Using digital health technology to evaluate the impact of chocolate on blood pressure: Results from the COCOA-BP study

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BACKGROUND High blood pressure (BP) is a major risk factor for cardiovascular disease (CVD). Consumption of dark chocolate, which is high in flavonoids that may reduce CVD risk, is an attractive intervention to reduce to BP. Additionally, the use of mobile health (mHealth) technologies (eg, telehealth, smartphones, and wearable devices) can improve outcomes in patients with CVD.

OBJECTIVE The purpose of this study was to investigate the impact of dark chocolate intake on BP, subject use of mHealth, and integration of mHealth into a clinical trial.

METHODS The COCOA-BP (ChOcolate COnsumption And Blood Pressure) study was a prospective, single-center, pre-/postintervention study that enrolled 62 healthy volunteers. The study consisted of 3 phases: smartwatch/smart BP monitor familiarization and washout from chocolate (week 1); control (week 2); and intervention (weeks 3 and 4). During the intervention phase, subjects consumed 50 g of dark chocolate per day. The primary endpoint was change in resting systolic BP between the intervention and control phases. Additional endpoints included device accuracy and correlation with physical activity.

RESULTS Mean resting systolic BP was 116.4 mm Hg before chocolate intake among 62 participants (mean age 37 years; 61% female). After chocolate intake, mean resting systolic BP was 116.0 mm Hg (difference −0.4; $P = .69$). These findings suggest that 2 weeks of dark chocolate intake did not reduce resting systolic BP. There was poor agreement between mHealth device and standard (nurse-performed) measurements.

CONCLUSION In this study, short-term dark chocolate intake did not seem to reduce BP. mHealth technology shows great potential for use in clinical studies, but challenges related to device accuracy and compliance need to be addressed.

KEYWORDS Chocolate; Clinical study; Heart rate determination; Home blood pressure monitoring; Wearable electronic devices

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Introduction

High blood pressure (BP) is a major risk factor for cardiovascular disease (CVD) and stroke.[1] More than one-third of American adults have CVD, which accounts for more deaths than any other cause worldwide.[1] Even small reductions in BP can reduce CVD risk.[1,2] New methods to evaluate BP may improve assessment of risk and impact of treatments over standard methods.[3]

Epidemiologic studies have suggested that intake of foods/beverages containing high amounts of flavonoids may reduce the risk of CVD.[4] Major sources of these antioxidants include fruit, vegetables, wine, and dark chocolate, which contains the highest amount.[5] As such, flavanol-rich chocolate and cocoa products have attracted interest as a nonpharmacologic treatment option for high BP.[6] Although the mechanism of action remains under investigation, flavonoids exhibit antihypertensive and anti-inflammatory effects.[7] A meta-analysis found evidence that flavanol-rich chocolate and cocoa products can reduce BP by a small amount in the short term.[2]

Consumer digital health devices have become common, with 1 in 6 US consumers currently owning and using them.[8] Smartwatches accounted for nearly 60% of the wearable market share in 2018.[9] Data derived from these wireless mobile health (mHealth) tools have the potential to supplement and improve clinical investigations on several levels, including physician–patient relationships, study cost reduction, and patient management.[10,11] The use of mHealth tools has the potential to precisely measure and track BP, thus playing a supplemental role in managing hypertension.

The COCOA-BP (ChOcolate COnsumption And Blood Pressure) study used mHealth devices to evaluate the impact of dark chocolate intake on BP. Measurements derived from

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KEY FINDINGS

- The goal of the COCOA-BP (ChOcolate COnsumption And Blood Pressure) study was to evaluate the impact of dark chocolate on blood pressure (BP) while assessing difficulties in using mobile health (mHealth) technology in the context of a clinical study. In this subject population, 2 weeks of dark chocolate intake did not seem to reduce resting systolic BP.
- The use of mHealth technology in clinical studies has great potential, including reduction of the number of clinic visits and overall costs as well as the development of augmented or novel endpoints. However, there was poor agreement between mHealth device and standard (nurse-performed) measurements related to BP and heart rate in our study.
- Several additional challenges need to be addressed before mHealth technology can be incorporated into clinical trials, including subject compliance, device usability, and data management.

the mHealth devices were compared to standard nurse assessment and correlated to physical activity. The study also assessed the feasibility of using these technologies in clinical investigations.

Methods

Population

COCOA-BP was a prospective, single-center, single-arm, pre/post study that assessed the impact of daily dark chocolate intake on BP and compared data derived from mHealth devices to that obtained by standard methods. COCOA-BP was conducted at 1 site (Boston Scientific Corporation headquarters, Marlborough, MA) using employee volunteers as participants. A communication was provided to employees notifying them of the study. Subjects were screened and met all inclusion criteria and no exclusion criteria. Subjects were $\geq$18 years of age, had an iPhone 5 or higher (Apple Corporation, Cupertino, CA), understood and were willing to comply with all study requirements, and provided written informed consent. Individuals were excluded if they were part of the study execution team; were current or recent smokers; had a history of diabetes, medically treated hypertension, persistent/frequent irregular heartbeat, or permanent pacemaker or defibrillator; currently was pregnant; or had an allergy to chocolate, cacao products, or skin adhesives. The study was conducted in accordance with 21 Code of Federal Regulations (CRF) Part 50 and the relevant parts of International Council for

Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines for Good Clinical Practices, ethical principles that have their origins in the Declaration of Helsinki (as revised in 2013). The data and study protocol for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (http://www.bostonscientific.com/en-US/data-sharing-requests.html).

Intervention

Subjects were followed through 3 phases over 4 weeks after an initial office visit (Figure 1A). At the enrollment visit, subjects received and were trained on use of the mHealth devices. This included downloading the study and device applications (apps), setting daily reminders/notifications, and completing a baseline questionnaire related to diet and technology perception. Subjects also received the chocolate (50 g/d; 5 pieces of chocolate; 147 mg flavonoids total) for consumption during the intervention phase (weeks 3 and 4). Subjects were considered enrolled once an informed consent form had been signed and the study app was successfully downloaded onto their cell phone.

Subjects were required to wear their study-provided smartwatch every day, obtain at least 1 smart BP monitor measurement per day, and enter daily study-related tasks into the app. Week 1 was a period of device familiarization for the subjects as well as a washout period during which participants did not consume any chocolate. Week 2 was the control phase. Weeks 3 and 4 were defined as the intervention phase, during which subjects consumed 50 g of dark chocolate daily.

At the end of study visit (14 $\pm$ 7 days from the start of week 3), BP and heart rate (HR) were measured by an on-site nurse, the devices were returned, and the end of study questionnaire was completed. Devices were then unpaired, sanitized, charged, and repackaged by study personnel for reuse.

Device description

Participants were given the Qardioarm portable BP cuff ("Smart BP Monitor," Qardio, San Francisco, CA) and the Apple Watch ("SmartWatch," Apple) for the duration of the study.

Study protocol

Endpoints and additional measurements

The primary endpoint of COCOA-BP was the change in mean resting systolic BP after 2 weeks of dark chocolate intake. Secondary endpoints included comparison of BP and HR measured by a nurse or the mHealth device as well as correlation to physical activity (number of steps) measured by the SmartWatch.

Subjects were instructed to perform daily resting BP and HR measurements in the morning, at a similar time, before ingestion of coffee or tea. For the measurements, the SmartWatch was switched to "workout" mode, and the Smart BP Monitor BP cuff was placed and tightened on the upper arm. The subjects were to rest for 5 minutes with both feet flat on the floor, arm at the same level as the heart, before initiating the Smart BP Monitor measurement. The

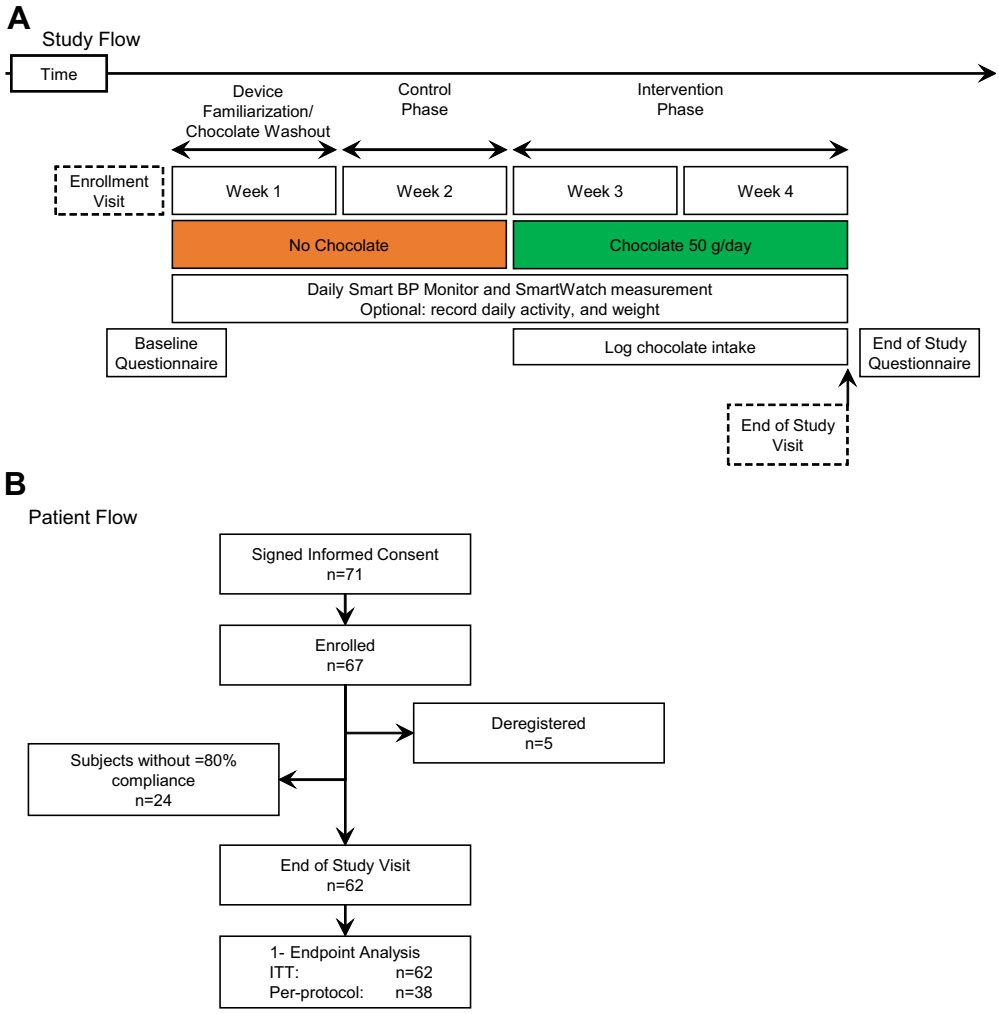


Figure 1 **A:** COCOA-BP (ChOcolate COnsumption And Blood Pressure) study design. **B:** Patient flow and disposition in the COCOA-BP study. Enrollment was defined as patients who signed the consent form, completed training, and downloaded the application. BP = blood pressure; ITT = intention to treat.

SmartWatch workout mode measures HR more frequently than standard mode; total time in this mode was ~7.5 minutes including the BP measurement.

For the standard measurement of BP and HR at the end of the study, subjects were seated for 5 minutes with their arm supported and at level of the heart. The manual BP measurement was the mean of 3 measurements taken by a nurse using a manual pressure cuff. The manual HR measurement was obtained by taking the radial pulse. Two BP and HR measurements were obtained from the Smart BP Monitor between the standard measurements.

Data analysis

The primary endpoint was the change in resting systolic BP after 2 weeks of dark chocolate intake. Resting systolic BP was an average of 3 consecutive automated measurements taken by the Smart BP Monitor. The primary endpoint was analyzed by comparing the (1) last day of the intervention phase (week 4; day 28) to the last day of the control phase (week 2; day 14); and (2) average of the last 3 days of weeks 4 and 2 (days 26 to 28 vs 12 to 14). Based on a minimum expected change of 3 mm Hg and an expected standard deviation of 8 mm Hg, 58 patients were required for 80% power. A paired, 2-sided Student t test was used to test the hypothesis ($\alpha = 0.05$). If $P < .05$ and 2-sided 95% upper confidence bound of the mean difference in resting systolic BP between the intervention and control phases was <0 mm Hg, then dark chocolate treatment would be concluded to significantly reduce BP in this subject population. Enrollment of up to 70 subjects was planned to allow for subject dropout and missing data. The primary endpoint was analyzed on an intention-to-treat (ITT) basis. For ITT analysis, all subjects who were enrolled in the study were included in the analysis regardless of their compliance to chocolate intake. The per protocol population included subjects who were $\geq$80% compliant for chocolate intake during weeks 3 and 4 determined by the chocolate intake log. A per protocol analysis of the primary endpoint also was performed.

Compliance with chocolate intake and method of BP measurement were analyzed descriptively. Discrete variables were reported as counts and percentages. Physical activity, defined as the average number of steps per day during the control phase (week 2) measured by the SmartWatch, was

Table 1 Baseline characteristics of the COCOA-BP study population (n = 62)

Characteristic	All patients (n = 62)
Female	61
Age (y)	37 ± 12
Height (in)	68 ± 4
Weight (lb)	162 ± 34
BMI (kg/m^2)	25 ± 4
Former smoker	6.5
Hyperlipidemia	8.1
Takes daily multivitamin	37.1
Ethnicity	
Caucasian	79
Asian	16
Hispanic/Latin	3
Not disclosed	2
Owns a fitness tracker	51

Values are given as % or mean ± SD.

BMI = body mass index; COCOA-BP = ChOcolate COnsumption And Blood Pressure.

correlated with resting systolic BP and resting HR during the same phase (ITT analysis set). A Bland-Altman plot was used to evaluate agreement between manual (nurse-assessed) and mHealth device measurements (ITT analysis set).[12] Bias, the mean difference between manual and Smart BP Monitor measurements, and limits of agreement (95%; ±1.96 SD of bias) were calculated.[12,13]

Results

Study population and baseline characteristics

A total of 71 subjects signed the consent form, and 67 subjects were enrolled between March 22, 2017, and September 12, 2017. Five patients were deregistered because no data were available (3 malfunctioning app, 1 phone issue, 1 personal issue), for an ITT population of 62. Of these patients, 24 did not comply with chocolate intake at the prespecified level of ≥80%, leading to a per protocol subject population of 38 (Figure 1B). In the ITT subject population, mean age was 37 ± 12 years; 21% were non-Caucasian or did not disclose their ethnicity, 61% were female; and average body mass index was 25 ± 4 kg/m^2 (Table 1). Approximately one-half of the study participants owned a fitness tracker at the start of the study, and of those patients, 72% indicated that fitness tracking had influenced their eating, sleeping, or physical activity levels.

Primary endpoint: Impact of dark chocolate on BP

The primary endpoint—change in resting systolic BP after 2 weeks of dark chocolate intake—is shown in Figure 2A. In the ITT population, average systolic BP on the last day of the control phase was 116.4 mm Hg (95% confidence interval [CI] 2.8 mm Hg) and 116.0 mm Hg (95% CI 3.0 mm Hg) on the last day of the intervention phase, for a difference of –0.4 (P = .69). When the last 3 days of the control and intervention phases were averaged and compared, mean systolic BP was 116.0 mm Hg (95% CI 2.4 mm Hg) and 116.5 mm Hg (95% CI 2.7 mm Hg), respectively, with a difference 0.50 (P = .51). Neither assessment of the primary endpoint was statistically significant (P >.05). Per protocol chocolate intake was defined as subjects who were ≥80% compliant during the intervention phase (weeks 3 and 4); a total of 61% (38) of subjects met this level. Twelve subjects were between 70% and 80% compliant, and 12 subjects were <70% compliant (Supplemental Figure 1). Similar results were observed when the per protocol study population was analyzed for the primary endpoint (Figure 2B).

Most participants (94%) performed the protocol-mandated daily resting BP and HR measurements, although some inconsistencies were observed. The median time of day at which resting BP and HR were taken ranged between 6:30 AM and 8:30 AM. Over the course of the study, the time became more widely distributed, with a greater number of measurements taken later in the day. To measure resting HR, participants were asked to put the SmartWatch in workout mode for 5 minutes before measuring resting BP (total ~7.5 minutes in workout mode). This mode measured HR more frequently than standard mode. One-third of HR measurements occurred with the requisite amount of time in workout mode (32%); 72% of measurements occurred with a partial premeasurement rest (>4 minutes). Compliance to workout mode improved with more thorough training in the latter half of the study (top vs bottom of Supplemental Figure 2).

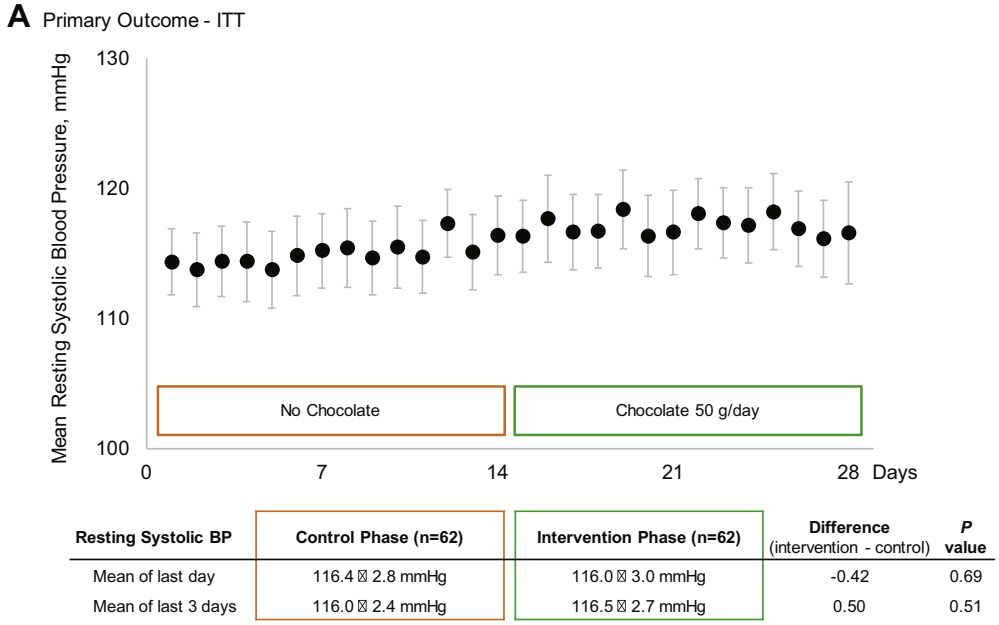
Secondary measurements

As a secondary endpoint, the correlations between activity levels and BP or HR were evaluated. The level of activity was estimated as the average number of steps per day during the control phase collected by the SmartWatch. Mean resting systolic BP and mean resting HR were measured by the Smart BP Monitor. No correlations were found between the average number of steps per day and resting systolic BP or HR (Figure 3).

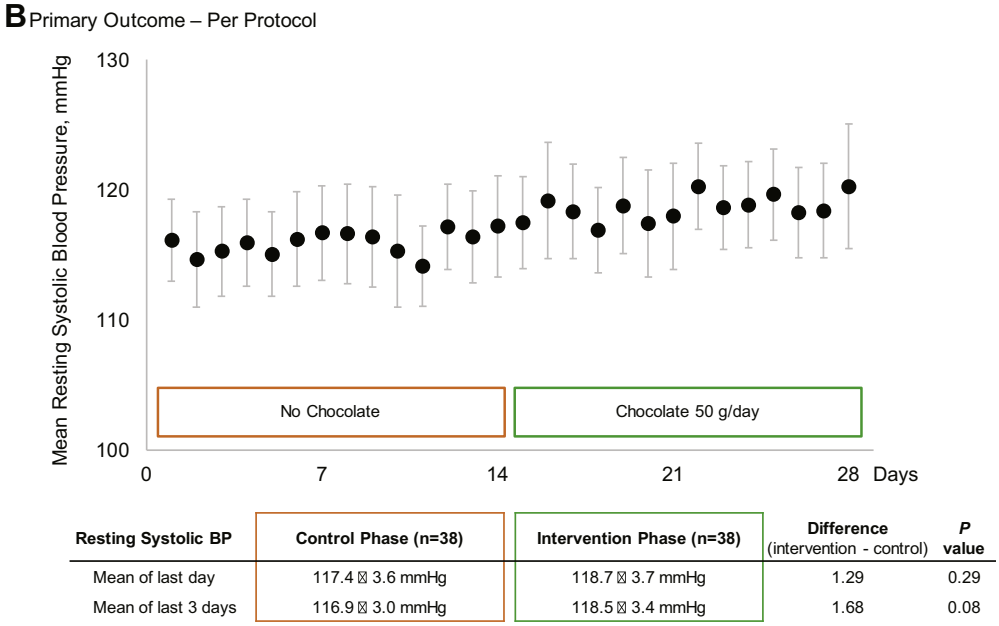
Agreement was evaluated between BP and HR assessed by a nurse using standard methods or by the Smart BP Monitor at the end of study visit. Bland-Altman plots of agreement are shown in Figures 3C and 3D. On average, manual measurement of resting systolic BP using standard methods was 4.6 mm Hg lower than device-derived measurements (mean bias –4.6 mm Hg; limits of agreement ±14.2 mm Hg) (Figure 3C). Nurse assessment of BP was lower than device-derived BP in 69% of subjects. For HR, mean bias was –2.4 bpm (limits of agreement ±11.0 bpm); 64% of subjects had a lower HR with manual methods vs the device. No positive or negative trends were observed.

Technology perception

Device features were ranked for importance at the time of enrollment and again after the study was completed (Figure 4A). Small positive shifts in the importance of battery life, data viewability, location on the body, and device capabilities were found. Fitness tracking became less important to the participants after the study. At the end of the study, more



Resting Systolic BP	Control Phase (n=62)	Intervention Phase (n=62)	Difference (intervention - control)	*P* value
Mean of last day	116.4 ± 2.8 mmHg	116.0 ± 3.0 mmHg	-0.42	0.69
Mean of last 3 days	116.0 ± 2.4 mmHg	116.5 ± 2.7 mmHg	0.50	0.51



Resting Systolic BP	Control Phase (n=38)	Intervention Phase (n=38)	Difference (intervention - control)	*P* value
Mean of last day	117.4 ± 3.6 mmHg	118.7 ± 3.7 mmHg	1.29	0.29
Mean of last 3 days	116.9 ± 3.0 mmHg	118.5 ± 3.4 mmHg	1.68	0.08

Figure 2 Primary endpoint of mean resting systolic blood pressure (BP) measured with the Smart BP Monitor after 2 weeks of dark chocolate intake in the intention-to-treat (primary analysis) **(A)** and per protocol **(B)** subject populations. Mean resting systolic BP (±95% confidence interval) is shown over the course of the study. Two paired analyses (table) compare mean systolic BP in week 2 (no chocolate) and week 4 (chocolate) using either the last day of each week or the average of the last 3 days of each week. *P* value from a 2-sided paired Student *t* test. ITT = intention to treat.

than 50% of participants were somewhat or very engaged/satisfied with the SmartWatch and more than 80% with the Smart BP Monitor (Figure 4B). Most subjects did not feel either device interfered with their daily life. When asked if they would continue to wear or use the devices on their own (if they purchased one), 40% of participants indicated they would consider continuing with the SmartWatch and 60% with the Smart BP Monitor.

Discussion

The goal of COCOA-BP was to evaluate the impact of dark chocolate on BP while assessing difficulties in using mHealth technology in the context of a clinical study. The impact of dark chocolate on health was an appealing study that attracted engaged and motivated subjects interested in mHealth or participation in a clinical study. Our study had mixed success. Dark chocolate intake did not seem to reduce resting systolic BP, although the use of mHealth devices in this study did show promise.

The health benefits of dark chocolate have been praised in the mainstream media, although studies of its impact on BP have been equivocal.[14] An updated Cochrane meta-analysis downgraded the evidence for chocolate intake reducing systolic BP from high to moderate quality due to significant

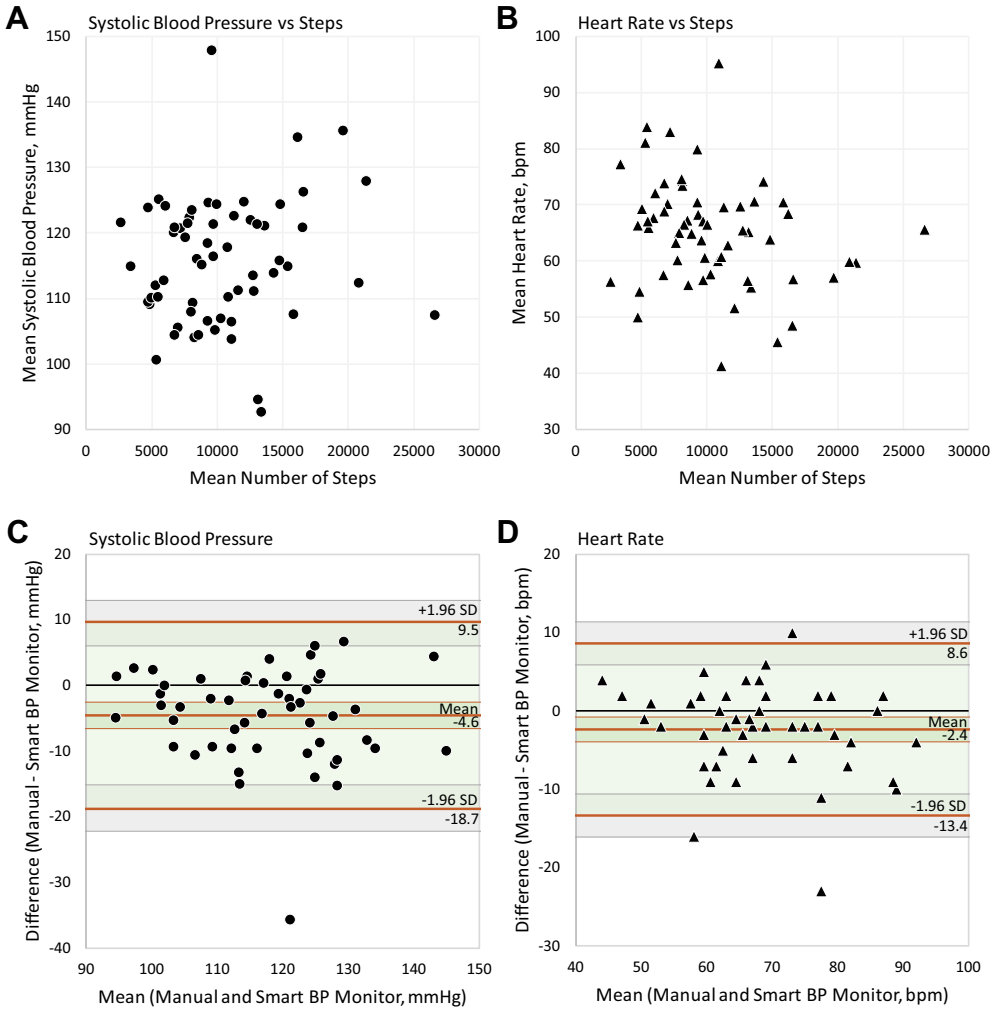


Figure 3 Secondary measurements. Correlation between number of steps and mean resting systolic blood pressure (BP) **(A)** or mean resting heart rate (HR) **(B)** measured during week 2. Bland-Altman plot of agreement between manual and Smart BP monitor measurements of systolic BP **(C)** and HR **(D)** at the end of study visit. *Red dotted lines* indicate limits of agreement (±1.96 SD of the difference). *Gray shading* indicates confidence limits of the mean and limits of agreement.

heterogeneity between studies.[2,15] The authors found a larger effect size in hypertensive/prehypertensive subjects, younger subjects, and longer studies (>6 weeks).[2,15] As such, any reduction in BP in our study could have been diluted by the short length of treatment, type (solid bar vs drink) and amount of chocolate consumed, flavanol content of the chocolate, and normotensive participants.[2] Compliance to chocolate consumption was lower than expected. Anecdotally, subjects stated that it was hard and/or not enjoyable to eat 50 g of dark chocolate per day. The primary endpoint also may have been impacted by the time the BP measurement was taken. Subjects were directed to measure BP after waking up and before consumption of coffee/tea. Compliance declined over the course of the study for most participants. BP is dynamic and reactive to many impulses (physical or emotional), which makes it challenging to detect small differences. More continuous measurements might decrease issues related to the variability of BP over time due to activity and stress.

Our results did not show a correlation between activity and either resting systolic BP or HR. These variables were averaged over the control phase of the study, and comparing HR and BP preactivity and postactivity might have been more informative. The accuracy limitations of mHealth devices may have influenced these outcomes. A secondary endpoint of the study compared measurements taken with the mHealth devices to standard methods. There was low precision of the BP and HR measurements taken by the smart devices and suboptimal agreement to those taken by a nurse.

The use of mHealth technology in clinical studies may reduce costs.[10,11] Because data collection and monitoring can be done remotely, the number of clinic visits could be reduced, thus saving time and money for participants, clinicians, and sponsors.[10,11] This technology may lead to novel or augmented endpoints, with potential for early detection of disease or decompensation.[16] Recent experience from the Apple Heart Study demonstrated benefits of mHealth

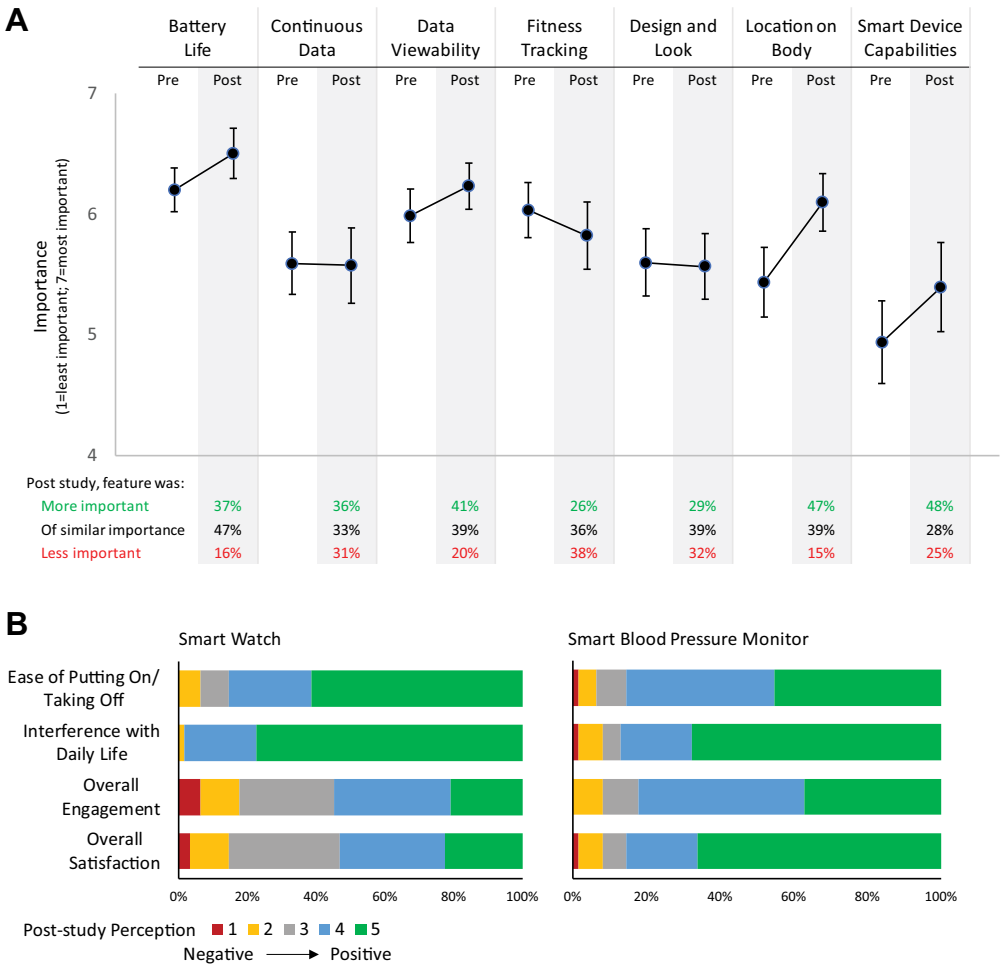


Figure 4 Technology perception. **A:** Study participants were asked, "Assuming you could have an ideal wearable device used for health management, please rank the importance of each of the following features" before and after the study, where rank 1 = not important and 7 = very important. Mean ± 95% confidence interval at the enrollment visit (pre) and end of the study (post) are given. **B:** Perception of different aspects of the wearable devices at the end of the study: ease of putting on/taking off the device (ranked 1 = difficult to 5 = very easy); interference with daily life (ranked 1 = could not complete daily routine/I would refuse to wear the device to 5 = did not or only mildly interfered with daily routine); and overall engagement and overall satisfaction (ranked 1 = not engaged/very dissatisfied to 5 = engaged all the time/very satisfied).

with regard to enrolling a large and engaged population in a short time.[17]

Common to this and other clinical studies, mHealth devices demonstrated potential, but issues need to be overcome before they become a standard part of clinical studies.[18–20] First and foremost, even in a young, healthy, engaged study population, compliance ultimately relies on human behavior. From the perspective of study participants, it was taxing to log chocolate intake and perform the measurement for resting BP each day. There are additional challenges with usability of mHealth devices by older subjects. For example, it may be challenging for this cohort to consistently wear the device or follow protocol-defined measurements and prompts. As such, devices and apps need to be extremely easy to use and reliable. If possible, processes should be passive or automated, and methods to increase subject compliance may need to be implemented (reminders, virtual rewards, visual displays).[8] From the perspective of those running the clinical trial, processes to manage data sharing, privacy, and security issues related to mHealth devices need to be in place.[8,16] Ample and appropriate resources are needed to handle and analyze the large and dense datasets collected from mHealth devices.[21] Finally, the accuracy of mHealth devices used in this study compared to those used in the clinic must be confirmed.[22]

Study limitations

Compliance to chocolate intake was low, and the subject population was young and normotensive. Confounding factors that can impact BP, such as salt intake and alcohol consumption, were not assessed in the study. Additionally, the study followed participants for only 4 weeks.

Conclusion

In this study, short-term dark chocolate intake did not seem to reduce resting systolic BP. The use of digital health technologies in clinical studies is promising and warrants further investigation.

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Disclosures

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.cvdhj.2020.08.002.

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