Prognosis in Relation to Blood Pressure Variability

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Blood pressure variability includes short-term, circadian, and long-term components. Assessment of blood pressure variability requires multiple readings obtained within a single or several visits, by home or 24-hour ambulatory blood pressure monitoring, or by beat-to-beat recordings. Factors that affect visit-to-visit and diurnal blood pressure variability, as reviewed elsewhere, include ethnicity, sex, age, hypertension, body mass index, use of β-blockers, a history of cardiovascular disease, renal dysfunction, diabetes mellitus, a sedentary lifestyle, and socioeconomic position.

The prognostic significance of blood pressure variability remains controversial. Some studies reported association of end-organ damage, cardiovascular events, or mortality with blood pressure variability, whereas others failed to do so or found variability to be inferior to the level of blood pressure. Several publications proposing that the magnitude of the morning blood pressure surge predicted stroke, in particular cerebral hemorrhage, or cardiovascular endpoints remained unconfirmed in recently published large-scale observational studies. This review will address the current controversy on the morning blood pressure surge, highlight the methodological problems in capturing blood pressure variability, and illustrate how large international population studies and a clinical trial do not support blood pressure variability as target in the management of hypertension.

Methodological Issues

Current indexes of blood pressure variability raise methodological issues related to their poor reproducibility, their interdependence, and their association with the level of blood pressure.

Morning Surge—Inconsistent Definitions and Poor Reproducibility

We will use the morning surge in blood pressure as a showcase to highlight how inconsistent definitions and poor reproducibility limit the clinical applicability of indexes of blood pressure variability. In 2003, Kario et al introduced 2 definitions of the morning surge in blood pressure (Figure 1A). The sleep-through morning surge is the difference between the morning pressure (the average blood pressure during the 2 hours after awakening) and the lowest nighttime blood pressure (the average of the lowest pressure and the readings immediately preceding and following the lowest value). The pre-awakening morning surge is the difference between the morning blood pressure (the average blood pressure during the 2 hours after waking up) and the preawakening blood pressure (the average blood pressure during the 2 hours before waking up). Other investigators redefined the preawakening morning surge because the blood pressure differences >1-hour interval prior and after awakening or the blood pressure difference between all readings during sleep and those obtained >2 hours after awakening. Several investigators reported that an exaggerated morning surge predicted outcome. However, using a variety of definitions of a single index of blood pressure variability induces confusion and raises the suspicion that definitions were revised to serve the hypothesis to be proven.
In 2008, we analyzed the substudy on ambulatory blood pressure monitoring to the Systolic Hypertension in Europe (Syst-Eur) trial. Patients underwent 24-hour ambulatory blood pressure monitoring twice before randomization at a 1-month interval and once 10 months after randomization to double-blind placebo. In 173 patients with repeat recordings within 33 days (median), the short-term repeatability coefficients, expressed as percentages of maximal variation, ranged from 35% to 41% for the daytime and nighttime blood pressure, but from 52% to 75% for the sleep-through and the preawakening morning surge, higher values representing worse reproducibility. In 219 patients with repeat recordings within 10 months (median), the corresponding long-term estimates ranged from 45% to 75% for the sleep-through and the preawakening morning surge, higher values representing worse reproducibility. Within individuals, blood pressure levels differ between rapid eye movement sleep and non–rapid eye movement sleep. Rapid eye movement sleep is accompanied by neural sympathetic and electroencephalographic activity similar to that when awake, with distinct cardiovascular effects. In contrast, non–rapid eye movement sleep is characterized by a suppression in neural sympathetic activity, resulting in a decrease in blood pressure. Ambient temperature and season influence blood pressure levels during sleep and during daytime. Cold conditions result in higher morning blood pressure surge and in later sleep stage transition and delayed sympathetic activation. The position of the cuff relative to the heart level introduces variability, in particular during sleep, when subjects cannot consciously control body position. Getting up methods, such as using an alarm clock,

Figure 1. Derivation of the morning blood pressure surge (A) and ARV_{24} (B) from 24-hour ambulatory blood pressure recordings. The sleep-through morning surge is the difference between the morning pressure and the lowest nighttime blood pressure. The preawakening morning surge is the difference between the morning blood pressure and the preawakening blood pressure (see text for more details). The ARV_{24} averages the absolute differences between consecutive readings and thereby accounts for the order of the blood pressure readings. For distinct blood pressure signals, SD can be the same, whereas ARV_{24} is not. ARV_{24} indicates average real variability over 24 hours. Reprinted from Kario et al and Hansen et al. 17
being waked up, or natural awakening, affect blood pressure rising at awakening. For patients on antihypertensive drugs, the times of dosing (eg, morning versus evening) and the duration of action of the drugs administered influence blood pressure level and the diurnal blood pressure variability, including the magnitude of the morning surge.

**Blood Pressure Variability—Association with Blood Pressure Level**

A major problem in many reports is that they assessed target organ damage or the incidence of events as a function of blood pressure variability indexes that are highly dependent on blood pressure level. In the early 1970s, Clement et al assessed blood pressure variability from the SD and the coefficient of variation of blood pressure measurements obtained every 5 minutes for 3 hours in 70 untreated hypertensive patients. Sympathetic activity correlated with the level and the SD of blood pressure, but not with the coefficient of variability, a measure of variability that is less dependent on level than the SD. In the 1980s, Mancia et al, by analyzing continuous 24-hour intra-arterial recordings replicated the observation that SD, but not coefficient of variation, is highly dependent on the blood pressure level. Nevertheless, until today, investigators continue using the SD to capture blood pressure variability.

Other measures of variability, such as the weighted SD, the difference between the maximum minus minimum blood pressure level (MMD) and average real variability (ARV), remains highly dependent on blood pressure level. The weighted SD is the mean of day and night SD values weighted for the number of hours covered by these 2 periods during ambulatory monitoring. ARV is the average of the absolute differences between consecutive readings, weighted for the between-reading time intervals and accounting for the order of the blood pressure readings (Figure 1B). More recently, Rothwell et al proposed blood pressure variability independent of the mean (VIM) as a new index. VIM is the within-subject SD divided by the within-subject mean blood pressure level to the power x and multiplied by the population mean blood pressure level to the power x. The power x is obtained by fitting a curve through a plot of SD against mean blood pressure level, using the model SD=axmean, where x is derived by nonlinear regression. The correlation of VIM with the other indexes of blood pressure variability is high, but VIM does not correlate with the blood pressure level. VIM therefore allows assessing association of outcome with blood pressure variability with little confounding by blood pressure level.

**Morning Blood Pressure Surge**

**Initial Studies**

Kario et al studied stroke prognosis in 519 patients with hypertension on office measurement (63.6% women; mean age, 72.5 years). They assessed silent cerebral infarction by MRI. For analysis, patients were dichotomized according to the 90th percentile of the sleep-through distribution (≥55 mm Hg). During an average follow-up of 41 months (range, 1–68 months), 44 patients experienced a stroke, of whom 2 had a silent stroke. The 53 patients in the top 10th of the sleep-through morning surge distribution, compared with the 466 remaining patients, had a higher baseline prevalence of multiple infarcts (57% versus 33%; P=0.001) and a higher stroke incidence (19% versus 7.3%, P=0.004) than the 466 remaining patients. The top 10 patients were also older (77 versus 72 years), had higher office (171 versus 163 mm Hg) and 24-hour (143 versus 138 mm Hg) systolic blood pressures, and were followed up for a longer period (41 versus 37 months). Because of these disparities, Kario et al matched 46 patients with exacerbated morning surge with 145 control patients for age and 24-hour systolic blood pressure. After matching, the relative risk of stroke in the morning surge compared with the control group was 2.71 (95% confidence interval [CI], 1.05–7.21; P=0.047).

Studies published shortly after Kario’s seminal report were not confirmatory. Among 1430 Japanese recruited in the framework of the Ohkama population study, the preawakening morning surge in systolic blood pressure marginally predicted cerebral hemorrhage (hazard ratio [HR] per 1-SD increase [13.8 mm Hg], 1.34; CI, 0.95–1.89), whereas the prognostic value for ischemic stroke was far from significant (HR, 0.97; CI, 0.79–1.19). Gosse et al recorded 31 cardiovascular events among 507 white hypertensive patients with a mean follow-up of 92 months. With adjustments applied for age and 24-hour systolic blood pressure, the risk of cardiovascular events was not associated with the preawakening systolic blood pressure, calculated as the difference of the first systolic blood pressure after standing up minus the last supine systolic blood pressure at awakening. For each 1-mm Hg increase, the estimate of relative risk amounted to 3.3% (95% CI, 0.8–5.8%).

**Recent Evidence**

Verdecchia et al investigated the relation between the day-to-night blood pressure dip and the early morning surge in a cohort of 3012 initially untreated subjects with essential hypertension. The day-to-night reduction in systolic blood pressure showed a direct association (P<0.0001) with the sleep-through (r=0.56) and the preawakening (r=0.55) morning surge in systolic blood pressure. During a mean follow-up period of 8.4 years, 220 patients died and 268 experienced a cardiovascular event. A blunted sleep-through (≤19.5 mm Hg; the lowest quartile) and preawakening (≤9.5 mm Hg) blood pressure surge were both associated with an excess risk of events (HRs, 1.66 [CI, 1.14–2.42] and 1.71 [CI, 1.12–2.71], respectively). However, neither patients with a high sleep-through (>36.0 mm Hg; the highest quartile) nor those with a high preawakening (>27.5 mm Hg) systolic blood pressure had an increased risk of death or a cardiovascular complication.

We analyzed the International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO). This resource included 12 randomly recruited population cohorts with follow-up of both fatal and nonfatal outcomes. During a median follow-up of 11.4 years, 785 deaths and 611 fatal and nonfatal cardiovascular events occurred in 5645 IDACO participants (mean age, 53.0 years; 54.0% women). Although accounting for covariables and the night:day ratio of systolic blood
pressure, the HR expressing the risk of all-cause mortality in the top 10th of the sleep-through morning surge distribution (≥37.0 mm Hg) compared with the remainder of the study population was 1.32 (CI, 1.09–1.59; Figure 2). For cardiovascular and noncardiovascular mortality, the corresponding HRs were 1.18 (CI, 0.87–1.61) and 1.42 (CI, 1.11–1.80); for all cardiovascular, cardiac, coronary, and cerebrovascular events, the HRs amounted to 1.30 (CI, 1.06–1.60; Figure 2), 1.52 (CI, 1.15–2.00), 1.45 (CI, 1.04–2.03), and 0.95 (CI, 0.68–1.32), respectively. Analyses of the risk associated with the top 10th of the distribution of the preawakening systolic morning surge (≥28.0 mm Hg) generated similar results (Figure 2). Furthermore, the risk of death or a major cardiovascular event in the 50th percentile group of the sleep-through morning surge was over 35% lower (P<0.01) than the average risk in the whole study population.\textsuperscript{21}

In the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study, Bombelli et al\textsuperscript{23} analyzed ambulatory blood pressure data of 2011 people. Cardiovascular mortality showed a positive relation with the sleep-through morning surge in unadjusted analyses (HR, 1.3; CI, 1.1–1.6), which disappeared after adjustment for covariables (HR, 0.9; CI, 0.7–1.1). Cardiovascular mortality, irrespective of adjustment, was unrelated to the preawakening morning surge (P≥0.12). Along similar lines, in this Italian population study,\textsuperscript{23} there were no differences in the risks of total and cardiovascular mortality when the bottom and top tenths of the distributions of the sleep-through and preawakening morning surge were compared (P≥0.39).
Blood Pressure Variability

In addition to the morning surge, diurnal blood pressure variability encompasses the day-to-night changes in the blood pressure level and reading-to-reading blood pressure variability in 24-hour ambulatory blood pressure recordings. Beat-to-beat recordings allow capturing blood pressure variability, even during short-time intervals.41

Diurnal Blood Pressure Variability

In 1988, O’Brien et al41 reported for the first time that an abnormal circadian blood pressure profile with decreased nighttime dipping had a more frequent history of stroke. Subsequent studies of populations36–39 and hypertensive cohorts41–43 usually corroborated that an elevated nocturnal blood pressure is a harbinger of an unfavorable outcome. In spite of the apparent concordance between these previously published large-scale outcome studies,36–46 several potential limitations required further clarification of the prognostic accuracy of the daytime versus the nighttime ambulatory blood pressure. Many studies considered only fatal outcomes36,37,44,45 or did not have the power to study cause-specific cardiovascular end points.36,37,39,43 Investigators dichotomized the night:day blood pressure ratio or applied widely different definitions of dipping status or of the daytime and nighttime intervals.

The IDACO consortium therefore assessed the prognostic accuracy of day versus night ambulatory blood pressure in 7458 people enrolled in prospective population studies in Europe, China, and Uruguay.47 Median follow-up was 9.6 years. Adjusted for daytime blood pressure, confounders, and cardiovascular risk factors, nighttime blood pressure predicted (P<0.01) total (n=983), cardiovascular (n=387), and noncardiovascular (n=560) mortality.47 Conversely, adjusted for nighttime blood pressure and other covariates, daytime blood pressure predicted only noncardiovascular mortality (P<0.05), with lower blood pressure levels being associated with increased risk. Both daytime and nighttime blood pressure consistently predicted (P<0.05) all cardiovascular events (n=943) and stroke (n=420).47 Adjusted for nighttime blood pressure, daytime blood pressure lost prognostic significance for cardiac events (n=525; P≥0.07). Adjusted for the 24-hour blood pressure, the night:day blood pressure ratio predicted mortality, but not fatal combined with nonfatal events. Participants with a systolic night:day blood pressure ratio value of ≥1 were older, at higher risk of death, and died at an older age than those whose night:day ratio was normal (≥0.80 to <0.90).47

In contrast to commonly held views, the IDACO analysis showed that daytime blood pressure adjusted for nighttime blood pressure predicted fatal combined with nonfatal cardiovascular events, except in treated patients, in whom antihypertensive drugs probably reduced blood pressure during the day, but not at night.47 The increased mortality in patients with higher nighttime than daytime blood pressure probably indicated reverse causality. The IDACO findings confirmed that both daytime and nighttime blood pressure hold valuable prognostic information.47 They supported the conclusion that recording blood pressure during the whole day should be the standard in clinical practice.

A 2014 IDACO publication48 highlighted that identification of truly low-risk white-coat hypertension requires setting thresholds simultaneously to 24-hour, daytime, and nighttime blood pressures. In line with the 2007 report,47 we also demonstrated that isolated nocturnal hypertension predicted cardiovascular outcome even in patients who are normotensive on office or on ambulatory daytime blood pressure measurement.49

Reading-to-Reading Blood Pressure Variability

We also assessed blood pressure variability from the SD and ARV (Figure 3) in 24-hour ambulatory recordings in the IDACO population.17 Higher diastolic ARV in 24-hour ambulatory blood pressure recordings predicted (P≤0.03) total (HR, 1.13; CI, 1.07–1.19) and cardiovascular (HR, 1.21; CI, 1.12–1.31) mortality and all types of fatal combined with nonfatal end points (HR, ≥1.07), with the exception of cardiac and coronary events (HR, ≤1.02; P≥0.58). Similarly, higher systolic ARV in 24-hour ambulatory recordings predicted (P<0.05) total (HR, 1.11; CI, 1.04–1.18) and cardiovascular (HR, 1.17; CI, 1.07–1.28) mortality and all fatal combined with nonfatal end points (HR, ≥1.07), with the exception of cardiac and coronary events (HR, ≤1.03; P≥0.54). SD predicted only total and cardiovascular mortality. The incremental cardiovascular risk explained by adding ARV to models already including 24-hour ambulatory blood pressure level and other covariates was <1%. Our report established that reading-to-reading blood pressure variability is an independent risk factor, significant in a statistical but not in a clinically meaningful manner. It highlighted that the level of the 24-hour blood pressure remains the primary blood pressure–related risk factor to account for in clinical practice.17

Within-Visit and Between-Visit Blood Pressure Variability in a Prospective Study

In a randomly recruited Flemish population sample (n=2944; mean age, 44.9 years; 50.7% women), highly trained observers measured blood pressure 5× consecutively at each of 2 home visits and recorded the incidence of adverse health outcomes in relation to the variability of systolic blood pressure at enrolment.5 We computed VIM, MMD, and ARV for within-visit variability (WVV) and for within-visit combined with between-visit variability. We captured between-visit variability from VIM and MMD. During a median follow-up of 12 years, 401 deaths occurred and 311 participants experienced a fatal or nonfatal cardiovascular event. Overall (10 readings ≥2 visits), systolic blood pressure variability averaged (SD) 5.45 (2.82) units for VIM, 15.9 (8.4) mm Hg for MMD, and 4.08 (2.05) mm Hg for ARV. In multivariable-adjusted analyses, overall and within- and between-visit blood pressure variability did not predict total or cardiovascular mortality or the composite of any fatal plus nonfatal cardiovascular end point. For instance, the HRs for all cardiovascular events combined in relation to overall variability as captured by VIM, MMD, and ARV were 1.05 (CI, 0.96–1.15), 1.06 (CI, 0.96–1.16), and 1.08 (CI, 0.98–1.19), respectively. By contrast, mean systolic blood pressure level was a significant predictor of all end points under
study, independent of blood pressure variability. These findings suggest that, in the general population, within-subject blood pressure variability does not have any prognostic significance over and beyond systolic blood pressure level.

Within-Visit and Between-Visit Blood Pressure Variability in Syst-Eur

Results from randomized clinical trials constitute the strongest evidence for the role and reversibility of any cardiovascular...
risk factor. In the Syst-Eur trial (NCT02088450), we investigated whether systolic blood pressure variability determines prognosis over and beyond level. Using a double-blind design, we randomly allocated 4695 patients (≥60 years) with isolated systolic hypertension (160–219/95 mm Hg) to active treatment or matching placebo. Active treatment consisted of nitrendipine (10–40 mg/d) with possible addition of enalapril (5–20 mg/d) and hydrochlorothiazide (12.5–25.0 mg/d). We assessed whether on-treatment systolic blood pressure level predicted all end points (P<0.0003). Active treatment reduced cardiovascular complications by decreasing systolic blood pressure level (+0.69 mm Hg, P<0.001) more than placebo, whereas the between-group differences in systolic blood pressure variability were not significant, averaging 0.29 units (P=0.20) for VIM and 0.07 mm Hg (P=0.47) for WVV (Figure 4). Active treatment reduced (P≤0.048) cardiovascular (−28%), cerebrovascular (−40%), and cardiac (−24%) end points. In analyses dichotomized by the median, patients with low versus high VIM had similar event rates (P=0.14). Low versus high WVV was not associated with event rates (P≥0.095), except for total and cardiovascular mortality on active treatment, which were higher with low WVV (P≤0.0003). In multivariable-adjusted Cox models, systolic blood pressure level predicted all end points (P≤0.0043), whereas VIM did not predict any adverse outcome (P=0.058). Except for an inverse association with total mortality (P=0.042), WVV was not predictive (P=0.15). Sensitivity analyses, from which we excluded blood pressure readings within 6 months after randomization, 6 months before an event, or both, were confirmatory. The double-blind placebo–controlled Syst-Eur trial irrefutably demonstrated that blood pressure lowering treatment reduces cardiovascular complications by decreasing systolic blood pressure level but not systolic variability and that higher systolic blood pressure level predicted risk without material contribution of variability.

**Beat-to-Beat Blood Pressure Variability**

In 256 untreated Chinese patients referred to a hypertension clinic, we assessed the association of target organ with VIM, MMD, and ARV, determined from 10-minute beat-to-beat, 24-hour ambulatory, and 7-day home blood pressure recordings. Effect sizes (standardized β) were computed using multivariable regression models. In beat-to-beat recordings, left ventricular mass index (n=128) was not (P=0.18) associated with systolic blood pressure level, but increased with all 3 systolic variability indices (+2.97–3.53 g/m², P<0.04). The urinary albumin:creatinine ratio increased (P≤0.03) with systolic blood pressure level (+1.14–1.17 mg/mmol, according to the model) and MMD (+1.18 mg/mmol), and aortic pulse wave velocity increased with systolic blood pressure level (+0.69 m/s, P<0.001). In 24-hour recordings, all 3 indexes of organ damage increased (P<0.03) with systolic blood pressure.
level, whereas the associations with systolic blood pressure variability were nonsignificant (P≥0.15) except for an increase in aortic pulse wave velocity (P<0.05 with VIM (+0.16 m/s) and MMD (+0.17 m/s). In home blood pressure recordings, the urinary albumin:creatinine ratio (+1.27–1.30 mg/mmol) and aortic pulse wave velocity (+0.36–0.40 m/s) increased (P<0.05) with systolic blood pressure level, whereas all associations of target organ damage with the variability indexes were nonsignificant (P≥0.07). In summary, while accounting for systolic blood pressure level, associations of target organ damage with systolic blood pressure variability were readily detectable in beat-to-beat recordings, least noticeable in home recordings, with 24-hour ambulatory monitoring being informative only for aortic pulse wave velocity.34

Conclusions
The recent evidence with regard to the prognostic value of the morning surge highlighted important issues. First, the morning surge of blood pressure, irrespective of its definition, is only a weak predictor of cardiovascular risk, attaining significance only in the top 10% of the distribution in studies with large sample size.10-21 Second, the risk associated with the morning surge is confounded by the day-to-night blood pressure difference or ratio and therefore by the timing of intake of blood pressure lowering medications.22 Finally, assessment of the risk of the morning surge requires a sufficient number of blood pressure readings during sleep and the completion of a diary that differentiates the awake from the sleeping period of the day.21 In the IDACO analyses, these 2 requirements eliminated 4850 of 11786 available participants.21 We are therefore on the side of the conclusion of Bombelli et al23 that the morning surge seems to be an epiphenomenon of 24-hour blood pressure variability, and that the morning surge represents only a tiny part of the whole-day blood pressure variability.34

Moving to blood pressure variability in general, recent publications8,11-13 reviewed elsewhere33,34 suggested that clinicians might reduce stroke incidence more by targeting systolic blood pressure variability along with level, preferentially using calcium-channel blockers,6,11-13 which might result in less blood pressure variability than other antihypertensive drugs classes. These recommendations, not endorsed by current guidelines,20 largely originated from observational population studies,5,56 or cohort analyses that enrolled high-risk patients with hypertension,31 diabetes mellitus,57-58 a history of stroke or transient ischemic attack,11 or renal failure.98-61 Other methodological issues that might have confounded are categorization of continuous variability measures for risk prediction,51 the application of variability indexes that are dependent on blood pressure level,51 and the limitation of end points to mortality. While addressing these issues in our population studies,3,17 we were never able to identify blood pressure variability as a clinically meaningful cardiovascular risk factor. In particular, our Syst-Eur analysis,52 in line with current recommendations, is strong evidence supporting the idea that blood pressure level, not variability, remains centerfold in the primary and secondary prevention of blood pressure–related cardiovascular complications. Although this does not preclude that blood pressure variability remains a target in clinical research, in particular if captured by beat-to-beat recordings,34 the current large international population studies and the Syst-Eur randomized clinical trial52 do not support blood pressure variability as prime target in the management of hypertension in clinical practice.

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None.

References


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### Response to Prognosis in Relation to Blood Pressure Variability: Con Side of the Argument

**Kazuomi Kario**

I agree with the opinion of Asayama et al. that blood pressure (BP) variability (BPV) is not yet a well-validated prime target that is superior to the average of BP values. However, intermittent BP measurement at 30-minute intervals by ambulatory BP monitoring may underestimate the impact of BP variability and morning BP surge (MBPS), and the inconsistent MBPS and BPV results obtained by ambulatory BP monitoring may be attributable to the different populations examined in the relevant studies. MBPS is one of the phenotypes of BPV. BPV is most extensively exaggerated in the morning, and the risk of cardiovascular events is highest in the morning, suggesting that MBPS is the important phenotype of BPV. The clinical relevance of MBPS and BPV is different between younger normotensive adults of the population study and the high-risk elderly hypertensive subjects with advanced arterial stiffness. Thus, population-based studies that include normotensive younger adults may underestimate the impact of BPV on cardiovascular events.

The effect of recent antihypertensive treatment using home morning BP values may have contributed to the negative MBPS results evaluated only at the baseline in the recent prospective study by Verdeccchia et al. The large International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes (IDACO) database clearly demonstrated that the top 10th percentile of MBPS values remained a significant independent risk for coronary artery disease, suggesting that the risk of BPV would be curvilinear rather than linear with the pathological threshold, as found for stroke in our Japanese study. The IDACO database demonstrates that MBPS is not an independent risk for stroke. This may be because of racial differences in the demographics of patients with cardiovascular disease. Because the cardiovascular risk is the highest and the BP-lowering effect of the conventional antihypertensive medication used once-daily is the lowest in the morning, we should now focus on the treatment of morning hypertension in consideration of morning BP levels and variability as the therapeutic target.

### References


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