

Review

Open Access



State-of-the-art rapid review of the current landscape of digital hypertension

Kazuomi Kario, Noriko Harada, Ayako Okura

Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi 329-0498, Japan.

Correspondence to: Prof. Kazuomi Kario, Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan. Email: kkario@jichi.ac.jp

How to cite this article: Kario K, Harada N, Okura A. State-of-the-art rapid review of the current landscape of digital hypertension. *Conn Health* 2022;1:46-58. <https://dx.doi.org/10.20517/ch.2022.02>

Received: 13 Jan 2022 **First Decision:** 7 Feb 2022 **Revised:** 21 Feb 2022 **Accepted:** 7 Mar 2022 **Published:** 7 Mar 2022

Academic Editors: Stefano Omboni, Raj S. Padwal **Copy Editor:** Xi-Jun Chen **Production Editor:** Xi-Jun Chen

Abstract

“Digital hypertension” is a new information and communication technology (ICT)-based research field of digital healthcare that adds significant value to the management of hypertension by integrating multidimensional and time-series data. It includes the study of pathogenesis and predictive, individualized, and preemptive treatments, and its clinical outcomes can be introduced in telemedicine. The ICT in digital hypertension includes the research and development of blood pressure (BP) monitoring, e.g., wearable, cuff-less BP monitoring, a platform for digital transformation and transmission systems, and artificial intelligence. A recent clinical trial demonstrated the significant BP-lowering effect of digital therapeutics that facilitate lifestyle modification at the individual level via the patient’s smartphone. One of the goals of digital hypertension is personalized anticipation medicine that identifies the timing, place, and behavior that may trigger the onset of a cardiovascular event. This narrative review aims to address and discuss the cutting-edge information on the technology and concept of “digital hypertension”.

Keywords: Digital hypertension, digital health, telemonitoring, blood pressure monitoring, wearable device, digital therapeutics, anticipation medicine, rapid review, state-of-the-art review

INTRODUCTION

The recent exponential development of digital health information and communication technology (ICT) has resulted in a significant evolution in the approach to hypertension treatment. Global guidelines now



© The Author(s) 2022. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, sharing, adaptation, distribution and reproduction in any medium or format, for any purpose, even commercially, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.



recommend the use of hypertension diagnoses based on 24 h ambulatory blood pressure monitoring (ABPM) and home blood pressure (BP) measurement rather than conventional office BP. In addition, a new system of medical care has been generated that incorporates wearable BP monitoring and multidimensional digital information processing to link the patient's background information with analysis programs^[1-3]. The COVID-19 pandemic has also contributed to the recognition of the usefulness of telemedicine for the management of hypertension, due to its strict lockdowns and withholding of face-to-face consultations^[2,4-6].

Against this backdrop, the concept of “digital hypertension management” was introduced to create added value in hypertension treatment and its related healthcare. Specifically, digital hypertension management is a new science proposed by the Japanese Society of Hypertension (JSH) that comprehensively considers the development of new technologies and analysis methods such as sensors, information processing, and machine learning, as well as the creation of platforms to integrate and apply these concepts and technologies^[7,8]. One of the goals of digital hypertension management is personalized anticipation medicine. Anticipation medicine is the integration of multidimensional time-series data of each individual, including his or her BP monitoring; it will lead to improve the accuracy of hypertension diagnoses and help prevent the occurrence of cardiovascular events through effective interventions in real time along with the prediction of future BP fluctuations^[1,7].

This narrative review aims to address and discuss the cutting-edge information on the technology and concept of “digital hypertension”.

DIGITAL HYPERTENSION AND TELEMONITORING

Digital health refers to a wide range of activities for storing, retrieving, sharing, and exchanging health information using ICT. Various technologies and services related to medical care have been applied and tested. In recent years, ICT has enabled the dramatic development of high-speed, large-capacity, and multiple connections and the wide dissemination of mobile devices; remote medical care and services via the Internet have thus expanded too^[9]. For example, diagnoses and prescriptions are now routinely conducted face-to-face on a computer screen, and medical data are promptly sent and received between patients and their physicians and other healthcare staff; education or guidance is also provided via smartphone applications (apps)^[10]. The terms applicable to digital health-related hypertension treatment are defined in [Table 1](#).

What is digital hypertension management?

Digital hypertension management can be perceived as an academic field of digital health encompassing e-health services, ICT-based treatments and services for hypertension, clinical research, and artificial intelligence (AI)-based big data analyses^[1,11]. From a macroscopic perspective, the information generated and exchanged in digital hypertension management could also be used to advance initiatives that benefit government healthcare policies and public welfare. For example, information on the medical care and health checkups of a community's residents can be centralized and used for both the patients' healthcare and the community's healthcare services. From a microscopic perspective, the digital management of hypertension attempts to improve the quality of care by collecting and managing data on each individual across time, so that their BP characteristics and background can be assessed to optimize their medical care. In these efforts, telemonitoring, which is the continuous and safe collection and management of information related to medical care and lifestyle - including individuals' daily BP readings [[Figure 1](#)] - is the most basic function for improving the accuracy of diagnosis and treatment of hypertension. The use of telemonitoring can also help reduce the severity of hypertension and cardiovascular events.

Table 1. Definition of the terms related to digital health

Terms	Definition
Anticipation medicine ^[1,7]	Anticipation medicine is used to implement risk reduction measures promptly and proactively by predicting the timing and location of potential cardiovascular events in an individual and warn both the physician and patient. It analyzes the patient's time-series and individual-based big data, such as lifestyle, environmental factors, and biomarkers
Digital health/electronic health (e-Health) ^[9]	This is a field of knowledge and practice to improve healthcare associated with the development and use of digital technologies. Digital healthcare expands the concept of e-Health to include digital consumers, with a wider range of smart devices and connected equipment. It also encompasses other digital technologies for health, such as the Internet of things, artificial intelligence, big data, and robotics
Digital hypertension ^[8]	This is an academic concept that applies rapidly evolving digital health technologies and artificial intelligence to hypertension care and research. It includes the study of pathogenesis and predictive, individualized, and preemptive treatments
Digital medicine	This aspect of digital healthcare relates specifically to medical care and treatment. Digital medicine encompasses both the objectives of digital healthcare and the means of dealing with them
Digital therapeutics (DTx)/digital therapy ^[6,65]	Evidence-based treatment interventions are applied via high-quality software programs. DTx/digital therapy is generally approved by regulatory authorities with the aim of treating and managing the disease. The patient is prescribed this therapy or therapeutics by their healthcare provider and follows the guidance of an app downloaded to their smartphone or tablet to monitor and improve their lifestyle and manage their medication between visits to the healthcare provider
Electronic health record (EHR)/personal health record (PHR)	A patient's electronic health record (EHR) is entered and stored in a network of medical information among medical institutions for mutual use. A patient's personal health record (PHR) is the information that unifies his or her personal medical records, medical checkup data, biometric information monitored in daily life, and nursing care records, and the PHR can be managed and utilized throughout the patient's life. Analysis of such big data can be used in future medical policy and clinical evidence
Environmental sensing/environmental sensor ^[1]	Environmental sensors (room temperature, barometric pressure, humidity, brightness, etc.) can be installed to identify aspects of a living or working environment that pose risks for the development of disease. Simultaneous analyses with biomonitoring may reveal the extent of the risks
Mobile health (m-Health)	Digital healthcare using mobile devices and apps. m-Health is the general term for health management through portable or wearable devices and smartphone apps
Precision medicine ^[1,7]	Customized medicine in which medical decisions, treatment, and management are tailored to each patient based on the evidence of risk factor identification and treatment methods constructed using resident-based big data such as genetic information and cohort data is called precision medicine
Telecare ^[3]	Telecare is the provision of assistance to a patient at home based on continuous and automatic monitoring of the patient from a distance with ICT. In the event of an accident or the need for urgent medical treatment, an alert is sent to the patient's healthcare provider, and assistance is arranged
Telemedicine ^[3]	Telemedicine is the remote exchange of medical data between patients and healthcare professionals for diagnoses, treatments, and prescriptions. It improves patients' access to healthcare and provides effective medical services in remote areas. It also includes the exchange of valid information and education materials among healthcare professionals for the purposes of medical collaboration and education
Telemonitoring ^[3]	This is a system in which medical professionals remotely manage the health of patients. Patient's data are transmitted to medical institutions and shared with medical professionals using medical devices connected to an ICT system
Wearable device/biosensor/biosensing device ^[1]	Portable or wearable devices with biometric sensors are used outside of healthcare facilities. By connecting the devices to an ICT system, the data can be managed on a server and shared between the patient and his or her doctor

ICT: Information and communication technology.

BLOOD PRESSURE MONITORING TO DETECT CARDIOVASCULAR RISK

BP is constantly fluctuating, and fluctuations in cardiovascular risks occur in tandem. Many factors influence BP variability. The precise relationships between BP measurements and potentially elevated pressure triggers such as environmental factors, physical activity, and psychological stress must therefore be established.

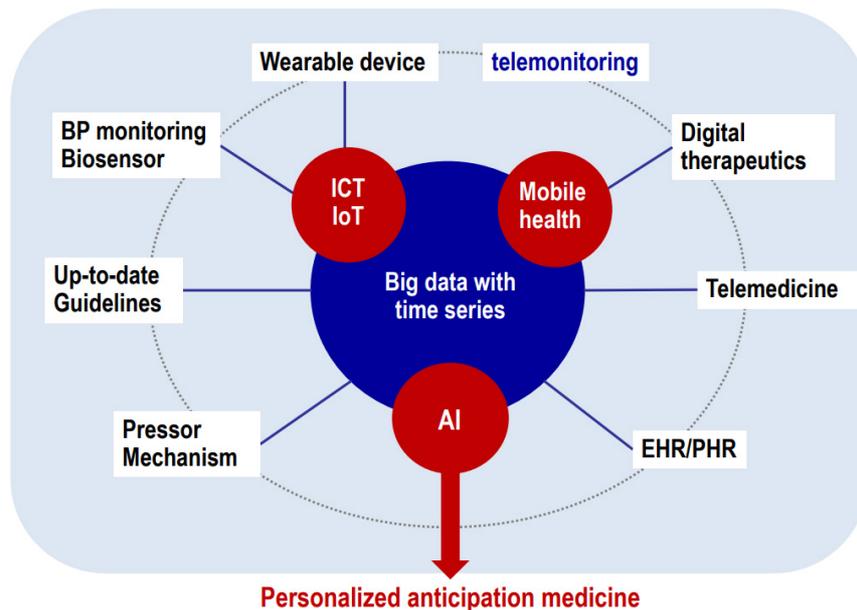


Figure 1. The concept and contents of digital hypertension: telemonitoring is combined with digital hypertension for anticipation medicine. Used with permission from Kario et al. *Hypertension Res.* 2022, in press.

The 24 h BP variability profile and the resonance hypothesis of BP surges

The BP resonance hypothesis is as follows: the peak of BP fluctuations at different times (e.g., by heartbeat, during the 24 h day, and across days, seasons, and years) resonates when various triggers for BP elevation (e.g., temperature, mental stress, sleep apnea, and exercise) happen simultaneously, producing an enormous dynamic BP surge that induces cardiovascular disease [Figure 2]^[12]. Patients with advanced arterial stiffness, who are unable to “attenuate” the surge in peripheral blood vessels, are particularly susceptible to the resonance of BP surges^[13]. Since the 24 h BP variability profile and the factors or “triggers” for BP surges vary from patient to patient [Figure 2]^[12], there are large individual differences in diurnal BP and BP responses to stressful situations. In addition, the acti-sensitivity (i.e., the slope of the regression line of free-running BP against the logarithm of physical activity) of hypertensive patients varies with the season, and the BP surge during exercise in winter is higher than that in summer^[14].

In general, BP shows a diurnal variation, with higher values in the early morning and lower values at night. Nocturnal hypertension of the “riser” type, in which BP rises at night, is an abnormal pattern of diurnal variation in BP. Both nocturnal hypertension and the riser type assessed by ABPM increase the risk of organ damage and cardiovascular events^[15]. The riser type of nocturnal hypertension tends to have the greatest impact, especially as it poses a clear risk for heart failure independent of the BP level^[16]. Nocturnal hypertension is more common in Asians and is also associated with salt-sensitive hypertension and sleep apnea syndrome. Excessive BP morning surges, even in the absence of nocturnal hypertension, contribute to an increased risk of stroke and cerebral hemorrhage, as well as organ damage^[15].

Evidence, guidelines, and limitations of BP monitoring

The JSH2019 Guidelines for the Treatment of Hypertension and other major guidelines including the American College of Cardiology/American Heart Association (ACC/AHA) guidelines and the European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines recommend the out-of-office measurement of BP using 24 h ABPM and home BP monitoring for the diagnosis and treatment of hypertension^[17-19]. Home BP and 24 h ambulatory BP are better prognostic predictors of organ damage and

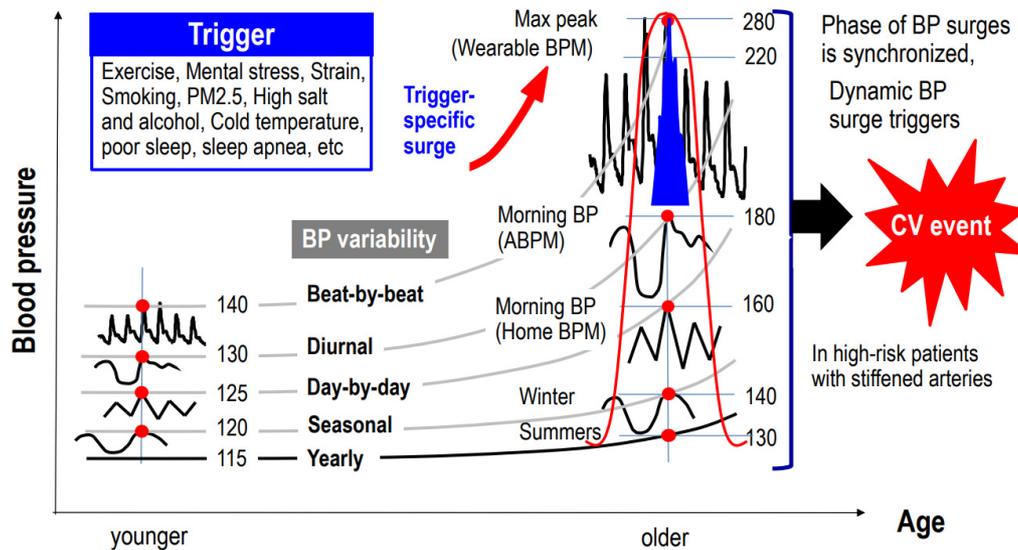


Figure 2. The synergic resonance hypothesis of blood pressure variability. Used with permission from Kario et al.^[12]

cardiovascular disease risk than office BP in various stages of hypertension^[1,20-22], including in drug-resistant hypertensive patients^[23-26]. Long-term home BP monitoring can detect seasonal variations of BP, which can trigger cardiovascular events in winter^[27,28]. These advantages make it possible that BP monitoring should be managed seamlessly to shift from a spot at the doctor's office to consecutive daily measurements. Telemonitoring is thus an indispensable tool for collecting and managing these data.

Nonetheless, there are limitations and restrictions in the use of BP measurements by the currently available devices; for example, home BP is almost always monitored at limited regular intervals, and an ABPM device tends to interfere with sleep at night. There are also issues of patient comfort, convenience, and medical cost. There is an urgent need for innovations in wearable BP measurement technology in order to realize continuous BP measurement with less stress to the patient, along with validated evidence of the accuracy and reliability of the technologies. We believe that accurate wearable BP monitoring incorporating digital technology which facilitates continuous BP management can minimize the risk of cardiovascular events in individuals. Such wearable devices will support the maintenance of “perfect 24 h BP control”: (1) 24 h BP < 130/80 mmHg; (2) normal BP circadian rhythm; and (3) moderate BP variability^[1,3,7].

WEARABLE BP MONITORING DEVICES AND DIGITAL PLATFORMS

Cuff-less wearable BP monitoring

The development of wearable BP monitors to accurately detect BP variability profiles and triggers that differ among individuals is thriving. While various wearable BP monitors have been researched and developed, including wrist- or finger-type devices, the measurement approach based on oscillometric and tonometric methods is more accurate in principle. The oscillometric method is widely used in office BP, home BP, and ambulatory BP monitoring.

Arterial tonometry has recently been a focus in the development of cuff-less wearable devices; arterial tonometry measures the arterial BP waveform with arterial wall appplanation of the radial artery at the wrist^[7,29,30]. The wearable tonometry device can measure BP values in real time at each heartbeat under free movement conditions. If the accuracy of this device can be sufficiently validated, it may be possible to evaluate the BP variability, which is not captured by the conventional oscillometric device. However, there

are limitations to this method^[7,29,30]. Hydrostatic pressure arising from misalignment of the wrist and heart position can affect the BP values, and the device must be calibrated with a validated cuff-based device before use in each patient^[31].

Cuff-less wearable devices using different methodologies, such as photoplethysmography, pulse transit time, and pulse wave analysis, are also available. However, the reliability of the measurements using these technologies is still limited^[11], and the accuracy is lower under free movement than by the cuff-based ABPM, although some devices and apps have been validated in accordance with common clinical standards^[31]. A cuff-less device using the new techniques is currently at the research and development stage^[29,32-34].

Therefore, cuff-less BP monitoring devices should not be used for diagnostic or treatment decisions in clinical practice until the accuracy of the absolute values of BP in ambulatory conditions is confirmed.

Wrist-cuff BP monitoring

A new wrist-cuff device based on the oscillometric method (model HEM6410T; Omron, Kyoto, Japan) has been in development and is expected to provide more comfort and less muscle pressure than the conventional upper-arm cuff. The accuracy of the wristwatch BP monitor was recently evaluated under guideline 59 of the American National Standards Institute/Association for the Advancement of Medical Instrumentation/International Organization for Standardization (ANSI/AAMI/ISO) 81060-2:2013^[35].

In addition to accuracy evaluation tests in the office according to the standard method, there is also a need for comparisons between the wearable BP monitor and conventional devices for measuring out-of-office BP, ambulatory BP, and home BP. To this end, we compared the BP values of outpatients who were simultaneously wearing a wristwatch-type wearable BP monitoring device (HEM6410T) and a conventional ABPM in the office and out of the office^[36]. No statistically significant difference was identified between the BP values measured by the two devices, indicating that the accuracy of the wristwatch-type device is acceptable^[36]. This BP monitor can capture daily psychological stress and elevated BP in the workplace^[37], and the BP data obtained by the wearable device are significantly correlated with the wearer's left ventricular mass values^[38].

Nocturnal home oscillometric BP monitors that automatically measure BP at regular intervals during sleep have been developed, and several clinical trials using these devices have provided evidence on the risks of nocturnal BP^[39-44]. A wrist-type oscillometric BP monitoring method has also been developed and well validated. In direct comparison studies in patients' home settings, this wrist device was associated with less sleep disturbance than a brachial type device, and the nighttime BP data are reproducible and comparable between the two devices^[45-49]. These findings support one of the above-described aims of digital hypertension management, i.e., to provide appropriate management and potential interventions for nocturnal hypertension and nocturnal BP variability.

The development and progress of digital platforms

The latest ACC/AHA guidelines state that healthcare ICT solutions will play a significant role in the diagnosis and management of hypertension in the near future^[18]. Telemedicine solutions are increasingly practical for the management of hypertension with wearable device technology. Although telemedicine has presented the possibilities of reducing BP and cardiovascular risk compared to more traditional care^[1-3,50,51], much more evidence is needed regarding how to best incorporate interactive digital interventions into diverse healthcare settings, including the cost-effectiveness. The following are some of the results of research conducted in Japan thus far.

Once specific residential environmental risks have been identified, it may be possible to perform simultaneous monitoring of residential environment data and individual time series data using a multisensor ICT system and, thereby, reduce cardiovascular risk through more comprehensive BP management [Figure 3] (http://www.jichi.ac.jp/usr/card/research/index_en.html)^[52]. For example, cold temperature is a residential environmental risk that might be targeted. Cold temperatures can increase BP via activation of the sympathetic nervous system, vasoconstriction, and reduced vascular endothelial function, and cold temperatures have consistently been shown to be associated with early morning hypertension, increased BP variability, and an increased risk of cardiovascular disease events^[53-56].

One example of a practical application of the remote management of hypertension is a study conducted in the areas affected by the Great East Japan Earthquake on 11 March 2011. In light of the evidence that the BP and cardiovascular event risks of individuals increase after a catastrophic disaster^[57,58], we established the Disaster Cardiovascular Prevention (DCAP) network, a remote ICT BP monitoring system using cloud computing that was introduced to a town devastated by the earthquake and subsequent tsunami^[59]. This network helped the participants follow strict BP control at the disaster shelters and home and enabled them to share their daily BP values with their physicians; the physicians could thus change their patients' medications immediately as needed. The introduction of the DCAP network contributed to the minimizing of seasonal variations in the BP of participants for months and years after the disaster [Figure 4]^[60]. These reports indicate that a similar network could be applied to routine BP monitoring in any community.

ADVANCE OF ANTICIPATION MEDICINE

Anticipation medicine is a concept of medical treatment that enables proactive intervention for early event avoidance and risk reduction. In practice, anticipation medicine consists of identifying increased risk factors by collecting a series of long-term, "big data" in a backward-looking manner and using it to predict the onset of cardiovascular events in a forward-looking manner^[1,7,11]. By combining anticipation medicine with precision medicine (customizing treatment and management for each patient, including determining a treatment strategy), we can achieve optimal individualized hypertension treatment by predicting the pathogenesis of individuals' hypertension and risks of BP variability in real time^[7].

The prediction of specific times and places conferring risk of cardiovascular events would need to be coupled with available preventative measures, including the titration of medications, and desynchronization of BP pressure surges generated by synergistic resonance of individual BP surges in different time phases, which are triggered by various pressor stimuli, *etc.*^[14].

Prediction models with AI

The mastery of AI using real-time big data obtained from wearable BP monitoring and digital technology is an innovative and developing field^[1,3,7,61]. Using machine learning methods, we developed a highly accurate model to predict the development of hypertension in the general population using data from 18,258 individuals^[62]. The results allowed us to identify individuals at risk of developing hypertension. Another AI-based prediction model using time-series BP data and a multi-input multi-output deep neural network also showed the possibility of predicting elevations of both mean BP and BP variability^[63]. Considering that abnormal BP variability is a serious risk factor for cardiovascular disease, the developed predictive model for the onset of the disease is a hallmark of AI applications that can lead to early interventions, such as lifestyle improvement, to prevent the onset of hypertension.

The future of digital therapeutics

Smartphone applications that modify lifestyle habits as a form of digital therapeutics have been put to

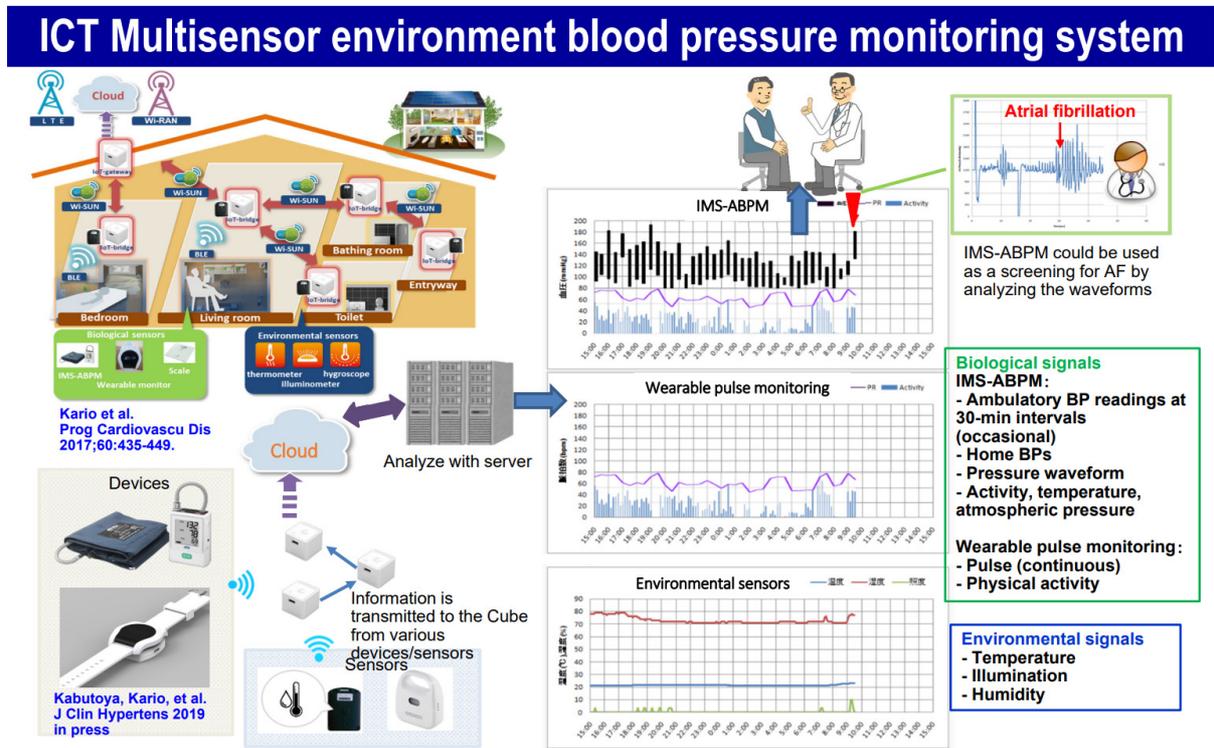


Figure 3. An ICT multisensor environment blood pressure monitoring system. The monitoring of residential environment data can be effective for hypertension management. Used with permission from Kario *et al.*^[52]. ICT: Information and communication technology.

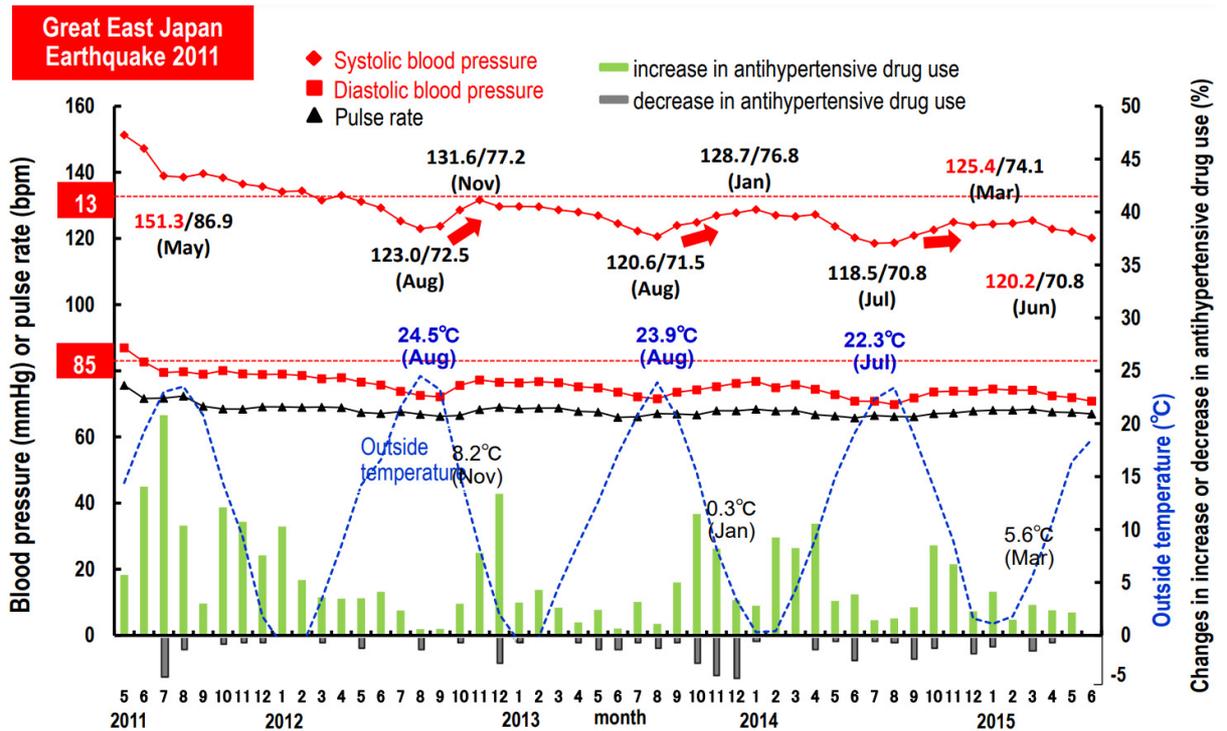


Figure 4. Changes in home blood pressure in participants ($n = 351$) in the Disaster Cardiovascular Prevention (DCAP) network after the 2011 Great East Japan Earthquake. Used with permission from Nishizawa *et al.*^[60].

practical use, and a new “application for hypertension treatment” was confirmed to have an antihypertensive effect^[64]. This application analyzes the medical background of the patient and determines the patient’s BP trends via telemonitoring; it suggests lifestyle modifications suitable for each individual and supports behavioral changes. This type of digital therapeutics will radically modify the practice of medicine from a “spot” in the doctor’s office to a “line” that tracks behavior and data in chronological order, and then to a “surface” that obtains and analyzes multifaceted data for each individual and feeds back appropriate guidance to each individual^[65]. The multidimensional data collected in the application for hypertension treatment will enable the prediction of BP characteristics and risk factors by deriving factors that affect the BP of individuals, which will lead to the realization of personalized anticipation medicine.

Interactions between patients and healthcare providers, and treatment via telemonitoring

Sharing information and collaboration regarding goals and implementation plans between patients and healthcare providers are essential to enhance the effectiveness of treatment. These actions maintain a patient’s motivation concerning his or her hypertension treatment and the sharing of information about antihypertensive goals, lifestyle modifications, and medication adherence, even outside the office. Telemonitoring is a tool to facilitate two-way communication between patients and healthcare providers, as digital technology bridges the gaps of geographic distance and time to share real-time patient information^[1-3]. The establishment of mutual trust between patients and medical professionals and the collaboration of medical teams will help eliminate the “hypertension paradox” (i.e., although the treatment of hypertension has greatly improved, the total number of individuals with uncontrolled hypertension has continued to increase) and avoid clinical inertia, thus contributing to the effectiveness of hypertension treatment. As a result, individualized anticipation medicine will be realized in the near future [Figure 5]^[14].

Evidence and penetration gaps

There are significant evidence gaps between digital hypertension research and clinical practice. While most of the world now has access to phones, there are obvious inequalities and barriers to accessing more specialized technologies that are important to consider (ideally sooner rather than later). There are significant disparities among different countries. There are also important disparities within individual countries. For example, lower socioeconomic status and older age are barriers to realizing the benefits of ICT-based connected health.

CONCLUSION AND PERSPECTIVES

Hypertension is a considerable and measurable risk factor for cardiovascular disease. In recent years, large-scale natural disasters and infectious diseases have made it challenging to continue to provide appropriate medical care around the world. In response, the development of digital hypertension management consisting of telemonitoring and AI applications have the potential to realize the seamless provision of medical care unconstrained by time and distance. The digital management of hypertension will also upgrade the accuracy of hypertension diagnoses and the quality of BP management, which will contribute to the amelioration of the hypertension paradox. Such progress in personalized anticipation medicine is also expected to decrease the incidence of cardiovascular disease events.

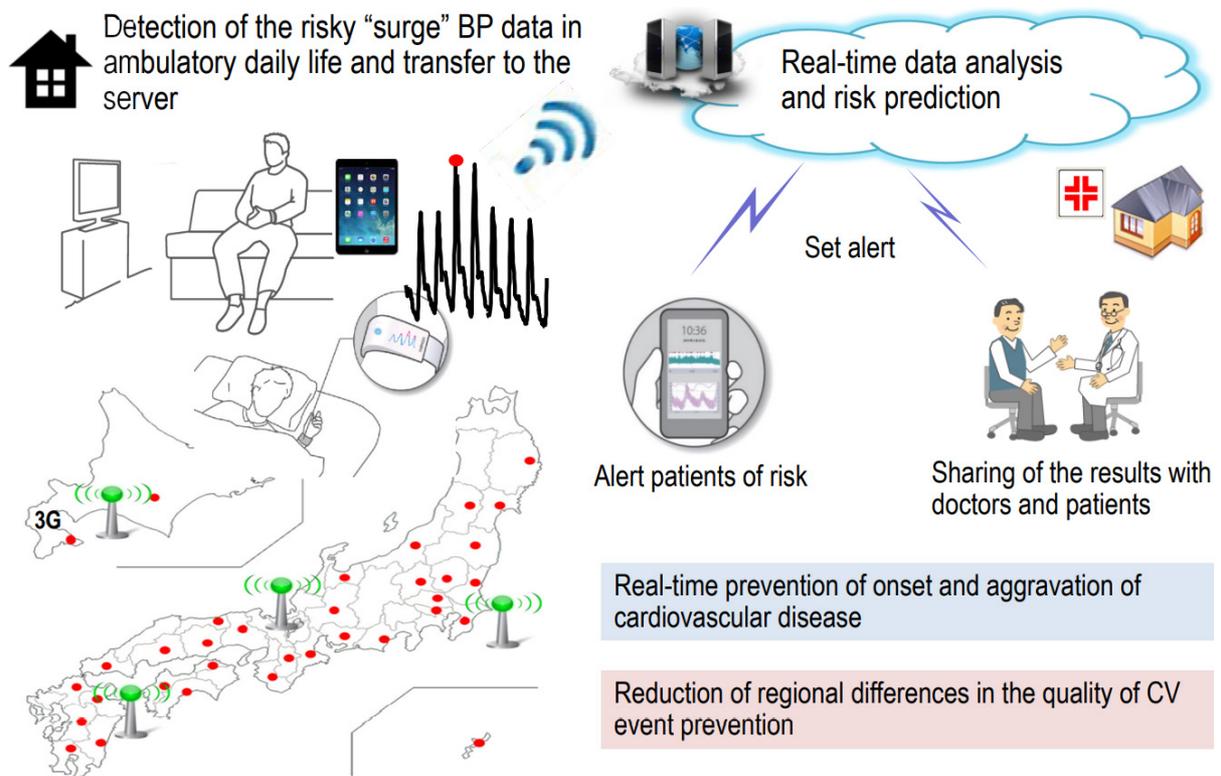


Figure 5. The model of ICT-based real-time anticipation telemedicine of cardiovascular disease. Used with permission from Kario et al.^[14]. ICT: Information and communication technology.

DECLARATIONS

Authors' contributions

Conceptualized the manuscript: Kario K
 Wrote the 1st draft: Kario K, Harada N
 Edited the manuscript style: Okura A
 All the authors reviewed and edited the final manuscript.

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Kario K received research grants from A&D Co. (Tokyo) and from Omron Healthcare (Kyoto, Japan), and a consulting fee from CureApp, Inc. (Tokyo). Other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Copyright

© The Author(s) 2022.

REFERENCES

1. Kario K. Essential manual of perfect 24-hour blood pressure management from morning to nocturnal hypertension. UK: Wiley Black Well; 2022. p. 1-384. DOI
2. Pellegrini D, Torlasco C, Ochoa JE, Parati G. Contribution of telemedicine and information technology to hypertension control. *Hypertens Res* 2020;43:621-8. DOI PubMed
3. Omboni S, McManus RJ, Bosworth HB, et al. Evidence and recommendations on the use of telemedicine for the management of arterial hypertension: an international expert position paper. *Hypertension* 2020;76:1368-83. DOI PubMed
4. Kario K, Morisawa Y, Sukonthasarn A, et al; Hypertension Cardiovascular Outcome Prevention; Evidence in Asia (HOPE Asia) Network. COVID-19 and hypertension-evidence and practical management: guidance from the HOPE Asia Network. *J Clin Hypertens (Greenwich)* 2020;22:1109-19. DOI PubMed PMC
5. Shibata S, Arima H, Asayama K, et al. Hypertension and related diseases in the era of COVID-19: a report from the Japanese Society of Hypertension Task Force on COVID-19. *Hypertens Res* 2020;43:1028-46. DOI PubMed PMC
6. Wang JG, Li Y, Chia YC, et al; Hypertension Cardiovascular Outcome Prevention; Evidence (HOPE) Asia Network. Telemedicine in the management of hypertension: Evolving technological platforms for blood pressure telemonitoring. *J Clin Hypertens (Greenwich)* 2021;23:435-9. DOI PubMed PMC
7. 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;59:262-81. DOI PubMed
8. Matsuoka R, Akazawa H, Kodera S, Komuro I. The dawning of the digital era in the management of hypertension. *Hypertens Res* 2020;43:1135-40. DOI PubMed
9. World Health Organization. WHO Guideline; recommendations on digital interventions for health system strengthening. Available from: <https://www.who.int/reproductivehealth/publications/digital-interventions-health-system-strengthening/en/> [Last accessed on 11 Mar 2022].
10. Yatabe J, Yatabe MS, Ichihara A. The current state and future of internet technology-based hypertension management in Japan. *Hypertens Res* 2021;44:276-85. DOI PubMed PMC
11. Kario K. Management of hypertension in the digital era: small wearable monitoring devices for remote blood pressure monitoring. *Hypertension* 2020;76:640-50. DOI PubMed PMC
12. 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;29:14-6. DOI PubMed
13. Kario K, Chirinos JA, Townsend RR, et al. Systemic hemodynamic atherothrombotic syndrome (SHATS) - coupling vascular disease and blood pressure variability: proposed concept from pulse of Asia. *Prog Cardiovasc Dis* 2020;63:22-32. DOI PubMed
14. Kario K, Tomitani N, Kanegae H, et al. 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;60:435-49. DOI PubMed
15. Kario K, Thijs L, Staessen JA. Blood pressure measurement and treatment decisions. *Circ Res* 2019;124:990-1008. DOI PubMed
16. Kario K, Hoshida S, Mizuno H, et al; JAMP Study Group. Nighttime blood pressure phenotype and cardiovascular prognosis: practitioner-based nationwide JAMP study. *Circulation* 2020;142:1810-20. DOI PubMed PMC
17. Umemura S, Arima H, Arima S, et al. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019). *Hypertens Res* 2019;42:1235-481. DOI PubMed
18. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018;71:1269-324. DOI PubMed
19. Williams B, Mancia G, Spiering W, et al; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39:3021-104. DOI PubMed
20. Kario K, Shimbo D, Hoshida S, et al. Emergence of home blood pressure-guided management of hypertension based on global evidence. *Hypertension* 2019. DOI PubMed PMC
21. Kario K. Global Impact of 2017 American Heart Association/American College of Cardiology Hypertension Guidelines: a perspective from Japan. *Circulation* 2018;137:543-5. DOI PubMed
22. Kubozono T, Akasaki Y, Kawasoe S, et al. The relationship between day-to-day variability in home blood pressure measurement and multiple organ function. *Hypertens Res* 2022;45:474-82. DOI PubMed
23. Nagai M, Dote K. Treatment-resistant hypertension assessed by home blood pressure monitoring: a new target for intervention? *Hypertens Res* 2022;45:167-9. DOI PubMed
24. Narita K, Hoshida S, Kario K. Difference between morning and evening home blood pressure and cardiovascular events: the J-HOP Study (Japan Morning Surge-Home Blood Pressure). *Hypertens Res* 2021;44:1597-605. DOI PubMed
25. Kario K, Hoshida S, Narita K, Okawara Y, Kanegae H; Investigators' network. Cardiovascular prognosis in drug-resistant hypertension stratified by 24-hour ambulatory blood pressure: the JAMP study. *Hypertension* 2021;78:1781-90. DOI PubMed
26. Narita K, Hoshida S, Kario K. Nighttime home blood pressure is associated with the cardiovascular disease events risk in treatment-

- resistant hypertension. *Hypertension* 2022;79:e18-20. DOI PubMed
27. Narita K, Hoshide S, Kario K. Seasonal variation in blood pressure: current evidence and recommendations for hypertension management. *Hypertens Res* 2021;44:1363-72. DOI PubMed
 28. Stergiou GS, Palatini P, Modesti PA, et al. Seasonal variation in blood pressure: evidence, consensus and recommendations for clinical practice. Consensus statement by the European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability. *J Hypertens* 2020;38:1235-43. DOI PubMed
 29. Kokubo A, Kuwabara M, Ota Y, et al. Nocturnal blood pressure surge in seconds is a new determinant of left ventricular mass index. *J Clin Hypertens (Greenwich)* 2021. DOI PubMed
 30. Ota Y, Kokubo A, Yamashita S, Kario K. Development of small and lightweight beat-by-beat blood pressure monitoring device based on tonometry. *Annu Int Conf IEEE Eng Med Biol Soc* 2021;2021:5455-8. DOI PubMed
 31. Bard DM, Joseph JI, van Helmond N. Cuff-less methods for blood pressure telemonitoring. *Front Cardiovasc Med* 2019;6:40. DOI PubMed PMC
 32. Watanabe T, Hoshide S, Kario K. Noninvasive method to validate the variability of blood pressure during arrhythmias. *Hypertens Res* 2022;45:530-2. DOI PubMed
 33. Hoshide S, Yoshihisa A, Tsuchida F, et al. Pulse transit time-estimated blood pressure: a comparison of beat-to-beat and intermittent measurement. *Hypertens Res* 2022.
 34. Miao F, Zhou B, Liu Z, Wen B, Li Y, Tang M. Using noninvasive adjusted pulse transit time for tracking beat-to-beat systolic blood pressure during ventricular arrhythmia. *Hypertens Res* 2022;45:424-35. DOI PubMed
 35. Kuwabara M, Harada K, Hishiki Y, Kario K. Validation of two watch-type wearable blood pressure monitors according to the ANSI/AAMI/ISO81060-2:2013 guidelines: Omron HEM-6410T-ZM and HEM-6410T-ZL. *J Clin Hypertens (Greenwich)* 2019;21:853-8. DOI
 36. Kario K, Shimbo D, Tomitani N, Kanegae H, Schwartz JE, Williams B. The first study comparing a wearable watch-type blood pressure monitor with a conventional ambulatory blood pressure monitor on in-office and out-of-office settings. *J Clin Hypertens (Greenwich)* 2020;22:135-41. DOI PubMed PMC
 37. Tomitani N, Kanegae H, Suzuki Y, Kuwabara M, Kario K. Stress-induced blood pressure elevation self-measured by a wearable watch-type device. *Am J Hypertens* 2021;34:377-82. DOI PubMed PMC
 38. Kario K, Tomitani N, Morimoto T, Kanegae H, Lacy P, Williams B. Relationship between blood pressure repeatedly measured by a wrist-cuff oscillometric wearable blood pressure monitoring device and left ventricular mass index in working hypertensive patients. *Hypertens Res* 2022;45:87-96. DOI PubMed
 39. Kario K. Nocturnal hypertension: new technology and evidence. *Hypertension* 2018;71:997-1009. DOI PubMed
 40. Kario K, Kanegae H, Tomitani N, et al. Nighttime blood pressure measured by home blood pressure monitoring as an independent predictor of cardiovascular events in general practice. *Hypertension* 2019;73:1240-8. DOI PubMed PMC
 41. Fujiwara T, Hoshide S, Kanegae H, Kario K. Cardiovascular event risks associated with masked nocturnal hypertension defined by home blood pressure monitoring in the J-HOP nocturnal blood pressure study. *Hypertension* 2020;76:259-66. DOI PubMed
 42. Kario K. Home blood pressure monitoring: current status and new developments. *Am J Hypertens* 2021;34:783-94. DOI PubMed PMC
 43. Kario K, Hoshide S, Nagai M, Okawara Y, Kanegae H. Sleep and cardiovascular outcomes in relation to nocturnal hypertension: the J-HOP Nocturnal Blood Pressure Study. *Hypertens Res* 2021;44:1589-96. DOI PubMed
 44. Hoshide S, Kanegae H, Kario K. Nighttime home blood pressure as a mediator of N-terminal pro-brain natriuretic peptide in cardiovascular events. *Hypertens Res* 2021;44:1138-46. DOI PubMed
 45. Kuwabara M, Harada K, Hishiki Y, Ohkubo T, Kario K, Imai Y. Validation of a wrist-type home nocturnal blood pressure monitor in the sitting and supine position according to the ANSI/AAMI/ISO81060-2:2013 guidelines: Omron HEM-9601T. *J Clin Hypertens (Greenwich)* 2020;22:970-8. DOI
 46. Kario K, Tomitani N, Iwashita C, Shiga T, Kanegae H. Simultaneous self-monitoring comparison of a supine algorithm-equipped wrist nocturnal home blood pressure monitoring device with an upper arm device. *J Clin Hypertens (Greenwich)* 2021;23:793-801. DOI PubMed PMC
 47. Tomitani N, Kanegae H, Kario K. Comparison of nighttime measurement schedules using a wrist-type nocturnal home blood pressure monitoring device. *J Clin Hypertens (Greenwich)* 2021;23:1144-9. DOI PubMed PMC
 48. Tomitani N, Kanegae H, Kario K. Reproducibility of nighttime home blood pressure measured by a wrist-type nocturnal home blood pressure monitoring device. *J Clin Hypertens (Greenwich)* 2021;23:1872-8. DOI PubMed PMC
 49. Tomitani N, Hoshide S, Kario K. Accurate nighttime blood pressure monitoring with less sleep disturbance. *Hypertens Res* 2021;44:1671-3. DOI PubMed
 50. Margolis KL, Dehmer SP, Sperl-Hillen J, et al. Cardiovascular events and costs with home blood pressure telemonitoring and pharmacist management for uncontrolled hypertension. *Hypertension* 2020;76:1097-103. DOI PubMed PMC
 51. McManus RJ, Little P, Stuart B, 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 PubMed PMC
 52. Kario K, Tomitani N, Kanegae H, Yasui N, Nagai R, Harada H. The further development of out-of-office BP monitoring: Japan's ImPACT Program Project's achievements, impact, and direction. *J Clin Hypertens (Greenwich)* 2019;21:344-9. DOI PubMed PMC
 53. Umishio W, Ikaga T, Kario K, et al; SWH Survey Group. Cross-sectional analysis of the relationship between home blood pressure and indoor temperature in winter: a nationwide smart wellness housing survey in Japan. *Hypertension* 2019;74:756-66. DOI PubMed

54. Umishio W, Ikaga T, Kario K, et al; SWH survey group. Impact of indoor temperature instability on diurnal and day-by-day variability of home blood pressure in winter: a nationwide Smart Wellness Housing survey in Japan. *Hypertens Res* 2021;44:1406-16. DOI PubMed PMC
55. Modesti PA. The shifted focus of interest in the temperature-blood pressure relationship: from load to variability. *Hypertens Res* 2021;44:1548-50. DOI PubMed
56. Yano Y. Blood pressure management in an ecosystem context. *Hypertens Res* 2020;43:989-94. DOI PubMed
57. Kario K. Disaster hypertension - its characteristics, mechanism, and management-. *Circ J* 2012;76:553-62. DOI PubMed
58. Narita K, Hoshide S, Kario K. Time course of disaster-related cardiovascular disease and blood pressure elevation. *Hypertens Res* 2021;44:1534-9. DOI PubMed
59. Kario K, Nishizawa M, Hoshide S, et al. Development of a disaster cardiovascular prevention network. *Lancet* 2011;378:1125-7. DOI PubMed
60. Nishizawa M, Hoshide S, Okawara Y, Matsuo T, Kario K. Strict blood pressure control achieved using an ICT-based home blood pressure monitoring system in a catastrophically damaged area after a disaster. *J Clin Hypertens (Greenwich)* 2017;19:26-9. DOI PubMed PMC
61. Tsoi K, Yiu K, Lee H, et al; Hope Asia Network. Applications of artificial intelligence for hypertension management. *J Clin Hypertens (Greenwich)* 2021;23:568-74. DOI PubMed PMC
62. Kanegae H, Suzuki K, Fukatani K, Ito T, Harada N, Kario K. Highly precise risk prediction model for new-onset hypertension using artificial intelligence techniques. *J Clin Hypertens (Greenwich)* 2020;22:445-50. DOI PubMed PMC
63. Koshimizu H, Kojima R, Kario K, Okuno Y. Prediction of blood pressure variability using deep neural networks. *Int J Med Inform* 2020;136:104067. DOI PubMed
64. Kario K, Nomura A, Harada N, et al. Efficacy of a digital therapeutics system in the management of essential hypertension: the HERB-DH1 pivotal trial. *Eur Heart J* 2021;42:4111-22. DOI PubMed PMC
65. Digital Therapeutics Alliance. Digital Therapeutics Definition and Core Principles. Available from: https://dtxalliance.org/wp-content/uploads/2021/01/DTA_DTx-Definition-and-Core-Principles.pdf [Last accessed on 11 Mar 2022].