patients' individual needs and preferences.

A growing number of patients have wearable devices for activity tracking and, hence, an increased healthy lifestyle awareness. These trackers have high potential; however, relatively little evidence is currently available regarding long-term health effects (2). Most digital health solutions at this moment focus on only one aspect of cardiovascular prevention (most often physical activity). More scientific research is needed on integrated solutions that can monitor the whole spectrum of cardiovascular risk factors (diabetes mellitus, arterial hypertension, smoking, inactivity, obesity, etc).

In this chapter, we will focus on studies from 2015 to 2019 that examine the effectiveness of smartphone and Internet applications in improving selected cardiovascular risk factors: arterial hypertension, diabetes mellitus, smoking, obesity, and sedentary lifestyle., obesity and sedentary lifestyle.

Hypertension

Hypertension, also known as high or raised blood pressure (BP), is a condition in which the blood vessels have persistently raised pressure (3). BP is created by the force of blood pushing against the blood vessel walls (arteries) as it is pumped by the heart. The higher the pressure, the harder the heart has to pump (3). Long-term hypertension can lead to heart damage and even heart failure (HF). Furthermore, high BP is associated with cardiovascular events such as IHD (4-5). European guidelines recommend BP goals of <140/90 mmHg in all patients or even 130/80 mmHg if treatment is well tolerated (6). The first step in hypertension management is a healthy lifestyle. Salt restriction, moderate alcohol consumption, weight reduction, smoking cessation, physical activity, and high consumption of fruits and vegetables have proven to be effective in lowering BP (6).

Nineteen trials and three meta-analyses conducted from 2015 until the end of 2019 looked at BP telemonitoring, and 72% of those studies showed a significant reduction in BP. More research and larger trials are needed to show the effectiveness and cost-effectiveness of these interventions. Details on the research review are provided in Annex 1.

Self-monitoring of BP already plays a big role in diagnosing hypertension and improving BP control. Telemonitoring is a remote interaction between patients and health professionals without the need for face-to-face consultation. It is in addition to self-monitoring. Margolis et al. (7) demonstrated in 2018 that home BP telemonitoring is effective, and the effects are sustained for twelve months after the end of the intervention. An integrated ICT-based system, which included home BP telemonitoring and a smartphone application, was tested by Albini et al. (8) in 2016. After a randomised control trial (RCT) with 690 patients, they concluded that this intervention could be effective in improving hypertension management and lowering clinical inertia (8). The TASMIN-4 trial conducted in 2018 was based on a randomised set of 1182 patients in three different categories: control (394 patients), self-monitoring (395 patients), or telemonitoring and self-monitoring (393 patients) (9). McManus et al. (9) demonstrated that both self-monitoring and telemonitoring resulted in significantly lower BP. The TASMIN-4 trial revealed that self-monitoring is more cost-effective than usual care. There was no clarity whether the addition of telemonitoring further improves the cost-effectiveness (10).

The effectiveness of telemonitoring was confirmed in 2017 in a meta-analysis by Duan et al. (11).

Fourteen trials and one meta-analysis conducted from 2015 until the end of 2019 investigated the effectiveness of smartphone applications in reducing BP. Of these studies, 73% showed that the use of smartphone applications can result in a significant BP reduction. More research and larger trials are necessary to determine which specific features of the smartphone applications are the most (cost-)effective. More details on the research review are described in Annex 1.

Smartphone applications are used in the management of hypertension. However, most corresponding trials have had small sample sizes. In 2016, Kang et al. (12) reported that a smartphone application was effective in improving medication adherence in hypertensive

patients, and in 2019, Lee et al. (13) tested a smartphone self-monitoring application and demonstrated that it resulted in significant reductions, compared with usual care.

Eight trials conducted from 2015 until the end of 2019 studied the effectiveness of text messaging in reducing BP. Of these trials, 75% showed that text messaging can lead to a significant reduction in BP. More research with preferably larger trials is required to confirm the observed reduction and to assess the cost-effectiveness of these interventions. More detailed information is provided in Annex 1.

In 2016, Bobrow et al. (14) reported on the effectiveness of weekly short message service (SMS) messages based on an RCT with 1372 patients. They postulated a small reduction in systolic BP control after twelve months.

In conclusion, current evidence suggests that telemonitoring could be effective in reducing BP. However, more research is required to confirm the added value of telemonitoring to self-monitoring alone. Furthermore, smartphone application and text-messaging have high potential for hypertensive patients in remote follow-up of blood pressure and improving medication adherence. However, there is currently insufficient evidence regarding the effectiveness of mHealth applications in hypertension management.

Diabetes mellitus type 2

Type 2 diabetes is a chronic disease that occurs either when the pancreas does not produce sufficient insulin or when the body cannot effectively utilise the insulin it produces. Insulin is one of the hormones that regulate blood sugar. Long-term uncontrolled diabetes can seriously damage many organs, especially the nerves and blood vessels (15).

Type 2 diabetes mellitus (T2DM) is associated with an increased risk of CVD. Therefore, intensive management of T2DM is required to prevent CAD or stroke. Possible additional complications are renal failure, diabetic ulcers, and even amputations (16). The prevalence of T2DM is high and increasing. It is estimated that nearly one out of ten people in Europe has diabetes, implying approximately 60 million people. By 2045, this number is expected to increase to 81 million (22%) (17). HbA1c is often used as an outcome in diabetes trials. Glycated haemoglobin, or HbA1c, is used to monitor the average blood glucose levels of the

last three months. This provides a useful longer-term gauge of blood glucose control. Twenty-four trials and seven meta-analyses conducted from 2015 until the end of 2019 investigated the effectiveness of telemonitoring for T2DM patients in reducing HbA1c. Of these studies, 90% indicate that text messaging can lead to a reduction in HbA1c. Nonetheless, more research or larger trials are required to confirm the effectiveness and cost-effectiveness in comparison with standard care and self-monitoring. Further details on the research reviews are provided in Annex 1.

Telemonitoring of diabetes mellitus is the remote monitoring of blood glucose levels by health professionals. Telemonitoring enables continuous monitoring and enables quicker interventions (for example medication change) by health professionals compared to self-monitoring in combination with regular visits to the health professionals.

Telemonitoring of diabetes mellitus patients has been studied in multiple trials. Unfortunately, these are mainly small, single-centre trials. Telemonitoring of blood glucose in T2DM patients seems to improve control of glycaemia, health-related QoL, and HbA1c (18-22). Some trials suggest that telemonitoring of T2DM patients can potentially reduce costs in comparison with usual care (22), but more evidence is needed. A meta-analysis in 2015 concluded that further trials are needed to prove the benefits of telemonitoring in enhancing diabetes management (23).

Fifteen trials and three meta-analyses conducted from 2015 onwards studied the effectiveness of text messaging in reducing HbA1c for T2DM patients. In 66% of these analyses, it was shown that text messaging can lead to a reduction in HbA1c. More research or larger trials will be indispensable to confirm the effectiveness and cost-effectiveness in comparison with standard care. More detailed information on the corresponding research reviews is provided in Annex 1.

Text messaging interventions can also play a potential role in the chronic management of T2DM. The former could increase therapy adherence and improve lifestyle choices. In 2019, Huang et al. (24) and Haider et al. (25) both demonstrated in meta-analyses that text messaging results in declined HbA1c and improved blood glucose control. Moreover, it is considered as a low-cost initiative to motivate T2DM patients to adhere to a healthier lifestyle.

Twenty-three trials and five meta-analyses conducted from 2015 to 2019 explored the effectiveness of smartphone applications for reducing HbA1c in T2DM patients. In 82% of the trials, it was concluded that smartphone applications can result in reduced HbA1c. The five meta-analyses demonstrated that these applications might effectively improve HbA1c control. Nevertheless, more research or larger trials are required to assess and confirm its long term effectiveness and cost-effectiveness in comparison with standard care. More details on the research review can be found in Annex 1.

Smartphone applications can provide T2DM patients with educational content, self-monitoring, and direct communication with health professionals. In 2019, Zhang et al. (26) demonstrated the difficulty in achieving long-term effective glucose improvement solely by using a self-management app. But in combination with interactive management, it can support rapid and sustained glycaemic control. Another trial conducted in 2019 by Yu et al. (27) reported the effectiveness of a smartphone application in reducing HbA1c.

Unfortunately, firm conclusions cannot be drawn in view of the relatively small trial sample size. A meta-analysis by Hou et al. (28) in 2018 claimed a 0.57% reduction in HbA1c for T2DM patients using smartphone applications. This observation indicates that smartphone applications could play a role in T2DM management in the future. Smartphone applications may also play a role in clinical decision-support systems or in the prevention and treatment of T2DM in remote or less-developed areas (29, 30).

Smoking Cessation

Smoking is a major modifiable risk factor for IHD, certain cancers, and multiple other diseases (31). Smoking cessation is a major part of every prevention programme. Current cessation interventions consist of pharmacological treatment and cognitive behaviour therapy. These rely heavily on health professionals initiating the treatment. Digital health could provide opportunities to engage less-motivated and/or remote smokers as well as enable long-term monitoring.

Internet-based interventions are an innovative way to deliver smoking cessation interventions. Sixteen trials and one meta-analysis conducted from 2015 to 2019 studied the effectiveness of Internet-based interventions for effective smoking cessation. Of these trials, 59% revealed

that Internet-based interventions can lead to smoking cessation. More research or larger trials are necessary to assess and confirm the effectiveness in comparison with standard care. More details on the related research review are described in Annex 1.

A number of small trials indicated a positive effect of Internet intervention on cessation rates (32, 33). On the other hand, large RCTs with more than 1000 patients suggest that Internet-based interventions have no additional effect on cessation rates in comparison with usual care. Graham et al. (34) demonstrated in 2018 that the use of an Internet-based intervention combined with social networks can enhance all three recommended components of an evidence-based smoking cessation programme (skills training, social support, and pharmacotherapy use). However, no higher cessation rates were observed. In 2016, Neri et al. (35) and Harrington et al. (36) came to the same conclusion. A tailored Internet-based intervention trial in 2017 reported an increase in hard-core smokers' receptivity to smoking cessation information and a decrease in cigarette consumption by only one cigarette per day (37).

A recent meta-analysis report by McCrabb et al. (38) on the effectiveness of an Internet-based smoking cessation intervention claimed that these interventions increased the odds of cessation by 29% in the short term and by 19% in the long term. In conclusion, more evidence is necessary to implement an Internet-based intervention in regular care.

Seventeen trials and three meta-analyses (2015–2019) showed that in 80% of the trials, text messaging can be effective in achieving smoking cessation. However, more research or larger trials are required to assess the long term effectiveness of these interventions. More detailed information is provided in Annex 1.

The use of text messages is an alternative innovative way to increase cessation rates. Multiple trials have demonstrated a positive effect of text messaging as a smoking cessation intervention (39-43). This conclusion was confirmed by an RCT (2017) with 8000 Chinese patients (44) and in two meta-analyses (45, 46). There is sufficient evidence that text messaging is an effective intervention for improving cessation rates. Hence, it could be a standard element of smoking cessation interventions.

Three out of four trials (2015–2019) reported the effectiveness of smartphone applications in achieving smoking cessation. More detailed information on the reviews can be found in Annex 1.

Crane et al. (47) demonstrated in 2019 that a smartphone application could result in higher self-reported three-month continuous smoking cessation. The evidence-based behaviour-change therapies implemented in the full version of the application were:

- 1) Supporting identity change: users thinking of themselves as non-smokers.
- 2) Rewarding cessation by praise, virtual prizes, and showing users the amount of money they save each day they are not smoking.
- 3) Changing routines: advising on ways to avoid smoking cues by changing routine.
- 4) Advising on medication use: promoting the use of one of the evidence-based smoking cessation medicines (47).

The above conclusion was confirmed in a study by Masaki et al. (48) in 2019. Their application consisted of a smoking cessation diary, messages and educational videos, and counselling chat sessions with an artificial intelligence nurse (48).

Weight loss management

Overweight and obesity are independent predictors for IHD (49). Weight loss interventions are not only important to reduce obesity; these interventions also influence a number of “major” risk factors including hypertension, high cholesterol, and T2DM (50). Weight loss programmes consist of physical activity training and dietary advice.

Internet-based weight loss interventions have been assessed in multiple large trials. Harden et al. (51) demonstrated in 2015 that an Internet-based worksite weight loss programme was able to reduce weight in 22% of the participants. Plaete et al. (52) showed in 2015 that a digital health intervention was able to improve physical activity levels as well as fruit and vegetable intake. Other trials confirmed the positive effects of Internet-based weight loss interventions on diet choices, physical activity, or weight (53-56).

Smartphone applications are another way to deliver weight loss interventions. Twenty-five trials and three meta-analyses conducted from 2015 until the end of 2019 looked at the effectiveness of smartphone applications for weight loss, and 89% of the trials showed that smartphone applications can lead to weight loss. More research or larger trials are needed to

confirm the long-term results and to assess the cost-effectiveness of these interventions. Details on the research review are provided in Annex 1.

Goldstein et al. (57) and Muralidharan et al. (58) showed in 2019 that smartphone applications can help to achieve a moderate short-term weight loss. Three other trials demonstrated the positive effects of smartphone applications on weight loss (59-61). The short-term efficacy of smartphone-based interventions was confirmed in two recent meta-analyses (62, 63). However, all of these RCTs had relatively small sample sizes (between 100 and 833 patients).

Kurtzman et al. (64) performed an interesting trial in 2018, testing the combination of social incentives and gamification within digital health devices. Gamification is the use of game-design elements. They demonstrated that using digital health devices to track behaviour led to significant weight loss through 36 weeks, but the gamification interventions were not effective at promoting weight loss when compared to the control group (64).

The effectiveness of text messaging interventions for weight loss remains debatable. Eight trials and two meta-analyses conducted from 2015 until the end of 2019 looked at the effectiveness of text messaging for weight loss, and 75% of the trials showed that text messaging can lead to weight loss. More research or larger trials are needed to confirm the long-term results and to assess the cost-effectiveness of these interventions. Details on the research review are provided in Annex 1.

An RCT conducted by Sidhu et al. (65) concluded that text message intervention was not successful in the maintenance phase of a weight intervention. Two meta-analyses demonstrated a small effect of text messaging interventions in short-term weight loss (66, 67). However, a lack of long-term results indicates that further efficacy studies are required.

Physical activity

A sedentary lifestyle and physical inactivity are important risk factors for IHD (68). Physical activity is, therefore, an important part of primary and secondary prevention programmes. Regular physical activity is associated with beneficial effects on insulin sensitivity, metabolic syndrome, weight, BP, and QoL (69). Current guidelines recommend a minimum of 150

minutes of moderate-intensity aerobic physical activity or at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week (70).

Seventeen trials and two meta-analyses conducted from 2015 until the end of 2019 looked at the effectiveness of pedometers in increasing physical activity, and all of the trials showed that pedometers can lead to increased physical activity. More research or larger trials are needed to confirm the long-term maintenance of higher physical activity. Details on the research reviews are provided in Annex 1.

Pedometers or activity trackers can be used to collect objective data on physical activity, which health professionals can use to give feedback to patients. Macniven et al. (71) demonstrated in 2015 that a pedometer-based programme is effective in reducing occupational sedentary behaviour. In 2016, Finkelstein et al. (72) confirmed that a pedometer-based programme combined with cash incentives was successful in increasing short-term physical activity. A meta-analysis by Qui et al. (73) in 2015 also concluded that step counter-based programmes are associated with reduced sedentary time among adults. Current evidence suggests the possible effectiveness of these interventions; however, more large trials and cost-effectiveness analysis are needed.

Twenty-two trials and four meta-analyses conducted from 2015 until the end of 2019 looked at the effectiveness of smartphone applications in increasing physical activity, and 81% of the trials showed that smartphone applications can lead to increased physical activity. More research or larger trials are needed to confirm the long-term maintenance of higher physical activity. Details on the research reviews are provided in Annex 1.

All recent smartphones have a built-in accelerometer which can be used as an objective measure of physical activity. Multiple studies have researched the effect of smartphone applications in motivating people to move more. Most of these studies are single-centre and have only small sample sizes, so it is difficult to draw a conclusion about their effectiveness. Direito et al. (74) conducted a meta-analysis in 2017 on physical activity promoted by digital health technologies and concluded that they only had small effects in improving physical activity and reducing sedentary time. This conclusion was confirmed by a meta-analysis published in 2019 by Romeo et al. (75).

Fourteen trials conducted from 2015 until the end of 2019 looked at the effectiveness of text messaging on increased physical activity, and 79% of the trials showed that text messaging

can lead to increased physical activity. Details on the research reviews are provided in Annex 1.

The effect of online social networks, gamification, and incentives were also investigated in multiple small trials. Most of these interventions show modest improvement in physical activity. Again, more evidence is needed to confirm the effectiveness and to justify implementation in standard care (76-78).

Conclusions

Digital health can have an impact on different cardiovascular risk factors to reduce the risk for a future CVD. Blood pressure telemonitoring could be effective approach for the diagnosis of arterial hypertension and for the follow-up of BP. More research is required to demonstrate the value of adding telemonitoring to self-monitoring alone. There is currently insufficient evidence to confirm the effectiveness of mHealth applications in hypertension management. Telemonitoring of T2DM patients has been studied in multiple small, single-centre trials. Most of these studies show positive effects of telemonitoring on HbA1c. Text messaging interventions can also play a potential role in the chronic management of T2DM. Smartphone applications for T2DM management seem to have high potential however most trials had small sample size and short follow-up. More long-term studies with large sample size are required to confirm the effectiveness of digital health in the management of T2DM. Internet-based interventions are an innovative way to deliver smoking cessation. Numerous studies show contradictory results, so more evidence is necessary to implement an Internet-based intervention in regular care. Multiple trials demonstrate the effectiveness of text messaging for improving cessation rates. Hence, it could be a standard element of smoking cessation interventions. Internet-based weight loss interventions seem to have positive effects on diet choices, physical activity, or weight. Numerous smartphone applications show positive effects on short-term weight loss. However, larger trials are needed to confirm the long-term results and to assess the cost-effectiveness of these interventions. The effectiveness of text messaging interventions for weight loss remains debatable. Pedometer-based and smartphone-based interventions seem an effective method to improve physical activity in primary prevention. The long-term maintenance of the higher physical activity level of both interventions is still uncertain.

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Chapter 2: Digital Health in secondary prevention of ischaemic heart disease (IHD)

Premature CVD mortality is decreasing in most European countries due to better medical care and prevention. However, the reduction in mortality rates has slowed down (1-3). Suspected causes are the rising prevalence of obesity and diabetes, along with an ageing population (3,4).

CVD recurrence rates are also high (up to 5–15% recurrence rate in the first year after myocardial infarction), partially due to insufficient implementation of secondary prevention measures, as shown recently in the EuroAspire audits (1,5). This high prevalence of CVD events leads to an immense economic burden (6).

Secondary prevention consists of two pillars: optimal medical therapy and a healthy lifestyle (7,8). Multiple trials have confirmed the positive effects of aspirin, statins, and BP-lowering agents on recurrent CVD events (9-11). Healthy lifestyle counselling is often incorporated in cardiac rehabilitation (CR). Therefore, current European guidelines recommend CR for all patients with CAD (7,8). CR comprises different core components such as physical activity, risk factor modification, nutritional counselling, and psychosocial wellbeing (7,8).

Unfortunately, only a few eligible patients participate in CR mainly due to transport and schedule constraints (12).

Digital health has the potential to overcome these barriers and to improve CR access and uptake. Recent publications have demonstrated that telerehabilitation (delivery of cardiac rehabilitation by digital means) can be as effective as centre-based CR and can improve participation (13-15). This could be important in remote areas or areas with few CR services. Furthermore, it has the potential to empower patients and keep cardiovascular care affordable (7).

Exercise training at home and Telerehabilitation of IHD

The beneficial effects of physical activity on a daily basis in primary and secondary prevention is well established (16,17). Physical activity has positive effects on blood lipid profiles, BP, insulin resistance, inflammation, etc. (7,16-18). Therefore, exercise training is a central part of CR and secondary prevention of IHD. Despite the protective and beneficial effects, participation rates after an IHD event remain low; less than 50% of eligible patients attend CR (12,19). Multiple trials studied the predictors of poor participation in CR; these include distance to the CR centre, lower socio-economic status, older age, and female gender (12,19). Home-based exercise programmes have been studied since the 1980s (20-21), but our focus is on studies from 2000 on.

Thirty-two trials and five meta-analyses conducted from 2000 until the end of 2019 looked at the effectiveness of home rehabilitation for IHD, and all trials showed that home rehabilitation for IHD could be an effective alternative for centre-based CR. Details on the research review are provided in Annex 2.

Ades et al. (22) demonstrated in 2000 that home-based, trans-telephonically monitored CR had comparable effects on QoL and exercise capacity (EC) as an on-site CR programme. In 2001, a retrospective analysis showed that stable post coronary artery bypass grafting (CABG) patients receiving a detailed exercise prescription to follow at home do as well as those in supervised rehabilitation (23). Arthur et al. (24) confirmed in 2002 that home CR was efficient for low-risk CABG patients. In 2006, Kortke et al. (25) conducted one of the first studies to investigate the cost-effectiveness of trans-telephonic ambulatory rehabilitation in cardiac surgery patients. They concluded that the intervention could reduce total rehabilitation costs by 58% (25). In 2007, Jolly et al. (26) conducted one of the largest RCTs showing that home-based CR programmes for low- to moderate-risk patients do not produce inferior outcomes compared with traditional CR programmes.

Several meta-analyses have reviewed the evidence on home-based CR. They concluded that home-based CR results in short-term improvements in EC and health-related QoL compared to usual care (27-30). A meta-analysis by Buckingham et al. (30) in 2016 concluded that costs of home-based and centre-based CR are equivalent for patients with IHD.

One way to supervise home-based exercise training in secondary prevention of myocardial infarction (MI) is the use of pedometers. In 2010, Furber and his team (31) conducted an RCT

with 215 patients and demonstrated that a pedometer-based telephone intervention could be offered as an effective option for patients not attending CR to increase and maintain their physical activity levels after hospitalisation. Sangster et al. (32) tested the same intervention in 2015 with a larger RCT, confirming that this low-contact intervention was feasible to provide CR in underserved rural areas. A recent trial in 2019 using a pedometer feedback intervention in phase III CR demonstrated that pedometer feedback was superior to providing usual physical activity recommendations without follow-up (33).

Thirty-four trials and three meta-analyses conducted from 2000 until the end of 2019 looked at the effectiveness of telerehabilitation for IHD, and 97% of all trials showed that telerehabilitation for IHD does not have significantly inferior outcomes compared to a centre-based supervised programme. Details on the research review are provided in Annex 2.

More recent approaches use mHealth technology such as smartphones, text messaging, Internet, and virtual reality in telerehabilitation programmes. Dalleck et al. (34) demonstrated that a videoconference-delivered CR programme is feasible for risk factor modification and exercise monitoring. In 2011, Worringham et al. (35) demonstrated that a smartphone, ECG, and GPS-based system for remotely monitoring exercise could be used effectively for remote CR.

A trial called TELEREHAB III by Frederix et al. (36) was published in 2015. They used accelerometer monitoring in combination with text messaging to deliver telerehabilitation as an add-on to standard CR. This RCT showed that a six-month telerehabilitation programme leads to larger improvement in both physical fitness and QoL (36). Frederix et al. (37) demonstrated in 2017 that this intervention induced persistent health benefits and remained cost-effective up to two years after the intervention ended. Maddison et al. (38) performed a randomised controlled telerehabilitation trial in 2019 which comprised a smartphone and chest-worn sensor to monitor and educate patients. They demonstrated that the intervention was an effective and cost-effective delivery model that could improve overall CR utilisation rates by increasing reach and satisfying unique participant preferences (38).

Several meta-analyses reviewed the effect of mHealth-supported telerehabilitation. Huang et al. (39) demonstrated in 2015 that telehealth-delivered CR was not inferior to centre-based CR. Rawstorn et al. (40) and Claes et al. (41) came to the same conclusion in 2016 and 2017, respectively. Rawstorn et al. (40) concluded that telerehabilitation was as effective as

traditional CR for improving modifiable cardiovascular risk factors and functional capacity. In 2018, a meta-analysis by Wu et al (42) had a comparable message that the efficacy of hybrid CR (a combination of centre-based CR with telerehabilitation) is similar to that of standard CR, and a 2019 meta-analysis by Su et al. (43) concluded that mHealth CR is effective in engaging patients in an active lifestyle, improving QoL, and reducing rehospitalisation.

Reflecting on the current evidence, the conclusion can be made that home-based exercise training or telerehabilitation for IHD patients is an effective way to deliver exercise training in patients who cannot attend centre-based CR and as an add-on to centre-based CR to increase its long-term effects. Most trials demonstrate comparable results in EC between centre-based CR and telerehabilitation with often a better impact on QoL for the telerehabilitation intervention. Several trials suggest that telerehabilitation as a standalone or as an add-on is cost-effective. However, larger studies in different healthcare systems, as well as more research on cost-effectiveness, are needed.

Lifestyle management in secondary prevention of IHD

Improving physical activity is a major part of secondary prevention programmes and CR but tackling other cardiovascular risk factors is also crucial to prevent recurrent events. Other components of lifestyle management programmes in CR are smoking cessation, stress and mental health management, nutritional counselling, and medication adherence. Participation in CR programmes can often help to improve the risk factor status of IHD patients, and digital health tools may help to maintain the long-term self-management of IHD after CR with an array of personal smartphone-based technologies (44).

In 2002, Vale et al. (45) demonstrated that a telephone coaching intervention is effective for increasing medication adherence. With the sequel RCT of 792 patients in 2003, Vale et al. (46) demonstrated that a telephone coaching intervention is a highly effective strategy to reduce total cholesterol and address other coronary risk factors. Multiple other studies demonstrated that telephone counselling and follow-up are effective options for long-term lifestyle management (47-51). Hansen et al. (52) showed in 2007 that a nurse-led systematic telephone follow-up intervention also could improve the physical dimension of health-related QoL compared with usual care. A large observational trial in 2013 by Nymark et al. (53)

showed that telephone counselling led to a 27% reduction in utilisation and a 22% reduction in-hospital care costs. In 2014, Kotb et al. (54) demonstrated that a telephone support intervention for IHD patients led to reduced feelings of anxiety and depression and improved systolic BP control and the likelihood of stopping smoking.

In 2003, Southard et al. (55) tested an Internet-based case management system. They concluded that it could be used as a cost-effective intervention for patients with CVD. Levine et al. (56) performed a cluster RCT of 15847 patients in 2011 using an Internet-delivered intervention. After two years, only one of seven clinical indicators of cardiovascular risk factor management was improved. This result corresponds to a 2008 study by Holmes-Rovner et al. (57) concluding that coaching post-hospitalisation for acute coronary syndrome (ACS) was modestly effective in accomplishing short-term but not long-term lifestyle behaviour change. Norlund et al. (58) demonstrated in 2018 that an Internet-based cognitive behavioural therapy (iCBT) for a myocardial infarction (MI) population did not result in lower levels of symptoms of depression or anxiety compared with the standard as usual. Possibly, low adherence to the Internet intervention could have influenced the effects of the iCBT.

A meta-analysis by Devi et al. (59) in 2015 concluded that there was not enough evidence for the impact of Internet-based interventions for secondary prevention of IHD on healthcare utilisation and cost-effectiveness to draw conclusions.

The introduction of smartphones and smartphonses gave health professionals the opportunity to deliver 'pocket-size' secondary prevention programmes. Blasco et al. (60) demonstrated in 2012 that a telemonitoring programme via smartphone messages appears to be useful in improving the risk profile of ACS patients. In 2013, Quilici et al. (61) used motivational smartphone SMS messages to improve the rate of antiplatelet medication intake after stent implantation. Three recent large RCTs using text messaging interventions for lifestyle promotion in secondary prevention of IHD demonstrated significant improvements in risk factor profiles (62-64).

Smartphone applications provide other opportunities in addition to text messaging. In 2014, Forman et al. (65) showed that a smartphone application for CR delivery was safe and agreeable to patients and clinicians. A 2019 RCT by Santo et al. (66) including 163 patients concluded that patients with IHD who used medication reminder apps had better medication adherence compared with usual care. In a study using 176 IHD patients, Johnston et al. (67)

demonstrated in 2016 that a smartphone application can improve patient self-reported drug adherence and may be associated with a trend towards improved cardiovascular lifestyle changes and QoL. In 2018, Coorey et al. (44) investigated the effect of smartphone applications on CVD self-management in a meta-analysis of ten trials. Multiple behaviours and CVD risk factors seemed modifiable in the shorter term with the use of smartphone apps (44).

In 2019, Jin et al. (68) published a meta-analysis of thirty studies investigating telehealth interventions for secondary prevention, showing no significant difference in all-cause mortality but a significant reduction in rehospitalisation in the intervention group. They concluded that telehealth interventions with a range of delivery modes could be offered to patients who cannot attend CR, or as an adjunct to CR for effective secondary prevention.

Conclusions

Home-based exercise training and telerehabilitation can be effective ways to increase physical activity in CAD patients. They can be provided as standalone programmes or as an add-on to centre-based CR to increase the long-term effects of CR. There is some evidence that these interventions can be cost-effective, but more research is needed to confirm that. Important to mention is the fact that most trials have had relatively small sample sizes.

Lifestyle management of IHD with the help of digital health tools is an effective way to optimise the risk factor profile of patients. Telephone counselling, text messaging, and smartphone applications are especially effective, while Internet-based interventions, as yet, have failed to prove effective. Smartphone applications have the potential to provide accessible pocket-size interventions.

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Chapter 3: Digital health in heart failure management

Heart Failure (HF) can be defined as the heart's reduced ability to pump or fill with blood, and therefore, the heart cannot create sufficient cardiac output (1). HF has recently been classified into three subtypes, namely, HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF), and HF with mid-range ejection fraction (HFmrEF), according to the ejection fraction, natriuretic peptide levels, the presence of structural heart disease, and diastolic dysfunction (2).

HF is the leading cause of hospitalisation in Europe (3) and accounts for a large part of the healthcare expenditure. A study conducted in 2012 by a research group at the International Centre for Circulatory Health at Imperial College London estimated the costs related to HF in 24 EU member states in one year to be US\$33.14 billion (~ €29 billion) (4,5). The bulk of the costs are driven by frequent, prolonged, and repeat hospitalisations. HF is associated with high rehospitalisation rates; up to 50% of patients are readmitted to the hospital within six months of discharge (6). This has a large impact on QoL and on healthcare budgets across Europe.

Acute HF, or decompensated HF, is often preceded by signs and symptoms such as weight gain, dyspnoea, reduction in physical activity, etc. Remote patient management or monitoring in patients with HF might help to detect early signs and symptoms of cardiac decompensation, thereby enabling a prompt initiation of the appropriate treatment and avoiding hospitalisation (7).

Telemonitoring of HF is one of the most researched and implemented topics within digital health. Multiple studies have demonstrated the feasibility and effectiveness of remote monitoring of HF patients (7,8), but the possibilities for digital health in HF reach much further. For example, biosensors can be used to measure thoracic impedance to predict HF decompensation, and smartphone applications can be used to educate patients and enable self-management.

Telemedicine in HF

Telemonitoring

It is well established that long-term follow-up of HF patients and disease management programmes for self-management enhance survival rates and QoL. Face-to-face disease management programmes are successful but require significant resources and patient efforts (9). Therefore, new technologies are being researched to allow remote disease management programmes which might be more cost-effective than face-to-face programmes.

Sixty-three trials and seven meta-analyses conducted from 2000 until the end of 2019 looked at the effectiveness of telemonitoring in HF patients, and 63% of the trials showed that it is effective in reducing mortality and healthcare utilisation. All seven meta-analyses concluded that telemonitoring seems to reduce mortality and rehospitalisation. Details on the research review are provided in Annex 3.

Telemonitoring can reduce patient-professional contact and, therefore, make long-term HF care more accessible as well as decrease healthcare costs. Cleland et al. (10) performed one of the first telemonitoring trials for HF in 2005. In an RCT with 426 patients, they demonstrated that home telemonitoring can play a valuable role in the management of selected patients with HF. In 2017, Pinna et al. (11) tested telemonitoring in an RCT of 461 patients. The study showed that telemonitoring of both vital signs and respiration was feasible in patients with HF. Giordano et al. (12) in 2007 and Woodend et al. (13) in 2008 both carried out RCTs with HF patients and demonstrated that a home-based tele-management strategy could reduce hospital readmissions and costs (12) as well as improve functional status and QoL (13).

In 2010, Chaudry et al. (14) included 1653 patients in a multicentre RCT where telemonitoring was performed with a telephone-based interactive voice response system. They reported no significant differences between the telemonitoring group and the usual care group in rehospitalisation, number of days in the hospital, and the number of hospitalisations and deaths. These results from one of the largest telemonitoring trials were surprising, considering that other trials at the time demonstrated the effectiveness of telemonitoring for HF patients. One of the potential reasons is the fact that adherence to the telemonitoring system was low at the end of the study period; in its final week, only 55% of the patients were still using the system at least three times per week (14).

In the same period, three other RCTs found no significant effects (15-17). A 2011 study by Wade (15) demonstrated that an Internet-based telehealth intervention in an elderly HF population did not result in better outcomes than usual care. Boyne et al. (16) performed an RCT in 2012 with 382 patients, and no significant differences were found regarding time to first HF hospitalisation. The authors hypothesised that the ‘disappointing results’ could be due to a relative underpowering of the intervention group combined with a very well-treated control group (16). However, they revealed in a 2014 sub-analysis that tailored telemonitoring was an effective way to educate patients with HF and to improve their self-care abilities and sense of self-efficacy (18). The third trial in 2011 that failed to show the effectiveness of telemonitoring was the TIM-HF trial (17). This RCT with 710 patients tested a telemedical management system using portable devices for electrocardiogram (ECG), BP, and body weight. They concluded that this strategy was not associated with a reduction in all-cause mortality compared with usual care (17).

In 2012, Dendale et al. (8) demonstrated that a telemonitoring-facilitated collaboration between the general practitioner and HF clinic reduced mortality and number of days lost to hospitalisation, death, or dialysis in HF patients. The TIM-HF 2 trial (7), which included 1,571 patients, was published in 2018 and demonstrated that a structured remote patient management intervention used in a well-defined HF population reduced the number of days lost due to unplanned cardiovascular hospital admissions and all-cause mortality. Moreover, three meta-analyses were published in 2014 (19) and 2018 (9,20) evaluating, respectively, remote monitoring and telemonitoring of HF patients. Nakamura et al. (19) concluded that remote monitoring for HF patients was effective. Yun et al. (9) demonstrated that telemonitoring of HF patients reduced mortality risk, and intensive monitoring with more frequent transmissions of patient data increased its effectiveness. In this recent meta-analysis, thirty-seven RCTs were included.

Pekmezaris et al. (20) also published a meta-analysis on home telemonitoring for HF patients. They concluded that home telemonitoring decreased the odds of all-cause mortality and HF-related mortality at 180 days but not at 365 days. This was also concluded by Frederix et al. (21) in 2019, demonstrating that an initial six-month telemonitoring programme was not associated with reduced all-cause mortality in HF patients at long-term follow-up (after the monitoring period ended) but resulted in a reduction in the number of days lost due to HF readmissions. So, telemonitoring intervention for HF seem only to have a positive effect in a

short period after the intervention has ended. This suggest that long-term telemonitoring is needed for HF patients.

In conclusion, many trials have demonstrated the effectiveness of telemonitoring in reducing rehospitalisation and improving QoL for HF patients. In addition, meta-analyses of these trials demonstrate significant improvement in outcomes for the telemonitoring interventions, especially in the short term. However, some large multi-centre trials failed to demonstrate telemonitoring effectiveness. Potential reasons can be patient selection, low adherence to the telemonitoring approach, or less intense intervention in these studies. Therefore, new multi-centre studies are needed to determine how to make telemonitoring effective for all patients and feasible for health professionals.

Telephone follow-up

Telemedicine or remote monitoring was introduced as a potential way to reduce the likelihood of deteriorating cardiac illness or the prospect of hospital readmissions (22). Next to telemonitoring systems, which involve the transmission of information on symptoms and signs, structured telephone support is another option for long-term monitoring (22).

Forty-two trials conducted from 2000 until the end of 2019 looked at the effectiveness of telephone follow-up for HF patients, and 69% of these trials showed that it is effective in reducing mortality or healthcare utilisation. Details on the research review are provided in Annex 3.

Clark et al. (23) demonstrated in 2007 that telephone monitoring is well accepted by elderly HF patients. Furthermore, Smith et al. (24) confirmed the effectiveness of a telephone-supported HF patient approach in 2008. However, they also concluded that organising such an approach was costly and did not lead to reduced healthcare utilisation.

In a 2016 prospective observational study of 1816 patients, Laborde-Casterot et al. (25) showed that multi-disciplinary HF disease management delivered by phone may improve survival. The TEACH-HF, a 2015 RCT with 1033 patients, demonstrated that home follow-up phone calls were associated with significantly fewer hospital readmissions (26). Furthermore, Baker et al. (27) showed in 2011 that progressive, reinforcing telephone

education for HF patients was effective in improving knowledge, health behaviours, and HF-related QoL compared to a single education session. A recent trial in 2018 by Grustam et al. (28) demonstrated that nurse telephone support approaches are viable options for chronic HF patient follow-up. They even showed that the nurse telephone support approach was cost-effective in comparison with usual care.

To conclude, trials show that telephone counselling can be an effective option in long-term HF management. Telephone counselling can be effective in reducing HF patient admission but seems most effective in improving patients' knowledge and self-care. A question remains regarding the cost-effectiveness of a structured telephone counselling approach.

Smartphone applications in heart failure

Smartphone applications and text messaging are more recent tools for remote monitoring of HF patients. Text messaging gives health professionals the opportunity to interact with patients in a less intrusive way. Smartphone applications have the potential to enable pocket-size delivery of multidisciplinary HF patient care. Cajita et al. (29) performed a survey in 2017 considering the acceptance of an mHealth application by elderly HF patients. For applications, they underline the importance of co-creation to ensure that the developed mHealth-based interventions will not only address the patient's needs but also be user-friendly for this mainly elderly population.

Most trials using smartphone applications or text messaging for HF patients only assess feasibility or patient and healthcare professional satisfaction. Below, the studies reporting health outcomes are provided.

Scherr and his team showed in 2006 (30) and 2009 (31) that smartphone-based telemonitoring of HF patients has the potential to reduce the frequency and duration of HF hospitalisations. Multiple studies confirmed that smartphone technology is suitable for continuous and secure medical data transmission in HF telemonitoring (32,33). Smartphones can also play a role as an electronic pillbox or be used as an mHealth intervention (smartphone application) for improving medication adherence in HF patients (34). Nundy et al. (35) showed in 2013 that text messaging was associated with a high rate of satisfaction and possible improvements in HF self-management. In 2012, Austin et al. (36) tested a smartphone-based interactive voice

response system (IVRS) with daily self-management and clinical monitoring messages. In this single cohort study of sixty patients, they concluded that an IVRS self-management support system can be an effective technology to reduce HF readmissions (36).

In 2017, Dang et al. (37) tested a smartphone intervention in an RCT with sixty-one patients from a minority population. Interestingly, they concluded that the smartphone intervention offered a modality to help reduce ethnic disparity and could lead to improvements in QoL and self-efficacy (37). Athilingam et al. (38) tested the HeartMapp application in 2017 in a small pilot feasibility RCT. HeartMapp was downloaded on the patient's smartphone, and the patient was trained to use the application features including daily weighing, symptom assessment, responding to tailored alerts, vital sign monitoring using a BioHarness-3 chest strap, HF education, performing a breathing exercise, and walking. They concluded that the results warrant further exploration of the use of HeartMapp to improve HF patient outcomes.

In conclusion, there is not yet strong evidence for the use of smartphones in long-term management of HF for long-term outcomes. Acceptance by patients, however, is good. Most trials have small sample sizes and short follow-up periods. The potential of smartphone use in long-term management of HF seems enormous; however, there is a need for large multi-centre trials to demonstrate the effectiveness and cost-effectiveness for these interventions.

Telerehabilitation in HF

The HF guidelines of the European Society of Cardiology suggest that HF management must be holistic, containing appropriate pharmacological and device therapy, CR, remote monitoring of cardiac implantable electronic devices (CIEDs), and regular follow-up (39). CR is often an underestimated part of long-term HF management.

Taylor et al. (40) demonstrated in a 2019 meta-analysis that exercise-based CR can lead to reductions in the risk of all-cause and HF-specific hospitalisation as well as potential important gains in QoL for people with HF. Like in CR for IHD, there are many possible barriers to participation (41). Telerehabilitation could be a promising solution to overcome some of the barriers and provide guideline-consistent monitoring of physical activity (42).

Thirty-five trials and three meta-analyses conducted from 2000 until the end of 2019 looked at the effectiveness of home rehabilitation for HF patients, and 91% of the trials showed that home rehabilitation for HF is effective in improving EC and QoL or reducing healthcare utilisation. Details on the research review are provided in Annex 3.

In 2000, Oka et al. (43) researched a home-based (walking) exercise programme for HF patients, monitoring adherence and progress as well as providing individualised feedback by weekly phone calls. They demonstrated that this intervention lowered fatigue and improved emotional function. Gary et al. (44) showed in 2004 that home-based, low-to-moderate-intensity exercise is an effective strategy for improving functional capacity and QoL. Another interesting trial was conducted by Smart et al. (45) in 2005. They used heart rate monitors, exercise diaries, and weekly telephone calls to monitor home-based exercise and concluded that this intervention was feasible for HF patients.

After these first three trials, Evangelista et al. (46) performed an RCT with ninety-nine patients in 2006. They demonstrated the beneficial effects of a low-level, home-based walking programme on weight loss in overweight and obese patients with advanced HF. A home-based walking programme was also investigated in 2007 by Dracup et al. (47) with a cohort of 173 patients with systolic HF. However, they concluded that the intervention did not result in improved clinical outcomes at the one-year follow-up.

An RCT in 2009 demonstrated that a home-based exercise programme was as effective as standard CR and provided a similar improvement in QoL (48). However, a study by Jolly et al. (49) in the same year failed to demonstrate any benefit from the addition of a home-based exercise programme in a community-based HF population. (49). Piotrowicz et al. (50) demonstrated in 2015 that home-based telerehabilitation was safe and effective for HF patients. Furthermore, the telerehabilitation intervention had an effect that was similar to standard care on QoL and was well accepted by the HF patients (51). In 2015, Piotrowicz et al. (52) also tested a home-based Nordic walking exercise programme for HF patients. They included 111 patients with HF, including those with a CIED, and demonstrated that home-based telemonitored Nordic walking was safe and effective (52).

The year 2019 was productive for telerehabilitation trials. Dalal et al. (53) conducted the REACH-HF trial in which home-based telerehabilitation was assessed in an RCT with 216 HF_rEF patients. They concluded that a home-based IT-facilitated intervention for HF_rEF

patients was clinically superior for disease-specific health-related QoL at twelve months and offered an affordable alternative to traditional centre-based programmes to address current low CR uptake rates for HF patients (53). Piotrowicz et al. (42) carried out the TELEREH-HF trial, which has been the largest telerehabilitation study for HF patients yet. In this trial, the effects of a nine-week programme of hybrid telerehabilitation for patients with HF were not associated with an increase in the percentage of days alive and out of the hospital and did not reduce mortality and hospitalisation over a follow-up period of fourteen to twenty-six months in comparison with usual care (42).

The cost-effectiveness of telerehabilitation for HF patients was assessed by Hwang et al. (54) in 2019 in a small RCT (53 patients). HF patient telerehabilitation was found to be less costly and as effective for the healthcare provider as traditional centre-based rehabilitation.

In conclusion, there is still debate on whether telerehabilitation is effective in reducing rehospitalisation and mortality in HF patients. Two trials published in 2019 agree that telerehabilitation for HF patients is effective in increasing QoL, but neither trial found significant differences in rehospitalisation or percentage of days alive. More research in home-based exercise training for HF patients is needed to investigate the long-term effects.

Conclusions

Many trials have studied telemonitoring for HF patients, and many of them show that it is effective in reducing rehospitalisation and in improving QoL. However, some large multi-centre trials have failed to demonstrate the effectiveness of telemonitoring. Therefore, future studies must investigate ways to make telemonitoring effective for patients and feasible for health professionals. Telephone follow-up can be an effective way to reduce healthcare utilisation. The effectiveness of smartphone applications and text messaging for long-term follow-up still needs much research. Current research suggests that it is a feasible and well-accepted intervention to possibly improve HF outcomes. Most studies demonstrate that home-based rehabilitation is effective in improving EC and QoL. However, only a few studies have investigated the long-term outcomes, and these studies show contradictory results. More research is needed to investigate the long-term effects.

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Chapter 4: Home-hospitalisation of heart failure patients

Heart Failure (HF) is associated with a high rate of rehospitalisation in a population with a low life expectancy (five-year life expectancy around 50%) (1-5). Frequent rehospitalisation of HF patients not only leads to increased healthcare costs, but it is also associated with functional decline, confusion, and in-hospital infections. As such, innovative delivery care models for HF patients are researched due to this important socio-economic burden and negative impact on QoL (1-5). Limited research shows that hospital-at-home programmes could reduce hospital admissions and allow patients to stay at home as much as possible.

Hospital-at-home, or home hospitalisation, is the delivery of acute hospital-level care in a home setting. Hospital-at-home comprises only the treatment of an acute HF decompensation at home, which normally takes place in the hospital and should be distinguished from permanent follow-up, telemonitoring, telerehabilitation, and early discharge interventions. During the home hospitalisation intervention, a physician or healthcare professional delivers daily home care during the acute decompensation of HF. Daily home care can consist of diagnostic tests including clinical examination, ECGs, blood samples, and administering HF therapy such as intravenous fluids or medications (6).

At this moment, there is little evidence regarding the effects of the hospital-at-home intervention for HF patients. A previous systematic review and meta-analysis based on six studies concluded that a hospital-at-home care programme foresees possible benefits in reducing acute hospital readmission and costs (6). The quality and quantity of the included studies were modest, which makes it difficult to gather real evidence for this model's efficacy.

However, with the implementation of digital health and the development of new technologies for distant surveillance, hospital-at-home interventions for HF patients (and potentially also for those with other indications in cardiology) may play an important role in reducing HF rehospitalisation and in improving QoL for HF patients in the future. Details on the research review are provided in Annex 4.

Conclusions

Home hospitalisation supported by IT technology could potentially reduce the need for hospital beds and improve HF patients' outcomes and QoL. However, the research is still in its infancy, awaiting strong proof from RCTs. The necessary technology and organisation can be used to help safely discharge HF patients earlier.

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Chapter 5: Digital health in cardiac arrhythmia diagnosis and management

Cardiac arrhythmia is defined as an irregular, very fast or very slow heart rate. Tachycardia is the presence of a fast heart rate (above 100 beats per minute). Bradycardia is a very slow heart rate (below sixty beats per minute). Common symptoms of cardiac arrhythmias are palpitations (sensations of an uncomfortable, irregular heartbeat), chest pain, dizziness, dyspnoea, and syncope.

The most prevalent arrhythmia is atrial fibrillation (AF), especially in elderly people. AF happens when electrical impulses fire off from different places in the top chambers of the heart (the atria) in a disorganised way. These irregular impulses cause the atria to quiver or twitch, which is known as fibrillation. This results in an irregular and often rapid heart rate that can increase the risk of strokes, HF, and other heart-related complications. Therefore, cardiac arrhythmias are associated with substantial morbidity, mortality, and economic costs (1).

Every day, patients visit general practitioners or emergency departments for palpitations, (pre) syncope, or feeling of irregular pulsations (2). Diagnosis of cardiac arrhythmia is, however, difficult because cardiac arrhythmias are often intermittent. Ambulatory ECG monitoring is therefore used to monitor ECG data over an extended period of time. This permits an evaluation of the dynamic and transient differences in the heart rhythm. However, ambulatory Holter monitoring is still limited in duration and can therefore still miss a significant portion of cardiac arrhythmias. The use of smartphone or smartwatch applications and handheld devices could help in long-term monitoring of intermittent cardiac arrhythmias. The advantage of these tools is that patients can monitor their own heart rhythm every time they feel symptoms.

Digital health can also be useful in the treatment of cardiac arrhythmias, especially in AF. Anticoagulation therapy is crucial in preventing strokes in patients with AF. However, making decisions about anticoagulation for individual patients remains a difficult area of clinical practice, balancing the risk of ischaemic stroke against that of major bleeding (3). Digital health can provide education, telemonitoring of adherence, or even allow self-management of anticoagulation therapy.

Telemedicine may also play an important role in cardiac emergencies. Multiple trials have investigated the role of prehospital ECG transmission in the triage of acute coronary syndromes. This comprises e-transmission of ECGs taken by the emergency staff with portable ECG devices and sent to the physician for quicker diagnosis and treatment.

Smartphone for arrhythmia detection

The last five years have seen an explosion of new trials testing smartphone applications for the detection of cardiac arrhythmia, mainly, AF. Most smartphone applications use photoplethysmography (PPG) for the detection of heartbeats. PPG is an optical technique that analyses changes in skin colour and light absorption (4).

Twenty-three trials conducted from 2000 until the end of 2019 looked at the effectiveness of smartphone applications for AF screening, and all trials showed that smartphone applications are effective for AF screening and detection. Details of the research review are provided in Annex 5.

In 2015, Haberman et al. (5) published one of the first trials testing the feasibility and accuracy of cardiac arrhythmia detection with the use of PPG in a smartphone application. They concluded that smartphone ECGs accurately detect baseline intervals, atrial rate, and rhythm and enable screening in diverse populations. In 2013, Harrington et al. (6) tested a smartphone application on an iPhone and found that the application was able to accurately detect and classify an irregular pulse from signals in the patients' fingertips.

Fibrichk is an FDA-approved application for AF detection. Patients place the left index finger over the flashlight and camera, holding the finger horizontally and keeping it in place for one min (4,7). The smartphone camera is used to obtain a PPG measurement to calculate the local arteriole blood volume pulse variation. The pulse rhythm is then identified based on the RR interval (4). PPG signal quality was sufficient for analysis in 93%, and single-lead ECG quality was sufficient in 94% of the participants (8). However, arrhythmia detection with smartphones has still some issues such as artefacts due to patient movement and positional variability (9).

The Apple Heart study (10), published in 2019, was one of the most anticipated trials in the field of digital health. Smartwatches were used to identify AF based on the PPG signal combined with an irregular pulse notification algorithm. When AF was detected by the smartwatch during this study, a telemedicine visit was automatically initiated. After that, an ECG patch was mailed to the participant to be worn for up to seven days to confirm the diagnosis of AF. The researchers of the Apple Heart study demonstrated that this diagnostic approach was feasible for AF screening. However, the effectiveness of this approach in diagnosis was slightly disappointing. AF could be confirmed by the ECG patch in only 34% of the patients who were diagnosed with AF by the smartwatch. This suggests that there is a large number of false-positive results, which can cause unnecessary healthcare costs and anxiety (10). More studies on using smartwatches for mass AF screening and the cost-effectiveness of this approach are needed.

Tison et al. (11) published another trial in 2018 which investigated the detection of AF with a commercially available smartwatch. The smartwatch used in this study also combined a PPG signal with an algorithm based on artificial intelligence. The authors concluded that the smartwatch was able to detect AF but had some loss of sensitivity and specificity in comparison with a standard ECG (11).

These studies show that smartphones and smartwatches could be promising tools for permanent ambulatory monitoring of heart rhythm; however, improvements in accuracy are still needed. The PPG signal-based approach offers the advantage that it can be used without the need for additional devices other than widely available smartphones.

Handheld ECG devices or single-lead ECGs are other tools that can be used for mass screening or for long-term monitoring of intermittent palpitations. A trial of 1001 patients using the AliveCor Kardia monitor (handheld single-lead ECG device) combined with a smartphone application demonstrated the efficacy of this approach for AF screening in patients with a high risk of stroke (12). Another study using the Kardia Mobile device (handheld single-lead ECG device) in combination with a smartphone application demonstrated the capability of handheld ECG devices to screen for and detect AF with high sensitivity and specificity (13).

Hendriks et al. (14) performed a prospective cross-sectional study in 2012 with the Zenicor handheld ECG device. They showed that intermittent short ECG recordings for four weeks

were more effective than 24-hour Holter monitoring in detecting AF and paroxysmal supraventricular tachycardia (14). A cohort study in 2015 confirmed that handheld ECG recorders might play a role in mass screening for AF in elderly people (15). Jacobs et al. (16) demonstrated in 2018 that AF screening using a handheld ECG recorder during influenza vaccination is likely to be cost-saving for the Dutch population aged 65 years and over.

In 2016, Chan et al. (17) performed a community screening trial of 13122 patients in Hong Kong. The study team concluded that AF screening using a smartphone-based wireless single-lead ECG was feasible for large cohorts and that it was able to diagnose a significant proportion (0.5–3.0%) of citizens with AF. Early detection of AF can have a significant impact on health outcomes and costs. Lowres et al. (18) demonstrated in 2014 that screening of cardiac arrhythmias in pharmacies using a smartphone application with an automated algorithm is both feasible and cost-effective. Furthermore, mass screening for AF has also been proven to be well accepted by patients (19).

Handheld single-lead ECG devices in combination with smartphones can provide the opportunity to deliver low-cost mass screening for prevalent arrhythmias such as AF.

Lastly, bio patches have been developed to continuously measure ECGs over an extended period. Most of these patches are also capable of monitoring other parameters such as respiratory rate, body position, temperature, and quality of sleep or physical activity (4). In 2013, Rosenberg et al. (20) tested the single-use, non-invasive, waterproof, long-term continuous monitoring Zio® Patch, concluding that it improved clinical accuracy (20). A 2018 RCT with 2,659 patients demonstrated that a self-applied wearable ECG patch resulted in a higher rate of AF diagnosis compared with delayed monitoring (21).

In conclusion, the field of ambulatory monitoring is evolving rapidly, with new tools becoming available for screening and long-term monitoring. Smartwatches, handheld devices, and bio patches show some promising results for long-term monitoring and mass screening. However, more research is still needed to confirm the cost-effectiveness of these interventions. More research is also needed to investigate the role and implementation of digital health screening in current workflow and care pathways.

Prehospital emergency ECG

Prehospital ECGs involve the use of telemedicine to transmit an ECG to the physician before the patient arrives at the hospital. The ECG can be taken at the patient's home or from the ambulance. E-transmission of the ECG accelerates the IHD diagnosis. This can optimise referral to the right centre (centres that are able to perform percutaneous coronary intervention (PCI) and speed up the start of treatment. The European guidelines for managing an ST-segment elevation acute myocardial infarction (STEMI) recommend that all patients presenting with symptoms suggestive of an ACS receive a 12-lead ECG before arriving at the hospital. This prehospital ECG allows them to determine which hospital the patient should be referred to in order to start the right treatment early (22,23).

For patients with MI, the current guidelines recommend timely (<90 min) reperfusion therapy. In research, this is often measured as door-to-balloon time, which is the time between the arrival of a patient with STEMI in the emergency room and the time that a balloon is inflated to revascularise the occluded coronary artery. A shorter door-to-balloon time is associated with better survival. Therefore, a prehospital ECG could help to improve quick and correct referral to the right hospital for revascularisation.

Forty-two trials and one meta-analysis conducted from 2000 until the end of 2019 looked at the effectiveness of prehospital ECGs, and 91% of these trials showed that they are effective in reducing door-to-balloon time and mortality. Details on the research review are provided in Annex 5.

The prehospital ECG can be transmitted through telemedicine devices, telephones, smartphones, etc. Multiple studies have demonstrated that prehospital ECGs are associated with lower door-to-balloon time and increased survival (23-27). Rasmussen et al. (24) demonstrated in 2014 that telemedicine for prehospital triaging and treatment of STEMI was feasible and allowed 89% of patients living up to 95 km from the invasive centre to be treated with primary PCI within 120 min of the emergency medical service call. A cohort study of 288,990 patients in 2014 confirmed that prehospital ECGs led to increased survival in STEMI and non-STEMI patients (25).

Digital Health for anticoagulation treatment in atrial fibrillation

Atrial fibrillation (AF) can lead to blood pooling in the atria, which can cause blood clots to form. These blood clots can migrate to your brain and occlude a brain artery, causing a stroke.

Therefore, adherence to oral anticoagulation (OAC) therapy is important in preventing strokes and systemic thromboembolism in AF (28,29). Non-adherence or failed persistence can result in poor clinical outcomes and increased healthcare costs (30). Education and telemonitoring may help in increasing adherence to OAC therapy. In vitamin K antagonists (VKA) therapy (a type of oral anticoagulation medication), close monitoring of the international normalised ratio (INR) and regular adaptation of medication dosage is important due to the difficult balance of bleeding risk when patients take too much VKA and thromboembolic risk when patients do not take enough VKA.

Eighteen trials and two meta-analyses conducted from 2000 until the end of 2019 looked at the effectiveness of digital health interventions in reducing bleeding complications, and 85% of these trials showed that digital health interventions are at least as safe as usual care. Details on the research review are provided in Annex 5.

The first telemedicine trials demonstrated in 2001 that telephone-based OAC therapy can be endorsed by primary-care physicians and had a positive impact on patients' satisfaction and knowledge about their antithrombotic therapy (31). Furthermore, Witt et al. (32) demonstrated in 2005 that telephone-based OAC therapy reduced the risk of anticoagulation therapy-related complications compared to usual care. Desteghe et al. (28) in 2018 and Proschaska et al. (33) in 2015 demonstrated that telemonitoring of OAC therapy increases medication adherence. Smartphone applications can be used for education, reminders, and monitoring. Stephan et al. (34) demonstrated in 2018 that a smartphone application can improve disease knowledge and enable a shared decision process. Two meta-analyses published respectively in 2006 and 2011 showed that patient self-management and self-testing of INR is associated with significantly fewer deaths and thromboembolic events (35,36).

In conclusion, the use of digital health technology can help to increase the quality of OAC therapy in patients with AF. No good cost-effectiveness studies are available, but it may be expected that these low-cost interventions will prove to be cost-saving.

Conclusions

Digital health provides many opportunities in the field of cardiac arrhythmia. Smartphones, smartwatches, and bio patches are exciting new technologies for ambulatory monitoring and screening of AF. Multiple studies have already demonstrated promising results; however, more research is still needed to confirm the cost-effectiveness of these interventions.

It is important to always check if the digital health tools are clinically validated before using them in clinical practice. E-transmission of prehospital ECGs could improve the triage of patients presenting with chest pain. This can result in better door-to-balloon times and possibly better survival of ACS. Lastly, digital health could play a vital role in improving adherence to OAC therapy in patients with AF. Most studies show promising results; however, studies with higher sample sizes are needed as well as cost-effectiveness analyses of digital interventions.

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Chapter 6: Digital health for cardiovascular implantable devices

Cardiovascular implantable electronic devices (CIEDs) include pacemakers, implantable cardioverter defibrillators (ICDs), and cardiac resynchronisation therapy (CRT). A pacemaker device is used to generate electrical impulses to regulate the electrical conduction system of the heart in patients with bradycardia or an atrioventricular block. The goal of an ICD is to prevent sudden cardiac death. ICDs keep track of the heart rate, and when an abnormal heart rhythm is detected, the device will deliver an electric shock to restore a normal heart rhythm. A CRT is the insertion of two electrodes in the left and right ventricles of the heart, respectively, to treat HF by coordinating the function of both ventricles. A CRT device is indicated when patients suffer from a low ejection fraction or when the electrical activity of the heart has been compromised.

In 2015, the Heart Rhythm Society recommended that remote monitoring (RM) should be offered to all patients with CIEDs. RM of CIEDs was originally devised to decrease the need for in-hospital follow-up and to increase access, but new research has established that RM is also an efficient method to improve patient outcomes (1-4).

Currently, CIEDs contain multiple sensors and technologies that enable daily monitoring of several important parameters in HF and cardiac arrhythmias (1). Most current CRTs and defibrillator devices can monitor daily physical activity, arrhythmias, and thoracic impedance, which helps in the early detection of HF decompensation. Furthermore, pacemakers and internal loop recorders permit long-term monitoring of cardiac rhythm and can help to detect paroxysmal AF or severe ventricular arrhythmias.

Next to CRT devices, pacemakers, and defibrillators, new wireless implantable hemodynamic monitoring systems are being developed. The CardioMEMS system consists of a miniaturised, wireless monitoring sensor that is implanted in the pulmonary artery (PA) during a minimally invasive procedure to directly measure PA pressure. Increases in PA pressure detected by the CardioMEMS system can predict an HF decompensation. This allows for a more personalised and proactive management to reduce the likelihood of hospitalisation (4).

In conclusion, early detection of cardiac arrhythmias and HF decompensation has the potential to prevent hospitalisations, major adverse cardiovascular events, and even death (1-4).

Remote monitoring of cardiac implantable electronic devices

Eighteen RCTs, twenty-four observational studies, and three meta-analyses conducted from 2000 until the end of 2019 looked at the effectiveness of RM of CIEDs on reducing healthcare utilisation and mortality, and 80% of these trials showed that it is effective in reducing healthcare utilisation and mortality. Sixteen cost-effective analyses showed that RM of CIEDs is a long-term cost-effective solution. Details on the research review are provided in Annex 6.

The ATTITUDE trial in 2010 (5) and the IN-TIME (6) trial in 2014 were early publications reporting improved survival among patients assigned to remote management of CIEDs. Saxon et al. (5) performed an observational study of 185778 patients with a CIED. The 69556 patients receiving remote follow-up had higher one- and five-year survival rates compared with patients who only received in-hospital device follow-up (50% reduction; $P < 0.0001$). The IN-TIME trial (6) was a randomised trial with 664 patients comparing implant-based, multiparameter telemonitoring (333) vs standard care. Hindricks et al. (6) concluded that telemonitoring of CIEDs can significantly improve clinical outcomes for patients with HF (odds ratio 0.63, 95% CI 0.43-0.90).

These early results were confirmed by several other studies. In 2015, Varma et al. (3) observed 269471 consecutive CIED patients, 127706 of whom (47%) used RM. They demonstrated that RM was associated with improved survival, irrespective of device type. Interestingly, a graded relationship with the level of adherence was found, which suggests that intensive use of RM is needed to further improve patient outcomes. The EFFECT study (7) in 2015 was an RCT enrolling 987 consecutive patients with ICDs. De Simone and his team demonstrated that RM reduces death and cardiovascular hospitalisations. The 2013 ECOST trial randomised 433 patients (8) and concluded that long-term RM of ICDs was as safe as standard ambulatory follow-up.

More recent trials by Morgan et al. (9) and Boriani et al. (10) failed to confirm the beneficial effect of RM in two large RCTs. The 2017 REM-HF trial (9) recruited 1650 patients and had

a median follow-up time of 2.8 years. This study showed no significant improvements in outcomes for patients followed by RM. Better usual care of CIEDs in England and a lower NYHA classification in this cohort were proposed by Morgan et al. (9) as possible reasons. The MORE-CARE trial in 2017 (10) demonstrated no beneficial effect of RM of CIEDs. In this RCT, 865 patients were enrolled, and the median follow-up time was two years. Even though RM did not improve patient health outcomes in the MORE-CARE trial, it did lead to a non-significant reduction in the use of healthcare resources due to a marked reduction in in-office visits (10).

In 2016, Böhm et al. (11) performed an RCT investigating a telemedicine system to alert fluid status in ICD patients by inaudible text message alerts to the responsible physician. This study did not demonstrate improved outcomes in the telemedicine group, possibly due to low adherence to the treatment protocol by both physicians and patients. In a 2015 study by Lüthje et al. (12) using fluid states, RM also could not demonstrate a significant effect on HF-related hospitalisations, ICD shocks, or mortality (12). The DOT-HF trial (13) in 2011 was an RCT with 335 patients using CIEDs to measure intrathoracic impedance. Patients were alerted with a sound when increases in pulmonary fluid retention were detected. This study showed that an implantable diagnostic tool to measure intrathoracic impedance with an audible patient alert did not improve outcomes and increased HF patients' hospitalisations and outpatient visits (13).

In 2017, Hindricks et al. (14) performed a pooled analysis of three large trials that investigated the role of daily RM of ICDs: IN-TIME (6), TRUST (15), and ECOST (8). The study concluded that daily RM reduced all-cause mortality mainly by preventing HF exacerbations (14). Klersy et al. (16) carried out a meta-analysis of eleven RCTs (5,702 patients) in 2016 to investigate the safety and effects of implantable device telemonitoring. An important conclusion of this meta-analysis was that RM was as safe as standard care and was associated with a marked reduction in planned hospital visits. Furthermore, RM also resulted in lower costs (16).

Guédon-Moreau et al. (17) demonstrated in a 2014 RCT with 310 patients that an RM system for ICDs was cost-saving from the French health insurance perspective. Lorenzoni et al. (18) also demonstrated in a 2014 observational study with 15254 patients that RM of CIEDs was cost-saving. Hummel et al. (19) in 2019 and Capucci et al. (20) in 2017 confirmed the cost-effectiveness in lifelong RM of ICDs. In 2016, Piccini et al. (21) conducted a nationwide

cohort study in Italy with 92566 patients who received RM for CIEDs and concluded that RM was associated with a reduction in hospitalisation and healthcare utilisation.

In conclusion, most trials and meta-analyses demonstrate that RM of CIEDs is effective in reducing rehospitalisation, mortality, and healthcare costs. However, the use of intrathoracic impedance monitoring with CIEDs, an early warning of impending decompensation in HF patients, needs further investigation.

Patient and staff experiences of remote monitoring of cardiac implantable electronic devices

Experience and acceptance by healthcare providers and patients using RM for CIEDs are important for implementation in regular care. The REMOTE-CIED trial (1) in 2019 investigated whether remote follow-up had an effect on patient-reported outcomes and acceptance of the ICD. Versteeg et al. (1) concluded that patient-reported health status and ICD acceptance did not differ between patients on RM and those receiving usual care. Petersen et al. (22) reported in 2012 that 95% of the patients were satisfied with the remote follow-up.

A survey study by Timmermans et al. in 2019 (23) demonstrated high satisfaction with RM, but a subgroup preferred in-clinic follow-up. Patients with a preference for RM were more likely to be higher educated ($P = 0.04$) and employed ($P = 0.04$). This suggests that physicians should also include patients' preferences and concerns to tailor device follow-up to individual patients' needs and preferences (23). In 2015, Mairesse et al. (24) demonstrated that physicians regard RM of CIEDs as a clinically useful technology that affords significant benefits for patients and healthcare organisations.

Wireless implantable hemodynamic monitoring systems

Intracardiac pressures are an important predictor for impending pulmonary congestion and could help to predict HF decompensations in time to prevent hospital admissions (25). Three RCTs, thirteen observational and cost-effect studies, and one meta-analysis conducted from 2000 until the end of 2019 looked at the effectiveness of wireless implantable hemodynamic

monitoring systems in effectively monitoring HF patients. All of these studies showed promising results. Details on the research review are provided in Annex 6.

In 2002, Magalski et al. (26) published one of the first studies to evaluate the accuracy of an implantable hemodynamic monitor in HF patients. They concluded that the implantable hemodynamic monitor was accurate over time to monitor the patient's hemodynamic condition. The COMPASS-HF trial was one of the first RCTs that investigated the clinical outcomes of implantable hemodynamic monitor-guided care. Bourge et al. (25) concluded in 2008 that the intervention did not significantly reduce all HF-related events compared with the control group.

Later, the CHAMPION trial was conducted using the CardioMEMS Heart Sensor. In 2011, Abraham et al. (27) demonstrated a large reduction in hospitalisation after six months of follow-up for patients with severe HF who were managed with the wireless implantable haemodynamic monitoring system. The monitoring system was able to reduce decompensation leading to hospitalisation compared with standard HF management strategies after a median of 17.6 months of follow-up (28). High pulmonary artery pressure (known as pulmonary hypertension) is when the pressure lung arteries becomes abnormally high. This strains the right side of the heart and could lead to heart failure. Pulmonary artery pressure-guided HF management used in the CHAMPION trial led to a 49% reduction in total HF hospitalisations and a 58% reduction in all-cause thirty-day readmissions (29). Later, several papers confirmed that in populations similar to those of the CHAMPION trial, the CardioMEMS device is cost-effective if the effectiveness is sustained over sufficiently long periods (30-32).

More research is needed to consistently implement implantable hemodynamic monitors in standard care, but most trials show promising results.

Arrhythmia detection with implantable devices

Remote monitoring of CIEDs may help in early detection of cardiac arrhythmias and, in that way, reduce decompensation, risk of stroke, and sudden cardiac death. A 2019 study by Perino et al. (33) showed a high prevalence of device-detected AF after pacemaker implantation (45% AF >6 minutes, 39% >1 hour, 32% >6 hours, 24% >24 hours). In 2006,

Cheung et al. (34) demonstrated that AF was detected in 24% of patients without a history of AF within one year after implantation. Ventricular high rate episodes (suggestive of AF) are frequently encountered in RM of pacemakers (35). A meta-analysis by Mahajan et al. (36) in 2018 demonstrated that RM of CIEDs detected subclinical AF in 35% of new CIED implants and that the presence of subclinical AF was associated with elevated stroke risk.

Multiple studies demonstrated that cardiac arrhythmias diagnosed during RM of CIEDs have a significant influence on major health outcomes. In 2017, Van Gelder et al. (37) showed that subclinical AF present for more than 24 hours is associated with an increased risk of ischaemic stroke or systemic embolism. A pooled analysis by Boriani et al. (38) in 2014 confirmed that device-detected AF burden is associated with an increased risk of ischaemic stroke. Lorenzoni et al. (19) showed that RM not only provides a potential to reduce the risk of stroke by early detection of new-onset AF but is also a cost-saving follow-up. A small qualitative study in 2017 showed that RM had a significant positive impact on health-related QoL for pacemaker patients (39).

RM can be used to adapt anticoagulation therapy in paroxysmal AF patients. The ANGELS AF trial in 2012 (40) demonstrated that it was possible to improve OAC use by supplying attending physicians with reports about the patient's risk factors and AF information from continuous ICD monitoring. Furthermore, Waks et al. (41) showed in 2018 among patients with rare AF episodes and low-to-moderate stroke risk that changing the OAC administration based on arrhythmia detection by the pacemaker or the implantable cardiac device is feasible and decreased anticoagulation utilisation by 75%. Mascarenhas (42) demonstrated in 2019 that AF burden assessment by CIEDs allows an individualised disease-guided approach to safely withdraw long-term OAC in patients with high bleeding risk.

Lastly, an RCT by Martin et al (43) in 2015 with 2718 patients showed that RM in ICD can be used for early initiation and interruption of anticoagulation without resulting in a significantly high level of strokes. However, there was also no significant reduction in bleeding complications (43).

In conclusion, arrhythmias detected by RM are predictive of adverse events, but it is unclear if treatment based on the detected abnormalities has a positive influence on outcomes.

Physical activity monitoring with implantable devices

Almost all CIEDs contain a single axis accelerometer to estimate daily physical activity. Palmisano et al. (44) in their 2018 study of 770 patients, showed that lower device-measured physical activity was associated with a higher risk of atrial arrhythmias, hospitalisations, and death. Device-based telerehabilitation should be studied to improve physical activity in patients with CIEDs.

Implantable loop recorder monitoring

Thirty-nine trials and two meta-analyses conducted from 2000 until the end of 2019 looked at the effectiveness of implantable loop recorders (ILRs) in increasing the diagnostic yield in patients with unexplained syncope, and 93% of these trials showed that it is effective in increasing the diagnostic yield. Details on the research review are provided in Annex 6.

ILRs have become increasingly popular for long-term cardiac rhythm monitoring. Multiple studies have demonstrated that ILR can play an important role in the diagnosis of unexplained syncope (45-49). Krahn et al. (46) showed in 2004 that long-term monitoring of patients with unexplained syncope led to the detection of more significant asymptomatic arrhythmias than anticipated. A meta-analysis by Solbiati et al. (50) in 2017 confirmed that in about half of all unexplained syncope subjects implanted with an ILR, the device made a diagnosis possible (50).

Thirty-two trials and one meta-analysis conducted from 2000 until 2019 looked at the effectiveness of ILRs in increasing the diagnosis of paroxysmal AF, and 91% of these trials showed that they are effective. Details on the research review are provided in Annex 6.

ILRs can also help to diagnose paroxysmal AF, and it is well established that Holter monitoring test (electrocardiogram) frequently misses this. A Holter monitor is a small, chest-worn wearable device that records all your heartbeats. Doctors often ask to wear a Holter for monitoring for one to two days. ILRs are implanted in the thorax and will also record all your heartbeats. However, ILRs can be used to monitor your heartbeats for a longer period which can increase the diagnostic yield of paroxysmal cardiac arrhythmias.

ILRs provide the opportunity for long-term rhythm monitoring (51). A 2019 study by Diederichsen et al. (52) demonstrated that a considerable burden of previously unknown AF

was detected when long-term monitoring was applied in at-risk patients. Two recent RCTs in 2016 and 2017 showed that, compared to usual care, ILR monitoring achieved a more rapid diagnosis of unexplained syncope and atrial tachycardia (53,54). Lastly, Rincoig et al. (55) used in 2019 a Markov model to establish that the use of ILRs is cost-effective for the UK NHS in identifying AF in a high-risk population.

ILRs can play an important role in the diagnosis of unexplained syncope, paroxysmal AF, and life-threatening arrhythmias in patients with recurrent complaints of syncope or palpitations.

Conclusions

Cardiovascular implantable electronic devices are becoming more common in cardiac patients as the indications for device placement continue to expand and the research data supports device placement compared to medical therapy (56). Multiple trials have reported the effectiveness of remote monitoring of CIEDs in reducing rehospitalisation, mortality, and healthcare costs in combination with high satisfaction from patients and health professionals. The use of devices that measure pulmonary artery pressure, such as the CardioMEMS system, seems to be effective. The role of CIEDs in detecting arrhythmias is still unclear. It is well established that device-detected arrhythmias are predictive of adverse events, but it is unclear if treatment based on the detected abnormalities has a positive influence on outcomes. Lastly, it is well established that ILRs should play an important role in the diagnosis of unexplained syncope, paroxysmal AF, and life-threatening arrhythmias in patients with recurrent complaints of syncope or palpitations.

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Chapter 7: Big data and artificial intelligence in cardiology

Big data

An increasing amount of data, including health data, is collected all over the world, and the use of digital health tools will only increase data flows (1). The introduction of electronic medical records (EMRs) has caused exponential growth in data availability in hospitals (2). This data can be collected not only from the EMRs in clinical practice but also from wearable devices, biosensors, genome sequencing, patient-reported outcomes, data about Internet use, and much more (2). This digital revolution is steering medicine away from manual data entry and relatively basic statistical tools to a bottom-up data management that involves real-time data extraction and analysis of various sources (3).

Big data can be defined as large datasets that cannot be analysed, searched, interpreted, or stored using traditional data-processing methods (4). These datasets are mostly processed and analysed by applying artificial intelligence and machine learning algorithms (5), but the most-used definition of big data was introduced by Doug Laney in 2001 and known as the 3V's: volume, variety, and velocity (5,6). Currently, big data is defined as the 4V's after the addition of veracity.

In most big datasets, the volume surpasses one petabyte of data (2). Nowadays, data can be stored in countless variations, can come from multiple sources, and often exist in unstructured formats (5). Structured data are highly organised and, therefore, easy to analyse (e.g. ECG data, age, drug dose, etc.). Unstructured data can be textual or non-textual and can be human- or machine-made (7). Unstructured data for healthcare can potentially give a more comprehensive view of a patient by integrating social and environmental information which possibly correlates with health.

The high speed at which data are generated increases the gap between the volume of data available and our ability to analyse and interpret them in time (5). The risk is that physicians are inundated with data that require a more sophisticated interpretation while being expected to perform more efficiently (5).

Artificial intelligence and machine learning may help to process and analyse big data sets and present them as smaller lumps of understandable information, enabling doctors to provide

more efficient, convenient, personalised, and effective care (8). Evidence for the use of big data analytics is increasing. Big data analytics can be used for predictive risk models, pharmacogenomics, ECG diagnosis, and image analysis as well as to facilitate research.

Artificial intelligence

Artificial intelligence is defined by the European Commission as: “Systems that display intelligent behaviour by analysing their environment and taking actions – with some degree of autonomy – to achieve specific goals. Artificial intelligence-based systems can be purely software-based, acting in the virtual world (e.g. voice assistants, image analysis software, search engines, speech and face recognition systems) or artificial intelligence can be embedded in hardware devices (e.g. advanced robots, autonomous cars, drones or Internet of Things applications) (1).”

Artificial intelligence is increasingly integrated into our daily lives in areas such as transportation, computer gaming, and digital voice assistants (e.g. Alexa, Siri) (9). Nowadays, artificial intelligence is also trending in medicine to improve patient care by speeding up processes and achieving greater accuracy, opening the path to providing better healthcare overall (9).

Machine learning is an extension of artificial intelligence and is defined as a system’s ability to autonomously acquire knowledge by extracting patterns from large data sets (10). Machine learning has three important forms: supervised machine learning, unsupervised machine learning, and reinforcement. Supervised learning uses a human-labelled classification of an observation (e.g. ‘Does this ECG represent sinus rhythm or atrial fibrillation?’) to predict the desired and known outcome; it helps in classification and regression problems but requires significant amounts of data and is time-consuming because the data have to be labelled by humans (8). Unsupervised learning focuses on discovering underlying hidden patterns in the dataset without human feedback. Lastly, reinforcement is a hybrid technique with the objective of maximising the algorithms’ accuracy using trial and error (8,10).

The most recent innovation in the field of artificial intelligence is deep learning and neural networks. Deep learning mimics the human brain by using multiple layers of artificial neural networks that can generate automated predictions from the input. Activated neuronal layers

continue to pass a value to the next layer of neurons until the final ‘output layer’ of neurons is reached (8). Simply put, deep learning is a more advanced technique within machine learning that requires bigger data and stronger computers, but it can offer automatic improvement and a high accuracy level.

Use of artificial intelligence in cardiology

Imaging

Artificial intelligence can play a role in detection, classification, segmentation, tracking, and even report generation in cardiovascular imaging (11). A 2019 study by Seah et al. (12) of a dataset of 103489 chest radiographs demonstrated that a machine learning algorithm was able to detect and highlight the cardiomegaly and pleural effusions with an area under the curve (AUC) of 0.82.

The deep learning algorithm of Madani et al. (13) in 2018 had an accuracy of 91.7% in comparison with the 79% accuracy of four board-certified echocardiographers in analysing fifteen standard echocardiographic views. (13). Samad and his colleagues (14) demonstrated in 2018 that a deep learning algorithm was able to predict survival with higher accuracy after analysing the echocardiography of multiple cases. Playford et al. (15) showed, also in 2018, that artificial intelligence was able to calculate the aortic valve area without left ventricular outflow tract measurements in evaluating aortic stenosis. Narula et al. (16) used machine learning in 2016 to differentiate hypertrophic cardiomyopathy from normal heart hypertrophy in 2D-echocardiography with an overall sensitivity of 87% and specificity of 82%. In a large retrospective study of 8000 echocardiograms, Zhang et al. (17) demonstrated in 2018 that artificial intelligence was able to classify hypertrophic cardiomyopathy (AUC 0.93), cardiac amyloid (AUC 0.87), and pulmonary hypertension (AUC 0.85) with high accuracy.

Gonzalez et al. (18) demonstrated in 2018 that a neural network is able to calculate Agatston scores from unenhanced chest CT exams without prior segmentation of coronary artery calcifications. Furthermore, it is faster and more accurate in comparison with standard methods.

Tao et al. (19) showed in 2019 that an artificial intelligence tool trained on a dataset of 596 magnetic resonance imaging (MRI) examinations is able to outperform manual segmentation.

In 2017, Dawes et al (20) used cardiac MRI scans and blood tests from 256 heart disease patients. The artificial intelligence tool measured the movement of 30,000 points that are marked on the heart structures in each heartbeat. By combining these data with the patients' eight-year health records, the artificial intelligence tool was able to predict the patients' survival rates for the next five years with an accuracy of 80% as compared to 60% for clinicians. In 2019, Otha et al. (21) evaluated myocardial-delayed enhancement on MRIs with an accuracy of 78.9–82.1%.

In 2017, Nakajima and his team (22) trained an artificial neural network to classify potentially abnormal areas on myocardial perfusion images as true or false. The diagnostic accuracy of the artificial neural network was compared with 364 expert interpretations. The artificial intelligence tool was diagnostically as accurate or more accurate in various clinical settings, including patients with previous MI and coronary revascularisation.

Deep learning has been used to predict obstructive disease from myocardial perfusion SPECT (23). In 2018, Betancur et al. (23) used myocardial perfusion imaging of 1638 patients to train the deep learning tool. This resulted in significantly better diagnoses of coronary obstructive disease.

These studies show the significant potential of artificial intelligence in cardiac imaging analysis.

Electrocardiogram (ECG)

In 2017, Isin et al. (24) used a deep learning algorithm for automated arrhythmia detection on an ECG using an online dataset of over 4000 long-term ECG Holter recordings, including rare conditions. It showed a correct recognition rate of 98.5% and an accuracy of 92% (24).

Rapjukar et al. (25) developed a deep learning tool in 2017 from 64000 single-lead ECGs to assess arrhythmia. Single-lead ECGs only use two electrodes and it is often used in smartwatches or handheld ECG devices.

Their results showed that the deep learning tool was non-inferior to six cardiologists. In 2019, Hannun et al. (26) developed a deep neural network to classify twelve rhythm classes using 91232 single-lead ECGs from 53549 patients who used a single-lead ambulatory ECG monitoring device. It was validated against an independent test dataset annotated by a

consensus committee of board-certified practising cardiologists; the deep neural network achieved an AUC of 0.97. Galloway et al. (27) used ECGs and artificial intelligence in 2019 to screen for high levels of potassium.

Risk assessment and risk prediction models

In 2018, Kwon et al. (28) developed a deep learning tool to detect in-hospital death without attempted resuscitation. The tool outperformed standard methods, showing higher sensitivity and lower false alarm rates. In 2017, Motwani et al. (29) evaluated the five-year risk of death in 10,030 suspected coronary heart disease patients. The artificial intelligence tool was superior to traditional clinical judgement and coronary computed tomographic angiography.

In 2019, Alaa et al. (30) showed a better risk prediction as compared to the Framingham score using a model with 473 variables. Interestingly, the tool was also able to detect new possible risk factors such as individual usual walking pace.

Conclusions

Artificial intelligence and big data hold great potential for improving certain healthcare functions, e.g. routine screening and diagnostics, avoiding medical errors and adverse reactions, understanding disease transmission pathways, supporting chronic disease management, and improving patient safety (1). Furthermore, they will allow more personalised healthcare and boost clinical and pharmacological research. However, more attention needs to be paid to the ethical considerations of artificial intelligence and for a balanced regulatory structure to regulate new innovations and protect personal data.

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Chapter 8 Considerations for implementation of Digital Health

This report has demonstrated the potential of digital health interventions in improving health outcomes and saving costs for cardiovascular prevention, detection, and management (1). The facilitators and barriers for the step between digital health research and implementation will be discussed in this chapter. Furthermore, it is important to consider the potential impact of digital health on social inequalities. Low health or digital literacy, the lack of user-friendliness, and doubts over the meaningfulness of information can also create new health inequalities (2).

Patient-related considerations

Important barriers for patients include accessibility, privacy, data security concerns, lack of personal motivation, and low digital literacy (1,3). Access to the Internet in the EU has increased significantly in the last ten years (4). For many people in the EU, using the Internet has become an increasingly important part of their daily lives; 84% of the EU's population are Internet users, with smartphones being the most frequently used device. However, digital literacy is still surprisingly low. Only 57% of the EU's population aged 16–74 had a basic level of digital literacy in 2017 (5). Low digital and health literacy are especially associated with older age and low socio-economic status.

Older people often feel isolated, and the older they get, the more they tend to depend on medical and social care without family support structures (2,6). Being able to use the Internet can be life-transforming and can improve QoL for seniors who possess the know-how to navigate it. Therefore, the introduction of digital health is only beneficial for those who have sufficient digital literacy. Attention is needed so that elderly people with lower digital literacy are not forgotten.

In 2012, Kontos et al. (7) demonstrated that patients with lower levels of education had significantly lower odds of going online to look for a healthcare provider; using email or the Internet to communicate with a doctor; tracking their personal health information online; using a website to help track diet, weight, and physical activity; or downloading health information to a mobile device. Digital health and patient empowerment go hand-in-hand. However, for some patients with a lower educational background, it is hard to master the

skills they need to use digital health tools. One important reason is that many digital health solutions are developed for people who already possess a much broader set of ‘health skills’, including awareness, attention, ambition, and self-discipline, to use new technologies for better health outcomes (2). New technology thus enhances already existing skills, which makes digital health particularly attractive and amenable to the educated—and potentially impenetrable for people with lower education.

Migrants are often a vulnerable population with sometimes little to no access to health services. In addition, poverty, discrimination, and cultural and language barriers are regularly present. There are many differences between ethnic minorities and migrant communities in their technology use, but even if they possess the needed technology for digital health services, several other barriers are present that could turn into inequalities. Language is one of the most important barriers, but many migrants are also not used to the format, style, and ‘candidness’ of information found on European websites, which may not fit their own cultural or religious values (2).

The previous examples show that it is important to ensure that digital health tools do not lead to increased inequalities in health. Therefore, patients should be involved in creating new digital health tools because of the important role they play in health decisions. The involvement of health professionals and patients in developing new digital tools is called co-creation. However, at this moment, most healthcare innovations are mainly technology-driven. In the future, digital health research and innovation must be driven more by patients’ and physicians’ needs. Next to co-creation, tailoring interventions to individual levels of health and digital literacy or to specific target groups can improve the adoption of digital health (8,9).

Recommendations for reducing patient-related considerations

1. Increasing access to digital health technology

Governments must invest in an infrastructure where all citizens can have access to affordable healthcare. One of the key initiatives will be co-creation. This means that various categories of end users have a say in the design of digital health tools.

There is also a need for cultural change whereby patients check with their doctors and do not take all information on the Internet at face value. In addition, implementation of video consultations, chatterbots, and similar tools would allow better patient-health professional communication (2). Last but not least, individuals must be better aware of data protection and safety because these could become important inhibitors for patients and even health professionals.

2. Reduce technological pressure

Technology is evolving faster than ever, and the result is that hardware and software are almost outdated from the moment people buy them. Not everybody is able to afford or to use all new technologies. Governments must create frameworks to make all digital health tools accessible for everyone, including to people who only have access to outdated technology. National health authorities and social security administrations could consider offering such patients appropriate digital health tools either as a donation or via financial subsidies that would allow them to purchase everything necessary to manage their conditions more effectively through digital health technology (2).

3. Improve digital literacy

Individuals only feel empowered if they are able to use digital health tools confidently. Since digital literacy comprises a whole set of different literacies, there is a growing need to educate and train individuals in all these elements, especially members in vulnerable and at-risk groups. In addition, there must be more focused information campaigns and training activities directed to the general public since average literacy levels in all categories tend to be low, and digital health literacy is a blurry notion for most people. There is a lack of understanding of what it entails and how it can add value, and there is even less information on common solutions and issues in a cross-border context, combined with concerns over data protection and confidentiality (2).

Physician-related considerations

Digital health allows physicians to diagnose, monitor, and treat patients remotely. Furthermore, digital health could reduce healthcare professionals' workload by taking over some of the daily tasks. In reality, however, digital health is often added to existing care

rather than being streamlined into it, leading to an increased workload (1). This results in the perception that digital health implementation always means a higher workload. Change is difficult in most healthcare organisations because healthcare professionals and, indeed, patients can be resistant to changes in the care they deliver or receive. This resistance can arise from the fear of losing something of value or the fear they will not be able to adapt to the new ways. Therefore, it is important to pay attention to integration in the clinical workflow during the development of digital health tools.

Evidence that a new intervention improves patient health outcomes is also crucial for implementation in medicine. Many physicians only implement new treatments or diagnostic strategies when there is overwhelming evidence that they are better than the current care. Therefore, more research and especially larger RCTs are needed to demonstrate the effectiveness of digital health interventions which will convince physicians of the positive effects. Improved patient health outcomes are also important to persuade governments and healthcare organisations to invest in these digital health strategies (1).

Another important consideration is the fact that current healthcare professionals are not trained to use digital health in patient care. Therefore, current and future healthcare professionals must be educated about the opportunities and the use of digital health.

In most EU countries, there is no reimbursement for digital health, and healthcare professionals are not paid for digital health services (1). Healthcare professionals can be hesitant to use innovative digital health when they are not compensated for these efforts.

Lastly, at this moment, a clear regulatory framework for the use of digital health and artificial intelligence in healthcare is lacking (1). This results in uncertainties such as who is responsible for decisions made by artificial intelligence systems or who is responsible for data leakage when an RM system is hacked.

Technical considerations

Digital health is trending not only in cardiology but in most medical disciplines. The result could be that physicians become overwhelmed by digital tools and data. Interoperability and integration in EMRs are important facilitators for implementation. Another barrier is the fact

that technology development is moving much faster than scientific validation is performed. Therefore, digital tools are often only validated when the technology is already outdated.

Digital health tools are used in decision-support systems, patient monitoring, diagnosis, and treatment choices. Therefore, system reliability and trustworthiness are important in persuading physicians to use these tools (1,10,11).

Legal and ethical considerations

In 2014, the European Commission launched a strategic reflection on the use of big data in healthcare (12,13). This resulted in ten policy recommendations formulated to stimulate the EU and national level deployment of big data without compromising people's privacy and safety (12). Only recently (June 2019), the Joint Action supporting the eHealth Network that was created under the Cross-border Patient's Rights Directive 2011/24/EU published a report on policy action for the innovative use of big data in health with a long-term goal to develop a European cross-national exchange format for EMRs (12,14,15). Furthermore, it is the ambition of the 2019-2024 European Commission to develop a legislative European approach to the human and ethical implications of artificial intelligence in the first 100 days of the new European Commission (12).

A legal framework for the use of digital health and artificial intelligence in healthcare is important because they can play a big role in risk prediction, diagnosis, and treatment choices within the field of cardiology. It must be ensured that these tools are of high quality. A legal framework can provide regulatory bodies with the information needed to monitor and assess the quality of digital health tools to make sure that the tools used in European healthcare are safe and compliant with the General Data Protection Regulation (GDPR).

This legal framework is not only necessary to ensure quality control but also to clarify questions about responsibility. For example, should health professionals be fully responsible for decisions suggested or made by artificial intelligence algorithms (16)? This dilemma creates issues such as when an algorithm suggests an intervention that seems banal but is also unhelpful, useless, and expensive or dangerous, should the provider second-guess the recommendation? Obviously, the first thought is 'Yes', but on the other hand, if providers

only implement the choices they would have made on their own, we lose all the benefits of the artificial intelligence analysis of big data.

Lastly, a legal framework is also important to ensure privacy and data security. Patients are becoming more aware of the value of their medical data and often only feel comfortable sharing their medical information with their health providers (16,17). A study of Kalkman et al (17) demonstrated that patients reported multiple concerns when asked to share medical data for research projects. Patients were more willing to share data when privacy-protecting measures were present and when the data handling, responsibilities and accountability was transparent (17).

The European Commission has already taken big leaps to establish a legal framework to ensure data security and protection of personal data with the introduction of the GDPR and ePrivacy (18,19).

Legal issues aside, there are also ethical considerations for implementing digital health and artificial intelligence in healthcare. Their potential is evident; however, they may pose a possible threat to patient preference, privacy, and safety.

Conclusions

Co-creation of digital health tools with all relevant stakeholders, including most notably patients and health professionals, is needed to overcome common barriers such as lack of personal motivation, low digital literacy, lack of interoperability, and increased workload. Furthermore, integration in EMRs is important to prevent overwhelming physicians with digital health tools and data. A European legal framework is needed to regulate digital health and artificial intelligence in healthcare to ensure quality and data security. The European Commission aims to create a clear framework which will help to implement digital health in standard practice.

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Chapter 9 Conclusions

The burden of cardiovascular disease (CVD) in the EU and Europe is high. Each year cardiovascular disease causes over 1.8 million deaths in the European Union (36% of all deaths) (1,2). This results in a significant challenge for healthcare systems regarding qualified personnel and infrastructure. For this reason, innovative ways to address these challenges, such as digital health are explored to deliver sufficient and better care to patients at a reasonable cost.

In primary prevention, evidence suggests that digital health can be used in lifestyle management intervention to reduce cardiovascular risk and play an important role in screening of patients with high cardiovascular risk, especially in remote areas and in less developed countries.

In secondary prevention multiple trials suggest that telerehabilitation can be as effective as centre-based CR. However, more trials with larger sample sizes are needed to confirm this. Lifestyle management programmes delivered with digital health could be effective to prevent recurrent heart attacks. Research suggest that text messaging is more effective than internet-based interventions.

The role of digital health in heart failure management remains under discussion especially in telemonitoring. Many trials suggest that telemonitoring is effective in HF, however some large multi-centre trials failed to demonstrate the effectiveness of telemonitoring. Also, more research is needed to prove the effectiveness of telerehabilitation in a HF population. Recent telerehabilitation trials in HF show conflicting results.

Digital health for AF detection is a relatively new field. There is still a need for more multi-centre RCTs, but current evidence suggest that it can be a valuable tool for AF detection and mass screening. It can also be important in improving adherence to OAC treatment.

Remote monitoring of CIEDs is effective in reducing rehospitalisation, mortality and healthcare costs. However, the use of intrathoracic impedance monitoring with CIEDs as an early warning of impending decompensation in heart failure patients, needs further investigation. AF detection by remote monitoring is a predictor for adverse events but it is

still unclear if it is effective to adapt OAC treatment on the basis of the CIED-detected arrhythmias.

Digital health gives patients and health professionals the chance to transform current healthcare models. However, there is still need for big multi-centre trials to confirm the effectiveness and the cost-effectiveness of these digital interventions in cardiology. Lastly, Digital health has great potential, but it is important not to forget patients with lower digital literacy. Attention to the needs of elderly, disabled and cultural differences between ethnic groups is needed.

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This paper relates to an activity that received funding under an operating grant from the European Union's Health Programme (2014-2020). The content represents the views of the authors only and is their sole responsibility; it cannot be considered to reflect the views of the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.