Digital Therapeutics in Hypertension: Evidence and Perspectives
Kazuomi Kario, Noriko Harada, Ayako Okura

ABSTRACT: Digital therapeutics refers to the use of evidence-based therapeutic interventions driven by high-quality software programs to treat, manage, or prevent a medical condition. This approach is being increasingly investigated for the management of hypertension, a common condition that is the leading preventable cardiovascular disease risk factor worldwide. Digital interventions can help facilitate uptake of important guideline-recommended lifestyle modifications, reinforce home blood pressure monitoring, decrease therapeutic inertia, and improve medication adherence. However, current studies are only of moderate quality, and are highly heterogeneous in the interventions evaluated, comparator used, and results obtained. Therefore, additional studies are needed, focusing on the development of universally applicable and consistent digital therapeutic strategies designed with health care professional input and evaluation of these interventions in robust clinical trials with objective end points. Hopefully, the momentum for digital therapeutics triggered by the coronavirus disease 2019 pandemic can be utilized to maximize advancements in this field and drive widespread implementation.

Key Words: blood pressure, cardiovascular diseases, digital technology, hypertension, mobile applications

Digital health essentially refers to the use of digital technologies for health. It involves the use of information and communications technology (ICT; ie, digital technologies) to support health and health-related fields. Digital health is facilitated by access to real-time information via constantly evolving digital technologies. In addition to improving the quality of patient care, this approach can also help to increase the productivity, efficiency, and accessibility of health care provision. Digital health is a broad term that covers digital medicine (the subset of digital health that relates to the use of technology to facilitate medical care and treatment) and then, more specifically, both software as a medical device (software used for medical purposes that are not part of a hardware medical device) and digital therapeutics (Figure 1). Digital therapeutics “deliver to patients evidence-based therapeutic interventions that are driven by high-quality software programs to treat, manage, or prevent a medical disorder or disease. They are used independently or in concert with medications, devices, or other therapies to optimize patient care and health outcomes.”

Digital medicine and digital therapeutics approaches to patient management have already been widely utilized in the areas of smoking cessation, mental health, diabetes, and hypertension. Recently, monitoring of blood pressure (BP) at home and associated digital solutions received a big push due to the requirement for remote patient management during lockdowns implemented in response to the COVID-19 pandemic. Hypertension has a high global prevalence and is the leading preventable cardiovascular disease risk factor worldwide. However, despite the availability of a range of pharmacological treatment options, BP control is often suboptimal. This means that there is a potential role for digital therapeutic interventions as a complementary strategy to optimize the management of hypertension.

Despite the widespread availability of apps claiming to facilitate hypertension control or medication adherence, not many have been developed in collaboration with health care professionals, been validated, or undergone rigorous scientific assessment of BP-lowering efficacy. Furthermore, despite current applications, there is a relative lack of data relating to digital therapeutics in hypertension management. However, it is essential that digital solutions for hypertension management are evidence-based and effective to minimize the impact of
Nonstandard Abbreviations and Acronyms

| Abbreviation | Definition |
|--------------|------------|
| App          | application |
| BP           | blood pressure |
| HBPM         | home BP monitoring |
| ICT          | information and communications technology |
| mHealth      | mobile health |
| SBP          | systolic BP |
| STEP         | Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients |

This important contributor to the worldwide epidemic of noncommunicable diseases. This narrative review article provides an overview of digital therapeutics in hypertension, including the design and features of different digital therapeutics platforms, current randomized controlled studies for mobile application (app) use, limitations, and potential apps. Key publications in the field were identified by PubMed searches conducted in October 2021 using the search terms “Digital therapeutics” or “mobile app” or “digital health” and “hypertension”. Search hits were restricted to English language publications. Reference lists of articles identified in the search were also reviewed to identify additional relevant publications. However, it should be noted that this process may result in some biases, including publication bias and the exclusion of non-English language materials.

**ICT PLATFORM FOR DIGITAL THERAPEUTICS**

In digital therapeutics, ICT is used to store, retrieve, share, and exchange health-related information to support the prevention, diagnosis, treatment, and monitoring of hypertension. This is facilitated by the now widespread availability of smartphones and tablets. In addition, a shared internet-based platform enables collaborative care and interactions between stakeholders. This connected infrastructure of health systems and services is also referred to as the “Internet of Medical Things.” Contributors to the Internet of Medical Things include the patient, health care professionals involved in their care, and devices that collect medical information (e.g., smartphone, tablet, connected BP monitor), and potentially other environmental signals (e.g., temperature, humidity, air pollution). With data storage in the cloud, all this information is then available to stakeholders involved in patient care, including the hospital/clinic/health care provider, the patient, and relevant health care professionals (e.g., physician, nurse, pharmacist).

Elements of a digital therapeutics platform for hypertension include patient-app interaction, app-doctor interaction, and patient-doctor interaction, all of which combine to facilitate a shared goal of lifestyle improvement and target BP attainment (Figure 2). There are several key steps including obtaining individual patient data and providing interactive education, providing personalized intervention based on these data, and self-planning and evaluation (supported by the personalized intervention). The course of the intervention may not always be linear, with a role for things like education multiple times during the process. Together, these features help to establish a personalized approach based on real-world data and evidence (Figure 3).

The wide variety of potential data inputs into an ICT platform for digital therapeutics in hypertension means that there is currently a large array of mobile applications and software technologies that have been designed to aid in the management of the disease. This means that there is a general lack of consistency in approach, and no one method currently predominates.

**POTENTIAL BP-LOWERING MECHANISMS OF DIGITAL THERAPEUTICS IN HYPERTENSION**

Effective digital therapeutics for hypertension include specific mechanisms to decrease BP, independent of pharmacotherapy and adherence. One of the broad mechanisms underlying the benefits of digital therapeutics is biofeedback to improve monitoring and management. More specifically, there are many potential mechanisms that contribute to the BP-lowering effects of digital therapeutic interventions in patients with hypertension. First, there is the impact of these interventions on the implementation of, and adherence to, guideline-driven/evidence-based important nonpharmacological interventions for reducing BP. These include consumption of a healthy diet (reduced intake of saturated fatty acids and cholesterol; increased intake of polyunsaturated fatty acids and low-fat dairy products), reducing dietary salt intake, increasing dietary consumption of potassium, increasing physical activity, reducing body weight, moderating alcohol intake, stress management, and good sleep hygiene (Figure 3). There are good levels of evidence to support all these approaches to BP reduction. Of the lifestyle modifications recommended by the guidelines, decreasing salt intake is particularly important in reducing BP, especially in Asian patients with hypertension. Decreasing salt intake by use of a salt substitute was recently shown to reduce rates of cardiovascular disease events, stroke, and all-cause mortality in rural Chinese adults aged ≥60 years with hypertension and a history of cardiovascular disease. The different components may also interact. For example, both stress reduction and decreased alcohol intake could contribute to better sleep quality. In addition, exercise might make a greater contribution to
weight loss, which in turn reduces BP, rather than having a direct BP-lowering effect. However, there is not yet enough data to draw any firm conclusions.

Self-monitoring of BP using a home BP monitoring (HBPM) device is another essential component of digital therapeutics in patients with hypertension (Figure 3). Use of out-of-office BP monitoring, including HBPM, is preferred over office BP monitoring for the diagnosis and management of hypertension in major hypertension guidelines. This is because home BP has been shown to be a better predictor of cardiovascular outcomes than office BP. Transmission of objective HBPM data is essential for the evaluation of changes in BP over time (eg, after the initiation of lifestyle modifications or drug therapy), and provides important information on BP variability (beat-to-beat, day-to-day, seasonal, etc), which is another important cardiovascular risk factor. However, home BP recordings are only useful if they are accurate. Therefore, use of a validated HBPM device is essential to allow high-quality measurements of home BP. Increasing use of digital therapeutics could help to facilitate access to appropriately validated HBPM devices, something that is currently an important issue. Despite their value, HBPM devices are not currently reimbursed in any country, which limits access to those who have the ability to pay for one. Access issues such as this are a key factor that needs to be overcome if digital therapeutics are to be implemented in a widespread and equitable manner.

Meta-analysis data show that self-monitoring of BP by itself can reduce both systolic and diastolic BP, and increase the proportion of patients with normalization of BP. Furthermore, data from randomized clinical trials indicate that app-related interventions for enhanced BP self-monitoring and feedback are beneficial for improving BP control, especially when BP control is inadequate. The addition of other interventions such as education, management of drug therapy, adherence monitoring, counseling, and behavioral interventions—all of which could be incorporated into a digital therapeutics intervention—decreased BP to a greater extent than BP monitoring alone. On the basis of these meta-analysis findings, it was concluded that implementation of self-monitoring of BP should be accompanied by other interventions to facilitate sufficient and optimal BP lowering. This suggests that high-quality digital therapeutic interventions that address a wide range of measures are needed to effectively reduce BP and lower cardiovascular risk in patients with hypertension.
Finally, improvements in medication adherence and optimization of antihypertensive drug therapy are additional potential mechanisms by which digital therapeutic interventions could contribute to reductions in BP in patients with hypertension. Both medication nonadherence and prescribing inertia are important contributors to suboptimal control of BP in patients with hypertension.42,43 Therapeutic inertia in hypertension refers to the failure of providers to initiate new therapy or titrate existing therapy when BP targets are not achieved.44 Improving medication adherence or reducing therapeutic inertia (or ideally both of these factors) would be expected to improve the utilization and effectiveness of pharmacological antihypertensive therapy. In fact, better compliance with antihypertensive medication has been shown to reduce cardiovascular risk.45

CURRENT RANDOMIZED CONTROLLED STUDIES
The body of evidence for the BP-lowering effects of mobile health (mHealth) app interventions in patients with hypertension is growing, with the majority of studies published in the last 3 years (Table). Currently available studies are of moderate quality only, with the main issue that could introduce bias being lack of blinding. Although this might be difficult to achieve in digital intervention trials, it is something that will need to be addressed to ensure that trials in this field provide high-quality, unbiased data that can be used to inform clinical practice.

Another important thing to note about currently available data on mHealth app intervention in hypertension is the lack of consistency. This includes lack of consistency in the interventions evaluated, the definition of the standard care comparator, and in study findings. The resulting heterogeneity, along with the potential for bias, makes it difficult to draw conclusions regarding the usefulness of interventions overall and to determine which aspects of digital health strategies might be most important for facilitating reductions in BP. In addition, there are not yet any truly large-scale clinical trials of mHealth app interventions in patients with hypertension.

Three randomized studies have included a sample size of >300 patients (Table).46–48 Of these 2 showed a significant reduction in BP in the digital therapeutics...
The largest positive study was conducted in untreated patients with essential hypertension (n=390) and used a digital therapeutics intervention specifically designed to promote lifestyle modifications (the HERB system; CureApp, Inc). App users created a personalized profile that included data on age, sex, lifestyle, social background, and behavior patterns. This information was combined with home BP measurements to develop a personalized program of lifestyle modifications designed to reduce BP. This included an interactive education program (step 1), specific instructions to implement lifestyle modifications (step 2), and self-planning and evaluation (step 3). Mean changes in ambulatory systolic BP (SBP) from baseline to 12 weeks (the primary end point) were significantly greater in the intervention versus control group (managed using standard lifestyle modifications), as were home and office SBP. The mobile app engagement rate was high (98.1%) and no program-related safety events occurred. A smaller study has also shown the utility of a mobile app for helping patients adhere to lifestyle modifications and improve medication adherence. Another small study of a mobile app–based disease management program showed that positive changes in measures of patient activation were significantly associated with improvement in lifestyle measures including alcohol consumption and cigarette smoking, as well as SBP and diastolic BP.

The other large, positive study utilized a more comprehensive app, which included reminders to measure BP, take medicine and exercise, alerts when physician visits were due, records of BP, BP control and drug use, education modules, and health evaluations, and allowed users to have remote physician consultations. A total of 480 patients were enrolled and followed for 6 months; the primary end point was the change from baseline in SBP and diastolic BP in the intervention group compared with control (no use of digital interventions). Both SBP and diastolic BP decreased from baseline to a significantly greater extent in the digital therapeutics versus control group, and the proportion of patients with BP control at the end of the study was also significantly higher in the intervention group.

The large study that did not show any significant benefit from digital therapeutics usage included patients with uncontrolled or poorly controlled hypertension. It used a smartphone coaching app designed to promote behavioral changes associated with hypertension self-management. There were no significant differences in the change from baseline in SBP compared with the control group in either study, although the self-management app did significantly improve patient confidence in BP control. Another intervention that has been shown to significantly reduce BP compared with standard care in a smaller study is a tablet-based disease self-monitoring system.

Overall, there is a growing body of data on the use of mHealth app interventions in hypertension management,
although the quality of evidence is moderate. Aggregating available data, a recent meta-analysis reported decreases in BP and increases in medication adherence in patients with hypertension who used smartphone apps.52 However, the heterogeneous nature of current studies with respect to both interventions and results means that additional research is needed. This should focus on the development of more universally applicable and consistent digital therapeutic strategies with input from both health care professionals and patients (the latter do not appear to have been involved in the design of currently available digital tools) and evaluation of these interventions in robust clinical trials with objective end points. The ultimate goal would be to investigate and document a beneficial effect of digital interventions that are acceptable to both patients and health care professionals not only on BP but also on cardiovascular outcomes.

### COMPREHENSIVE DIGITAL APPROACH FOR BP VARIABILITY

Although hypertension is a well-documented cardiovascular risk factor, there are multiple mechanisms

---

**Table.** Summary of Studies Reporting the Effects of mHealth App Interventions Relating to Lifestyle Interventions on Blood Pressure in Patients With Hypertension

| Author, year | Patients (n) | Design (duration of follow-up) | Primary outcome (key secondary outcome) | Digital intervention/ control | Findings | Quality of evidence* |
|--------------|--------------|-------------------------------|----------------------------------------|-------------------------------|----------|----------------------|
| Kario et al, 2021 | HTN (n=148) | Multicenter, randomized, open, pilot study (24 wk) | Mean change in 24-h SBP by ABPM at 24 wk (mean change in 24-h SBP by ABPM at 16 wk) | Mobile app–based support for lifestyle modifications (HERB)/Std care | Mean change from baseline in 24-h ambulatory BP did not differ significantly between the DTx and std care groups (adjusted difference, −0.66 [95% CI, −5.34 to 3.9; P=0.78]) | 3 |
| Kario et al, 2021 | Untreated HTN (n=390) | Multicenter, randomized, open (12 wk) | Mean change in 24-h SBP by ABPM at 12 wk (Mean changes in office and home BP at 12 wk) | Mobile app–based support for lifestyle modifications (HERB)/Std care | Between-group differences (95% CI) in the change from baseline in 24-h ambulatory, home, and office SBPs were −2.4 (−4.5 to −0.3) [P=0.034], −4.3 (−6.7 to −1.9) [P<0.001], and −3.6 (−6.2 to −1.0) mm Hg [P=0.006], respectively. The proportion of patients achieving morning home BP<135/85 mmHg was 22.2% in the DTx group and 10.4% in the control group. The mobile app engagement rate was 98.1%. | 3 |
| Bozorgi et al, 2021 | HTN (n=120) | Randomized, open (24 wk) | Adherence to antihypertensive medication (Regular BP monitoring) | Mobile app–based education support/ Std care | MAP decreased over time by 3.4 mm Hg (95% CI, 1.6 to 5.2), and adherence to treatment was better, in the mHealth app vs std care group | 3 |
| Gong et al, 2020 | HTN (n=480) | Multicenter, randomized, open (6 mo) | SBP and DBP changes at 6 mo (Medication adherence) | Mobile app–based HTN management/ Std care | Mean change from baseline in SBP was −8.9±6.42 in the mHealth app group and −5.92±9.5 mm Hg in the std care group (P<0.05 for between-group difference in change from baseline). The proportion of pts with BP control at the end of the study was 77% in the mHealth app group vs 67% in the std care group (P<0.001) | 3 |
| Persell et al, 2020 | Uncontrolled HTN (n=333) | Randomized, open (6 mo) | SBP at 6 mo with prespecified adjustment for baseline SBP, sex, and age (self-reported antihypertensive medication adherence) | Mobile coaching app/BP-tracking app (control) | Adjusted between-group difference in mean SBP at 6 mo was −2.0 mmHg (95% CI, −4.9 to 0.8); P=0.16; self confidence in controlling BP score was greater in the mobile Coaching app vs control group (P<0.001) | 3 |
| Kim et al, 2016 | HTN (n=95) | Randomized (sub-study), open (6 mo) | Not predefined | Mobile app–based disease management program/Std care | In multivariable models, the interaction between wireless self-monitoring and positive changes in the patient activation measure was a significant contributor to improvements in cigarette smoking, alcohol consumption, SBP, and DBP | 2 |
| Or et al, 2016 | T2D±HTN (n=83) | Randomized, open, pilot study (3 mo) | HbA1c level, fasting blood glucose level, SBP, DBP, chronic disease knowledge, and frequency of self-monitoring at 1, 2, and 3 mo. | Tablet-based interactive self-monitoring system including reminders and education materials/ Self-monitoring only (std care) | The decrease from baseline in mean SBP (95% CI) was −13.0 mm Hg (−19.1 to −6.9) in the mHealth app group vs −5.4 mm Hg (−12.0 to 1.1) in the std care group (P=0.043). There were no significant between-group differences in frequency of BP and fasting blood glucose monitoring, chronic disease knowledge, or levels of fasting blood glucose or glycosylated hemoglobin | 3 |

ABPM indicates ambulatory BP monitoring; app, application; BP, blood pressure; DBP, diastolic BP; DTx, digital therapeutics; HbA1c, glycated hemoglobin; HTN, hypertension; MAP, mean arterial pressure; mHealth, mobile health; pts, patients; SBP, systolic blood pressure; std, standard; and T2D, type 2 diabetes.

*Jadad score, on a scale from 0 to 5 where higher scores indicate higher quality and less risk of bias.
underlying this increased risk. Elevated BP itself is a risk factor for progressive endothelial dysfunction and atherosclerosis.\textsuperscript{53,54} Then, in the presence of existing cardiovascular disease, exaggerated BP variability can trigger acute cardiovascular events.\textsuperscript{58} These relationships have been described using the resonance hypothesis.\textsuperscript{56}

In the context of cardiovascular disease, anticipation medicine is defined as practices that help to predict the time and place of cardiovascular event onset by record- ing relevant parameters and providing alerts when risk is increasing, thus allowing proactive, real-time risk reduction.\textsuperscript{57,58} Therefore, a digital therapeutics system that utilizes ICT to monitor both BP measurements and BP variability taking into account other stressors, including environmental factors, would be ideally suited to facilitate anticipation medicine.

Such a system has been developed, known as ICT-based multisensory ambulatory BP monitoring (IMS-ABPM; A&D Co, Tokyo, Japan). It includes a high-sensitivity actigraph that detects the wearer’s fine-scale physical movements in three directions, a thermometer and a barometer.\textsuperscript{59} The system stores BP and waveform data from intracuff pressure, which is transmitted to a data center for analysis, and the results are shared with both the patient and their doctor. Artificial intelligence could be applied to the cloud-based big data (Internet of Medical Things) to assess time-series of BP changes to predict future BP variability. For a comprehensive digital approach, this system could be combined with an app that stores personalized data on knowledge, attitude, and practice relating to hypertension and cardiovascular disease, and required lifestyle modifications (such as, for example, the recently developed HERB system\textsuperscript{60}). Taken together, the data obtained and generated by this digital solution would provide real-time feedback to patients and physicians and potentially contribute to the prevention of adverse BP-related and BP variability–related cardiovascular outcomes. This is an important area for future research.

**IDENTIFYING RESPONDERS**

Based on the limited amount of current data, patients with hypertension who are motivated to change their health behavior might be the best candidates for mobile app–based self-monitoring of health.\textsuperscript{50} Otherwise, it is not yet clear which patients will respond best to mHealth app interventions. This is made even more challenging by the lack of consistency in the digital strategies studied to date and the heterogeneous results of those studies. Grouping patients, or patient phenotyping, based on factors or characteristics known to be associated with hypertension, including salt or alcohol intake, stress, sleep quality, and environmental factors (eg, temperature, air pollution) may be helpful. Another approach to identifying those likely to respond to digital intervention might be evaluation of day-by-day interactions between the patient’s behavior and the BP response during use of a digital tool. This might be facilitated by the use of wearable sensors, including cuff-less BP monitoring.\textsuperscript{61}

**USE WITH OTHER ANTIHYPERTENSIVE THERAPIES**

Digital therapeutics have a role across the continuum of hypertension management, from the early stage right through to end-stage cardiovascular or renal disease. As a result, they are almost certain to be combined with other pharmacological or nonpharmacological treatments for hypertension. Renin-angiotensin system inhibitors or diuretics might have synergistic effects in combination with digital therapeutic strategies with respect to salt reduction, but this needs to be evaluated further. In early-stage hypertension, there is the potential for utilization of digital therapeutics promoting lifestyle modifications to delay or eliminate the need for drug therapy, or to allow this to be initiated at a lower dosage. Then, when needed, digital monitoring can facilitate adherence to, and optimization of, drug therapy as has been already reported.\textsuperscript{49,62} Digital therapeutic strategies might also help physicians to identify good candidates for renal denervation, and could be continued to support BP reductions after this procedure (Figure 4). Additionally, digital therapeutics modules that specifically target other cardiometabolic risk factors, such as obesity, diabetes, and hyperlipidemia, could be added to those targeting hypertension to further reduce risk.

---

**Figure 4.** Potential mechanisms contributing to the blood pressure (BP)–lowering effects of digital therapeutic interventions for hypertension, including lifestyle modifications (blue boxes), BP monitoring (purple box), and optimization of pharmacological therapy (black boxes). DTx indicates digital therapeutics.
LIMITATIONS

Despite the promise of digital therapeutic interventions, there are several limitations that can impact on the dissemination and adoption of these approaches in routine clinical practice. Access to technology such as a smartphone and the internet, from both cost and logistical perspectives, may be an issue that precludes the widespread implementation of ICT-based digital therapeutics in some regions or in specific vulnerable populations. There is also the issue of reimbursement, which would be required to facilitate more widespread accessibility and uptake. Issues relating to reimbursement of health care professionals for services and consultations as part of digital interventions also need to be evaluated and addressed.

Another important systems-related limitation is that none of the digital therapeutics approaches studied to date have been fully integrated into existing health care systems. Therefore, the impact of these interventions in the context of overall health management and their ability to be integrated into existing infrastructure (eg, electronic medical records) is not yet known. As noted by the World Health Organization, increasing interest in digital health solutions for services and consultations as part of digital interventions also need to be evaluated and addressed.

Digital therapeutics relies on technology and equipment that should be developed, validated, and certified based on regulatory requirements. Regulatory bodies in the United States and Europe have outlined the conditions under which medical software is classified as a medical device and, as a result, the regulation and validation process. However, there are currently no specific regulatory standards for digital therapeutics, either within or across countries. These standards and quality control guidelines will be important to ensure that things like the educational components of digital therapeutic interventions are scientifically accurate and evidence-based. In addition, systems that incorporate self-measurement of BP are only going to be as good as the BP data recorded, which reinforces the need for the use of validated measurement tools as part of digital therapeutics in hypertension. Further research and development are needed to support the development of validated, guideline-driven digital therapeutic strategies in hypertension. One tool that might be useful to inform this process is artificial intelligence, potentially in combination with data from wearable monitoring devices. However, it is important to note that there are several hurdles to overcome before artificial intelligence can be reliably implemented to transform the management of hypertension. In addition, there is the potential for unintended consequences with exclusive use of predictive artificial intelligence-based models if correlations are mistaken for causation. Other relevant issues in the application of artificial intelligence are the quality of data used to inform machine learning and models, and the potential for machine learning to reflect existing societal biases to the disadvantage of those already experiencing health disparities (eg, ethnic minorities).
An individual’s health-related information is highly sensitive, and this is especially relevant when data are being collected and stored on digital platforms. Concerns about these issues may prevent some patients from participating in digital therapeutic solutions. Therefore, safeguards are needed to ensure the privacy and safety of patient data and to minimize the risk of any data leaks or breaches. These reassurances then need to be passed on to patients. Applicable laws and regulations in Europe and the Health Insurance Portability and Accountability Act in the United States currently do provide a level of protection and can help to guide the development of secure digital interventions for patients with hypertension.

CONCLUSIONS

Digital health solutions have already impacted health care delivery and will continue to transform disease management in patients with hypertension (Figure 5). The adoption of technological innovations, such as wearable devices and health apps, and other digital solutions can also facilitate processes requiring big data and data analytics to generate new approaches to patient management and increase the potential for personalized care. Despite the technological advances that have already taken place, more work is needed to fully realize the benefits of digital solutions in the management of hypertension, and to ensure that these approaches do not create a digital divide between high and low-income groups and those with versus without access technology (regardless of the reasons for this). In addition, although innovative digital technologies are likely to have an important role in improving treatment outcomes and facilitating access to health care, it is also important that these new digital interventions are appropriately evaluated to ensure that investment in these technologies and their integration into existing health systems does not inappropriately divert limited resources away from other, proven nondigital therapeutic strategies.

Validated programs need to be developed, researched, and implemented so that physicians and patients can confidently expect and obtain consistent benefits. Hopefully, the momentum for digital therapeutics triggered by the COVID-19 pandemic can be utilized to maximize advancements in digital therapeutics and their widespread implementation into clinical practice. This will allow effective management of hypertension for as many people as possible, helping to limit the negative effects of high BP and contribute to attenuating the worldwide epidemic of cardiovascular disease.

ARTICLE INFORMATION

Affiliation
Division of Cardiovascular Medicine, School of Medicine, Jichi Medical University, Tochigi, Japan.

Acknowledgments
Medical writing assistance was provided by Nicola Ryan, independent medical writer, funded by Jichi Medical University, K. Kario and N. Harada conceptualized this review and researched for contents. A. Okura assisted in the literature search. All authors contributed to the writing of the final article.

Sources of Funding
None.

Disclosures
K. Kario reports grants from CureApp Inc. outside the submitted work. The other authors report no conflicts.

REFERENCES

1. World Health Organization. WHO guideline: recommendations on digital interventions for health system strengthening. Geneva, 2019. Accessed May 11, 2022. https://www.who.int/publications/i/item/9789241550505
2. Marques ICP, Ferreira JJM. Digital transformation in the area of health: systematic review of 45 years of evolution. Health and Technology. 2020;10:575–586. doi: 10.1002/10253-019-00402-8
3. Digital Therapeutics Alliance. Digital Therapeutics Definition and Core Principles. (Nov 2019). Accessed November 22, 2021. https://dtaalliance.org/wp-content/uploads/2021/01/DTA_DTx-Definition-and-Core-Principles.pdf
4. Whittaker R, McRobbie H, Bullen C, Rodgers A, Gu Y. Mobile phone-based interventions for smoking cessation. Curr. Database Syst Rev. 2016;4:CD006611. doi: 10.1002/14651858.CD006611.pub4
5. Linardon J, Cuijpers P, Caribbring P, Messer M, Fuller-Tayskewicz M. The efficacy of app-supported smartphone interventions for mental health problems: a meta-analysis of randomized controlled trials. World Psychiatry. 2019;18:325–336. doi: 10.1002/wps.20673
6. Tchero H, Kangambega P, Briatte C, Brunet-Houdard S, Retaili GR, Rusch E. Clinical effectiveness of telemedicine in diabetes mellitus: a meta-analysis of 42 randomized controlled trials. Telemed J E Health. 2019;25:569–583. doi: 10.1089/tmj.2018.0128
7. Wu X, Guo X, Zhang Z. The efficacy of mobile phone apps for lifestyle modification in diabetes: systematic review and meta-analysis. JMI Health UHealth. 2019;7:e12297. doi: 10.2196/12297
8. Han H, Guo W, Lu Y, Wang M. Efficacy of mobile applications on blood pressure control and their development in China: a systematic review and meta-analysis. Public Health. 2020;185:356–363. doi: 10.1016/j.puhe.2020.05.024
9. Bhaskar S, Bradley S, Chattru VK, Adivesh A, Nurtazina A, Kyrkyybeva S, Sakhamum S, Yuya S, Sunil T, Thomas P, et al. Telemedicine across the globe-position paper from the COVID-19 pandemic health system resilience PROGRAM (REPROGRAM) International Consortium (Part 1). Front Public Health. 2020;8:556720. doi: 10.3389/fpubh.2020.556720
10. Bhaskar S, Bradley S, Chattru VK, Adivesh A, Nurtazina A, Kyrkyybeva S, Sakhamum S, Moguliner S, Pandya S, Schroeder S, et al. Telemedicine as the new outpatient clinic gone digital: position paper from the pandemic health system resilience PROGRAM (REPROGRAM) International Consortium (Part 2). Front Public Health. 2020;8:410. doi: 10.3389/fpubh.2020.00410
11. Monaghesh E, Hajizadeh A. The role of telehealth during COVID-19 outbreak: a systematic review based on current evidence. BMC Public Health. 2020;20:1193. doi: 10.1186/s12889-020-09301-4
12. Keersa S, Jonas A, Schulman K. Covid-19 and Health Care’s Digital Revolu- tion. N Engl J Med. 2020;382:62. doi: 10.1056/NEJMp2005836
13. Lafti R, Doarn CR. Perspective on COVID-19: Finally, Telemedicine at Center Stage. Telemed J E Health. 2020;26:1106–1109. doi: 10.1089/tmj.2020.0132
14. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol. 2020;16:223–237. doi: 10.1038/s41581-019-0244-2
15. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, Chen J, He J. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. Circulation. 2016;134:441–450. doi: 10.1161/CIRCULATIONAHA.115.018912
16. Goldberg EM, Levy PD. New Approaches to Evaluating and Monitoring Blood Pressure. Curr Hypertens Rep. 2016;18:49. doi: 10.1007/s11906-016-0650-9
17. Kumar N, Khunger M, Gupta A, Garg N. A content analysis of smartphone-based applications for hypertension management. J Am Soc Hypertens. 2015;9:130–136. doi: 10.1016/j.jash.2014.12.001
Kario K, Tomitani N, Matsumoto Y, Hamasaki H, Okawara Y, Kondo M, Harsha DW, Bray GA. Weight loss and blood pressure control (Pro). Chen TL, Chang SC, Hsieh HF, Huang CY, Chuang JH, Wang HH. The effect of smartphone app-based interventions for hypertension: a meta-analysis of randomized controlled trials. Harsha DW, Ford GA. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. Semlitsch T, Jeitler K, Berghold A, Horvath K, Posch N. The effect of alcohol on quality of sleep. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. The effect of self-monitoring of blood pressure on the self-management of hypertension: review and content analysis. Dickinson HO, Mason JM, Nicolson DJ, Campbell F, Beyer FR, Cook JV, et al. Better compliance to antihypertensive medications reduces blood pressure variability. Kario et al. Systemic hemodynamic atherothrombotic syndrome and resolvin hypothesis of blood pressure variability: triggering cardiovascular events.
56. Kario K. New insight of morning blood pressure surge into the triggers of cardiovascular disease: synergistic resonance of blood pressure variability. *Am J Hypertens*. 2016;29:14–16. doi: 10.1093/ajh/hpv114

57. Kario K. Evidence and perspectives on the 24-hour management of hypertension: hemodynamic biomarker-initiated ‘anticipation medicine’ for zero cardiovascular event. *Prog Cardiovasc Dis*. 2016;59:262–281. doi: 10.1016/j.pcad.2016.04.001

58. Kario K. Hemodynamic biomarker-initiated anticipation medicine in the future management of hypertension. *Am J Hypertens*. 2017;30:226–228. doi: 10.1093/ajh/hpw160

59. Kario K, Tomitani N, Kanegae H, Yasui N, Nishizawa M, Fujiwara T, Shigezu T, Nagai R, Harada H. Development of a new ICT-based multisensor blood pressure monitoring system for use in hemodynamic biomarker-initiated anticipation medicine for cardiovascular disease: the national IMPACT program project. *Prog Cardiovasc Dis*. 2017;60:435–449. doi: 10.1016/j.pcad.2017.10.002

60. Kario K, Nomura A, Kato A, Harada N, Tanigawa T, So R, Suzuki S, Hida E, Satake K. Digital therapeutics for essential hypertension using a smartphone application: A randomized, open-label, multicenter pilot study. *J Clin Hypertens (Greenwich)*. 2021;23:923–934. doi: 10.1111/jch.14191

61. Kario K. Management of hypertension in the digital era: small wearable monitoring devices for remote blood pressure monitoring. *Hypertension*. 2020;76:640–650. doi: 10.1161/HYPERTENSIONAHA.120.14742

62. McManus RJ, Little P, Stuart B, Morton K, Kafferty J, Kelly J, Bradbury K, Zhang J, Zhu S, Murray E, et al. HOME BP investigators. Home and Online Management and Evaluation of Blood Pressure (HOME BP) using a digital intervention in poorly controlled hypertension: randomised controlled trial. *BMJ*. 2021;372:m4858. doi: 10.1136/bmj.m4858

63. The Bellagio eHealth Evaluation Group. Call to action on global eHealth evaluation: consensus statement of the WHO Global eHealth Evaluation Meeting, Bellagio, Italy, September 2011. Accessed May 11, 2022. https://cdn.who.int/media/docs/default-source/a-future-for-children/who-bellagio-ehealth-evaluation-call-to-action.pdf?sfvrsn=99788e45_1&download=true

64. Zhang W, Zhang S, Deng Y, Wu S, Ren J, Sun G, Yang J, Jiang Y, Xu X, Wang TD, et al. STEP Study Group. Trial of intensive blood-pressure control in older patients with hypertension. *N Engl J Med*. 2021;385:1268–1279. doi: 10.1056/NEJMoa2111143

65. Omboni S, McManus RJ, Bosworth HB, Chappell LC, Green BB, Kario K, Logan AG, Magid DJ, Mckinstry B, Margolis KL, et al. Evidence and recommendations on the use of telemedicine for the management of arterial hypertension: an international expert position paper. *Hypertension*. 2020;76:1386–1383. doi: 10.1161/HYPERTENSIONAHA.120.15873

66. European Parliament and Council. Regulation (EU) 2017/745 on medical devices (2017). Accessed October 28, 2021. https://eur-lex.europa.eu/eli/reg/2017/745/2017-05-05

67. US Food and Drug Administration. Policy for device software functions and mobile medical applications. Guidance for industry and Food and Drug Administration staff (2019). Accessed October 28, 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-device-software-functions-and-mobile-medical-applications

68. Padmanabhan S, Tran TOB, Dominiczak AF. Artificial intelligence in hypertension: seeing through a glass darkly. *Circ Res*. 2021;128:1100–1118. doi: 10.1161/CIRCRESAHA.121.318106

69. European Parliament and Council. General Data Protection Regulation (GDPR) compliance guidelines. Accessed October 28, 2021. https://gdpr.eu

70. US Department of Health and Human Services. Health information privacy. Accessed October 28, 2021. https://www.hhs.gov/hipaa/index.html