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EDITORIAL

Special Issue: Current evidence and perspectives for hypertension management in Asia

Latest hypertension research to inform clinical practice in Asia

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Abstract

Despite the challenges associated with the coronavirus pandemic, the last 2 years have been active periods for hypertension research and initiatives in Asia. There are new hypertension guidelines from the World Health Organization that can be interpreted and applied locally. This is also the case for data from the latest Blood Pressure Lowering Treatment Trialists' Collaboration meta-analysis, which showed that greater reductions in systolic blood pressure (BP) are associated with lower risks of cardiovascular events. The randomized controlled Strategy of Blood Pressure Intervention in the Elderly Hypertensive study and the Salt Substitute and Stroke Study provide local data to inform practice. Other initiatives to help reduce high salt intake in Asia are also underway. Both drug-resistant and nocturnal hypertension are appropriate areas of focus in Asia, and there are an increasing number of pharmacological and non-pharmacological treatment options for these conditions. Digital therapeutics to promote uptake and implementation of lifestyle interventions are showing promise, and other digital-based strategies such as telemedicine, wearable BP monitors to detect beat-by-beat BP and artificial intelligence will no doubt become integral parts of future strategies to reduce the burden of hypertension and hypertension-related disease. A number of initiatives from the Hypertension Cardiovascular Outcome Prevention and Evidence in Asia Network and Japanese Society of hypertension are underway, and there is good reason for optimism regarding the ongoing and future management of hypertension in Asia based on these and the active research activities in the region.

Keywords Hypertension · Antihypertensives · Cardiovascular risk · Digital therapeutics · Artificial intelligence · Blood pressure monitoring

Introduction

As the second year of the coronavirus pandemic comes to an end, global issues around low rates of achievement of blood pressure (BP) control have not improved, and hypertension remains a prevalent and significant health issue worldwide [1, 2]. This is due, at least in part, to the reluctance of patients with chronic diseases to seek medical care due to fear of infection with SARS-CoV-2, and the worsening economic situation. However, the greater burden of coronavirus illness (COVID-19) in patients with comorbid diseases such as hypertension [3] highlights the importance of continuing to pursue important hypertension goals, including the global non-communicable disease target of reducing the prevalence of elevated BP by 25% compared with 2010 levels by 2025 [4].

Despite these challenges, the last 2 years have been active periods of hypertension research [5] and implementation of hypertension-related action plans in Asia. These data continue to highlight the need for both population-based primary prevention strategies and more effective treatments for high-risk patients with hypertension [6], something that should be achievable in all countries [2]. As has been documented previously, effective prevention and management of hypertension in Asia requires country- and region-specific approaches that take into account the Asia-specific characteristics of hypertension [7–9].

This article provides an up-to-date overview on the latest hot topics, clinical trial data, new pharmacological and non-pharmacological treatment options, and technological advances (including digital therapeutics, wearable monitoring

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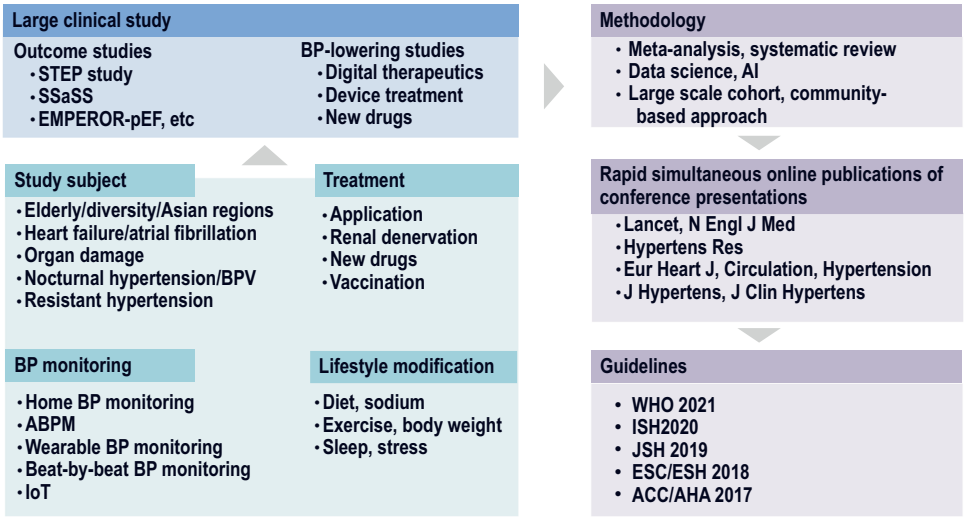

Fig. 1 Summary of hypertension research activities to inform clinical practice. ABPM ambulatory blood pressure monitoring, ACC American College of Cardiology, AHA American Heart Association, AI artificial intelligence, BP blood pressure, BPV blood pressure variability, EMPEROR-pEF EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction, ESC European Society of Cardiology, ESH European Society of Hypertension, IoT Internet of Things, ISH International Society of Hypertension, JSH Japanese Society of Hypertension, WHO World Health Organization

devices, the Internet of Things [IoT] and artificial intelligence [AI]) (Fig. 1). Asian action approaches to improve the management of hypertension are also highlighted.

Latest WHO guidelines

In 2021, the World Health Organization (WHO) published new guidelines for the pharmacological treatment of hypertension [10]. Summarizing the evidence to date, the guidelines recommend that high-risk patients should be treated promptly and reliably, starting earlier, at lower BP levels, and that the BP target should be gradually decreased. Initiation of antihypertensive therapy is recommended when BP is ≥140/90 mmHg, even in the absence of cardiovascular disease or risk factors. For patients who do have existing cardiovascular disease or cardiovascular disease risk factors and/or comorbid conditions (e.g., diabetes mellitus or chronic kidney disease [CKD]), antihypertensive drug treatment should be initiated when systolic BP (SBP) is 130–139 mmHg. In order to achieve a reliable antihypertensive effect, thiazide and thiazide-like diuretics, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and long-acting dihydropyridine calcium channel blockers (CCBs) are recommended as first-line agents. In addition, fixed-dose single pill combinations (SPCs) are recommended to reduce the number of tablets taken and improve adherence. Target BP during treatment is <140/90 mmHg in all patients without comorbidities, while reducing SBP to <130 mmHg is recommended in patients with known cardiovascular disease or those with high cardiovascular risk [10].

BPLTTC meta-analysis data

The results of the largest ever meta-analysis of antihypertensive therapy, including data from the Systolic Blood Pressure Intervention Trial (SPRINT) [11], were published in 2021 by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) [12]. This included data from 344,716 patients who participated in 48 randomized controlled trials that compared antihypertensive drug therapy versus placebo, different classes of antihypertensive agents, or intensive versus standard antihypertensive therapy [12].

Although changes in office SBP varied between studies, the meta-analysis showed that greater reductions in SBP were associated with lower risks of cardiovascular disease events. A 5-mmHg reduction in SBP was associated with an approximately 10% reduction in the rate of major vascular events, although the magnitude of risk reduction varied by the type of event (Fig. 2). The beneficial cardiovascular effects of BP lowering were consistent across baseline SBP categories and occurred regardless of baseline cardiovascular disease status [12, 13]. Pharmacological reduction of BP was also found to be effective across all age groups (including participants aged ≥85 years) [13].

Overall, the BPLTTC meta-analysis findings suggest that a fixed degree of BP lowering is effective for both the primary and secondary prevention of major cardiovascular

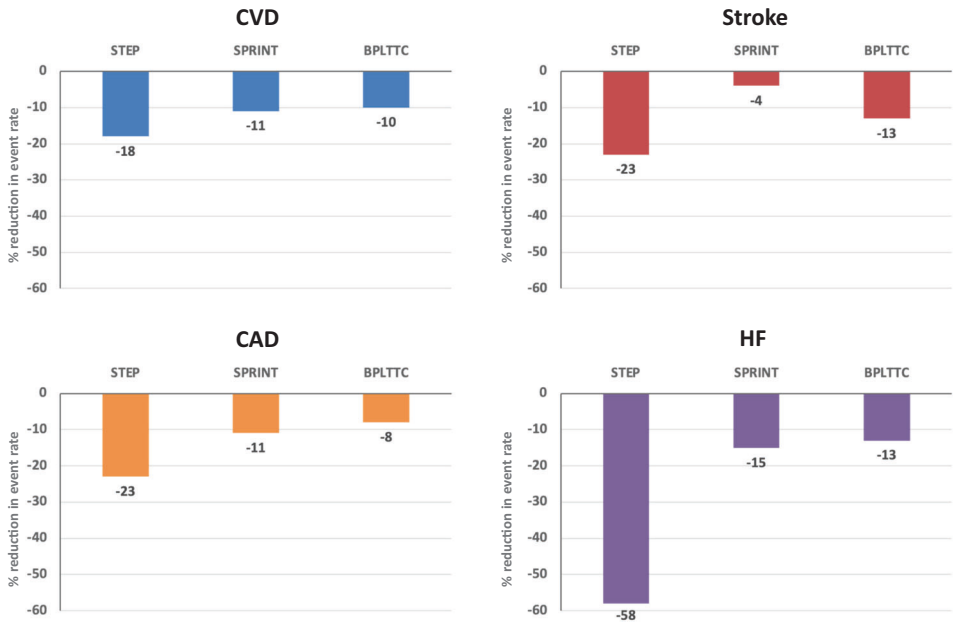

Fig. 2 Estimated cardiovascular risk reduction associated with a 5-mmHg reduction in office systolic blood pressure (SBP) in the STEP [17] and SPRINT [11] studies, and the BPLTTC meta-analysis [12]. BPLTTC Blood Pressure Lowering Treatment Trialists' Collaboration, CAD coronary artery disease (myocardial infarction [MI]/acute coronary syndrome), CVD cardiovascular disease, HF heart failure, SPRINT Systolic Blood Pressure Intervention Trial, STEP Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients. *CVD definitions as follows: STEP—composite of stroke (ischemic or hemorrhagic), acute coronary syndrome (acute MI and hospitalization for unstable angina), acute decompensated HF, coronary revascularization, atrial fibrillation, or death from cardiovascular causes; SPRINT—composite of MI, acute coronary syndrome not resulting in MI, stroke, acute decompensated HF, or death from cardiovascular causes; BPLTTC—composite of fatal or non-fatal stroke, fatal or non-fatal MI or ischemic heart disease, or heart failure causing death or requiring hospital admission

events, and that these benefits are seen even at BP levels that are below currently recommended thresholds for antihypertensive treatment initiation [12]. In addition, drug treatment of hypertension should be considered for patients of all ages, and the removal of age-related BP thresholds from international treatment guidelines was recommended [13]. The utility of antihypertensive drug therapy in older individuals is also highlighted by data showing that regimens designed to achieve intensive BP lowering tended to be more effective than standard BP-lowering treatment in trials of older patients with hypertension (age ≥70 years) (Fig. 3) [14]. Furthermore, BPLTTC data show that reducing BP is an effective strategy for preventing new-onset type 2 diabetes mellitus in patients with hypertension, especially when treatment includes an ACE inhibitor or ARB [15].

Another BPLTTC meta-analysis investigated the usefulness of antihypertensive treatment with SPCs for the primary prevention of cardiovascular disease [16]. Data from three large, randomized trials were included, and the results showed that treatment strategies including an SPC substantially reduced rates of cardiovascular disease, including myocardial infarction, revascularization, stroke and cardiovascular death. These findings were consistent for SPCs that did or did not include aspirin, and occurred irrespective of the presence of cardiometabolic risk factors [16].

High-impact clinical trials in Asia

The Strategy of Blood Pressure Intervention in the Elderly Hypertensive (STEP) [17] and Salt Substitute and Stroke Study (SSaSS) [18] were both conducted in China and the results were published in 2021.

STEP study

The randomized, controlled STEP study is a Chinese version of the SPRINT trial [11], providing specific data on the value of intensive BP lowering in an Asian population [17]. It enrolled 8511 older patients with hypertension (age 60–80 [mean 66] years) who were treated with intensified (target SBP 110–130 mmHg) or standard (target SBP 130–150 mmHg) antihypertensive therapy [17]. All subjects used smartphones and home BP monitors to continuously monitor BP, and worked with physicians to adjust medications. Over a mean follow-up of 3.34 years, the mean reduction in SBP was 19.4 mmHg in the intensified treatment group and 10.1 mmHg in the standard

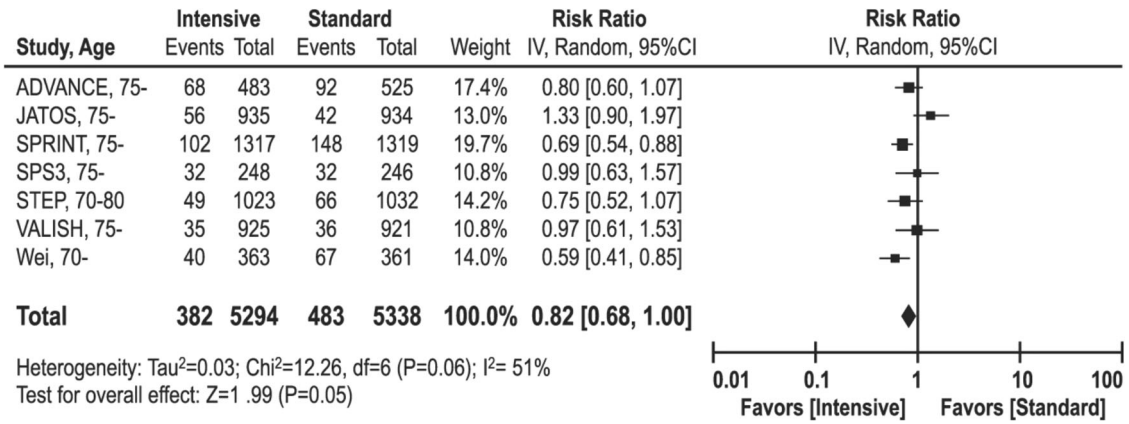

Fig. 3 Effect of intensive blood pressure-lowering during pharmacological antihypertensive therapy on the risk of composite cardiovascular events in older patients. Boxes and horizontal lines represent the risk ratio (RR) and 95% confidence interval (CI) values for individual trials, and the size of boxes is proportional to the weight of that trial result. The diamond represents the pooled RR and 95% CI for pooled estimates of effect. Reproduced, with permission, from Rakugi et al. (2022) [14]

treatment group (between-group difference: 9.3 mmHg). The difference between treatment groups in SBP was seen early after treatment initiation and was maintained throughout the study [17].

In China, as in Japan, early morning hypertension is attracting attention, and BP in the morning before taking antihypertensive medication is widely recognized as a blind spot for drug treatment. In the STEP study, there was initially almost no difference in early morning home SBP between the two treatment groups, but this difference gradually increased over time, such that the mean SBP reduction during the study period was about 7.5 mmHg greater in the intensified versus standard treatment group [17]. The risk of the composite primary outcome (a composite of stroke, acute coronary syndrome, acute uncompensated heart failure, coronary revascularization, atrial fibrillation (AF), and cardiovascular death) was reduced by 26% in patients managed using intensified treatment compared with standard treatment (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.60–0.92]; $p = 0.007$). Both stroke and acute coronary syndrome risk was reduced by 33% with intensive versus standard treatment (HR 0.67, 95% CI 0.47–0.97 and HR 0.67, 95% CI 0.47–0.94, respectively), and intensified treatment reduced the risk of acute uncompensated heart failure was reduced by almost three-quarters compared with standard therapy (HR 0.27, 95% CI 0.08–0.98). These results clearly demonstrate the benefits of intensive BP lowering.

In the STEP study, a 5-mmHg reduction in SBP was associated with an 18% reduction in the risk of major cardiovascular disease events. This is nearly twice the reduction seen in the BPLTTC meta-analysis (Fig. 2). Reductions in the risk of individual endpoint events were also numerically greater in the STEP study compared with the BPLTTC meta-analysis [12] and SPRINT [11] (Fig. 2), indicating that the benefits of BP reduction may be greater in elderly Asian populations compared with western patients. However, this issue needs to be evaluated in future studies.

The STEP study was discussed during a Super-Express Session at the Japanese Society of Hypertension (JSH) 2021 conference, and has been the subject of several editorial comments published in *Hypertension Research* [14, 19, 20]. Dr Hiromi Rakugi noted that mean BP achieved in the intensified treatment group of the STEP study (127.5 mmHg) should prompt reconsideration of the target BP level for elderly patients with hypertension in a variety of international guidelines [14]. He also noted that the results of this study should be used to educate physicians and help overcome clinical inertia [14], which is a contributing factor to low treatment rates and poor BP control [21]. Although antihypertensive medication titration and BP targets were based on office measurements, Dr Takayoshi Okubo highlighted the importance of collecting home BP data using smartphone applications, as performed in the STEP study [20]. However, the study population was limited to those able to competently use a smartphone and relevant applications, which may not be the case in unselected patients treated during routine clinical practice [20]. As noted by the author (K. Kario) in another editorial, data from the online supplement accompanying the STEP study publication showed that the prevalence of masked morning hypertension appeared to increase in the standard treatment group over time, whereas this was not the case in the intensive BP control group [19]. This shows that standard treatment based on office BP is insufficient to provide good control of morning BP during long-term follow-up. Thus, the STEP study findings, along with data showing a close association between poorly controlled morning BP and cardiovascular events [22–25], highlight the importance of controlling morning BP and the use of digital hypertension management strategies focusing on early morning BP [19, 26, 27].

SSaSS

Higher salt intake and salt sensitivity are likely to be key factors driving high rates of hypertension and the BP profile in Asia. In addition to being genetically predisposed to salt sensitivity [28], Asians also have a high salt intake [29], which exceeds the WHO-recommended level of <5 g/day [30]. Use of a salt substitute in which a proportion of the sodium chloride is replaced by potassium chloride is a valid way to reduce dietary salt intake. This also has the benefit of decreasing the urinary sodium/potassium ratio. Increases in the urinary sodium/potassium ratio have been shown to be associated with increases in both SBP and diastolic BP (DBP) [31, 32], and is a useful indicator of adherence to WHO-recommended sodium intake levels [33].

In addition to increasing BP, high salt intake has been linked to a variety of negative cardiovascular outcomes. For example, household salt intake was significantly associated with the long-term risk of all-cause, cardiovascular, cerebrovascular and stroke mortality over 24 years of follow-up in a representative Japanese population [34]. Although both dietary sodium reduction and dietary potassium supplementation have been shown to have BP-lowering effects [35, 36], the effects of these approaches on the cardiovascular disease burden had not previously been investigated.

SSaSS was a cluster randomized trial that evaluated the effects of using a salt substitute (25% potassium chloride/75% sodium chloride) compared with standard salt (100% sodium chloride) on rates of stroke, major cardiovascular events and death in patients with hypertension plus age ≥60 years or a history of stroke from a group of 60 villages in China [18]. Villages were randomly assigned to the intervention (salt substitute) or control (standard salt) groups. The intervention groups used salt substitute instead of regular salt for all cooking, seasoning and food preservation purposes at similar amounts to their usual salt usage. The mean follow-up was 4.74 years. Patients who used the salt substitute showed a 14% reduction in stroke risk, a 30% reduction in rates of a non-fatal acute coronary syndrome, and a 12% reduction in total mortality compared with the standard salt group [18]. The observed benefits from the salt substitute were broadly consistent across participant subgroups and prespecified exploratory outcome analyses of stroke, other vascular events, and death [18]. The absence of any increased risk of clinical hyperkalemia in the intervention group supports the safety of salt substitution in this patient population [18].

Other salt intake-related studies and initiatives

A study conducted in rural India randomized patients to the use of a salt substitute (30% potassium chloride/70% sodium chloride) or regular salt [37]. Over the 3-month follow-up period, mean SBP/DBP was 4.66/1.14 mmHg lower in participants using the salt substitute compared to those using standard salt ($p < 0.001/p = 0.02$). In addition, compared with the control group, there was a significant increase in 24-h urinary potassium excretion and a significant decrease in the urinary sodium/potassium ratio in the salt substitute group.

Asian countries have implemented many programs to reduce population salt intake. The Chinese government has included the reduction of salt intake as a key component of "Healthy Lifestyle for All", which is part of the country's health development agenda [38]. A series of programs were created and implemented nationwide by Action on Salt China, a unit funded by the National Institute of Health Research. These included a salt awareness campaign, education on salt reduction at home, and reducing salt usage in restaurants and processed food [38]. In addition, a significant reduction in salt intake for both children and adults was achieved through the School-based Education Program to Reduce Salt Intake in Children and Their Families (School-EduSalt) [39].

Multi-component strategies have been a feature of most successful dietary sodium intake reduction programs. For example, the JSH set up at Salt Reduction Committee in 2005 to promote the reduction of population salt consumption. In 2019, the JSH announced the "Tokyo Declaration in Promotion of Salt Reduction" [40]. This included a six-strategy action plan designed to reduce salt intake to <6 g/day. Key components were: (1) educate citizens on the harms of excessive salt intake and the importance of reducing salt intake; (2) recommend assessment of salt intake of individuals or populations, and propose adequate methods to reduce salt intake; (3) promote salt reduction in children as a part of dietary education at school; (4) promote salt reduction in restaurant meals, prepared dishes, canteens, and school lunches; (5) encourage companies to develop and spread low-salt foods; and (6) encourage the government to take measures to promote salt reduction. In addition, the JSH hypertension management guidelines include clear recommendations around reducing salt intake [41]. More broadly, The Okinawa Declaration on the unity of hypertension societies in Asian countries and regions to overcome hypertension and hypertension-related diseases was announced in 2021 [42].

Hypertension and atrial fibrillation

After heart failure, aging and valvular heart disease, hypertension is the fourth-most common risk factor for AF [43]. However, as by far the most prevalent of these risk factors, hypertension is an important contributor to AF burden in the population [44, 45]. Data from epidemiological studies show

that hypertension is associated with a 1.8-fold increase in the risk of developing new-onset AF and a 1.5-fold increased risk of progression to permanent AF [43, 46]. In an elderly Chinese population, there was a U-shaped relationship between both SBP and DBP and prevalent AF, with the lowest risk of AF seen with high-normal BP levels [47]. AF alone increases the risk of stroke and systemic emboli, but the risk is even greater in presence of both AF and hypertension [48, 49]. Nevertheless, a recent study conducted in China showed that even after AF is detected, the proportion of patients treated with appropriate oral anticoagulant therapy was extremely low [50]. Therefore, the early detection and appropriate treatment of AF and associated comorbidities such as hypertension are essential.

Detection of AF in patients with hypertension

A home BP monitoring (HBPM) device equipped with a new algorithm for pulse wave analysis for the detection of AF was evaluated in 75 subjects with confirmed AF based on an echocardiogram and 205 who were in sinus rhythm [51]. Based on the pulse wave extracted by changing each pulse pressure after cuff deflation in three consecutive home BP measurements, the interval of pulse peak (IPP15) was defined as: [interval of pulse peak – the average of the interval of the pulse peak] ≥ the average of the interval of the pulse peak × 15%, and irregular heart beat (IHB) was defined as beats of IPP ≥ total pulse × 20%. The sensitivities of IPP15 for diagnosing AF defined as two or three IHBs of three readings were 1.0 and 0.99, and the corresponding specificities were 0.97 and 0.99, respectively. This shows that this AF detection algorithm mounted on a HBPM device had high diagnostic accuracy for detecting AF [51]. Its association with a standard and widely available technique for monitoring home BP suggests that it could be widely implemented to monitor heart rhythm as well as BP in patients with hypertension over the long term, although additional research is needed to facilitate implementation of this potential tool into clinical practice.

A wrist-type pulse wave monitor also showed high sensitivity and specificity for the diagnosis of AF in patients with hypertension in a case–control study that used similar definitions for IPP and IHB [52]. This is another promising approach to facilitate AF detection in patients with hypertension.

BP management in patients with AF

Current guidelines recommend a target BP of 130/80 mmHg in patients with AF receiving anticoagulant therapy [41, 53, 54]. However, patients with AF have often been excluded from hypertension treatment trials because of their fluctuating and unstable BP. The prospective, multicenter, observational, longitudinal All Nippon AF In Elderly Registry was designed to collect data on the clinical status of elderly patients with nonvalvular AF [55]. A total of 5204 patients aged ≥75 years were included and evaluated using HBPM. This allows the white coat effect to be eliminated and a high frequency of measurements allowed the impact of BP on embolic and hemorrhagic events in patients with AF to be assessed over approximately 2 years of follow-up. Overall, 77.5% of patients with nonvalvular AF had hypertension. Office BP was ≥130 mmHg (i.e., uncontrolled based on guideline recommendations) in 48.9% of patients, and even in the 51.1% of patients who had office BP < 130 mmHg, more than half (52.5%) still had uncontrolled morning home BP [55]. This shows that a high proportion of high-risk elderly patients with nonvalvular AF have inadequate control of morning home BP, which could contribute to a higher risk of morning cerebrovascular and cardiovascular events in these patients.

Another study from Japan highlights the importance of good BP control in patients with hypertension before the development of AF [56]. Using data from the Japan Medical Data Center Co., Ltd database, this retrospective analysis investigated the impact of pre-existing hypertension and BP control status prior to AF onset on subsequent prognosis [56]. Based on data from 7885 patients with new-onset nonvalvular AF and BP data from prior to AF onset, those with pre-existing hypertension has a significantly higher rate of AF-related cardiovascular endpoint events compared to those without hypertension (10.3 vs. 4.4 per 1000 patient-years; $p < 0.001$). In addition, there was a significant association between lower SBP before AF onset (<120 mmHg) and a lower incidence of cardiovascular events after the development of AF [56]. This highlights the importance of tight BP control for reducing not only the development of AF but also the risk of subsequent cardiovascular events after an AF diagnosis.

There are a number of mechanisms by which antihypertensive therapy has the potential to prevent AF. These include the improvement of structural and electrical cardiac remodeling, and prevention of heart failure, all of which contribute to the development of AF [57]. Analysis of data from the SPRINT study suggested that intensive antihypertensive treatment (target SBP < 120 mmHg) in patients with hypertension at high risk of cardiovascular disease has the potential to reduce the risk of AF [58]. However, patients with AF still appear to be at increased cardiovascular risk even when BP is reduced to <120/80 mmHg during antihypertensive therapy [59]. Therefore, additional data from prospective clinical trials are needed to clearly define the role of antihypertensive therapy in the prevention and management of AF.

Drug-resistant hypertension defined using out-of-office BP measurement

Definition

Resistant hypertension is defined as a BP level that exceeds goal despite concurrent treatment with agents from three different antihypertensive drug classes, usually including a renin-angiotensin system blocker, a CCB and a diuretic, or when treatment with ≥4 agents is needed to achieve BP control [41, 53, 54, 60]. However, making a true diagnosis of resistant hypertension requires the measurement of out-of-office BP (i.e., home and/or ambulatory BP) [60]. This allows white coat hypertension, where patients have an elevated office BP reading but normal out-of-office readings, to be excluded. In clinical practice, this is relevant to management decisions because patients with uncomplicated white coat hypertension do not have increased cardiovascular risk compared with normotensive individuals [61]. Thus, patients with true resistant hypertension have uncontrolled BP based on both office and out-of-office measurements, as defined in recent studies [62, 63].

Prognosis

Treatment-resistant hypertension confirmed using HBPM or 24-h ambulatory BP monitoring (ABPM) has been shown to be a risk factor for cardiovascular disease, including heart failure [62, 63].

The Japan Morning Surge Home BP study was the first to report an association between treatment-resistant hypertension based on HBPM and cardiovascular risk [63]. The study included 4261 Japanese subjects who performed HBPM in the morning and evening for 14 days. Treatment-resistant hypertension was defined as uncontrolled home BP using three classes of medications including diuretics or controlled/uncontrolled home BP during treatment with ≥4 classes of medication. Over a mean 6.2 ± 3.8 years of follow-up, the adjusted total cardiovascular disease risk was significantly increased in patients with treatment-resistant hypertension compared with those whose BP was controlled using <3 antihypertensive drug classes (HR 2.20, 95% CI 1.38–2.94 using a home BP of 135/85 mmHg, and HR 1.81, 95% CI 1.23–2.65 using a home BP of 130/80 mmHg) [63].

Most recently, the Japan Ambulatory Blood Pressure Monitoring Prospective (JAMP) study investigated the effects of uncontrolled resistant hypertension diagnosed using ABPM on the risk of heart failure and overall cardiovascular events in 5839 patients [62]. True treatment-resistant hypertension was defined as a 24-h ambulatory BP of ≥130/80 mmHg. The adjusted risk of total cardiovascular events (HR 1.66, 95% CI 1.12–2.48; $p = 0.012$), and especially HF events (HR 2.24, 95% CI 1.17–4.30; $p = 0.015$), was significantly increased in patients with true resistant versus controlled nonresistant hypertension [62]. The findings from both of these studies confirm the importance of diagnosing treatment-resistant hypertension using out-of-office BP measurement, and then determining a treatment regimen that reduces BP to target.

Nocturnal hypertension

Heart failure risk

When BP rises, a large amount of salt is eliminated from the body, but if the body is prone to storing salt (e.g., Asians, and patients with CKD, metabolic syndrome and/or obesity), salt intake increases BP not only during the day but also at night. This compensatory increase in nighttime BP increases cardiac workload and has adverse effects on the cardiovascular system and kidneys.

Control of elevated nighttime BP (nocturnal hypertension) is a key component of managing patients with hypertension and heart failure [64–67]. There are several mechanisms by which nocturnal hypertension has negative effects in patients with heart failure, as summarized previously [64, 68]. Briefly, when the patient is in the supine position during sleep, circulating blood volume shifts from the periphery to the upper body by about 800 mL, causing the heart to expand and increasing preload. In this situation, high nighttime BP (i.e., afterload) further increases preload, and increases strain on the left ventricular wall.

There are four different circadian patterns of nighttime BP variability: dipper (nighttime BP decreases by 10–20 mmHg compared with the daytime); non-dipper (nighttime BP does not decrease); riser (nighttime BP increases); and extreme dipper (nighttime BP decreases significantly). In the JAMP study, 6359 Japanese subjects underwent 24-h ABPM at baseline to determine the nighttime BP dipping pattern and were then followed for a mean of 4.5 years [69]. The results showed that each 20-mmHg increase in nighttime SBP was associated with a 21% increase in the risk of stroke and coronary artery disease, and a 36% increase in the risk of heart failure [69]. In addition, the risk of developing heart failure was 2.45 times higher in patients with a riser versus dipper pattern of nighttime BP ($p = 0.004$), even after adjustment for 24 h, daytime, and nighttime BP. Even in patients with well-controlled BP, those with a riser or non-dipper pattern of nighttime BP still showed substantially and significantly elevated heart failure risk [69]. This highlights the importance of monitoring and controlling nighttime BP even if BP otherwise appears to be well controlled. Effective control of nighttime BP can also help to attenuate left ventricular hypertrophy and renal dysfunction, further reducing heart failure risk [64].

New sodium-releasing drugs

Reducing circulating volume is an important part of strategies to reduce nighttime BP and ameliorate nocturnal hypertension. The heart failure drugs sodium-glucose cotransporter 2 (SGLT2) inhibitors, angiotensin receptor-neprilysin inhibitors (ARNI) and selective mineralocorticoid receptor antagonists (MRA) are now covered by insurance in Japan for the treatment of hypertension. Recent data are summarized below.

SGLT2 inhibitors

This group of agents is currently only indicated in patients with heart failure or diabetes mellitus. However, there is a growing body of evidence to suggest that they also have benefits beyond their hypoglycemic activity, including beneficial effects on BP [70]. The Japanese SGLT2 inhibitor and Angiotensin Receptor Blocker Combination Therapy in Patients With Diabetes and Uncontrolled Nocturnal Hypertension (SACRA) study [71], the EMPA-REG BP trial [72], the LUSCAR study [73], the Y-AIDA trial [74], other studies with dapagliflozin and empagliflozin [75, 76], and a post-hoc analysis of data from the Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation (CREDENCE) trial [77] have all reported reductions in out-of-office BP measurements (including nighttime BP) during treatment with a variety of SGLT2 inhibitors. Taken together, these recent data make this class of agents a potential new option for reducing BP, along with cardiovascular risk, in patients with heart failure—although more studies are needed in this area [78, 79].

ARNI

Dual inhibition of the angiotensin-1 receptor and neprilysin has multiple beneficial effects on the cardiovascular system [80]. The first-in-class ARNI sacubitril/valsartan is being seen as a potential treatment option for resistant hypertension and may be ideally suited to a salt-sensitive hypertension phenotype, which is common in Asia [80]. Sacubitril/valsartan was approved in Japan for the treatment of hypertension in September 2021 [81]. This approval was supported by data from several rigorous clinical studies showing the BP-lowering effects of sacubitril/valsartan, especially over the important nighttime period [82–85]. In the most recent publication, data from a multicenter, randomized, double-blind, parallel-group study conducted in Japanese patients with mild to moderate systolic hypertension experienced a greater reduction in mean seated SBP and achieved a higher BP control rate during treatment with sacubitril/valsartan compared with olmesartan [83]. However, as recently noted, additional follow-up data are required to confirm the role of sacubitril/valsartan for the long-term treatment of hypertension [86].

MRA

MRAs are effective for the treatment of resistant hypertension, but use of earlier generation agents was associated with problematic adverse events, including hyperkalemia (with both spironolactone and eplerenone) and gynecomastia (spironolactone) [87–89]. Esaxerenone is a newer non-steroidal selective MRA that received approval in the hypertension indication in Japan in January 2019 [90]. In addition to studies documenting BP reductions in patients with hypertension treated with esaxerenone [91–96], a recent Japanese analysis highlighted the BP-lowering activity of esaxerenone through the important nighttime period [97]. Nighttime SBP decreased in all patients after 28 weeks' treatment with esaxerenone 2.5–5 mg/day, regardless of nocturnal BP dipping status, although BP reductions were greatest in those with a riser pattern. In addition, the prevalence of the undesirable riser and non-dipper patterns of nighttime BP decreased during esaxerenone therapy [97]. Therefore, esaxerenone may be a useful treatment option for patients who have nocturnal hypertension, and especially those with a riser pattern of nighttime BP.

Renal denervation

Renal denervation (RDN) is a non-drug option for reducing nocturnal BP via suppression of the sympathetic nervous system and improving salt sensitivity. This technique showed great theoretical promise, but progress was stalled by the equivocal results of early sham-controlled trials. These sometimes conflicting results have recently been summarized in a meta-analysis and systematic review to provide a more accurate estimate of the effects of this non-pharmacological intervention on BP in patients with hypertension [98]. Taken together, data from 1555 patients (885 treated with RDN and 670 with a sham control) suggest a modest but statistically significant reduction in both office (−3.31 mmHg) and 24-h ambulatory (−5.25 mmHg) BP at 26 months after RDN (Fig. 4), and this was consistent across devices and in the presence or absence of antihypertensive medication [98]. This analysis also showed that RDN significantly reduced nighttime SBP by 3.2 mmHg from baseline [98]. The authors suggested that this may be clinically relevant for reducing cardiovascular event risk in patients with hypertension given the limitations of pharmacological treatment for effectively lowering nighttime BP [98].

There are several Asia-specific characteristics of hypertension that mean that RDN may be particularly suited to the Asian hypertension phenotype [99, 100]. Subanalyses from

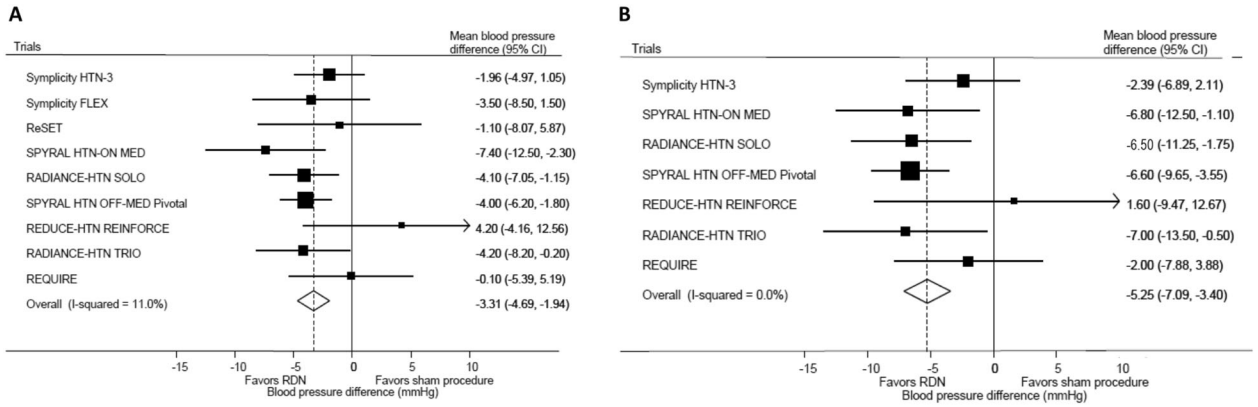

Fig. 4 Effects of renal denervation (RDN) on 24-h ambulatory (**A**) and office (**B**) blood pressure in patients with hypertension (reproduced, with permission, from Ogoyama et al. (2021)) [98]. Horizontal lines show 95% confidence intervals (CI) with the point estimate at the center of the box. Boxes are proportional to the sample size from each study. Diamonds represent summary data centered on the pooled estimate and their width spans the corresponding 95% CI

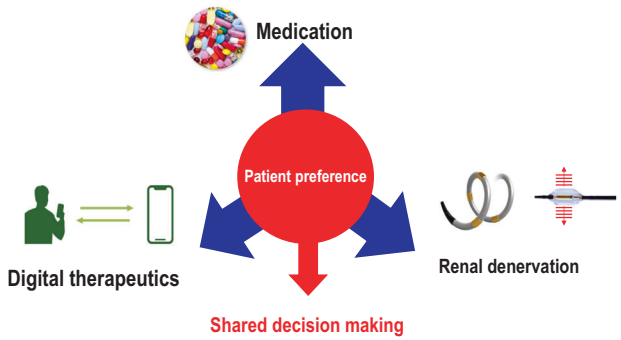

Fig. 5 Patient preference and shared decision making for the future management of hypertension (adapted from Kario (2020) [108], with permission)

the Global SYMPLICITY Registry showed significant and sustained BP reductions after RDN in treated individuals from Korea and Taiwan [101–103]. In addition, the magnitude of BP reductions in patients from Korea was greater than that in a matched group of European patients [101, 102]. Based on these data, the Asia Renal Denervation Consortium has suggested that RDN could be considered as an initial therapy option for the treatment of hypertension in Asia, either alone or in combination with antihypertensive medication [99].

A survey conducted recently in Japan determined patient preference for treatment with RDN, and included 2393 patients with hypertension [104]. A total of 755 survey participants (31.6%) stated a preference for RDN to treat their hypertension; males, younger individuals, and those with higher SBP, poor adherence to antihypertensive medication, heart failure and adverse effects during antihypertensive treatment were more likely to express a preference for RDN.

Going forward, challenges to be overcome with respect to the implementation of RDN in clinical practice include procedural guidance, identification of responders, and durability of effects [105]. Based on currently available data, Asian patients with hypertension might be good candidates for RDN, but additional research is needed.

Advances in non-pharmacological treatment

As highlighted by the RDN-related survey findings above and other research, individual patients will have different preferences for antihypertensive therapy [106, 107]. This means that patient preference should be central to decisions regarding the management of hypertension, and is a key component in shared decision making (Fig. 5) [108]. As part of this strategy, there are a growing number of other non-pharmacological options that can be utilized to facilitate the management of hypertension. Some of these are highlighted below.

Digital therapy with hypertension treatment application

Digital therapeutics refer to the use of evidence-based therapeutic interventions driven by high-quality software programs to treat, manage, or prevent a medical condition [109]. In the field of hypertension, new non-pharmacological digital methods of lowering BP are now approaching clinical implementation.

The world's first application for hypertension treatment, HERB, is an approach to hypertension management that aims to lower BP by encouraging patients to change their behavior [110]. The app contains information on non-pharmacological therapies that have evidence to support their effectiveness in the treatment of hypertension (salt reduction, weight loss, reducing alcohol intake, exercise, stress management and sleep). The aim of the program is to

help patients to acquire the correct knowledge about these lifestyle modifications and implement changes in their daily life. Patients record home BP and other information in the app, and their physicians check treatment status on the internet and provide individual guidance [110].

In a pivotal study of treatment-motivated patients who were not receiving pharmacological antihypertensive therapy (HERB-DH1), patients managed using the HERB digital system had a significantly greater reduction in 24-h BP at 12 weeks than the control group (who were managed conventionally with home BP recording) (−4.9 vs. −2.5 mmHg; between-group difference: 2.4 mmHg, $p = 0.024$) [110]. The greatest difference between groups was seen in early morning BP (−10.6 vs. −6.2 mmHg; between-group difference: 4.3 mmHg, $p < 0.001$) [110]. Normally, BP can be lowered by about 2 mmHg by monitoring home BP alone, and by about 6 mmHg with general guidance and individualized instruction from a physician. This matches the reduction in early morning BP seen in the HERB-DH1 study control group who were managed in this way, but BP reductions in the intervention group exceeded this by 4.3 mmHg. These findings support a bright future for app-based individualized therapy to promote lifestyle modifications that support hypertension management.

Hypertension vaccine

Vaccines addressing several different targets are being investigated for the prevention and treatment of hypertension [111]. One such agent is a modified angiotensin II DNA vaccine (AGMG0201) that was recently evaluated in a double-blind randomized, placebo-controlled phase I/IIa trial [112]. Patients aged 18–79 years with mild to moderate hypertension received two vaccine injections 30 days apart and were monitored for 360 days after the second dose. Treatment-related adverse events were generally mild or moderate in severity, and included injection site pain and erythema. Vaccination triggered the production of anti-angiotensin II antibodies, especially at the highest dose [112]. This is an innovative area of research that is of future interest.

Digital hypertension research and anticipation medicine

The JSH has defined digital hypertension as the application of rapidly evolving digital health technologies and AI to hypertension healthcare and research [113]. This approach shows great promise for providing further insights into the pathophysiology of this significant public health issue and identifying potential new therapeutic targets [114]. In addition, it is central to the implementation of predictive, personalized, and preemptive approaches in clinical practice [114].

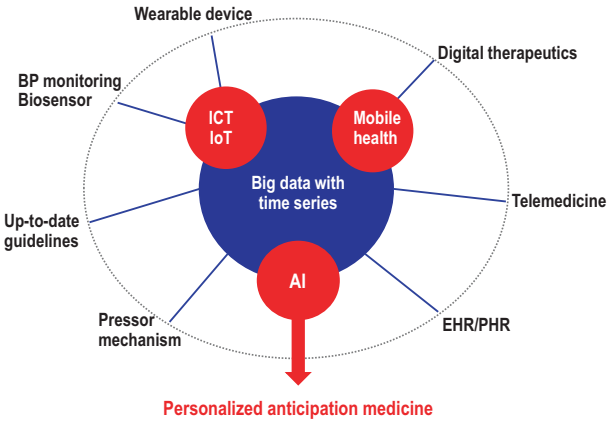

Fig. 6 Digital hypertension management to facilitate personalized anticipation medicine. AI artificial intelligence, BP blood pressure, EHR electronic health record, ICT information and communication technology, IoT Internet of Things, PHR personal health record

Digital hypertension encompasses many aspects, including BP monitoring, wearable devices, digital therapeutics (as described above), telemedicine, big data, and mobile health (Fig. 6). Ultimately, information obtained from these sources using a digital hypertension approach is to predict cardiovascular events using AI. This is particularly relevant in hypertension due to the regular variations in BP (beat-by-beat, orthostatic, diurnal, daily, short term, between-visit and seasonal) and the important contribution that this makes to cardiovascular risk [115]. The goal is to use digital information to create personalized solutions for anticipation medicine, thereby substantially reducing (or even eliminating) cardiovascular risk [116].

Telemedicine and digital patient management

HBPM is a central component in telemedicine strategies for hypertension management. It has been shown to significantly reduce BP and improve BP control [117]. However, remote monitoring of BP is just one component of digital hypertension strategies. HBPM can be combined with other support/interventions, as documented with the HERB digital therapeutics program [110].

As recently summarized [118], there is a growing body of evidence for the beneficial effects of telemedicine strategies on a variety of indices, including BP, mediation adherence and lifestyle modification. Telemedicine has a number of advantages, including patient engagement/empowerment and enhanced patient–physician relationships [118, 119]. In addition, telemedicine strategies have shown their value for the management of chronic medical conditions to ensure continuity of care during the COVID-19 pandemic and associated restrictions on face-to-face interactions

[120–124]. However, there are also a number of barriers and challenges that need to be overcome. These include access to equipment and internet connectivity, technological competence of users, data privacy, and the need for relevant training, certification and licensing [118, 125].

Thus, although additional work is needed to fully define the role of telemonitoring and telemedicine in routine clinical care across a range of settings, it is clear that these approaches have an important part to play in the future management of hypertension.

Wearable wrist-type BP monitoring

There are a wide variety of factors that can impact BP at any one time, including physical activity, mental stress, environmental factors, and sleep disturbance. These are important because, for example, seasonal factors such as changes in temperature have been shown to have an important effect on BP and cardiovascular risk [126–134]. The combination of one or more of these factors with other periods where BP might increase naturally, such as the early morning period, could elevate BP enough to trigger a series of events, starting with plaque disruption or hemorrhage, that culminate in a cardiovascular event (referred to as the synergistic resonance hypothesis) [135], even when office BP is apparently controlled. Previously, the only way to get regular data on changes in BP throughout the 24-h period was to use ABPM. Automated HBPM devices capable of determining nighttime BP are also available, and are being developed to also monitor other risk factors such as environmental conditions and physical activity, and may have the potential to detect arrhythmias [126, 131, 136–138]. However, conventional upper arm measurement of BP can be inconvenient for patients and is associated with sleep disturbance [139].

This highlights the value of small wearable BP monitoring devices that can provide regular or continuous data on BP status, and potentially other triggers, in an individual patient [140]. One of these devices has been shown to be able to detect changes in BP under different conditions, including emotional stress, location, body position and physical activity [141]. BP was found to increase by a mean of 7.9 mmHg during negative emotions (anxiety, tension) compared with positive emotions (happiness, calm), by 4.6 mmHg at work versus at home, and by 4.5 mmHg during moderate exercise compared with rest [141]. Furthermore, BP determined using a wearable device correlated well with the left ventricular mass index on cardiac magnetic resonance imaging in patients with hypertension [142].

To prepare for more widespread usage of wearable BP devices, it is important that these are validated and accurate compared with conventional methods of measuring out-of-office BP. The first comparison of a wrist-worn watch-type oscillometric BP monitoring device (HeartGuide; Omron Healthcare) with traditional ABPM found that the wearable device produced BP readings that showed an acceptable level of similarity to brachial cuff inflation ABPM [143]. In addition, patients found the wearable device more comfortable, less burdensome, and less intrusive than ABPM [143].

The use of wearable devices to continuously monitor nighttime BP is an important potential application, given the close association between nighttime BP and cardiovascular risk [144–146]. In a recent Japanese study, use of a new algorithm-equipped wrist nocturnal HBPM device (HEM-9601T, NightView; Omron Healthcare) was found to record BP values that were similar to those obtained with an upper arm HBPM device and be clinically reliable. Further studies such as this will help to better define the role and application of wearable BP monitoring devices in real-world clinical settings.

Beat-by-beat continuous BP monitoring

There are a number of methods by which small wearable monitoring devices determine beat-by-beat continuous BP. One of these is applanation tonometry [147]. The radial artery at the wrist is ideally suited to this method because it is fixed on a radial bone and is shallow beneath the skin [116]. A small beat-by-beat monitoring device based on tonometry has been shown to provide continuous BP readings that correlate well with other validated conventional devices [147]. Although wearable devices using tonometry appear to do well under static conditions [148], accuracy is lower under ambulatory conditions due to the movement of the sensor during measurements [149]. This is something that will clearly need to be resolved before this can be widely utilized in clinical settings.

Another method that can be used to continuously monitor BP is pulse transit time (PTT). This is the interval of the pulse wave propagation between two arterial sites, is inversely proportional to BP, and has been shown to provide a good estimate of BP [150–154]. PTT can be estimated without the need for an ECG using an array of bioimpedance sensors placed on the wrist [155]. This has been shown to allow continuous and accurate BP measurement in a way that patients found comfortable [155]. In addition, beat-to-beat monitoring using a PTT approach showed good agreement with intermittent measurements, especially with respect to average BP values and BP variability [156].

Artificial intelligence for prediction

Combining the data that can be obtained from digital platforms and wearable BP monitoring devices with AI is an

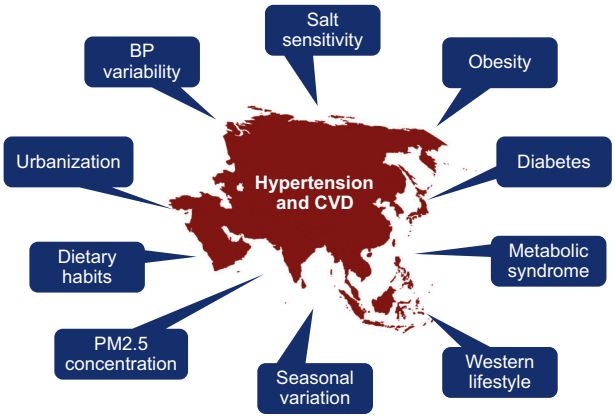

Fig. 7 Factors contributing to hypertension and cardiovascular disease in Asia (reproduced, with permission, from Kario et al. (2020)) [7]. BP blood pressure, CVD cardiovascular disease, PM2.5 fine particulate matter <2.5 μg

area with great potential. Such approaches have already been shown to facilitate the development of a model predicting the development of hypertension in a general population based on information on vascular stiffness [157], and to predict both mean BP and BP variability [158]. With respect to BP variability, morning home SBP data over 56 days, plus data on prescription medications, age, height, weight, past BP changes and temperature changes, were used to develop an algorithm for predicting future BP changes using AI (deep neural network) [158]. This model was able to predict changes in BP over the next month within a range of about 10 mmHg on a weekly basis; the accuracy of the model was greater when patient information and time-series environmental information were included [158].

Other potential applications of AI in the field of hypertension include predicting disease incidence and related clinical outcomes, and the prediction of BP levels with new technologies (such as the wearable devices highlighted above) [159]. Although there is much research still needed into applying developing AI technology to facilitate the diagnosis and management of hypertension, it is likely that it will make an important contribution to the future digital management of this common condition.

Actions for better hypertension management in Asia

The Asian continent is large and diverse but hypertension is a prevalent and burdensome condition throughout the region [1]. Absolute BP levels in Asia are now amongst the highest in the world and BP control rates are relatively low [1, 6, 8], although there is variation within the region [160–162]. Thus, while Asian peoples not only share some cultures, customs and genetic factors, this diversity between regions also influences the development and treatment of hypertension and hypertension-related diseases in Asian countries and regions.

A variety of factors contribute to the development and severity of hypertension in Asia (Fig. 7) [7]. This highlights the need for a coordinated approach to hypertension management in the region, with the tailoring of approaches for each individual country/region.

The Hypertension Cardiovascular Outcome Prevention and Evidence in Asia (HOPE Asia) Network was established in 2016 and is now both a member of the organization of the World Hypertension League (WHL) and affiliated with the International Society of Hypertension. To help contribute to the WHL's mission of confronting the global hypertension epidemic and associated burden of disability and premature mortality, the HOPE Asia Network's goal is to improve the management of hypertension to protect against target organ damage, with the ultimate aim of reducing the number of cardiovascular events in Asia to zero [163, 164]. To facilitate this, the HOPE Asia Network has published several consensus documents and Asia-specific guidelines covering a variety of topics relating to hypertension and its management [165–169].

HOPE Asia Network action approach

Most recently, the HOPE Asia Network has outlined seven action approaches for improving the management of hypertension in Asia [170]. These are as follows:

1. Strict reduction of sodium intake.
2. Strict BP control.
3. Use of home BP to guide hypertension management.
4. Reduce morning home BP first, followed by nighttime BP, in high-risk patients.
5. Choose appropriate antihypertensive agents for local populations.
6. Implement widespread screening to improve awareness.
7. Use telemedicine strategies.

It is hoped that these strategies will make a significant contribution to reducing the burden of hypertension in Asia.

Okinawa declaration

To date, collaborative research in Asian countries and regions, including Japan, has contributed much to hypertension research. As part of the next stage, the "Okinawa Declaration of the Asian Hypertension Network" was presented at the 43rd Annual Meeting of the JSH in 2021 [42]. Its aim is to build a network to overcome hypertension and hypertension-related diseases in Asia by sharing evidence

and experience. The hypertension societies of Asian countries and regions will continue their efforts to achieve this goal by creating and cooperating on a concrete action plan, as follows:

1. Actively promote clinical and experimental investigations for hypertension research to encourage participation from researchers and practitioners from Asia.
2. Share Asian evidence to promote the establishment of standardized management of hypertension in Asia.
3. Continue to work toward developing Asian consensus guidance for the management of hypertension, using a collaborative approach and taking into account diversities within Asia.
4. Create an Asian multidisciplinary network for the management of hypertension and hypertension-related diseases.

JSH future plan in the "new normal" with COVID-19

In 2018, the JSH formulated a plan for the future in terms of overcoming hypertension with the slogan "Healthy 100-year life with good blood pressure" [113]. However, the plan was recently revised due to the COVID-19 pandemic and now includes the phrase "new normal", and promotion of the three pillars—medical system, academic research and social awareness—was accelerated [171, 172].

With respect to the healthcare system, this focuses on the establishment of a telemedicine system to accurately assess BP and the complications of hypertension complications. In addition, the need for the establishment of a multidisciplinary telemedicine team is recognized. This will help to ensure that lifestyle changes required to prevent infection with SARS-CoV-2 do not lead to suboptimal eating and exercise habits, and increased mental stress. Having a robust telemedicine system will also contribute to preventing the spread of COVID-19 because patients can be managed remotely rather than face-to-face.

It is suggested that academic research focuses on strategies to enable the prevention, prediction and control of hypertension using AI, big data, and IoT-based telemedicine. Bioinformatics obtained from continuous digital information regarding BP and heart rate can be applied to BP management, and also could be used to predict the onset of cerebral infarction and myocardial infarction, and worsening of heart failure. In addition, research on hypertension in aging-related diseases such as frailty and dementia, and prevention of cardiovascular diseases in the elderly, will be promoted.

A key component of social awareness is the development of a society where citizens take responsibility for managing their own BP. In Asia, reducing salt intake is a key component of this. Thus, the JSH is focusing on self-monitoring of salt intake, issuing health guidance in this area, and improving access to low-salt foods.

All of these activities, both in Japan and elsewhere in Asia, will be facilitated by the dedication of Asian countries to the Kyoto declaration on hypertension research in Asia, which aspires to generate novel solutions for common hypertension-related problems in Asia based on a deeper understanding of Asian hypertension through cooperative efforts [173].

Conclusion

There is good reason for optimism regarding the ongoing and future management of hypertension in Asia based on the active research activities and initiatives taking place in the region. Both regional and international collaborations will continue to drive advances in technology and patient care that contribute to reducing the burden of hypertension and hypertension-related disease. Challenges still remain, but the increased usage of digital approaches and therapeutics, the drive towards personalized medicine and shared decision making, and treatment advances are key contributors to improved patient outcomes.

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Compliance with ethical standards

Conflict of interest KK reports research grant from A&D, Omron Healthcare, Fukuda Denshi, Otsuka Pharmaceutical, Otsuka Holdings, CureApp, Sanwa Kagaku Kenkyusho, Daiichi Sankyo, Taisho Pharmaceutical, Sumitomo Dainippon Pharma, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, Teijin Pharma, Boehringer Ingelheim Japan, Pfizer Japan, Fukuda Lifetec, Bristol-Myers Squibb, Mochida Pharmaceutical, Roche Diagnostics; and Consulting fees from A&D, JIMRO, Omron Healthcare, CureApp, Kyowa Kirin, Sanwa Kagaku Kenkyusho, Terumo, Fukuda Denshi, Mochida Pharmaceutical; and Honoraria from Idorsia, Omron Healthcare, Daiichi Sankyo, Novartis Pharma, Mylan EPD; and Participation in Advisory Board of Daiichi Sankyo, Novartis Pharma, Fukuda Denshi outside the submitted work. All other authors declare no conflict of interest.

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