The use of mobile health to evolve outpatient thoracic surgical care: a focus on implementation, patient engagement, arrhythmia detection and cardiovascular risk reduction

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CHAPTER VII

Summary and General Discussion

The aim of this thesis was to evaluate the effects of mHealth in patients who underwent cardiac surgery, and provide an insight in the requirements for the implementation of an mHealth project in the clinical setting. Project *The Box* was successfully started by colleague and co-supervisor Treskes, who obtained his doctorate in 2018. At the time of his defense, Treskes described eHealth to be a relatively new concept, with not much data being available. The rising number of publications in the field of mHealth, along with innovation in digital technology, has changed the currently available information significantly.

Chapter II provides an overview of the currently available evidence regarding the detection of atrial fibrillation (AF) with single-lead ECG devices and ECG patches. These devices enable patients to register an ECG without the need for assistance or supervision of trained healthcare staff. A systematic review was conducted, selecting 14 studies in a total of 4617 adult patients with an indication for ECG follow-up. The main purpose was to evaluate the detection rate of AF by mHealth devices compared with regular follow-up, which was defined as follow-up via the general practitioner or regular outpatient clinic visits with a standard 12-lead ECG or Holter monitoring. The intervention groups of the selected studies registered a single-lead ECG at scheduled moments, mostly twice a week to twice daily. In case an ECG patch was used, patients wore this patch for the duration of 14 to 28 days. Due to a considerable clinical heterogeneity (i.e. heterogeneity in patient population, type of intervention and follow-up protocol) with a Q of 34.1 and an I^2 of 61.9, it was decided not to pool the results, thus not to perform a meta-analysis. A total of 13 out of 14 studies found an increased AF detection rate in the intervention group as compared to the control group, with Odds Ratios ranging from 1.77 (0.96 - 3.26) to 35.71 (1.70 - 750.18).

Consequently, conducting more (spot) measurements via mHealth lead to an increased likelihood of detecting AF despite the unfeasibility to pool all results into a meta-analysis. This, however, does not mean that all patients in whom AF was detected should also be put on anticoagulant therapy. European guidelines define AF as an irregular arrhythmia without visible P waves lasting 30 seconds or more, documented on a standard 12-lead ECG or via Holter monitoring. The clinical significance of short paroxysms is debated. The new way of diagnosing rhythm disturbances mHealth allows could, especially in the case of ECG patches, potentially best be compared with AF detection in patients with a cardiac device. In these patients, the AF burden is known to be more important than short paroxysms, although there is a correlation between AF duration and total AF burden. The clinical relevance of AF detection by mHealth devices will therefore have to be addressed in further research. Until then, clinicians must beware of overdiagnosis of AF and, sequentially, overtreatment with oral anticoagulants.

Chapter III provides an overview of the first four years of project *The Box* at the department of Cardiology of the LUMC. The main purpose of this Chapter is to describe the implementation process of an mHealth project in day-to-day clinical care and present real world results from this implementation process. The paper describes some logistical hazards that have to be overcome for implementation. For instance, it is important for patients to be able to receive help installing the devices and offer the opportunity for them to contact a helpdesk in case of device-issues at home. Equally important is the automatic connectibility of mHealth devices to the electronic medical record of the hospital to allow care providers insight in measurement data without requiring patients to actively send their data by pressing a button, while also providing timely feedback to the patient. Care providers have yet another requirement: easy insight in measurement data, preferably in combination with an automatic filter that makes data irregularities stand out.

Another purpose of this Chapter is to provide insight in Box user characteristics and experiences from both patients and care providers. Over the course of the first four years of *The Box*, 1140 patients were equipped with a Box. As described in the introduction to this thesis, *The Box* started as a randomized controlled trial for patients after myocardial infarction in 2016, and was continued as a clinical project after inclusion was completed. At the end of 2017, inclusion for *The Box 2.0* was started, a study which is further described in **Chapters IV to VI**. Shortly thereafter, in the first half of 2018, patients with a cardiac device and those after ablation were also eligible to receive a Box. Finally, at the end of 2019, heart failure patients and grown-ups with congenital heart disease could also receive a Box. The average age of Box users was 60.8 years, the majority was male (73.6%). The oldest patient to receive a Box was 83 years of age. Over the course of follow-up, the median number of measurements was 260 on a median of 189 unique measurement days. The growth was almost exponential, and for 2020 an expected 1100 Boxes were to be handed out. Patients praised the ease of use of the devices and felt more involved with their illness and care. Professionals reported more interactive and productive outpatient consultations as well as improved insight in health parameters such as blood pressure and weight.

Chapter IV discusses the rationale and design of *The Box 2.0*. The aim of this study was already highlighted in the introduction of this thesis: to assess the effect of *The Box* on clinical outcomes and patient satisfaction after cardiac surgery. Patients who underwent cardiac surgery via sternotomy, performed in the LUMC, were eligible for enrollment. Starting in November 2019, patients were prospectively included in the intervention group. A historical control group was used for comparison. Duration of follow-up was 3 months. The selected mHealth devices for this study were a weight scale, blood pressure monitor, thermometer and pedometer watch (all Withings, Issy les Moulinaux, France), a blood oxygen saturation monitor (Masimo, Irvine, CA, USA), a single lead I ECG moni-

tor (Alivecor Inc., San Francisco, CA, USA), and an EASI-derived ECG device (Cardiosecur, Personal Medsystems, Frankfurt am Main, Germany).

Participants of the intervention group received all mHealth devices before discharge. If necessary, they received help from specialized help desk support staff to install these devices on their smartphone. Patients could also contact the help desk if they ran into problems with the mHealth devices at home. Two weeks after discharge, patients were seen by a nurse practitioner (NP). Control group patients were seen back at the outpatient clinic. Intervention group patients were seen back via the webcam (eVisit), at which time their sternal wound was visually checked. During the first two weeks patients took measurements daily, and 2-3 times per week after these initial two weeks unless there was a reason to do this differently. The NP checked these measurement data 2-3 times per week. The final outpatient contact moment took place at the outpatient clinic after three months, because patients underwent a transthoracic echo and a blood sample was taken. Patients handed in the Cardiosecur device; the other mHealth devices were gifted to the participants.

The power calculation was based on the primary outcome; the detection of postoperative AF (POAF), which was expected to increase from 15% to 25%. POAF was defined as AF shown on an EASI ECG, made with the Cardiosecur device. A power of 0.9 yielded a sample size of 335 patients per group, which was increased to 365 due to expected loss-to-follow-up. Secondary outcomes include blood pressure and lipid levels at three months, readmission rates, number of cardiology-related visits to the emergency department (ED), quality of life (five-level EuroQol, EQ5D), and patient satisfaction of care. The results were agreed to be analyzed according to the intention-to-treat principle. This means that patients who did not consent to the intervention, but consented to the researchers using their data, were included in the analyses in order to reduce selection bias. For the same reason, data of patients who dropped out of the intervention were also used in the analyses.

Thirty months after inclusion of the first patient, *The Box 2.0* was completed. **Chapter V** presents the main results of this study. Due to logistical issues, the blood oxygen saturation monitor could not be included in *The Box*. This was the only protocol deviation. After screening 419 patients for eligibility, 365 patients were included in the intervention group. COVID-19 caused an inclusion delay, and a difference between the intervention and control group at baseline due to the effect on the intensive care capacity and, as a result, cancellations of elective cardiac surgery. The mean age of this group was 62 years, versus 66 years in the control group. A total of 74,767 mHealth measurements were recorded by 319 intervention group patients over the course of almost 17,926 unique measurement days. The other 46 intervention group patients did not consent to mHealth

measurements, but have been included in the intervention arm due to the intention-to-treat design. These patients gave signed consent for the use of their data.

In the intervention group, 61 patients were diagnosed with POAF versus 25 in the control group. After correction, a significant Risk Ratio (RR) of 1.95 (95% confidence interval (CI): 1.33 - 3.03) was found. A per-protocol analysis was also carried out, showing a corrected RR of 2.38 (95% CI: 1.55 - 3.97). The Kaplan-Meier curve showed this effect mainly resulted from the first two weeks of follow-up. Another significant effect of the intervention was seen when evaluating ED-visits; 48 intervention group patients had at least one unplanned ED-visit, versus 86 controls (Odds Ratio 0.50; 95% CI: 0.34 – 0.74; P = 0.0005). This difference is hypothesized to be due to an improved patient engagement and empowerment, where the possibility for patients to register an ECG and measure the vital parameters have a comforting effect, as the NP checked 2-3 times per week and provided feedback when needed. Overcrowding of emergency departments is a problem worldwide, and is associated with worse patient outcomes and increased costs. Therefore, it is important to reduce unnecessary ED visits as much as possible. Finally, intervention group patients were significantly more satisfied compared to controls. Intervention group patients scored an 8.2 out of a possible 10 points, versus a 7.9 for controls (P = 0.02).

Finally, **Chapter VI** presents the results of a substudy of *The Box 2.0* regarding blood pressure, weight and cholesterol management. Only patients who underwent coronary artery bypass grafting were selected for this substudy. Concomitant surgery was an exclusion criterium, as well as incomplete blood pressure data at the end of follow-up. This yielded a total of 228 patients; 117 controls and 111 intervention group patients. Mean age in the intervention group was 63 years, versus 65 years for controls (P = 0.05). Cholesterol levels did not differ at baseline, yet significantly more controls (N = 74) had a history of hypertension compared to the intervention group (N = 51; P = 0.01).

Patients registered a median of 222 measurements (interquartile range (IQR): 164-304) on a median of 52 out of a possible 92 days (IQR: 37-84). The primary endpoints were systolic and diastolic blood pressure, weight and LDL at the end of follow-up. The systolic blood pressure was significantly lower in intervention group (mean: 129.5 mmHg versus 137.4 mmHg for controls; P = 0.03). The diastolic blood pressure showed no significant difference, although it was lower in intervention group patients than in controls (mean: 76.8 mmHg versus 77.9 mmHg, respectively; P = 0.17). During follow-up, intervention group patients lost an average of 1.76 kg (SD: 3.23), while controls on average gained 0.31 kg (SD: 2.55; P = 0.002). LDL-C levels at the end of follow-up were significantly lower in the intervention group versus controls (median: 1.8 mmol/L versus 2.0 mmol/L, respectively; P = 0.0005). A Spearman's analysis showed no correlation between the number of mHealth measurements, or measurement days, and the individual endpoints. The decrease in LDL

is hypothesized to be related to an educational consequence of the intervention, resulting in an increased patient engagement and empowerment.

Interestingly, although this study found significant blood pressure differences between the intervention and control group, *The Box* RCT by Treskes did not find a significant difference in blood pressure outcomes between Box users and controls. This may be explained by several factors. As project *The Box* project aged, it became a standard in the management of outpatients of the cardiology department of the LUMC. Over the years, improvements have been made on the client side as well as for the staff. Currently, NP's have an easier overview of patients' measurements, and measurement alerts have been introduced. This has improved the detection of data irregularities and, as such, may have led to an improvement in efficiency regarding adjustments in the therapeutic regimen during follow-up. As to the observed differences in LDL cholesterol between the intervention and control group, it is hypothesized that this difference is due to the difference in weight reduction on one hand, and an educational effect of the intervention on the other hand; patients likely became more engaged and empowered by the intervention. This was extensively discussed in **Chapter V**.

GENERAL DISCUSSION

This thesis has demonstrated the positive effect mHealth can have on the detection of (de novo) AF. Mobile health devices, used in *The Box 2.0*, were found to increase POAF detection in post-cardiac surgery patients, which may also positively impact complications such as ischemic stroke. Additionally, the systematic review conducted in this thesis showed other patient groups at risk for cardiovascular events to benefit from mHealth interventions for the detection of (de novo) AF as well, as 13 out of 14 studies with different populations, interventions, and (primary) outcomes found an increased number of AF diagnoses with the use of an mHealth intervention compared with standard care. Moreover, as stroke is found to be the first symptom of AF in 37% of patients aged younger than 75 years with no history of cardiovascular diseases[1], screening risk groups for de novo AF may also be of clinical relevance.

However, no consensus exists within the scientific community whether each episode of AF should be deemed clinically significant. Most mHealth ECG devices register the heart rhythm during 10 to 30 seconds, and are most often used by patients immediately after symptoms arise. The clinical significance of a short paroxysm of AF is debated. For patients who underwent an AF ablation, it is known that the quality of life response is proportional to the AF burden rather than to a short-lived event, and that AF burden is also a better predictor for stroke risk compared solely with a history of AF[2]. The eCardiology working group of the European Society of Cardiology (ESC) has recently published a position paper in which is stated that, in the context of AF management, documentation of cardiac rhythm is pivotal for decision regarding the need for re-ablation procedures or self-administration of rhythm-control drugs in situations when pill-in-the-pocket strategy is employed[3]. The current ESC guidelines discuss that although caution is needed in the clinical use of mHealth ECG devices, as many are not clinically validated, a single-lead ECG tracing of ≥30 seconds or a 12-lead ECG showing AF suffices to definitively diagnose AF[4]. However, when considering prescribing anticoagulant therapy, clinicians should realize that overtreatment is looming when the diagnosis of AF is solely based on one mHealth reading.

This thesis has also shown the use of mHealth in cardiovascular risk management. The eCardiology working group of the ESC lately also recommended using mHealth interventions to address (residual) cardiovascular risk factors[5]. **Chapter VI** has demonstrated a positive impact of an mHealth intervention on the systolic and diastolic blood pressure of cardiac surgery patients, which is in line with research that has been performed in other patient groups[6-8], reducing the systolic BP by 7 mmHg. Although further research is needed to assess long-term outcomes of *The Box*, it is known that a 3 mmHg reduction in systolic BP can reduce stroke mortality by 8%[9]. The American Heart Association

has recently released a statement concerning self-measured blood pressure monitoring at home[10], supporting this form of monitoring based on available literature (*Class of Recommendation I; Level of Evidence A*)[11]. However, BP device data is not always easily shared with healthcare professionals. The use of mHealth devices could solve this problem, as they allow for an automatic incorporation of device data in the hospital's electronic medical records. Moreover, mHealth can be used more extensively to reduce cardiovascular risk factors. The American Heart Association stated it to be reasonable to use self-measured BP monitoring in case of white coat hypertension, to discover masked uncontrolled hypertension, and to replace standard 24-hour ambulatory BP monitoring in outpatients. Therefore, it is important to develop mHealth further, focusing on mHealth literacy in both patients and healthcare providers, data integration and, importantly, data safety.

However, cardiovascular risk management does not only entail blood pressure management. Reducing a patient's weight and cholesterol levels are equally important. Although no previous studies assessing weight reduction with eHealth devices were found, several small trials have found positive effects of web-based eHealth interventions on weight loss in patients with coronary artery disease[12-14]. The positive impact of mHealth on cholesterol levels we found, however, could not be traced in earlier research. No studies have investigated the role of mHealth on cholesterol management in patients with cardiovascular disease. As of recently, in other patient groups, gamification is often used as a method to induce positive lifestyle changes, with several studies showing a positive effect on body weight reduction[15-17]. One gamification study in diabetic patients focused on body weight reduction and increased physical activity, showing decreased cholesterol levels at the end of a one-year follow-up period.[17] The authors hypothesize these observed changes to be a result of an increased incentive to improve on one's lifestyle. In **Chapter VI**, we call this *'increased patient engagement'*. Engaging patients in improving on lifestyle factors is important as, for instance, even small increases or light-intensity physical activity can lead to health benefits, in particular a decreased risk of cardiovascular disease[18,19].

Finally, this thesis demonstrated mHealth implementation to be feasible in daily outpatient care, as well as its positive impact on patient satisfaction. Mobile health enables better quality of care, it increases patient involvement and safety, and it optimizes access to healthcare. This thesis showed that mHealth is generally well accepted by patients, which is demonstrated by the high median number of mHealth measurements during the follow-up period, the fact that 90% of all patients adhered to the mHealth protocol, and the high satisfaction scores after follow-up was completed. Importantly, the results of qualitative interviews indicate that patients become more active mHealth participants as they were asked to measure their own vitals daily. Providers commended on the ability of mHealth to enhance patient engagement and medical literacy, as they received

fewer and more to-the-point questions from patients. After more than 4 years of The Box, mHealth has been incorporated in the daily outpatient care of all kinds of patient groups, not only on the cardiology and thoracic surgery departments. It is now also used for the follow-up of pregnant women, patients with diabetes, and organ transplantation patients. The Dutch government actively stimulates the use of eHealth and mHealth by healthcare providers. In 2021, the Dutch Healthcare Authority (NZA) has increased eHealth funding and made regulations more flexible[20]. For instance, to increase and sustain the use of eHealth, care providers can apply for a grant from the eHealth at home scheme. Another example is the grant that is available for healthcare institutions to train digicoaches, to help patients increase their eHealth literacy[21]. As is demonstrated in this thesis, eHealth literacy is important for adherence and patient satisfaction, and therefore has a significant effect on the feasibility of implementing an e/mHealth intervention.

Importantly, when looking at feasibility, care providers have to notice that eHealth is not the solution to all clinical (outpatient) issues. The risks of eHealth are underexposed in literature as well as hospital-wide and nation-wide decision-making. The Dutch National Institute for Public Health observed a lack of academic interest for risk assessment in eHealth, which has been reported to be a matter of concern[22]. At present, risks often only emerge as secondary findings in the minority of eHealth studies. Therefore, when developing an mHealth care-track, clinicians and researchers should not only look at potential benefits but also at risk factors and pitfalls such as patient safety, data safety and economic costs.

FUTURE RESEARCH

Electronic and mobile health are healthcare areas that have been increasingly researched over the last decade. Although eHealth and mHealth were once part of a hype cycle, and the definition of eHealth still is not clear, eHealth and mHealth are being implemented worldwide and patients, care providers and governments are positive towards the potential mHealth holds. However, researchers and clinicians are advised not to implement mHealth as an interesting new feature for patients to try, but as a solution for a clinical problem that cannot be solved in an easier way.

As to the future research of devices that can detect AF, it is important to understand that many solutions have been marketed over the last 5-10 years. Plenty of research has been done in the direction of the effect of mHealth on the detection of AF in the home-setting, which was mainly done with single-lead ECG devices. Lately, studies that used photophletysmography have been published as well, showing a comparable effect on AF detection. Both solutions are primarily used for AF detection, but could also be used for the detection of other atrial rhythm disturbances, and perhaps also for ventricular arrhythmias. Importantly, with the development of mHealth devices such as the Cardiosecur, it may be possible to pinpoint the origin of premature ventricular complexes or ventricular tachycardias, enabling electrophysiologists with ambulatory ventricular mapping. This potential needs to be addressed in future research.

Moreover, as AF can now be more easily detected with the use of mHealth, these solutions can be hypothesized to reduce the risk of stroke. As AF is known to cause ischemic stroke, early treatment with anticoagulant medication is important. However, future research will have to address if the use of mHealth after cardiac surgery can indeed reduce the 5 or 10 year risk of stroke. This was not the scope of the current thesis, as larger patient groups are needed and a longer duration of follow-up is required. As The Box has now been incorporated as a standard follow-up method of the cardiology department of the LUMC, however, this topic can be addressed in the (near) future.

Finally, it is not yet known why exactly mHealth participants become so engaged and empowered that they reach their targets as to cardiovascular risk factors in such a short time after the start of their mHealth follow-up. **Chapter VI** as well as the **General Discussion** discussed the hypothesis of gamification to play a role, as several studies have shown a potential benefit on patient behaviour in cardiovascular risk management. Gamification is, however, not yet part of The Box.

Moreover, it is not yet known which personality types respond well to mHealth, and which do not. These patient characteristics are very important for the future development of

The Box, and will have to be addressed before a bespoke mHealth track can be made for each individual patient. This is hypothesized to increase adherence and satisfaction even further, potentially influencing other outcomes as an effect.

In conclusion, the future of eHealth and mHealth seems to be bright. It has become a standard follow-up method of several patient groups of the LUMC, and is used increasingly often worldwide. Mobile health has been demonstrated to be feasible for AF detection as well as cardiovascular risk management. Future researchers are advised to focus on patient and care provider factors to further improve eHealth and mHealth interventions.

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