Clinical Aspect of Morning Blood Pressure Surge

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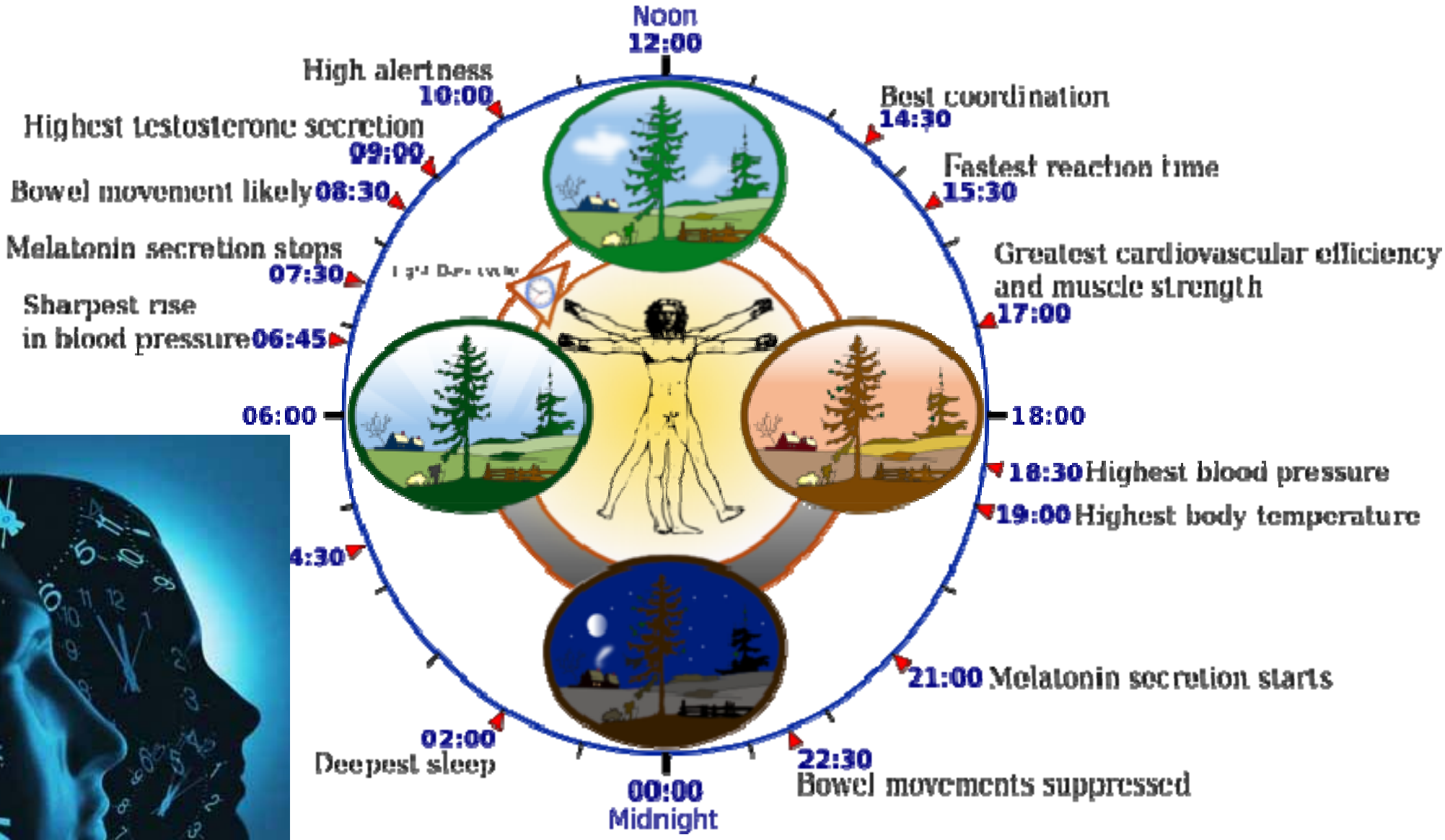
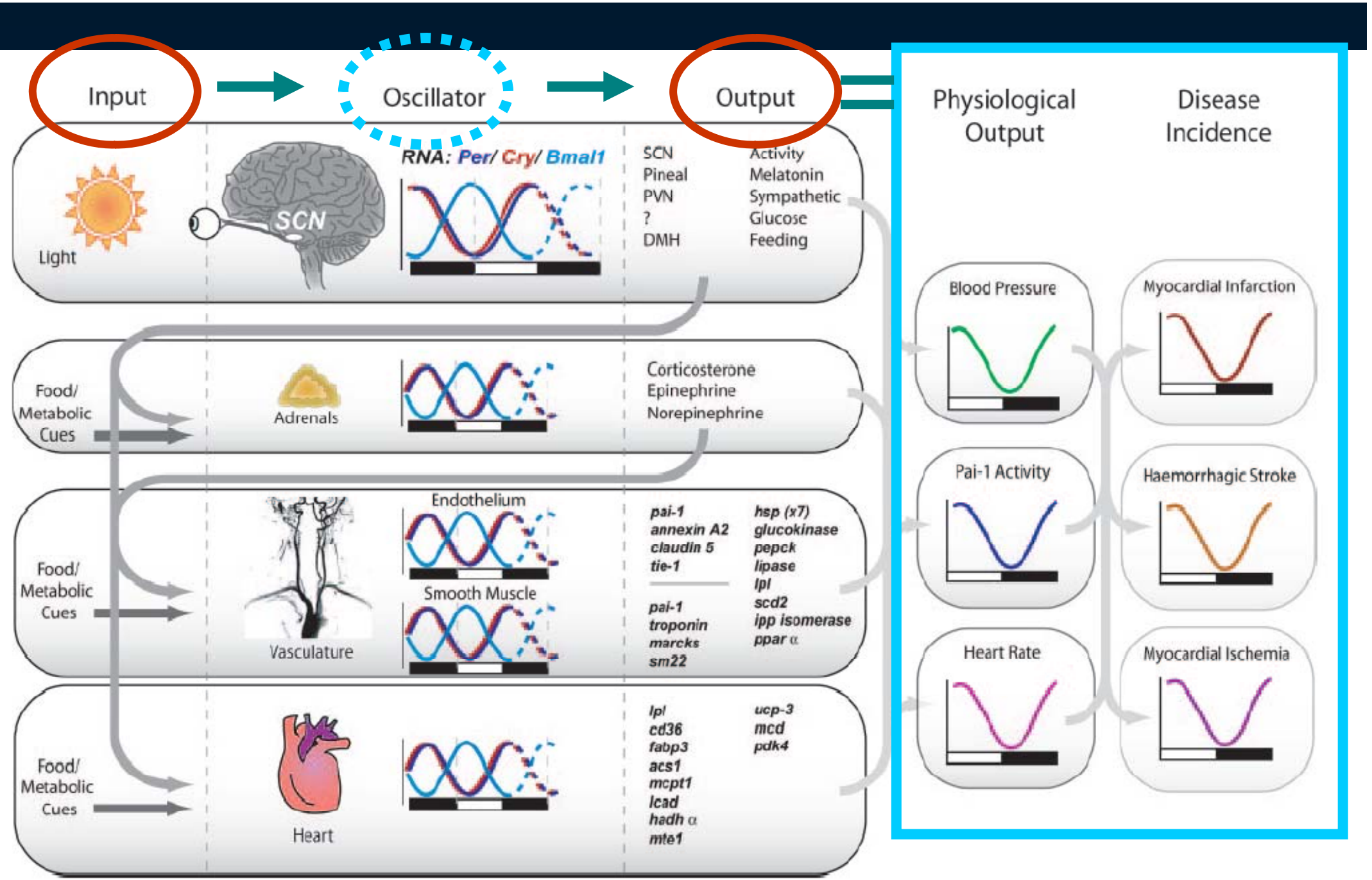

Noon
12:00
High alertness
10:00
Highest testosterone secretion
09:00
Bowel movement likely
08:30
Melatonin secretion stops
07:30
Sharpest rise
in blood pressure
06:45
06:00
4:30
02:00
Deepest sleep
00:00
Midnight
22:30
Bowel movements suppressed
21:00
Melatonin secretion starts
19:00
Highest body temperature
18:30
Highest blood pressure
18:00
17:00
Greatest cardiovascular efficiency
and muscle strength
15:30
Fastest reaction time
14:30
Best coordination

Circadian Rhythm

- Daily cycles of physiology and behavior that are driven by an endogenous oscillator with a period of approximately (*circa-*) one day (*dies or diem*).



SCN, suprachiasmatic nucleus

ATVB 2007;27:1694

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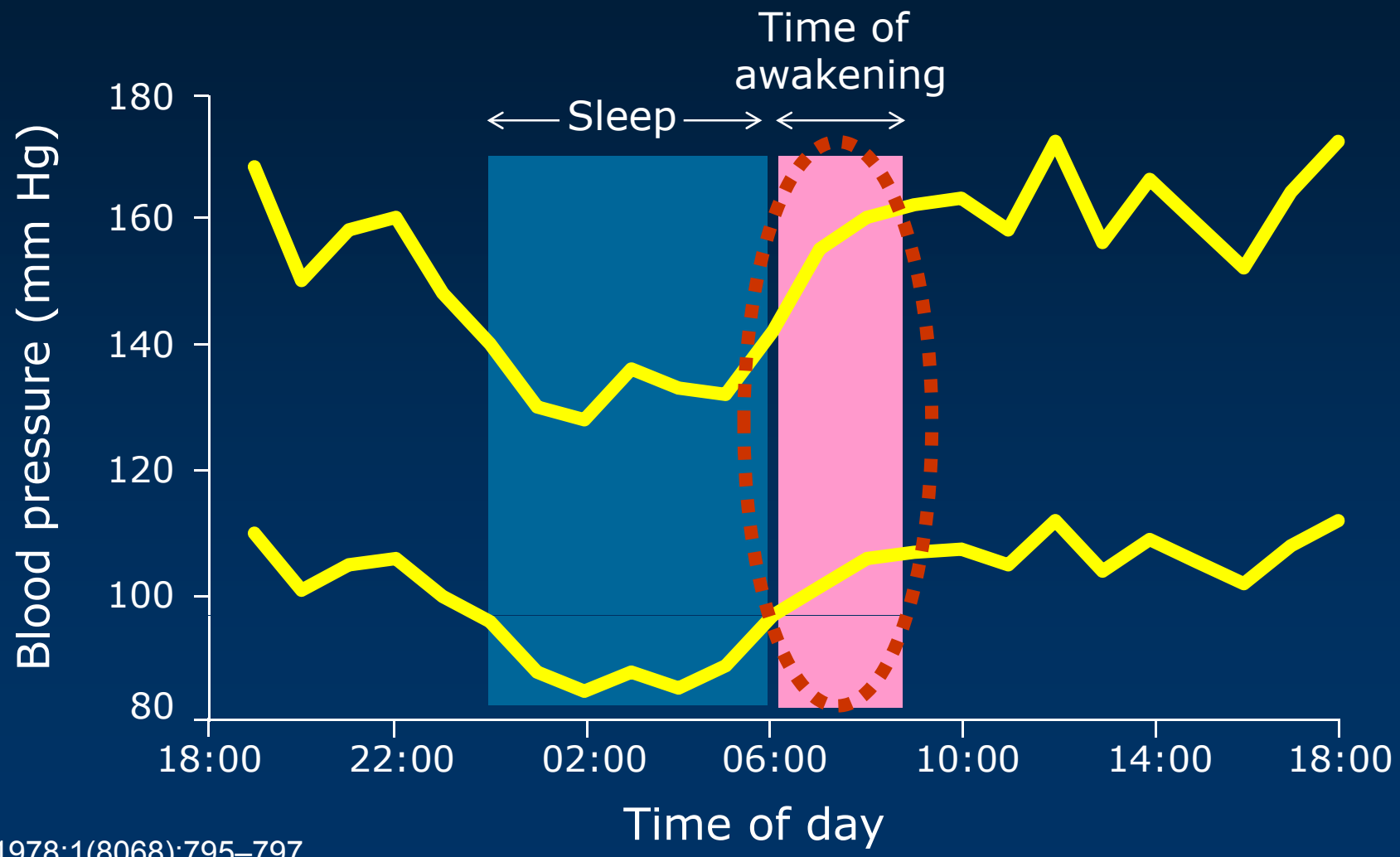
- CV or hemodynamic parameters such as **HR, BP, endothelial function**, and **fibrinolytic activity** exhibit variations consistent with **circadian rhythm**.

Diurnal Variation of BP



Lancet 1978;1(8068):795–797
Circ Res 1983;53:96–104

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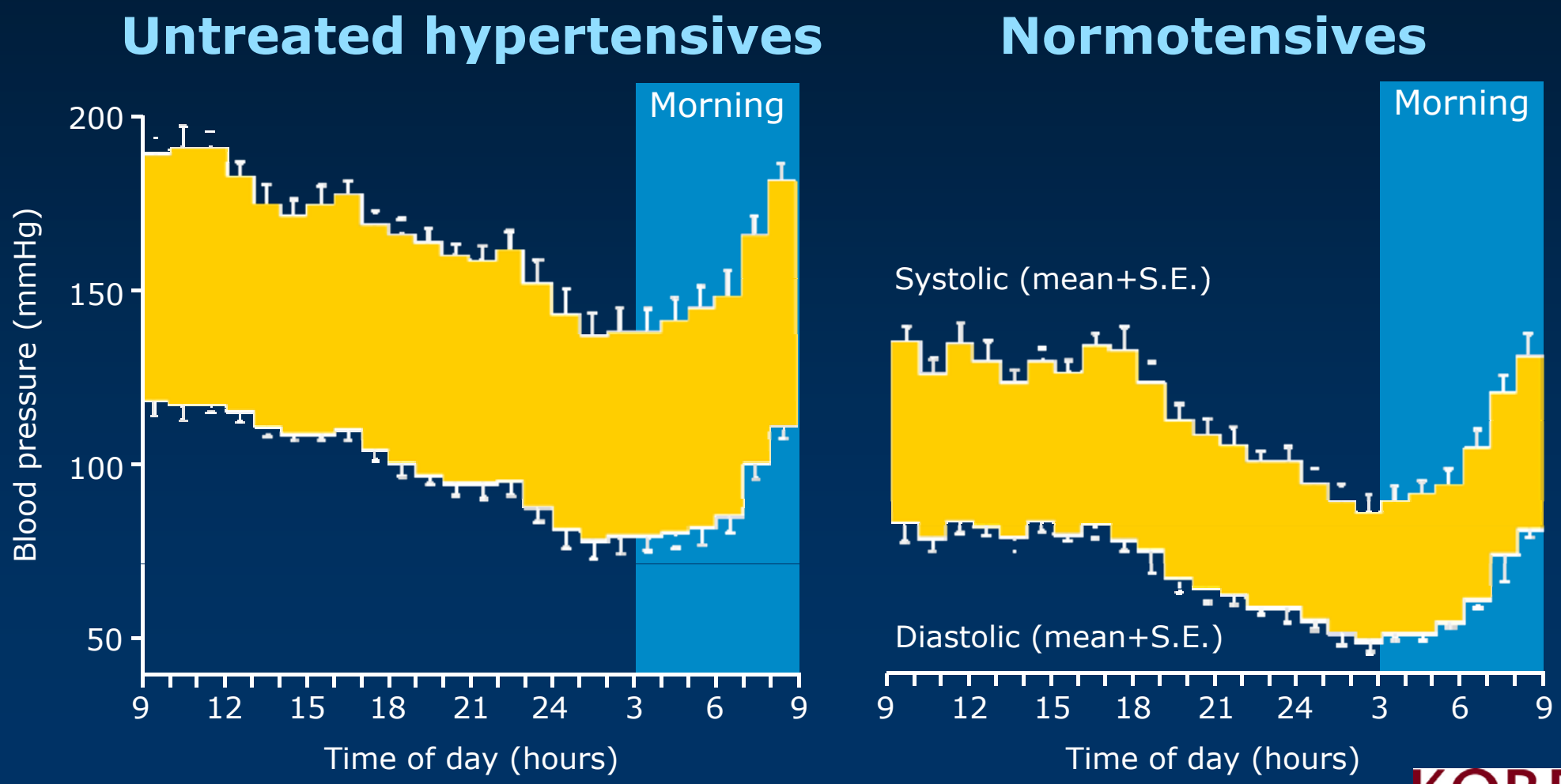
Early Morning BP Surge



Lancet 1978;1:795–797

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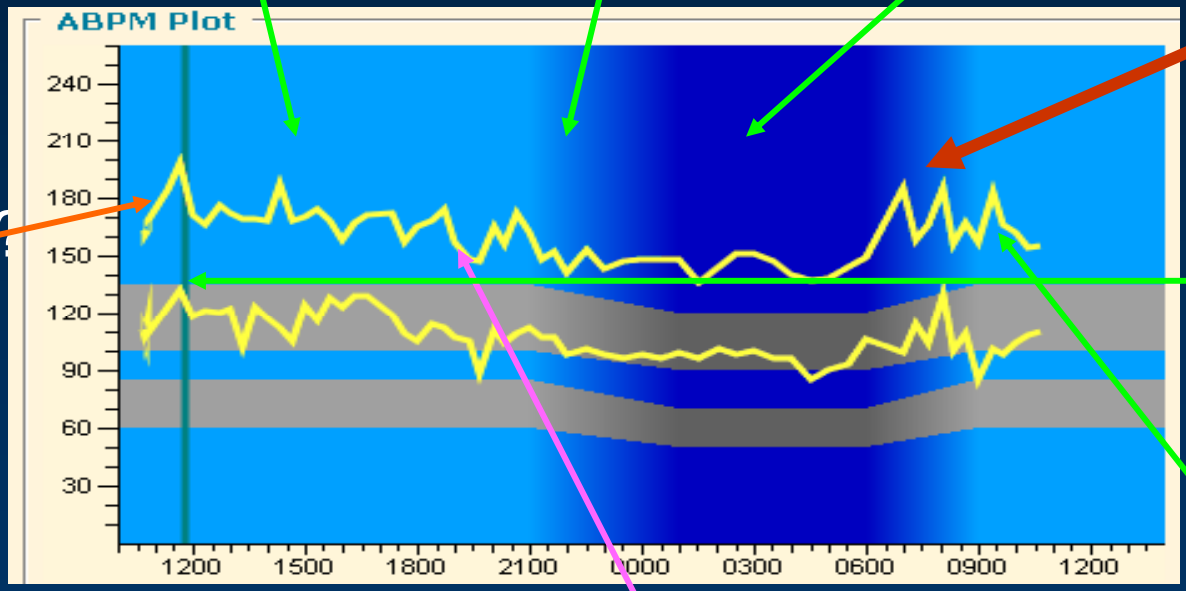
Various Types of BP

Daytime BP?

Dipping Pattern?

Nighttime BP?

Morning Surge?



Clinic BP?

24 Hr Average BP?

Variability of BP?

Home BP?

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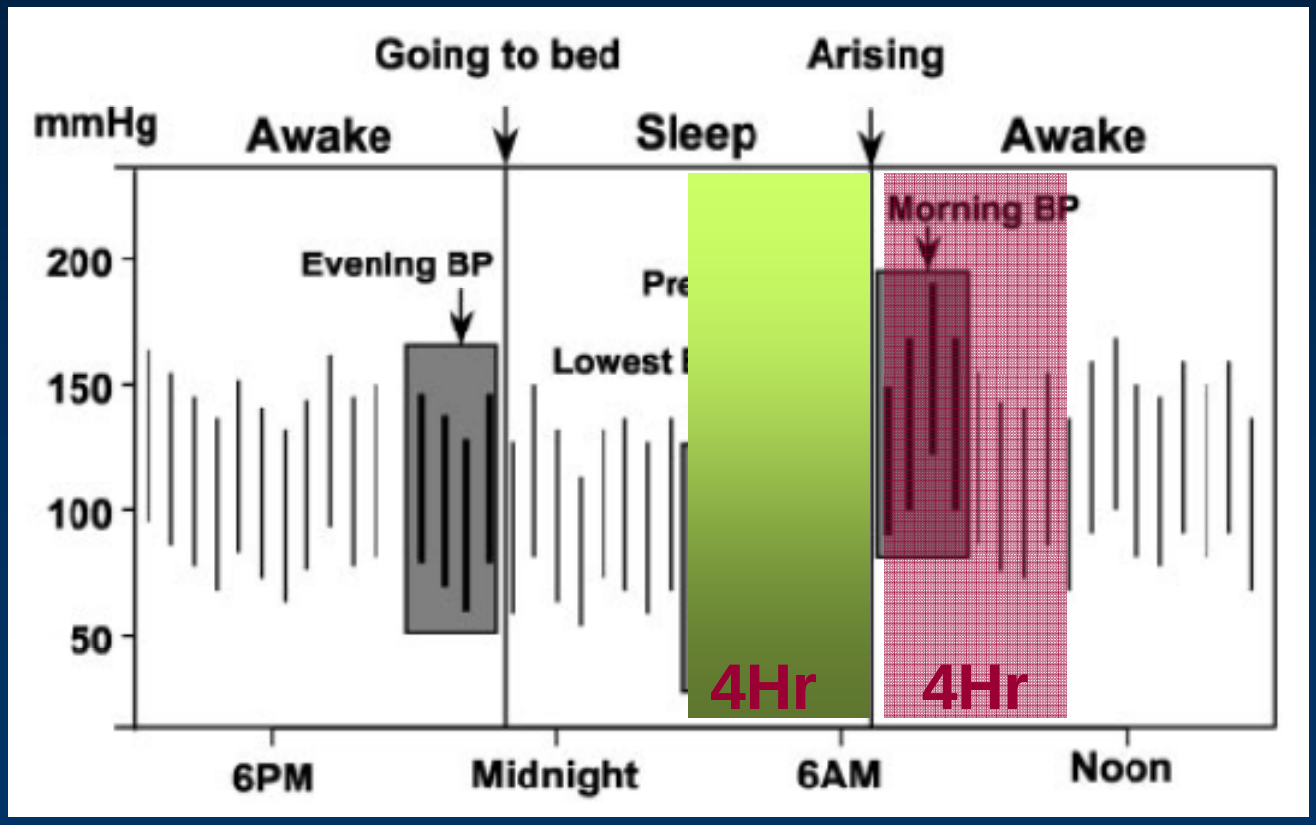
Definition

- There is no universally recognized definition of the morning surge



Kario et al. Circulation 2003;107:1401

Leary et al. J HTN 2002;20:865

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Morning BP Surge & Subclinical Organ Damage

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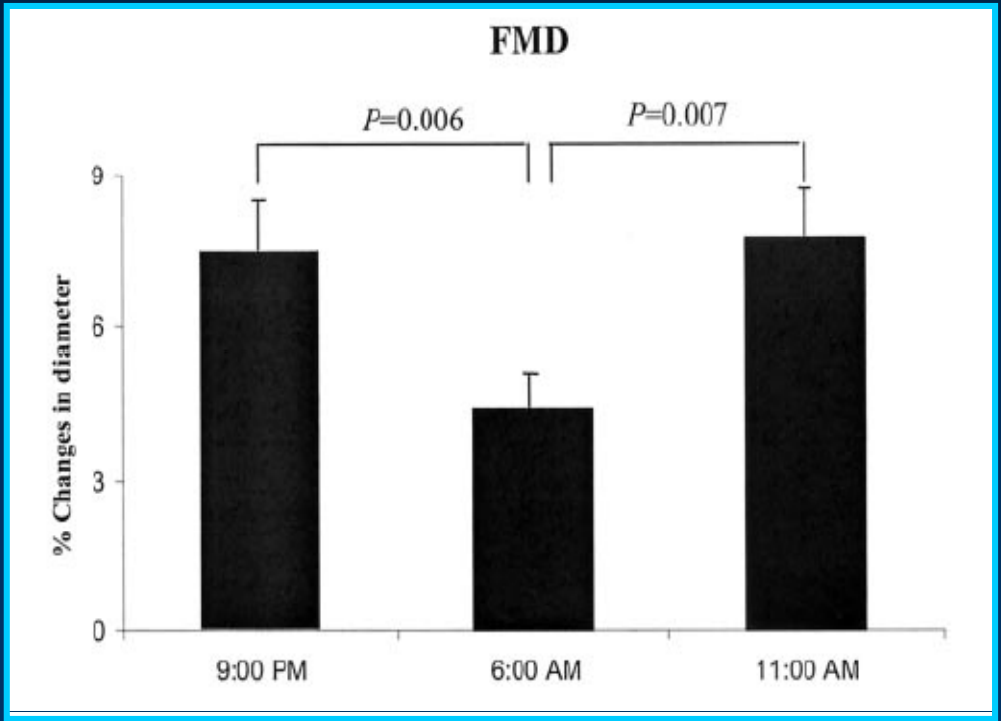
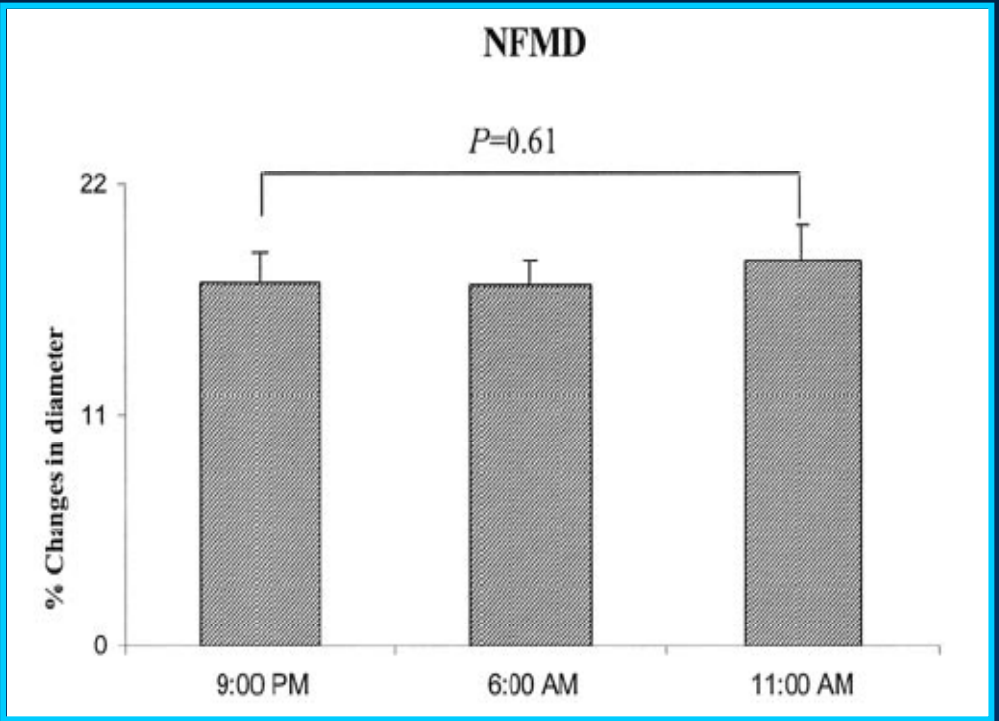
MBPS Causes TOD

- MBPS → hemodynamic stress → TOD
- High MBPS more likely to have LVH
- BP in the morning is a better predictor than office BP of:
  - the decline in GFR
  - albuminuria in patients with type 1 diabetes
  - albuminuria in patients with type 2 diabetes

J Hypertens 2004;22:1113–1118
Clin Exp Hypertens 2002;24:249–260
Diabetes Care 2002;25:2218–2223
Diabetes Care 2003;26:2473–2475

Early Morning Attenuation of Endothelial Function in Healthy Humans





Circulation 2004;109:2507–2510

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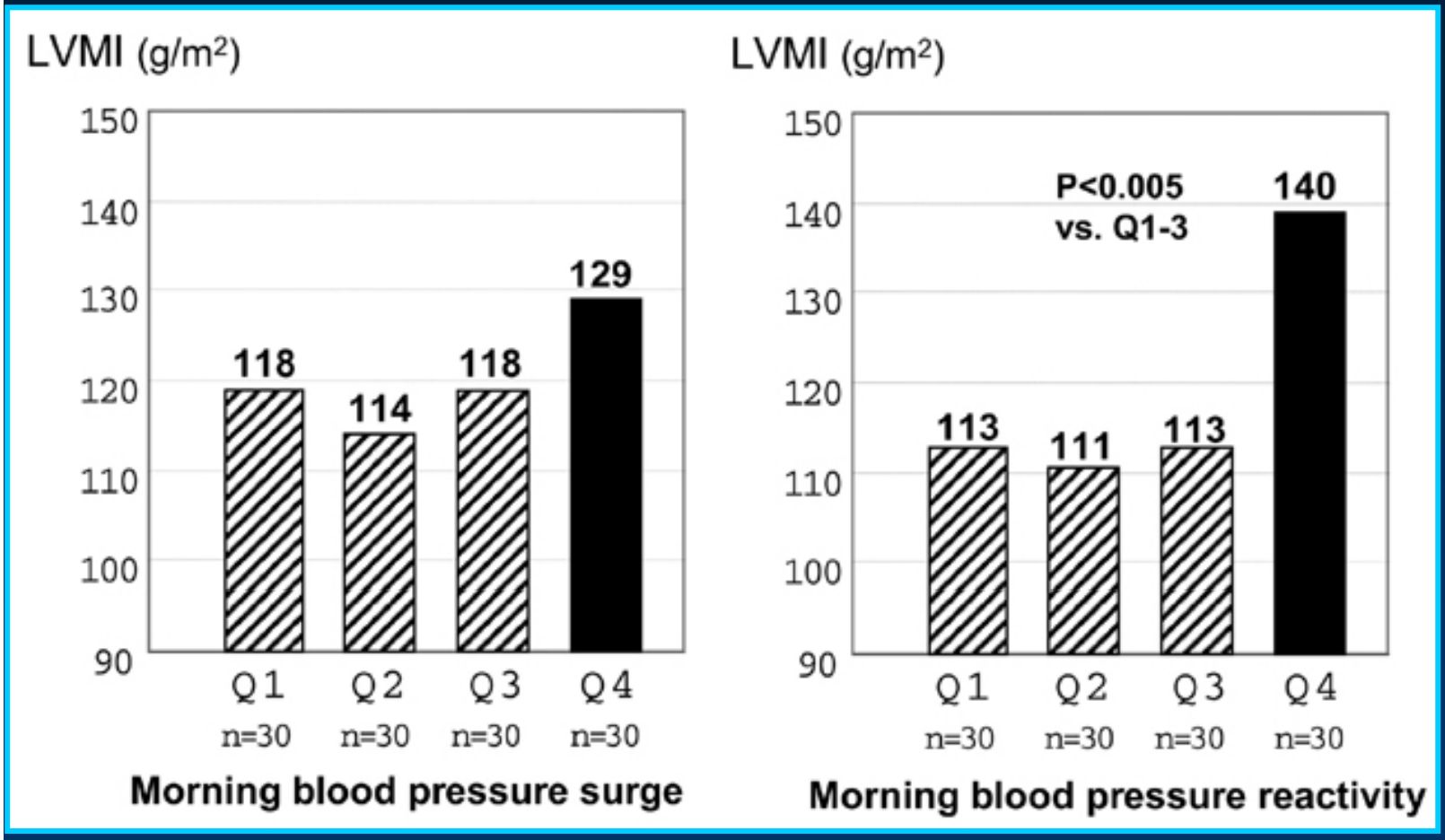
Morning BP Surge or Reactivity and LVH



MBPR

= MBPS /

(sum of 2-h activity after arising)$^{0.5}$

Am J Hypertens 2005;18:1528–1533

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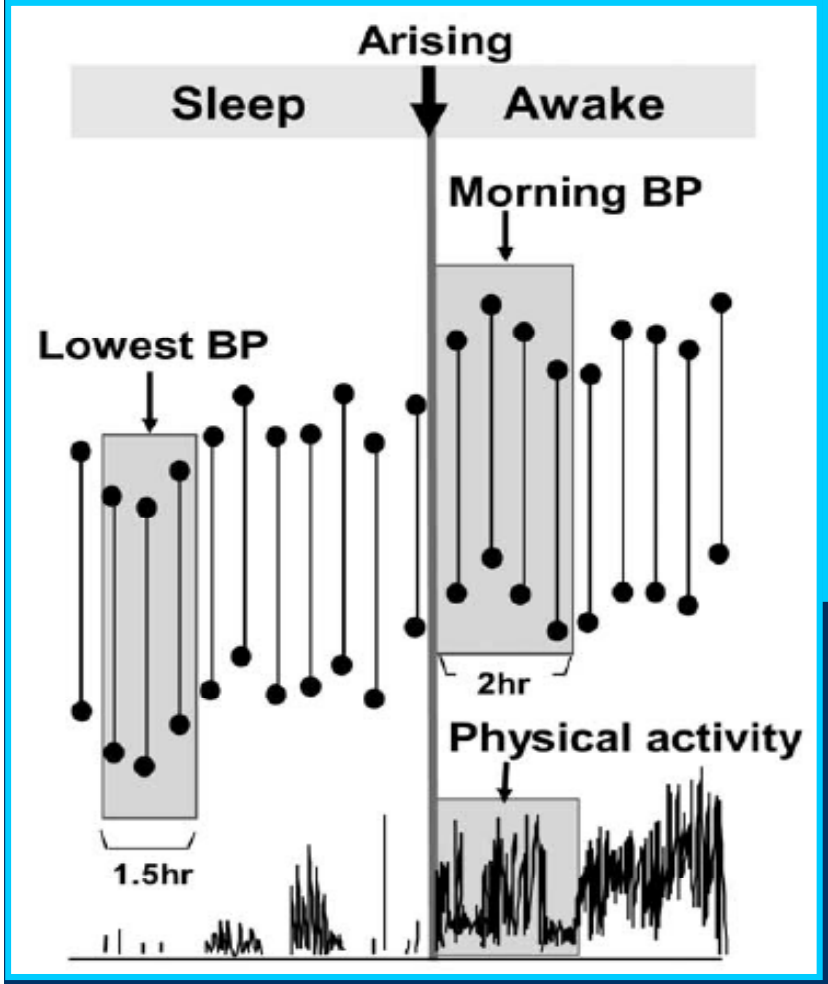
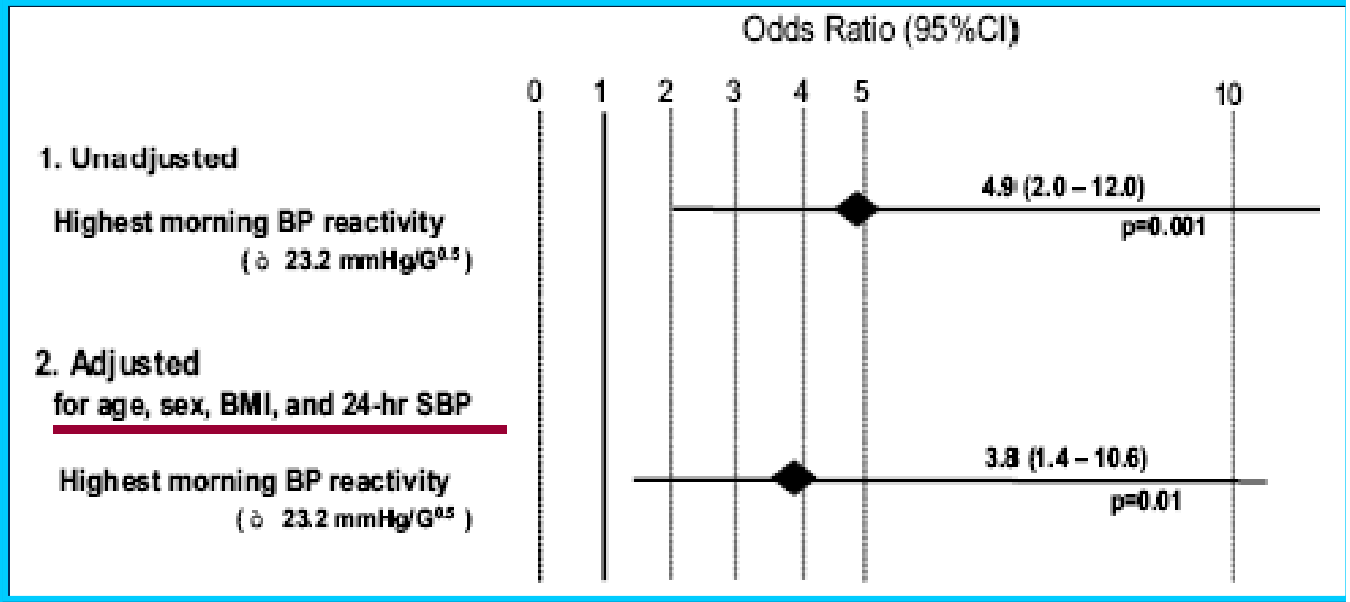
Morning BP Hyper-Reactivity and LVH





Morning BP Reactivity was **independently** associated with **cardiac hypertrophy**

Am J Hypertens 2005;18:1528–1533

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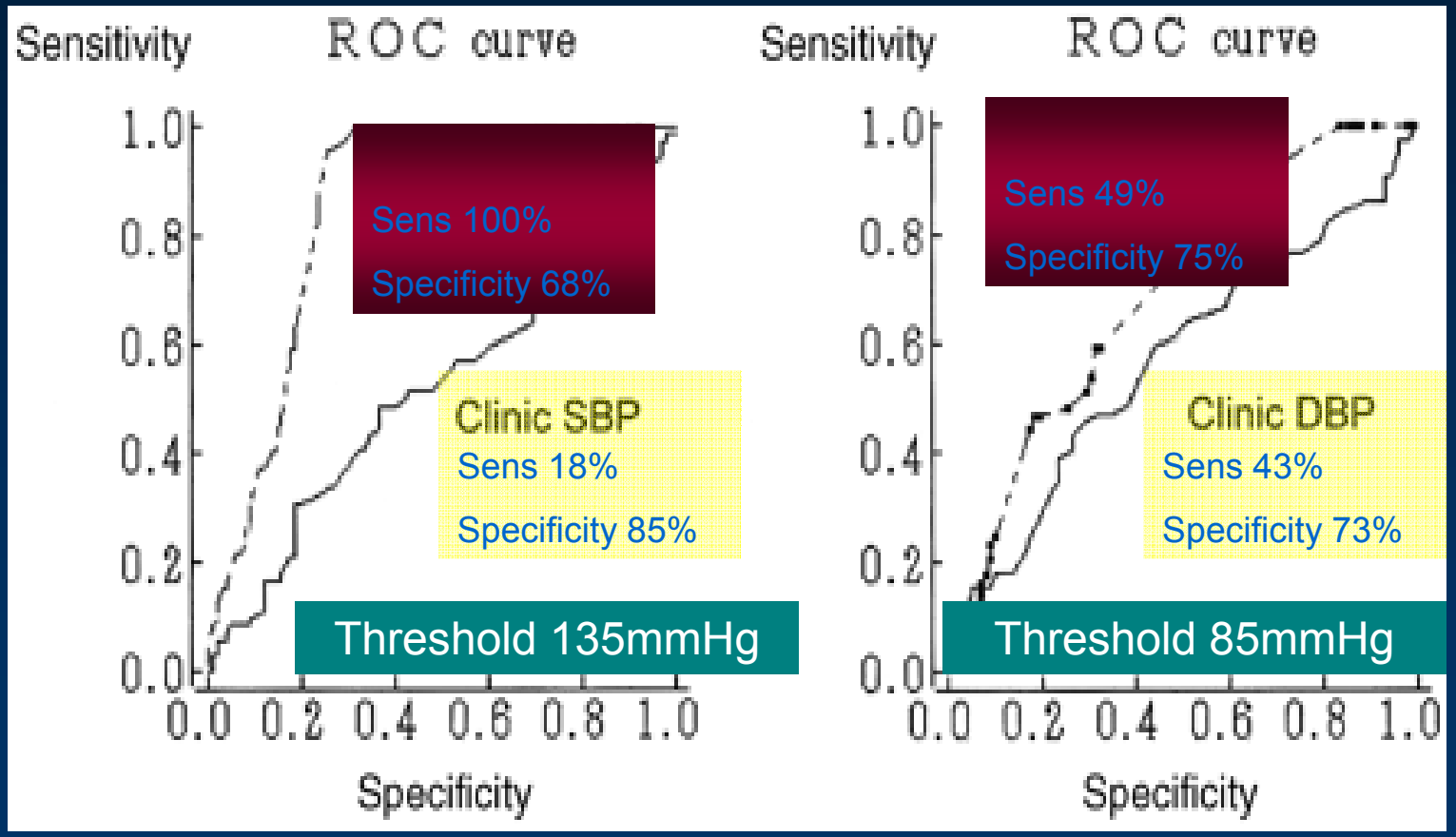
Morning BP is a Better Predictor than Clinic BP of Albuminuria in Type 2 DM



Diabetes Care 2002;25:2218–2223

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CV Events Occur More Frequently In the Morning !

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The Early Morning BP Surge

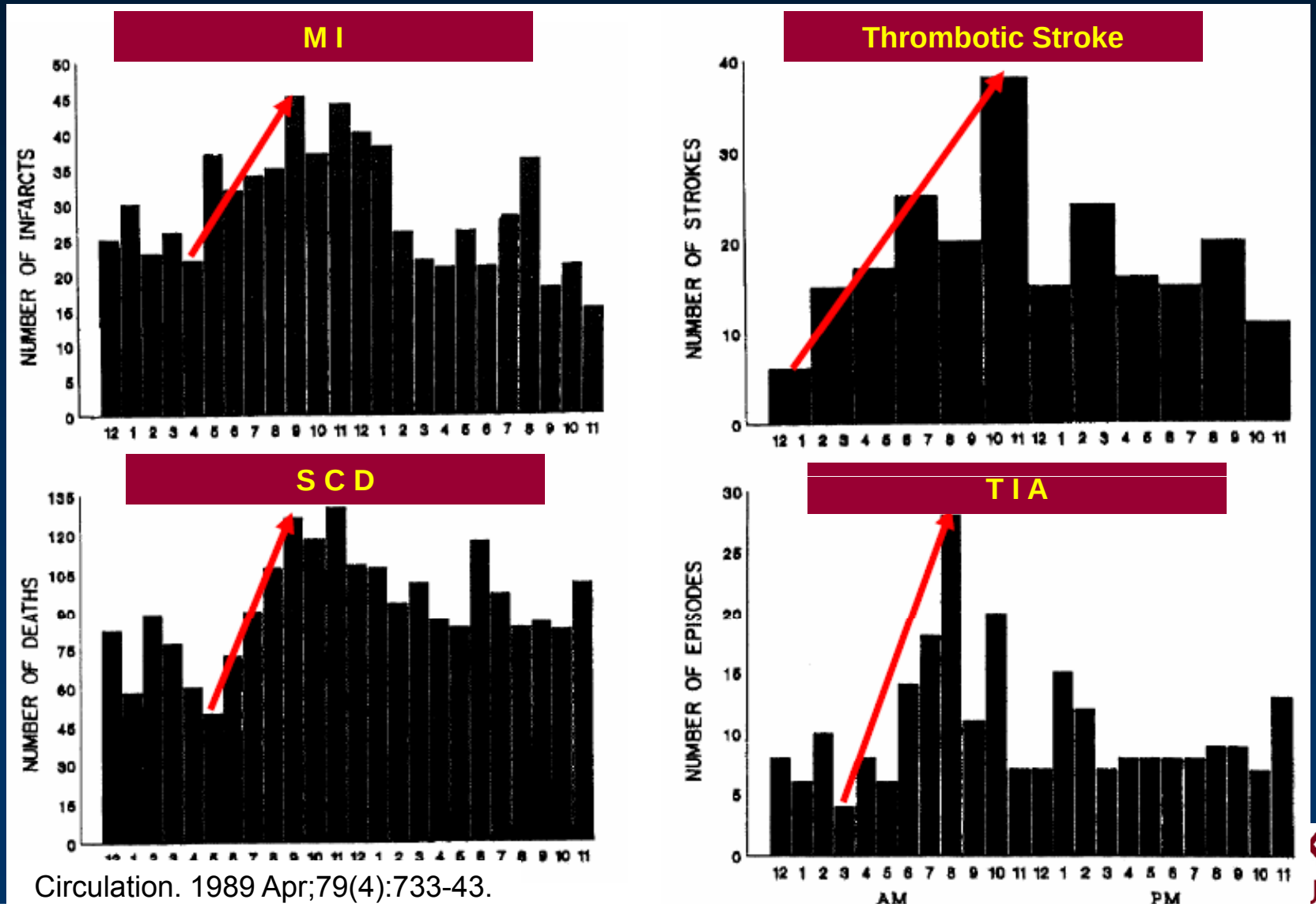
Coincides with peak time of cardiovascular complications

- Sudden death
- Acute myocardial infarction
- Typical angina pectoris
- Silent ischemia
- Total ischemic burden
- Ischemic stroke
- Variant angina pectoris (02:00-04:00)
- Platelet aggregability

06:00–12:00

Lancet. 1988;2:755–759; *Am Heart J*. 1989;118:1098–1099; *Stroke*. 1989;20:473–476; *Circulation*. 1989;80:1617–1626; *Ter Arkh* 2000;72:47–51

Circadian Variation of Acute CVD



Circulation. 1989 Apr;79(4):733-43.

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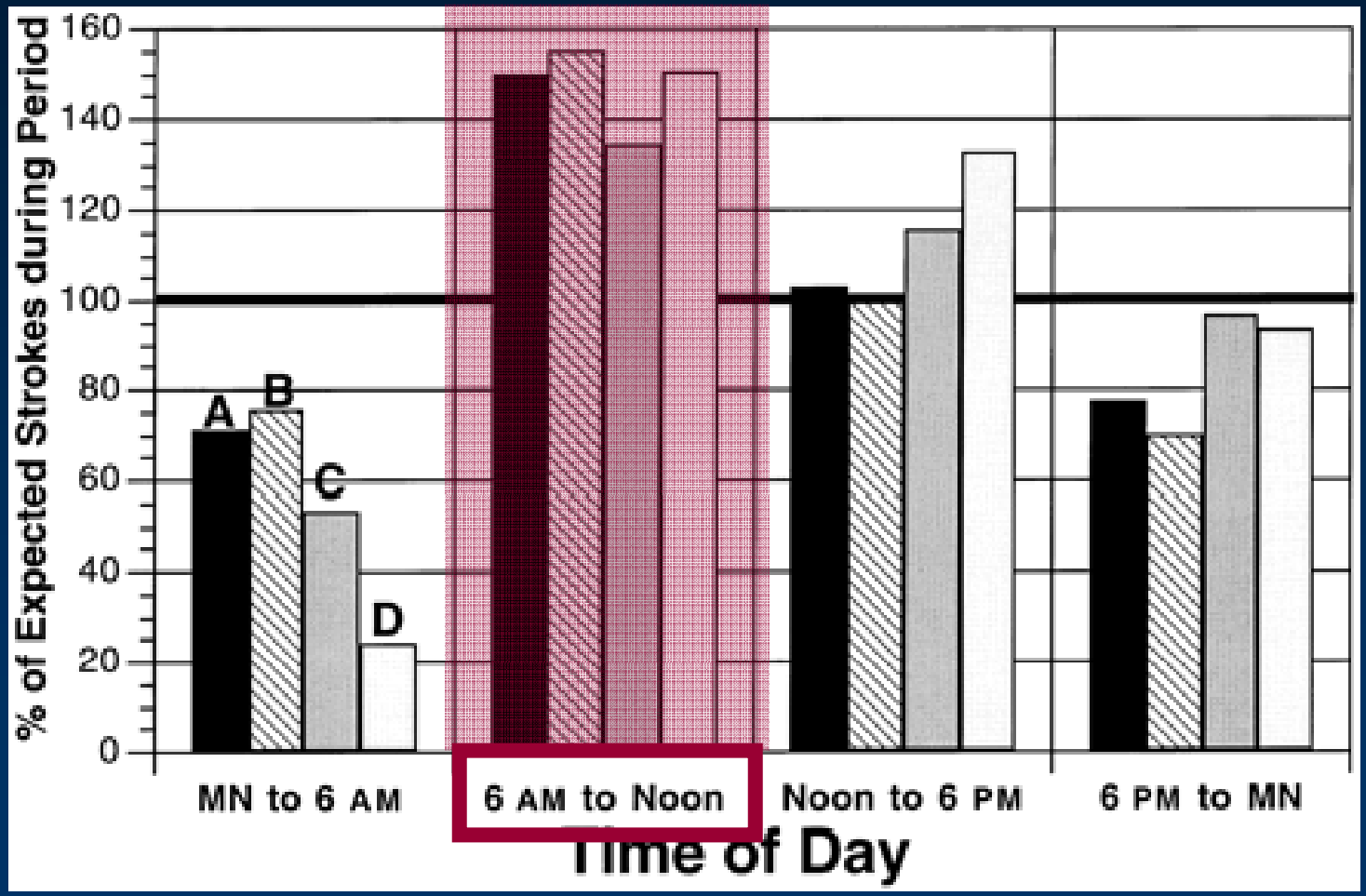
Circadian Patterns of Onset of Symptoms of Stroke

A: all

B: Ischemic

C: Hemorrhagic

D: TIA



Stroke. 1998 May;29(5):992-6

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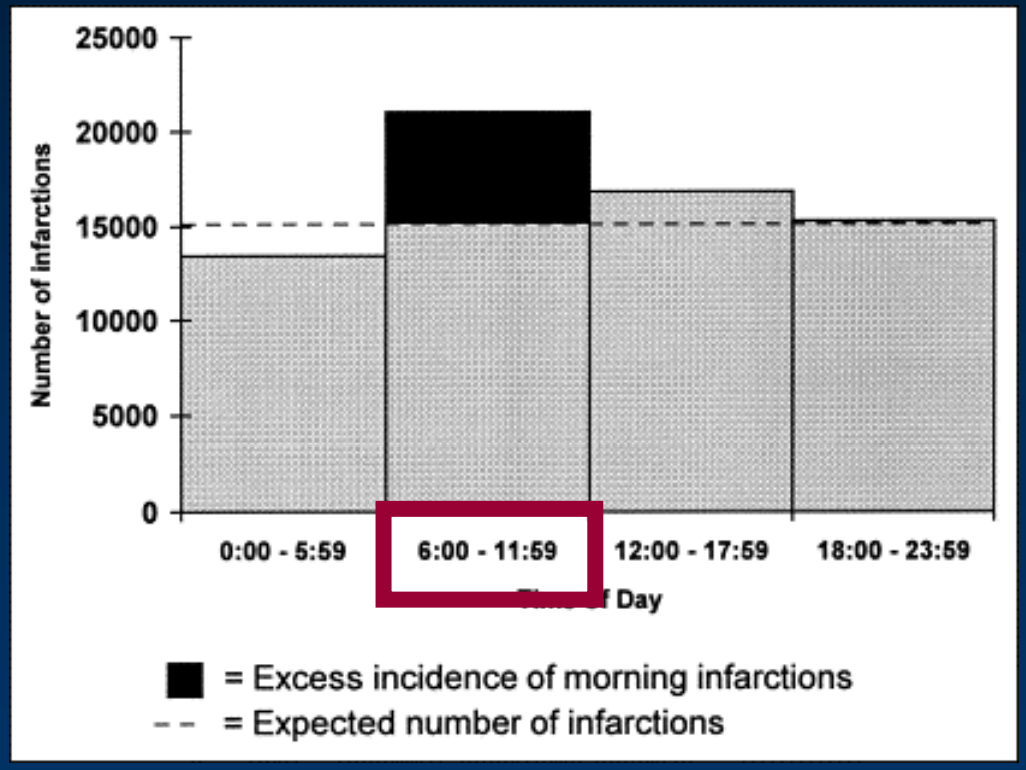
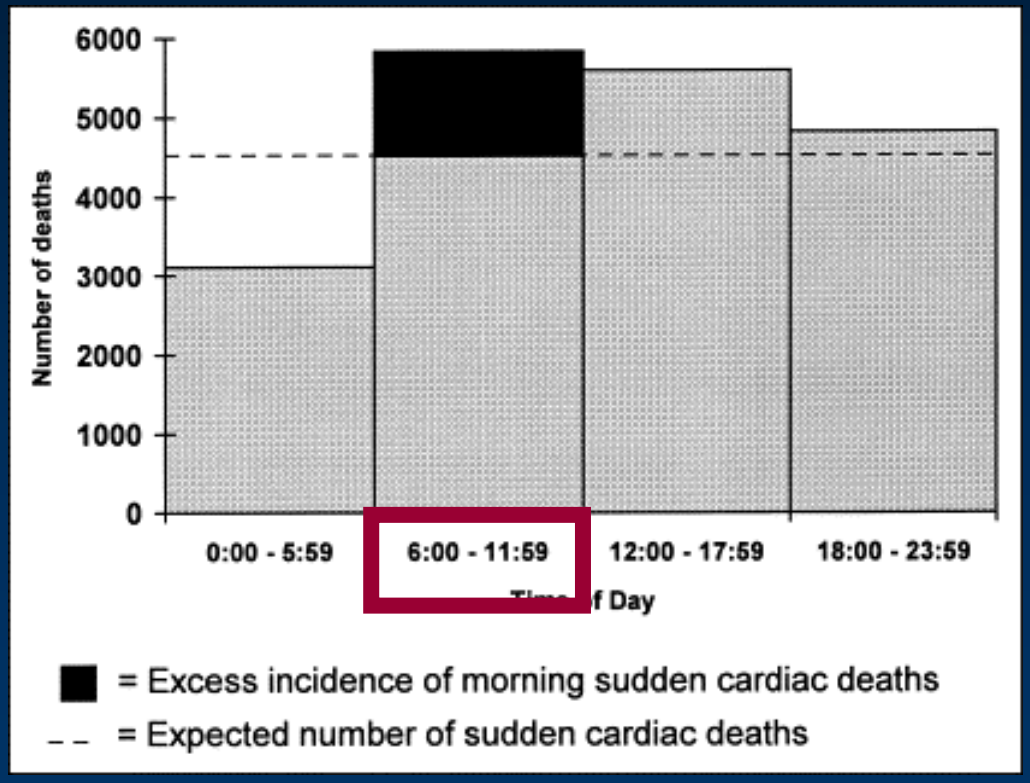
Morning Excess of AMI and Sudden Cardiac Death





Am J Cardiol. 1997 Jun 1;79(11):1512-6

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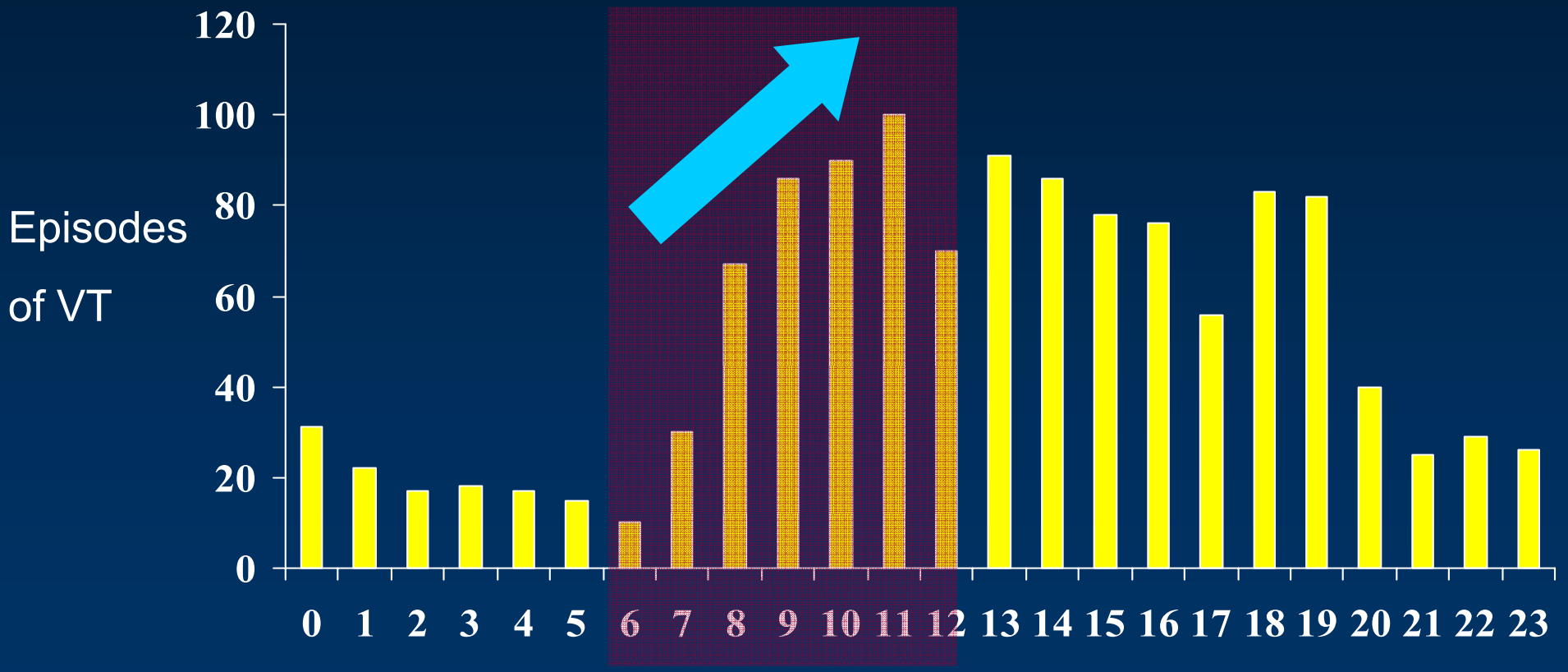
Morning Peak of VT Detected by ICD



Circulation 1995;92: 1203

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Morning BP Surge is Independently Associated With…

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MBPS is Independently Associated With CV Complications

	RR	95% CI	P
Univariate analysis			
Age (years)	1.066	1.033–1.101	< 0.001
24-h SBP (mmHg)	1.042	1.022–1.062	< 0.001
SBP change on rising (mmHg)	1.043	1.021–1.066	< 0.001
LVM/$h^{2.7}$	1.031	1.006–1.057	0.01
Multivariate analysis			
24-h SBP (mmHg)	1.042	1.022–1.062	0.003
SBP change on rising	1.033	1.008–1.058	0.009
Age (years)	1.044	1.005–1.085	0.026

- Baseline
  : Untreated 507 HTN
- Then treated
- Mean 7yr f/u

- **CV Cx: MI, Angina, CVA, SCD, CRF, HF, PAD, AAA, Carotid stenosis**

Journal of Hypertension 2004, 22:1113–1118

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MBPS is Independently Associated With Stroke

Covariates	Model 1 Relative Risk (95% CI)	Model 1 *P*	Model 2 Relative Risk (95% CI)	Model 2 *P*
Age (10 y)	1.75 (1.20–2.55)	0.004	1.69 (1.15–2.50)	0.008
24-Hour SBP (10 mm Hg)	1.38 (1.17–1.64)	<0.001	1.35 (1.13–1.60)	<0.001
SCI*	4.50 (1.99–10.2)	<0.001	4.02 (1.73–9.30)	0.001
Sleep-trough MS (10 mm Hg)†	1.22 (1.05–1.40)	0.008	1.25 (1.06–1.48)	0.008
Dipping status				0.025‡
Extreme-dippers vs dippers			1.43 (0.59–3.43)	0.426
Nondippers vs dippers			1.76 (0.78–4.01)	0.175
Risers vs dippers			2.71 (1.02–7.21)	0.047

22-25% / 10mmHg

- 519 older HTN
- Mean 41mo f/u

After controlling for age, sex, BMI, 24h SBP

Circulation. 2003;107:1401-1406

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Why Morning Surge ?

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ts ; Mechanism

Vascular Remodeling

➔↑ oscillatory shear

Cardiac Remodeling

Other CV Risk Factors ↑ in Morning

CV Events !

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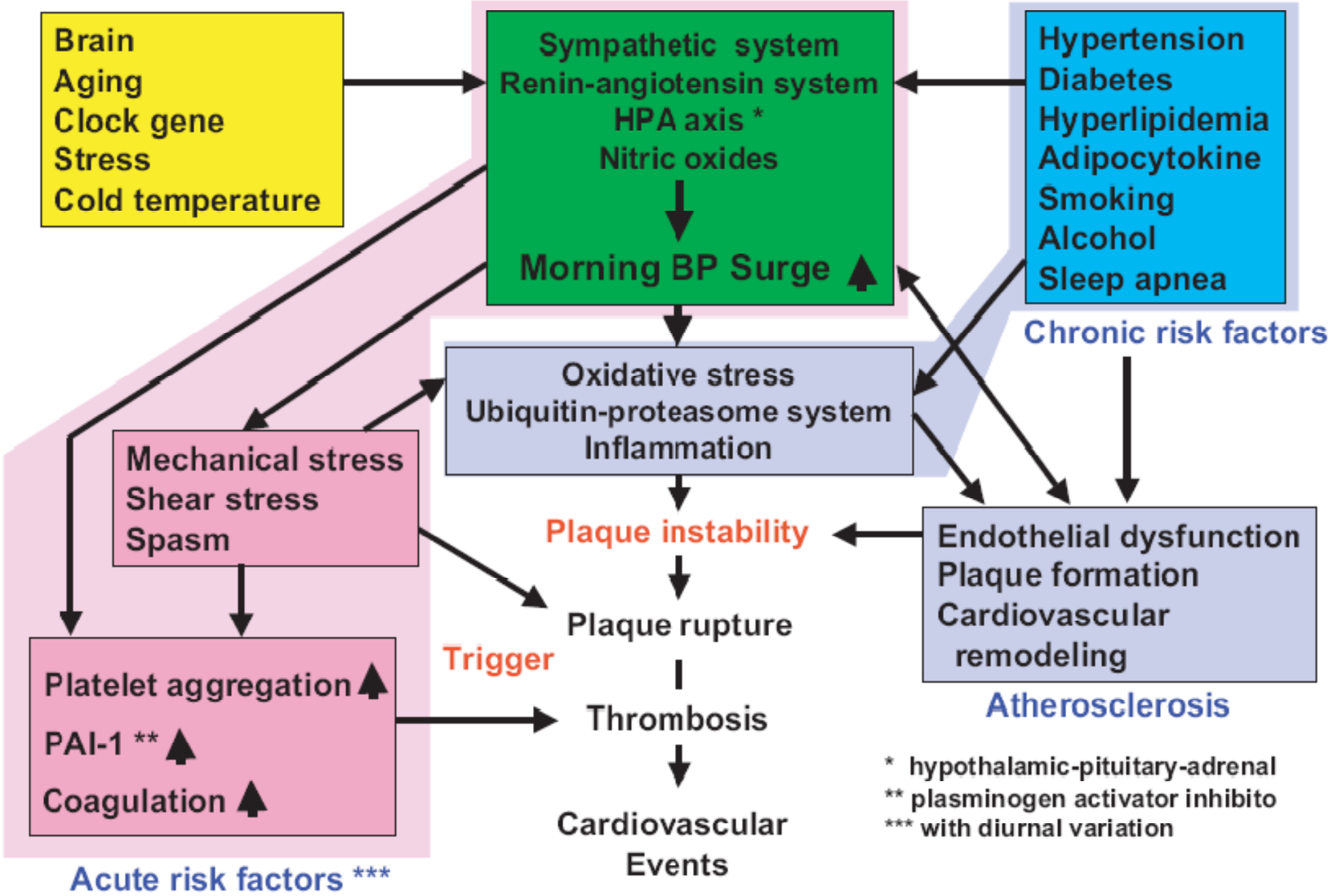
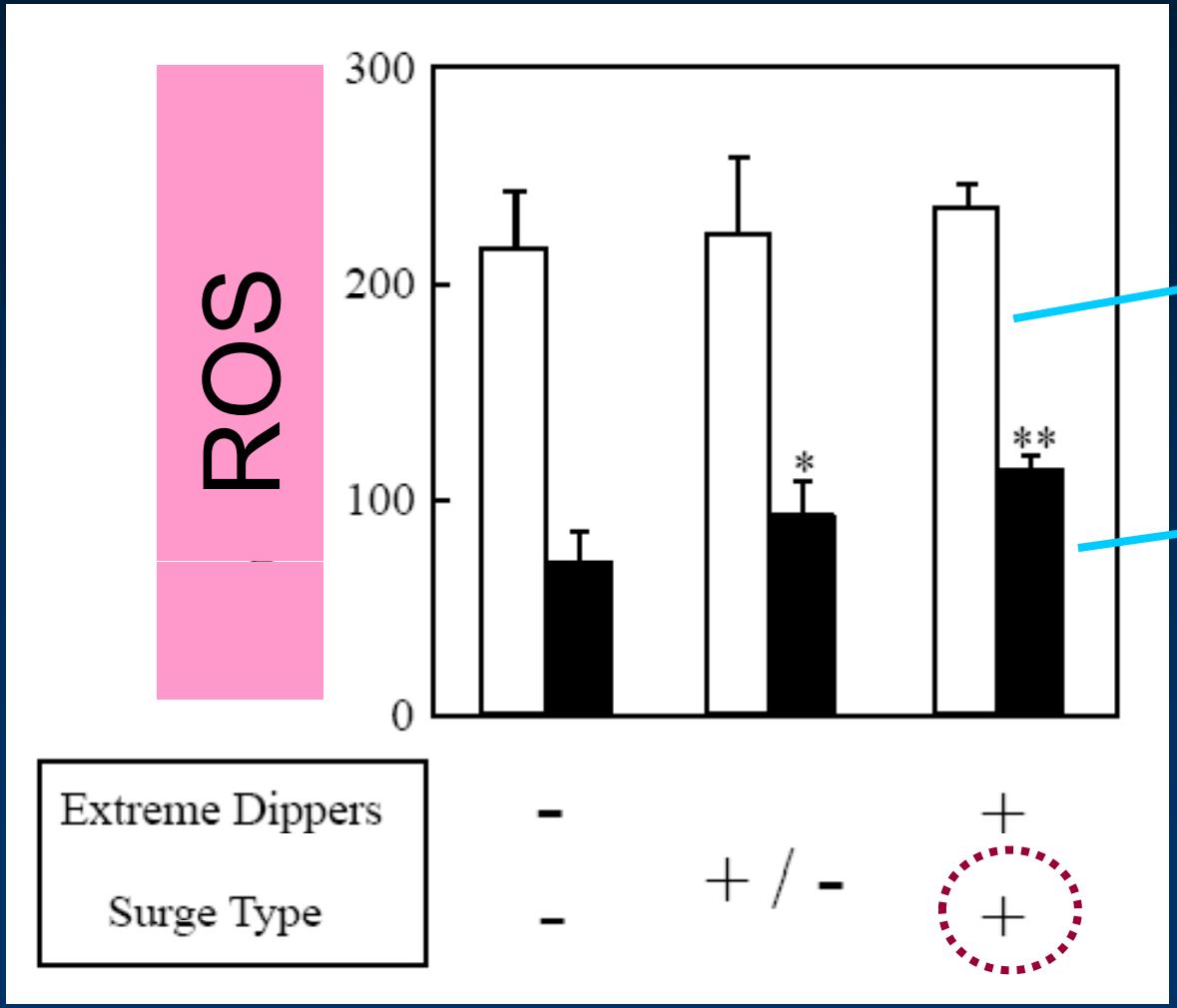
Morning Blood Pressure Surge – related Cardiovascular Risk



MBPS – Oxidative Stress

HTN

N= 31



Hypertens Res 2005;28:755-761

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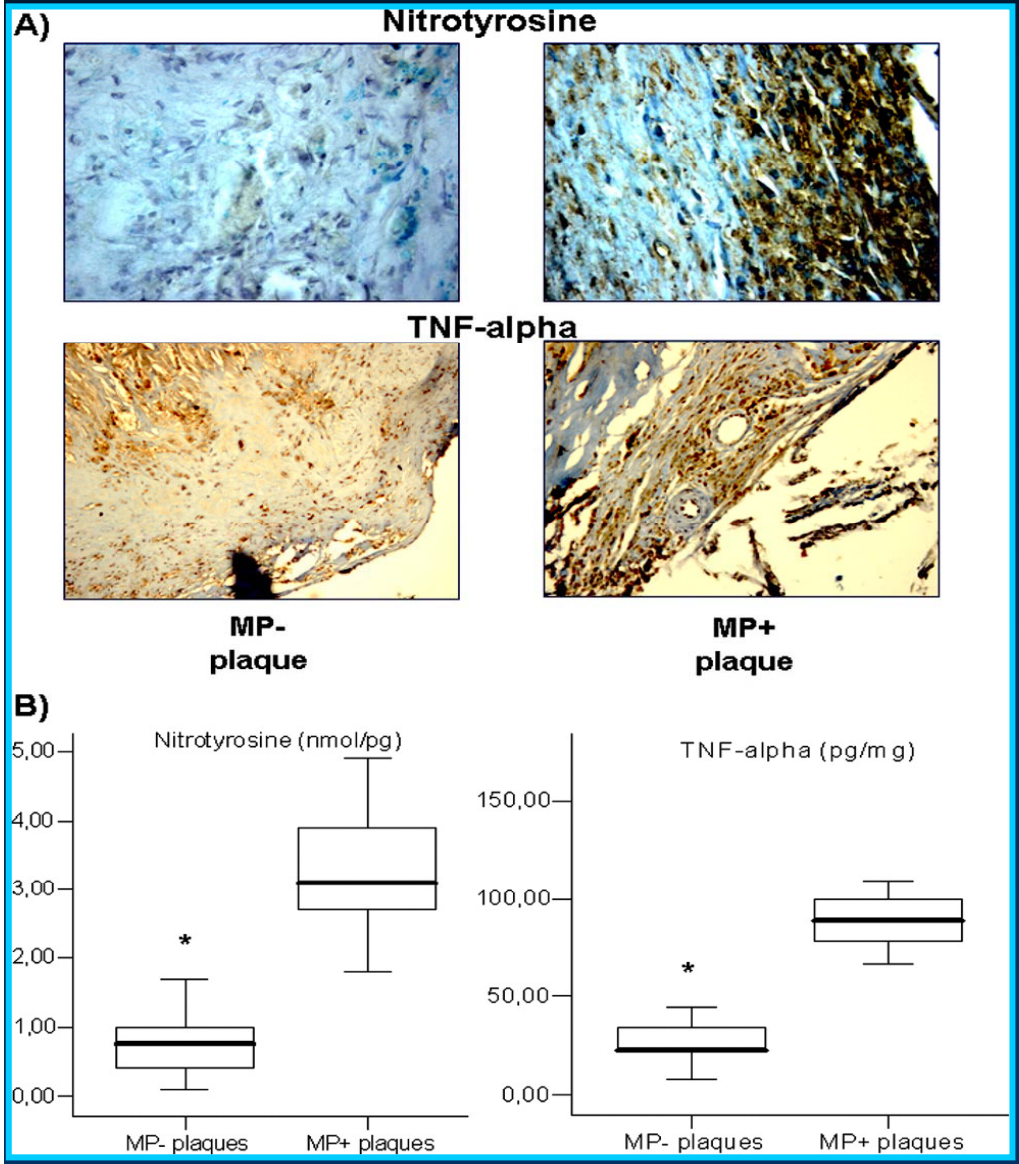
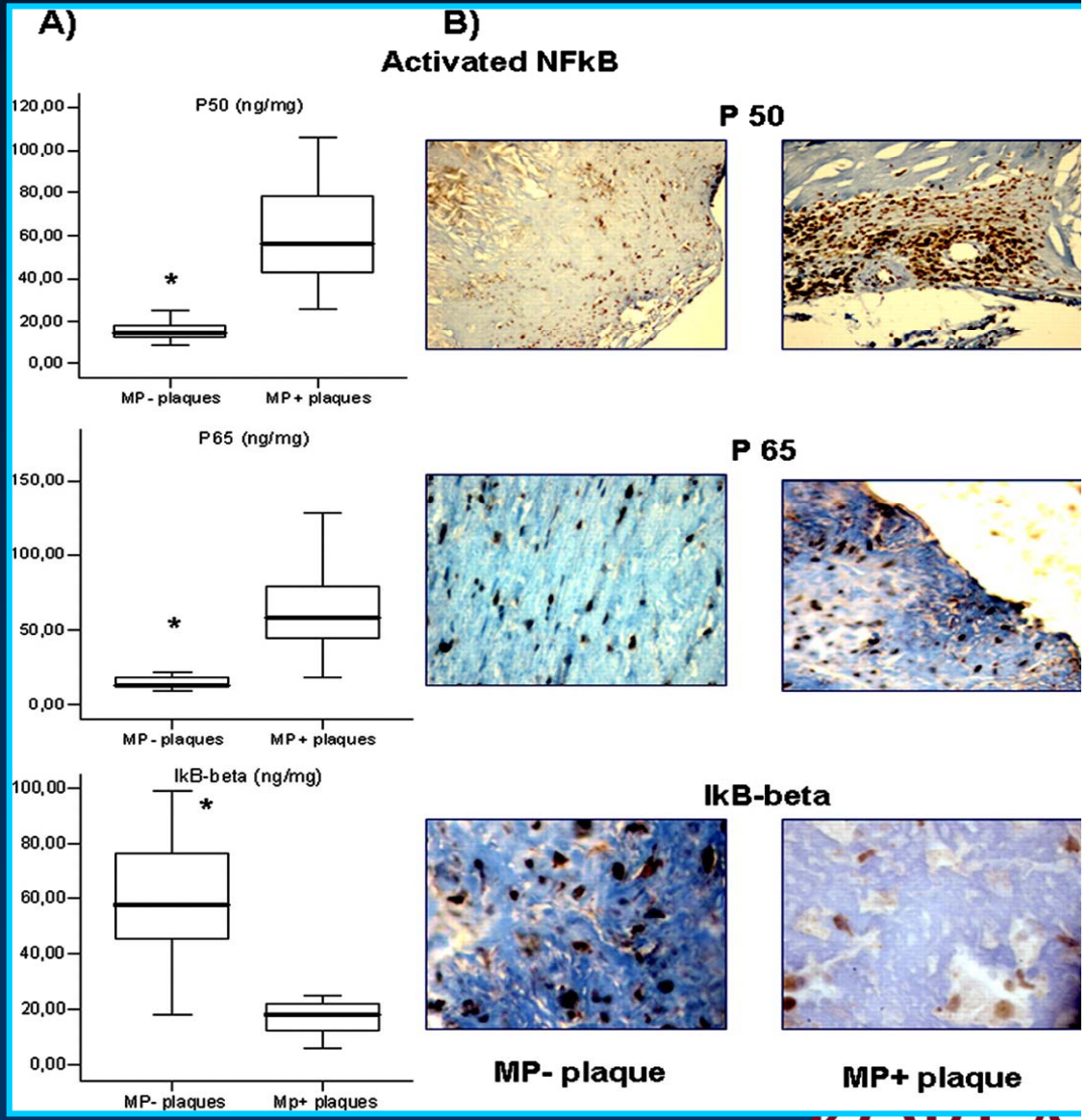
in Carotid Plaque of MBPS





Hypertension 2007;49:784-791

Hypertensives

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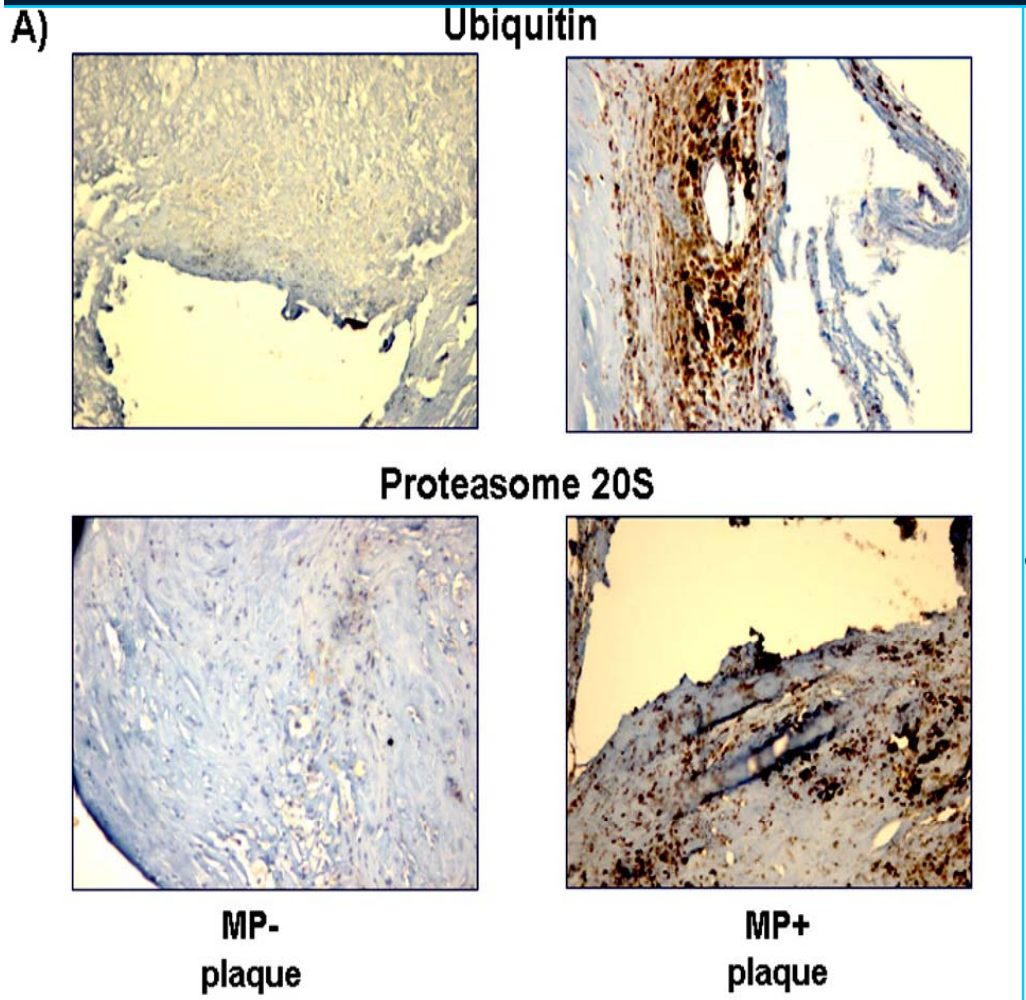
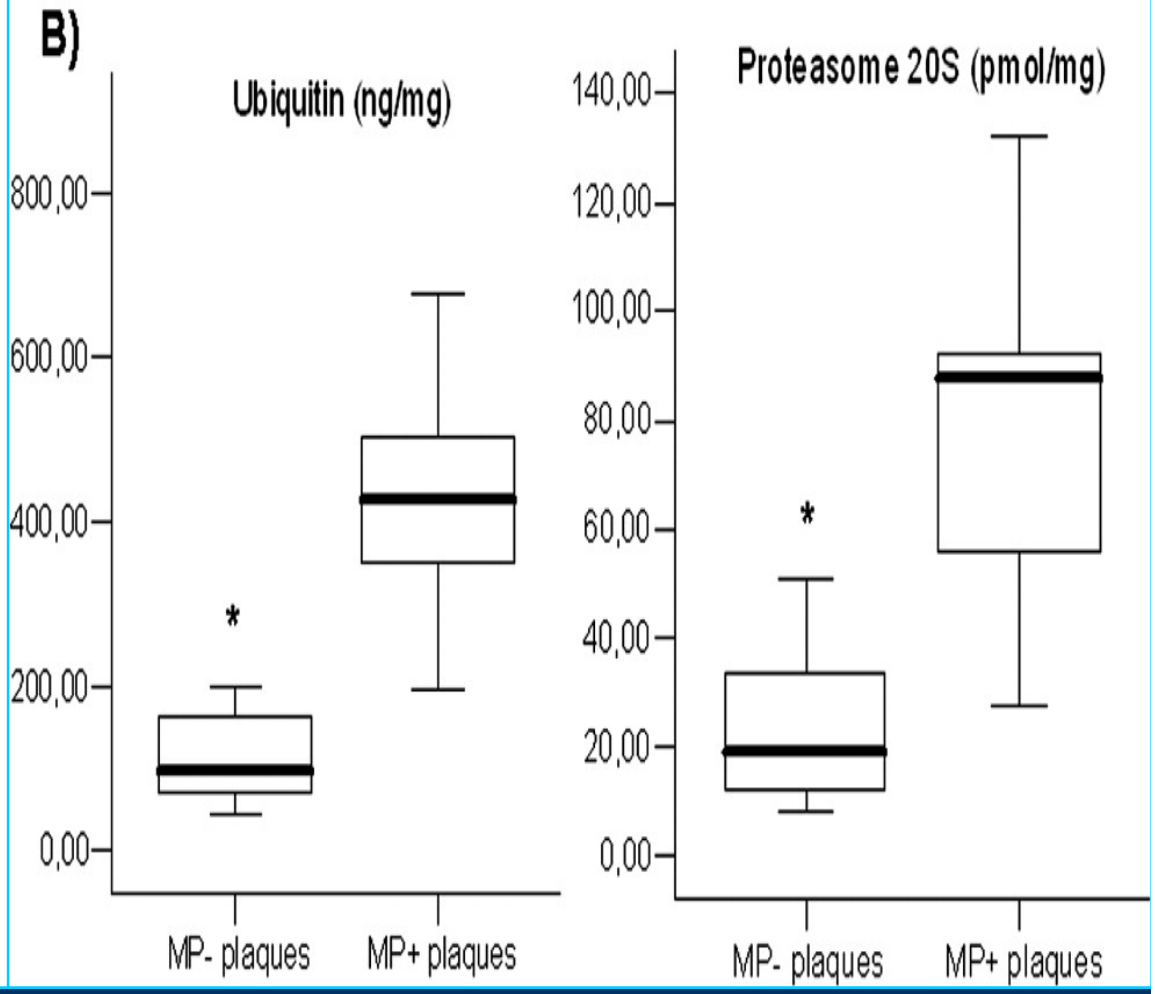
↑ UP in Carotid Plaque of MBPS





Hypertension 2007;49:784-791

Hypertensives

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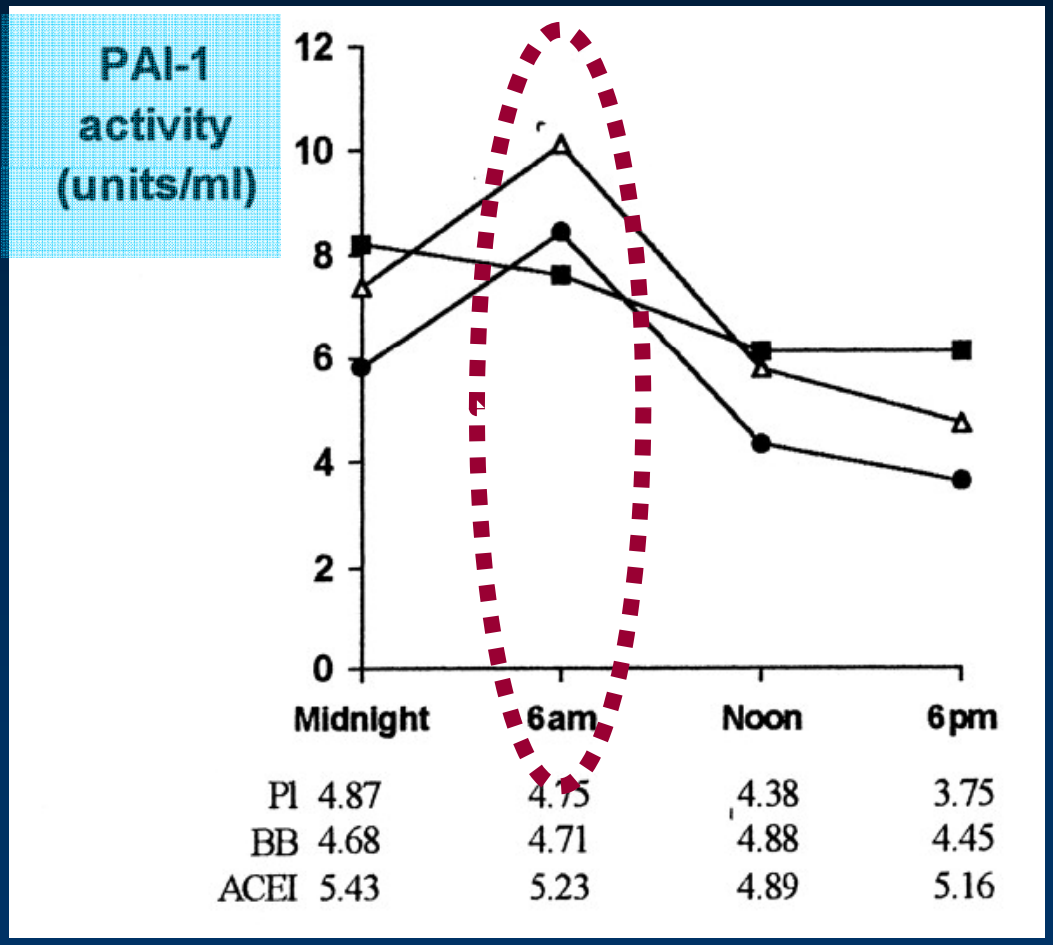
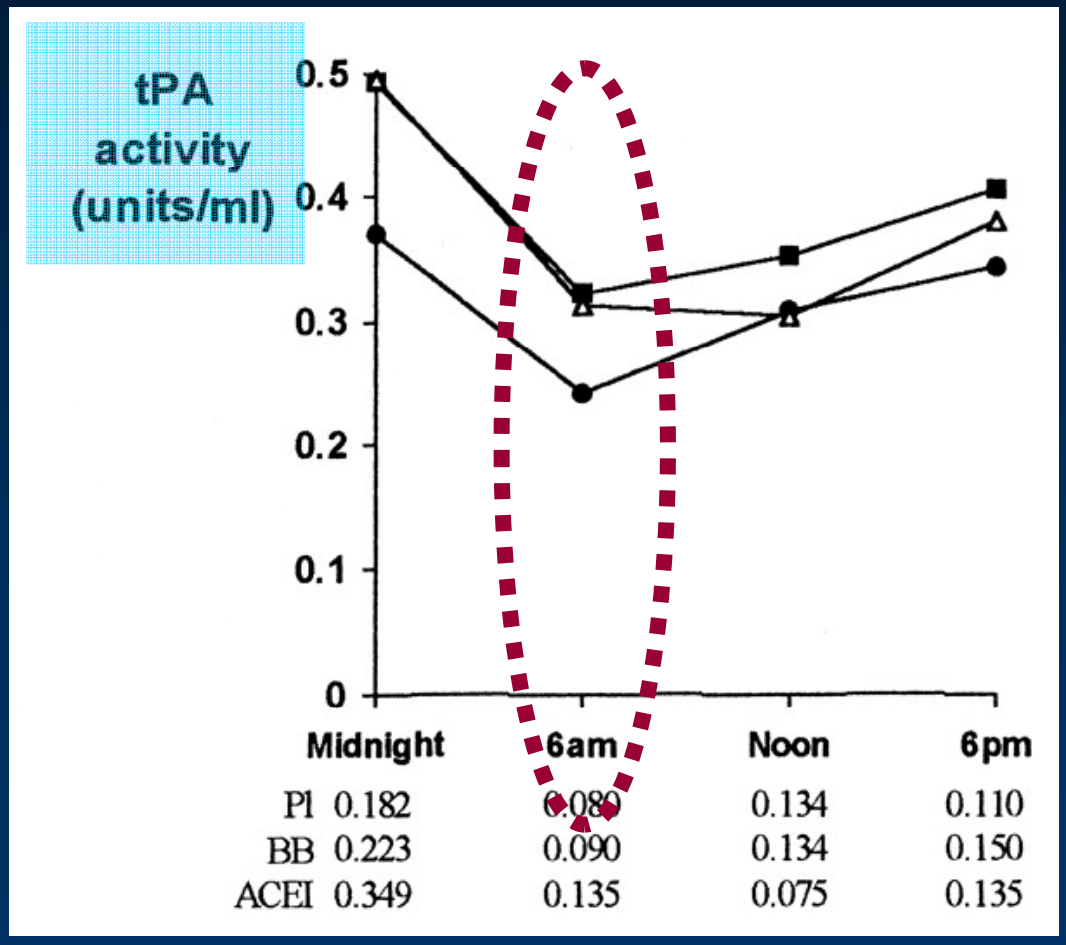
Circadian Variation of PAI-1 and tPA Activities



	Midnight	6am	Noon	6pm
PI	4.87	4.75	4.38	3.75
BB	4.68	4.71	4.88	4.45
ACEI	5.43	5.23	4.89	5.16



	Midnight	6am	Noon	6pm
PI	0.182	0.080	0.134	0.110
BB	0.223	0.090	0.134	0.150
ACEI	0.349	0.135	0.075	0.135

J Am Coll Cardiol, 1998; 32:1962-1968

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Therapeutic Strategies to Control MBPS

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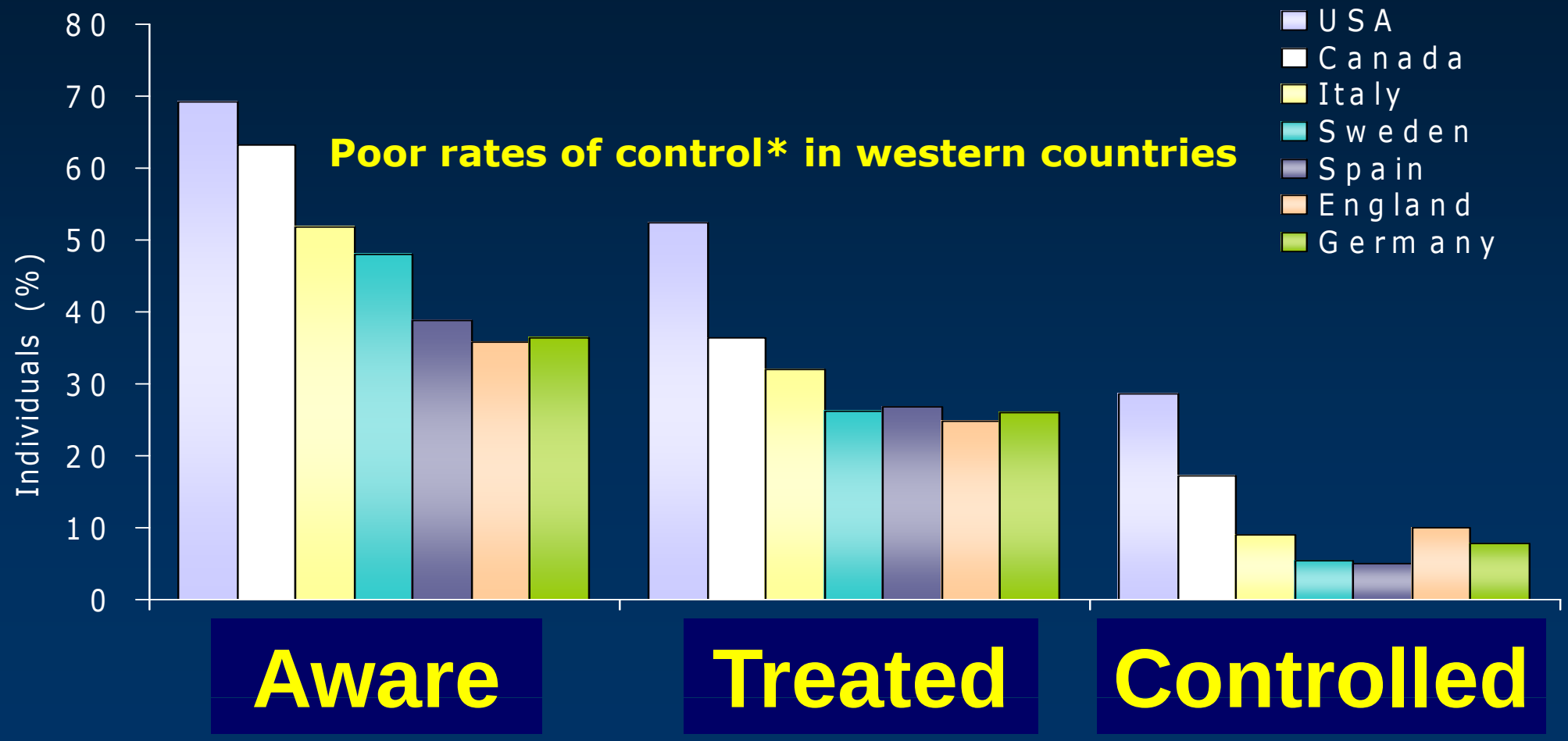
Hypertension Awareness, Treatment and Control



* Threshold of SBP/DBP 140/90 mm Hg

Wolf-Maier et al. *Hypertension* 2004;43:10–17

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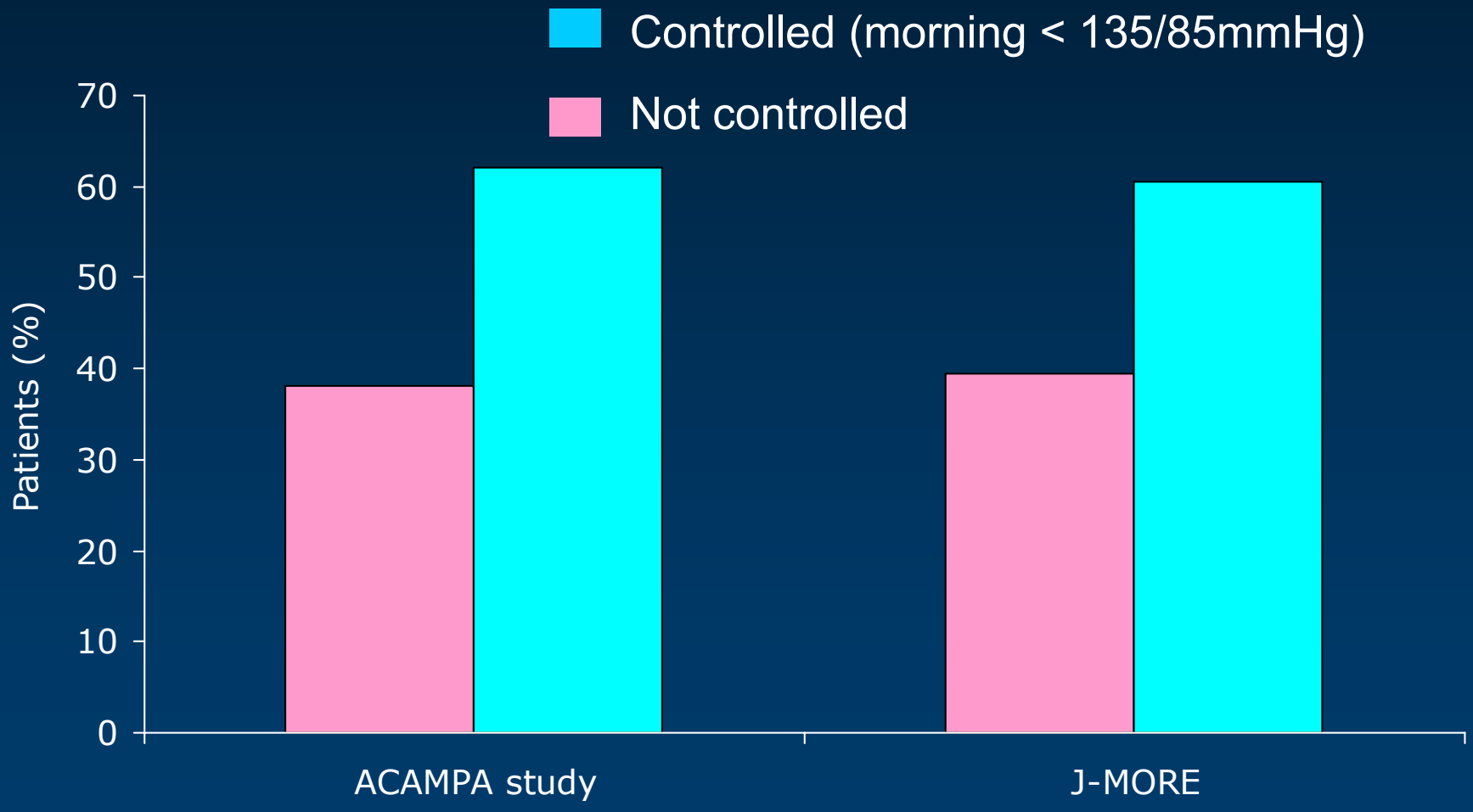
In Pts with Controlled Office BP; Also During Morning Hours ?



Redón et al. *Blood Press Monit* 2002;7:111–116
Kario et al. *Circulation* 2003;108:72e–73e

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Early Morning BP Surge as a Target for Therapy

Consider…

- Pharmacokinetic profile with morning dosing
- Underlying mechanisms for MBPS

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A Therapeutic Blind Spot With Current Therapy in the Morning

- **One** of the suggested **reasons for morning hypertension in treated subjects.**

- **Insufficient duration of action (short T1/2)** of antihyertensive drugs, leaving patients vulnerable.

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Chronotherapeutic Tx Strategies

- Choose drug with **long half-life** with **high trough-to-peak ratios**, ensuring coverage during the morning surge
- **Extended-release, delayed-onset, bedtime dosing**
- **Twice** daily doses
- Coupled **with a diuretic**

Half-lives of Various Blood Pressure Medications

J Clin Hypertens 2008;10:140-145

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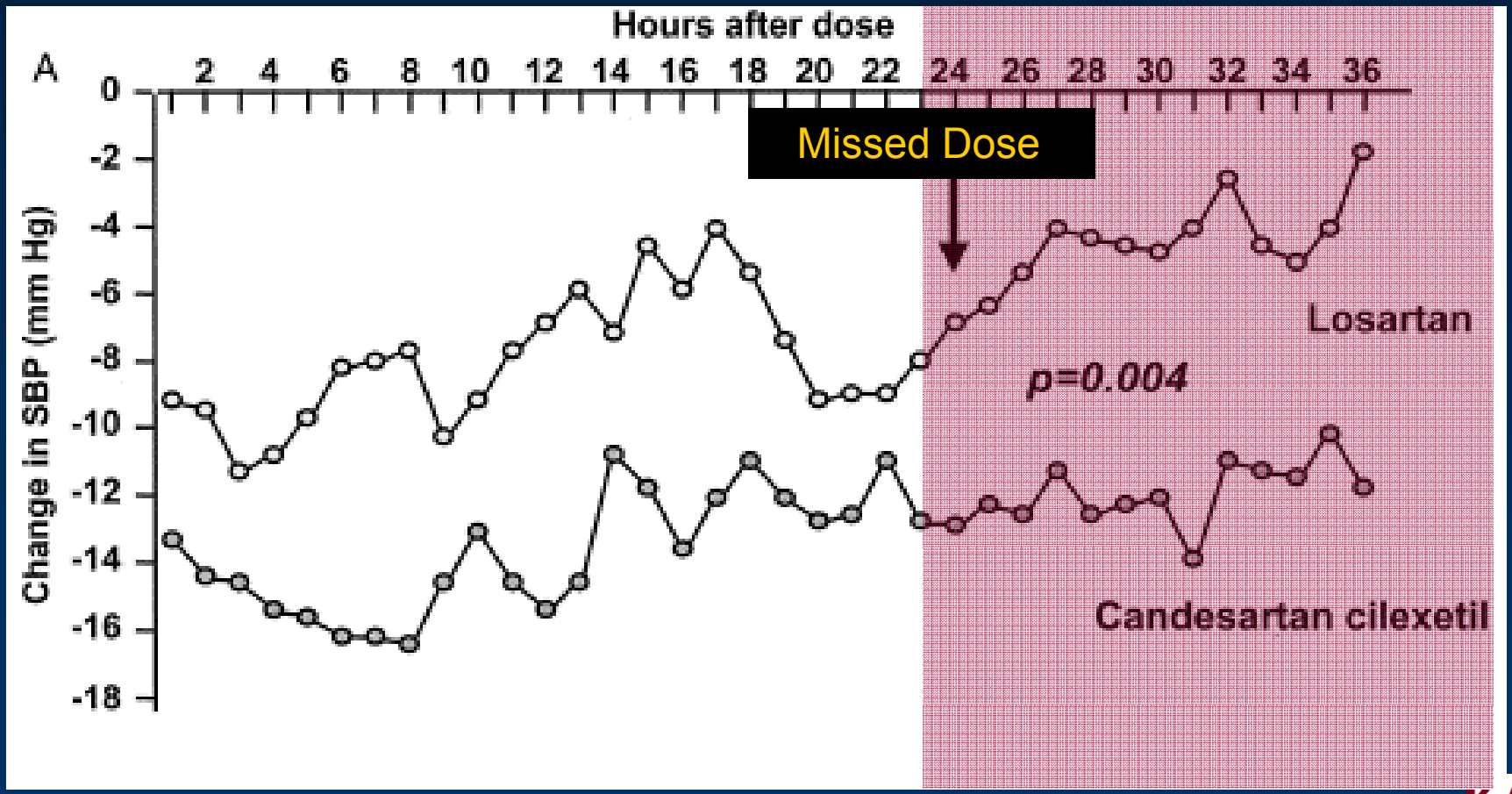
Effects of Two ARBs Approved for Once Daily Dosing on 24 Hour BP



Mancia et al AJC 1999: 84; 28S

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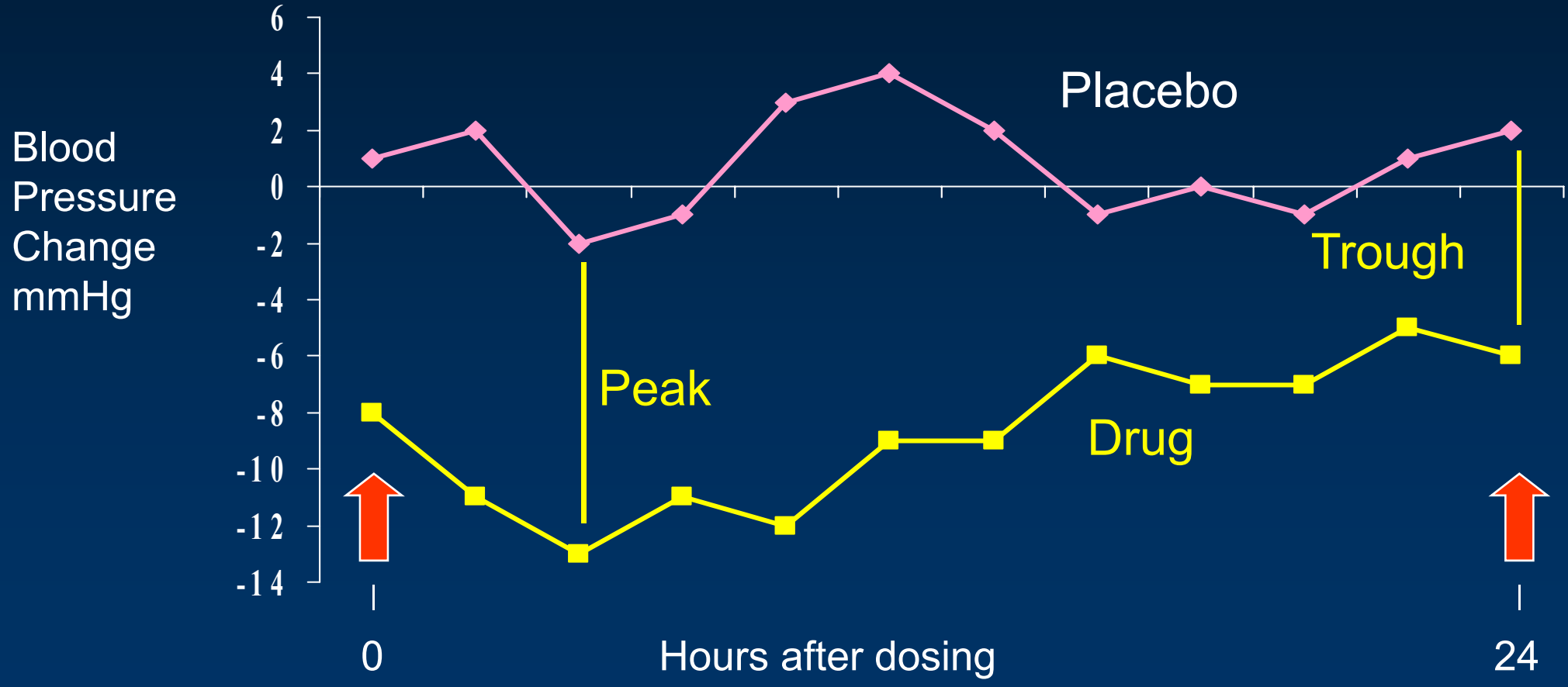
Duration of Action by Trough:Peak Ratio



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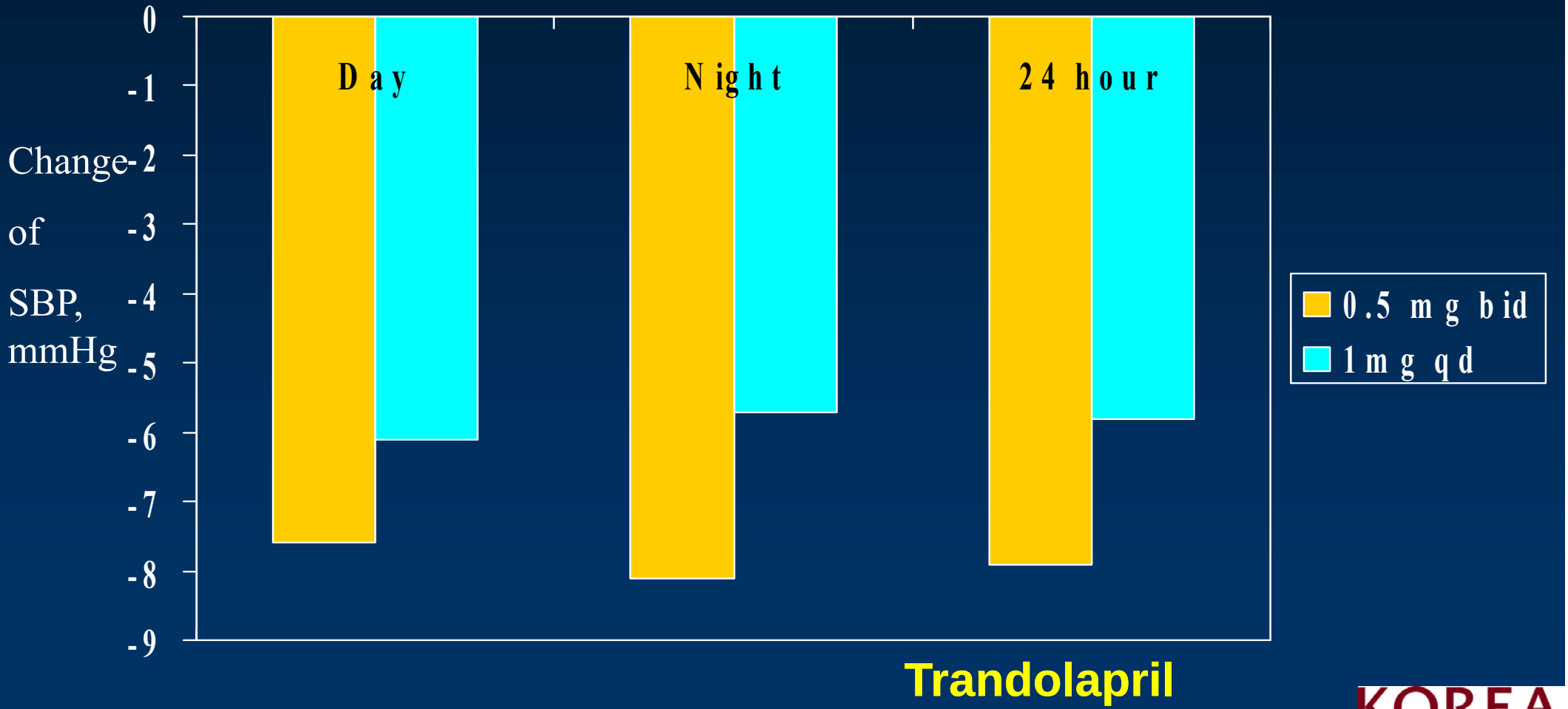
Effects of Time of Administration on Diurnal Changes of BP



Poirier J Clin Pharm 1993: 33:832

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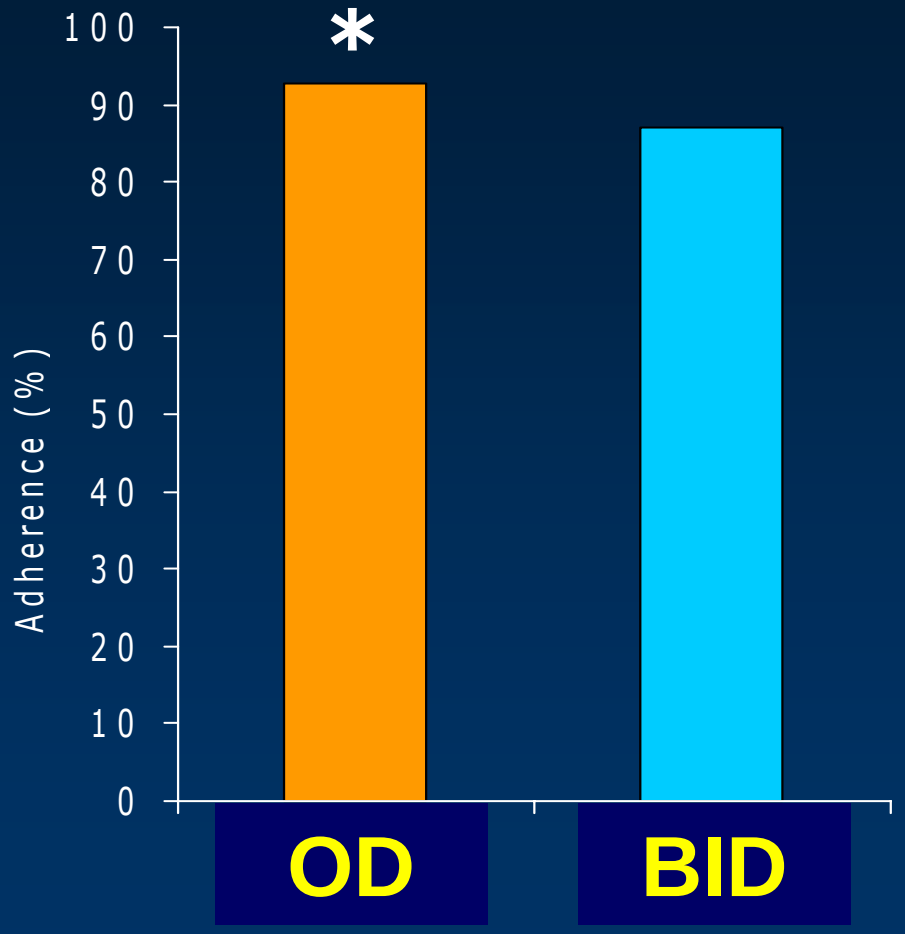
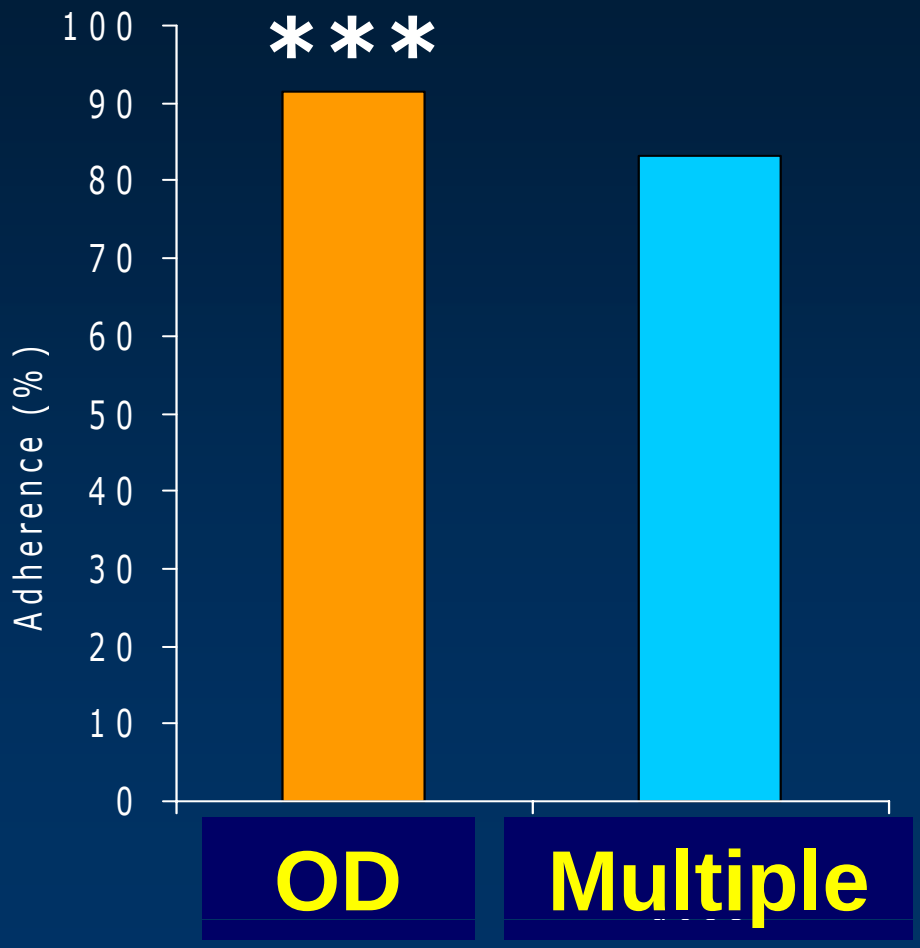
Adherence to Treatment Greater with Once-daily Dosing





* P<0.05 vs twice-daily dosing
*** P<0.001 vs multiple daily doses

Clin Ther 2002;24:302–316

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Targeting Mechanisms Responsible for MBPS

- **Sympathetic Nervous System**
  - ↑ Morning BP surge
  - Platelet hyperactivation
  - Endothelial cell dysfunction
  - ↑ Blood viscosity
- **Renin-Angiotensin-Aldosterone System**
  - ↑ Morning BP surge

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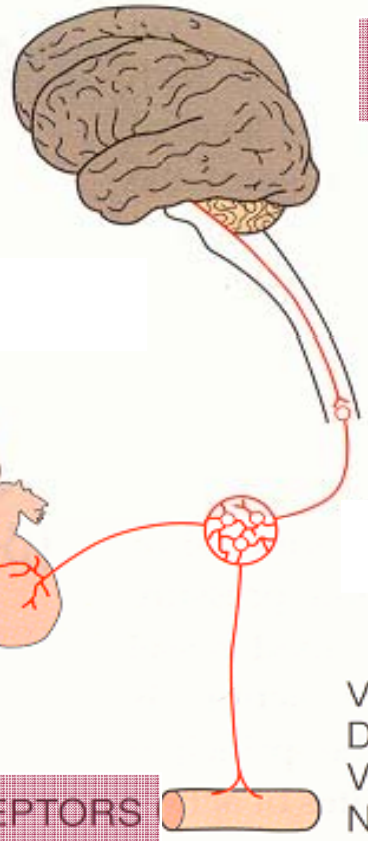
SNS
RAAS



VASOMOTOR CENTRE
α_2 -Adrenoceptor agonists
Imidazoline receptor agonists

β-ADRENOCEPTORS ON HEART
β-adrenoceptor antagonists

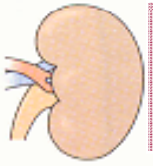
VASCULAR SMOOTH MUSCLE
Diuretics
Vasodilators
Nitrovasodilators
Calcium channel blockers
Potassium channel openers

ANGIOTENSIN RECEPTORS ON VESSELS
ACE inhibitors
AT1 receptor blockers

α-ADRENOCEPTORS ON VESSELS
α_1 blockers

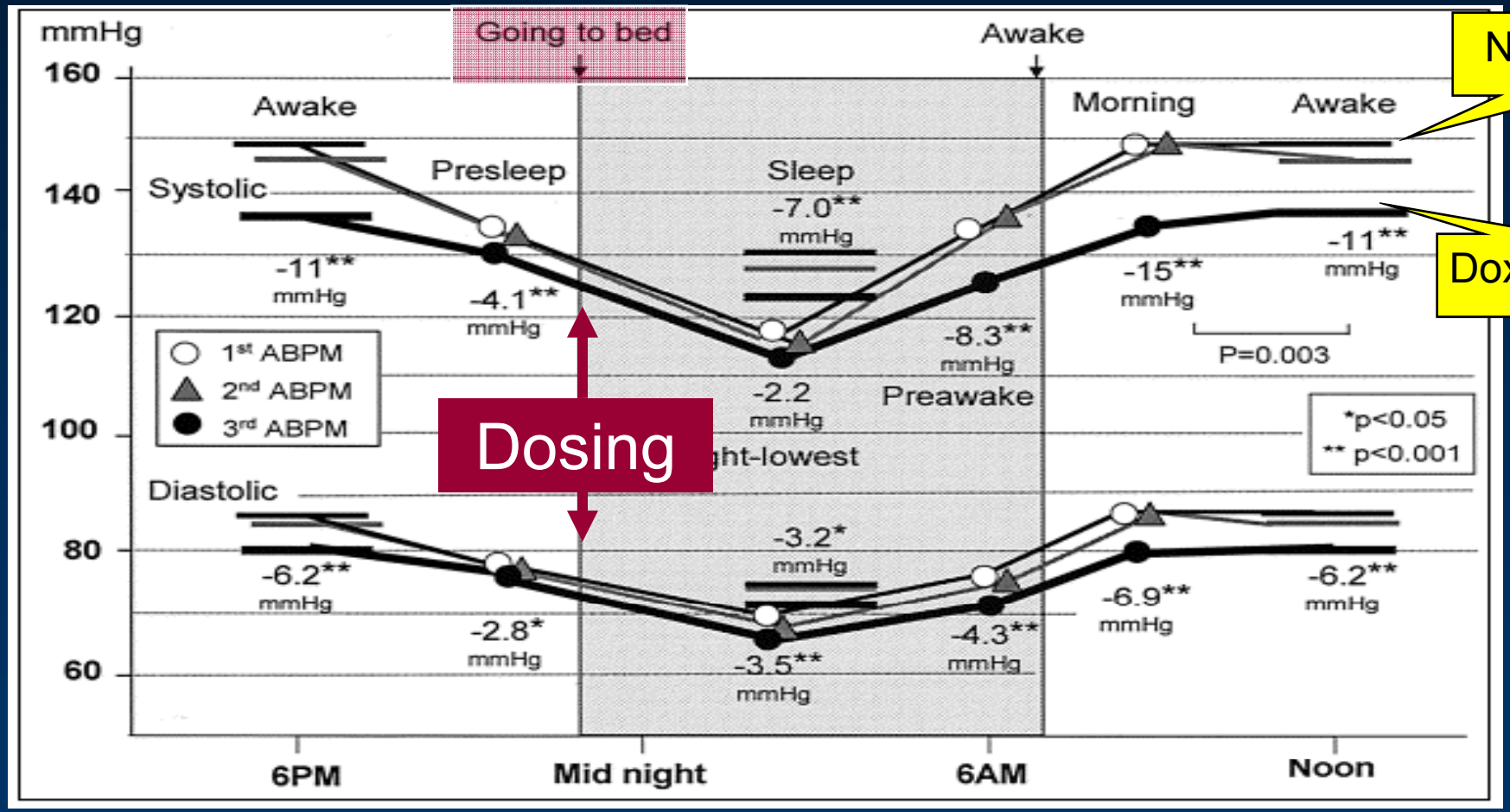
ADRENAL CORTEX
ACE inhibitors of angiotensin II formation
AT1 receptor blockers

KIDNEY TUBULES
Diuretics
ACE inhibitors



JUXTAGLOMERULAR CELLS THAT RELEASE RENIN
β-Adrenoceptor antagonists

Effects of α-Blockade on the Morning Surge of BP



Kario, Pickering, et al Am J Hypertens 2004;17; 668

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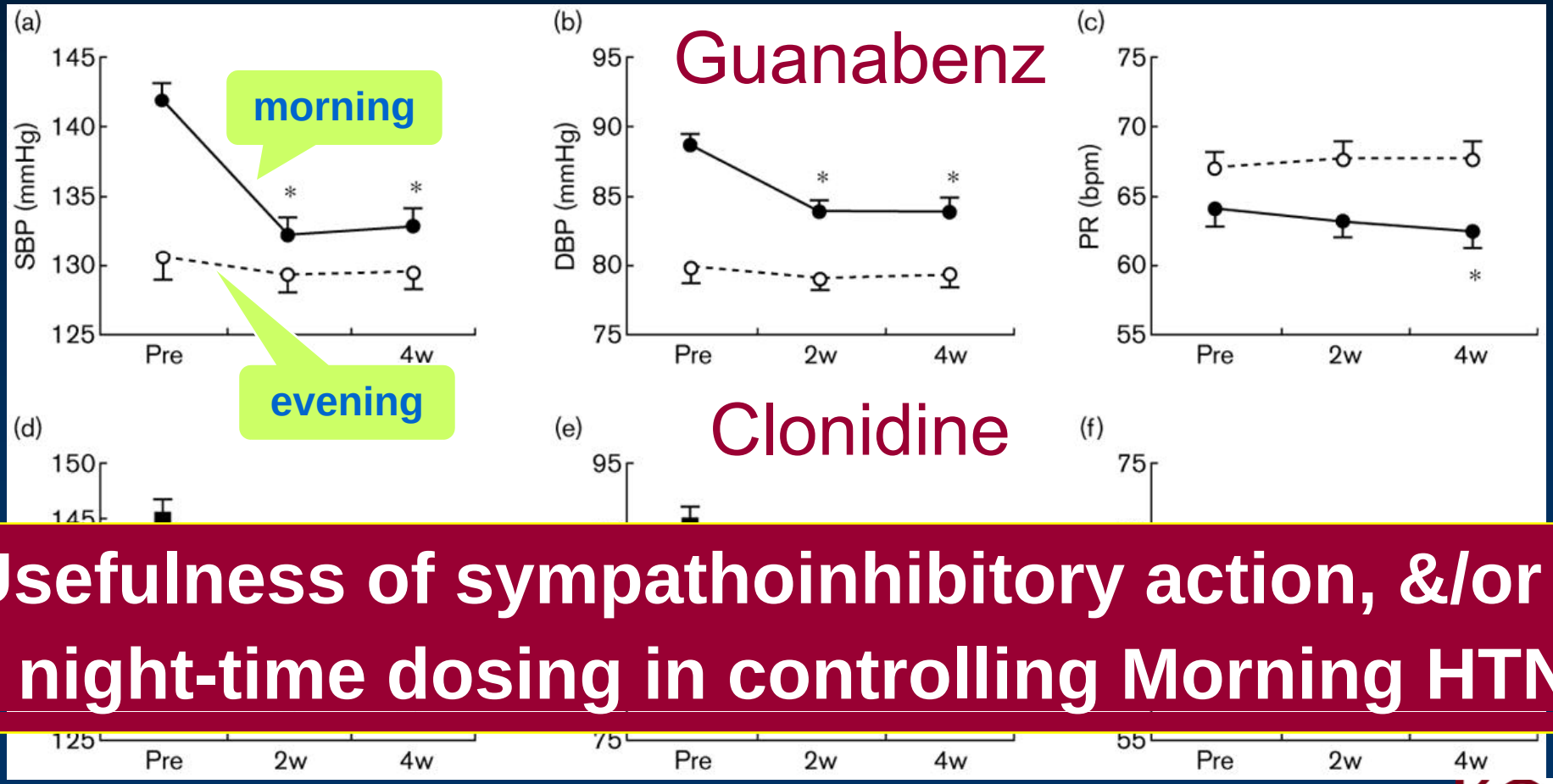
Effects of Bedtime Dosing of Centrally Acting α2-agonists on Morning HTN



Usefulness of sympathoinhibitory action, &/or of night-time dosing in controlling Morning HTN

J HTN 2003;21:805-811

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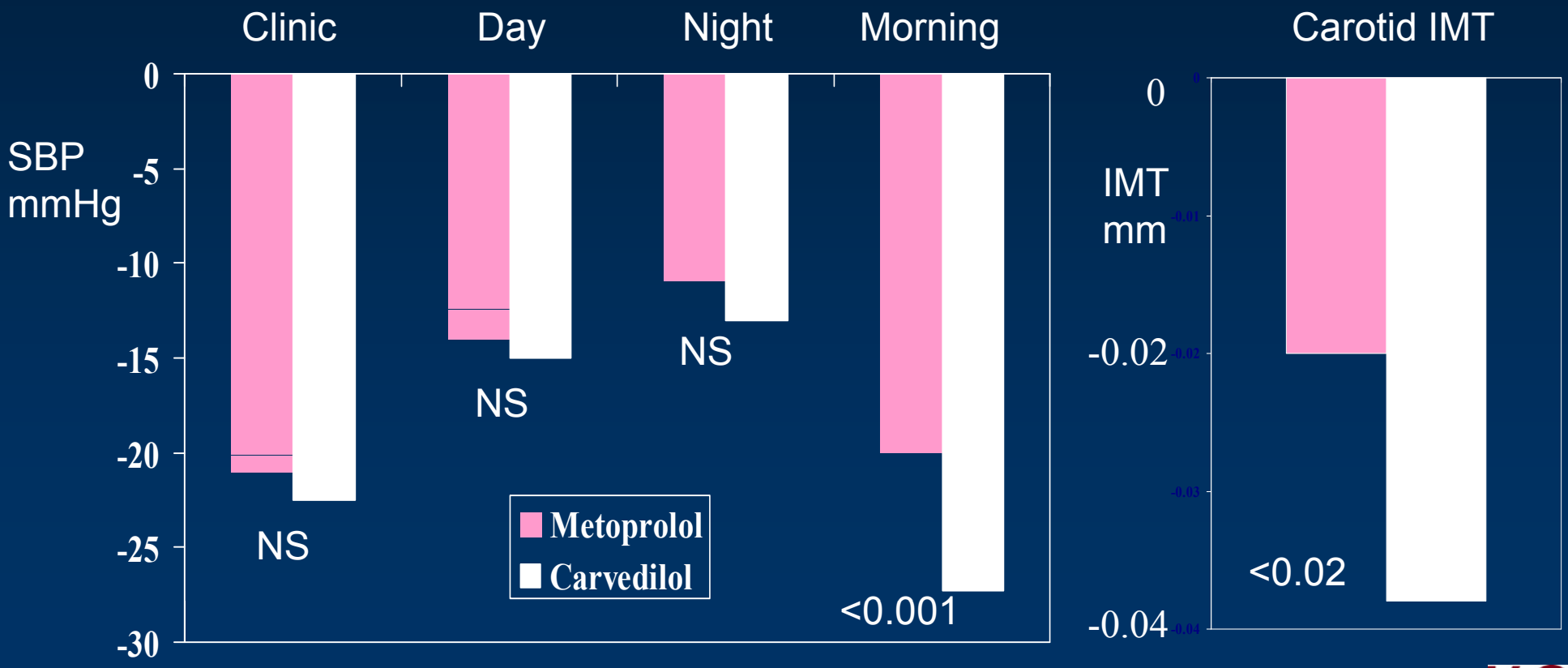
Regression of Carotid Atherosclerosis by Controlling Morning BP by α1/ß Antagonist



Marfella et al, Am J Hypertens 2005: 18: 308

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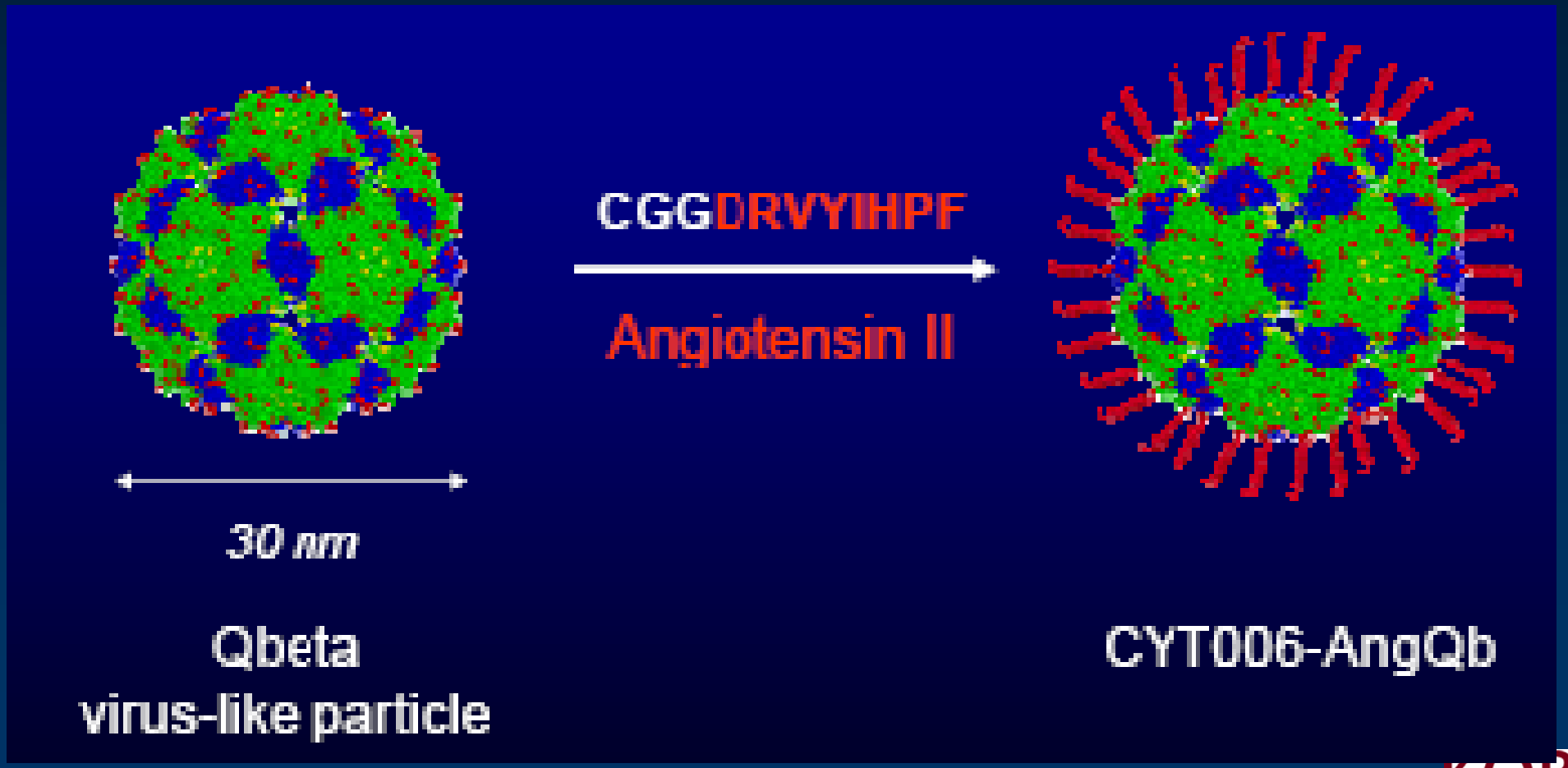
CYT006-AngQb, a Vaccine Against Hypertension Targeting Angiotensin II



Lancet 2008;371:821-827

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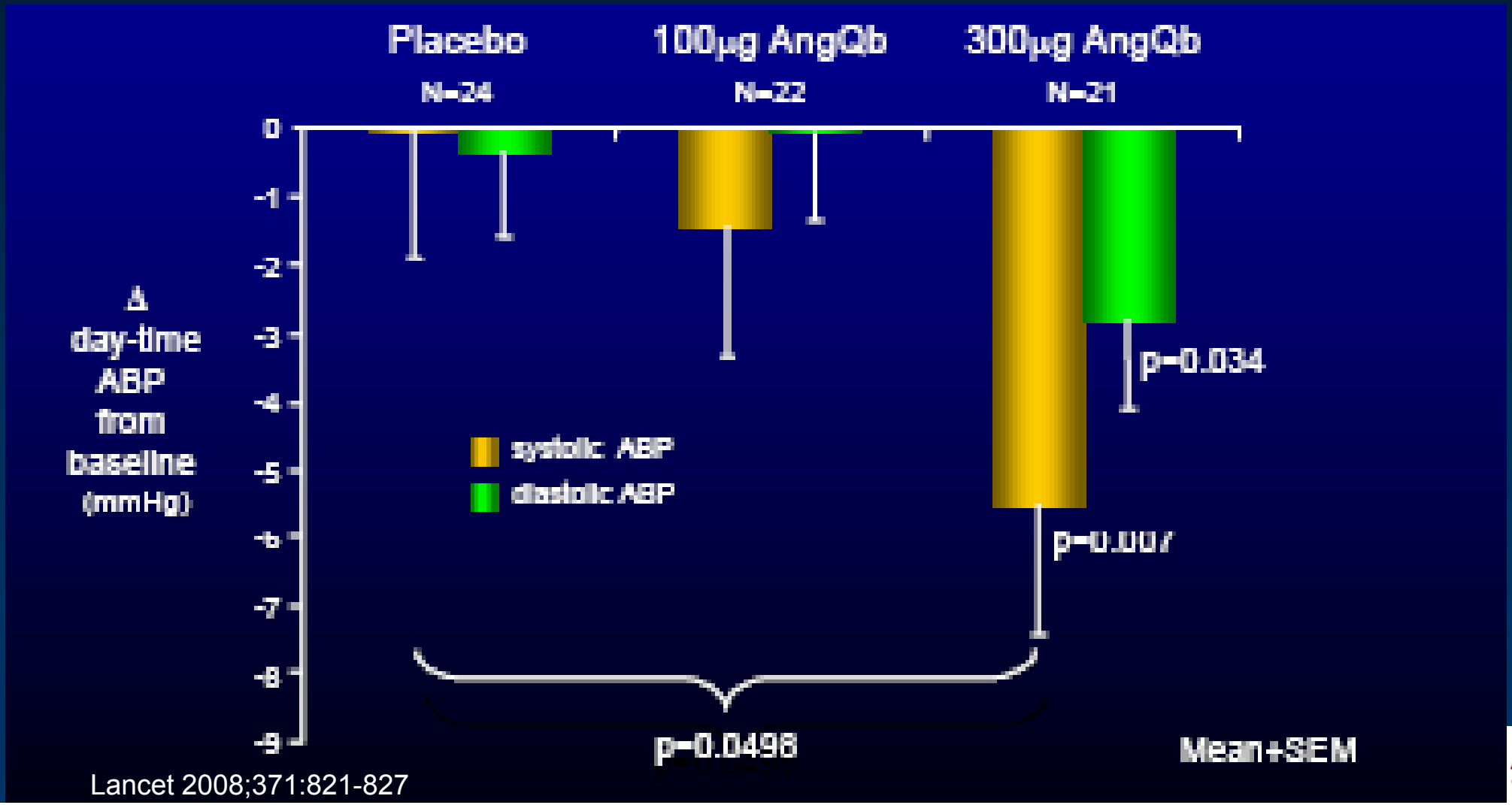
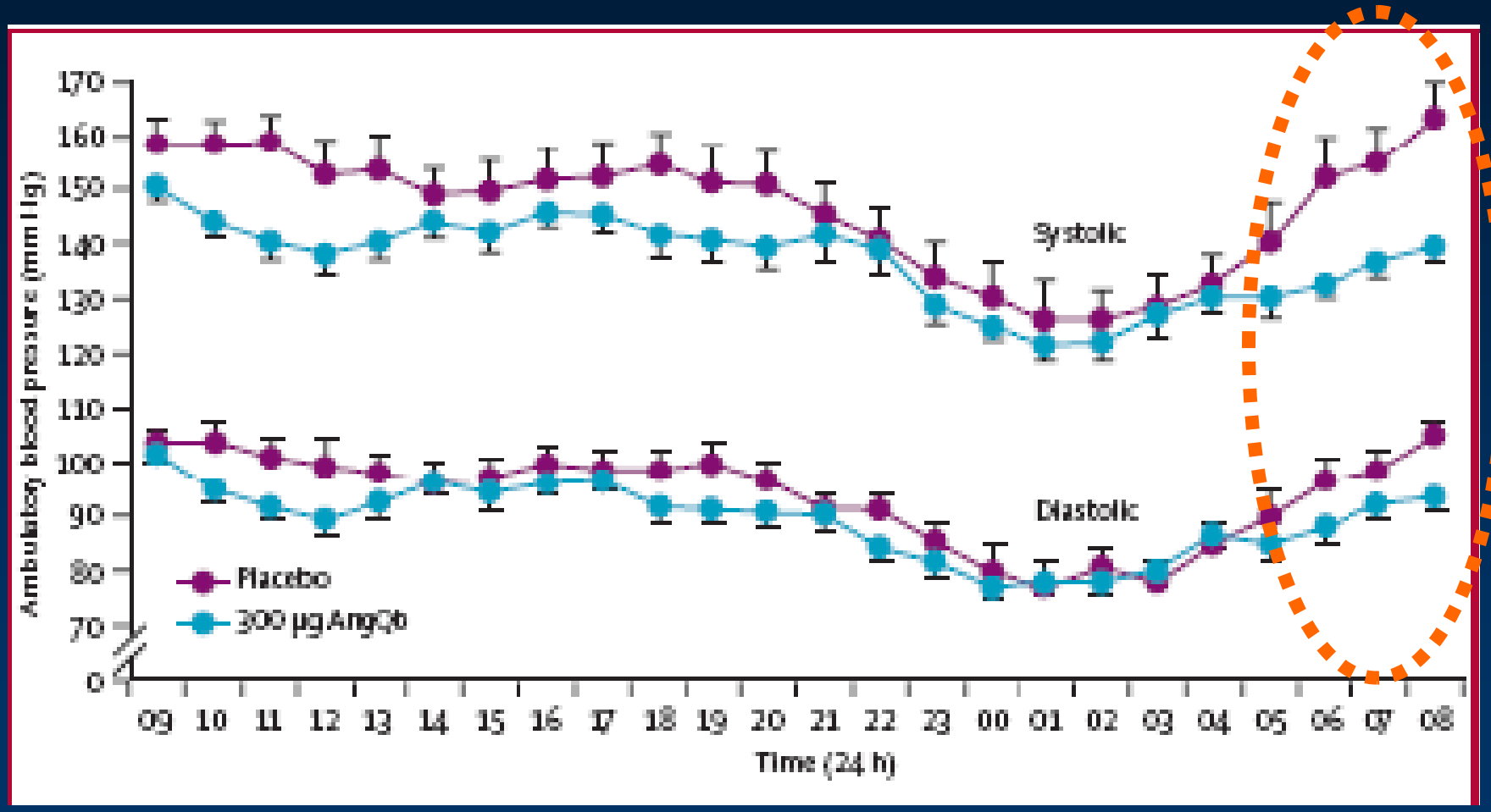
Change of Daytime BP
(week 14 vs. Baseline)



Lancet 2008;371:821-827

24hr BP Profile at Week 14



Lancet 2008;371:821-827

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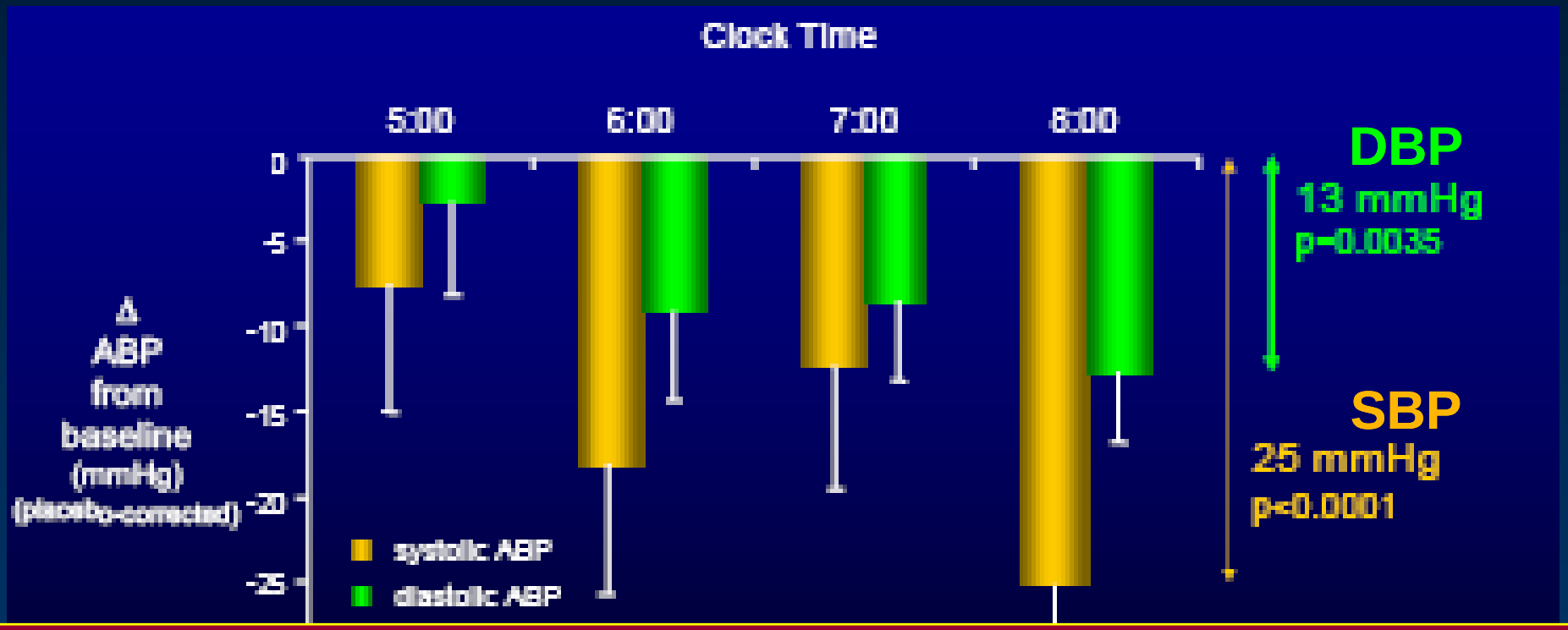
Change of Early Morning BP
(week 14 vs. Baseline. 300µg CYT006-AngQb)



Usefulness of RAAS-inhibitory action, &/or of long T1/2 in controlling Morning HTN

Lancet 2008;371:821-827

Summary (I)

- There is a pronounced diurnal rhythm of **BP and CV events**, with a **peak** of both in the **morning** hours, and a decrease during the night.
- **Drugs** approved for once daily dose may have **different durations of action**, particularly after missed doses.
- With some antihypertensive drugs the **time of dosing** may have significant effects on the diurnal pattern of BP.

Summary (II)

- **Inhibition of SNS or RAAS may be useful for controlling MBPS**
- **Different antihypertensive drugs** may have **different effects on the morning** surge of BP.

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Conclusions

- Morning BP surge is an independent risk for advancing the atherosclerosis process , TOD and triggering CV events.

- In addition to strict BP control, antihypertensive therapy targeting MBPS could achieve more beneficial effect for prevention of CV disease in high-risk hypertensive patients.

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KOREA UNIVERSITY GURO HOSPITAL

제1회 임상의사를 위한
최신 심장학
Core Review

일시 2008. 5.10(토) 14:00~18:30

장소 고려대학교 구로병원 대강당

주관 | 고려대학교 구로병원 심장혈관센터

문의 | 심장내과 의국 (02)2626-1108

행사안내

연수평점

→ 대한의사협회 연수평점 3점

→ 순환기내과분과 연수평점 4점

등록비(등록비는 없습니다.)

사전등록안내

→ 당일 현장에서의 등록은 오후 1시 30분부터 입니다.

고려대학교구로병원
KOREA UNIVERSITY GURO HOSPITAL

제1회 임상의사를 위한
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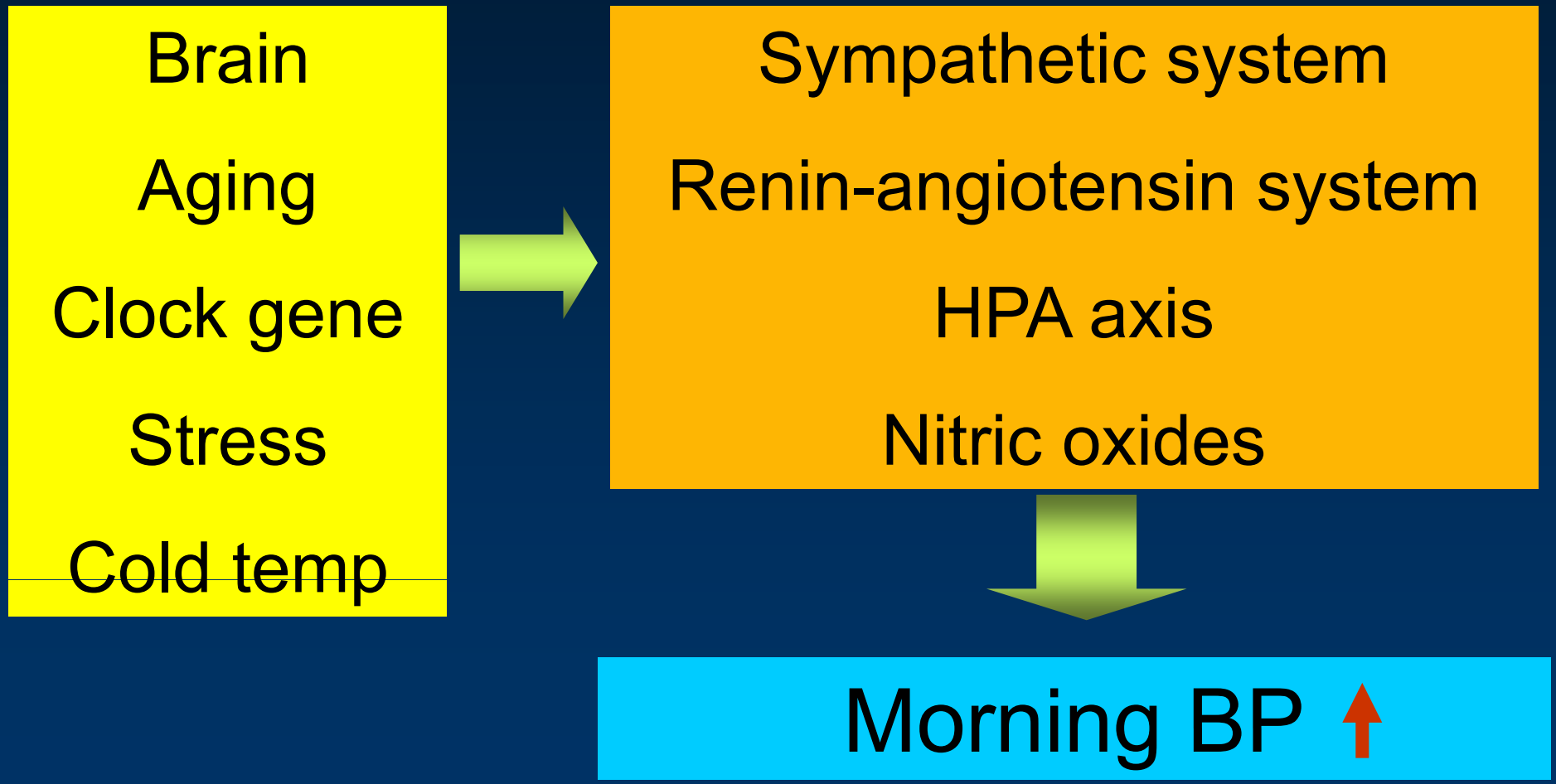
주관 | 고려대학교 구로병원 심장혈관센터 문의 | 심장내과 의국 (02)2626-1108

등록비(등록비는 없습니다.)

KOALA Symposium


Thank you
for your
attention !

Factors Influencing Morning Surge



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Factors Influencing Exaggerated Morning Surge

- Age (> 70 yr)
- African-American Ethnicity
- Day of week (Mon) / Season of year (Winter)
- Tobacco / Alcohol use
- Sodium / Caffeine / Medication (e.g. oral contraceptives)

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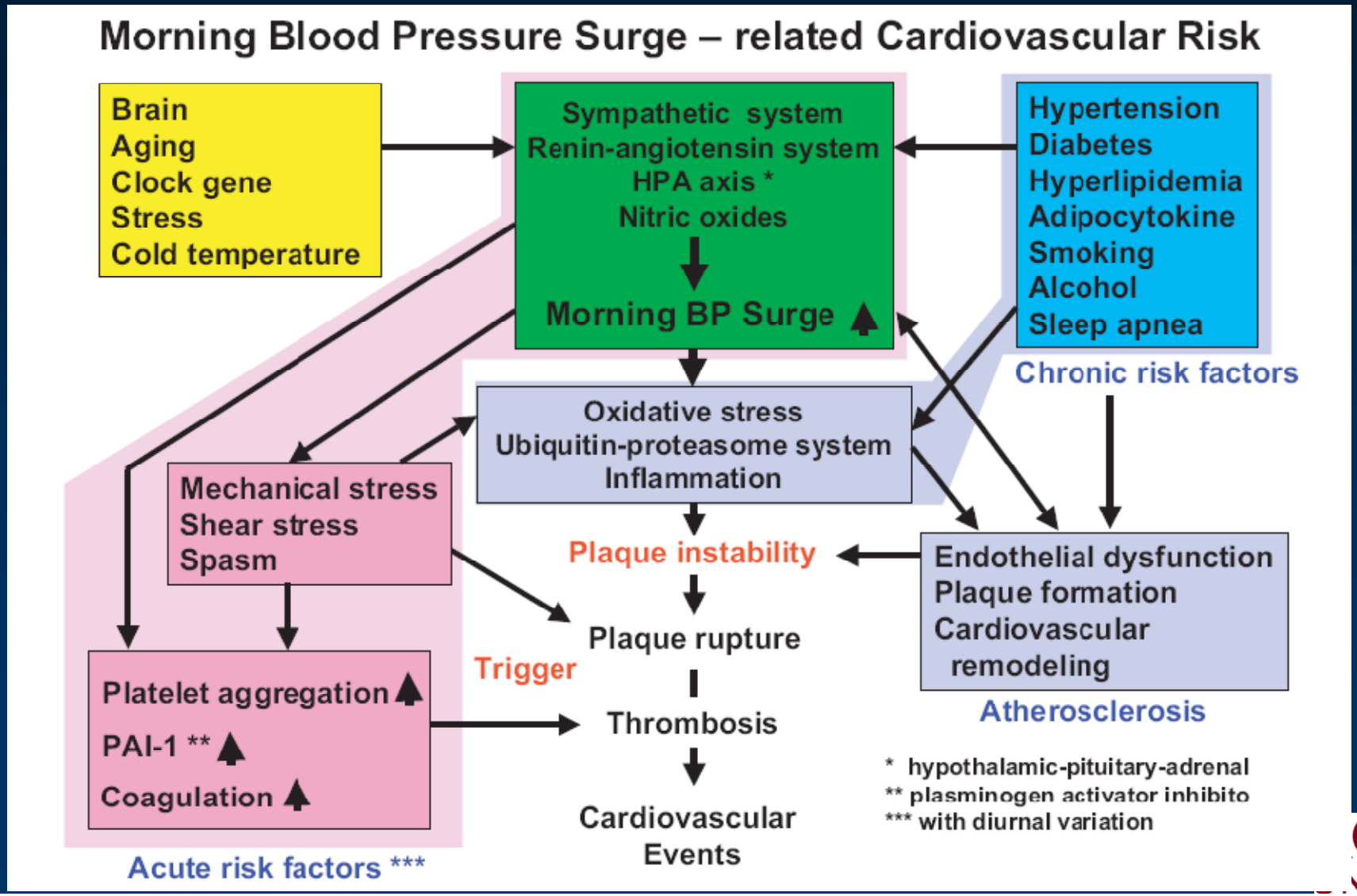
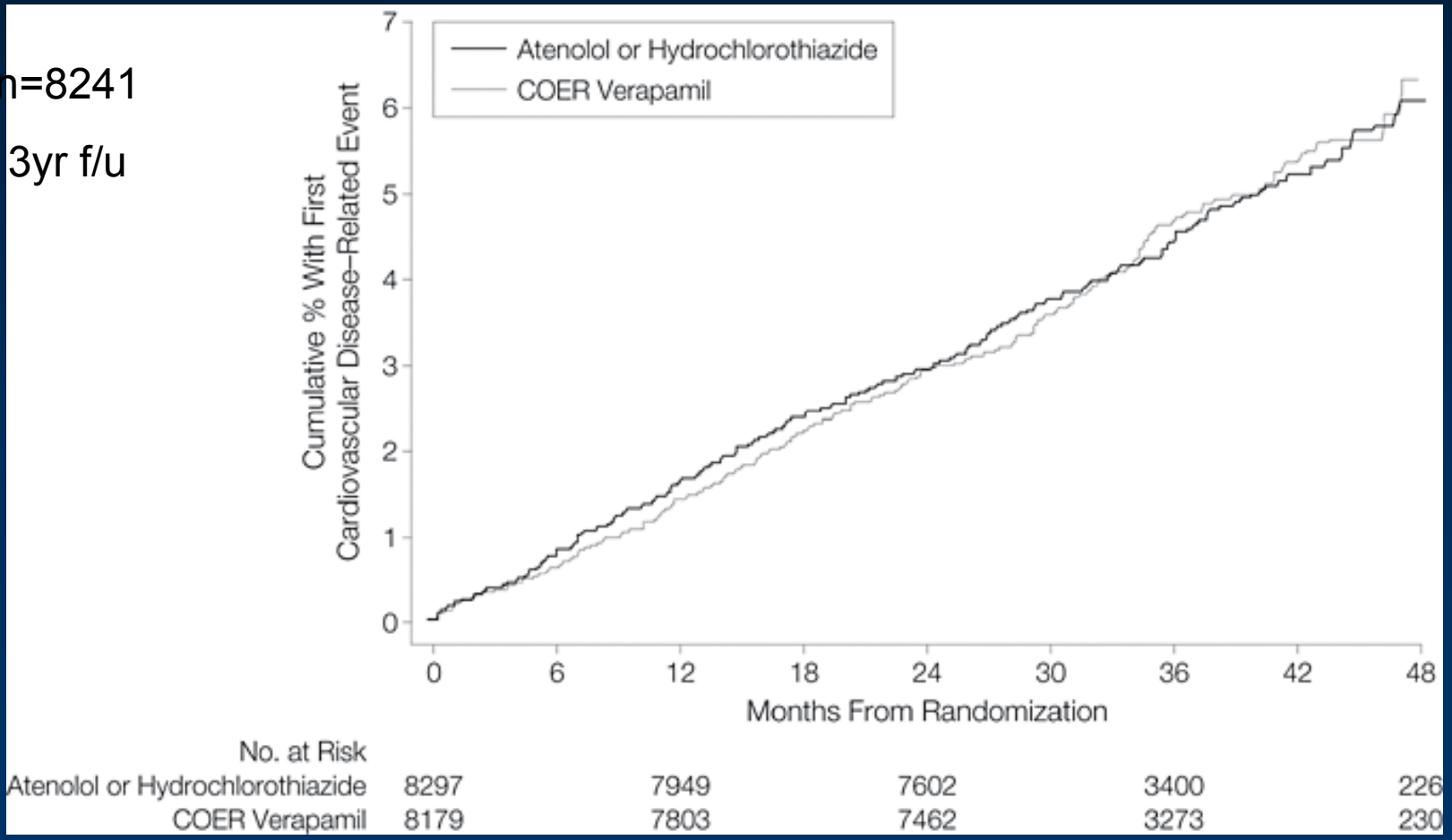

Morning Blood Pressure Surge – related Cardiovascular Risk
Brain
Aging
Clock gene
Stress
Cold temperature
Sympathetic system
Renin-angiotensin system
HPA axis *
Nitric oxides
Morning BP Surge
Hypertension
Diabetes
Hyperlipidemia
Adipocytokine
Smoking
Alcohol
Sleep apnea
Chronic risk factors
Oxidative stress
Ubiquitin-proteasome system
Inflammation
Mechanical stress
Shear stress
Spasm
Plaque instability
Endothelial dysfunction
Plaque formation
Cardiovascular
remodeling
Atherosclerosis
Plaque rupture
Trigger
Platelet aggregation
PAI-1 **
Coagulation
Thrombosis
Cardiovascular
Events
Acute risk factors ***
* hypothalamic-pituitary-adrenal
** plasminogen activator inhibito
*** with diurnal variation

Controlled onset extended release Verapamil vs. Atenolol or Hydrochlorthiazide

n=8241

3yr f/u



JAMA 2003;289:2073-2082

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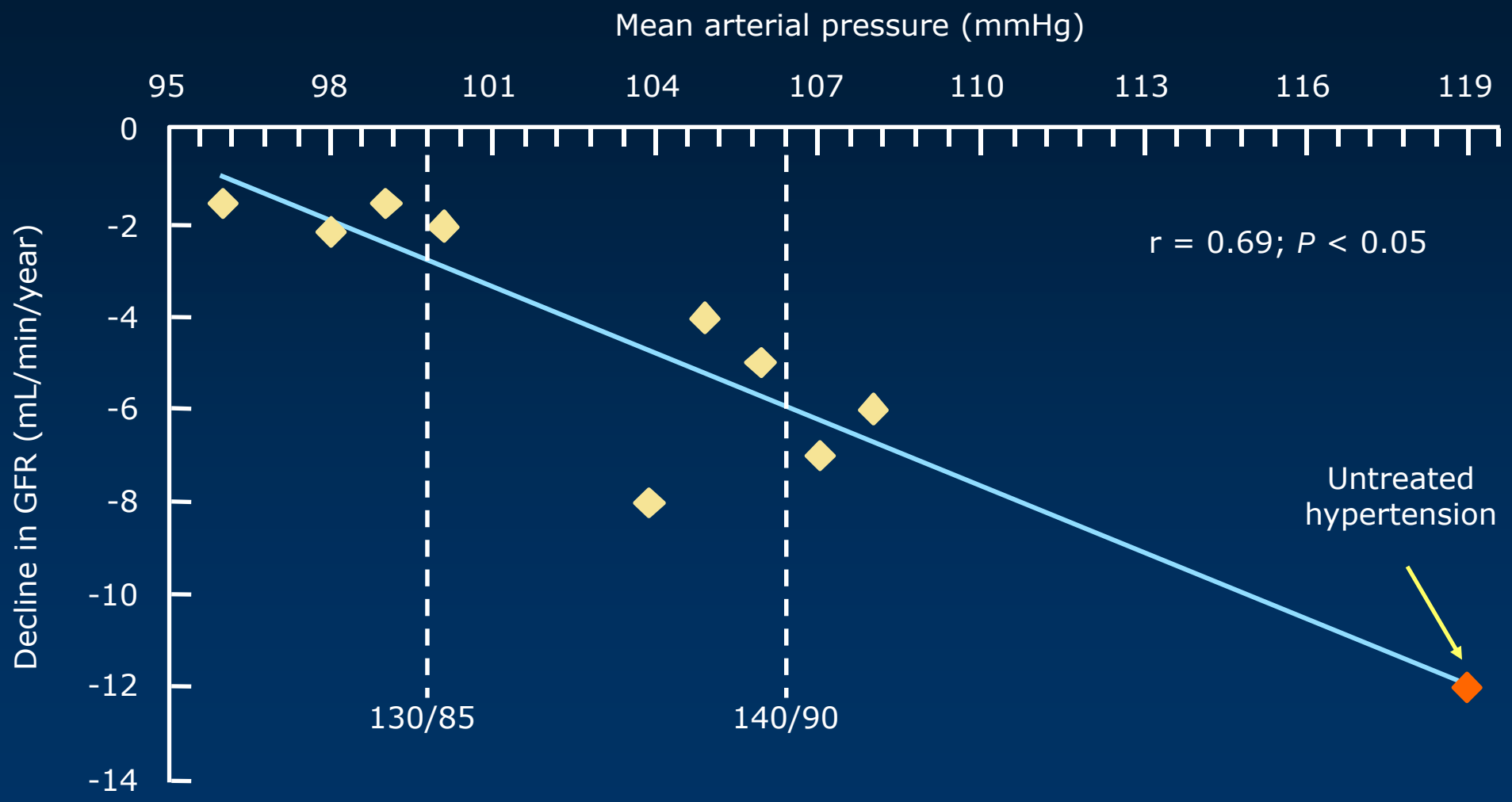
Reducing target-organ damage

Reduced blood pressure slows the rate of GFR decline



Bakris et al. *Am J Kidney Dis* 2000;36:646-661

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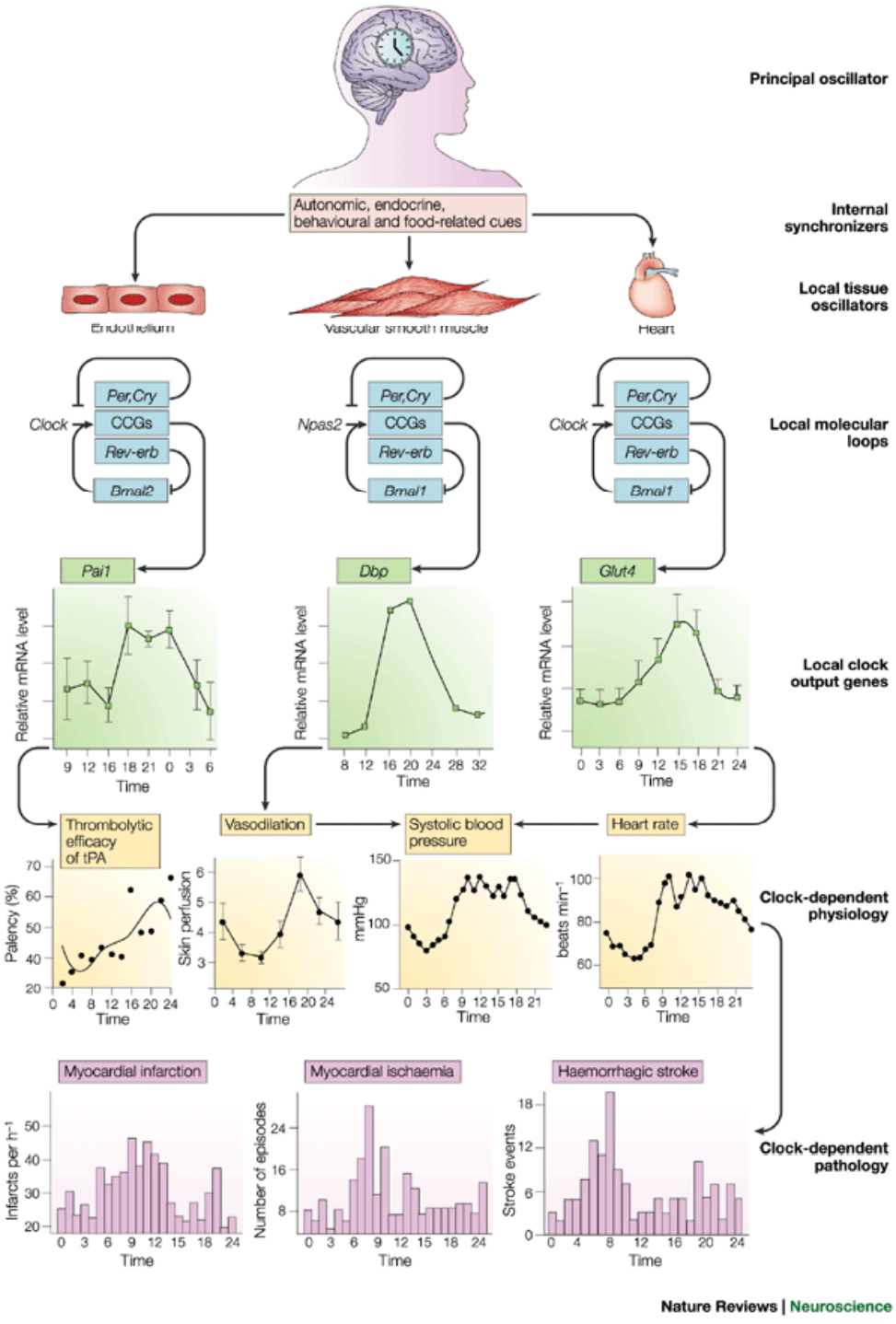

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Morning BP Surge & CV Events

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Target-organ Damage Increases Cardiovascular Risk

Endothelial dysfunction

- Endothelium plays a key role in controlling peripheral arteriolar resistance
- Endothelial dysfunction can be observed as an inapropriate response to vasodilators/vasoconstrictors
  - Nitric oxide is a key endogenous vasodilator
- It is one of the earliest markers for target-organ damage
- It contributes to cardiovascular dise

Klahr, Morrissey. *Kidney Int Suppl* 2000;75:S7-S14

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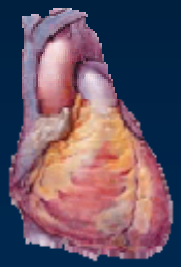
Target-Organ Damage Precedes Clinical Events

Risk factors: diabetes, obesity, smoking, age

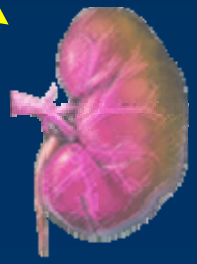
Vasoconstriction
Vascular hypertrophy
Endothelial dysfunction
Atherosclerosis



Apoptosis
LVH
Fibrosis

Hypertension
Thrombosis

Vascular disease



Decreased GFR
Proteinuria/albuminuria
Glomerulosclerosis

Arrhythmia
Heart failure
MI

Stroke
Cognitive dysfunction

Renal failure

Death

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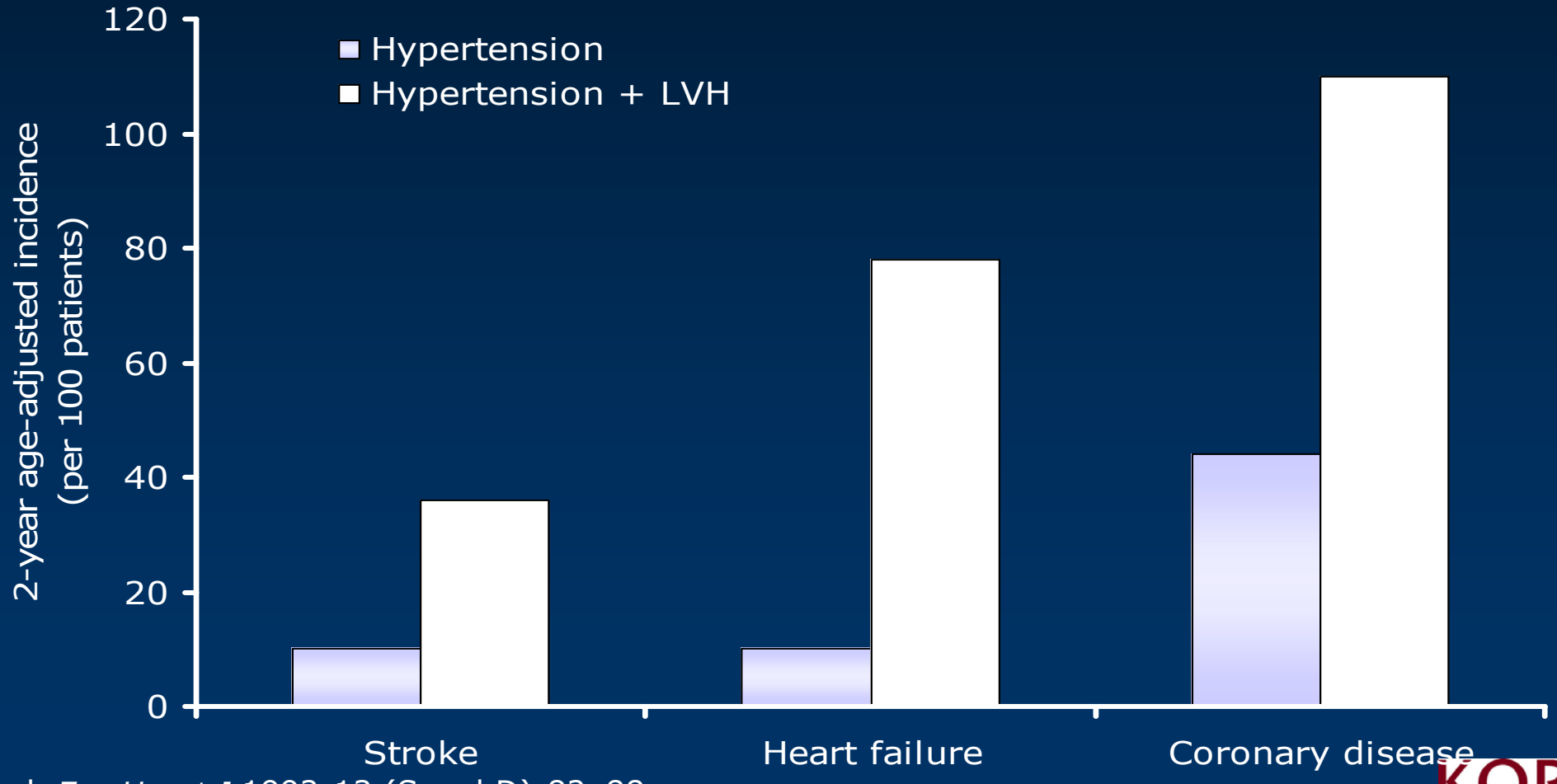
Target-organ Damage Increases Cardiovascular Risk

Left ventricular hypertrophy



Kannel. *Eur Heart J* 1992;13 (Suppl D):82–88

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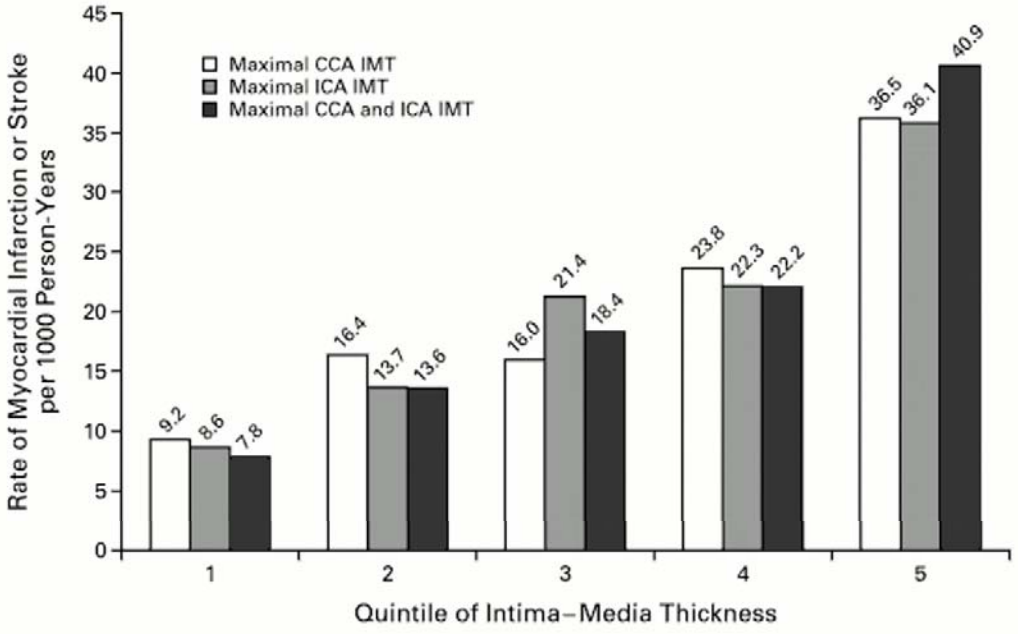
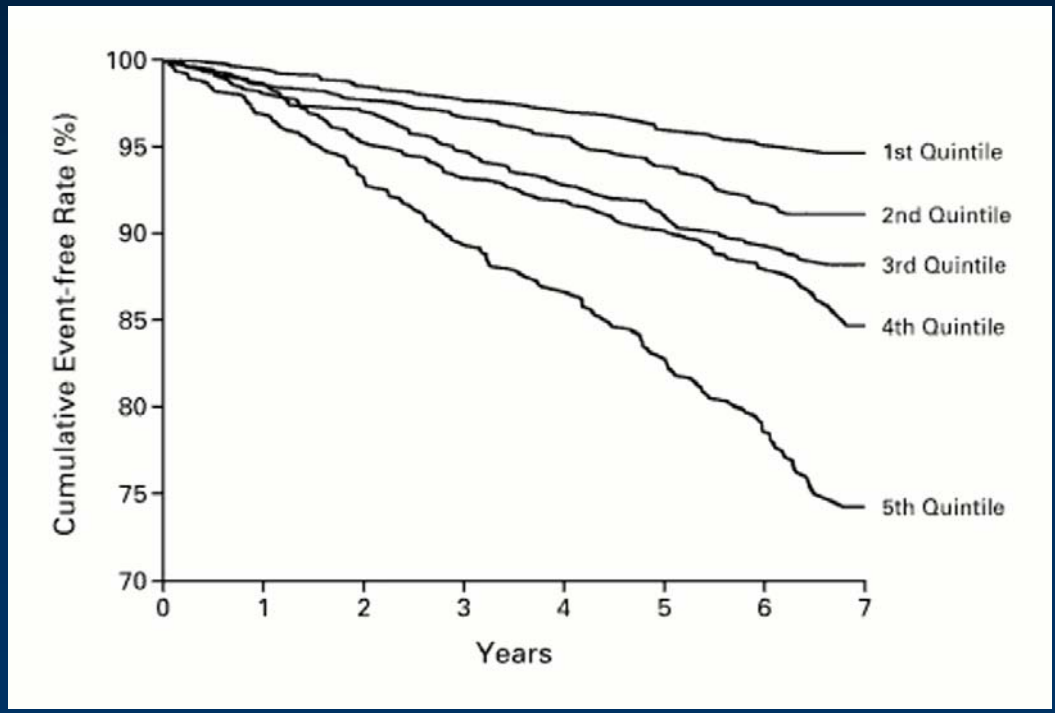
Target-organ Damage Increases Cardiovascular Risk

Carotid IMT





Daniel HO et al. *NEJM* 1997;340:14-22

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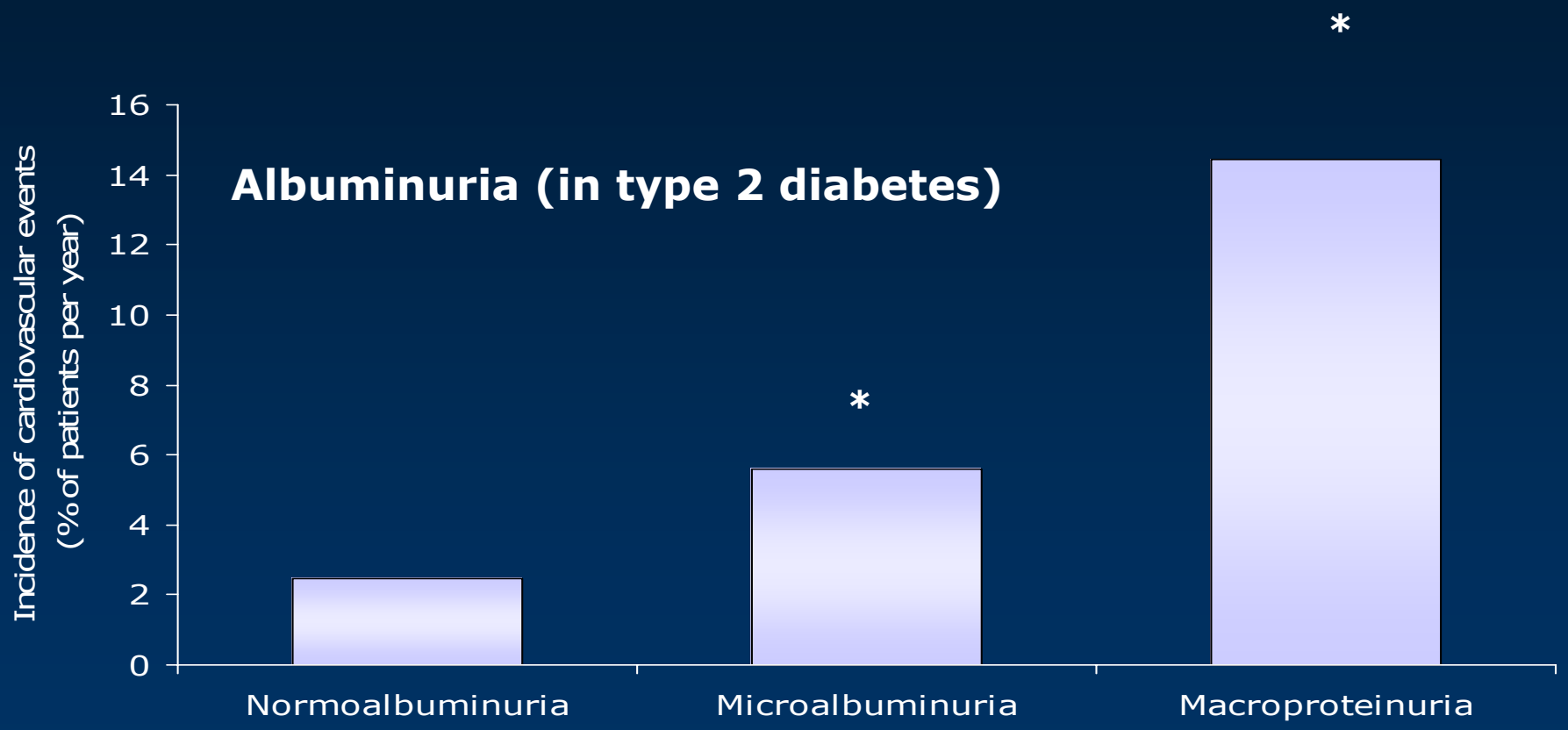
Target-organ Damage Increases CV Risk



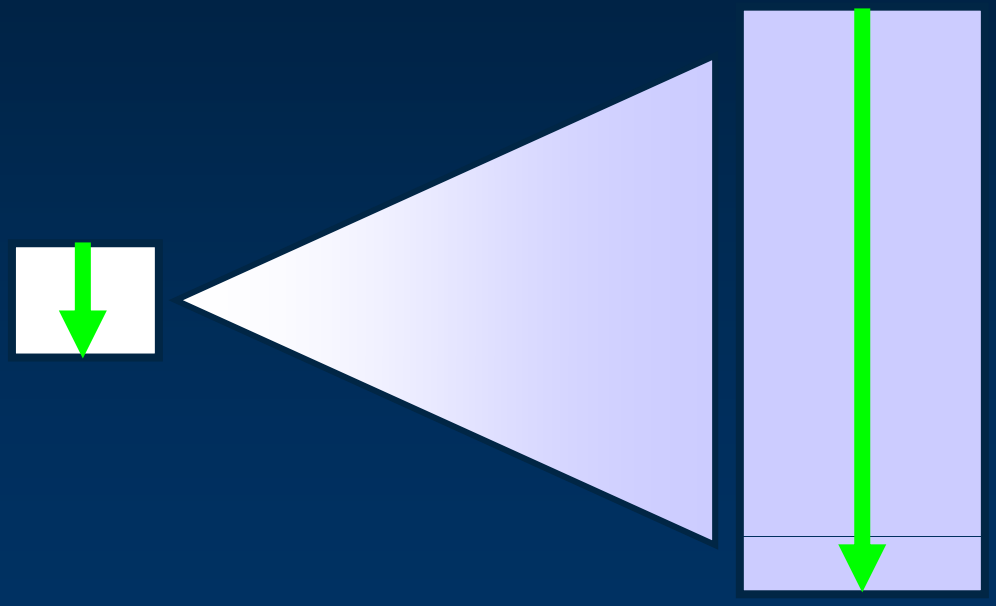
*P<0.05 versus normoalbuminuria after adjusting for other risk markers

Gimeno Orna et al. *Rev Clin Esp* 2003;203:526–531

Lowering BP reduces CV risk

Meta-analysis of 61 prospective, observational studies
One million adults, 12.7 million person-years

2 mmHg decrease in mean SBP



7% reduction in risk of ischaemic heart disease mortality

10% reduction in risk of stroke mortality

Lewington et al. *Lancet.* 2002;360:1903–1913.

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Characteristics of Morning BP Reactivity Subgroup

	Nonreactive Group Q1–3		Hyperreactive Group Q4
Number	90		30
Age (yr)	59 ± 10	<	65 ± 13*
Male, *n* (%)	41 (46)		15 (50)
Sustained hypertension, *n* (%)	30 (33)		19 (63)
24-h systolic BP (mm Hg)	121 ± 13	<	133 ± 17†
24-h diastolic BP (mm Hg)	74 ± 8	<	78 ± 10*
24-h pulse rate (/min)	68 ± 7		67 ± 8
SD of 24-h systolic BP (mm Hg)	17 ± 5		20 ± 4*
SD of awake systolic BP (mm Hg)	17 ± 6		19 ± 4*

Am J Hypertens 2005;18:1528–1533

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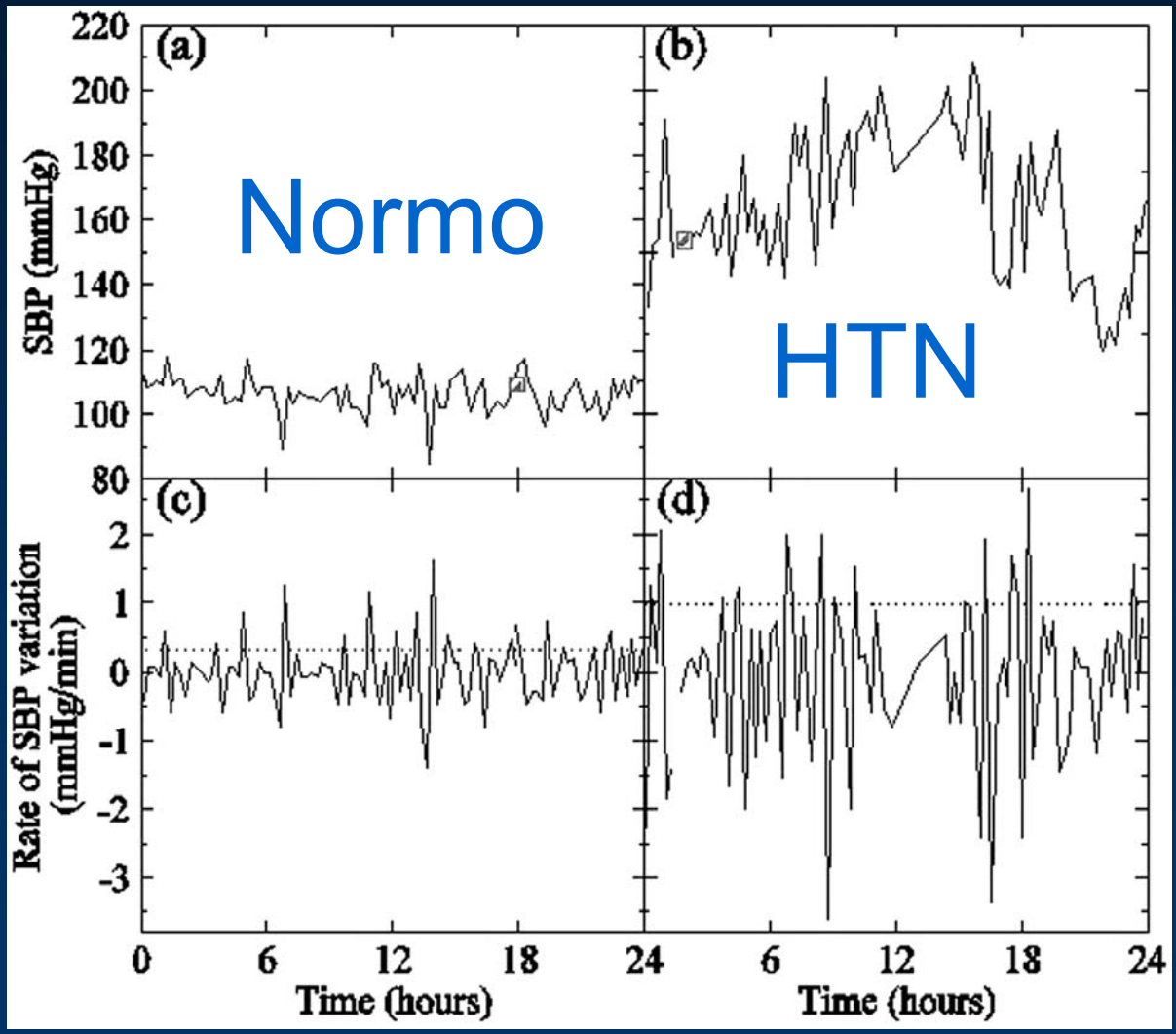
24h Profiles of SBP & SBP Variation



Hypertension. 2005;45:505-512.

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Rate of SBP Variation During Morning BP Surge Correlated Independently to Larger CCA-IMT

	Multiple Linear Regression Analysis†	
Variable*	Regression Coefficient (95% CI)	*P*
SBP‡	+0.017 (0.003−0.031)	0.018
DBP‡	−0.018 (−0.037−0.002)	0.103
HR§	−0.006 (−0.022−0.009)	0.421
SBP variability	+0.003 (−0.002−0.008)	0.290
DBP variability	+0.004 (−0.001−0.010)	0.109
HR variability	−0.002 (−0.005−0.001)	0.162
Rate of SBP variation‖	+0.010 (0.003−0.017)	0.008

Hypertension. 2005;45:505-512.

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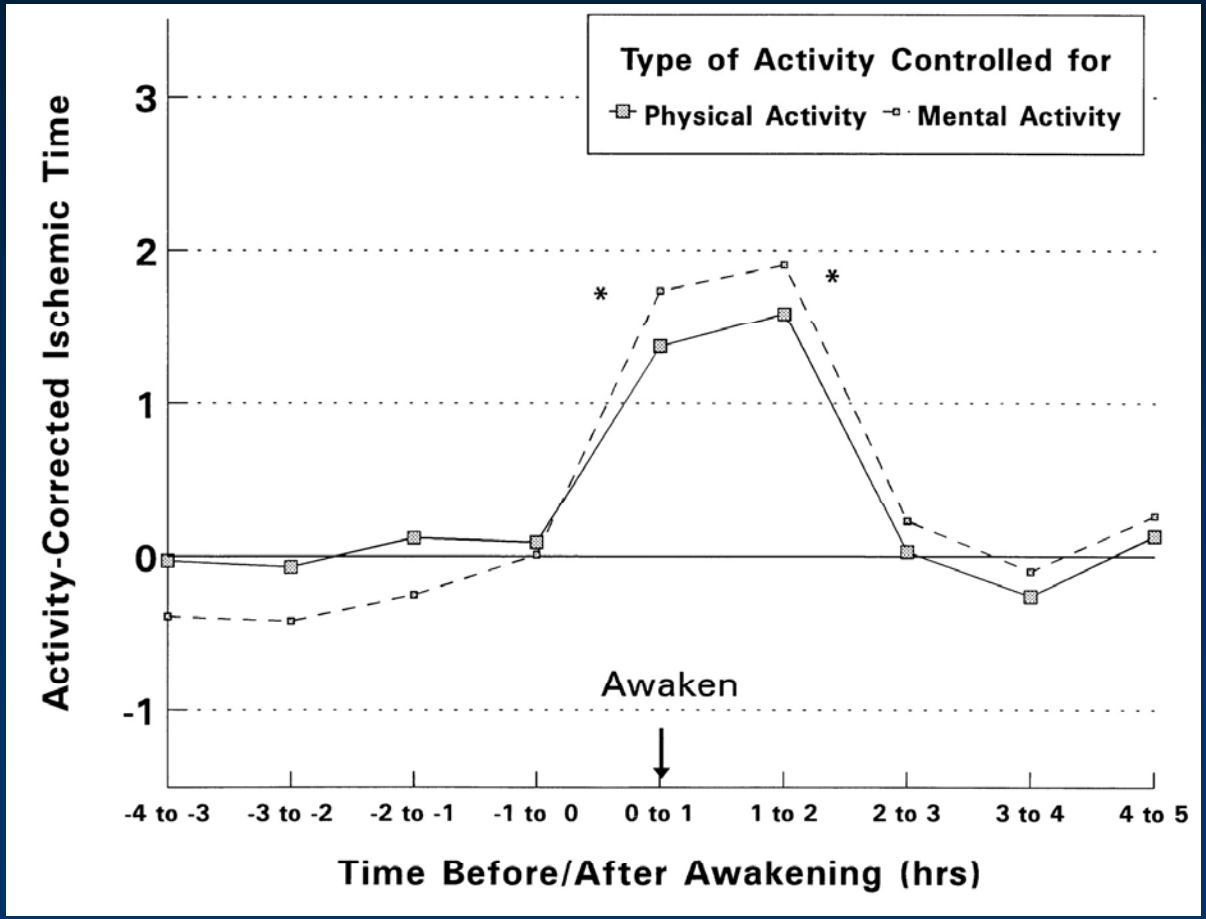
A significant increase in physical and mental activity–adjusted ischemic time at the hour of awakening



Circulation. 1996;93:1364-1371

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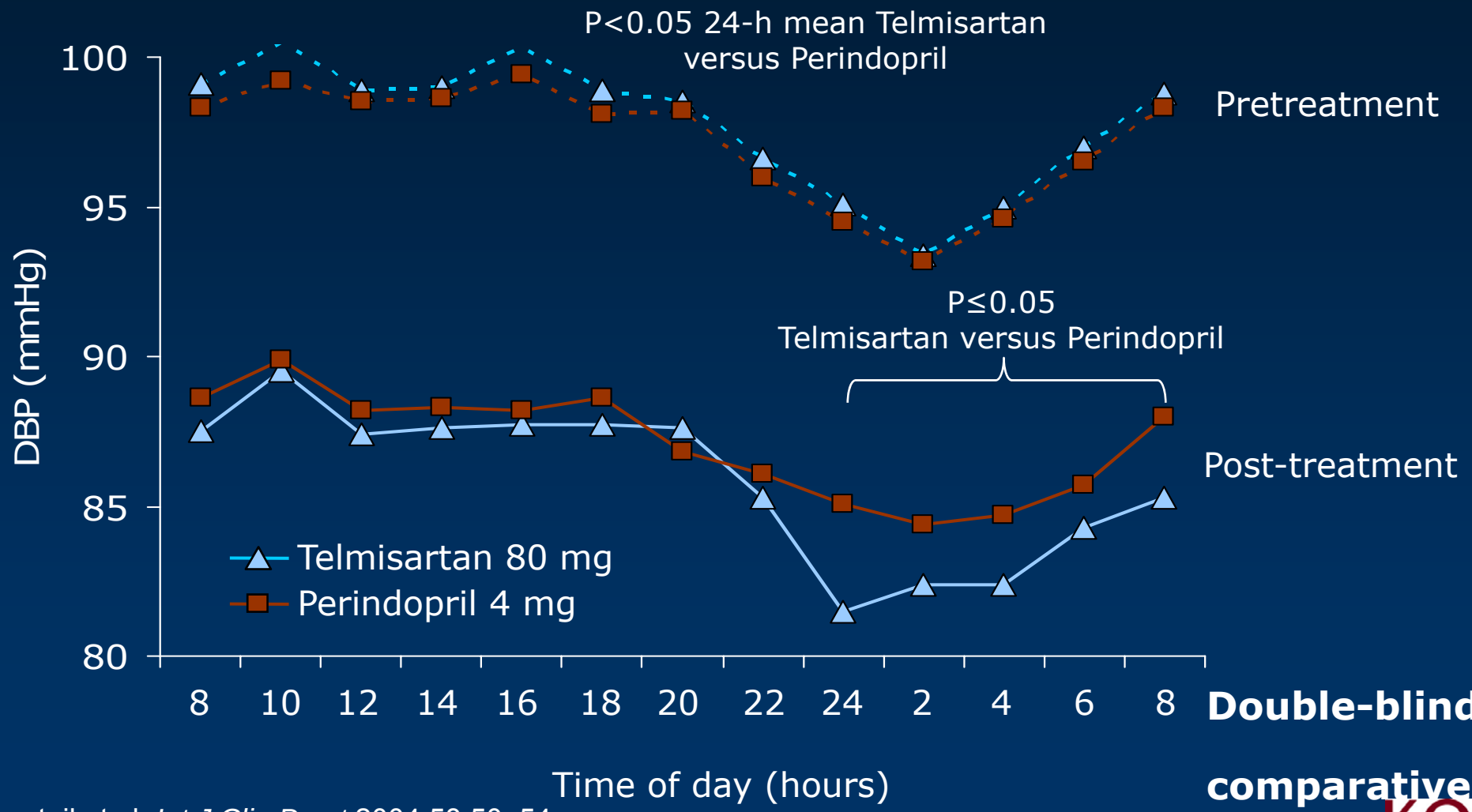
Telmisartan compared with Perindopril – last 8 hours



Double-blind comparative study

Nalbantgil et al. *Int J Clin Pract* 2004;58:50–54

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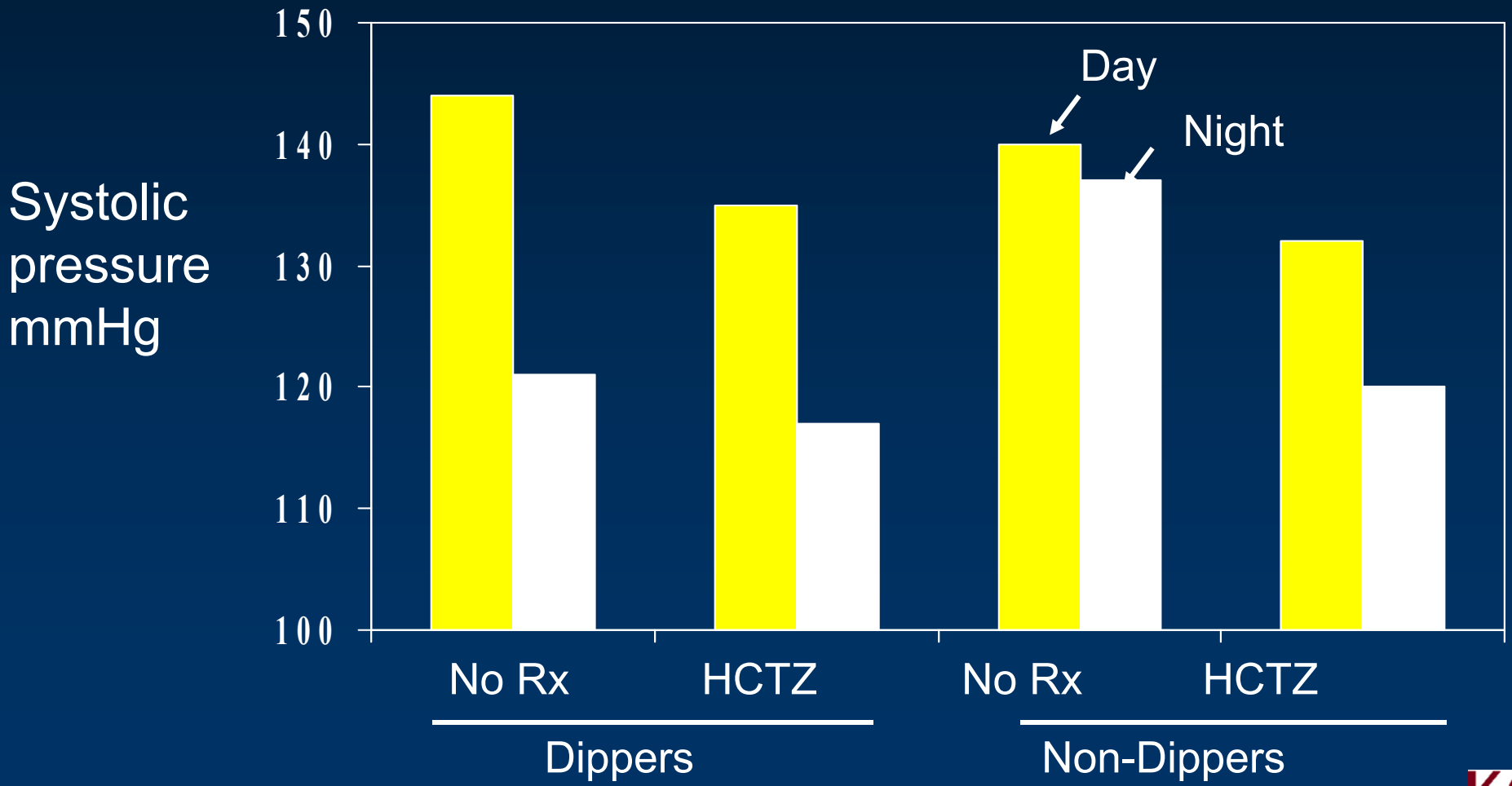
Diuretics Convert Non-Dippers to Dippers



Uzu & Kimura Circ 1999; 100:1635

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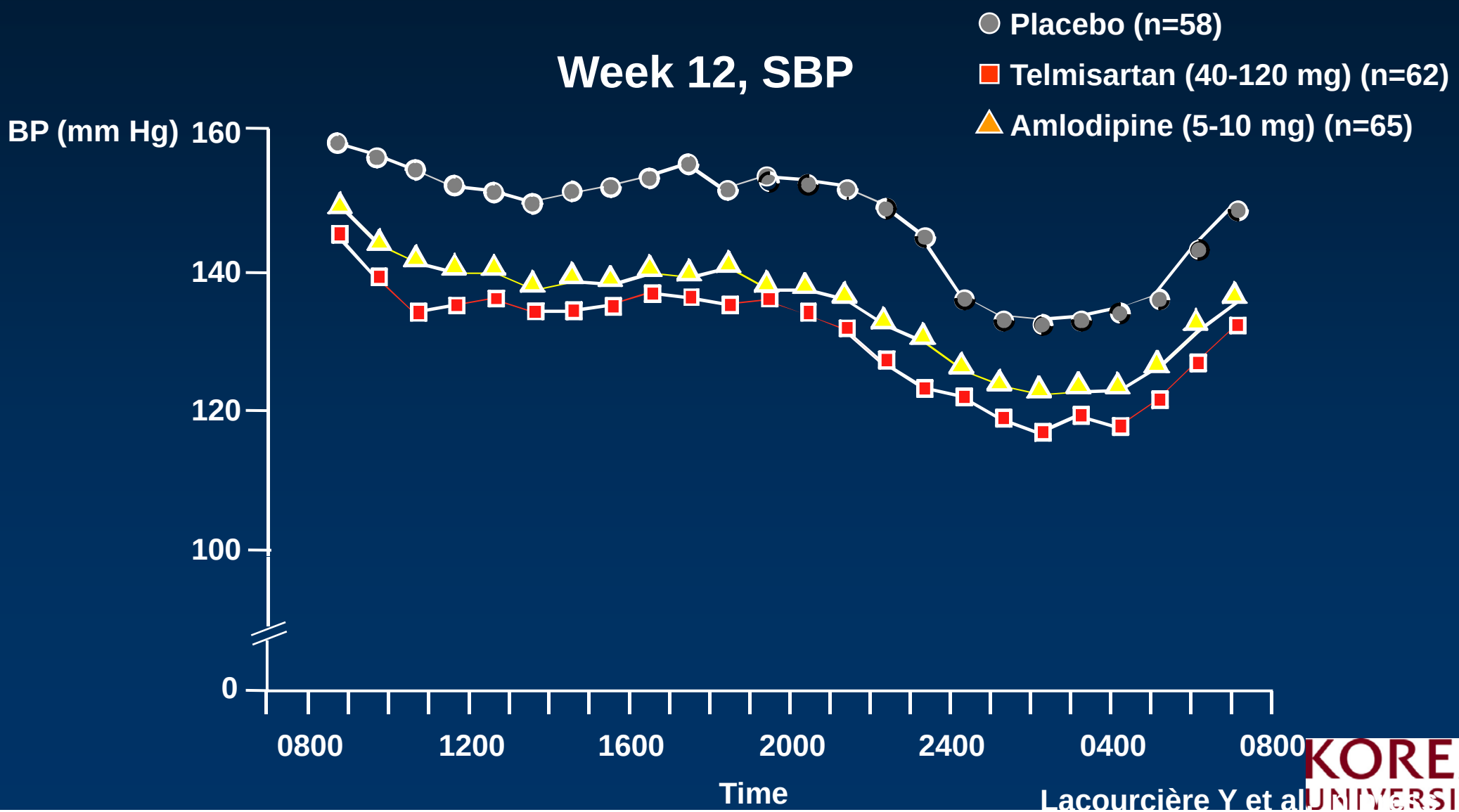
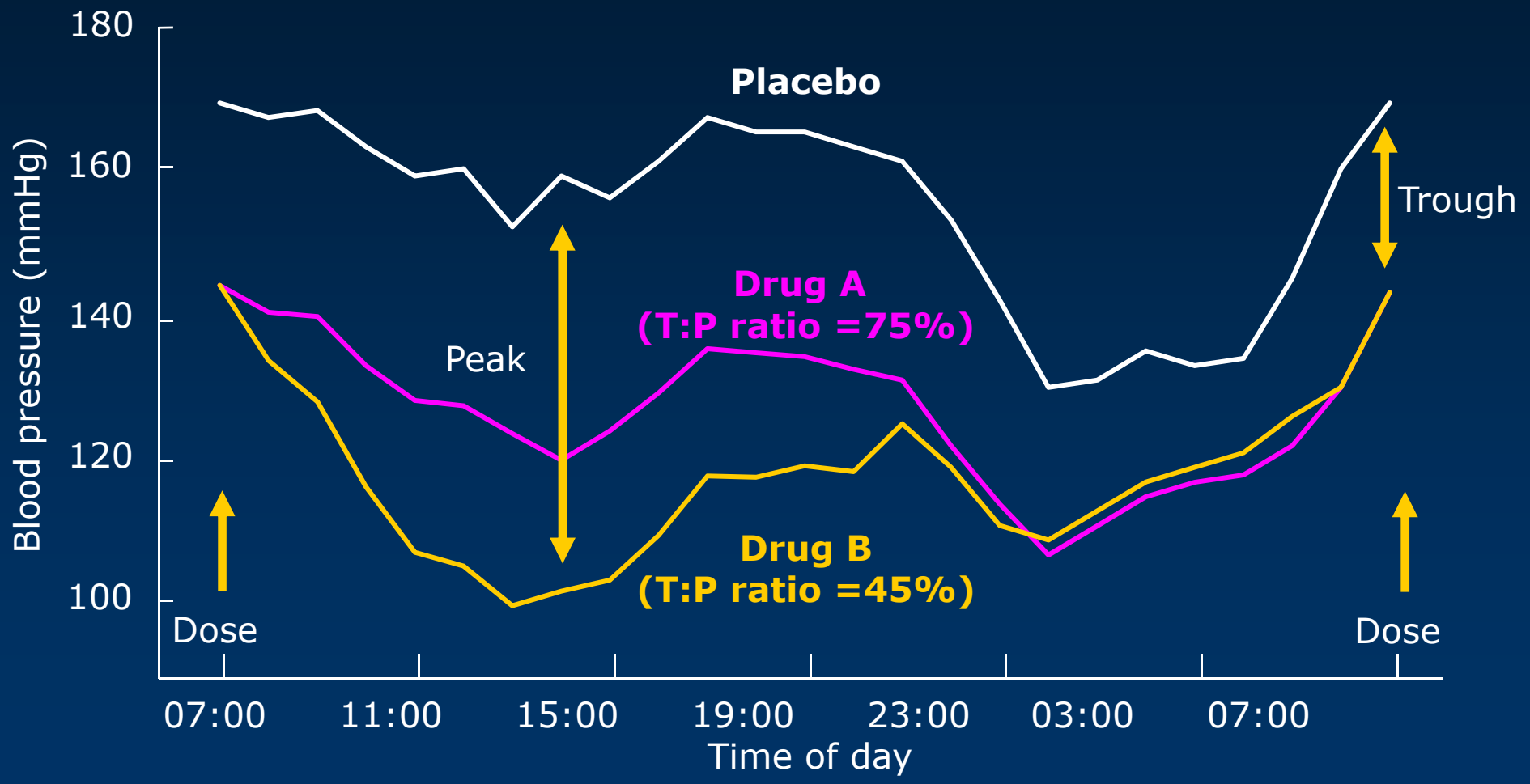
Telmisartan vs Amlodipine using 24-h ABPM



Lacourcière Y et al

Relevance of trough:peak ratios to 24-h BP control



Ellioit, Meredith. *J Hypertension* 1995;13:279–283

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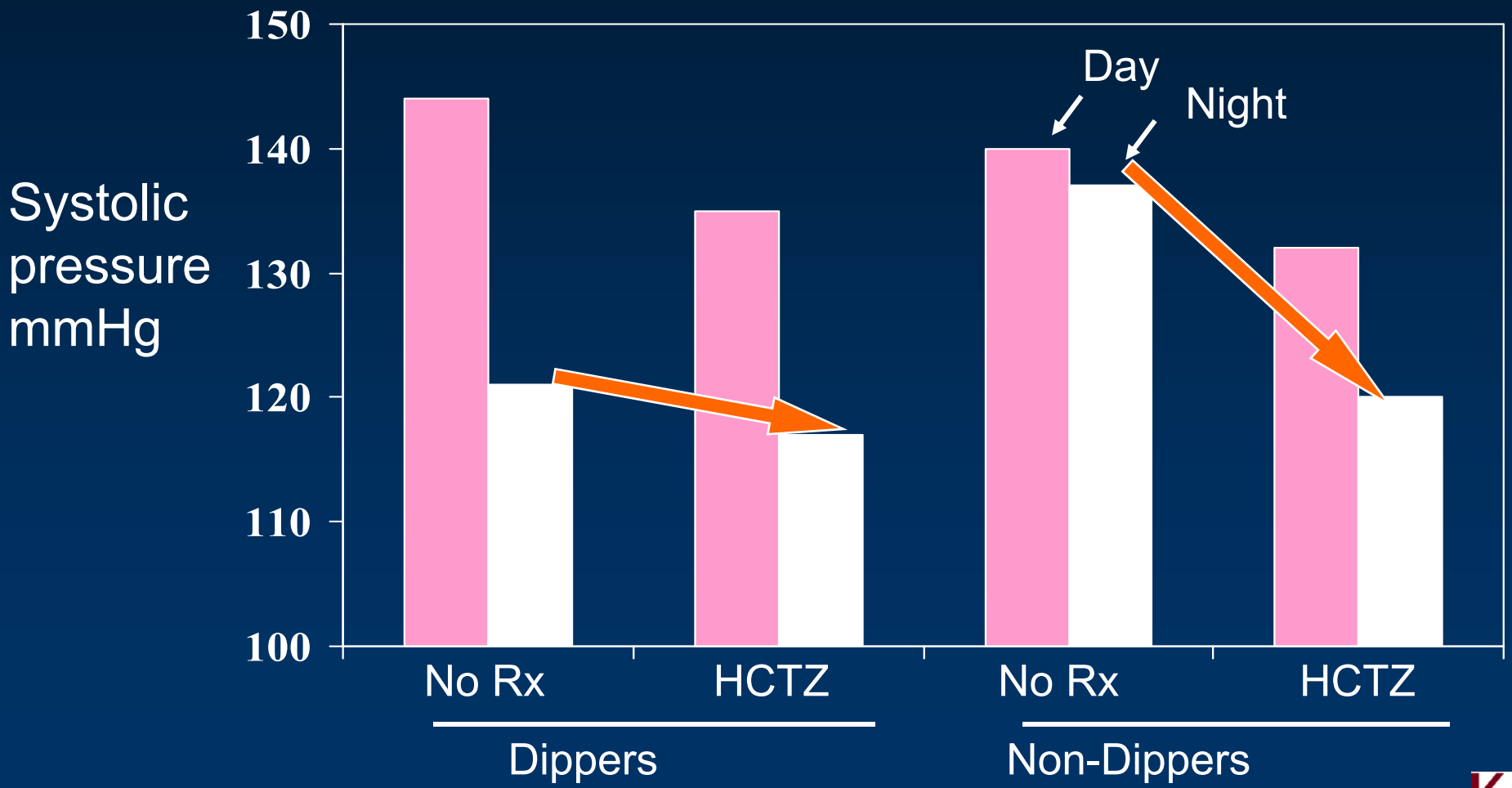
Diuretics Convert Non-Dippers to Dippers



Uzu & Kimura Circ 1999; 100:1635

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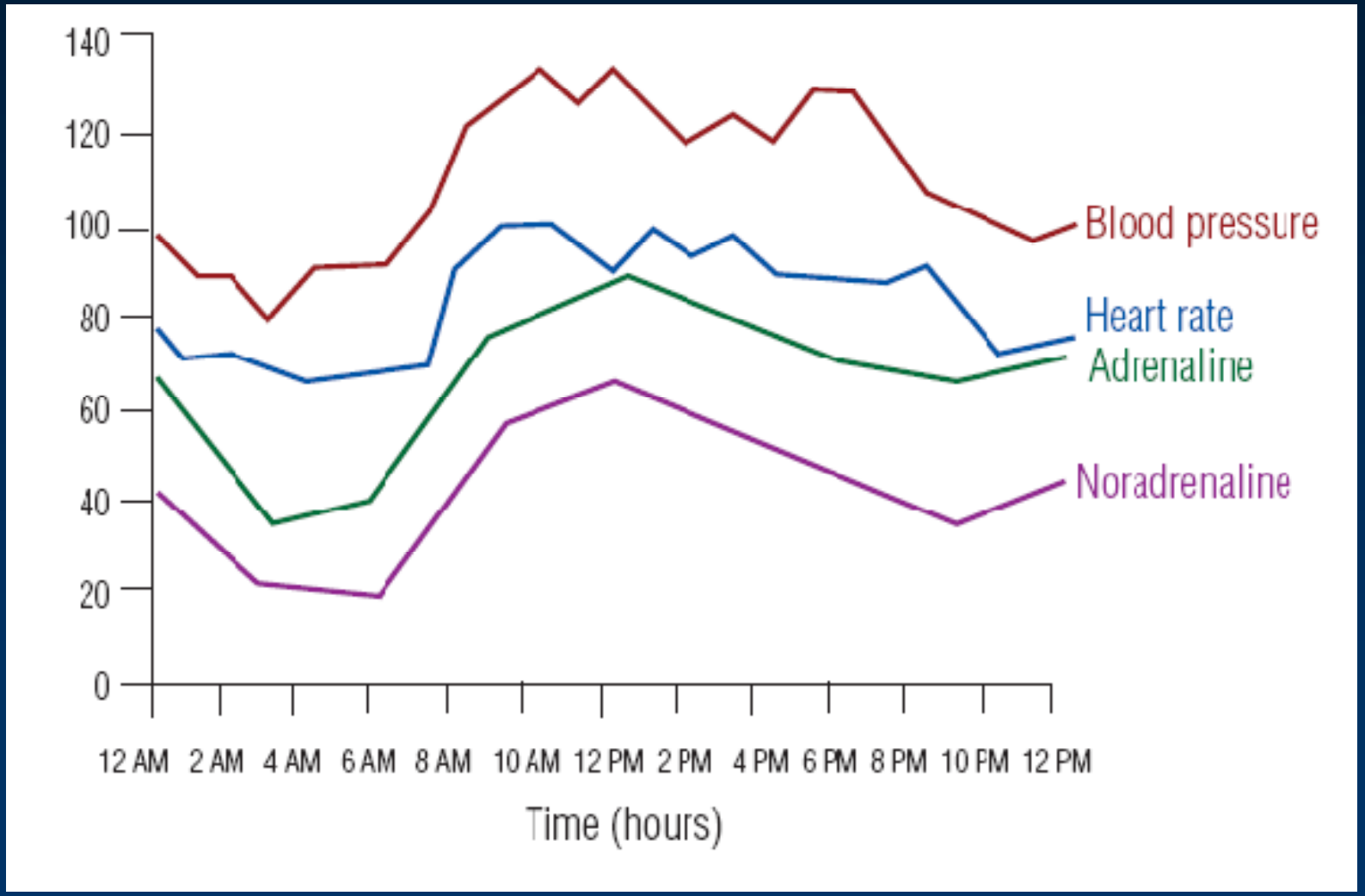
Circadian Change



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Adverse Events of CYT006-AngQb

	Placebo (n=24)	100 µg (n=24)	300 µg (n=24)	p value
Injection-site erythema	20 (83·3%)	24 (100%)	22 (91·7%)	0·15
Injection-site induration	16 (66·7%)	23 (95·8%)	19 (79·2%)	0·045
Injection-site oedema	8 (33·3%)	18 (75·0%)	21 (87·5%)	0·0003
Injection-site pain	11 (45·8%)	17 (70·8%)	17 (70·8%)	0·16
Headache	8 (33·3)	6 (25·0%)	15 (62·5%)	0·024

	Placebo (n=24)	100µg (n=24)	300µg (n=24)	p
Injection-site induration	16 (66.7%)	23 (95.8%)	19 (79.2%)	0.045
Injection-site edema	8 (33.3%)	18 (75.0%)	21 (87.5%)	0.0003
Headache	8 (33.3%)	6 (25.0%)	15 (62.5%)	0.024

Limb injury	0	0	2 (8·3%)	0·32
Erythema	0	2 (8·3%)	0	0·32

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