

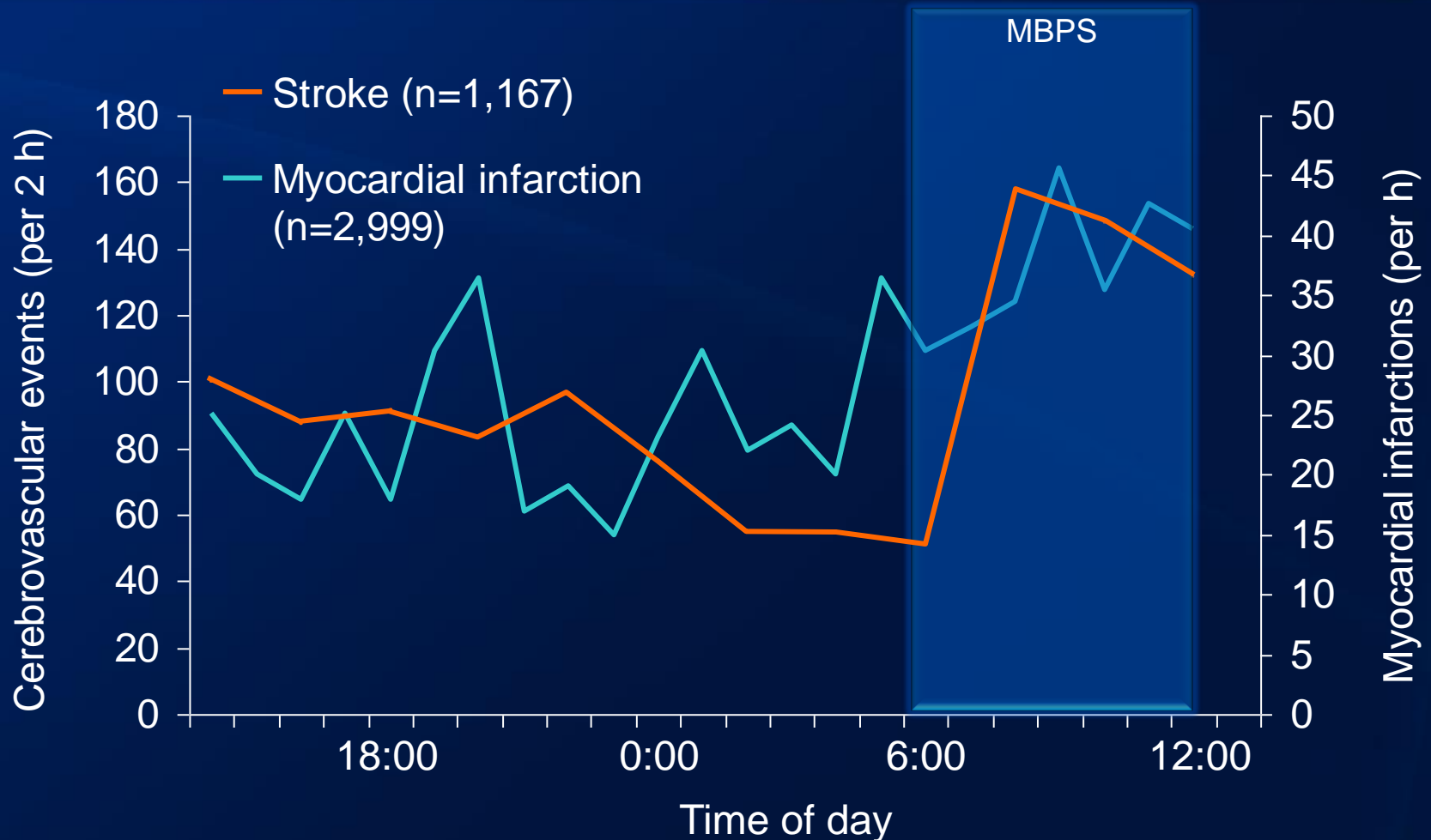
2017 춘계심혈관통합학술대회

Optimal Treatment Strategy for Morning Blood Pressure Surge and Nocturnal Hypertension

Jae Hyuk Choi, MD

Hangang Sacred Heart Hospital
Hallym University, College of Medicine

Increased risk of Stroke and Myocardial infarction during the morning



Muller et al. *N Engl J Med* 1985;313:1315–1322

Marler et al. *Stroke* 1989;20:473–476

Morning Surge in Blood Pressure as a Predictor of Silent and Clinical Cerebrovascular Disease in Elderly Hypertensives

A Prospective Study

Kazuomi Kario, MD; Thomas G. Pickering, MD; Yuji Umeda, MD; Satoshi Hoshide, MD; Yoko Hoshide, MD; Masato Morinari, MD; Mitsunobu Murata, MD; Toshio Kuroda, MD; Joseph E. Schwartz, PhD; Kazuyuki Shimada, MD

Background—Cardiovascular events occur most frequently in the morning hours. We prospectively studied the association between the morning blood pressure (BP) surge and stroke in elderly hypertensives.

Methods and Results—We studied stroke prognosis in 519 older hypertensives in whom ambulatory BP monitoring was performed and silent cerebral infarct was assessed by brain MRI and who were followed up prospectively. The morning BP surge (MS) was calculated as follows: mean systolic BP during the 2 hours after awakening minus mean systolic BP during the 1 hour that included the lowest sleep BP. During an average duration of 41 months (range 1 to 68 months), 44 stroke events occurred. When the patients were divided into 2 groups according to MS, those in the top decile (MS group; MS \geq 55 mm Hg, n=53) had a higher baseline prevalence of multiple infarcts (57% versus 33%, $P=0.001$) and a higher stroke incidence (19% versus 7.3%, $P=0.004$) during the follow-up period than the others (non-MS group; MS <55 mm Hg, n=466). After they were matched for age and 24-hour BP, the relative risk of the MS group versus the non-MS group remained significant (relative risk=2.7, $P=0.04$). The MS was associated with stroke events independently of 24-hour BP, nocturnal BP dipping status, and baseline prevalence of silent infarct ($P=0.008$).

Conclusions—In older hypertensives, a higher morning BP surge is associated with stroke risk independently of ambulatory BP, nocturnal BP falls, and silent infarct. Reduction of the MS could thus be a new therapeutic target for preventing target organ damage and subsequent cardiovascular events in hypertensive patients. (*Circulation*. 2003;107:1401-1406.)

Key Words: blood pressure ■ stroke ■ hypertension ■ cerebral infarction ■ cerebral ischemia

Morning Surge as a predictor of SCI

Measures	MS Group (n=53)	Non-MS Group (n=466)
Baseline data		
SCI	Relative Risk 2.7	
Prevalence, %	70†	48
Average number	2.3±2.6†	1.3±2.6
Multiple SCIs‡		
Prevalence, %	57*	33
Prospective data		
Clinical stroke incidence, %	19†	7.3

Data are shown as mean±SD or percentages.

* $P < 0.001$, † $P < 0.01$.

‡ > 2 silent infarcts.

Kario K. Circulation. 2003;107: 1401-1406

519 elderly
hypertensive
patients (mean 72
yrs)

F/U average of 41
Ms

Morning Surge
group

- MS > 55 mmHg

Kario K,

**“Morning Hypertension:
The Strongest Independent Risk
Factor for Stroke in Elderly
Hypertensive Patients”**

**Sleep-trough morning BP
Top decile >55 mmHg
77-year old**

Morning Blood Pressure Surge, Dipping, and Risk of Ischemic Stroke in Elderly Patients Treated for Hypertension

Sante D. Pierdomenico,^{1,2} Anna M. Pierdomenico,² and Franco Cuccurullo^{1,2}

BACKGROUND

The independent prognostic significance of morning surge (MS) in blood pressure (BP) is not yet clear. We investigated the association between MS in systolic BP (SBP) and risk of ischemic stroke in elderly patients treated for hypertension.

METHODS

Occurrence of ischemic stroke was evaluated in 1,191 elderly patients treated for hypertension (aged 60–90 years). Patients were divided according to tertiles of MS in SBP in the population as a whole, dipping status, and group-specific tertiles of MS in SBP in dippers and nondippers.

RESULTS

During follow-up (9.1 ± 4.9 years, range 0.4–20 years), 139 ischemic strokes occurred. The event rate per 100 patient-years was 1.28. After adjustment for various covariates, Cox regression analysis showed that stroke risk was not significantly associated with tertiles of MS in SBP in

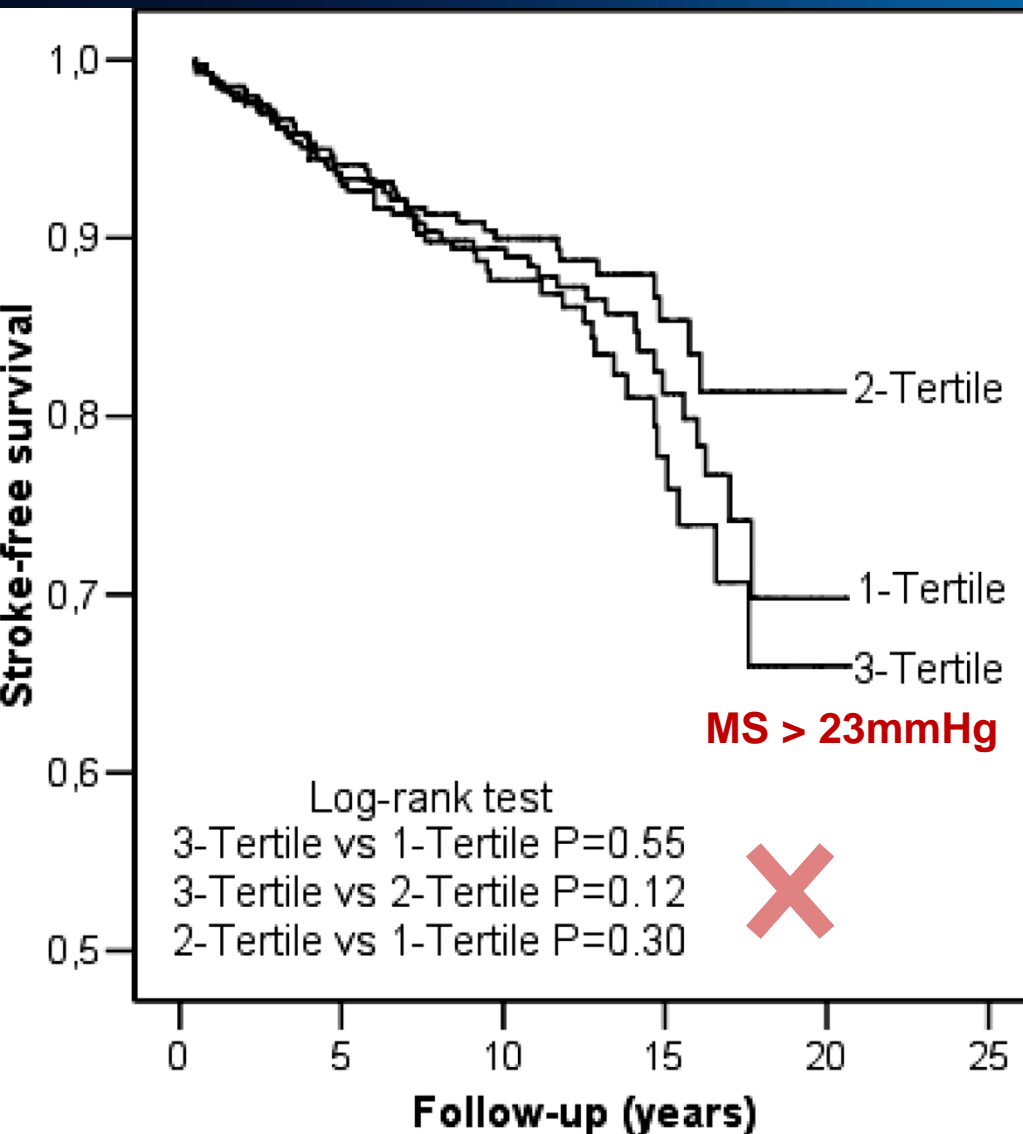
the population as a whole. When nondippers and dippers were analyzed separately by group-specific tertiles of MS in SBP, stroke risk was not associated with MS in nondippers. Conversely, in dippers, stroke risk was significantly higher in the third tertile (>23 mm Hg) of MS in SBP (hazard ratio, 2.08; 95% confidence interval, 1.03–4.23; $P = 0.04$). Additional analysis showed that stroke risk was significantly and similarly higher in dippers with MS >23 mm Hg and in nondippers than in dippers with MS <23 mm Hg.

CONCLUSIONS

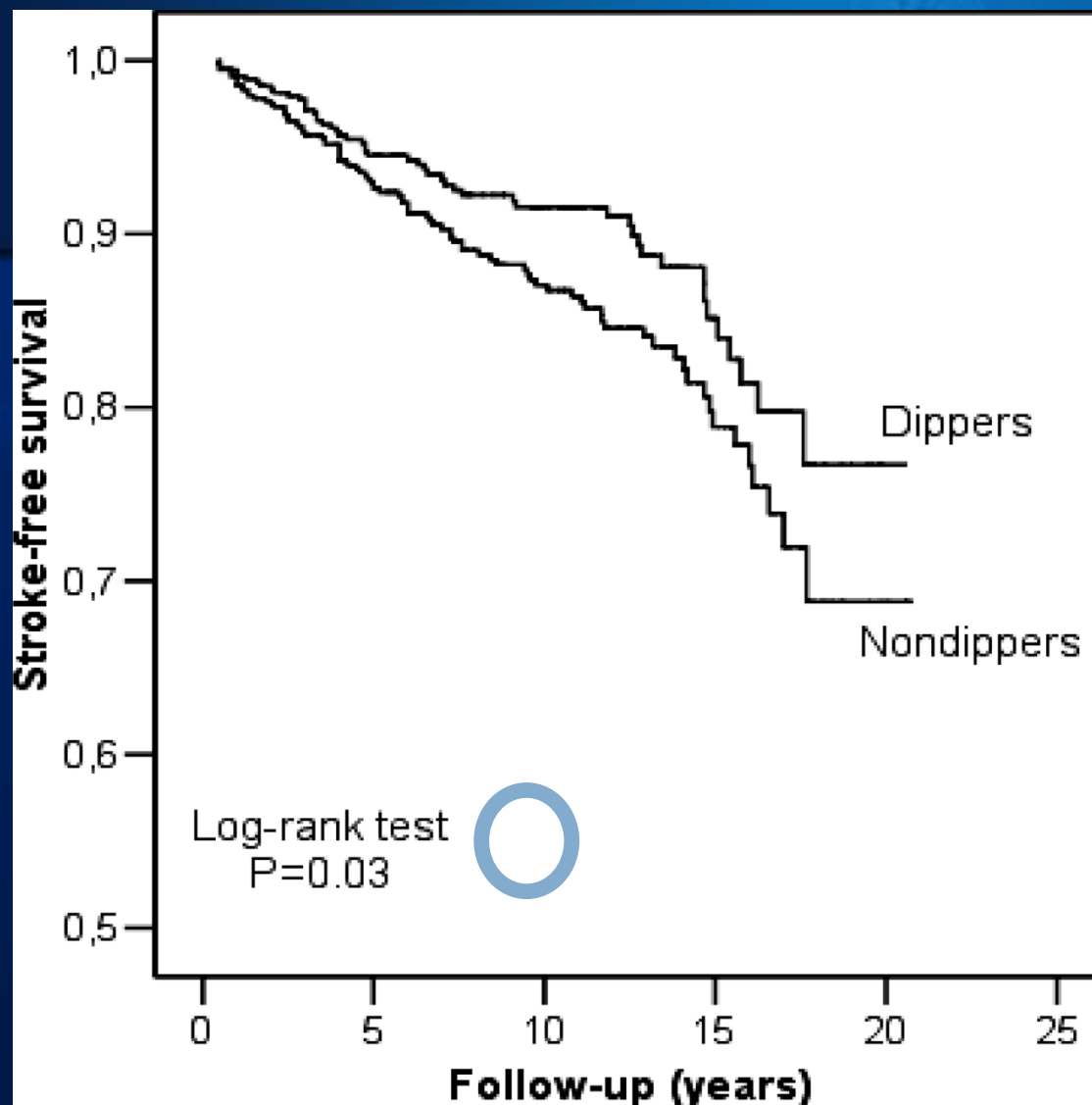
In elderly patients treated for hypertension, high MS in SBP predicts stroke in dippers but not in nondippers. Nondippers are at high stroke risk with or without MS >23 mm Hg.

Keywords: ambulatory blood pressure; blood pressure; dippers; hypertension; nondippers; morning surge; stroke.

doi:10.1093/ajh/hpt170



- ▶ 1,191 elderly patients treated for hypertension (60–90 yrs)
- ▶ F/U (9.1 ± 4.9 years)
- ▶ 139 ischemic strokes occurred



Pierdomenico et al. American Journal of Hypertension 27(4) April 2014

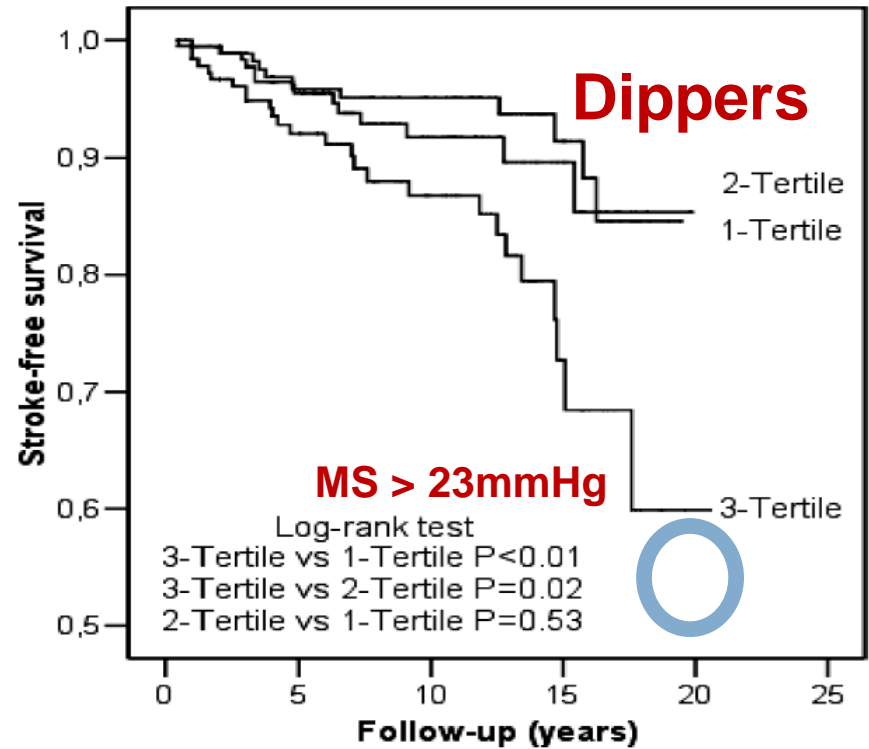
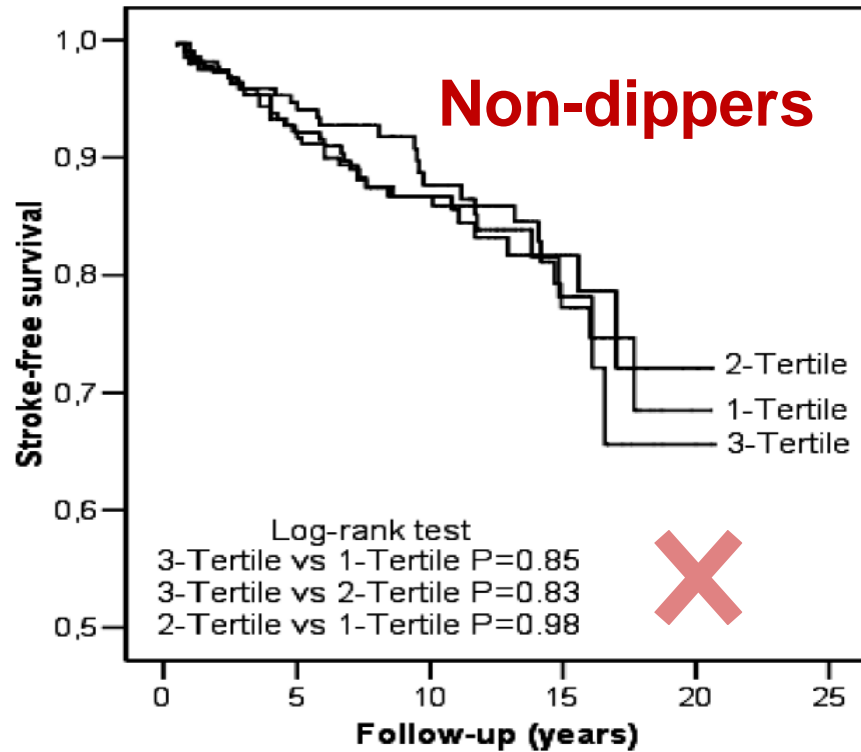


Figure 3. Stroke-free survival curves for nondippers by group-specific tertiles of morning surge in systolic blood pressure.

Figure 4. Stroke-free survival curves for dippers by group-specific tertiles of morning surge in systolic blood pressure.

CONCLUSIONS

In elderly patients treated for hypertension, high MS in SBP predicts stroke in dippers but not in nondippers. Nondippers are at high stroke risk with or without MS >23 mm Hg.

Relationship Among Morning Blood Pressure Surge, 24-Hour Blood Pressure Variability, and Cardiovascular Outcomes in a White Population

Michele Bombelli, Danilo Fodri, Elena Toso, Mario Macchiarulo, Matteo Cairo, Rita Facchetti, Raffaella Dell’Oro, Guido Grassi, Giuseppe Mancia

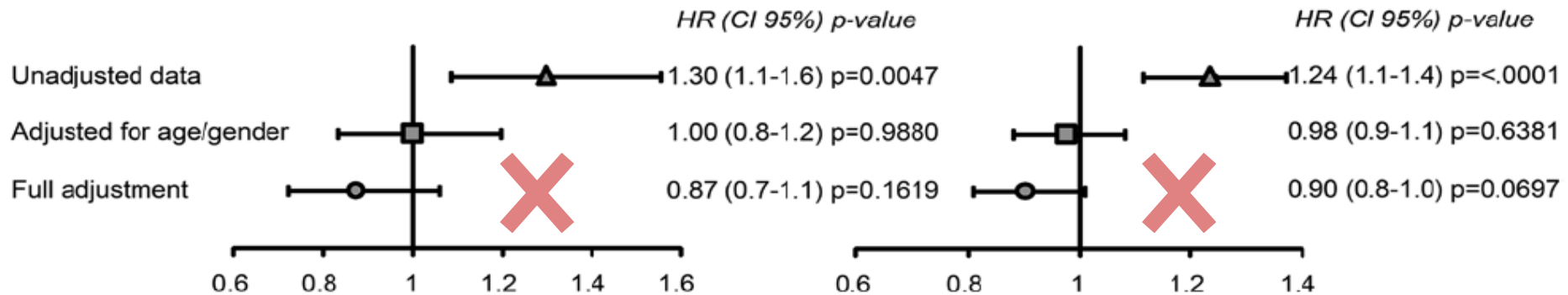
Abstract—Cardiovascular events have their greatest prevalence in the early morning period. Whether this is attributable to an arousal-dependent blood pressure (BP) increase is far from being clear. It is also not clear to what extent this phenomenon reflects overall 24-hour BP variability. In 2051 subjects (aged 25–74 years) representative of the population of Monza (Italy), we measured 24-hour ambulatory systolic BP (SBP) and calculated the difference between the 2-hour average values after morning arousal and the lowest 3 or average 2-hour values before arousal (morning BP surge 1 and 2, respectively). For either measure, we sought the relationship with a variety of indices of 24-hour SBP variability and collected information on (1) the occurrence of cardiovascular and all cause deaths during a follow-up of ≈16 years and (2) the appearance of echocardiographic left ventricular hypertrophy after 10 years from the baseline visit. Morning SBP surge 1 was directly related to indices of 24-hour SBP variability, including those made independent on the magnitude of the day–night SBP difference. There was a weak positive relationship between morning SBP surge 1 and the risk of cardiovascular and all-cause death, which disappeared after adjustment for confounders. This was the case also for development of left ventricular hypertrophy. Morning SBP surge 2 was smaller, inconsistently related to 24-hour SBP variability and not at all related to fatal events or new-onset left ventricular hypertrophy. In a white population, morning BP surge was not found to be an independent predictor of cardiovascular death, all-cause death, or development of high cardiovascular risk (as documented by new-onset cardiac damage) even when appropriately assessed by measures that reflect its association with 24-hour BP variability. (*Hypertension*. 2014;64:943-950.) • [Online Data Supplement](#)

Key Words: blood pressure ■ blood pressure monitoring, ambulatory ■ cardiovascular diseases
■ morbidity ■ mortality

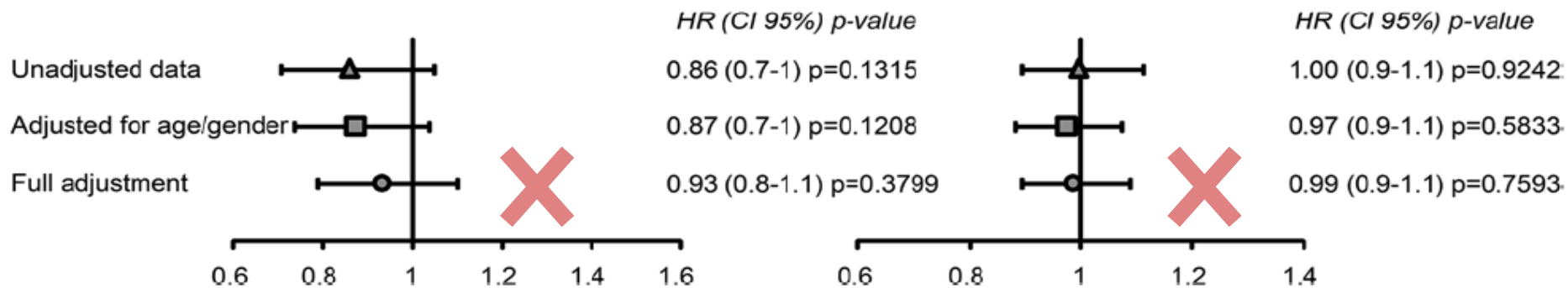
CV death

All cause death

Sleep-trough Surge

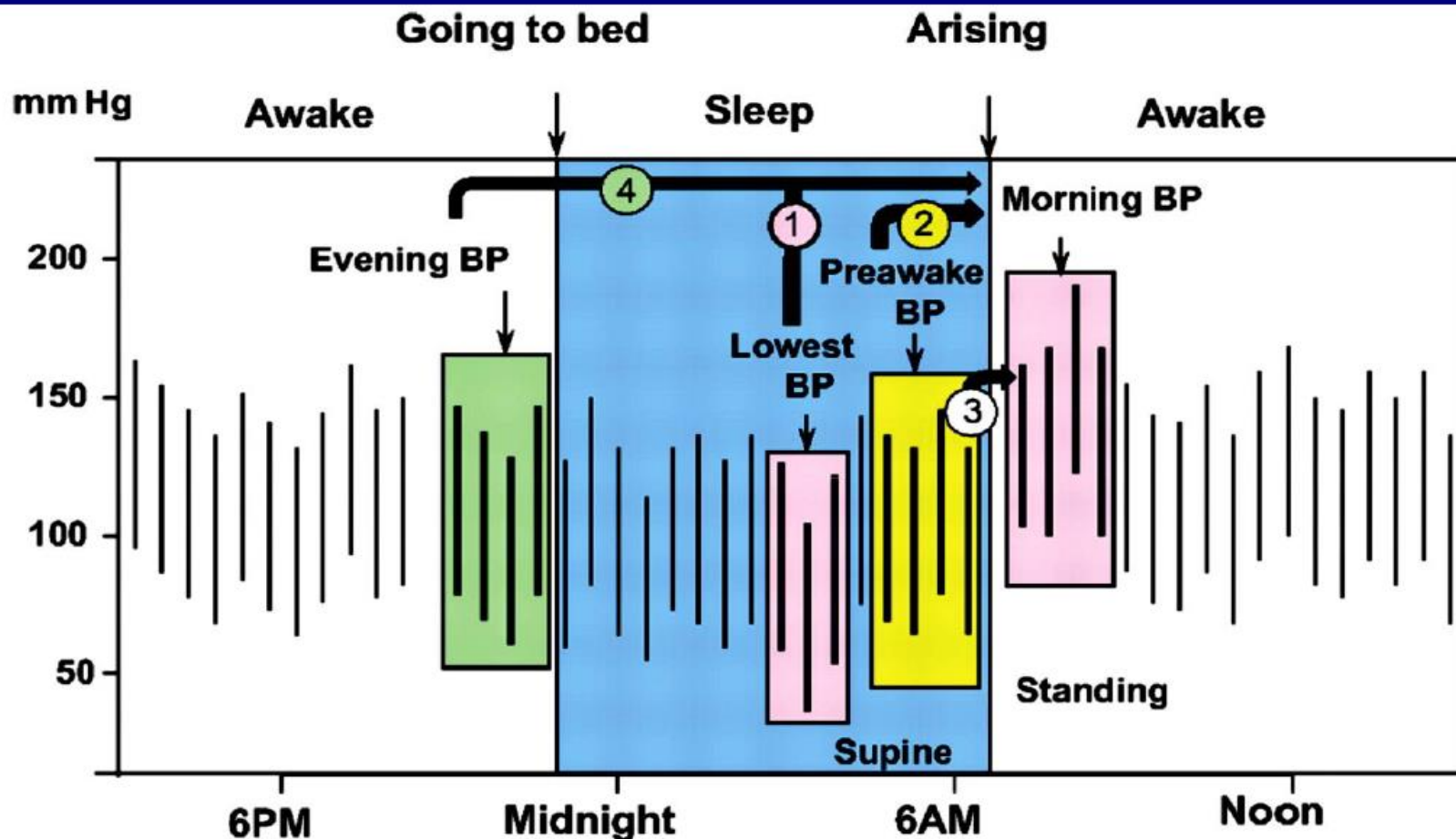


Pre-waking Surge



variability and not at all related to fatal events or new-onset left ventricular hypertrophy. In a white population, morning BP surge was not found to be an independent predictor of cardiovascular death, all-cause death, or development of high cardiovascular risk (as documented by new-onset cardiac damage) even when appropriately assessed by measures that reflect its association with 24-hour BP variability. (*Hypertension*. 2014;64:943-950.) • [Online Data Supplement](#)

Definitions of morning, nighttime, and evening blood pressure measurements and morning blood pressure surge



- ① Sleep-trough surge = Morning SBP - Lowest nighttime SBP
- ② Prewaking surge = Morning SBP - Preawake SBP
- ③ Rising BP surge = Morning SBP on rising - SBP on supine <30 min before rising
- ④ ME difference = Morning SBP - Evening SBP (by home BP self-measured)

SBP, systolic BP

TIME Available

Ambulatory Blood Pressure Monitoring

Day-Night Dip and Early-Morning Surge in Blood Pressure in Hypertension Prognostic Implications

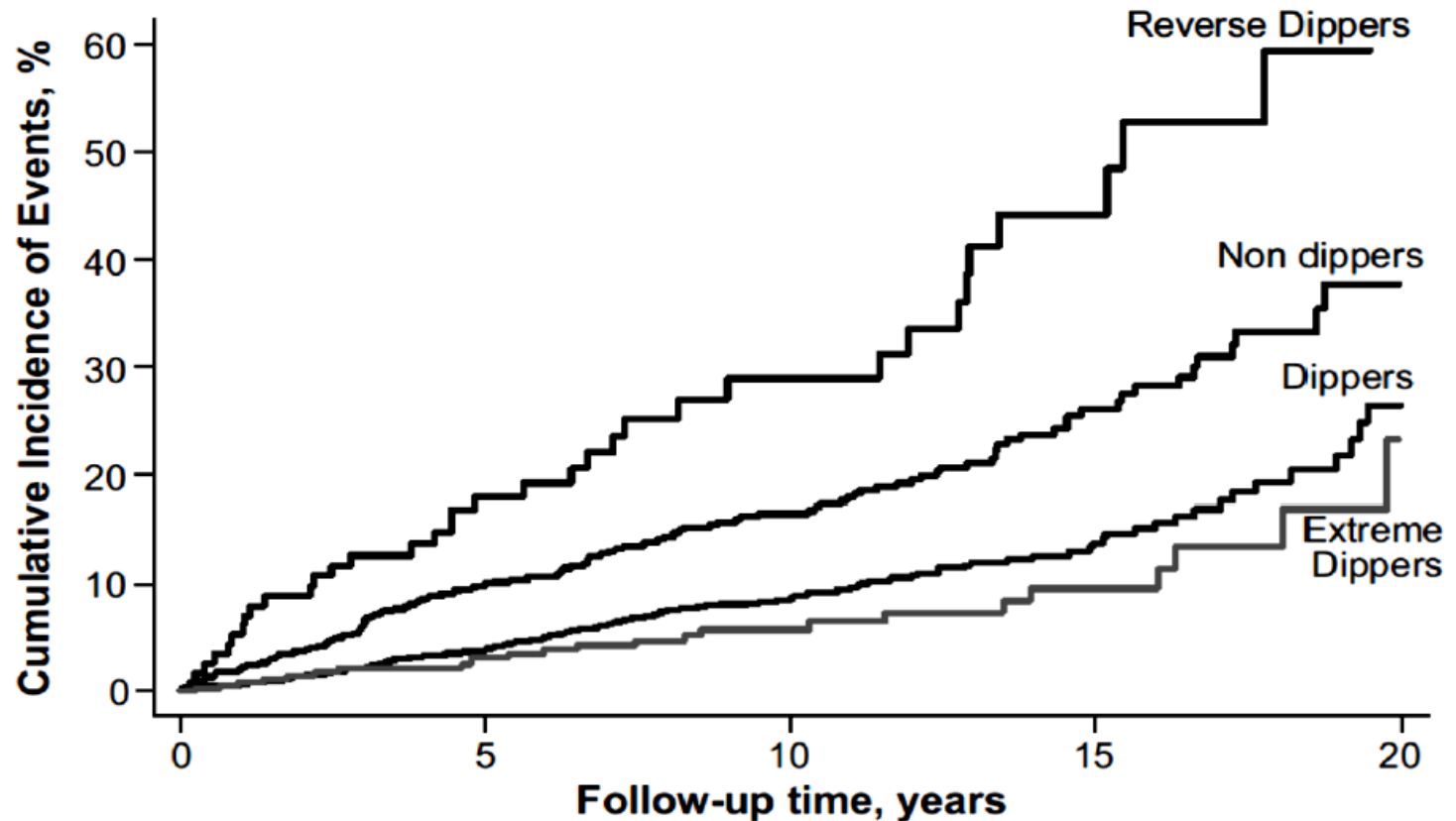
Paolo Verdecchia, Fabio Angeli, Giovanni Mazzotta, Marta Garofoli, Elisa Ramundo, Giorgio Gentile, Giuseppe Ambrosio, Gianpaolo Reboldi

See Editorial Commentary, pp 8–9

Abstract—We investigated the relationship between the day-night blood pressure (BP) dip and the early morning BP surge in an cohort of 3012 initially untreated subjects with essential hypertension. The day-night reduction in systolic BP showed a direct association with the sleep trough ($r=0.564$; $P<0.0001$) and the preawakening ($r=0.554$; $P<0.0001$) systolic BP surge. Over a mean follow-up period of 8.44 years, 268 subjects developed a major cardiovascular event (composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and heart failure requiring hospitalization) and 220 subjects died. In a Cox model, after adjustment for predictive covariates, including age, sex, diabetes mellitus, cigarette smoking, total cholesterol, left ventricular hypertrophy on ECG, estimated glomerular filtration rate, and average 24-hour systolic BP, a blunted sleep trough (≤ 19.5 mm Hg; quartile 1) and preawakening (≤ 9.5 mm Hg; quartile 1) BP surge was associated with an excess risk of events (hazard ratio, 1.66 [95% CI, 1.14–2.42]; $P=0.009$; hazard ratio, 1.71 [95% CI, 1.12–2.71]; $P=0.013$). After adjustment for the same covariates, neither the dipping pattern nor the measures of early morning BP surge were independent predictors of mortality. In conclusion, in initially untreated subjects with hypertension, a blunted day-night BP dip was associated with a blunted morning BP surge and vice versa. In these subjects, a blunted morning BP surge was an independent predictor of cardiovascular events, whereas an excessive BP surge did not portend an increased risk of events. (*Hypertension*. 2012;60:34-42.)

Key Words: hypertension ■ dippers ■ nondippers ■ blood pressure monitoring ■ sleep
■ morning blood pressure surge ■ ambulatory blood pressure

Kaplan-Meier curves reporting the cumulative incidence of cardiovascular disease in the 4 categories of dipping pattern



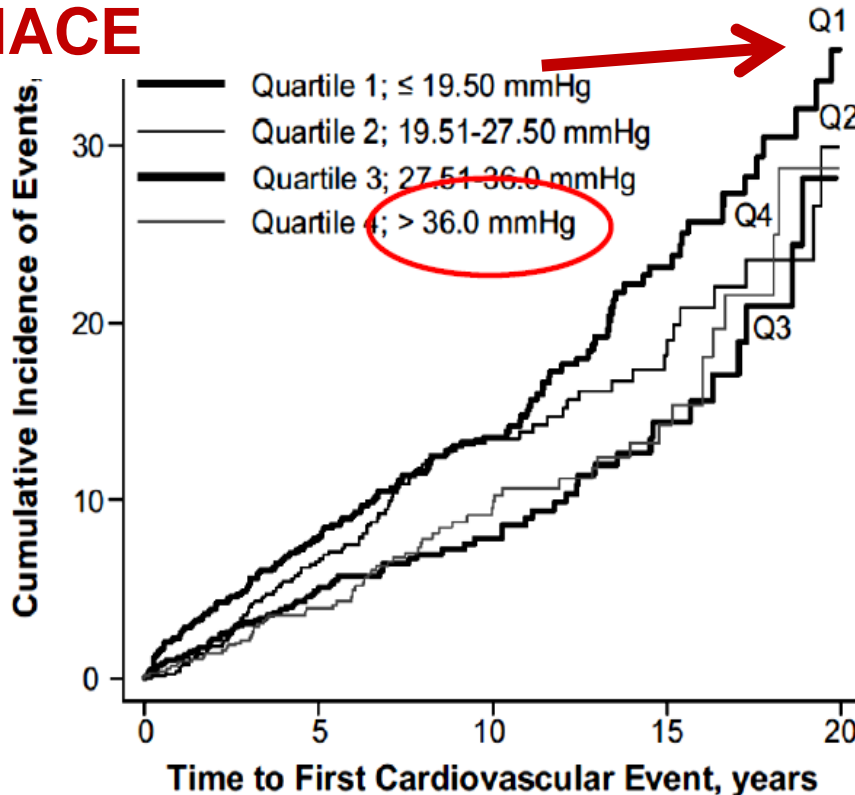
Number at risk

Reverse dippers	116	72	34	14	4
Non dippers	835	552	303	117	20
Dippers	1647	1140	583	211	34
Extreme dippers	408	286	135	59	11

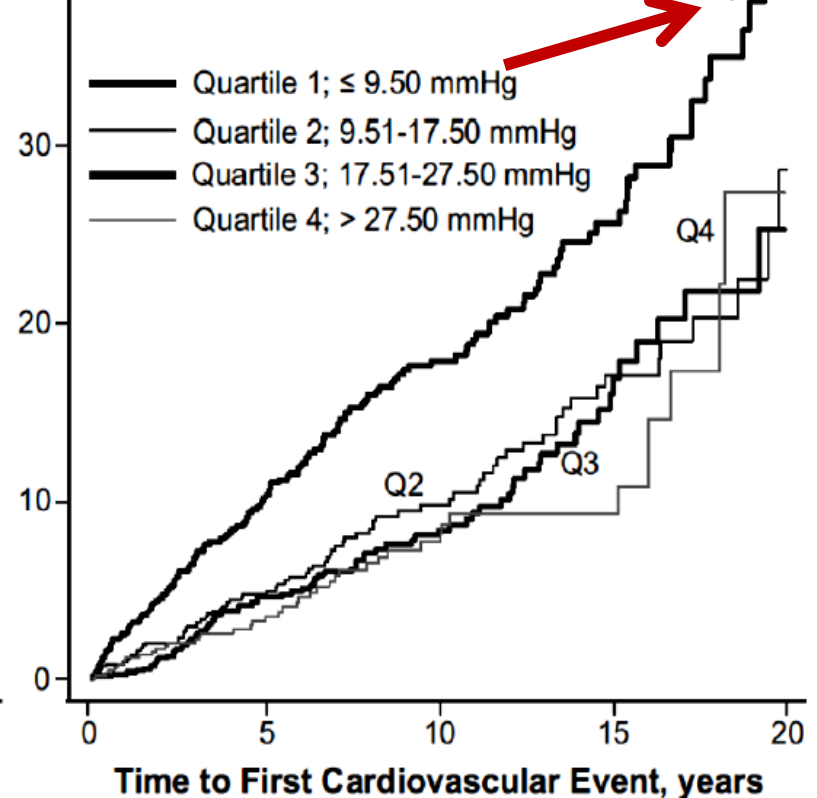
Kaplan-Meier curves reporting the cumulative incidence of cardiovascular disease in the 4 quartiles

MACE

40 | Sleep-Trough Systolic BP Surge



40 | Pre-Awakening Systolic BP Surge



Number at risk

Quartile 1	780	544	306	136	36
Quartile 2	776	520	249	97	10
Quartile 3	715	490	262	87	14
Quartile 4	737	499	240	81	9

Number at risk

Quartile 1	773	534	290	126	32
Quartile 2	753	531	270	118	19
Quartile 3	879	587	315	95	11
Quartile 4	603	401	182	62	7

Verdecchia P,

“In these subjects, a blunted morning BP surge was an independent predictor of cardiovascular events, whereas an excessive BP surge did not portend an increased risk of events.”

Morning Blood Pressure Surge



Benign physiologic response?

OR

Poor prognostic pathologic response?

Prognostic Significance of the Morning Blood Pressure Surge in Clinical Practice: A Systematic Review

James Peter Sheppard,^{1,2} James Hodgkinson,² Richard Riley,³ Una Martin,⁴ Susan Bayliss,³ and Richard J. McManus¹

BACKGROUND

An exaggerated morning blood pressure surge (MBPS) may be associated with stroke and other cardiovascular events, but the threshold at which an MBPS becomes pathological is unclear. This study aimed to systematically review the existing literature and establish the most appropriate definition of pathological MBPS.

METHODS

A MEDLINE search strategy was adapted for a range of literature databases to identify all prospective studies relating an exaggerated MBPS to cardiovascular endpoints. Hazard ratios (HRs) were extracted and synthesized using random-effects meta-analysis.

RESULTS

The search strategy identified 2,964 unique articles, of which 17 were eligible for the study. Seven different definitions of MBPS were identified; the most common was a prewaking surge (mean blood pressure for 2 hours after wake-up minus mean blood pressure for 2 hours before wake-up; n = 6 studies). Summary meta-analysis gave no clear

evidence that prewaking MBPS (defined by a predetermined threshold: >25–55 mm Hg) was associated with all cardiovascular events (n = 2 studies; HR = 0.94, 95% confidence interval (CI) = 0.39–2.28) or stroke (n = 2 studies; HR = 1.26, 95% CI = 0.92–1.71). However, using a continuous scale, which has more power to detect an association, there was evidence that a 10 mm Hg increase in MBPS was related to an increased risk of stroke (n = 3 studies; HR = 1.11, 95% CI = 1.03–1.20).

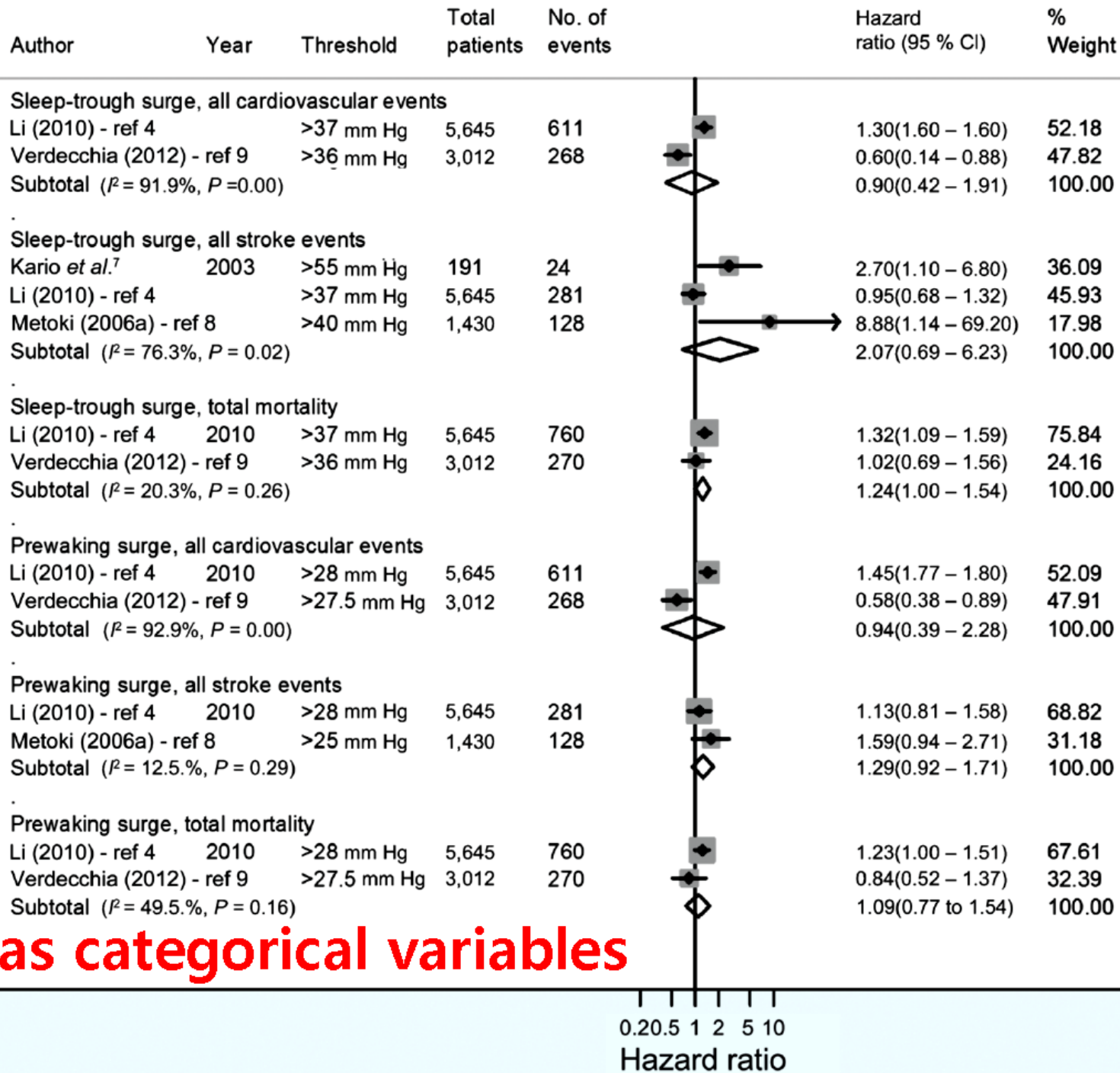
CONCLUSIONS

These findings suggest that when measured and analyzed as a continuous variable, increasing levels of MBPS may be associated with increased risk of stroke. Large, protocol-driven individual patient data analyses are needed to accurately define this relationship further.

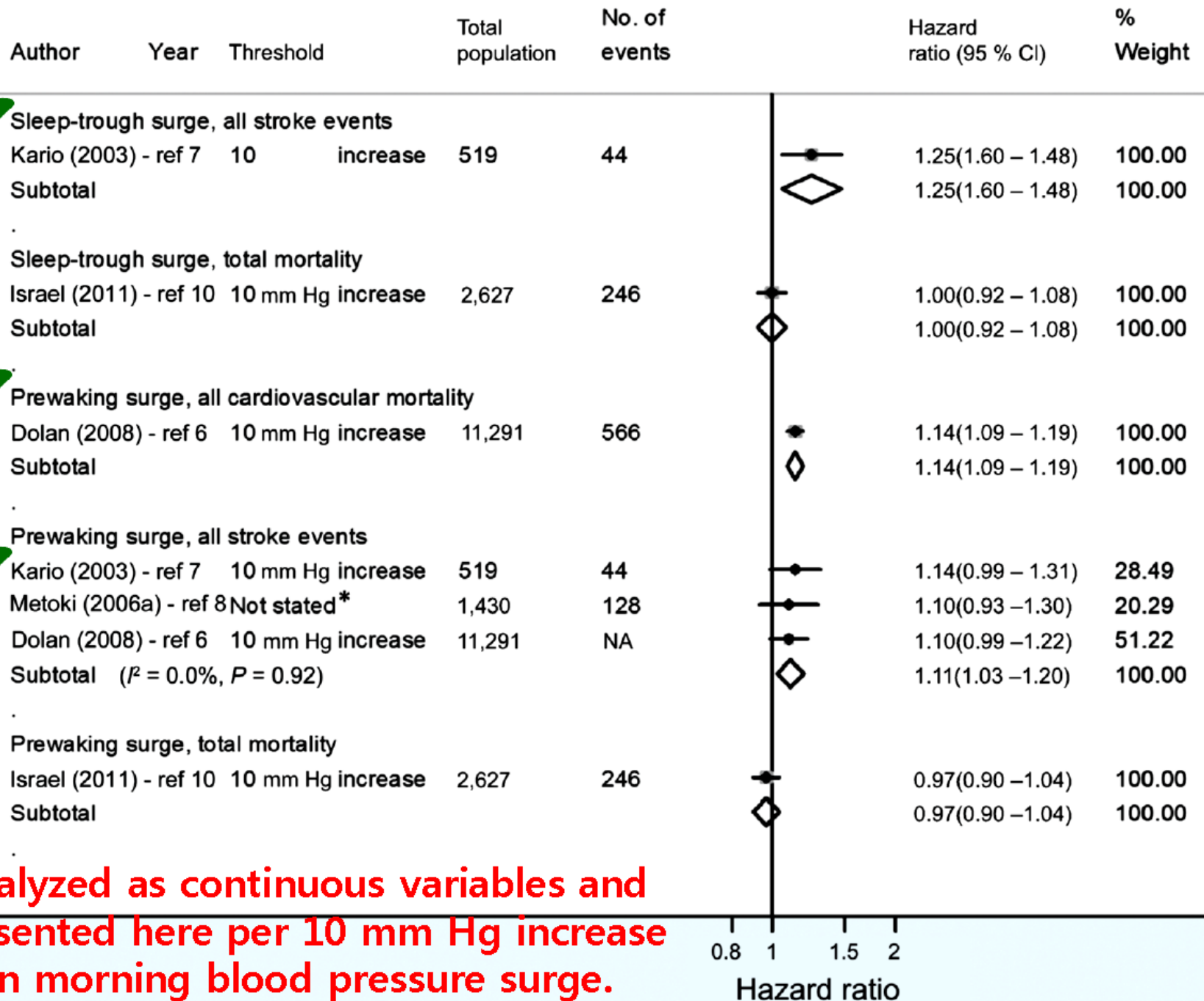
Keywords: ambulatory blood pressure monitoring; blood pressure; cardiovascular diseases; cardiovascular disease risk factors; circadian rhythm; hypertension; stroke.

doi:10.1093/ajh/hpu104

Forest plot of adjusted hazard ratios (HRs) depicting the risk of cardiovascular morbidity and/or mortality with an exaggerated morning BP surge.



analyzed as categorical variables

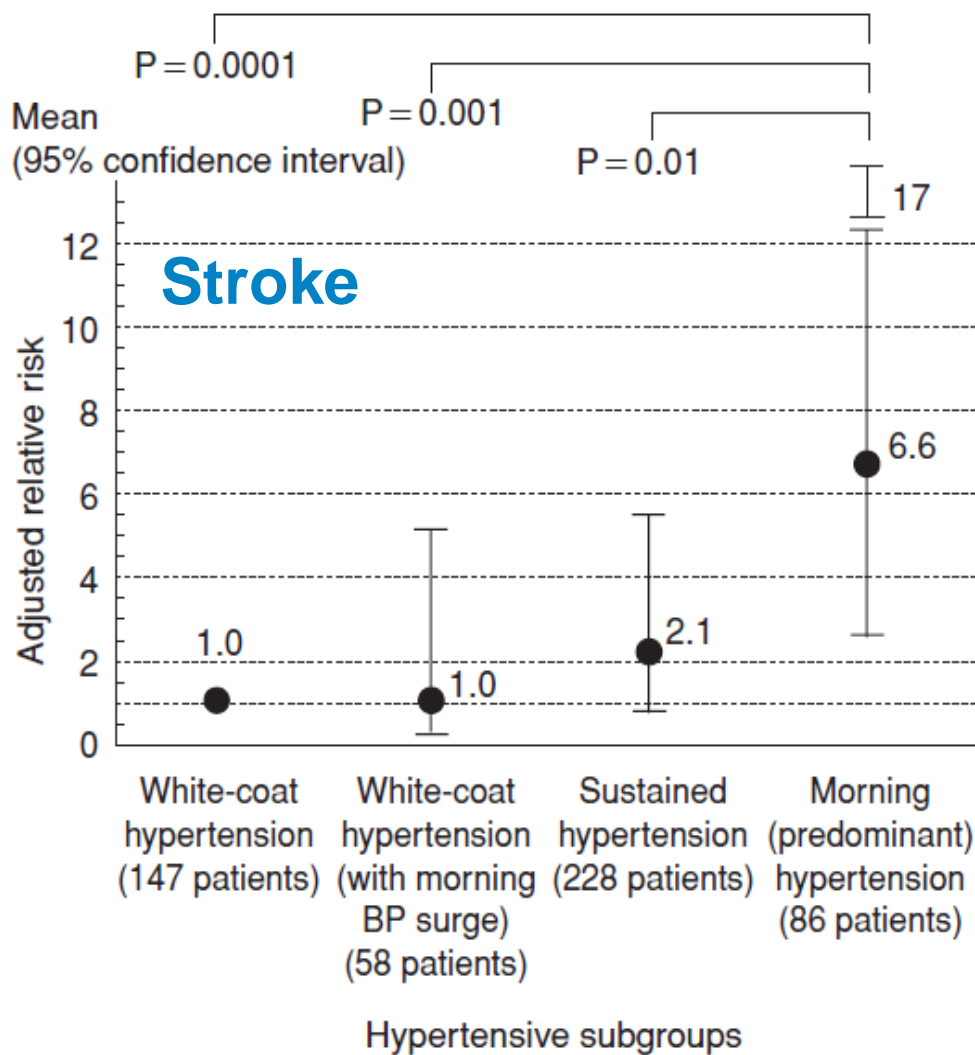


analyzed as continuous variables and presented here per 10 mm Hg increase in morning blood pressure surge.



- ▶ It may not be sure that **the MBPS** is Guilty or not.
- ▶ Then, How are the **Morning Hypertension**?

(Total of 529 hypertensive patients. Correction factors: age, sex, BMI, smoking, diabetes mellitus, hyperlipidemia, asymptomatic cerebral infarction, antihypertensive therapy)



- ▶ 519 Hypertensive patients
- ▶ Mean age, 72yrs
- ▶ Mean F/U, 41Ms
- ▶ Cut-off value

ME average-135mmHg

ME difference-20mmHg

Fig. 3 Stroke risk of Japanese hypertensive patients (JMS ABPM study, Wave 1)

[Kario K, et al. Morning hypertension. (in preparation)]

Total of 969 hypertensive patients in treatment,
mean age 66.5 years, 42% males,
45 participating physicians in 33 facilities

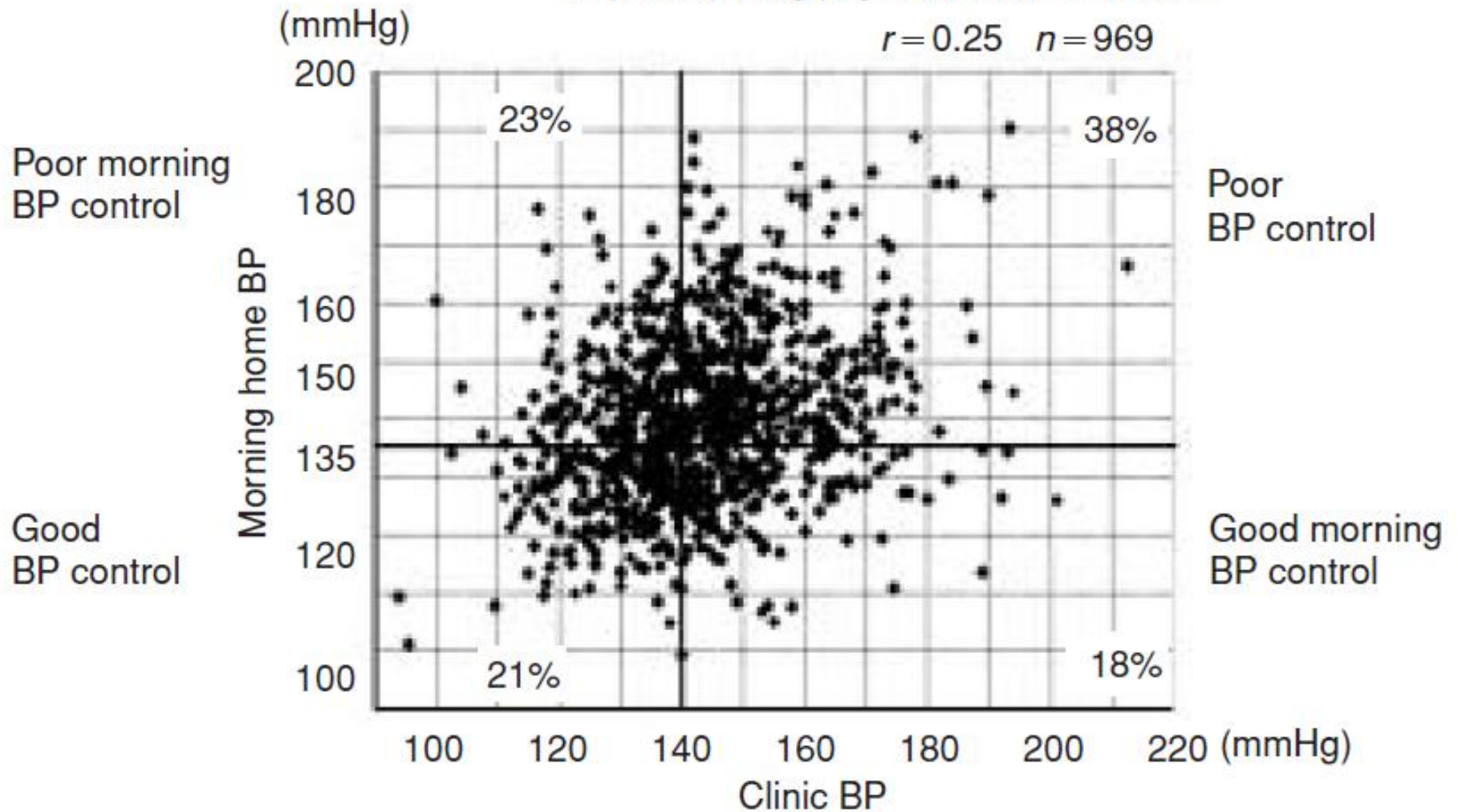


Fig. 1 Jichi morning hypertension research (J-MORE) study
(From Kario K, et al. *Circulation*. 2003;108:e72–e73)

Epidemiology/Population

Home Blood Pressure and Cardiovascular Outcomes in Patients During Antihypertensive Therapy Primary Results of HONEST, a Large-Scale Prospective, Real-World Observational Study

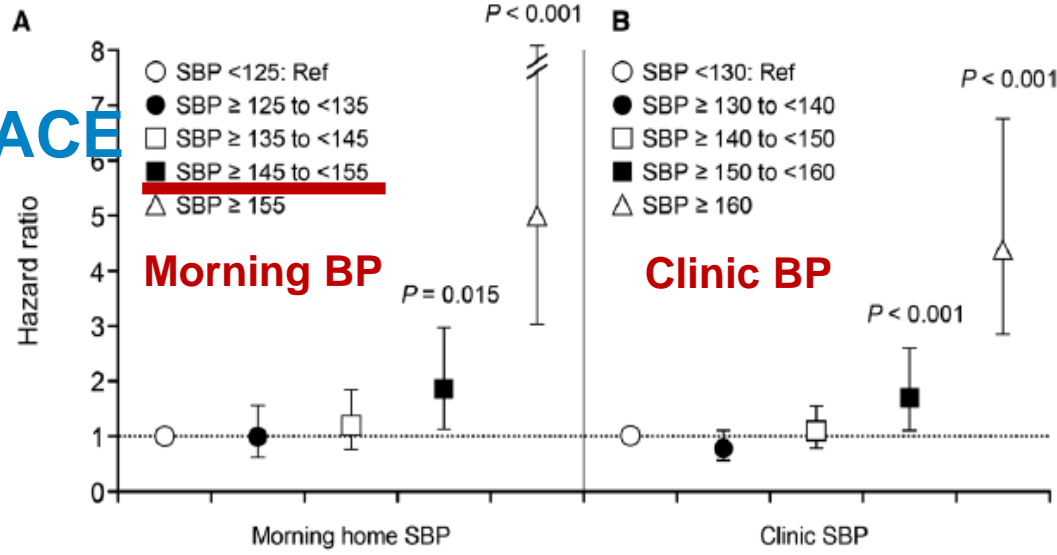
Kazuomi Kario, Ikuo Saito, Toshio Kushiro, Satoshi Teramukai, Yusuke Ishikawa, Yoshihiro Mori, Fumiaki Kobayashi, Kazuyuki Shimada

Abstract—This study aimed to investigate the relationship between on-treatment morning home blood pressure (HBP) and incidence of cardiovascular events using data from the Home Blood Pressure Measurement With Olmesartan Naive Patients to Establish Standard Target Blood Pressure (HONEST) study, a prospective observational study of 21 591 outpatients with essential hypertension (mean age, 64.9 years; women, 50.6%) enrolled between 2009 and 2010 at clinics and hospitals in Japan. They received olmesartan-based treatment throughout. The primary end point was major cardiovascular events. After a mean follow-up period of 2.02 years, cardiovascular events occurred in 280 patients (incidence, 6.46/1000 patient-years). The risk for the primary end point was significantly higher in patients with on-treatment morning HBP ≥ 145 to < 155 mmHg (hazard ratio [HR], 1.83; 95% confidence interval [CI], 1.12–2.99) and ≥ 155 mmHg (HR, 5.03; 95% CI, 3.05–8.31) than < 125 mmHg and with on-treatment clinic blood pressure ≥ 150 to < 160 mmHg (HR, 1.69; 95% CI, 1.10–2.60) and ≥ 160 mmHg (HR, 4.38; 95% CI, 2.84–6.75) than < 130 mmHg. Morning HBP associated with minimum risk was 124 mmHg by spline regression analysis. Cardiovascular risk was increased in patients with morning HBP ≥ 145 mmHg and clinic blood pressure < 130 mmHg (HR, 2.47; 95% CI, 1.20–5.08) compared with morning HBP < 125 mmHg and clinic blood pressure < 130 mmHg. In conclusion, it is essential to control morning HBP to < 145 mmHg, even in patients with controlled clinic blood pressure.

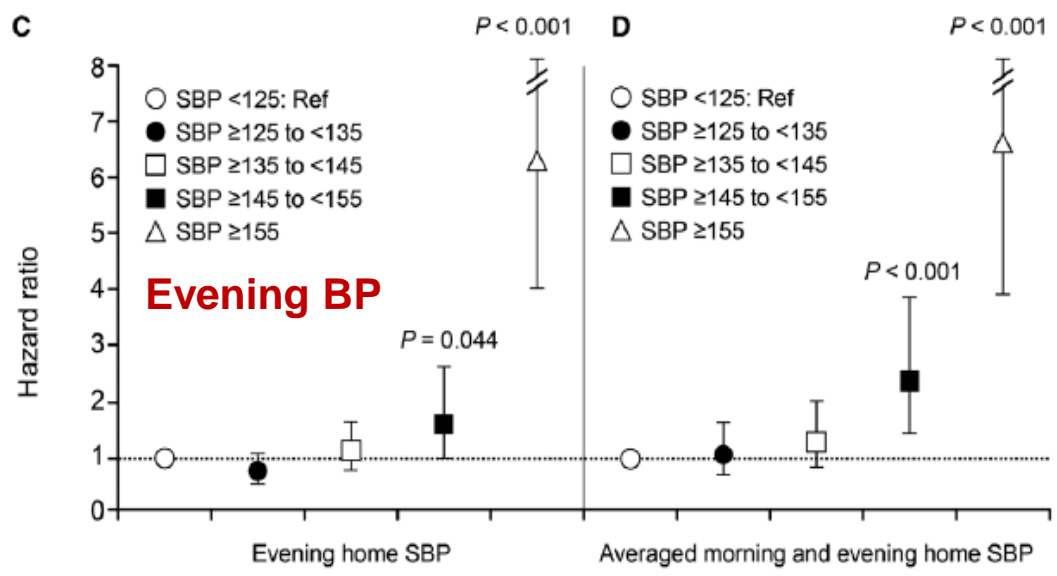
Clinical Trial Registration—URL: <http://www.umin.ac.jp/ctr/index.htm>. UMIN Clinical Trials Registry, trial No. UMIN000002567. (*Hypertension*. 2014;64:989-996.) • [Online Data Supplement](#)

Key Words: antihypertensive agents ■ blood pressure monitoring, ambulatory ■ cardiovascular diseases ■ hypertension ■ masked hypertension ■ observational study

MACE



No. of patients	3008	7338	7165	2565	925	6548	8197	4436	1517	648
Incidence [†]	4.08	4.15	5.27	9.37	26.50	5.68	4.26	6.30	10.12	25.73
Hazard ratio	1	0.98	1.18	1.83	5.03	1	0.78	1.09	1.69	4.38



No. of patients	6038	7491	4426	1333	447	3820	7886	5821	1674	519
Incidence [†]	4.98	3.80	6.13	9.44	38.91	3.81	4.27	5.48	10.83	32.38
Hazard ratio	1	0.77	1.15	1.63	6.32	1	1.08	1.31	2.36	6.60



Morning Versus Evening and Av-ME

Among morning HSBP, evening HSBP, and Av-ME HSBP, morning HSBP showed the greatest discrepancy between mean SBP during follow-up and the SBP associated with minimum risk, as determined by spline regression analysis. And with the Cox proportional hazards model, the ratio of patients with SBP ≥ 145 mm Hg was highest in morning HSBP. Those findings indicate insufficient control of morning HSBP compared with other types of SBP in real-world clinical practice. Circadian changes in BP, such as morning surge,¹³ may underlie uncontrolled morning HSBP, so strict monitoring of morning HSBP is recommended.

MACE

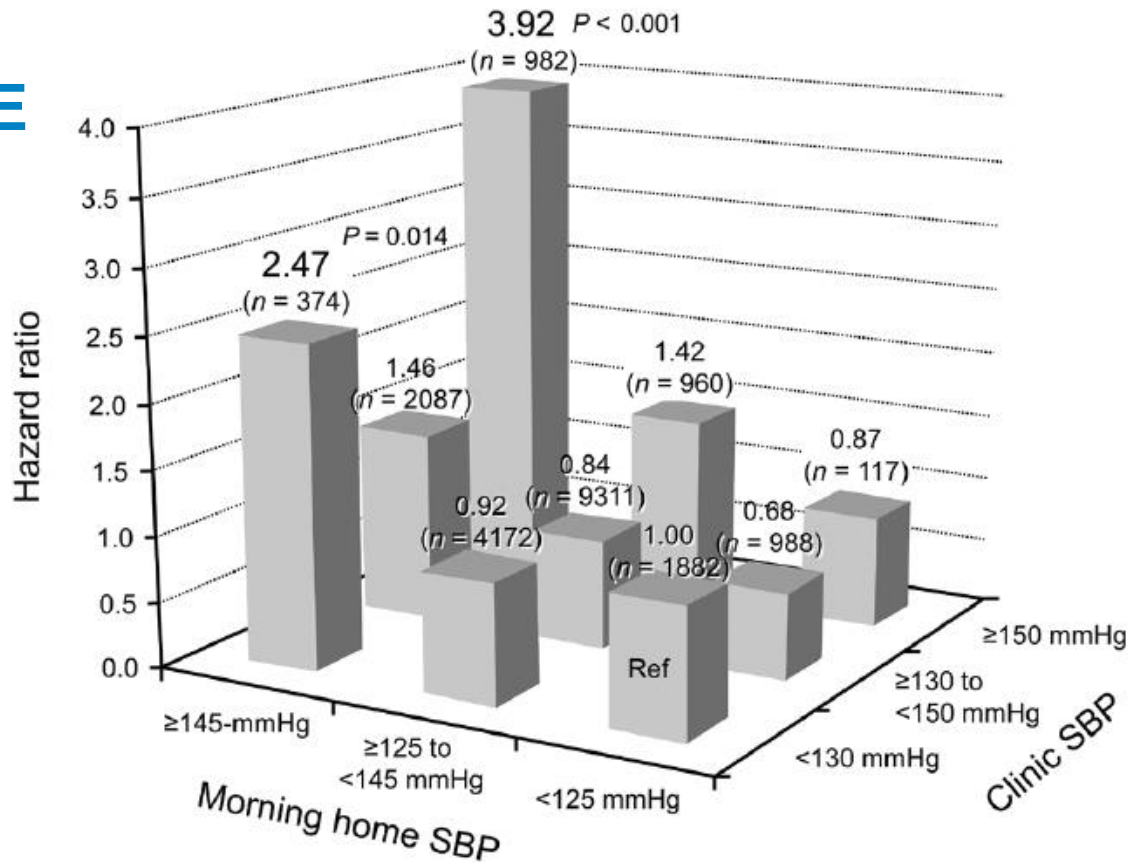


Figure 3. Relationship between the primary end point and systolic blood pressure (SBP) divided into 9 categories. The Cox proportional hazards model was used, adjusting for sex, age, family history of cardiovascular disease, dyslipidemia, diabetes mellitus, chronic kidney disease, history of cardiovascular disease, and smoking status. Morning home SBP <125 mmHg and clinic SBP <130 mmHg were used as a reference.

The results of previous studies have shown that masked hypertension is associated with higher cardiovascular risk as with sustained hypertension.^{4,5,15,16} This is consistent with the findings of the present study, which used on-treatment BP as an indicator. Therefore, we strongly recommend measuring and monitoring HBP in real-world clinical practice so as to identify masked hypertension, which can be described as a pitfall in the treatment of hypertension.

Morning Home Blood Pressure Is a Strong Predictor of Coronary Artery Disease



The HONEST Study

Kazuomi Kario, MD,^a Ikuo Saito, MD,^b Toshio Kushiro, MD,^c Satoshi Teramukai, PhD,^d Yasuhiro Tomono, MS,^e Yasuyuki Okuda, MS,^e Kazuyuki Shimada, MD^f

ABSTRACT

BACKGROUND Few studies have evaluated out-of-office blood pressure (BP) measurements as predictors of coronary artery disease (CAD) events.

OBJECTIVES The aim of this study was to determine morning home blood pressure (HBP) as a predictor of CAD events.

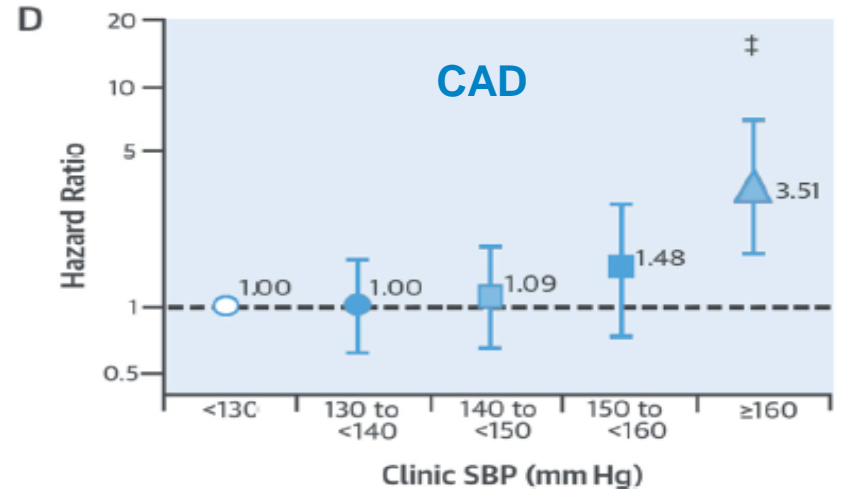
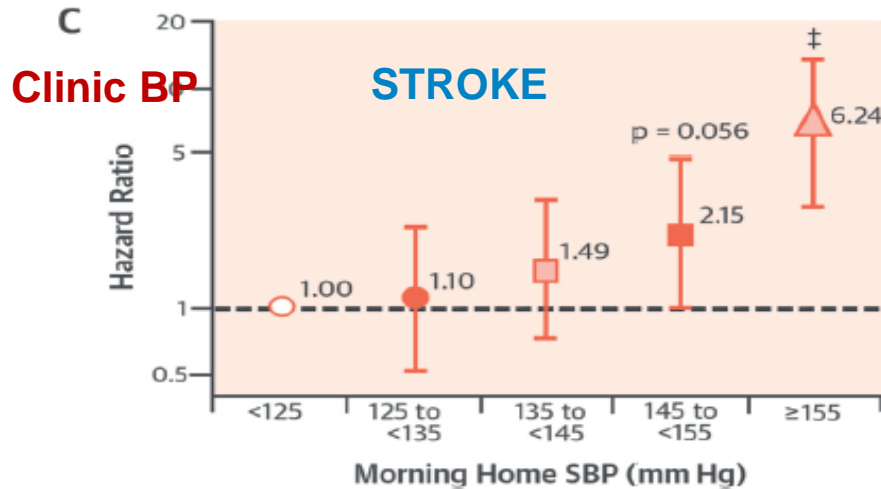
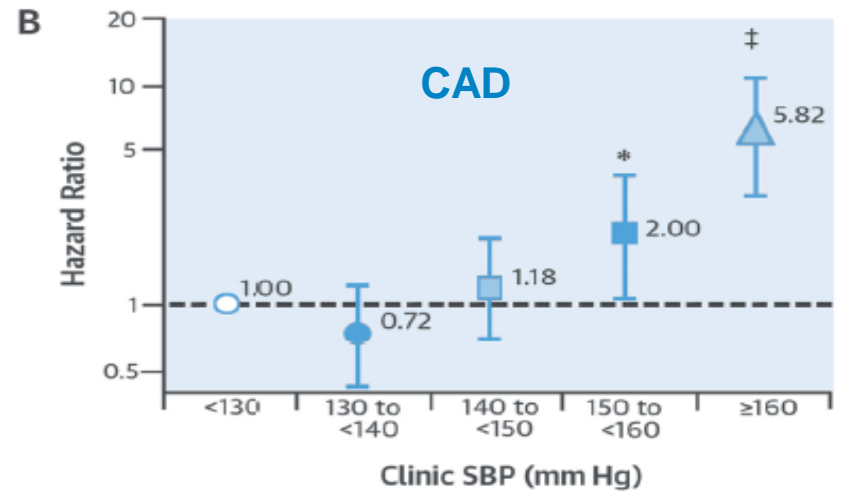
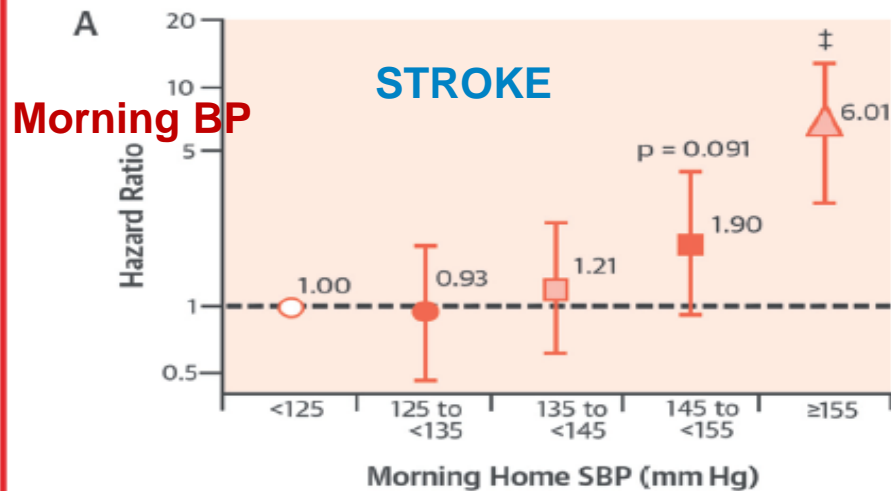
METHODS Using data from the HONEST (Home blood pressure measurement with Olmesartan Naive patients to Establish Standard Target blood pressure) study, we investigated the relationship between morning HBP and incidence of stroke and CAD events.

RESULTS In 21,591 treated hypertensive patients (mean age 64.9 years; mean follow-up 2.02 years), 127 stroke events (2.92 per 1,000 patient-years), and 121 CAD events (2.78 per 1,000 patient-years) occurred. The incidence of stroke events was significantly higher in patients with morning home systolic blood pressure (HSBP) ≥ 145 mm Hg compared with < 125 mm Hg, and in patients with clinic systolic blood pressure (CSBP) ≥ 150 mm Hg compared with < 130 mm Hg. Hazard ratios (HRs) were 6.01 (95% confidence interval [CI]: 2.85 to 12.68) between patients with morning HSBP ≥ 155 mm Hg and those with morning HSBP < 125 mm Hg and 5.82 (95% CI: 3.17 to 10.67) between patients with CSBP ≥ 160 mm Hg and those with CSBP < 130 mm Hg; morning HSBP predicted stroke events similarly to CSBP. Incidence of CAD events was significantly higher in patients with morning HSBP ≥ 145 mm Hg compared with < 125 mm Hg and in patients with CSBP ≥ 160 mm Hg compared with < 130 mm Hg. The HR for morning HSBP ≥ 155 mm Hg was 6.24 (95% CI: 2.82 to 13.84) and for CSBP ≥ 160 mm Hg was 3.51 (95% CI: 1.71 to 7.20); therefore, compared with morning HSBP, CSBP may underestimate CAD risk. Goodness-of-fit analysis showed that morning HSBP predicted CAD events more strongly than CSBP.

CONCLUSIONS Morning HBP is a strong predictor of future CAD and stroke events, and may be superior to clinic BP in this regard. There does not appear to be a J-curve in the relationship between morning HBP and stroke or CAD events. (Home blood pressure measurement with Olmesartan Naive patients to Establish Standard Target blood pressure Study [HONEST]; [UMIN00002567](#)) (*J Am Coll Cardiol* 2016;67:1519-27)

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CENTRAL ILLUSTRATION Morning Home Blood Pressure and CAD: SBP and HR for Stroke and CAD Events During Follow-Up



Kario, K. et al. J Am Coll Cardiol. 2016;67(13):1519-27.

Morning HBP is a strong predictor of future CAD and stroke events, and may be superior to clinic BP in CAD prediction

The Morning Hypertension is Guilty !!

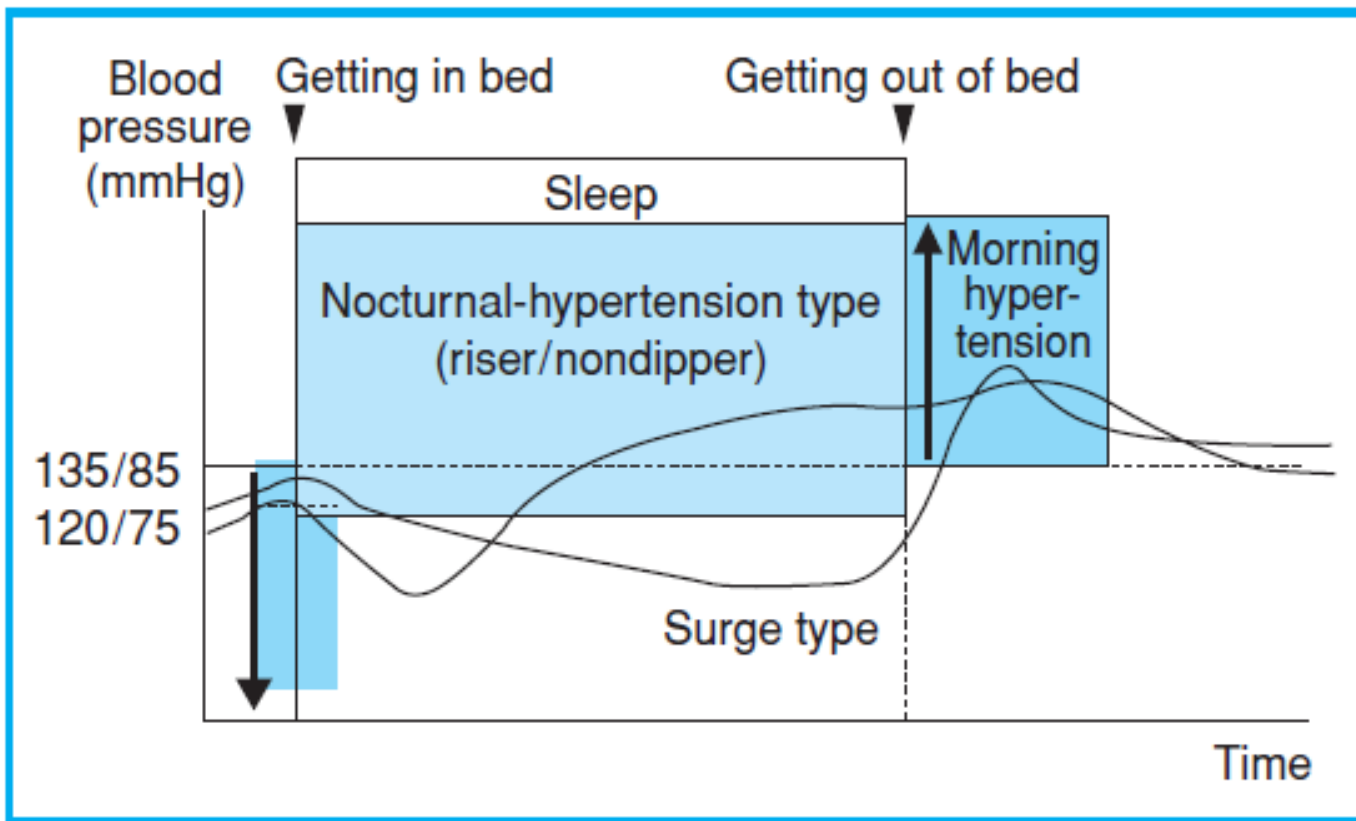


Fig. 5 Abnormal diurnal variation in blood pressure in two types of morning (predominant) hypertension

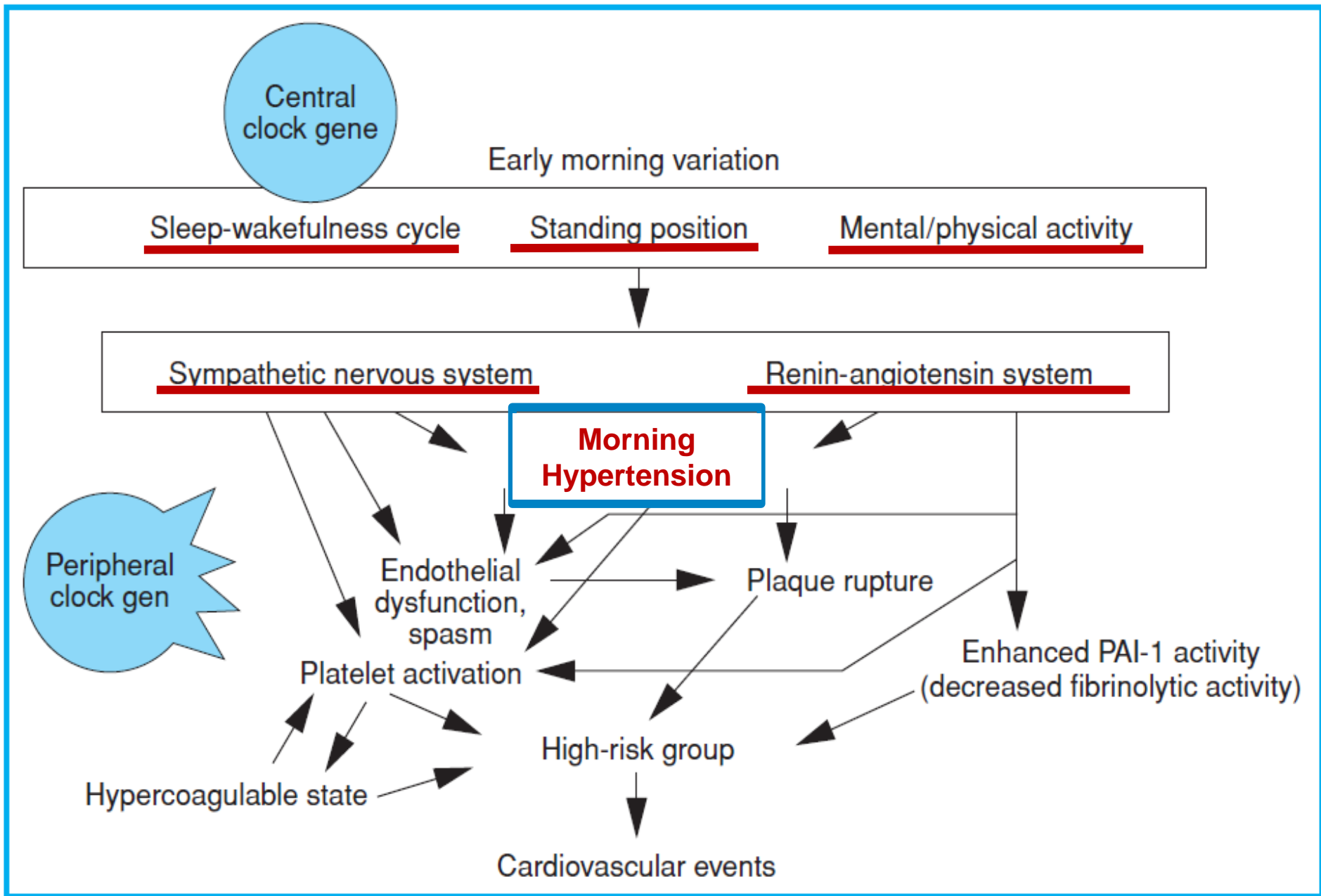


Fig. 6 Mechanism of the morning onset of cardiovascular events

[Kario K, et al. J Cardiovasc Pharmacol. 2003;42(Suppl 1):S87–S91]

Morning Blood Pressure Surge and Hypertensive Cerebrovascular Disease

Role of the Alpha Adrenergic Sympathetic Nervous System

Kazuomi Kario, Thomas G. Pickering, Satoshi Hoshide, Kazuo Eguchi, Joji Ishikawa, Masato Morinari, Yoko Hoshide, and Kazuyuki Shimada

Background: The morning surge of blood pressure (BP) is associated with α -adrenergic activity. We studied the association between the α -adrenergic morning surge in BP and silent cerebrovascular disease in elderly patients with hypertension.

Methods: We conducted ambulatory BP monitoring three times (twice at baseline and after nighttime dosing of the α_1 -blocker doxazosin) in 98 elderly hypertensive patients in whom the presence of silent cerebral infarcts (SCI) was assessed by brain magnetic resonance imaging. The morning BP surge (MBPS) was calculated as the mean systolic BP during the 2 h after waking minus the mean systolic BP during 1 h that included the lowest sleep BP. The α -adrenergic MBPS was calculated as the reduction of MBPS by doxazosin.

Results: The prevalence of multiple SCI was higher in the Surge group (top quartile: MBPS ≥ 45 mm Hg, $n = 24$) than in the Nonsurge group (MBPS < 45 mm Hg, $n = 74$) (54% v 31%, $P = .04$), and in the higher α -adrenergic

surge group (top quartile: α -adrenergic MBPS ≥ 28 mm Hg, $n = 25$) than in the lower α -adrenergic surge group (< 28 mm Hg, $n = 73$) (68% v 26%, $P < .0001$). In the Surge group, subjects with higher α -adrenergic surge ($n = 17$) had a markedly higher frequency of multiple SCI, whereas none in the lower α -adrenergic surge group had multiple SCI ($n = 7$) (77% v 0%, $P = .001$). The α -adrenergic MBPS was closely associated with multiple SCI (10 mm Hg increase: OR = 1.96, $P = .006$), independently of age, MBPS, 24-h systolic BP, and other confounding factors.

Conclusion: The morning BP surge, particularly that dependent on α -adrenergic activity, is closely associated with advanced silent hypertensive cerebrovascular disease in elderly individuals. Am J Hypertens 2004;17:668–675 © 2004 American Journal of Hypertension, Ltd.

Key Words: Hypertension, elderly, morning surge, sympathetic activity, cerebrovascular disease.

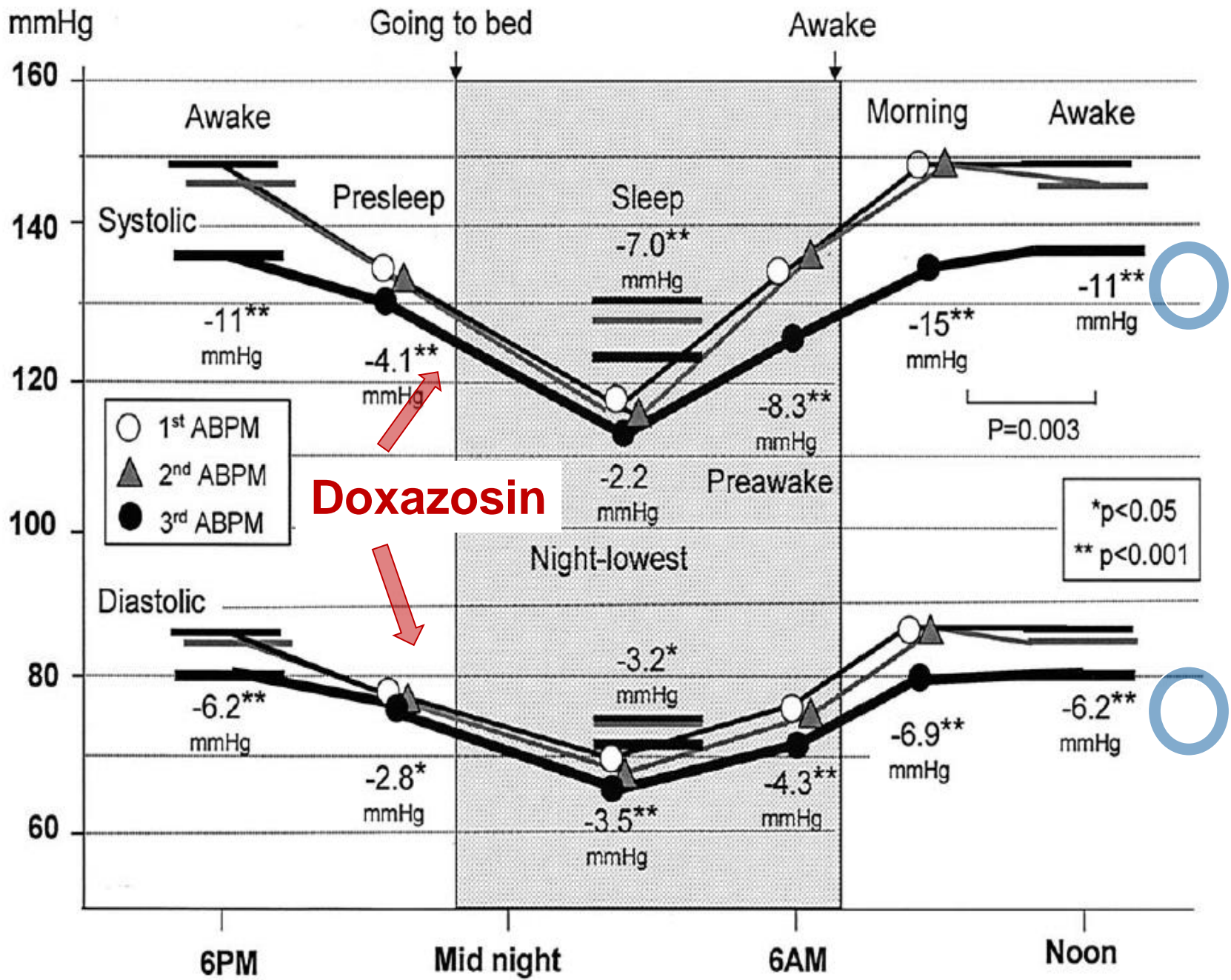
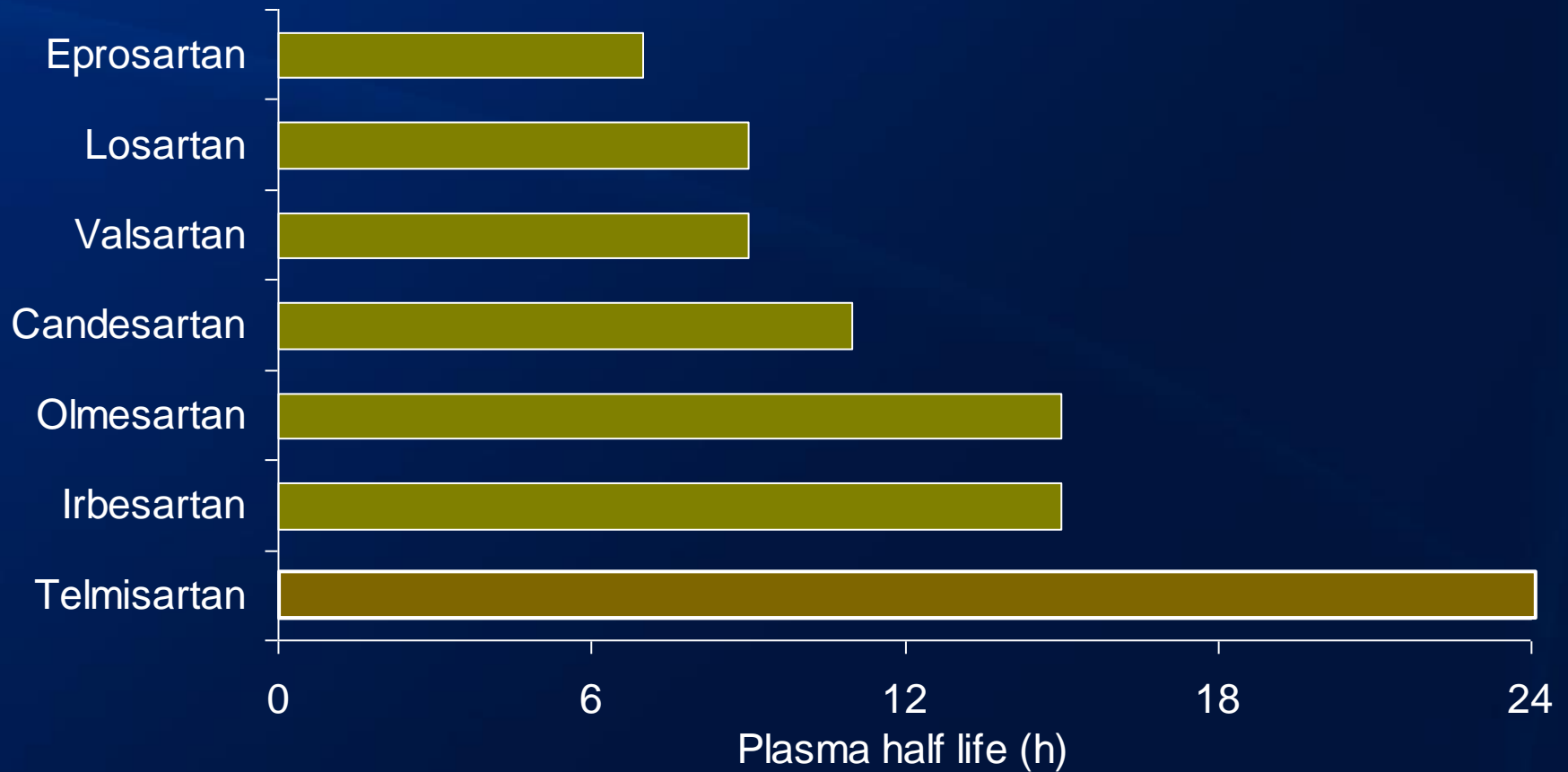


FIG. 1. Ambulatory blood pressure (BP) values during the two baseline recordings and after doxazosin therapy.

Plasma half-life

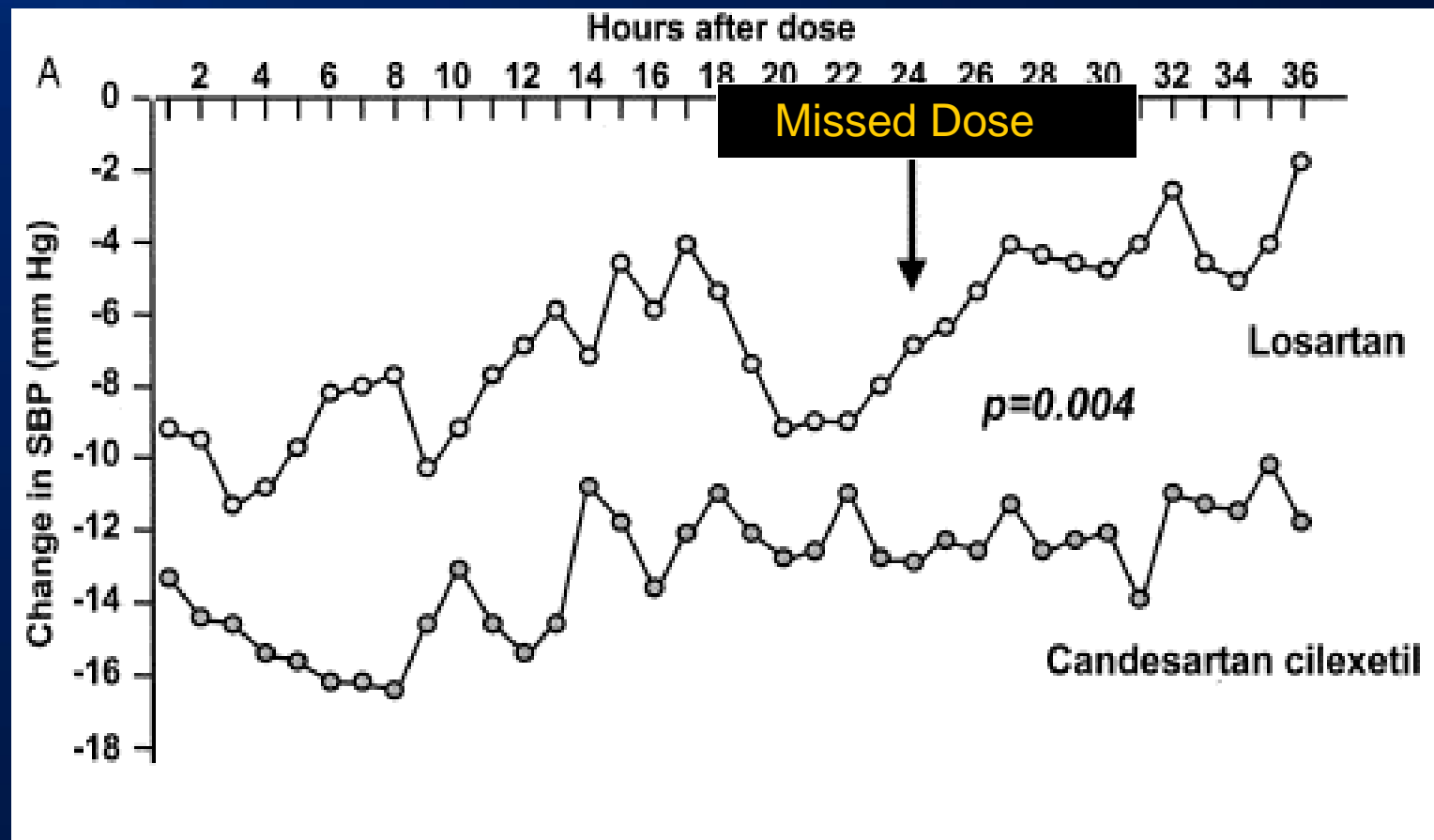
Longest half-life of clinically available ARBs



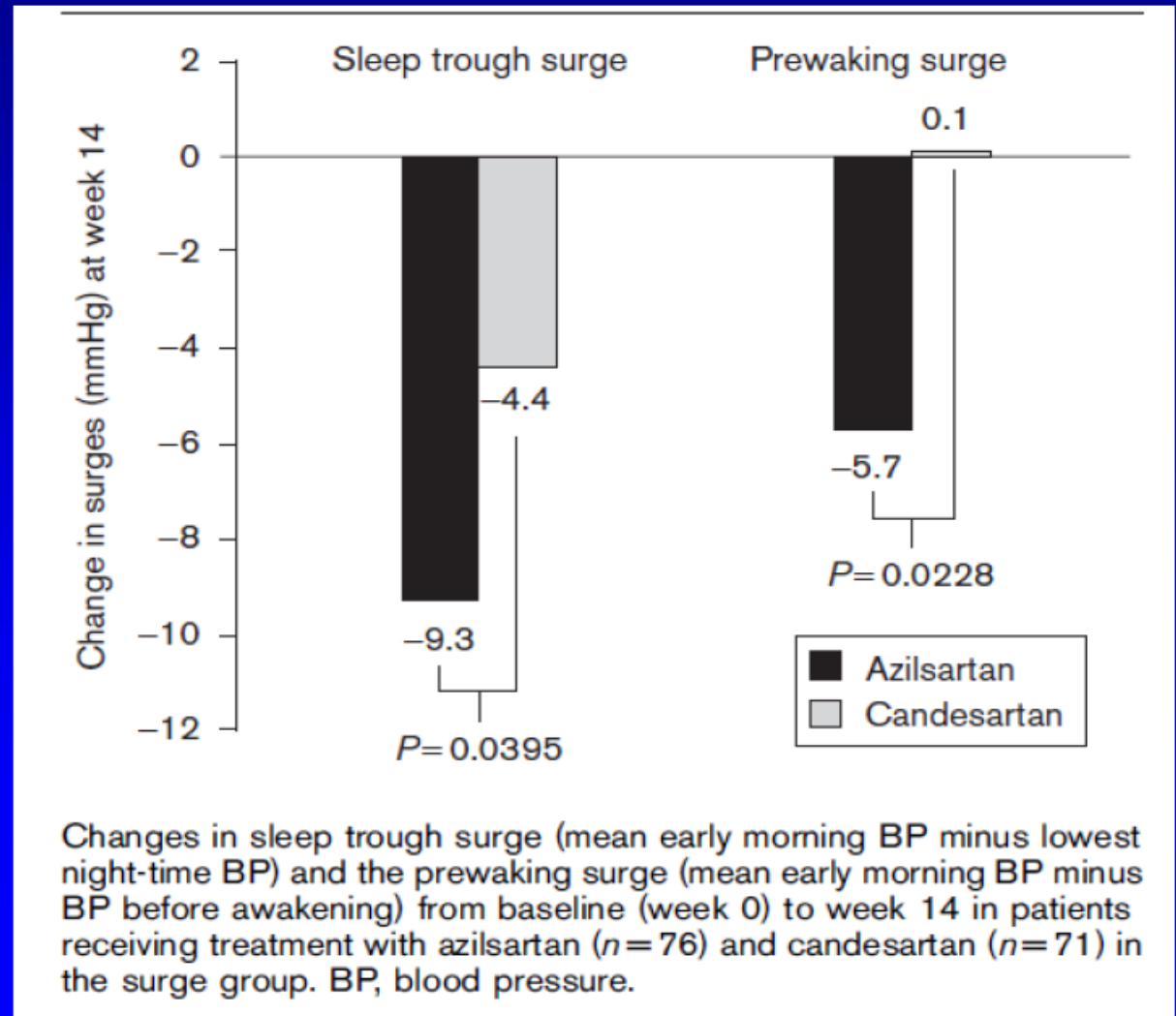
Burnier, Brunner. *Lancet* 2000;355:637–645
Brunner. *J Hum Hypertens* 2002;16 (Suppl 2):S13–S16

Effects of Two ARBs Approved for Once Daily Dosing on 24 Hour Blood Pressure

(Mancia et al AJC 1999: 84; 28S)

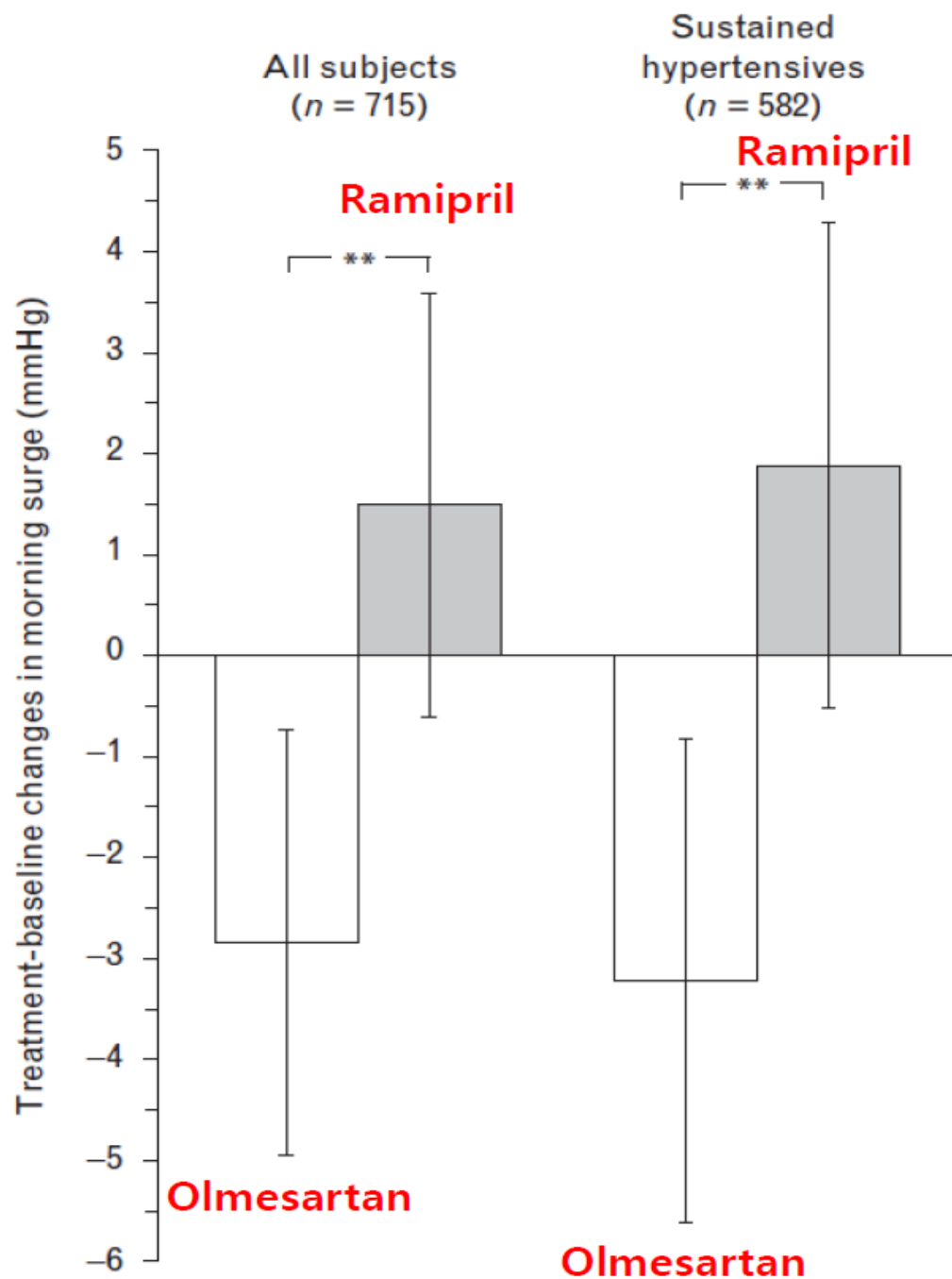


Sustained acting drug Is useful for controlling the Morning BP surge



Blood Press Monit
2014;19:164-169

Morning surge after 12 weeks of treatment



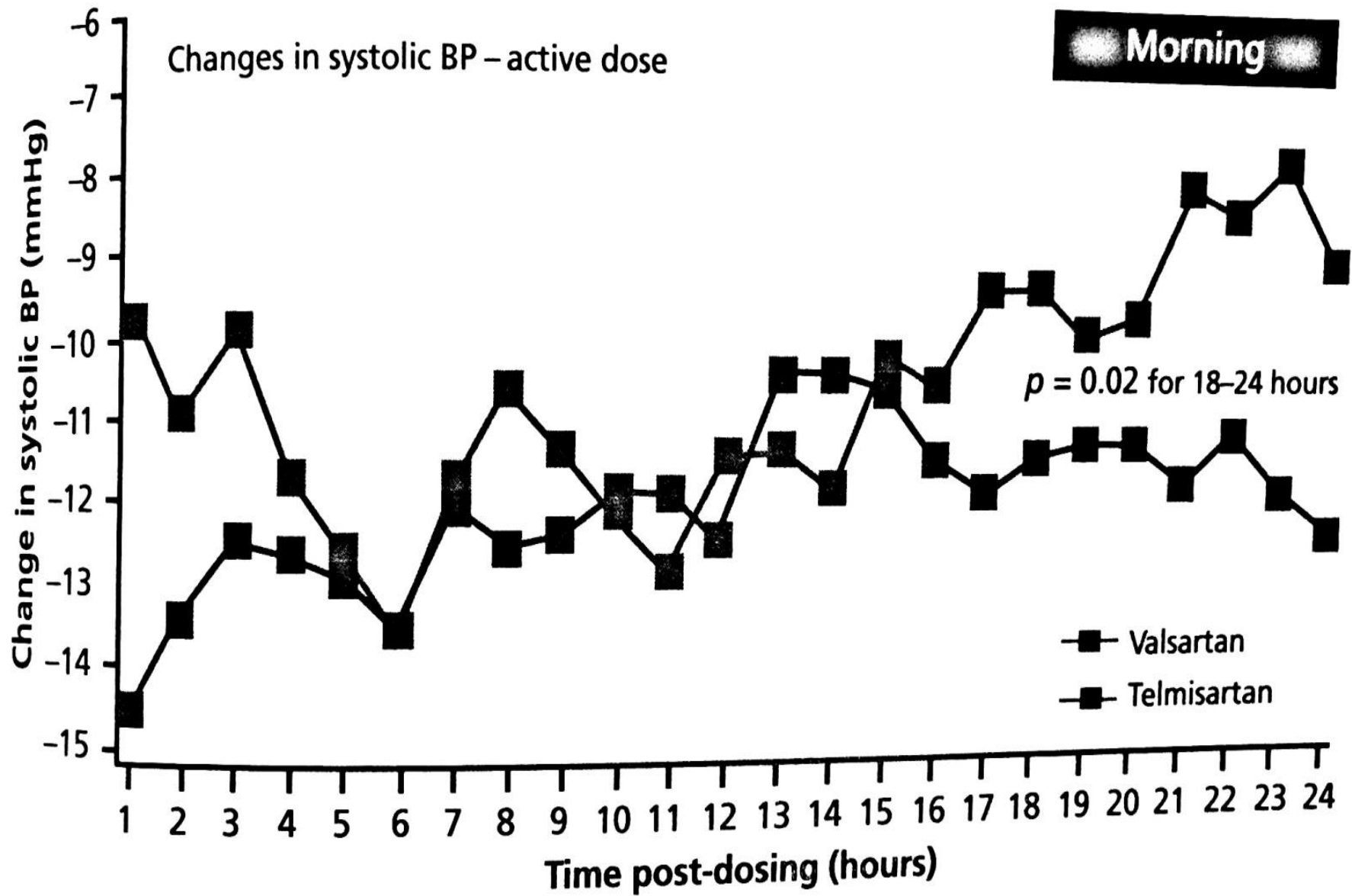


Figure 8.9 Different BP lowering effects of telmisartan versus valsartan on morning BP in hypertensive patients. *Source:* White et al. 2004 [143].

The prospective, randomized investigation of the safety and efficacy of telmisartan versus ramipril using ambulatory blood pressure monitoring (PRISMA I)

Bryan Williams^a, Philippe Gosse^b, Linda Lowe^c and Ruth Harper^c, on behalf of the PRISMA I Study Group

Objective To compare the efficacy and safety of once-daily telmisartan and ramipril on blood pressure (BP) reductions during the last 6 h of the dosing interval.

Patients and methods In a prospective, randomized, open-label, blinded-endpoint study using ambulatory BP monitoring, 801 patients with mild-to-moderate hypertension were randomly assigned to once-daily treatment with telmisartan 80 mg for 14 weeks or ramipril 5 mg for 8 weeks and then force titrated to ramipril 10 mg for the last 6 weeks. Primary endpoints were the reduction from baseline in the last 6-h mean ambulatory systolic BP (SBP) and diastolic BP (DBP). Secondary endpoints included changes in 24-h, morning, daytime and night-time mean ambulatory BP and ambulatory BP response rates.

Results Telmisartan 80 mg produced greater reductions in the last 6-h mean ambulatory SBP and DBP compared with ramipril 5 mg ($P < 0.0001$) and 10 mg ($P < 0.0001$), and was superior to ramipril for all secondary ambulatory SBP and DBP endpoints ($P < 0.05$). Ambulatory BP response rates (24-h mean ambulatory SBP/DBP $< 130/80$ mmHg or reduction from baseline ≥ 10 mmHg) were greater with telmisartan 80 mg ($P < 0.01$) than with ramipril 5 and 10 mg.

Ramipril was associated with a higher incidence of treatment-related cough (5.7 versus 0.5% for telmisartan).

Conclusions Telmisartan was significantly more effective than ramipril in reducing BP throughout the 24-h dosing interval and particularly during the last 6 h, a time when patients appear to be at greatest risk of cerebro- and cardiovascular events. Both drugs were well tolerated, although ramipril was associated with a higher incidence of cough. *J Hypertens* 24:193–200 © 2006 Lippincott Williams & Wilkins.

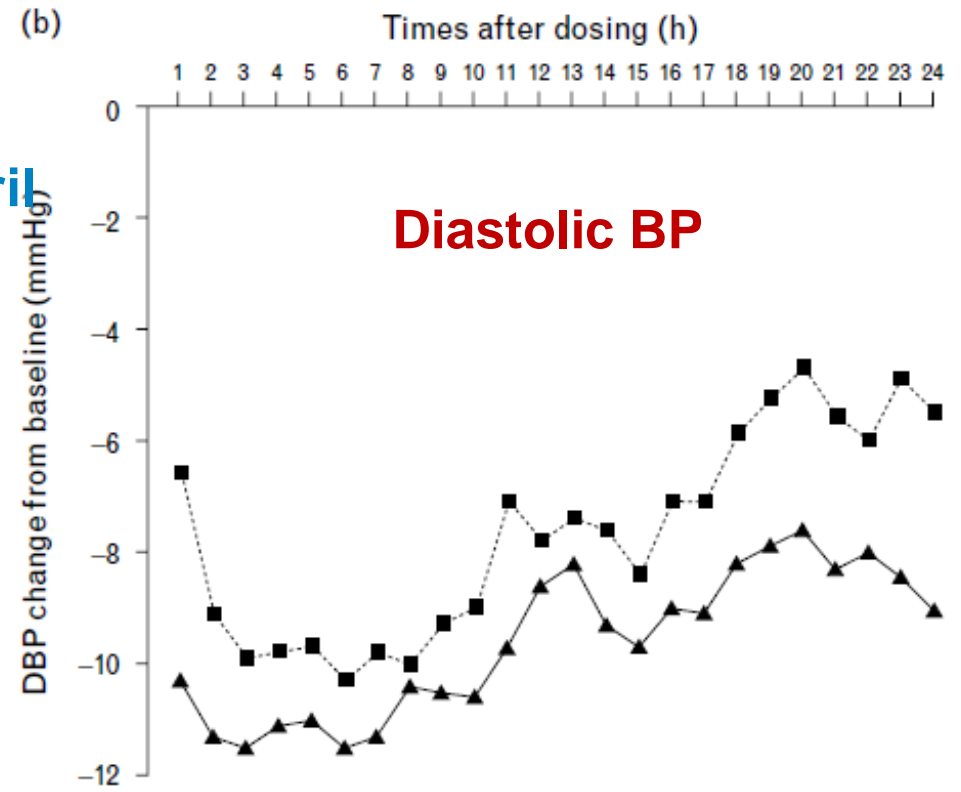
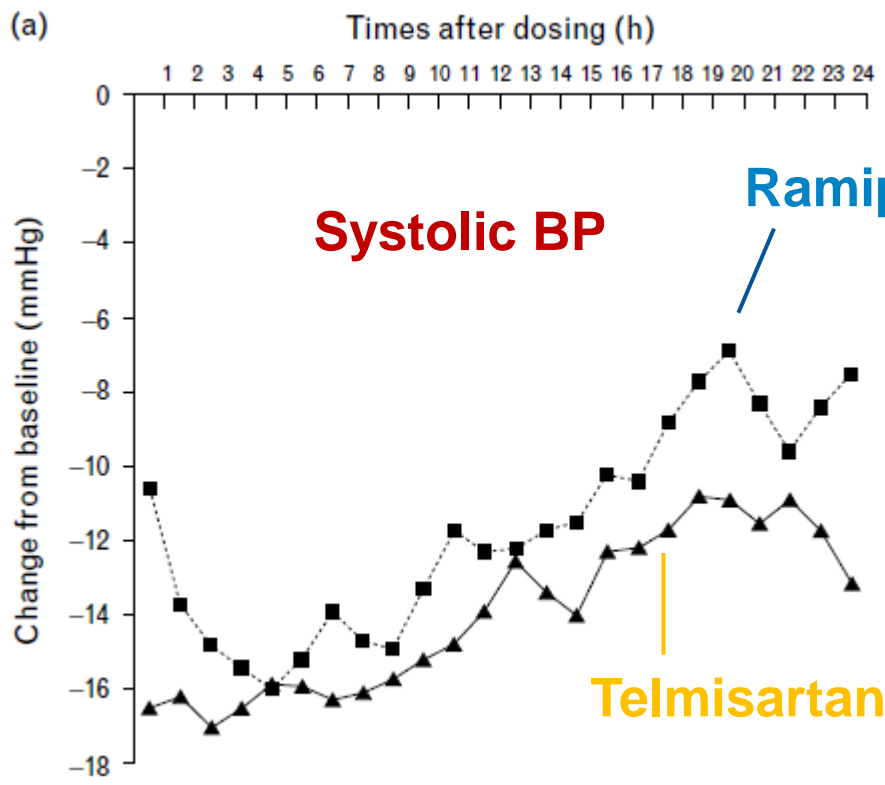
Journal of Hypertension 2006, 24:193–200

Keywords: angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, circadian blood pressure, ramipril, telmisartan

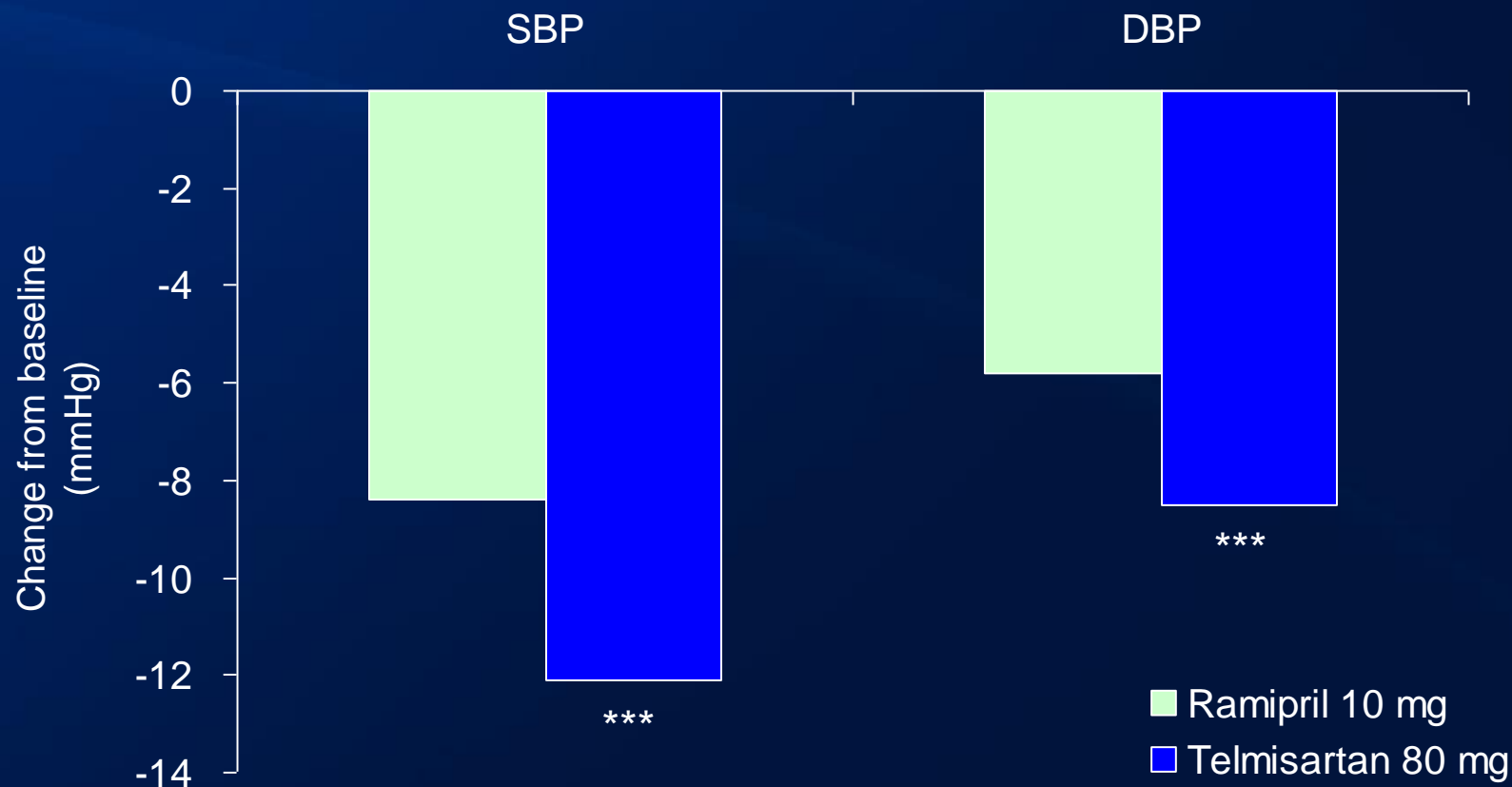
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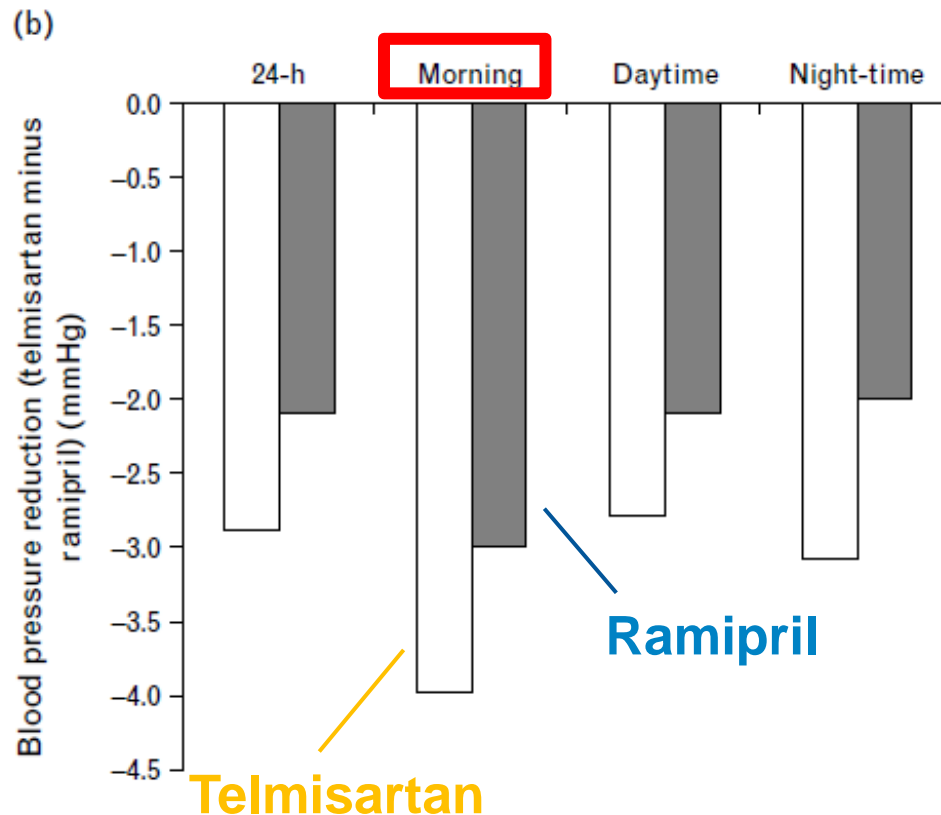
Received 8 March 2005 Revised 20 July 2005
Accepted 13 September 2005



Reductions in BP in last 6 h of dosing interval



***p < 0.0001 Telmisartan vs Ramipril

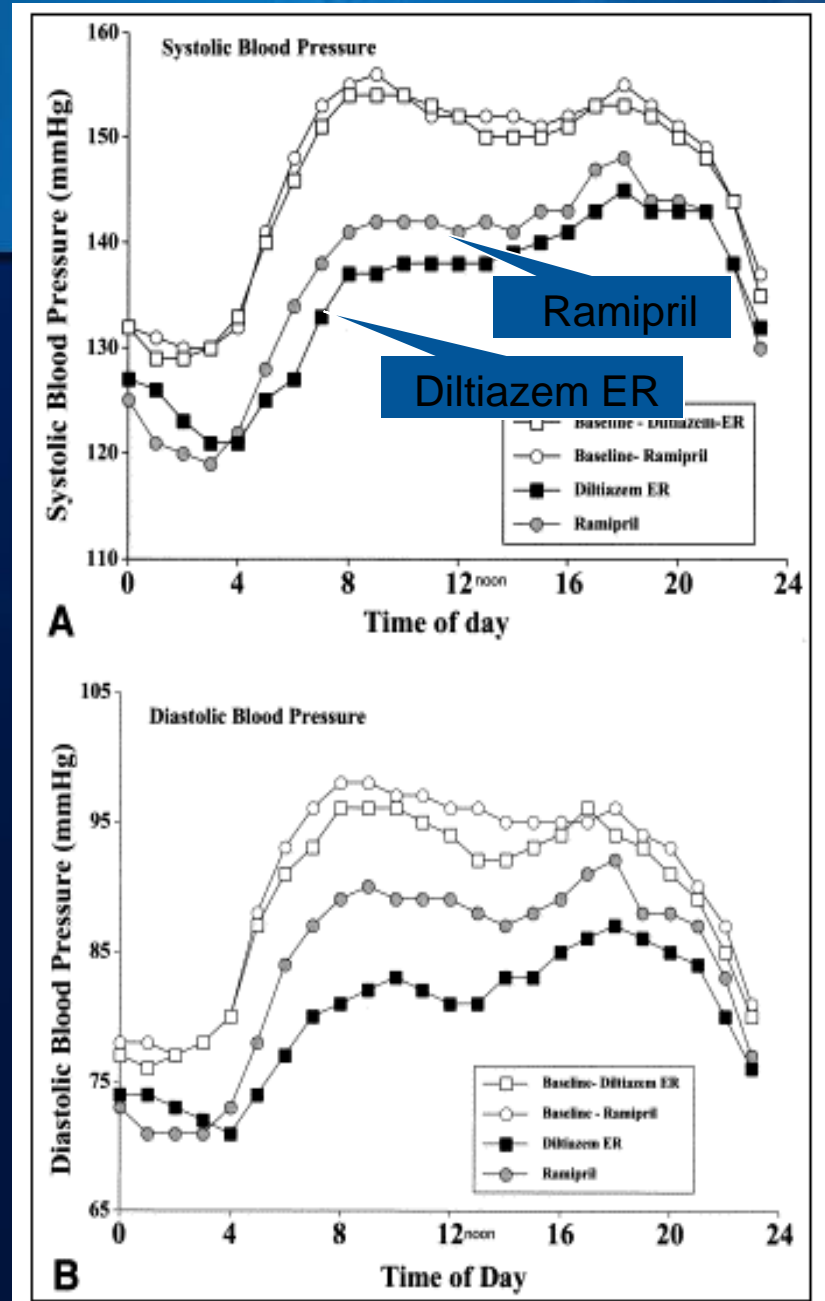


Differences between telmisartan 80 mg and (a) ramipril 5 mg at 8 weeks and (b) ramipril 10 mg at 14 weeks in the reductions from baseline in mean ambulatory systolic blood pressure and diastolic blood pressure over different periods of the once-daily dosing interval. □ systolic blood pressure; ■ diastolic blood pressure.

Conclusions Telmisartan was significantly more effective than ramipril in reducing BP throughout the 24-h dosing interval and particularly during the last 6 h, a time when

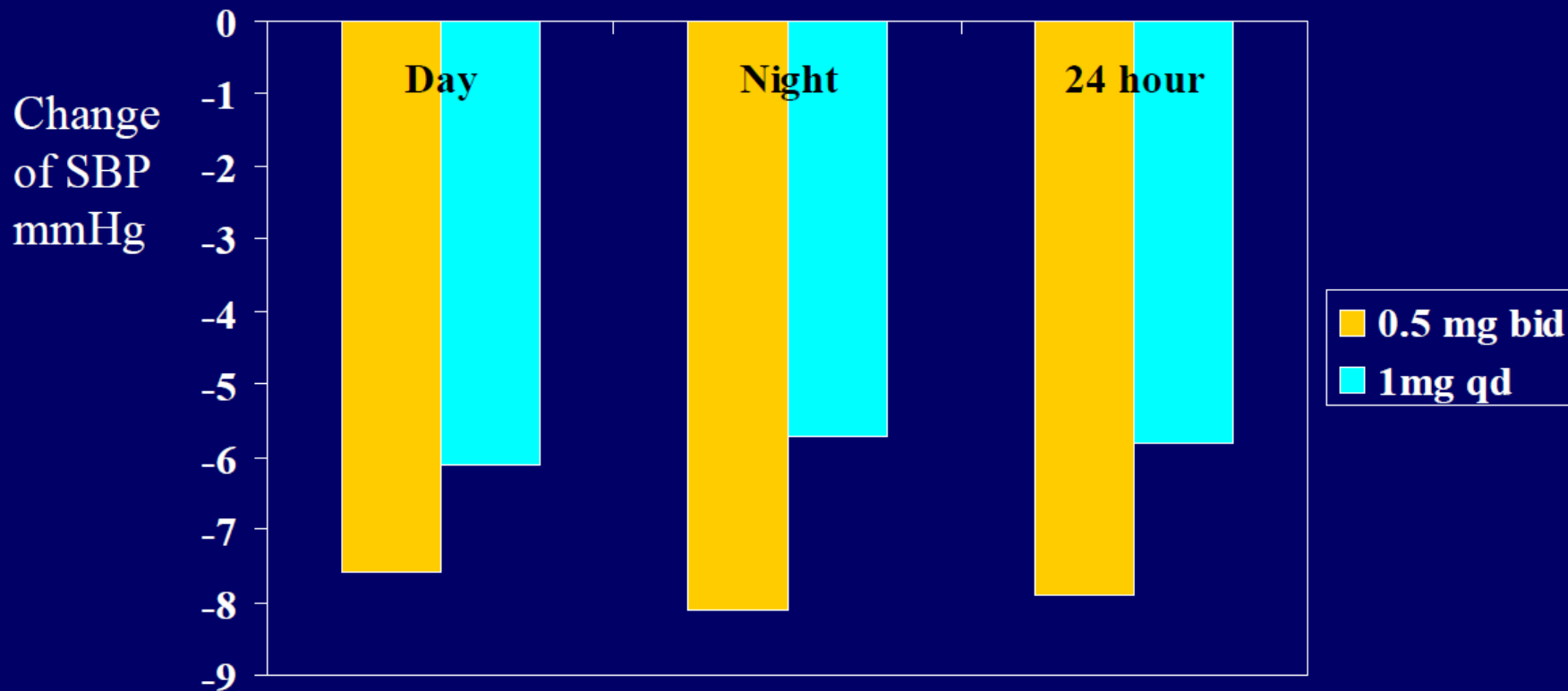
Effects of graded release Diltiazem vs. Ramipril on Morning BP

(White et al, Am Heart J 2004; 148: 628)



Effects of Time of Administration of Trandolapril on Diurnal Changes of BP

(Poirier J Clin Pharm 1993: 33:832)



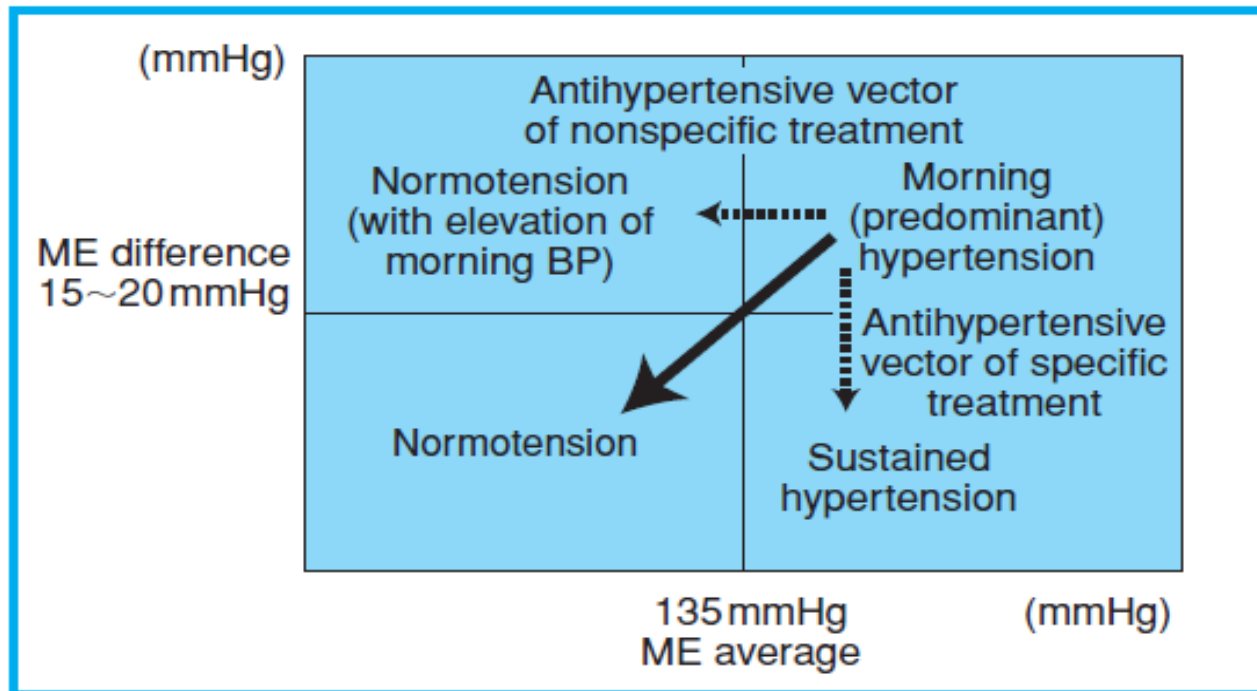


Fig. 7 Specific antihypertensive treatment for morning (predominant) hypertension using home BP monitoring

Nonspecific treatment: long-acting antihypertensive drugs (twice-daily, morning and evening, doses should also be considered), diuretics

Specific treatment: α -blockers used at bedtime

Renin-angiotensin-aldosterone system inhibitors (dosing at bedtime should also be considered)

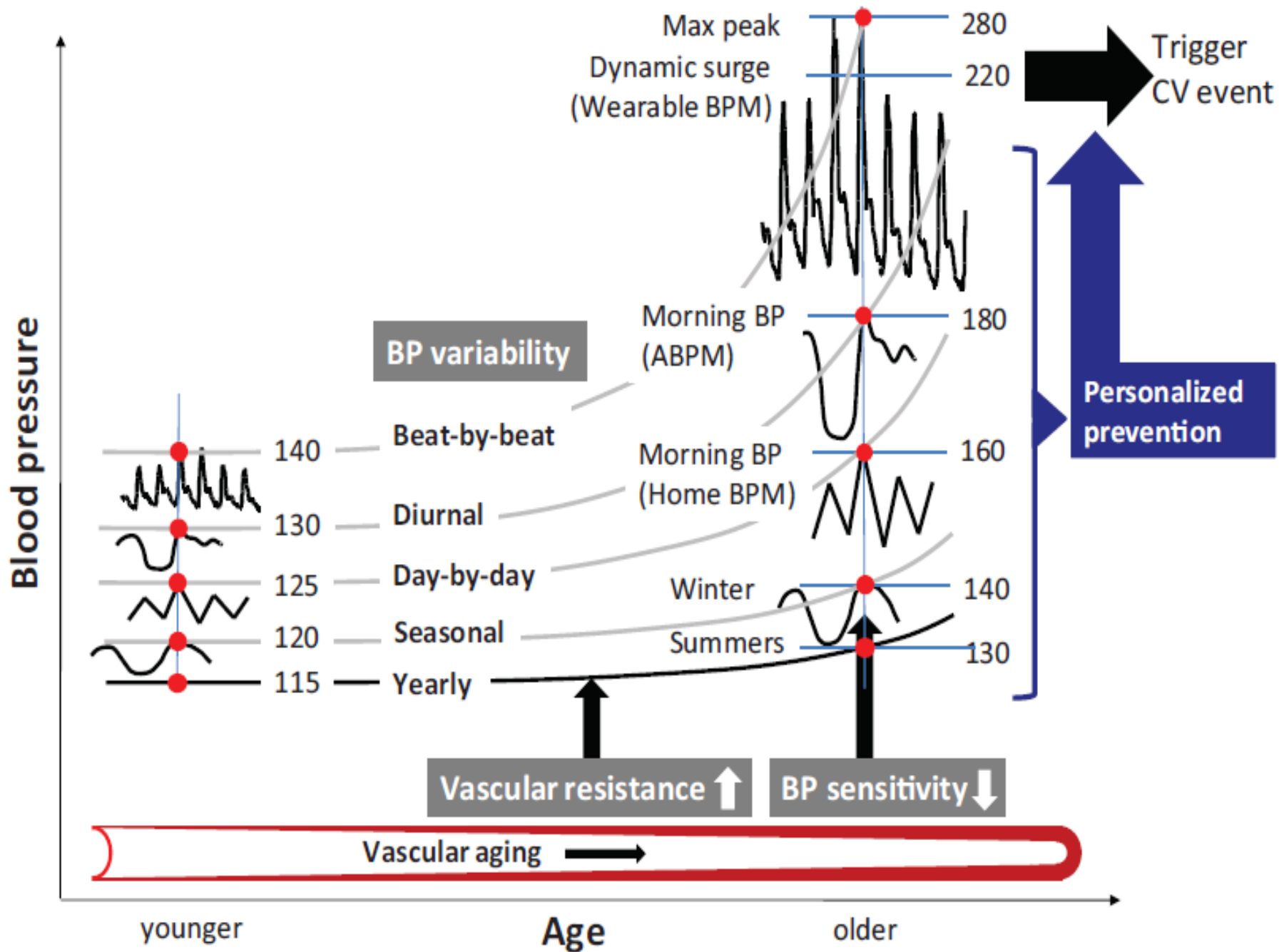
Heart rate-controlling calcium antagonists (cilnidipine, azelnidipine, diltiazem)

Conclusions:

1. There is a pronounced **diurnal rhythm** of BP and cardiovascular events, with a **peak of both in the morning hours**, and a decrease during the night.
2. In some categories of patients the **normal dipping pattern of BP is lost or reversed**; this *may* be associated with increased risk.
3. Drugs approved for once daily dose may have different durations of action, particularly after missed doses.
4. Most classes of antihypertensive drugs lower daytime BP more than nighttime BP.

Conclusions:

5. Long acting antihypertensive drugs, twice daily, a-blocker, RAS blocker, Non-DHP CCB may be effective to control morning blood pressure.
6. With some antihypertensive drugs the **time of dosing** may have significant effects on the diurnal pattern of BP.
7. The implications of these **time-dependent differences** of antihypertensive drugs for CV morbidity are largely unknown, and need to be more fully investigated.



Thank you !

