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## **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 VI

## Mobile Health for Cardiovascular Risk Management After Cardiac Surgery: Results of a Sub-analysis of The Box 2.0 Study

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# ABSTRACT

## Introduction

Patients after Coronary Artery Bypass Grafting (CABG) are at high risk to develop adverse events. Lowering low density lipoprotein (LDL-C) and blood pressure (BP) levels to guideline recommended values reduces the risk of major adverse cardiac events in this patient population. The aim of this study is to evaluate the effects of mHealth on BP and cholesterol levels in patients after standalone CABG, in order to improve cardiovascular risk management.

## Methods

We performed an observational cohort study among 228 adult patients who underwent standalone CABG surgery at a tertiary care hospital in The Netherlands. In a consecutive rather than randomized version, 117 patients received standard care (two in office outpatient clinic visits), and 111 patients underwent an mHealth intervention. This consisted of frequent BP and weight monitoring with regimen adjustment in case of high blood pressure. One outpatient clinic visit was replaced by an electronic visit. Primary outcome was difference in systolic BP and LDL-C between baseline and value after three months of follow-up.

## Results

Mean age in the intervention group was 62.7 years, 98 (88.3%) patients were male. A total of 26,449 mHealth measurements were recorded. At three months, systolic BP decreased by 7.0 mmHg (SD: 15.1) in the intervention group versus -0.3 (SD: 17.6;  $P < 0.00001$ ) in controls, and body weight decreased by 1.76 kg (SD: 3.23) in the intervention group versus -0.31 (SD: 2.55;  $P = 0.002$ ) in controls. Serum LDL-C levels were significantly lower in the intervention group versus controls (median: 1.8 versus 2.0;  $P = 0.0002$ ).

## Conclusions

This study showed an association between daily home monitoring after CABG and a reduction in systolic BP, body weight and serum LDL-C. The causality of the association between the observed weight loss and decreased LDL-C in intervention group patients remains to be investigated. Furthermore, as this study had three months of follow-up, long-term effects of mHealth on lifestyle and cardiovascular risk management need to be addressed in further research.



## ABBREVIATIONS

AF	Atrial Fibrillation
BP	Blood Pressure
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
ECG	Electrocardiogram
eHealth	Electronic Health
EMR	Electronic Medical Record
eVisit	Electronic Visit
mHealth	Mobile Health
NP	Nurse Practitioner
LDL-C	Low Density Lipoprotein C
LUMC	Leiden University Medical Center
RCT	Randomized Controlled Trial

## INTRODUCTION

After coronary artery bypass grafting (CABG), patients remain at high risk of adverse events due to coronary artery disease (CAD). All-cause mortality is 6.2% within the first year after isolated CABG, and 30.7% within 10 years[1,2]. Of these deaths, 65% have a cardiac cause, with non ST-elevation myocardial infarction to be the leading cause of death, followed by heart failure[3,4]. Clinical trials have shown that a 5 mmHg reduction of systolic blood pressure reduces the risk of major cardiovascular events by about 10%[5]. Adequate regulation of serum LDL-C levels is also of importance. In a meta-analysis of 49 clinical trials with 312,175 participants, each 1-mmol/L (38.7 mg/dL) reduction in LDL-C was associated with a relative risk (RR) of major vascular events of 0.77[6]. Therefore, current European guidelines on cardiovascular disease prevention stress the importance of reducing LDL-C and BP levels in patients who underwent CABG[7]. However, a study in 16,646 patients in 24 European countries found that only a minority of patients achieved adequate control of these risk factors 6 months after CABG or percutaneous coronary intervention (PCI): 48.6% continued smoking, 42.7% had a BP  $\geq$ 140/90 mmHg, and 80.5% had an LDL-C of  $\geq$ 1.8[8]. Moreover, only one-third of all patients with CAD attended cardiac rehabilitation after undergoing CABG or PCI[8,9].

Interactive mobile health (mHealth) has been shown to be an effective intervention on lifestyle through health education[10-12]. Mobile health is defined as the use of mobile phone and wireless technologies to support the achievement of health objectives[13]. The eHealth working group of the European Society of Cardiology (ESC) now recommends the use of mHealth to support remote clinical care and improve psychosocial health, diet and smoking cessation, in the primary, secondary and tertiary prevention of CAD[7,14,15]. However, positive effects of mHealth on cardiovascular risk management has not yet been definitively demonstrated: several randomized controlled trials (RCTs) suggested a beneficial effect of mHealth interventions on patient self-management[16-21], although other studies found no statistically significant improvement[22-26]. Moreover, no published results are available on the use of mHealth in patients after CABG.

The use of mHealth devices, such as a BP monitor and weight scale, may be beneficial in the outpatient follow-up of patients with a high (residual) CAD risk. In order to improve cardiovascular risk management, the aim of the present study – The Box 2.0 – is to evaluate the effects of mHealth on BP, body weight and cholesterol levels in patients after standalone CABG surgery.

## METHODS

### Study design, recruitment and population

As previously described, The Box 2.0 was a non-randomized observational cohort study with a prospective intervention group and a historical control group for comparison[27]. This study was conducted at the department of cardiothoracic surgery of the Leiden University Medical Center (LUMC), a tertiary care hospital in The Netherlands, and registered under NCT03690492 (ClinicalTrials.gov) and NL65959.058.18 (ToetsingOnline.nl). The study complied with the Declaration of Helsinki, and was approved by the ethics committee.

As lack of attainment of lipid target levels following CABG is associated with long-term mortality[28], frequent lipid level measurements are performed in patients after CABG. However, not all cardiac surgery patients need this form of cardiovascular risk management. In order to improve comparability, solely patients who underwent CABG were selected for the present sub-study to ensure comparability regarding BP and lipid level outcomes. As a wide variety of concomitant surgical procedures could be performed, affecting outcomes, patients undergoing concomitant procedures were excluded, as well as those with incomplete BP data at the end of follow-up. We deemed BP data to be complete if there was an available BP measurement at the last outpatient clinic visit. The aim of introducing these selection criteria was to optimize comparability between both study groups. Other exclusion criteria were: pregnancy, incapacitation or mechanical support at the moment of inclusion, ventricular septal rupture, implantation of a ventricular assist device, and emergency cardiac surgery defined as a score 1 or 2 at the Interagency Registry for Mechanically Assisted Circulatory Support scale.

Between December 2017 and September 2018, 365 adult patients who underwent cardiac surgery via sternotomy were consecutively screened and included in the control group, 117 of whom underwent standalone CABG surgery. From September 2018 until November 2020, another 365 patients were consecutively screened and included in the intervention group, 111 of whom underwent standalone CABG surgery. Study results of all 730 patients are described separately[29]. Eligible patients were recruited at the outpatient clinic before surgery, 4 to 6 weeks before surgery, or on the ward during admission, 1 to 5 days before surgery or between 3 days after surgery and 1 day before discharge. Eligible patients were given oral and written study information, and were given at least 24 hours to consider participation. All patients were recruited by a nurse practitioner (NP) and signed the informed consent form before discharge. To ensure all eligible patients were approached with study information and informed consent forms, the study team reviewed the weekly surgery schedule of the thoracic surgery department, and a weekly meeting with this department was held. Discharge from the department of cardiothoracic surgery marked the start of follow-up. The total duration of follow-up was 92 days.

## Control group

Control group patients underwent standardized follow-up, defined as two physical outpatient clinic visits; one visit 2 weeks after initial discharge and one visit 3 months after discharge. The 2-week visit consisted of an examination of the sternal wound and, if applicable, the vein harvesting wound, and a 12-lead 10 second electrocardiogram (ECG) was made. At 3 months, another ECG was made, the BP and a laboratory test for cholesterol levels were taken, and a transthoracic echocardiogram was performed. No mHealth was used in these patients.

## Intervention group

Intervention group patients received mHealth intervention The Box, consisting of an activity tracker, BP monitor, thermometer, and a weight scale (all from Withings, Issy les Moulineaux, France). These devices are shown in Figure 1. During the first two weeks of follow-up, patients were requested to take daily measurements with the Withings devices. For the remainder of the 3-month follow-up, measurements were taken 3 times a week.



Figure 1: the Box and its contents.

Furthermore, the standard first outpatient clinic visit, 2 weeks after discharge, was replaced by an electronic visit (eVisit). This eVisit consisted of an identical patient interview compared to the standard outpatient clinic follow-up and was performed by the same NP, who also checked the sternum wound and, if applicable, also the vein harvesting wound via the webcam. During follow-up, the therapeutic regimen could be revised based on the results of mHealth measurements such as BP as well as on symptoms. The outpatient clinic visit, 3 months after discharge, was identical to the outpatient clinic visit of control group patients, and marked the end of follow-up.

The NP checked all sent-in data 3 times per week. An automated alarm was triggered in case of a data irregularity, which made these irregularities stand out from other measurements. In case of an irregularity, the NP contacted the patient within 48 hours after the data were received. An overview of data irregularities has been published previously[29]. Based on these irregularities, the NP could amend the medication regime if necessary. Importantly, patients were instructed to contact emergency services if needed, as The Box served to support their convalescence.

## Medication

Patients were discharged with either metoprolol or sotalol, unless they were on bisoprolol or other beta-blockers before surgery. As internal cardiothoracic guidelines changed in 2019, we expected significantly more intervention group patients to be discharged with sotalol instead of metoprolol. BP medication was based on daily BP readings during the admission period, and updated until the day of discharge. As the NP could act on data irregularities, BP medication could be amended accordingly during follow-up. This was done in case patients registered three consecutive measurements above either 140 mmHg (systolic BP) or 90 mmHg (diastolic BP), unless a reading was deemed to be incorrect. The NP always discussed medication changes with one supervising cardiologist, who was dedicated to this project.

Cholesterol levels were checked before surgery and medication was either started or amended based on these results. As cholesterol levels were only measured before surgery and after follow-up, not during follow-up, cholesterol medication was only changed in case of potential side-effects.

## Connectibility and technical assistance

The Box 2.0 was handed out before discharge from the LUMC; required mobile applications were installed by eHealth-technicians if necessary. A helpdesk was available throughout the duration of each patients' participation in the study, to assist with technical issues. Patients who did not own a smartphone, were equipped with a loan device free of charge. To warrant the privacy of all study patients, patients were provided with an @hlc.nl email address based on a randomly generated code as the individual's login name, combined with a randomly generated password. The @hlc.nl domain is owned and maintained by the LUMC, its data are stored on LUMC servers. Online data from the mHealth devices were accessed via the Application Programming Interface (API; Withings). The Withings API allowed all device data to be automatically imported in the electronic medical records of the LUMC, via a protected authentication protocol (OAuth2). Patients were phoned by eHealth-technicians after two weeks of not receiving any mHealth measurement, reminding them of the importance of these measurements.

## Study endpoints

The primary endpoints of this study were the systolic and diastolic BP, as well as body weight and serum LDL-C levels at the end of follow-up. Secondary endpoints were total cholesterol, HDL, LDL-C/cholesterol ratio and triglycerides at the end of follow-up, as well as BP control and the percentage of patients with an adequate LDL-C at the end of follow-up. These parameters were all measured at the end of follow-up. BP control was defined as a BP below the threshold of hypertension - <140/<90 mmHg - as it was defined by the European Society of Cardiology (ESC) guidelines[30], measured with a manual sphygmomanometer (Welch Allyn 707) at the outpatient clinic. ESC guidelines were also used to define LDL-C adequacy: in patients with a very high cardiovascular risk, the treatment target for LDL-C is <1.8 mmol/L or a reduction of at least 50% from baseline LDL-C[31].

## Statistical analysis

Demographic and baseline characteristics are summarized for all subjects as mean  $\pm$  standard deviation (SD), median and interquartile range (IQR), or frequencies for continuous and categorical variables, respectively. Variables with a skewed distribution were compared using a Mann-Whitney U test. Categorical variables were compared with Fisher exact tests. Multivariable logistic regression was used to assess binary endpoints, multivariable linear regression was used to assess continuous endpoints. We adjusted for age, gender, BMI, hypertension at baseline, and antihypertensive treatment at baseline, as these were confounding variables, as well as for baseline differences: length of hospital stay, and either systolic BP at baseline for the analyses of systolic BP endpoints, or diastolic BP at baseline for the analyses of diastolic BP endpoints. All analyses were performed with SPSS version 25.0 (released 2017, IBM SPSS Statistics for Windows, IBM Corp, Armonk, NY, USA).

# RESULTS

## Patient characteristics

A total of 228 patients were enrolled in this sub study; 117 controls and 111 intervention group patients. All baseline characteristics are presented in Table 1. In both groups, 98 patients were male (84% of controls and 88% of intervention group patients, respectively;  $p=0.35$ ). Mean age in the intervention group was 62.7 years versus 65.3 years for controls ( $p=0.05$ ) and significantly more controls had a history of hypertension ( $n=74/117$ , 63% versus  $n=51/111$ , 46%;  $p=0.01$ ). Diastolic BP at discharge was higher in intervention patients than in controls (81.2 mmHg versus 75.6 mmHg;  $p=0.0005$ ). As expected, significantly more intervention group patients were discharged with sotalol compared to controls ( $n=80/117$ , 68% versus  $n=96/111$ , 87%;  $p=0.002$ ), and as a result less metoprolol was used ( $n=31/117$ , 27% versus  $n=11/111$ , 10%;  $p=0.002$ ). At baseline, serum cholesterol levels did not differ significantly between both groups, nor did the percentage of patients treated with cholesterol lowering medication. Importantly, there were no cases of familial hypercholesterolemia in the study population. None of the patients had a contra-indication for the use of statins.

## Protocol adherence

A total of 26,449 mHealth measurements have been recorded by all intervention group patients, on 6,295 unique measurement days. Patients registered a median of 222 measurements (IQR: 164-304) on a median of 52 of out 92 days (IQR: 37-84). A summary of all measurement totals is provided in the Appendix. Figure 2 presents the protocol adherence for all intervention group patients. A total of 16 (14.4%) Box patients registered no measurements for  $\geq 21$  consecutive days and were considered non-adherent. Data of all non-adherent patients was used for the analyses; no patients dropped out of the study.

Table 1: baseline characteristics.

	Control (n=117)	Intervention (n=111)	P value
Gender, male (%)	98 (83.8%)	98 (88.3%)	0.347
Age, years (SD)	65.3 (9.9)	62.7 (9.3)	<b>0.046</b>
BMI, kg/m <sup>2</sup> (SD)	27.8 (4.1)	26.8 (3.9)	<b>0.043</b>
History of smoking (%)	67 (57.3%)	65 (58.6%)	0.894
Hypertension (%)	74 (63.2%)	51 (45.9%)	<b>0.011</b>
Hypercholesterolemia (%)	50 (42.7%)	51 (45.9%)	0.690
Diabetes Mellitus (%)	40 (34.2%)	28 (25.2%)	0.150
History of myocardial infarction (%)	46 (39.3%)	57 (51.4%)	0.084

**Table 1: baseline characteristics. (continued)**

	Control (n=117)	Intervention (n=111)	P value
History of PCI (%)	37 (31.6%)	37 (33.3%)	0.888
History of CABG (%)	3 (2.6%)	0 (0.0%)	0.247
History of CVA/TIA (%)	9 (7.7%)	10 (9.0%)	0.812
Peripheral arterial disease (%)	6 (5.1%)	9 (8.1%)	0.430
Urgent operation (%)	49 (41.9%)	43 (38.7%)	0.686
Resternotomy (%)	9 (7.7%)	6 (5.4%)	0.597
Length of hospital stay, days (IQR) [Range]	6 (4-7) [2-24]	6 (6-7.5) [5-16]	<b>&lt;0.0001</b>
Readmission (%)	8 (6.8%)	2 (1.8%)	0.103
MACE before initial discharge (%)	5 (4.3%)	4 (3.6%)	1.000
LVEF, % (SD) (wel of niet?)	54.4 (8.8)	54.9 (8.3)	0.640
Systolic BP, mmHg (SD)	139.2 (20.6)	141.0 (18.3)	0.478
Diastolic BP, mmHg (SD)	75.6 (11.3)	81.2 (12.5)	<b>0.0005</b>
Use of ≥1 antihypertensive drug (%)	99 (84.6%)	86 (77.5%)	0.168
<i>ACE inhibitor</i>	64 (54.7%)	62 (55.9%)	
<i>Angiotensin receptor blocker</i>	27 (23.1%)	16 (14.4%)	
<i>Calcium antagonist</i>	37 (31.6%)	14 (12.6%)	
<i>Diuretic</i>	27 (23.1%)	12 (10.8%)	
Antiarrhythmics / betablockers			
<i>Amiodarone (%)</i>	2 (1.7%)	3 (2.7%)	0.273
<i>Sotalol (%)</i>	80 (68.4%)	96 (86.5%)	<b>0.002</b>
<i>Metoprolol (%)</i>	31 (26.5%)	11 (9.9%)	<b>0.002</b>
<i>Bisoprolol (%)</i>	3 (2.6%)	1 (1.0%)	0.340
Total cholesterol, mmol/L (IQR) [Range]	4.6 (3.7-5.5) [2.0-7.5]	4.4 (3.8-5.4) [2.4-8.6]	0.867
LDL, mmol/L (IQR) [Range]	2.9 (2.0-3.6) [1.0-5.6]	2.4 (2.0-3.4) [0.9-6.1]	0.297
HDL, mmol/L (IQR) [Range]	1.1 (0.9-1.3) [0.5-2.4]	1.1 (1.0-1.3) [0.7-2.7]	0.307
Cholesterol ratio (IQR) [Range]	4.2 (3.2-5.2) [1.8-9.0]	3.8 (3.2-4.8) [2.0-9.5]	0.288
Triglycerides, mmol/L (IQR) [Range]	1.5 (1.0-2.2) [0.5-5.6]	1.5 (1.0-2.0) [0.4-5.5]	0.521
Use of cholesterol lowering drug(s) (%)	114 (97.4%)	109 (98.2%)	0.694
<i>Statin</i>	97 (82.9%)	96 (86.5%)	
<i>Ezetimibe</i>	6 (5.1%)	4 (3.6%)	
<i>Statin + ezetimibe</i>	8 (6.8%)	8 (7.2%)	
<i>PCSK9 inhibitor + ezetimibe</i>	3 (2.6%)	1 (1.0%)	

\*No other antiarrhythmics or betablockers were used in the study population.



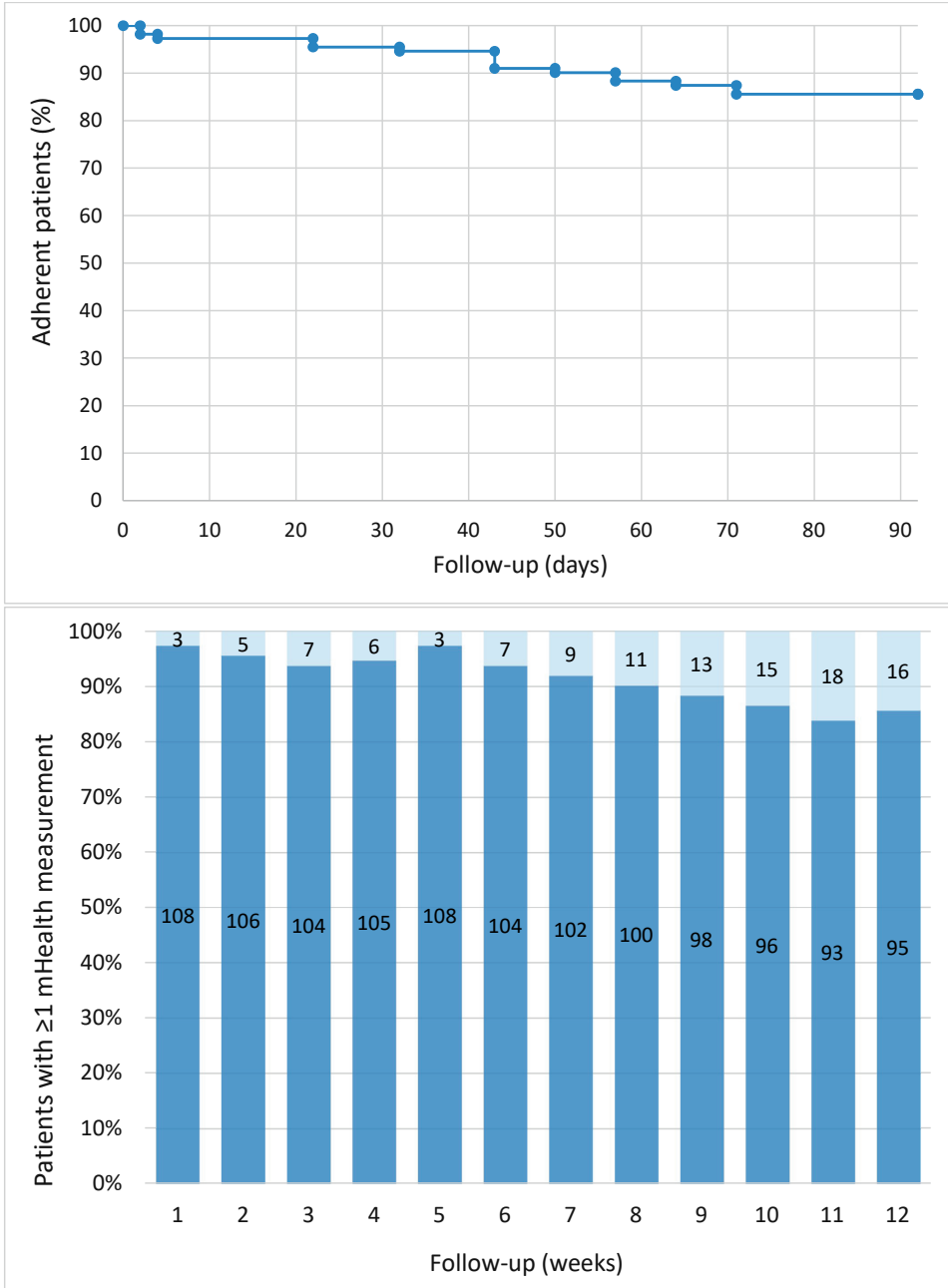


Figure 2: mHealth device use and Kaplan-Meier estimates of non-adherence, defined as ≥21 consecutive days without at least one registered mHealth measurement regarding BP, weight, temperature or ECG. Step count measurements were not included in this analysis.

## Medication

During follow-up, BP medication was unchanged in 105 (89.7%) control group patients versus 72 (34.9%) intervention group patients ( $P<0.00001$ ). This is presented in Table 2. In significantly more intervention group patients (26; 23.4%) versus controls (4; 3.5%;  $P<0.00001$ ), BP medication was added or the dose was increased. On the other hand, BP medication was removed or the dose was reduced in 11 (10.0%) of all intervention group patients versus 6 (5.1%) controls ( $P=0.21$ ).

**Table 2: blood pressure medication regime during follow-up.**

BP medication <b>added</b>	3 (2.6%)	15 (13.5%)	<b>&lt;0.00001</b>
Dose increased	1 (0.9%)	11 (9.9%)	
BP medication <b>removed</b>	6 (5.1%)	10 (9.0%)	0.21
Dose reduced	0 (0.0%)	1 (1.0%)	
BP medication <b>unchanged</b>	105 (89.7%)	72 (64.9%)	<b>&lt;0.00001</b>
Medication <b>switch</b> , comparable dose	2 (1.7%)	2 (1.8%)	1

Cholesterol medication was amended in 4 (3.6%) intervention group patients and 4 (3.4%) controls ( $P=0.96$ ). Reasons were myalgia ( $n=3$ ), inadequate initial treatment ( $n=3$ ), drug interactions ( $n=1$ ) and dizziness on atorvastatin ( $n=1$ ). All medication changes are presented in the Appendix.

## Endpoint: blood pressure

Results of the BP endpoints are presented in Table 3. The primary endpoints, being systolic and diastolic BP at the end of follow-up, were both lower in the intervention group. The systolic BP was significantly lower in intervention patients than in controls (mean: 129.5 mmHg versus 137.4 mmHg, respectively;  $P=0.02$ ). The diastolic BP showed no significant difference, although it was lower in intervention patients than in controls (mean: 76.8 mmHg vs 77.9 mmHg, respectively;  $P=0.17$ ). Notably, in the intervention group, both systolic and diastolic BP were significantly lower at the end of follow-up than at baseline: -7.0 (SD: 15.1) and -3.5 (SD: 16.8), respectively. In the control group, systolic and diastolic BP were slightly higher at the end of follow-up than at baseline: 0.3 (SD: 17.6) and 4.7 (SD: 17.3), respectively. When comparing both study groups, the systolic BP difference was significant ( $P=0.016$ ) while the diastolic BP difference was not ( $P=0.30$ ).

**Table 3: blood pressure outcomes.**

	Controls (n=117)	Intervention (n=111)	P Value
Systolic BP, mmHg (SD)	137.4 (19.1)	129.5 (17.2)	<b>P=0.02</b>
Diastolic BP, mmHg (SD)	77.9 (10.5)	76.8 (9.6)	P=0.17
Adequate BP (%)*	67 (57.3%)	91 (82.0%)	<b>P=0.0004</b>
Systolic BP difference from baseline, mmHg (SD)	0.3 (17.6)	-7.0 (15.1)	<b>P=0.02</b>
Diastolic BP difference from baseline, mmHg (SD)	4.7 (17.3)	-3.5 (16.8)	P=0.30

\*Adequate BP is defined as a systolic BP <141 and a diastolic BP <91.

For the secondary endpoints, 82% of intervention patients had an adequate BP (n=91/111) versus 57% of the control group (n=67/117; p=0.0004). Antihypertensive treatment was amended in 39 intervention group patients (35%) versus 11 controls (9%; P<0.0001). No correlation was found between adherence (measurement days) and systolic or diastolic BP at the end of follow-up (p=0.24).

### Endpoint: body weight and cholesterol levels

Results of the body weight and cholesterol endpoints are presented in Table 4. 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). Serum LDL-C levels at the end of follow-up were significantly lower in the intervention group versus controls (median: 1.8 versus 2.0, respectively; P=0.0002).

**Table 4: weight and cholesterol outcomes.**

	Controls (n=117)	Intervention (n=111)	P value
Weight loss during follow-up, kg (SD)	-0.31 (2.55)	1.76 (3.23)	<b>0.002</b>
Total cholesterol, mmol/L (IQR) [Range]	3.7 (3.3-4.4) [2.0-8.1]	3.6 (3.3-4.2) [2.3-6.6]	0.15
LDL, mmol/L (IQR) [Range]	2.0 (1.7-2.7) [1.0-6.0]	1.8 (1.4-2.2) [0.3-4.7]	<b>0.0002</b>
HDL, mmol/L (IQR) [Range]	1.1 (0.9-1.3) [0.5-3.7]	1.1 (0.9-1.3) [0.4-2.1]	0.47
Cholesterol ratio (IQR) [Range]	3.4 (2.8-4.1) [0.9-7.8]	3.4 (2.7-4.0) [1.9-7.2]	0.27
Triglycerides, mmol/L (IQR) [Range]	1.4 (1.0-1.9) [0.5-4.7]	1.4 (1.1-2.4) [0.5-5.6]	0.12
Adequate LDL (%)*	44 (37.6%)	65 (58.6%)	<b>0.002</b>
LDL <1.8 mmol/L (%)	37 (31.6%)	61 (55.0%)	<b>0.0003</b>
LDL decreased by >50% (%)	20 (17.1%)	24 (21.6%)	0.41
LDL difference from baseline, % (IQR) [Range]	-16,7 (46.2 - 6.3) [-67.3-181.8]	-28.0 (-49.6 - -4.2) [-90.7-43.3]	<b>0.04</b>
Cholesterol medication amended (%)	4 (3.4%)	4 (3.6%)	0.96

\*Adequate LDL is defined as an LDL <1.8 mmol/L or a >50% reduction compared with the previous measurement.

For the secondary endpoints, 59% of intervention patients had an adequate LDL-C (n=65/111) versus 38% (n=44/117; p=0.002) of all controls. Both groups saw a decrease in serum LDL-C levels compared to baseline, with a 28.0% reduction (IQR: 4.2% – 49.6%) in the intervention group versus a 16.7% reduction (IQR: -6.3% – 46.2%) in controls. This was a significantly greater decrease in the intervention group compared to controls (P=0.04). No correlation was found between adherence (measurement days) and LDL-C at the end of follow-up (P=0.57).

## DISCUSSION

### Main findings

This study reports the effects of an mHealth intervention on cardiovascular risk factors, in which patients made 26,449 measurements over the course of 6,295 unique measurement days. A significant decrease of systolic and diastolic BP as well as serum LDL-C was observed in the intervention group. As the mHealth intervention caused BP levels to be available throughout the follow-up period, BP medication could be amended whenever needed. As expected, this was done in significantly more intervention group patients as compared to controls. This is the main explanation for the significant decrease in systolic and diastolic BPs at the end of follow-up. The same cannot be said of the significant decrease in serum cholesterol levels, as these levels were only assessed before and after follow-up. The observed decrease in serum LDL-C levels is, however, hypothesized to be partly related to an educational consequence of the intervention, such as increased patient engagement and empowerment, and partly to the weight loss at the end of follow-up that has been observed in intervention group patients but not in controls. The reason for this significant difference between intervention and control group patients may be related to the frequent confrontation to the intervention group patients' body weight, as they were requested to weigh themselves multiple times per week.

### Protocol adherence

Patients were instructed to take mHealth measurements every day for the first 2 weeks after discharge, followed by 3 times a week after these initial 2 weeks. This should lead to 47 unique measurement days and 235 total measurements. Our intervention group patients measured a median of 222 total measurements (IQR: 164-304) during a median of 52 unique days (IQR: 37-84); 95 (85.6%) intervention group patients remained adherent over the course of 3 months. As is shown in Figure 2, however, protocol adherence decreased over time as did the number of patients who logged at least one mHealth measurement per week. Disengagement is a known factor in mHealth[32], and has been reported before[33]. Consistent feedback may positively impact the patient's engagement. As the LUMC recently developed its own app for Box patients to use, further increasing the engagement is currently being studied.

### Comparison with literature

To our best knowledge, no results of other studies have been published regarding the effect of mHealth on BP, body weight or cholesterol levels in post-cardiac surgery patients. In other populations with an increased cardiovascular risk, mHealth interventions have been found to significantly decrease both systolic and diastolic BPs[34-36]. The differences in systolic BP after an mHealth intervention were found to be -3.9 to -7.5 mmHg, which is

in line with the 7.0 mmHg systolic BP reduction of the current study. Importantly, studies have shown that a 3 mmHg reduction in systolic BP can reduce stroke mortality by 8%[37].

Although we found a significant impact of The Box on BP outcomes, an earlier RCT that evaluated The Box in myocardial infarction patients found no significant difference in these outcomes between Box users and controls[38]. However, The Box became a standard of care in the management of various outpatient groups of the cardiology department of the LUMC due to the appreciation by both patients and care providers[39]. Over these years, The Box has been continuously improved on the patients' side as well as for staff members. 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 BP treatment during follow-up.

While numerous studies have evaluated mHealth interventions for BP management, very few studies have evaluated mHealth for the management of weight or hyperlipidemia. Studies that have been conducted, often used SMS or phone calls as an intervention and have been mostly unable to show significant benefit. More recent studies have shown the effect of gamification on cardiovascular health outcomes: in 2021, two RCTs were published that demonstrated significant effects on medication adherence[40], as well as increased physical activity and reduced HbA1c levels[33]. The latter RCT provided patients with a Withings activity tracker and weight scale for the duration of one year, and an app that provided them with points and levels based on patients meeting their weekly goals and measurement frequencies. As is also seen in the current study, adherence was very high at the start of the intervention and then slowly declined. However, the RCT as well as the current study show an indirect educational effect of the mHealth intervention; the selected outcome measures were not influenced by medication changes that could have directly impacted these outcomes. This indirect educational effect is hypothesized to be caused by an increased patient engagement and empowerment; due to taking daily measurements, patients are confronted with their lifestyle and (the management of) their illness on a daily basis. However, modifying cardiovascular risk factors with the use of gamification is a new area and more research is needed to determine the scale of this effect and the psychology behind it.

## **Strengths and limitations**

The main strength of this study is the protocol adherence of the intervention group, with a high mHealth measurement count and a high number of unique measurement days. Although patients were consecutively included and the exclusion criteria were the same for both the intervention and control group, selection bias may have occurred due to the impact of COVID-19 after March 2020. This is the main reason for some differences at

baseline, such as age, history of hypertension and length of stay. We corrected for these parameters in the statistical analyses.

Another factor to take into consideration is the cost of The Box, which is around €350 (\$350) and currently not refunded by the Dutch healthcare system as well as most healthcare systems around the world, making this intervention less accessible to patients. If cardiovascular risk management is the only requirement, these costs can be reduced as in this case, only a BP monitor, activity tracker and potentially a weight scale would have to be handed out.

## **CONCLUSIONS**

This study demonstrated mHealth to be a potentially useful intervention strategy for BP, weight and cholesterol management. However, long-term effects of mHealth on lifestyle and cardiovascular risk management could not yet be assessed and need to be addressed in further research.



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## APPENDIX

**Table: measurement totals.**

	<b>Total</b>	<b>Median</b>	<b>IQR</b>	<b>Range</b>
Blood pressure	6767	45	29 - 87	1 - 307
Weight	5939	47	28 - 84	0 - 172
Temperature	4482	32	9 - 76	0 - 116
Step count days	7975	90	64 - 92	0 - 92
ECG's	1289	11	5 - 14	0 - 102
Measurement total	26449	222	164 - 304	1 - 561
Unique measurement days	6295	52	37 - 84	0 - 92

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**Table: blood pressure medication at baseline and at the end of follow-up.**

	<b>Control (n=117)</b>	<b>Intervention (n=111)</b>	<b>P value</b>
<u>Baseline</u>			
No BP medication	18 (15.4%)	25 (22.5%)	0.17
1 BP medicine	53 (45.3%)	68 (61.3%)	
2 BP medicines	36 (30.8%)	18 (16.2%)	
3 BP medicines	10 (8.5%)	0 (0.0%)	
ACE inhibitor	64 (54.7%)	62 (55.9%)	
Angiotensin receptor blocker	27 (23.1%)	16 (14.4%)	
Calcium antagonist	37 (31.6%)	14 (12.6%)	
Diuretic	27 (23.1%)	12 (10.8%)	
<u>End of follow-up</u>			
No BP medication	19 (16.2%)	26 (23.4%)	0.19
1 BP medicine	55 (47.0%)	64 (57.7%)	
2 BP medicines	33 (28.2%)	21 (18.9%)	
3 BP medicines	10 (8.5%)	0 (0.0%)	
ACE inhibitor	56 (47.9%)	67 (60.4%)	
Angiotensin receptor blocker	30 (25.6%)	17 (15.3%)	
Calcium antagonist	35 (29.9%)	15 (13.5%)	
Diuretic	27 (23.1%)	10 (9.0%)	

## Medication changes

Effect	Study arm	Treatment at discharge	Treatment end of follow-up	Reason for change
Medication switch	Control 1	Atorvastatin 40mg once daily	Ezetimib 10mg once daily	Persistent costo-myalogenous pain during follow-up
Medication switch	Control 2	Atorvastatin 40mg once daily	Atorvastatin 40mg + ezetimib 10mg once daily	During follow-up, a high LDL (4.6 mmol/L) at discharge was noticed
Medication switch	Control 3	Atorvastatin 40mg once daily	Rosuvastatin 10mg once daily	Generalized myalgia
Medication switch	Control 4	Simvastatin 40mg once daily	Atorvastatin 40mg once daily	Inadequate treatment according to ESC guidelines
Medication switch	Intervention 1	Pravastatin 40mg once daily	Rosuvastatin 10mg once daily	Inadequate treatment according to ESC guidelines
Medication switch	Intervention 2	Atorvastatin 40mg once daily	Rosuvastatin 20mg once daily	After consultation of a otorhinolaryngologist for dizziness, it was advised to switch from atorvastatin to a different statin
Medication switch	Intervention 3	Atorvastatin 40mg once daily	Rosuvastatin 20mg once daily	Generalized myalgia
Medication switch	Intervention 4	Atorvastatin 40mg once daily	Rosuvastatin 20mg once daily	Amiodarone was started during follow-up. As a result, atorvastatin was switched as it is known to interact with amiodarone.

<b>Effect</b>	<b>Study arm</b>	<b>Treatment at discharge</b>	<b>Treatment end of follow-up</b>	<b>Reason for change</b>
<b>Effect</b>	<b>Study arm</b>	<b>BP treatment at discharge</b>	<b>Treatment end of follow-up</b>	<b>Reason for treatment change</b>
Medication switch, comparable dose	Control 1	Sotalol 3x40mg + perindopril 2mg	Metoprolol 50mg + valsartan 2x40mg	A bothersome cough during follow-up
Medication switch, comparable dose	Control 2	Metoprolol 2x25mg + perindopril 2mg	Metoprolol 2x25mg + losartan 25mg	A bothersome cough during follow-up
Medication switch, comparable dose	Intervention 1	Sotalol 3x40mg + perindopril 2mg	Sotalol 3x40mg + losartan 50mg	A bothersome cough during follow-up
Medication switch, comparable dose	Intervention 2	Sotalol 2x80mg + perindopril 4mg	Sotalol 2x80mg + losartan 50mg	A bothersome cough during follow-up
BP medication added	Control 1	Sotalol 3x80mg + perindopril 4mg	Sotalol 3x80mg + perindopril 4mg + nifedipine 2x30mg	Persistent hypertension during follow-up
BP medication added	Control 2	Metoprolol 2x25mg + perindopril 2mg	Metoprolol 2x25mg + candesartan 8mg + hydrochlorothiazide 25mg	Persistent hypertension during follow-up
BP medication added	Control 3	Metoprolol 50mg	Metoprolol 25mg + perindopril 2mg	Persistent hypertension during follow-up
BP medication added	Intervention 1	Sotalol 2x80mg + perindopril 4mg	Sotalol 2x80mg + perindopril 4mg + amlodipine 5mg	Persistent hypertension during follow-up
BP medication added	Intervention 2	Sotalol 2x80mg + lisinopril 10mg	Sotalol 2x80mg + lisinopril 20mg + amlodipine 10mg	Persistent hypertension during follow-up
BP medication added	Intervention 3	Metoprolol 25mg	Metoprolol 25mg + perindopril 2mg	Persistent hypertension during follow-up
BP medication added	Intervention 4	Propranolol 2x10mg + hydrochlorothiazide 25mg	Propranolol 2x10mg + hydrochlorothiazide 25mg + perindopril 2mg	Persistent hypertension during follow-up

<b>Effect</b>	<b>Study arm</b>	<b>Treatment at discharge</b>	<b>Treatment end of follow-up</b>	<b>Reason for change</b>
BP medication added	Intervention 5	Sotalol 3x40mg	Sotalol 3x40mg + perindopril 2mg	Persistent hypertension during follow-up
BP medication added	Intervention 6	Sotalol 3x80mg + diltiazem 300mg	Sotalol 3x80mg + diltiazem 300mg + irbesartan 75mg	Persistent hypertension during follow-up
BP medication added	Intervention 7	Sotalol 2x80mg	Sotalol 2x80mg + amlodipine 10mg	Persistent hypertension during follow-up
BP medication added	Intervention 8	Sotalol 3x80mg + lisinopril 2.5mg	Sotalol 3x80mg + lisinopril 2x10mg + hydrochlorothiazide 12.5mg	Persistent hypertension during follow-up
BP medication added	Intervention 9	Sotalol 2x80mg	Sotalol 2x80mg + perindopril 2mg	Persistent hypertension during follow-up
BP medication added	Intervention 10	Sotalol 2x80mg + perindopril 2mg	Sotalol 2x80mg + amlodipine 5mg + valsartan 160mg	Persistent hypertension during follow-up
BP medication added	Intervention 11	Sotalol 2x80mg	Sotalol 2x80mg + perindopril 2mg	Persistent hypertension during follow-up
BP medication added	Intervention 12	Sotalol 3x80mg	Metoprolol 100mg + perindopril 4mg	Persistent hypertension during follow-up
BP medication added	Intervention 13	Sotalol 2x80mg	Sotalol 2x80mg + perindopril 2mg	Persistent hypertension during follow-up
BP medication added	Intervention 14	Metoprolol 75mg + hydrochlorothiazide 25mg	Metoprolol 75mg + hydrochlorothiazide 25mg + valsartan 80mg	Persistent hypertension during follow-up
BP medication added	Intervention 15	Sotalol 2x80mg + perindopril 4mg	Sotalol 2x80mg + perindopril 8mg + amlodipine 10mg	Persistent hypertension during follow-up
Dose increased	Control 1	Sotalol 3x40mg + losartan 25mg	Sotalol 3x40mg + losartan 50mg	Persistent hypertension during follow-up



<b>Effect</b>	<b>Study arm</b>	<b>Treatment at discharge</b>	<b>Treatment end of follow-up</b>	<b>Reason for change</b>
Dose increased	Intervention 1	Sotalol 3x80mg + perindopril 4mg	Bisoprolol 2.5mg + perindopril 8mg	Persistent hypertension during follow-up
Dose increased	Intervention 2	Sotalol 2x80mg + enalapril 10mg	Sotalol 2x80mg + enalapril 2x10mg	Persistent hypertension during follow-up
Dose increased	Intervention 3	Sotalol 2x80mg + perindopril 2mg	Sotalol 2x80mg + perindopril 4mg	Persistent hypertension during follow-up
Dose increased	Intervention 4	Sotalol 3x80mg + perindopril 1mg	Sotalol 3x80mg + perindopril 2mg	Persistent hypertension during follow-up
Dose increased	Intervention 5	Sotalol 2x80mg + enalapril 2.5mg	Sotalol 2x80mg + enalapril 20mg	Persistent hypertension during follow-up
Dose increased	Intervention 6	Sotalol 2x80mg + perindopril 2mg	Sotalol 2x80mg + perindopril 6mg	Persistent hypertension during follow-up
Dose increased	Intervention 7	Sotalol 2x40mg + perindopril 6mg	Metoprolol 12.5mg + perindopril 8mg	Persistent hypertension during follow-up
Dose increased	Intervention 8	Sotalol 2x80mg + candesartan 4mg	Sotalol 2x80mg + candesartan 2x4mg	Persistent hypertension during follow-up
Dose increased	Intervention 9	Sotalol 2x40mg + irbesartan 75mg	Sotalol 2x40mg + irbesartan 150mg	Persistent hypertension during follow-up
Dose increased	Intervention 10	Perindopril 4mg	Perindopril 6mg	Persistent hypertension during follow-up
Dose increased	Intervention 11	Sotalol 2x80mg + perindopril 2mg	Sotalol 2x80mg + perindopril 4mg	Persistent hypertension during follow-up
BP medication removed	Control 1	Sotalol 3x40mg + lisinopril 2x5mg + amlodipine 5mg	Sotalol 3x40mg + lisinopril 10mg	Hypotension during follow-up
BP medication removed	Control 2	Metoprolol 25mg + perindopril 2mg + diltiazem 200mg	Diltiazem 200mg	Hypotension during follow-up

<b>Effect</b>	<b>Study arm</b>	<b>Treatment at discharge</b>	<b>Treatment end of follow-up</b>	<b>Reason for change</b>
BP medication removed	Control 3	Metoprolol 50mg + lisinopril 5mg + nifedipine 30mg	Lisinopril 5mg	Hypotension during follow-up
BP medication removed	Control 4	Metoprolol 50mg + losartan 100mg + hydrochlorothiazide 25mg	Losartan 100mg	Hypotension during follow-up
BP medication removed	Control 5	Metoprolol 25mg + perindopril 2mg	None	Hypotension during follow-up
BP medication removed	Control 6	Metoprolol 2x25mg + lisinopril 5mg + amlodipine 5mg	None	Hypotension during follow-up
BP medication removed	Intervention 1	Metoprolol 75mg + losartan 50mg + hydrochlorothiazide 12.5mg	None	Hypotension during follow-up
BP medication removed	Intervention 2	Sotalol 2x80mg + perindopril 2mg	Sotalol 2x80mg	Hypotension during follow-up
BP medication removed	Intervention 3	Sotalol 3x80mg + perindopril 4mg	Sotalol 2x80mg	Hypotension during follow-up
BP medication removed	Intervention 4	Metoprolol 25mg + enalapril 2x20mg	None	Hypotension during follow-up
BP medication removed	Intervention 5	Sotalol 3x80mg + enalapril 10mg + amlodipine 5mg	Sotalol 3x80mg + enalapril 10mg	Hypotension during follow-up
BP medication removed	Intervention 6	Sotalol 2x80mg + losartan 50mg + diltiazem 300mg	Sotalol 2x80mg	Hypotension during follow-up
BP medication removed	Intervention 7	Sotalol 2x80mg + perindopril 2mg	Sotalol 2x80mg	Hypotension during follow-up
BP medication removed	Intervention 8	Sotalol 3x40mg + amlodipine 5mg Sotalol 2x80mg +	Sotalol 3x40mg	Hypotension during follow-up
BP medication removed	Intervention 9	hydrochlorothiazide 12.5mg	Sotalol 2x80mg	Hypotension during follow-up
BP medication removed	Intervention 10	Sotalol 3x40mg + losartan 50mg	Sotalol 3x40mg	Hypotension during follow-up
Dose decreased	Intervention 1	Metoprolol 150mg + olmesartan 20mg + amlodipine 15mg	Metoprolol 150mg + olmesartan 20mg + amlodipine 10mg	Hypotension during follow-up

