Hipertansiyon Tedavisinde Etkin Doz ARB Kullanımı ve Kan Basıncı Kontrolünün Ötesindeki Faydalar

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Kardiyoloji Anabilim Dalı

Anti-hipertansif ilaç tercihinizde aşağıdakilerden hangisi en etkin faktördür?

a. Ucuz olması
b. Üretici Firması
c. Kan Basıncını düşürmesi
d. Klinik kanıtlarının olması
e. Yan etkisinin az olması

Evre 2 Hipertansiyon Tedavisinde en sık tercih ettiğiniz kombinasyon nedir?

a. ACE inh + diüretik
b. ARB + diüretik
c. ARB + Kalsiyum kanal bloker
d. Beta Bloker + Kalsiyum kanal bloker
e. Beta Bloker + ACE inh

Aşağıdaki ARB lerden hangisinin MI geçirmiş hastalarda ve/veya Konjestif Kalp Yetmezliği Hastalarında İndikasyonu vardır?

a. Losartan 100 mg/g

b. Valsartan 320 mg/g

c. Irbesartan 300 mg/g

d. Olmesartan 40 mg/g

e. Telmisartan 80 mg/g

Hipertansif Hastada Hedeflerimiz Ne Olmalı ?

1. HEDEF:

Kan basıncının düşürülmesi

Komplike olmayan HT	**< 140/90 mmHg**
Diabetes Mellitus	**< 130/80 mmHg**
Hedef Organ Hasarı	**< 130/80 mmHg**
Proteinüri > 1gr	**< 125/75 mmHg**

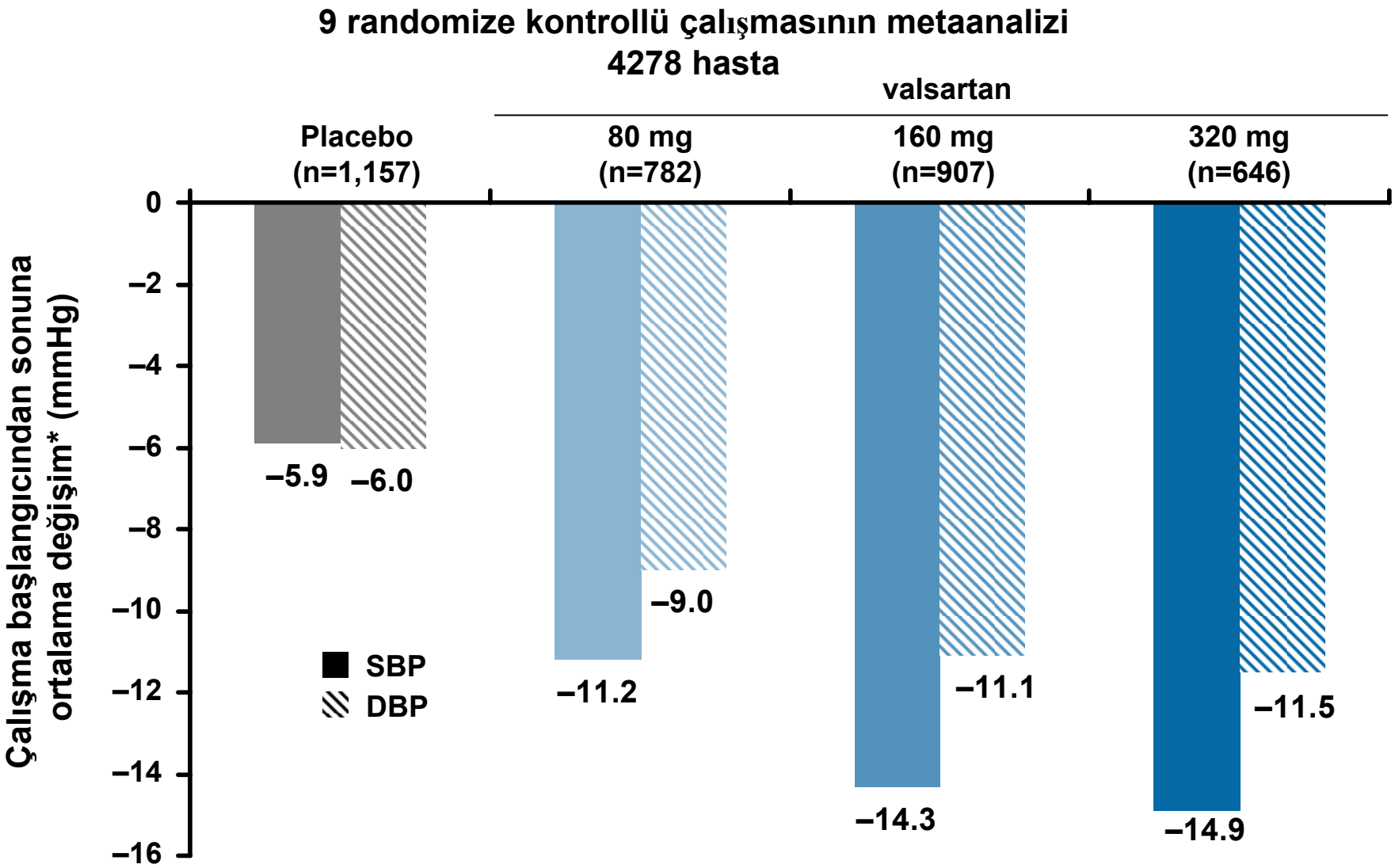
Anti-Hipertansif Tedavi

Etkinlik: 354 çalışma metaanalizi- Doza göre KB (mmHg) değişimi vs plasebo

	Yarım	Standard	İki kat
Tiazid	7.4/3.7	8.8/4.4	10.3/5.0
BB	7.4/5.6	9.2/6.7	11.1/7.8
CCB	5.9/3.9	8.8/5.9	11.7/7.9
ACEI	6.9/3.7	8.5/4.7	10.0/5.7
ARB	7.8/4.5	10.3/5.7	12.3/6.5

Wald NJ et al. *BMJ. 2003; 326: 1419*.

Doza bağlı KB düşüşü



*Tedavi süreleri 4-8 hafta

Weir et al. J Clin Hypertens 2007;9:103–12

AJH 2007; 20:807–815

Time to Achieve Blood-Pressure Goal: Influence of Dose of Valsartan Monotherapy and Valsartan and Hydrochlorothiazide Combination Therapy

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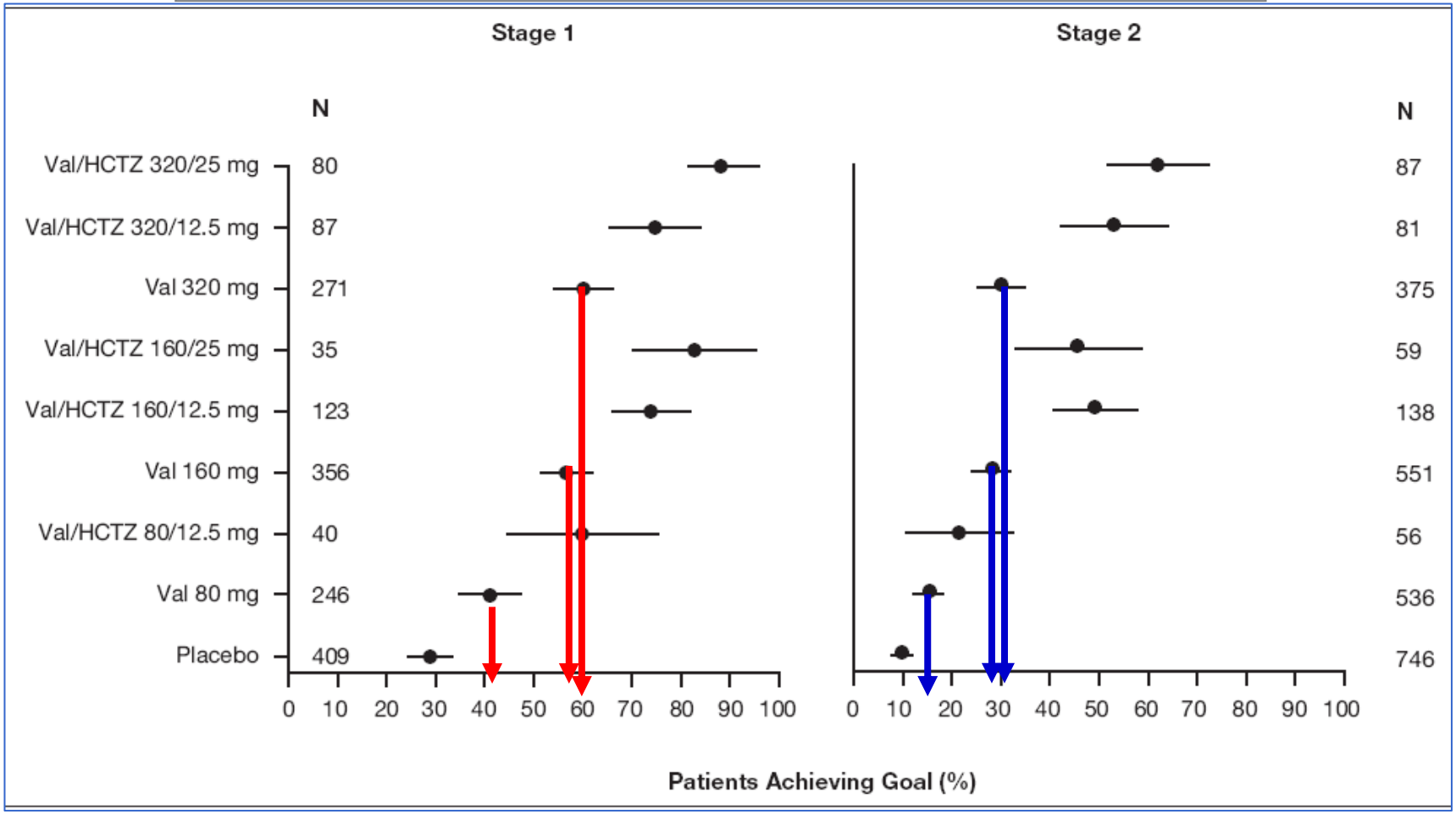
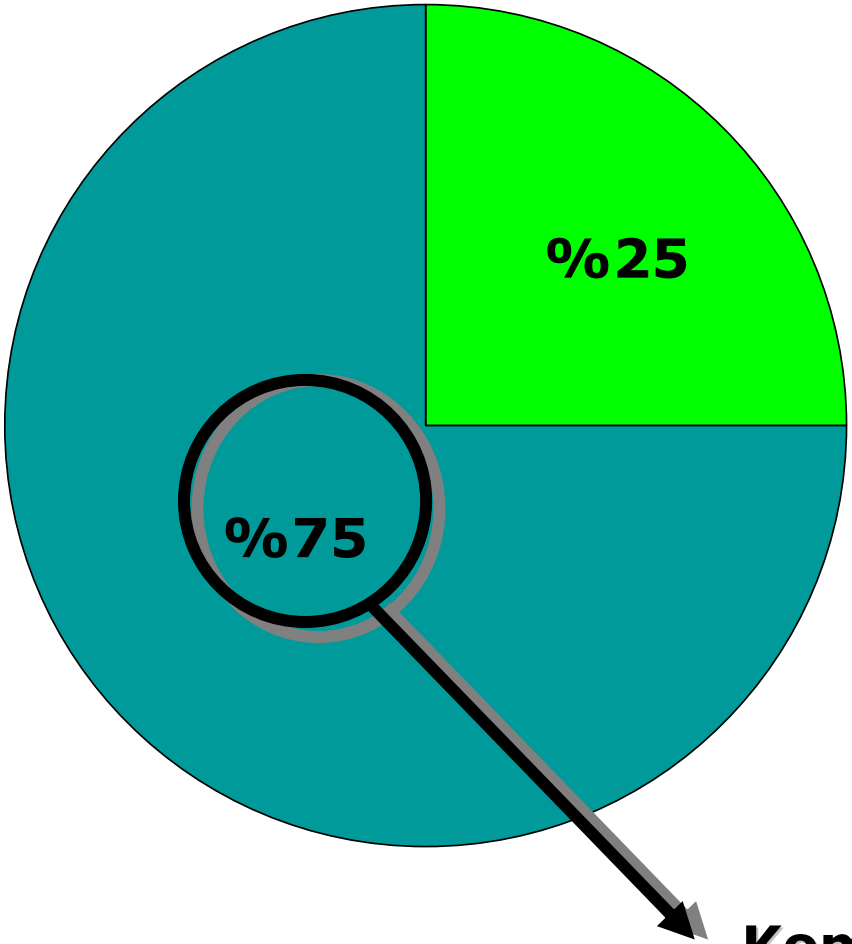


Hipertansiyon Evre Oranları



Evre 1 HT

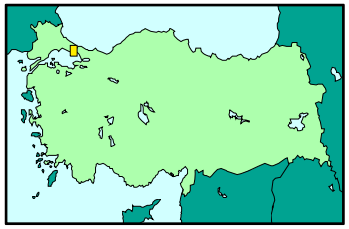
140-159/90-99

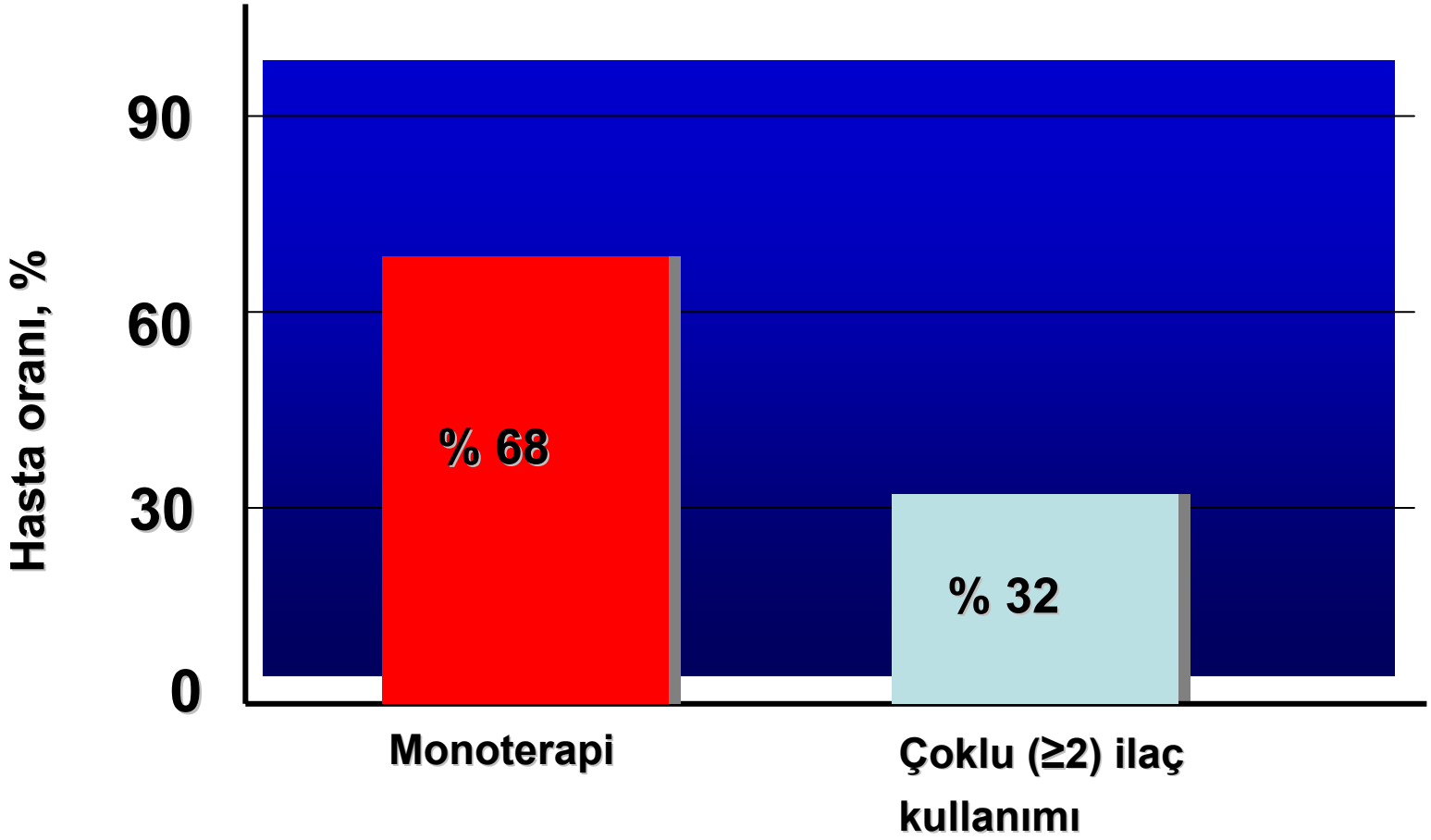
≥ Evre 2 HT

≥ 160/100

Kombinasyon başlanmalı

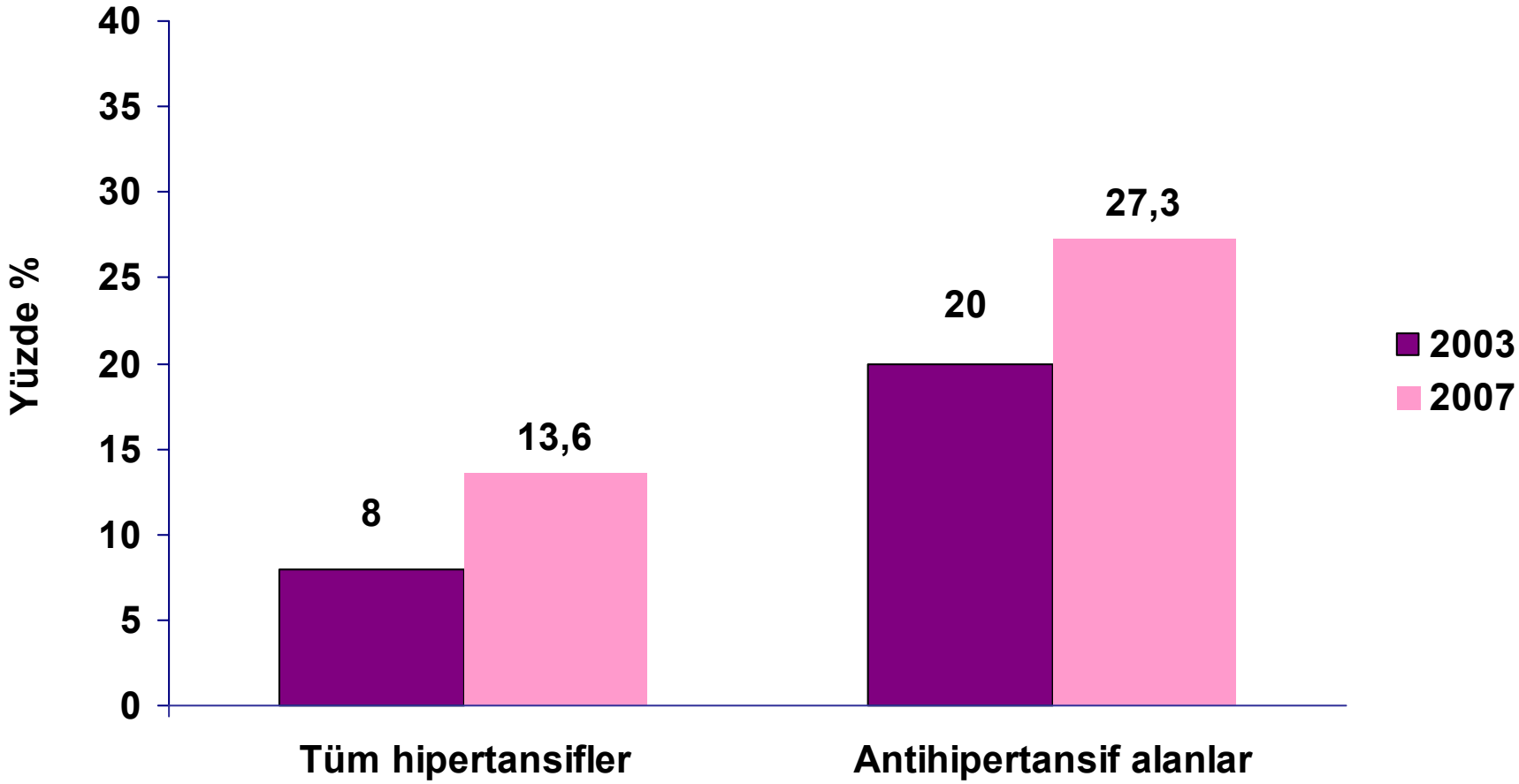
Türk hipertansiyon prevalans çalışması. J Hypertens 2005





Türk hipertansiyon prevalans çalışması. J Hypertens 2005

Hipertansiyon Kontrolü 2003-2007



Türk Hipertansiyon ve Böbrek Hastalıkları Derneği, 2008

Dirençli Hipertansiyon

Tedaviye Yanıt Vermeyen HT Hastası

Dirençli Hipertansiyon

Maksimum dozda üç farklı anti-HT tedaviyi aldığı halde KB>140/90 mmHg

“Dirençli Hipertansiyon” da kombinasyonda mutlaka olması gereken ilaç hangisidir?

a. Beta Bloker
b. Kalsiyum kanal bloker
c. Diüretik
d. ACE İnhibitör
e. Angiotensin reseptör bloker

Türk Toplumunda Tuz Tüketimi Çalışması SALTURK

NaCl Alımı

	Cinsiyet	Sayı	Ortalama	SD
NaCl Alımı (gr/gün)	Tüm grup	1767	18.04	8.34
	Erkek	857	19,31	8,67
	Kadın	910	16,83	7,86

Türk Hipertansiyon ve Böbrek Hastalıkları Derneği, 2008

Türk Toplumunda Tuz Tüketimi Çalışması SALTURK

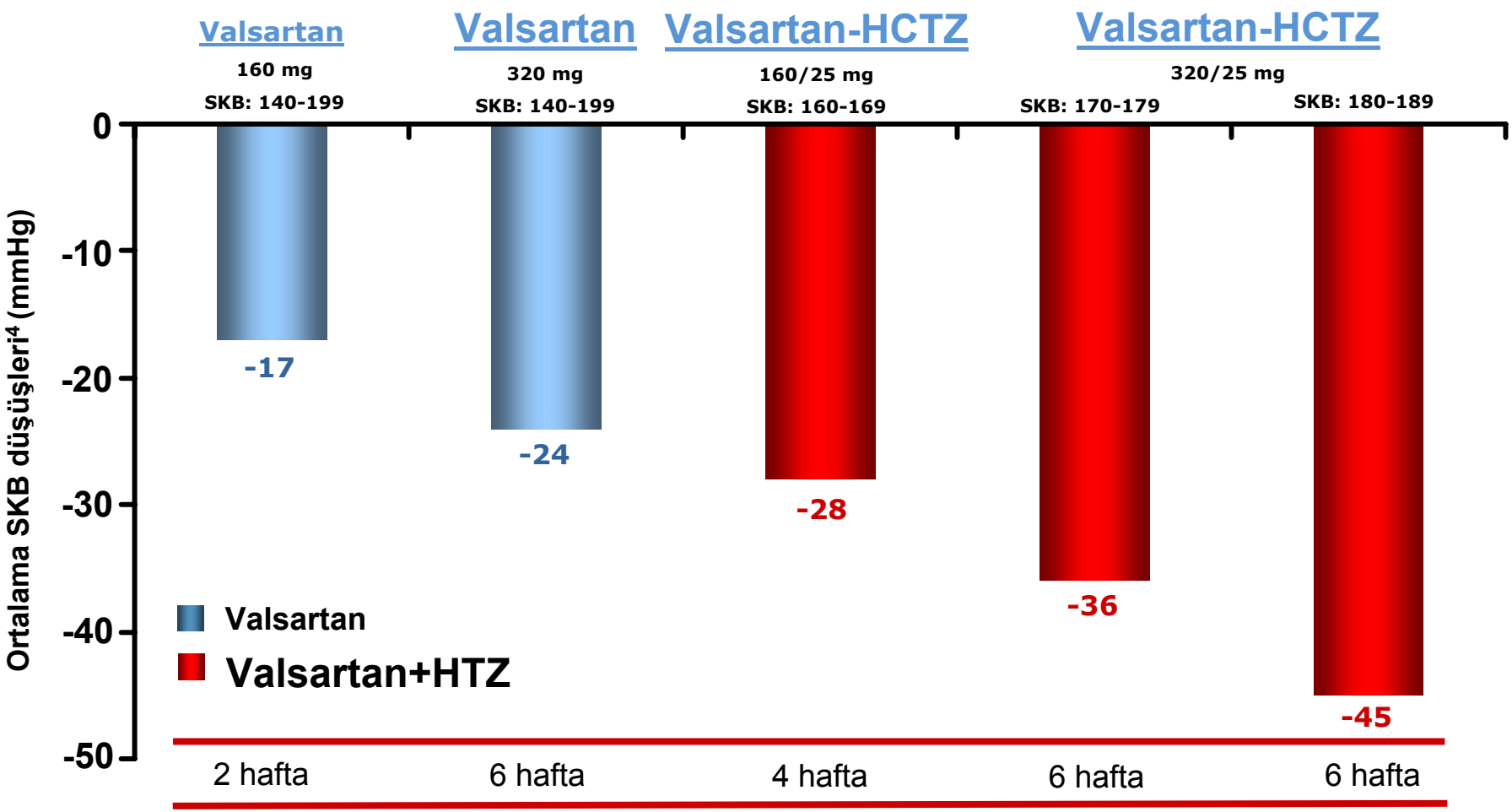
Hipertansiyon & NaCl Alımı (gr/gün)

	HT (TA ≥140/90 mmHg)	Sayı	Ortalama	SD	Ortanca
NaCl Alımı	HT var	622	18,08	8,01	16,64
	HT yok	1145	18,01	8,54	16,70

NaCl alımı p=0,853

Türk Hipertansiyon ve Böbrek Hastalıkları Derneği, 2008

Valsartan - Valsartan-HCTZ artan dozlarda artan kan basıncı düşüşleri sağlar.[1,2,3]



1. Weir MR et al. J Clin Hypertens. 2007 Feb;9(2):103-12. **2.** Pool J et al. Clin Ther. 1998 Nov-Dec;20(6):1106-14. **3.** Calhoun DA. et al. Curr. Med. Res. Opin. 2008;24(8):2303-11. **4.** Data on file - Study CVAH631D2301.

AJH 2007; 20:807–815

Time to Achieve Blood-Pressure Goal: Influence of Dose of Valsartan Monotherapy and Valsartan and Hydrochlorothiazide Combination Therapy

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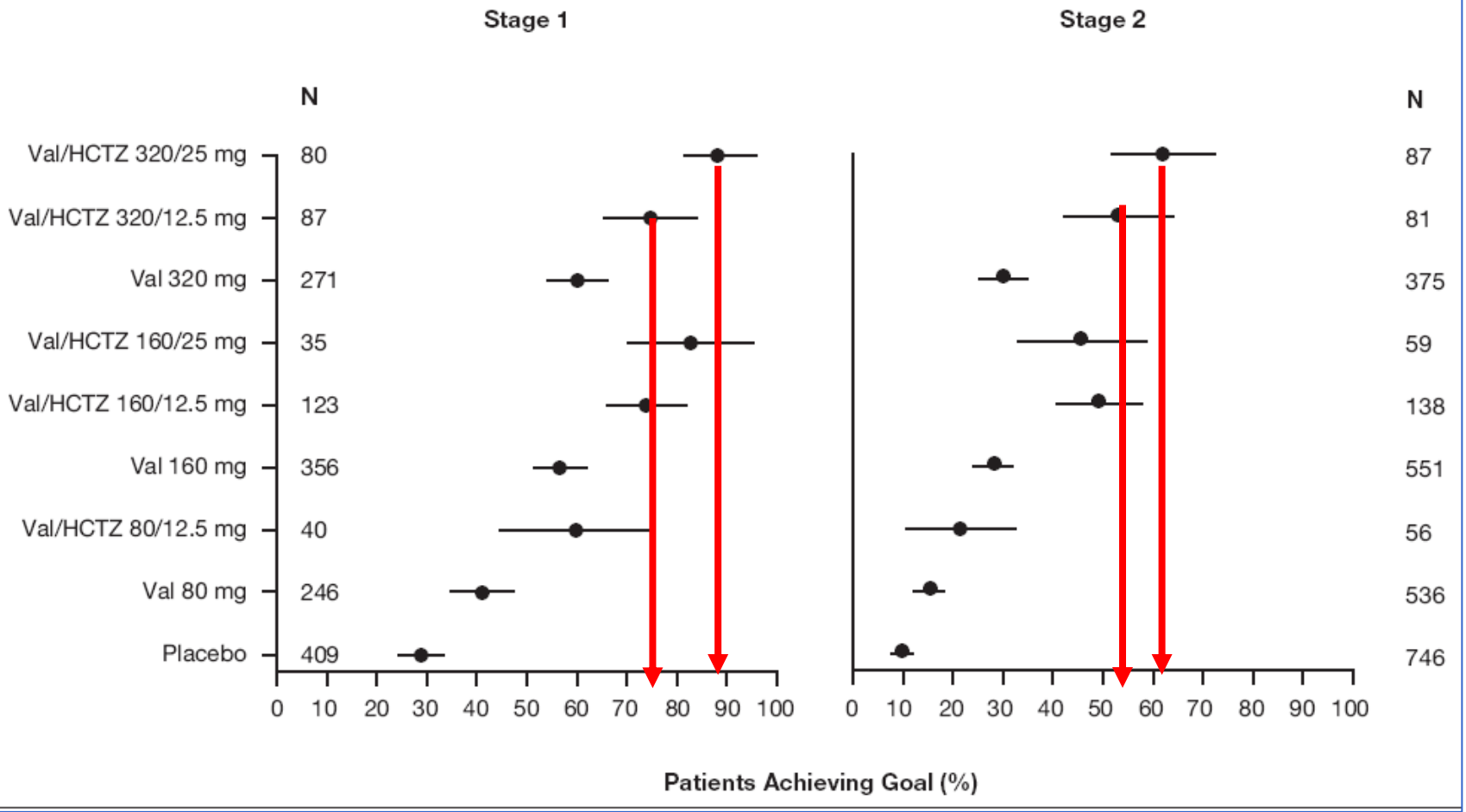
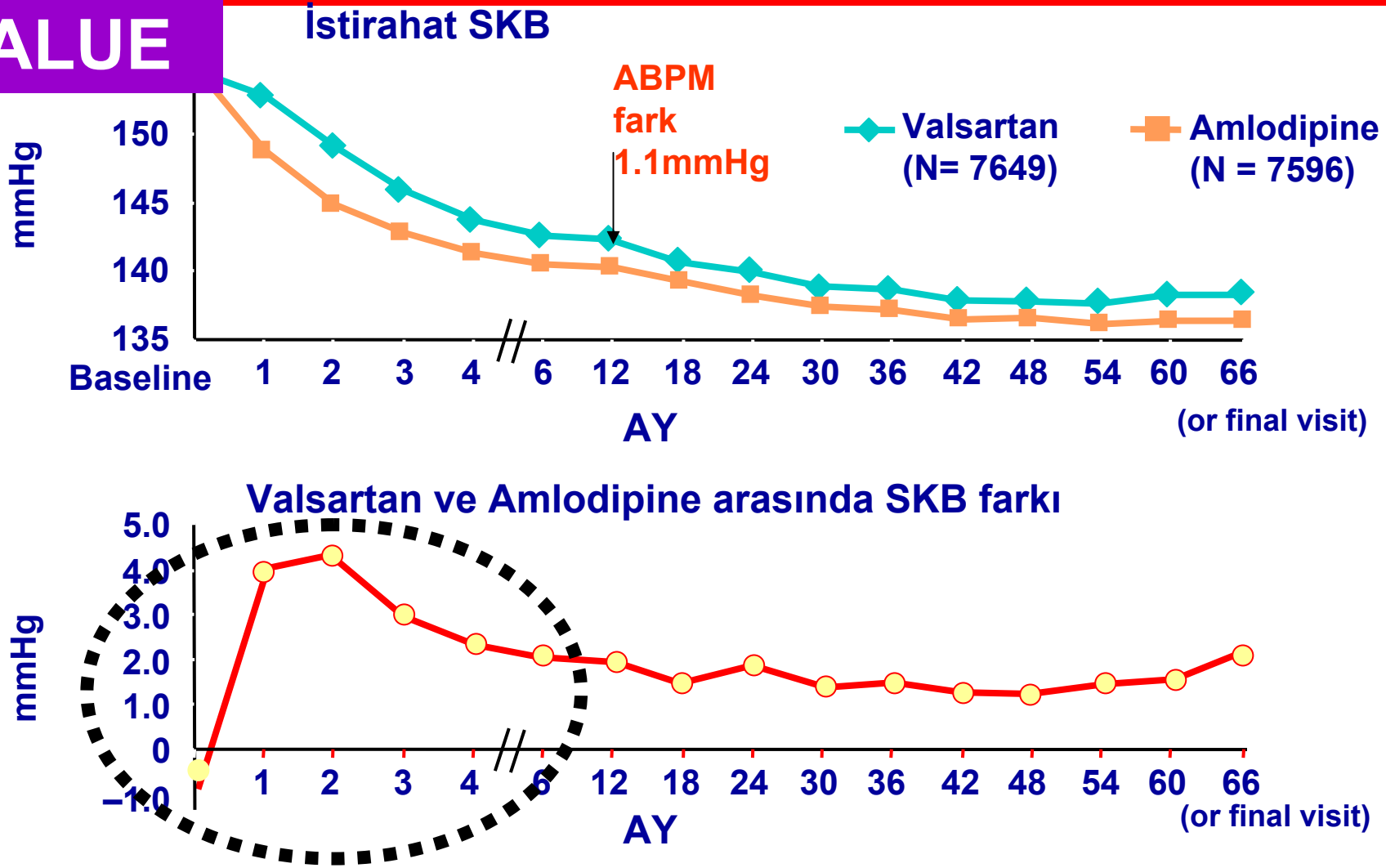


Hedef Kan Basıncına Ulaşma Süresi ÖNEMLİ MİDİR?

Hedef Kan Basıncına Ulaşma Süresi ÖNEMLİ MİDİR?

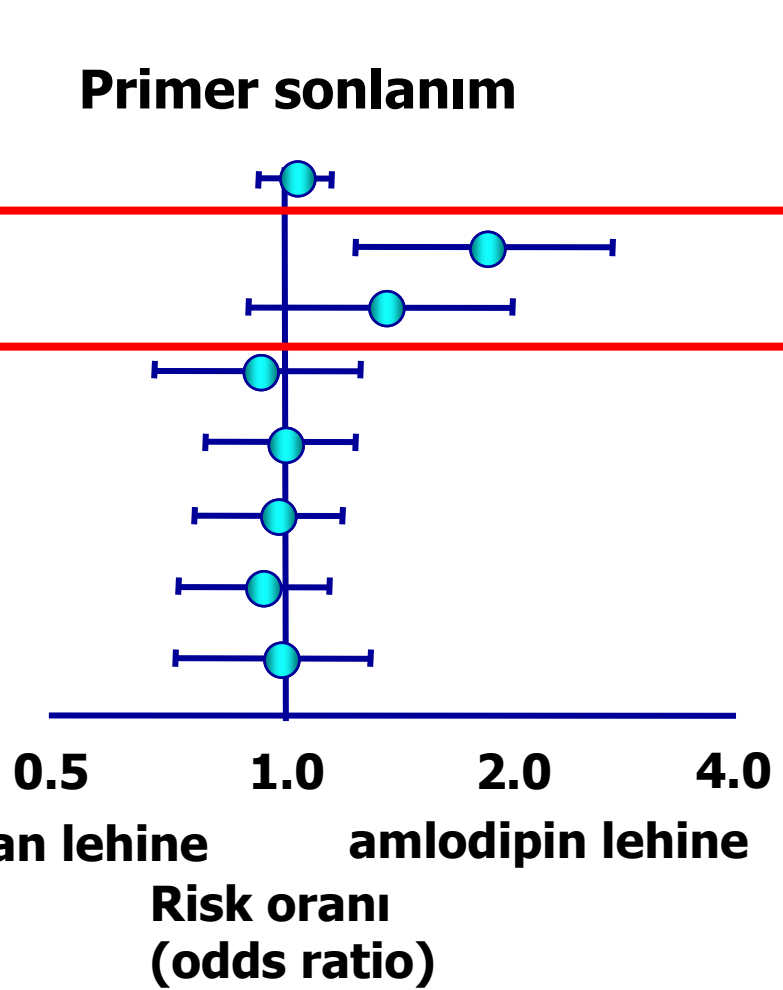
VALUE



Julius S et al. *Lancet*. June 2004;363.

Belirli Zaman Aralıklarında SKB ve Sonuç Değişiklikleri: *Miyokard İnfarktüsü*

Süre (ay)	Δ SKB mmHg
Çalışma Boyunca	2.2
0–3	3.8
3–6	2.3
6–12	2.0
12–24	1.8
24–36	1.6
36–48	1.4
48- çalışma sonu	1.7

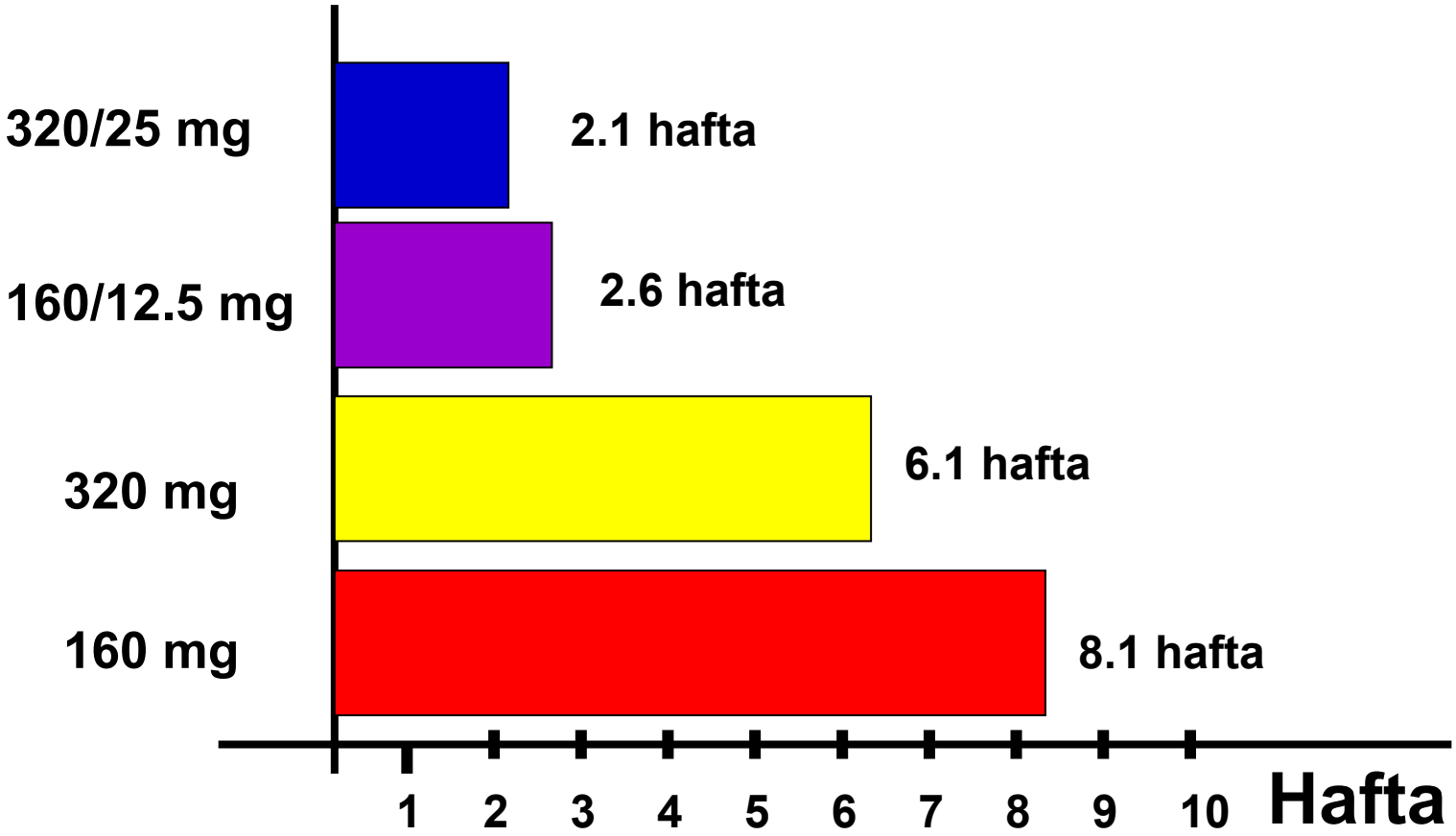


Julius S et al. Lancet. June 2004;363.

Kan Basıncını Kontrol Altına Alma Süresi Önemlidir

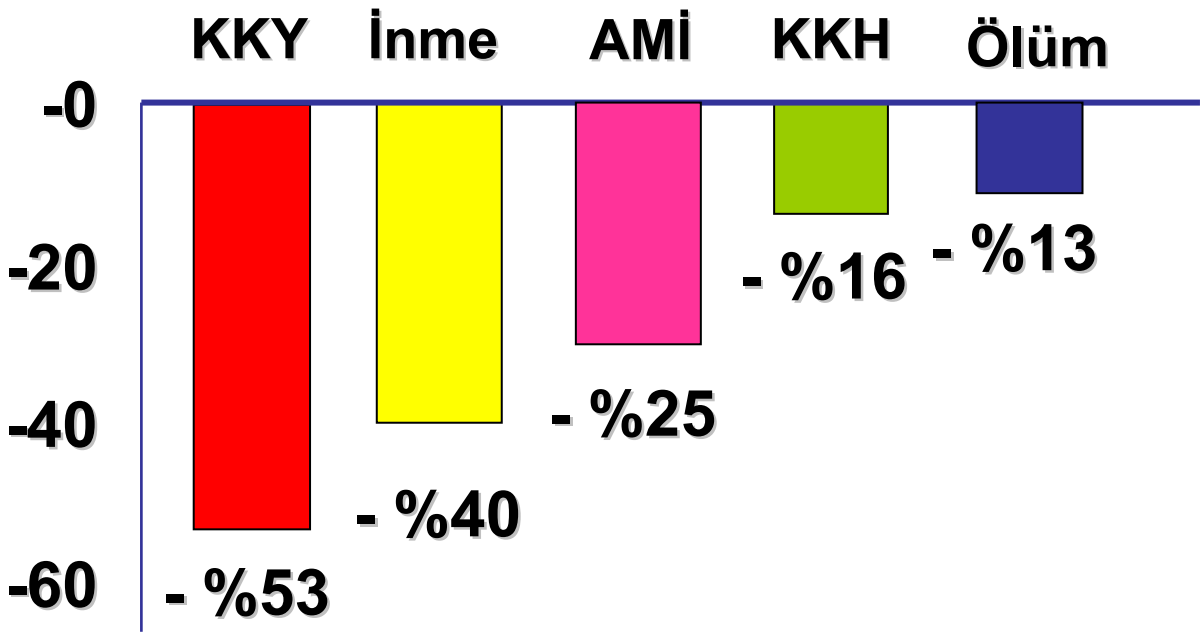
Kan Basıncını Kontrol Altına Alma Süresi Önemlidir

Valsartan ve Valsartan/HCTZ ile KB hedefine ulaşma süresi



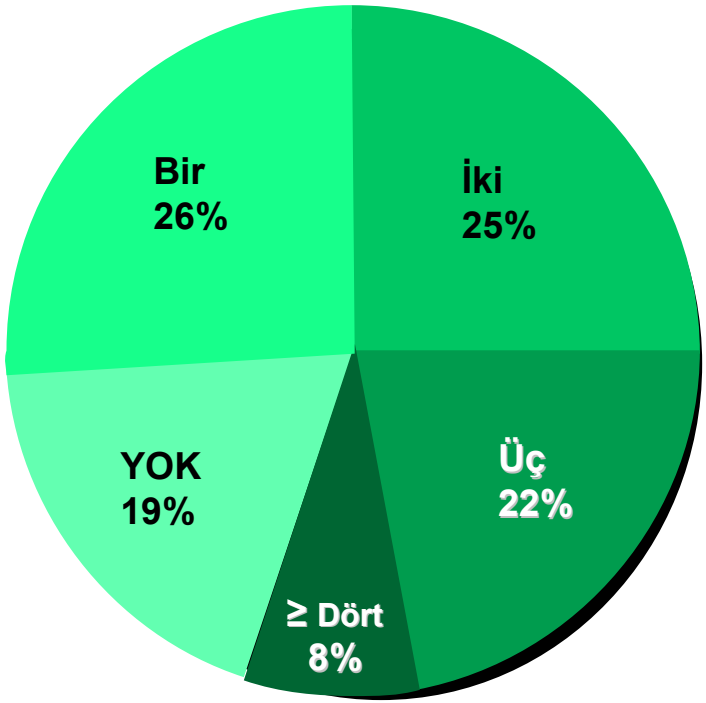
Weir M AJH 2007:20:807

Meta-analiz: KB<140/90 mmHg
Kan Basıncı Tedavisi Sonucu



Hipertansif Hastalarda >%80 Ek Komorbidite VARDIR

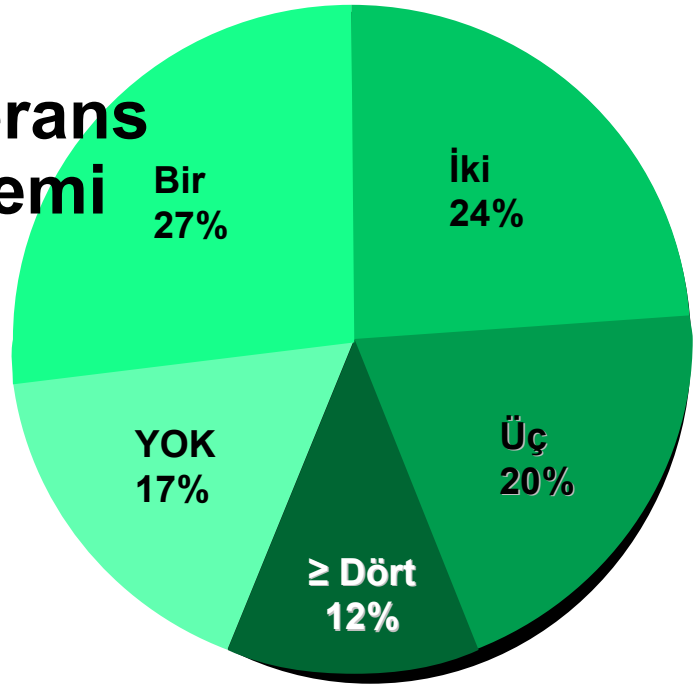
Erkek



Komorbideteler:

- Obesite
- Glukoz intolerans
- Hyperinsulinemi
- Dislipidemi
- KAH
- KKY
- MI
- İnme
- Aritmi

Kadın

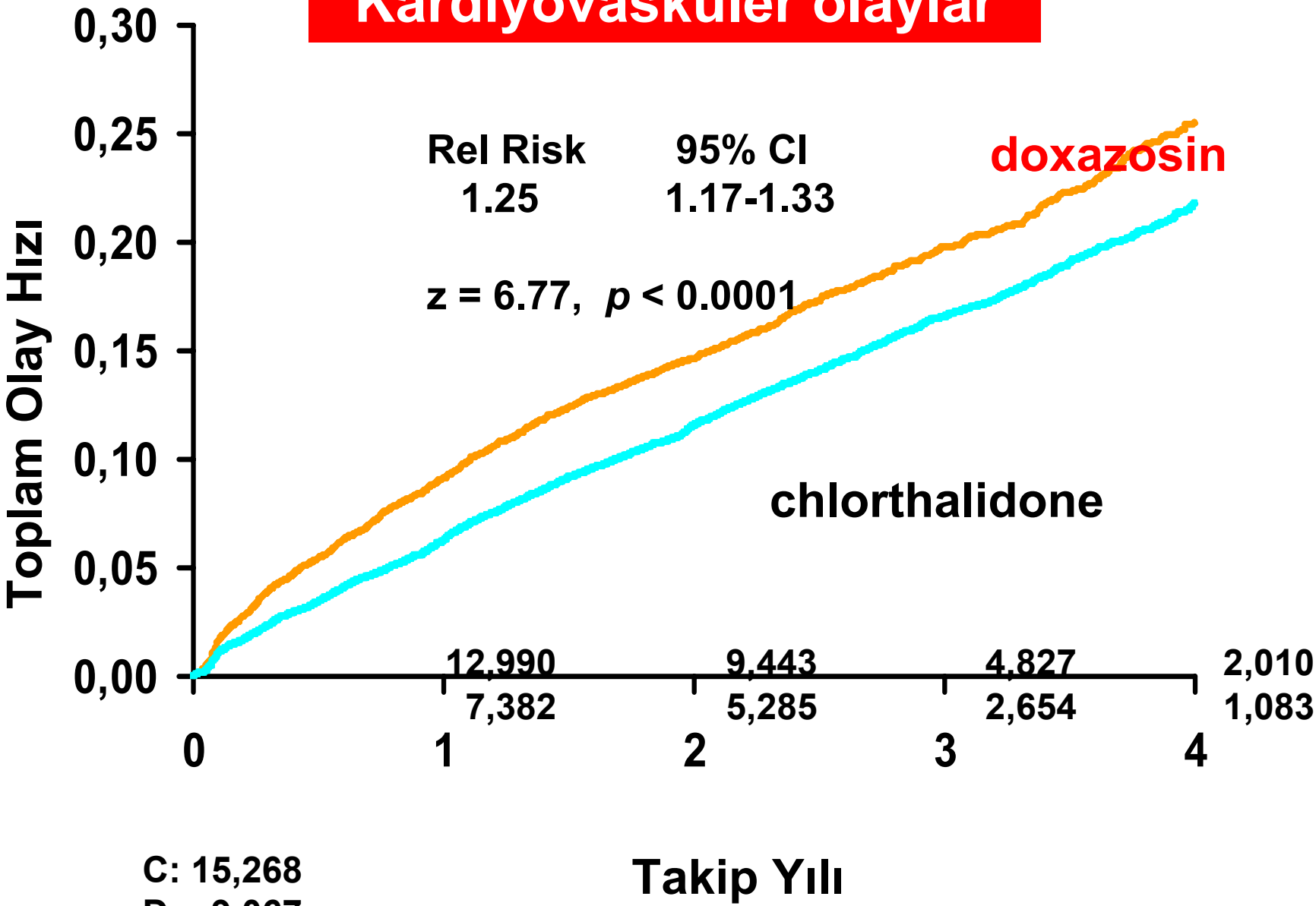


>50% HT Hastası ≥2 Komorbiditeye sahip

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; TG, triglycerides.

Kannel WB. *Am J Hypertens.* 2000:13:3S-10S.

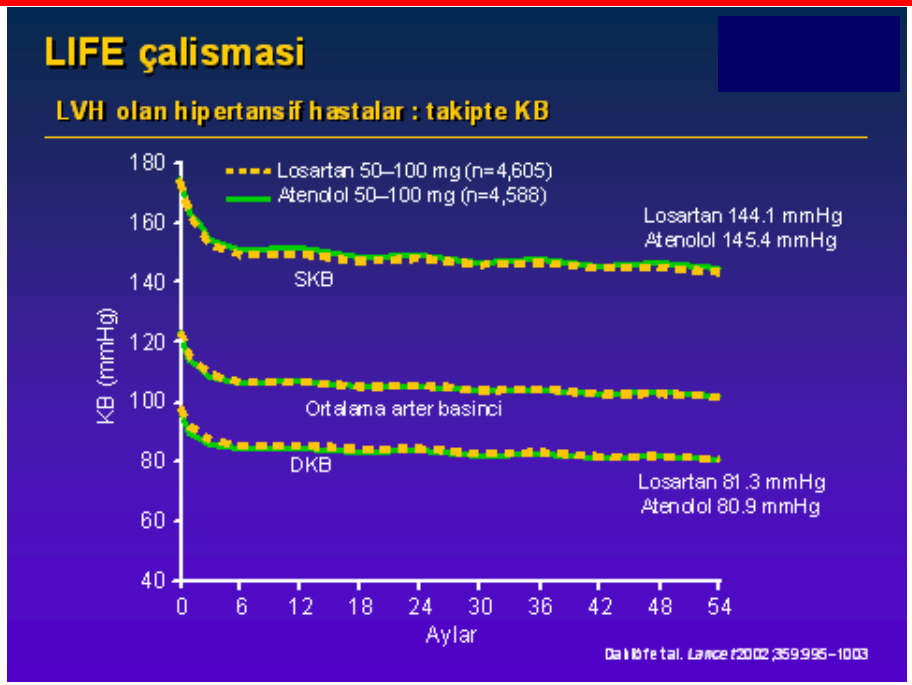
ALLHAT
Kardiyovasküler olaylar

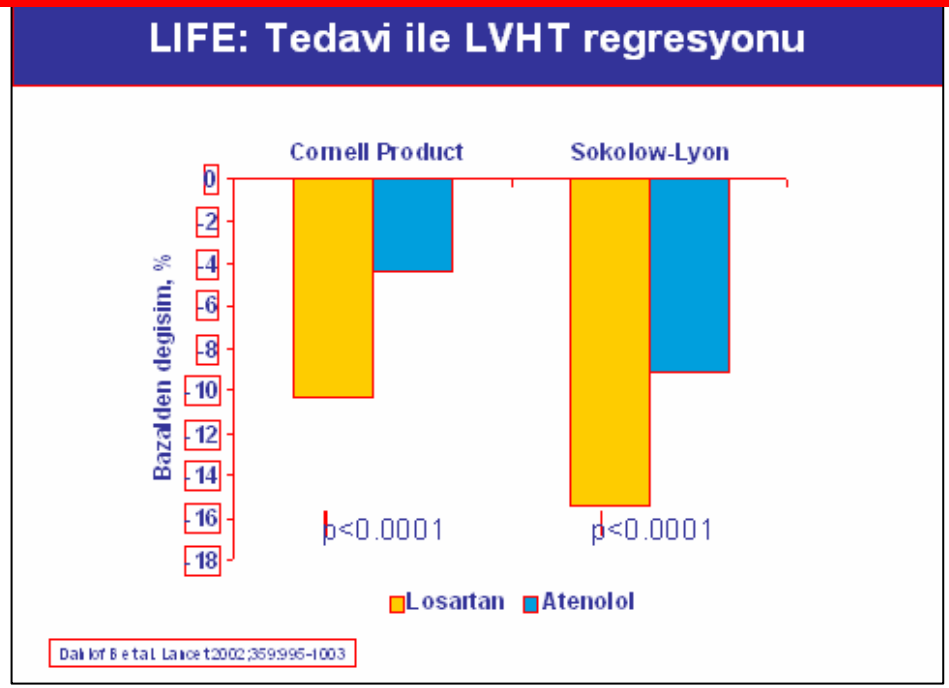


C: 15,268
D: 9,067

JAMA. 2000;283:1967-1975

LIFE Çalışması
EKG de LVHT olan Hipertansif Hastalar





	Losartan* (n = 4605)	Atenolol* (n = 4588)	*P*
• Primer sonlanma**	11%	13%	0.021
• CV ölüm	4%	5%	0.21
• İnme	5%	7%	0.001
• MI	4%	4%	0.49
• Tüm Ölümler	8%	9%	0.13

Tüm Antihipertansifler Aynı Değil

Farklı anti-hipertansif tedavilerle

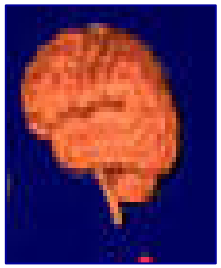
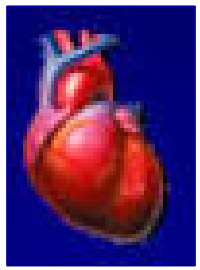
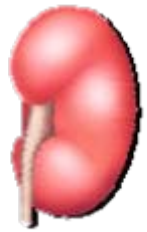
Kan Basıncı eşit olarak düşürülse bile prognozlar

farklı olmaktadır.....

HİPERTANSİYON TEDAVİSİNDE SEÇİLECEK İLAÇ

1. **Etkin – Sürekli Kan Basıncı Kontrolü**
2. **Kan Basıncını Düşürme dışında olumlu etkiler**

HEDEF ORGAN KORUMA

Metabolik Olumlu Etkiler

VAKA

- **63y Erkek**

Şikayet: **Nefes darlığı ve çabuk yorulma**

- **Hikayesi:** **Yol yürümekle nefes darlığı varmış. Gün içinde ayaklarında şişlik oluyormuş.**

  - 6 aydır şiddetli gıcık tarzında öksürük varmış.

  - Kan basıncı genelde yüksek olurmuş.

  - 5 yıl önce KAG yapılmış ve kalp damarlarından birisinin tıkalı olduğu söylenmiş ve stent takılmış.

  2 yıl önce geçici bir felç geçirmiş.

Özgeçmiş: **HT (15 yıl), Hiperlipidemi, MI, SVO**

Soygeçmiş: **Baba HT,**

İlaç Kullanımı:

Aspirin 300 mg,

Ramipril 5 mg/g,

Metoprolol 50 mg/g

Simvastatin 20 mg/g

Sigara: 1 paket/g (30 yıl)

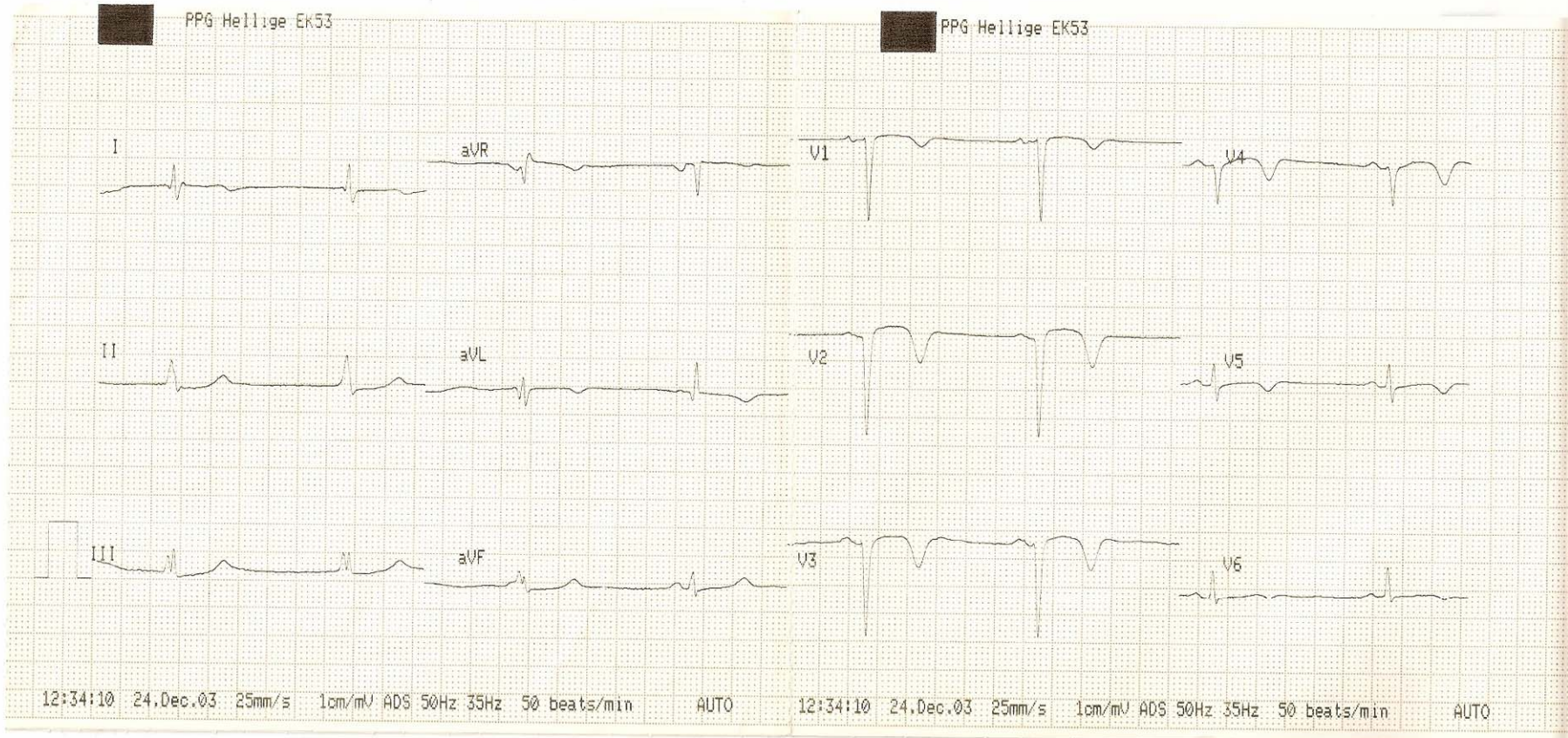
Fizik Muayene

Genel durum iyi
Kilo: 94 kg Boy: 165 cm

Kan Basıncı: 160/95 mmHg
Kalp Hızı: 52/dak/ritmik

KVS: Apikal 1/6 sistolik üfürüm

Solunum Sistemi: Bilateral krepitan ral
Batın: Doğal
Ödem: +/+


PPG Hellige EK53
I
aVR
II
aVL
III
aVF
12:34:10 24.Dec.03 25mm/s 1cm/mV ADS 50Hz 35Hz 50 beats/min AUTO
PPG Hellige EK53
V1
V4
V2
V5
V3
V6
12:34:10 24.Dec.03 25mm/s 1cm/mV ADS 50Hz 35Hz 50 beats/min AUTO

LABORATUVAR

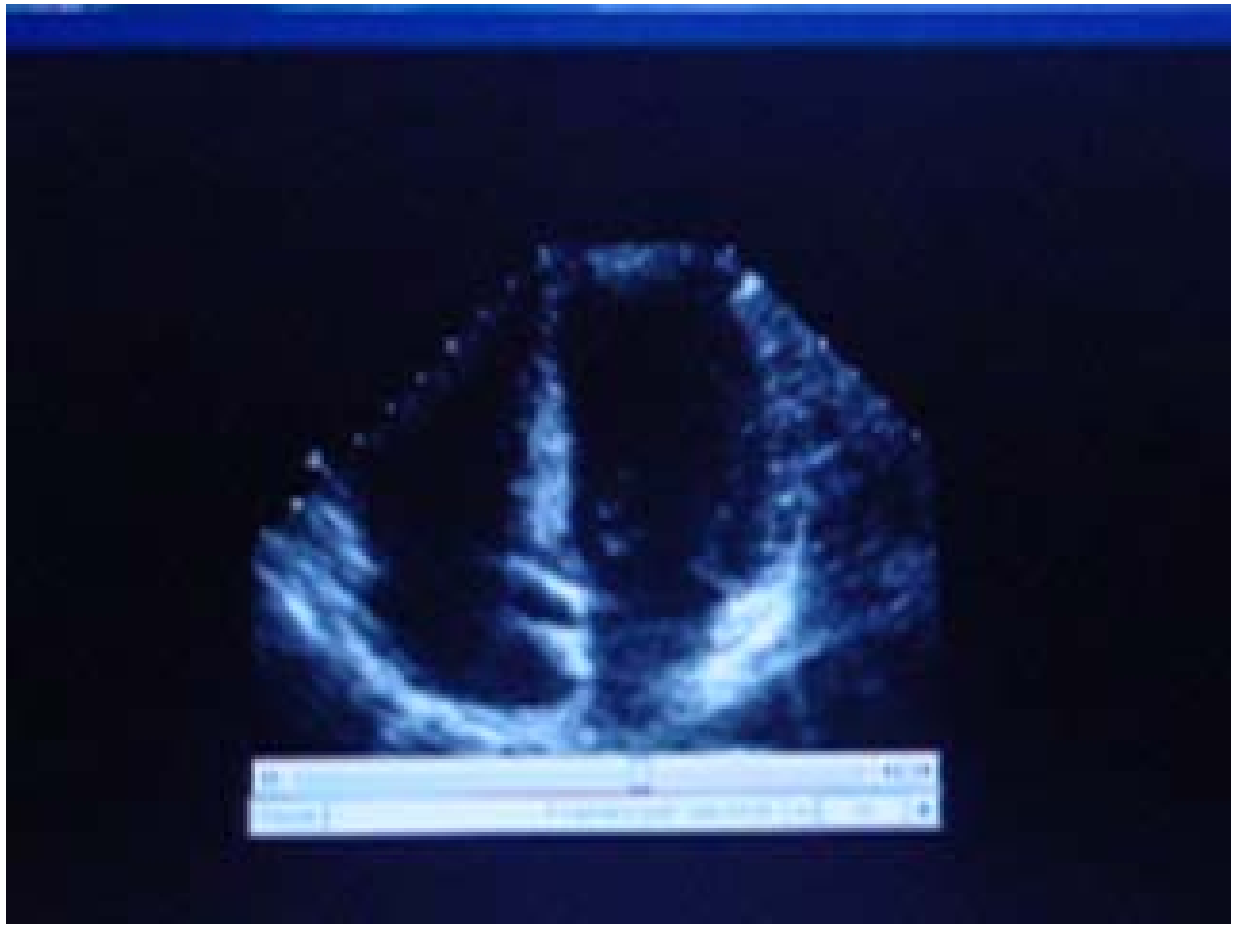
- **Kan Sayımı:** Hb: 14.4 gr BK: 8600/mm^3
- **Biyokimya:**

  Kreatinin 1.1 mg/dl BUN 18 mg/dl
  AST: 21 U/L ALT: 24 U/L
  K+: 4.7 mEq/L Ürik asit: 6.4 mg/dl
  Kan Şekeri: 96 mg/dl

  T-Kolesterol: 231 mg/dl Trigliserid: 179 mg/dl
  LDL-K: 133 mg/dl HDL-K: 42 mg/dl

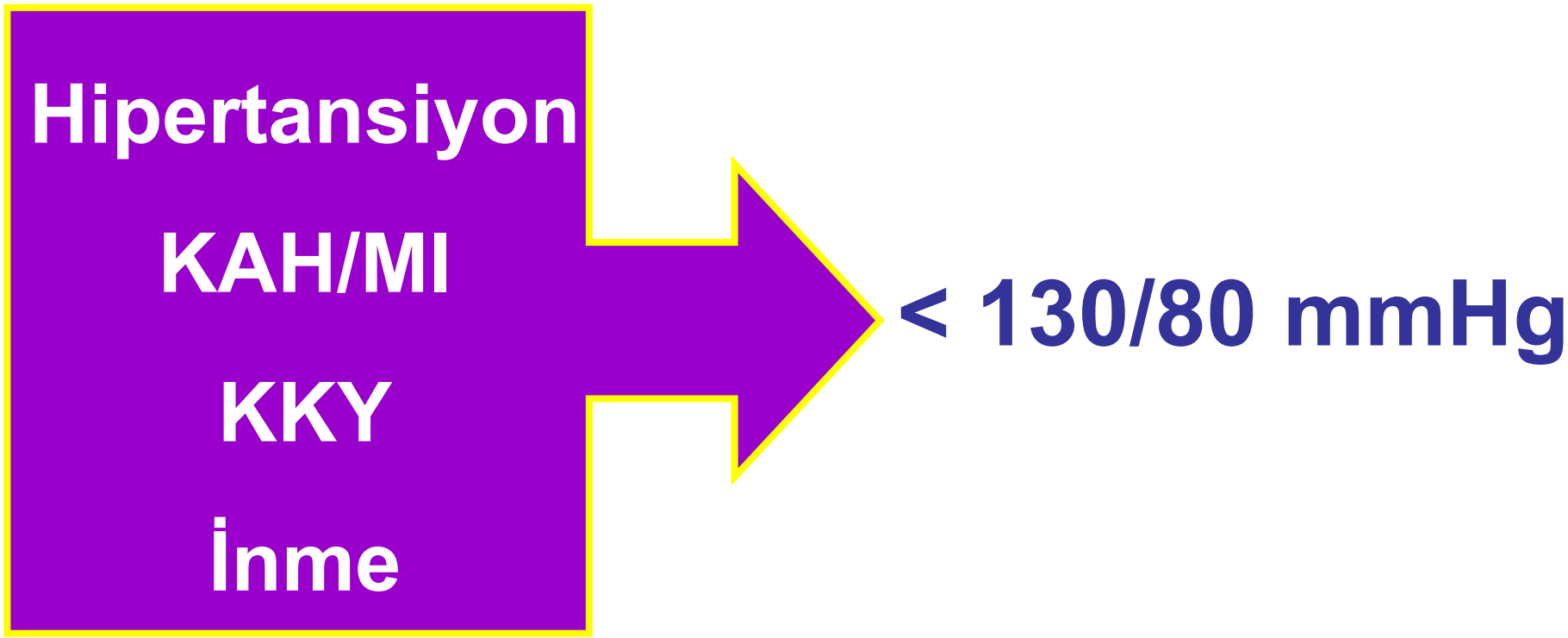
- **İdrar Tetkiki:** Protein negatif

Ekokardiyografi



Kardiyomegali-LV disfonksiyon

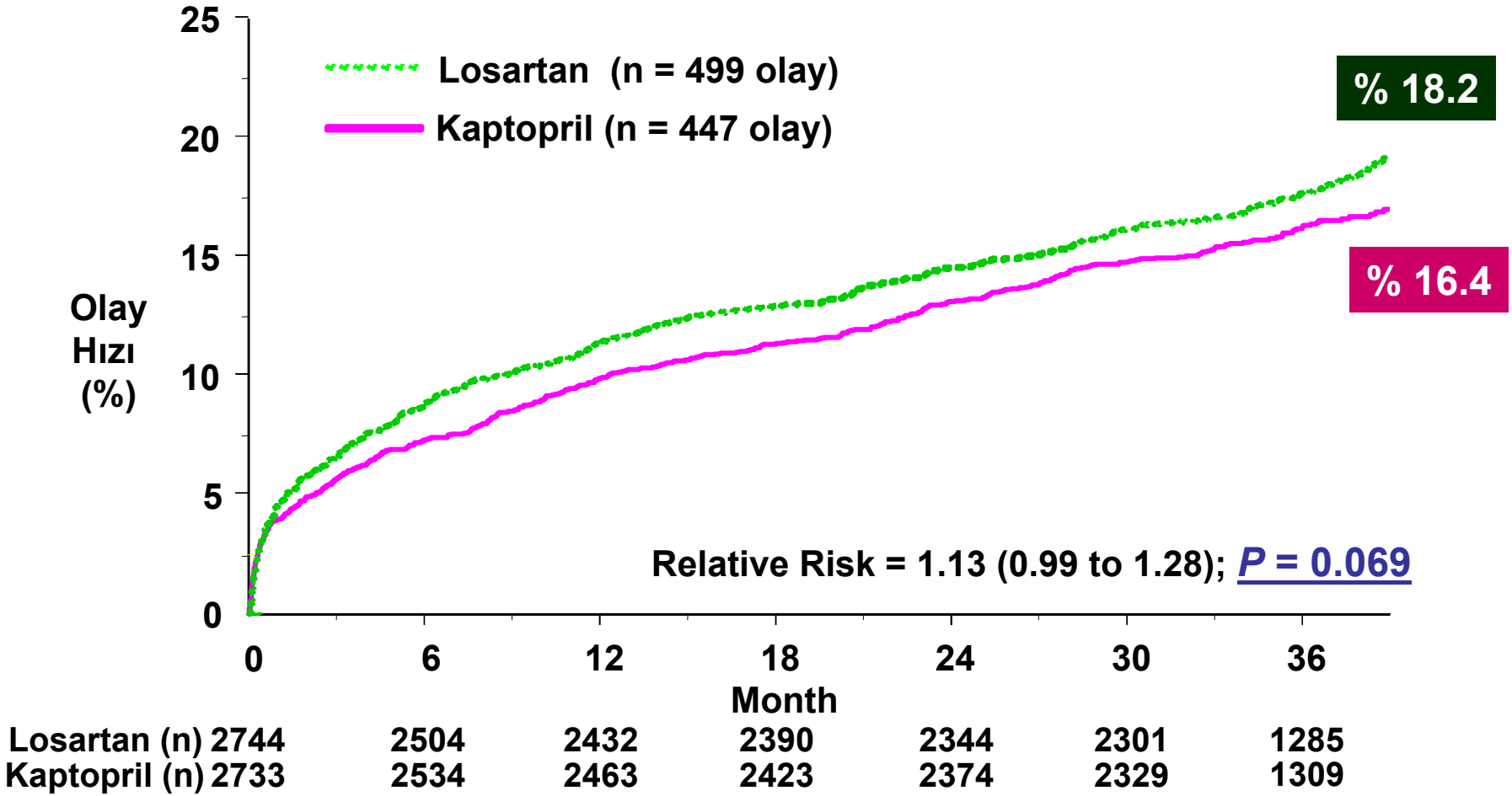
HEDEF KAN BASINCI



Hangi ARB verelim ?

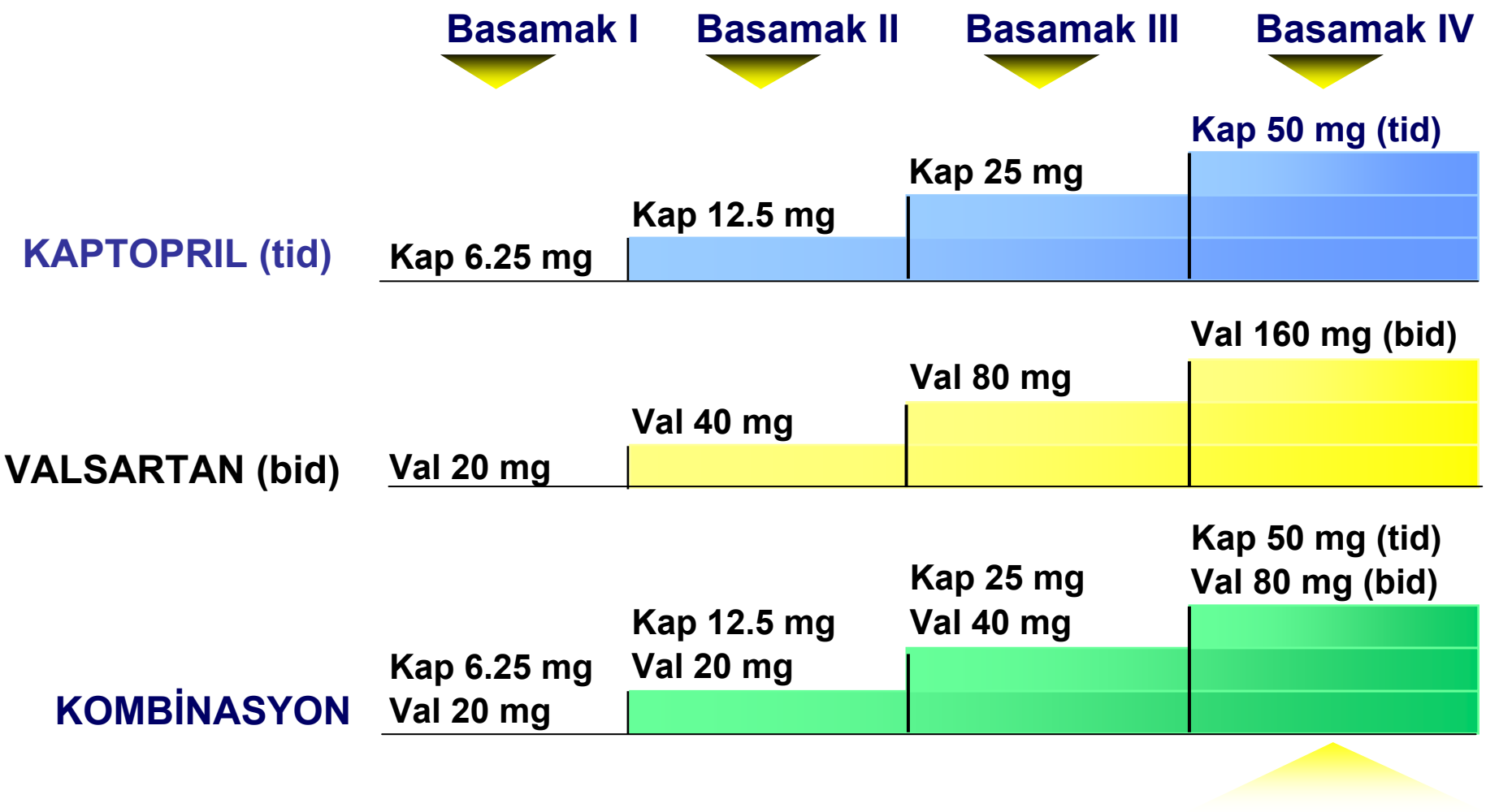
a. Losartan
b. Irbesartan
c. Kandesartan
d. Valsartan
e. Olmesartan

OPTIMAAL: Tüm nedenlere bağlı ölüm



Dickstein K et al. *Lancet*. 2002;360:752-60.

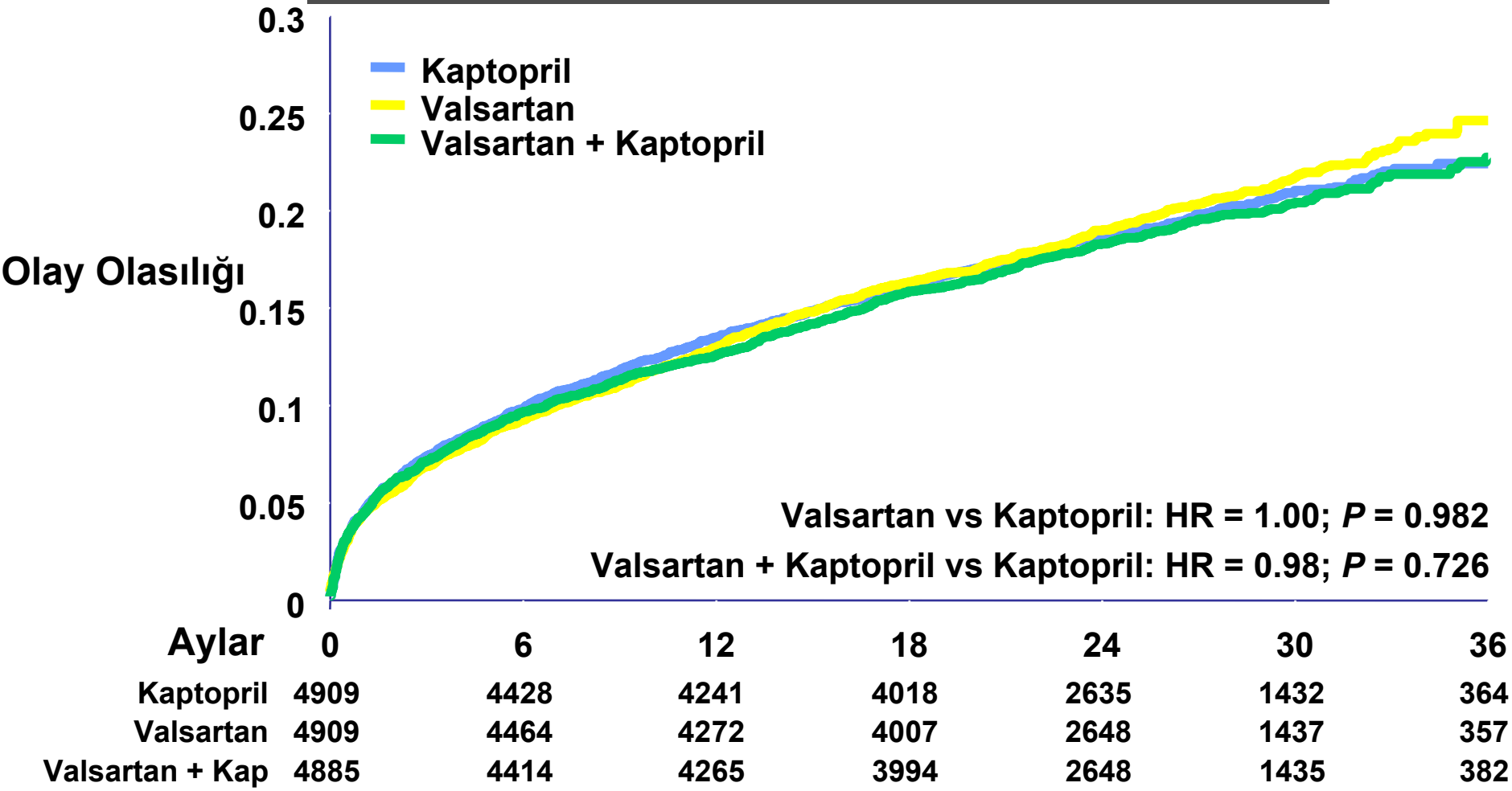
VALIANT: Titrasyon



Pfeffer MA et al. *Am Heart J.* 2000;140:727-734.

VALIANT
AMI Sonrası Valsartan Kullanımı: Mortalite

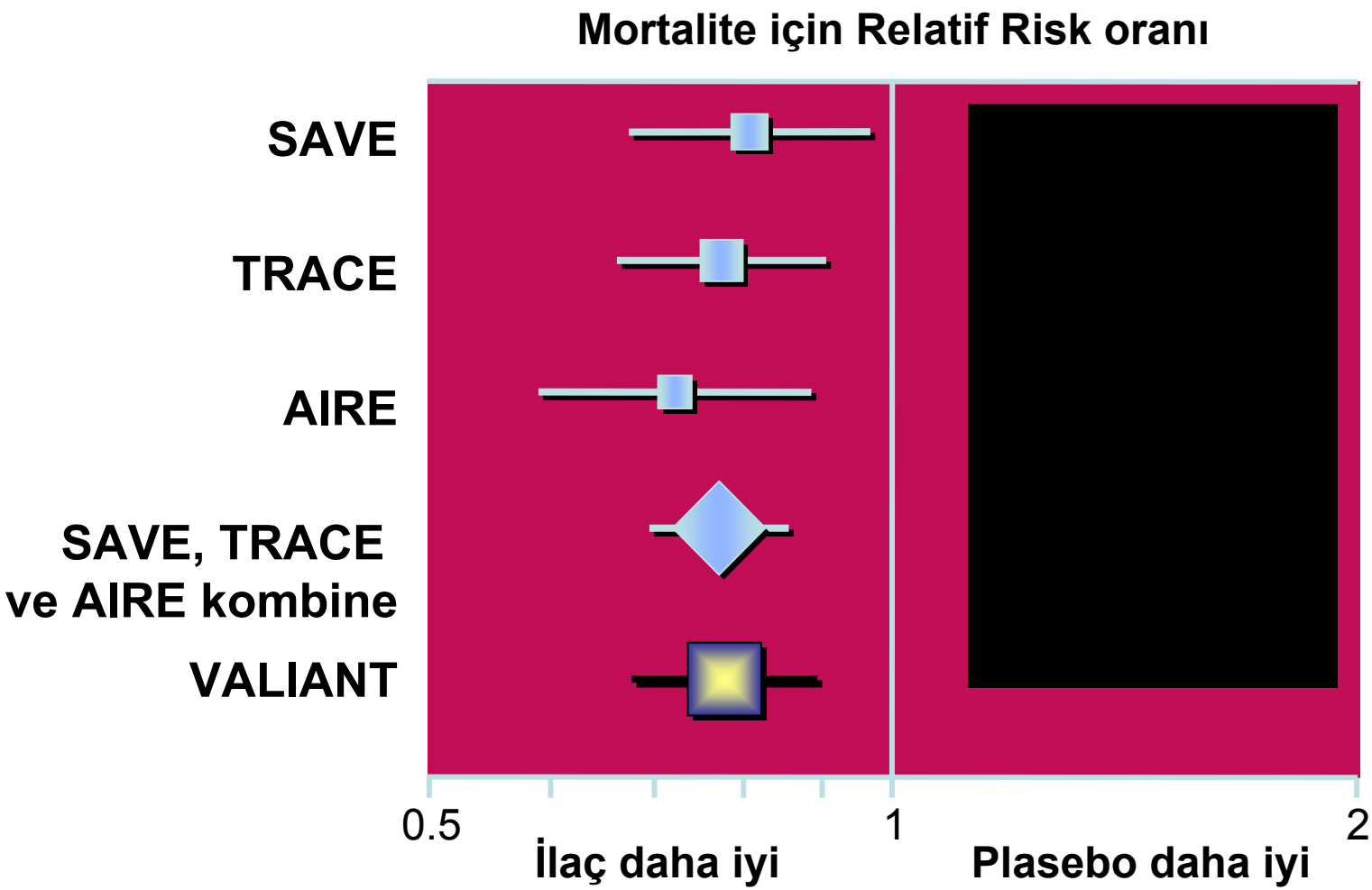
Valsartan dozu: 320 mg/g



Aylar	0	6	12	18	24	30	36
Kaptopril	4909	4428	4241	4018	2635	1432	364
Valsartan	4909	4464	4272	4007	2648	1437	357
Valsartan + Kap	4885	4414	4265	3994	2648	1435	382

Pfeffer MA et al. *N Engl J Med.* 2003;349:1893-1906.

Mortalite oranları: SAVE, TRACE, AIRE ve VALIANT



Pfeffer, McMurray, Velazquez, *et al. N Engl J Med* 2003;349

ACC/AHA PRACTICE GUIDELINES—FULL TEXT

ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction)

Developed in Collaboration With the Canadian Cardiovascular Society

Klas I indikasyonlar

ACE inhibitorüne toleransı olmayan STEMI hastalara ve klinik veya radyolojik olarak KKY bulgusu olana veya LVEF<%40 olan STEMI hastalara angiotensin receptor blocker (ARB) tedavisi kullanılabilir. ((Valsartan ve kandesartanın bu durum için etkinliği gösterilmiştir)

Sınıf IIa İndikasyonlar

ACE inhibitorünü tolere edebilen STEMI hastalara

ARB, klinik veya radyolojik olarak KKY bulgusu veya LVEF<%40 varsa, yararlı bir alternatif olabilir

(Valsartan ve kandesartan)

Kalp Yetmezliğinde Tedavi Yaklaşımı

Evre A

Yüksek Risk,

Yapısal Kalp hastalığı

YOK

Tedavi

- Hipertansiyon tedavisi
- Dislipidemi tedavisi
- Düzenli Egzersiz
- Alkol alımında kısıtlama
- Sigara bırakma
- ACE inhibisyonu
- **ARB**

Evre B

Yapısal hastalık VAR, Asemptomatik

Tedavi

- Evre A dakilerin hepsi
- Uygun hastaya ACE inh.
- Uygun hastaya Beta bloker
- Uygun hastaya **ARB**
- Uygun hastaya aldesteron blokajı

Evre C

Yapısal hastalık VAR + Şimdi/önce KKY semptomları

Tedavi

- Evre A dakilerin hepsi
- **Diuretik**
- Beta-bloker
- **ACE inhibitor**
- **ARB**
- Aldesteron blokajı
- Digital
- Tuz kısıtlama

Evre D

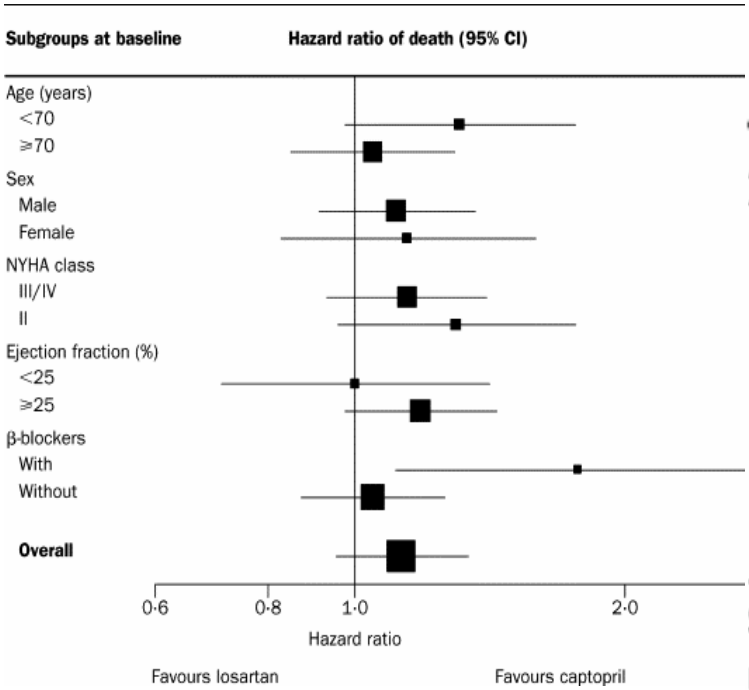
Özel girişim gerektiren ciddi Refrakter KKY

Tedavi

Evre A-B-C dekilerin hepsi

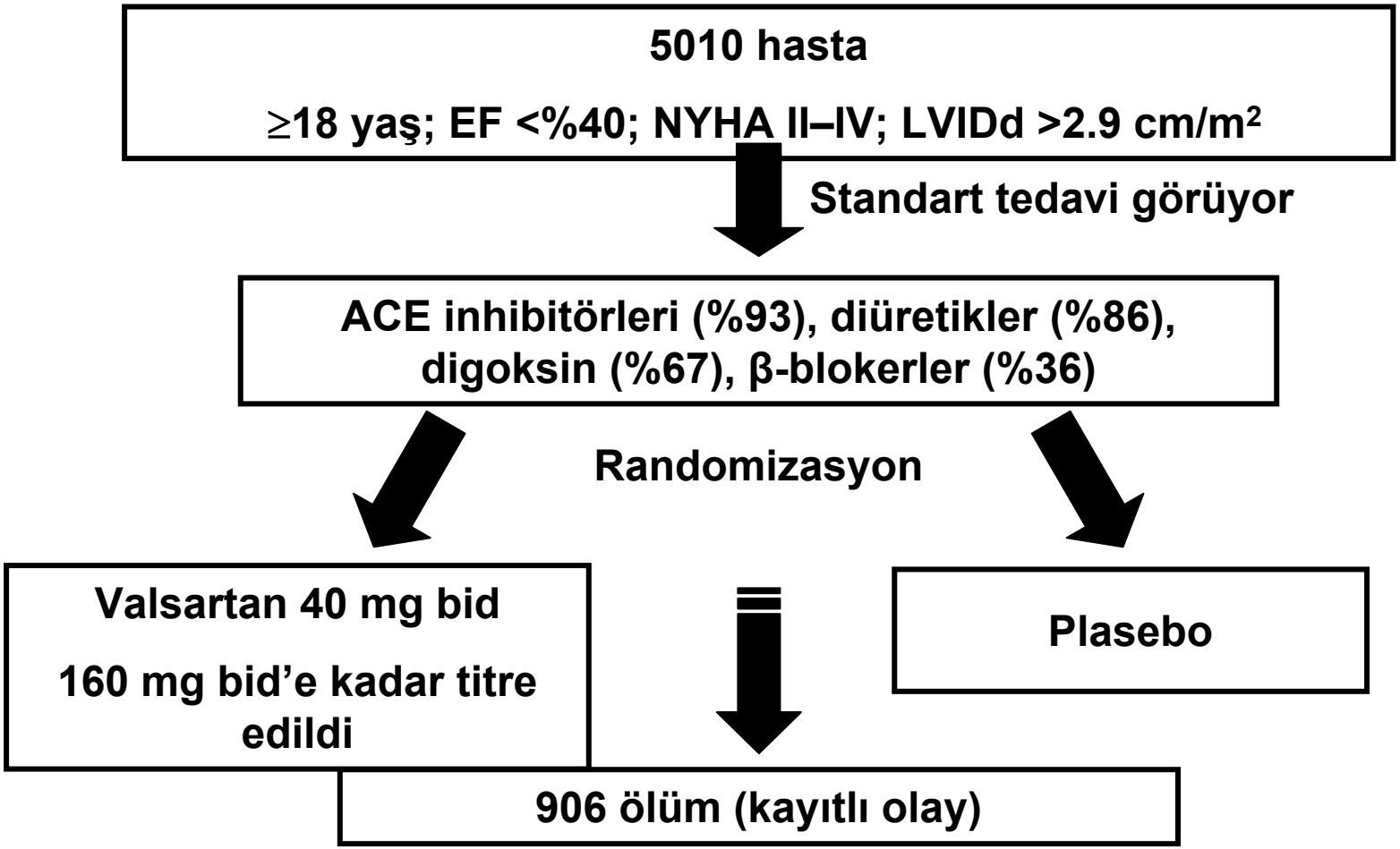
- Mekanik asist devices
- Kalp transplantasyonu
- IV inotropik
- EECP

Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II



Endpoint	Losartan (n=1578)	Captopril (n=1574)	Hazards ratio (CI)*	p
All-cause mortality (primary endpoint)				
Total mortality	280 (17·7%)	250 (15·9%)	1·13 (0·95–1·35)	0·16
Sudden death	130 (8·2%)	101 (6·4%)	1·30 (1·00–1·69)	
Progressive heart failure	46 (2·9%)	53 (3·4%)	0·88 (0·59–1·30)	
Myocardial infarction	31 (2·0%)	28 (1·8%)	1·11 (0·66–1·85)	
Stroke	18 (1·1%)	11 (0·7%)	1·65 (0·78–3·49)	
Other cardiovascular	5 (0·3%)	6 (0·4%)	0·84 (0·26–2·76)	
Non-cardiovascular	50 (3·2%)	51 (3·2%)	0·99 (0·67–1·47)	
Sudden death or resuscitated cardiac arrest	142 (9·0%)	115 (7·3%)	1·25 (0·98–1·60)	0·08

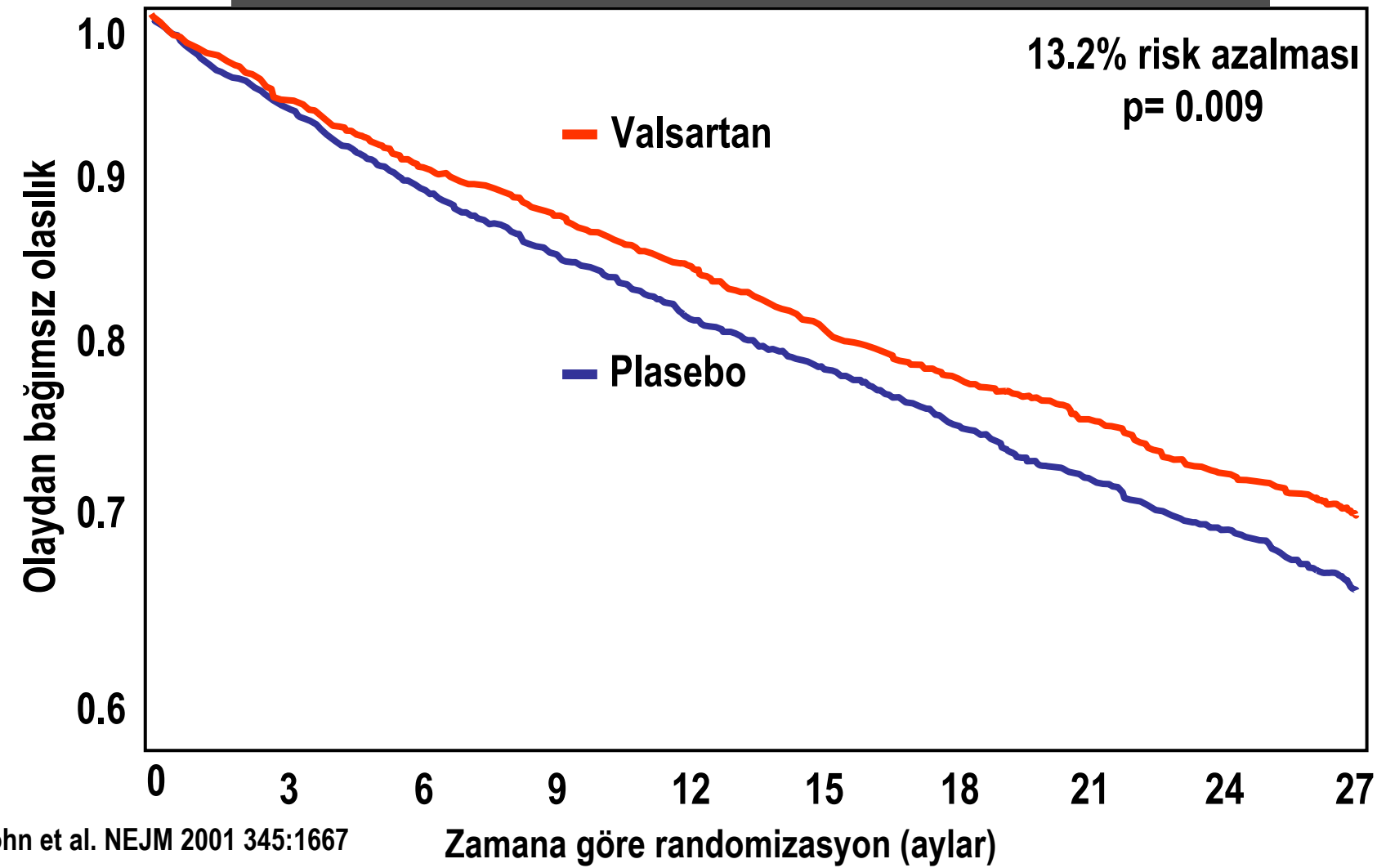
KY'de Valsartan + ACE-İ: Valsartan Kalp Yetersizliği Çalışması (Val-HeFT)



EJ = ejeksiyon fraksiyonu; LVIDd = sol ventrikül içi diyastolik çap.
Cohn JN et al. *Eur J Heart Fail*. 2000;2:439-446.

VAL-HeFT Çalışması:
Mortalite / Morbidite: Birleşik mortalite/ morbidite

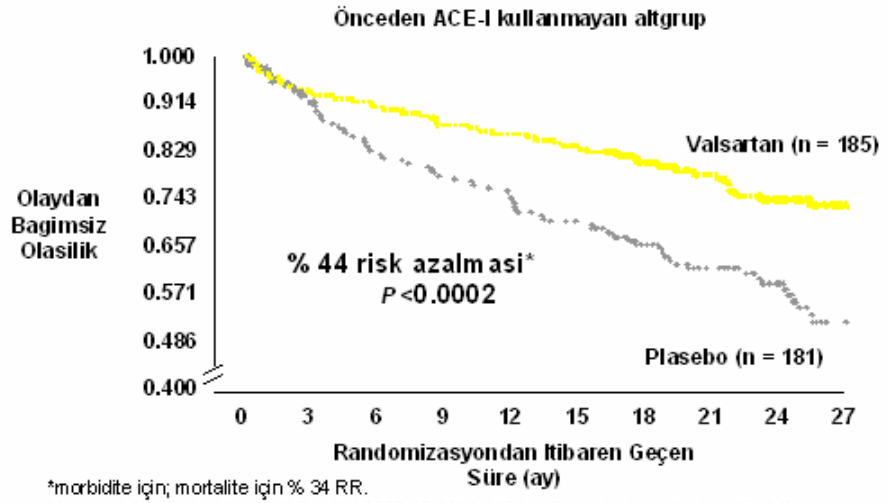
Valsartan dozu: 320 mg/g



Cohn et al. NEJM 2001 345:1667

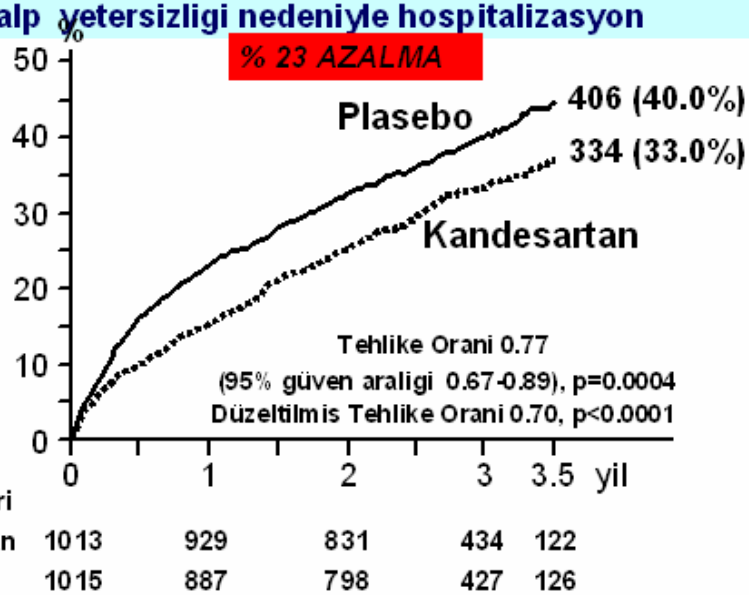
Konjestif Kalp Yetmezliğinde ARB

Val-HeFT
Kombine Morbidite Sonlanim Noktasi



*morbidite için; mortalite için % 34 RR.
Maggioni AP et al. *J Am Coll Cardiol.* 2002;40:1414-1421 çalismasindan adapte edilmistir.

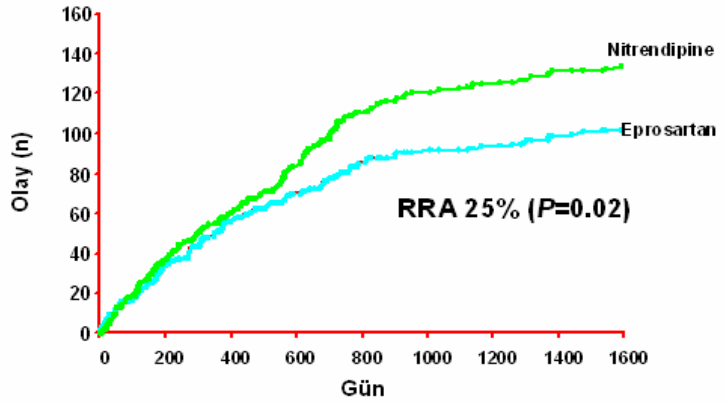
CHARM-Alternatif: Primer sonlanma noktasi
Kardiyovasküler ölüm veya kalp yetersizligi nedeniyle hospitalizasyon



Risk Sayilari					
Kandesartan	1013	929	831	434	122
Plasebo	1015	887	798	427	126

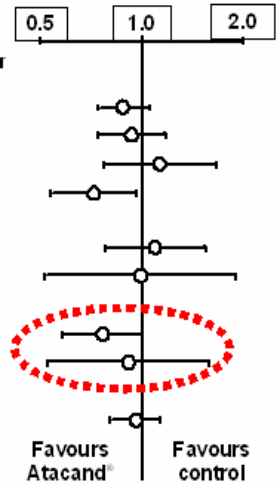
ARB Serebrovasküler Korunma

MOSES: Serebrovasküler olay Sikligi



SCOPE: Kardiyovasküler Olay - Inme

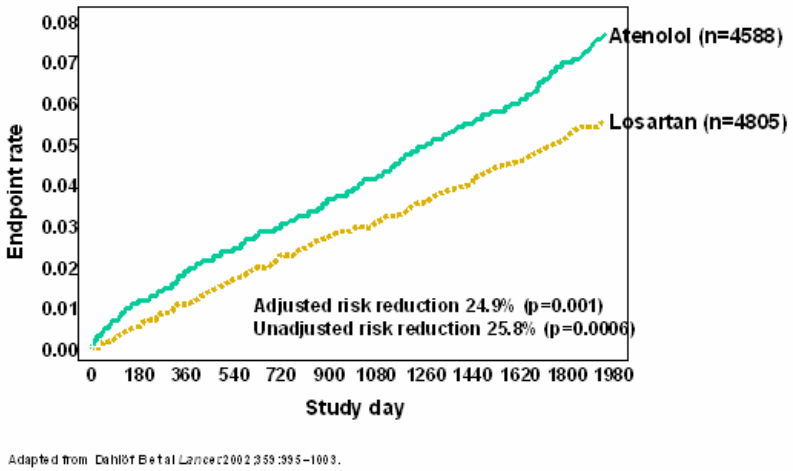
	Atacand® n	Atacand® n/1000 pts year	Control n	Control n/1000 pts year
Major CV events	242	26.7	268	30.0
CV deaths	145	15.6	152	16.6
Non-fatal MI	54	5.9	47	5.2
Non-fatal stroke	68	7.4	93	10.3*
All MI	70	7.6	63	6.9
Fatal MI	18	1.9	18	2.0
All stroke	89	9.7	115	12.8
Fatal stroke	24	2.6	26	2.8
Total mortality	259	27.9	266	29.0



* 28% risk reduction, $p = 0.04$

Lithell et al, J Hypertens in press

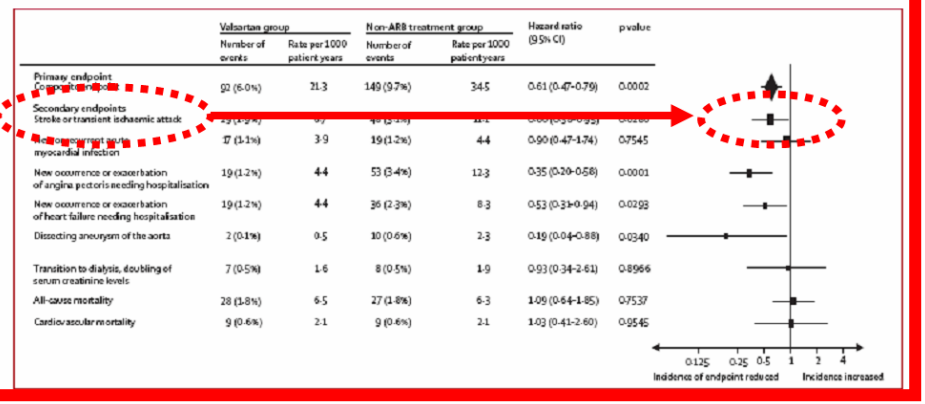
LIFE: Losartan Inme Sikligini Azaltir



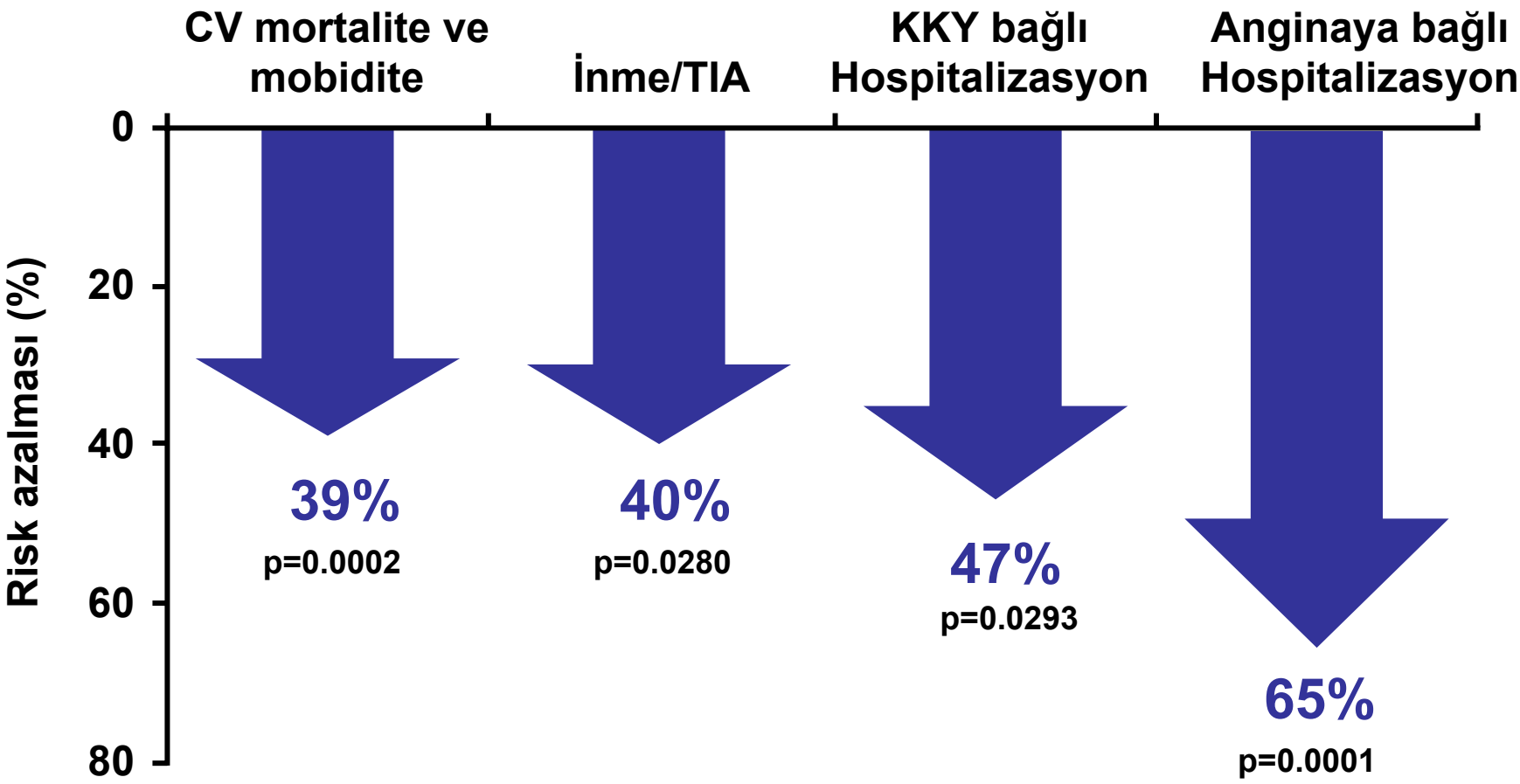
Adapted from Dahlöf B et al Lancet 2002; 359: 995–1003.

Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study

Lancet 2007; 369: 1431-39



JIKEI HEART Çalışması



With valsartan-based therapy compared with non-ARB therapy †Primary endpoint

TIA = transient ischemic attack

Mochizuki et al. Lancet 2007;369:1431–9

Uygun Tedavi Planımız

Aspirin 300 mg

Ramipril → **Valsartan 160 mg/g**

Diüretik → **Tiazid 25 mg/g**

Metoprolol 50 mg/g

Simvastatin 20 mg/g → **Statin değiştirilmesi veya + Ezetemib**

1 ay sonra kontrol

Şikayeti YOK

Kan Basıncı: 130/80mmHg **N: 55/dak/r**

Solunum Sistemi: Ral Yok

Batın: Doğal

Pretibiyal Ödem: Yok

Kreatinin 1.1 mg/dl **BUN 19 mg/dl**

AST: 24 U/L **ALT: 26U/L**

K+: 4.8 mEq/L **Ürik asit: 6.7 mg/dl**

LDL-K: 80 mg/dl **HDL-K: 46 mg/dl**

Ne yapalım ?

a. İlaçlara aynen devam ederim

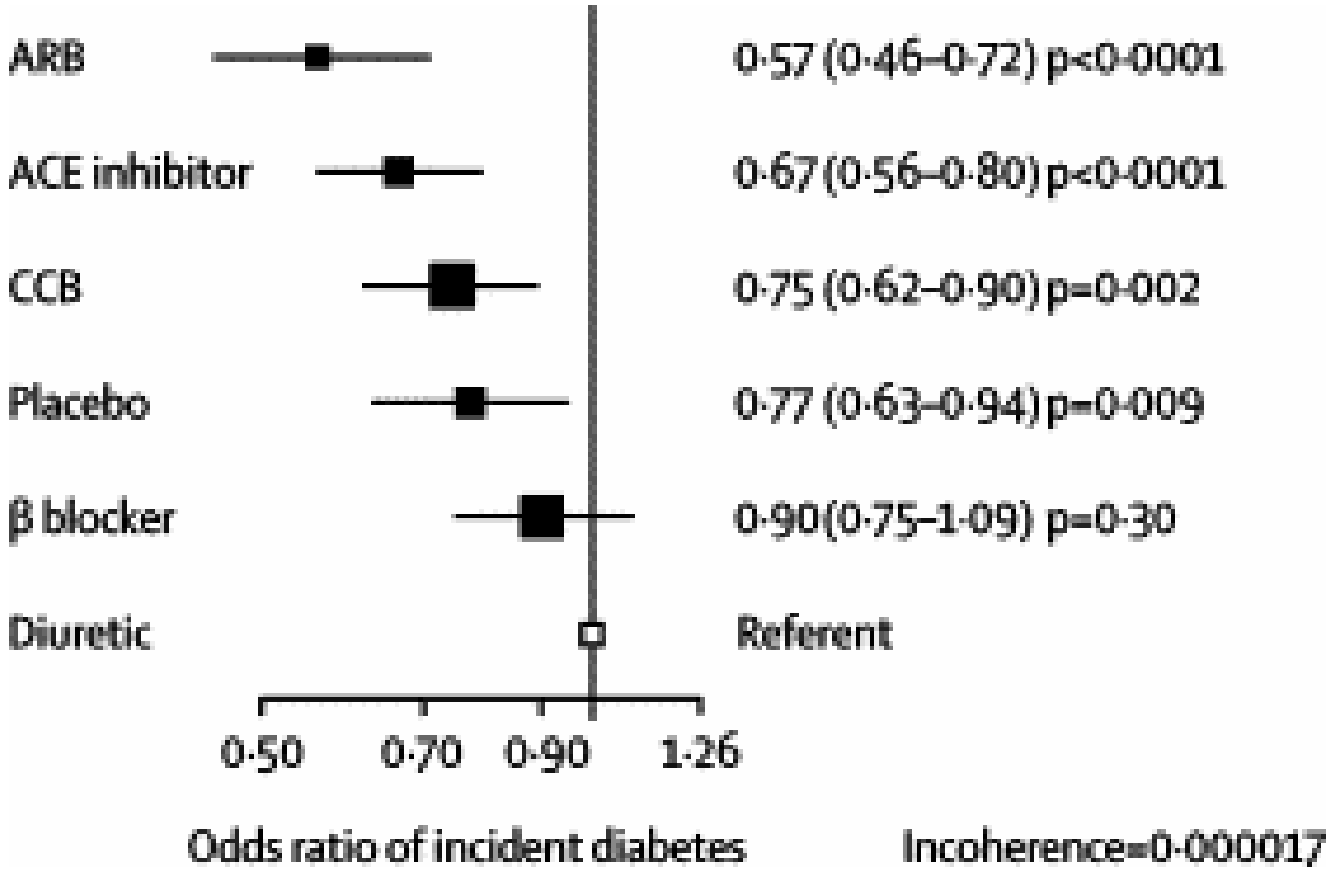
b. Kalsiyum Kanal Bloker (amlodipin) eklerim

c. Alfa bloker eklerim (doksazosin 2 mg/g)

d. Beta Bloker dozunu artırırım (100 mg/g)

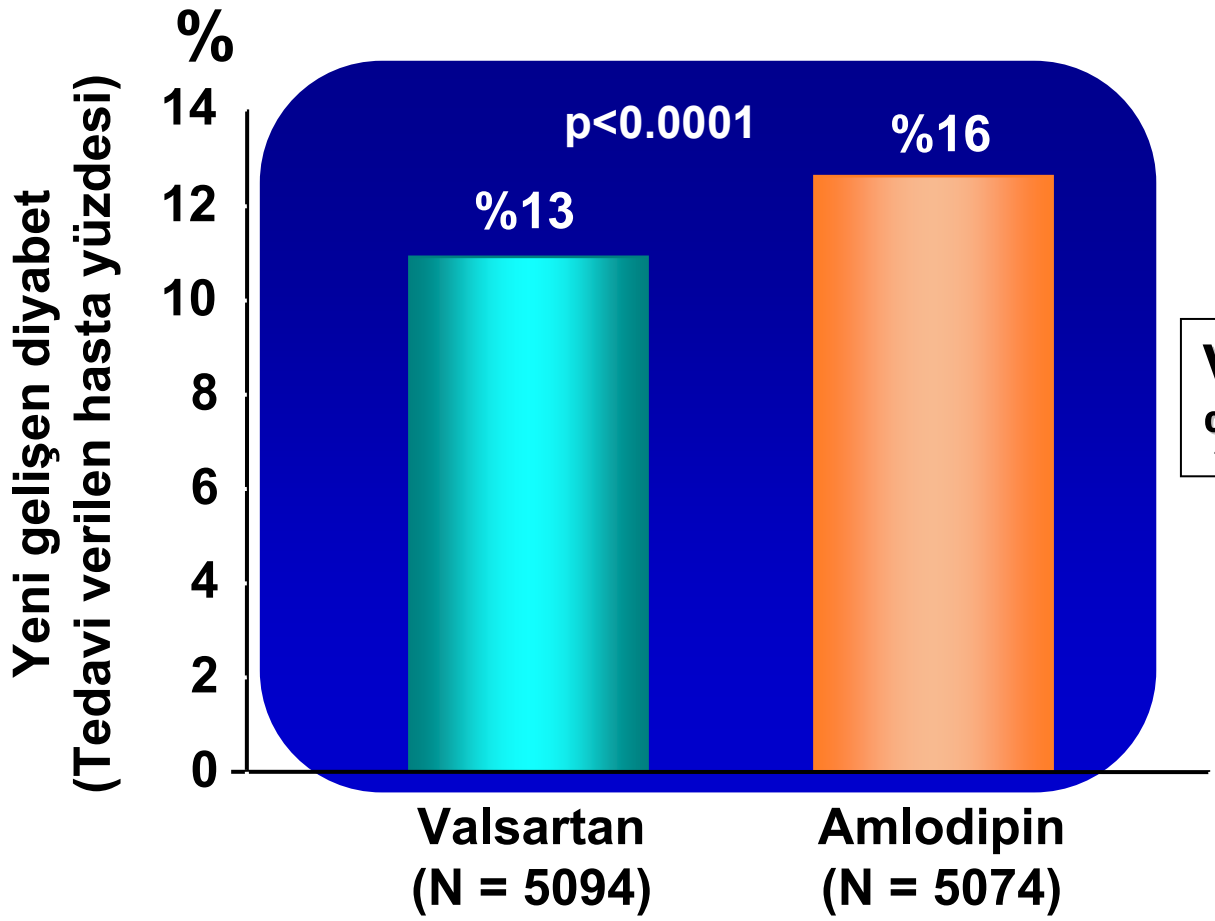
e. Valsartan dozunu artırırım (320/25 mg/g)

Antihipertansif Tedavinin DM gelişimine etkisi (Metaanaliz n=143,154 hasta)



Elliott WJ, *et al. Lancet* 2007; 369: 201-7.

VALUE:
Yeni Gelişen Diyabet



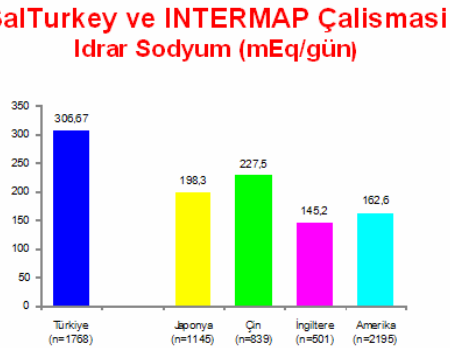
Valsartan ile %23 risk azalması

Julius S et al. *Lancet*. June 2004;363.

SONUÇ

- **Etkin ve Hızlı KB kontrolü için ve**
- **Kan basıncı düşürmenin ötesinde kardiyovasküler, renal ve serebral yarar için,**
  - ➔ **çalışmalarla KANITLANMIŞ olan ilaç,**
  - ➔ **çalışmalarla KANITLANMIŞ olan TAM doz (optimal) İlaç kullanılmalıdır.**

SONUÇ

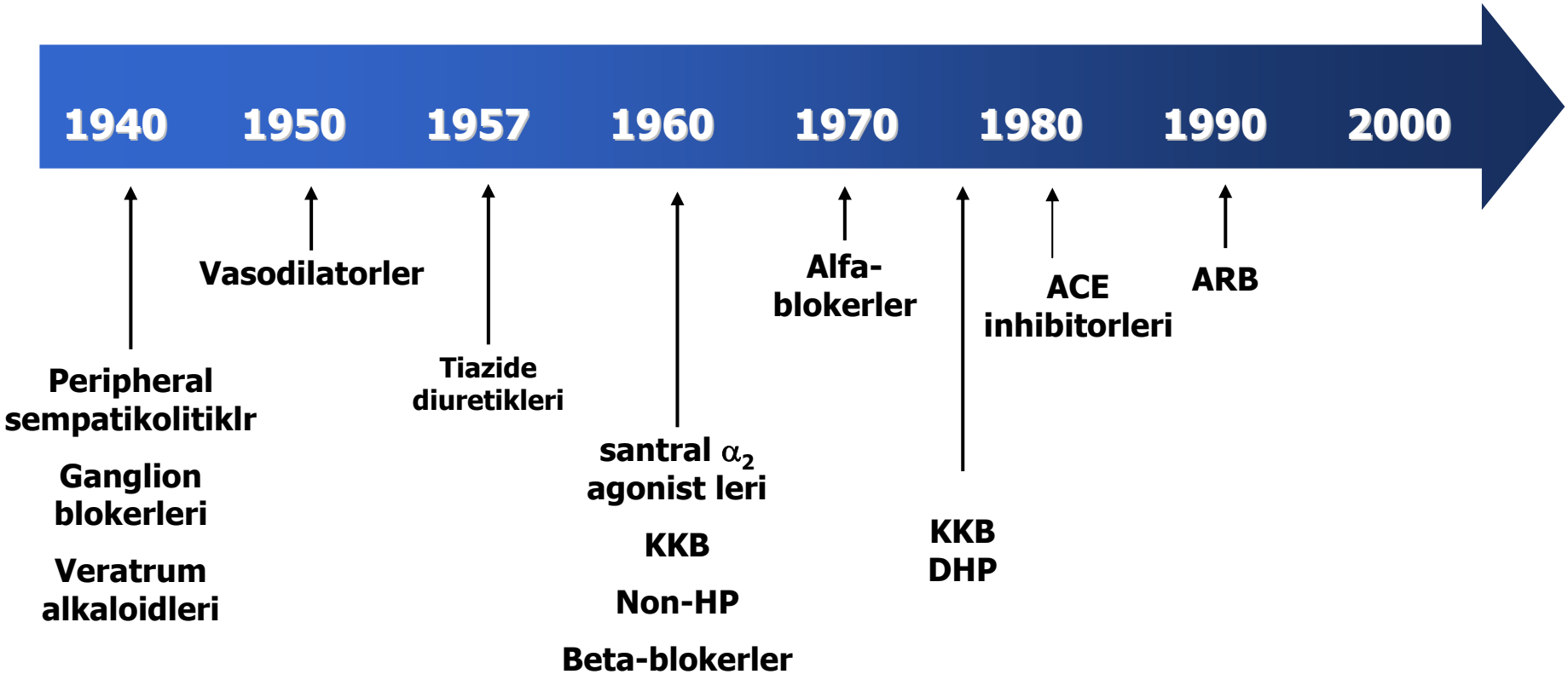


Türk Hipertansiyon ve Böbrek Hastal?klar?Dernek?i, 2008
Arch Intern Med. 2006;166:79-87

- **Yüksek tuz tüketimi olan toplumumuzda, ARB (Valsartan) ile 12.5/25mg HCTZ kombinasyonu, hızlı ve güçlü KB düşürücü etkinlik**

Beni Türk Hekimlerine Emanet Ediniz

Anti-Hipertansif Tedavi



1996 valsartan 80 mg FDA onayı aldı

1998 valsartan 80 mg Türkiye'de piyasada

2000 valsartan160mg ve
valsartan/HKTZ 80/12,5 mg

2002 valsartan/HKTZ 160/12,5 mg,

2004 valsartan/HKTZ 160/25 mg,

2008 valsartan 320 mg

Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: efficacy and safety compared with placebo and enalapril.

J Hypertens. 1996 Sep;14(9):1147-51.

- Holwerda NJ, Fogari R, Angeli P, Porcellati C, Hereng C, Oddou-Stock P, Heath R, Bodin F.
- St Elizabeth Hospital, Tilburg, The Netherlands.

- OBJECTIVE: To compare the antihypertensive efficacy and systemic tolerability of valsartan, a new angiotensin II receptor antagonist, with placebo and with an angiotensin converting enzyme (ACE) inhibitor, enalapril. DESIGN: A total of 348 adult outpatients with mild-to-moderate uncomplicated essential hypertension participated in this double-blind, parallel, study. Patients were allocated randomly in a ratio of 2:2:1 to receive 80 mg valsartan once a day, 20 mg enalapril once a day, or placebo for 8 weeks in general practice. Patients were assessed at 4 and 8 weeks of therapy. MAIN OUTCOME MEASURES: The primary efficacy variable was the change from baseline in mean sitting diastolic blood pressure (SDBP) after 8 weeks of therapy. Secondary variables included the change in sitting systolic blood pressure (SSBP) and response rates at 8 weeks. RESULTS: Valsartan and enalapril produced statistically significant reductions in diastolic and systolic blood pressures compared with placebo. Similar falls were found in both of the active treatment groups with mean changes in SDBP at 8 weeks of -9.5 mmHg for valsartan and -9.4 mmHg for enalapril (-4.5 mmHg for placebo). No significant differences between valsartan and enalapril were found for reductions in SDBP or SSBP. Response rates at 8 weeks were significantly greater for valsartan (54%) and enalapril (58%) than for placebo (20%), with no significant difference between the two active treatments. Both valsartan and enalapril demonstrated a consistent antihypertensive effect over time, with 90% of patients with a response at 4 weeks responding at 8 weeks. Both of the treatments were tolerated well. Although the incidence of coughing was generally low in the study, more cases were reported with enalapril (three) than with valsartan (one) or placebo (none).
- CONCLUSIONS: **The data show 80 mg valsartan once a day to be as effective as 20 mg enalapril once a day in the treatment of mild-to-moderate hypertension**. Valsartan is tolerated well and does not appear to be associated with any increase in the incidence of coughing.

The efficacy and safety of valsartan compared with placebo in the treatment of patients with essential hypertension.

Clin Ther. 1996 Sep-Oct;18(5):797-810.

- Oparil S, Dyke S, Harris F, Kief J, James D, Hester A, Fitzsimmons S.
- University of Alabama at Birmingham, Alabama, USA.

- A multicenter, randomized, placebo-controlled, double-masked, parallel-group study was performed to compare the efficacy and safety of valsartan 20, 80, 160, and 320 mg with placebo in the treatment of patients with essential hypertension. A total of 736 adults with uncomplicated essential hypertension stages 1 to 3 were randomized to receive placebo or valsartan 20, 80, 160, or 320 mg daily for 8 weeks. Assessments were made at baseline, after 4 and 8 weeks of treatment, and 2 to 3 days after stopping treatment. The primary efficacy variable was change from baseline in mean sitting diastolic blood pressure (MSDBP). Other variables included change from baseline in mean sitting systolic blood pressure (MSSBP) and responder rates (ie, MSDBP < 90 mm Hg or decrease of > or = 10 mm Hg from baseline). All doses of valsartan produced statistically significant reductions in both MSDBP and MSSBP at end point compared with placebo. A dose-response effect was seen, although the incremental reduction in blood pressure with doses of valsartan > 80 mg was relatively small. Statistically significant differences in responder rates at end point were seen for doses of valsartan of 80 mg and above compared with placebo, whereas the responder rates for valsartan 20 mg was not significantly different from that for placebo. Safety and tolerability variables included data on adverse experiences, rebound hypertension, and clinical laboratory evaluations. Tolerability was good, with headache being the most common complaint and occurring most frequently in placebo patients. The incidence of dizziness was similar among the placebo (5.4%) and valsartan 20-mg to 160-mg groups (2.1% to 3.4%); there was an increase in the incidence of dizziness in the 320-mg group (9.3%). No cases of symptomatic orthostatic hypotension occurred. Analysis of rebound showed that 11.6% of patients receiving placebo and 16.6% receiving valsartan had an increase in MSDBP to baseline levels or above 2 to 3 days after stopping treatment. No clinically significant adverse experiences were noted after stopping treatment. There were no clinically or statistically significant changes in laboratory values during treatment.
- **Thus valsartan proved to be both effective and safe in reducing blood pressure in adults with essential hypertension. The optimal dose range is 80 to 160 mg, given once daily.**

Valsartan and hydrochlorothiazide in patients with essential hypertension. A multiple dose, double-blind, placebo controlled trial comparing combination therapy with monotherapy.

J Hum Hypertens. 1998 Dec;12(12):861-6.

- Benz JR, Black HR, Graff A, Reed A, Fitzsimmons S, Shi Y.
- Clinical Research, Cedar Rapids, IA 52401, USA.

- OBJECTIVE: This study compares the antihypertensive efficacy and tolerability of valsartan, a novel angiotensin II antagonist, given with hydrochlorothiazide (HCTZ) vs placebo or vs valsartan or HCTZ alone. DESIGN: 871 adult out-patients with essential hypertension participated in this double-blind study. Patients were randomised in equal number to receive either combination therapy of valsartan (80 mg or 160 mg) and HCTZ (12.5 mg or 25 mg), or valsartan (80 mg or 160 mg) or HCTZ (12.5 mg or 25 mg) alone, or placebo. Patients were treated once daily for 8 weeks and assessed at 2, 4 and 8 weeks after randomisation. MAIN OUTCOME MEASURES: The primary efficacy variable was change from baseline in mean sitting diastolic blood pressure (MSDBP) at end-point. The secondary variable was change in mean sitting systolic blood pressure (MSSBP) from baseline to end-point. RESULTS: All active treatments produced a statistically significant difference in MSDBP ($P < 0.001$) from baseline to end-point compared with placebo. Similar results were obtained for MSSBP. All combination regimens produced a statistically significantly greater reduction in MSDPB and MSSBP than the corresponding monotherapies. Dizziness and headache were the most common treatment-related adverse experiences reported. Hypokalaemia, associated with the use of thiazide diuretics, was more commonly reported in the higher dose HCTZ 25 mg groups. CONCLUSIONS: **Valsartan 80 mg and 160 mg act additively with HCTZ 12.5 mg or 25 mg to lower MSDBP and MSSBP in patients with essential hypertension**. The addition of HCTZ to valsartan 80 mg or 160 mg was well tolerated.

Effects of the angiotensin II antagonist valsartan on blood pressure, proteinuria, and renal hemodynamics in patients with chronic renal failure and hypertension.

J Am Soc Nephrol. 1998 Dec;9(12):2223-34

- Plum J, Bünten B, Németh R, Grabensee B.
- Department of Nephrology and Rheumatology, Medizinische Einrichtungen der Heinrich Heine Universität, Düsseldorf, Germany.

- Angiotensin II receptor antagonists have become clinically available for the treatment of arterial hypertension. Presently, there is little information about their effects on BP, proteinuria, and renal function in patients with moderate or advanced renal failure. This study examines the effects of the angiotensin II antagonist **Valsartan (80 mg/d**) on proteinuria and glomerular permselectivity in patients with chronic renal failure during a 6-mo treatment, using a double-blind, randomized, placebo-controlled study (treatment group [V-group]: n = 5, age 57 +/- 7 yr, serum creatinine 365 +/- 122 micromol/L; placebo group [P-group]: n = 4, age 62 +/- 11 yr, serum creatinine 346 +/- 61 micromol/L). Study parameters included BP, 24-h proteinuria, GFR, and effective renal plasma flow (ERPF) as determined by inulin and para-aminohippurate clearance. Changes in glomerular permselectivity were assessed by measuring the fractional clearances of neutral dextrans by HPLC gel-permeation chromatography. Valsartan lowered the mean arterial pressure on average by 13 +/- 7 mmHg during the 6-mo treatment ($P < 0.05$). GFR and ERPF remained almost unchanged. However, after 6 mo of Valsartan treatment, proteinuria was reduced by 396 +/- 323 mg/24 h (26 +/- 18%) and albuminuria by 531 +/- 499 mg/24 h (41 +/- 21%) with regard to baseline values ($P < 0.05$). In the P-group, both proteinuria and albuminuria increased slightly with time (by 30 +/- 43% and 30 +/- 54%, respectively, NS). The fractional clearances of high molecular weight dextrans >66 A were significantly reduced after 6 mo of Valsartan treatment ($P < 0.05$), indicating a reduction of the glomerular shunt volume by 54 +/- 20% ($P < 0.05$) according to the model of Deen et al. (Am J Physiol 249: 347-389, 1985). The mean pore size radius of the glomerular membrane remained unchanged. This effect was independent of glomerular hemodynamic changes. **Valsartan persistently lowered proteinuria in patients with chronic renal failure..**

Dose-response efficacy of valsartan, a new angiotensin II receptor blocker.

J Hum Hypertens. 1999 Apr;13(4):275-81.

- Pool JL, Glazer R, Chiang YT, Gatlin M.
- Baylor College of Medicine, Houston, TX, USA.

- OBJECTIVE: To study the efficacy and tolerability of a range of valsartan doses in patients with mild-to-moderate hypertension. DESIGN: 122 adult out-patients were randomised in equal numbers to receive **valsartan 10 mg, 40 mg, 80 mg, 160 mg or placebo** once daily (OD) for 4 weeks in this multicentre, double-blind, fixed-dose, parallel trial. Patients were assessed at 0, 2 and 4 weeks. MAIN OUTCOME MEASURES: The primary efficacy variable was change from baseline in trough mean supine diastolic blood pressure (MSuDBP). Other variables included change from baseline in trough mean supine systolic blood pressure (MSuSBP), responder rates and trough/peak ratio. RESULTS: All treatments significantly reduced MSuDBP and MSuSBP at 4-week end-point compared to baseline ($P < 0.001$). The magnitude of blood pressure lowering was greater with increasing doses of valsartan (least square mean change from baseline for placebo, valsartan 10 mg, 40 mg, 80 mg, 160 mg respectively: MSuDBP -4.4 mm Hg, -4.9 mm Hg, -6.5 mm Hg, -8.2 mm Hg, -9.1 mm Hg; MSuSBP -1.3 mm Hg, -3.6 mm Hg, -7.0 mm Hg, -11.1 mm Hg, -11.9 mm Hg). A fitted quadratic curve, to predict relationship between dose and change from baseline in trough MSuDBP, indicated a positive dose response. Responder rates were 16%, 24%, 33%, 46%, 54% for placebo, valsartan 10 mg, 40 mg, 80 mg, 160 mg respectively, which also indicated a positive dose response in the dose range of 10 mg to 160 mg. Greater than 50% of the antihypertensive effect measured at peak persisted at trough for each of the four active treatment groups, confirming efficacy over a 24-h period. No dose-related adverse experiences were observed, with overall incidence (regardless of relationship to trial medication) of 44% with placebo and 44%, 36%, 22%, 21% for valsartan 10 mg, 40 mg, 80 mg, 160 mg respectively. The most common adverse experience reported was headache which occurred most frequently with placebo (12%). No trial drug-related cough was observed. Treatment with valsartan did not produce clinically significant orthostatic changes in diastolic or systolic blood pressure. One case of symptomatic orthostatic hypotension was observed on placebo.
- **CONCLUSIONS: The results of this trial show valsartan to effectively lower blood pressure in patients with mild-to-moderate hypertension, and demonstrate that the reduction in blood pressure increases with increasing dose levels.**

Angiotensin II antagonism and the heart: valsartan in left ventricular hypertrophy.

Cardiology. 1999;91 Suppl 1:3-7

- Thürmann PA.
- Institute of Clinical Pharmacology, University Witten/Herdecke, Wuppertal, Germany. thuermann@klinikum-wuppertal.de

- Left ventricular hypertrophy (LVH) represents an independent risk factor for cardiovascular morbidity and mortality, and normalization of left ventricular mass has become a desirable goal of antihypertensive treatment. In a randomized, double-blind study the angiotensin II (AT(1) receptor) antagonist valsartan (**Diovan((R)); 80 mg/160 mg q.d.**) was compared with the beta-blocker atenolol (50 mg/100 mg q.d.) over 8 months in predominantly previously untreated patients with essential hypertension and LVH. Sixty-nine patients were randomized, of whom 58 were evaluated with echocardiographic data. After 8 months of treatment in the atenolol group [n = 8 with additional hydrochlorothiazide (HCTZ)], initial blood pressure was reduced from 160/103 to 147/92 mm Hg ($p < 0.0001$), and in the valsartan group (n = 9 with additional HCTZ) blood pressure decreased from 163/101 to 146/90 mm Hg ($p < 0.0001$). Left ventricular mass index decreased from 127 to 117 g/m(2) in the atenolol group and from 127 to 106 g/m(2) in the valsartan group.
- **Long-term treatment with valsartan resulted in a significant reduction of LVH in patients with essential hypertension**.

Rationale and design of the Valsartan Heart Failure Trial: a large multinational trial to assess the effects of valsartan, an angiotensin-receptor blocker, on morbidity and mortality in chronic congestive heart failure.

J Card Fail. 1999 Jun;5(2):155-60.

- Cohn JN, Tognoni G, Glazer RD, Spormann D, Hester A.
- Department of Medicine, University of Minnesota Medical School, Minneapolis 55455, USA.

- BACKGROUND: To investigate the role of persistent angiotensin activity despite angiotensin-converting enzyme inhibitor therapy in the progression of heart failure, the Valsartan Heart Failure Trial has been designed to investigate the effect of the angiotensin-receptor blocker, valsartan, on morbidity and mortality. METHODS AND RESULTS: Nearly 5,000 patients with New York Heart Association classes II to IV heart failure, while receiving all standard therapy, are being randomized to treatment with **valsartan, 160 mg twice daily**, or placebo in a worldwide study. Follow-up will be continued until 906 deaths have been recorded. Additional end points will include the need for hospitalization, other major morbid events, quality--of life measurement, changes in neurohormone levels, and changes in left ventricular size and function. Substudies will explore exercise tolerance, arrhythmias, and magnetic resonance imaging.
- CONCLUSION: **This study should help establish the role of angiotensin-receptor blockade in the treatment of heart failure.**

Valsartan in acute myocardial infarction trial (VALIANT): rationale and design.

Am Heart J. 2000 Nov;140(5):727-50.

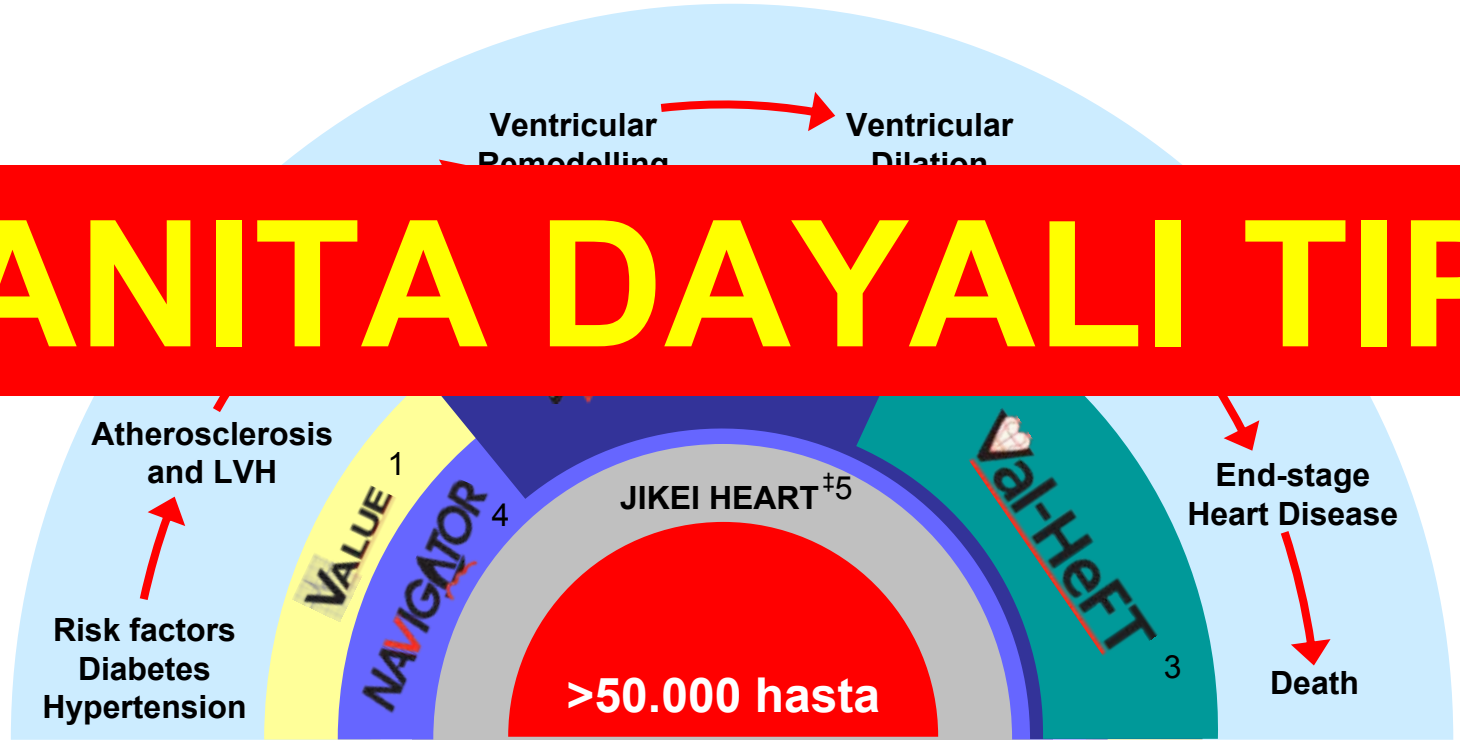
- Pfeffer MA, McMurray J, Leizorovicz A, Maggioni AP, Rouleau JL, Van De Werf F, Henis M, Neuhart E, Gallo P, Edwards S, Sellers MA, Velazquez E, Califf R.
- Cardiovascular Division, Brigham and Women's Hospital, Boston, MA 02115, USA. mpfeffer@rics.bwh.harvard.edu

- BACKGROUND: Survivors of acute myocardial infarction (MI) complicated by heart failure and/or resulting in left ventricular dysfunction are at heightened risk for subsequent death and major nonfatal cardiovascular events. Inhibition of the renin-angiotensin system with an angiotensin-converting enzyme inhibitor has consistently been demonstrated to result in reductions in these risks by approximately 20%. The development of angiotensin II receptor blockers offers a new, more specific, and theoretically more complete pharmacologic mode to inhibit the adverse influence of angiotensin II. METHODS: Valsartan in Acute Myocardial Infarction (VALIANT) is a multicenter, double-blind, randomized, active controlled parallel group study comparing the efficacy and safety of long-term treatment with valsartan, captopril, and their combination in high-risk patients after MI. The trial is designed with 3 arms, giving equal statistical consideration to survival comparisons of captopril versus the angiotensin II receptor blocker valsartan, as well as the combination of captopril plus valsartan, compared with a proven effective dose of captopril. This 14,500-patient trial is designed with an 86% power to detect a 15% reduction in mortality rate with either use of valsartan compared with captopril. The trial encourages optimal individualization of other proven therapies in acute and chronic infarction, and the international patient body ensures good representation of multiple practice patterns.
- CONCLUSION: **VALIANT is a large international investigative effort that will evaluate the role of valsartan in the management of patients with MI associated with heart failure and/or left ventricular dysfunction.** The use of a proven dose of captopril and the comparator arms with valsartan alone or in combination with captopril provides a unique test of whether the angiotensin II receptor blocker can make an additional improvement in clinical outcomes beyond angiotensin-converting enzyme inhibitors.

Nefrologlara Teşekkürler


ТУАЛЕТ
ЖЕНСКИЙ
ВХОД

Kardiyovasküler Süreçte Valsartan



*Not all patients in these studies received valsartan
‡Independent, investigator-initiated study

1. Julius et al. Lancet 2004; 363:2022–31; 2. Pfeffer et al. N Engl J Med 2003;349:1893–906; 3. Cohn et al. N Engl J Med 2001; 345:1667–75
4. Califf et al. Am Heart J 2008;156:623–32; 5. Mochizuki et al. Lancet 2007;369:1431–9; 6. Viberti et al. Circulation 2002;106:672–8
7. Karalliedde et al. Hypertension 2008;51:1617–23; 8. SMART Group. Diabetes Care 2007;30:1581–3; 9. Hollenberg et al. J Hypertens 2007;25:1921–6

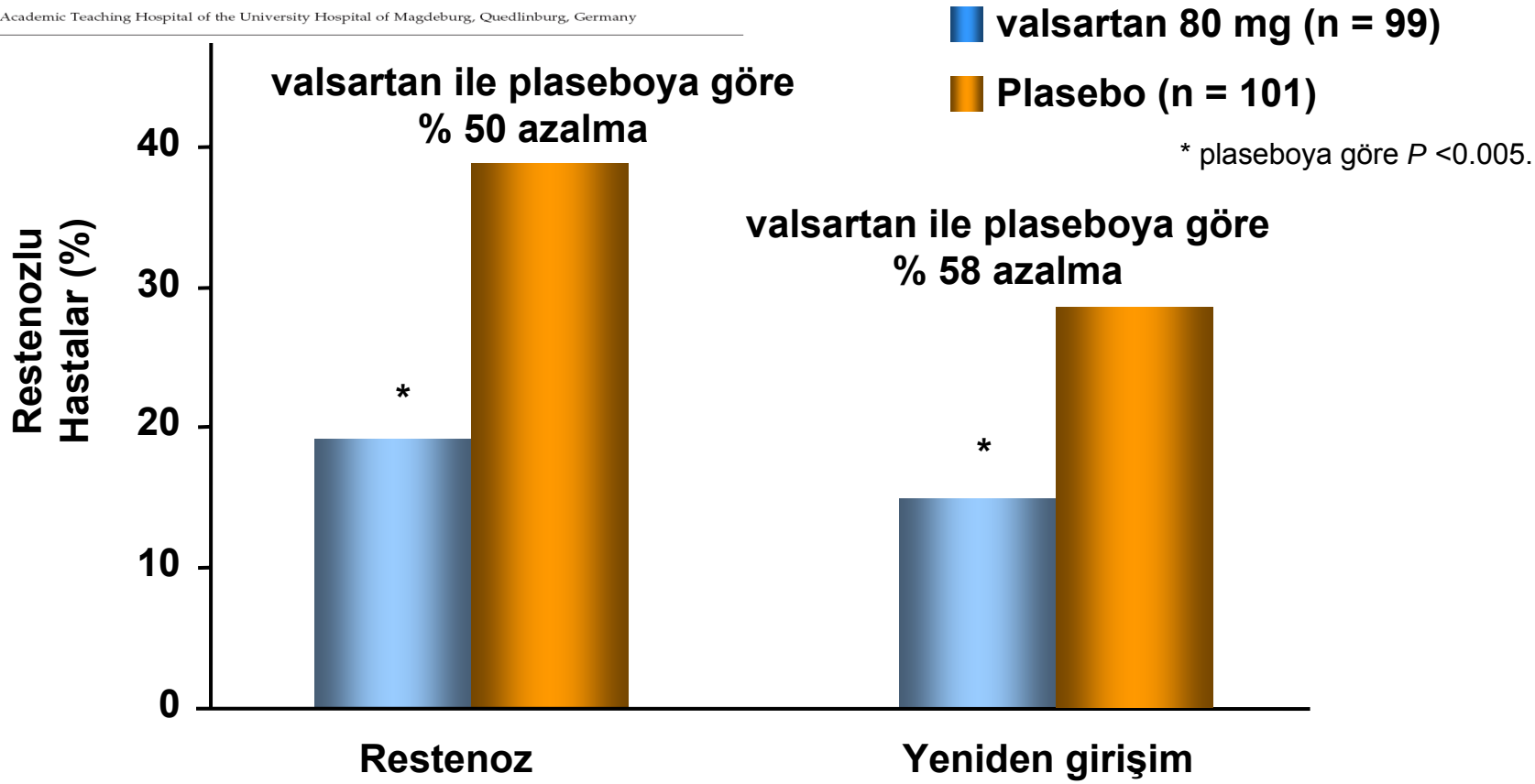
ORIGINAL RESEARCH ARTICLE

Am J Cardiovasc Drugs 2008; 8 (2): 83-87
1175-3277/08/0002-0083/$48.00/0

Comparison of Efficacy of Low- (80 mg/day) and High- (160–320 mg/day) Dose Valsartan in the Prevention of In-Stent Restenosis after Implantation of Bare-Metal Stents in Type B2/C Coronary Artery Lesions

Stefan Peters

Klinikum Quedlinburg, Academic Teaching Hospital of the University Hospital of Magdeburg, Quedlinburg, Germany



Val-PREST: 6 aylık stent içi restenoz ve yeniden girişim oranlarını

Peters S et al *J Invasive Cardiol.* 2001;13:93-97

Am J Cardiovasc Drugs 2008; 8 (2): 83-87
1175-3277/08/0002-0083/$48.00/0

Comparison of Efficacy of Low- (80 mg/day) and High- (160–320 mg/day) Dose Valsartan in the Prevention of In-Stent Restenosis after Implantation of Bare-Metal Stents in Type B2/C Coronary Artery Lesions

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Table II. In-stent restenosis rate, mean late lumen loss, target lesion revascularization (TLR) and target vessel revascularization (TVR) rates, and major adverse cardiac event (MACE) rate in high- and low-dose[2] valsartan groups

Clinical endpoints	Low-dose valsartan (80 mg/day)[2]	High-dose valsartan (160–320 mg/day)	p-Value
In-stent restenosis [no. (%)]	78 (19.5)	27 (7.3)	<0.0001
TLR and TVR [no. (%)]	36 (9)	16 (4.3)	<0.01
MACE [no. (%)]	7 (1.5)	0	<0.01
Mean late lumen loss [mm (mean ± SD)]	0.53 ± 0.31	0.37 ± 0.3	<0.01