**ONLINE SUPPLEMENT**

# Efficacy of a digital therapeutics system in the management of essential hypertension: the HERB-DH1 pivotal trial

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## SUPPLEMENTARY FIGURES

**Figure S1.** Individual changes in 24-hour ambulatory systolic blood pressure (BP) from baseline to 12 weeks.

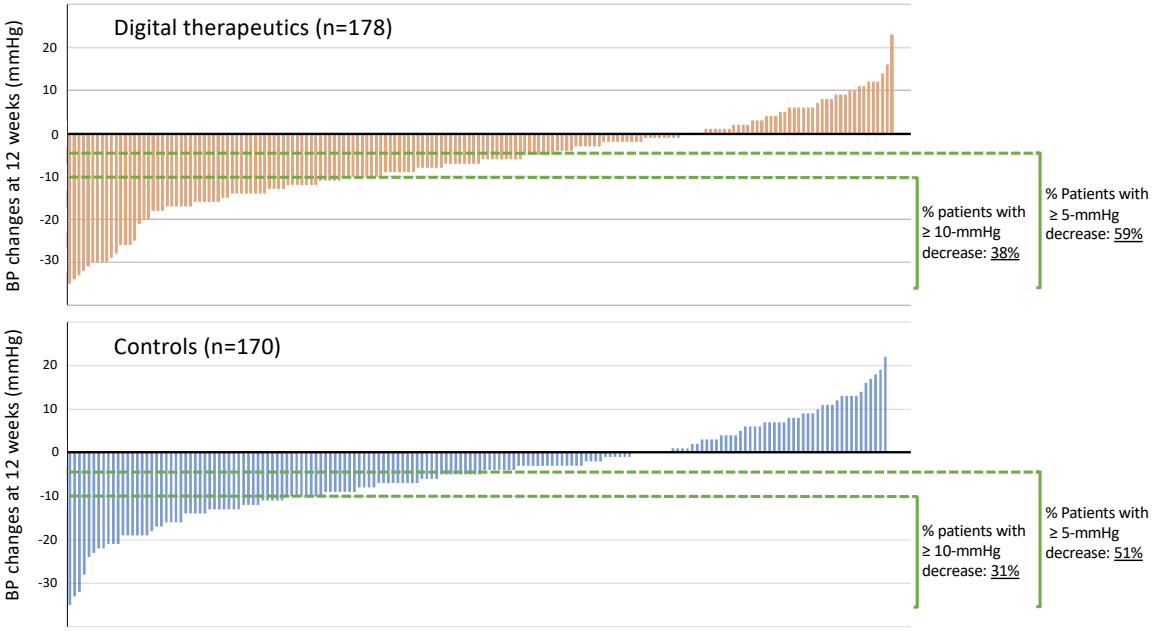



**Figure S2.** Changes from baseline to 12 weeks in 24-hour, daytime and nighttime diastolic blood pressure (DBP) based on ambulatory blood pressure monitoring (ABPM), morning and evening home DBP, and office DBP. Values are reported as mean [95% confidence interval].

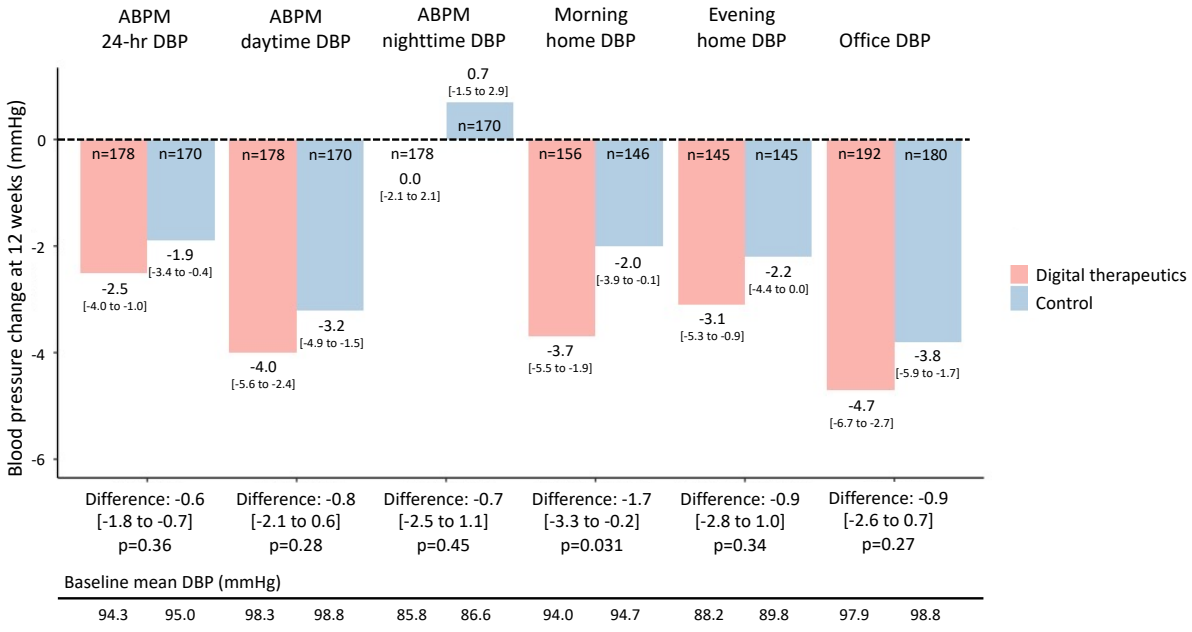


**Figure S3.** Changes from baseline to 12 weeks in 24-hour, daytime and nighttime heart rate (HR) based on ambulatory blood pressure monitoring (ABPM), morning and evening home HR, and office HR. Values are reported as mean [95% confidence interval].

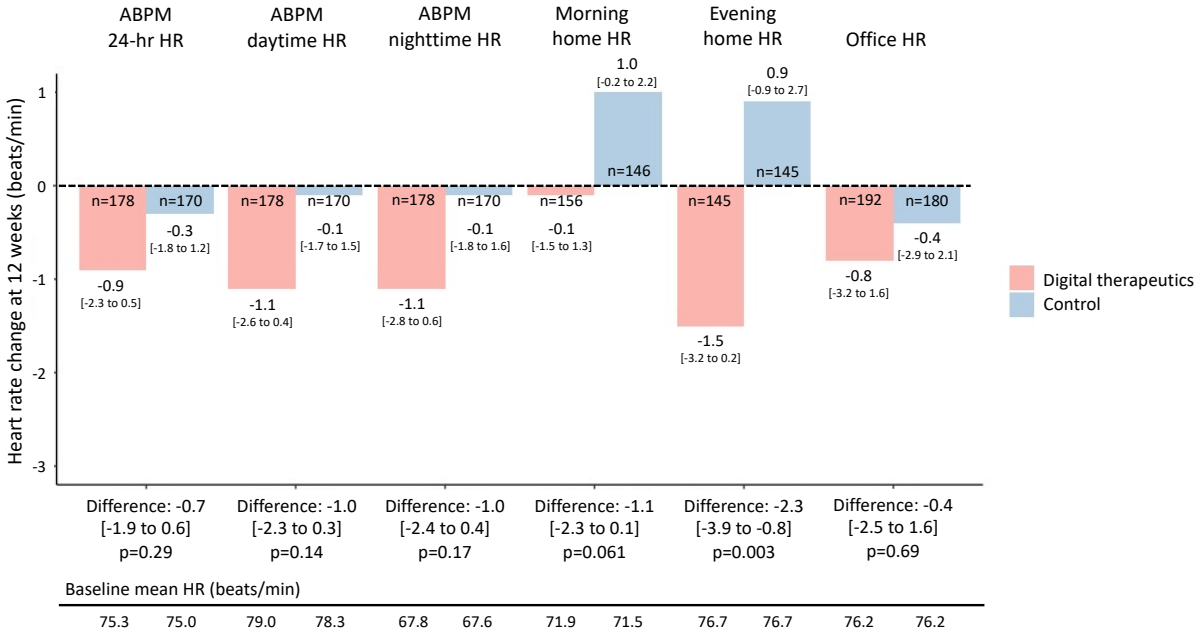
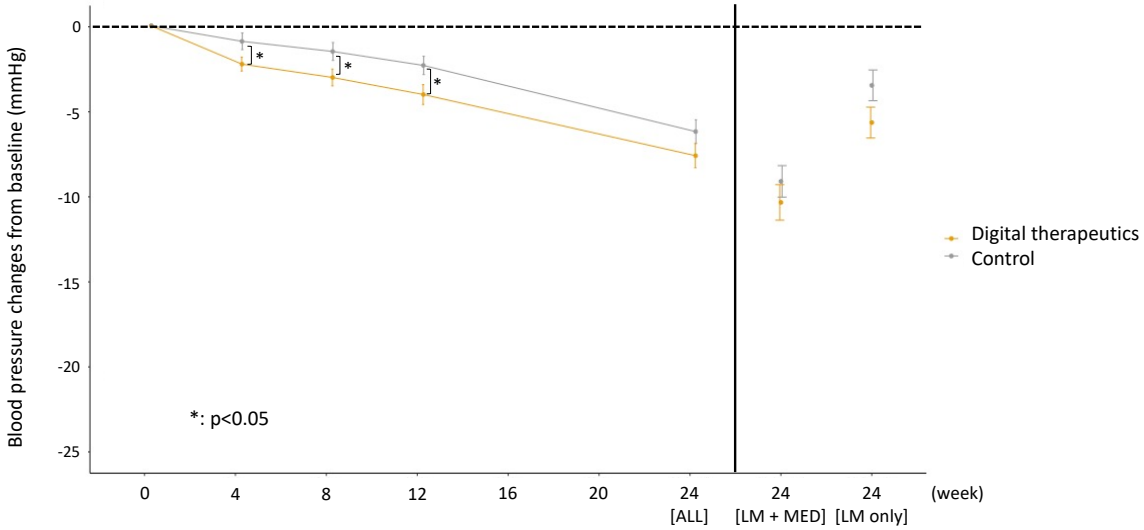


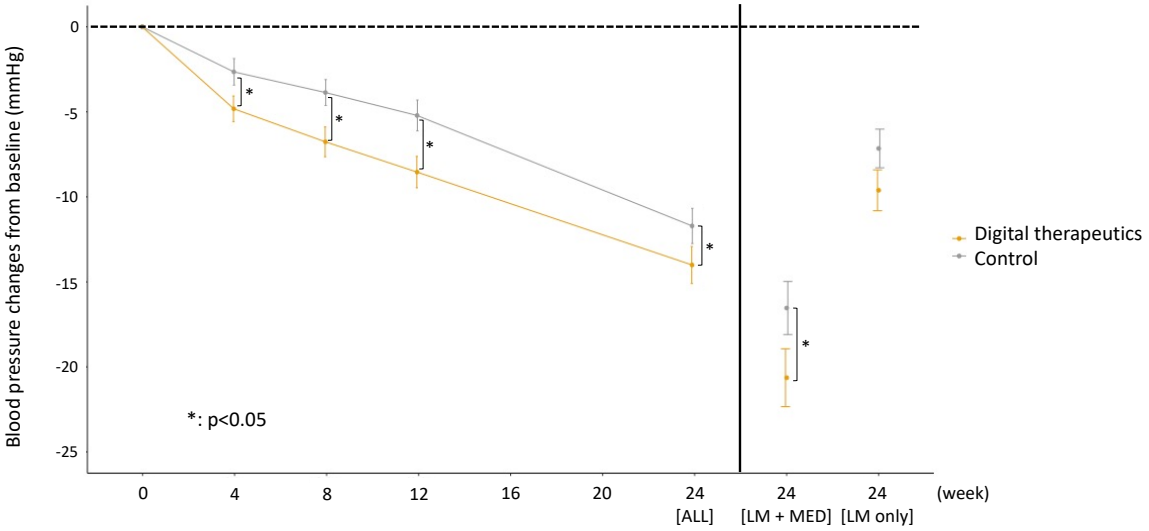

**Figure S4.** Change in morning home diastolic blood pressure (DBP) from baseline to 24 weeks. Values are reported as mean and standard error (bars). p-values are for differences between groups in the change from baseline to each time point using ANCOVA adjusted for study site, previous antihypertensive drug use and baseline systolic blood pressure on ambulatory blood pressure monitoring. LM, guideline-based lifestyle modification; MED, prescribed antihypertensive medications at 12 weeks.




Mean crude morning home diastolic blood pressure (mmHg)

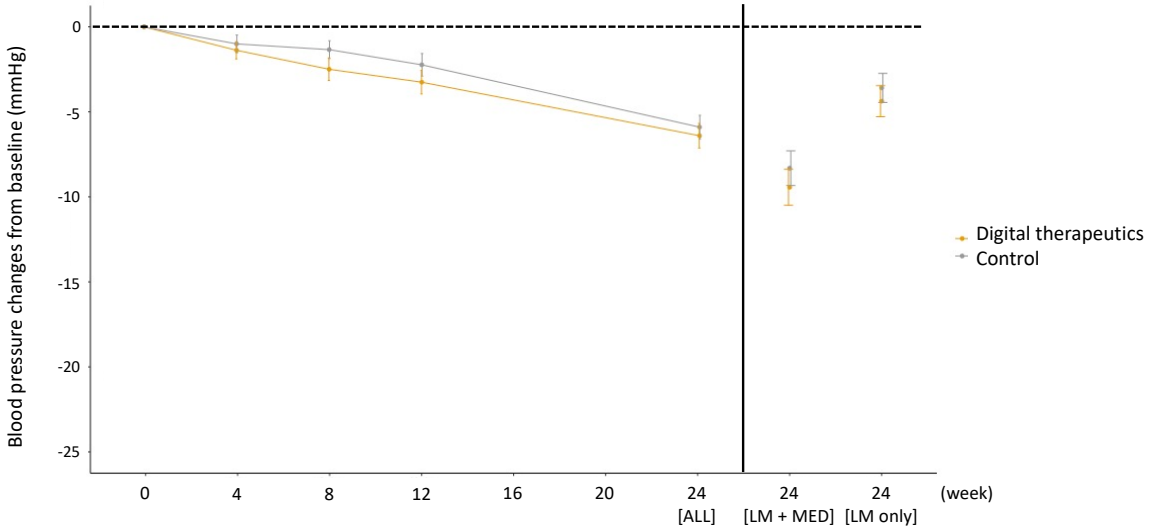
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Digital therapeutics | 94.0 | 91.6 | 90.7 | 89.8 | 86.3 | 86.2 | 86.3 |
| Control | 95.7 | 94.9 | 93.9 | 93.0 | 89.1 | 90.1 | 88.0 |
| p for difference | - | p=0.035 | p=0.033 | p=0.031 | p=0.10 | p=0.26 | p=0.14 |

**Figure S5.** Change in evening home systolic blood pressure (SBP) from baseline to 24 weeks. Values are reported as mean and standard error (bars). p-values are for differences between groups in the change from baseline to each time point using ANCOVA adjusted for study site, previous antihypertensive drug use and baseline SBP on ambulatory blood pressure monitoring. LM, guideline-based lifestyle modification; MED, prescribed antihypertensive medications at 12 weeks.



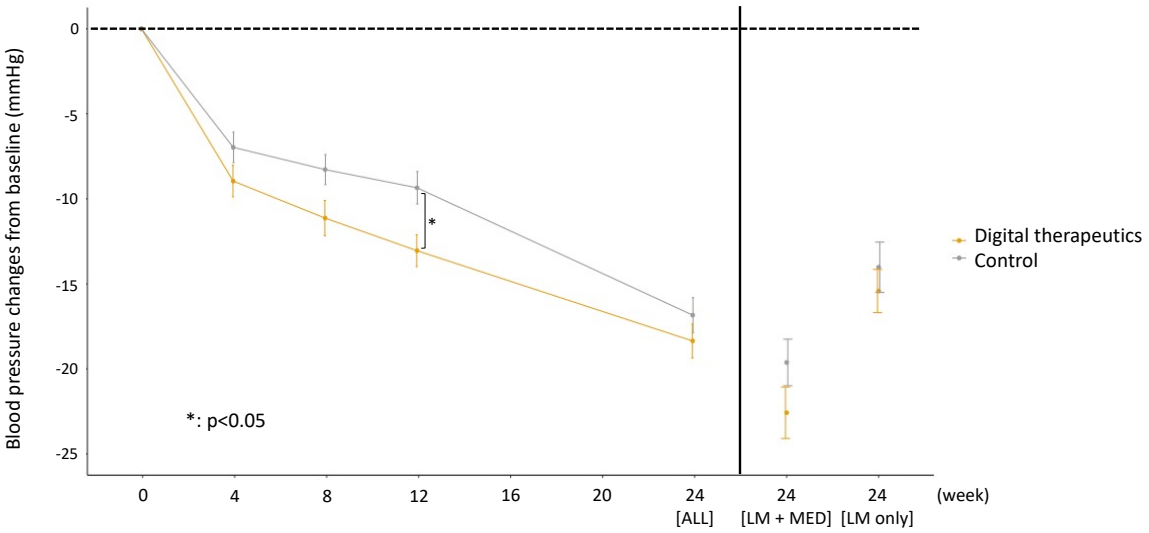

| Mean crude evening home systolic blood pressure (mmHg) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Digital therapeutics | 140.6 | 135.3 | 133.4 | 132.2 | | 126.0 | 124.4 | 127.1 |
| Control | 143.3 | 140.7 | 139.6 | 137.8 | | 130.6 | 131.2 | 129.9 |
| p for difference | - | p=0.028 | p=0.007 | p=0.013 | | p=0.038 | p=0.006 | p=0.24 |

**Figure S6.** Change in evening home diastolic blood pressure (DBP) from baseline to 24 weeks. Values are reported as mean and standard error (bars). p-values are for differences between groups in the change from baseline to each time point using ANCOVA adjusted for study site, previous antihypertensive drug use and baseline systolic blood pressure on ambulatory blood pressure monitoring. LM, guideline-based lifestyle modification; MED, prescribed antihypertensive medications at 12 weeks.



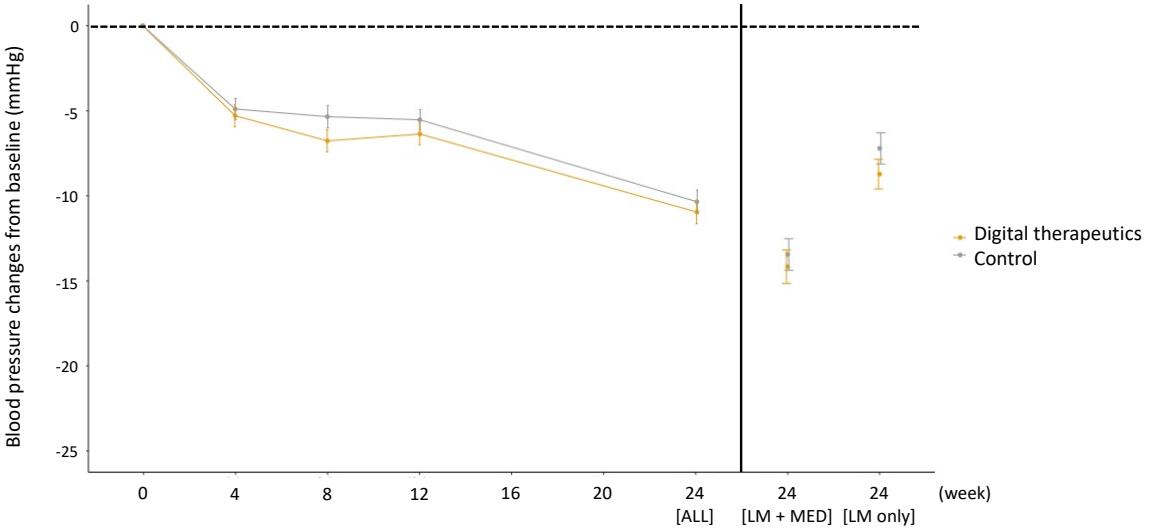

| Mean crude evening home diastolic blood pressure (mmHg) | | | | | | | |
|---|---|---|---|---|---|---|---|
| Digital therapeutics | 88.2 | 86.3 | 85.3 | 84.8 | 86.3 | 80.2 | 82.0 |
| Control | 89.8 | 88.7 | 88.3 | 87.6 | 89.1 | 84.7 | 81.8 |
| p for difference | - | p=0.48 | p=0.18 | p=0.34 | p=0.36 | p=0.12 | p=0.55 |

**Figure S7.** Change in office systolic blood pressure (SBP) from baseline to 24 weeks. Values are reported as mean and standard error (bars). p-values are for differences between groups in the change from baseline to each time point using ANCOVA adjusted for study site, previous antihypertensive drug use and baseline SBP on ambulatory blood pressure monitoring. LM, guideline-based lifestyle modification; MED, prescribed antihypertensive medications at 12 weeks.



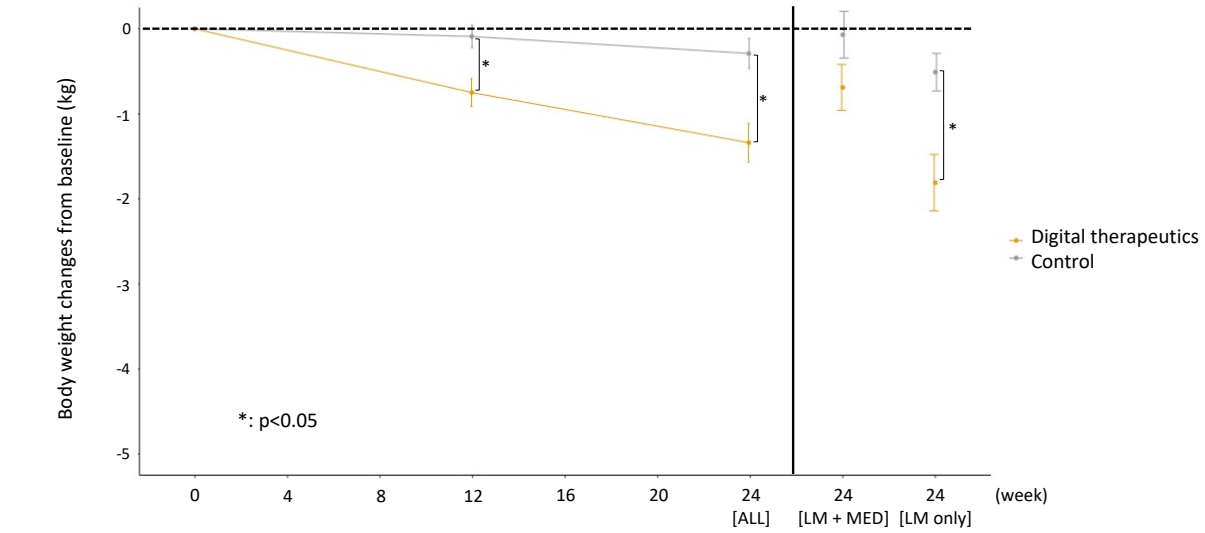

| Mean crude office systolic blood pressure (mmHg) | | | | | | | |
|---|---|---|---|---|---|---|---|
| Digital therapeutics | 153.2 | 143.8 | 141.6 | 140.2 | 134.7 | 131.0 | 137.3 |
| Control | 154.1 | 147.1 | 146.1 | 144.4 | 136.7 | 132.8 | 140.8 |
| p for difference | - | p=0.18 | p=0.063 | p=0.006 | p=0.33 | p=0.15 | p=0.47 |

**Figure S8.** Change in office diastolic blood pressure (DBP) from baseline to 24 weeks. Values are reported as mean and standard error (bars). p-values are for differences between groups in the change from baseline to each time point using ANCOVA adjusted for study site, previous antihypertensive drug use and baseline SBP on ambulatory blood pressure monitoring. LM, guideline-based lifestyle modification; MED, prescribed antihypertensive medications at 12 weeks.



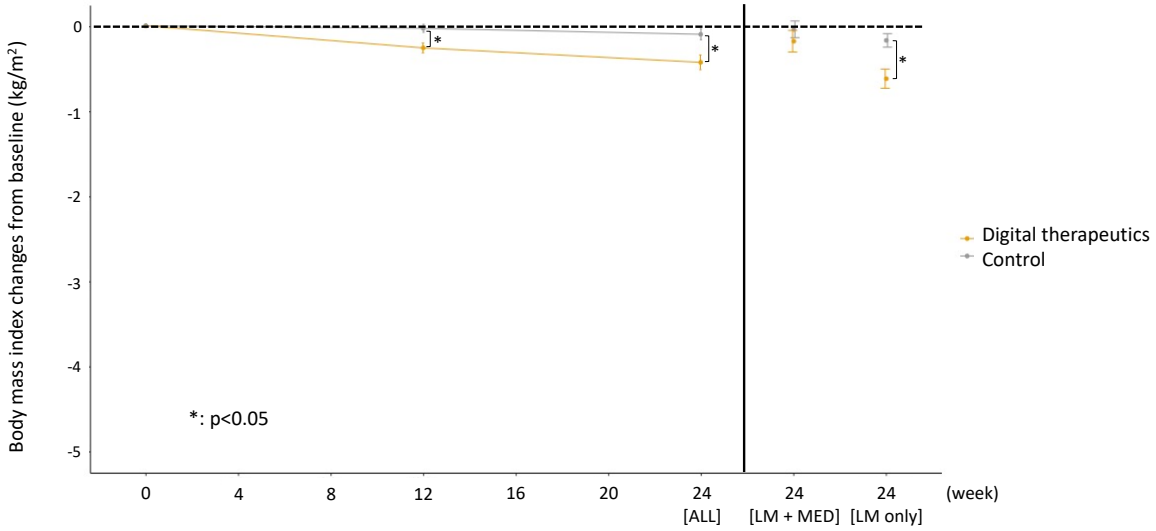

| Mean crude office diastolic blood pressure (mmHg) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Digital therapeutics | 97.9 | 92.6 | 91.5 | 91.6 | | 87.1 | 84.7 | 88.8 |
| Control | 98.8 | 94.0 | 93.6 | 93.0 | | 88.3 | 86.6 | 90.0 |
| p for difference | - | p=0.74 | p=0.13 | p=0.27 | | p=0.41 | p=0.78 | p=0.14 |

**Figure S9.** Change in body weight from baseline to 24 weeks. Values are reported as mean and standard error (bars). p-values are for differences between groups in the change from baseline to each time point using ANCOVA adjusted for study site, previous antihypertensive drug use and baseline systolic blood pressure on ambulatory blood pressure monitoring. LM, guideline-based lifestyle modification; MED, prescribed antihypertensive medications at 12 weeks.



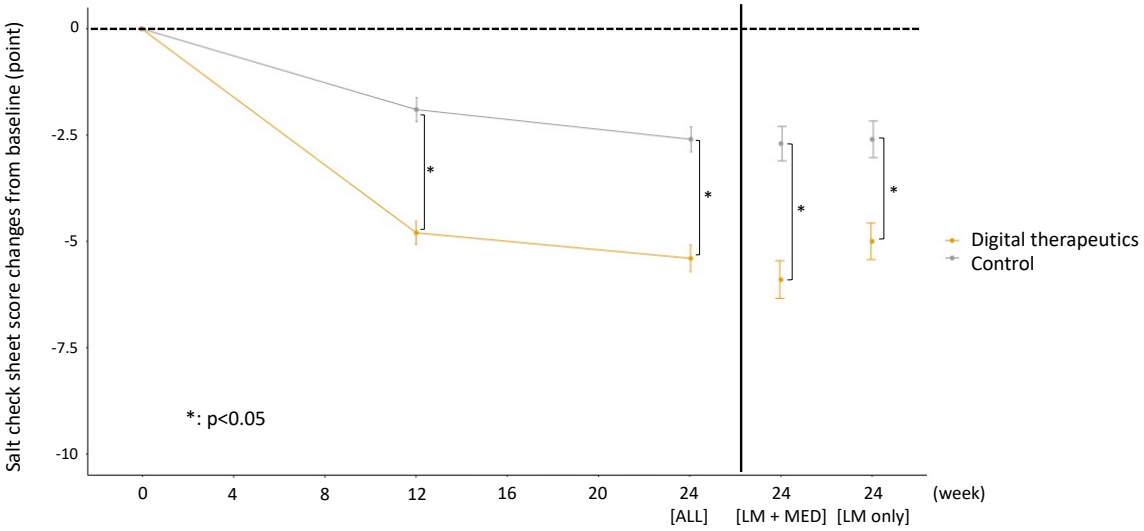

| Mean crude body weight (kg) | | | | | |
|---|---|---|---|---|---|
| Digital therapeutics | 73.3 | 72.5 | 71.9 | 71.9 | 72.0 |
| Control | 73.0 | 73.0 | 72.5 | 74.9 | 70.2 |
| p for difference | - | p=0.003 | P<0.001 | p=0.17 | p=0.014 |

**Figure S10.** Change in body mass index from baseline to 24 weeks. Values are reported as mean and standard error (bars). p-values are for differences between groups in the change from baseline to each time point using ANCOVA adjusted for study site, previous antihypertensive drug use and baseline systolic blood pressure on ambulatory blood pressure monitoring. LM, guideline-based lifestyle modification; MED, prescribed antihypertensive medications at 12 weeks.



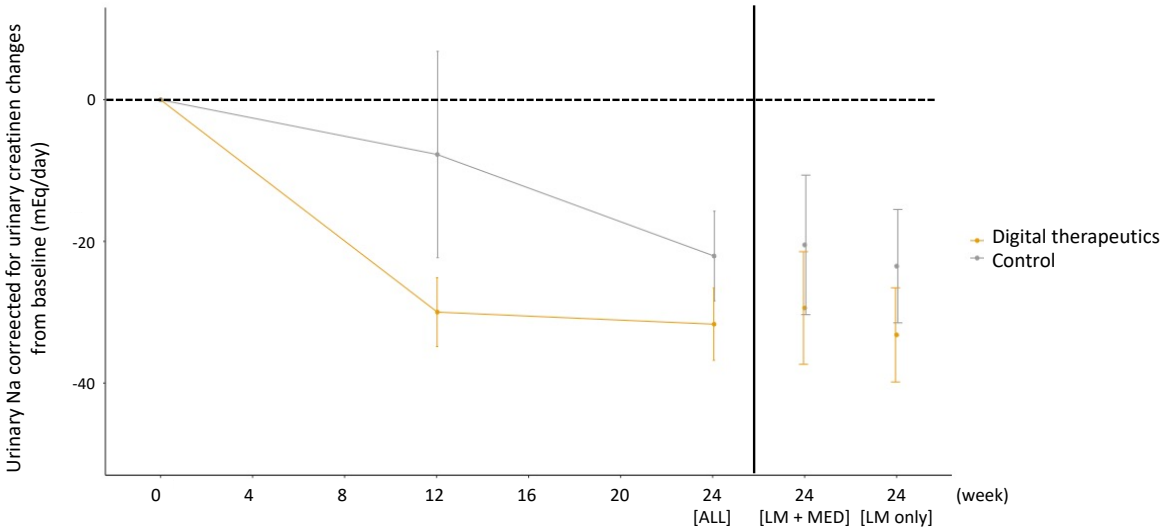

| Mean crude body mass index (kg/m²) | | | | | |
|---|---|---|---|---|---|
| Digital therapeutics | 25.7 | 25.5 | 25.3 | 25.5 | 25.1 |
| Control | 25.8 | 25.7 | 25.6 | 26.1 | 25.1 |
| p for difference | - | p=0.005 | p=0.005 | p=0.52 | p=0.014 |

**Figure S11.** Change in salt intake from baseline to 24 weeks. Values are reported as mean and standard error (bars). p-values are for differences between groups in the change from baseline to each time point using ANCOVA adjusted for study site, previous antihypertensive drug use and baseline systolic blood pressure on ambulatory blood pressure monitoring. LM, guideline-based lifestyle modification; MED, prescribed antihypertensive medications at 12 weeks.



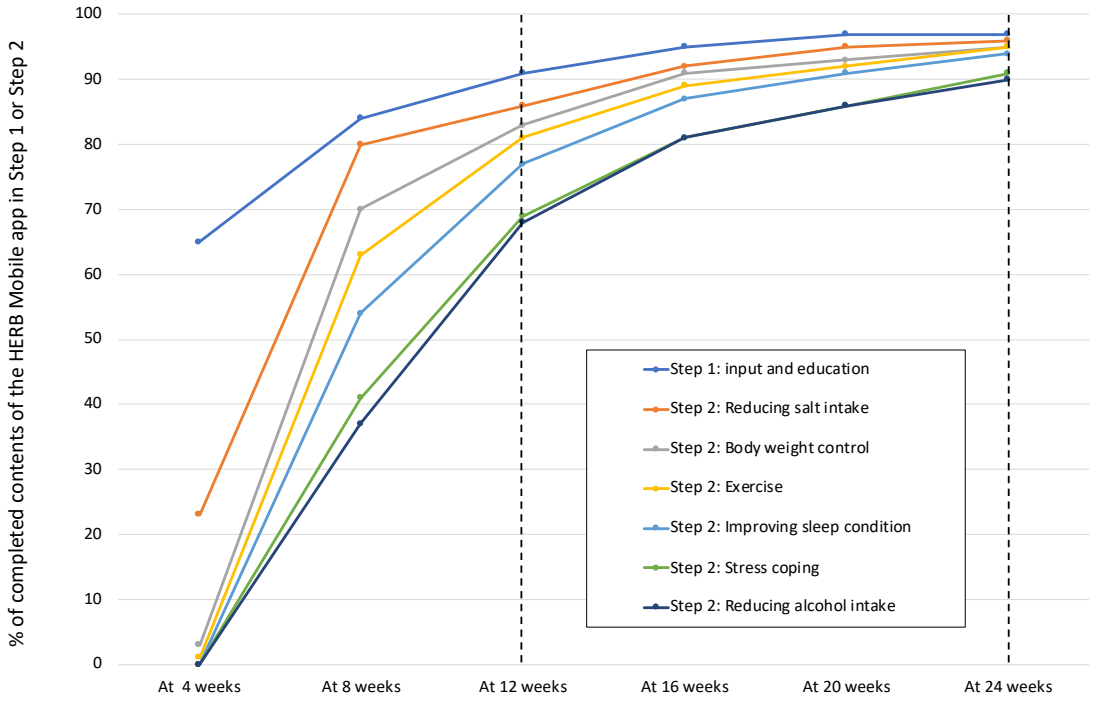

| Mean crude salt check sheet score (point) | | | | | |
|---|---|---|---|---|---|
| Digital therapeutics | 14.5 | 9.7 | 9.1 | 8.8 | 9.4 |
| Control | 14.3 | 12.4 | 11.7 | 11.8 | 11.5 |
| p for difference | - | P<0.001 | P<0.001 | P<0.001 | P<0.001 |

**Figure S12.** Change in urinary sodium corrected for urinary creatinine from baseline to 24 weeks. Urinary creatinine-corrected urinary sodium was calculated as the urinary sodium level divided by the urinary creatinine level. Values are reported as mean and standard error (bars). p-values are for differences between groups in the change from baseline to each time point using ANCOVA adjusted for study site, previous antihypertensive drug use and baseline systolic blood pressure on ambulatory blood pressure monitoring. LM, guideline-based lifestyle modification; MED, prescribed antihypertensive medications at 12 weeks.




| Mean crude urinary Na corrected for urinary creatinine (mEq/day) | | | | | |
|---|---|---|---|---|---|
| Digital therapeutics | 209.0 | 180.7 | 178.6 | 174.9 | 181.2 |
| Control | 210.9 | 205.0 | 188.5 | 191.2 | 185.8 |
| p for difference | - | p=0.16 | p=0.24 | p=0.46 | p=0.37 |

**Figure S13.** Progress of app-supported lifestyle modification. Completion of Step 1 was defined as receiving all 14 interactive education chapters, and completion of Step 2 was defined as the app user having successfully experienced and achieved three consecutive recommended goals in each category.



# SUPPLEMENTARY TABLES

**Table S1.** (**A**) Research organization and roles (each team and committee was independently organised and responsible for their own work. (**B**) Study sites, principal investigators (PI) and center personnel.

**A**

| Role | Investigators and personnel | Institute |
|---|---|---|
| **Steering Committee** | | |
| Chairman, Coordinating investigator | Kazuomi Kario MD, PhD | Jichi Medical University, Tochigi |
| Medical expert | Akihiro Nomura, MD, PhD | Kanazawa University, Kanazawa |
| Coordinator | Noriko Harada, BE | Jichi Medical University, Tochigi |
| ,Coordinator | Ayako Okura, BA | Jichi Medical University, Tochigi |
| **Biostatistical Committee** | | |
| Director of biostatistical analysis | Eisuke Hida, PhD | Osaka University, Osaka |
| Biostatistical analysis | Kunitake Komatsu, BSc | Intage Healthcare Inc., Tokyo |
| Data management | Ryoichi Muraoka, DVM | Intage Healthcare Inc., Tokyo |
| **Clinical Trial Management** | | |
| Assignment manager | Ryoichi Muraoka, DVM | Intage Healthcare Inc., Tokyo |
| Manager, Contact for public queries | Kiyose Nakagawa, MPharm | CureApp, Inc., Tokyo |
| Safety information management | Katsunori Sakai, BSc | CureApp, Inc., Tokyo |
| Medical expert | Tomoyuki Tanigawa, MD, MPH | CureApp, Inc., Tokyo |
| **Data Safety Monitoring Board** | | |
| Monitoring | Wataru Muto, BPharm | Intage Healthcare Inc., Tokyo |
| Audit | Susumu Kato, MPharm | Intage Healthcare Inc., Tokyo |
| **Clinical trial sponsor** | Kota Satake, MD, MBA, MPH | CureApp, Inc., Tokyo |

**B**

| Site, prefecture | Investigators and personnel |
|---|---|
| Hatori Clinic, Kanagawa | PI: Yutaka Hatori |
| Jichi Medical University Hospital, Tochigi | PI: Kazuomi Kario |
| Kita Shin-yokohama Internal Medicine Clinic, Kanagawa | PI: Uguri Kamiya |
| Kyosokai AMC NISHI-UMEDA Clinic, Osaka | PI: Yoshimitsu Yamasaki |
| Maekawa Medical Clinic, Kanagawa | PI: Hiromitsu Maekawa |
| Medical corporation Shirayurikai Swing Nozaki Clinic, Tokyo | PI: Minoru Nozaki |
| Sasaki Clinic, Hyogo | PI: Ryotaro Sasaki |
| Shimokitazawa Tomo Clinic, Tokyo | PI: Tomofumi Murakami |
| Sone Clinic Shinjuku, Tokyo | PI: Masayoshi Sone |
| Tokyo Center Clinic, Tokyo | PI: Hirotaka Nagashima |
| Tokyo-Eki Center-building Clinic, Tokyo | PI: Arihiro Kiyosue |
| Yotsuya Internal Medicine Clinic, Tokyo | PI: Takahiro Yokoyama |

**Table S2.** List of prescribed medications at 3 months after registration.

| Prescribed medications, n (%) | Control (n=180) | Digital therapeutics (n=192) |
|---|---|---|
| Prescribed antihypertensive drugs | 87 (48.3) | 78 (40.6) |
| Calcium channel blocker | 74 (41.1) | 68 (35.4) |
| Angiotensin-2 receptor blocker | 22 (12.2) | 12 (6.3) |
| Diuretics | 2 (1.1) | 2 (1.0) |

**Table S3.** Differences in change from baseline to 12 and 24 weeks between the digital therapeutics and control groups in 24-hour systolic and diastolic blood pressure (mmHg), and 24-hour heart rate (beats/min) based on ambulatory blood pressure monitoring.

| At 12 weeks | | | | At 24 weeks | | | |
|---|---|---|---|---|---|---|---|
| | Difference | 95% CI | p-value | Medication-use evaluation at 12 weeks | Difference | 95% CI | p-value |
| **24-hour SBP** | –2.4 | –4.5 to 0.3 | 0.024 | All | –1.8 | –4.1 to 0.5 | 0.12 |
| | | | | Lifestyle modification and medication | –3.2 | –6.8 to 0.4 | 0.085 |
| | | | | Lifestyle modification only | –1.4 | –4.4 to 1.5 | 0.33 |
| **24-hour DBP** | –0.6 | –1.8 to 0.7 | 0.36 | All | –1.0 | –2.4 to 0.4 | 0.17 |
| | | | | Lifestyle modification and medication | –1.6 | –4.0 to 0.7 | 0.17 |
| | | | | Lifestyle modification only | –1.0 | –2.8 to 0.7 | 0.25 |
| **24-hour HR** | –0.7 | –1.9 to 0.6 | 0.29 | All | –0.9 | –2.2 to 0.4 | 0.19 |
| | | | | Lifestyle modification and medication | 1.0 | –1.0 to 3.0 | 0.31 |
| | | | | Lifestyle modification only | –2.1 | –3.9 to –0.4 | 0.019 |

CI, confidence interval; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

**Table S4.** Differences in change from baseline to 12 and 24 weeks between the digital therapeutics and control groups in home systolic and diastolic blood pressure (mmHg), and heart rate (beats/min).

| At 12 weeks | | | | At 24 weeks | | | |
|---|---|---|---|---|---|---|---|
| | **Difference** | **95% CI** | **p-value** | **Medication-use evaluation at 12 weeks** | **Difference** | **95% CI** | **p-value** |
| **Morning home SBP** | –4.3 | –6.7 to –1.9 | <0.001 | All | –4.9 | –7.8 to –2.0 | 0.001 |
| | | | | Lifestyle modification and medication | –7.3 | –11.4 to –3.1 | <0.001 |
| | | | | Lifestyle modification only | –3.7 | –7.7 to 0.3 | 0.067 |
| **Morning home DBP** | –1.7 | –3.3 to –0.2 | 0.031 | All | –1.6 | –3.6 to 0.3 | 0.10 |
| | | | | Lifestyle modification and medication | –1.6 | –4.4 to 1.2 | 0.26 |
| | | | | Lifestyle modification only | –1.9 | –4.5 to 0.6 | 0.14 |
| **Morning home HR** | –1.1 | –2.3 to 0.1 | 0.061 | All | –1.6 | –2.9 to –0.2 | 0.023 |
| | | | | Lifestyle modification and medication | –0.8 | –2.7 to 1.2 | 0.42 |
| | | | | Lifestyle modification only | –1.8 | –3.7 to 0.1 | 0.065 |
| **Evening home SBP** | –3.3 | –5.8 to –0.7 | 0.013 | All | –3.0 | –5.8 to –0.2 | 0.038 |
| | | | | Lifestyle modification and medication | –6.6 | –11.2 to –2.0 | 0.006 |
| | | | | Lifestyle modification only | –2.1 | –5.5 to 1.4 | 0.24 |
| **Evening home DBP** | –0.9 | –2.8 to 1.0 | 0.34 | All | –0.9 | –2.9 to 1.1 | 0.36 |
| | | | | Lifestyle modification and medication | –2.4 | –5.5 to 0.6 | 0.12 |
| | | | | Lifestyle modification only | –0.8 | –3.4 to 1.8 | 0.55 |
| **Evening home HR** | –2.3 | –3.9 to –0.8 | 0.003 | All | –2.3 | –4.1 to –0.6 | 0.010 |
| | | | | Lifestyle modification and medication | –1.9 | –4.5 to 0.8 | 0.16 |
| | | | | Lifestyle modification only | –2.1 | –4.7 to 0.4 | 0.10 |

CI, confidence interval; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

**Table S5.** Differences in change from baseline to 12 and 24 weeks between the digital therapeutics and control groups in office systolic and diastolic blood pressure (mmHg), and heart rate (beats/min).

| At 12 weeks | | | | At 24 weeks | | | |
|---|---|---|---|---|---|---|---|
| | **Difference** | **95% CI** | **p-value** | **Medication-use evaluation at 12 weeks** | **Difference** | **95% CI** | **p-value** |
| **Office SBP** | –3.6 | –6.2 to –1.0 | 0.006 | All | –1.4 | –4.1 to 1.4 | 0.33 |
| | | | | Lifestyle modification and medication | –2.9 | –6.9 to 1.0 | 0.15 |
| | | | | Lifestyle modification only | –1.4 | –5.3 to 2.4 | 0.47 |
| **Office DBP** | –0.9 | –2.6 to 0.7 | 0.27 | All | –0.7 | –2.5 to 1.0 | 0.41 |
| | | | | Lifestyle modification and medication | –0.4 | –2.9 to 2.2 | 0.78 |
| | | | | Lifestyle modification only | –1.8 | –4.2 to 0.6 | 0.14 |
| **Office HR** | –0.4 | –2.5 to 1.6 | 0.69 | All | –0.1 | –2.2 to 1.9 | 0.91 |
| | | | | Lifestyle modification and medication | 0.1 | –3.2 to 3.4 | 0.95 |
| | | | | Lifestyle modification only | –0.6 | –3.3 to 2.0 | 0.63 |

CI, confidence interval; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

**Table S6.** Proportion of patients achieving target BP control criteria at 12 and 24 weeks.

| **% Patients** | **At 12 weeks** | | **At 24 weeks** | | |
|---|---|---|---|---|---|
| | **Digital therapeutics** | **Controls** | **Medication-use evaluation at 12 weeks** | **Digital therapeutics** | **Controls** |
| **>5 mmHg decrease in ambulatory BP from baseline** | 59.0% | 50.6% | All | 72.2% | 66.3% |
| | | | Lifestyle modification and medication | 82.9% | 82.9% |
| | | | Lifestyle modification only | 65.1% | 51.2% |
| **Morning home BP <135/85 mmHg** | 22.2% | 10.4% | All | 35.1% | 19.0% |
| | | | Lifestyle modification and medication | 37.7% | 17.9% |
| | | | Lifestyle modification only | 33.3% | 20.3% |

**Table S7.** Changes in obesity-related metabolic risk factors and measures of fatty liver from baseline to 24 weeks in the digital therapeutics (DTx) and control groups.

| | | Baseline | 12 weeks | 24 weeks | | |
|---|---|---|---|---|---|---|
| | | | | All | LM + MED | LM only |
| Total cholesterol (mg/dL) | DTx | 213.9 ± 37.5 | 217.3 ± 37.0 | 215.1 ± 34.6 | 217.6 ± 35.7 | 213.3 ± 33.8 |
| | Control | 213.8 ± 33.5 | 218.0 ± 36.7 | 214.4 ± 33.4 | 211.6 ± 33.3 | 217.3 ± 33.5 |
| | p for difference | - | 0.81 | 0.64 | 0.46 | 0.37 |
| Triglycerides (mg/dL) | DTx | 137.0 ± 107 | 150.2 ± 110 | 144.0 ± 120 | 149.9 ± 106 | 139.8 ± 123 |
| | Control | 131.5 ± 102 | 156.0 ± 160 | 139.7 ± 92.2 | 140.70 ± 93.4 | 138.60 ± 91.6 |
| | p for difference | - | 0.42 | 0.96 | 0.57 | 0.50 |
| HDL cholesterol (mg/dL) | DTx | 60.3 ± 16 | 59.9 ± 17 | 61.0 ± 18 | 61.4 ± 17 | 60.7 ± 19 |
| | Control | 59.6 ± 15 | 58.7 ± 15 | 58.7 ± 15 | 57.5 ± 13 | 59.8 ± 16 |
| | p for difference | - | 0.88 | 0.43 | 0.13 | 0.09 |
| Fasting plasma glucose (mg/dL) | DTx | 98.0 ± 19 | 96.8 ± 17 | 96.4 ± 14 | 99.7 ± 25 | 95.9 ± 13 |
| | Control | 99.7 ± 23 | 99.8 ± 24 | 101.6 ± 25 | 101.9 ± 29 | 100.8 ± 28 |
| | p for difference | - | 0.45 | 0.045 | 0.31 | 0.02 |
| Uric acid (mg/dL) | DTx | 6.13 ± 1.3 | 6.27 ± 1.3 | 6.13 ± 1.2 | 6.13 ± 1.3 | 6.14 ± 1.2 |
| | Control | 5.99 ± 1.2 | 6.10 ± 1.2 | 6.04 ± 1.2 | 6.25 ± 1.2 | 5.82 ± 1.3 |
| | p for difference | - | 0.63 | 0.70 | 0.79 | 0.73 |
| AST (IU/L) | DTx | 25.3 ± 11 | 24.7 ± 12 | 24.8 ± 12 | 25.8 ± 13 | 24.2 ± 11 |
| | Control | 25.9 ± 12 | 26.1 ± 11 | 27.3 ± 18 | 26.9 ± 12 | 27.7 ± 22 |
| | p for difference | - | 0.72 | 0.30 | 0.63 | 0.39 |
| ALT (IU/L) | DTx | 28.5 ± 21 | 27.4 ± 19 | 27.6 ± 21 | 31.2 ± 23 | 25.1 ± 19 |
| | Control | 28.4 ± 18 | 29.5 ± 20 | 31.6 ± 24 | 33.4 ± 24 | 29.7 ± 24 |
| | p for difference | - | 0.72 | 0.30 | 0.63 | 0.39 |
| γ-GTP (IU/L) | DTx | 46.5 ± 45 | 46.7 ± 50 | 47.2 ± 57 | 57.3 ± 77 | 40.2 ± 35 |
| | Control | 53.0 ± 72 | 54.9 ± 85 | 56.0 ± 71 | 60.1 ± 86 | 51.8 ± 52 |
| | p for difference | - | 0.47 | 0.46 | 0.41 | 0.21 |

Values are mean ± standard deviation.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GTP, gamma-glutamyl transpeptidase; HDL, high-density lipoprotein; LM, lifestyle modification; MED, medication.

**Table S8.** Baseline characteristics in patient subgroups based on baseline 24-hour ambulatory SBP (≥145 versus <145 mmHg); p-values were calculated using unpaired *t*-test for continuous variables and Chi-square test for categorical variables.

| | **Baseline 24-hour ambulatory SBP** | | |
|---|---|---|---|
| | **<145 mmHg (n=213)** | **≥145 mmHg (n=177)** | **p-value** |
| Age, years | 51.7 ± 8.6 | 52.7 ± 6.7 | 0.21 |
| Male, n (%) | 170 (80%) | 142 (80%) | 0.92 |
| Body mass index, kg/m$^2$ | 25.0 ± 3.7 | 26.6 ± 4.2 | <0.0001 |
| Waist circumference, cm | 87.5 ± 10 | 91.0 ± 11 | 0.0012 |
| Current smoking, n (%) | 28 (13%) | 34 (19%) | 0.10 |
| Previous antihypertensive drug treatment, n (%) | 22 (10%) | 35 (20%) | 0.0086 |
| Comorbidities, n (%) | | | |
| Dyslipidaemia | 102 (48%) | 93 (53%) | 0.36 |
| Diabetes | 13 (6%) | 13 (7%) | 0.62 |
| Proteinuria | 11 (5%) | 16 (9%) | 0.13 |
| Non-valvular atrial fibrillation | 1 (1%) | 2 (1%) | 0.46 |
| Blood pressure, mmHg | | | |
| 24-hour ambulatory SBP | 136.8 ± 4.3 | 153.9 ± 7.6 | <0.0001 |
| 24-hour ambulatory DBP | 90.8 ± 5.9 | 99.2 ± 7.0 | <0.0001 |
| Morning home SBP | 142.8 ± 11 | 154.9 ± 12 | <0.0001 |
| Morning home DBP | 92.3 ± 7.8 | 98.0 ± 10 | <0.0001 |
| Evening home SBP | 136.7 ± 12 | 148.9 ± 13 | <0.0001 |
| Evening home DBP | 87.0 ± 9.5 | 91.5 ± 11 | <0.0001 |
| Office SBP | 151.4 ± 9.7 | 156.4 ± 10 | <0.0001 |
| Office DBP | 97.2 ± 7.3 | 99.7 ± 6.6 | 0.0007 |

DBP, diastolic blood pressure; SBP, systolic blood pressure.

**Table S9.** Morning and evening home blood pressure (BP) measurement rates in the digital therapeutics and control groups. Home BP measurement rate was calculated as the number patients with successful home BP monitoring for ≥5 days in the week (7 days) immediately prior to a study visit divided by the number of patients completed their follow-up at each visit.

| | Baseline | 4 weeks | 8 weeks | 12 weeks | 24 weeks | | |
|---|---|---|---|---|---|---|---|
| | | | | | All | LM + MED | LM only |
| **Digital therapeutics group** | | | | | | | |
| N completed follow-up at each visit | 199 | 197 | 196 | 192 | 191 | 78 | 113 |
| N with morning BP measured | 167 | 187 | 191 | 187 | 181 | 76 | 105 |
| Morning BP measurement rates (%) | 83.9 | 94.9 | 97.4 | 97.4 | 94.8 | 97.4 | 92.9 |
| N with evening BP measured | 160 | 181 | 180 | 180 | 171 | 70 | 101 |
| Evening BP measurement rates (%) | 80.4 | 91.9 | 91.8 | 93.8 | 89.5 | 89.7 | 89.4 |
| **Control group** | | | | | | | |
| N completed follow-up at each visit | 191 | 190 | 186 | 180 | 175 | 87 | 88 |
| N with morning BP measured | 158 | 170 | 177 | 178 | 168 | 85 | 83 |
| Morning BP measurement rates (%) | 82.7 | 89.5 | 95.2 | 98.9 | 96.0 | 97.7 | 94.3 |
| N with evening BP measured | 159 | 162 | 172 | 174 | 166 | 85 | 81 |
| Evening BP measurement rates (%) | 83.2 | 85.3 | 92.5 | 96.7 | 94.9 | 97.7 | 92.0 |

LM, lifestyle modification; MED, medication.

**Table S10.** Safety outcomes and adverse events by patients during the trial period.

| **Patients (%)** | **Control (n=194)** | **Digital therapeutics (n=200)** |
|---|---|---|
| Patients with any adverse event | 54 (27.8%) | 91 (45.5%) |
| Haematological or lymphatic | 0 (0%) | 1 (0.5%) |
| Anaemia | 0 | 1 |
| Cardiovascular | 0 (0%) | 2 (1.0%) |
| Angina | 0 | 1 |
| Cardiovascular disease | 0 | 1 |
| Ophthalmologic | 2 (1.0%) | 1 (0.5%) |
| Chalazion | 0 | 1 |
| Conjunctival bleeding | 1 | 0 |
| Visual impairment | 1 | 0 |
| Gastrointestinal | 9 (4.6%) | 21 (10.5%) |
| Abdominal distention | 0 | 1 |
| Abdominal pain | 1 | 5 |
| Upper abdominal pain | 1 | 3 |
| Constipation | 0 | 1 |
| Caries | 1 | 1 |
| Diarrhoea | 1 | 9 |
| Gastritis | 1 | 0 |
| Gastro-oesophageal reflux | 1 | 1 |
| Bloody stool | 0 | 1 |
| Haemorrhoid | 1 | 0 |
| Oral ulcer | 0 | 1 |
| Impaired dental development | 1 | 0 |
| Dental pain | 1 | 2 |
| Vomiting | 0 | 1 |
| General | 1 (0.5%) | 8 (4.0%) |
| Powerlessness | 1 | 0 |
| Chest pain | 0 | 1 |
| Exhaustion | 0 | 2 |
| Fatigue | 0 | 4 |
| Fever | 0 | 4 |
| Hepatobiliary | 4 (2.1%) | 3 (1.5%) |
| Elevated hepatic enzyme levels | 3 | 3 |
| Fatty liver | 1 | 0 |
| Immunological | 0 (0%) | 2 (1.0%) |
| Anaphylactic reaction | 0 | 1 |
| Seasonal allergy | 0 | 1 |
| Infectious diseases | 15 (7.7%) | 33 (16.5%) |

| | | |
|---|---|---|
| Cellulitis | 0 | 1 |
| Cystitis | 0 | 1 |
| Gastroenteritis | 1 | 2 |
| Viral gastroenteritis | 0 | 1 |
| Gingivitis | 2 | 0 |
| Shingles | 1 | 0 |
| Hordeolum | 1 | 0 |
| Influenza virus infection | 1 | 0 |
| Nasopharyngitis | 6 | 24 |
| Periodontitis | 0 | 2 |
| Pharyngitis | 2 | 2 |
| Rhinitis | 1 | 1 |
| Sinusitis | 1 | 0 |
| Dental infection | 0 | 1 |
| Injuries | 3 (1.5%) | 12 (6.0%) |
| Arthropod bite | 0 | 2 |
| Leg bone fracture | 1 | 1 |
| Skin damage | 0 | 1 |
| Sprain | 1 | 1 |
| Bruise | 1 | 2 |
| Scratch | 1 | 0 |
| Heatstroke | 0 | 4 |
| Foreign body in airway | 0 | 1 |
| Laboratory data | 1 (0.5%) | 5 (2.5%) |
| Aspartate aminotransferase elevation | 0 | 1 |
| Gamma glutamyl-transferase elevation | 0 | 1 |
| Positive for urine glucose | 0 | 1 |
| Positive for occult haematuria | 0 | 1 |
| White blood cell count elevation | 0 | 1 |
| Hepatic enzyme elevation | 1 | 0 |
| Metabolic | 6 (3.1%) | 7 (3.5%) |
| Diabetes | 1 | 1 |
| Gout | 1 | 2 |
| Hyperuricaemia | 1 | 3 |
| Dyslipidaemia | 2 | 0 |
| Hyperlipidaemia | 1 | 1 |
| Musculoskeletal | 8 (4.1%) | 28 (14.0%) |
| Joint pain | 0 | 7 |
| Arthritis | 0 | 1 |
| Back pain | 2 | 10 |

| | | |
|---|---|---|
| Fasciitis | 0 | 1 |
| Joint effusion | 1 | 0 |
| Cramp | 1 | 1 |
| Musculoskeletal pain | 0 | 1 |
| Myalgia | 2 | 7 |
| Neck pain | 0 | 1 |
| Nodal osteoarthritis | 0 | 1 |
| Osteoarthritis | 0 | 1 |
| Limb pain | 1 | 1 |
| Arthritis deformans | 0 | 1 |
| Snapping finger | 0 | 1 |
| Fibromyalgia | 1 | 0 |
| Myofascial pain syndrome | 0 | 1 |
| Neoplasms | 1 (0.5%) | 1 (0.5%) |
| Lymphoma | 1 | 0 |
| Skin papilloma | 0 | 1 |
| Neurological | 6 (3.1%) | 21 (10.5%) |
| Dizziness | 3 | 2 |
| Dysgeusia | 1 | 0 |
| Head discomfort | 1 | 1 |
| Headache | 3 | 16 |
| Intracranial aneurysm | 1 | 0 |
| Migraine | 0 | 3 |
| Presyncope | 0 | 1 |
| Renal and urinary tract | 2 (1.0%) | 1 (0.5%) |
| Haematuria | 1 | 0 |
| Renal dysfunction | 1 | 1 |
| Genital | 2 (1.0%) | 3 (1.5%) |
| Dysmenorrhoea | 1 | 3 |
| Prostatitis | 1 | 0 |
| Respiratory | 3 (1.5%) | 4 (2.0%) |
| Asthma | 1 | 0 |
| Cough | 2 | 1 |
| Voice impairment | 1 | 0 |
| Dyspnoea | 0 | 1 |
| Pulmonary embolism | 0 | 1 |
| Upper respiratory tract inflammation | 0 | 1 |
| Oropharyngeal pain | 1 | 1 |
| Skin | 4 (2.1%) | 12 (6.0%) |
| Blister | 0 | 1 |

| | | |
|---|---|---|
| Dermatocyst | 0 | 1 |
| Dermatitis | 0 | 1 |
| Allergic dermatitis | 1 | 0 |
| Contact dermatitis | 2 | 2 |
| Eczema | 0 | 1 |
| Miliaria | 0 | 1 |
| Pityriasis rosea | 0 | 1 |
| Pruritus | 2 | 1 |
| Skin rush | 0 | 2 |
| Hives | 0 | 1 |
| Blood vessels | 1 (0.5%) | 1 (0.5%) |
| Orthostatic hypotension | 1 | 0 |
| Hot flash | 0 | 1 |