

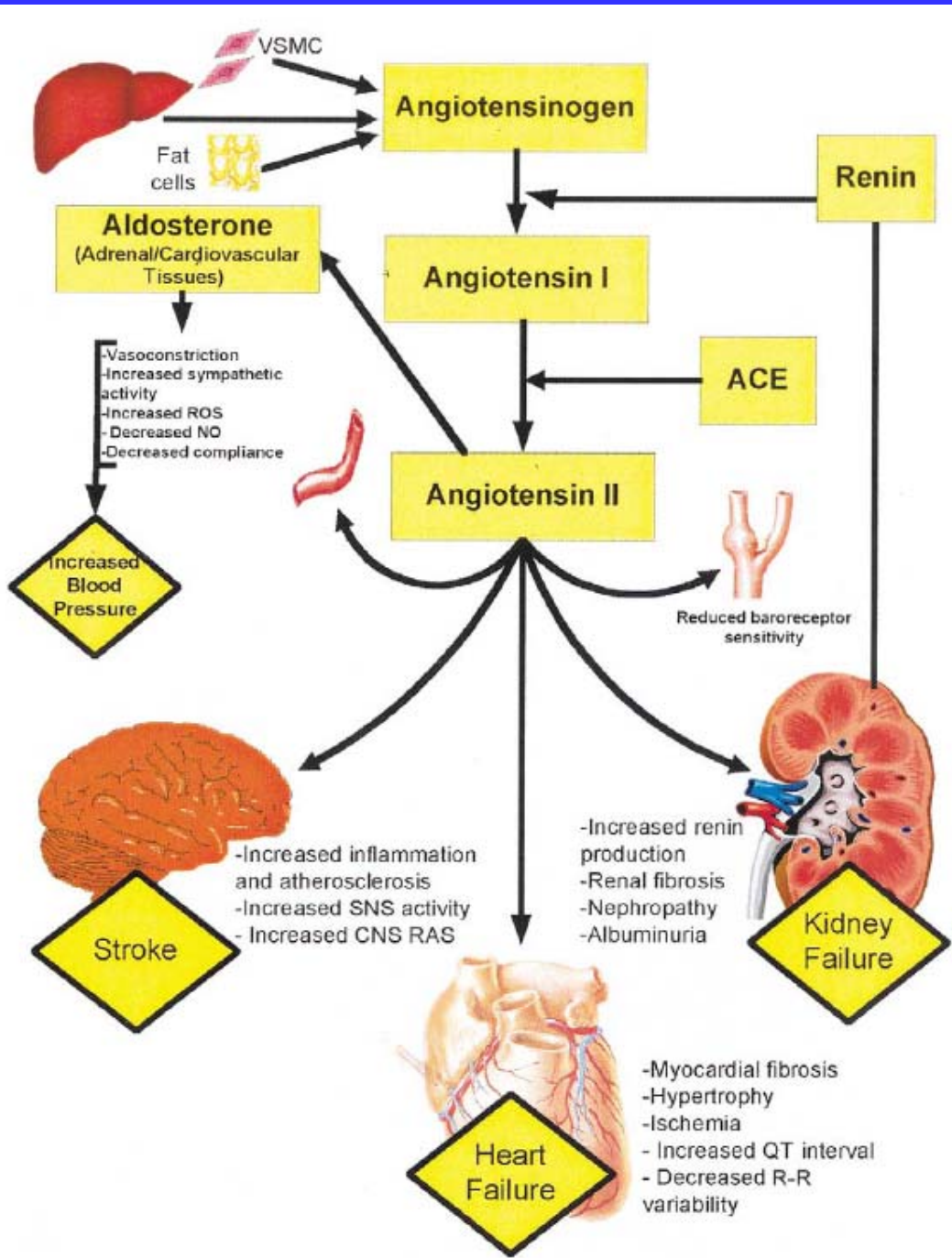
RAS Blokajını
ACEI ile mi ARB ile mi
Yapalım?

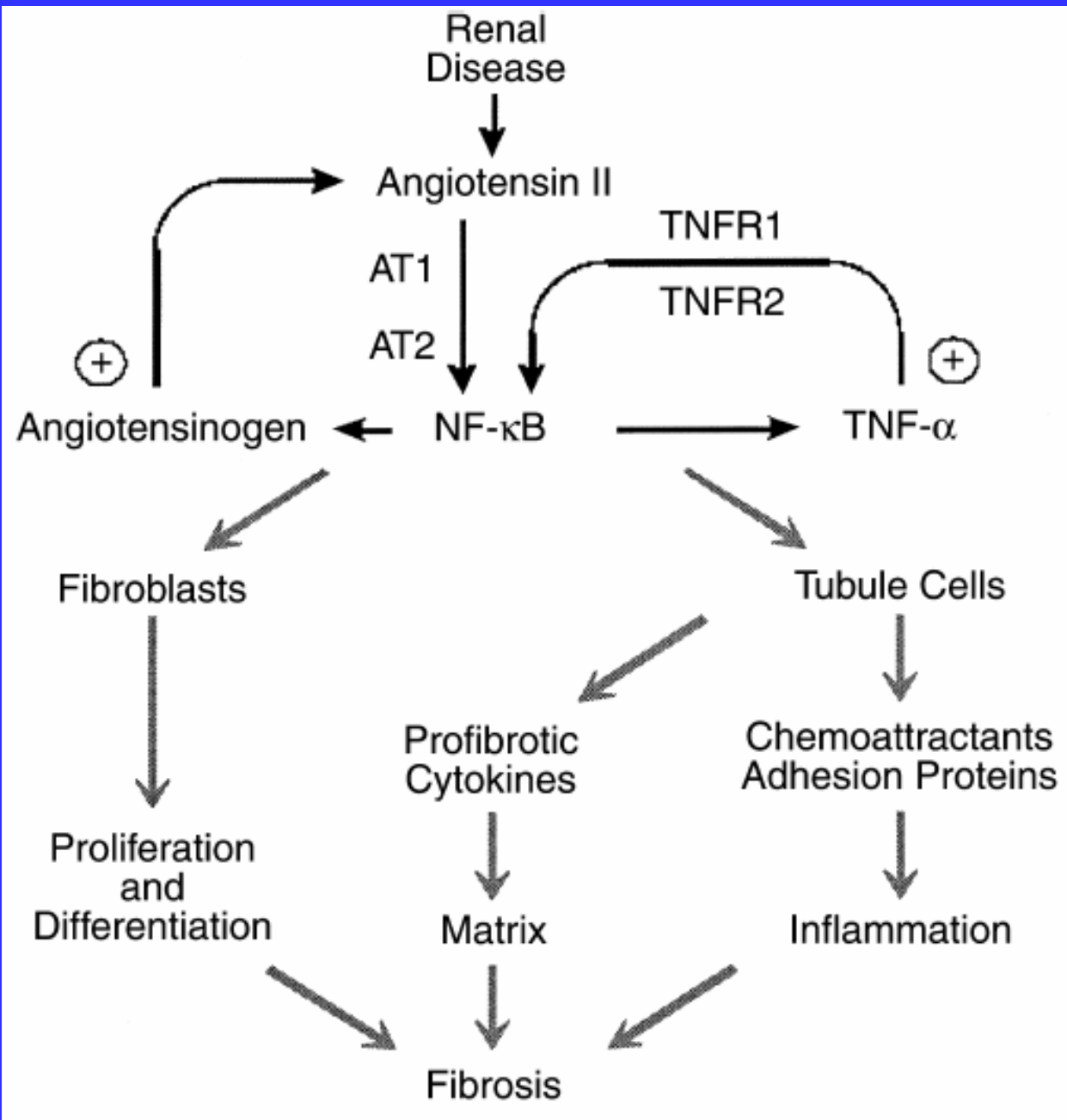
Dr.Mehmet KOÇ

Marmara Üniversitesi Tıp Fakültesi

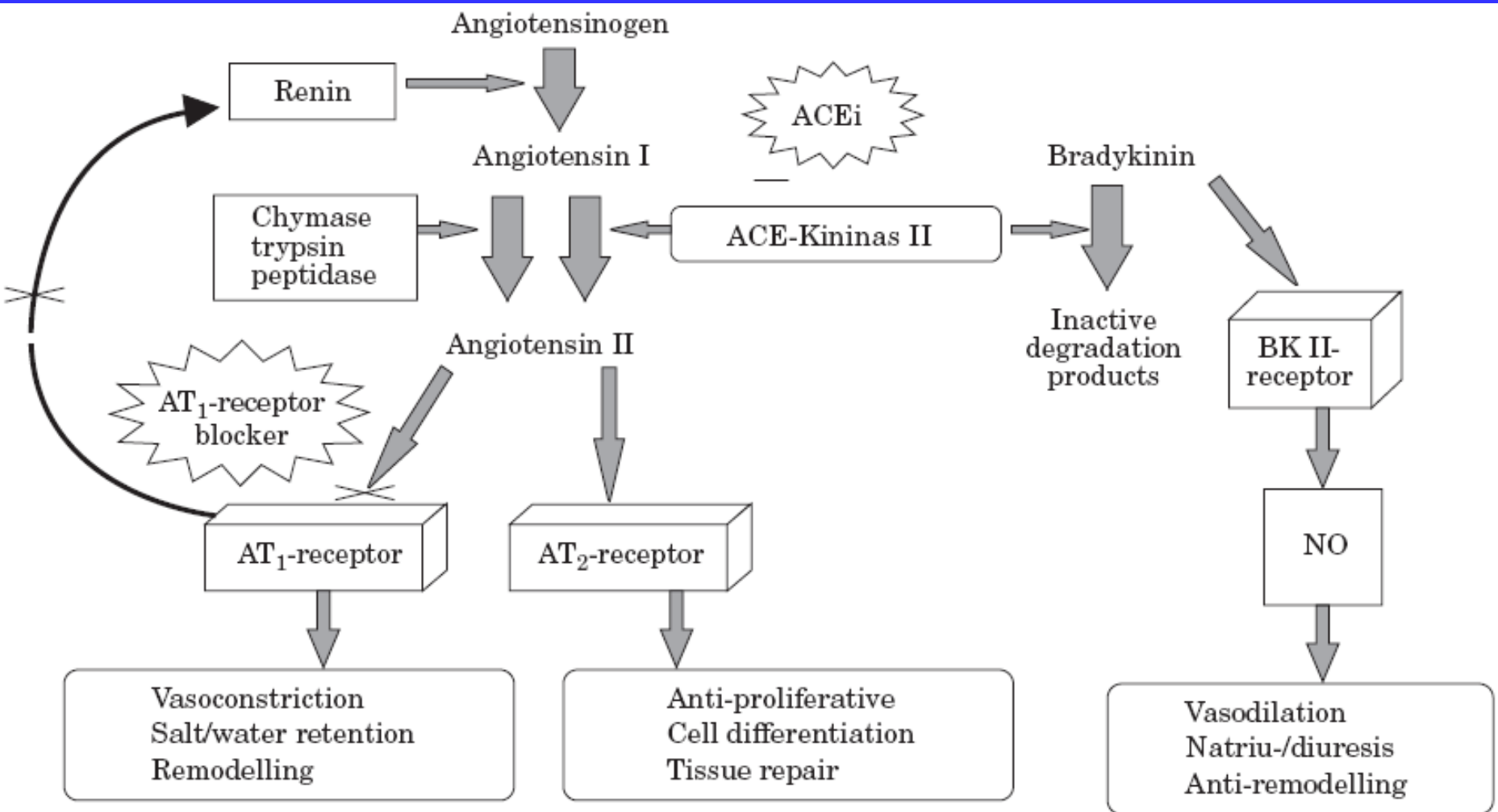
Nefroloji Bilim Dalı

Angiotensin-II'nin Hastalıkların Patogenezindeki Yeri

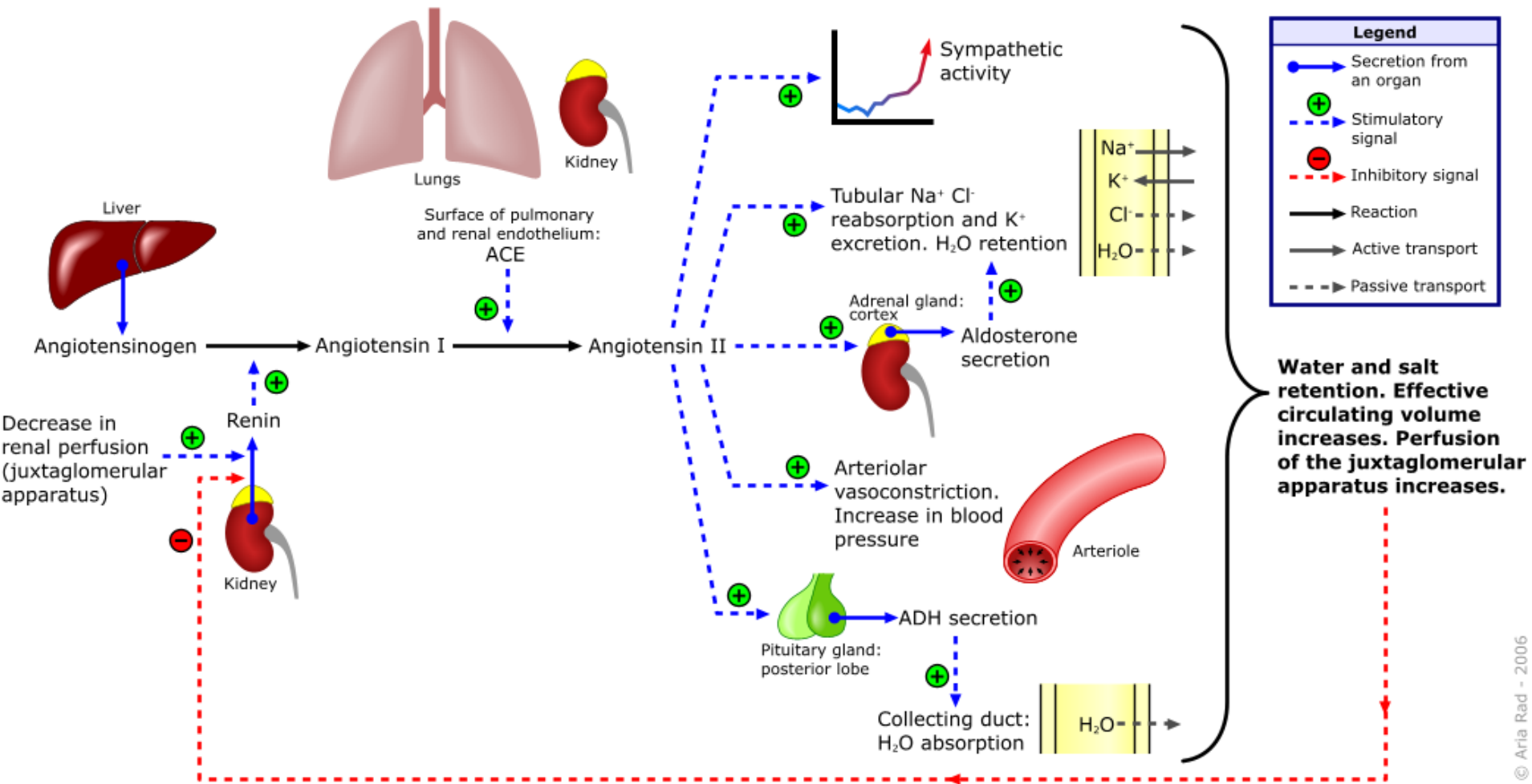




Renin Anjiotensin Sistemi



Renin-angiotensin-aldosterone system

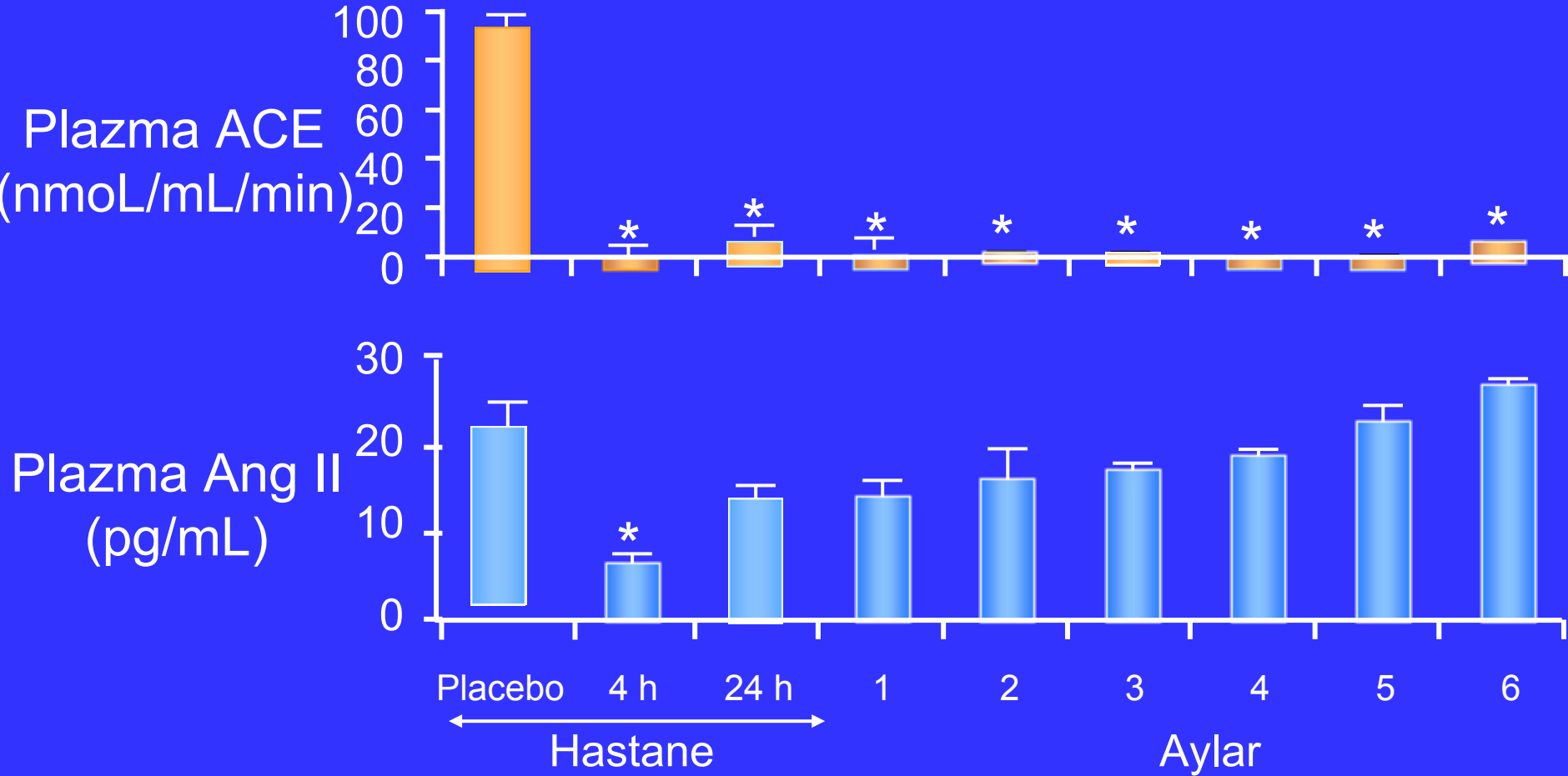


Anjiyotensin Dönüştürücü Enzim (ACE)

- Vücutta, ACE büyük oranda iki şekilde bulunur:
- **Plazma**
- **Dokular**

- İkinci şekil ilkinden daha hızlı bir dönüştürme süreci gerçekleştirir.

ACE İnhibisyonu Altında Angiotensin II Kaçış Fenomeni



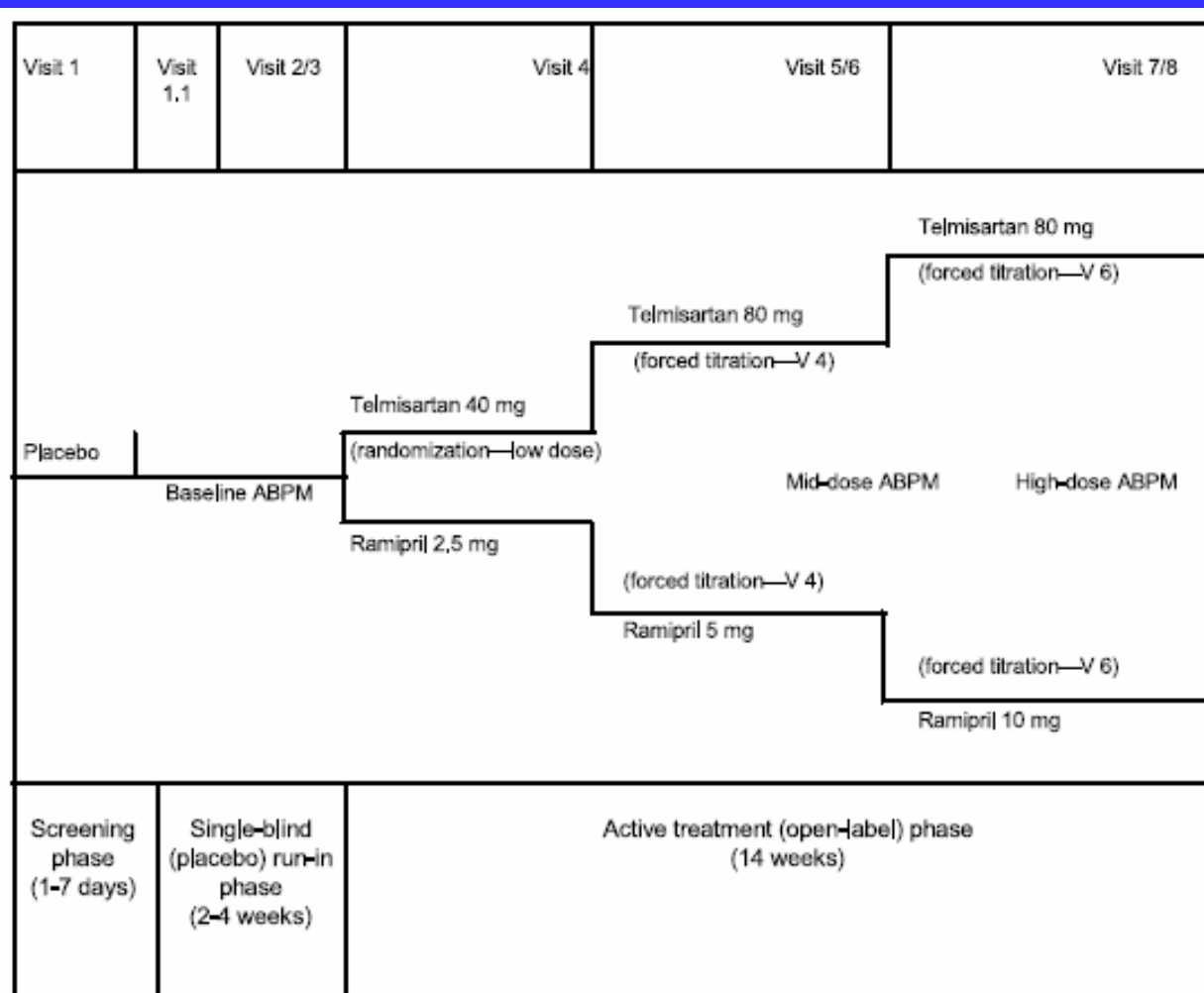
* $P < .001$ vs plasebo

Ang- II'nin Üretilmesinde Alternatif Yollar

- **Renin dışı anjiyotensinojenazlar** anjiyotensinojen üzerinde etki ederek anjiyotensin I ya da anjiyotensin II üretirler.
- Doku plazminojen aktivatörü (t-PA)
- Katepsin G
- Tonin
- Elastaz
- **ACE dışı “dönüştürücü” enzimler** anjiyotensin II üretmek üzere anjiyotensin I üzerinde etki ederler.
- Katepsin G
- Tonin
- Doku plazminojen aktivatörü (t-PA)
- Kimostatin-duyarlı anjiyotensin II oluşturuucu enzim (CAGE)
- Kimaz

Antihipertansif Etki Karşılaştırmaları

A Multicenter, 14-Week Study of Telmisartan and Ramipril in Patients With Mild-to-Moderate Hypertension Using Ambulatory Blood Pressure Monitoring

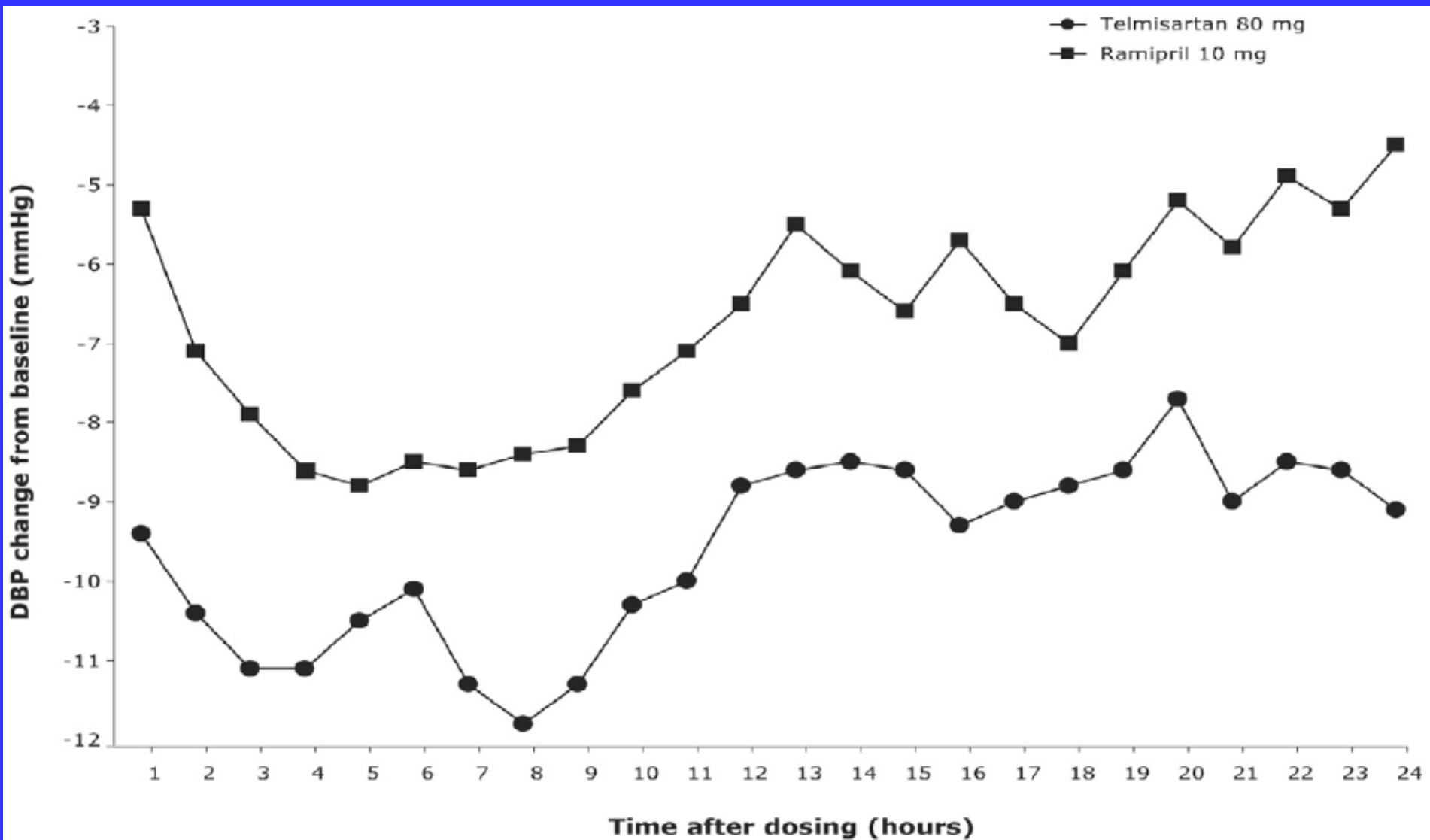


ABPM, ambulatory blood pressure monitoring; V, visit.

FIG. 1. Study design.

Table 2. Antihypertensive effects of telmisartan 80 mg and ramipril 5 mg or 10 mg on mean systolic/diastolic ambulatory blood pressure (mm Hg) at week 8 and week 14 compared with baseline

Variable/Drug	Baseline Mean	Week 8	Week 14	P Value v Ramipril
Mean last 6-h				
Telmisartan	142.2/88.6	131.1/80.9	129.5/79.8	<.0000
Ramipril	141.9/89.2	136.3/85.1	134.0/83.8	<.0001
Mean 24-h				
Telmisartan	148.2/92.5	135.3/83.6	133.4/82.6	<.0000
Ramipril	147.6/92.5	138.9/87.0	136.9/85.8	<.0001
Mean morning				
Telmisartan	152.8/97.2	140.1/88.5	138.5/87.5	<.0000
Ramipril	152.3/97.4	144.6/92.6	143.0/91.6	<.0001
Mean daytime				
Telmisartan	153.3/96.8	139.9/87.7	138.3/86.7	<.0000
Ramipril	152.7/96.9	143.0/90.7	141.5/89.9	<.0001
Mean night-time				
Telmisartan	137.8/83.6	126.1/75.4	124.7/74.7	<.0000
Ramipril	137.1/83.9	130.8/79.5	127.9/77.7	<.0001



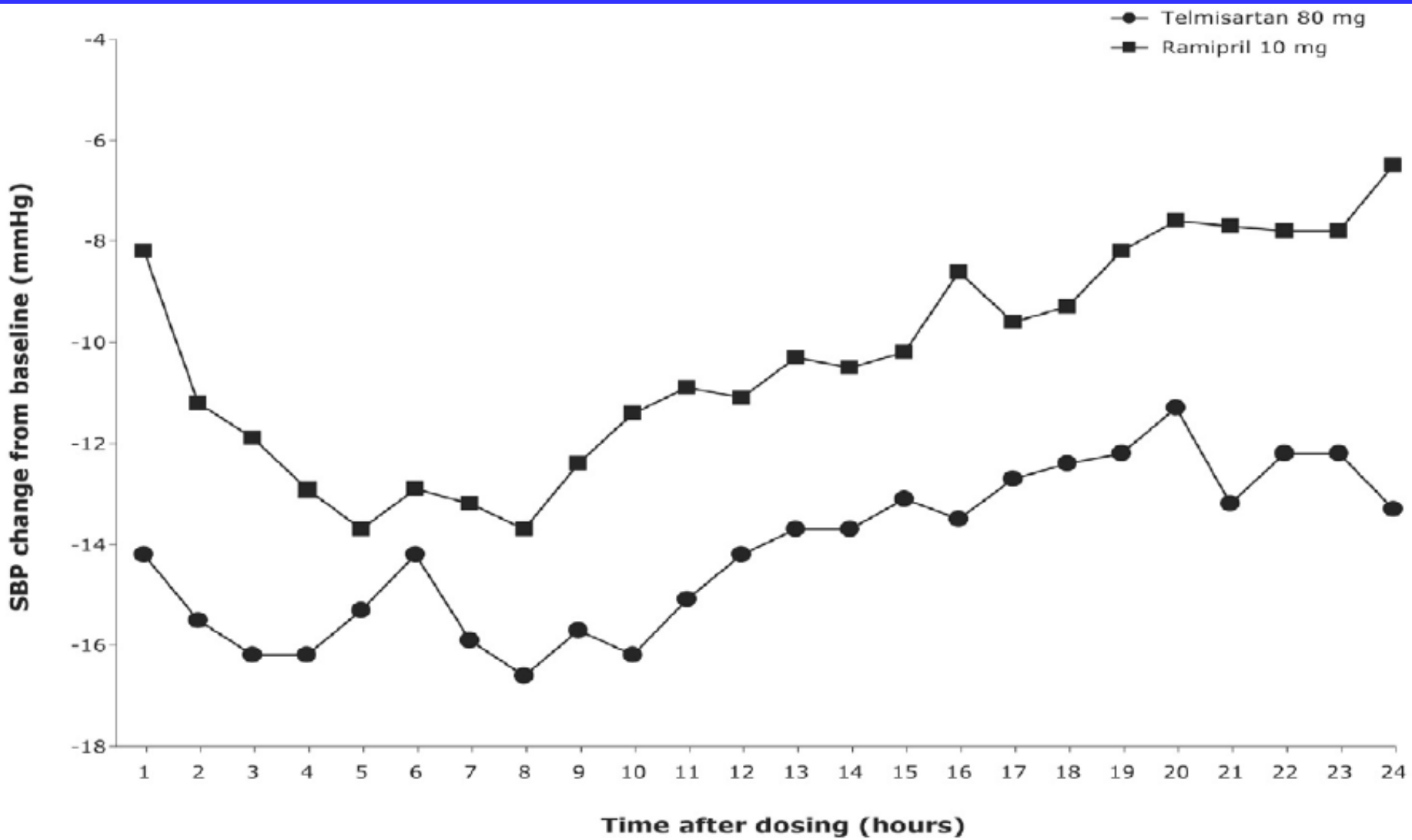


Table 3. Antihypertensive effects of telmisartan 80 mg and ramipril 5 mg or 10 mg on clinical blood pressure (mm Hg)

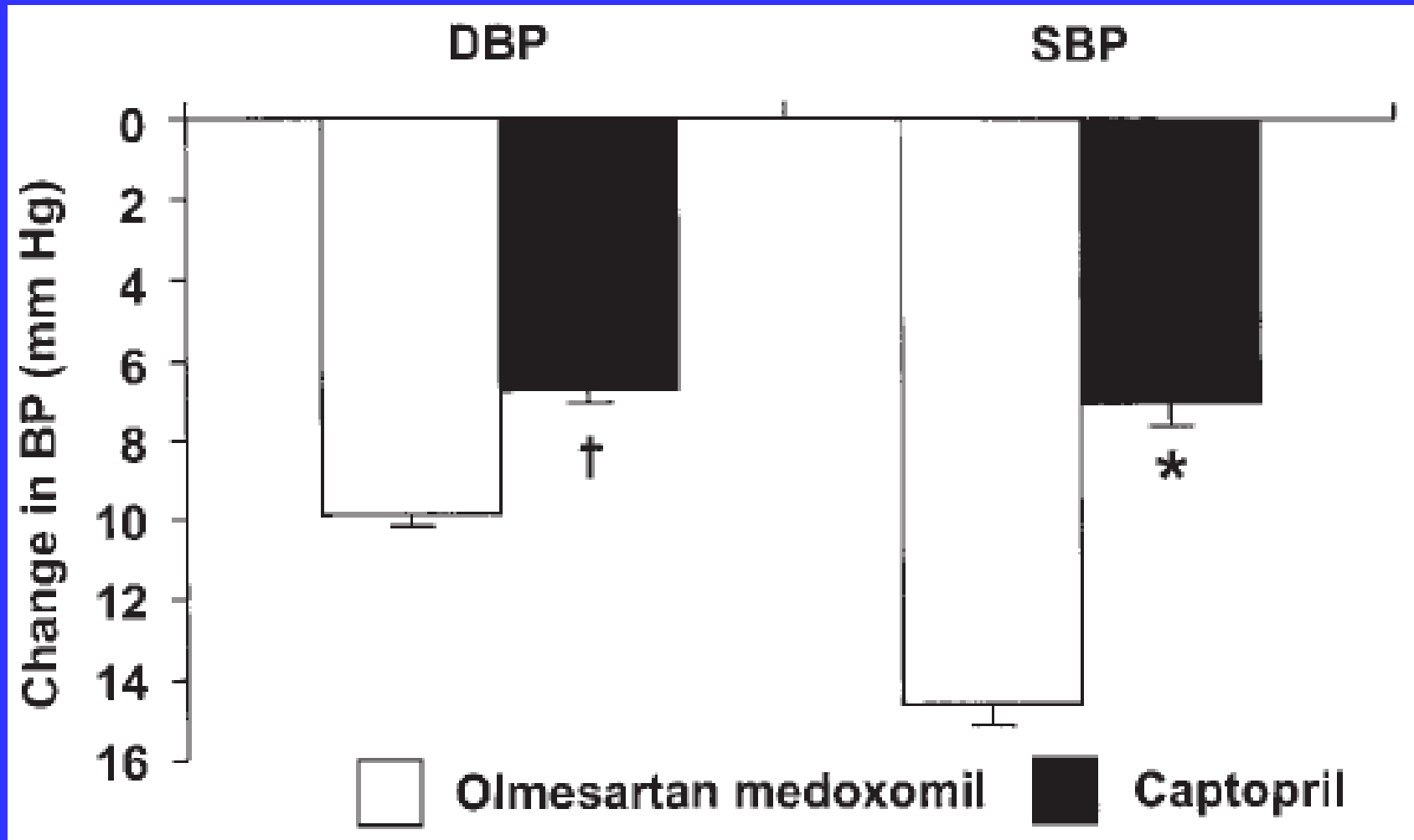
Variable	Telmisartan	Ramipril	P Value v Ramipril
Baseline			
Systolic BP	153.9	152.5	NS
Diastolic BP	99.7	99.8	NS
Week 8			
Systolic BP	140.2	145.1	<.0000
Diastolic BP	89.4	93.3	<.0001
Change from baseline (systolic/diastolic)	-13.7/10.3	-7.4/6.5	<.0001
Week 14			
Systolic BP	139.6	143.4	<.0000
Diastolic BP	88.7	92.0	<.0001
Change from baseline (systolic/diastolic)	-14.3/11.0	-9.1/7.8	<.0001

BP = blood pressure; NS = not significant.

Öksürük oranı:

Ramipril grubu %10.1, telmisartan grubu %1.5

Antihypertensive efficacy of olmesartan compared with other antihypertensive drugs



Losartan and Perindopril Effects on Plasma Plasminogen Activator Inhibitor-1 and Fibrinogen in Hypertensive Type 2 Diabetic Patients

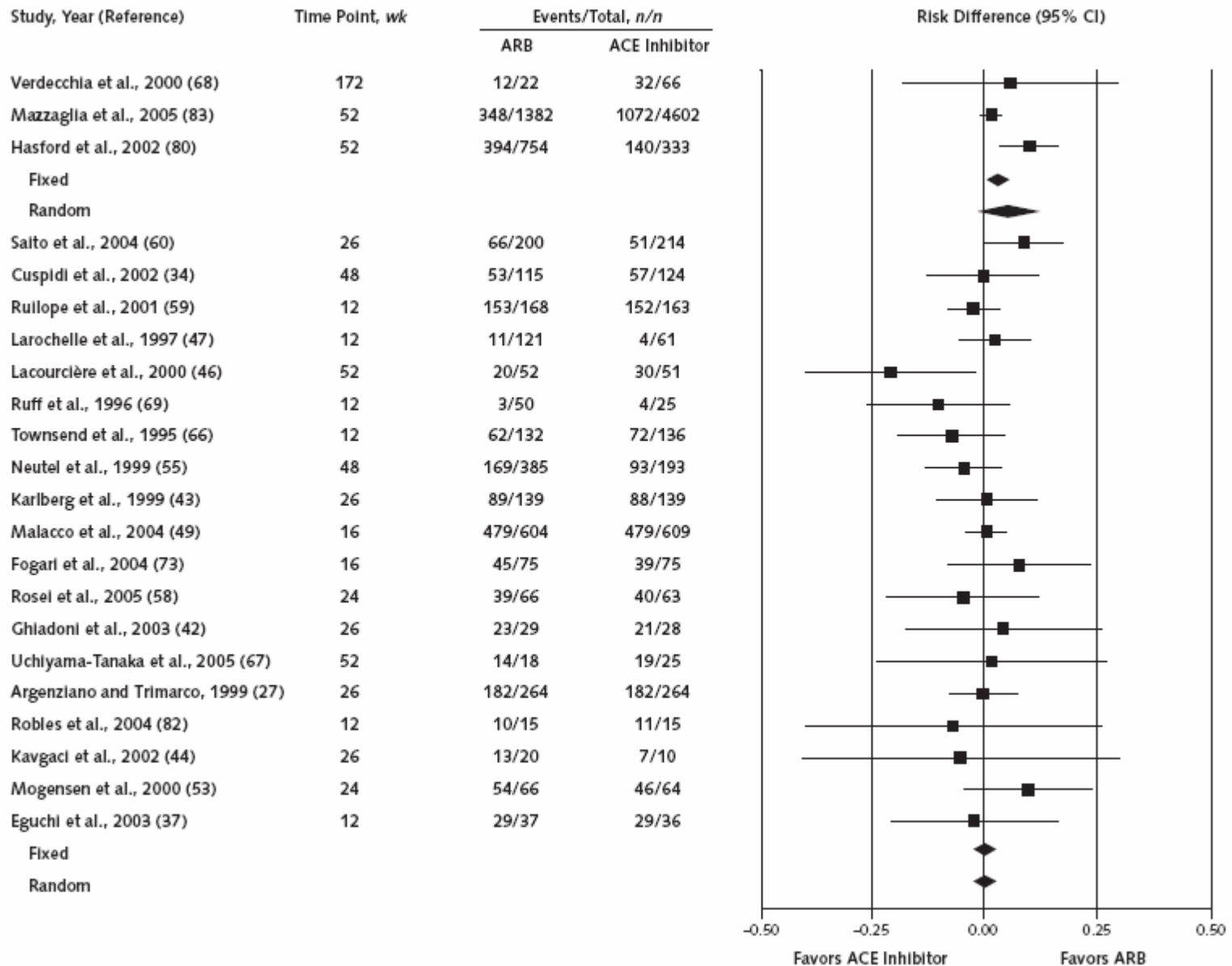
Table 2. Effects of treatment with perindopril and losartan

	Placebo	Perindopril	<i>P</i>	Placebo	Losartan	<i>P</i>	Comparison Between Treatments
SBP (mm Hg)	162 ± 13	146 ± 10	.001	162 ± 14	147 ± 11	.001	NS
DBP (mm Hg)	102 ± 6	87 ± 5	.001	102 ± 6	88 ± 5	.001	NS
BMI (kg/m ²)	26 ± 0.9	27 ± 0.8	NS	26 ± 0.8	26 ± 0.7	NS	NS
PAI-1 (ng/mL)	42 ± 21	32 ± 17	.028	41 ± 19	45 ± 22	NS	.01
Fibrinogen (mg/dL)	356 ± 74	312 ± 59	NS	344 ± 67	333 ± 59	NS	NS
FBG (mg/dL)	112 ± 7.3	107 ± 6.9	NS	113 ± 7.5	111 ± 7.0	NS	NS
Serum creatinine (mg/dL)	1.1 ± 0.4	1.1 ± 0.4	NS	1.1 ± 0.5	1.1 ± 0.4	NS	NS
Total cholesterol (mg/dL)	197 ± 23	186 ± 19	NS	191 ± 20	188 ± 19	NS	NS
HDL cholesterol (mg/dL)	44 ± 5	46 ± 6	NS	44 ± 5	44 ± 6	NS	NS
Triglycerides (mg/dL)	142 ± 49	127 ± 44	NS	145 ± 50	140 ± 48	NS	NS
HbA _{1c} (%)	7.2 ± 1.9	7.1 ± 1.7	NS	6.9 ± 2.0	7.0 ± 1.8	NS	NS

NS = not significant; BMI = body mass index; PAI-1 = plasminogen activator inhibitor; FBG = fasting blood glucose; HbA_{1c} = glycosylated hemoglobin; other abbreviations as in Table 1.

Data are given as mean ± SD.

Figure 2. Successful monotherapy: angiotensin-converting enzyme (ACE) inhibitors versus angiotensin II receptor blockers (ARBs).



The first group is observational studies and the second group is randomized, controlled trials.

Renal Koruma Karşılaştırmaları

Additive Effect of ACE Inhibition and Angiotensin II Receptor Blockade in Type I Diabetic Patients with Diabetic Nephropathy

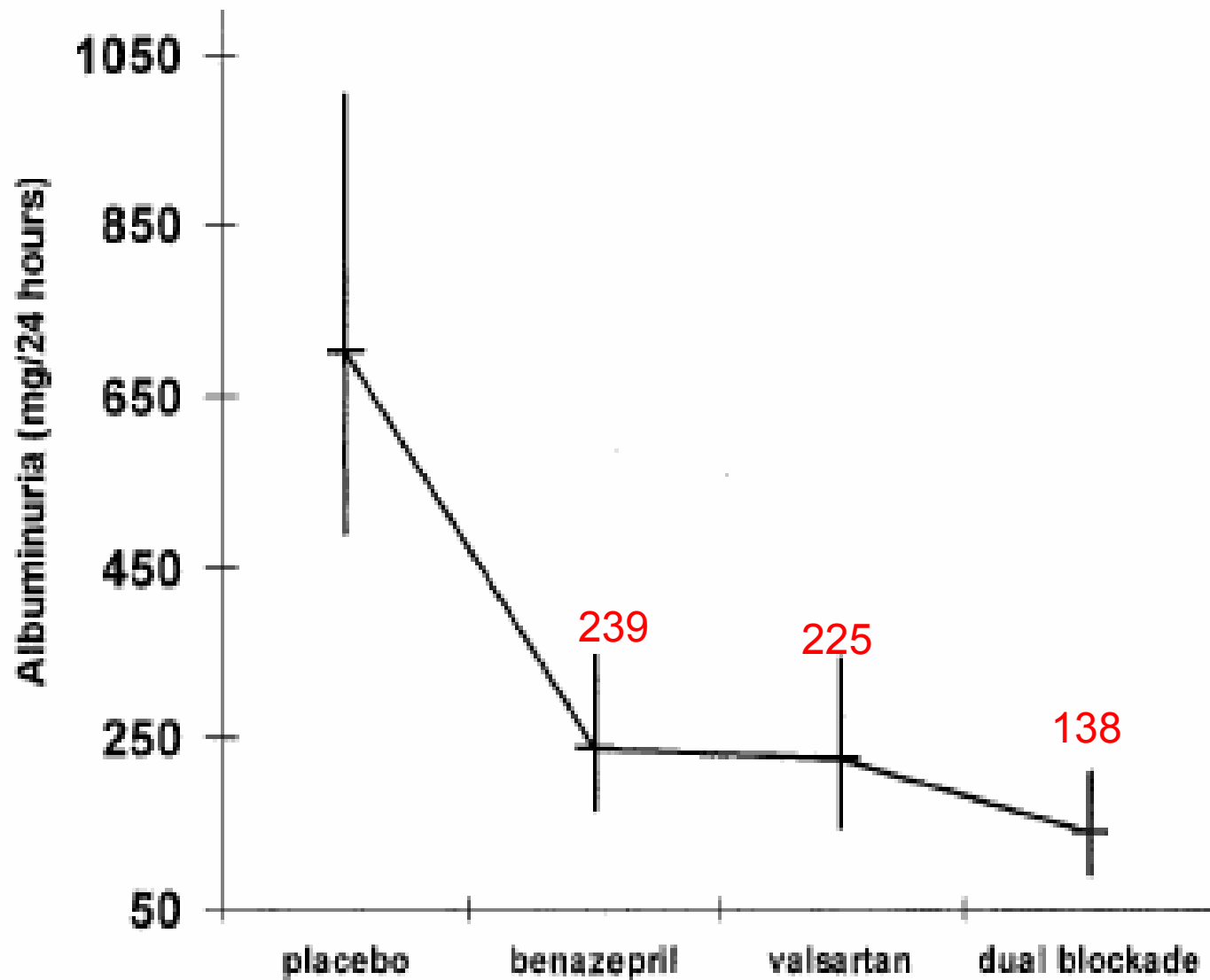
Table 2. Effects on kidney function and arterial BP of blockade of the renin angiotensin system in 18 type I diabetic patients with diabetic nephropathy

Parameter	Placebo Values	Decline from Placebo		
		Benazepril 20 mg	Valsartan 80 mg	Benazepril 20 mg + Valsartan 80 mg
Albuminuria	701 (490 to 1002) mg/24 h ^a	65 (56 to 72)% ^b	65 (56 to 72)% ^b	80 (75 to 84)% ^{bd}
GFR (ml/min per 1.73 m ²)	82 (7)	3 (-1 to 7)	4 (-1 to 8)	10 (6 to 14) ^{bd}
P-creatinine (μmol/L)	115 (7)	-1 (-8 to 6)	2 (-5 to 9)	-9 (-16 to -2) ^{ce}
Albuminuria/([p-albumin] × [GFR])	172 (109 to 270) 10 ^{-6a}	65 (57 to 72)% ^b	64 (55 to 71)% ^b	78 (73 to 82)% ^{bd}
24-h systolic BP (mmHg)	144 (4)	15 (9 to 22) ^b	15 (8 to 21) ^b	22 (15 to 28) ^b
day (7 to 23)	149 (3)	15 (8 to 21) ^b	15 (9 to 21) ^b	22 (15 to 28) ^{be}
night (23 to 7)	133 (4)	16 (7 to 25) ^b	13 (5 to 22) ^c	21 (13 to 30) ^b
24-h diastolic BP (mmHg)	79 (2)	6 (3 to 9) ^b	6 (3 to 9) ^b	13 (10 to 16) ^{bd}
day (7 to 23)	82 (2)	7 (4 to 10) ^b	7 (4 to 10) ^b	14 (11 to 17) ^{bd}
night (23 to 7)	72 (2)	5 (1 to 9) ^c	4 (0 to 8)	11 (7 to 15) ^{bd}

Placebo values are mean (SEM) and changes are mean (95% CI).

^a Geometric mean (95% CI); ^b *P* < 0.001 versus placebo; ^c *P* < 0.05 versus placebo; ^d *P* < 0.01 dual blockade versus mono-therapy;

^e *P* < 0.05 dual blockade versus mono-therapy.



Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study

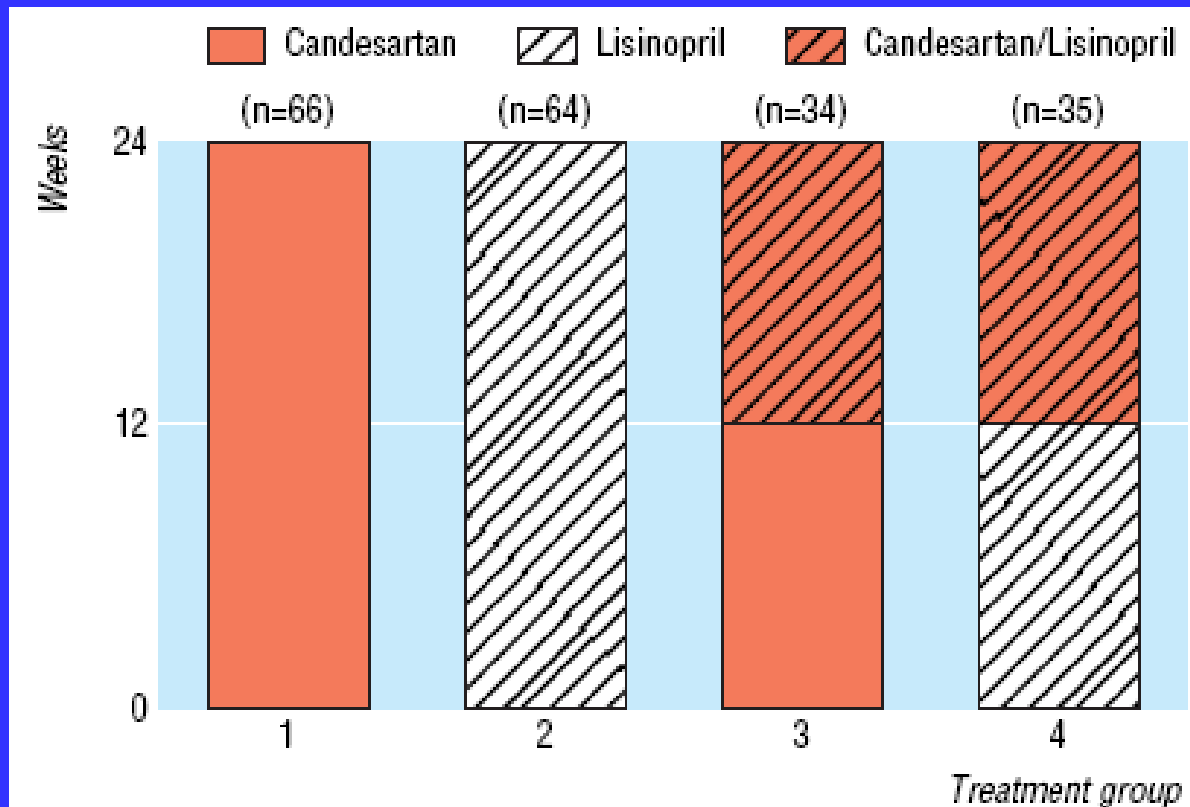


Fig 1 Distribution of participants in study. Doses were: candesartan 16 mg once daily, lisinopril 20 mg once daily, or their combination

Table 1 Baseline characteristics of patients with hypertension, microalbuminuria, and type 2 diabetes followed from baseline to 12 weeks. Figures are means (SD) unless stated otherwise

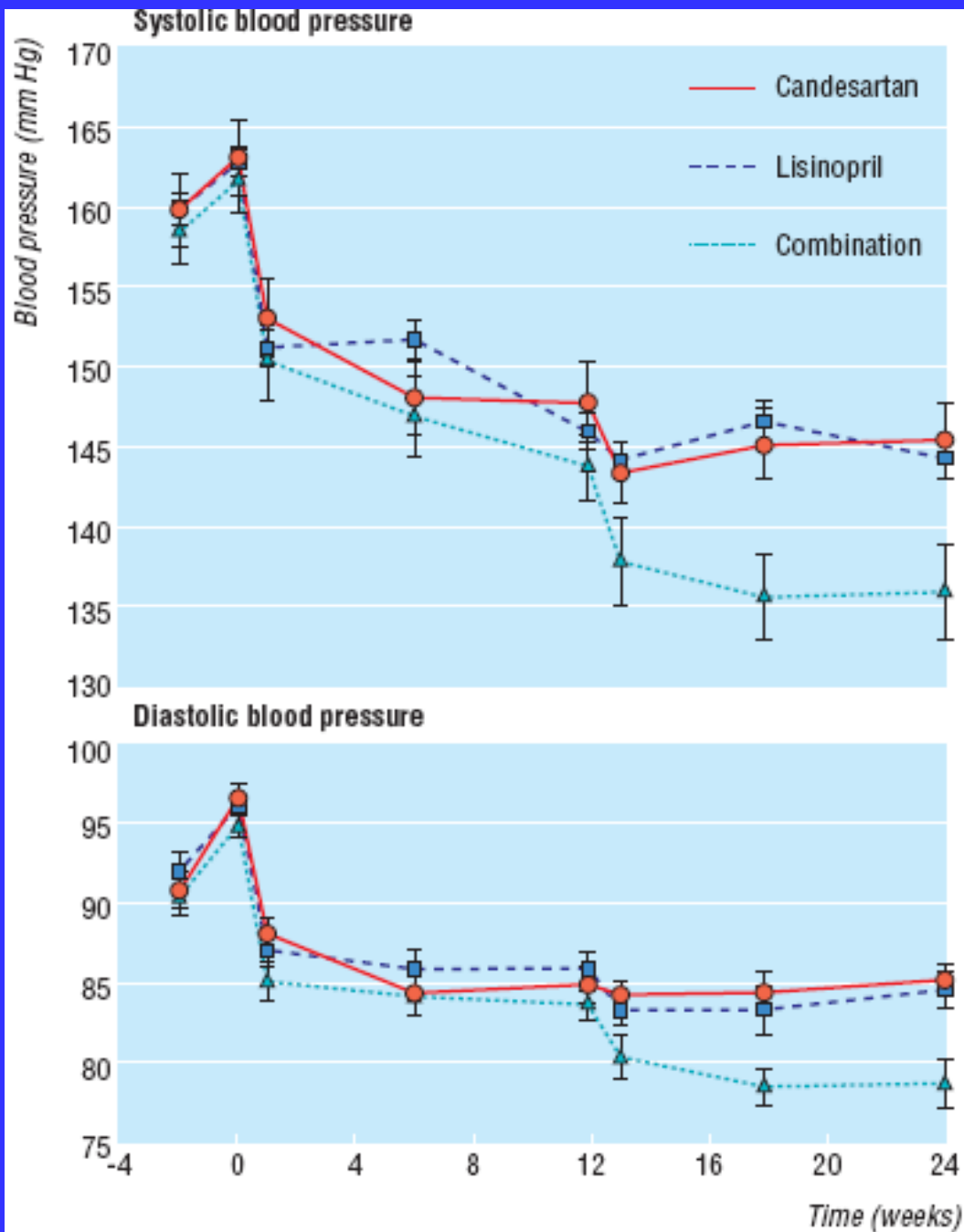
	Candesartan	Lisinopril
No of patients	99	98
Age (years)	59.7 (9.9)	60.0 (8.5)
No of men	66/33	62/36
Body mass index (kg/m ²)	30.7 (4.3)	29.8 (3.8)
Duration of hypertension (years)	8.3 (8.8)	9.0 (8.9)
Duration of diabetes (years)	9.8 (7.5)	8.4 (7.3)
Systolic blood pressure (mm Hg)	162.7 (17.7)	162.6 (17.6)
Diastolic blood pressure (mm Hg)	96.0 (6.2)	95.7 (6.2)
Urinary albumin:creatinine ratio (mg/mmol)*	5.9 (1.1)	6.6 (1.1)
Serum creatinine (μmol/l)	85.8 (18.9)	85.0 (16.8)
Creatinine clearance (ml/min)	103.1 (37.7)	96.0 (28.7)
Haemoglobin A _{1c} (%)	7.6 (1.2)	7.6 (1.6)

Table 2 Adjusted* mean reductions in blood pressure and urinary albumin:creatinine ratio from baseline to 12 weeks in patients with hypertension, microalbuminuria, and type 2 diabetes

	Candesartan	Lisinopril	Adjusted mean difference between treatments
Sitting diastolic blood pressure (mm Hg)	9.5 (7.7 to 11.2); P<0.001	9.7 (7.9 to 11.5); P<0.001	0.2 (-2.3 to 2.7); P>0.20
Sitting systolic blood pressure (mm Hg)	12.4 (9.1 to 15.8); P<0.001	15.7 (12.2 to 19.2); P<0.001	3.3 (-1.5 to 8.2); P=0.18
Urinary albumin:creatinine ratio (%)	30 (15 to 42); P<0.001	46 (35 to 56); P<0.001	30 (1 to 71); P=0.058†

*Adjusted for centre, treatment, baseline value, weight, and change in diastolic blood pressure.

†Relative reduction.



Angiotensin-Receptor Blockade versus Converting-Enzyme Inhibition in Type 2 Diabetes and Nephropathy

Table 1. Baseline Characteristics of the Subjects.*

Variable	Telmisartan Group (N=120)	Enalapril Group (N=130)
Age — yr	61.2±8.5	60.0±9.1
Male sex — no. of subjects (%)	87 (72.5)	95 (73.1)
White race — no. of subjects (%)†	118 (98.3)	128 (98.5)
Body-mass index‡	30.8±4.4	30.6±5.1
Blood pressure — mm Hg		
Systolic	152.6±16.6	151.6±15.8
Diastolic	85.4±8.8	85.9±7.8
Heart rate — beats/min	73.6±10.2	75.7±10.0
Duration of hypertension — yr		
Median	8.0	5.5
Range	0–34	0–49
Duration of diabetes — yr		
Median	8.0	8.0
Range	0–25	0–37
History of cardiovascular disease — no. of subjects (%)	59 (49.2)	63 (48.5)
Glomerular filtration rate — ml/min/1.73 m ²	91.4±21.5	94.3±22.1
Serum creatinine — mg/dl	1.02±0.21	0.99±0.20
Urinary albumin excretion rate — μg/min		
Median	46.2	60.0
Range	4–1011	9–969
Microalbuminuria — no. of subjects (%)§	98 (81.7)	106 (81.5)
Macroalbuminuria — no. of subjects (%)§	22 (18.3)	23 (17.7)

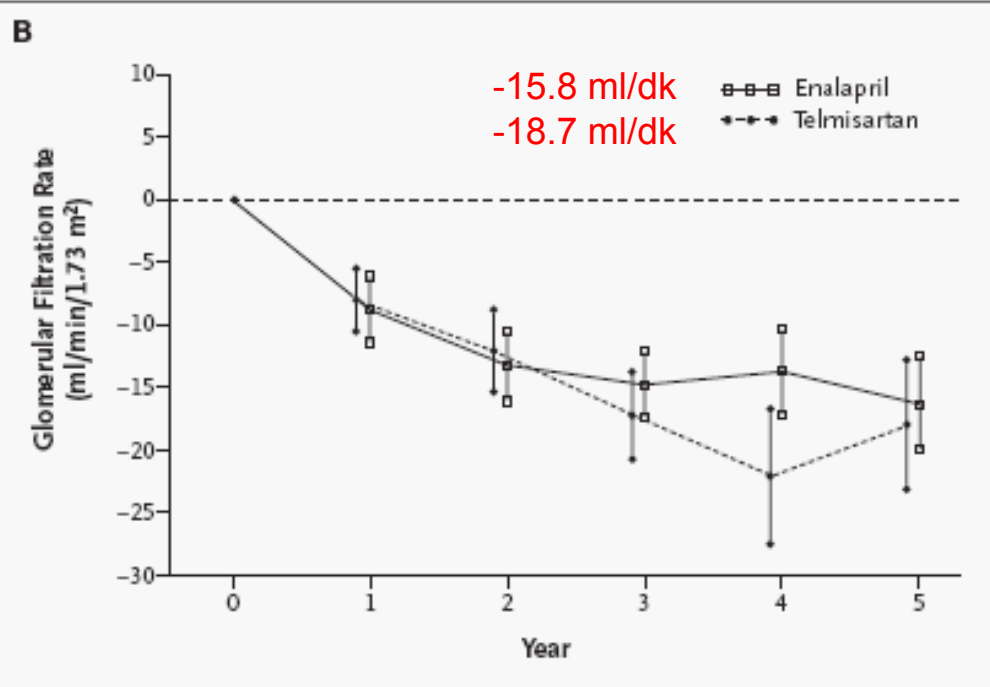
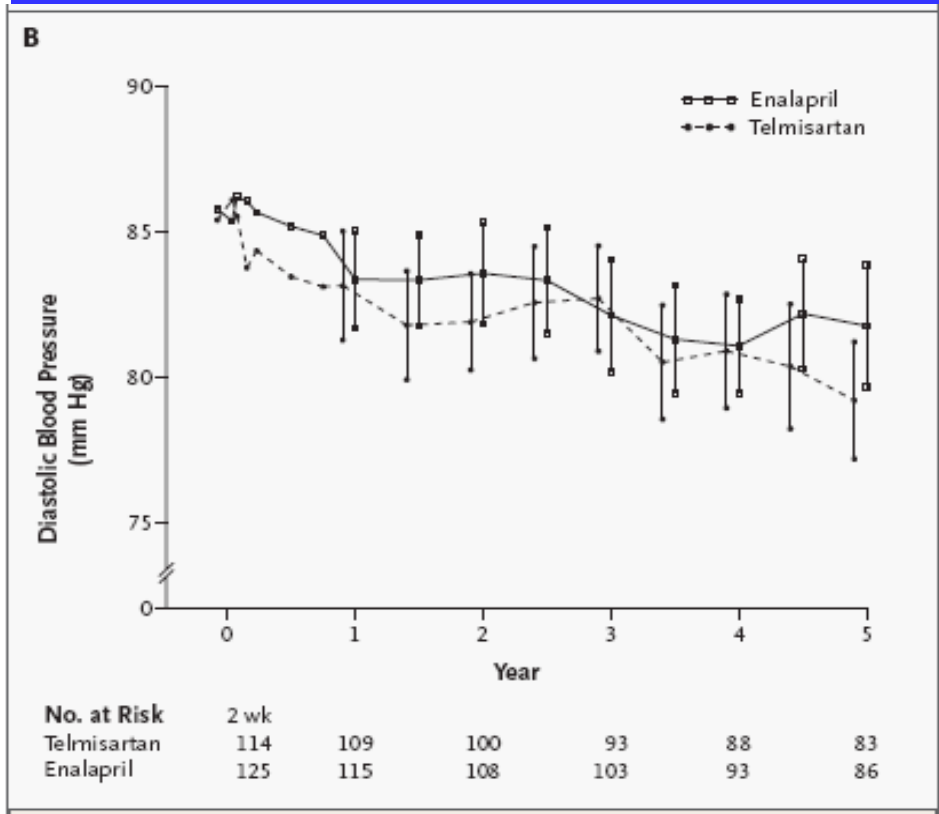
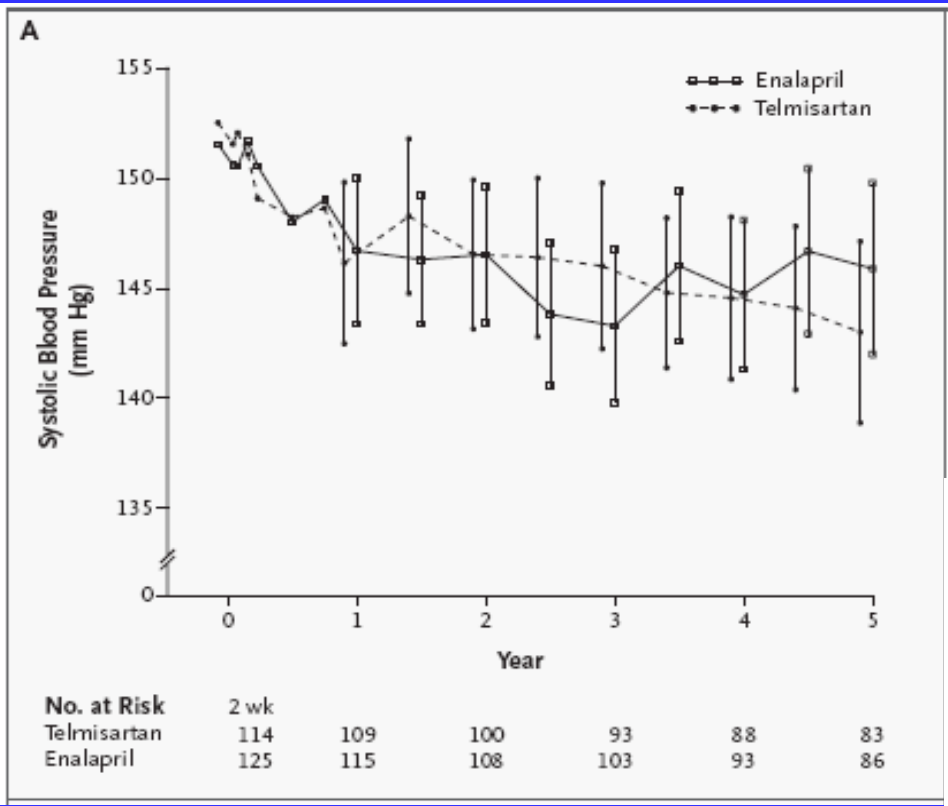


Figure 1. Changes from Baseline in the Glomerular Filtration Rate, Based on Analyses of the Last Observation Carried Forward (Panel A) and Complete Five-Year Data (Panel B), According to Treatment Group.

The vertical bars represent the standard deviation.

Table 3. Secondary Renal End Points after Five Years of Treatment, According to Analysis of the Last Observation Carried Forward.[§]

End Point	Change from Baseline		Difference between Groups (95% CI)
	Telmisartan Group	Enalapril Group	
Serum creatinine (mg/dl)	0.10	0.10	0 (-0.66 to 0.65)
Urinary albumin excretion (ratio) [†]	1.03	0.99	1.04 (0.71 to 1.51) [‡]



Effects of dual blockade of the renin-angiotensin system in primary proteinuric nephropathies

Table 1. Summary of baseline characteristics of patients with proteinuric nephropathies

	Candesartan (<i>N</i> = 15)	Lisinopril (<i>N</i> = 14)	Candesartan + lisinopril (<i>N</i> = 16)
Men/women <i>N</i>	10/5	12/2	9/7
Age years	45 ± 18	50 ± 16	42 ± 13
BMI <i>kg/m</i> ²	26.7 ± 2.6	26.4 ± 3.9	27.1 ± 5.6
Blood pressure <i>mm Hg</i>			
Systolic	133 ± 14	135 ± 20	135 ± 20
Diastolic	80 ± 11	80 ± 14	84 ± 10
Serum/plasma			
<i>S</i> _{Cr} <i>mg/dL</i>	1.08 ± 0.5	1.26 ± 0.5	1.15 ± 0.3
<i>K</i> <i>mmol/L</i>	4.3 ± 0.3	4.3 ± 0.3	4.5 ± 0.3
Albumin <i>g/dL</i>	3.6 ± 0.4	3.6 ± 0.5	3.5 ± 0.5
Urine			
<i>C</i> _{Cr} <i>mL/min</i>	104 ± 36	84 ± 26	96 ± 34
Protein/creatinine	4.0 ± 2.5	3.6 ± 2.9	3.8 ± 2.1

Data are means ± SD. *P* > 0.05 for all comparisons by chi-square, ANOVA or Kruskal-Wallis tests, as appropriate.

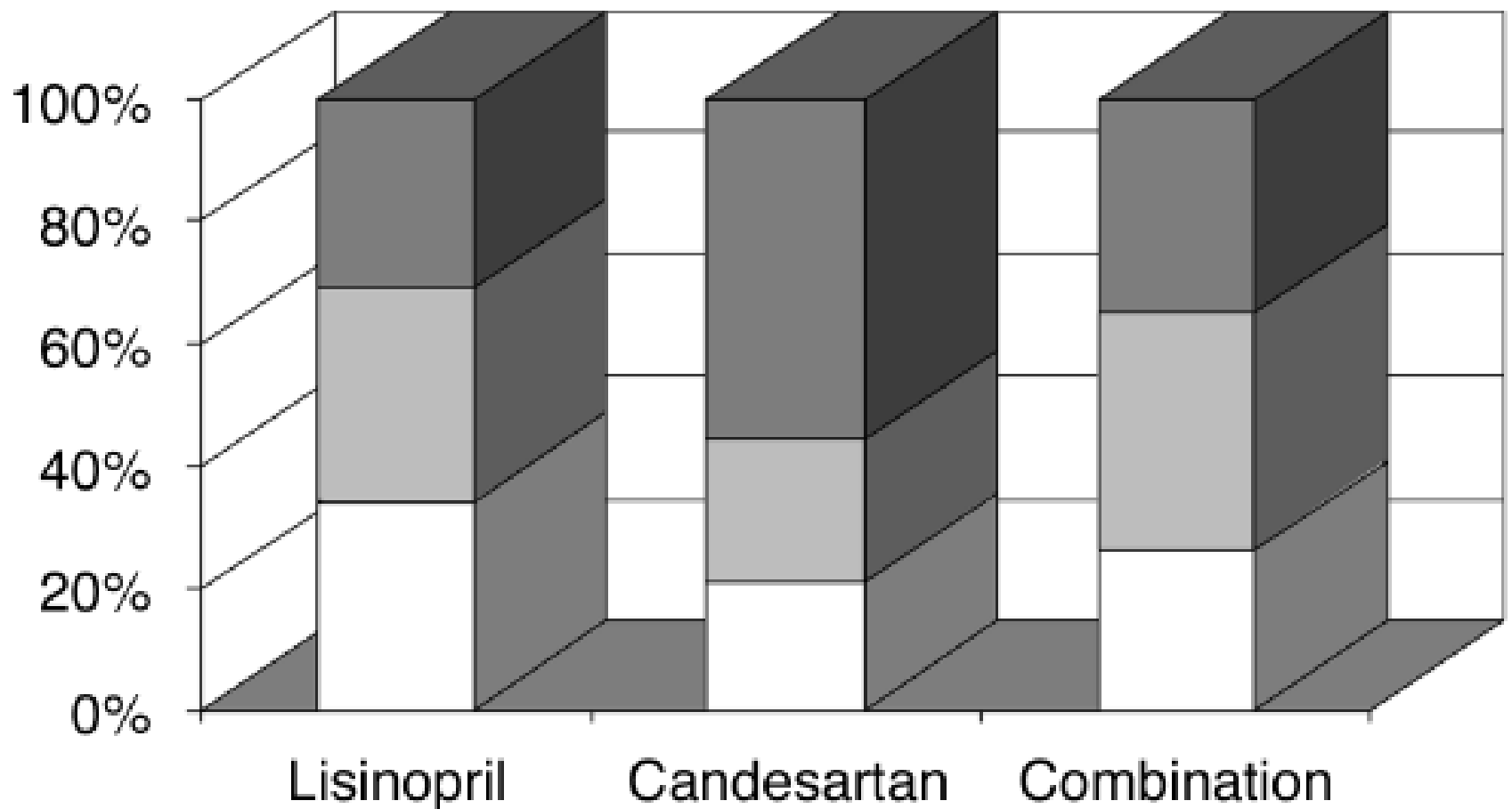


Fig. 1. Percentage of patients who achieved the maximum, medium and minimum dose of medication in each study group. Symbols are: (■) maximum; (▒) medium; (□) minimum.

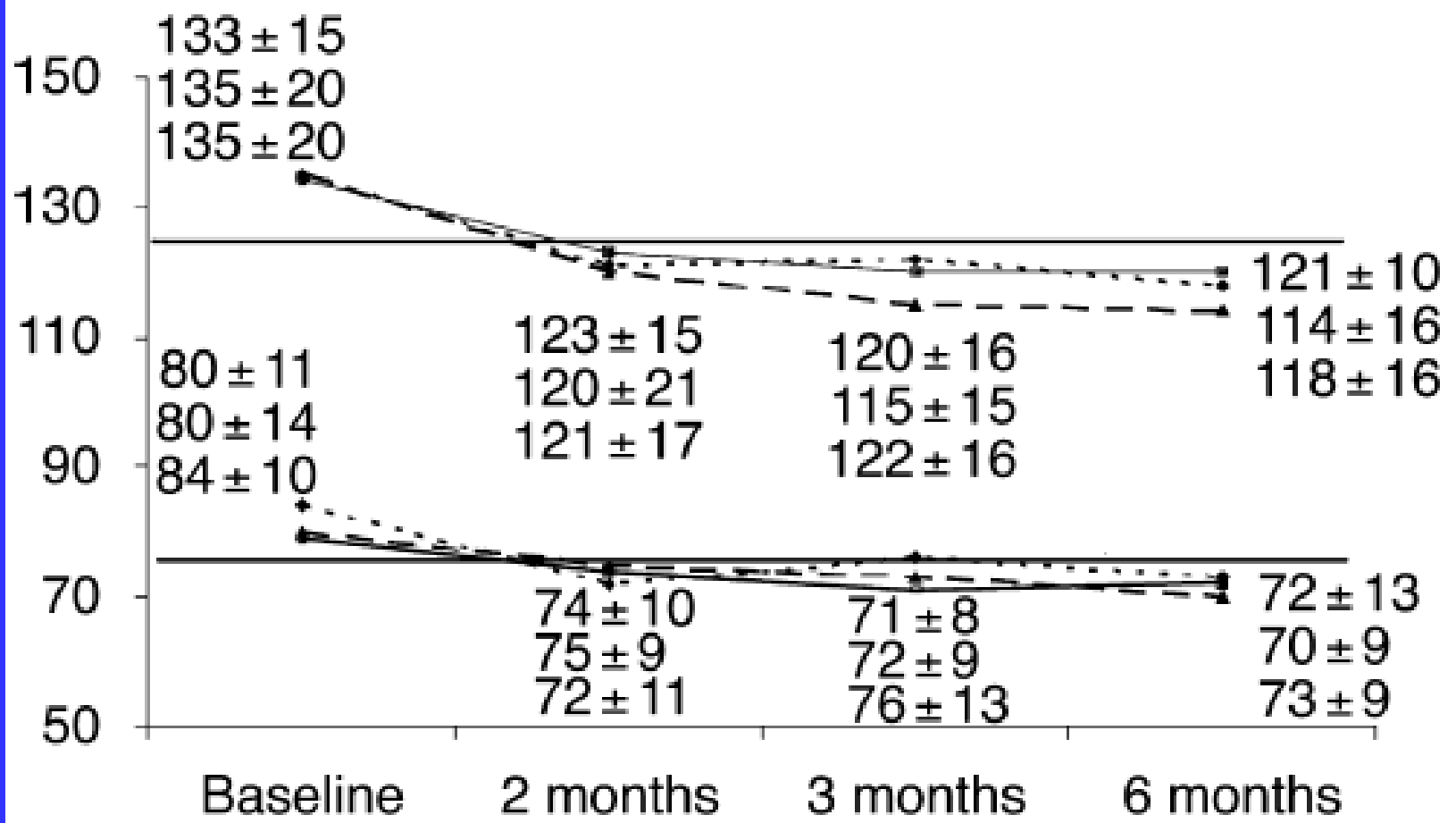


Fig. 4. Blood pressure changes (mm Hg) by treatment groups throughout the study period. *P* < 0.005 from first month until end of follow-up for both systolic and diastolic compared to baseline, *P* was non-significant between groups at any time point. Symbols are: (solid line) candesartan; (dashed line) lisinopril; (dotted line) combination of candesartan and lisinopril therapy.

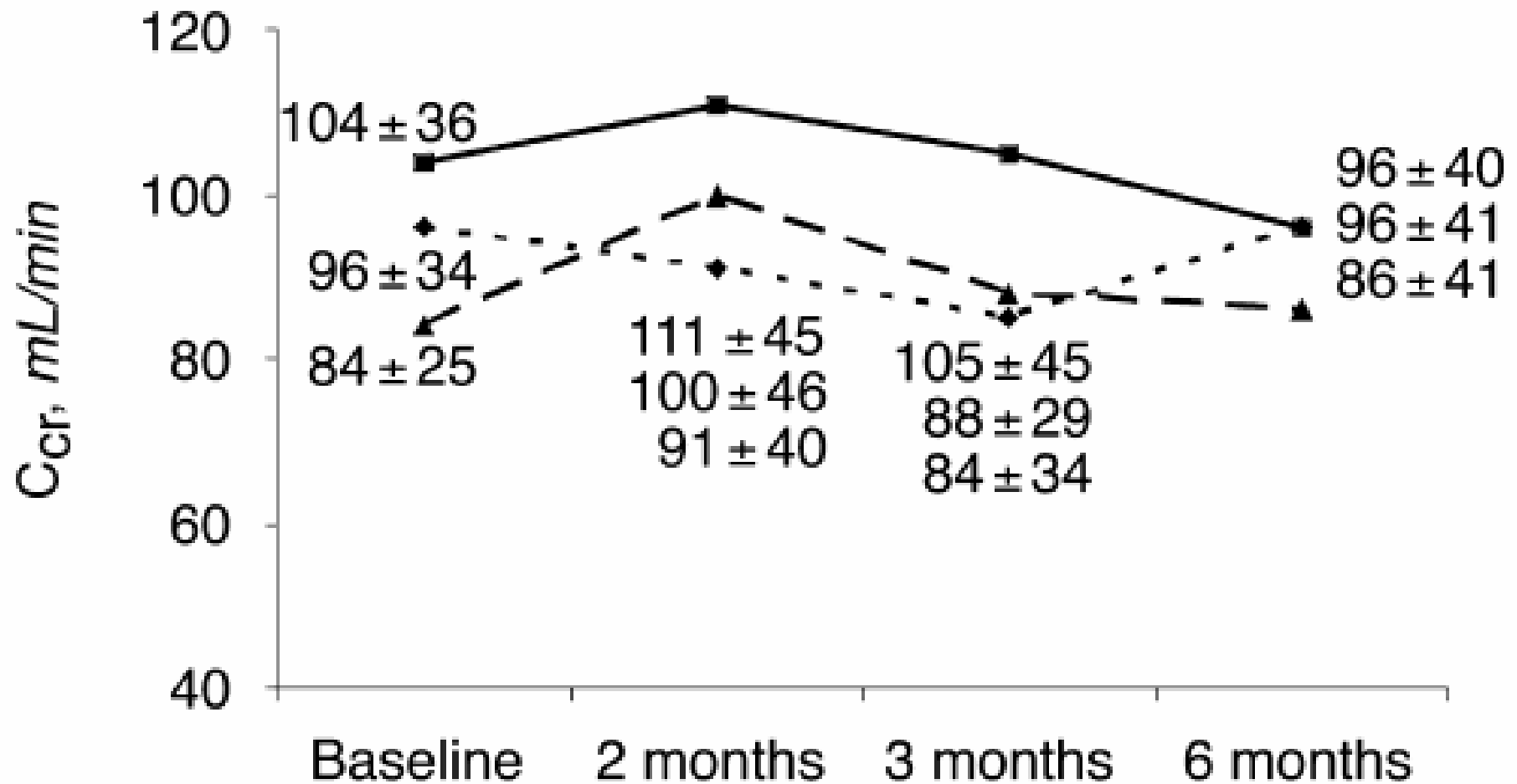


Fig. 2. Changes in creatinine clearance (C_{Cr}) by treatment groups throughout the study period. Symbols are: (solid line) candesartan; (dashed line) lisinopril; (dotted line) combination of candesartan and lisinopril therapy. There were not significant changes between groups at any time.

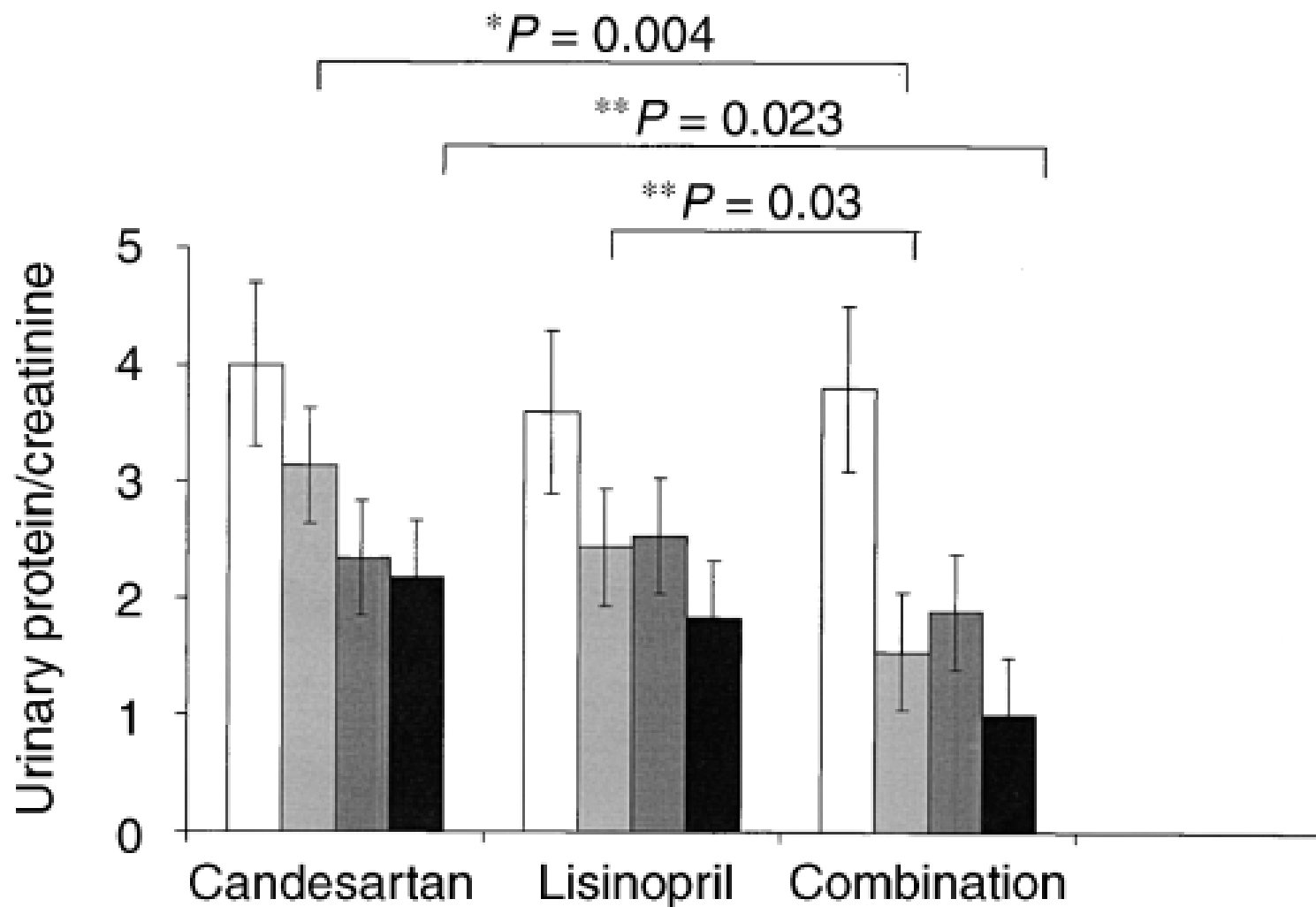


Fig. 5. Mean \pm SE of urinary protein/creatinine ratio (g/g) by treatment groups during study period two, three and six months comparing with baseline. Symbols are: (□) baseline data; (◻) two months; (◻) three months; (■) six months.

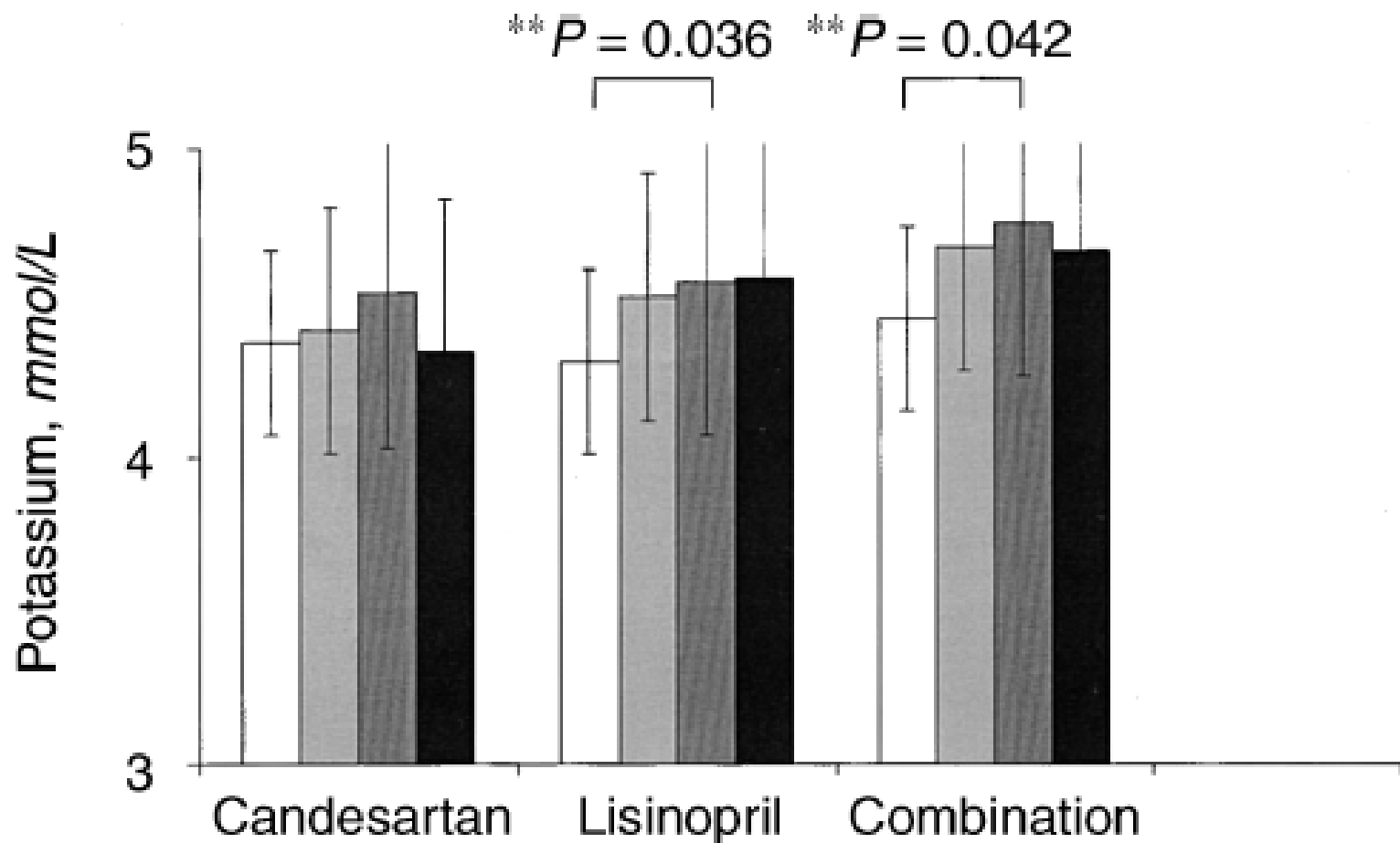
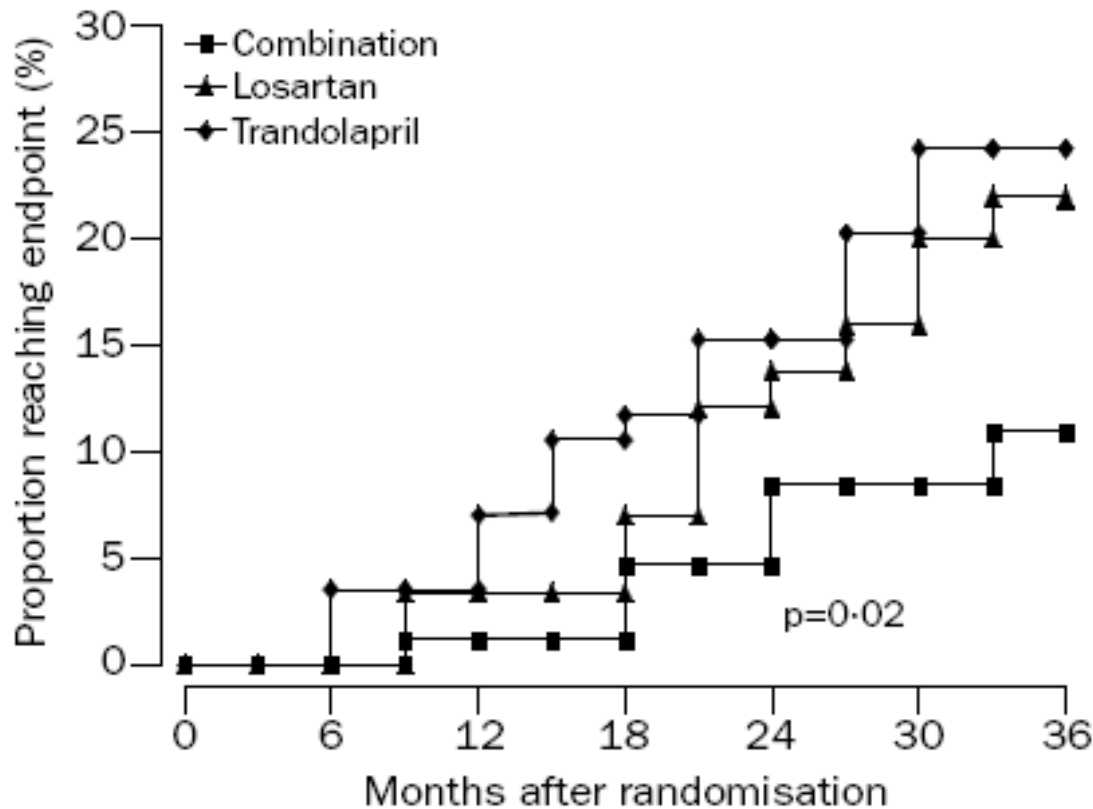


Fig. 3. Mean \pm SD serum potassium (mmol/L) by treatment groups during the study period. $*P = 0.036$ comparing mean serum potassium in the lisinopril group at 3 months with baseline data. $**P = 0.042$ comparing mean serum potassium in the combination therapy group at 3 months with baseline data. Symbols are: (□) baseline data; (▤) two months; (▥) 3 months; (■) 6 months.

Ⓜ Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial

	Losartan (n=89)	Trandolapril (n=86)	Combination (n=88)
Demographic			
Age (years, mean [SD])	44.8 (4.8)	45.9 (5.8)	45.2 (4.9)
Sex (M/F)	48/41	46/40	47/41
Renal disease			
Glomerular	58 (65%)	56 (65%)	57 (65%)
Hypertension	15 (17%)	16 (19%)	15 (17%)
Polycystic kidney interstitial	3 (3%)	5 (6%)	4 (5%)
Unknown	13 (15%)	9 (10%)	12 (14%)
Renal function			
Serum creatinine ($\mu\text{mol/L}$, mean [SD])	265 (10.3)	267 (9.5)	271 (9.9)
Calculated glomerular filtration rate (mL/min per 1.73 m ² , mean [SD])	38.4 (4.0)	37.9 (3.7)	37.5 (3.9)
Urinary protein excretion (g/day, mean [SD])	2.4 (1.1)	2.5 (1.2)	2.5 (1.1)
≥ 3	20 (22%)	18 (21%)	20 (23%)
1 to <3	35 (39%)	36 (42%)	35 (40%)
<1	34 (38%)	32 (37%)	33 (38%)
Urinary urea excretion (g/day, mean [SD])	5.1 (1.4)	5.2 (1.5)	5.4 (1.8)
Urinary sodium excretion (mEq/day, mean [SD])	140.5 (13.2)	145.5 (14.2)	143.6 (13.6)
Arterial blood pressure			
Systolic (mm Hg, mean [SD])	130.0 (9.3)	129.9 (10.2)	130.3 (10.5)
Diastolic (mm Hg, mean [SD])	74.3 (5.6)	75.9 (4.9)	75.1 (5.1)



23% Trandolapril grup

%23 losartan grup

%11 Kombinasyon grup

Number at risk

Losartan	89	88	84	79	65	59	47
Trandolapril	86	85	83	75	72	63	58
Combination	88	87	86	83	76	73	67

Figure 2: Proportion of patients reaching endpoint

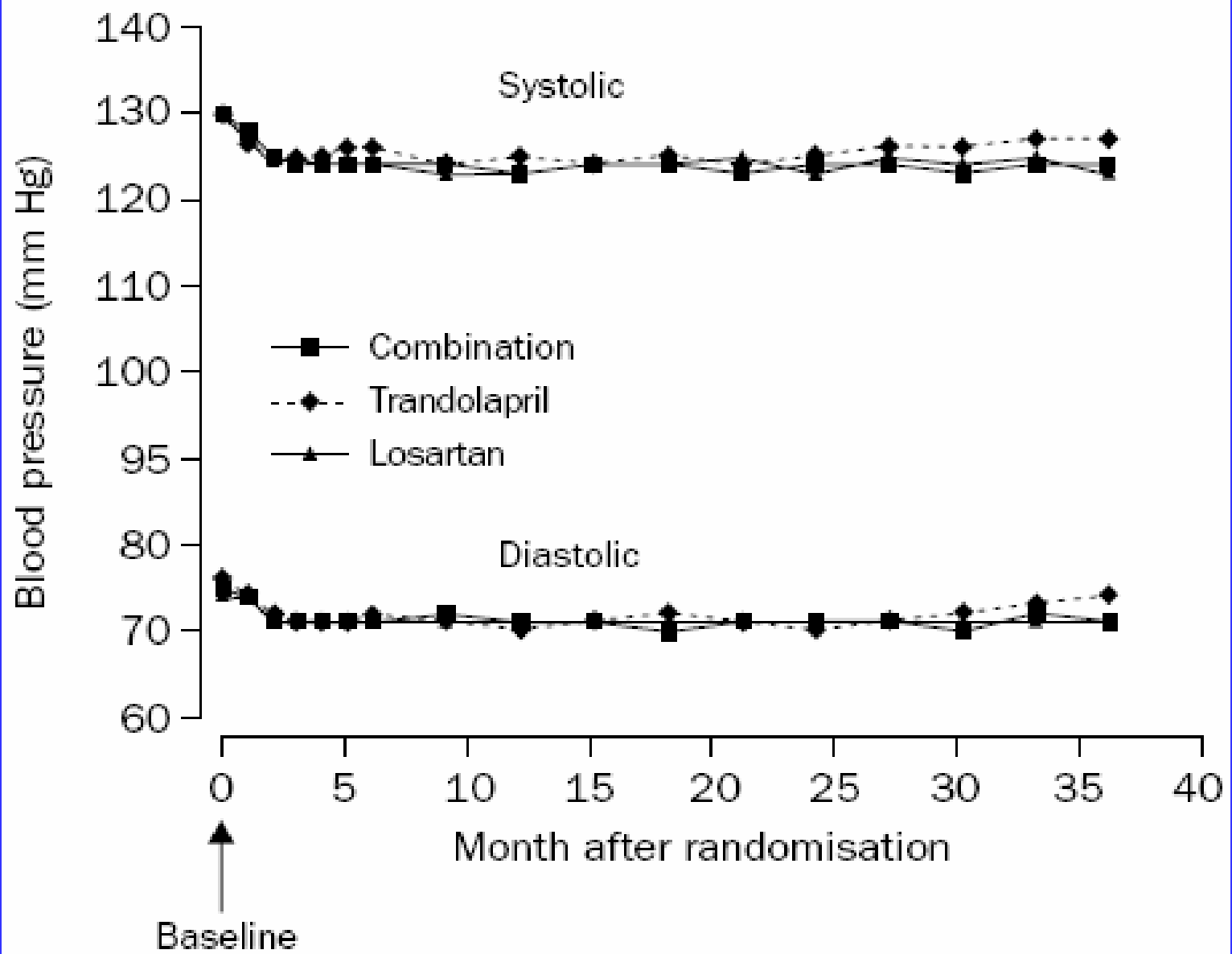


Figure 3: **Blood pressure by treatment group**

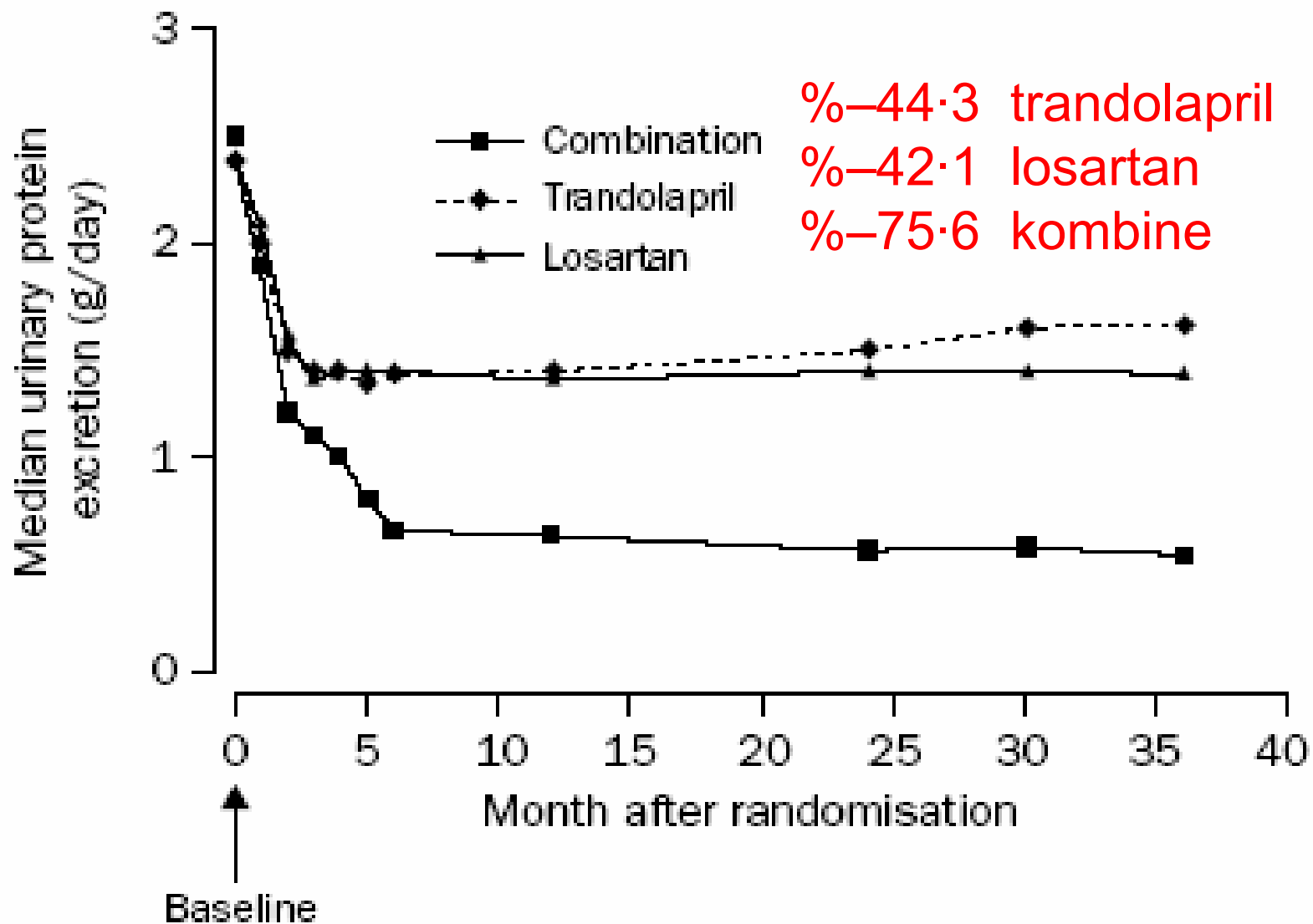


Figure 4: Median urinary protein excretion by treatment group

Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial

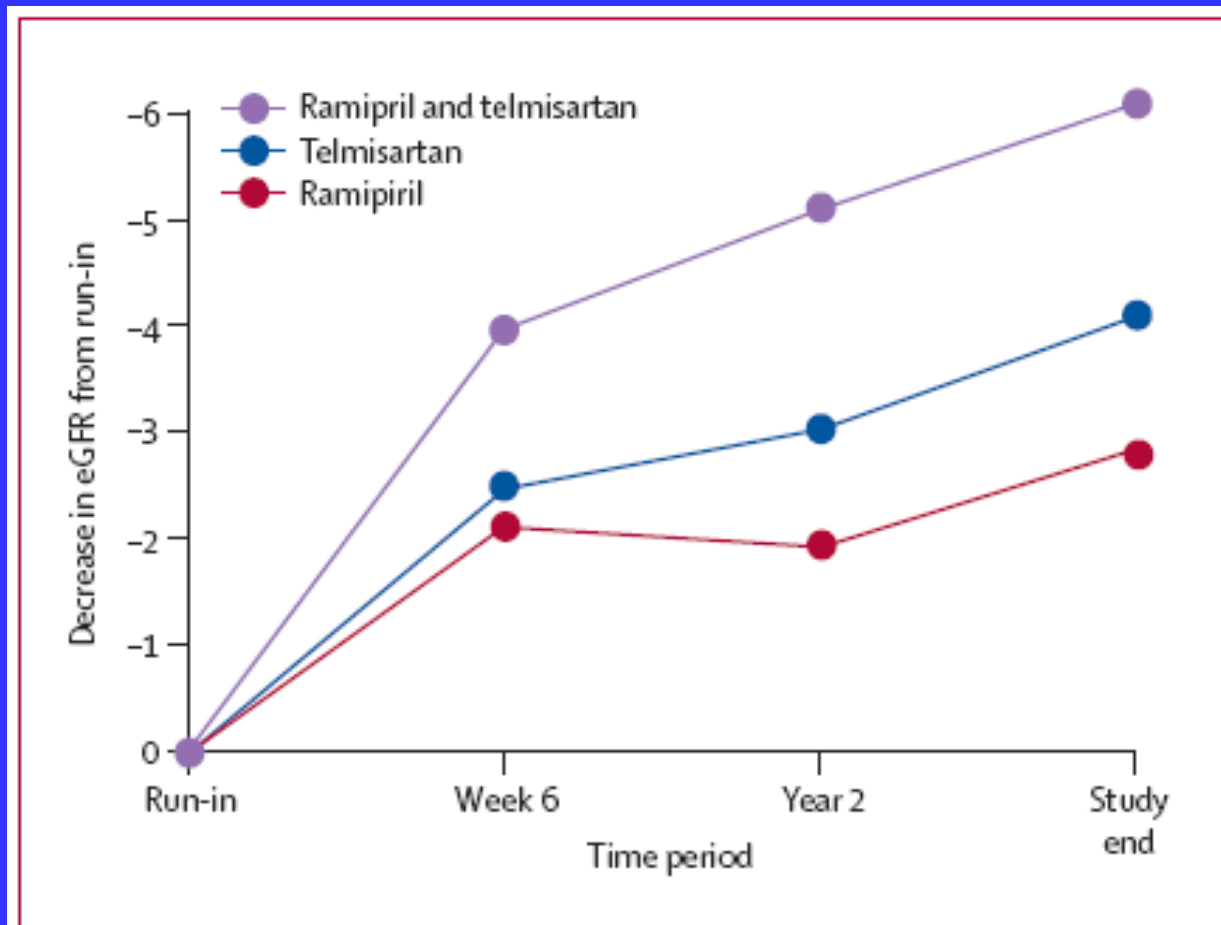


Figure 2: Decrease in estimated glomerular filtration rate (eGFR) during the trial, from baseline to study end

	Ramipril	Telmisartan	Ramipril+ telmisartan	Telmisartan vs ramipril p	Ramipril+telmisartan vs ramipril p
eGFR, baseline	73.7 (19.3)	73.6 (19.9)	73.4 (19.5)	0.915	0.388
eGFR change baseline to 6 weeks	-2.14 (12.9)	-2.51 (13.2)	-4.01 (13.3)	0.070	<0.0001
eGFR change baseline to 2 years	-1.96 (15.1)	-3.05 (15.1)	-5.12 (15.7)	<0.0001	<0.0001
eGFR change 6 baseline to final	-2.82 (17.2)	-4.12 (17.4)	-6.11 (17.9)	<0.0001	<0.0001
eGFR change 6 weeks to final	-1.17 (17.1)	-2.06 (17.1)	-2.49 (17.4)	0.0032	<0.0001

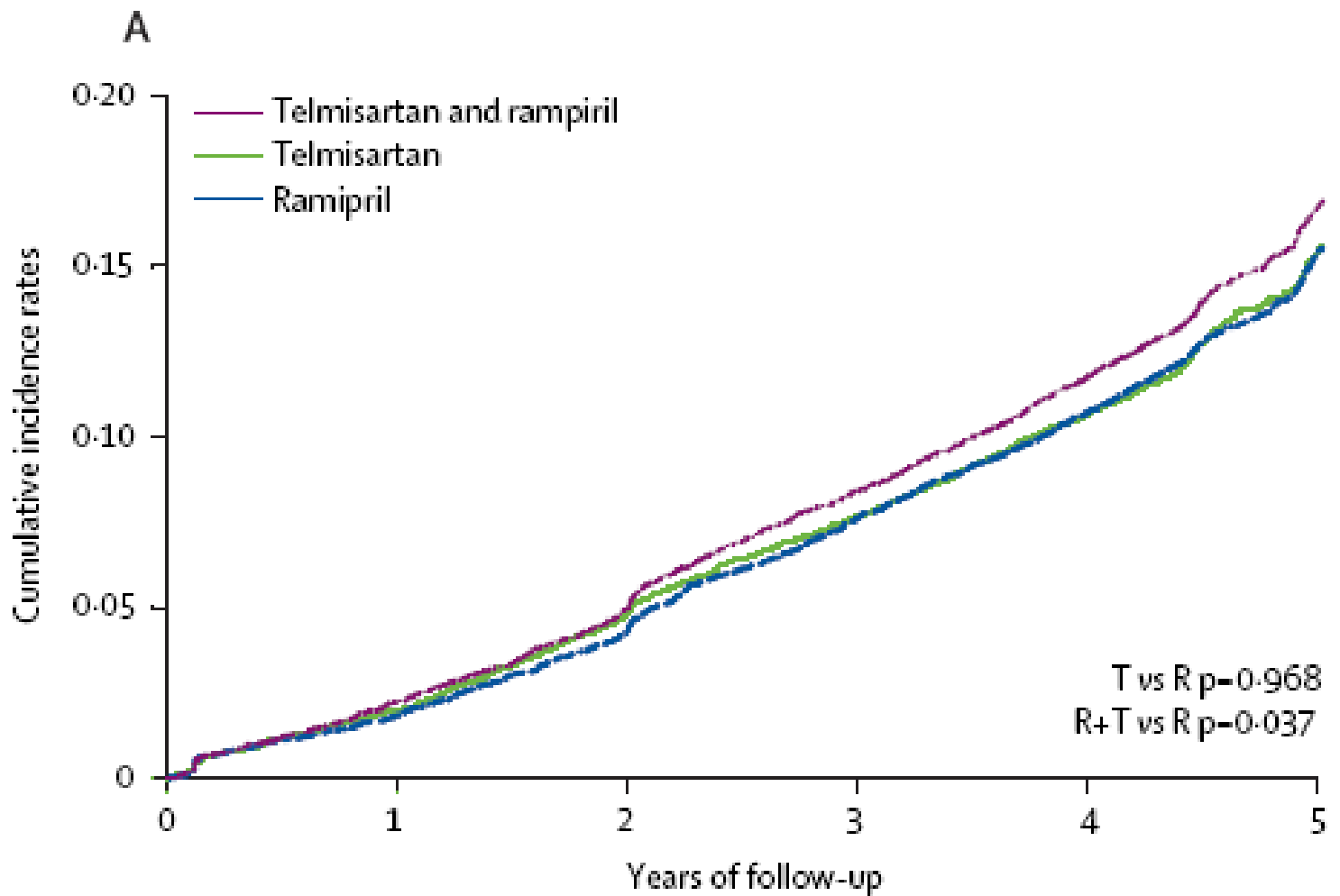
eGFR—estimated glomerular filtration rate (mL/min/1.73 m² [SD]). Number of participants with measurements—25 551 at baseline, 24 970 at 6 weeks, 22 573 at 2 years, 19 601 at study end.

Table 1: Estimated glomerular filtration rate at baseline and changes of eGFR

	Ramipril n (%)	Telmisartan n (%)	Ramipril+ telmisartan n (%)	Telmisartan vs ramipril HR (95% CI)	p	Ramipril+ telmisartan vs ramipril HR (95% CI)	p
All dialysis, doubling, death	1150 (13.4)	1147 (13.4)	1233 (14.5)	1.00 (0.92-1.09)	0.968	1.09 (1.01-1.18)	0.037
All dialysis and doubling	174 (2.03)	189 (2.21)	212 (2.49)	1.09 (0.89-1.34)	0.420	1.24 (1.01-1.51)	0.038
All dialysis	48 (0.56)	51 (0.60)	63 (0.74)	1.07 (0.72-1.58)	0.747	1.33 (0.92-1.94)	0.133
All death	1014 (11.8)	989 (11.6)	1065 (12.5)	0.98 (0.90-1.07)	0.641	1.07 (0.98-1.16)	0.144
Doubling	140 (1.63)	155 (1.81)	166 (1.95)	1.11 (0.88-1.39)	0.378	1.20 (0.96-1.50)	0.110
Acute dialysis	13 (0.15)	20 (0.23)	28 (0.33)	1.55 (0.77-3.11)	0.221	2.19 (1.13-4.22)	0.020
Chronic dialysis	33 (0.39)	31 (0.36)	34 (0.40)	0.94 (0.58-1.54)	0.817	1.05 (0.65-1.69)	0.854

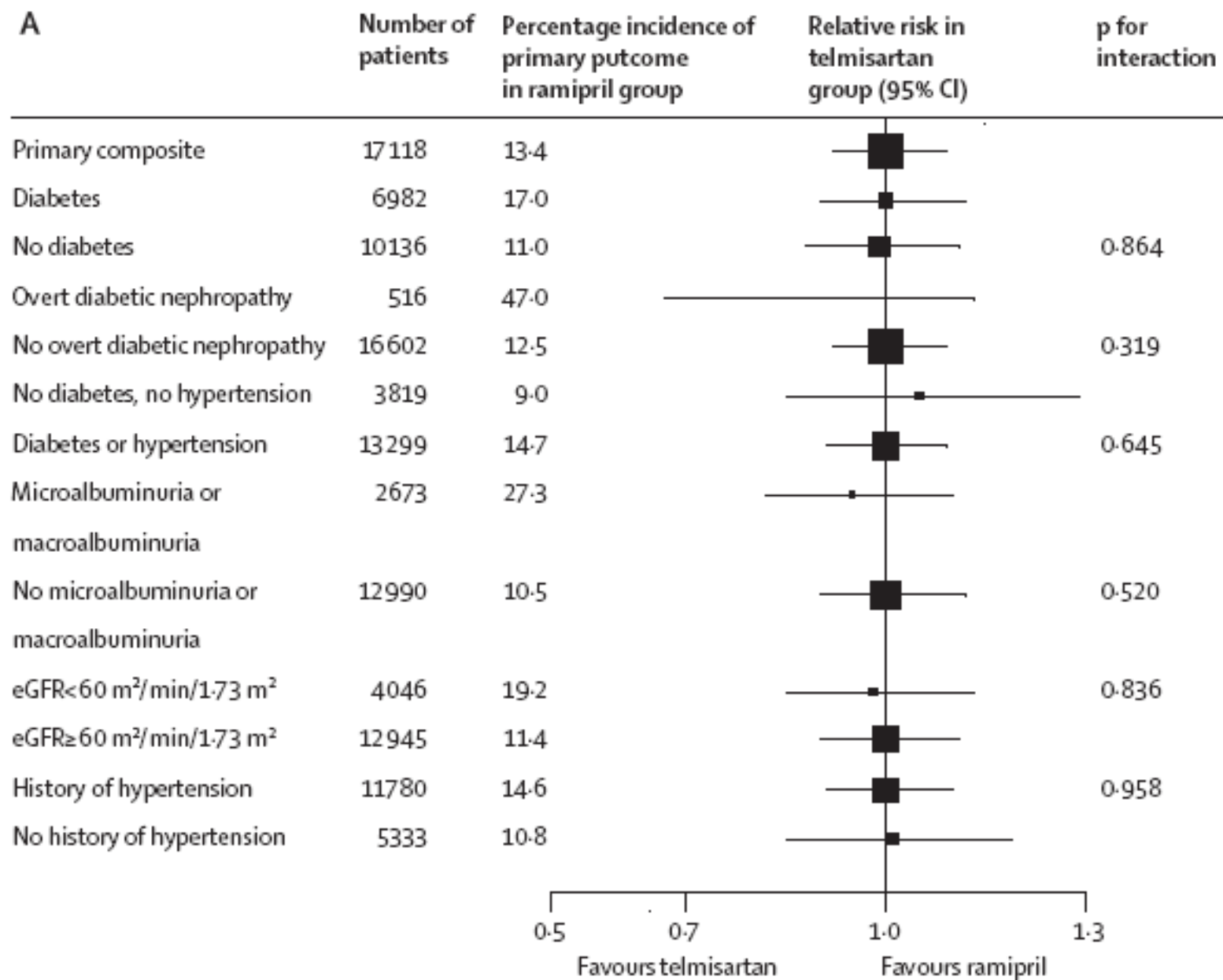
Dialysis—at least one dialysis. Chronic dialysis—more than 2 months. Acute dialysis—2 months or less. Doubling—doubling of serum creatinine from baseline values. HR—hazard ratio. Reasons for acute dialysis were reported as severe infection (n=22), volume depletion (n=9), post-surgery (n=7), drugs (n=5), specific renal diseases (n=5), and other reasons (n=23). In three of 165 originally reported cases of dialysis,⁶ detailed analysis revealed that no dialysis took place. In three of the 162 cases of dialysis, we got no information on duration of dialysis. Investigators could report several reasons for acute dialysis.

Table 2: Incidence of primary and secondary renal outcomes and of its components



Number at risk

Telmisartan	8542	8362	8123	7895	7643	4999
Ramipril	8576	8406	8194	7933	7670	4968
Telmisartan and ramipril	8502	8301	8074	7797	7526	4850



	Ramipril gMean (95% CI)	Telmisartan gMean (95% CI)	Ramipril+telmisartan gMean (95% CI)	Telmisartan vs ramipril p	Telmisartan+ramipril vs ramipril p
UACR, Baseline	0.81 (0.78–0.84)	0.83 (0.80–0.86)	0.81 (0.78–0.84)	0.246	0.923
2-year ratio to baseline	1.17 (1.13–1.20)	1.08 (1.05–1.12)	1.05 (1.02–1.08)	0.0013	<0.0001
Final ratio to baseline	1.32 (1.27–1.37)	1.25 (1.20–1.29)	1.22 (1.17–1.26)	0.033	0.0028
LO ratio to baseline	1.31 (1.26–1.35)	1.24 (1.20–1.28)	1.21 (1.17–1.25)	0.027	0.0009

UACR=urine albumin to creatinine ratio (mg/mmol); Final=study end. gMean=geometric mean. LO=last observation value; for patients with at least one follow-up value, changes from baseline to last observation were compared between groups. All UACR values were log-transformed before analyses; gMean-values are back-transformed. Differences were calculated using an ANOVA model adjusted for baseline values. Number of participants with measurements= 21 076 at baseline, 19 397 at 2 years, 16 098 at study end.

Table 3: Changes in log urine albumin to creatinine ratio

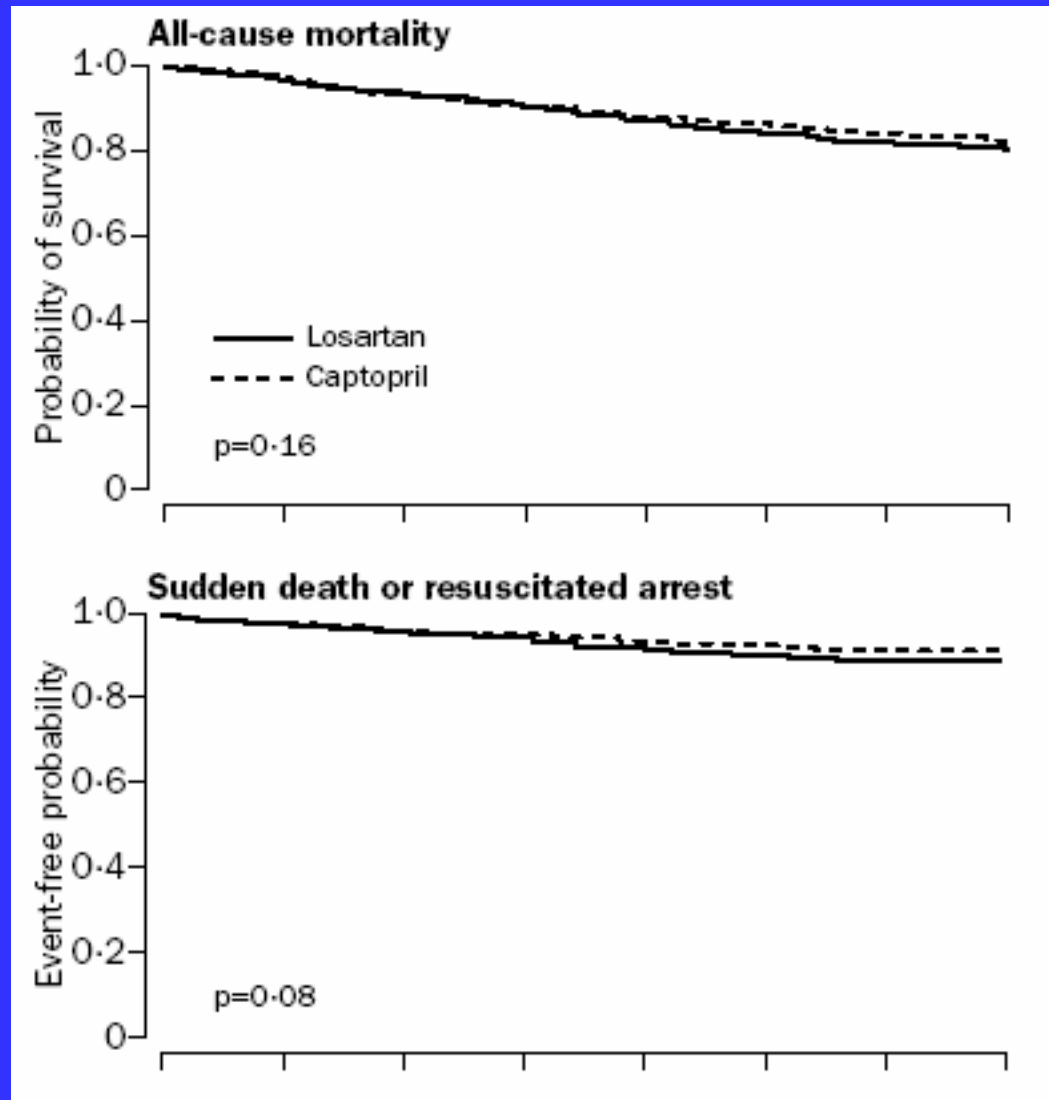
Table 1. Clinical Studies with Comparison Between ACEI and ARB

Authors	No of Patients	Maximal dose	last BP	follow-up	Results
Reference	diseases		(mmHg)		
Gansevoort [9]	11, nonDMCKD	enalapril 10, 20mg losartan 50, 100mg	MAP 96, 93 MAP 100, 96	8 weeks	equivalent proteinuria reduction
Ferrari [10]	11, non-DM CGN	fosinopril 20mg irbesartan 150mg	136/84 131/85	4 weeks	equivalent proteinuria reduction
Russo [11]	10, IgAGN	enalapril 10, 20mg Losartan 50, 150mg	118/65 115/73	4 weeks	equivalent proteinuria reduction
Campbell [12]	24, non-DM,CKD	benazepril 20mg Valsartan 160mg	126/80 129/79	8 weeks	equivalent proteinuria reduction
Nakao [8]	263, non-DM	trandrapril 3mg Losartan 100mg	130/76 130/75	36 weeks	equivalent proteinuria reduction equivalent renal survival

Shoda [4]	68, non-DM	benasepril 5mg or Trandraprol 4mg Candesartan 8mg or Losartan 100mg	128/77 130/76	5 years	ACEI is priority for proteinuria ACEI provides better survival
Mogensen [7]	199, type 2 DM	lisinopril 20mg Candesartan 16mg	MR -10.7 MR -10.4	12 weeks	equivalent proteinuria reduction
Lacourciere [13]	103, type 2 DM	enarapril 10mg Losartan 50mg	145/84 148/86	52 weeks	equivalent proteinuria reduction equivalent GFR
Barnett [14]	250, type 2 DM	enelapril 20mg Telmisartan 80mg	MR -2.9 MR -6.9	5 years	equivalent renal protection

KKY ve MI Sonrası ACE ve ARB Kullanımı

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



%11.7 losartan
%10.4 captopril
p=0.16

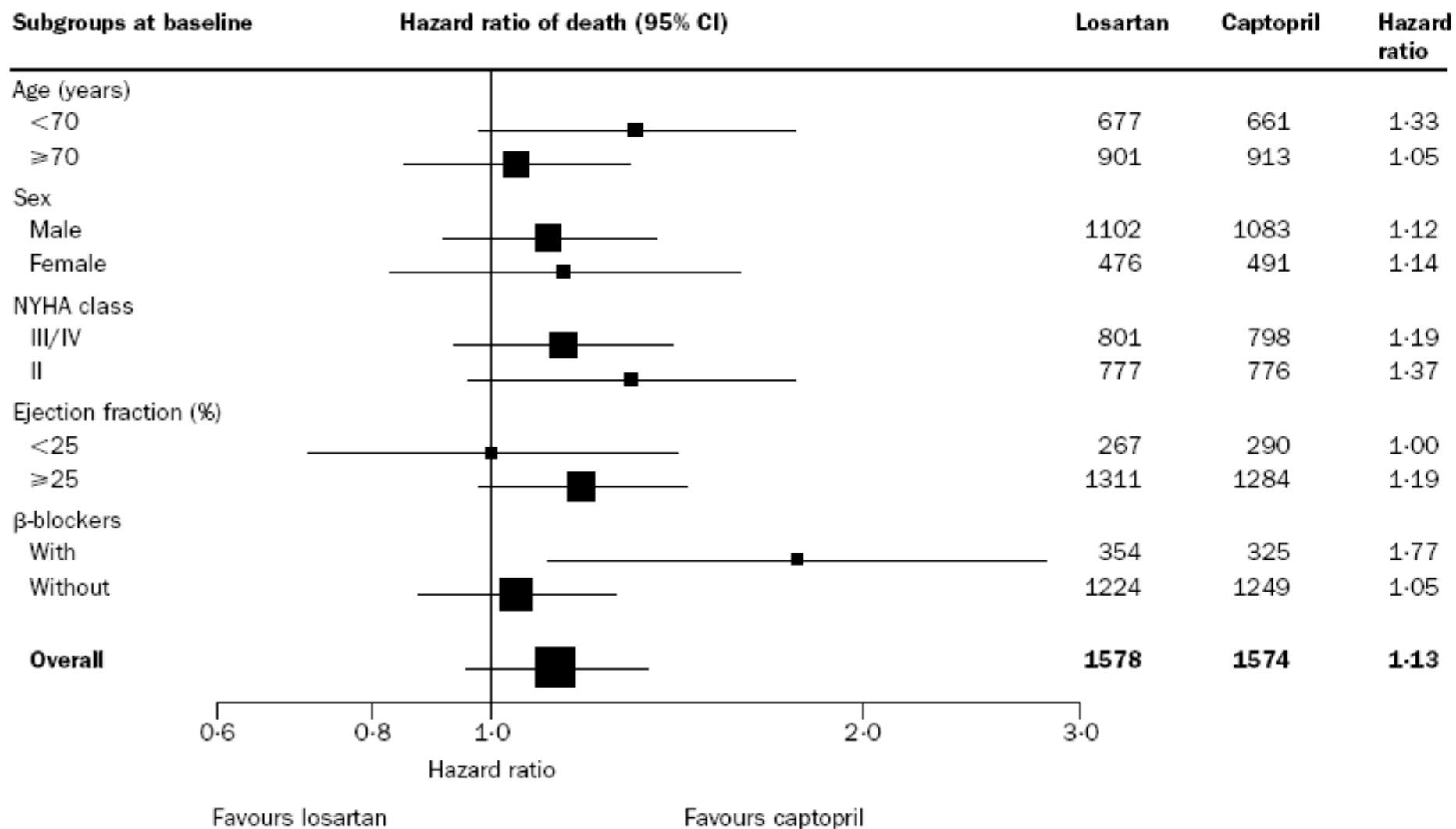
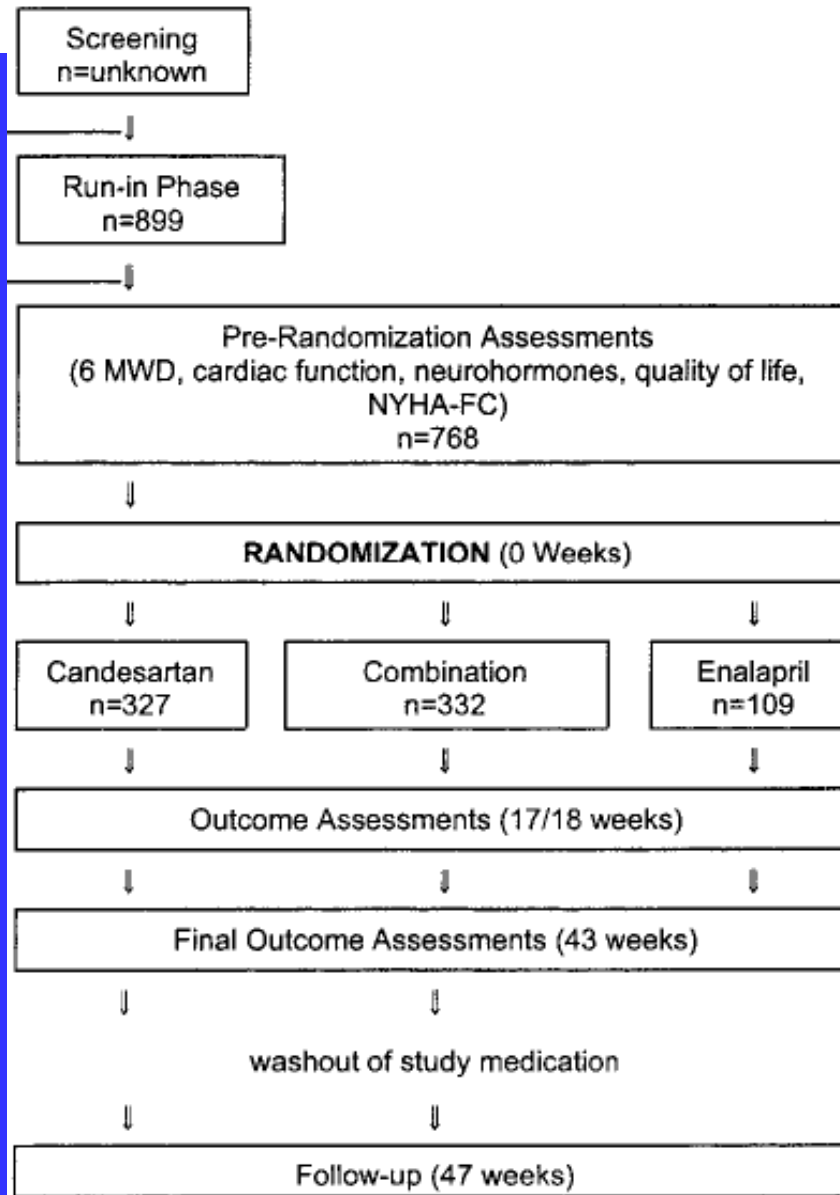


Figure 3: **Mortality by subgroup**

Size of box is proportional to number of events in each category; numbers reflect number of patients in each category.

Comparison of Candesartan, Enalapril, and Their Combination in Congestive Heart Failure

Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) Pilot Study



Study Design

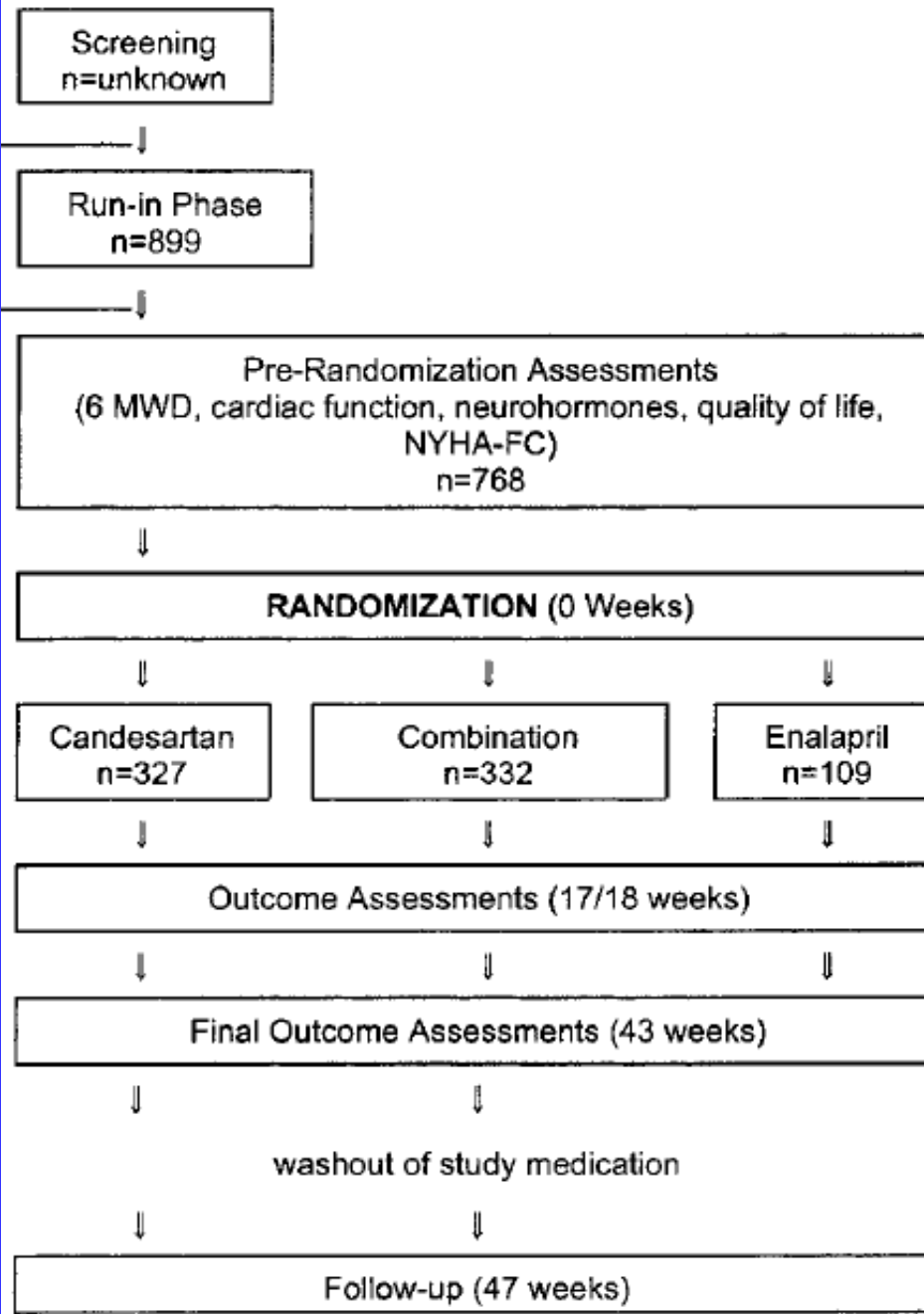


TABLE 3. Clinical Events up to Week 43

	Candesartan				Combination*			Enalapril 20 mg (n=109), n (%)	P†
	Total Group (n=327), n (%)	4 mg (n=111), n (%)	8 mg (n=108), n (%)	16 mg (n=108), n (%)	Total Group (n=332), n (%)	4 mg (n=165), n (%)	8 mg (n=167), n (%)		
Death	20 (6.1)	7 (6.3)	8 (7.4)	5 (4.6)	29 (8.7)	10 (6.1)	19 (11.4)	4 (3.7)	0.15
Any CHF hospitalization	43 (13.1)	11 (9.9)	20 (18.5)	12 (11.1)	31 (9.3)	18 (10.9)	13 (7.8)	7 (6.4)	0.09
Any hospitalization	87 (26.6)	22 (19.8)	37 (34.3)	28 (25.9)	80 (24.1)	42 (25.5)	38 (22.8)	24 (22.0)	0.58
Death/any CHF hospitalization	55 (16.8)	17 (15.3)	22 (20.4)	16 (14.8)	58 (17.5)	27 (16.4)	31 (18.6)	10 (9.2)	0.11
Death/any hospitalization	96 (29.4)	27 (24.3)	38 (35.2)	31 (28.7)	102 (30.7)	48 (29.1)	54 (32.3)	26 (23.9)	0.39
Renal dysfunction	2 (0.6)	1 (0.9)	1 (0.9)	0 (0)	2 (0.6)	0 (0)	2 (1.2)	0 (0)	0.72
Symptomatic hypotension	3 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)	4 (1.2)	1 (0.6)	3 (1.8)	1 (0.9)	0.93

*Combination includes enalapril 20 mg daily with the candesartan dose.

†Based on a χ^2 comparison across the total in the 3 main groups of candesartan, combination, and enalapril. Of the 10 pairwise comparisons of candesartan alone vs enalapril or the combination group vs enalapril, none were statistically significant except for the outcome of death/any CHF hospitalization between combination vs enalapril ($P=0.037$).

© Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial

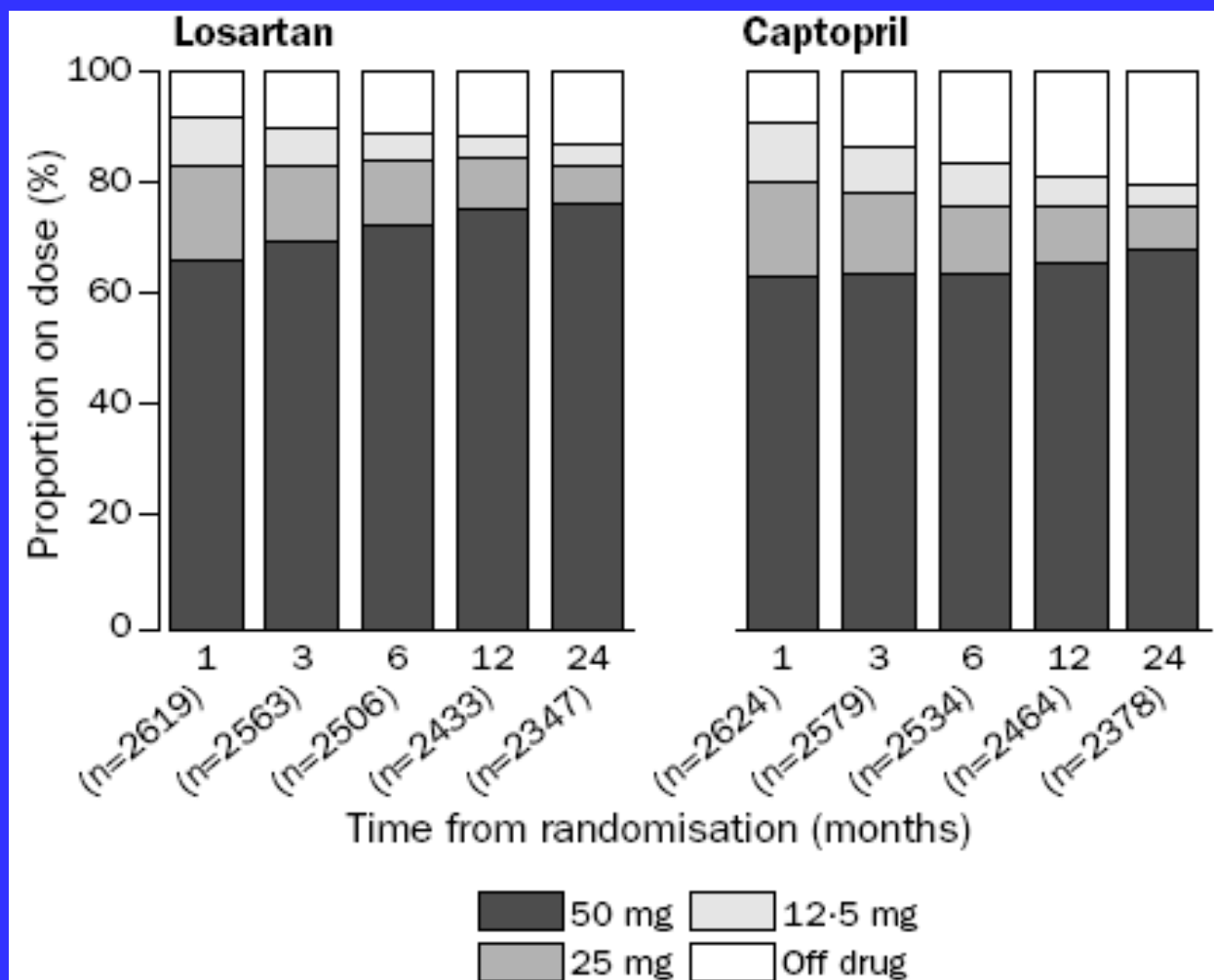


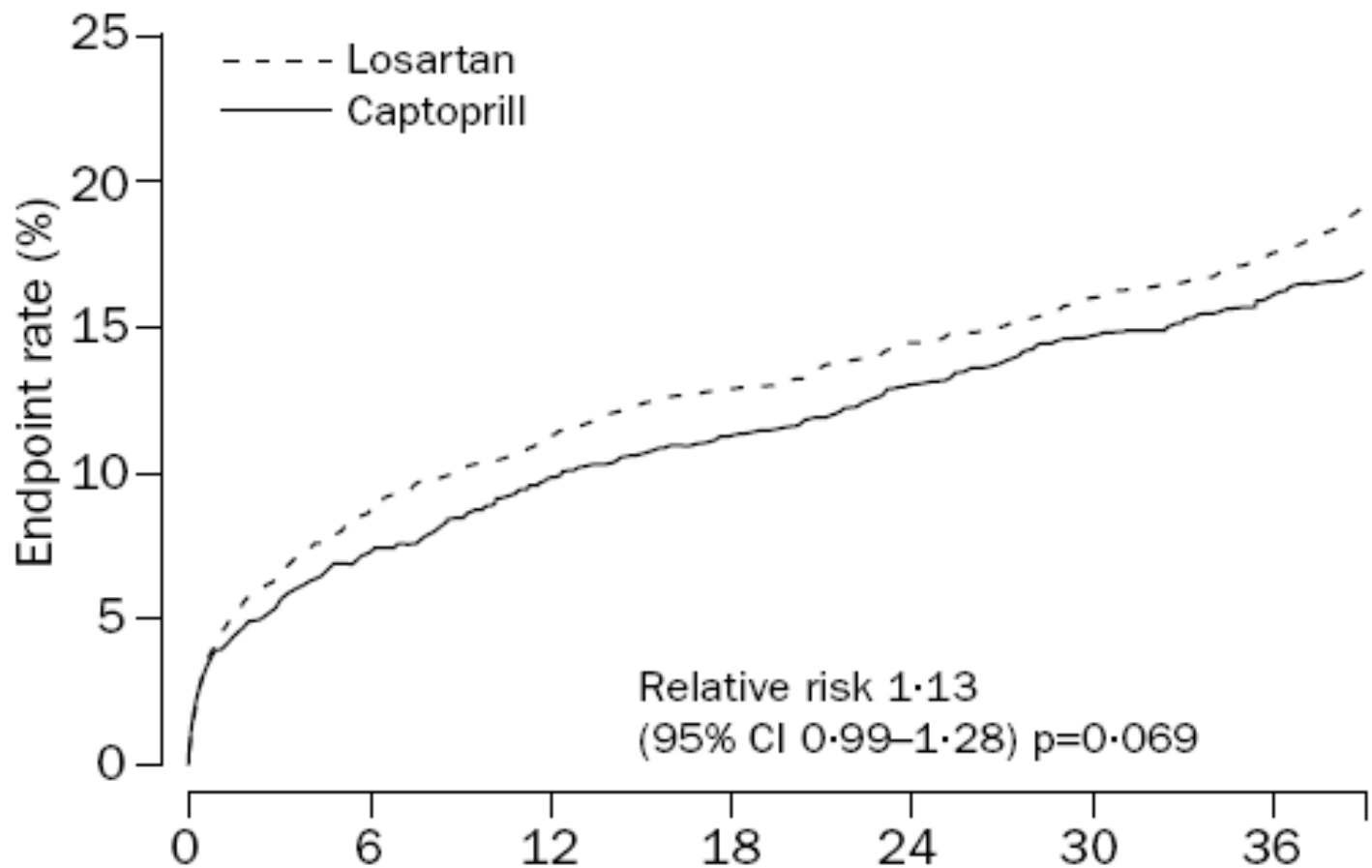
Figure 2: **Dose of study drug**

Losartan was administered once daily and captopril three times daily.

	Losartan (n=2744)	Captopril (n=2733)	Relative risk (95% CI)	p
All-cause mortality	499 (18.2%)	447 (16.4%)	1.13 (0.99–1.28)	0.069
SCD/RCA	239 (8.7%)	203 (7.4%)	1.19 (0.99–1.43)	0.072
Myocardial reinfarction (fatal/ non-fatal)*	384 (14.0%)	379 (13.9%)	1.03 (0.89–1.18)	0.722
Other prespecified endpoints				
MI/total mortality	746 (27.2%)	689 (25.2%)	1.10 (0.99–1.22)	0.085
Cardiovascular death	420 (15.3%)	363 (13.3%)	1.17 (1.01–1.34)	0.032
Stroke (fatal/ non-fatal)	140 (5.1%)	132 (4.8%)	1.07 (0.84–1.36)	0.587
CABG	404 (14.7%)	375 (13.7%)	1.09 (0.95–1.26)	0.228
PTCA	466 (17.0%)	492 (18.0%)	0.94 (0.83–1.07)	0.358
Revascularisation	845 (30.8%)	827 (30.3%)	1.03 (0.93–1.13)	0.620
First all-cause admission	1806 (65.8%)	1774 (64.9%)	1.03 (0.97–1.10)	0.362
First admission for heart failure	306 (11.2%)	265 (9.7%)	1.16 (0.98–1.37)	0.072
Cardiovascular admission	1480 (53.9%)	1421 (52.0%)	1.06 (0.99–1.14)	0.108
Non-cardiovascular admission	885 (32.3%)	905 (33.1%)	0.98 (0.90–1.08)	0.719

SCD=sudden cardiac death; RCA=resuscitated cardiac arrest; MI=myocardial infarction; CABG=coronary-artery bypass grafting; PTCA=percutaneous transluminal coronary angioplasty. *Definite or probable as defined by endpoint classification committee.

Table 3: Crude rates and relative risks for prespecified endpoints



Number at risk

Losartan	2744	2504	2432	2390	2344	2301	1285
Captoprill	2733	2534	2463	2423	2374	2329	1309

Figure 4: Kaplan-Meier curve for primary endpoint (all-cause mortality)

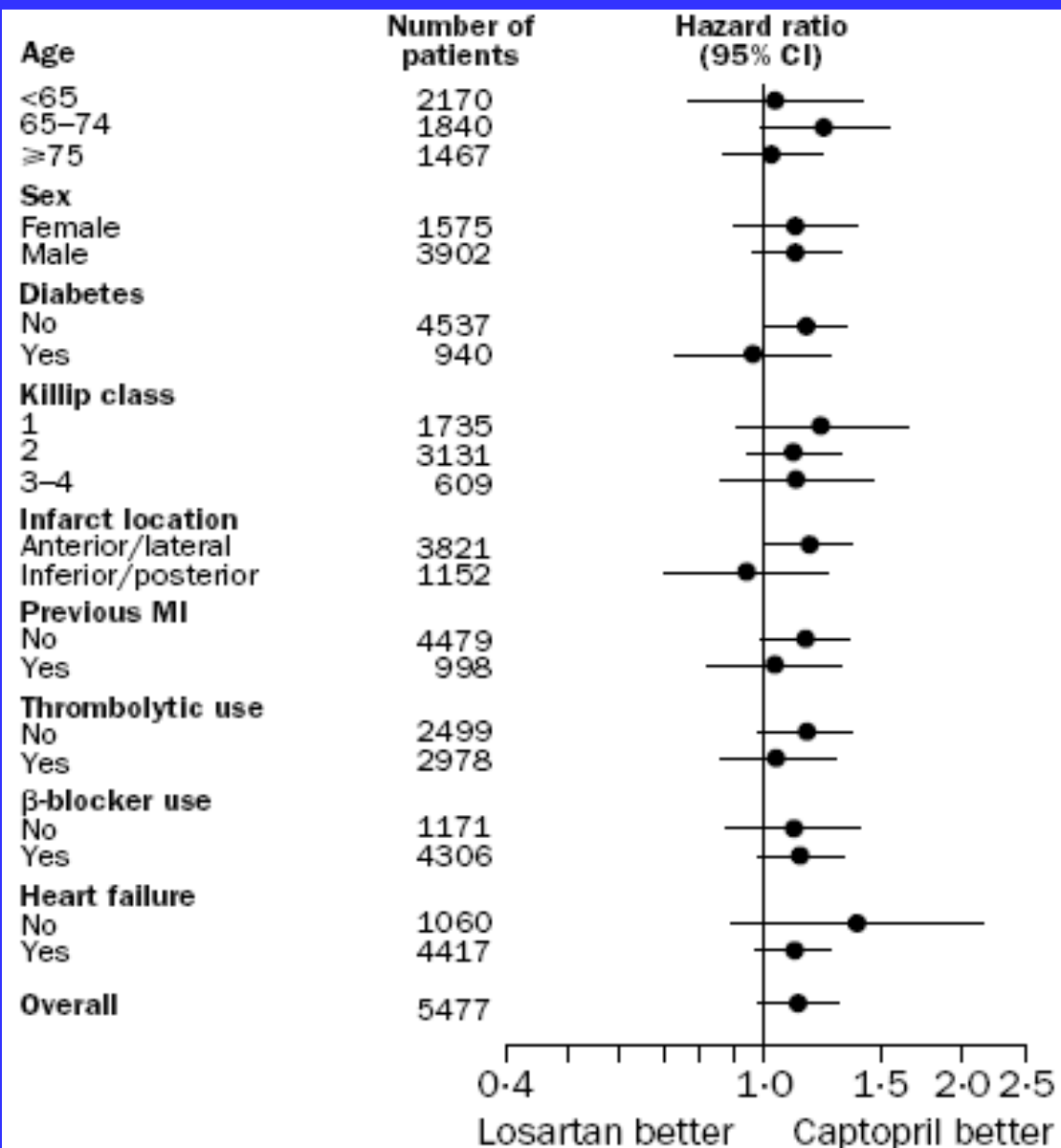


Figure 5: **Subgroup analyses for primary endpoint**

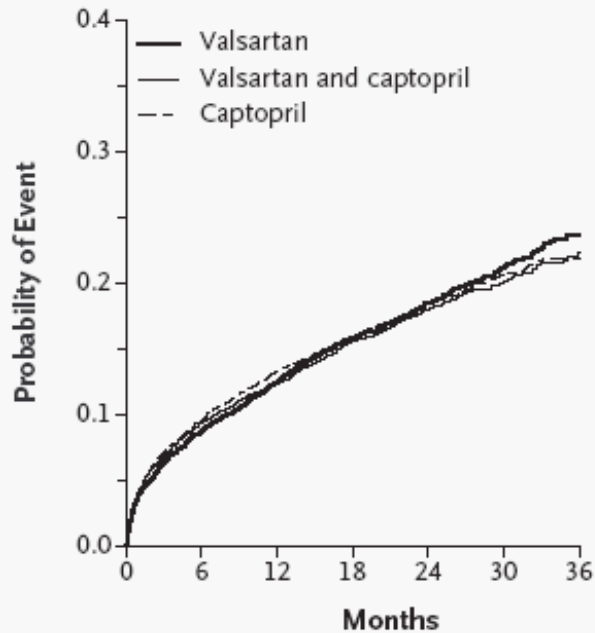
MI=myocardial infarction.

Valsartan, Captopril, or Both in Myocardial Infarction Complicated by Heart Failure, Left Ventricular Dysfunction, or Both

Table 1. Base-Line Characteristics of the Patients.*

Characteristic	Valsartan Group (N=4909)	Valsartan-and-Captopril Group (N=4885)	Captopril Group (N=4909)
Age — yr	65.0±11.8	64.6±11.9	64.9±11.8
Race — no. (%)			
White	4604 (93.8)	4553 (93.2)	4591 (93.5)
Black	125 (2.5)	137 (2.8)	145 (3.0)
Asian	44 (0.9)	53 (1.1)	44 (0.9)
Other	136 (2.8)	142 (2.9)	129 (2.6)
Female sex — no. (%)	1544 (31.5)	1490 (30.5)	1536 (31.3)
Blood pressure — mm Hg			
Systolic	122.7±16.8	122.5±17.1	122.8±17.0
Diastolic	72.3±11.3	72.3±11.4	72.4±11.2
Heart rate — beats/min	76.2±13.0	76.2±12.7	76.2±12.8
Body-mass index†			
Median	27.34	27.24	27.14
Interquartile range	24.69–30.47	24.62–30.35	24.54–30.22
Left ventricular ejection fraction — %‡	35.3±10.4	35.3±10.3	35.3±10.4
Killip class — no. (%)			
I	1294 (26.5)	1381 (28.4)	1424 (29.1)
II	2401 (49.2)	2329 (47.9)	2346 (48.0)
III	874 (17.9)	842 (17.3)	813 (16.6)
IV	313 (6.4)	312 (6.4)	306 (6.3)
Medical history — no. (%)			
Myocardial infarction	1395 (28.4)	1376 (28.2)	1333 (27.2)
Hypertension	2732 (55.7)	2700 (55.3)	2690 (54.8)
Diabetes mellitus	1134 (23.1)	1146 (23.5)	1120 (22.8)
Heart failure	759 (15.5)	701 (14.4)	714 (14.5)
Stroke	292 (5.9)	305 (6.2)	298 (6.1)
Smoking	1556 (31.7)	1546 (31.6)	1562 (31.8)
Coronary-artery bypass grafting	355 (7.2)	327 (6.7)	344 (7.0)
Percutaneous coronary intervention	376 (7.7)	337 (6.9)	354 (7.2)

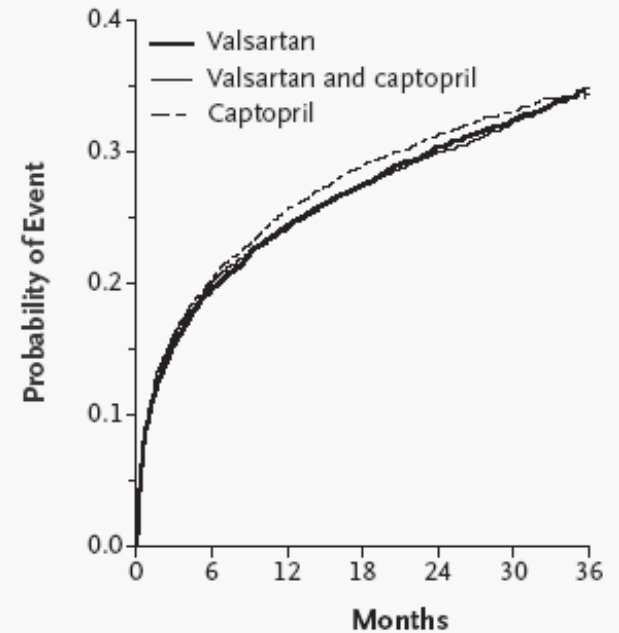
A Death from Any Cause



No. at Risk

Valsartan	4909	4464	4272	4007	2648	1437	357
Valsartan and captopril	4885	4414	4265	3994	2648	1435	382
Captopril	4909	4428	4241	4018	2635	1432	364

B Combined Cardiovascular End Point



No. at Risk

Valsartan	4909	3921	3667	3391	2188	1204	290
Valsartan and captopril	4885	3887	3646	3391	2221	1185	313
Captopril	4909	3896	3610	3355	2155	1148	295

Valsartan: 979 ölüm (%19.9) HR: 1.00 vs captopril, p=0.98

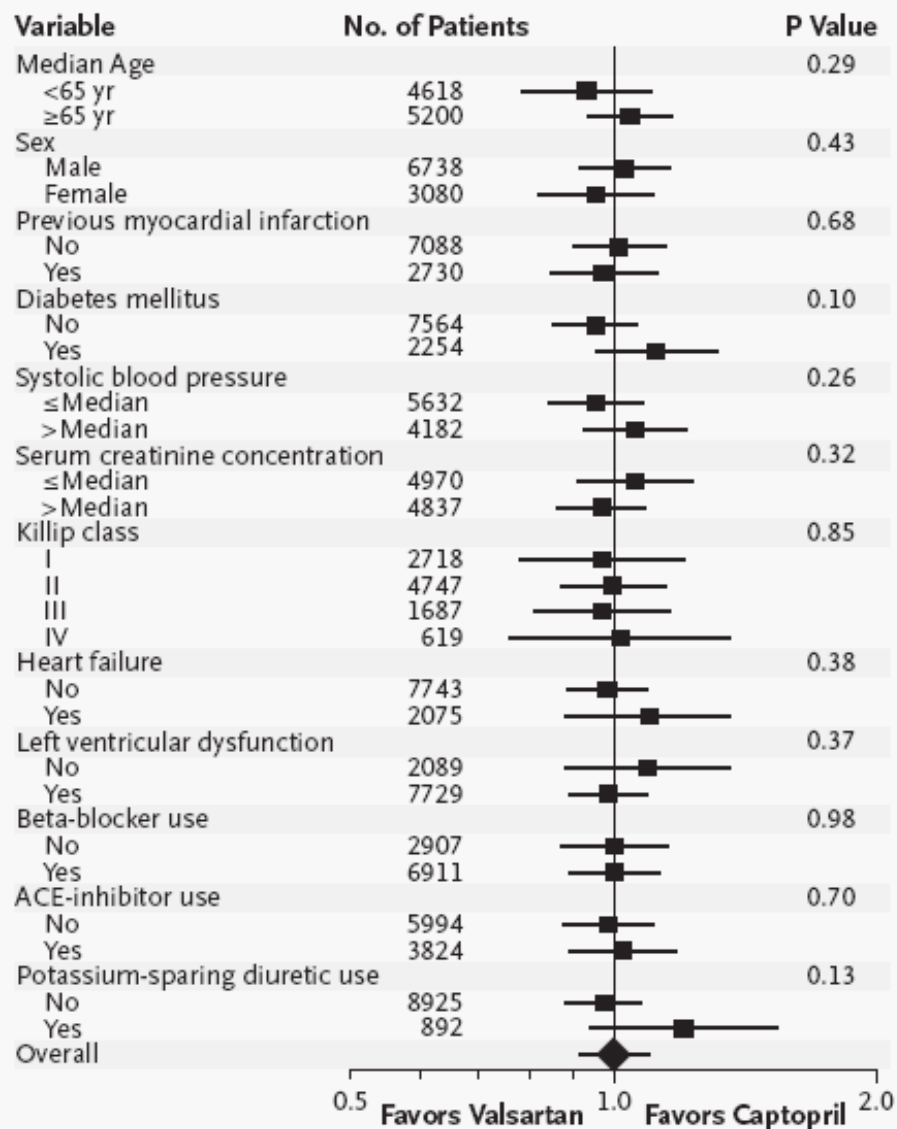
Captopril: 958 ölüm (%19.5)

Vals-Capt: 941 (%19.3) HR: 0.98 vs captopril p=0.73

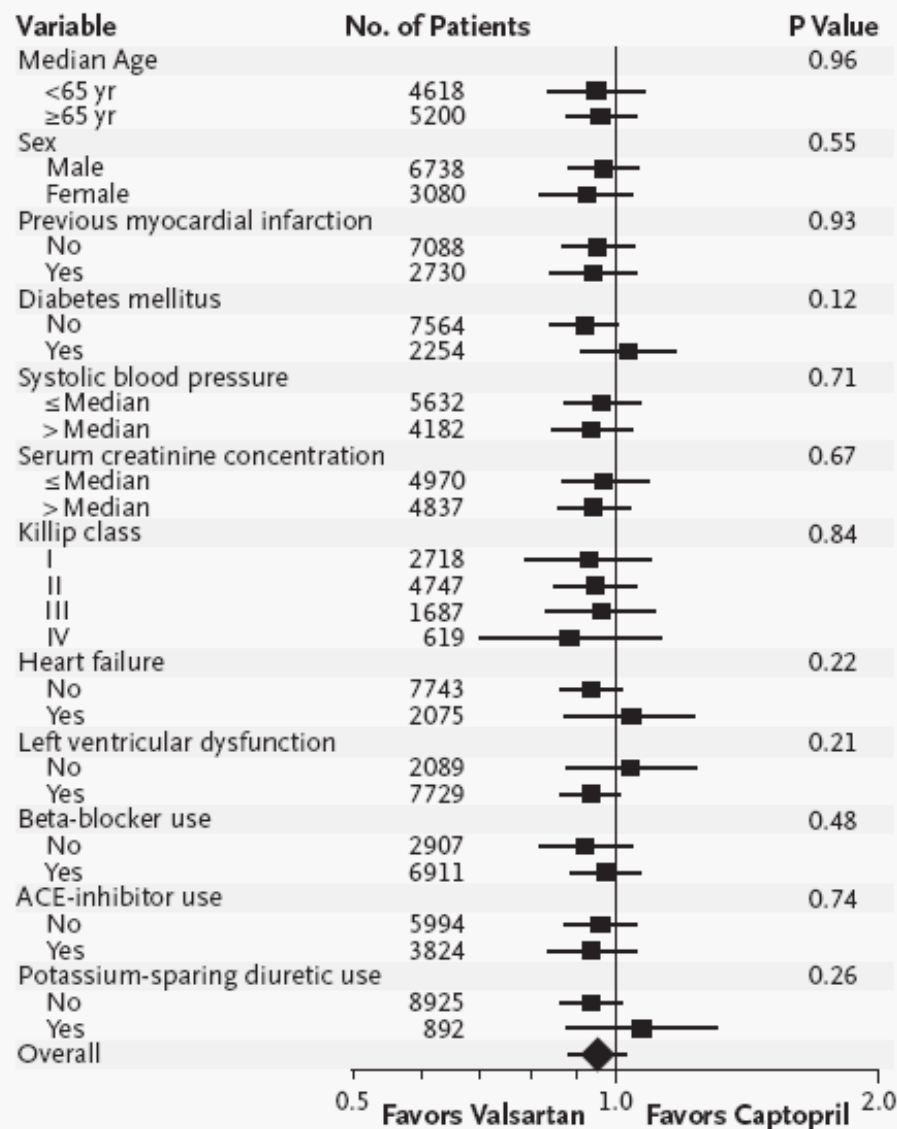
Table 2. Cardiovascular Mortality and Morbidity.*

End Point	Valsartan Group (N=4909)	Valsartan-and-Captopril Group (N=4885)	Captopril Group (N=4909)	Valsartan vs. Captopril			Valsartan and Captopril vs. Captopril	
				Hazard Ratio (97.5% CI)	P Value for Non-Value inferiority	P Value	Hazard Ratio (97.5% CI)	P Value
	<i>number (percent)</i>							
Death from cardiovascular causes	827 (16.8)	827 (16.9)	830 (16.9)	0.98 (0.87–1.09)	0.62	0.001	1.00 (0.89–1.11)	0.95
Death from cardiovascular causes or myocardial infarction	1102 (22.4)	1096 (22.4)	1132 (23.1)	0.95 (0.87–1.05)	0.25	<0.001	0.96 (0.88–1.06)	0.40
Death from cardiovascular causes or heart failure	1326 (27.0)	1331 (27.2)	1335 (27.2)	0.97 (0.90–1.05)	0.51	<0.001	1.00 (0.92–1.09)	0.94
Death from cardiovascular causes, myocardial infarction, or heart failure	1529 (31.1)	1518 (31.1)	1567 (31.9)	0.95 (0.88–1.03)	0.20	<0.001	0.97 (0.89–1.05)	0.37
Death from cardiovascular causes, myocardial infarction, heart failure, resuscitation after cardiac arrest, or stroke	1612 (32.8)	1580 (32.3)	1641 (33.4)	0.96 (0.89–1.04)	0.25	<0.001	0.96 (0.89–1.04)	0.26

A Death from Any Cause



B Combined Cardiovascular End Point



Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events

The ONTARGET Investigators*

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Ramipril (N=8576)	Telmisartan (N=8542)	Combination Therapy (N=8502)
Age — yr	66.4±7.2	66.4±7.1	66.5±7.3
Blood pressure — mm Hg†	141.8±17.4/82.1±10.4	141.7±17.2/82.1±10.4	141.9±17.6/82.1±10.4
Heart rate — beats/min	67.9±12.2	68.0±12.3	67.7±12.2
Body-mass index‡	28.1±4.5	28.1±4.6	28.0±4.5
Cholesterol — mmol/liter			
Total	4.9±1.1	4.9±1.1	5.0±1.2
LDL	2.9±1.0	2.9±1.0	2.9±1.0
HDL	1.3±0.4	1.3±0.4	1.3±0.4
Triglycerides — mmol/liter	1.7±1.1	1.7±1.1	1.7±1.1
Glucose — mmol/liter	6.7±2.6	6.7±2.5	6.7±2.6
Creatinine — μmol/liter	93.5±22.8	93.8±22.8	93.8±22.8
Potassium — mmol/liter	4.4±0.4	4.4±0.4	4.4±0.5
Female sex — no. (%)	2331 (27.2)	2250 (26.3)	2250 (26.5)

Clinical history — no. (%)

Coronary artery disease	6382 (74.4)	6367 (74.5)	6353 (74.7)
Myocardial infarction	4146 (48.3)	4214 (49.3)	4189 (49.3)

Angina pectoris

Stable	3039 (35.4)	2958 (34.6)	2960 (34.8)
Unstable	1257 (14.7)	1296 (15.2)	1264 (14.9)

Stroke or transient ischemic attacks	1805 (21.0)	1758 (20.6)	1779 (20.9)
--------------------------------------	-------------	-------------	-------------

Peripheral artery disease	1136 (13.2)	1161 (13.6)	1171 (13.8)
---------------------------	-------------	-------------	-------------

Hypertension	5918 (69.0)	5862 (68.6)	5827 (68.5)
--------------	-------------	-------------	-------------

Diabetes	3146 (36.7)	3246 (38.0)	3220 (37.9)
----------	-------------	-------------	-------------

Left ventricular hypertrophy	1085 (12.7)	1120 (13.1)	1082 (12.7)
------------------------------	-------------	-------------	-------------

Microalbuminuria¶	929 (13.1)	923 (13.2)	929 (13.3)
-------------------	------------	------------	------------

Previous procedures — no. (%)

Coronary-artery bypass grafting	1862 (21.7)	1920 (22.5)	1893 (22.3)
---------------------------------	-------------	-------------	-------------

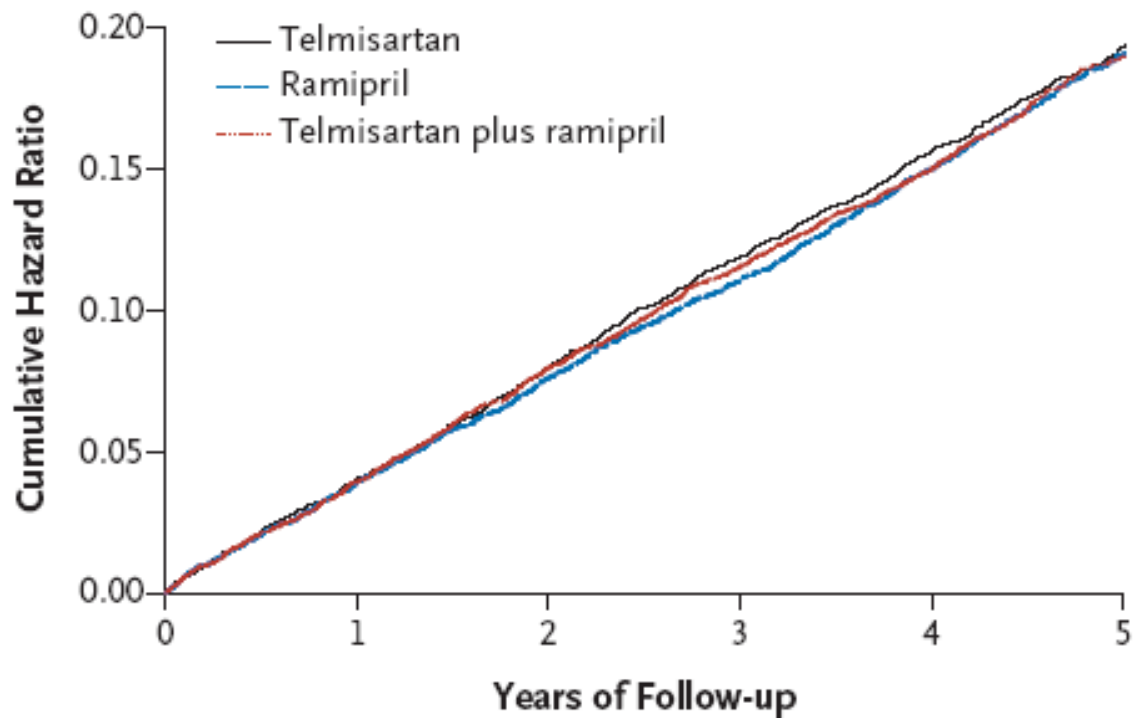
Percutaneous transluminal coronary angioplasty	2527 (29.5)	2476 (29.0)	2434 (28.6)
--	-------------	-------------	-------------

Table 1. (Continued.)

Characteristic	Ramipril (N = 8576)	Telmisartan (N = 8542)	Combination Therapy (N = 8502)
Medication — no. (%)			
Statin	5234 (61.0)	5294 (62.0)	5255 (61.8)
Beta-blocker	4847 (56.5)	4860 (56.9)	4876 (57.4)
Aspirin	6473 (75.5)	6469 (75.7)	6461 (76.0)
Clopidogrel or ticlopidine	927 (10.8)	966 (11.3)	931 (11.0)
Antiplatelet agent	6903 (80.5)	6926 (81.1)	6898 (81.1)
Diuretic	2454 (28.6)	2359 (27.6)	2351 (27.7)
Calcium-channel blocker	2821 (32.9)	2787 (32.6)	2864 (33.7)

Table 3. Incidence of the Primary Outcome, Its Components, and Death from Any Cause.

Outcome	Ramipril (N=8576)	Telmisartan (N=8542)	Combination Therapy (N=8502)	Telmisartan vs.	Combination Therapy	
				Ramipril	vs. Ramipril	
			<i>number (percent)</i>		<i>risk ratio (95% CI)</i>	
Death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure*	1412 (16.5)	1423 (16.7)	1386 (16.3)	1.01 (0.94–1.09)	0.99 (0.92–1.07)	
Death from cardiovascular causes, myocardial infarction, or stroke†	1210 (14.1)	1190 (13.9)	1200 (14.1)	0.99 (0.91–1.07)	1.00 (0.93–1.09)	
Myocardial infarction‡	413 (4.8)	440 (5.2)	438 (5.2)	1.07 (0.94–1.22)	1.08 (0.94–1.23)	
Stroke‡	405 (4.7)	369 (4.3)	373 (4.4)	0.91 (0.79–1.05)	0.93 (0.81–1.07)	
Hospitalization for heart failure‡	354 (4.1)	394 (4.6)	332 (3.9)	1.12 (0.97–1.29)	0.95 (0.82–1.10)	
Death from cardiovascular causes	603 (7.0)	598 (7.0)	620 (7.3)	1.00 (0.89–1.12)	1.04 (0.93–1.17)	
Death from noncardiovascular causes	411 (4.8)	391 (4.6)	445 (5.2)	0.96 (0.83–1.10)	1.10 (0.96–1.26)	
Death from any cause	1014 (11.8)	989 (11.6)	1065 (12.5)	0.98 (0.90–1.07)	1.07 (0.98–1.16)	



No. at Risk						
Telmisartan	8542	8177	7778	7420	7051	1687
Ramipril	8576	8214	7832	7472	7093	1703
Telmisartan plus ramipril	8502	8133	7738	7375	7022	1718

Figure 1. Kaplan–Meier Curves for the Primary Outcome in the Three Study Groups.

The composite primary outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.

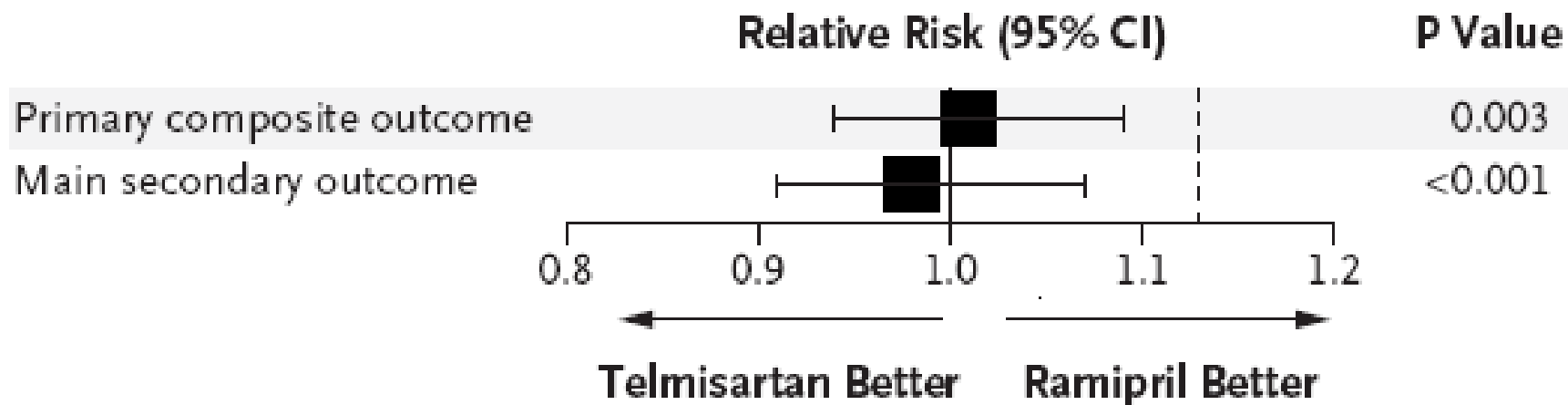
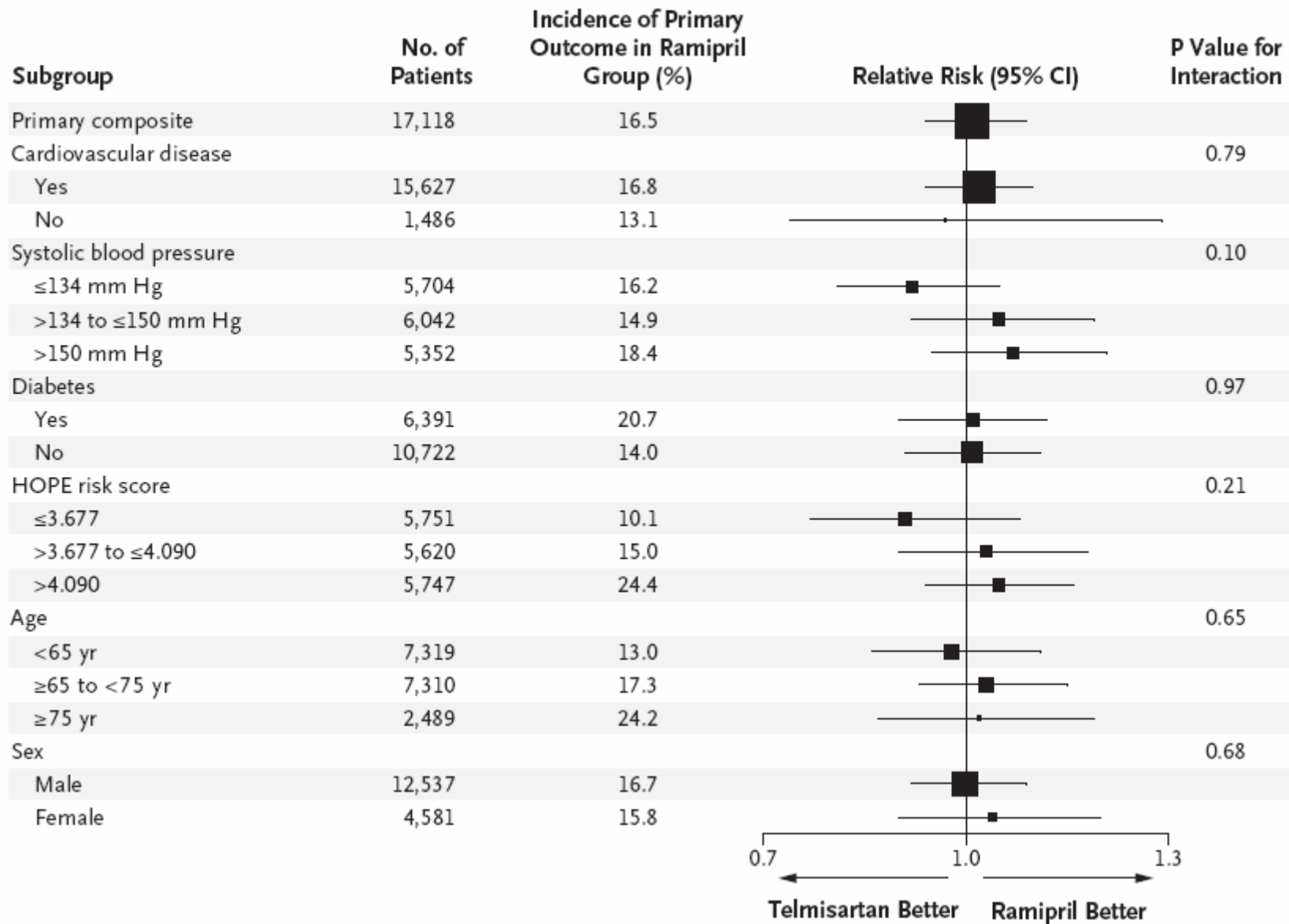


Figure 2. Relative Risk of the Primary Outcome and of the Main Secondary Outcome.

The primary composite outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. The main secondary outcome was death from cardiovascular causes, myocardial infarction, or stroke, which was used as the primary outcome in the Heart Outcomes Prevention Evaluation (HOPE) trial.⁵ The P value is for the comparison with the noninferiority margins.

A



Diyabet Gelişimini Önleme

Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers for Prevention of Type 2 Diabetes

Table 1. Prevention of Type 2 Diabetes by ACE Inhibitors or ARBs

Trial (Ref. No.)	No. of Patients	Years of Follow-Up*	Percent of New Diabetics	Risk Ratio (95% Confidence Interval)†
CAPPP (15)	10,985	6.1	Captopril 337/5,183 (6.5%) Diuretic/beta-blocker 380/5,230 (7.3%)	0.79 (0.67–0.94)
STOP-2 (16)	6,614	5	Conventional drugs 97/1,961 (4.9%) ACE inhibitors 93/1,969 (4.7%)	0.96 (0.72–1.27)
HOPE (17)	9,297	5	Ramipril 102/2,837 (3.6%) Placebo 155/2,883 (5.4%)	0.66 (0.51–0.85)
LIFE (18)	9,193	4.8	Losartan 241/4,019 (6%) Atenolol 319/3,979 (8%)	0.75 (0.63–0.88)
ALLHAT (19)	33,357	4.9	Lisinopril 119/4,096 (8.1%) Chlorthalidone 302/6,766 (11.6%)	0.70 (0.56–0.86)
ANBP2 (20)	6,083	Median 4.1	Enalapril 138/2,800 (4.9%) HCTZ 200/2,826 (7.1%)	0.66 (0.54–0.85)
SCOPE (21)	4,937	3.7 Maximum 5	Candesartan 93/2,167 (4.3%) Placebo 115/2,175 (5.3%)	0.81 (0.61–1.02)
ALPINE (22)	392	1	Candesartan ± felodipine 1/196 (0.5%) Atenolol ± HCTZ 8/196 (4%)	0.13 (0.03–0.99)
CHARM (23)	7,599	3.2	Candesartan 163/2,715 (6%) Placebo 202/2,721 (7%)	0.78 (0.64–0.96)
SOLVD (24)	4,228	3.4	Enalapril 9/153 (5.9%) Placebo 31/138 (22.4%)	0.26 (0.13–0.53)
VALUE (25)	15,245	4.2	Valsartan 690/5,267 (13.1%) Amlodipine 845/5,152 (16.4%)	0.77 (0.69–0.86)
PEACE (26)	8,290	Maximum 7 Median 4.8	Trandolapril 335/3,432 (9.8%) Placebo 399/3,472 (11.5%)	0.83 (0.72–0.96)

Yeni tanı DM insidansında;

ACE inhibitörleri: %27

ARB: %23

Risk azalması

Diđer Olumlu Etkiler

Losartan and Perindopril Effects on Plasma Plasminogen Activator Inhibitor-1 and Fibrinogen in Hypertensive Type 2 Diabetic Patients

Table 2. Effects of treatment with perindopril and losartan

	Placebo	Perindopril	P	Placebo	Losartan	P	Comparison Between Treatments
SBP (mm Hg)	162 ± 13	146 ± 10	.001	162 ± 14	147 ± 11	.001	NS
DBP (mm Hg)	102 ± 6	87 ± 5	.001	102 ± 6	88 ± 5	.001	NS
BMI (kg/m ²)	26 ± 0.9	27 ± 0.8	NS	26 ± 0.8	26 ± 0.7	NS	NS
PAI-1 (ng/mL)	42 ± 21	32 ± 17	.028	41 ± 19	45 ± 22	NS	.01
Fibrinogen (mg/dL)	356 ± 74	312 ± 59	NS	344 ± 67	333 ± 59	NS	NS
FBG (mg/dL)	112 ± 7.3	107 ± 6.9	NS	113 ± 7.5	111 ± 7.0	NS	NS
Serum creatinine (mg/dL)	1.1 ± 0.4	1.1 ± 0.4	NS	1.1 ± 0.5	1.1 ± 0.4	NS	NS
Total cholesterol (mg/dL)	197 ± 23	186 ± 19	NS	191 ± 20	188 ± 19	NS	NS
HDL cholesterol (mg/dL)	44 ± 5	46 ± 6	NS	44 ± 5	44 ± 6	NS	NS
Triglycerides (mg/dL)	142 ± 49	127 ± 44	NS	145 ± 50	140 ± 48	NS	NS
HbA _{1c} (%)	7.2 ± 1.9	7.1 ± 1.7	NS	6.9 ± 2.0	7.0 ± 1.8	NS	NS

NS = not significant; BMI = body mass index; PAI-1 = plasminogen activator inhibitor; FBG = fasting blood glucose; HbA_{1c} = glycosylated hemoglobin; other abbreviations as in Table 1.

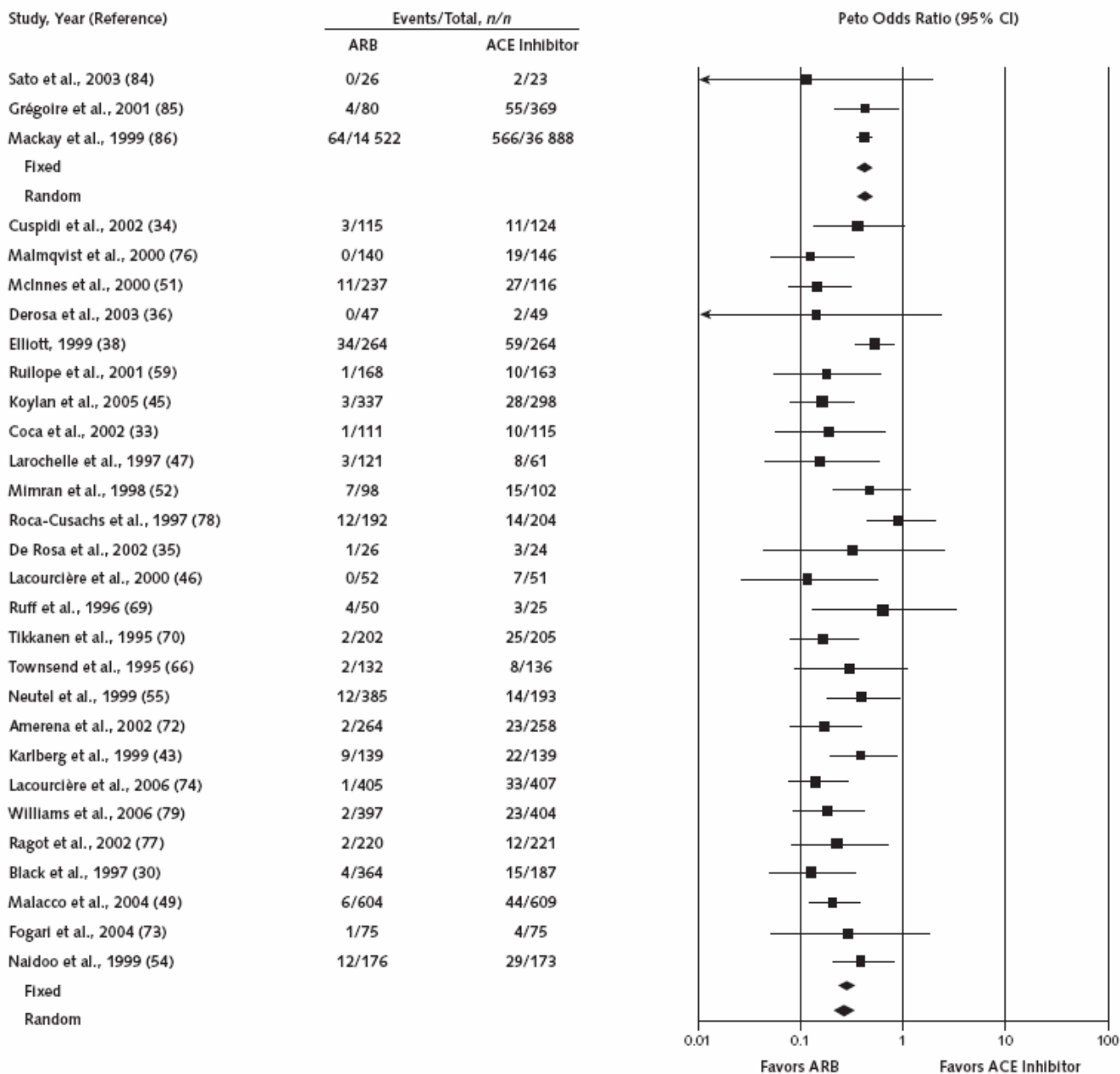
Data are given as mean ± SD.

Yan Etki Profileri

Table 2. Discontinuation of Study Medications and Selected Reasons for Permanent Discontinuation.*

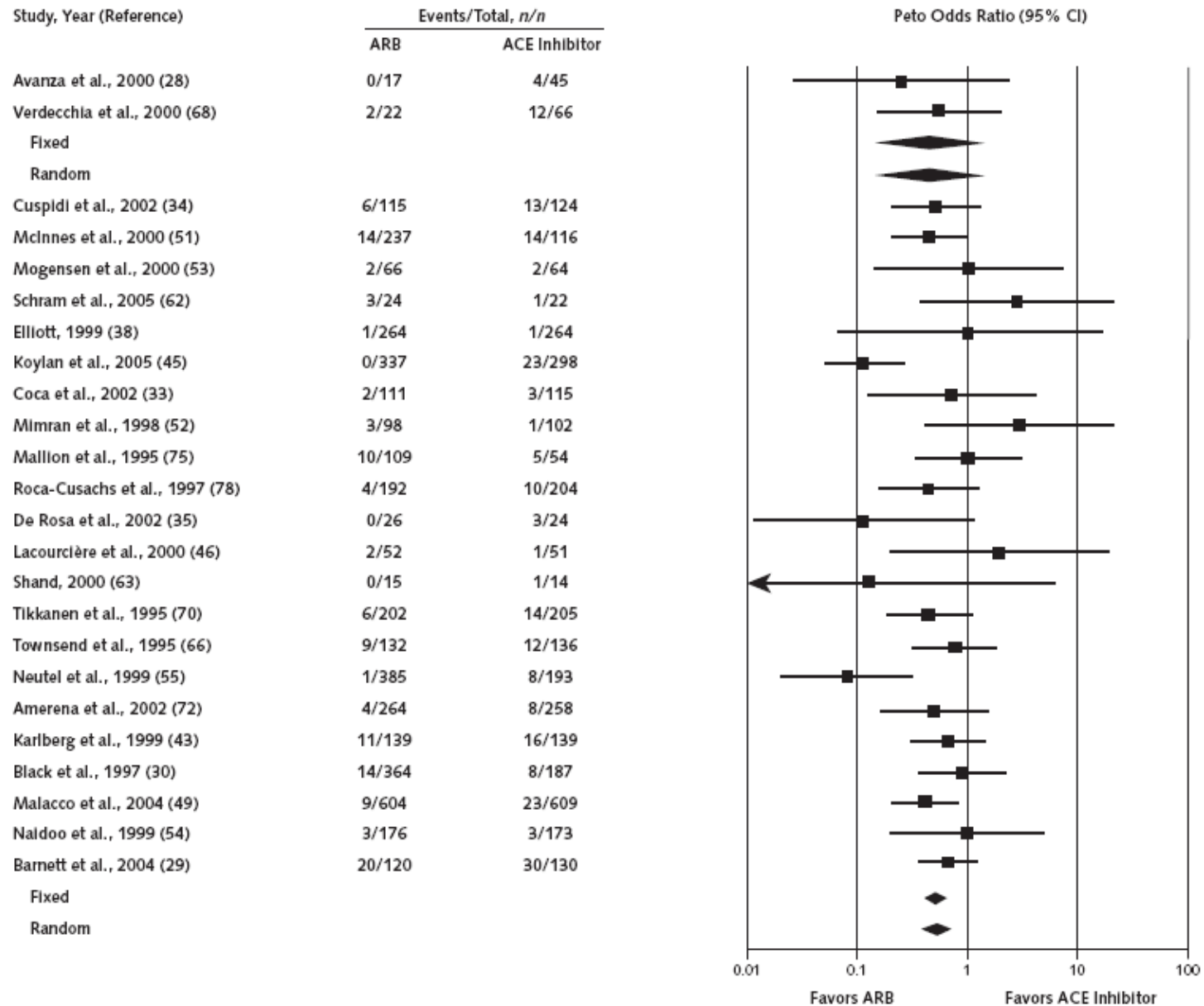
Variable	Ramipril (N = 8576)	Telmisartan (N = 8542)	Combination Therapy (N = 8502)	Telmisartan vs. Ramipril		Combination Therapy vs. Ramipril	
				Relative Risk	P Value	Relative Risk	P Value
	<i>number (percent)</i>						
Total no. of discontinuations†	2099 (24.5)	1962 (23.0)	2495 (29.3)	0.94	0.02	1.20	<0.001
Reason for permanent discontinuation							
Hypotensive symptoms	149 (1.7)	229 (2.7)	406 (4.8)	1.54	<0.001	2.75	<0.001
Syncope	15 (0.2)	19 (0.2)	29 (0.3)	1.27	0.49	1.95	0.03
Cough	360 (4.2)	93 (1.1)	392 (4.6)	0.26	<0.001	1.10	0.19
Diarrhea	12 (0.1)	19 (0.2)	39 (0.5)	1.59	0.20	3.28	<0.001
Angioedema	25 (0.3)	10 (0.1)	18 (0.2)	0.4	0.01	0.73	0.30
Renal impairment	60 (0.7)	68 (0.8)	94 (1.1)	1.14	0.46	1.58	<0.001

Figure 3. Cough as an adverse event: angiotensin-converting enzyme (ACE) inhibitors versus angiotensin II receptor blockers (ARBs).



The first group is observational studies and the second group is randomized, controlled trials.

Figure 4. Withdrawals due to adverse events: angiotensin-converting enzyme (ACE) inhibitors versus angiotensin II receptor blockers (ARBs).



The first group is observational studies and the second group is randomized, controlled trials.

ÖZET

- Esansiyel HT tedavisine benzer etkiler
- Diyabetik hastalarda benzer proteinüri azalması ve renal koruma
- KKY hastalarında istatistiksel farklılık yok.
- Yan etkiler ve ilaca bağlı tedaviyi bırakma ACE'lerde daha fazla.

TEŞEKKÜRLER