Real-world long-term effects on blood pressure and other cardiovascular risk factors for patients in digital therapeutics

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Purpose **Hypertension is a leading causeof premature death worldwide and a major public health problem. This study investigated the long-term effects (>1 year) of digital hypertension monitoring by home blood pressure (HBP) measurements in combination with individualized remote treatment via a Swedish Digital Therapeutics platform in a large patient population.**

Methods **The primary endpoint, HBP, and exploratory endpoints, BMI, alcohol consumption, stress level, physical activity, and smoking, were assessed every 3 months for 540 and 360 days, respectively, in 7752 Swedish primary hypertension patients. Patients received individualized medical treatments and lifestyle advice via asynchronous text-based communication in an app. Changes from baseline in endpoints were calculated for the whole population and for subgroups defined by baseline SBP ≥135 (high SBP), 125–135 (suboptimal SBP), 115–125 (optimal SBP), and <115 mmHg (low SBP).**

Results **After 360 days of treatment, the whole population showed a significant increase of 57% (from 37 to 58%) in the proportion of patients with controlled SBP (i.e. SBP of 115–135 mmHg). The largest reduction in SBP of 13.8 mmHg was observed for the high SBP subgroup, whereas for the low SBP subgroup, SBP increased by 13.4 mmHg. BP improved most in the first three months, and for both the high and low BP subgroups, the improvement continued during the 540-day study period. Significant beneficial changes were also observed for some exploratory endpoints including BMI and smoking.**

Conclusions **In conclusion, the digital therapeutics platform was associated with significant improvement in BP control and associated risk factors, which were maintained over a longer period. *Blood Press Monit* XXX: XXXX–XXXX Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Hypertension is the leading preventable risk factor for cardiovascular diseases (CVDs) and premature death worldwide [1]. The financial burden attributed to high blood pressure (BP) was estimated to be around 370 billion US dollars globally in 2001 for inpatient and outpatient care, or about 10% of the global healthcare expenditure [2]. The global prevalence of hypertension (defined as SBP ≥140 mmHg orDBP ≥90) was estimated to 30% in adults in 2010 [3].

In Sweden, approximately 1.8 million people are affected by hypertension [4] and the prevalence appears to be rising [5]. Andersson *et al.* found that hypertension was the most costly CVD-related diagnosis in Swedish inpatient care in 2019, costing 1.4 billion Swedish kronor (almost 140 million Euro) [6]. Moreover, a study of Swedish registry data covering the years 2010–2017 found that, despite the widespread availability of effective and affordable treatments in Sweden, only 10% of hypertension patients reached treatment targets for hypertension risk factors including controlled BP (i.e. office-based BP of <140/90 mmHg) and low-density lipoprotein cholesterol of <2.6 mmol/L, while also being non-smokers [7]. Several barriers may contribute to hypertension treatment failures including the requirement of long-term patient adherence to lifestyle recommendations or drug treatment in combination with regular BP measurements and systematic follow-ups by caregivers [8,9]. Overcoming these barriers and increasing BP control in the population can contribute to better health and substantial cost offsets.

In recent years, new applications based on home BP (HBP) monitoring have been developed to facilitate simple and effective hypertension management for patients and healthcare providers [10]. HBP is a practical and less expensive alternative to office and ambulatory BP

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measurements and is particularly valuable for long-term monitoring of patients treated for hypertension [11]. A meta-analysis of 46 randomized controlled trials (RCT) of home BP telemonitoring showed clinically important BP reductions in hypertensive individuals, with the largest reductions reported for studies that combined BP telemonitoring with case management (e.g. counseling and medication management) [12]. Extensive digitalization, including the wide use of smartphones, has provided new possibilities for remote HBP monitoring and hypertension management by digital therapeutics (DTx). With DTx, patients can receive effective healthcare services, including regular feedback from healthcare professionals based on BP readings sent electronically, without physical interaction between healthcare providers and patients [11]. Recent studies evaluating the use of digital interventions for hypertensive patients have demonstrated favorable effects on BP; a meta-analysis by Xu *et al.* including six RCTs of smart-phone based interventions showed a mean reduction in SBP of –2.28 mmHg over 3–12 months compared to controls [13], and in another RCT, digital home BP monitoring in combination with guided self-management of 622 hypertension patients resulted in a reduction in BP of 3.4/0.5 mmHg compared to usual care [14].

A DTx platform that manages hypertension using an in-house developed conformité européene (CE)-marked medical technology system combining regular HBP measurements, structured anamnesis, and laboratory measurements with virtual physician interactions that provide individualized patient supervision, education, and treatment showed promising effects on BP in a pilot study; among 117 subjects with uncontrolled HBP at treatment initiation, SBP was reduced by 4.6 mmHg ($P < 0.001$) and DBP by 2.7 mmHg ($P < 0.001$) after using the DTx for 3 months [15]. The objective of this real-world retrospective study was to investigate the long-term effects (up 540 days) of the same DTx platform on HBP and other related clinical outcomes in a large population of Swedish primary hypertension patients ($n = 7752$).

Methods

Hypertension treatment by digital therapeutics

The DTx platform for treatment of hypertension and other risk factors related to CVDs evaluated in this study is under development by Blodtrycksdoktorn.se. The DTx platform is provided as part of the public healthcare system and is reimbursed by the county councils in Sweden per digital consultation by physician. The technical functions of the app are described in more detail in Supplementary Methods, Supplemental Digital Content 1, http://links.lww.com/BPMJ/A184. Eligibility criteria for onboarding the DTx platform at the time of the study were age between 35 and 75 years old, a self-reported diagnosis of primary hypertension, an absence of diagnosed secondary hypertension, stroke history, myocardial infarction history, heart failure history, cardiac arrhythmia, severe renal failure (defined as estimated glomerular filtration rate <30 mL/min/1.73 m^2), and on-going pregnancy.

At onboarding to the DTx platform, the patient downloads the DTx smartphone app and receives, free of cost by mail, a validated and CE-labelled, Bluetooth-equipped oscillometric BP monitor with individually adjusted cuff size (Truly Instrument Limited, Hong Kong, China) that connects to the app via Bluetooth. Through the app, the patient uploads baseline HBP measurements (see section 'Study variables and endpoints' below) and answers structured anamnesis questions. Patients are also asked to report any medication they may use and answer questions regarding medical compliance. Each patient is also asked to provide a blood and urine sample for analysis of fifteen routine pre-treatment screening tests including fasting blood glucose and lipid profile.

The intervention (treatment program) begins at onboarding. At this point, the patient can communicate with a physician and receive feedback on his/her medical situation, including interpretations of HBP and laboratory values. In the case of patients with highly elevated BP, medication adjustments can be done, and new prescriptions can be made using asynchronous text communication and a web-based digital tool for drug prescription (Alfa eCare Recept AB, Malmö, Skåne, Sweden), which enables e-prescriptions reaching all pharmacies in Sweden. Moreover, all patients receive educational materials that focus on smoking and moist powder tobacco cessation, salt and liquorice restriction, alcohol intake, the dietary approaches to stop hypertension diet, weight reduction, physical exercise, and stress management. Additional educational materials discussing factors important for good BP control are provided via a weekly digital newsletter. Furthermore, patients who report risk factors (e.g. smoking, high salt- or liquorice intake, high alcohol consumption, and BMI >25 kg/m^2 or waist circumference in women/men of >88/102 cm) of hypertension at onboarding, can receive individual education and advice around BP and lifestyle factors supported by gamification.

Following baseline measurements at onboarding, participants are asked to measure HBP on at least seven days in the morning (before breakfast) and at least seven days in the evening for the first two weeks after registration (onboarding). Physicians work in a combined patient record and clinical decision support system that leverages all the data from the patient to provide effective treatment based on medication and lifestyle intervention. The patient-responsible physician is alerted through automated notifications if HBPs become exceedingly high (>190 SBP or >115 mmHg DBP) or low (SBP <110 mmHg). Two weeks after the onboarding process, all patients are scheduled for a first treatment control, where they receive individualized treatment programs by the patient-responsible physician, which includes initiation of lifestyle intervention

and medicine adjustment when needed, based on trends of their HBP during the first two weeks. If the initial mean BP values are above target (defined as mean HBP >135/85 mmHg), antihypertensive medications can be adjusted according to European Society of Cardiology (ESC) guidelines [9] and a follow-up is planned after two weeks. Patients can also be referred for extra laboratory tests if judged necessary following medication adjustments. Patients can provide more than just the standard BP measurements to alert the physician about symptoms such as dizziness, palpitations, or headaches. BP measurements performed without prior rest were not included in the mean BP measurement computed for this study (see 'Study variables and endpoints' below). If SBP indicates hypotension (defined as SBP <110 mmHg), or if dizziness is reported, patients are asked to perform additional orthostatic BP measurements. If orthostatic hypotension is confirmed (defined as a decline of SBP ≥20 mmHg or a decline of DBP ≥10 mmHg within three min of standing), medication can be adjusted by the treating physician.

After the first treatment control, regular and standardized follow-ups and treatment controls are performed by the physician based on regular HBP measurements performed every three months following baseline BP measurement. Laboratory values are scheduled for collection on a yearly basis, but participants can be referred for extra laboratory tests as necessary (though most patients chose not to be tested during the COVID-19 pandemic). As part of the care model, patients can contact their responsible physician at any time using a chat function in the app and the physician usually responds within 24 h on weekdays.

Study data

Study population

The date of onboarding to the DTx platform for the first patient was 28 June 2018, and the data were harvested on 8 April 2021. During this period, 7922 subjects meeting the eligibility criteria for the DTx (see full list of eligibility criteria above) initiated the treatment program and completed their 3-month follow-up measurement, which was an inclusion criterion for the study. No significant changes that could affect the study results were made to the application over the study period. No patient fee was paid by the study participants during the study period. Ethical approval was obtained for this retrospective analysis from the Swedish Ethical Review Authority (Dnr 2021-06301-01) subject to providing an option for subjects to opt out of study participation. This resulted in a loss of 170 patients who opted out and a final sample size of 7752.

On the basis of baseline HBP measurements, the study population was divided into four subgroups representing different grades of hypertension classified according to European Society of Hypertension/ESC Guidelines [9]. However, as HBP measurements (both SBP and DBP) are generally 5 mmHg lower compared to conventional office BP measurements [9], the BP thresholds were adjusted accordingly by 5 mmHg. Because SBP is the primary treatment focus for physicians, we maintained a reasonable number of patient subgroups by defining groups based on SBP only (classifying by both SBP and DBP control would have led to four times as many categories). Age-dependent hypertension thresholds were not considered for group definitions to simplify the interpretation of the study results. The SBP-based subgroups were defined as follows:

(1) High SBP; SBP ≥135 mmHg
(2) Suboptimal SBP; SBP = 125–135 mmHg
(3) Optimal SBP; SBP = 115–125 mmHg
(4) Low SBP; SBP <115 mmHg.

Study variables and endpoints

Sex, age, height, weight, diabetes, country of birth (see supplementary methods, Supplemental Digital Content 1, http://links.lww.com/BPMJ/A184 for further description of data collection), and timing of first medical treatment for hypertension, were collected by self-reporting at baseline (i.e. through a structured anamnesis in the app at the time of onboarding the DTx platform).

The primary endpoint was HBP measured at baseline, initial assessment (two weeks after baseline), and thereafter every three months from baseline up to 540 days. Baseline BP level was calculated as the mean value of two registered measurements (i.e. four individual measurements) during onboarding. In general, all registered BP measurements were based on the mean of two readings with a one-min interval performed in a sitting position after five min of rest. If the two measurements differed by more than 7 mmHg, one more measurement was performed, and HBP was calculated as the mean of the last two measurements. Secondary endpoints were DBP, pulse pressure (PP; defined as the difference between SBP and DBP in mmHg), and proportion of patients having HBP measurements within the target for controlled hypertension defined as SBP between 115 and 135 mmHg.

Self-reported exploratory endpoints measured at baseline and thereafter every three months up to 360 days included BMI (created from self-reported height and weight), physical activity level (physically active defined as self-reported levels of physical activity as 'frequently active' or 'pretty frequently active'), high alcohol consumption (based on self-reported consumption of more than 9/14 standard units of alcohol/week for females/males), high-stress level (defined as the self-reported frequency of stressful episodes as 'all the time' or 'most of the time'), and smoking (defined as self-reported 'smoking daily' or 'smoking but not daily'). Other patient characteristics and endpoints relevant to the dataset are described in Supplementary Methods, Supplemental Digital Content 1, http://links.lww.com/BPMJ/A184.

Treatment effects

Exposure to the intervention was defined as starting at onboarding to the DTx platform and ending at discontinuation of treatment or end of the study data (i.e. censored). The length of exposure varied across subjects. Subjects contributed data for the time they participated (i.e. no requirement for completion of the maximum follow-up time). Treatment effects of primary, secondary, and exploratory endpoints were analyzed for the population as a whole and for the four SBP-based subgroups separately. Treatment effects of primary and secondary endpoints were also analyzed in the following exploratory subgroups:

(1) Diabetes (self-reported or fasting plasma glucose ≥7.0 mmol/L)
(2) Pre-diabetes (fasting plasma glucose ≥6.1 and <7.0 mmol/L)
(3) Overweight (defined as BMI 25.0–29.9 kg/m^2)
(4) Obese (defined as BMI ≥30 kg/m^2)
(5) Age >65 years
(6) Age <65 years
(7) High alcohol consumption (defined as self-reported consumption of more than 9 standard units of alcohol per week for females and 14 standard units for males)
(8) Low alcohol consumption (defined as self-reported consumption of less than 9 standard units of alcohol per week for females and 14 standard units for males).

Statistical analysis

Descriptive statistics

Descriptive statistics were computed for the baseline values of each study variable for the full study population as well as for the four SBP-based subgroups. The descriptive statistics consisted of sample size, mean, and SD for continuous variables and sample size and proportion for categorical variables.

Mean change from baseline

Mean change from baseline was calculated for all endpoints at two weeks from baseline (first treatment control) and every three months from baseline up to 540 days for primary and secondary outcomes, and 360 days for exploratory endpoints. For primary and secondary endpoints, initial assessment at two weeks after baseline was also included as a time point. The mean change from baseline for each continuous endpoint was computed, together with *P* values and SEs. As there is no control arm, the patients served as their own control group. While this reflects treatment by the DTx platform in the real-world setting, the ability to control for confounding factors (including patient self-selection into treatment and secular trends that may be ongoing before and during the study period) was limited. Because non-random subject attrition (e.g. due to death, goal attainment, or treatment dissatisfaction but include censoring due to late study entry for otherwise ongoing treatment) can bias the comparison (i.e. informed censoring), we additionally calculated mean values for the primary outcomes for completers and differences versus all subjects, by duration and SBP-based subgroup. Statistical significance was tested using *t*-tests performed on the sub-group of patients with complete follow-up data to the tested time point. The significance level was set to $P < 0.05$.

Evolution curves

All endpoints were plotted over time separately by SBP-based subgroup from baseline and at every 3-month interval. Mean and 95% confidence interval at each time point were plotted. Categorical endpoints were described with bar charts for each point in time.

Results

Patient characteristics at baseline

A total of 7752 initiating on the DTx platform during the period 2018–2021 participated in the retrospective study. Baseline characteristics for the whole patient population, and for SBP-based subgroups, are presented in Table 1. Sixty-nine percent were born in Sweden, 12% in other European countries, and 19% outside Europe. All patients had a hypertension diagnosis for which they received treatment before initiating onboarding the DTx platform and 79 % of the patients had received previous medication for their hypertension. Moreover, 57, 36, and 19% had had their first medication for hypertension ≥2, ≥5, and >10 years, respectively, before enrolling in the study while 19% had not yet received medication for hypertension. The majority of the participants (58%) had SBP above the defined diagnostic target for uncontrolled SBP (i.e. SBP ≥135).

As expected, mean SBP/DBP differed between SBP-based subgroups ranging from 149/92 in the high SBP subgroup to 109/72 in the low SBP subgroup. Some differences in patient characteristics were observed between subgroups; the low SBP subgroup differed from the whole study population by having fewer male patients and a higher proportion of patients with a high-stress level, as well as a smaller proportion of patients with high alcohol consumption. With increased mean SBP, we also observed an increase in the proportion of males and people born in Sweden as well as an increase in BMI of approximately one unit between each subgroup.

Treatment effects

As per inclusion criteria, all 7752 study participants were represented in HBP measurements at three months after baseline. However, as the recruitment was continuous and data harvested at a fixed time point, the number of patients with HBP measurements declined for every additional three-month interval from baseline. Over the study period, there was also a small proportion of patients (7%) who were lost to follow-up (reasons included death, serious complications, drop-out, and moving abroad) and

Table 1 Baseline characteristics for SBP-based subgroups and for the whole study population

		High SBP (>135 mmHg)			Suboptimal SBP (125–135 mmHg)			Optimal SBP (115–125 mmHg)			Low SBP (<115 mmHg)			All participants		
Variable	Unit	*N*	Mean/%	SD	*N*	Mean/%	SD	*N*	Mean/%	SD	*N*	Mean/%	SD	N	Mean/%	SD
Age	Years	4502	57.6	9.6	1768	57.5	9.4	1084	56.7	9.9	396	56.9	9.8	7750	57.4	9.6
Sweden	%	3232	71.8%	–	1173	66.4%	–	694	64.0%	–	237	59.8%	–	5336	68.9%	–
Nordic (except Sweden)	%	151	3.4%	–	43	2.4%	–	38	3.5%	–	10	2.5%	–	242	3.1%	–
EU (except Nordic)	%	199	4.4%	–	73	4.1%	–	48	4.4%	–	20	5.1%	–	340	4.4%	–
Europe (except EU and Nordic)	%	199	4.4%	–	91	5.2%	–	60	5.5%	–	23	5.8%	–	373	4.8%	–
Africa	%	88	2.0%	–	42	2.4%	–	32	3.0%	–	13	3.3%	–	175	2.3%	–
Asia	%	264	5.9%	–	159	9.0%	–	111	10.2%	–	48	12.1%	–	582	7.5%	–
North America	%	23	0.5%	–	10	0.6%	–	5	0.5%	–	1	0.3%	–	39	0.5%	–
Oceania	%	0	0.0%	–	1	0.1%	–	1	0.1%	–	0	0.0%	–	2	0.0%	–
South America	%	39	0.9%	–	32	1.8%	–	14	1.3%	–	5	1.3%	–	90	1.2%	–
Male	%	2473	54.9	–	847	47.9	–	469	43.3	–	131	33.1	–	3920	50.6	–
SBP	mmHg	4502	148.9	11.7	1 768	129.7	2.9	1084	120.4	2.7	396	108.6	5.8	7 750	138.5	16.0
DBP	mmHg	4502	91.9	10.6	1 768	82.3	7.8	1084	78.5	7.0	396	71.9	7.5	7 750	86.8	11.4
PP[a]	mmHg	4502	57.0	10.5	1 768	47.5	7.78	1084	41.9	6.9	396	36.7	7.1	7 750	51.7	11.5
Proportion controlled SBP	%	4502	0.0	0.0	1 768	100	0.0	1084	100	0.0	396	0.0	0.0	7 750	37	1.0
BMI	kg/m^2	4401	29.6	5.2	1 727	28.5	4.8	1060	27.7	4.5	383	26.8	4.3	7 571	29.0	5.1
Diabetes	%	4055	9.5	–	1 617	10.7	–	975	9.3	–	351	8.8	–	6 998	9.8	–
High stress level[b]	%	4262	35.6	–	1 664	35.6	–	1026	40.1	–	363	42.4	–	7 315	36.6	–
High alcohol consumption[c]	%	4211	26.1	–	1 641	23.3	–	1014	22.7	–	356	18.0	–	7 222	24.5	–
Physically active[d]	%	4242	16.1	–	1 652	13.5	–	1020	14.2	–	362	15.2	–	7 276	15.2	–
Smoker[e]	%	4490	12.5	–	1 761	10.7	–	1078	11.8	–	393	12.2	–	7 722	12.0	–

PP, pulse pressure.

[a]PP = SBP − DBP.

[b]Self-reported frequency of stressful episodes as 'all the time' or 'most of the time'.

[c]Self-reported consumption of more than 9/14 standard units of alcohol/week for females/males.

[d]Self-reported physical activity levels as 'frequently active' or 'pretty frequently active'.

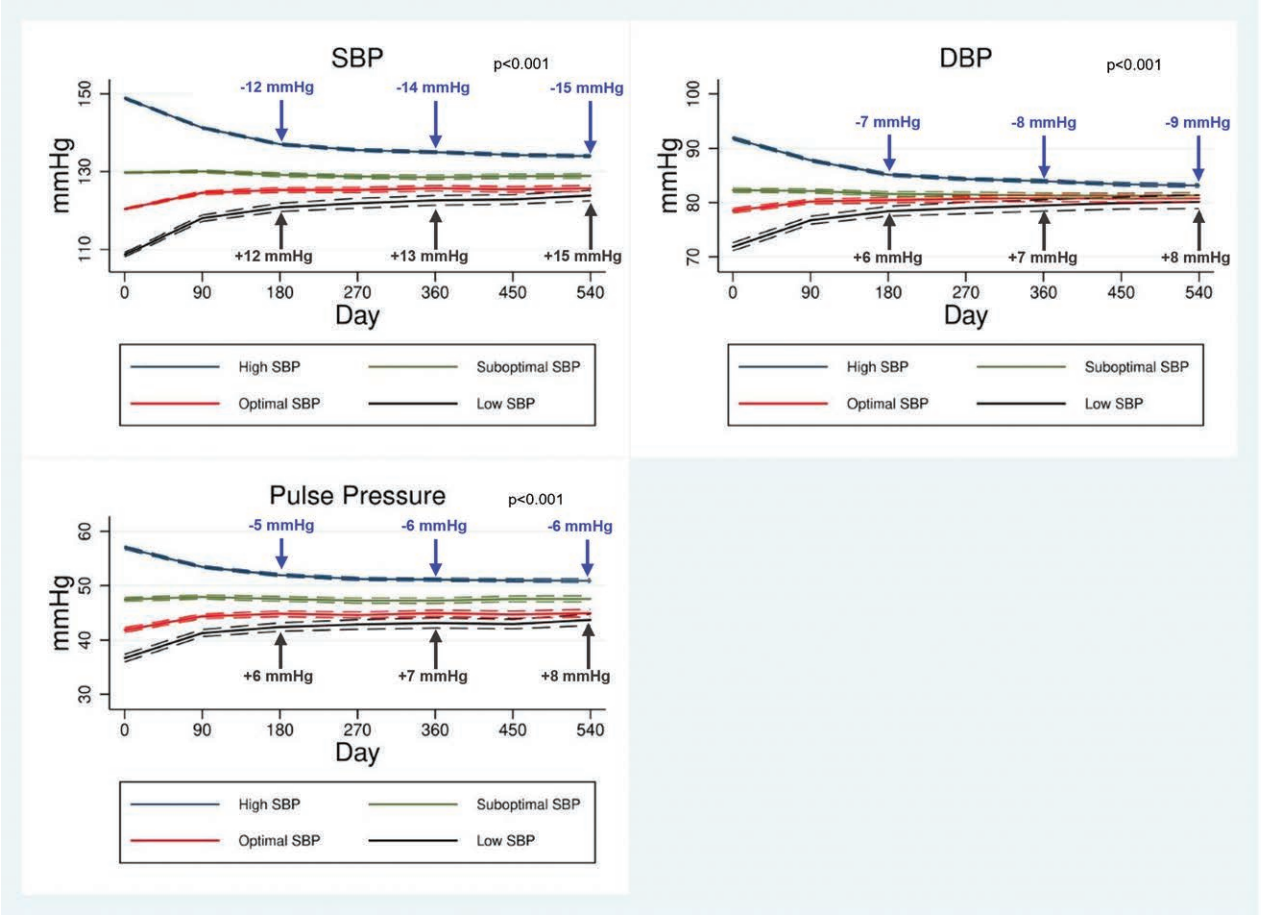
[e]Self-reported smoking status as 'smoking daily' or 'smoking but not daily'.

8% of the patients were inactive on the platform (e.g. due to travel) at some point during the study period, which further contributed to a loss of sample sizes over time. The number of patients with HBP measurements at 180, 360, and 540 days after baseline were 6164, 4827, and 3718, respectively (Supplementary Table S1, Supplemental Digital Content 1, http://links.lww.com/BPMJ/A184). To evaluate the potential of systematic bias in HBP values over time due to declining sample sizes, we compared mean baseline HBP for those subjects with complete follow-up data at the end of each three-month interval, and only minimal differences (<0.4 mmHg) were observed between these groups.

The values for SBP, DBP, and PP over time are depicted in Fig. 1 separately for the four SBP-based subgroups. Supplementary Figures S1 and S2 (Supplemental Digital Content 1, http://links.lww.com/BPMJ/A184) present the same for the exploratory endpoints. Mean changes from baseline in primary, secondary, and exploratory endpoints after 360 days of treatment with the DTx platform for the whole patient population and for SBP-based subgroups separately are presented in Table 2. Mean values and change from baseline at all timepoints are presented in Supplementary Table S1, (Supplemental Digital Content 1, http://links.lww.com/BPMJ/A184) for primary and secondary endpoints and in Supplementary Table S2, (Supplemental Digital Content 1, http://links.lww.com/BPMJ/A184) for exploratory endpoints. Mean values and change from baseline in primary and secondary outcomes for exploratory subgroups are presented in Supplementary Tables S3–S10, (Supplemental Digital Content 1, http://links.lww.com/BPMJ/A184.)

After 360 days from baseline, significant decreases in SBP, DBP, and PP were observed for the whole study population and the proportion of patients with controlled SBP (defined as SBP ≥115 and ≤135 mmHg) increased from 37 to 58% (Table 2, Supplementary Table S1, Supplemental Digital Content 1, http://links.lww.com/BPMJ/A184). Between SBP-based subgroups, the most profound changes in primary and secondary outcomes over the 360 days were, as expected, observed for the high SBP

Fig. 1



Changes in SBP, DBP, and PP over time for SBP-based subgroups. The graphs show mean values with confidence intervals. PP, pulse pressure.

Table 2 Change from baseline to 360 days of treatment with the DTx platform in primary, secondary, and exploratory outcomes for the whole study population and SBP-based subgroups

Outcomes	High SBP (>135 mmHg)				Suboptimal SBP (125–135 mmHg)				Optimal SBP (115–125 mmHg)				Low SBP (<115 mmHg)				All participants		
	N	Mean change	SE	*P*	*N*	Mean change	SE	*P*	*N*	Mean change	SE	*P*	*N*	Mean change	SE	*P*	*N*	Mean change	SE	*P*
Primary and secondary																				
SBP	2850	−13.8	0.24	<0.001	1083	−1.2	0.28	<0.001	674	5.3	0.35	<0.001	220	13.4	0.71	<0.001	4 827	−7.0	0.21	<0.001
DBP	2 850	−8.0	0.18	<0.001	1083	−1.2	0.24	<0.001	674	2.3	0.30	<0.001	220	6.6	0.57	<0.001	4 827	−4.4	0.14	<0.001
PP	2 850	−5.8	0.17	<0.001	1083	0.0	0.22	0.933	674	3.0	0.27	<0.001	220	6.7	0.51	<0.001	4 827	−2.7	0.13	<0.001
Proportion controlled SBP	2 850	0.5	0.01	<0.001	1083	−0.3	0.01	<0.001	674	−0.2	0.02	<0.001	220	0.7	0.03	<0.001	4827	0.2	0.009	<0.001
Exploratory																				
BMI	432	−0.47	1.45	<0.001	178	−0.46	1.08	<0.001	99	−0.40	1.27	0.002	28	−0.48	2.16	0.249	737	−0.46	1.38	<0.001
High stress level	437	−0.09	0.02	<0.001	180	−0.16	0.03	<0.001	101	−0.07	0.05	0.147	28	−0.17	0.08	0.071	746	−0.11	0.02	<0.001
High alcohol consumption	436	0.06	0.02	0.0112	180	0.02	0.03	0.605	99	0.07	0.05	0.137	28	0.03	0.08	0.649	743	0.05	0.02	0.004
Physically active	436	0.04	0.02	0.038	179	0.02	0.03	0.428	101	0.00	0.03	0.922	28	0.10	0.08	0.172	744	0.03	0.01	0.026
Smoker	437	−0.04	0.01	0.009	180	−0.05	0.02	0.029	101	−0.09	0.02	0.007	28	−0.05	0.05	0.423	746	−0.05	0.01	<0.001

Diff, difference from baseline; PP, pulse pressure.

subgroup (Table 2). For this subgroup, there was a reduction in both mean SBP and DBP, particularly in the first months of the study period (Fig. 1). The largest reduction was observed for SBP which decreased by an average of 13.8 mmHg over 360 days of treatment of which a considerable proportion [mean (SE) change −6.5 (0.143) mmHg] occurred already in the period between baseline and initial assessment (Table 2, Supplementary Table S1, Supplemental Digital Content 1, http://links.lww.com/BPMJ/A184). After Day 180, the values were largely stabilized with SBP in the range of 121–123 mmHg (Fig. 1, Supplementary Table S1, Supplemental Digital Content 1, http://links.lww.com/BPMJ/A184).

The decrease in DBP reached 8.0 mmHg at Day 360 (Table 2). The large reduction in SBP over time resulted in a concomitant lowering of PP and was also reflected by a considerable increase, from 0 to 48%, in the proportion of patients reaching controlled SBP after 360 days (Table 2).

In contrast to the high SBP subgroup, the low SBP subgroup showed an increase in both SBP and DBP over time, particularly in the first months of the study (Fig. 1). After Day 180, the mean SBP stabilized at around 121–123 mmHg for this group (Fig. 1, Supplementary Table S1, Supplemental Digital Content 1, http://links.lww.com/BPMJ/A184), and after 360 days of treatment, mean SBP and DBP had increased by 13.4 and 6.7 mmHg, respectively (Table 2). As a result of the raised SBP in the low SBP subgroup, the proportion of patients with controlled SBP increased from 0 to 74% after 360 days from baseline.

A small increase in mean SBP and DBP was also observed in the first months from baseline for the optimal SBP subgroup, and after 180 days, the SBP stabilized in the range of 125–126 mmHg. At day 360, SBP and DBP showed a mean increase of 5.3 and 2.3 mmHg, respectively. For the suboptimal group, mean SBP and DBP remained relatively stable over the 540-day period with SBP-values in the range of 129–130 mmHg; however, there was a small overall decrease of just over 1 mmHg for both SBP and DBP after the 360 days of treatment (Table 2). For the suboptimal and optimal BP subgroups, the percent of patients with controlled BP decreased over the 360-day treatment period by 30 and 24%, respectively.

Exploratory subgroups showed overall similar results as the main population (Supplementary Tables S3–S10, Supplemental Digital Content 1, http://links.lww.com/BPMJ/A184*)*, and for all subgroups, BP declined continuously with increasing time from baseline. However, a few differences were observed: Mean baseline DBP was lower for patients >65 years old (84 mmHg) compared with those aged <65 years (88 mmHg). Mean baseline DBP was also somewhat lower for patients with pre-diabetes (83 mmHg) compared to those with diabetes (86 mmHg). Moreover, a higher baseline SBP

(142 mmHg) and larger reduction in SBP after 360 days (–7.8 mmHg) was observed for obese patients compared with overweight patients (137/–6.7 mmHg). For patients with high alcohol consumption at baseline, BP was similar to those with low alcohol consumption at baseline (SBP of 139 mmHg and 138 mmHg, respectively) but the decline in BP for uncontrolled patients was higher for those with low alcohol consumption (–14.1 mmHg compared to –13.2 mmHg after 360 days).

Small but significant beneficial changes were also observed for some exploratory outcomes over the 360-day study period; there was an increase in the proportions of patients who were physically active (from 15 to 18%), and reductions were observed for BMI (mean reduction of 0.46 kg/m^2, corresponding to a mean reduction in weight of 1.6%) as well as for the proportions of smokers (from 12 to 7%) and patients with high-stress level (from 37 to 26%) (Table 2, Supplementary Table S2, Supplemental Digital Content 1, http://links.lww.com/BPMJ/A184). Undesirably, the proportion of patients with high alcohol consumption increased from 25 to 29%. Overall, these changes occurred across all SBP-based subgroups and began already in the first months of the study period (Table 2, Supplementary Table S2, Supplemental Digital Content 1, http://links.lww.com/BPMJ/A184). It should be noted that the response rates for exploratory outcomes decreased nearly 10-fold (from approximately 7500 to 750) between baseline and day 360 (Supplementary Table S2, Supplemental Digital Content 1, http://links.lww.com/BPMJ/A184).

Discussion

This is one of the first large studies to evaluate real-world treatment outcomes for an app-based DTx treatment strategy for chronic disease, and it is highly relevant for hypertension patients in Sweden. The combination of active patient engagement, education, and empowerment, continuous monitoring of health data with regular feedback, and early intervention by patient-responsible healthcare providers is a strong care concept that shows the way for future effective digital care models for the treatment of chronic disease. These features enable easily accessible, equal, and resource-efficient care of high quality for our largest patient groups. The study is an extension of an earlier pilot study by Wijkman *et al.* [14] in which 172 prospectively collected subjects were treated with the DTx platform's app-based therapy for hypertension, and which found that BP control improved for both initially hypertensive and hypotensive patients over 90 days. Using non-randomized data for more than 7500 DTx-treated patients followed for up to 540 days, we found significant beneficial effects on BP for patients with different degrees of hypertension (i.e. high and suboptimal BP subgroups) and for patients with hypotension (i.e. low BP subgroup), and these benefits were maintained over time. The effects observed for the high and low SBP subgroups were of considerable magnitudes with a change from baseline in SBP/DBP of –14/8 mmHg and +13/7 after 360 days, respectively. As a comparison, meta-analyses of results from RCTs have demonstrated that a reduction in SBP of 10 mmHg or DBP of 5 mmHg is associated with a reduction in the premature death of 10–15%, stroke of 35%, myocardial infarction of 20%, and heart failure of 40% [9,16–18]. A likely explanation for the long-term beneficial effects observed in this study is that the evaluated DTx provides regular and continuous contact with a caregiver in combination with encouraging patient empowerment. The latter is achieved by education and gamification, which engages patients in their treatment and supports lifestyle improvements and self-care. It should be noted that the intervention, in terms of medical treatment, differs between patient categories; for patients with high BP, medication will be increased to reduce BP, whereas for patients with hypotension, medication will be adjusted to increase BP. Thus, as BP changes for hypertensive and hypotensive patients may cancel each other out in the whole study population, it is more informative to evaluate the effect of the intervention in subgroups defined by baseline BP.

That a large part of the change in BP appeared already in the two weeks between baseline and first assessment may be partially explained by improved compliance to medication and treatment among patients after being onboarded to the DTx platform. Adherence to pharmacotherapy is generally low among hypertension patients and typically reported at <50% one year after treatment initiation [19]. The possibility of informed censoring election effects related to sample attrition was assessed by analyzing complete follow-up data at the end of each period for the base case scenario and found to be small (results available upon request). Moreover, the small increase in BP observed in the first weeks for the optimal SBP subgroup, and the reduction in the proportion of patients with BP control in the optimal and suboptimal subgroups, may be attributable to medical adjustments at the beginning of the treatment period for older patients with BP below the higher recommended target for patients ≥65 years (i.e. SBP of 130–139 mmHg, equivalent to home measured SBP of 125–135 mmHg [9]).

In addition to changes in BP, a selection of exploratory outcomes was evaluated. Although the response rate decreased considerably over time for these outcomes, small but significant beneficial effects were observed for stress level, physical activity, smoking, and BMI. The reduction in BMI corresponding to a decrease in weight of 1.6% may be close to clinical significance considering that improvement in triglycerides and SBP have been found among people with weight loss in the low interval of between 2 and 5% [20]. We also observed a small and unexpected significant increase in the proportion of

patients with high alcohol consumption in the high SBP subgroup. A potential explanation could be less controlled alcohol intake associated with the COVID-19 pandemic that has been observed in high-income countries during the pandemic [21].

Strengths of this real-world study include the large study population and long study period. The results reflect actual clinical practice which often represents a higher heterogeneity with respect to population characteristics, treatment regimens, and patient adherence compared to RCTs [22]. Also, subject retention was generally good, and patients contributed data for all timepoints possible (i.e. no selection based on the requirement for completion of the maximum follow-up time to be included in the study). Moreover, uncertainty in the primary outcomes, SBP and DBP, was reduced by averaging multiple measurements and the use of app-based reporting of SBP values using the validated and CE-labelled Bluetooth-equipped BP monitor with individually adjusted cuff size. Furthermore, subjects were followed at 90-day intervals, which permitted assessment of the robustness of the results over time.

A weakness of the study is the lack of a formal comparator (dictating an uncontrolled change from baseline analytical design) and the associated risk that the results are influenced by confounding factors. For example, the study results may be influenced by regression to the mean because treatment is more likely to be sought after when BP control is poor [23]. However, it should be noted that the patients included in the study were previously diagnosed with high BP and that 79% had received medical treatment before being included in the current study. Despite this, the intervention resulted in significantly improved BP control. Another limitation was the drop in sample size observed at the long-term follow-ups. However, for HBP, this drop related primarily to late-starting patients who had not completed the longer follow-ups at the study end date, whereas the proportion of patients lost to follow-up over the study period was small. Also, minimal differences in mean baseline HBP and changes in HBP were observed between patient groups with data at the different follow-ups which reduces the risk of systematic bias over time (see Supplementary Table S1, and Supplementary Figures S3 and S4, Supplemental Digital Content 1, http://links.lww.com/BPMJ/A184. Another limitation was the loss of laboratory values as endpoints due to the difficulty of collecting sufficient sample numbers during the COVID-19 pandemic. However, it should be noted that particularly important blood sampling (e.g. when adjusting medication) was largely maintained throughout the pandemic. Moreover, the creation of subgroups was based on SBP only, thus ignoring DBP. Although this simplified the interpretation of data and maintained power for the statistical analyses, it may have caused a loss of interesting findings. While not a limitation, the use of HBP measurements potentially limits the accuracy of comparisons with similar studies reporting clinic-based measurements. Additionally, with the available data it was not possible to evaluate changes in medication over time (i.e. increased or decreased medication) as changes in medication occur continuously and can take different forms (e.g. dose adjustment, switching to or from combination therapies, and switching between classes of BP medicine). Finally, generalizability to the full Swedish population is limited by the exclusion of non-Swedish-speaking patients.

The significant reduction in HBP reported in this study was in line with observations from previously published studies of digital HBP monitoring interventions, including the meta-analysis of smartphone applications by Xu *et al.* [12,13,24–26]. The reduction observed for the high SBP subgroup in our study (i.e. 14 mmHg) was on the higher end compared to the range of approximately 2.5–13.0 mmHg reported by previous studies. An important note is the considerable difference between previously published studies in study duration (range: 3–12 months) and mean baseline SBP values (range: <140 to >150 mmHg); larger effects on BP have generally been observed for studies with higher baseline SBP.

Conclusion

Digital remote hypertension monitoring by a virtual individualized online DTx platform was associated with beneficial effects on BP for both hypertensive and hypotensive patients, and these effects were maintained over a long period. The results indicate that the present DTx care model for hypertension could lead to improved real-world BP control.

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M.W., A.N., and P.L. are employees of the Swedish Institute for Health Economics, which provides consulting services for governmental bodies, academic institutions, and commercial life science enterprises (including Blodtrycksdoktorn AB). G.D., M.C., and J.W. are employees and co-owners of Blodtrycksdoktorn AB. M.C. has organized professional meetings and lectured for Lilly, Novo Nordisk, Sanofi, Roche, Novartis, and AstraZeneca. G.D. has served on advisory boards and/or lectured for Novartis and Novo Nordisk.
The data that support the findings of this study and which are not included in the main article or supporting information is available from the authors upon reasonable request.

Conflicts of interest

M.W. is the guarantor of this work and, as such, had full access to all the data in the study, and takes responsibility for the integrity of the data and accuracy of the data analysis. All authors confirm that they meet the International Committee of Medical Journal Editors (ICJME) uniform requirements for authorship and that they have contributed to the critical analysis and interpretation of the data, drafting and/or critically revising the article and sharing in the final responsibility for the content of the article, as well as the decision to submit it for publication. For the remaining authors, there are no conflicts of interest.

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