



## Update on Hypertension Research in 2021

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Received: 1 June 2022 / Accepted: 3 June 2022 / Published online: 5 July 2022  
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### Abstract

In 2021, 217 excellent manuscripts were published in Hypertension Research. Editorial teams greatly appreciate the authors' contribution to hypertension research progress. Here, our editorial members have summarized twelve topics from published work and discussed current topics in depth. We hope you enjoy our special feature, "Update on Hypertension Research in 2021".

**Keywords** Hypertension Research · Up-to-date · 2021

### Usefulness of vascular function tests for cardiovascular risk assessment and a better understanding of the pathophysiology of atherosclerosis in hypertension (see Supplementary Information 1)

**Supplementary information** The online version contains supplementary material available at <https://doi.org/10.1038/s41440-022-00967-4>.

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Vascular function tests and vascular imaging tests are useful for assessing the severity of atherosclerosis. Since vascular dysfunction and vascular morphological alterations are closely associated with the maintenance and progression of atherosclerosis, vascular tests may provide additional information for cardiovascular risk assessment (Fig. 1) [1–5]. Measurement of the ankle-brachial index (ABI) has been performed not only for screening for peripheral artery disease but also for cardiovascular risk assessment in clinical practice [6]. However, the

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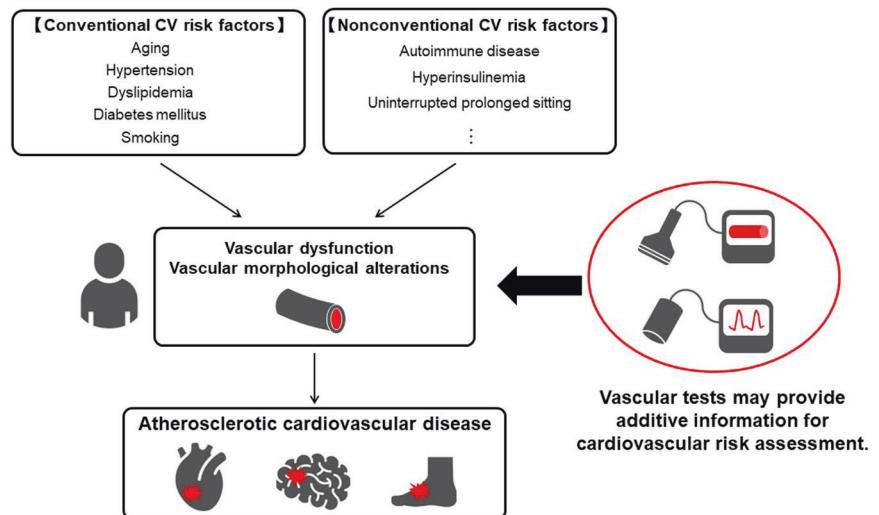
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**Fig. 1** Vascular function tests and vascular imaging tests for the assessment of cardiovascular risk. CV cardiovascular risk



ABI method does not always provide reliable data because the ABI value is falsely elevated despite the presence of occlusive arterial lesions in the lower extremities of patients with non-compressible lower limb arteries, which can lead to incorrect cardiovascular risk assessment [7–9]. Tsai et al. [10] reported that a combination of an ABI value  $<0.9$  and an interleg ABI difference  $\geq 0.17$  was more useful for predicting all-cause mortality and cardiovascular mortality than was an ABI value  $<0.9$  alone. Therefore, attention should be given not only to the ABI value but also to the interleg ABI difference for more precise cardiovascular risk assessment. Sang et al. [11] conducted a systematic review and meta-analysis to investigate the usefulness of brachial-ankle pulse wave velocity (baPWV), an index of arterial stiffness, for risk assessment and showed that higher baPWV was significantly associated with a higher risk of cardiovascular events, cardiovascular mortality, and all-cause mortality in patients with a history of coronary artery disease or stroke.

Vascular tests are also useful to achieve a better understanding of the underlying pathophysiology of cardiac disorders. Harada et al. [12] reported that short stature defined as height  $<155.0$  cm was associated with low flow-mediated vasodilation (FMD), an index of endothelial function, in Japanese men, supporting the association between short stature and high risk of cardiovascular events [13]. Cassano et al. [Supplementary Information 1-1] reported that low levels of endothelial progenitor cells (EPCs) at baseline were associated with impaired endothelial function assessed by the reactive hyperemia index (RHI) and impaired arterial stiffness assessed by carotid-femoral PWV (cfPWV) at baseline and that EPC levels at baseline were also associated with longitudinal changes in RHI and cfPWV three years after the initiation of antihypertensive drug treatment in patients with hypertension. Murai et al. [Supplementary Information 1-2] reported that a higher area under the curve value of insulin during a 75-g oral glucose tolerance test, but not insulin

sensitivity indices, was significantly associated with higher baPWV in young Japanese subjects aged  $<40$  years. Miyaoka et al. [14] reported that baPWV and central systolic blood pressure were significantly associated with renal microvascular damage assessed by using renal biopsy specimens in patients with nondiabetic kidney disease. Vila et al. [Supplementary Information 1-3] reported that carotid intima-media thickness (IMT) was significantly greater in male patients with autoimmune disease than in age-matched male controls without autoimmune disease, supporting a role for immune-mediated inflammation in the pathogenesis of atherosclerosis. Li et al. [Supplementary Information 1-4] showed in a cross-sectional study that increased carotid IMT was significantly associated with cognitive impairment assessed by the Mini-Mental State Examination in Chinese patients with hypertension, especially patients who were  $\geq 60$  years of age and patients with low high-density lipoprotein cholesterol levels ( $<40$  mg/dL).

Vascular function is profoundly affected by habitual behavior. Fryer et al. [Supplementary Information 1-5] reported that central arterial stiffness and peripheral arterial stiffness assessed by cfPWV and  $PWV_{\beta}$  were more deteriorated by uninterrupted prolonged sitting (180 min) combined with prior high-fat meal consumption (61 g fat, 1066 kcal) than by uninterrupted prolonged sitting combined with prior low-fat meal consumption (10 g fat, 601 kcal) in healthy nonsmoking male subjects, suggesting that high-fat meal consumption should be avoided before uninterrupted prolonged sitting to prevent the progression of arterial stiffening. Yamaji et al. [15] reported that endothelial function assessed by FMD and vascular smooth muscle function assessed by nitroglycerine-induced vasodilation of the brachial artery were more impaired in patients without daily stair climbing activity than in patients who habitually climbed stairs to the  $\geq 3^{\text{rd}}$  floor among patients with hypertension. Funakoshi et al. [16] reported that eating within 2 h

before bedtime  $\geq 3$  days/week was associated with the development of hypertension defined as blood pressure  $\geq 140/90$  mmHg or initiation of antihypertensive drug treatment during an average follow-up period of 4.5 years in the general Japanese population, suggesting that avoiding late dinners may be helpful for preventing the development of hypertension. These findings indicate the importance of lifestyle modifications for maintaining vascular function and preventing the development of hypertension and the progression of atherosclerosis.

(TM and YH)

**Keywords:** vascular function, endothelial function, arterial stiffness, carotid intima thickness, ankle-brachial index.

## Advances in hypertension management for better renal outcomes (See Supplementary Information 2)

In chronic kidney disease (CKD) patients, hypertension is a risk factor for end-stage renal disease (ESRD), cardiovascular events and mortality. Thus, the prevention and appropriate management of hypertension in CKD patients are important strategies for preventing ESRD and cardiovascular disease (Fig. 2).

### Risk factors for hypertension

Fibroblast growth factor 21 (FGF21) is an endocrine hormone that is mainly secreted by the liver. Circulating FGF21 levels are reported to be increased in CKD patients, while higher circulating FGF21 levels were reported to be

associated with all-cause mortality in ESRD patients [17, 18]. Additionally, Matsui et al. reported that higher circulating FGF21 levels partially mediate the association of elevated BP and/or aortic stiffness with renal dysfunction in middle-aged and older adults [19]. A study by Funakoshi et al. showed that eating before bed was correlated with the future risk of developing hypertension in the Iki Epidemiological Study of Atherosclerosis and Chronic Kidney Disease [Supplementary Information 2-1].

### Prognostic markers

Several promising prognostic markers for renal and cardiovascular outcomes have been suggested. Matsukuma et al. reported that a higher urinary sodium-to-potassium ratio was independently associated with poor renal outcomes in patients with CKD [Supplementary Information 2-2]. Chinese hypertensive patients with higher albumin-to-creatinine ratios had a significantly increased risk of first ischemic stroke [Supplementary Information 2-3]. The number of nephrons in hypertensive patients was significantly lower than that in controls [20]. Tsuboi et al. suggested the usefulness of methods to estimate the total nephron count and single nephron GFR in living patients, which helped to tailor patient care depending on age or disease stage as well as to predict the response to therapy and the disease outcome [21].

### Treatments

Mineralocorticoid receptor (MR) blockers (e.g., esaxerenone) are used in the treatment of essential hypertension and hyperaldosteronism. Recently, a new MR antagonist, finerenone, has been introduced as a treatment for CKD patients with type 2 diabetes. However, hyperkalemia has been recognized as a potential side effect during treatment with MR blockers. A recent review article by Rakugi et al. suggested that being aware of at-risk patient groups, choosing appropriate dosages, and monitoring serum potassium during therapy are required to ensure the safe clinical use of these agents [Supplementary Information 2-4].

The clinical use of sodium–glucose cotransporter-2 inhibitors (SGLT2is) has recently been expanded to non-diabetic patients with CKD and heart failure as well as diabetic patients [22, 23]. Several novel findings regarding the renal protective properties of SGLT2is were reported in 2021. In a real-world registry study of Japanese type 2 diabetes patients with CKD, SGLT2is were associated with significantly better kidney outcomes in comparison to other glucose-lowering drugs, irrespective of the presence or absence of proteinuria [24]. Kitamura et al. reported that the addition of metformin to SGLT2is blunts the decrease in eGFR but that the coadministration of RAS inhibitors

## Advantages of hypertension in CKD

### Risk factors for hypertension

Circulating fibroblast growth factor 21 elevation [18]  
Eating before bed [Supple 2-1]

### Prognostic markers

Urinary sodium-to-potassium ratio [Supple 2-2]  
Urinary albumin-to-creatinine ratio [Supple 2-3]  
Total nephron number and single nephron GFR [21]

### Treatments

MR blocker [Supple 2-4]  
• New drug launch: finerenone  
SGLT2 inhibitor [25, 30-35, Supple 2-5]  
• Expansion as a drug for CKD treatment  
• Postglomerular vasorelaxation  
• Fluid homeostatic mechanism

**Fig. 2** Advantages of hypertension in CKD. CKD chronic kidney disease, GFR glomerular filtration rate, MR mineralocorticoid receptor, SGLT2 sodium–glucose cotransporter 2

ameliorates this response [Supplementary Information 2-5]. Thomson and Vallon reported that (1) SGLT2i treatment reduces glomerular capillary pressure that is mediated through tubuloglomerular feedback (TGF) and (2) the TGF response to SGLT2is involves preglomerular vasoconstriction and postglomerular vasorelaxation [25].

SGLT2is have an antihypertensive effect, which is greater in subjects with higher salt sensitivity and BMI [26–28]. Furthermore, the degree of BP change in patients undergoing SGLT2i therapy depends on the baseline BP; a larger reduction is observed in patients with higher baseline BP, and a smaller reduction or slight increase is observed in patients with lower baseline BP [29]. These BP regulation mechanisms may partially depend on body fluid homeostasis by SGLT2is. SGLT2is ameliorate fluid retention through osmotic diuresis and natriuresis but are associated with a low rate of hypovolemia [30–33], which is evident by the compensatory upregulation of renin and vasopressin levels [33–35]. These fluid homeostatic mechanisms exerted by SGLT2is may contribute to the stabilization of BP. Moreover, recent clinical studies have shown that SGLT2is reduce BP without changes in urinary sodium and fluid excretion or plasma volume [35–37], suggesting the role of other factors, such as the inhibition of the sympathetic nervous system, restoration of endothelial function, and reduction of arterial stiffness [38, 39].

(TM and DN)

**Keywords:** fibroblast growth factor 21, nephron number, mineralocorticoid receptor blocker, SGLT2 inhibitor, fluid homeostasis.

### Hypertension and heart disease-focusing on the relationship with HFpEF (See Supplementary Information 3)

With the increasing longevity of ‘Westernized’ populations, heart failure (HF) in the elderly has become a problem of growing scale and complexity worldwide [40].

Stages of HF are classified from A to D [41]. HF patients are also divided into patients with preserved ejection fraction (EF) (HFpEF), those with mildly reduced EF and those with reduced EF (HFrEF). Persistent hypertension and increased arterial stiffness in stage A HF result in left ventricular (LV) hypertrophy (LVH), at which point it is classified as stage B HF. Although the etiology of HFpEF is diverse, patients with HFpEF have been reported to have a high prevalence of hypertension, which is closely associated with increased arterial stiffness, LVH and diastolic LV dysfunction [41].

In adult Sprague–Dawley rats, a novel flavoprotein, renalase, was increased in hypertrophic cardiac tissue, and recombinant renalase improved cardiac function and

suppressed myocardial fibrosis in the HF model [42]. In stroke-prone spontaneously hypertensive rats, carboxypeptidase X 2 (Cpxm2) was identified as a locus that affects LV mass. Analysis of endomyocardial biopsies from LVH patients showed significant upregulation of CPXM2 expression [43]. In this way, basic research applied to humans has shown in detail the pathophysiology of LVH.

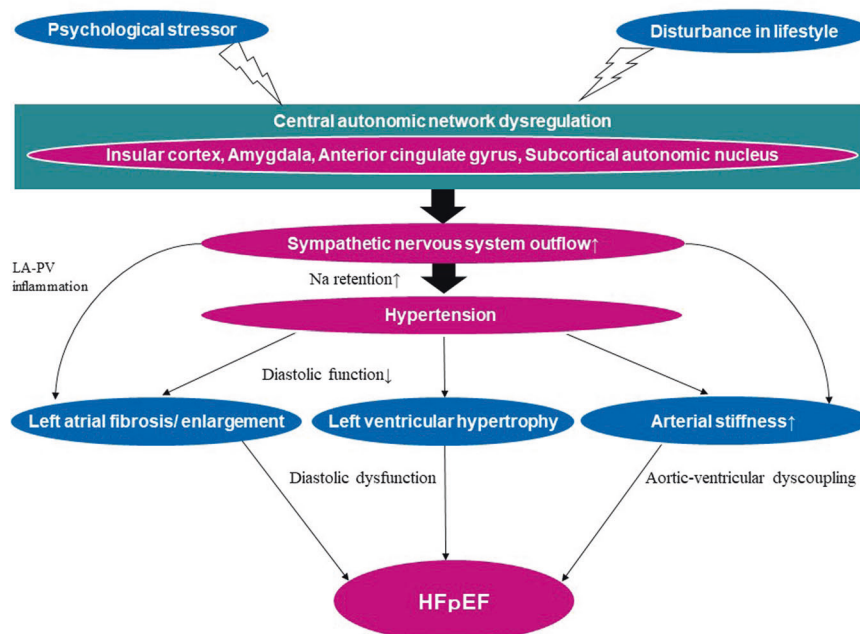
Left atrial (LA) enlargement (LAE) is also associated with HFpEF [44]. In response to proinflammatory mediators, microvascular endothelial cells become inappropriately activated, resulting in microvascular endothelial dysfunction, perpetuating the inflammatory process and LA fibrosis [45]. Manifestations of these mechanisms have been related to LAE, which can be detected prior to the incidence of atrial fibrillation. Sympathetic overdrive from the central autonomic network, including the insular cortex, causes LA-pulmonary vein (PV) border fibrosis. LA-PV border fibrosis was suggested to originate from local inflammation triggered by preganglionic fibers ending in ganglionated plexi [45, 46].

In the SPRINT study, intensive BP management was not associated with LA abnormalities defined based on ECG [47]. Although LA volume (LAV) according to body surface area was recommended to assess LA size [48], LAV indexed for height<sup>2</sup> was shown to be more sensitive for detecting subclinical hypertensive organ damage in females [49]. In the ARIC study, the minimum but not the maximum LAV index was significantly associated with the risk of incident HFpEF or death [50].

In the 2021 European Society of Cardiology guidelines for the treatment of HFrEF, angiotensin receptor/neprilysin inhibitor (ARNI) and sodium–glucose cotransporter 2 inhibitor (SGLT2i) are newly recommended for first-line treatment. In contrast, no guideline-directed treatment has been shown to convincingly reduce mortality and morbidity in HFpEF patients [44].

BP control is important to prevent adverse events in HFpEF patients with high BP. In a randomized study of hypertension patients, a significant reduction in systolic blood pressure (BP) (SBP) and diastolic BP was observed during daytime and nighttime in the ARNI group compared to the placebo group [51]. ARNI was also associated with reduced BP in patients with refractory hypertension with HFpEF [52]. In the PARAGON-HF trial, a decrease in pulse pressure, a marker of large arterial stiffness, during ARNI run-in was associated with a significant improvement in the prognosis of HFpEF [53]. On the other hand, the SACRA study showed that a significant reduction in BP occurred after adding SGLT2i to existing antihypertensive and antidiabetic agents in nonsevere obese diabetic elderly with uncontrolled nocturnal hypertension [54]. Recently, in the EMPEROR-Preserved Trial, SGLT2i improved the prognosis of patients with HFpEF

**Fig. 3** A scheme of the relationship between hypertension and HFpEF. The dysregulation of the central autonomic network is associated with enhanced sympathetic nervous system activity in hypertension linked to HFpEF via left atrial remodeling, left ventricular hypertrophy and increased arterial stiffness. HFpEF heart failure with preserved ejection fraction, LA left atrium, PV pulmonary vein



[55]. From the above, it is suggested that reducing nighttime BP and improving diurnal BP patterns improves the prognosis of HFpEF [56, 57].

Accumulated evidence from basic and clinical studies suggests that hypertension is a crucial risk factor for HFpEF (Fig. 3). These data may contribute to future studies aimed at elucidating the more detailed pathophysiology of HFpEF in hypertension research and the development of therapeutic agents and/or strategies that improve the prognosis of HFpEF in hypertension.

(MN)

**Keywords:** heart failure with preserved ejection fraction, arterial stiffness, left ventricular hypertrophy, diastolic left ventricular dysfunction, left atrial remodeling.

## Up-to-date preeclampsia knowledge; what we should know for mother and child (See Supplementary Information 4)

### Diagnostic criterion

In 2017, the American College of Cardiology/American Heart Association hypertension treatment guidelines identified hypertension as blood pressure (BP)  $\geq 130/80$  mmHg. The reference BP for hypertension during pregnancy as specified in international guidelines [e.g., the International Society for the Study of Hypertension in Pregnancy guidelines (ISSHP) [58] and the American College of Obstetricians and Gynecologists guidelines (ACOG) [59, 60]] is  $\geq 140/90$  mmHg. A large number of studies have examined the incidence of PE and fetal outcomes according

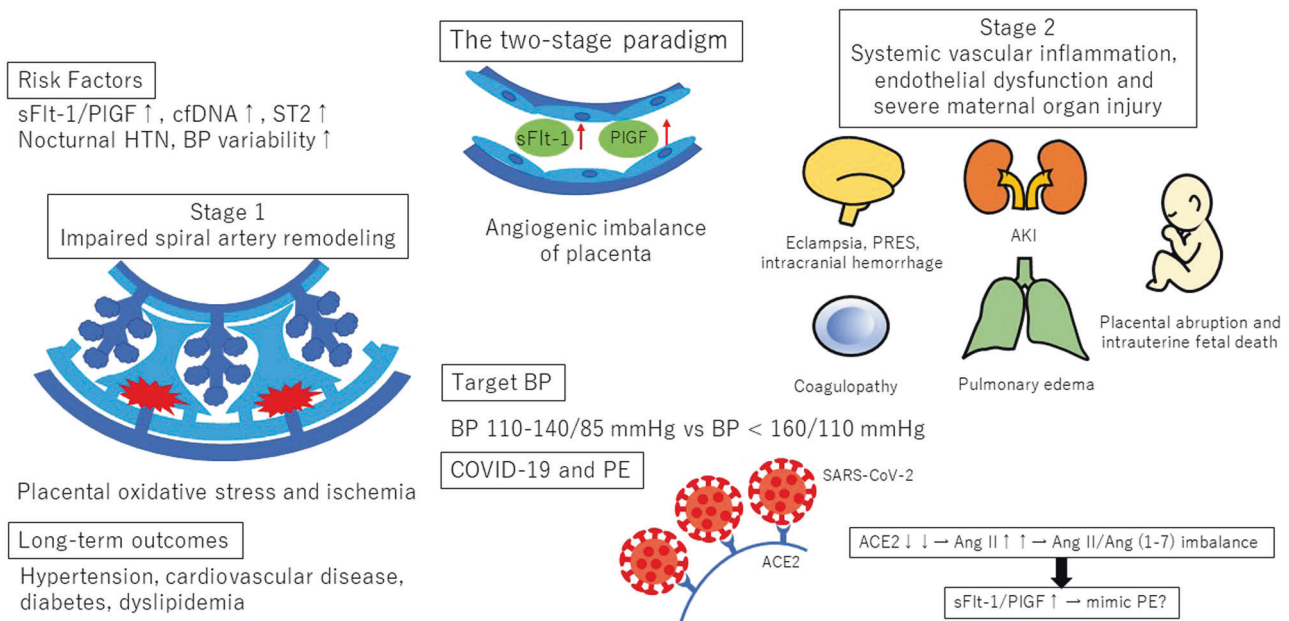
to BP levels. The meta-analysis of these studies has shown that BP  $\geq 120/80$  mmHg, particularly  $\geq 130/80$  mmHg, in early pregnancy is also associated with increased maternal and perinatal risks and proposed new BP categories of  $<120/80$  mmHg (normal),  $120\text{--}129/80$  mmHg (high normal), and  $130\text{--}139/80\text{--}89$  mmHg (elevated) for pregnant women [61].

### Prognostic tools

The predictive value of BP and other clinical characteristics for PE is relatively low [62, 63]. Soluble fms-like tyrosine kinase 1 (sFlt-1)/placental growth factor (PlGF) ratio testing resulted in reduced unnecessary hospitalization [64, 65]. Circulating cell-free DNA (cfDNA) and human suppression of tumorigenesis 2 (ST2) were increased in individual with gestational hypertension (GH) and PE and served as diagnostic biomarkers [Supplementary Information 4-1]. Nocturnal hypertension was a significant predictor of early-onset PE in high-risk pregnancies [66]. BP variability was higher in pregnant women with hypertensive disorders and was significantly associated with left ventricular mechanics [Supplementary Information 4-2]. Including these factors in multivariate models may improve the detection rates of PE and may identify women who could benefit from preventive interventions (Fig. 4).

### Management

The ISSHP recommends that BP  $\geq 140/90$  mmHg should be treated, with a goal BP of  $110\text{--}140/85$  mmHg, while the ACOG recommends antihypertensive medications when



**Fig. 4** Schematic presentation of the topics of preeclampsia 2021. HTN hypertension, PE preeclampsia, BP blood pressure, cfDNA cell-free DNA, ST2 human suppression of tumorigenesis 2, sFlt-1 soluble

fms-like tyrosine kinase-1, PlGF placental growth factor, PRES posterior reversible encephalopathy syndrome, AKI acute kidney injury, ACE angiotensinogen converting enzyme, Ang angiotensin

BP  $\geq 160/110$  mmHg, with goal BP below this threshold (Fig. 4). Systolic BP (sBP)  $< 130$  mmHg within 14 weeks of gestation reduced the risk of developing early-onset superimposed PE in women with chronic hypertension [67]. The Chronic Hypertension and Pregnancy (CHAP) project also showed that BP control to  $< 140/90$  was associated with a reduction in composite adverse outcomes, with no significant increase in small for gestational age infants [68].

### Long-term outcomes

PE is linked to major chronic diseases such as hypertension, type 2 diabetes mellitus, dyslipidemia, and cardiovascular disease (Fig. 4). The American Heart Association lists hypertension during pregnancy as a major cardiovascular risk factor and recommends that affected women undergo cardiovascular risk screening within 3 months after giving birth [69]. Since many cardiovascular risk factors are modifiable and related to lifestyle, all women with prior PE should be followed up by physicians even after the resolution of PE.

### COVID-19 and Pregnancy

Pregnancy could potentially affect the susceptibility to and severity of COVID-19. Severe cases of COVID-19 present with PE-like symptoms. PE mimicry by COVID-19 was confirmed following the alleviation of preeclamptic symptoms without delivery of the placenta [70]. In COVID-19, angiotensin-converting enzyme 2 (ACE 2) function

decreases, and subsequently, angiotensin II (Ang) activity increases [71]. Similar to PE, COVID-19 results in an increase in the sFlt-1/PlGF ratio due to pathologic Ang II/Ang (1-7) imbalance [72] (Fig. 4). Most experts believe that SARS-CoV-2 is likely to become endemic, and continued collection of data on the effects of COVID-19 during pregnancy is needed.

Further investigation is needed to decrease PE-related maternal and fetal deaths and to reduce maternal risks for chronic diseases in later life. The participation of physicians is necessary to offer appropriate medical care to women with prior PE, and continued publications of issues regarding PE in Hypertension Research are expected.

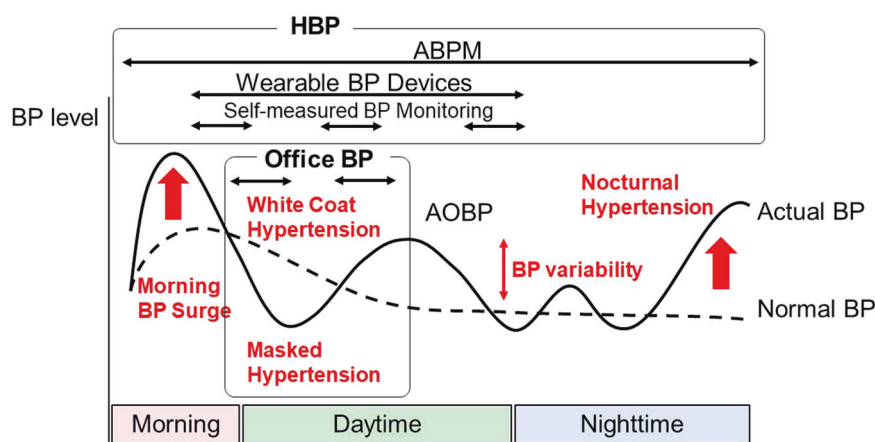
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**Keywords:** preeclampsia, gestational hypertension, chronic hypertension, soluble fms-like tyrosine kinase 1, placental growth factor.

### Appropriate blood pressure assessment methods for the prevention of hypertension complications (See Supplementary Information 5)

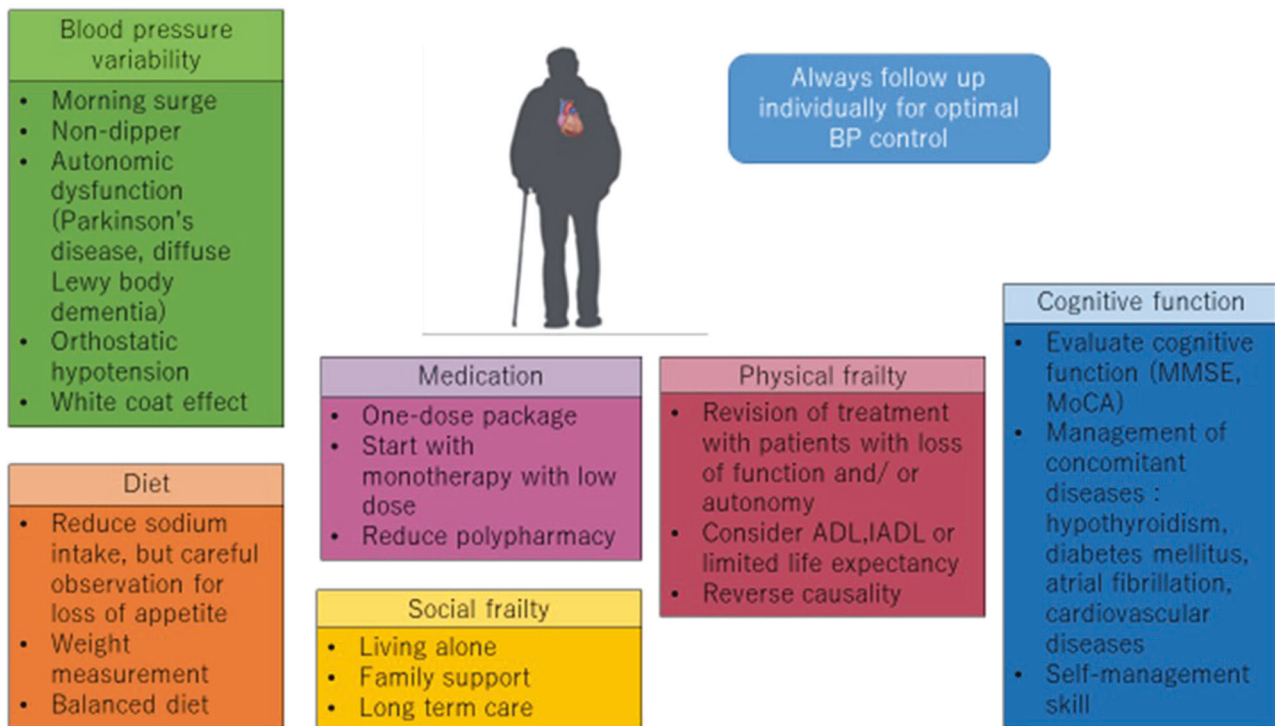
Blood pressure (BP) values can vary and fluctuate widely depending on the method and the environment of blood measurement. Via appropriate measurement and interpretation of BP values, hypertension can be correctly diagnosed, treated and guided [73]. To give an example, appropriate body posture is important for accurate BP

**Fig. 5** Methods of measuring variable blood pressure and evaluating factors associated with the prognosis of cardiovascular disease



measurement. Wan et al. [Supplementary Information 5-1] demonstrated that BP levels measured with the back in an unsupported position were 2.3/1.0 mmHg higher than those measured with the back in a supported position. Glenning et al. [Supplementary Information 5-2] demonstrated the feasibility of measuring diastolic blood pressure by the onset of the fourth Korotkoff phase (K4), when K5 is undetectable under exercise conditions in children and adolescents. In recent years, a variety of BP measurement devices and techniques have appeared, and accumulating evidence has shown the feasibility, reproducibility, and usefulness of these devices [74, 75]. Kario et al. [76] demonstrated the relationship between BP by a newly released wrist-cuff oscillometric wearable BP device and left ventricular hypertrophy. They concluded the feasibility and usefulness of wearable BP devices to detect masked daytime hypertension. Automated office blood pressure (AOBP) measurement includes recording of several BP readings using a fully automated oscillometric sphygmomanometer with the patient resting alone in a quiet place, thereby potentially minimizing the white-coat effect. The most comprehensive meta-analysis [77] reported that AOBP is equivalent to home BP (HBP), but the diagnostic value and viability of AOBP are still controversial. Lee et al. [78] assessed the diagnostic accuracies of two AOBP machines and manual office blood pressure measurements (MOBP) in Chinese individuals and clarified the lower diagnostic significance of AOBP than that of MOBP. Recent studies strongly recommended the wide use of self-measured HBP [79] because HBP has better reproducibility than office BP (OBP), improves adherence to treatment, enables us to detect high-risk populations and has prognostic value for cardiovascular disease (CVD) events [80–82]. Both elevated morning and nocturnal BP values and disrupted circadian BP rhythm assessed by each BP measurement method or devices are associated with worsened cardiovascular outcomes (Fig. 5). Zhan et al. [83] demonstrated

that HBP monitoring improved treatment adherence and BP control in stage 2 and 3 hypertension. Hoshida et al. [84] demonstrated the association of nighttime BP assessed by HBP and CVD events, independent of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, in the Japanese clinical population. Narita et al. [Supplementary Information 5-3] demonstrated that the elevated difference between morning and evening systolic BP was associated with a higher incidence of CVD events in the J-HOP study. Narita et al. [Supplementary Information 5-4] also demonstrated that treatment-resistant hypertension diagnosed by HBP monitoring was associated with increased CVD risk independent of cardiovascular damage in the same Japanese cohort. Oliveira et al. [Supplementary Information 5-5] demonstrated that the SAGE score calculated by systolic BP, age, fasting blood glucose and estimated glomerular filtration rate was associated with pulse wave velocity measured by oscillometric devices and concluded that a SAGE score  $\geq 8$  could be used to identify a high risk of CVD events. ABPM is currently regarded as the reference method for hypertension diagnosis in children and pregnancy. Salazar et al. [Supplementary Information 5-6] demonstrated nocturnal hypertension assessed by ABPM as a significant predictor of early-onset preeclampsia/eclampsia in high-risk pregnant women in a cohort study in Argentina. ABPM also helped us to notice abnormal circadian patterns in BP, which are associated with increased circulating volume, largely determined by salt sensitivity and salt intake. Understanding these pathogenic mechanisms under conditions of nocturnal hypertension and heart failure suggests several new antihypertensive pharmacotherapies, including sodium–glucose cotransporter 2 inhibitors, angiotensin receptor neprilysin inhibitors and mineralocorticoid receptor antagonists [56, 85, 86]. Kario et al. [Supplementary Information 5-7] demonstrated the effect of esaxerenone, a highly selective mineralocorticoid receptor blocker, for improving nocturnal hypertension and



**Fig. 6** Hypertension management in frail patients. ADL activities of daily living, IADL instrumental activities of daily living

NT-proBNP levels. Esaxerenon could be an effective treatment option, especially for nocturnal hypertensive patients with a riser pattern.

(YN)

**Keywords:** hypertension management, BP measurement devices, BP variability, home BP, cardiovascular disease

## Considering frailty and exercise in the management of hypertension and hypertensive organ damage (See Supplementary Information 6)

### Frailty

Frailty is defined as physiological decline and a state of vulnerability to stress and results in adverse health outcomes [87]. Frailty consists of multiple domains, such as physical, social, and psychological factors. Cognitive decline is one of the factors related to frailty, and blood pressure (BP) control significantly reduced dementia or cognitive decline in a meta-analysis [88]. However, in the elderly population above 80 years, the positive effect of antihypertensive therapy for preventing dementia was not proven [89–91].

A systematic review and meta-analysis of the prevalence of mild cognitive impairment (MCI) among hypertensive

patients was conducted by Quin et al. The prevalence of MCI was 30% in a sample of 47,179 hypertensive patients. Heterogeneity was seen due to ethnicity, study design (cross-sectional or cohort study), and cognition assessment tools [92]. Li. et al. investigated the association between carotid intima thickness (CIMT) and cognitive function in hypertensive patients [Supplementary Information 6-1]. CIMT was significantly and negatively associated with MMSE scores in people aged  $\geq 60$  years but not in those aged  $< 60$  years.

BP guidelines in various countries suggest that BP management should be carried out in the context of frailty or end of life, and careful observation, including personalized BP control among elderly individuals, is essential (Fig. 6). A total of 535 patients with hypertension (age 78 [70–84] years, 51% men, 37% with frailty) were prospectively followed for 41 months, and mortality associated with frailty and BP was evaluated by Inoue et al. [93]. Frailty was assessed by the Kihon checklist. Among 49 patients who died, mortality rates were lowest in those with systolic BP  $< 140$  mmHg and nonfrailty and highest in those with systolic BP  $< 140$  mmHg and frailty. The results indicate that frail patients have a higher risk of all-cause mortality than nonfrail patients, and BP should be managed considering frailty status, which is in line with previous reports [94]. Our latest study showed that in patients with preserved MMSE scores, higher BP was associated with



cognitive impairment, and those with MMSE scores below 24 points had the opposite results [95]. Elderly individuals with hearing impairment have higher rates of hospitalization, mortality, falls, frailty, dementia, and depression. Miyata et al. performed a study using data from medical records from health checkups: higher SBP levels were associated with an increased risk of objective hearing impairment at 1 kHz [Supplementary Information 6-2].

## Exercise

In the era of technical advancement, people are spending less time being active, which leads to cardiovascular risks, including hypertension. However, guidelines emphasize the importance of nonpharmacological strategies such as lifestyle modification and exercise to prevent diseases [96].

Sardeli et al. compared types of exercise that are beneficial to health. The study compared the effects of aerobic training (AT), resistance training (RT), and combined training (CT) in hypertensive older adults aged >50 years. There were extensive health benefits associated with exercise training, and CT was the most effective intervention at improving a wide spectrum of health conditions, including cardiorespiratory fitness, muscle strength BMI, fat mass, glucose, TC and TGs [97]. J Almeida et al. showed that isometric handgrip exercise training reduced systolic BP in treated hypertensive patients [Supplementary Information 6-3]. Stair climbing and vascular function were assessed by Yamaji et al. There was a significant difference in nitroglycerine-induced vasodilatation between the group with no habits of climbing stairs and the other groups with two or more climbing habits [Supplementary Information 6-4].

The safety of resistance training was studied by Hansford et al who concluded that isometric resistance training (IRT) was safe and led to a potentially clinically meaningful reduction in BP [Supplementary Information 6-5].

(AT)

**Keywords:** physical and social frailty, elderly, cognitive function, resistance training, cardiorespiratory function

## Blood pressure variability—therapeutic target for the prevention of cardiovascular disease (See Supplementary Information 7)

In the past three decades, there have been many reports on the associations of various parameters of blood pressure (BP) variability with increased risk of cardiovascular disease (CVD) events; these parameters include short-term BP variability (BPV), i.e., beat-by-beat BPV and ambulatory BPV, abnormality of nocturnal BP dipping pattern, and mid- to long-term BPV, i.e., day-by-day BPV, visit-to-visit BPV, and seasonal variations in BP [98–106]. In addition, BPV has been

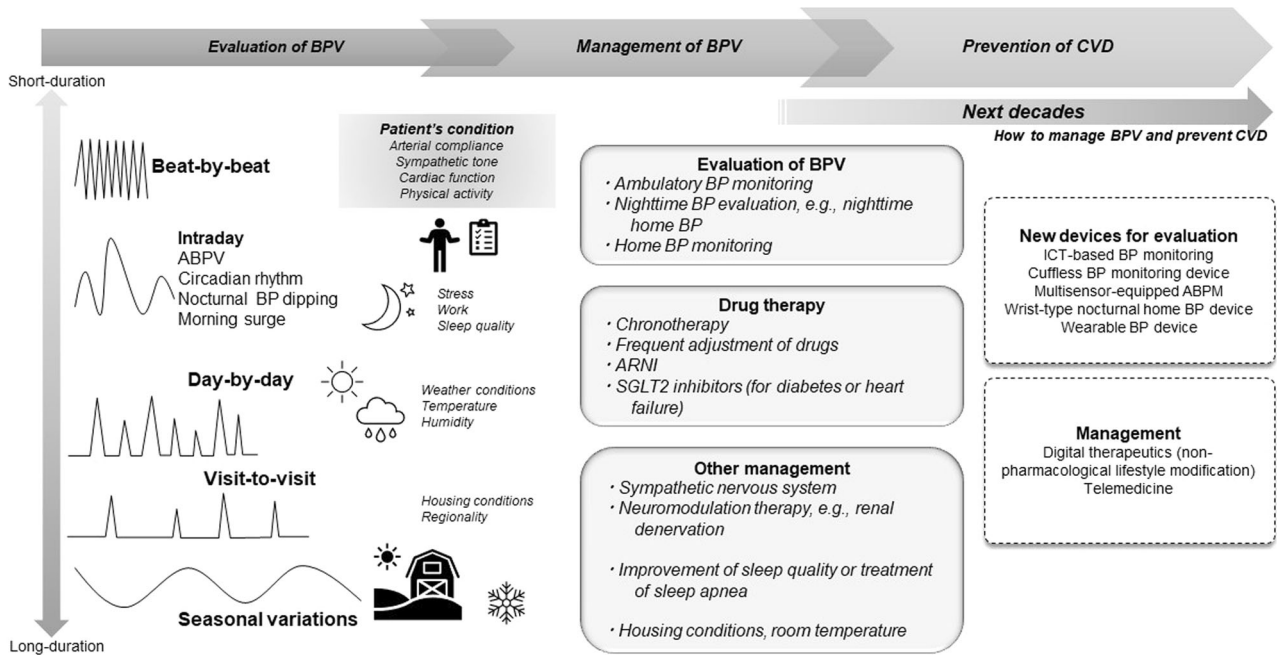
associated with the progression of endovascular organ damage related to heart failure, chronic kidney disease, and cognitive function [107–111] [Supplementary Information 7-1]. Several factors that are associated with abnormal BPV [112], as well as environmental factors such as cold or warm temperatures and seasonal changes in climate, increase fluctuations in BP. Individual intrinsic factors, such as sympathetic nervous tone, arterial stiffness, physical activity, and mental stress, also contribute to elevated BPV. According to evaluations of BPV abnormalities, out-of-office BP measurements, such as ambulatory and home BP monitoring, are needed. To evaluate nighttime BP levels, home BP monitoring devices equipped with a function for nighttime BP readings and new wrist-type nocturnal BP monitoring devices are available [76]. Although there are issues regarding measurement accuracy, cuffless BP monitoring devices, for example, those using pulse transit time, may be used to estimate nighttime BP levels [Supplementary Information 7-2]. Such cuffless BP devices can also evaluate beat-by-beat BPV. Moreover, by using the multisensor-equipped ambulatory BP monitoring device developed by our research group, it is possible to evaluate BPV associated with changes in temperature, physical activity, and/or atmospheric pressure [113].

Based on the mechanism(s) underlying a given patient's BPV abnormality, several methods may be considered for the management of that abnormality (Fig. 7). For example, improving excessive sympathetic nervous system activation may be useful in the management of BPV abnormalities [114], and renal denervation has been reported to decrease ambulatory BPV [115]. Abnormal nocturnal BP dips may be treated by decreasing nighttime BP. In patients with sleep apnea, improving sleep quality and implementing continuous positive airway pressure are recognized to be useful for nighttime BP control [116]. Moreover, early adjustment of antihypertensive drugs has been reported to be useful in suppressing seasonal variations in BP, leading to a decreased risk of CVD events [99]. Furthermore, housing conditions and room temperature are closely related to BP levels, and adaptive control of room temperature would be useful to suppress winter increases in BP [117, 118]. In clinical practice, we must not forget that BPV parameters are interrelated. For instance, frequent evaluation of BP levels and adjustment of antihypertensive drugs can suppress visit-to-visit BPV, which in turn leads to the suppression of seasonal variations in BP.

Over the next decade, more data on how to manage and control BPV need to be accumulated. Additionally, future studies should be conducted to verify whether the different types of BPV management are useful in preventing CVD events.

(KN, SH and KK)

**Keywords:** blood pressure variability, out-of-office blood pressure monitoring, cardiovascular disease



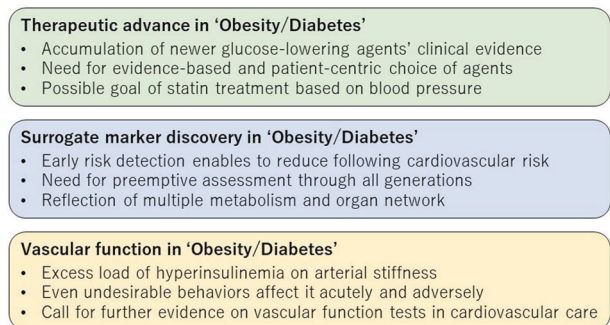
**Fig. 7** Current and future perspectives in the management of blood pressure variability. Short- and long-term BP variability is associated with CVD event risk independent of each BP level. Out-of-office BP measurements, such as ABPM and home BP monitoring, and other new BP devices are useful for evaluating the various types of BP variability. To suppress BP variability, several management methods, including new antihypertensive medications, chronotherapy, housing

condition, and sympathetic nervous denervation, are considered. ABPM ambulatory blood pressure monitoring, ABPV ambulatory blood pressure variability, ARNI angiotensin receptor neprilysin inhibitor, BP blood pressure, BPV blood pressure variability, CVD cardiovascular disease, ICT information and communication technology, SGLT2i sodium–glucose cotransporter 2 inhibitor

prevention, wearable blood pressure monitoring device, environmental factors.

### Optimal therapy and clinical management of obesity/diabetes (See Supplementary Information 8)

Obesity/diabetes is a major comorbidity in patients with hypertension, and these conditions often share common pathological conditions, such as insulin resistance and the risk of cardiovascular diseases (CVD). One of the biggest highlights of recent years in the area of obesity/diabetes has been the remarkable benefits of newer glucose-lowering agents seen in large-scale clinical trials on cardiorenal outcomes (Fig. 8), followed by the relevant clinical guideline updates and the expansion of the clinical application of those agents [119]. In particular, sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists are now preferentially recommended in patients with type 2 diabetes (T2D) and specific cardiorenal risk, independent of diabetes status or background use of metformin [120]. It is noteworthy, of course, that those agents reduced the risk of cardiorenal events, and their multifaceted effects beyond hypoglycemic effects are also



**Fig. 8** Schematic presentation of the topic 'Obesity/Diabetes' in 2021

attracting clinical attention. In a review series 'New Horizons in the Treatment of Hypertension' in Hypertension Research, Tanaka and Node [121] discussed the modest effects of those agents on blood pressure (BP)-reduction and the clinical perspectives. They also proposed a new-normal style care for diabetes and its complications using such evidence-based agents with multidisciplinary effects, partly aiming at reduced polypharmacy and avoidance of its possible harm. This action will improve the quality of hypertension care in patients with obesity/diabetes; however, a substantial population with treated hypertension still has inadequate blood pressure control, which is recognized as

resistant hypertension (RH). Due to the difficulty in distinguishing true RH from pseudo-RH due to nonadherence, little is known about the clinical characteristics of true RH. Chiu et al. from Boston [Supplementary Information 8-1] reported a notable prevalence (26.6%) of true RH in patients with T2D registered in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure trial and identified several independent predictors, such as higher baseline BP, higher number of baseline antihypertensives, macroalbuminuria, chronic kidney disease, and history of stroke. Moreover, patients with true RH exhibited poorer prognosis than those without, suggesting an emerging need for effective screening and intensified treatment for patients with true RH.

The BP treatment goal in patients with diabetes and hypertension is less than 130/80 mmHg [122], and intensified BP control was associated with reduced stroke risk [123–125]. Intensive lipid-lowering therapy is also recommended for patients with T2D at risk of CVD [126]; however, an original EMPATHY study investigating the effect of intensive lipid-lowering therapy (target of low-density lipoprotein cholesterol [LDL-C] < 70 mg/dL) on cardiovascular outcomes failed to show the clinical benefits of intensive statin therapy in patients with T2D, diabetic retinopathy, elevated LDL-C levels, and no known CVD [127]. In a subanalysis of the EMPATHY study, Shinohara et al. [128] revealed for the first time that intensive statin therapy was associated with a reduced risk of cardiovascular events compared with standard therapy (target of  $\geq 100$  to < 120 mg/dL) in a subgroup with baseline BP  $\geq 130/80$  mmHg but not in another subgroup with baseline BP < 130/80 mmHg. Their findings suggest that baseline BP is also a possible determinant of the target LDL-C in that patient population, although the precise reasons for the difference in the clinical benefits of intensive statin therapy between subgroups according to baseline BP levels are still uncertain.

Obesity is a crucial global health concern across generations. Obesity and insulin resistance cause several cardiometabolic disorders, including hypertension, and increase the risk of subsequent CVD. Hence, further actions against obesity and cardiometabolic disorders are urgently needed for individuals of all generations [129, 130]. In this context, Fernandes et al. from Brazil [Supplementary Information 8-2] revealed for the first time that Ang-(1-7) and des-Arg9BK metabolites were novel biological markers of adolescent obesity and relevant cardiovascular risk profiles, such as elevated BP, lipids, and inflammation. Thu et al. from Singapore [Supplementary Information 8-3] found a positive association between accumulated visceral adipose tissue and systolic BP in midlife-aged women, independent of burdens of inflammatory markers. Intriguingly, Haze et al. [131] clearly demonstrated that an increased ratio of visceral-to subcutaneous fat volume was

an independent risk factor for renal dysfunction in Japanese patients with primary aldosteronism. These findings should highlight the clinical importance and the need for further research to explore surrogate markers of obesity in the care of hypertension and its related conditions (Fig. 8).

Finally, we briefly introduce some exciting progress in vascular function in the area of “Obesity/Diabetes” (Fig. 8). Murai et al. [132] elegantly showed that postload hyperinsulinemia was independently associated with increased arterial stiffness as assessed by brachial-ankle pulse wave velocity (PWV) in young medical students at Jichi Medical University. Given the close pathological relationship between hyperinsulinemia and most CVDs, including heart failure [133, 134], their findings suggest that hyperinsulinemia-induced vascular failure is one of the key drivers of that pathological link. Interestingly, Fryer et al. from the UK [Supplementary Information 8-4] also found that arterial stiffness as assessed by carotid-femoral PWV was exacerbated by the consumption of a high-fat meal relative to a low-fat meal prior to 180 min of uninterrupted sitting. Importantly, arterial stiffness testing could accurately reflect even such a combination of unfavorable behaviors, and thus vascular function assessment has the potential to reflect a wide spectrum of cardiovascular risk and provide a clinical opportunity for better risk stratification and optimal modification [135]. We look forward to accumulating and consolidating evidence of vascular function tests and further applying them to actual cardiovascular care [136].

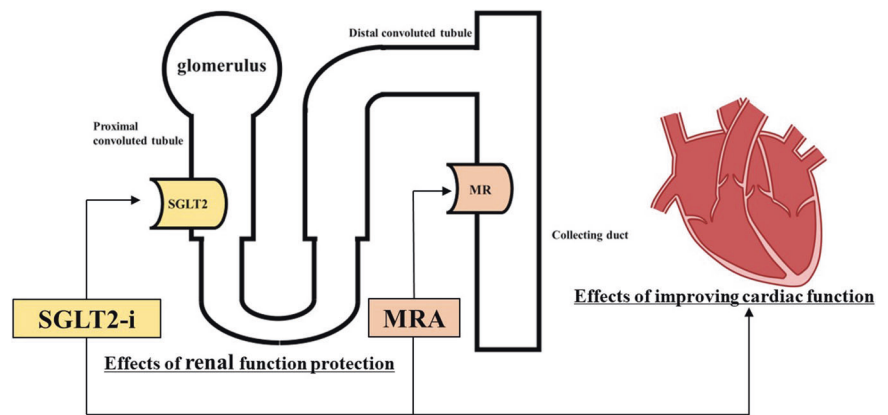
(AT and KN)

**Keywords:** glucose-lowering agent, resistant hypertension, statin, surrogate marker, vascular function

### **A new era of progress in primary aldosteronism treatment: mineralocorticoid receptor antagonists, a new aldosterone assay, and a clinical practice guideline (See Supplementary Information 9)**

A hot topic in 2021 was advances in the treatment of mineralocorticoid receptor (MR)-associated hypertension [137], particularly primary aldosteronism (PA). The non-steroidal MR antagonist (MRA) esaxerenone is now widely used in Japan. Kario et al. [138] reported that esaxerenone reduced nocturnal blood pressure in patients with essential hypertension, according to ambulatory blood pressure assessment and N-terminal pro-brain natriuretic peptide assays. Yoshida et al. [139] reported that MRAs such as esaxerenone improved quality of life in PA patients. Ito et al. [140] reported that add-on treatment using esaxerenone with maximal tolerable doses of a renin-angiotensin system (RAS) inhibitor reduced the urinary

**Fig. 9** Potential drug therapy regimen. Combined administration of an MRA and an SGLT2i may afford cardiac and renal protection. MRA mineralocorticoid receptor antagonist, SGLT2i sodium–glucose cotransporter 2 inhibitor



albumin-creatinine ratio in patients with type 2 diabetes mellitus (ESAX-DN), suggesting a renoprotective effect against diabetic nephropathy. Several clinical studies of another nonsteroidal MRA, finerenone (FIDELIO-DKD [141], FIGARO-DKD [142], and FIDELITY [143]), have shown its renoprotective effect against diabetic nephropathy as well as cardiovascular events, particularly hospitalization for heart failure in patients with type 2 diabetes and chronic kidney disease. Although there are no reports of clinical studies on finerenone for PA, finerenone may be used in the future for type 2 diabetes patients with PA, as obesity, glucose intolerance, and sleep apnea are common complications in patients with PA [144]. Similarly, sodium–glucose cotransporter 2 inhibitors (SGLT2i) have been demonstrated to improve the prognosis of cardiovascular disease and chronic kidney disease in individuals with type 2 diabetes (EMPA-REG OUTCOME [145], DECLARE-TIMI 58 [146], DAPA-HF [147], and DAPA-CKD [22]). As steroidal MRAs such as spironolactone and eplerenone are effective in the treatment of mild to severe stages of heart failure (RALES, EPHESUS [148], and EPHESUS-HF [149]), combined treatment with MRA and SGLT2i, in addition to an RAS inhibitor, may be a novel effective treatment for cardiac and renal protection in type 2 diabetic patients (Fig. 9). Second, radiofrequency ablation of macroscopic adrenal tumors [150–152] has been reported as an alternative treatment for PA to lower blood pressure and plasma aldosterone levels. This treatment has been covered by health insurance providers in Japan since April 2022, but long-term outcomes need to be validated.

Another hot topic was the launch of serum aldosterone measurement using a chemiluminescent enzyme immunoassay (CLEIA), which utilizes a two-step sandwich method. Previously, low aldosterone levels may have been measured incorrectly [153]. The new CLEIA figures are closely correlated with liquid chromatography/tandem mass spectrometry values; the new assay is more accurate than the previous radioimmunoassay, which overestimated serum aldosterone levels [154–156]. Thus, the Japan

Endocrine Society issued a Primary Aldosteronism Clinical Guideline in 2021 [157]. The CLEIA method is also used to measure urinary aldosterone levels; Ozeki et al. [158] proposed a PA diagnostic cutoff of  $\geq 3$   $\mu\text{g}/\text{day}$  for the oral salt loading test. The CLEIA method is currently available only in Japan.

Exosomes may serve as biomarkers of MR activity. Ochiai-Homma et al. [159] focused on pendrin, a  $\text{Cl}^-/\text{HCO}_3^-$  exchanger that is only expressed by renal intercalated cells. In a rat model, the pendrin level in the urinary exosome was reduced by therapeutic interventions favored for PA patients; the urinary level was correlated with the renal level. This model may help to elucidate the pathophysiology of PA-induced organ injury [160].

Finally, Haze et al. [Supplementary Information 9-1], Segawa et al. [Supplementary Information 9-2], Nishimoto et al. [Supplementary Information 9-3], Chen et al. [Supplementary Information 9-4], and Liu et al. [Supplementary Information 9-5] have conducted intriguing clinical studies regarding PA.

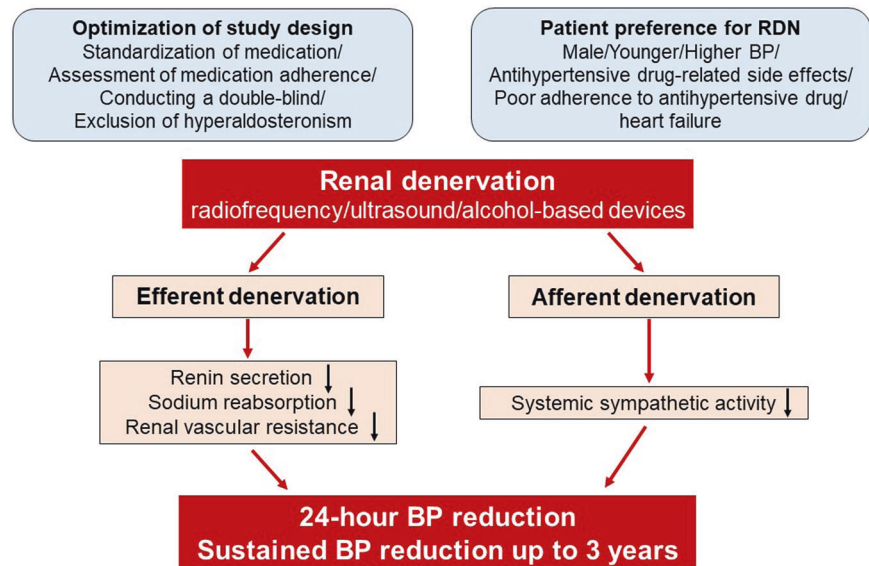
(YY and HS)

**Keywords:** mineralocorticoid receptor-associated hypertension, mineralocorticoid receptor antagonist, hypertension, primary aldosteronism, chemiluminescent enzyme immunoassay

### Advances in renal denervation for treating hypertension: current evidence and future perspectives (See Supplementary Information 10)

It is well established that renal denervation (RDN) decreases blood pressure (BP) in various models of hypertension in animals and in humans [161–165]. Here, we reviewed studies related to RDN published in Hypertension Research in 2021 (Fig. 10). The antihypertensive effect of RDN is mediated by interrupting both the efferent outputs from the brain to the kidney and the afferent inputs from the kidney

**Fig. 10** Topics on renal denervation. BP blood pressure, RDN renal denervation



to the brain, suppressing systemic sympathetic outflow [165, 166]. In basic research, there are two methods of RDN: total RDN (TRDN) performed by surgical cutting of renal nerves to ablate both efferent and afferent nerves and selective afferent RDN (ARDN) performed via capsaicin application to renal nerves to specifically ablate afferent nerves expressing capsaicin receptors [167, 168]. Katsurada et al. [169] reviewed previous reports that address the different effects of TRDN and ARDN in different animal models of hypertension, suggesting potentially complicated and diversified origins of hypertension. The potential therapeutic effects of TRDN and ARDN have also been reported in animal models of heart failure [170].

In clinical practice, radiofrequency, ultrasound, and alcohol-based RDN devices have been developed as second-generation catheter devices and evaluated in randomized control trials. Ogoyama et al. [171] reported a meta-analysis of nine randomized sham-controlled trials of RDN that showed that RDN significantly reduced a range of office, home and 24 h BP parameters in patients with resistant, uncontrolled, and drug-naïve hypertension. There were no significant differences in the magnitude of BP reduction between radiofrequency-based and ultrasound-based devices.

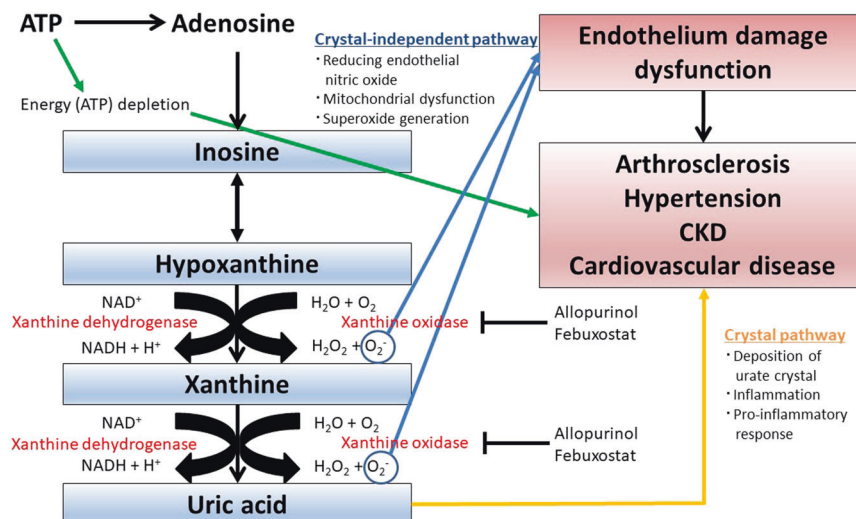
The Global SYMPPLICITY Registry (GSR) is a prospective all-comer registry to evaluate the safety and efficacy of RDN in a real-world population [172]. The overall GSR has enrolled over 2700 patients, and more than 2300 of these have now been followed for 3 years [173]. GSR Korea is a Korean registry substudy of GSR ( $N = 102$ ) [174]. Kim et al. [Supplementary Information 10-1] reported the 3-year follow-up outcomes from the GSR Korea showing that RDN led to sustained reductions in office systolic BP at 12, 24 and 36 months ( $-26.7 \pm 18.5$ ,  $-30.1$

$\pm 21.6$ , and  $-32.5 \pm 18.8$  mmHg, respectively) without safety concerns. Recently, the efficacy and safety of second-generation radiofrequency RDN up to 36 months have been reported [175].

The REQUIRE trial by Kario et al. [Supplementary Information 10-2] is the first trial of ultrasound RDN in Asian patients from Japan and South Korea with hypertension receiving antihypertensive therapy. The study findings were neutral for the primary endpoint, with similar reductions in 24 h systolic BP at 3 months in the RDN ( $-6.6$  mmHg) and sham control groups ( $-6.5$  mmHg). Although BP reduction after RDN was similar to other sham-controlled studies [161, 162, 164, 176], the sham group in this study showed much greater reduction. Unlike RADIANCE-HTN TRIO that used an ultrasound catheter system to measure its primary endpoint, REQUIRE did not standardize medications or measure medication adherence, which may lead to increased variability in BP outcome; moreover, REQUIRE was not a double-blind study, which may result in a substantial bias. Another important factor is that 32.4% of patients showed hyperaldosteronism in the REQUIRE trial. Patients with primary aldosteronism have decreased sympathetic nerve activity and are likely to respond poorly to RDN [177]. The lessons from REQUIRE will enable us to design a follow-up trial to make a definitive evaluation of the effectiveness of RDN in Asian patients with hypertension.

Another topic is the patient preference for RDN. Kario et al. [Supplementary Information 10-3] conducted a nationwide web-based survey in Japan and reported that preference for RDN was expressed by 755 of 2392 Japanese patients (31.6%) and was higher in males, in younger patients, in those with higher BP, in patients who were less adherent to antihypertensive drug therapy, in those who had

**Fig. 11** Mechanisms linking hyperuricemia and arteriosclerosis, hypertension, chronic kidney disease, and cardiovascular disease. ATP adenosine triphosphate, CKD chronic kidney disease



antihypertensive drug-related side effects, and in those with comorbid heart failure. This should be taken into account when making shared decisions about antihypertensive therapy.

(KK)

**Keywords:** renal nerves, hypertension, renal denervation, patient preference, heart failure

### Hot topics in uric acid research: the difficulties of managing hyperuricemia (See Supplementary Information 11)

The mechanisms linking hyperuricemia, arteriosclerosis, hypertension, chronic kidney disease, and cardiovascular disease are becoming clearer (Fig. 11) [178–181]. However, it remains unclear whether treatment of hyperuricemia improves these diseases. Some recent topics of uric acid research are introduced below.

First, urate-lowering treatment with allopurinol, a xanthine oxidase (XO) inhibitor, did not slow the decline in eGFR compared with placebo in either the PERL (Preventing Early Renal Loss in Diabetes) trial [182] or CKD-FIX (Controlled Trial of Slowing of Kidney Disease Progression from the Inhibition of Xanthine Oxidase) [183]. These results were similar to the results of FEATHER (Febuxostat Versus Placebo Randomized Controlled Trial Regarding Reduced Renal Function in Patients with Hyperuricemia Complicated by Chronic Kidney Disease Stage 3) from Japan [184]. Moreover, the PRIZE (Program of Vascular Evaluation Under Uric Acid Control by the Xanthine Oxidase Inhibitor Febuxostat: Multicenter, Randomized, Controlled) study showed that febuxostat did not delay the progression of carotid atherosclerosis in patients with asymptomatic hyperuricemia [185]. These results suggest the difficulties of

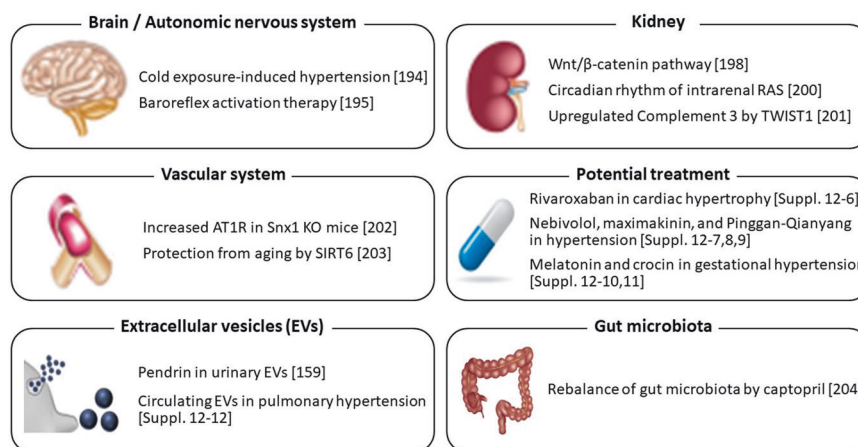
managing hyperuricemia for preventing chronic kidney disease (CKD) and/or arteriosclerosis.

Second, FAST (the Febuxostat versus Allopurinol Streamlined Trial) showed that febuxostat was noninferior to allopurinol therapy with respect to the primary cardiovascular endpoint, all-cause or cardiovascular deaths [186]. The results of FAST were different from the results of the CARES (The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities) trial [187], and the authors summarized that regulatory advice to avoid the use of febuxostat in patients with cardiovascular disease should be reconsidered and modified [186].

In Hypertension Research 2021, several important articles on uric acid research were published. Mori et al. reported that a high serum uric acid level is associated with an increase in systolic blood pressure in women but not in men in subjects who underwent annual health checkups [188]. Their group also reported that a low uric acid level is a significant risk factor for CKD over 10 years in only women, and an elevated UA level increases the risk of CKD in both sexes [Supplementary Information 11-1]. Moreover, Li et al. reported that elevated serum uric acid levels in subjects without stroke, coronary heart disease, and medication for hyperuricemia or gout aged 40–79 years were independent predictors of total stroke, especially ischemic stroke, in women but not in men in a 10-year cohort study [Supplementary Information 11-2]. These results suggested the possibility that both hyperuricemia and hypouricemia in women could be associated with a higher risk for hypertension, CKD, and stroke than those in men.

Azegami et al. reported a prediction model of high blood pressure in young adults aged 12–13 years followed up for an average of 8.6 years. The results showed that uric acid was an important predictor of high blood pressure [189].

**Fig. 12** Topics in basic research. Each ref. number indicates the reference paper cited in the text. AT1R angiotensin type 1 receptor, EV extracellular vesicles, KO knockout, RAS renin-angiotensin system, Snx1 sorting nexin 1, SIRT6 sirtuin 6, TWIST1 twist-related protein 1



Kawasoe et al. reported that high (4.1–5.0, 5.1–6.0, and  $\geq 6.1$  mg/dL) and low ( $\leq 2.0$  mg/dL) serum uric acid levels were significantly associated with an increased prevalence of high blood pressure compared to 2.1–4.0 mg/dL serum uric acid in subjects who underwent health checkups [190]. The results were compatible with a previous report stratified by sex [191]. Serum uric acid levels and the risks for diseases are largely different between men and women, and it is desirable to conduct every analysis by sex when conducting uric acid research.

Furuhashi et al. reported that plasma xanthine oxidoreductase (XOR) activity was associated with hypertension in 271 nondiabetic subjects in the Tanno–Sobetsu Study [192]. Kusunose et al. reported that additional febuxostat treatment in patients with asymptomatic hyperuricemia for 24 months might have potential prevention effects on impaired diastolic dysfunction in the subanalysis of the PRIZE study [193]. These reports suggested the potential direct antioxidant effects of the treatment as reflected in serum uric acid levels as well as its xanthine-oxidase-lowering properties in tissue [Supplementary Information 11-3]. Whether the preferential use of xanthine oxidoreductase XO inhibitors becomes a new therapeutic strategy for the prevention of cardiovascular disease in patients with asymptomatic hyperuricemia awaits further high-quality trials [Supplementary Information 11-4].

Finally, Nishizawa et al. reported a mini review article focusing on the relationship between hyperuricemia and CKD or cardiovascular diseases, and they summarized that high-quality and detailed clinical and basic science studies of hyperuricemia and purine metabolism are needed [Supplementary Information 11-5].

(MK and TK)

**Keywords:** uric acid, cardiovascular disease, chronic kidney disease, arteriosclerosis, xanthine oxidase

### Basic research: elucidation of the “mosaic” pathogenesis of hypertension (See Supplementary Information 12)

The pathogenesis of hypertension is multifactorial and highly complex, as described by the “mosaic theory” of hypertension. Basic research plays critical roles in elucidating the “mosaic” pathogenesis of hypertension and developing its treatment (Fig. 12).

In the field of the brain and autonomic nervous system, Chen et al. demonstrated that mild cold exposure elicits autonomic dysregulation, such as increased sympathetic activity, decreased baroreflex sensitivity, and poor sleep quality, causing blood pressure (BP) elevation in normotensive rats [194]. This finding may have critical implications for cardiovascular event occurrence at low ambient temperatures. In addition, Domingos-Souza et al. showed that the ability of baroreflex activation to modulate hemodynamics and induce lasting vascular adaptation is critically dependent on the electrical parameters and duration of carotid sinus stimulation in spontaneously hypertensive rats (SHRs) [195], proposing a rationale for improving baroreflex activation therapy in humans. Although only normotensive and hypertensive rats were used in these two studies, without comparing the two strains, previous studies have shown that neuronal function and activity in the cardiovascular sympathoregulatory nuclei, including the nucleus tractus solitarius and rostral ventrolateral medulla, which are involved in baroreflex regulation, are different between normotensive and hypertensive rats [196, 197]. Further studies comparing normotensive and various hypertensive animal models would be interesting.

In the kidney, Kasacka et al. showed that the activity of the Wnt/ $\beta$ -catenin pathway is increased in SHRs and two-kidney, one-clip (2K1C) hypertensive rats, while it is inhibited in deoxycorticosterone acetate (DOCA)-salt rats

according to kidney immunohistochemistry [198]. The intrarenal renin-angiotensin system (RAS) is also involved in BP regulation. In renal damage with an impaired glomerular filtration barrier, liver-derived angiotensinogen filtered through damaged glomeruli regulates intrarenal RAS activity [199]. Matsuyama et al. further showed that the glomerular filtration of liver-derived angiotensinogen depending on glomerular capillary pressure causes circadian rhythm of the intrarenal RAS with in vivo imaging using multiphoton microscopy [200]. Fukuda and his colleagues have shown that complement 3 (C3) is a primary factor that activates intrarenal RAS [Supplementary Information 12-1,2]. Otsuki and Fukuda et al. additionally demonstrated that TWIST1, a transcription factor that regulates mesodermal embryogenesis, transcriptionally upregulates C3 in glomerular mesangial cells from SHR [201].

The RAS in the vascular system, as well as in other organ systems, plays a major role in BP regulation. Sorting nexins (SNXs) are cellular sorting proteins that can regulate the expression and function of G protein-coupled receptors (GPCRs) [Supplementary Information 12-3,4,5]. Liu C et al. demonstrated that SNX1 knockout mice exhibit hypertension through vasoconstriction mediated by increased expression of AT1R, a GPCR mediating most of the effects of angiotensin II (Ang II), within the arteries [202]. Moreover, in vitro studies suggest that SNX1 sorts arterial AT1R for proteasomal degradation. These findings indicate that SNX1 impairment increases arterial AT1R expression, leading to vasoconstriction and hypertension. Liu X et al. found that sirtuin 6 (SIRT6) expression is downregulated in the aortae of aged rats and showed that SIRT6 knockdown enhances Ang II-induced vascular adventitial aging by activating the NF- $\kappa$ B pathway in vitro [203]. This study suggests that SIRT6 may be a biomarker of vascular aging and that activating SIRT6 can be a therapeutic strategy for delaying vascular aging.

Several reports indicate the potential treatment for hypertension and the associated organ damage. Narita et al. showed that rivaroxaban exerts a protective effect against cardiac hypertrophy by inhibiting protease-activated receptor-2 signaling in renin-overexpressing hypertensive mice [Supplementary Information 12-6]. In addition, the efficacy of nebivolol (a third-generation  $\beta$ -blocker), maximakinin (a bradykinin agonist peptide extracted from the skin venom of toad), and Pinggan-Qianyang decoction (a traditional Chinese medicine) were also shown in hypertensive animal models [Supplementary Information 12-7,8,9]. In animal models of gestational hypertension, melatonin and crocin have each exhibited an antihypertensive effect [Supplementary Information 12-10,11].

Studies investigating extracellular vesicles (EVs) have increased. Ochiai-Homma et al. showed that pendrin in urinary EVs can be a useful biomarker for the diagnosis and treatment of primary aldosteronism, which was supported by studies

using a rat model of aldosterone excess [159]. Another report indicated that pulmonary arterial hypertension induces the release of circulating EVs with oxidative content and alters redox and mitochondrial homeostasis in the brains of rats [Supplementary Information 12-12]. Studies on the role of gut microbiota in BP regulation have also been accumulating. Wu et al. demonstrated that captopril has the potential to rebalance the dysbiotic gut microbiota of DOCA-salt hypertensive rats, suggesting that the alteration of the gut flora by captopril may contribute to the hypotensive effect of this drug [204]. Moreover, important basic studies, including review papers, have been reported in Hypertension Research. See Supplementary Information.

(KS)

**Keywords:** autonomic nervous system, kidney, vascular system, renin-angiotensin system, extracellular vesicles, gut microbiota.

## Compliance with ethical standards

**Conflict of interest** The authors declare no competing interests.

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