

Antihipertansif ilaçlar sabah alınmalı

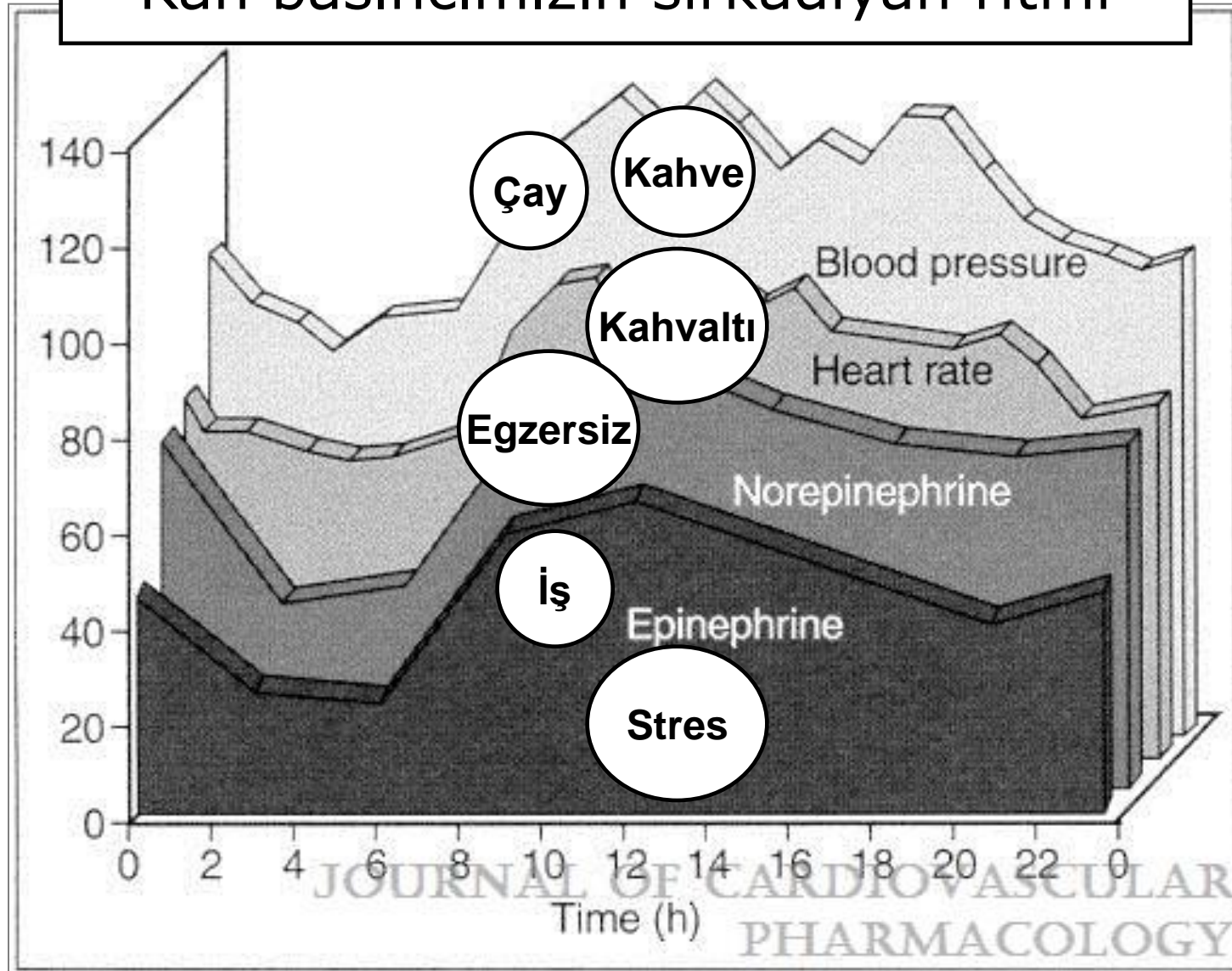
Dr. Ahmet Temizhan

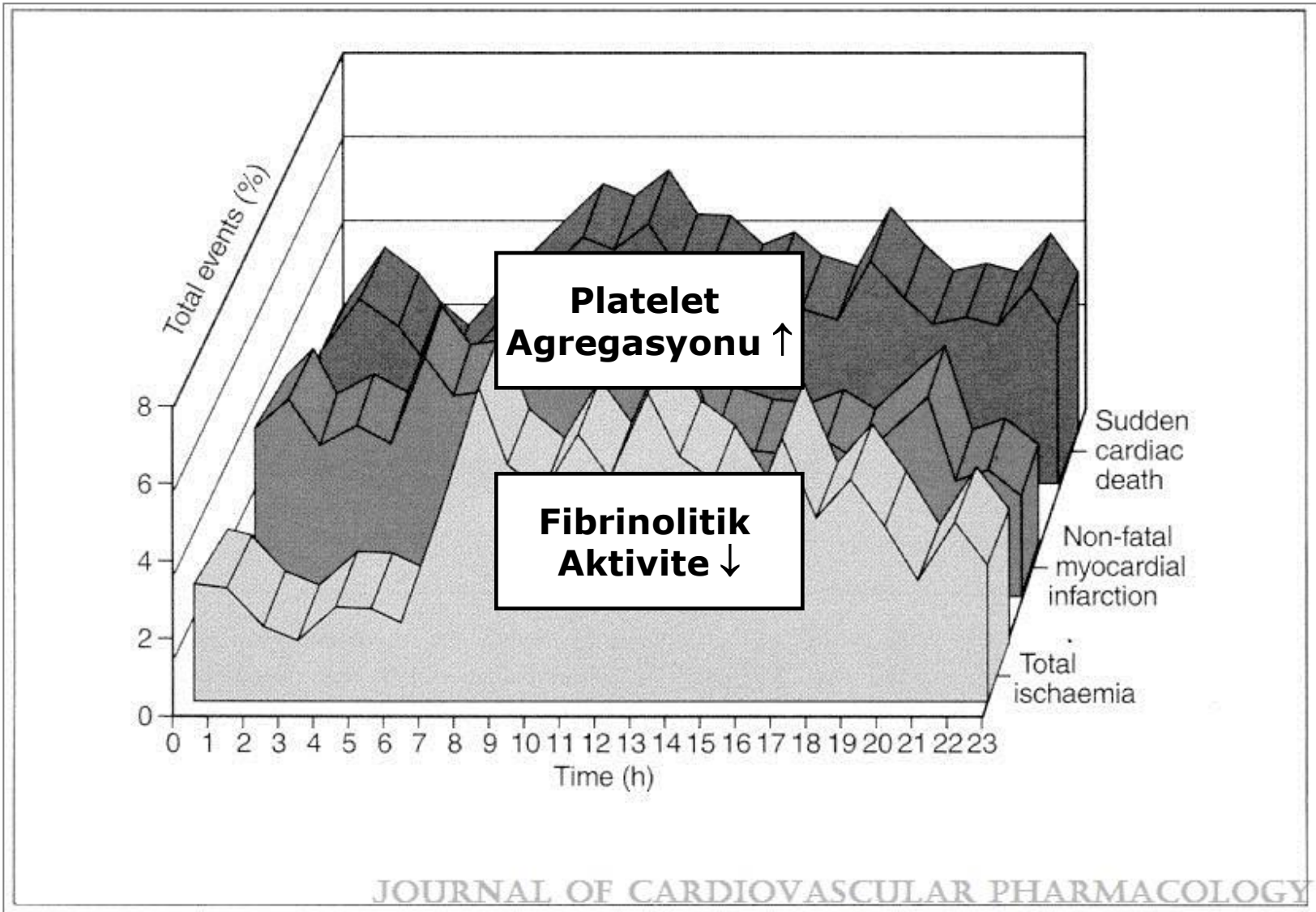
Türkiye Yüksek İhtisas EAH Kardiyoloji Kliniđi
Karabük Üniversitesi Tıp Fakültesi Kardiyoloji AD

Bir tane antihipertansif ilaç
kullanıyorum

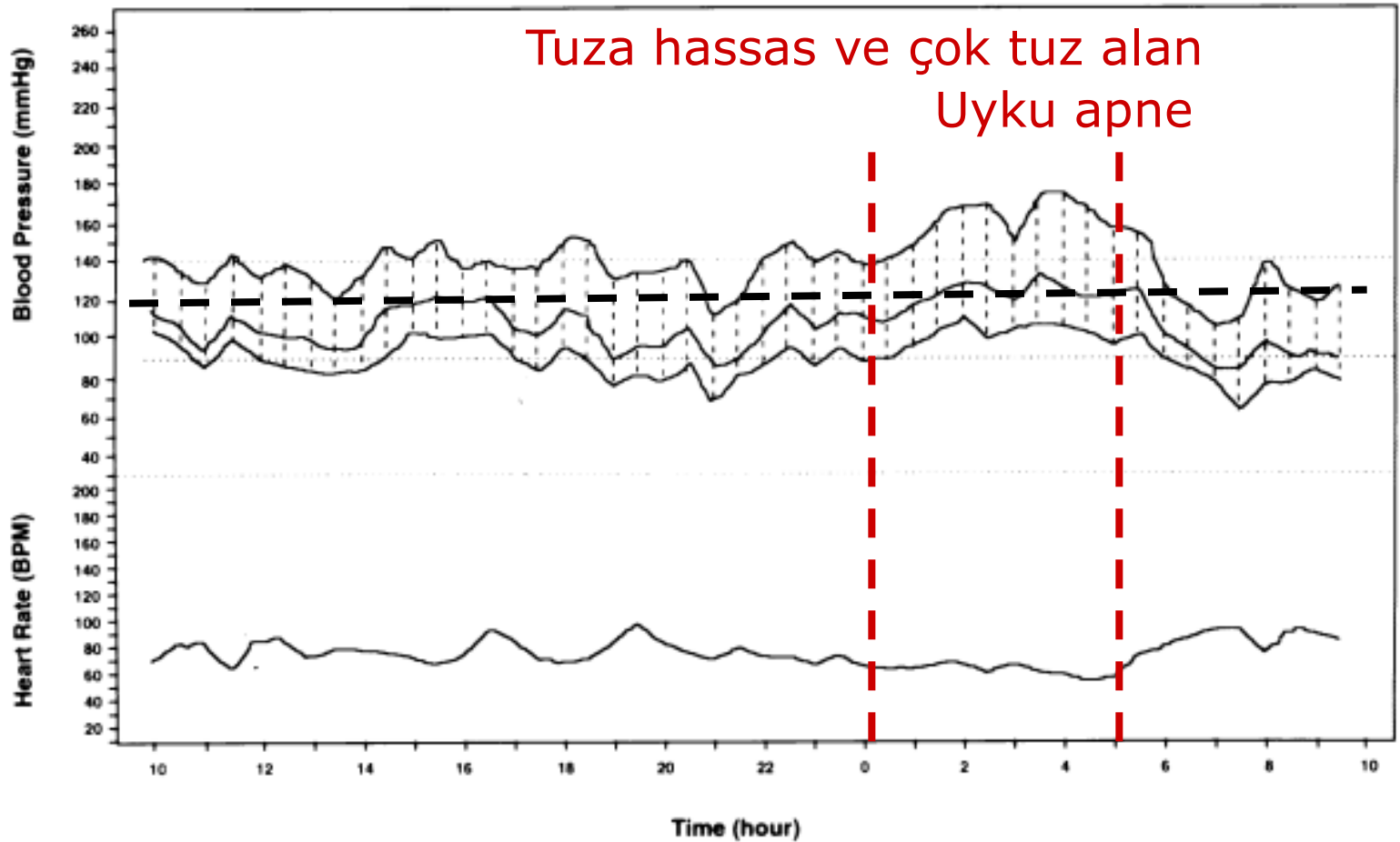
Bunu ne zaman alayım?
(kronoterapi)

Kan basıncımızın sirkadiyan ritmi



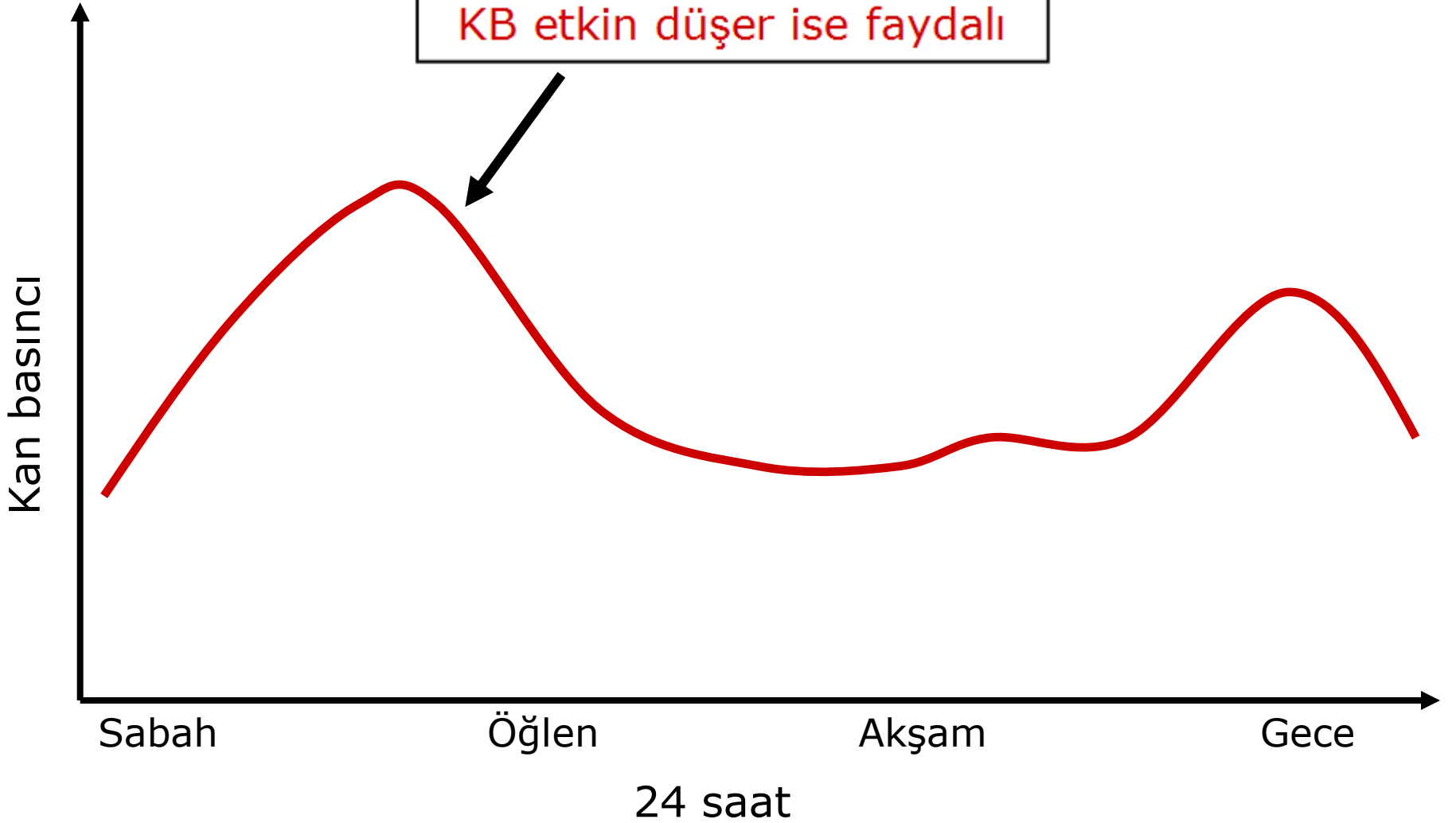


Non-dipper hastalarda artan KV risk



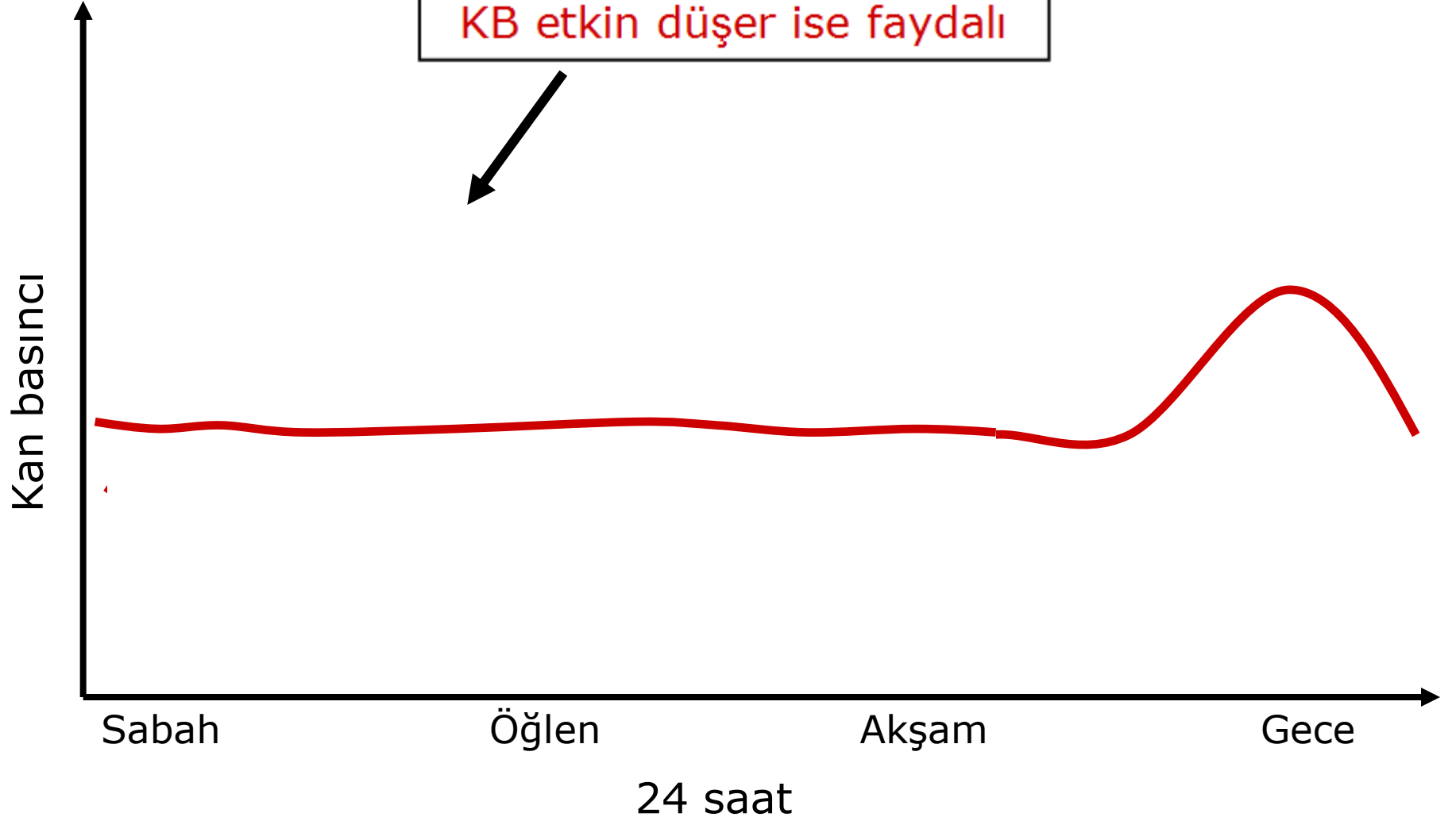
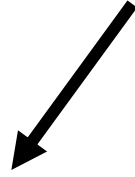
ACEİ ARB KKB
Diüretik BB

KB etkin düşer ise faydalı



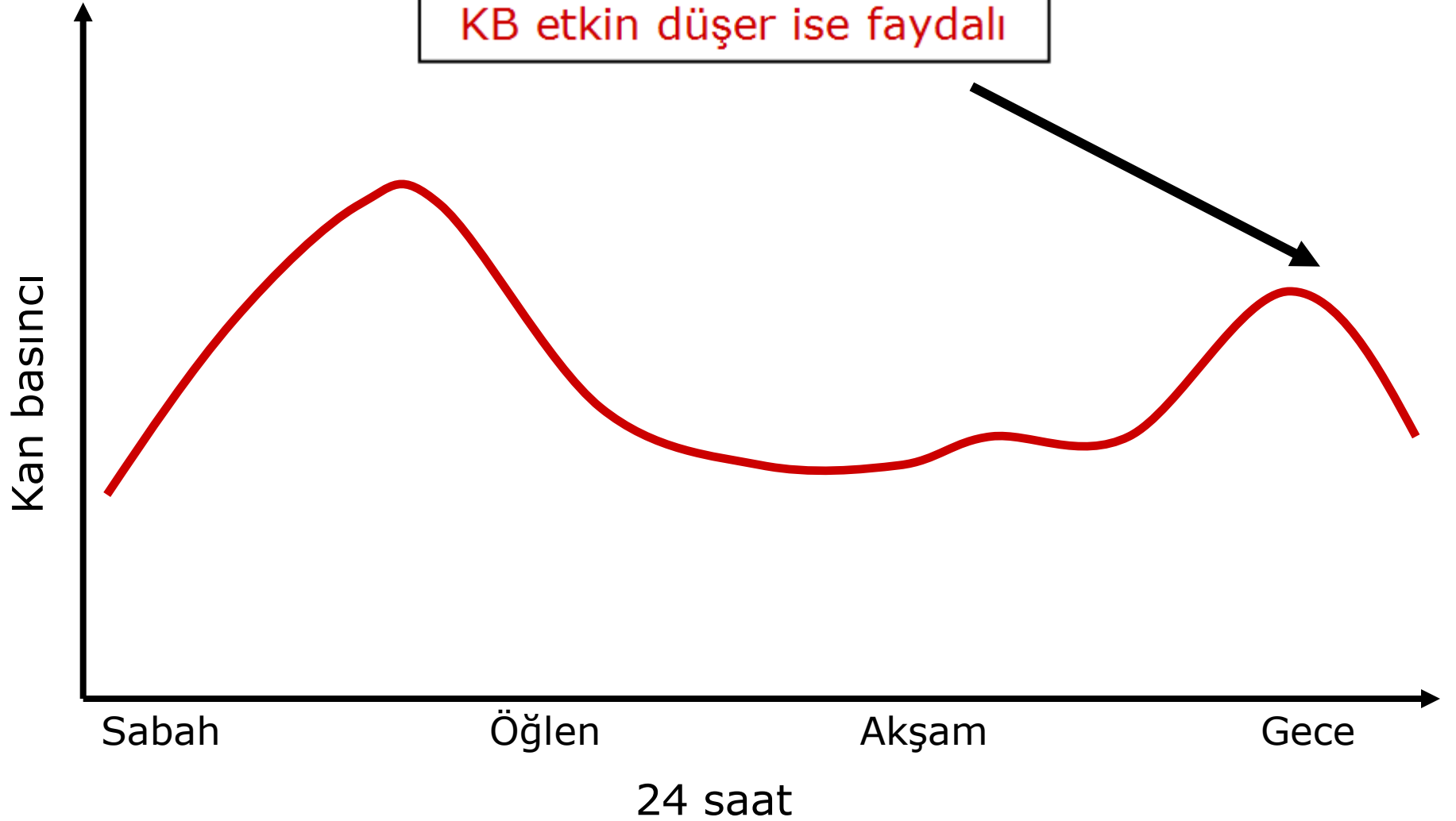
ACEİ ARB KKB
Diüretik BB

KB etkin düşer ise faydalı



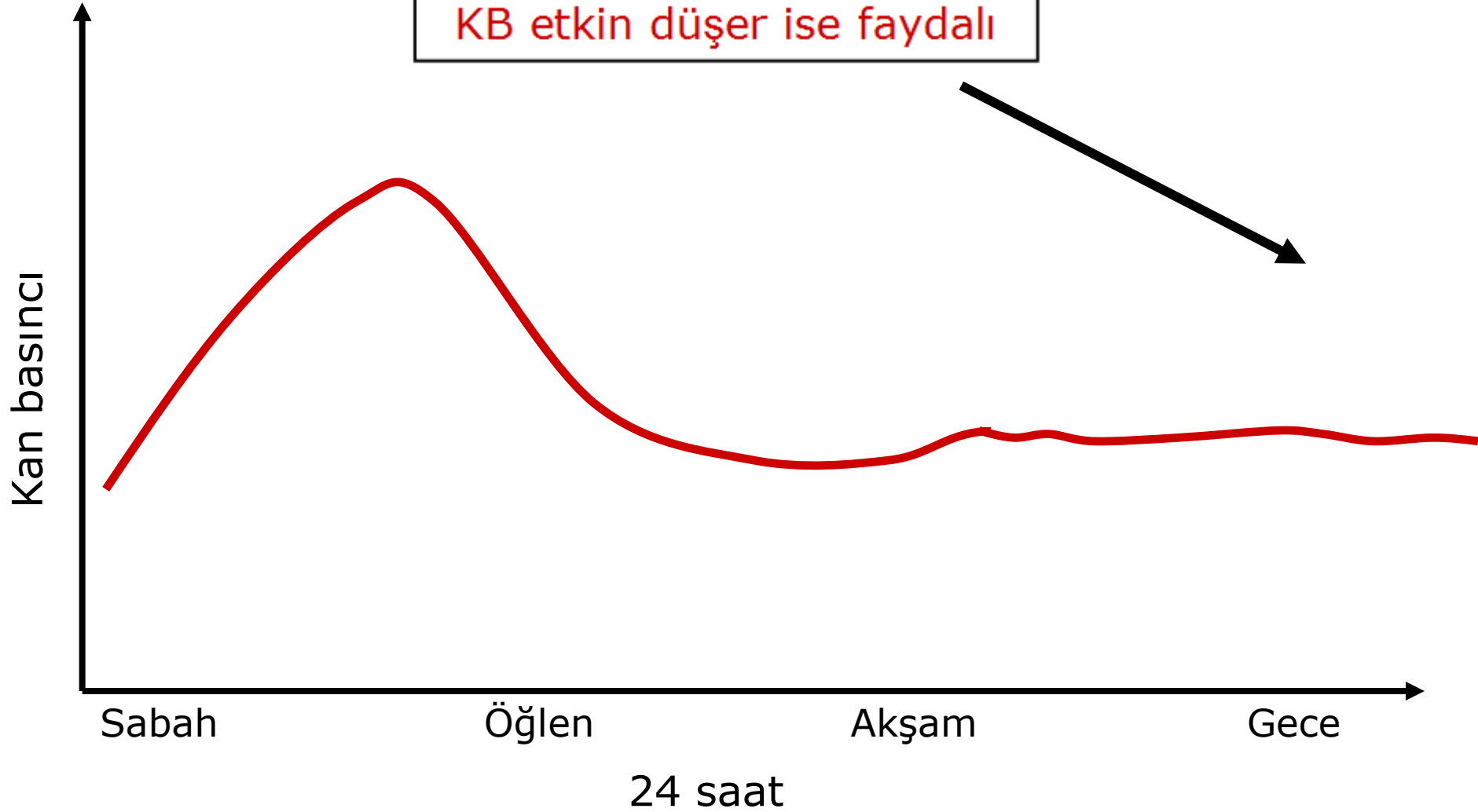
ACEİ ARB KKB
Diüretik BB

KB etkin düşer ise faydalı



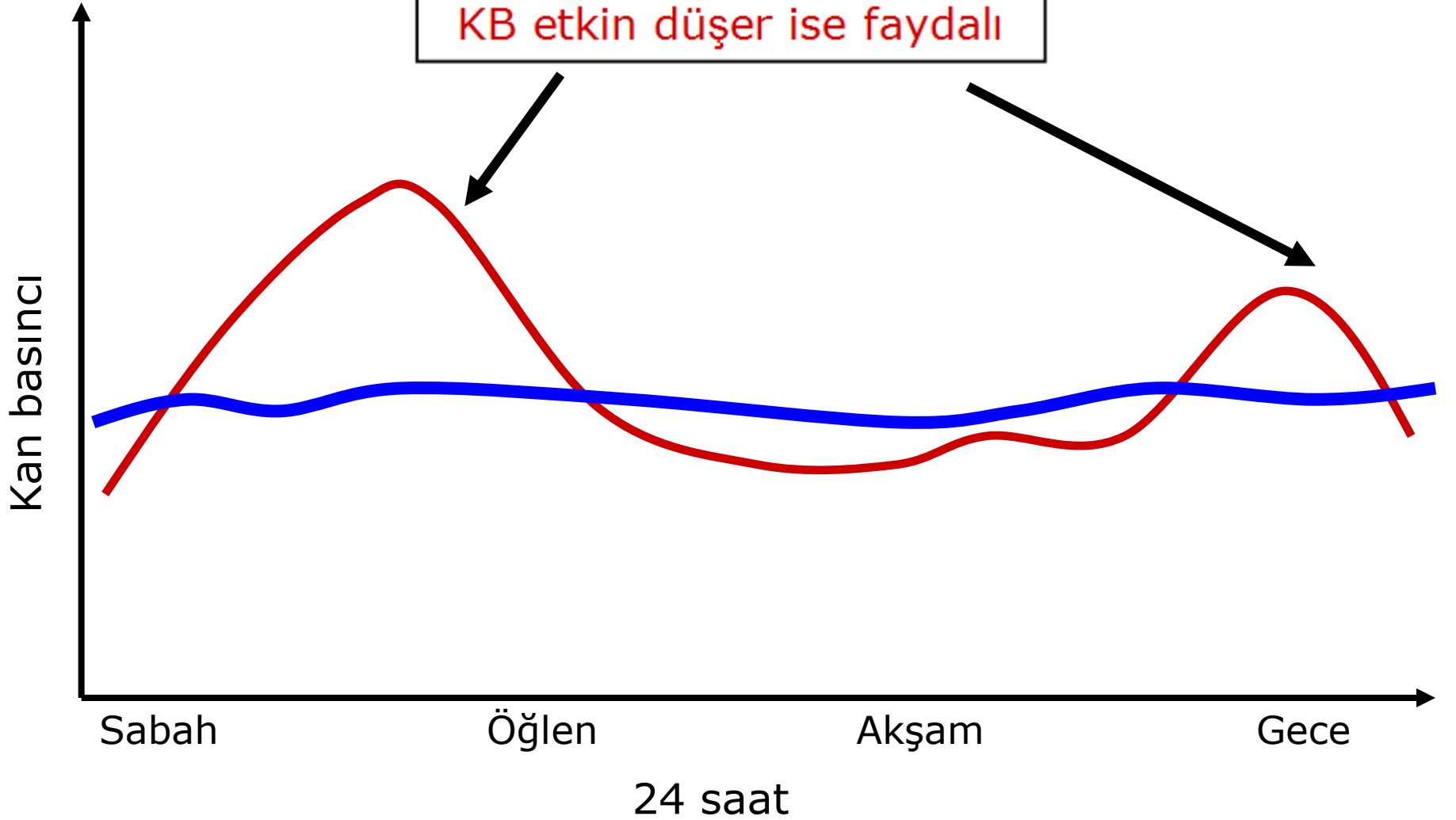
ACEİ ARB KKB
Diüretik BB

KB etkin düşer ise faydalı



ACEİ ARB KKB
Diüretik BB

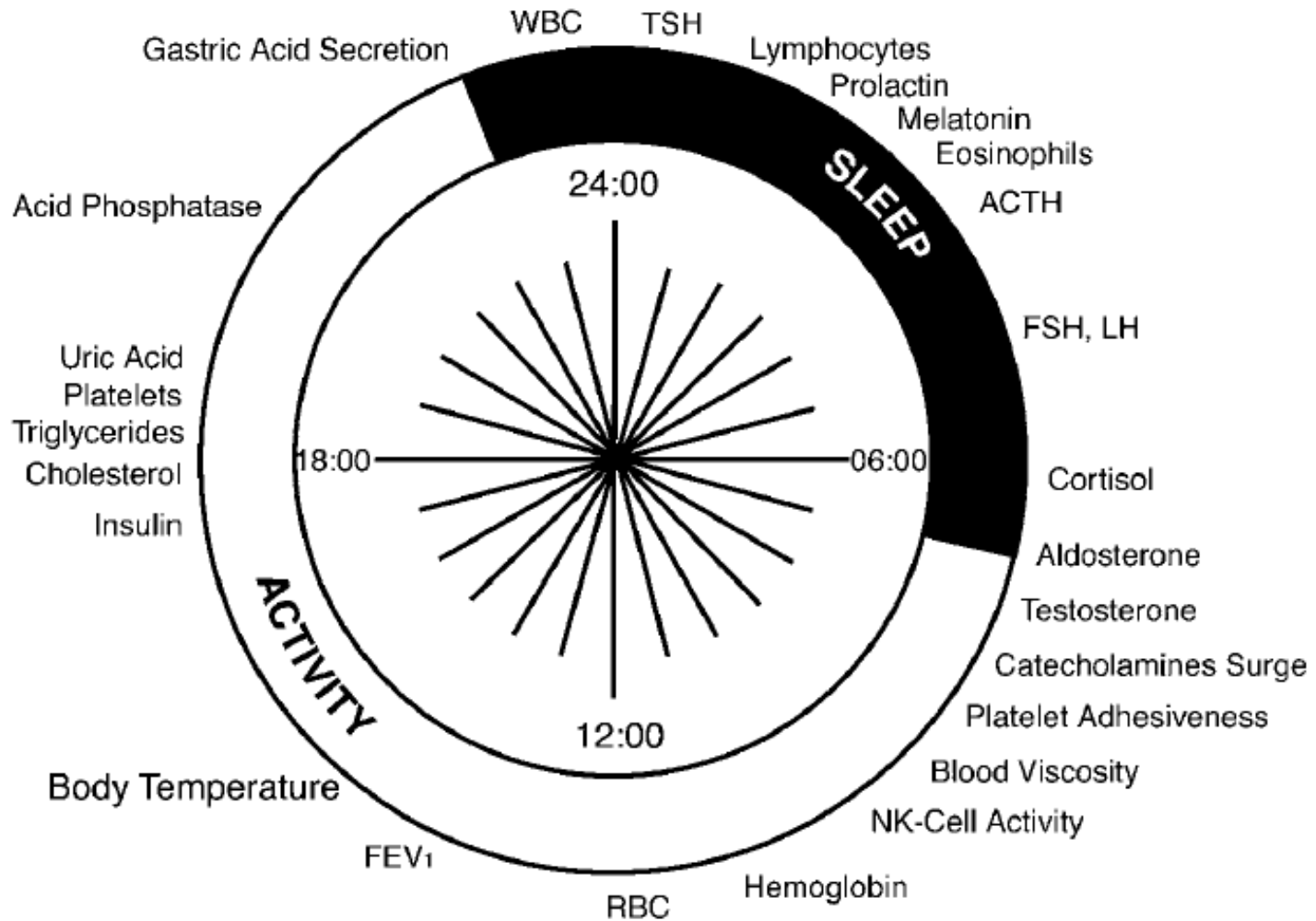
KB etkin düşer ise faydalı

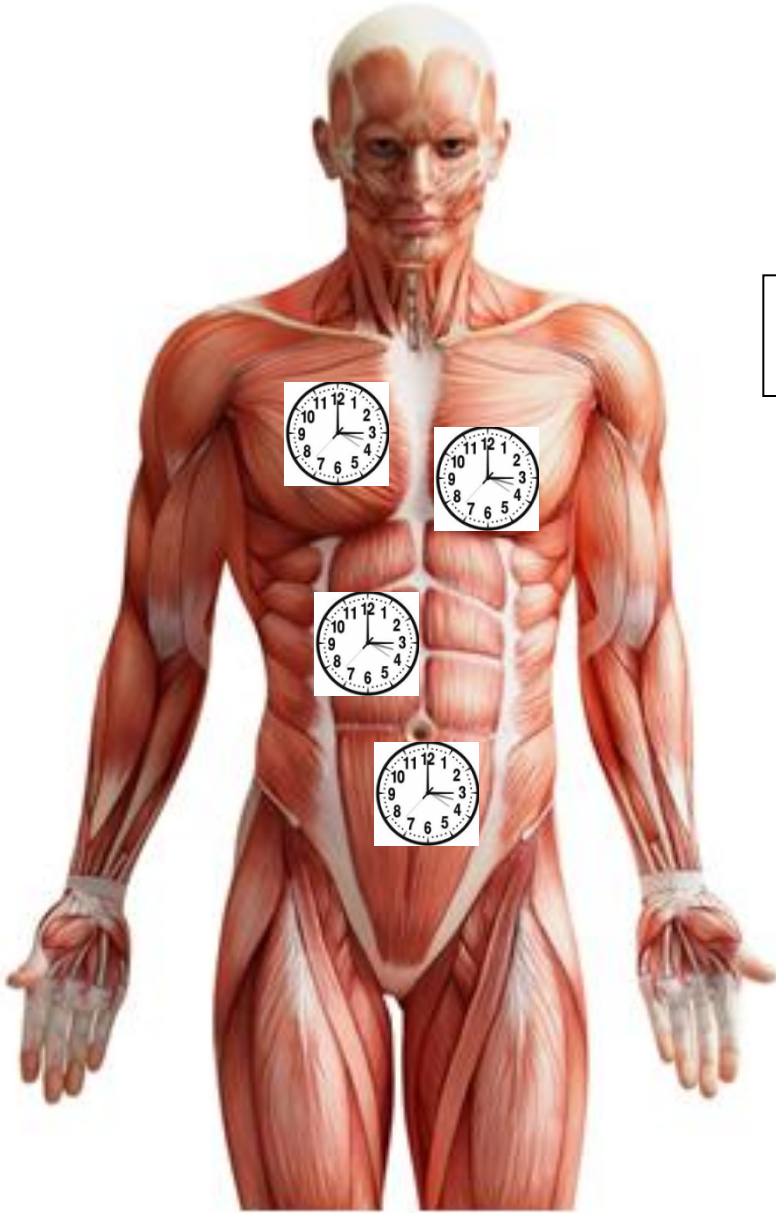


Klinik pratikteki uygulamalar; Kronoterapi

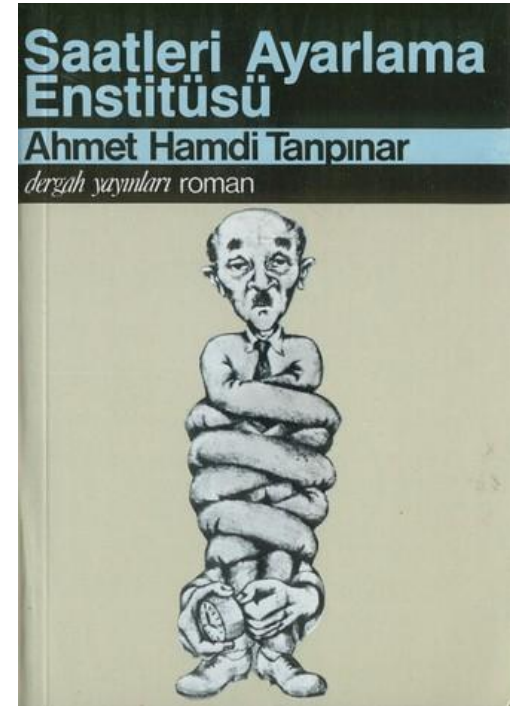
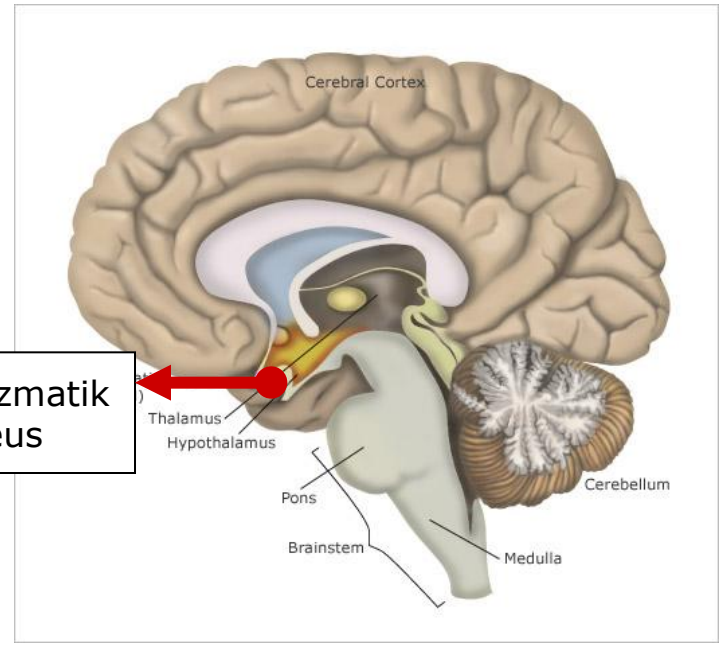
- Metilprednizolonun sabah verilmesi (1960)
- Nokturnal astma tedavisinde gece yatarken teofilin uygulaması
- Statinlerin gece yatarken verilmesi
- H₂ reseptör blokerlerinin gece yatarken, proton pompa inhibitörlerinin sabah verilmesi
- Androjen replasman tedavisinin sabah uygulanması

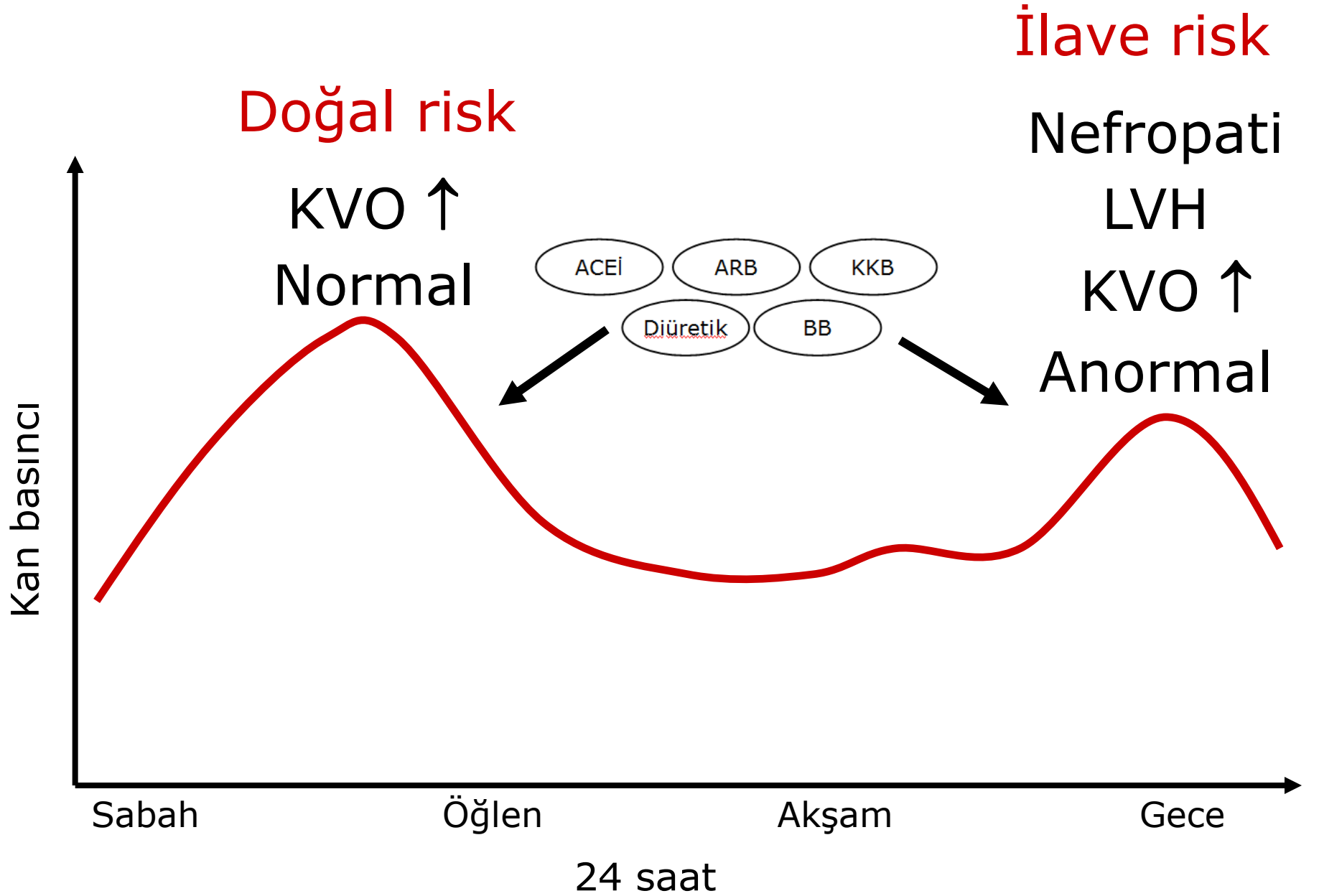
HT tedavisi için buna gerek var mı?

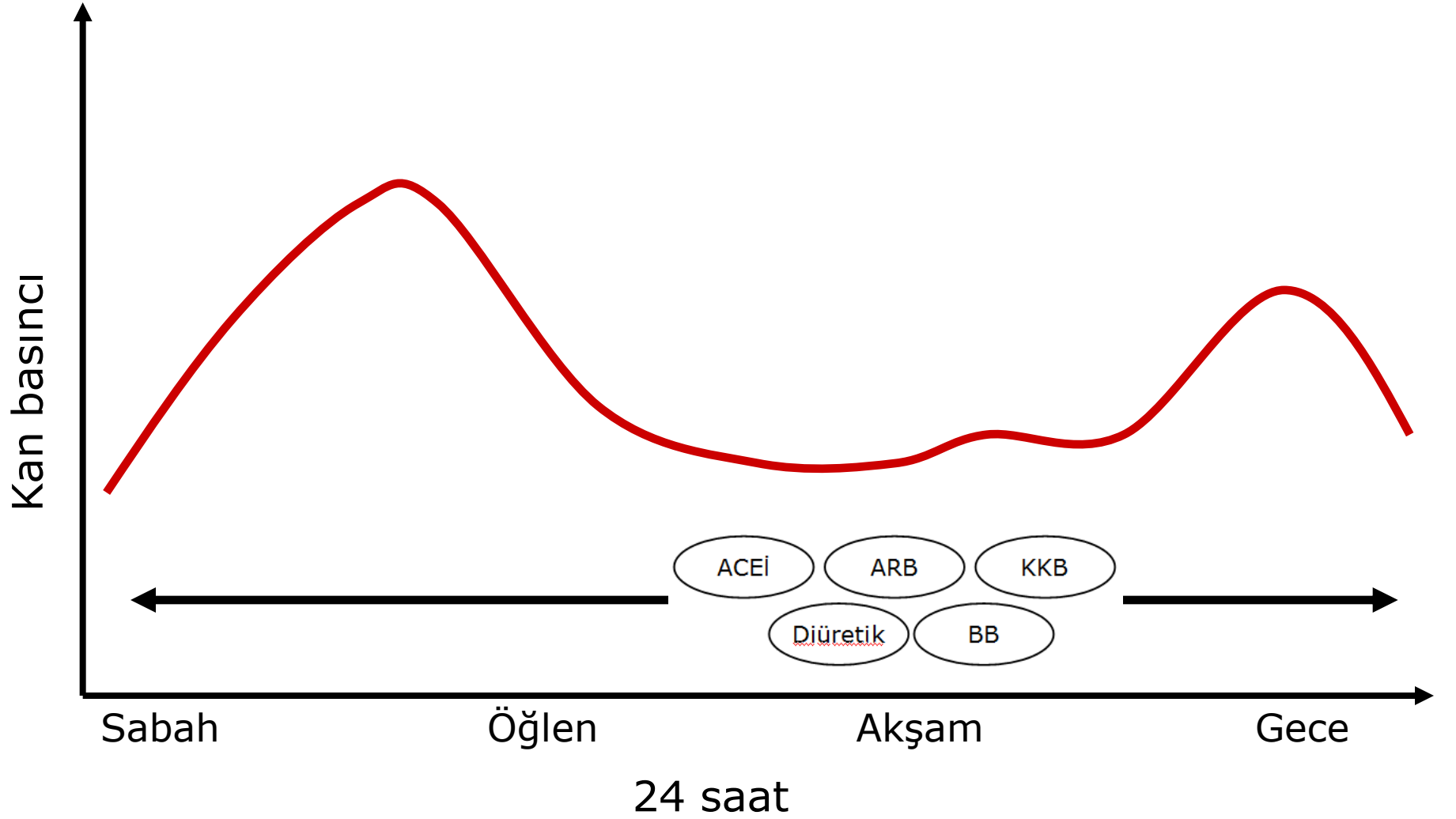


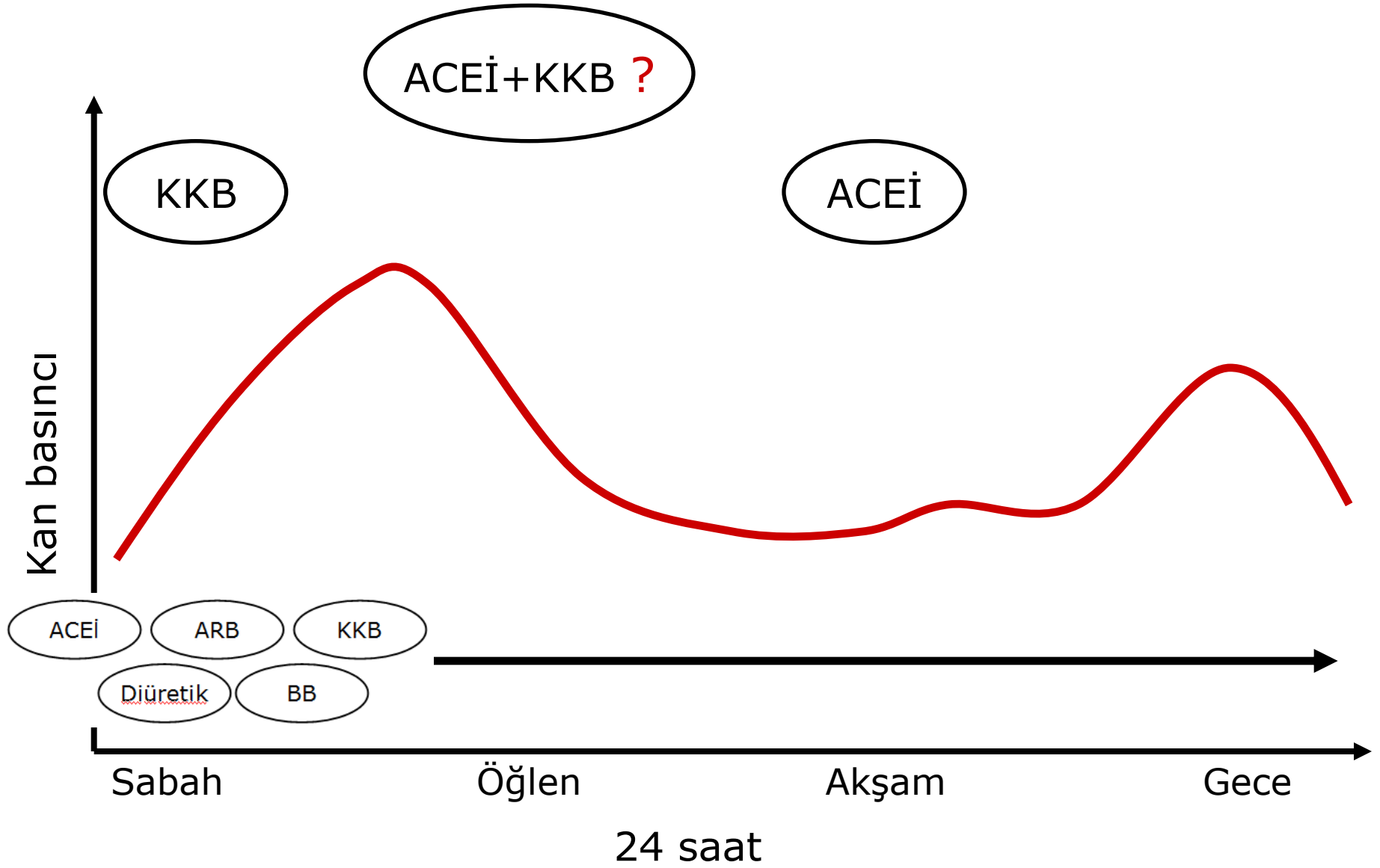


Suprakiazmatik
nükleus









The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

The JNC 7 Report

Table 4. Oral Antihypertensive Drugs*

Class	Drug (Trade Name)	Usual Dose, Range, mg/d	Daily Frequency
Thiazide diuretics	Chlorothiazide (Diuril)	125-500	1
	Chlorthalidone (generic)	12.5-25	1
	Hydrochlorothiazide (Microzide, HydroDIURIL)†	12.5-50	1
β-Blockers	Atenolol (Tenormin)†	25-100	1
	Betaxolol (Kerlone)†	5-20	1
	Bisoprolol (Zebeta)†	2.5-10	1
	Metoprolol (Lopressor)†	50-100	1-2

RKÇ neredeyse tümünde sabah verilmiştir

	Fosinopril (Monopril)	10-40	1
	Lisinopril (Prinivil, Zestril)†	10-40	1
	Moexipril (Univasc)	7.5-30	1
	Perindopril (Aceon)	4-8	1-2
	Quinapril (Accupril)	10-40	1
Calcium channel blockers—dihydropyridines	Amlodipine (Norvasc)	2.5-10	1
	Felodipine (Plendil)	2.5-20	1
	Isradipine (Dynacirc CR)	2.5-10	2
	Nicardipine sustained release (Cardene SR)	60-120	2
	Nifedipine long-acting (Adalat CC, Procardia XL)	30-60	1

Antihipertansiflerin sabah veya akşam verilmesi;

Table 1. Effects on the circadian pattern of blood pressure of chronotherapy with calcium-channel blockers

Drug	Dose	Treatment times	Subjects	Effect on the day/night ratio [†]	
				Morning	Evening
Amlodipine	5 mg	08.00 vs. 20.00	12 EH	=	=
Amlodipine	5 mg	Awakening vs. bedtime	49 EH	=	=
Amlodipine	5–10 mg	07.00 vs. 21.00	62 EH	=	=
Amlodipine	5 mg	Awakening vs. bedtime	87 EH-CT	=	=
Cilnidipine	10 mg	Awakening vs. bedtime	13 EH	=	=
Diltiazem retard	100–200 mg	08.00 vs. 19.00	13 EH	=	↓
Isradipine	5 mg	08.00 vs. 20.00	16 RH	=	↑
Isradipine	5 mg	07.00 vs. 19.00	18 EH	=	=
Nifedipine GITS	30 mg	10.00 vs. 22.00	10 EH	=	=
Nifedipine GITS	30–60 mg	Awakening vs. bedtime	80 EH	=	=
Nisoldipine	20 mg	08.00 vs. 22.00	85 EH	=	=
Nitrendipine	20 mg	Morning vs. evening	41 EH	=	=
Nitrendipine	10 mg	06.00 vs. 08.30 vs. 18.00	6 EH	=	↑

Dihidropridin KKB verilış zamanından bağımsız olarak gündüz ve gece homojen bir KB düşüşü sağlıyor

Antihipertansiflerin sabah veya akşam verilmesi;

Medication	Dose, mg	Treatment times	No. patients	Effect on sleep-time relative BP decline*	
				Morning R _x	Evening R _x
<i>α-Blockers</i>					
Doxazosin GITS	4	Awakening vs. bedtime	91	↓	=
<i>β-Blockers</i>					
Carvedilol	10	Morning vs. evening	9	=	↑
Nebivolol	5	Awakening vs. bedtime	173	↓	↓
Nebivolol	10	Morning vs. evening	38	=	=
<i>Diuretics</i>					
Torsemide	5	Awakening vs. bedtime	113	=	↓

Karvedilol ve nebivolol akşam verilir ise sabah pikine ve non-dipperlere etkili

Antihipertansiflerin sabah veya akşam verilmesi;

Medication	Dose, mg	Treatment times	No. patients	Effect on sleep-time relative BP decline*	
				Morning R _x	Evening R _x
Benazepril	10	09:00 h vs. 21:00 h	10	=	↑
Captopril + HCTZ [†]	25 + 12.5	08:00 h vs. 20:00 h	13	↓	↑
Enalapril	10	07:00 h vs. 19:00 h	8	↓	↑
Enalapril	5	10:00 h vs. 22:00 h	12	↓	↑
Enalapril	20	Morning vs. evening	10	↓	↑
Imidapril	10	07:00 h vs. 18:00 h	20	=	=
Lisinopril	20	08:00 h vs. 16:00 h vs. 22:00 h	40	=	↑
Perindopril	4	09:00 h vs. 21:00 h	18	=	↑
Quinapril	20	08:00 h vs. 22:00 h	18	↓	↑
Ramipril	2.5	08:00 h vs. 20:00 h	33	↓	↑
Ramipril	5	08:00 h vs. 14:00 h vs. 22:00 h	30	↓	↑
Ramipril	5	Awakening vs. bedtime	115	↓	↑
Spirapril	6	Awakening vs. bedtime	165	↓	↑
Trandolapril	1	Awakening vs. bedtime	30	↓	↑
Zofenopril	30	Awakening vs. bedtime	33	↓	↑

Antihipertansiflerin sabah veya akşam verilmesi;

Medication	Dose, mg	Treatment times	No. patients	Effect on sleep-time relative BP decline*	
				Morning R _x	Evening R _x
Irbesartan	100	Morning vs. evening	10	↓	↑
Olmesartan	20-40	08:00 h vs. 20:00 h	18	=	=
Olmesartan	20	Awakening vs. bedtime	133	=	↑
Olmesartan	40	Awakening vs. bedtime	40 [†]	=	↑
Olmesartan	40	Awakening vs. bedtime	72	=	↑
Telmisartan	40-80	06:00 h vs. 18:00 h	42	=	=
Telmisartan	80	Awakening vs. bedtime	215	=	↑
Valsartan	160	Awakening vs. bedtime	90	=	↑
Valsartan	160	Awakening vs. bedtime	100 [‡]	=	↑
Valsartan	160	Awakening vs. bedtime	200 [§]	=	↑

ACEİ ve ARB akşam saatlerinde verilir ise non-dipperlerde etkili

Benazepril

Sabah 09.00 vs akşam 09.00

Sabah verilenlerde daha iyi KB kontrolü

Int J Clin Pharmacol Ther Toxicol 1993; 31:295–300

Enalapril

Sabah 07.00 vs akşam 07.00

Benzer etkinlik

Clin Pharmacol Ther 1993; 54:177–186

Kinapril

Sabah 08.00 vs akşam 10.00

Akşam verilen kinapril ile daha iyi 24 sa KB kontrolü sağlandı. ACE aktivasyonu daha fazla azaldı

Clin Pharmacol Ther 1992; 52:378–383

Ramipril

Sabah verilirse gündüz ort KB düşüşü daha fazla, akşam verilirse gece ort KB düşüşü daha fazla (HOPE çalışmasında da böyle).

Sabah 04.00-08.00 arasındaki KB düşüşü her iki uygulamada da aynı.

Curr Ther Res 1995; 56:1298–1306

Perindopril

Sabah 09.00 vs akşam 09.00

Sabah verilenlerde 24 saat etkinlik daha iyi.

Akşam verilenlerde etkinlik 18 saat sürmüştü. Ancak sabah saatlerindeki KB düşüşü daha iyi.

J Hypertens 1997; 15:205–211

Trandolapril

Sabah ile gece yatarken verilen doz aynı etkinlikte

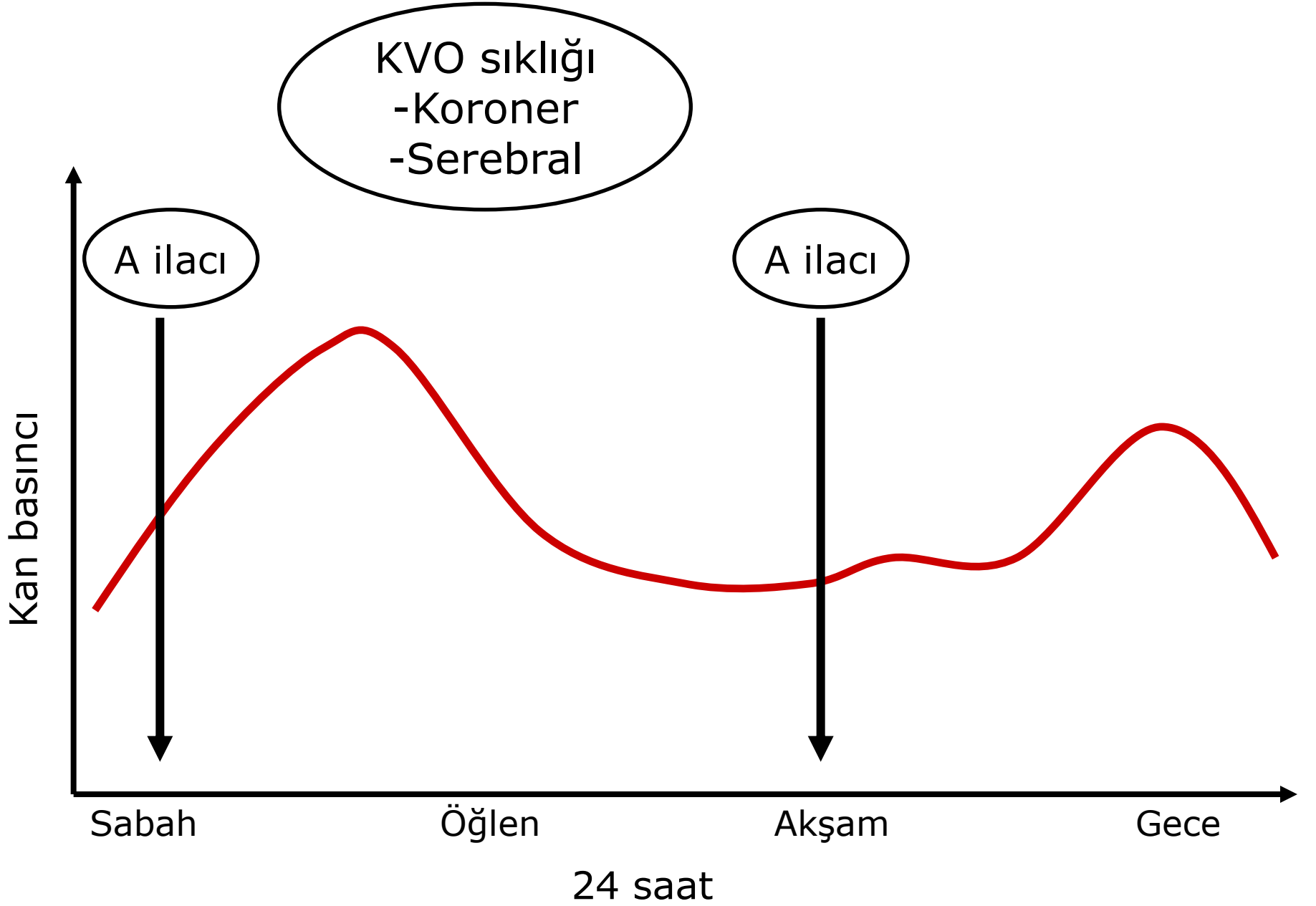
Hypertens Res 2004; 27:15–20

Valsartan

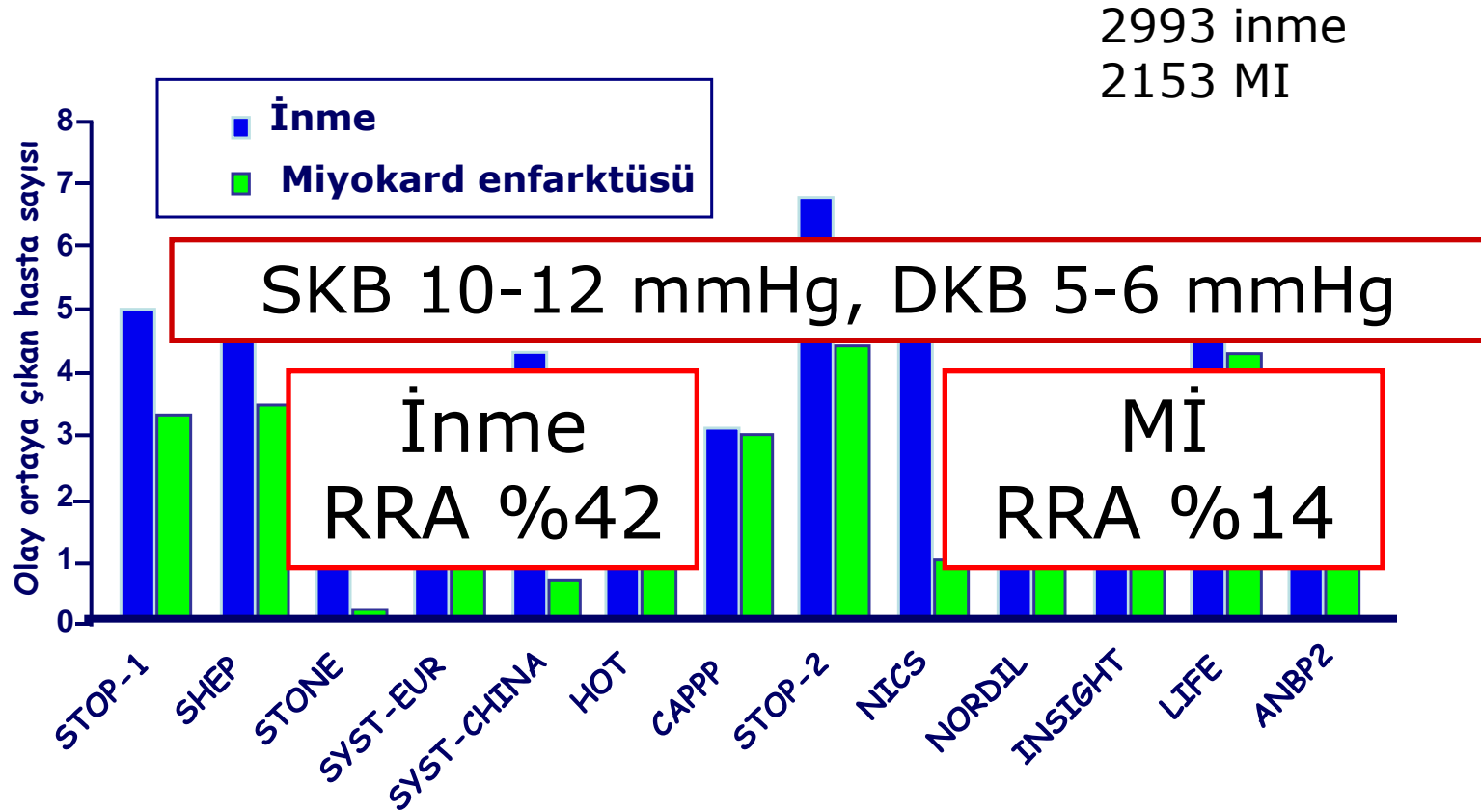
Sabah ve gece dozunda etkinlik farkı yok. Gece dozunda nondipper etkinlik daha iyi

Hypertension 2003; 42:283–290

Neden farklı sonuçlar elde edilmiştir?



Hipertansiyon Çalışmalarında İnme ve MI



1990'dan sonra yayınlanan büyük ve prospektif hipertansiyon çalışmalarında bildirilen fatal ve fatal olmayan inme ve fatal olmayan MI yüzdeleri.

Differences in circadian variation of cerebral infarction, intracerebral haemorrhage and subarachnoid haemorrhage by situation at onset

S Omama, Y Yoshida, A Ogawa, T Onoda, A Okayama



J Neurol Neurosurg Psychiatry 2006;77:1345–1349. doi: 10.1136/jnnp.2006.090373

Background: The precise time of stroke onset during sleep is difficult to specify, but this has a considerable influence on circadian variations of stroke onset.

Aim: To investigate circadian variations in situations at stroke onset—that is, in the waking state or during sleep—and their differences among subtypes.

Methods: 12 957 cases of first-ever stroke onset diagnosed from the Iwate Stroke Registry between 1991 and 1996 by computed tomography or magnetic resonance imaging were analysed. Circadian variations were compared using onset number in 2-h periods with relative risk for the expected number of the average of 12 2-h intervals in the waking state or during sleep in cerebral infarction (CIF), intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH).

Results: ICH and SAH showed bimodal circadian variations and CIF had a single peak in all situations at onset, whereas all three subtypes showed bimodal circadian variations of stroke onset in the waking state only. These variations were different in that CIF showed a bimodal pattern with a higher peak in the morning and a lower peak in the afternoon, whereas ICH and SAH had the same bimodal pattern with lower and higher peaks in the morning and afternoon, respectively.

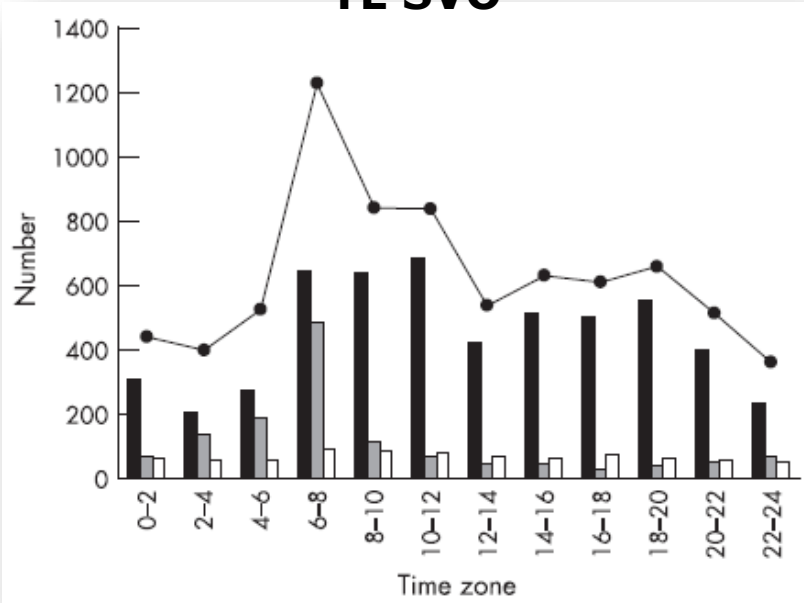
Conclusions: Sleep or status in sleep tends to promote ischaemic stroke and suppress haemorrhagic stroke. Some triggers or factors that promote ischaemic stroke and prevent haemorrhagic stroke in the morning cause different variations in the waking state between ischaemic and haemorrhagic stroke.

See end of article for authors' affiliations

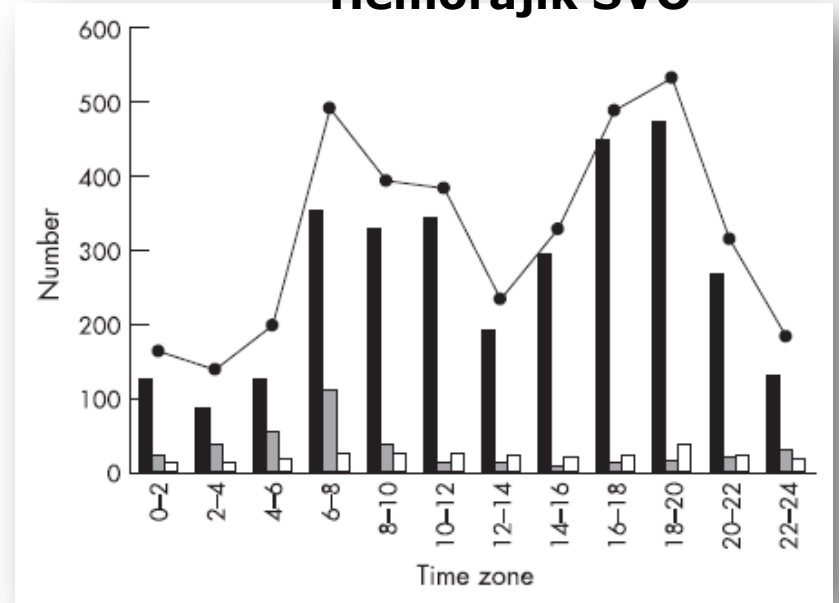
Correspondence to:
S Omama, Department of Neurosurgery, School of Medicine, Iwate Medical University, 19-1 Uchimaru, Morioka, Iwate 020-8505, Japan;
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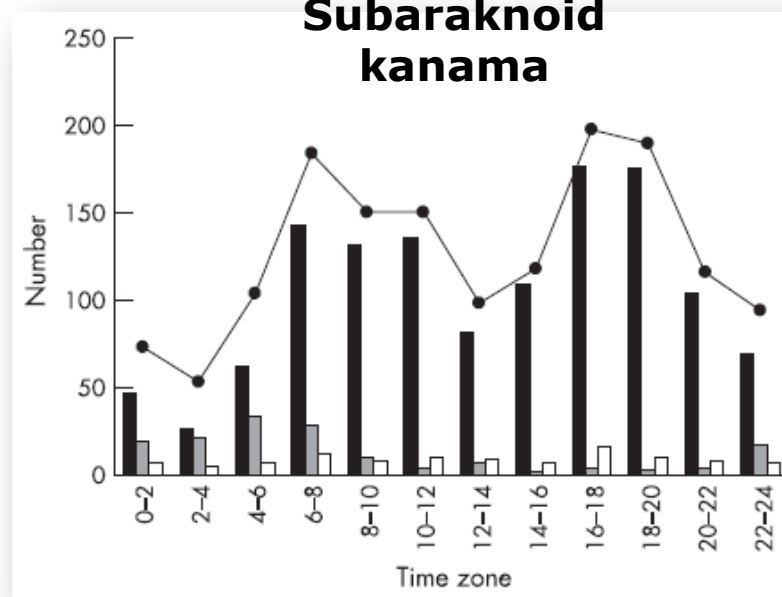
TE SVO



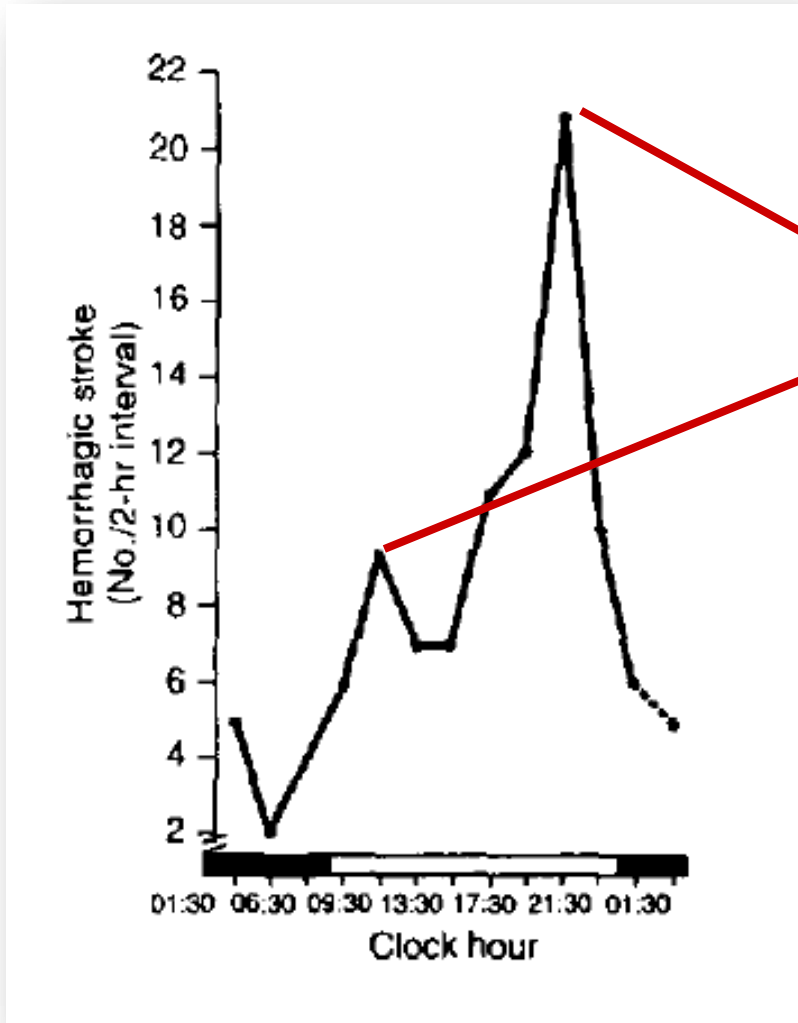
Hemorajik SVO



Subaraknoid kanama



Akşam hemorajik inme çok oluyor...



09.30 vs 19.30
3 kat daha fazla

Does Abnormal Circadian Blood Pressure Pattern Really Matter in Patients With Transient Ischemic Attack or Minor Stroke?

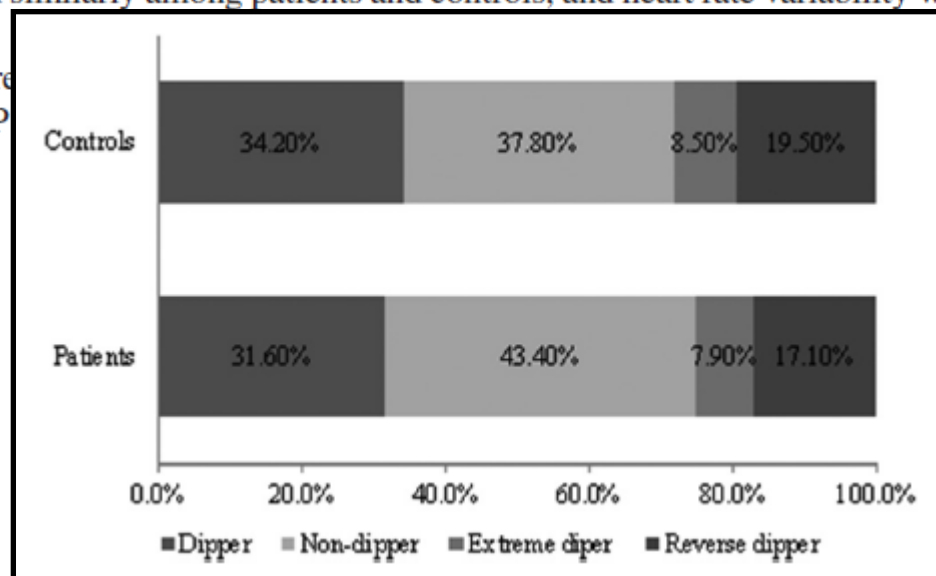
WenWen Zhang, PhD; Dominique A. Cadilhac, PhD; Leonid Churilov, PhD; Geoffrey A. Donnan, MD; Christopher O'Callaghan, PhD; Helen M. Dewey, PhD

Background and Purpose—Patients with stroke are more likely to have impaired autonomic nervous function and abnormal circadian blood pressure (BP) patterns. It remains unclear whether circadian BP patterns in patients with transient ischemic attack or minor stroke (National Institutes of Health Stroke Scale ≤ 3) differ from those in the normal population.

Methods—Participants were assessed using a 24-hour ambulatory BP monitor and a short-term measurement of heart rate variability.

Results—There were 76 patients (mean age, 67.2 years; 57.9% men; and 61.8% transient ischemic attack) and 82 controls (65.6 years; 54.9% men). A history of hypertension was more prevalent in patients (72.4%; controls 48.8%). Circadian BP patterns were distributed similarly among patients and controls, and heart rate variability was also consistent between patients and controls.

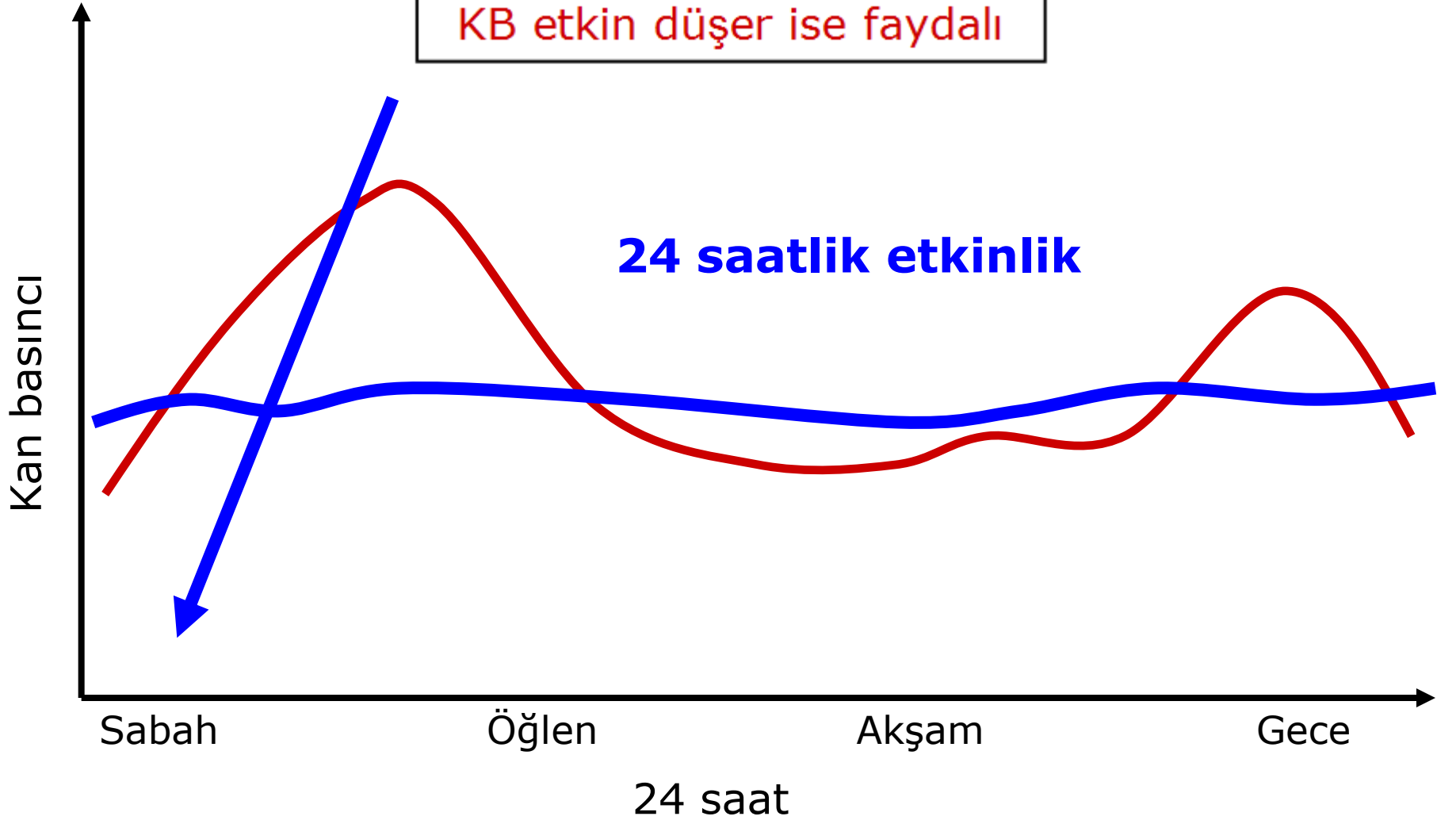
Conclusions—In contrast to previous studies, patients with transient ischemic attack or minor stroke had similar BP patterns compared with controls. (*Stroke*. 2014;45:865-867.)



transient ischemic attack or minor stroke had similar BP patterns compared with controls. (*Stroke*.

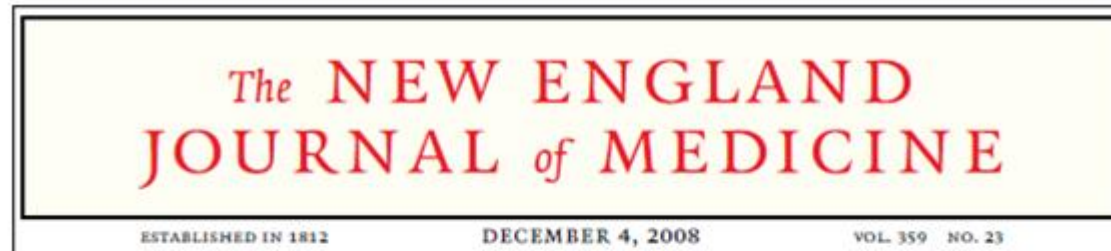


KB etkin düşer ise faydalı



Sabah verilmesinin kanıtı var mı?

Hemen tüm randomize kontrollü HT çalışmaları



Benazepril plus Amlodipine or Hydrochlorothiazide
for Hypertension in High-Risk Patients

RAS-blok+Amlodipin vs RAS-blok+Diüretik

ABSTRACT

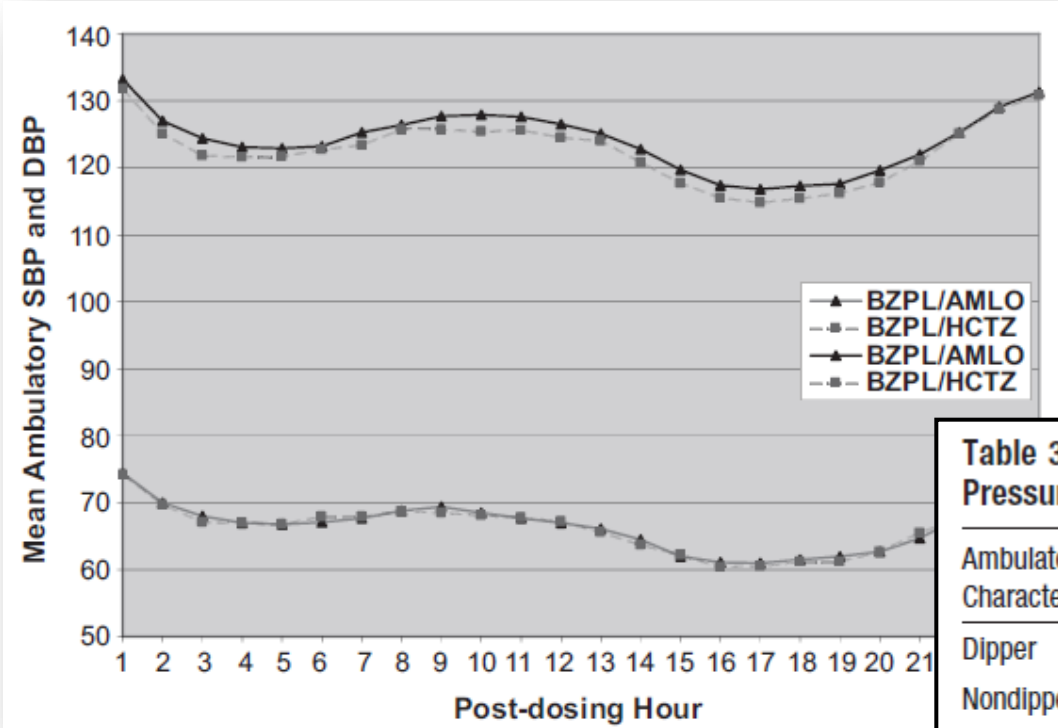
BACKGROUND

The optimal combination drug therapy for hypertension is not established, although current U.S. guidelines recommend inclusion of a diuretic. We hypothesized that treatment with the combination of an angiotensin-converting-enzyme (ACE) inhibitor and a dihydropyridine calcium-channel blocker would be more effective in reducing the rate of cardiovascular events than treatment with an ACE inhibitor plus a thiazide diuretic.

From the University of Michigan Health System, Ann Arbor (K.J., B.P.); the State University of New York Downstate Medical College, Brooklyn (M.A.W.); the University of Chicago Pritzker School of Medicine, Chicago (G.L.B.); Sahlgrenska University Hospital, Gothenburg, Sweden (B.D.); Novartis Pharmaceuticals, East

Efficacy and Duration of Benazepril Plus Amlodipine or Hydrochlorothiazide on 24-Hour Ambulatory Systolic Blood Pressure Control

(Hypertension. 2011;57:174-179.)



*:Gün içindeki KB seyri aynı

HCTZ yarı ömrü 12-15 saat

Amlodipin yarı ömrü 28-30 saat

Table 3. Twenty-Four-Hour Blood Pressure Profiles and Blood Pressure Control Rates After 2 Years of Treatment

Ambulatory Characteristics	B+A (n=288)	B+H (n=285)	All (n=573)	P Value
Dipper	29.2	31.6	30.4	0.530
Nondipper	70.8	68.4	69.6	...
Control at 2 years (ABMP <135/85 mm Hg)	81.3	84.9	83.1	0.243
Any hourly mean SBP reading >160 mm Hg	10.4	11.9	11.2	0.565
Nighttime hypertension >130 mm Hg	18.8	18.6	18.7	0.962
Morning surge*	2.8	3.5	3.1	0.616

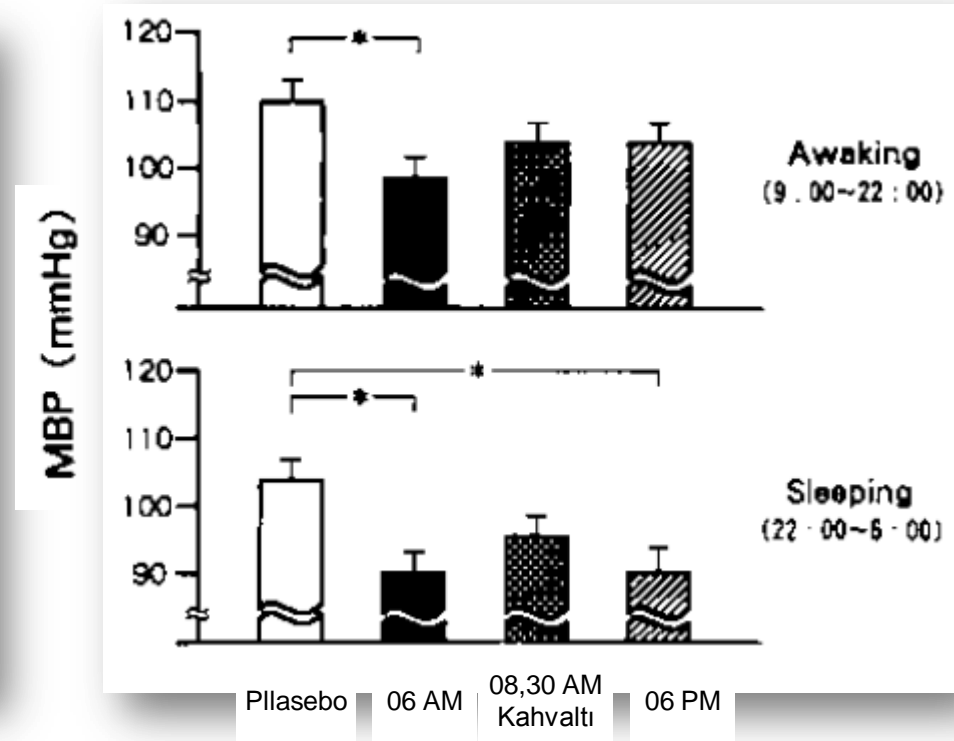
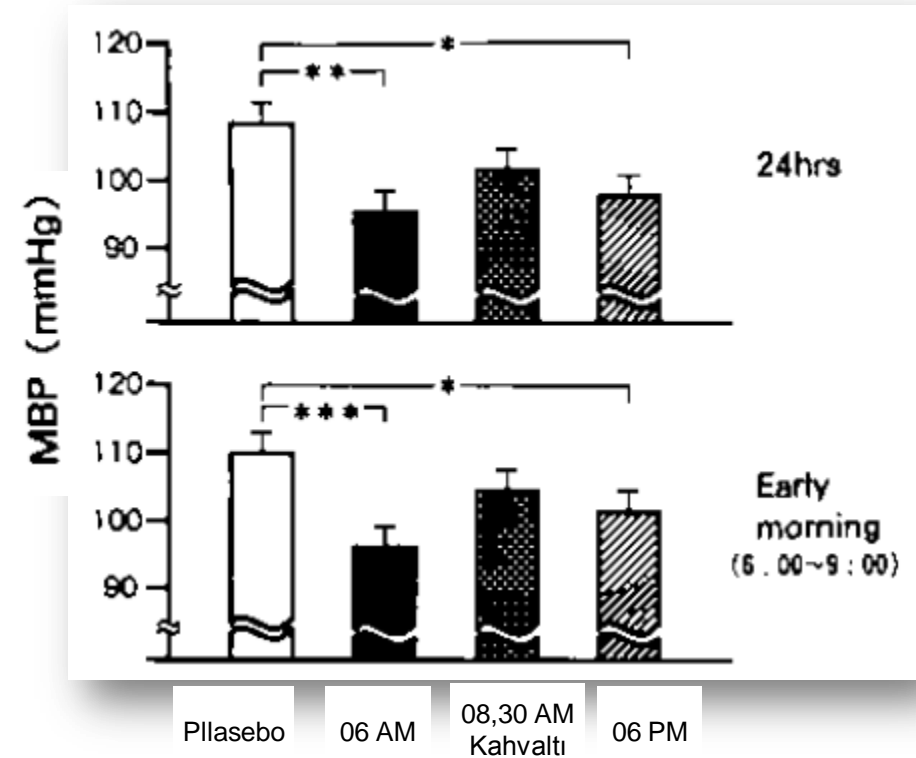
Timing for Administration of an Antihypertensive Drug in the Treatment of Essential Hypertension

Abstract To find the best timing for administration of long-acting antihypertensive drugs, we gave nitrendipine, a calcium antagonist of the dihydropyridine group, once a day to six hospitalized and drug-free patients with essential hypertension, changing the time of administration and studying the effects on the circadian rhythm of blood pressure. After control values of 24-hour blood pressure variations were taken with patients on placebo, a 10-mg tablet of nitrendipine was given for 3 days on three occasions — at 6 AM on awakening, at 8:30 AM after breakfast, and at 6 PM after supper; 24-hour blood pressure values for each period were recorded on the third day. The 24-hour blood pressure values during the control period showed a biphasic circadian rhythm, with higher values during wakefulness and lower values during sleep. The control period was also characterized by a rapid rise in blood pressure on awakening, the so-called morning surge of blood pressure, and a gradual decline during sleep at night. Although

the morning surge was not completely suppressed by nitrendipine given after breakfast, it was diminished by the drug given on awakening or after supper; the latter brought a deeper decline in blood pressure during sleep compared with other times. The average of 24-hour blood pressure values obtained by nitrendipine given on awakening was the lowest among the three occasions. Thus, administration of long-acting calcium antagonists with a rapid onset of action on awakening in the early morning seems to be a more rational and beneficial alternative than the conventional administration after breakfast. The earlier administration may prevent dangerous cardiovascular catastrophes, including stroke, myocardial infarction, and sudden death, known to occur often during the morning surge of blood pressure. (*Hypertension*. 1994;23[suppl 1]:I-211-I-214.)

Key Words • antihypertensive agents • nitrendipine • circadian rhythm • hypertension, essential • blood pressure

Antihipertansif ilacı sabah verelim ama sabah saat kaçta verelim?



Antihipertansif ilacı kronotropiye göre uygulamak!

İlacı akşam vermek!

Mantığı olan ancak kanıtı olmayan

Antihipertansif ilaçlar sabah alınmalı

Antihipertansif ilaçlar **sabah erken alınmalı**

