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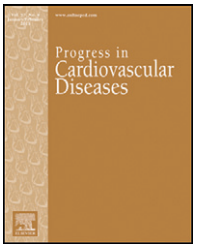

Evidence and Perspectives on the 24-hour Management of Hypertension: Hemodynamic Biomarker-Initiated 'Anticipation Medicine' for Zero Cardiovascular Event

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ABSTRACT

There are notable differences between Asians and Westerners regarding hypertension (HTN) and the relationship between HTN and cardiovascular disease (CVD). Asians show greater morning surges in blood pressure (BP) and a steeper slope illustrating the link between higher BP and the risk of CVD events. It is thus particularly important for Asian hypertensives to achieve 24-h BP control, including morning and night-time control. There are three components of 'perfect 24-h BP control:' the 24-h BP level, nocturnal BP dipping, and BP variability (BPV), such as the morning BP surge that can be assessed by ambulatory BP monitoring. The morning BP-guided approach using home BP monitoring (HBPM) is the first step toward perfect 24-h BP control, followed by the control of nocturnal HTN. We have been developing new HBPM devices that can measure nocturnal BP. BPV includes different time-phase variability from the shortest beat-by-beat, positional, diurnal, day-by-day, visit-to-visit, seasonal, and yearly changes. The synergistic resonance of each type of BPV would produce a great dynamic BP surge (resonance hypothesis), which triggers a CVD event, especially in the high-risk patients with systemic hemodynamic atherothrombotic syndrome (SHATS). In the future, the innovative management of HTN based on the simultaneous assessment of the resonance of all of the BPV phenotypes using a beat by beat wearable 'surge' BP monitoring device (WSP) and an information and communication technology (ICT)-based data analysis system will produce a paradigm shift from 'dots' BP management to 'seamless' ultimate individualized 'anticipation medication' for reaching a zero CVD event rate.

Global burden and ethnic differences

The aging of the population in Japan is the fastest in the world. As the older and elderly segments of Japanese society continue to expand, the public health concerns regarding cardiovascular disease (CVD) events and age-related diseases such as vascular dementia, heart failure (HF), and chronic kidney disease (CKD) are urgent matters that must be understood and addressed

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Abbreviations and Acronyms

ABPM = ambulatory blood pressure monitoring

BP = blood pressure

BPV = blood pressure variability

CHD = coronary heart disease

CKD = chronic kidney disease

CPAP = continuous positive airway pressure

CV = cardiovascular

CVD = cardiovascular disease

HBPM = home BP monitoring

HF = heart failure

HTN = hypertension or hypertensive

ICT = information and communication technology

LVH = left ventricular hypertrophy

OSA = obstructive sleep apnea

RAS = renin–angiotensin system

SBP = systolic blood pressure

T2D = type 2 diabetes

UACR = urine albumin-to-creatinine ratio

immediately. Hypertension (HTN) is one of the most widespread and powerful risk factors for these diseases, and its role in global health and that of the Japanese is of great interest.[1]

There are significant ethnic differences in the characteristics of HTN and CVD (Fig 1).[2,3] In Asian countries (e.g., Japan, China, Korea, Taiwan), the association of HTN and CVD is stronger than in Western countries (e.g., Europe and the U.S.). In Asians, stroke is more common than coronary heart disease (CHD), whereas in Westerners CHD is more common than stroke.[4] Hemorrhagic stroke in particular is more common in Asians than in Westerners, among both individuals medicated with anticoagulation therapy and those without such therapy.

In the series of medicated HTN patients enrolled in a recent nationwide prospective study, the Home Blood Pressure Measurement With Olmesartan-Naive Patients to Establish Standard Target Blood Pressure (HONEST) study, the incidence of CVD events (i.e., stroke, myocardial infarction/MI, angina pectoris with intervention, and sudden cardiac death/SCD) was 6.46 per 1000 person-years, and the incidence of stroke was three times higher than that of MI.[5] When angina pectoris and MI were combined as 'CHD,' the incidence of CHD was comparable to that of stroke.[5] The association slope of the blood pressure (BP) level against the risk of CVD events, especially stroke, is significantly steeper in Asians than in Westerners.[6]

Excess salt intake in combination with higher salt sensitivity is an important environmental risk for the predisposition to essential HTN. In addition to higher salt intake, salt sensitivity is genetically greater in Asian populations than Western populations. The gene frequency of candidate gene polymorphisms of salt-sensitive HTN such as angiotensinogen gene, alpha-adducin gene, promoter of the aldosterone synthase gene, G-protein beta3 subunit gene (GNB3), etc. was significantly higher in several Japanese populations than in Caucasians, indicating the enormous interracial differences in the frequency of salt-sensitive hypertension.[7]

The prevalences of obesity and related metabolic syndrome are now dramatically increasing in Asian countries. Obesity increases sympathetic activity and salt sensitivity. Obese Asians may be more prone to develop HTN compared to obese Caucasians. With even a mild increase in body mass index (BMI), the prevalence of preHTN increases in younger Asian adults. In fact, in our long-term population-based cohort (the Jichi Medical School (JMS) Cohort study), the subjects with a mild increase in BMI (23.0–24.9 kg/m^2) had an increased risk of preHTN,[8] which is associated with an increased 10-year risk of CVD, and this risk may be elevated during the second 5-year period in the nonelderly.[9] In addition, a recent international comparison study demonstrated that the Japanese HTN patients had significantly higher morning BP levels and morning BP surges than Italian and Spanish patients matched for age and office BP level.[10]

Although HTN is a great burden on healthcare globally, the country-based regional approach considering ethnic differences in the pathogenesis and clinical characteristics of HTN is important for effective practical management.[11] Considering the above-described Asian characteristics, the benefit of antiHTN medication would be greater in Asians and in Westerners, especially for stroke and HF. A meta-analysis of subjects with type 2 diabetes (T2D) and/or impaired fasting glucose demonstrated that more-intensive BP control (≤130 mmHg) was associated with a greater reduction in stroke, and that controlling BP to a systolic BP (SBP) of <120 mmHg resulted in continued risk reduction for stroke, although it did not reduce other CVD events.[12] The Japanese guidelines (JSH2014G) thus retain the target BP <130/80 mmHg for diabetic HTN patients,[1] whereas many international guidelines increased the target BP level of diabetic HTN patients.[13,14] The acquisition of global comparative evidence of the efficacy of different drugs could contribute to the development of country-based regional specific guidelines for the management of HTN.

Evidence of benefit of strict BP control

A recently published paper from the Systolic Blood Pressure Intervention Trial (SPRINT)[15] has triggered a discussion of some of the most important clinical topic: which BP level should be targeted as the treatment of HTN. Several international guidelines have been published recently that, compared with the previous guidelines, increased the target BP levels from 130/80 mmHg to 140/90 mmHg for high-risk patients with T2D and/or CKD and from 140/90 mmHg to 150/90 mmHg for elderly HTN patients.[13,14] However, at the end of 2015, strikingly opposing results from the SPRINT study were published.

In SPRINT, over 9000 patients with SBP >130 mmHg and an increased CVD risk (except T2D) were randomly assigned to a strict-control group (target SBP<120 mmHg) or standard-control group (<140 mmHg).[15] After a median follow-up of 3.26 years, the strict-control group, as compared with the standard-control group, had a 25% lower relative risks of major CVD events and 27% lower relative risks of death from any cause, but the rates of some serious adverse events – including hypotension and acute kidney injury or failure – were significantly higher in the strict-control group than in the standard-control group.

SPRINT excluded HTN patients with diabetes or a history of stroke, in light of the results of two trials that included these high-risk subgroups. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial examining diabetic hypertensive patients, there was no significant benefit of strict BP control at <120 mmHg compared to routine BP control at <140 mmHg for the suppression of the composite endpoints of CHD, stroke, and CVD death.[16] However, in this trial, the strict BP control significantly reduced stroke events (one of the secondary endpoints) by 40% compared to the standard control ($p = 0.01$). The effects of the strict BP control on individual outcomes in SPRINT and the ACCORD trial are generally consistent, suggesting that this strict BP control is superior for high-risk HTN patients, including diabetic HTN. In another randomized open-label trial, the Secondary Prevention of Small Subcortical Strokes (SPS3) study, patients with recent symptomatic lacunar infarctions were randomly assigned to a higher-target or lower-target BP group according to a SBP target of 130–149 mmHg or <130 mmHg, respectively. During the mean 3.7-year follow-up, non-significant difference in rate reductions between the 2 groups was seen for the primary endpoint, i.e., all stroke (hazard ratio 0.81, $p = 0.08$), but the rate of intracerebral hemorrhage was significantly reduced in the lower-target group than in the higher-target group (0.37, $p = 0.03$).[17]

In addition, a 2015 meta-analysis of over 613,000 HTN patients from randomized controlled trials clearly demonstrated that antiHTN medication reduced the rates of all CVD events and death in all patients, including those with SBP <130 mmHg, regardless of concomitant diseases.[18] This benefit was especially stronger for stroke and HF.[18] These results support the benefit of more strict BP control to at least <130 mmHg, not only in the SPRINT high-risk group but also in other high-risk groups. Thus, the guidelines for the management of HTN should modify the target BP level before the regularly scheduled revisions are conducted.[11]

Importance of '24-h BP control'

In my research group, we define the status of 'perfect 24-h BP control,' which minimizes the organ damage and risk of CVD events, as the achievement of the following three components: (1) the average of 24-h BP levels is <130/80 mmHg, (2) a normal circadian rhythm, i.e., adequate dipping of nocturnal BP (dipper-type) is observed, and (3) adequate BP variability (BPV) (e.g., morning BP surge <45 mmHg) is achieved (Fig 2).[19] The first component concerns the quantity of BP control, and the latter two components focus on the quality of BP control. In clinical practice, beyond the goal of strict office BP control, the three BP profiles of white-coat effect, BPV, and nocturnal BP should also be considered.

1. **Stroke, especially hemorrhagic stroke, more common than myocardial infarction**
2. **Steeper association between blood pressure and cardiovascular disease**
3. **Higher salt intake with higher salt sensitivity**
4. **Obesity and metabolic syndrome epidemic**
5. **Morning and nocturnal hypertension more common**

Fig 1 – Characteristics of hypertension in Asian populations (i.e., Japan, China, Korea, Taiwan, etc.). (Modified from Ref. 2).

White-coat effect

It is important to exclude the white-coat effect on office BP to assess the remaining BP overload to the cardiovascular (CV) system and to avoid a harmful excessive BP reduction by antiHTN medication. There are three different BP measurements which can exclude the white-coat effect in the current clinical practice.

The first is the gold standard, i.e., ambulatory BP monitoring (ABPM).[19–24] The 24-h BP (that is, the average of BPs) is more closely associated with HTN organ damage and the risk of future CVD events than office BP is among both community-dwelling populations and HTN patients. The 24-h SBP in particular is more important as a risk factor for CVD events in the elderly than 24-h diastolic BP,[22] In our prospective study, the Jichi Medical University ABPM (JMU-ABPM) study of elderly HTN, a 10-mmHg increase accounted for a 38% increase in the risk of CVD events.[22] ABPM is used in the definitions of 24-h HTN, i.e., 24-h BP (the average of 24-h BPs) values ≥130/80 mmHg; daytime HTN, i.e., daytime BP (the average of daytime BPs) ≥135/85 mmHg, and nocturnal HTN, i.e., nocturnal BP (the average of nocturnal BPs) ≥120/70 mmHg, regardless of office BP values. White-coat HTN (i.e., HTN for office BP, and normotension for 24-h BP) is at lower risk during the short-term period,[22,24] but it may deteriorate to sustained HTN and diabetes, resulting in an increased risk of future CVD events.[23] On the other hand, the CVD risk in untreated masked HTN (normotension for office BP, and HTN for 24-h BP) is similar to that from sustained HTN.[24] Thus, masked HTN should be regarded as a subtype of HTN, which should be treated.

The second type of BP measurement is automated office BP (AOBP) monitoring, which automatically measures an individual's BP while he or she is seated in a quiet room without the presence of medical staff. The SBP values that are obtained by AOBP are lower by 5–10 mmHg and the risk of future CVD events than standard doctor-measured office BP values.[25] The threshold of the diagnosis of HTN based on AOBP monitoring is 135/85 mmHg.[25] In the SPRINT, the office BP values were obtained by AOBP, not doctor-measured.

The third type of BP measurement is self-measured BP using HBPM,[26] and home BP measured in the morning (morning BP) is especially important.[19] In our prospective HONEST study using HBPM conducted by over 21,000 HTN patients, when home morning SBP was well-controlled at <125 mmHg during a follow-up, there was no increase in CVD events even among the HTN patients whose office SBP remained at ≥150 mmHg.[5] On the other hand, even when office SBP was well controlled at <130 mmHg, the hazard ratio of CVD events was 2.5 in the masked uncontrolled HTN group with morning SBP ≥145 mmHg compared to the well-controlled groups with morning SBP <125 mmHg. Morning home BP is a strong

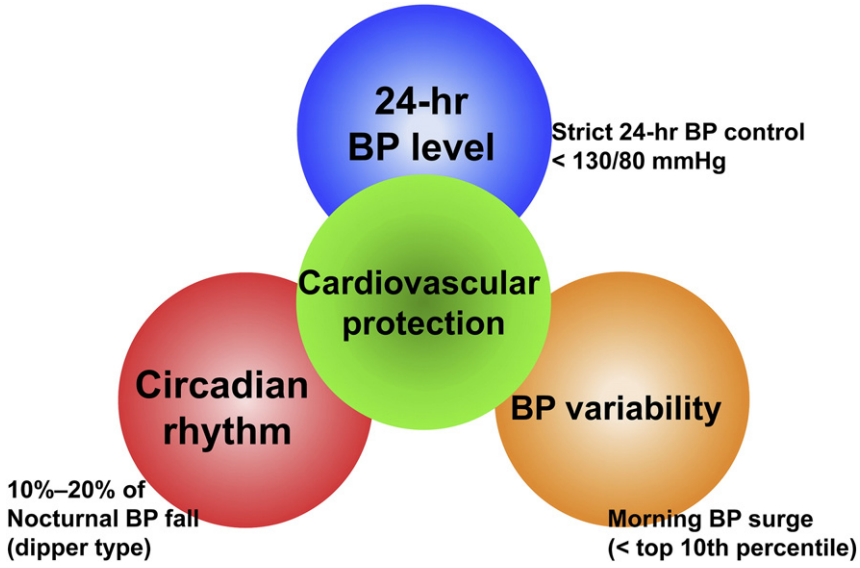

Fig 2 – The triad of perfect 24-h blood pressure control. BP, blood pressure. (Modified from Ref. 19).

predictor of CHD events, as well as stroke events, and may be superior to clinic BP in this regard.[27] In addition, there does not appear to be a J-curve in the relationship between morning home BP and CVD events. The Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure (HOMED-BP) study demonstrated that the 5-year risk of CVD events was minimal when the on-treatment home SBP was <132 mmHg.[28]

Although there is no consensus about the optimal target BP level, it may be recommended that these white-coat effect-excluded BP measurements should use <125 mmHg as the target, with the corresponding value of doctor-measured office SBP of 130 mmHg (Fig 3).[11]

Based on the findings of the HONEST study, we are now proposing the 3-step strategy of morning BP-guided management of HTN using HBPM (Fig 4).[19] The HONEST study revealed 144 mmHg as the threshold of on-treatment morning BP for a significant increase in CVD events, and approx. 125 mmHg as the minimum risk.[5] In addition, there was no J-curve until approx. 100 mmHg of morning SBP. Thus, as the first step, morning SBP should be treated using the target <145 mmHg for all HTN patients, and the second step is the guideline level, 135 mmHg. Approximately ≤125 mmHg presents the lowest risk of CVD events.

Morning BP (morning BP surge)

Morning SBP parameters are defined as follows. 'Morning BP' is the average of morning BP values during the first 2 h after arising or between 7 a.m. and 9 a.m. The 'moving peak morning BP' is defined as the highest 1-h moving average of consecutive BP values (3 points) during the first 2 h after arising, or between 6 a.m. and 10 a.m. The 'maximum morning BP' is the maximum morning BP value [a single BP value] during the first 3 h after arising or between 7 a.m. and 10 a.m.[19] The 'prewakening nocturnal BP' or 'minimal (or moving prewakening) morning BP' between 5 a.m. and 9 a.m. is used to calculate the prewakening morning BP surge. The definition of morning HTN is morning BP ≥135/85 mmHg regardless of office BP.[19,29,30] In elderly HTN patients, morning HTN, defined as morning BP ≥135/85 mmHg is most closely associated with CVD events among the office and ambulatory BP values measure during different time periods of the 24-h day.[30]

Controlling morning BP is the important first step of 'perfect 24-h BP control' in medicated HTN patients, because the risk of CVD events is the highest and the BP-lowering effect of conventional antiHTN drugs is the weakest in the morning.[19,29] Morning BP is more closely related to sympathetic nervous activity, and thus the bedtime dosing of alpha-blockers, doxazosin, and catheter-based renal denervation is effective for reducing morning BP.[31,32]

Morning BP surge parameters can be calculated as follows.[19] The 'sleep-trough morning surge' is calculated as the average morning BP value minus the moving lowest nocturnal BP value. The 'prewakening morning surge' is calculated as the average morning BP value minus the prewakening morning BP value. In our JMU-ABPM study, the ABPM-defined morning surge in SBP (sleep-through morning surge, and prewakening morning surge) was associated with MRI-detected silent cerebral infarcts and future clinical stroke events, independently of 24-h SBP and nocturnal BP dipping status (Fig 5).[33–36] As an adequate morning BP surge is physiological, the exaggerated morning BP surge above some threshold (e.g., the top 10th percentile of the study subjects) should be considered pathological. Asians are likely to have a higher degree of morning BP surge than Westerners.[10]

Nocturnal BP (nighttime BP) and dipping

Nocturnal BP parameters are defined as follows.[19] 'Nocturnal BP' is the average of nocturnal BP values. The 'average peak nocturnal BP' is the average of the three highest different nocturnal BP values. The 'maximum nocturnal BP' is the single peak BP value. The 'minimum nocturnal BP' is the single lowest BP value. The 'moving lowest nocturnal BP' is

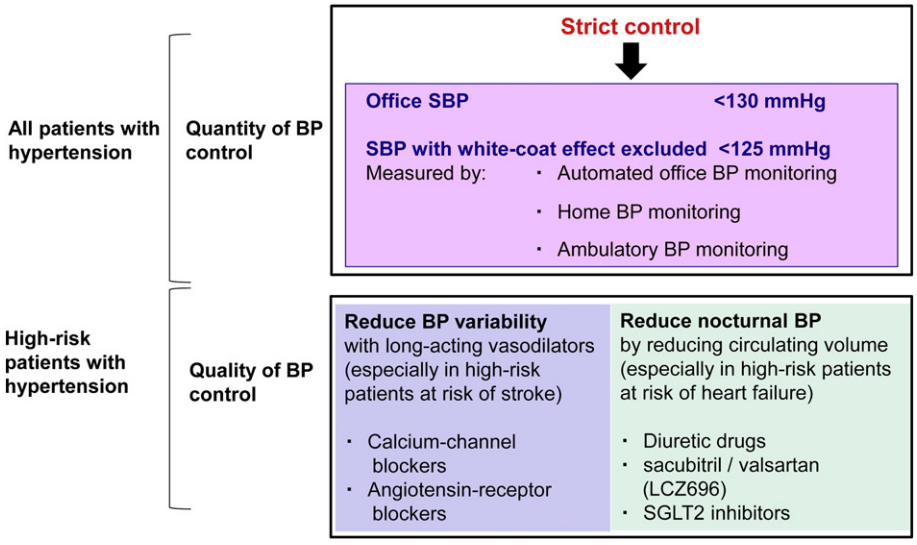

Fig 3 – Precision medication for the management of hypertension. The strict BP control (quantity of BP control) guided by white-coat effect-excluded BP <125 mmHg, as well as office BP <130 mmHg for all hypertensive patients. 'Perfect 24-h BP control' considering BP variability and nocturnal hypertension (quality of BP control) is recommended for high-risk patients with hypertension. The CCBs and ARBs may be protective against stroke by reducing BP variability, and drugs that reduce circulating volume such as diuretics, LCZ696, and SGLT2 inhibitors may be protective against heart failure by reducing nocturnal BP. SBP, systolic BP; SGLT2, Sodium-glucose co-transporter 2. (Modified from Ref. 11).

the lowest 1-h moving average of consecutive nocturnal BP values. The 'prewakening nocturnal BP' is the average of nocturnal BPs during the 2 h before arising. The definition of nocturnal HTN is nocturnal BP ≥120/70 mmHg, regardless of office, daytime and/or morning BP values.[1,19]

Nocturnal HTN is a risk factor for damage to the brain, heart, kidney, and large and small arteries and for all the CVD events including both hemorrhagic and ischemic stroke, CHD, HF (especially with preserved ejection fraction/HFpEF), CKD, and SCD, independently of office BPs, in both community-dwelling populations and HTN patients.[37–40] Nocturnal HTN is also associated with brain MRI-evaluated brain atrophy and silent cerebral disease, and physical and cognitive dysfunction in the elderly.[19] Even among completely normotensive community-dwelling subjects, those with isolated nocturnal HTN are likely to have LVH, especially concentric LVH, and to have increased plasma levels of atrial natriuretic peptide and B-type natriuretic peptide (BNP).[38] In both medicated or non-medicated individuals, masked uncontrolled nocturnal HTN with well-controlled office, home and/or daytime BP is associated with increases in arterial stiffness, the plasma level of BNP and the urinary albumin/excretion ratio,[40] suggesting that nocturnal HTN is an independent risk for future CVD events. Nocturnal BP is preferentially reduced by

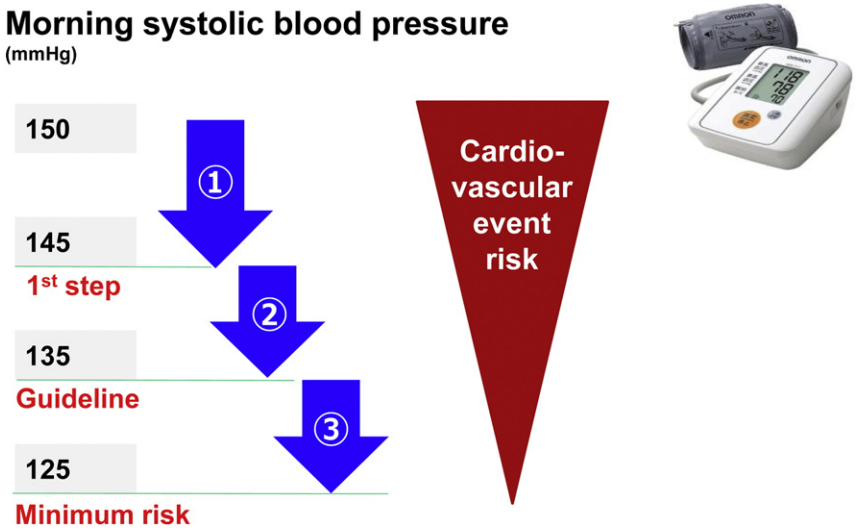

Fig 4 – Home blood pressure-guided three-step antihypertensive strategy for morning hypertension. (Modified from Ref. 19).

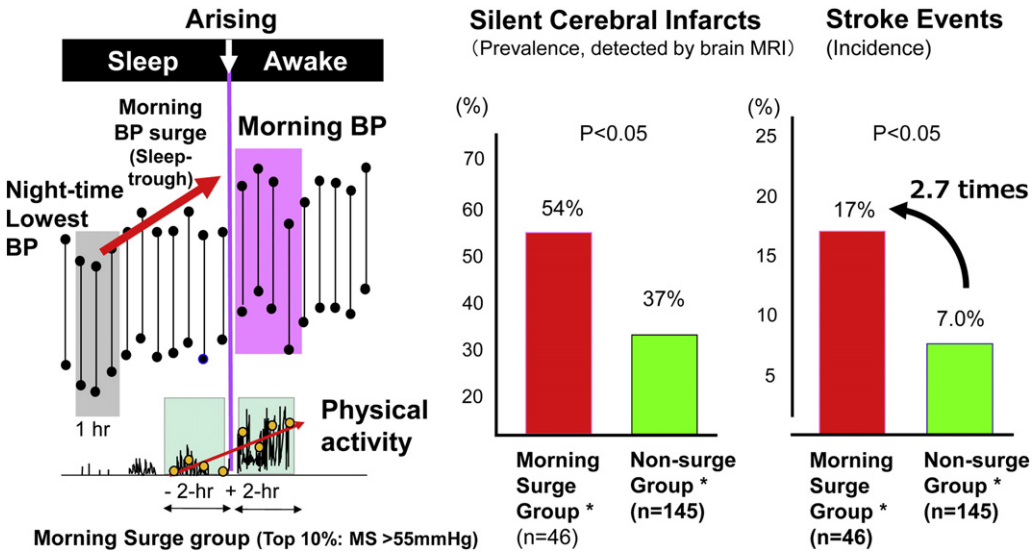

Fig 5 – Prevalence of MRI-detected silent cerebral infarcts and incidence of stroke events over a 42-month period in elderly hypertensive patients with or without morning surge in blood pressure: the Jichi Medical University ABPM study, Wave 1. *matching for age and 24-h systolic blood pressure (Modified from Ref. 33).

diuretics, indicating that the circulating volume may contribute to nocturnal HTN.[41,42] Renal denervation also significantly reduced nocturnal BP, indicating that sympathetic nervous activity may partly determine nocturnal BP by reducing sodium excretion and increasing peripheral vascular resistance.[32] The average peak and the maximum nocturnal BP values may be related to the nocturnal BP surge triggered by apnea/hypopnea episodes of obstructive sleep apnea (OSA),[43,44] and the moving lowest and minimum nocturnal BP values may be related to the circulating volume and/or vascular structure (both large and small arteries).[19]

Nocturnal BP dipping parameters can be calculated as follows. 'Nocturnal BP dipping (%)' is calculated as: (1 – the average nocturnal BP/average daytime BP) × 100. Based on the nocturnal dipping of SBP, the following subgroup classification: extreme dipper: >20%; dipper: ≤20%, >10%; non-dipper: ≤10%, >0%; riser: ≤0%. The non-dippers and riser classifications are associated with organ damage of the brain, heart and kidney and future CVD events in both younger normotensives and older HTN.[45–52] Among patients with HF, the riser pattern is more common in HFpEF than in those with reduced ejection, and the riser pattern is associated with mild cognitive impairment.[51,52] Even among community-dwelling normotensive subjects, non-dippers have advanced LVH, especially concentric LVH,[47] and poor CV prognoses.[48]

Extreme-dipping, another extreme edge of disrupted circadian BP rhythm, may be associated with silent cerebral disease and nonfatal stroke in elderly HTN patients.[45,46] Our JMU ABPM study was the first to demonstrate that extreme-dippers had advanced silent cerebral infarcts and white matter lesions, detected by brain MRI at the baseline, and an increased risk of future stroke during a follow-up, compared to normal dippers.[45,46] Young normotensive subjects who exhibited either the extreme-dipper or riser patterns at the baseline developed advance coronary calcium evaluated by computed tomography performed in their middle aged adults 10 years or more after the baseline ABPM.[50] In the Ambulatory Blood Pressure Collaboration in Patients with Hypertension (ABC-H) meta-analysis of 17,312 with HTN from three continents, the extreme-dippers' risk of CVD events was markedly modified by the treatment status. Extreme dipping relative to normal dipping carried a borderline reduced risk of CVD events (HR: 0.72; $p = 0.050$), whereas among cohorts of untreated patients, extreme dipping was hazardous (HR: 1.92; $p = 0.006$).[53] Therefore, disrupted diurnal variations (i.e., the extreme dipper and riser patterns) are risk factors for CVD, independently of 24-h BP.

Nocturnal BP surge parameters can be calculated as follows. The 'average nocturnal surge' is calculated as the average peak nocturnal SBP minus the average nocturnal SBP. The 'dynamic nocturnal surge' is the average peak nocturnal SBP minus the moving lowest nocturnal SBP. The 'maximum dynamic nocturnal surge' is defined as the maximum nocturnal SBP minus the minimum nocturnal SBP. An increase in the standard deviation (SD) of nocturnal BP values, one of the measures of nocturnal BPV, is associated with CVD events independently of the average of nocturnal BPs. The cut-off value of the pathological SD was 12.2 mmHg.[54] In addition, in HTN patients there is a synergistic increase in the CV risk with the combination of non-dipping of both the nocturnal BP and the heart rate. The nocturnal BP-non-dippers with the nocturnal heart rate non-dipper pattern exhibited worse CV prognoses.[55]

AntiHTN medication considering 24-h BP variability

The morning BP-guided approach using HBPM is the first step toward perfect 24-h BP control.[19,29] After controlling morning

HTN, nocturnal HTN is the second target. The recent largest meta-analysis of the randomized controlled trials of antiHTN medication revealed that among high-risk HTN patients (who are prone to stroke and HF), different classes of antiHTN drugs had different BP-lowering effects; calcium channel blockers (CCBs) were more effective for reducing stroke, and diuretics were more effective for reducing HF.[18] These findings may partly be explained by the different BP-lowering profile of each class of drugs. The CCBs and angiotensin receptor blockers (ARBs) may be superior to other classes for preventing stroke due to their strongest effects on reducing BPV (Fig 3).[11] The long-acting and lipophilic characteristics of antiHTN drugs may contribute to this benefit.

On the other hand, diuretics – including an aldosterone blocker and other new drugs such as an angiotensin receptor-neprilysin inhibitor, LCZ696 (sacubitril/valsartan),[56–59] and a sodium-glucose co-transporter 2 (SGLT2) inhibitor, which significantly reduce circulating volume – may be superior for preventing HF,[60] by their BP-lowering effect predominantly on nocturnal BP (Fig 3).[11] High nocturnal SBP increases the left ventricular wall stress more than daytime BP does, because the supine position during sleep increases the preload due to a fluid shift from the lower body to the upper body.

Considering the higher salt intake of Asians and its direct adverse effect,[61] salt restriction and diuretics can be expected to be especially effective in Asians.[2] In a intervention study, a 3-month education program by nutritionists along with salt restriction to ≤6 g per day (as recommended by the Japanese Society of Hypertension)[1] significantly lowered the 24-h urinary sodium excretion and 24-h SBP in treated HTN patients compared to the control group.[62] In Japan, the most commonly used classes of antiHTN drugs are CCBs, followed by ARBs.[63] It is important to choose a long-acting antiHTN drug with a longer half-life, such as amlodipine.[19] The BP-lowering effect of a CCB is independent of salt sensitivity and salt intake. Thus, a CCB is one of the most efficacious antihypertensive drugs for Asian patients.[64] In fact, in our previous comparison study, amlodipine was superior to valsartan, a short-acting ARB, for reducing the 24-h BP level including morning BP in HTN patients.[65] The Azilsartan Circadian and Sleep Pressure – the First (ACS1) study, a multicenter, randomized, open-label, two-parallel group study demonstrated that amlodipine was superior to azilsartan for reducing ambulatory BP in Japanese HTN patients.[66] This may be due in part to the greater salt intake by Asians, because of increased circulating volume, resulting in a reduction of the RAS activity.

A CCB lowers the higher baseline BP level more extensively than other antiHTN drugs of different classes including RAS inhibitors; however, a CCB does not reduce the low baseline BP very much, resulting in the most effective lowering effect of BPV among the different classes of antiHTN drugs. Thus, a CCB seems to be the best choice for older patients with structural HTN with increased BPV. On the other hand, a RAS inhibitor would be preferable for younger metabolic HTN patients with neurohumoral activation. Some international guidelines concerning the management of HTN recommend selecting different drugs depending on the patient's age, but no studies have investigated the relationship between drug selection and age-related differences. In fact, the ACS1 study demonstrated that azilsartan was superior to amlodipine for achieving a successful BP control rate in younger HTN. The post hoc analysis of the ACS1 study conducted to investigate age- and sex-related differences in the antiHTN effects of azilsartan and amlodipine revealed that azilsartan significantly reduced diastolic BP in male patients <60 years old compared to amlodipine, but amlodipine significantly reduced SBP in female patients ≥60 years old compared to azilsartan.[67] AntiHTN strategies considering these age- and sex-related differences may increase cost-effectiveness in the long-term management of HTN. Based on the above-described findings, a RAS inhibitor may be preferable in the early stage of HTN for younger adults with metabolic neurohumoral HTN, and a CCB would be preferable in the later stage of HTN for older patients with structural hypertension after their SBP has gradually increased to an uncontrolled status.

Diuretics may be more effective in Asians who consume higher amounts of salt than in Westerners who consume less salt. A recent double-blind, randomized, comparative study of diuretics in Indian HTN patients demonstrated that daily treatment with low-dose chlorthalidone (6.25 mg) more effectively reduced 24-h BP and nocturnal BP compared to hydrochlorothiazide (12.5 mg).[68] When combined with an ARB, a small dose of a diuretic, i.e., 6.25-mg hydrochlorothiazide, was effective in Japanese hypertensive patients with higher salt intake and higher salt sensitivity.[42]

There is a difference in diurnal BP-lowering effects between CCBs and diuretics. The use of a diuretic both as monotherapy and in ARB–diuretic combination therapy is more effective for reducing nocturnal BP, whereas the use of a CCB is more effective for reducing higher daytime BP levels and BPV.[69] If BP is not well-controlled, the three-drug combination of a RAS inhibitor, a CCB and a diuretic is the gold standard for the treatment of uncontrolled HTN in both Asians and Westerners.

Time of dosing

The bedtime dosing of antiHTN drugs is effective for morning and nocturnal HTN. In our Japan Morning Surge-1 (JMS-1) study, the bedtime dosing of doxazosin reduced morning BP values and the urinary albumin/creatinine ratio (UACR), and the reduction of the UACR was independent of the reduction of BP.[31] In the Japan Morning Surge-Target Organ Protection (J-TOP) study, the bedtime dosing of candesartan was more effective for reducing the UACR than morning dosing.[70] In RAS inhibitor combination therapy with a diuretic or CCB and bedtime or morning dosing therapy, the reduction of nocturnal BP is critically important for reducing the UACR.[19] In the recent multicenter, prospective, randomized open-label, ARB/CCB Longest Combination Treatment on Ambulatory and Home Blood Pressure in Hypertension with Atrial Fibrillation: Multicenter Study on Time Of Dosing (ACROBAT) study,[71] which investigated the difference in the BP-lowering effect of long-acting telmisartan/amlodipine combination tablets between morning and bedtime dosing in HTN with paroxysmal atrial fibrillation, significant reductions were revealed in 24-h, nighttime, and morning BP by ABPM and day-by-day home

SBP variability and maximum home SBP; in addition, the BP-lowering effects were similar regardless of the timing of administration. The N-terminal of the prohormone BNP (NT-proBNP) and UACR levels were significantly decreased only in the bedtime dosing group.

Device treatment

A catheter-based renal denervation technique was recently introduced for the management of drug-resistant HTN. The SYMPLICITY HTN-1 and HTN-2 trials demonstrated a marked office BP reduction by renal denervation, but the SYMPLICITY HTN-3 controlled trial using a sham group demonstrated no significant office BP-lowering effect by renal denervation compared with a sham group.[72] We conducted the SYMPLICITY HTN-Japan trial with Japanese patients with drug-resistant HTN.[73] In the SYMPLICITY HTN-Japan trial, the renal denervation arm tended to show more lowering of the 24-h SBP compared to the control arm. However, the trial was stopped because of the negative results of the SYMPLICITY HTN-3 trial. In the analysis of the combined ABPM data of the SYMPLICITY HTN-3 and HTN-Japan trials, renal denervation significantly reduced morning and nocturnal BP values, but it did not reduce daytime BP.[32] This can be partly explained by the close association between morning HTN and increased sympathetic activity. Nocturnal HTN is frequently observed in OSA patients, who are likely to have increased sympathetic activity. The SPYRAL HTN Global Trial is currently underway and is being conducted to determine the 24-h BP-lowering effect of renal denervation in the absence and presence of antiHTN medication.[74]

New concept of hemodynamic biomarker-initiated 'anticipation medicine'

In the recent guidelines, the diagnosis and management of HTN and the estimated risk of CVD are based on the average of BP values in consideration of concomitant risk factors and organ damage at a specific point of time. Beyond this current guideline-based standardized management, there are two perspectives on the 'perfect individualized medicine aiming at CVD event-zero' (Fig 6). One is 'precision medicine,' which is defined as an approach to disease treatment and prevention that seeks to maximize effectiveness by taking into account individual variability in genes, environment, and lifestyle.[75] This would be dramatically improved by powerful methods such as the use of large-scale biologic databases (e.g., the human genome sequence), proteomics, metabolomics, genomics, diverse cellular assays, and mobile health technology and computational tools for analyzing large sets of data.

Anticipation medicine

Another perspective is 'anticipation medicine,' which is defined as an approach to disease treatment and prevention that predicts future risk by taking into account longitudinal (time-domain) individual changes in markers and the status of disease against environmental and behavioral factors. One of the most promising approaches to 'perfect individualized medicine' is the combination of precision medicine and anticipation medicine by an information and communications technology (ICT)-based approach using hemodynamic biomarkers (i.e., the BP level and new the indexes of BP/heart rate variability and baroreceptor sensitivity) with different time-phases (Fig 6).

BP variability with different time-phase

Accumulating evidence indicates that independently of an individual's average BP levels, increased BPV presents risks of both CVD events and organ damage.[36,76–89] BPV can be examined in several time phases: orthostatic, beat-by-beat, psychological or physical stress-induced, diurnal, day-by-day, office or clinic visit-to-visit, seasonal, and yearly.[36,76] Nearly all of the BPV phenotypes correlate with each other to some degree, and nearly all have been reported to be CVD risk factors.[90–93] These varying forms of BPV can be examined by methods such as home, office, and ABPM measurements (Fig 7).[36,76]

BPV is both a sensor of cardiovascular dysregulation that is affected by an individual's characteristics, medication status, and the many daily stressors of environmental conditions and psychobehavioral factors, and a modifiable risk factor for CVD and organ damage.[94–98] BPV is thus considered a "master biomarker" in the healthcare field.

The components of BPV may have different clinical impacts on CVD. A long-term increase in the average of BP values would be considered a chronic risk factor for advancing endothelial dysfunction and subsequent atherosclerosis, whereas relatively short-term exaggerated BPV (e.g., the BP surge) would be considered an acute risk factor which triggers an atherothrombotic CVD event by a mechanical stress-induced plaque rupture. These different roles of the risks presented by BPV are similar to the risks of heart failure: chronically advancing LVH, and the triggering of acute HF afterload mismatch due to an abrupt increase in SBP. In combination with the conventional prevention of chronic risk factors, a real-time ICT-based acute CV risk prediction and alert system would provide a new hemodynamic biomarker-initiated way to prevent falling the cliffs to the onset, recurrence, and severity of CVD events, resulting in a healthy life and increased longevity (Fig 8).

The resonance hypothesis

We are now proposing the 'resonance hypothesis' of BPV.[94,99] On the basis of reduced baroreceptor sensitivity and small-artery remodeling according to aging, each type of BPV with different time phases increases. The degree of increase in each type of BPV may be different in different persons. When the timing of each type of BPV wave with different time phases is different, the total summation of BPV at each time phase is small. However, the timing of all of the BPV waves with different time phases is synchronized and resonance of the pulse wave occurs, resulting in the generation of a critically large dynamic BP surge that would trigger a CVD event (Fig 9).

For example, the morning BP surge is one of the several types of BPV.[36] The morning BP surge can be potentiated

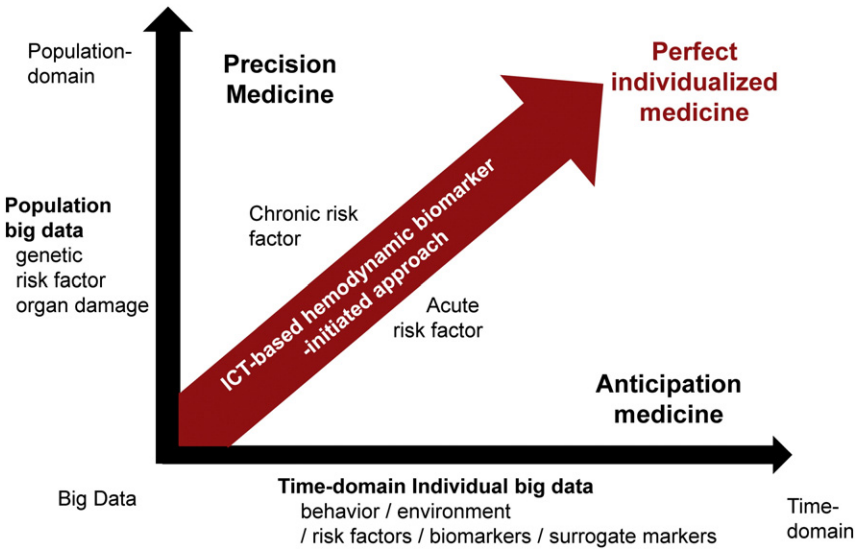

Fig 6 – Cardiovascular disease 'anticipation medicine.' There are two perspectives on 'perfect individualized medicine aiming at cardiovascular event-zero.' One is the precision medicine approach, and the other is anticipation medicine. ICT, information and communication technology.

synergistically by a resonance of various components of BPV, resulting in morning-onset CVD events.[99] In ABPM studies, the morning BP surge was exaggerated in the winter, especially in elderly patients (the winter morning surge in BP).[100] The coexistence of exposure of airborne PM2.5 and cold temperature may increase morning BP.[98] These changes in the morning BP surge may contribute to the increase in CVD events in the winter among the elderly and on Mondays among working adults.

Maximum SBP, one of the measures of day-by-day HBPM most frequently observed in the morning (in approx. 2/3 of observations), has been reported to be significantly associated with measures of CV remodeling (i.e., the left ventricular mass index and carotid intima-media thickness) even in HTN with a well-controlled average of home BPs <135/85 mmHg.[101] In addition, the increased standard deviation of morning BP is a significant independent predictor of CVD death.[77] Thus, an unstable morning BP surge synergistically augmented by the

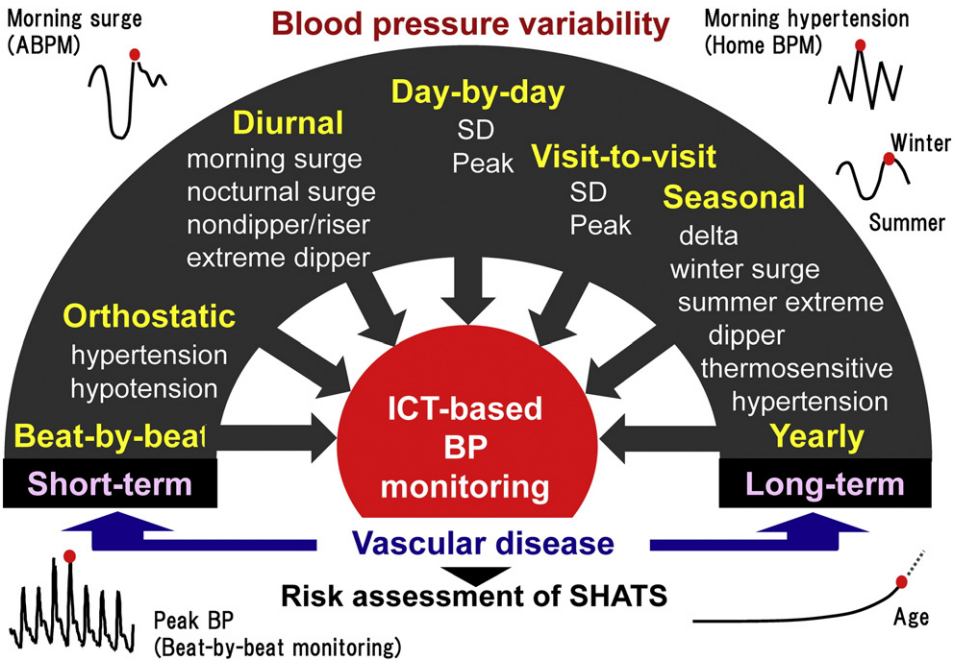

Fig 7 – ICT-based assessment of different blood pressure variability and vascular damage in systemic hemodynamic atherothrombotic syndrome (SHATS). ABPM, ambulatory blood pressure monitoring; BPM, blood pressure monitoring; ICT, information and communication technology. (Modified from Ref. 36).

resonance of other phenotypes of BPV may be more likely to advance organ damage and trigger CVD events than a stable and reproducible morning BP surge.

Systemic hemodynamic atherothrombotic syndrome (SHATS)

In 2013 we proposed a novel disease entity, systemic hemodynamic atherothrombotic syndrome (SHATS), which is also a risk factor for CVD events and organ damage (Fig 10).[2,19,36,102,103] Characterized by a vicious cycle between vascular disease and hemodynamic stress (based on BPV, the pulse wave form and blood flow variability), the presence of SHATS enhances the effects of BPV on peripheral organ damage and subsequent CVD events. A novel aspect of SHATS is its synergistic consideration of hemodynamic stress and the numerous types of BPV in relation to vascular disease. In addition, the standing test, HBPM, ABPM and other currently available methods can be used to detect the phenotypes of BPV in SHATS.

Large-artery disease and other types of vascular disease increase the impact of exaggerated BPV on CVD events. The triggering of CVD events and organ damage at peripheral atherosclerotic sites often follows an increase in large-artery stiffness, as such stiffness decreases the attenuation of pulses that are transmitted to the peripheral arteries. Even in patients without atherosclerosis in large artery, the next specific target of SHATS is strain vessels (small arteries of the brain, heart, kidney, and eyes), resulting in small-vessel diseases.[104] SHATS may also increase the risk of HF through an increase in the circulating volume due to baroreflex failure[105] and via an increase in the peak and variability of the afterload. In individuals with SHATS, synergistic resonance among the morning BP surge and different types of BPV may occur, and this could easily trigger CVD events in the morning.

The underlying mechanism of SHATS is thought to include impairments of vascular and neural components of the baroreflex caused by increased central sympathetic activity and decreased carotid dispensability, respectively. Increases in BPV are often due in part to small-artery remodeling as well as large-artery disease. Indeed, the three BP measures of SHATS are increased BPV, impaired baroreceptor sensitivity,

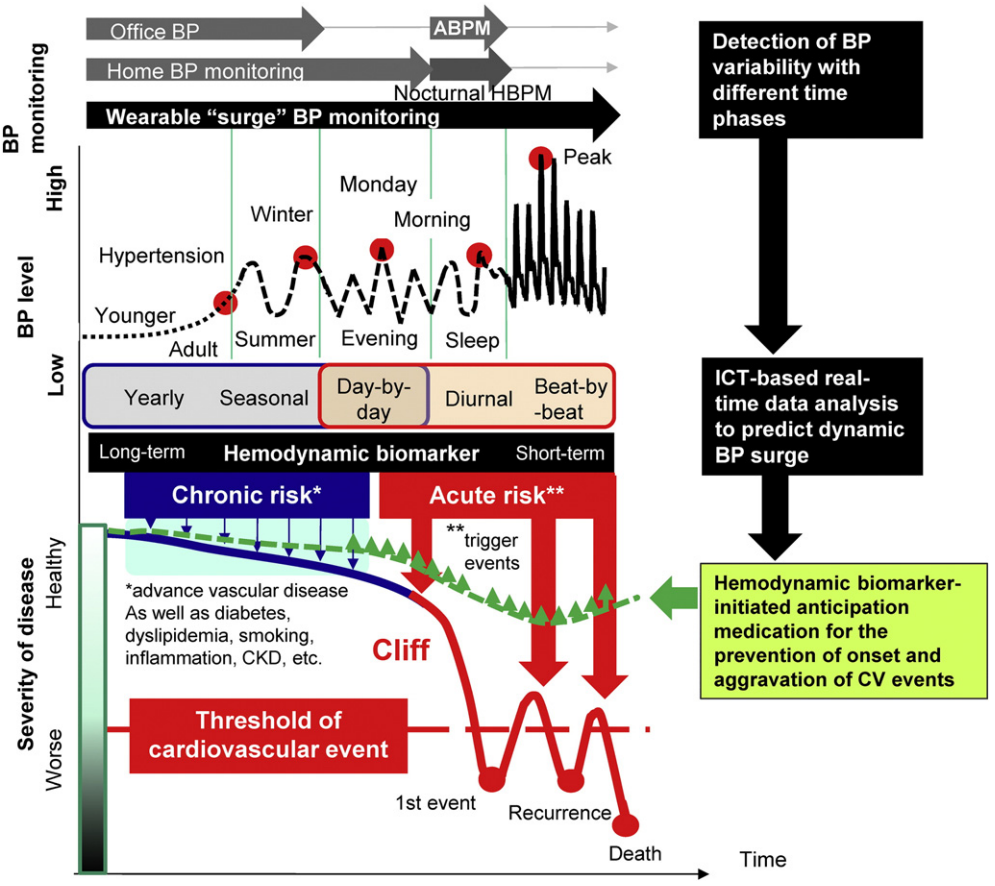

Fig 8 – Differential roles of acute vs chronic hemodynamic biomarker-initiated anticipation medicine of cardiovascular disease in the early vs late stages. By analysis of variability of hemodynamic parameters in combination with environmental conditions and individual characteristics, new hemodynamic biomarkers would be generated separately as chronic risk factor advancing vascular disease and as acute risk factor triggering cardiovascular events. The real-time ICT-based cardiovascular risk prediction and alert system would achieve the new hemodynamic biomarker-initiated prevention of falling the cliff of cardiovascular events resulting in healthy life for longevity. ABPM, ambulatory blood pressure monitoring; CKD, chronic kidney disease; CV, cardiovascular; HBPM, home blood pressure monitoring; ICT, information and communication technology.

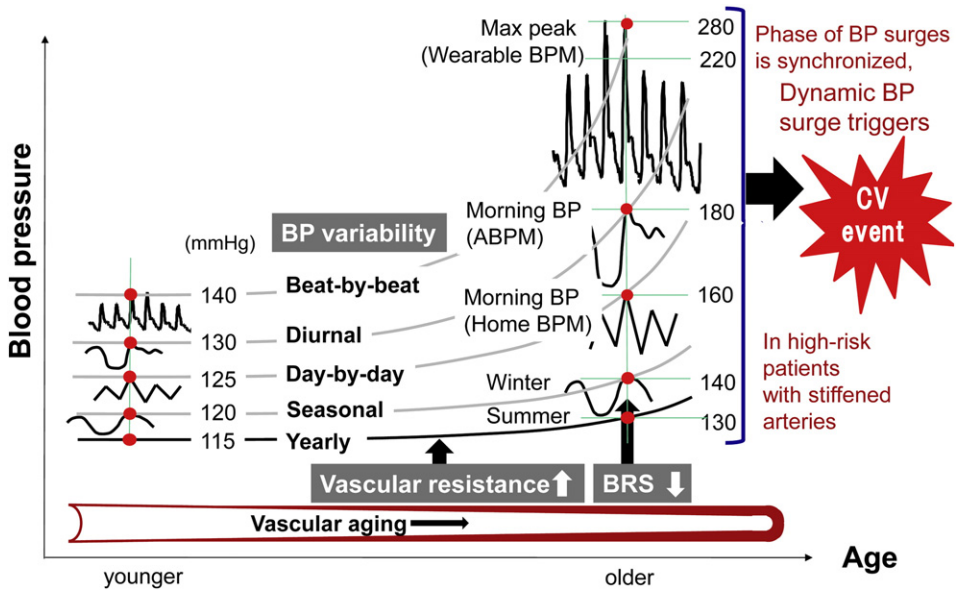

Fig 9 – Synergistic resonance hypothesis of blood pressure variability. ABPM, ambulatory blood pressure monitoring; BPM, blood pressure monitoring; CV, cardiovascular; BRS, baroreceptor sensitivity (Modified from Ref. 99).

and increased central BP; these measures are closely related.[93] The different phenotypes of BPV may be determined by the extent of peripheral and central neurohumoral activation and the cardiovascular reactivity in each specific condition.

The measurements of ambulatory BP, including the morning BP surge, reflect an individual's pulsatile hemodynamics as influenced by arterial stiffness and wave reflections, and two important components of pulsatile hemodynamics are arterial stiffness and pressure wave reflections. The concept of SHATS underscores that clinicians should recognize the synergistic risk posed by exaggerated BPV and vascular damage in clinical practice.

We are now conducting the prospective CardiOVascUlar Prognostic Coupling (COUPLING) study to investigate the serial interaction of subclinical CVD and vascular disease and its impact on CV prognosis in approx. 5000 patients with one or more risk factors, using a device (from Fukuda Denshi, Co. Ltd.) that simultaneously assesses electrocardiograph and vascular properties such as the cardio-ankle vascular index (CAVI) since 2015. The CAVI is correlated with the stiffness

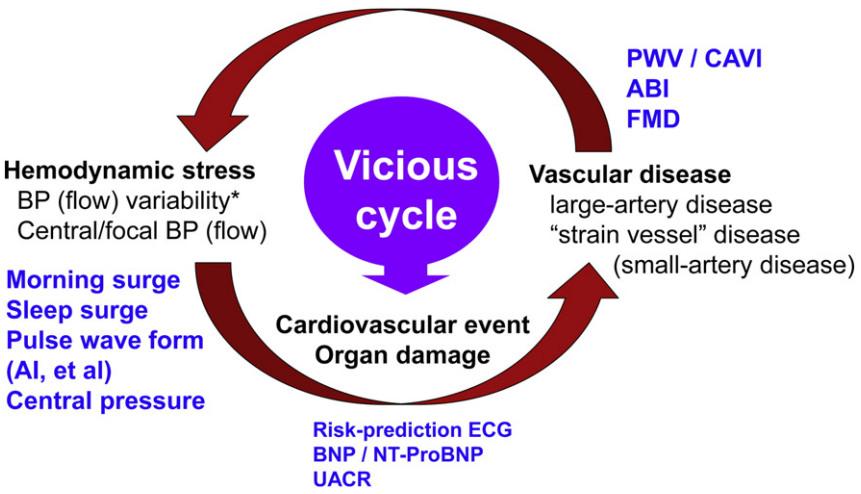

Fig 10 – Concept of systemic hemodynamic atherothrombotic syndrome (SHATS). SHATS is a disease condition that accelerates the risk of organ damage and cardiovascular events via a vicious cycle of hemodynamic stress and vascular disease. AI, augmentation index; ECG, electrocardiography; BNP, B-type natriuretic peptide; NT-ProBNP, N-Terminal-ProBNP; UACR, urinary albumin/creatinine ratio, PWV, pulse wave velocity; CAVI, cardio-ankle vascular index; ABI, ankle-brachial index; FMD, flow-mediated dilatation (Modified from Ref. 93).

parameter β in the thoracic aorta, indicating a potential role of the CAVI in evaluations of integrated arterial stiffness including that of the central aorta.[106]

The disaster cardiovascular prevention (DCAP) network – an ICT-based model

The next stage of the management of HTN is information and communication technology (ICT)-based approaches using HBPM. ICT-based HBPM per se improved the home BP control status even in remote geographic locations.[107] The graphic function of an ICT-based approach that demonstrates the trend of BP control status also helps to achieve faster home BP control.[108] Various types of BPV with different time phases can be detected by ICT-based monitoring, and the synergistic assessment of BPV in combination with a vascular evaluation will lead to more precise risk assessments of SHATS (Fig 7).

We developed an ICT-based BP monitoring system at the time of the Great East Japan earthquake (March 2011) to improve the BP control in people who had been affected by this disaster. A major disaster increases the thrombophilic tendency and BP values, both of which trigger disaster-induced CVD events such as stroke and cardiac events.[109–111] At the time of the Great Hanshin-Awaji earthquake (January 1995), I worked for the Awaji-Hokudan public clinic in areas near the earthquake's epicenter, and I observed the disaster-associated increase in BP.[109] Most of the HTN patients developed uncontrolled HTN, but their BP levels returned to the previous BP level within 1 month after the earthquake. However, some patients (especially those with CKD) developed persistent uncontrolled disaster HTN.[109,112]

At the time of Great East Japan earthquake, we established the web-based disaster cardiovascular prevention (DCAP) network (which provided a DCAP risk and prevention score assessment and self-measured BP monitoring) for survivors of the 2011 earthquake.[113] The DCAP network system used cloud computing on the Internet to monitor the individual BP data self-measured at home or at a shelter, and this system was first introduced to a shelter in one of the most damaged areas (Minami Sanriku).[113] It had been shown that disaster-induced increases in BP are affected by the increased white-coat effect (clinic BP minus home BP), and thus the BP measurement by an unknown medical volunteers under stressful conditions in a shelter may tend to result in overestimations; self-measured BP could therefore be considered for obtaining more accurate BP values under such conditions.[111,113] In most patients affected by a disaster, the increases in clinic BP and self-measured BP are transient, and the BP levels return to the pre-disaster baseline levels within 4 weeks.[109–111] Thus, it is recommended that the BP levels of individuals who are affected by a disaster should be monitored ideally by self-measured BP in the disaster shelter or at home, and the dose of antiHTN medication should be reconsidered every 2 weeks during the short-term period after the disaster situation.

The pressor effect observed after the 2011 East Japan Earthquake lasted far longer than that following the Hanshin-Awaji Earthquake in 1995, most likely due to the greater damage and sequelae of the three disasters in 2011 (i.e., the earthquake, the subsequent tsunami, and the radiation exposure from the Fukushima Daiichi nuclear disaster). Twenty-one months after the East Japan Earthquake, on December 7, 2012, the largest aftershock occurred and tsunami warnings sounded. An ABPM study of eight patients who lived in the disaster area was being conducted at that time, and it revealed a pressor effect followed by increased nocturnal and morning BP levels.[114] In addition, the nocturnal and morning BP values were significantly greater in the subjects who were staying in temporary housing compared to the subjects who continued to live in their own homes. The more difficult living conditions in the temporary housing after the disaster were likely to have been stressful, contributing to a greater risk of CVD events.

Minami Sanriku study

We have continued to monitor home BP using the DCAP system in approx. 350 outpatients of Minami Sanriku Hospital with Dr. Masafumi Nishizawa (the hospital's vice president) for over 5 years. After the 2011 earthquake, the outpatients' home BP levels gradually decreased and reached approx. <125 mmHg (Nishizawa, Hoshide, Kario et al., unpubl. data), resulting in an approx. 50% reduction of CVD events in this geographic area. The successful use of the DCAP network in the Minami Sanriku area validates our introduction of an ICT-based home BP-guided approach with the goal of reducing the incidence of CVD events. In the Minami Sanriku study, we have also followed the 24-h ambulatory BP twice-yearly (summer and winter) since the winter of 2012 toward the goal of achieving 'perfect 24-h BP control.'

Research and development of new BP monitoring

When using an ICT-based hemodynamic biomarker-initiated CVD prevention, the development of BP monitoring devices that can detect different types of hemodynamic stress on the CV system is important. We have been developing the following new ABPM and HBPM devices.

Home-activity-ICT-based ABPM (HAI-ABPM)

We have conducted the JMU-ABPM Study, Wave 1 at the Awaji-Hokudan Public Clinic since 1992,[22,30,33,45,46] and we began the Japan Ambulatory Blood Pressure Prospective study (JAMP) in 2009. The JAMP study is an ongoing prospective nationwide study using ABPM in approx. 7000 Japanese patients with one or more CVD risk factors. We developed a new IT-based home and ABPM device equipped with (1) high-sensitive actigraphy that can detect fine-scale physical movements in three directions, (2) a thermometer, and (3) a barometer (i.e., Home-activity-ICT-based ABPM [HAI-ABPM], A&D Co.Itd, Tokyo).

As ambulatory BP is partly determined by an individual's physical activity, this device automatically calculates two new indices, 'BP reactivity,' based on the slope of ambulatory BP increase against activity just before the BP measurement (actisensitivity),[19,34,115] and based on the slope of cold

temperature (thermosensitivity).[19,36] Using these indices, we have introduced the concepts of 'trigger-induced BP reactivity index' to identify specific high-risk patients as those with 'thermosensitive HTN' and 'actisensitive HTN,' respectively. This device can monitor both home and ambulatory BPs and send the data by ICT, and we are now starting a new nationwide cohort using this device, the HAI-JAMP (Home-Activity ICT-based Japan AMbulatory Blood Pressure Prospective) study.

Home nocturnal BP monitoring

Basic home nocturnal BP monitoring (Medinote→HEM-7252G-HP)
ABPM had once been the only available method for measuring a subject's nocturnal BP during his or her sleep, and as an alternative to ABPM, our development of the Medinote semi-automatic nocturnal HBPM device was a first step in obtaining basic nocturnal BP data. The Medinote (Omron Healthcare, Kyoto, Japan) measures the user's BP values automatically at fixed intervals while he or she sleeps.[2,19] The user simply places the Medinote's cuff on his or her arm just before going to bed. The user's BP data are stored in the device's memory file. The Japan Morning Surge Home Blood Pressure (J-HOP) study, a nationwide cohort study, was the first investigation to use the Medinote on a large scale.[63,116,117] The design for HBPM devices has already advanced to a new ICT-based nocturnal BP monitoring device, the HEM-7252G-HP (Omron).

In the J-HOP study, we recruited 4310 patients who had one or more CVD risk factors. The results of this study demonstrated that morning BP and evening BP provide equally useful information regarding subclinical target organ damage, yet multivariate modeling highlighted the stand-alone predictive ability of morning BP.[63] We successfully measured the nocturnal home BP of 2562 participants using the Medinote monitoring device three times during sleep (at 2:00, 3:00, and 4:00 a.m.) as well as three times each in the morning and evening for 14 days. The 4:00 a.m. SBP levels were slightly but significantly higher than those at the other two time points, by 1.5 mmHg ($p < 0.0001$), but there were no significant differences between the nocturnal home SBP levels at 2:00 and 3:00 a.m. Based on the J-HOP results, we concluded that it is feasible to have subjects self-measure their nocturnal BP at home.[117]. In our J-HOP sub-analysis, the nocturnal home BP values obtained were almost the same as those of nocturnal BP values obtained by ABPM.[116] In the J-HOP Study, the subjects' nocturnal home SBP was significantly correlated with measures of organ damage.[117] Twenty-seven percent of the subjects whose morning home BP was well-controlled at <135/85 mmHg showed masked home nocturnal HTN with nocturnal home SBP ≥120 mmHg, and these subjects also had higher NT-proBNP and UACR values.[117] Nocturnal home BP was also a better indicator of BP control during antiHTN treatment. In our Japan Morning Surge-Target Organ Protection (J-TOP) study, cardiac echography and electrocardiography revealed that the reduction of nocturnal home BP was more closely associated with the regression of left ventricular hypertrophy (LVH). The J-TOP findings indicate that remaining uncontrolled nocturnal HTN should be a focus of future antiHTN treatment even after a patient's morning BP is well-controlled by conventional home BP-guided treatment.

'ThermosensitiveHTN' – Detecting home BP device
The HEM-7252G-HP includes a thermosensor within the device. BP is partly associated with temperature. The morning BP level in particular is closely determined by cold temperatures, especially in the elderly. However, this characteristic varies among different HTN patients. Here I first used the term 'thermosensitive HTN'[19,36] to define HTN in which home BP is affected by seasonal temperature changes (e.g., $R^2 > 0.3$, change of morning SBP >10 mmHg/10 °C).[19] Individuals with thermosensitive HTN may experience a 'winter morning surge in BP'[100] that contributes to an increased rate of CVD events during the winter season. We are now conducting the Prediction of IT-Home BP Variability (PREDICT) study using ICT-based monitoring to examine the possibility of the prediction of near-future home BP values at the individual level based on the patient's characteristics, environmental conditions, and past day-by-day home BP values.

ICT-based triggering of home nocturnal BP monitoring (ITNP)
'Triggered BP measurement' in HBPM is a concept that we introduced in 2015.[19] The measurement of BP at a trigger signal based on specific conditions was not provided by any HBPM device prior to that time. The benefit of triggered BP measurement at home is that it can be used to repeatedly measure a subject's specific BP levels and BPV related to risky conditions. We hypothesized that since repeated measurements can be obtained by HBPM, repeated BP measurements taken at triggered conditions at home could improve the detection of abnormal BP peaks in specific conditions that are CVD risk-related.

In our development of triggered BP measurement, we devised a 'trigger nocturnal BP monitoring (TNP)' method based on the Medinote's automated fixed-interval measurements, with an added trigger function. With a pre-set threshold for oxygen desaturation (which is continuously monitored by pulse oximetry), the HBPM device is triggered to initiate BP measurements when the wearer's oxygen desaturation falls below the threshold.[2,19,103,118,119] OSA patients' nocturnal BP profile is characterized by increased nocturnal BPV, nocturnal HTN with the non-dipper/riser pattern, and exaggerated morning BP surges.[43] The higher nocturnal BP that is directly linked to OSA episodes could not be detected by earlier HBPM and ABPM methods, but the TNP method can successfully detect the OSA-specific exaggerated nocturnal BP surges triggered by hypoxic episodes (Fig 11).[118] Compared to the general population, OSA patients also experience sleep-onset CVD events more frequently during sleep, and their exaggerated nocturnal BP surges may partly explain this.[119]

We also added a trigger function to the Medinote to detect the 'basal BP,' which is based on the wearer's lowest heart rate. The basal BP, defined as the nocturnal BP values obtained after the signal triggered by the lowest heart rate during sleep (Fig 11),[2,19] is the nocturnal BP with the lowest sympathetic drive. The basal BP is determined based mainly on the circulating blood volume and structure of the vasculature.

Nocturnal HTN has shown heterogeneous pathophysiology. Two types of nocturnal BP with different clinical implications (i.e., cardiovascular structure-determined basal BP and sympathetic

activity-related BP) were revealed by the TNP method, which measures the double-trigger signals of hypoxia and heart rate. TNP monitoring may thus help achieve more effective control of nocturnal HTN with a different pressor mechanism by identifying the best class of antiHTN drugs. Nocturnal BP values with these different pressor mechanisms cannot be differentiated by conventional ABPM using fixed-interval measurements.

With our colleagues at Omron Healthcare, we developed an ICT-based TNP (ITNP) system (Fig 12)[103] that is a cloud computing-based composite analysis and management system using data sent from the BP device worn by a patient at home. Repeated and day-by-day variabilities in nocturnal BP are detected by the ITNP system, as are the basal nocturnal BP and morning BP values and the nocturnal BP surges linked to OSA episodes, the extent of which is often affected by daily environmental changes. In 2012 we began a prospective investigation using this ITNP system, the Sleep Pressure and Disordered Breathing in Resistant Hypertension and Cardiovascular Disease (SPREAD) study, to determine the clinical implications of nocturnal BP and nocturnal BP surges in high-risk patients with resistant HTN and/or CVD. Improved sensitivity for the diagnoses of OSA and the related nocturnal BP surge can be achieved based on repeated assessments using the ITNP system in real-life settings. The presence or severity of OSA could be missed or underestimated, respectively, by single-day polysomnography in alcohol-prohibited conditions in hospitals. Individuals with moderate OSA may thus not be identified in such conditions. In the SPREAD study, the degree of apnea/hypopnea episodes among the subjects who had mild-to-moderate OSA showed significant night-by-night variability, and on alcohol-intake days the nocturnal BP values and nocturnal BP surges of these subjects were increased.[19]

The ITNP system can also evaluate the efficacy of treatment. In our study of TNP, the bedtime dosing of nifedipine and carvedilol significantly reduced all of the measures of nocturnal BP, although the nocturnal BP-lowering properties of these two drugs are different. [44] Compared with nifedipine, carvedilol comparably reduced the peak nocturnal BP, while it significantly but less extensively reduced basal BP, resulting in a significant suppression of hypoxia-induced nocturnal BP surges.[44] In addition, the ITNP system was able to evaluate the efficacy of continuous positive airway pressure (CPAP). Effective CPAP reduces nocturnal SBP markedly greater when evaluated by measuring the hypoxia-peak nocturnal SBP.[19]

The detection of high-risk OSA patients with nocturnal HTN and/or a nocturnal BP surge will be improved by the use of the ITNP system. In addition, better BP control could be achieved in OSA patients who are using a CPAP and those who are under antiHTN treatment when the ITNP system is used. The development of organ damage and CVD events in OSA patients would be effectively suppressed by strict 24-h BP control (including these patients' hypoxia-induced peaks and nocturnal BP), and using the ITNP system will help reach this goal.

Beat by beat wearable 'surge' BP monitoring

Wearable noninvasive beat-by-beat BP monitoring has been the dream of doctors who manage HTN. A recent systematic review comparing continuous noninvasive arterial BP monitoring with invasive arterial BP monitoring demonstrated that the inaccuracy and imprecision of continuous noninvasive arterial BP monitoring devices are larger than what was defined as acceptable.[120] There are two methods that could be used for noninvasive continuous beat-by-beat BP monitoring. One is the applanation tonometry method, and the other is the pulse wave transit time (PWTT) method. There are several limitations of these methods.

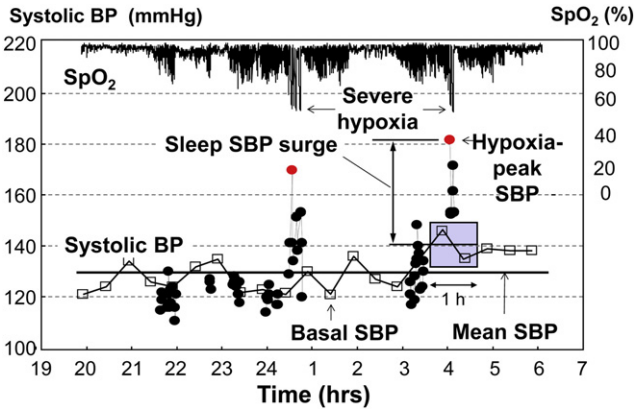

Fig 11 – Definition of nocturnal blood pressure parameters obtained by trigger nocturnal blood pressure monitoring (TNP). SBP, systolic blood pressure (Modified from Ref. 44).

The PWTT-method does not take direct measurements; it provides an indirect estimation of arteria BP or cardiac output.[121] However, the biggest problem with the PWTT method is that the PWTT is determined by the functional stiffness and the structural stiffness, and the impacts of functional versus structural components which determine the PWTT differ among individual patients. The PWTT method may be used for younger subjects whose arteries are soft, because the PWTT is predominantly determined by the intra-arterial BP and the PWTT could change very much according to the change in intra-arterial BP. However, in high-risk patients with stiffened arteries, the PWTT is predominantly determined by the structure of the stiffened arteries, and the PWTT should change little with changes in intra-arterial BP. Thus, the estimated BP values may be relatively accurate for healthy younger patients at the early stage of HTN without vascular disease, but the estimated BP values would likely be inadequate for high-risk patients with advanced vascular disease. In addition, theoretically, the change in the PWTT may not reflect the beat-by-beat changes in intra-arterial BP, because the PWTT method uses the mean pressure to estimate BP.

The applanation tonometry method provides direct measurements based on the law of Laplas. Effective applanation of the arterial wall is required to achieve accurate results. The radial artery is the best artery for effective applanation, because it is shallow beneath the skin and is fixed on a radial bone. However, for effective applanation, the position of the pressure sensor should be fixed exactly and stably without physical movement during measurement. A single sensor structure type (pencil-type) is used by the SphygmoCor®

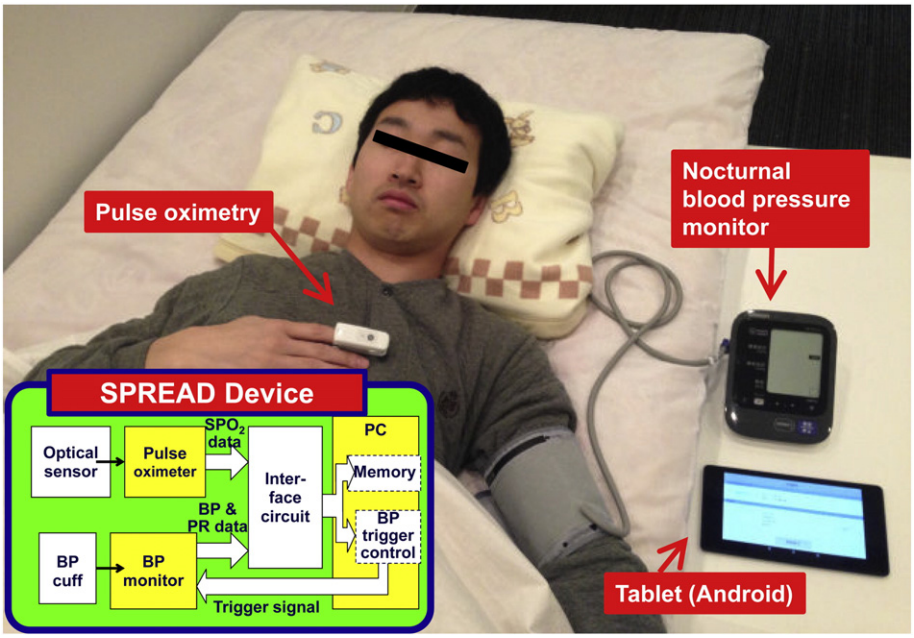

Fig 12 – ICT-based trigger nocturnal home BP monitoring system with oxygen and heart rate triggers and a cloud system (ITNP, 2015, developed by Jichi Medical University, Tochigi, and Omron Healthcare Inc., Kyoto, Japan). (Modified from Ref. 103).

Cardiovascular Management System to determine the radial pulse wave form, and this requires a skilled operator to obtain the accurate pulse wave form.[122]

In contrast, an arrayed sensor, once set on the subject's wrist, is servo-controlled to optimize the hold-down pressure in order to attain effective applanation of the artery and automatically select a sensor element outputting the highest-quality tonometric waveform. The accuracy of this blood pressure monitoring device (the JENTOW) is described elsewhere.[123] It is expected to enable ambulatory arterial tonometry. However, the weaknesses of a tonometry BP monitoring device are that (1) the position of the sensor to

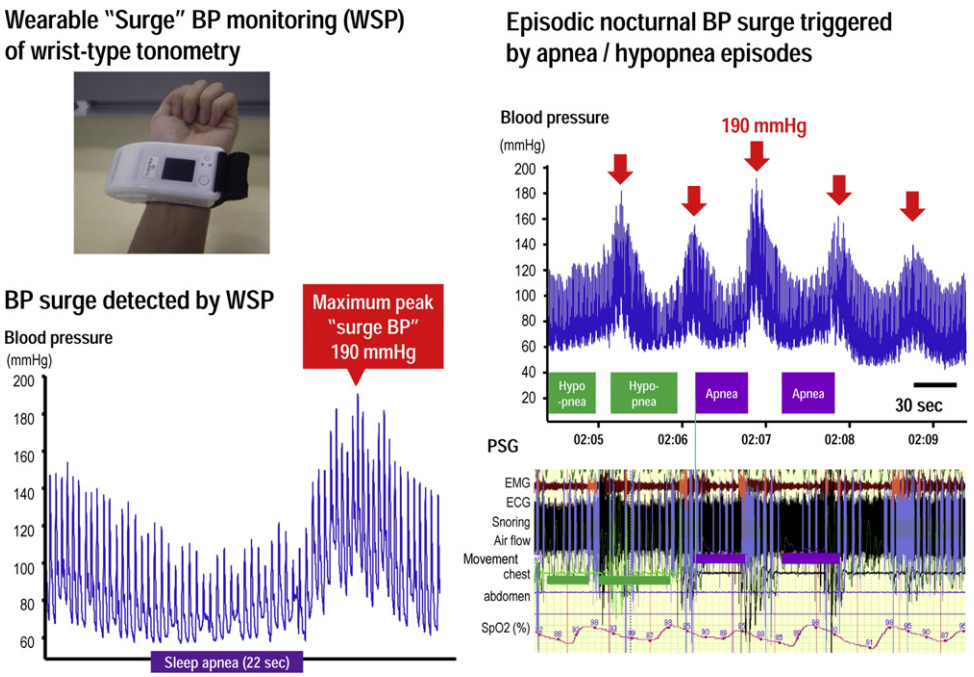

Fig 13 – Nocturnal blood pressure surges detected by wearable "surge" blood pressure monitoring of wrist-type tonometry (WSP) in a hypertensive patients with sleep apnea. BP = blood pressure, PSG = polysomnography.

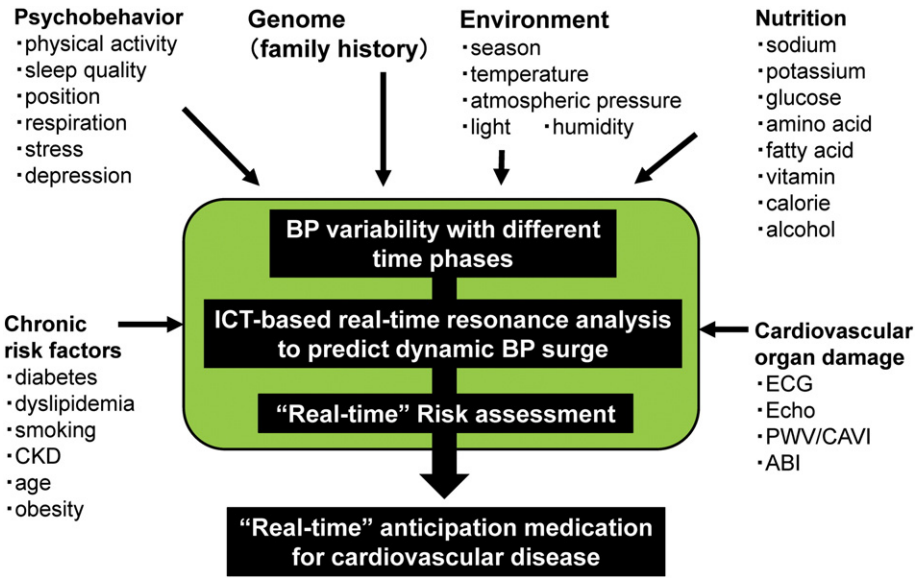

Fig 14 – Hemodynamic biomarker-initiated 'anticipation medication' for the prevention of onset and aggravation of cardiovascular events. CKD, chronic kidney disease; ECG, electrocardiography; Echo, cardiac and carotid echography; PWV, pulse wave velocity; CAVI, cardio-ankle vascular index; ABI, ankle-brachial index.

cover the artery is very strict, and (2) artifacts by the movement of the wrist, which disturb effective applanation, are frequent. There is also an inconstant positional relationship between the heart and the measurement site, which would introduce the influence of hydrostatic pressure alterations on the BP level.

Omron Healthcare Inc. recently publicized a prototype of a wearable wrist type of tonometry BP monitor that uses recent advances in automatically-controlled technology.

This prototype has two tonometery sensor plates and the angle of the arrayed sensor plate to cover the radial artery is automatically adjusted in order to obtain effective applanation.

We are testing this device and improving it in collaboration with Omron with the goal of developing more accurate beat-by-beat 'wearable surge BP monitoring (WSP),' which could measure the absolute values of the maximum peaks of beat-by-beat pressure (Fig 13).

Perspectives

BPV is an important measure of both 'precision medicine' and 'anticipation medicine' for CVD. Repeated exaggerated BPV triggered by specific conditions may advance organ damage, and one extremely large dynamic BP surge generated by the synergistic resonance of various BP surges with different time phases may trigger a cardiovascular event. Thus, in the future, the 'ICT-based 24-h anticipation management of HTN' in consideration of BPV and nocturnal HTN is a promising individualized approach against advancing atherosclerosis from early stages and against the triggering of CVD events at the final stage of CVcontinuum among high-risk patients. However, intermittent BP measurements at fixed intervals would underestimate the CVD risk of BPV and exaggerated BP surges. Finally, the advances in wearable 'beat-by beat' continuous BP monitoring and ICT-based real-time large-scale data resonance analyses and simultaneous feedback systems (Fig 14) will achieve a paradigm shift from 'dots' of BP management to 'seamless' event anticipation management.

Disclosures and conflict of interest

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Spring Scientific Meeting of the Japanese Society of Hypertension, Tokyo in May 2016. Some parts of this paper are significantly overlapped with the forthcoming review paper entitled "Research and development of information and communication technology-based home blood pressure monitoring from morning to nocturnal hypertension" (Annals of Global Health 2016).

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