The discovery of blood pressure was more important than the discovery of blood.

Blood Pressure Variability

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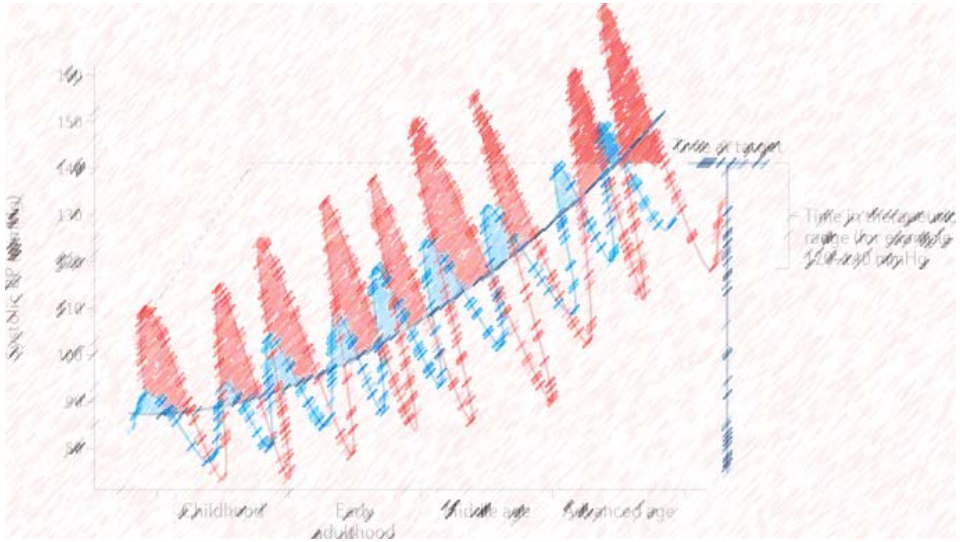
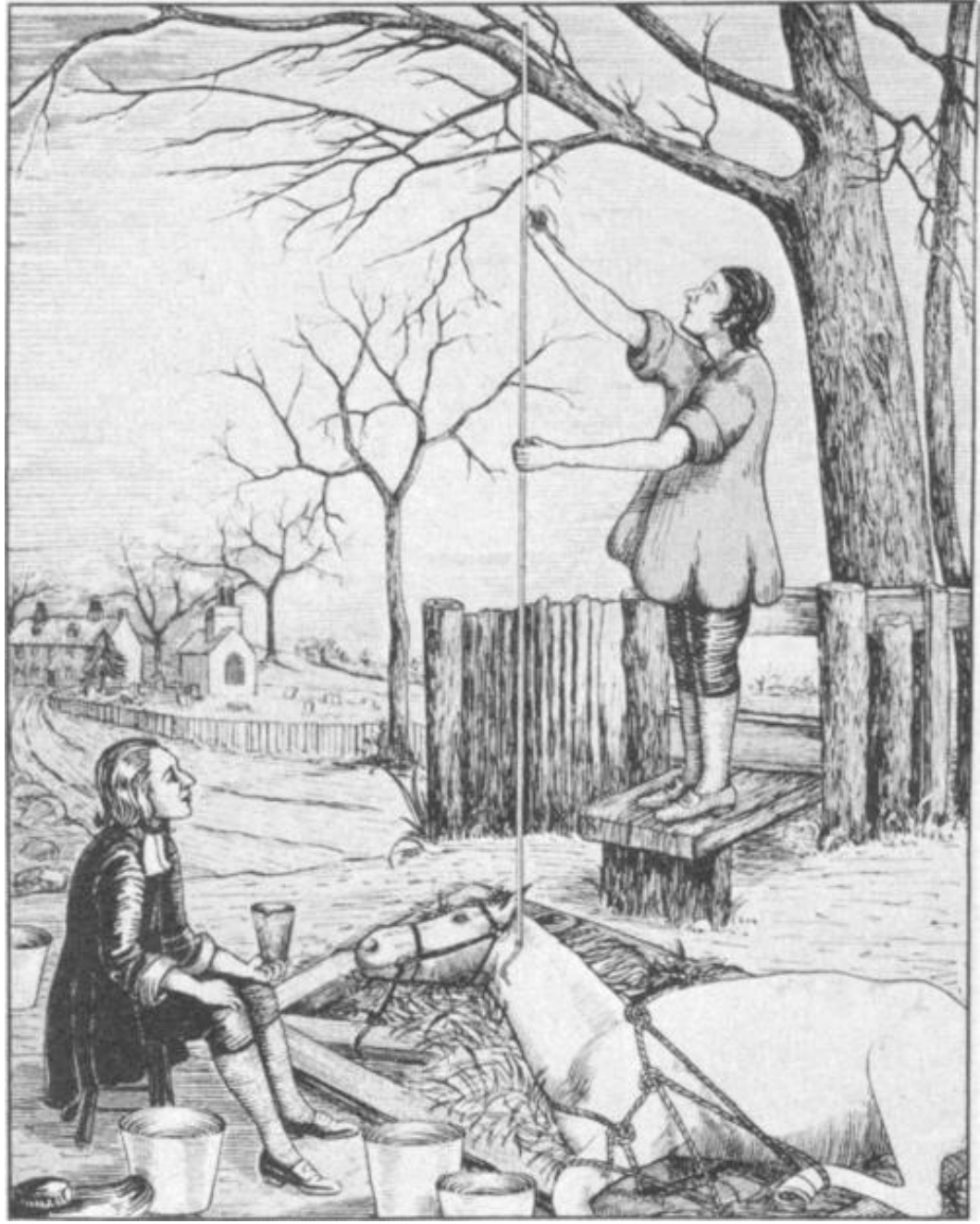
May 2023



Blood pressure is discovered.

- THE YEAR IS 1733 and the Enlightenment is in full force in England.
- Philosophers dream of a brighter age and scientists scramble to organize and establish their ranks amongst the new order of scientific academies.
- Cambridge scholar Stephen Hales calms an adolescent horse he's laid down on its side.
- He looks to his assistant and gives him the go-ahead.
- Complying with Stephen's request, the assistant proceeds to connect a 9 foot glass tube to a bypass Stephen had inserted into the crural artery of the horse's thigh.
- The connection had been made!
- The assistant points the glass tube vertical towards the sky.
- Stephen releases a tie.
- They both watch in anticipation as the warm blood of the horse's artery enters and climbs the walls of the glass tube.
- The blood quickly rises reaching a height of 8 feet 3 inches above the horse.
- Suddenly the blood level starts rising and falling about 3 inches in a continuous periodic nature that appears to be in synchrony with each of the horse's heart beats.



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MINI REVIEW

Mini review series: Current topic in Hypertension

Short- to long-term blood pressure variability: Current evidence and new evaluations

Keisuke Narita[1] · Satoshi Hoshide[1] · Kazuomi Kario[1]

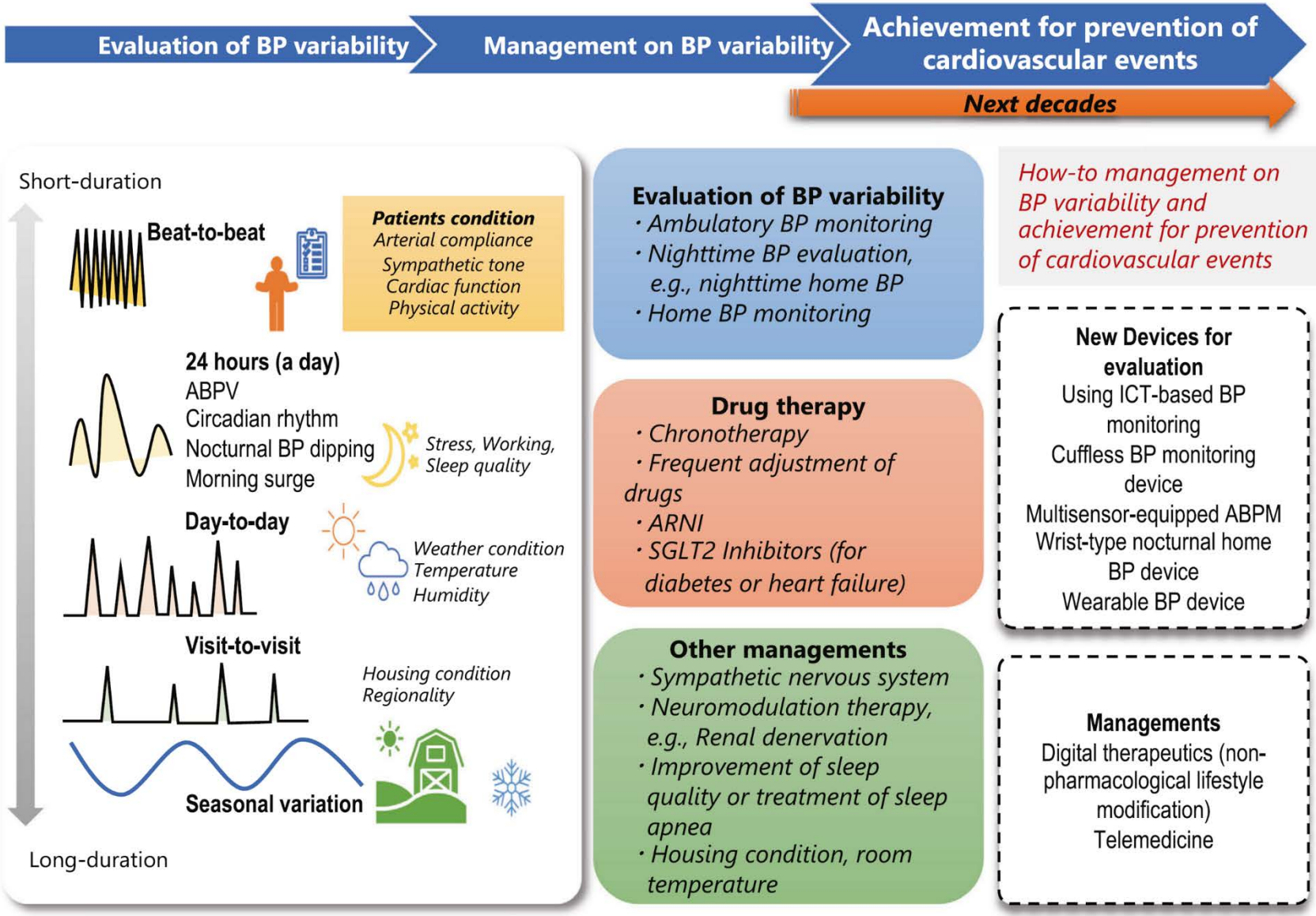
Received: 10 November 2022 / Revised: 5 January 2023 / Accepted: 19 January 2023 / Published online: 9 February 2023

Abstract

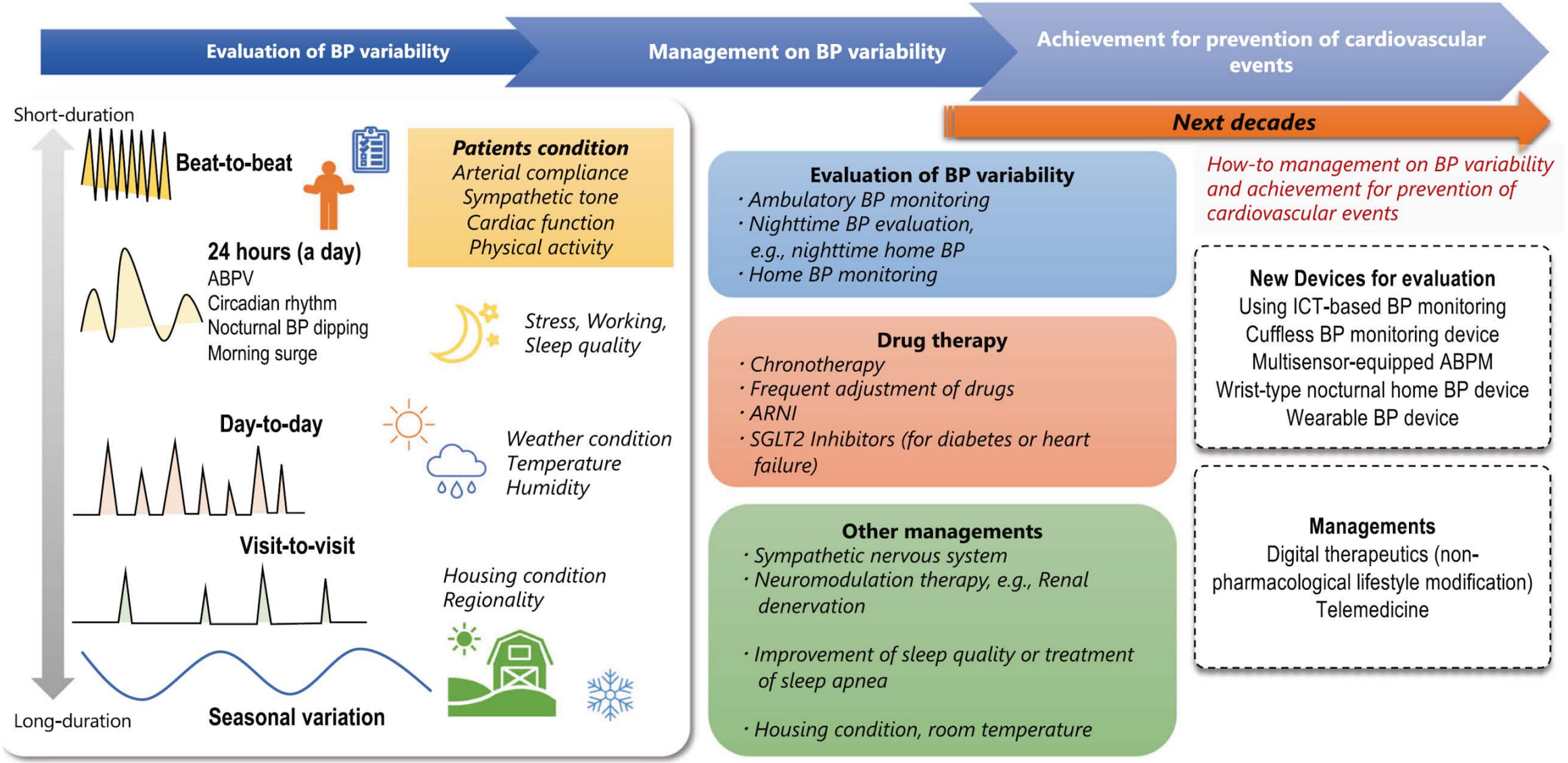
Increased blood pressure (BP) variability and the BP surge have been reported to be associated with increased cardiovascular risk independently of BP levels and can also be a trigger of cardiovascular events. There are multiple types of BP variation: beat-to-beat variations related to breathing and the autonomic nervous system, diurnal BP variation and nocturnal dipping related to sleep and physical activity over a 24-hr period, day-to-day BP variability with anomalous readings within a several-day period, visit-to-visit BP variability between outpatient visits, and seasonal variations. BP variability is also associated with the progression to hypertension from prehypertension and the progression of chronic kidney disease and cognitive impairments. Our research group proposed the "resonance hypothesis of blood pressure surge" as a new etiological hypothesis of BP variability and surges; i.e., the concept that when the time phases of surges and hypertension-inducing environmental influences coincide, resonance occurs and is amplified into a larger "dynamic surge" that triggers the onset of cardiovascular disease. New devices to assess BP variability as well as new therapeutic interventions to reduce BP variability are being developed. Although there are still issues to be addressed (including measurement accuracy), cuffless devices and information and communication technology (ICT)-based BP monitoring devices have been developed and validated. These new devices will be useful for the individualized optimal management of BP. However, evidence regarding the usefulness of therapeutic interventions to control BP variability is still lacking.

Keywords Blood pressure · Hypertension · Blood pressure variability · Blood pressure monitoring · Hypertension · Cardiovascular disease

Blood pressure variability
—New target for prevention of cardiovascular diseases

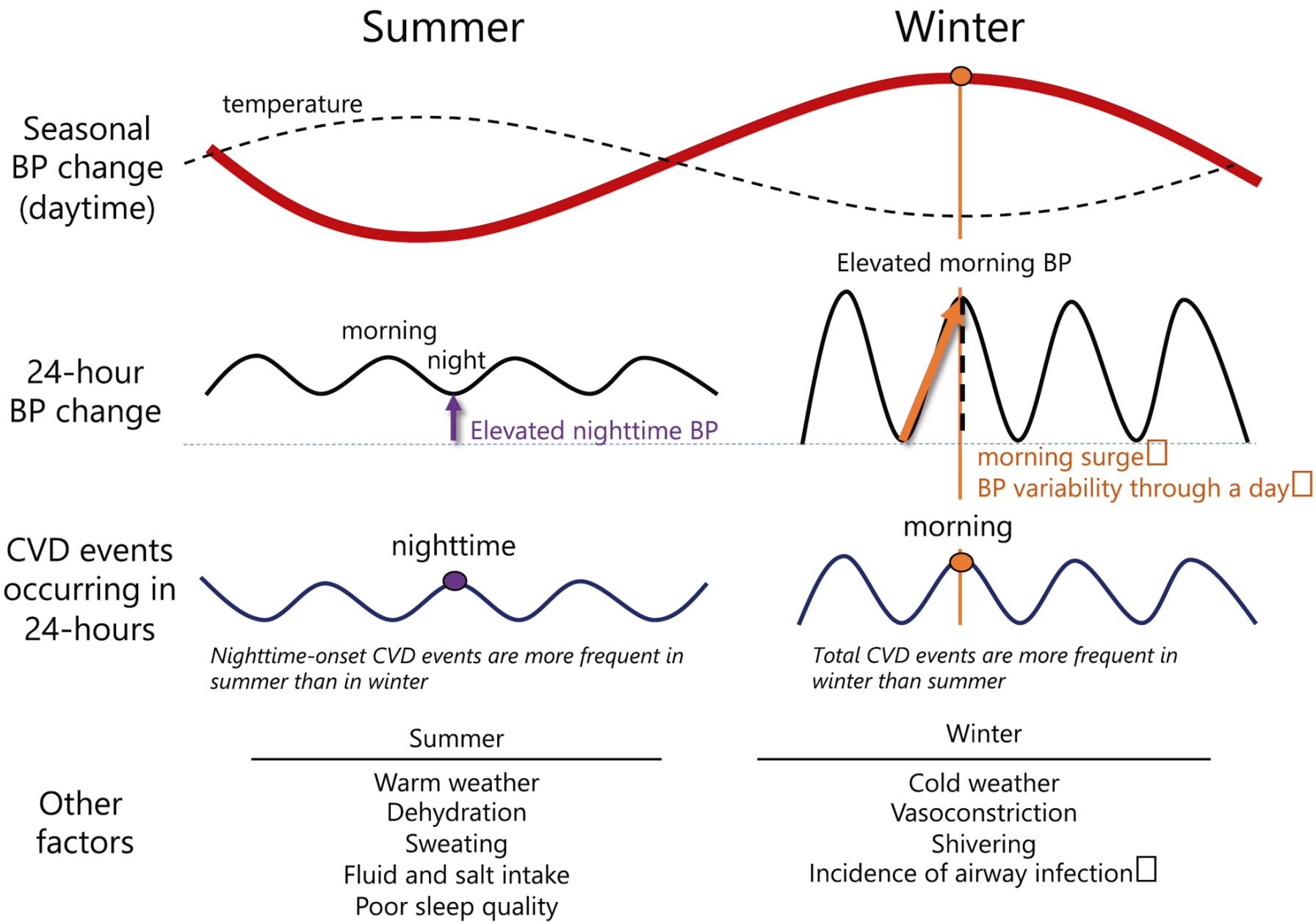


K. Narita, S. Hoshide, and K. Kario, Hypertens. Res., vol. 46, no. 4, pp. 950–958, 2023.



Blood pressure variability — A new target for the prevention of cardiovascular diseases. Blood pressure (BP) variability can be classified in terms of the time course. BP variability has a variety of mechanisms, and a detailed evaluation of these mechanisms is synonymous with assessing a patient's risk of cardiovascular disease. The development of new assessments and interventions for BP variability may be useful for the prevention of cardiovascular disease events

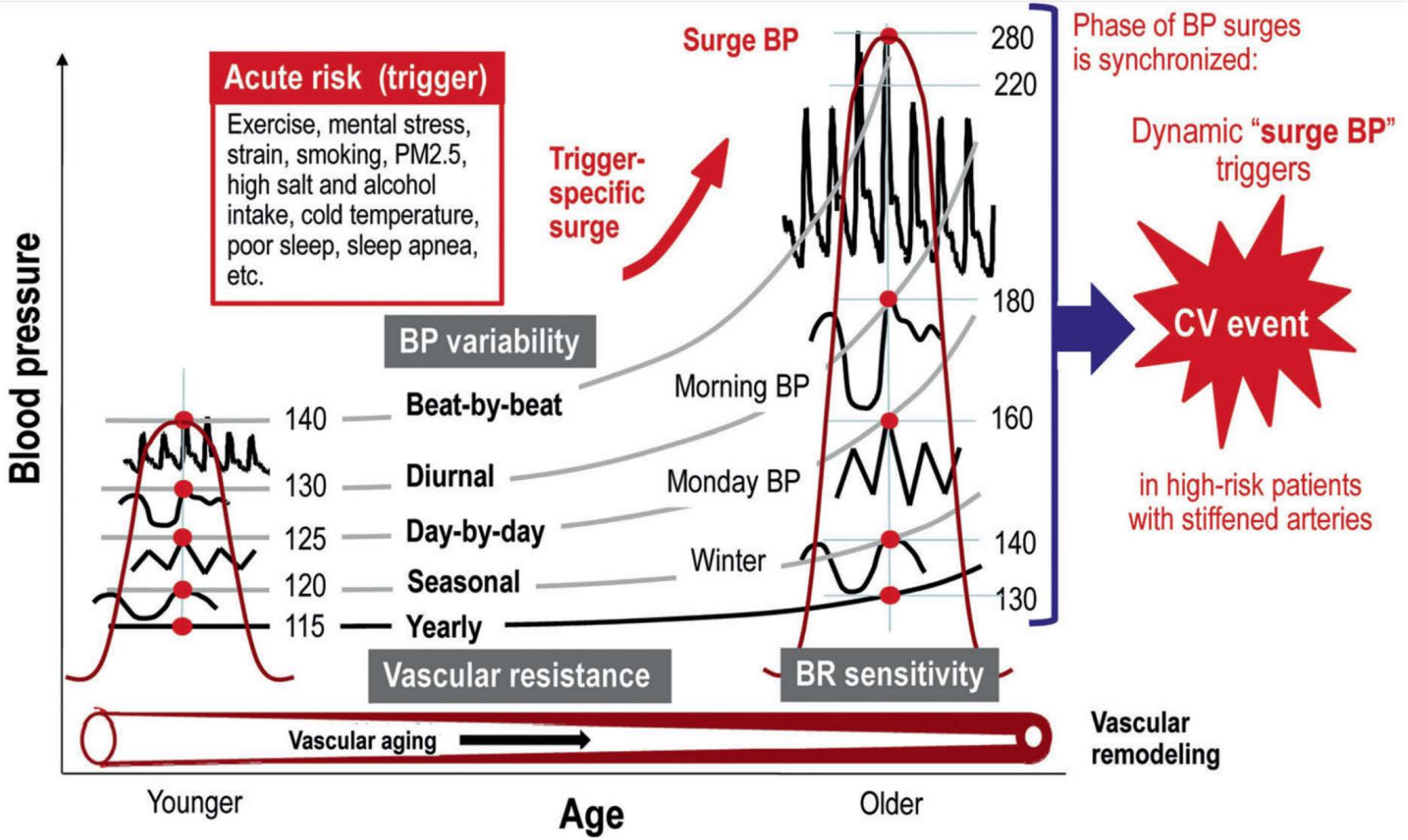
K. Narita, S. Hoshide, and K. Kario, Hypertens. Res., vol. 46, no. 4, pp. 950–958, 2023.



Seasonal variation of BP and its effect on cardiovascular risk. The incidence of cardiovascular disease is widely recognized to be higher in winter than other seasons. In winter, cold exposure induces BP increases, especially in the morning. The mechanisms of this phenomenon involve cold temperature, vasoconstriction, shivering, and other factors. In contrast, nocturnal blood pressure often increases in the Summer.

K. Narita, S. Hoshide, and K. Kario, Hypertens. Res., vol. 46, no. 4, pp. 950–958, 2023.

Blood pressure variability and cardiovascular disease risk -The resonance hypothesis of blood pressure surges. BP variability is related to progression from prehypertension to hypertension, and BP variability is worse in individuals with increased arterial stiffness and cardiovascular risk. Elevated BP variability is also considered an event trigger of cardiovascular disease



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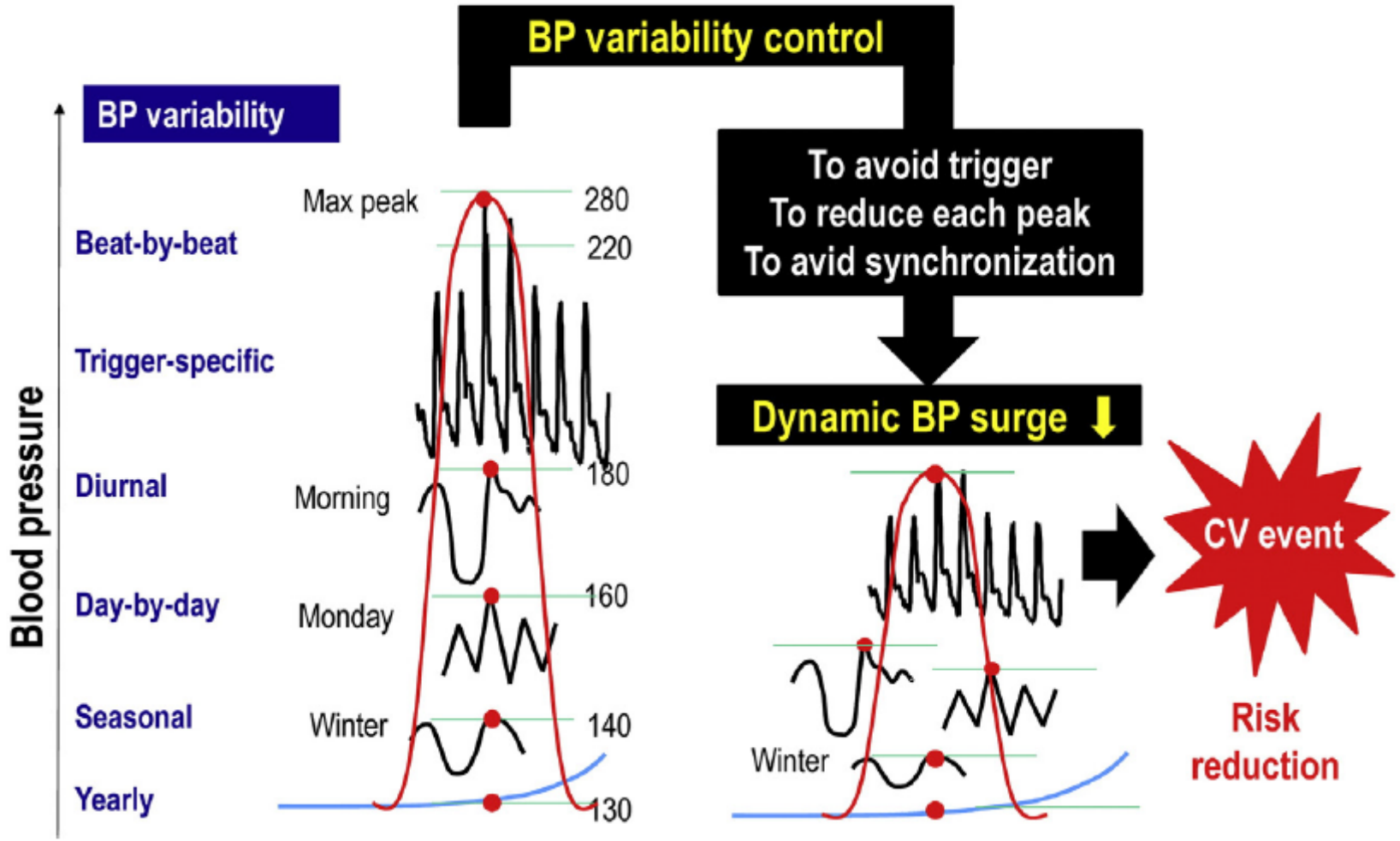
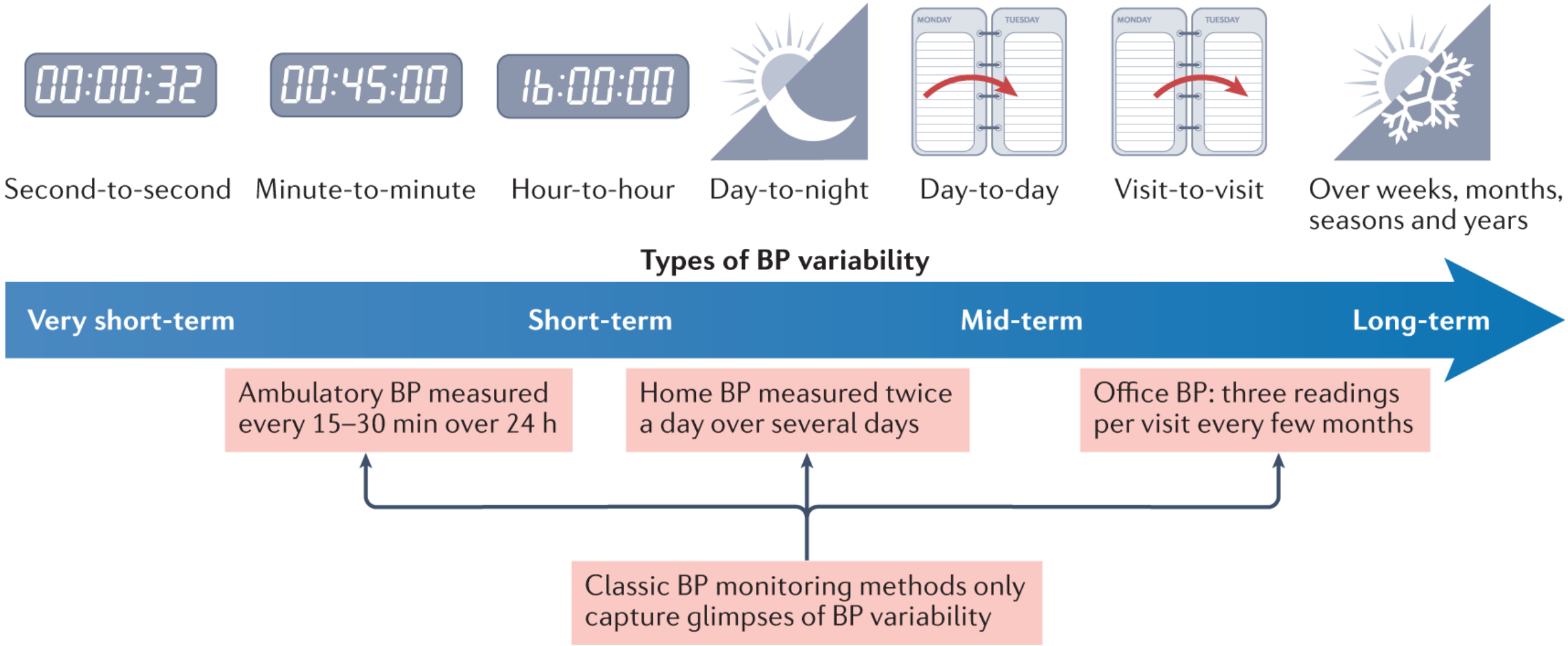
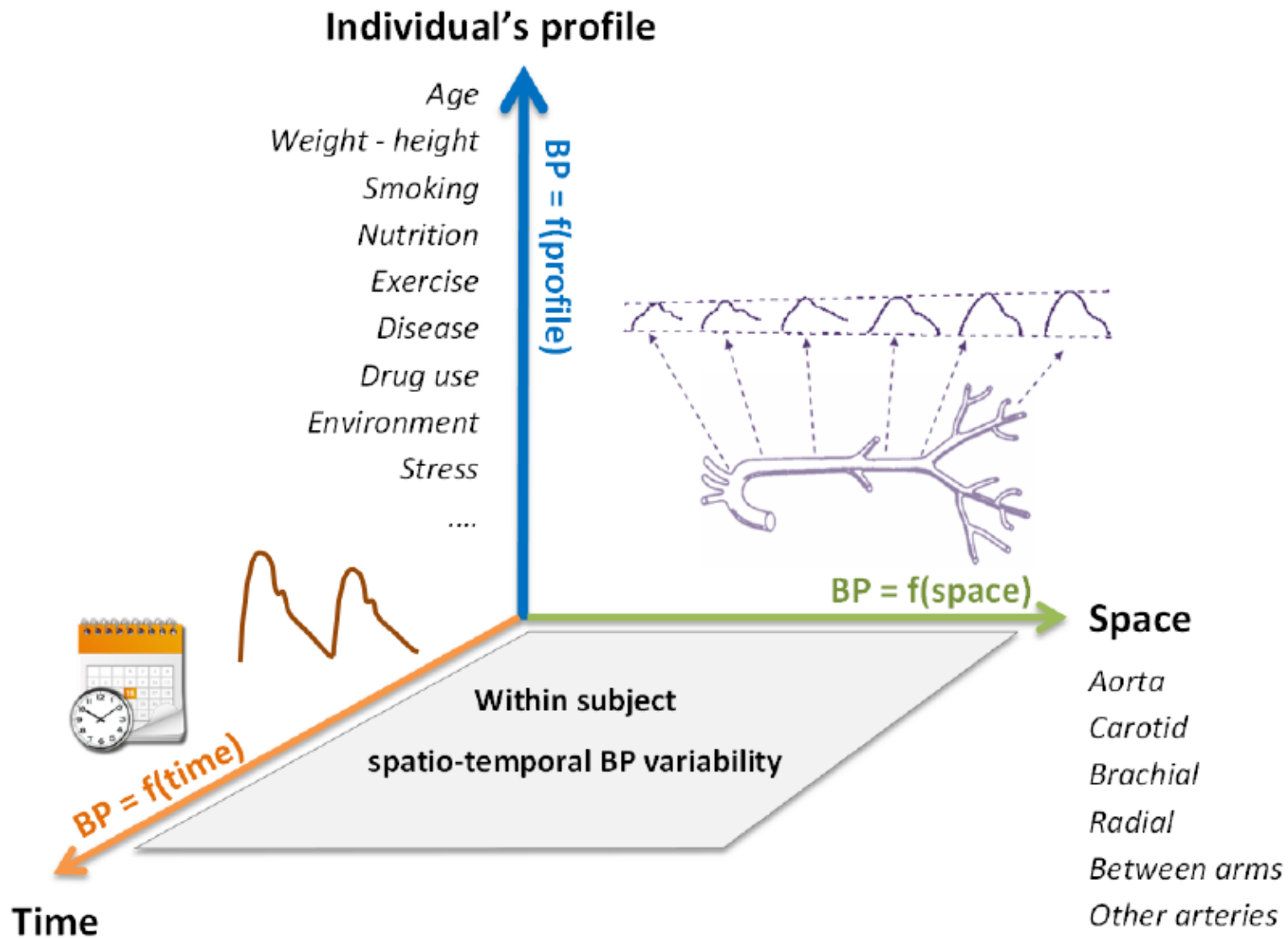


Fig 9 – Blood pressure-variability control strategy based on the synergistic resonance hypothesis and aiming at the prevention of cardiovascular-event onset. BP, blood pressure; CV, cardiovascular.

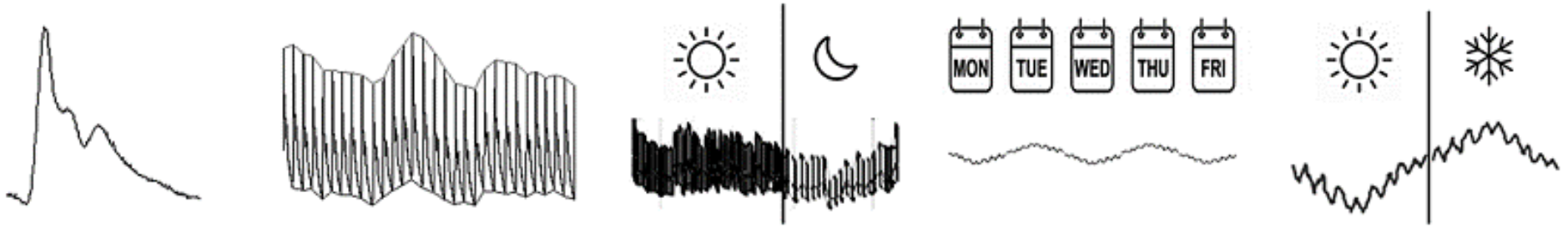

00:00:32
00:45:00
16:00:00
MONDAY
TUESDAY
MONDAY
TUESDAY
Second-to-second
Minute-to-minute
Hour-to-hour
Day-to-night
Day-to-day
Visit-to-visit
Over weeks, months, seasons and years
Types of BP variability
Very short-term
Short-term
Mid-term
Long-term
Ambulatory BP measured every 15–30 min over 24 h
Home BP measured twice a day over several days
Office BP: three readings per visit every few months
Classic BP monitoring methods only capture glimpses of BP variability



Different dimensions of intra-subject blood pressure variability.
BP value for each subject is a function (f) of
1. subject's current status -profile
2. time of measurement
3. arterial site of measurement.

Blood pressure variability: methodological aspects, clinical relevance and practical indications for management - a European Society of Hypertension position paper*

Gianfranco Parati[a,b], Grzegorz Bilo[a,b], Anastasios Kollias[c], Martino Pengo[a,b], Juan Eugenio Ochoa[a], Paolo Castiglioni[d,e], George S. Stergiou[c], Giuseppe Mancia[f], Kei Asayama[g,h,i], Roland Asmar[j], Alberto Avolio[k], Enrico G. Caiani[a,l], Alejandro De La Sierra[m], Eamon Dolan[n], Andrea Grillo[o], Przemysław Guzik[p], Satoshi Hoshide[q], Geoffrey A. Head[r], Yutaka Imai[i], Eeva Juhanoja[s,t], Thomas Kahan[u], Kazuomi Kario[q], Vasilios Kotsis[v], Reinhold Kreutz[w], Konstantinos G. Kyriakoulis[c], Yan Li[x,y], Efstathios Manios[z], Anastasia S. Mihailidou[aa], Pietro Amedeo Modesti[bb], Stefano Omboni[cc,dd], Paolo Palatini[ee], Alexandre Persu[ff], Athanasios D. Protogerou[gg], Francesca Saladini[ee,hh], Paolo Salvi[a], Pantelis Sarafidis[ii], Camilla Torlasco[a], Franco Veglio[jj], Charalambos Vlachopoulos[kk], and Yuqing Zhang[ll]



	Within beat BPV	Very short-term BPV	Short-term BPV	Mid-term BPV	Long-term BPV
recommended measurement interval	<0.02 s within single heartbeat	beat-by-beat hundreds of beats	every 15-30 min within 24h	day-by-day within one week	visit-to-visit
common measurement methods	Noninvasive tonometry intra-arterial recordings photoplethysmography	Noninvasive tonometry intra-arterial recordings photoplethysmography	Ambulatory BP monitoring	Home BP monitoring	Office/Home BP monitoring
typical measurement duration	Few seconds	From 5' to 60'	About 24h	From 3 to 7 days	Weeks to years
measurement includes	Waveform parameters	Overall BPV decomposed in time-/ frequency-domain indexes	Overall BPV, circadian patterns, activity related changes	Overall BPV	Overall BPV, seasonal patterns

Classification of blood pressure variability (BPV) based on temporal frame of reference. Key features of measurement methodology are summarized for each BPV subtype. ''Overall'' variability indicates total variance, including all components of BPV over a given time window.

G. Parati et al., J. Hypertens., vol. 41, no. 4, pp. 527–544, Apr. 2023.

Box 1. Factors determining BPV

INTRINSIC FACTORS

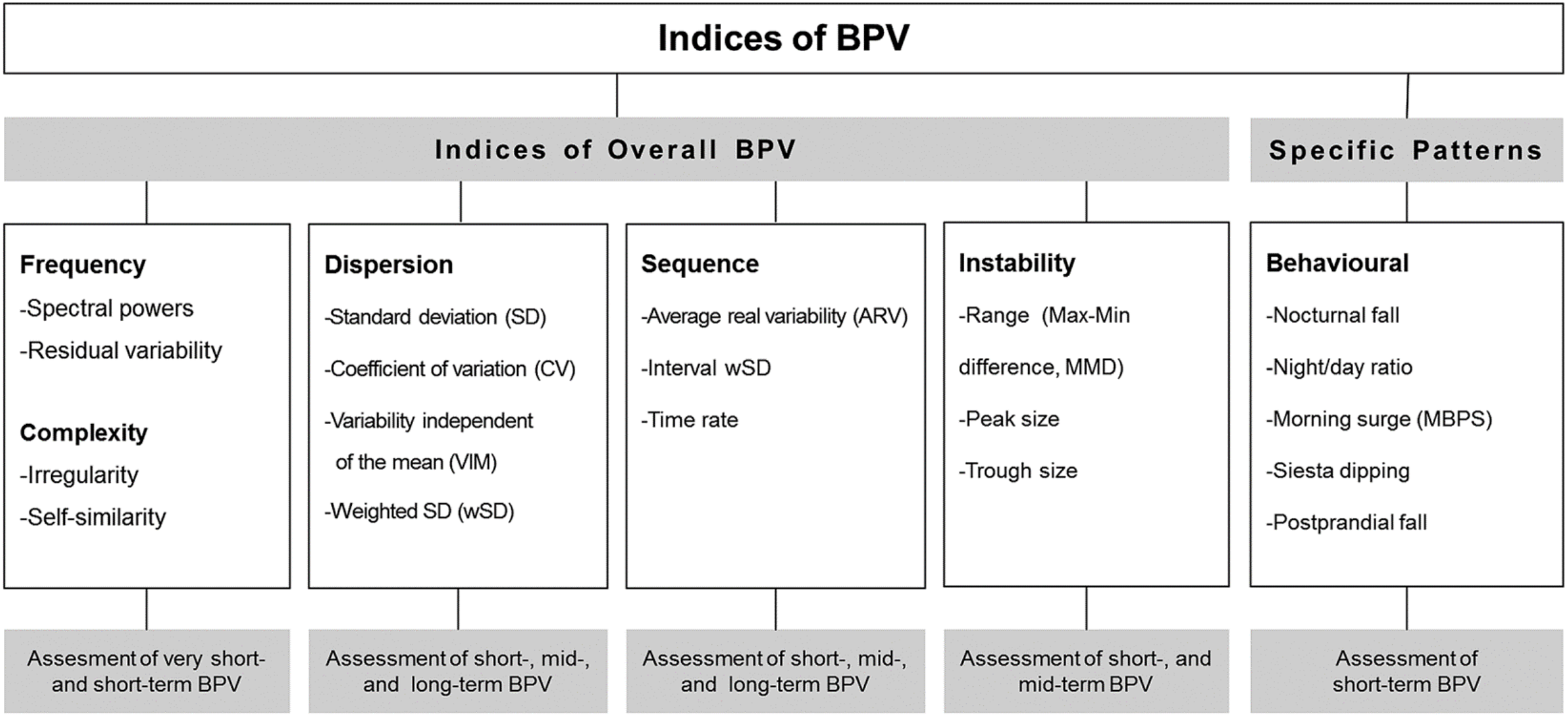
Neural mechanisms: central sympathetic drive, arterial and cardiopulmonary reflexes, chemoreflexes.
Humoral mechanisms: catecholamines, insulin, insulin resistance, renin, angiotensin II, bradykinin, cortisol, aldosterone and its metabolites, endothelin-1, nitric oxide, natriuretic peptides.
Vascular mechanisms: viscoelastic properties of large arteries, peripheral vasomotor modulation, endothelial dysfunction.
Cardiac function: changes in stroke volume and cardiac output caused by mechanical and hemodynamic factors, and arrhythmias.
Rheological mechanisms: changes in blood viscosity by anemia, hemodilution, erythrocytosis.
Metabolic activity: hypercapnia and hypoxia, acidosis and alkalosis.
Respiratory activity: spontaneous or device-induced changes in ventilatory mechanics.
Renal mechanisms: salt sensitivity, sodium excretion, renin secretion, tubuloglomerular feedback, hypo/hypervolemia
Genetic susceptibility: genes regulating the level of sympathetic cardiovascular modulation
Diseases affecting the autonomic function: neurodegenerative diseases (e.g.Parkinson's disease), sleep-related breathing disorders, carotid artery disease, arterial hypertension, chronic kidney disease, heart failure, diabetes mellitus, postural orthostatic tachycardia syndrome, orthostatic hypotension/ hypertension, post-COVID 19 syndrome.

EXTRINSIC FACTORS

Environmental factors: seasonal and altitude-related changes; barometric pressure changes (i.e. hypobaric hypoxia); changes in ambient temperature and humidity; sunshine, UV radiation, heat waves, wind chill, air pollution, noise.
Behavioural factors: job strain, physical activity, sleep/wakefulness cycles and jet lag, sleep quality and duration, postural changes, patterns of fluid and sodium intake, eating patterns, smoking/vaping, overeating, fasting, alcohol consumption, energy drinks, recreational drugs, screen time, e-gaming.
Emotional stimuli: psychological stress, depression, burnout.
Antihypertensive treatment factors: inconsistent BP control, poor patient's adherence; improper dosing/titration; dose omission or delays; differences in drugs class, pharmacokinetic and pharmacodynamic profiles.
Other treatments: drugs affecting BP.
Inappropriate BP monitoring: rare and irregular BP measurement; wrong brachial cuff size and placement; monitors sensitive to cardiac arrhythmias; not validated devices (finger/wrist monitors, cuffless devices).

G. Parati et al., J. Hypertens., vol. 41, no. 4, pp. 527–544, Apr. 2023.

Main BPV indices. BPV, blood pressure variability



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Type/time scale	Index [units]	Formula
Frequency domain/short-term and very short-term BPV	High frequency power [$mmHg^2$] [43]	$HF_P = \int_{HF_1}^{HF_2} P(f)df$ *where P(f) is the power spectrum of beat-by-beat BP values by Fast Fourier Transform or by AR modeling, HF_1=0.15 Hz and HF_2=0.40 Hz*
	Low frequency power [$mmHg^2$]	$LF_P = \int_{LF_1}^{HF_1} P(f)df$ *where LF_1=0.04 Hz*
	Very low frequency power [$mmHg^2$]	$VLF_P = \int_{VLF_1}^{LF_1} P(f)df$ *where VLF_1=0.003 Hz*
Frequency domain/short-term BPV	Residual variability [$mmHg^2$] [44]	$RV = \sum_{i=1}^{N}(BP_i - CC)^2$ *where BP_i are N ambulatory BP readings over 24-h, CC is the sum of the 1st and 2nd cycling components fitting the circadian BP pattern, with period of 24 and 12 h respectively, from Fourier analysis*
Complexity domain/short-term and very short-term BPV	Self-similarity scale exponents [45]	α_1 and α_2 *slopes of the regression line fitting in a log-log plot the variability of a detrended fluctuations function over small (<12 beats) and long (≥12 beats) blocks of BP segments respectively*
Complexity domain/short-term and very short-term BPV	Entropy [26]	SampEn *negative natural logarithm of the conditional probability that a BP sequence similar for m points remains similar at the next point*
Dispersion / short, mid, and long-term BPV	Standard deviation [mmHg]	$SD = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(BP_i - \overline{BP})^2}$ *with BP_i=N ambulatory home or office BP readings and $\overline{BP}$=their mean*
	Coefficient of variation [%]	$CV = 100 \times \frac{SD}{\overline{BP}}$
Dispersion / short-term BPV	Weighted standard deviation [mmHg] [46]	$SD_W = \frac{SD_{wake} \times n_{wake} + SD_{sleep} \times n_{sleep}}{n_{wake} + n_{sleep}}$ *where SD_{wake} and SD_{sleep} are the standard deviations of the n_{wake} and n_{sleep} ambulatory BP readings taken over the wake and sleep periods*
Dispersion/long-term BPV	Variability independent of the mean [mmHg] [47]	$VIM = \frac{SD}{\overline{BP}^x} \times [\overline{BP}]^x$ *with SD and* $\overline{\mathrm{BP}}$=standard deviation and mean of visit-to-visit BP measures in an individual, the power x calculated over a population fitting SD and $\overline{\mathrm{BP}}$ with a log-log regression line and $[\overline{BP}]$=*the population average of individual* $\overline{BP}$

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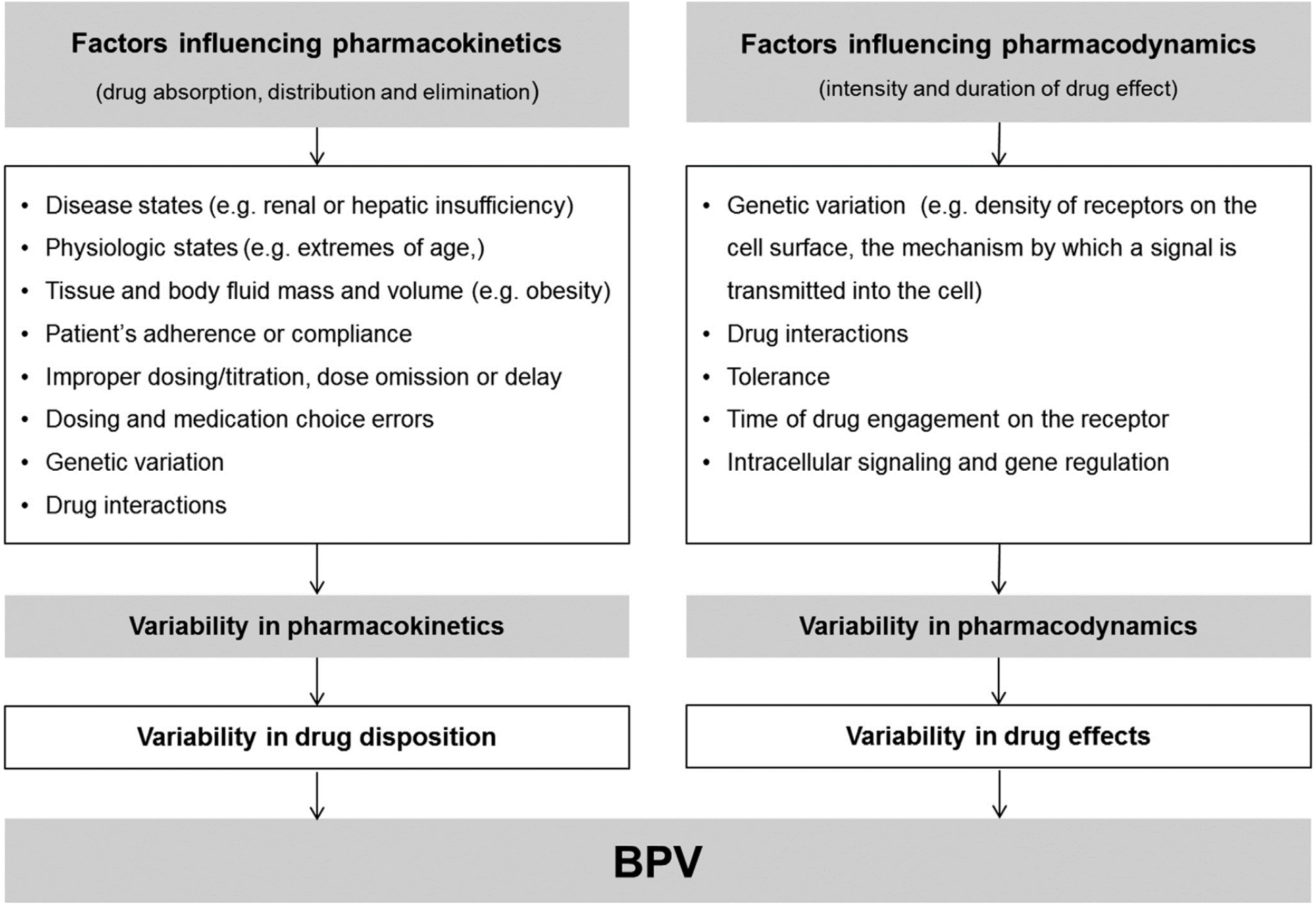
Type/time scale	Index [units]	Formula
Sequence/ short, mid, and long-term BPV	Average real variability [mmHg] [48]	$ARV = \frac{1}{N-1}\sum_{i=1}^{N-1}\lvert BP_{i=1} - BP_i\rvert$ *where BP_i are N ambulatory, or home-, or office- BP readings*
Sequence/ short-term BPV	Time rate [mmHg/min] [49]	$TR = \frac{1}{N-1}\sum_{i=1}^{N-1}\frac{\lvert BP_{i+1}-BP_i\rvert}{t_{i+1}-t_i}$ *where BP_i are N ambulatory BP readings and t_i the time of their measurement*
Instability/short and mid-term BPV	Range [mmHg]	$Range = Max(BP_i) - Min(BP_i)$ *where BP_i are N BP readings, Max and Min their highest and lowest value*
	Peak [mmHg]	$Peak = Max\langle BP_i\rangle - \overline{BP}$
	Through [mmHg]	$Through = \overline{BP} - Min\langle BP_i\rangle$
Patterns/short-term BPV	Nocturnal fall [%]	$NF = \frac{\overline{BP_{Day}} - \overline{BP_{Night}}}{\overline{BP_{Day}}}$ *with $\overline{BP_{Day}}$ and $\overline{BP_{Night}}$ means of ambulatory BP readings over day and night*
	Night/day ratio	$N/D = \frac{\overline{BP_{Night}}}{\overline{BP_{Day}}}$
	Morning surge [mmHg] [50,51]	$MorSur = BP_{Morning} - BP_{LowSleep}$ *$BP_{Morning}$= Average of BP readings during 2 h just after Wake-Up* *$BP_{LowSleep}$= average of 3 BP readings centered on the lowest nighttime reading*[a]
	Siesta dipping [%] [52]	$SieDip = \frac{\overline{BP_{DayW}} - \overline{BP_{DayS}}}{\overline{BP_{DayS}}}$ *where $\overline{BP_{DayW}}$ and $\overline{BP_{DayS}}$ are the mean values of 24-h ambulatory BP readings over the daytime wakeful period and the daytime sleep period*[a]
	Postprandial fall [mmHg] [53]	*difference between a single systolic BP reading just before lunch and a single systolic BP reading 30 min after the lunch*[a]

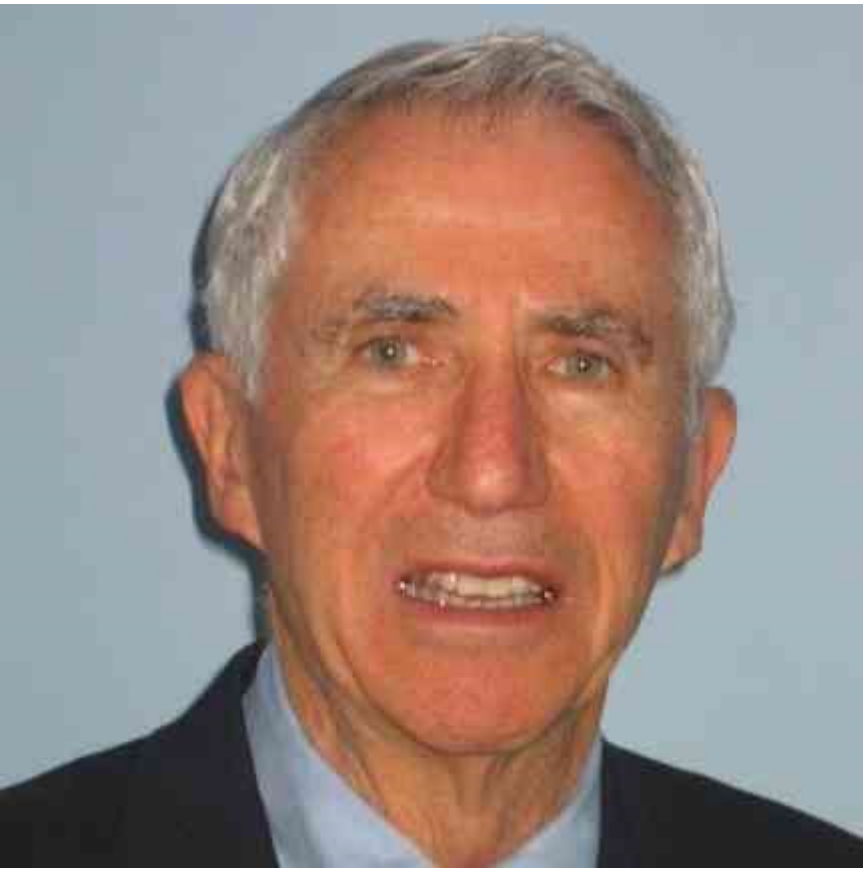
BPV, blood pressure variability.
[a]The literature proposes different formulas and a consensus has not yet been reached.

G. Parati et al., J. Hypertens., vol. 41, no. 4, pp. 527–544, Apr. 2023.



Impact of pharmacokinetic and pharmacodynamic features of antihypertensive drugs on BPV. BPV, blood pressure variability.

G. Parati et al., J. Hypertens., vol. 41, no. 4, pp. 527–544, Apr. 2023.



1930-2022
Nephrologist

NAA Stanley Franklin Debate:
BEST METHOD FOR OUT OF OFFICE BP ASSESSMENT

Con Position: "Home BP Monitoring is the Better Method for Out-of-Office BP Assessment"

Joseph E. Schwartz, PhD
Center for Behavioral and Cardiovascular Health
Columbia University Medical Center, NY

Pro Position: "24-hr Ambulatory BP Monitoring is the Best Method for Out-of-Office BP Assessment"

Ray Townsend, MD
University of Pennsylvania

2023 NAA CONFERENCE

Methodological

BPV ASSESSMENT

- What is the best BP measurement method for each BPV type ?
- What is the optimal frequency of BP measurement for short-term, mid-term or long-term BPV assessment ?
- Which BPV indices should be used for short-term, mid-term and long-term BPV?
- BP Recording conditions to estimate BPV
- Should individuals' behaviour be standardized while investigating short-term BPV over 24-h?
- How to properly assess long-term, visit-to-visit BPV

  - what is the minimum number of visits and BP measures?
  - how to account for changes in treatment ?
  - how relevant is the relationship between time of BP measurement and drug intake?

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ISSUES RELATED TO BPV DATA ANALYSIS

- How to best quantify differences in BPV while accounting for concomitant differences in average BP levels?
- How to explore the independent contribution of BPV to outcome accounting for possible confounders (age, sex, BP average level) ?
- How to assess the interaction between visit-to-visit long-term BPV and seasonal BP changes?
- How to assess the interaction between morning BP surge and nocturnal BP dipping?
- How do the different BPVs (short-term, mid-term, long-term) relate to each other?

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Clinical

BPV MECHANISMS

- What is the relationship of BPV with physiological variables (e.g. Baroreflex sensitivity, muscle sympathetic nerve activity, SpO2, arterial stiffness)?
- What are the main determinants of mid-term and long-term BPV?
- What is the impact of age, sex, genetic and racial factors on BPV indices and predictive power ?
- How do atrial fibrillation and cardiac arrhythmias influence BPV?
- How does cardiac pacing impact BPV?
- How is BPV in acute ischaemic stroke patients with high, normal and low BP?
- What is the link between BPV and white coat and masked hypertension?
- What is the interaction between visit-to-visit long-term BPV and seasonal BP changes?
- Is BP response to laboratory stressors or to office BP measurement (white coat effect) a predictor of daily life BPV?

BPV PROGNOSTIC IMPACT

- Are short-term, mid-term and long-term BPV predictors of cardiovascular disease risk?
- Are short-term, mid-term and long-term BPV predictors of non-cardiovascular outcomes (dementia, cancer, death)?
- Which BPV type is the best predictor of outcome?
- Are systolic and diastolic BPV comparable in risk prediction at different ages and gender?
- What are the threshold levels to identify elevated BPV?
- What is the clinical relevance of BPV changes in critical patients with hypotension/shock?

G. Parati et al., J. Hypertens., vol. 41, no. 4, pp. 527–544, Apr. 2023.

THERAPEUTIC ISSUES

- How to best assess the effects of treatment on BPV? Which indices should be used?
- Is drug-induced BPV reduction accompanied by reduction in events rate?
- How different drug classes affect BPV?
- Is there evidence to consider BPV as a target for treatment? If so, which indices should be the targeted?

G. Parati et al., J. Hypertens., vol. 41, no. 4, pp. 527–544, Apr. 2023.

Box 3 Indications for BPV management in research and clinical settings, based on currently available data and on experts' opinion

- **Standardized methodology for BPV assessment** must be used in terms of BP measurement and indices to estimate BPV
- Currently there are no universally accepted **cut-off values to define elevated BPV**, but some indications are available
- Different types of BP fluctuations may unveil **different patterns of cardiovascular modulation** by control mechanisms
- High BPV was shown to reclassify patients to higher risk category, suggesting a **role for elevated BPV in cardiovascular risk stratification**
- **Elevated short-term BPV and nocturnal BP non-dipping are associated with higher cardiovascular risk**, although no evidence-based specific therapeutic interventions can be recommended yet to reduce BPV and restore nocturnal BP fall

G. Parati et al., J. Hypertens., vol. 41, no. 4, pp. 527–544, Apr. 2023.

Box 3 Indications for BPV management in research and clinical settings, based on currently available data and on experts' opinion

- **Long-acting antihypertensive drugs and drug combinations including long-lasting compounds** may be preferred to avoid iatrogenic increase in BPV and to better smooth down the 24-h BP profile
- **Long-acting CCBs and diuretics** may be preferred to reduce elevated BPV, in absence of clinical indications to choose other specific drug classes
- **ABPM reports in clinical practice and in research** should include:
  -BPV estimates (e.g. 24-h weighted SD of SBP and DBP, or daytime SD and night-time SD of SBP and DBP)
  -An estimate of nocturnal SBP and DBP dipping (expressed as % reduction of daytime values or night/day SBP or DBP ratio)
  -Average 24-h, daytime and night-time HR values and their variability

Hypertension Research
https://doi.org/10.1038/s41440-023-01297-9

ARTICLE

Home Blood Pressure-Centered Management of Hypertension

Peak home blood pressure as an earlier and strong novel risk factor for stroke: the practitioner-based nationwide J-HOP study extended

Kazuomi Kario[1] · Naoko Tomitani[1] · Takeshi Fujiwara[1] · Yukie Okawara[1] · Hiroshi Kanegae[2] · Satoshi Hoshide[1]

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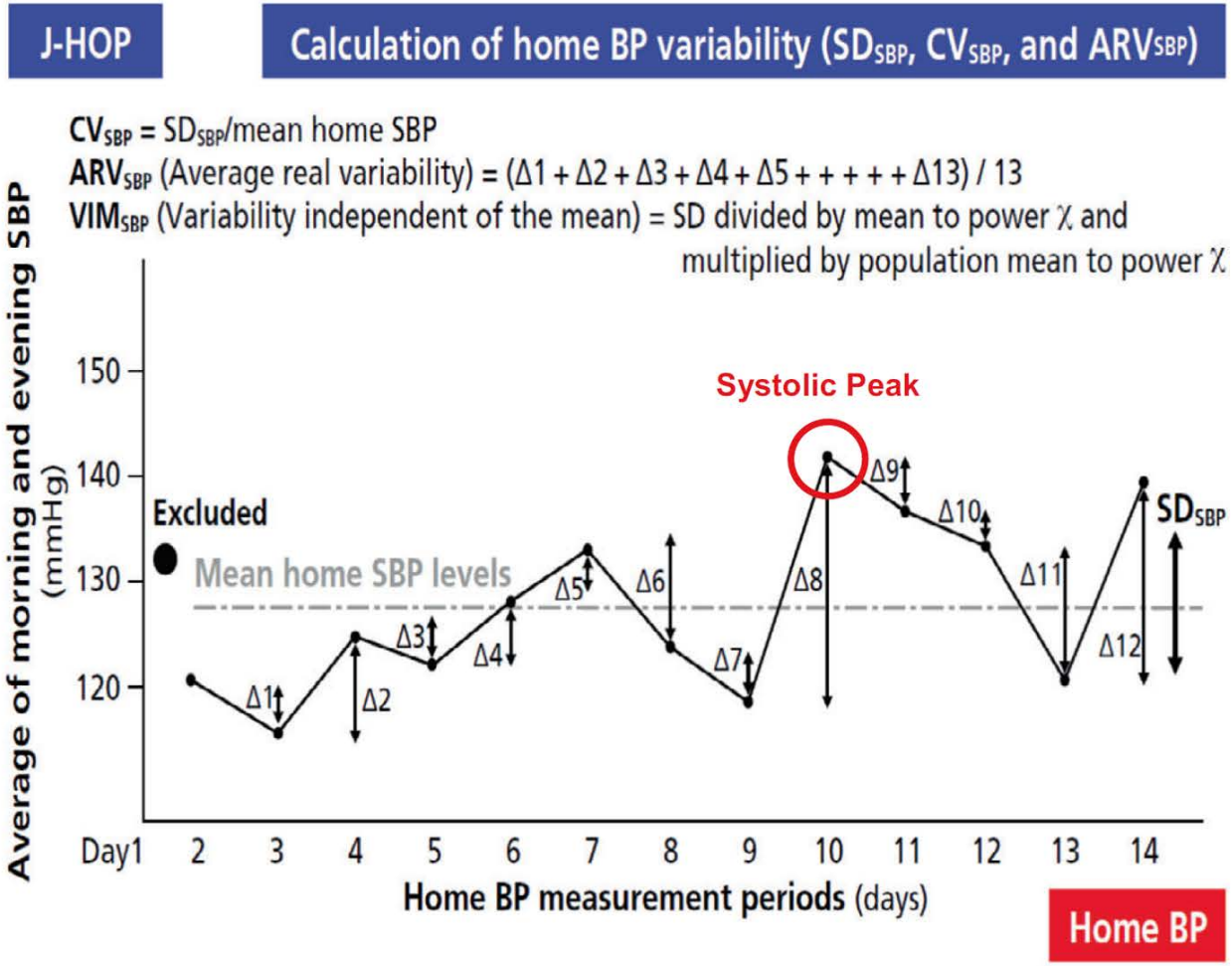
Home blood pressure measures of cardiovascular risk



Average home blood pressure (BP)

Morning (M)
Evening (E)
ME average

Cardiovascular risk

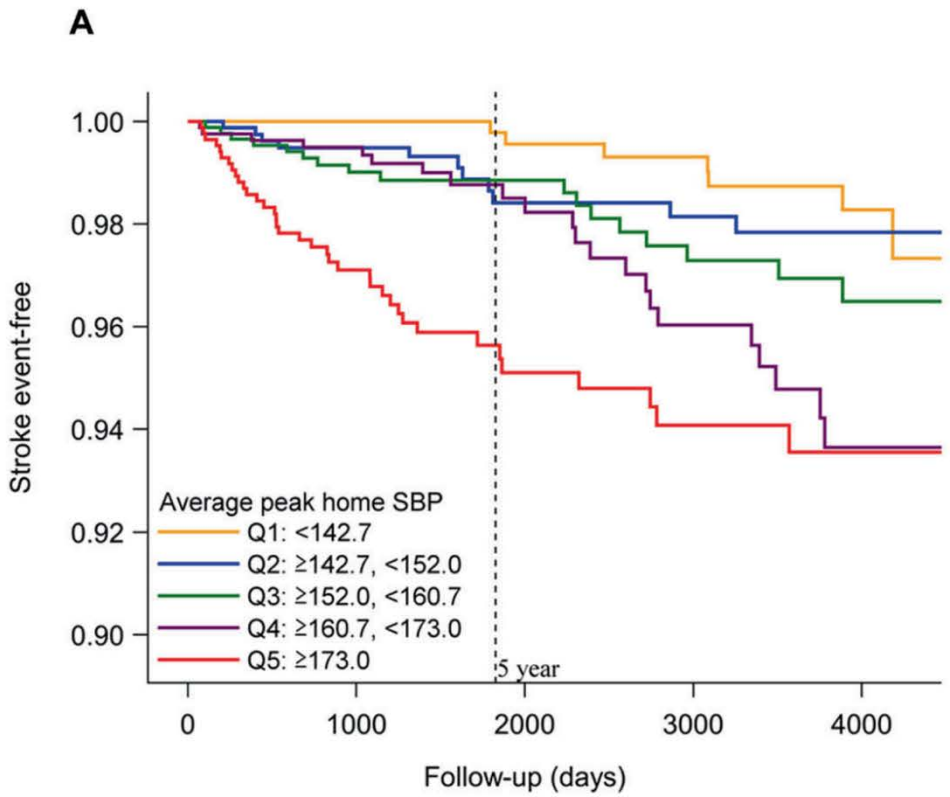
Home BP variability

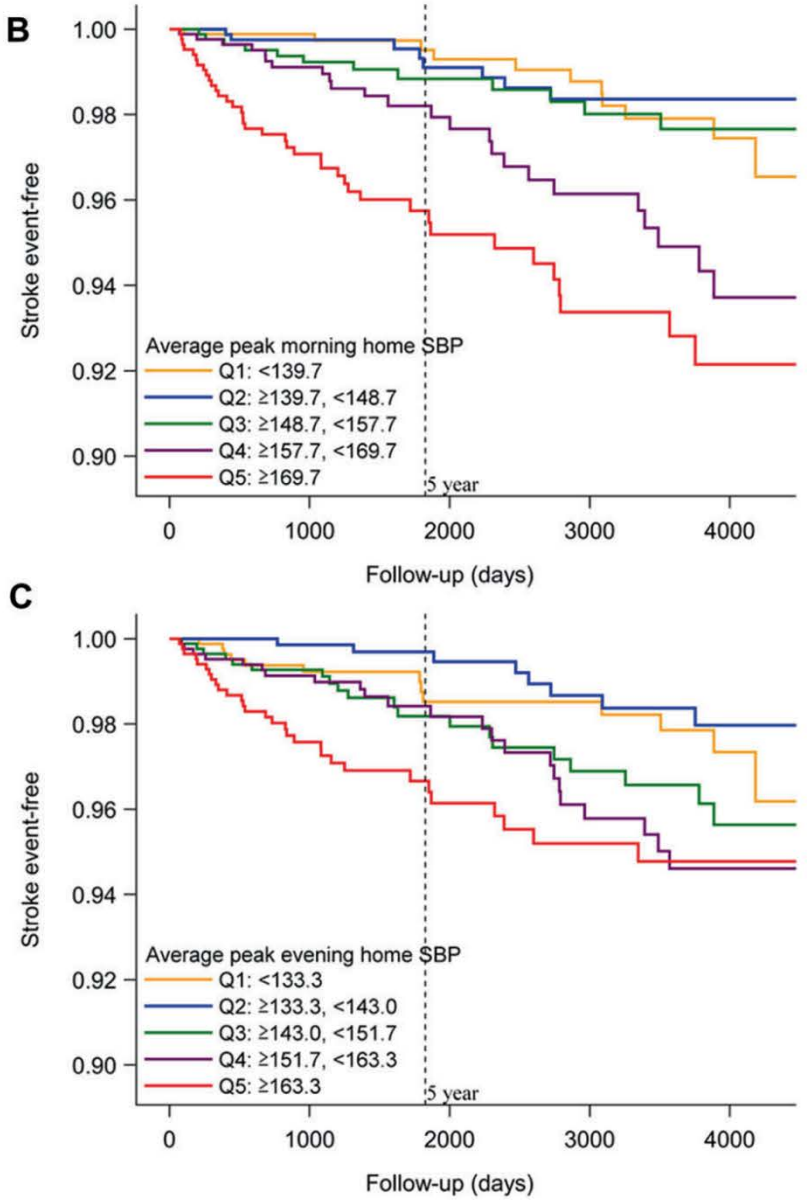
ME difference
Coefficient of variation (CV)
Average real variability (ARV)
Variability independent of the mean (VIM)

Surge home BP

Systolic peak

K. Kario, N. Tomitani, T. Fujiwara, Y. Okawara, H. Kanegae, and S. Hoshide, Hypertens. Res., pp. 1–11, Apr. 2023.





Cumulative incidence of stroke events by average peak home systolic blood pressure quintile (mean follow-up 6.2 ± 3.8 years; 26,205 person-years). Average peak home systolic blood pressure was calculated using both morning and evening home systolic blood pressure values (A), only morning home systolic blood pressure values (B), and only evening home systolic blood pressure values (C). Q indicates quartile; SBP systolic blood pressure

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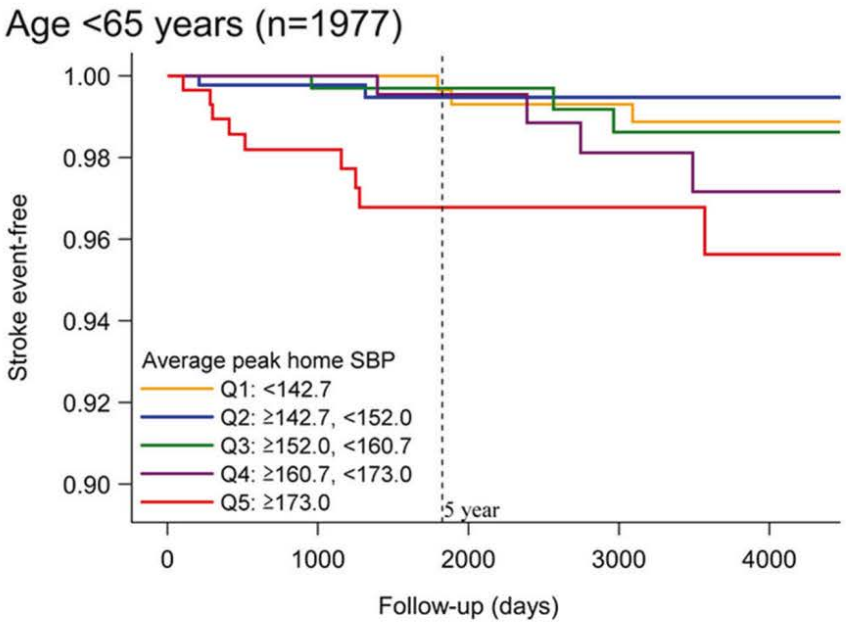

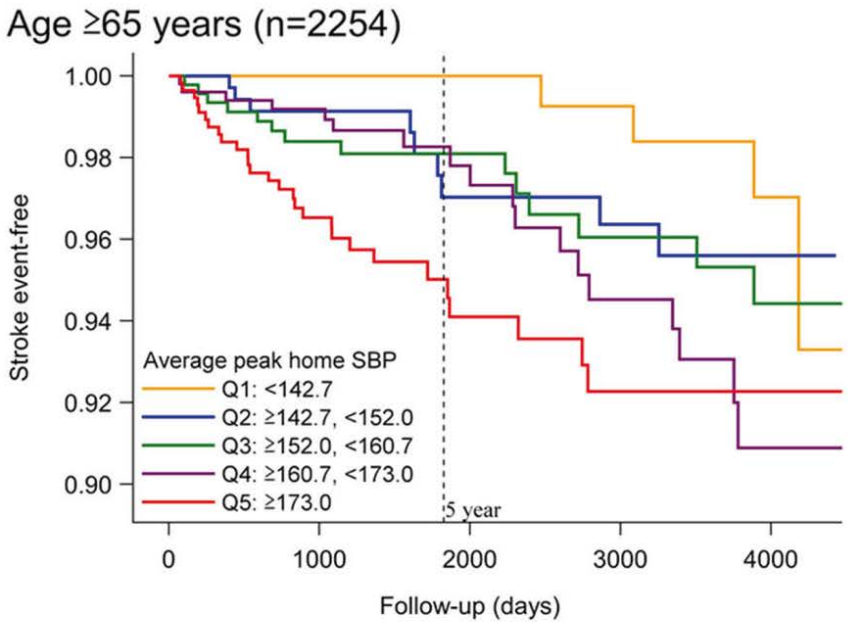

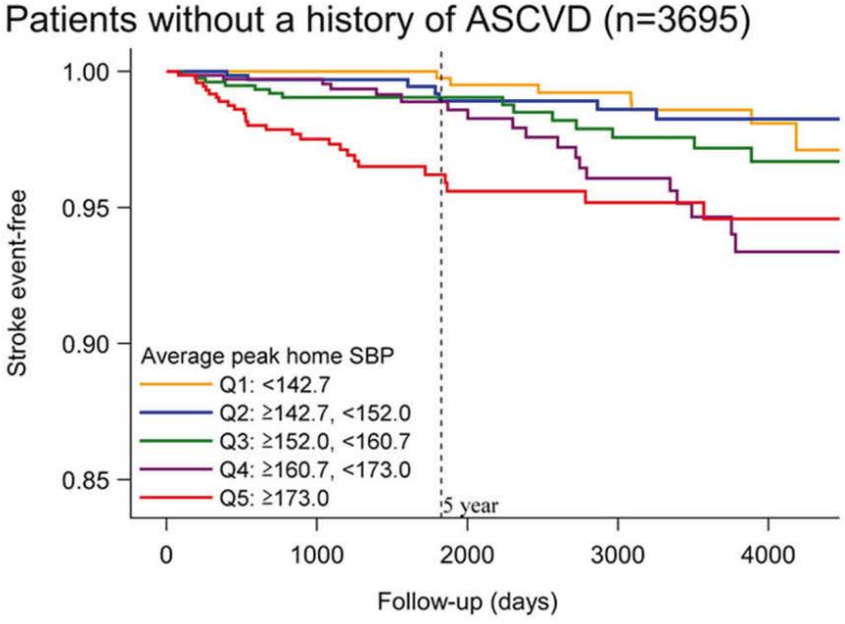

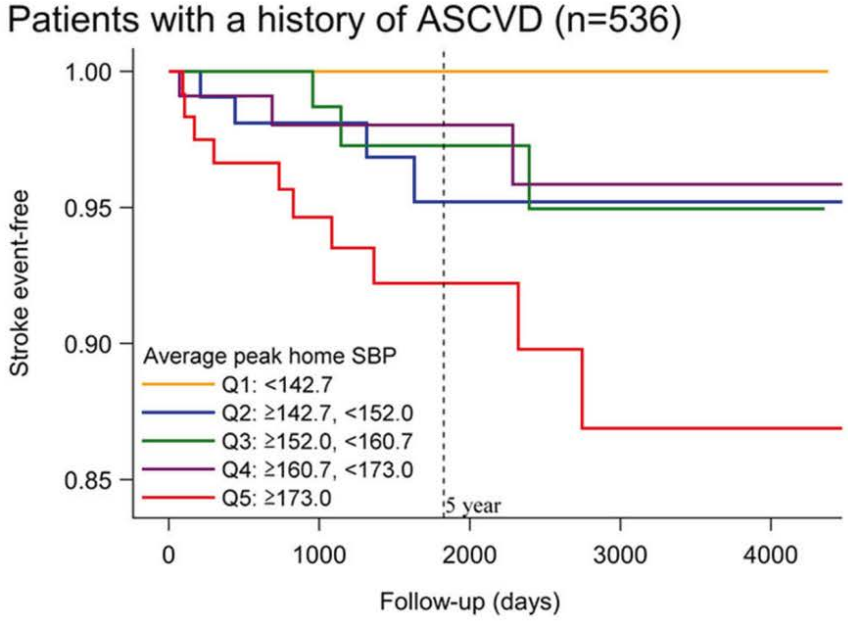

Cumulative incidence of stroke events by average peak home systolic blood pressure quintile, stratified by age or history of atherosclerotic cardiovascular disease. Average peak home systolic blood pressure was calculated using both morning and evening home systolic blood pressure values. ASCVD indicates atherosclerotic cardiovascular events (stroke and coronary artery disease); Q quartile, SBP systolic blood pressure

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Thank you