Morning surge in blood pressure accelerates TOD

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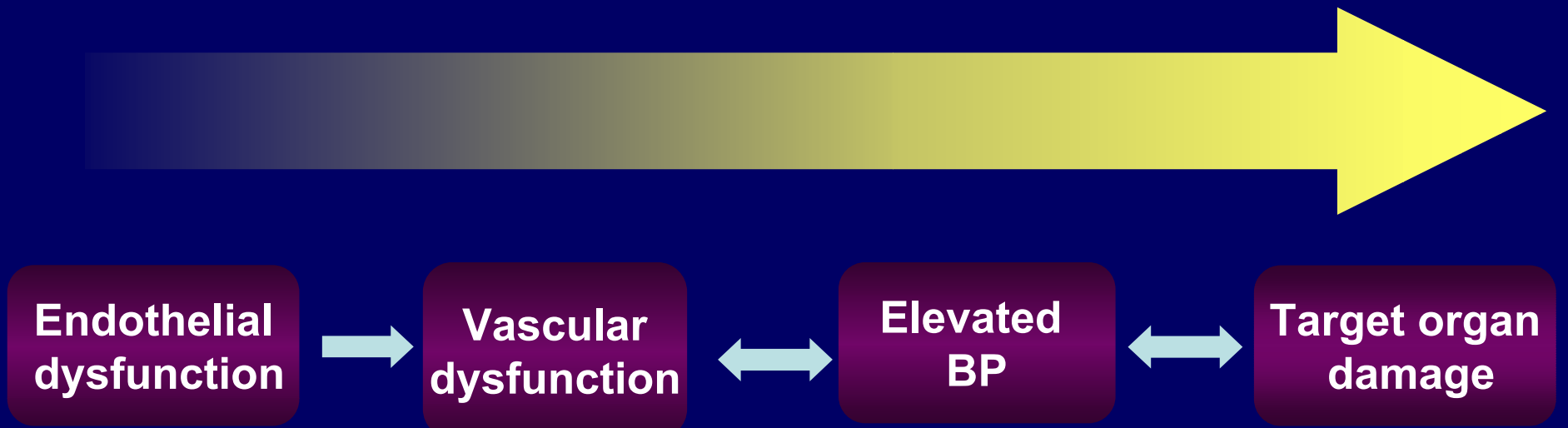
Natural history of hypertensive disease

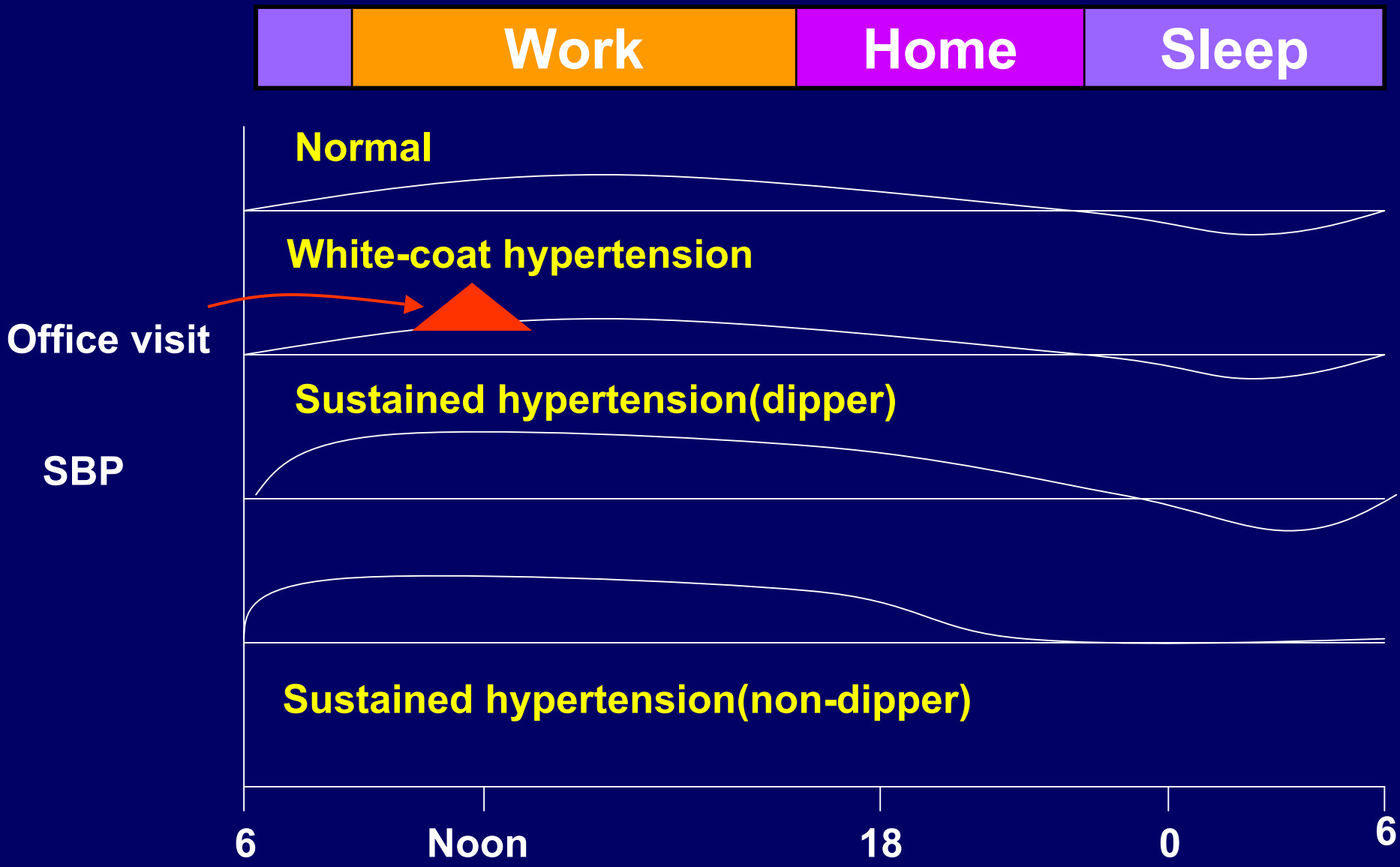
From endothelial dysfunction to target-organ damage



BLOOD PRESSURE VARIABILITY

- Blood pressure fluctuates continuously over time, either spontaneously or in responses to a variety of external stimulations.

- Average 24 h BP, as well as 24 h BP variability correlate with the hypertension-related alterations of the target-organ structure and function.



Circadian blood pressure patterns that may be obtained by ambulatory monitoring.

Recommendations for the use of home(self) and ambulatory blood pressure monitoring

BP Measure	NORMOTENSIVE (mmHg)	HYPERTENSIVE (mmHg)
Day-time (awake)	< 135/85	≥ 140/90
Night-time (asleep)	< 120/75	≥ 125/80
Average 24-h	< 130/80	≥ 135/85

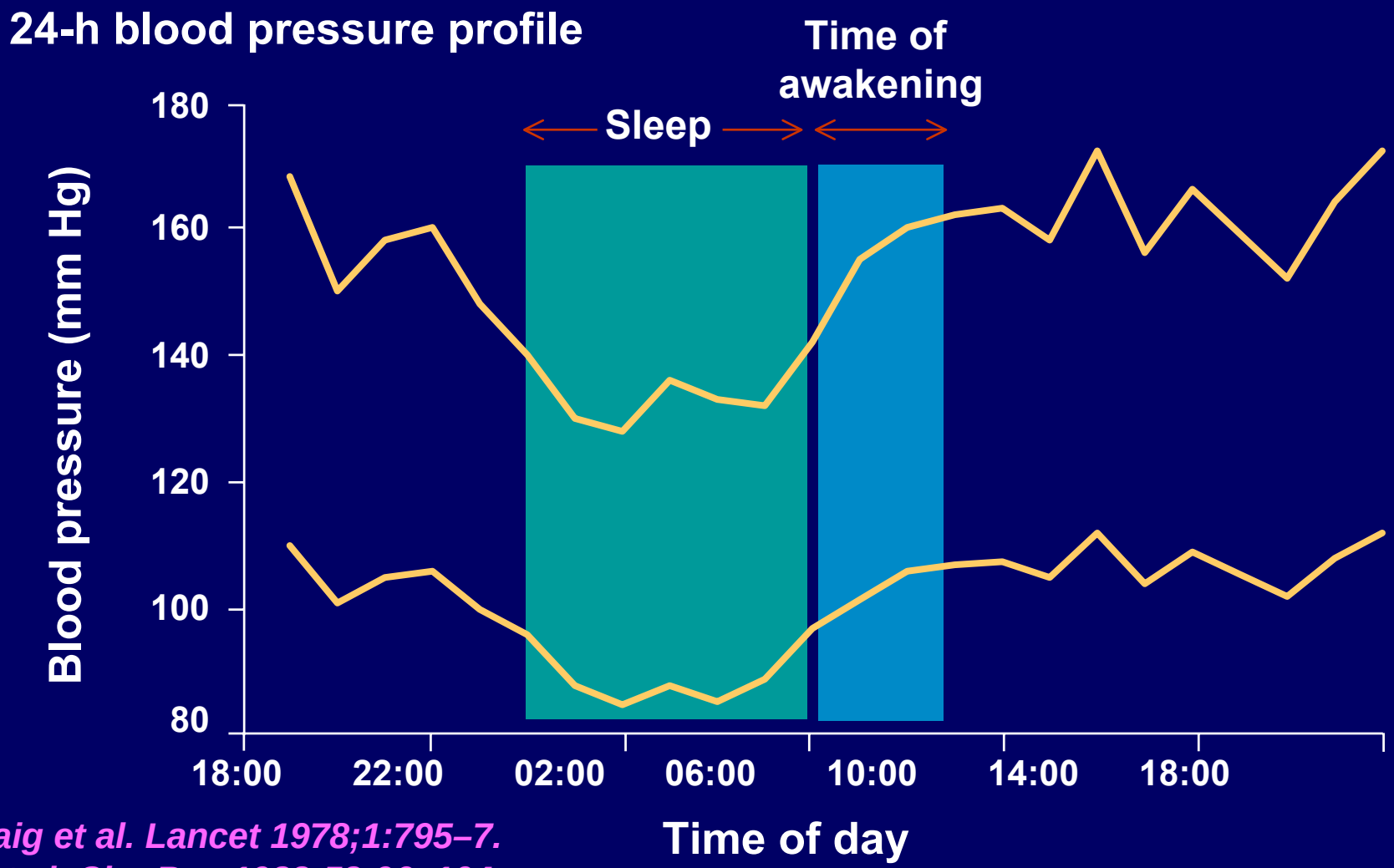
The difference between awake and asleep blood pressure is usually more than 15/10mmHg

Pickering T. Am J Hypertens 1995;9:1-11

Parameters influencing the normal circadian pattern of BP

›hic	Age > 70 years
ɛris	African-American ethnicity
External factors	Mental/ physical activity
	Postural changes
	Smoking
	Alcohol ingestion
	Sodium ingestion
	Caffeine ingestion
	Medication(e.g. oral contraceptives)
Neuroendocrine system	Sympathetic nervous system
	Renin-angiotensin-aldosterone system
	Plasma cortisol concentration
	Nitric oxide level

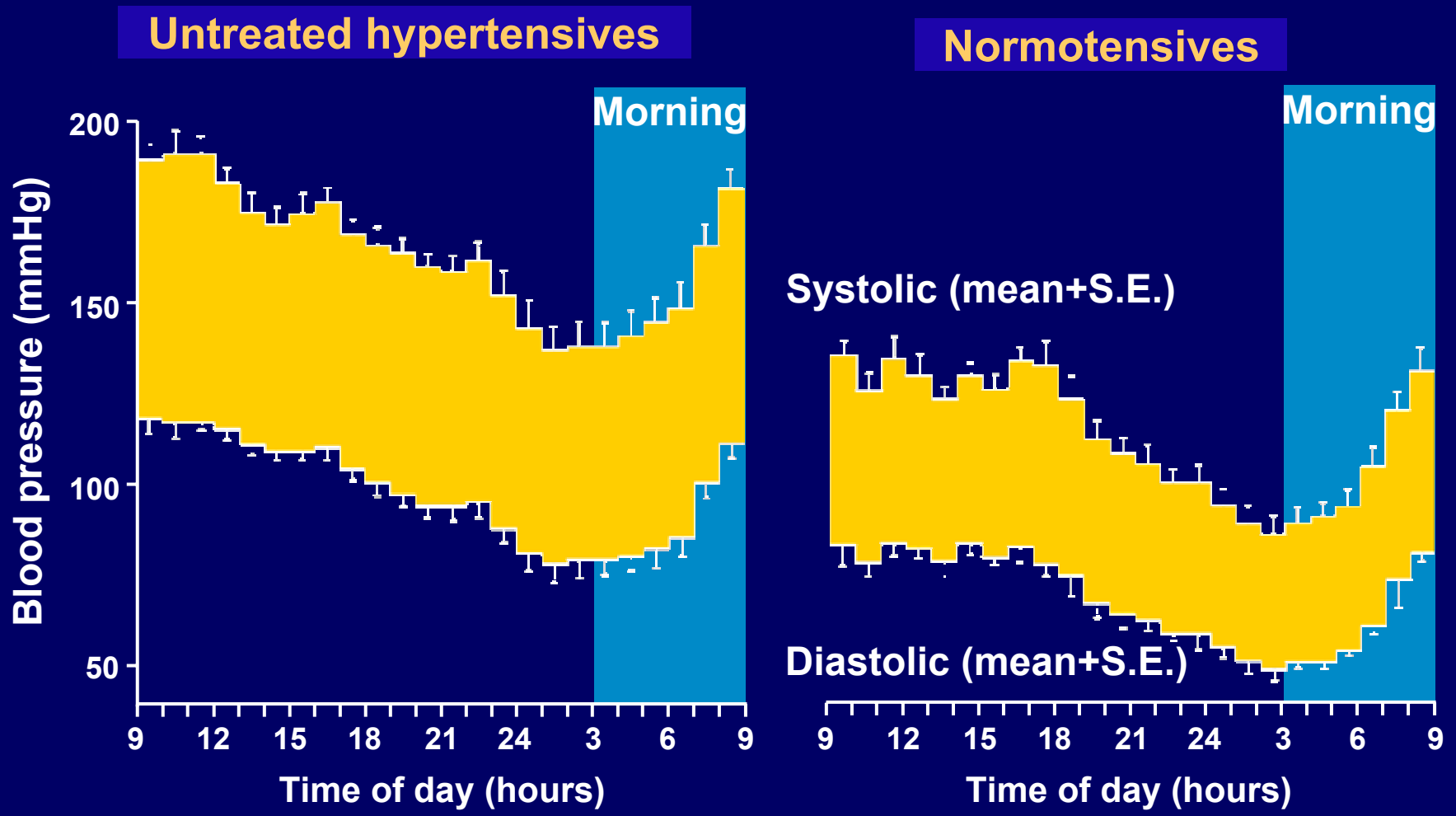
Morning blood pressure surge



Millar-Craig et al. Lancet 1978;1:795–7.
Mancia et al. Circ Res 1983;53:96–104.

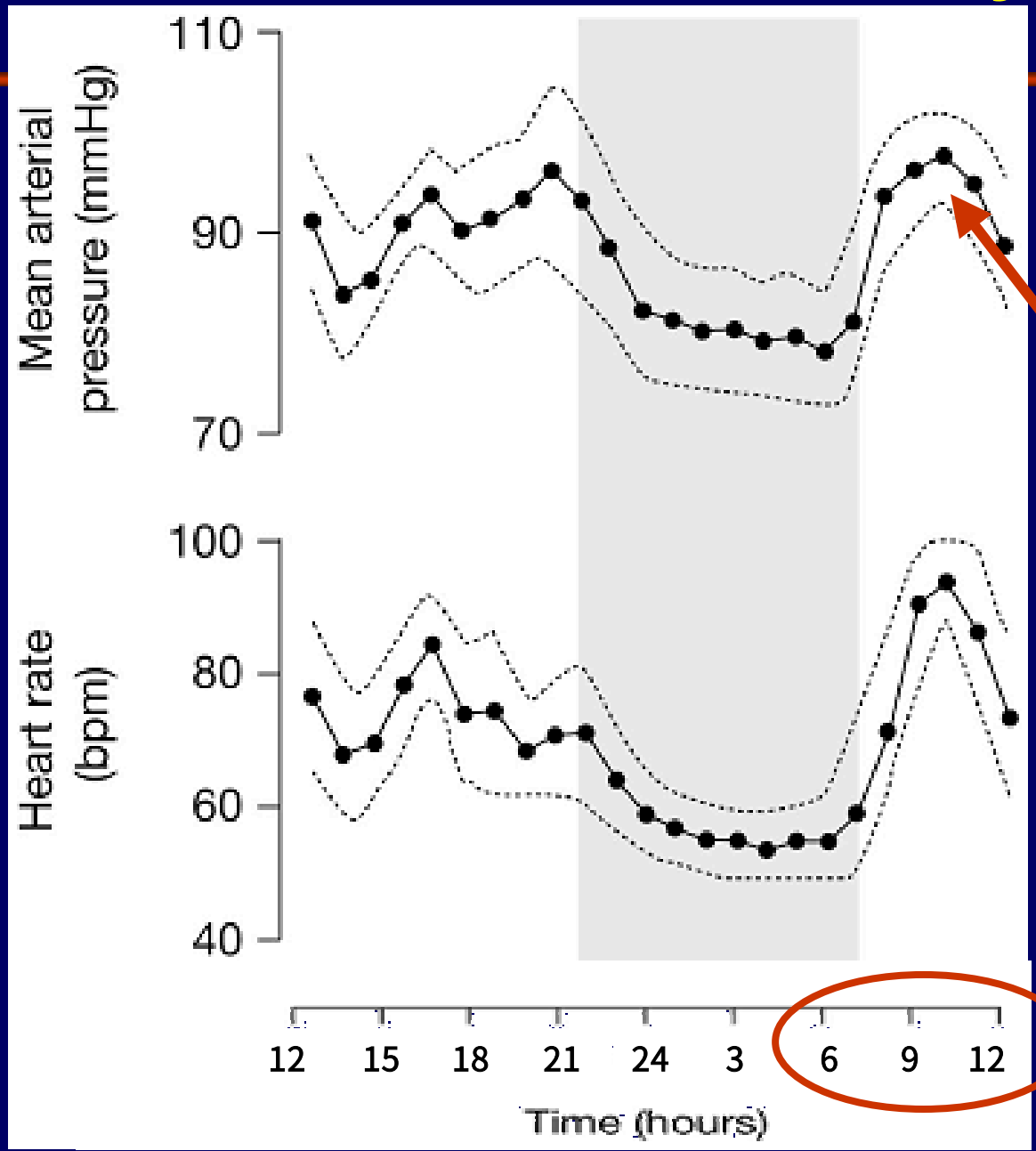
Morning blood pressure surge

increased morning blood pressure in norm- and hypertensives



Millar-Craig et al. Lancet 1978;1:795–7.

Circadian variation of BP in hypertension



Morning surge

Circadian variation in blood pressure

Morning surge in blood pressure

- Abrupt rise in BP that occurs after arising from sleep in both normotensive and hypertensive individuals

  → continues for 4-6 h after awakening

  → increases at a rate of about

  SBP: 3mmHg/h and DBP; 2mmHg/h

- May be associated with hypertensive target organ damage and subsequent cardiovascular risk in hypertensive patients

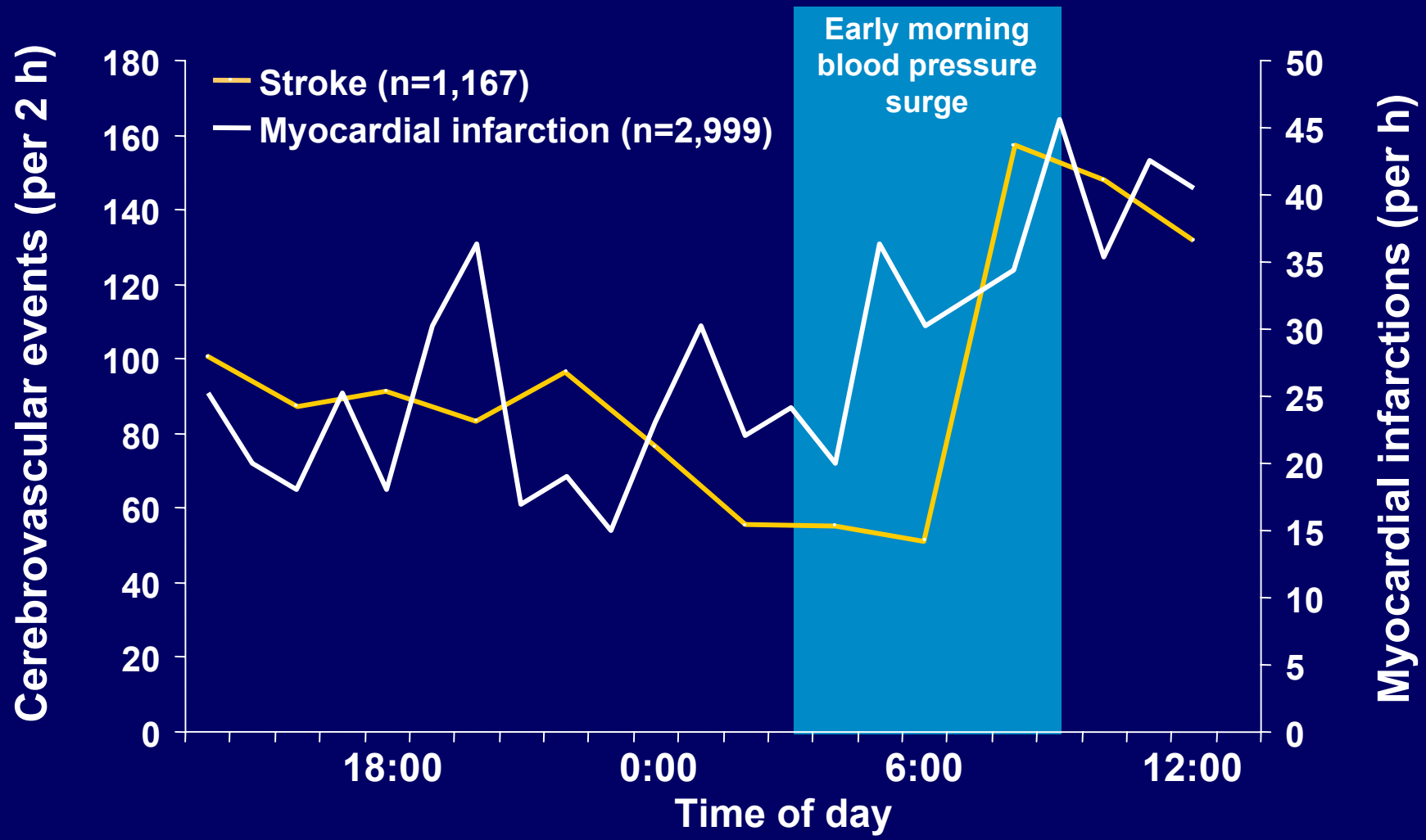
Morning blood pressure surge and CV events

A large number of studies have demonstrated that the incidence of MI, sudden death and stroke is the highest during the vulnerable period of 0600 to 1200 h.

Elliott WJ. Am J Hypertens 2001;14:291S-295S.

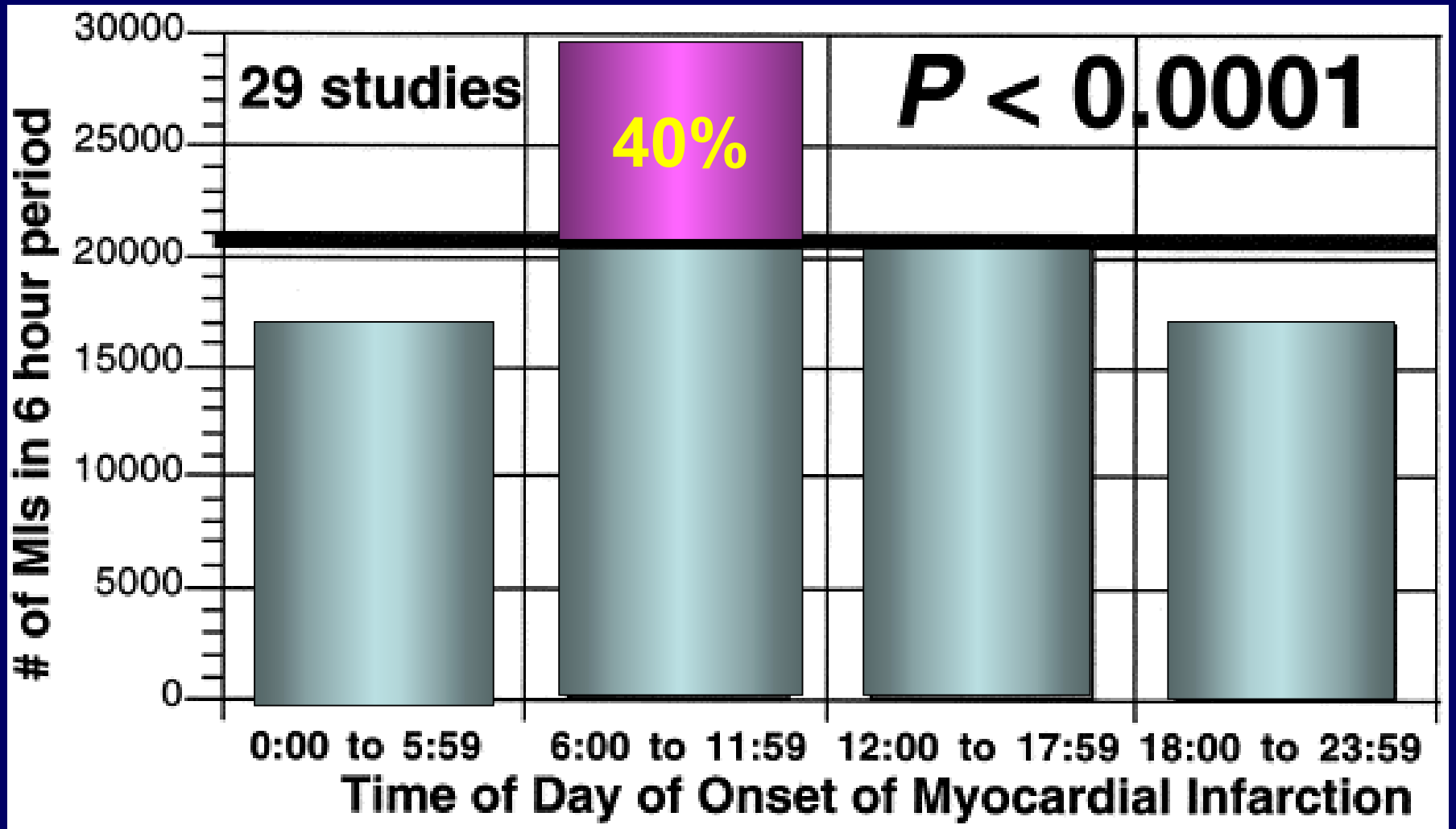
Morning blood pressure surge

Increased cardiovascular risk



Muller et al. N Engl J Med 1985;313:1315–22.
Marler et al. Stroke 1989;20:473–6.

Circadian variations of BP and CV events: Onset of MI



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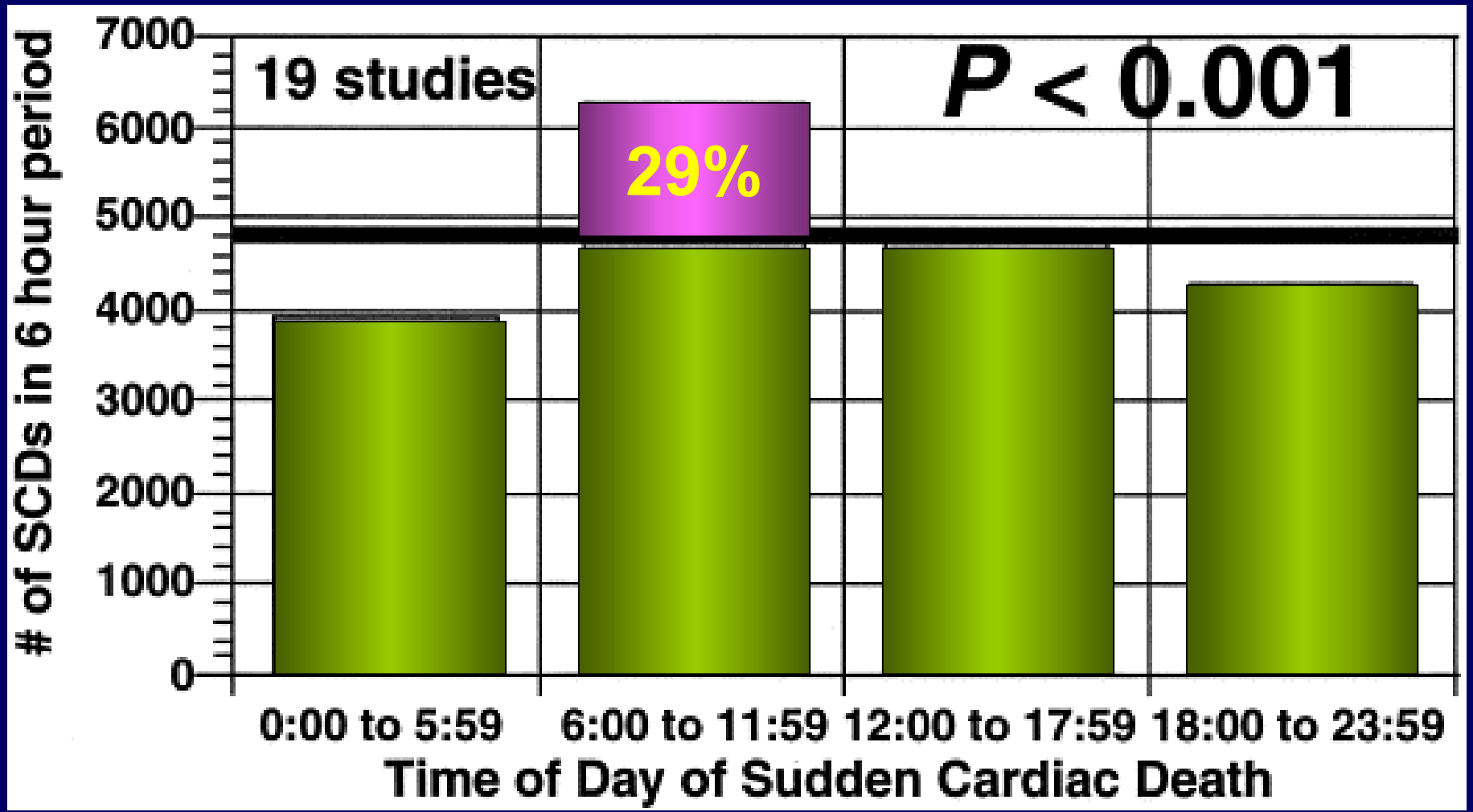
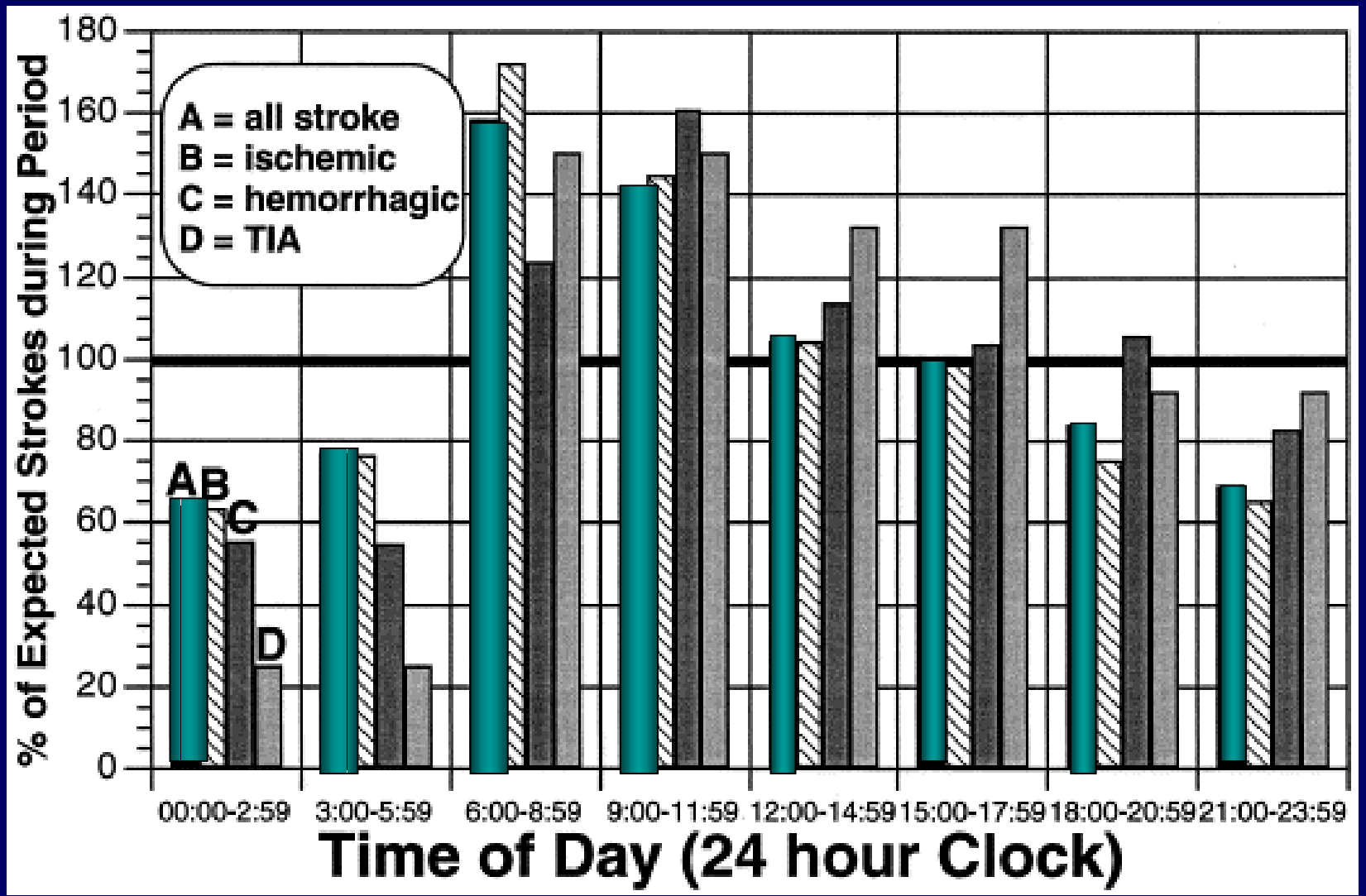
Circadian variations of BP and CV events: Onset of Sudden Death



Elliott WJ. Am J Hypertens 2001;14:291S-295S.

Circadian variations of BP and CV events: Distribution of Strokes



Elliott WJ. Am J Hypertens 2001;14:291S-295S.

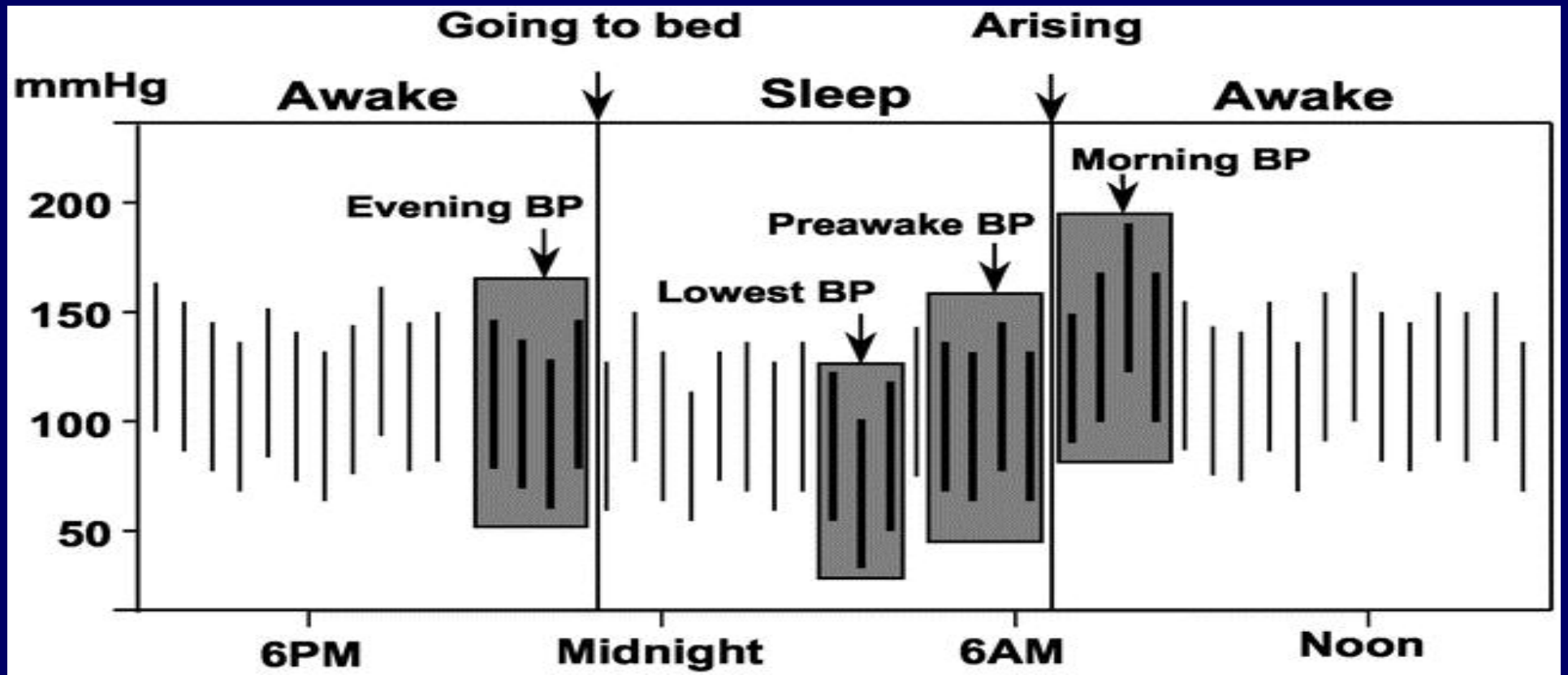
Definition of morning blood pressure surge(MBPS)

- Defined as the difference between the mean systolic blood pressure during the 2 hours after waking and arising minus the mean systolic blood pressure during the hour that included the lowest blood pressure during sleep
- Sleep-trough MBPS

  Prewaking MBPS

Kario K, et al. Circulation 2003;107:1401-6.

- **Sleep BP**; 자는 동안 기록한 혈압의 평균
- **Awake BP**; 깨어 있는 동안 기록한 혈압의 평균
- **Morning BP**; 기상 후 첫 2시간 동안 기록한 혈압의 평균
- **Lowest BP**; 취침 중에 가장 낮게 기록 된 혈압 전과 후의 평균
- **Evening BP**; 취침 2시간 전에 기록한 혈압의 평균
- **Preawake BP**; 기상 2시간 전에 기록한 혈압의 평균

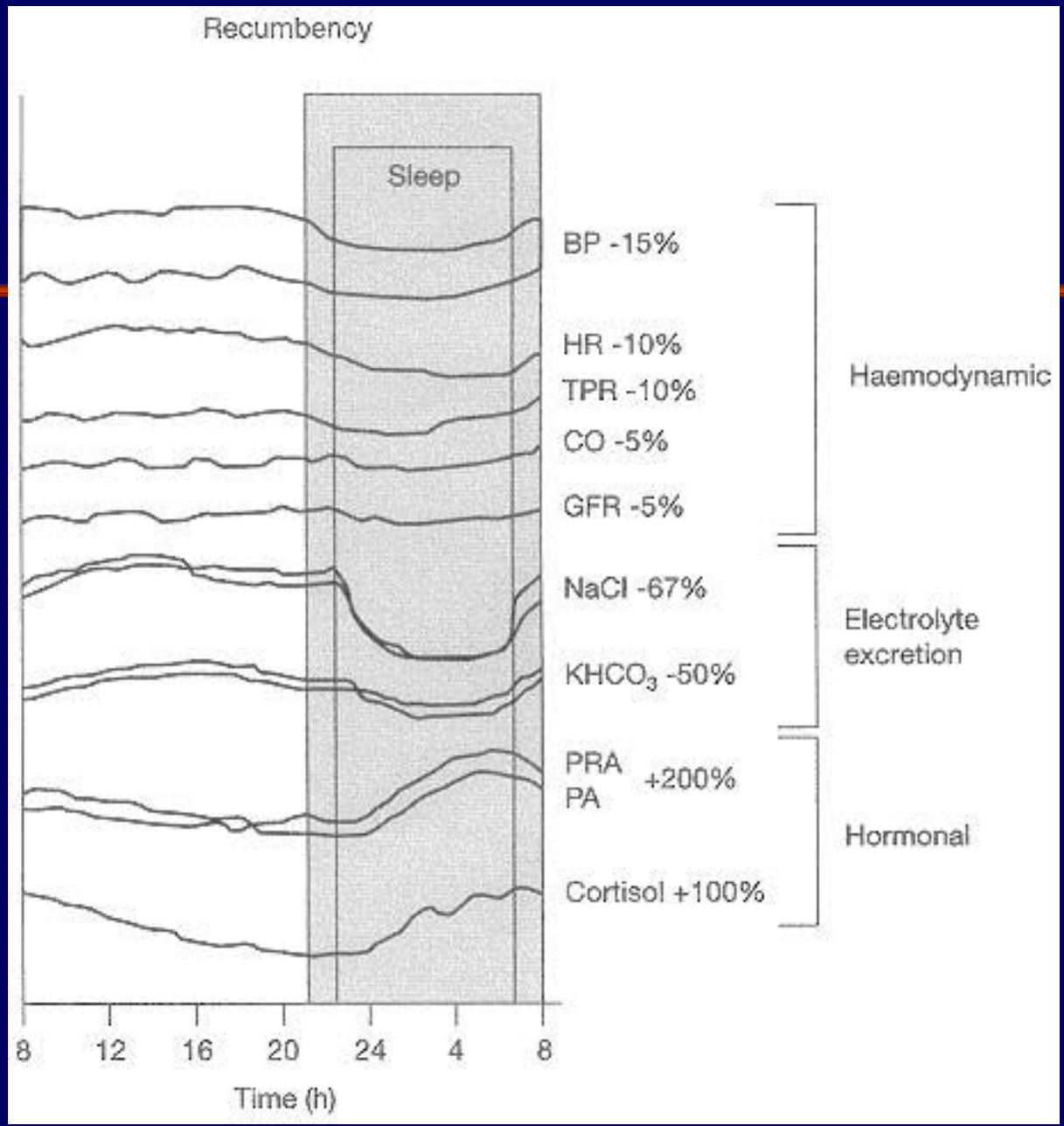


Definition of morning blood pressure surge(MBPS)

- **Sleep-trough MBPS:**
  morning SBP – lowest SBP
- **Prewaking MBPS:**
  morning SBP – preawake SBP
- **Noctunal BP fall:**
  evening BP – lowest BP

Kario K, et al. Circulation 2003;107:1401-6.

Mechanism of MBPS



Circadian variation of physiologic function

Pathomechanisms of Circadian Variation of Cardiovascular Events?

Hemodynamic

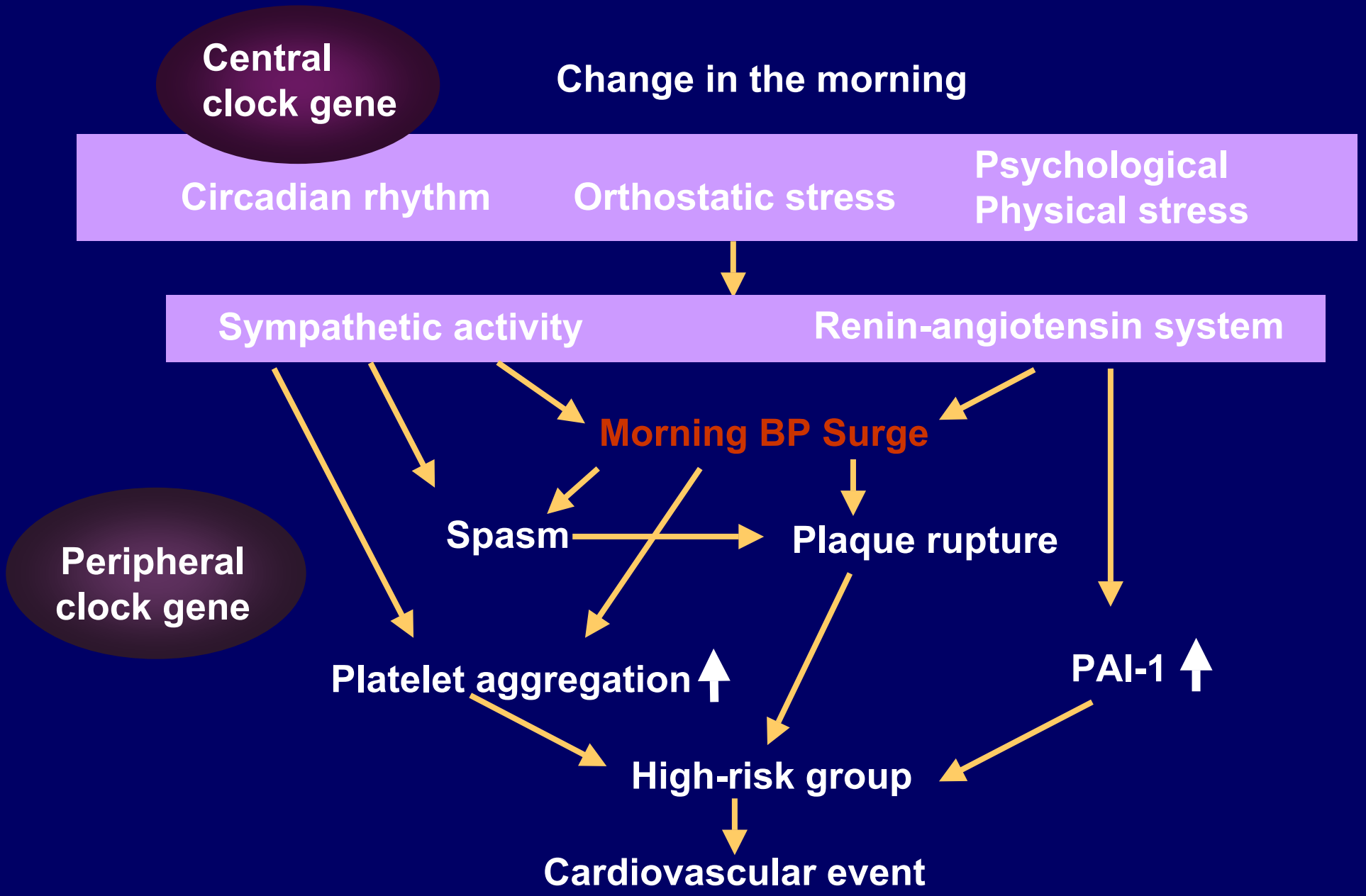
- Systolic BP ↑
- Heart rate ↑
- Workload SBP x HR ↑↑↑

Endothel. Dysfunction

- Norepinephrine ↑
- Epinephrine ↑
- α-Sympathomimetic Activity ↑
- Plasma Renin Activity ↑
- Cortisol ↑

Prothrombotic State

- Blood viscosity, Hematocrit ↑
- Platelet Aggregation ↑
- tissue Plasminogen activator (t-PA) ↓
- Plasminogen Activator Inhibitor 1 (PAI 1) ↑



Mechanism of morning-onset cardiovascular disease

Relationship between blood pressure morning surge and hypertensive complications

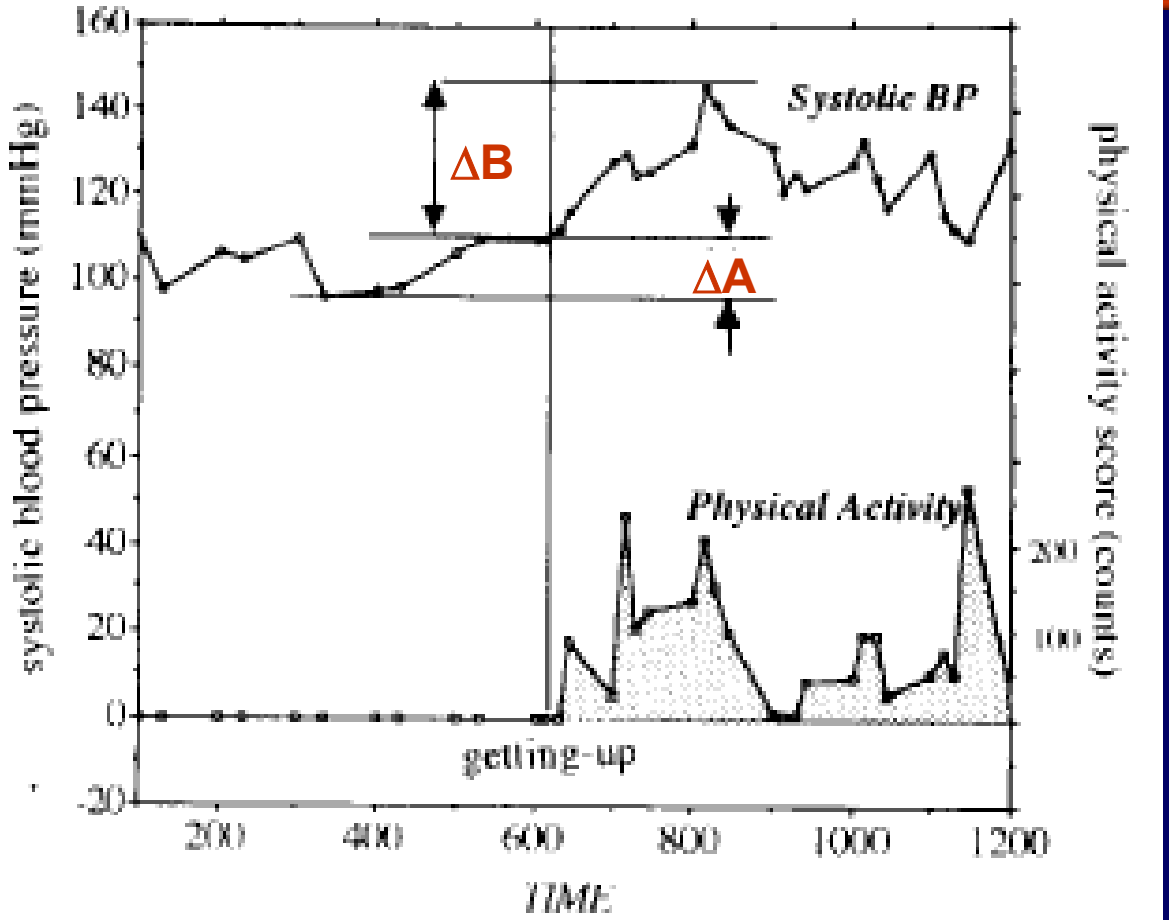
- **Heart:**

  Significant correlations with left ventricular mass and diastolic function independent of blood pressure before arising

- **Brain:**

  Significant associations with silent cerebrovascular disease and evidence of stroke independent of 24h average blood pressure

Cardiac Implications of the Morning Surge in Blood Pressure in Elderly Hypertensive Patients: Relation to Arising Time



Morning surge in SBP before and after arising time from bed.

ΔA represents the increase in SBP before arising.

ΔB represents the Increase in SBP after arising.

Kuwajima I, et al. Am J Hypertens 1995;8:29-33.

Cardiac Implications of the Morning Surge in Blood Pressure in Elderly Hypertensive Patients: Relation to Arising Time

Correlation between blood pressure change in the morning and cardiac parameters

	ΔSBP Before Arising		ΔSBP After Rising		ΔDBP Before Arising		ΔDBP After Rising	
Parameters	r	*P*	r	*P*	r	*P*	r	*P*
LAD	0.4	NS	0.4	NS	0.1	NS	0.1	NS
LVDd	0.1	NS	0.1	NS	0.1	NS	0.1	NS
LVDs	0.1	NS	0.3	NS	0.2	NS	0.3	NS
WT	0.3	NS	0.5	< .05	0.1	NS	0.3	NS
LVMI	0.2	NS	0.5	< .02	0.2	NS	0.3	NS
FS	0.2	NS	0.4	NS	0.4	NS	0.4	NS
A/E	0.4	NS	0.7	< .01	0.3	NS	0.2	NS

LAD; Left atrial dimension; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; WT, wall thickness; LVMI, left venticular mass index; FS, fractional shortening; A/E, ratio of diastolic transmitral valve flow.

Kuwajima I, et al. Am J Hypertens 1995;8:29-33.

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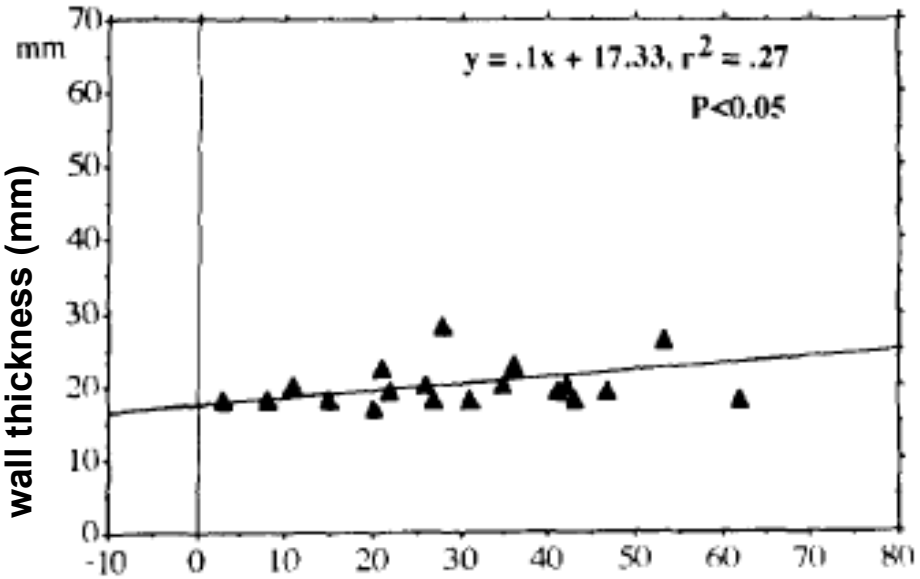
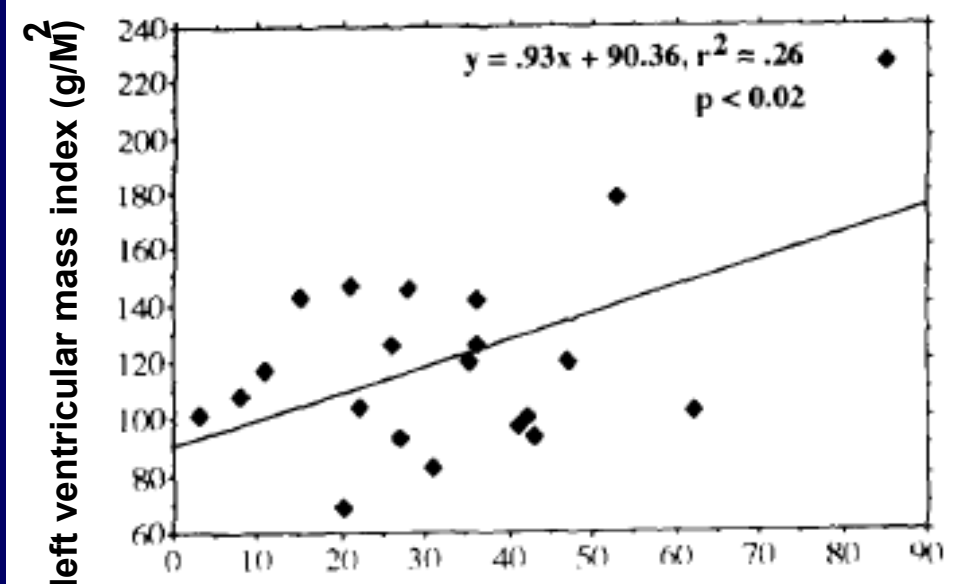




Correlation between the increase in systolic BP after arising from bed and wall thickness and left ventricular mass index.

Kuwajima I, et al. Am J Hypertens 1995;8:29-33.

Cardiac Implications of the Morning Surge in Blood Pressure in Elderly Hypertensive Patients: Relation to Arising Time

- The relation between the increase in BP before arising and cardiac parameters: No significant correlations
- The relation between the increase in BP after arising and cardiac parameters:

  - the higher the LV mass, the greater the increase in SBP after arising from bed

  - the more depressed the LV diastolic function, the greater the morning rise in SBP

Kuwajima I, et al. Am J Hypertens 1995;8:29-33.

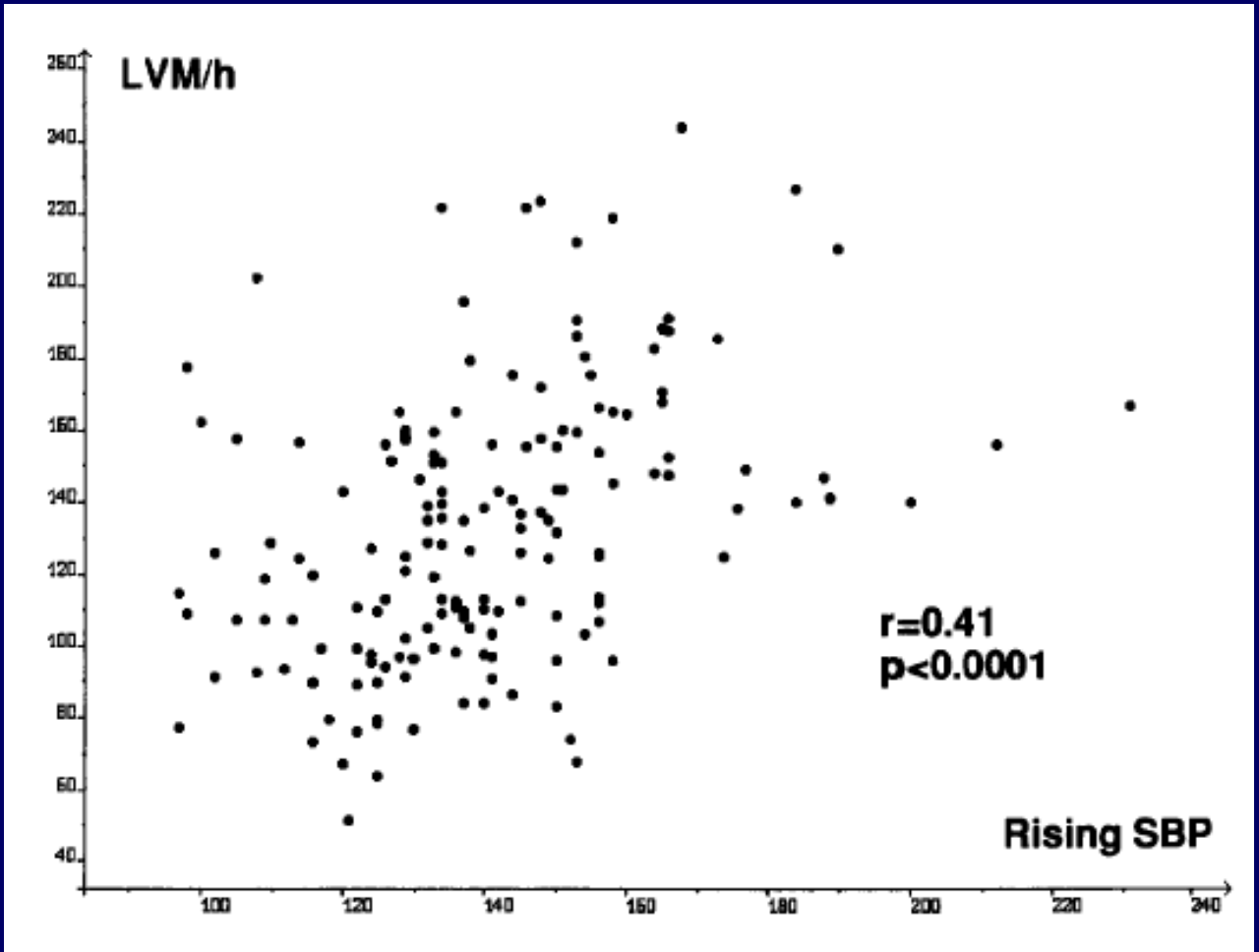
Conclusion

- **The higher the degree of LV hypertrophy and the more depressed diastolic LV function, the higher the BP increase after awaking and rising.**

The magnitude of morning surge in blood pressure after arising from bed was related with the severity of hypertensive target organ damage.

Kuwajima I, et al. Am J Hypertens 1995;8:29-33.

Left Ventricular Mass Is Better Correlated With Arising Blood Pressure Than With Office or Occasional Blood Pressure



A correlation between BP on arising and LV mass in 181 previously untreated hypertensive patients

Correlation between height-indexed LV mass and arising SBP

Gosse P, et al. Am J Hypertens 1997;10:505-510.

Left Ventricular Mass Is Better Correlated With Arising Blood Pressure Than With Office or Occasional Blood Pressure

- LV mass is a risk factor for CV complications, and a correlation with arising BP would have epidemiological implications

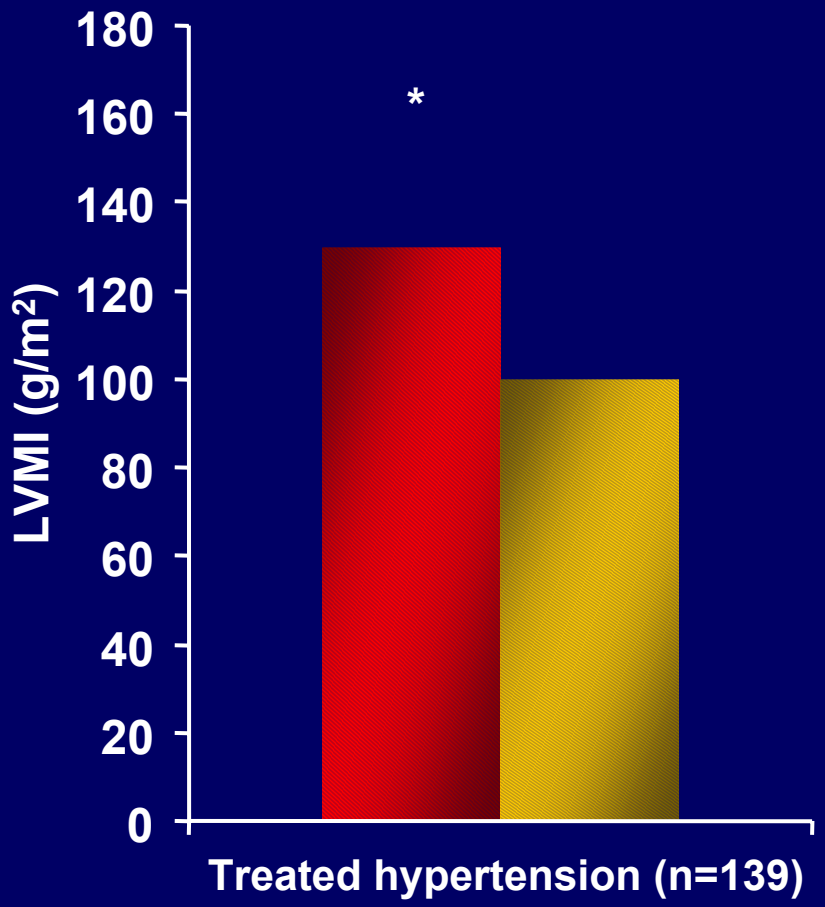
  → the significance of the arising BP

- The elevation in BP initiated on arising is enough to contribute to the development of LVH and may constitute a trigger for CV events.

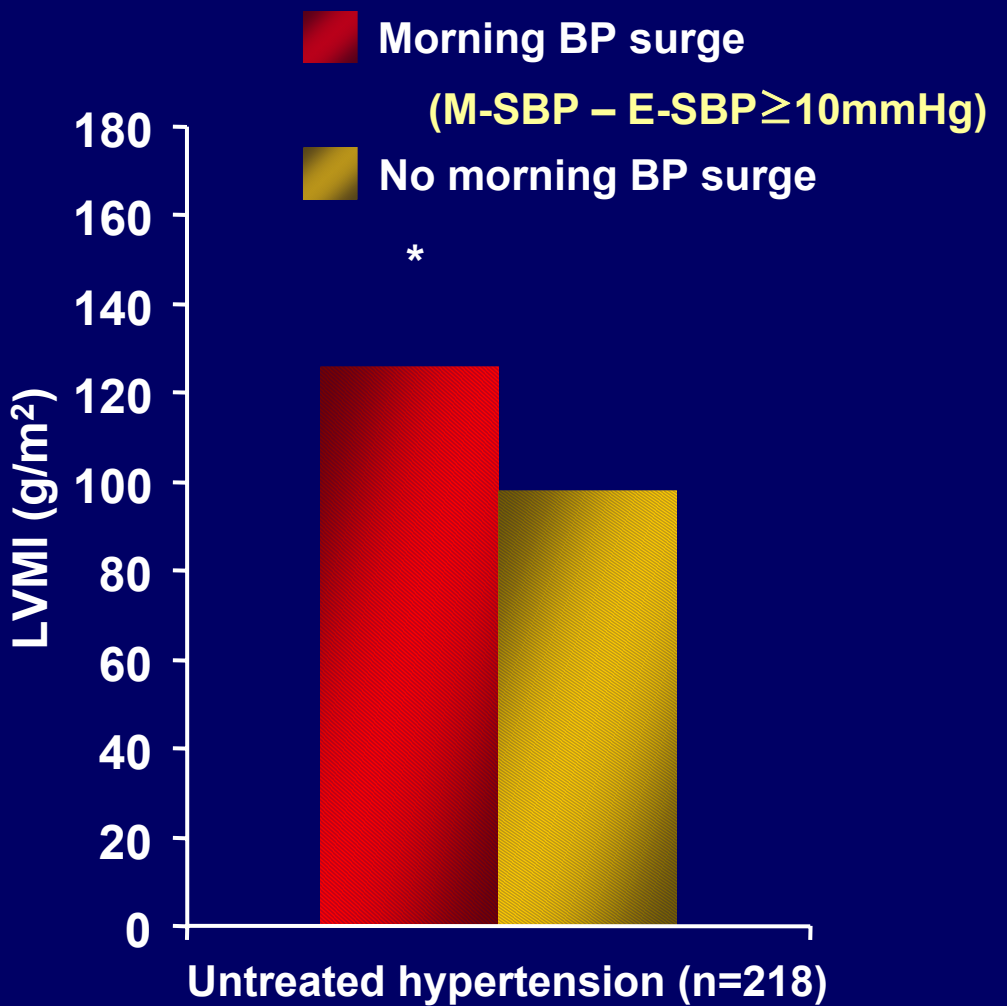
Gosse P, et al. Am J Hypertens 1997;10:505-510.

Morning BP surge increases the risk of developing LVH

*P<0.0001 vs no morning BP surge



Matsuo et al. J Hypertens 2002;20 (Suppl 4):S314



Ikeda et al. J Hypertens 2002;20 (Suppl 4):S150

Morning Surge in Blood pressure as a Predictor of Silent and Clinical Cerebrovascular Disease in Elderly Hypertensives: A Prospective Study

	MS Group (n=46)	Non-MS Group (n=145)	P-value
Age (years)	76	76	NS
24-h SBP (mmHg)	142	142	NS
Baseline data			
Silent cerebral infarct			
Prevalence (%)	70	49	0.02
Number (/person)	2.0	1.5	0.01
Multiple cerebral infarcts			
Prevalence (%)	54	37	0.04
Prospective data			
Stroke incidence (%) (relative risk=2.7)	17	7.0	0.04

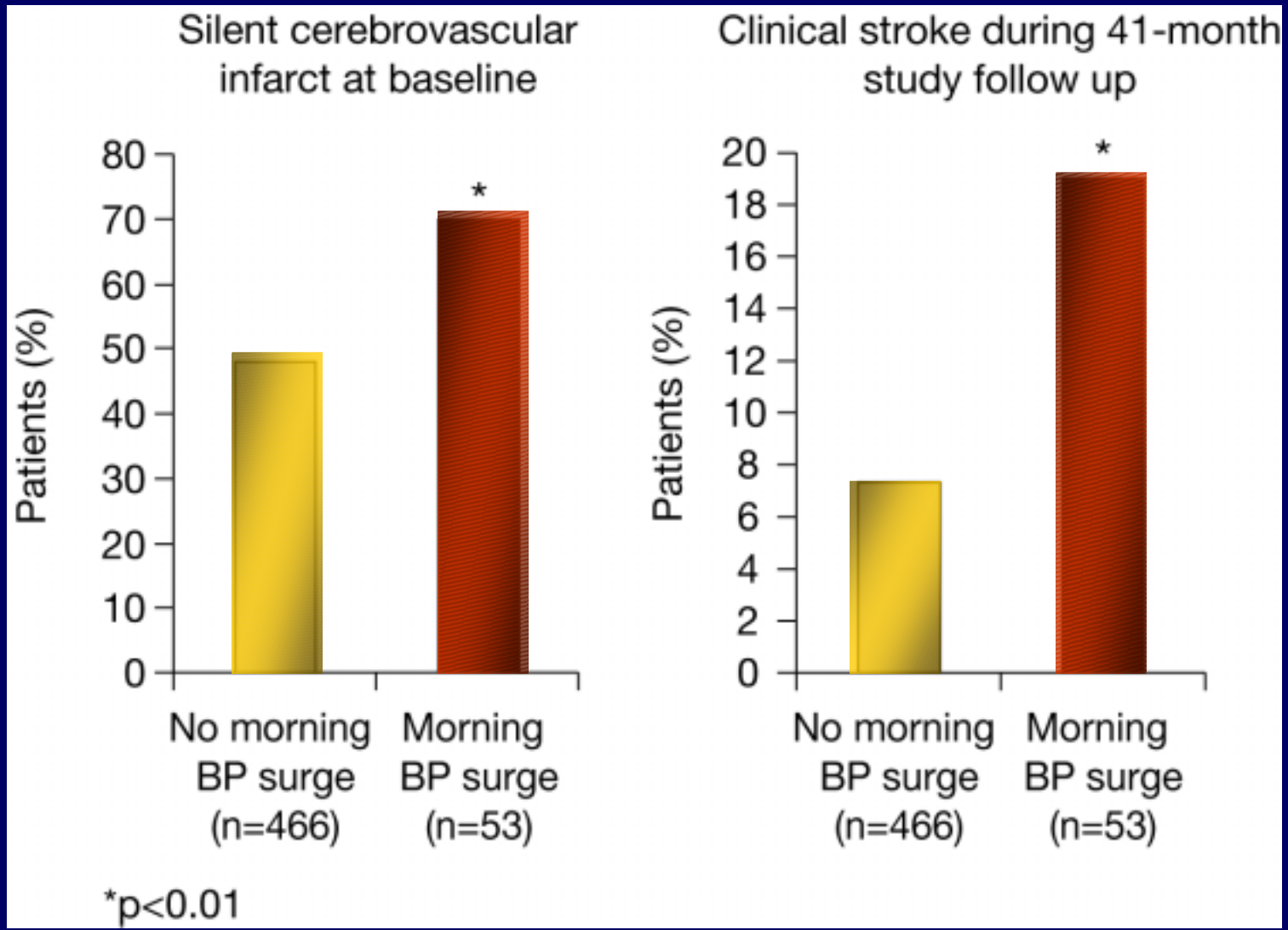
Kario K, et al. Circulation 2003;107:1401-6.

Morning Surge in Blood pressure as a Predictor of Silent and Clinical Cerebrovascular Disease in Elderly Hypertensives: A Prospective Study

Relative risk for stroke event in hypertension (n=519)

Covariates		
Age (10years)	1.75 (1.20-2.55)	0.004
24-h SBP (10mmHg)	1.38 (1.17-1.64)	<0.001
Silent cerebral infarct	4.50 (1.99-10.20)	<0.001
Morning SBP surge (10mmHg)	1.22 (1.05-1.40)	0.008

Kario K, et al. Circulation 2003;107:1401-6.



The prevalence of silent cerebrovascular infarct and incidence of clinical stroke in patients with and without morning blood pressure surge

Kario K, et al. Circulation 2003;107:1401–6.

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

A Prospective Study

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.

Ba ...tion

Me ...was ...ning ...tolic ...ths), ...(MS ...and ... MS ...us the non-MS ...troke events independently of ..., 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.)**

Early morning BP as a therapeutic target

- For antihypertensive agents taken once daily in the morning, the time of the trough plasma drug level and therefore the lowest pharmacodynamic effect often coincides with the early morning rise in BP and HR.

- CV risk is heightened at this time of day, so the morning surge itself could become a trigger for acute events.

Optimal treatment of hypertension

- Attenuate the early-morning surge in blood pressure
- Maintain the normal circadian pattern of blood pressure

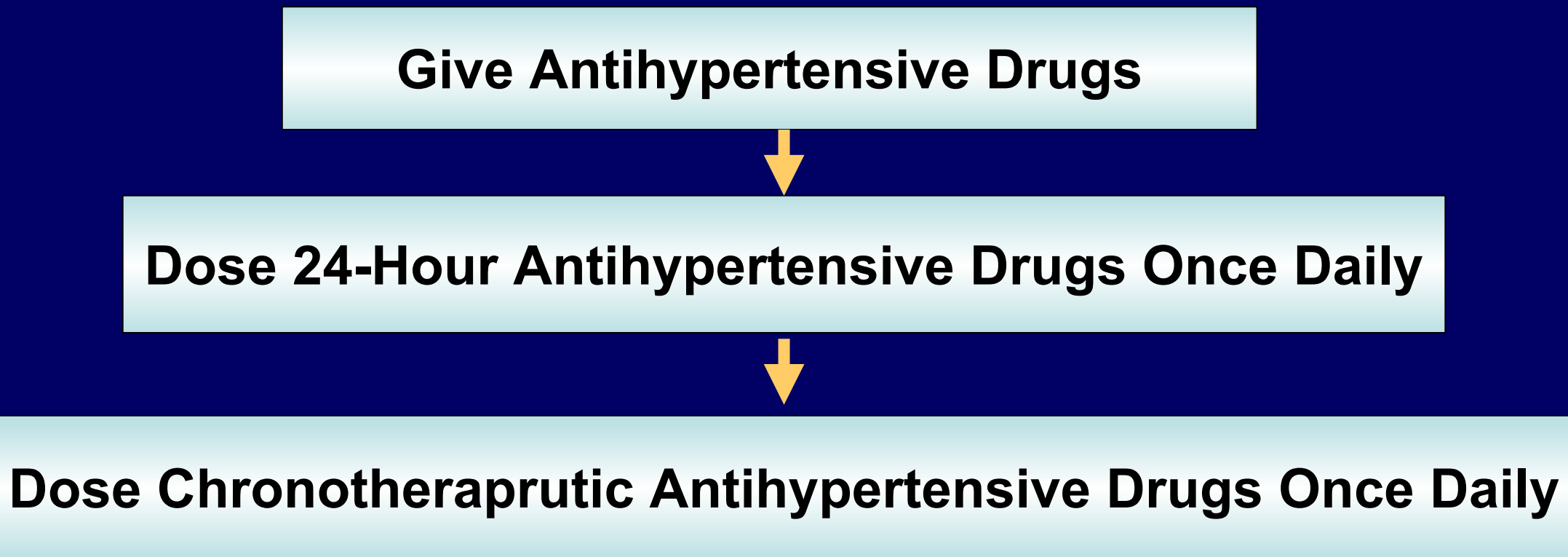
Antihypertensive agents with a longer duration of action appear preferable to those that provide intermittent blood pressure control

- **Intrinsically long-acting antihypertensive drugs**
  - characterized by long elimination half-lives with high T/P ratios for decreasing BP.
  - once daily in the morning

- **Long-acting chronoformulations**
  - incorporate sh… …ting antihypertensive drugs i… …layed on…
  - o…
  - COE…

‘ Chronotherapeutics ’ is the purposeful alteration of drug level to match rhythm to optimize therapeutic outcomes and minimize side effect

Hypertension and Chronotherapy: Shifting the Treatment Paradigm



Flowchart depicting a transition in therapeutics.

Summary

- The morning surge in BP appears to be a risk factor for subclinical hypertensive target organ damage and subsequent CV events in hypertensive patients, that is independent of the average BP levels.
- It is possible that the strict management of morning BP as well as of risk factors that show a similar morning surge might achieve a more effective prevention of CV disease