

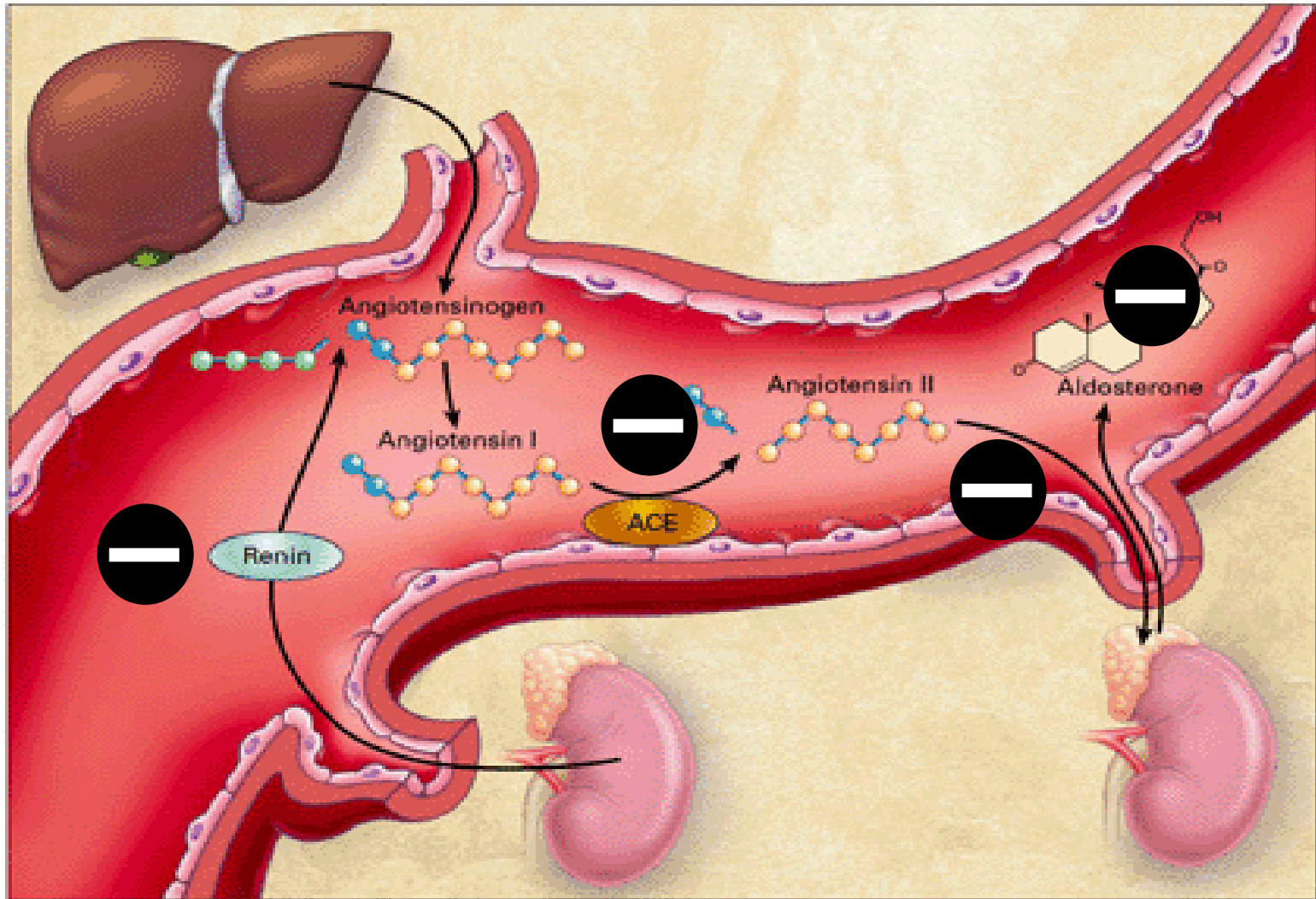
Nereye Kadar & Nasıl Koruma ?

Dr. Mustafa ARICI

Nereye Kadar & Nasıl Koruma ?

- **RAS Blokajında Nereye Kadar ?**
 - RAS'ın İkili Blokajı
 - RAS'ın Yüksek Doz Blokajı
 - RAS'ın Üçlü ve Daha Fazla Blokajı (?)
 - Yeni RAS İnhibitörleri (?)
- **Kan Basıncında Nereye Kadar ?**
- **Nasıl Koruma ?**

Renin-Angiotensin Sistemi



ACE Inhibisyonu & AT₁ Reseptör Blokajı

Hipertansiyon



ACE inhibitörleri

- Kalp yetersizliği
- sol V işlev bozukluğu
- Miyokard infarktüsü sonrası
- Diyabetik nefropati
- Diyabete bağlı olmayan nefropati
- sol V hipertrofi
- Karotis aterosklerozu
- Proteinüri/mikroalbüminüri
- Atriyal fibrilasyon
- Metabolik sendrom

Anjiyotensin reseptör antagonistleri

- Kalp yetersizliği
- Miyokard infarktüsü sonrası
- Diyabetik nefropati
- Proteinüri/mikroalbüminüri
- sol V hipertrofisi
- Atriyal fibrilasyon
- Metabolik sendrom
- ACEI ile indüklenen öksürük

ACE İnhibitor + ARB Çalışmaları

Hipertansiyon

Hypertension
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart
Association® 
Learn and Live™

Systematic Review of Combined Angiotensin-Converting Enzyme Inhibition and Angiotensin Receptor Blockade in Hypertension

Timothy W.R. Doultou, Feng J. He and Graham A. MacGregor
Hypertension 2005;45;880-886; originally published online Apr 4, 2005;
DOI: 10.1161/01.HYP.0000161880.59963.da

Çalışma	Metod		1 + 1 > ARB	1 + 1 > ACEI
Doultou (2005); Metaanaliz	14 çalışma (n=434)	Kan Basıncı	Evet (3.8/2.9 mmHg)	Evet (4.7/3.0 mmHg)

ONTARGET **Kan Basıncında Değişim (mmHg)**

	Ramipril	Telmisartan	Kombinasyon
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Sistolik	-6.0	-6.9	-8.4
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Diyastolik	-4.6	-5.2	-6.0
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ACE İnhibitor + ARB Çalışmaları

Kardiyovasküler Koruma

- **Kardiyak Koruma**
 - Çok çok az ek fayda
 - VaL-HeFT (+/-)
 - CHARM (+)
 - VALIANT (-)
 - Yan etkilerde artış
 - Hiperkalemi
 - Hipotansiyon
 - Renal fonksiyonlarda bozulma
 - İlaç bırakmada artış

ACE İnhibitor + ARB Çalışmaları

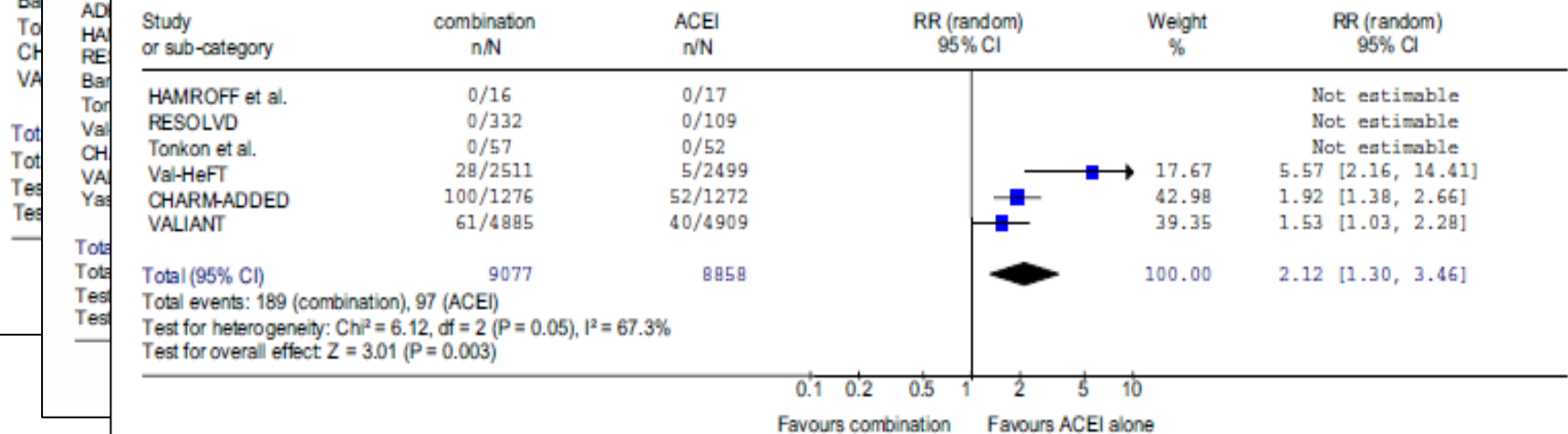
Kardiyovasküler Koruma

Review: Meta-analysis of the safety and tolerability of ACE-I versus ACE-I+ARB in Patients with HF)

Comparison: 01 Hyperkalemia

Review: Meta-analysis of the safety and tolerability of ACE-I versus ACE-I+ARB in Patients with HF
Comparison: 06 Hypotension

Review: Meta-analysis of the safety and tolerability of ACE-I versus ACE-I+ARB in Patients with HF
Comparison: 04 Renal Function
Outcome: Worsening renal function



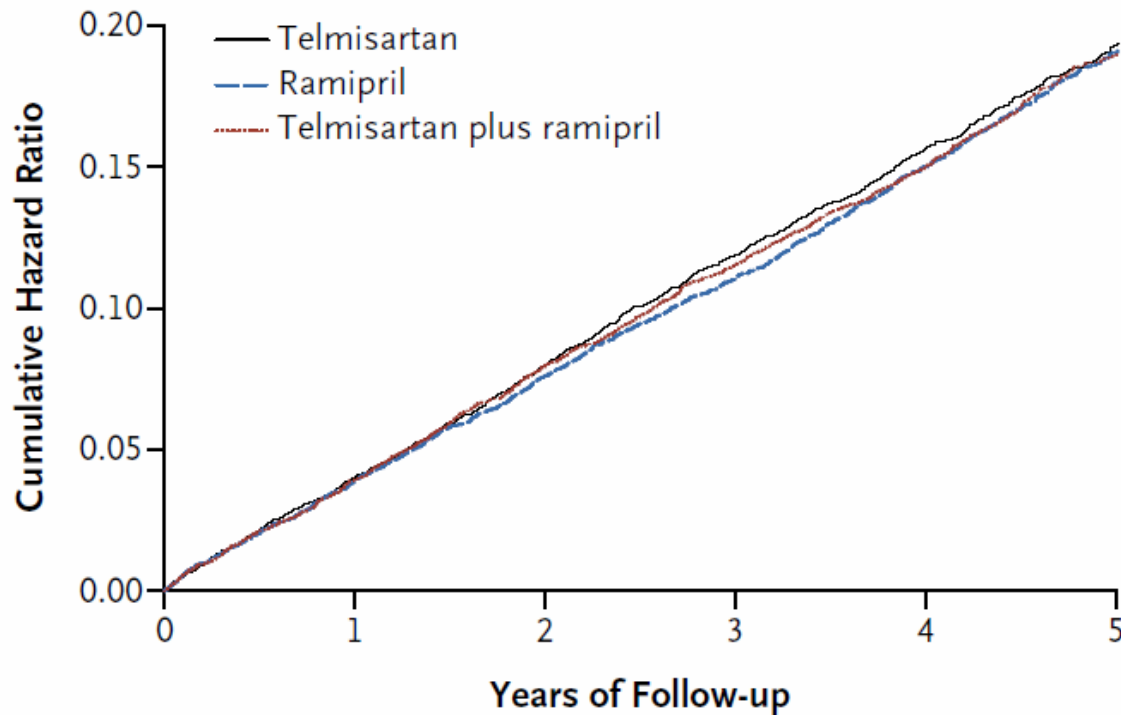
Hiperkalemi Riski (RR): 4.17

Hipotansiyon Riski (RR): 1.91

Böbrek Fonksiyonlarında Bozulma Riski (RR): 4.17

ACE İnhibitor + ARB Çalışmaları

Kardiyovasküler Koruma



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

Çalışma İlaçlarının Kalıcı olarak Bırakılmasının Nedenleri

	Ram N=8576	Ram + Tel N=8502	Ram + Tel vs. Ram	
			RR	P
Hipotansiyon	149	405	2.74	<0.0001
Senkop	15	29	1.95	0.032
Öksürük	359	392	1.10	0.176
Diyare	12	39	3.28	0.0001
Anjiyoödem	25	18	0.73	0.30
Renal yetmezlik	59	93	1.59	0.0047
Herhangi bir tedaviyi bırakma	2098	2492	1.20	<0.0001

ACE İnhibitor + ARB Çalışmaları

Renal Koruma

REVIEW

Annals of Internal Medicine

Meta-analysis: Effect of Monotherapy and Combination Therapy with Inhibitors of the Renin–Angiotensin System on Proteinuria in Renal Disease

Regina Kunz, MD, MSc(Epi); Chris Friedrich, MD; Marcel Wolbers, PhD; and Johannes F.E. Mann, MD

Çalışma	Metod	1 + 1 > ARB	1 + 1 > ACEI
Kunz (2008); Metaanaliz	44 çalışma (n=6181)	Evet (% 34 fark)	Evet (% 27 fark)

ACE İnhibitor + ARB Çalışmaları

Renal Koruma

- **Proteinürideki azalma son noktaları (SDBY'ne ilerleme ve/veya ölüm) etkiliyor mu ?**
- **Proteinüride azalma sağlanırken yan etkiler artıyor mu ?**
- **İlaç bırakma oranları daha yüksek mi ?**

THE LANCET

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

Johannes F E Mann, Roland E Schmieder, Matthew McQueen, Leanne Dyal, Helmut Schumacher, Janice Pogue, Xingyu Wang, Aldo Maggioni, Andrzej Budaj, Suphachai Chaithiraphan, Kenneth Dickstein, Matyas Keltai, Kaj Metsärinne, Ali Oto, Alexander Parkhomenko, Leopoldo S Piegas, Tage L Svendsen, Koon K Teo, Salim Yusuf, on behalf of the ONTARGET investigators

ONTARGET Sendromu ????

ONTARGET

Proteinüri

- Hasta grubunun ortalama ACR: 10 mg/g
- Hasta grubunun
 - % 13'ü mikroalbuminürik,
 - % 4'ü makroalbuminürik

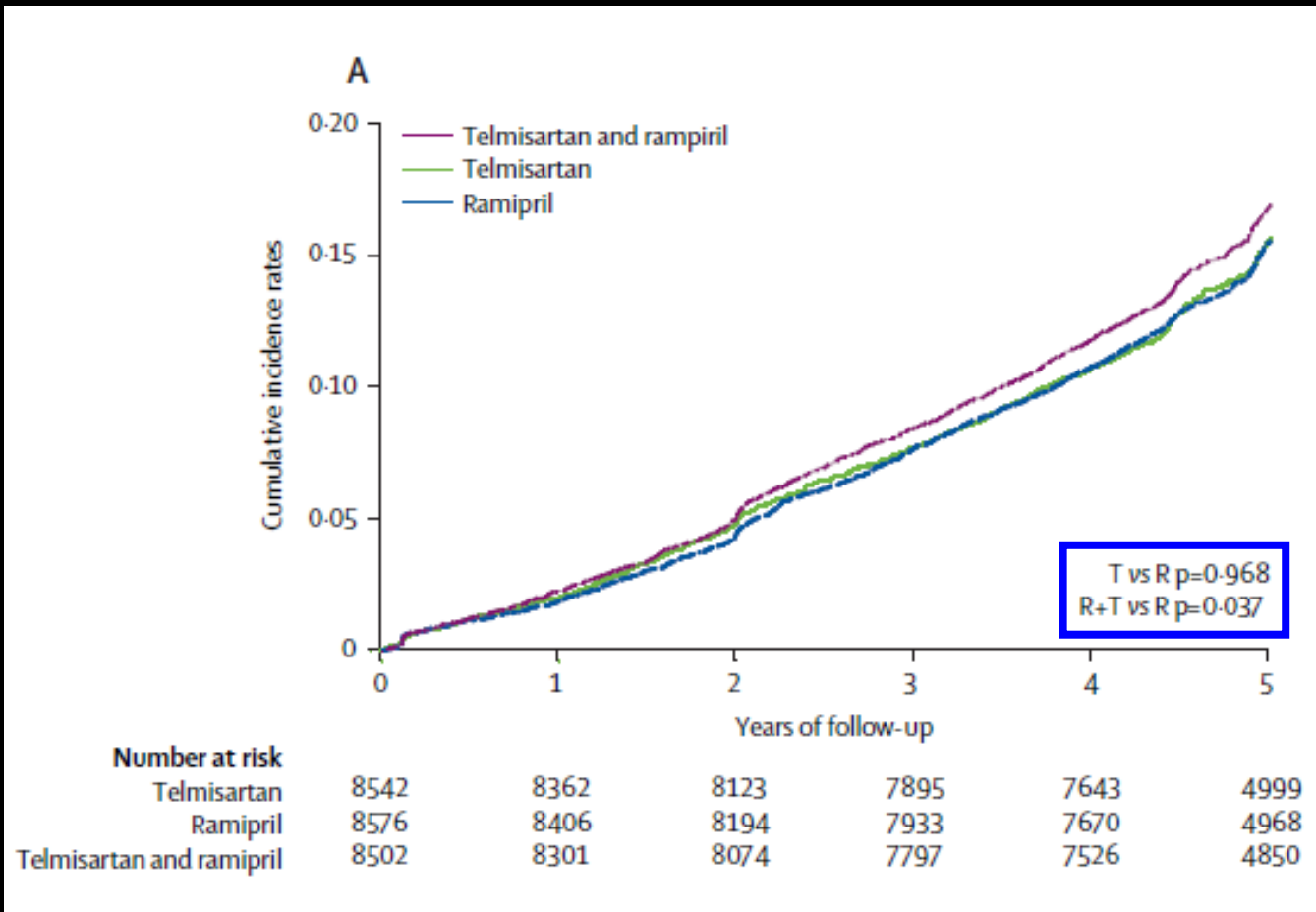
	Ramipril gMean (95% CI)	Telmisartan gMean (95% CI)	Ramipril+telmisartan gMean (95% CI)	Telmisartan vs ramipril p	Telmisartan+ramipril vs ramipril p
UACR, Baseline	0.81 (0.78–0.84)	0.83 (0.80–0.86)	0.81 (0.78–0.84)	0.246	0.923
2-year ratio to baseline	1.17 (1.13–1.20)	1.08 (1.05–1.12)	1.05 (1.02–1.08)	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

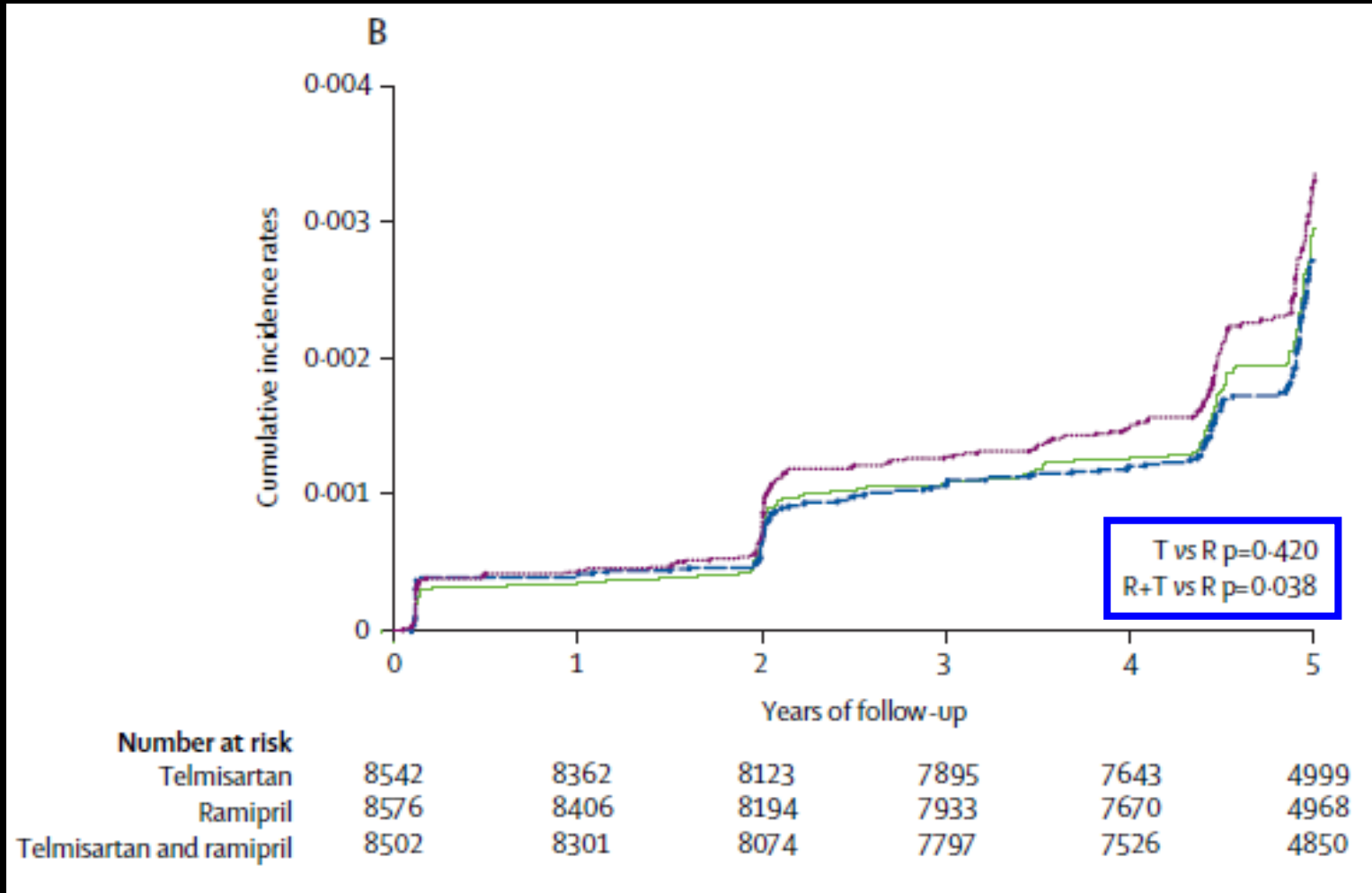
Primer Birleşik Son Nokta

*Diyaliz, renal transplantasyon, serum Cre değerinin
ikiye katlaması veya ölüm*



Sekonder Son Nokta

Diyaliz veya serum Cre değerinin ikiye katlanması



	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

PRESS RELEASES

Guideline alert for blood pressure patients as treatment combo fails

Toronto, Jan. 16, 2009

**These two popular categories
of hypertension medication
are each safe and effective
treatments – but not together**

Bu tartışma burada biter mi ?

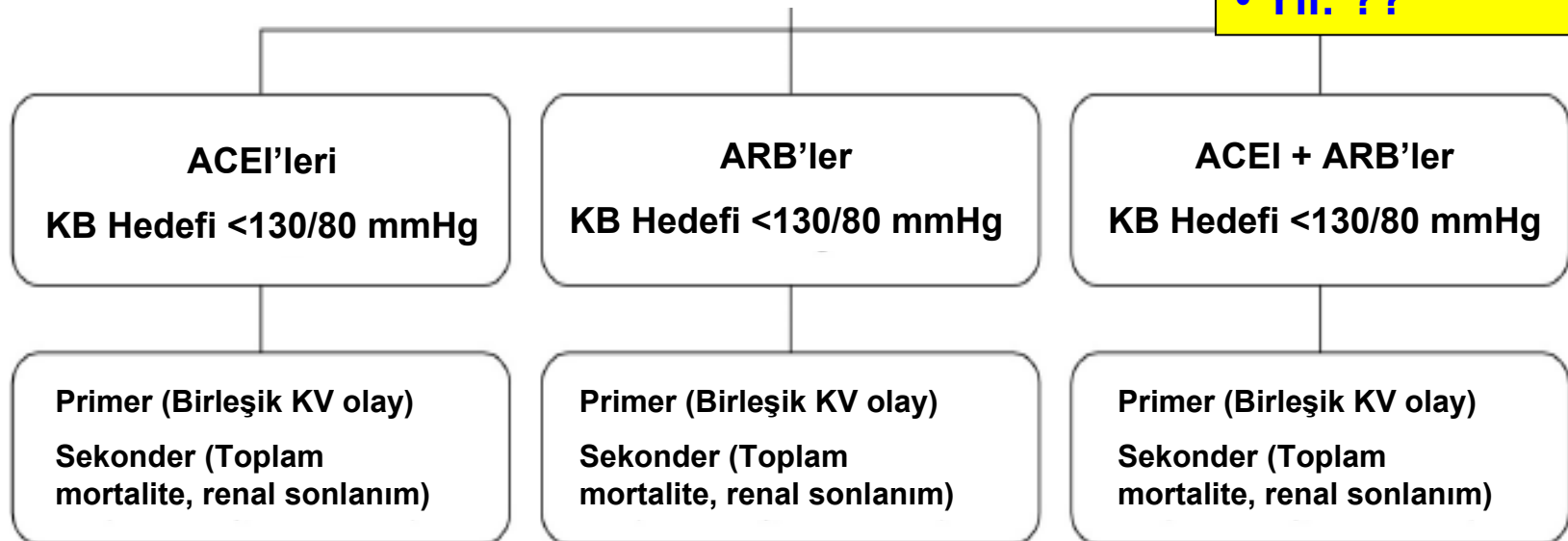
Protocol of the Long-term Impact of RAS Inhibition on Cardiorenal Outcomes (LIRICO) randomized trial

Ausilia Maione¹, Antonio Nicolucci¹, Jonathan C. Craig^{2,3},
Giovanni Tognoni¹, Antonio Moschetta^{4,5},
Giuseppe Palasciano⁴, Giuseppe Pugliese⁶,
Deni A. Procaccini⁷, Loreto Gesualdo⁸, Fabio Pellegrini¹,
Giovanni F.M. Strippoli^{1,2,3}

JNephrol 2007; 20: 646-655

www.sin-italy.org/jnonline – www.jnephrol.com

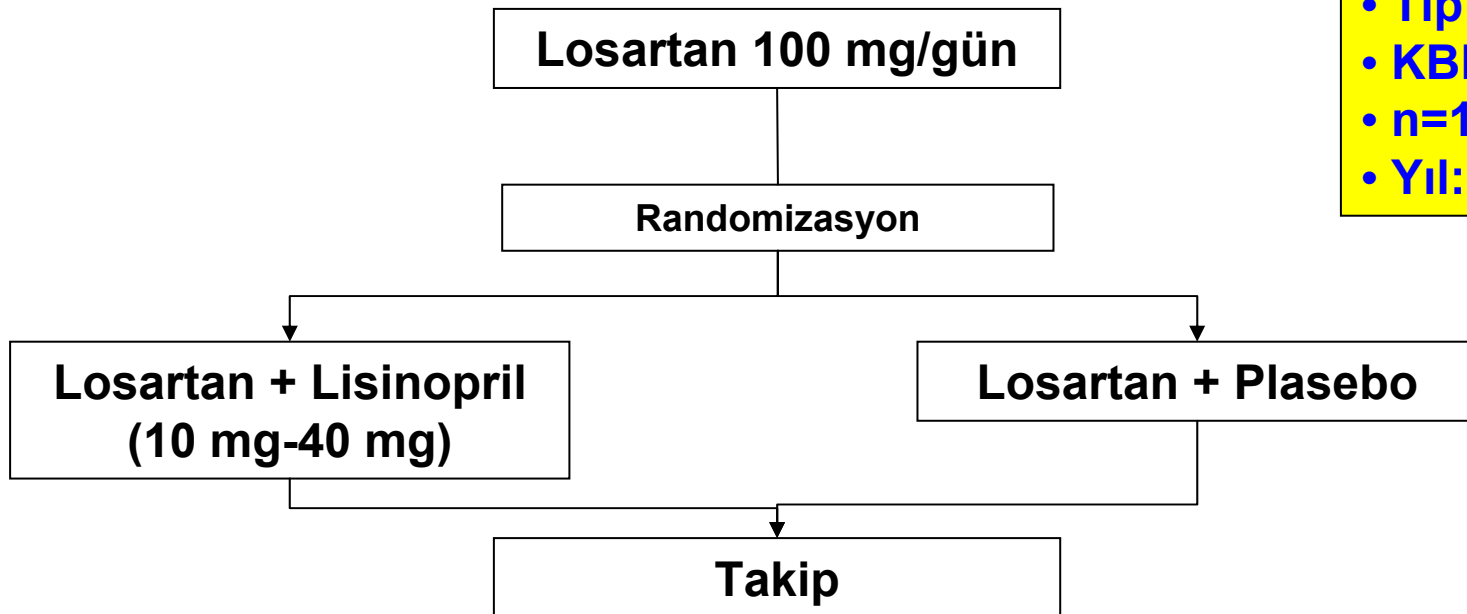
- Mikroalbuminürik
- n=2100
- Yıl: ??



Bu tartışma burada biter mi ?

Design of Combination Angiotensin Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy (VA NEPHRON-D)

Linda F. Fried,^{*} William Duckworth,[†] Jane Hongyuan Zhang,[‡] Theresa O'Connor,[‡] Mary Brophy,[§] Nicholas Emanuele,[¶] Grant D. Huang,^{||} Peter A. McCullough,^{**} Paul M. Palevsky,^{*} Stephen Seliger,^{††} Stuart R. Warren,^{‡‡} and Peter Peduzzi,[‡] for VA NEPHRON-D Investigators

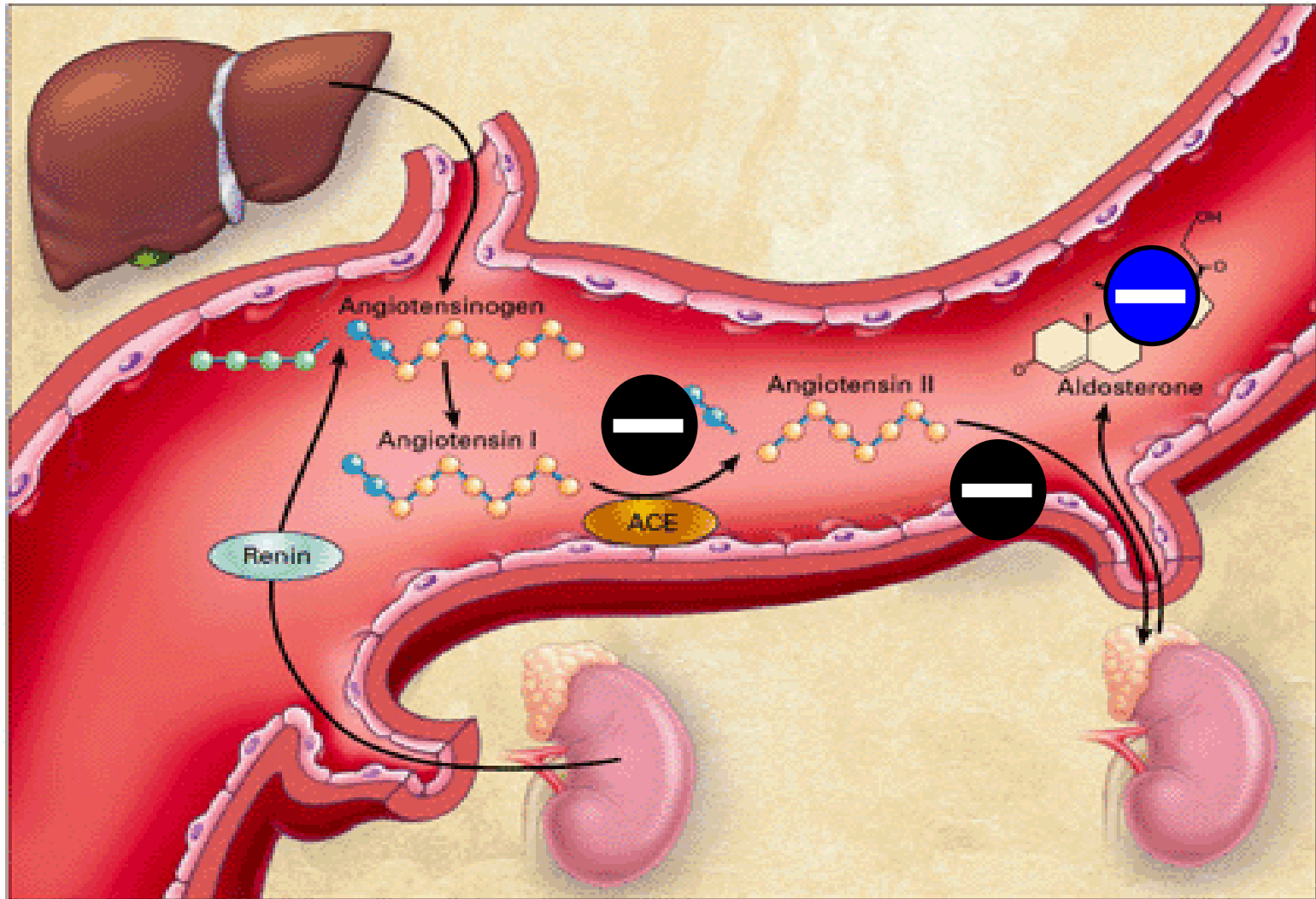


- Tip 2 DM
- KBH Evre 2-3
- n=1850
- Yıl: 2013

Yüksek Doz RAS Blokajı

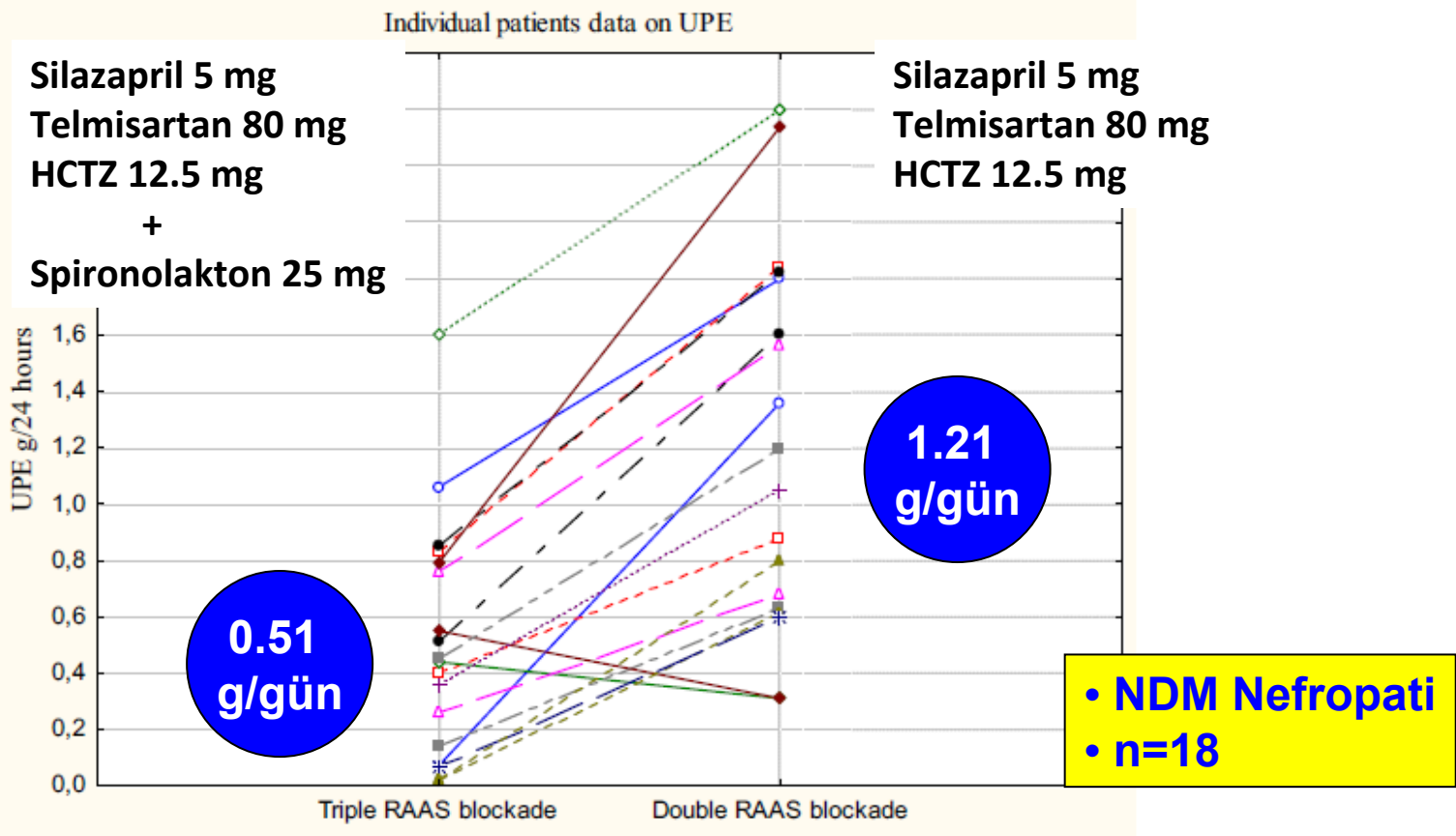
- **ACE İnhibitörleri**
 - Lisinopril 10-40 mg (40>10)
 - Lisinopril 10-40 mg (40=10)
 - Lisinopril 20-40-60 mg (60=40>20)
 - Benazepril 10-40 mg (40>10 mg)
- **ARB'ler**
 - Losartan 50-100-150 mg (100 mg)
 - Candesartan 8-16-32 mg (16 mg)
 - Candesartan 16-32-64 mg (64 mg)
 - Candesartan 16-64-128 mg (128 mg)
 - Irbesartan 300-600-900 mg (900 mg)
 - Valsartan 160-320-640 mg (320-640 mg)
 - Telmisartan 80-160 mg (160 mg)
 - Losartan 50 mg-200 mg (>100 mg)

Renin-Angiotensin Sistemi

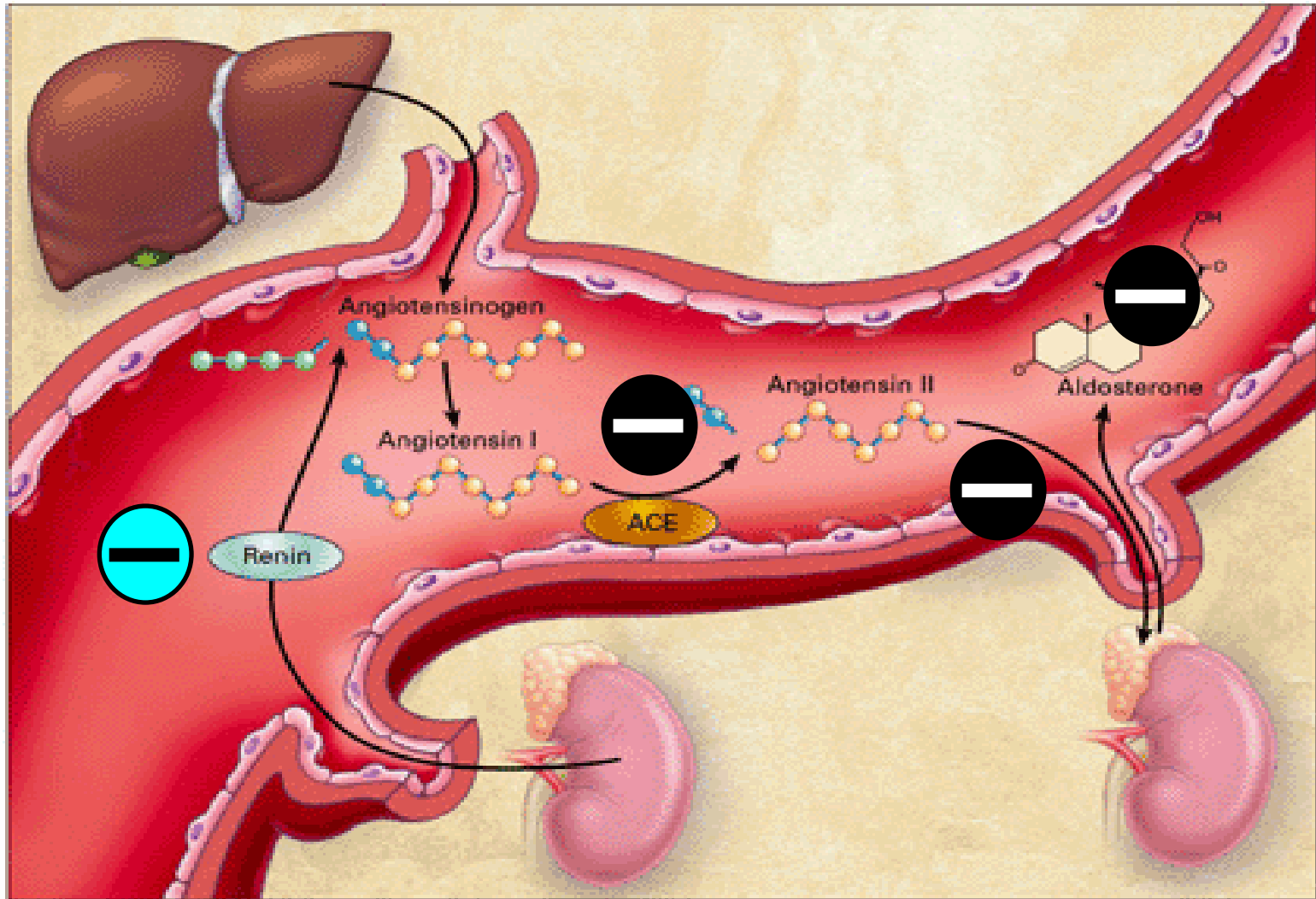


Triple Pharmacological Blockade of the Renin-Angiotensin-Aldosterone System in Nondiabetic CKD: An Open-Label Crossover Randomized Controlled Trial

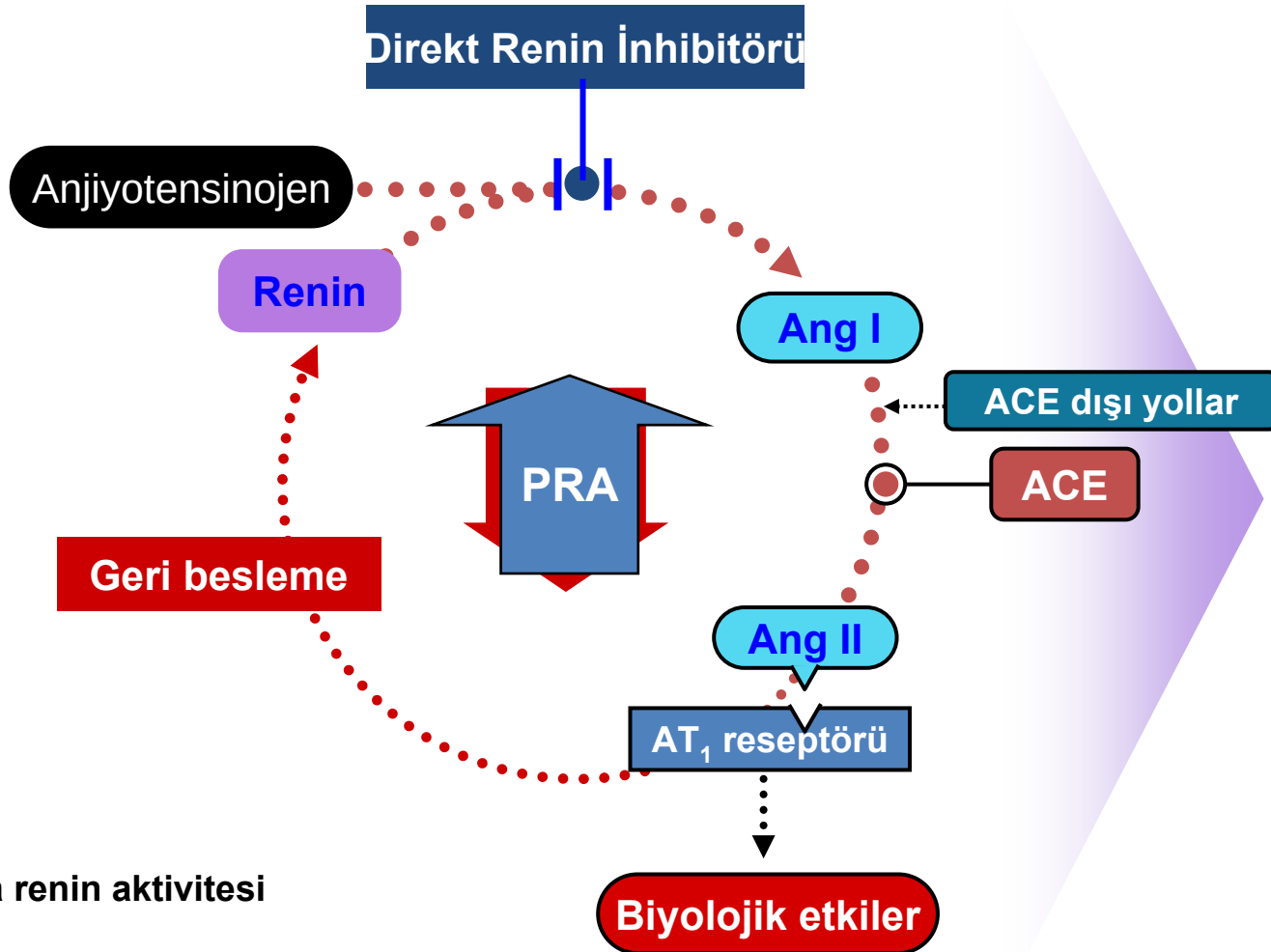
Leszek Tylicki, MD, PhD,¹ Przemysław Rutkowski, MD, PhD,¹ Marcin Renke, MD, PhD,¹ Wojciech Larczyński, MD,¹ Ewa Aleksandrowicz, PhD,² Wiesława Lysiak-Szydłowska, MD, PhD,² and Bolesław Rutkowski, MD, PhD¹



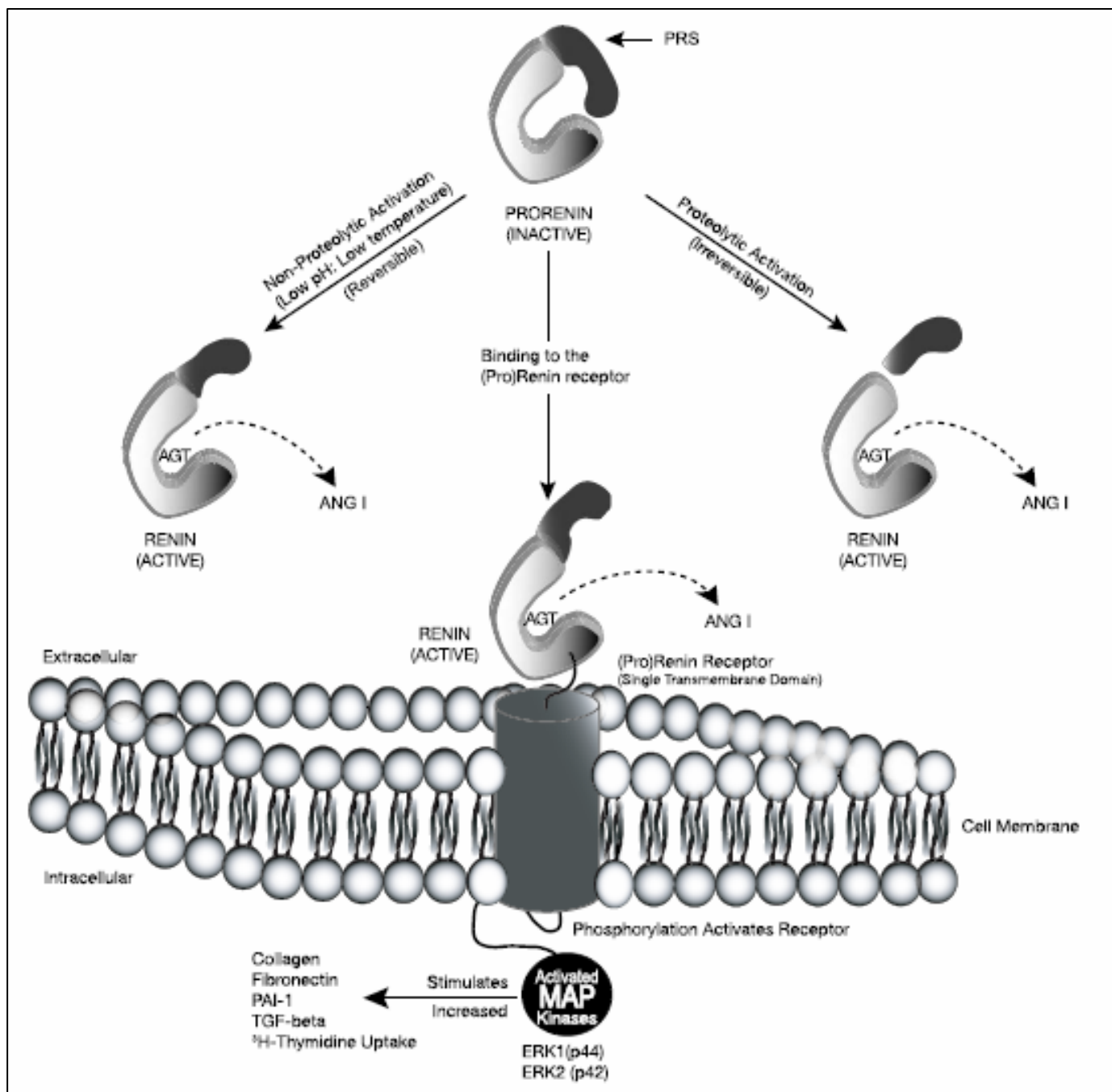
Renin-Angiotensin Sistemi



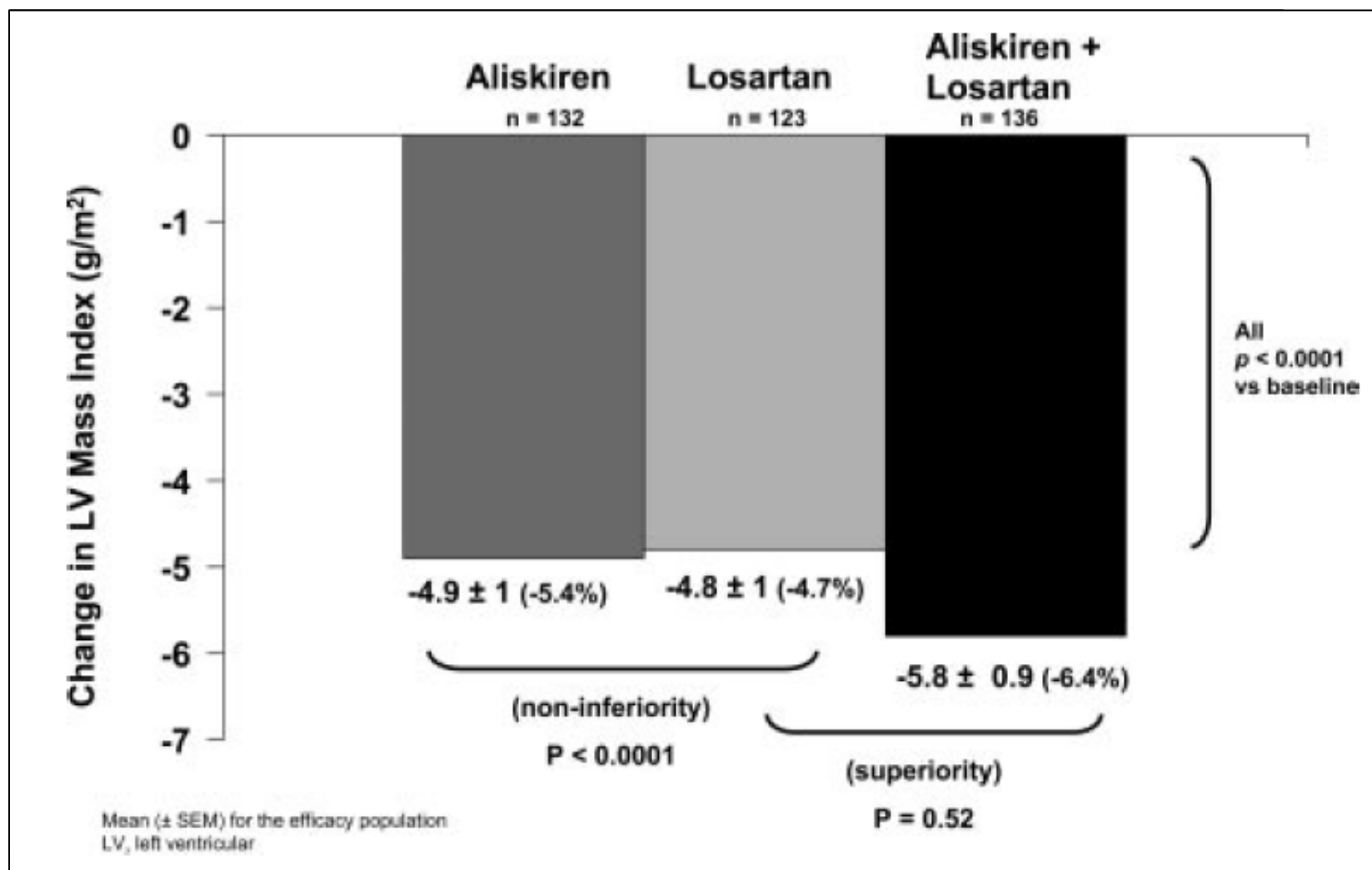
Direkt Renin İnhibisyonu



PRA = plazma renin aktivitesi

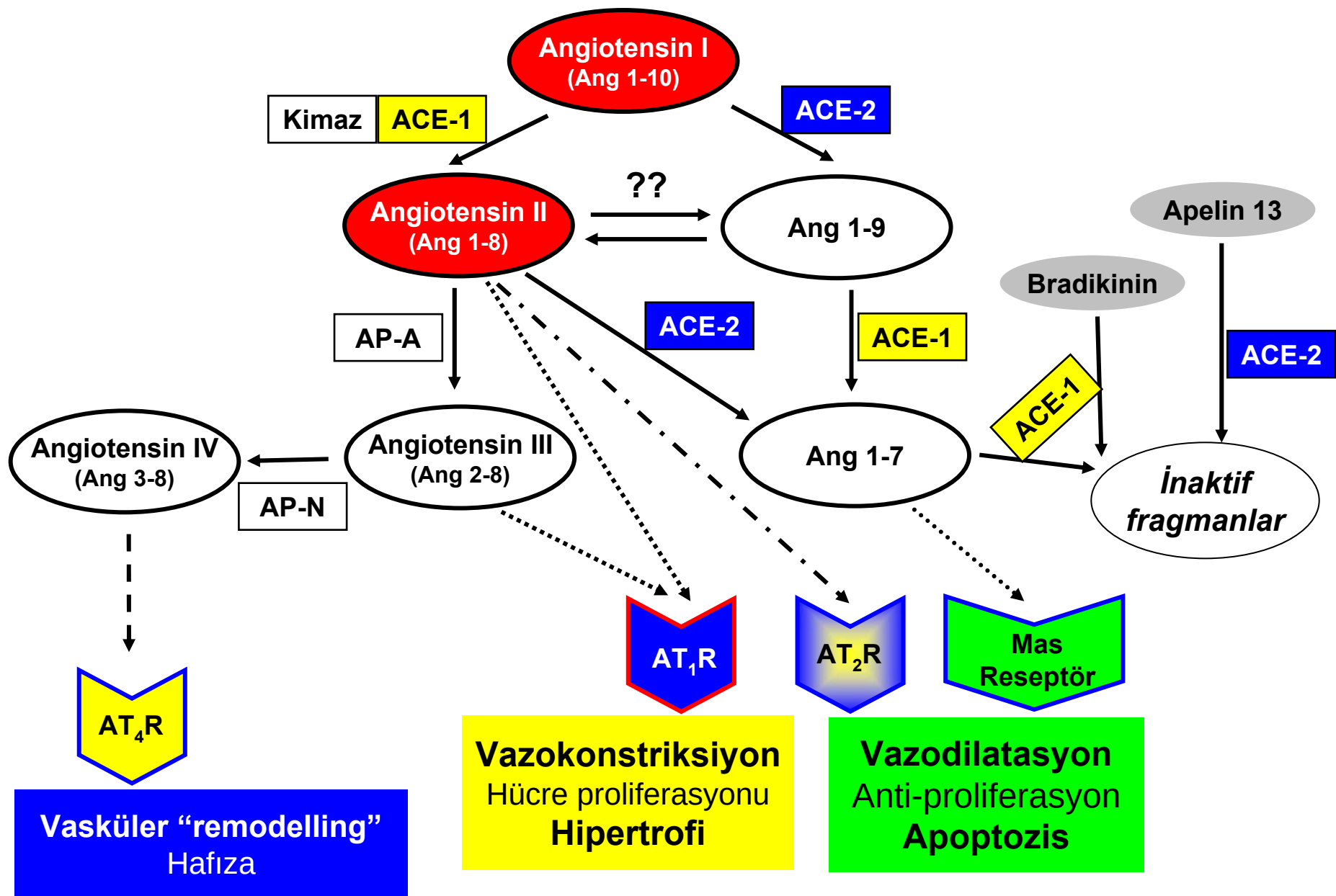


Direkt Renin Inhibisyonu



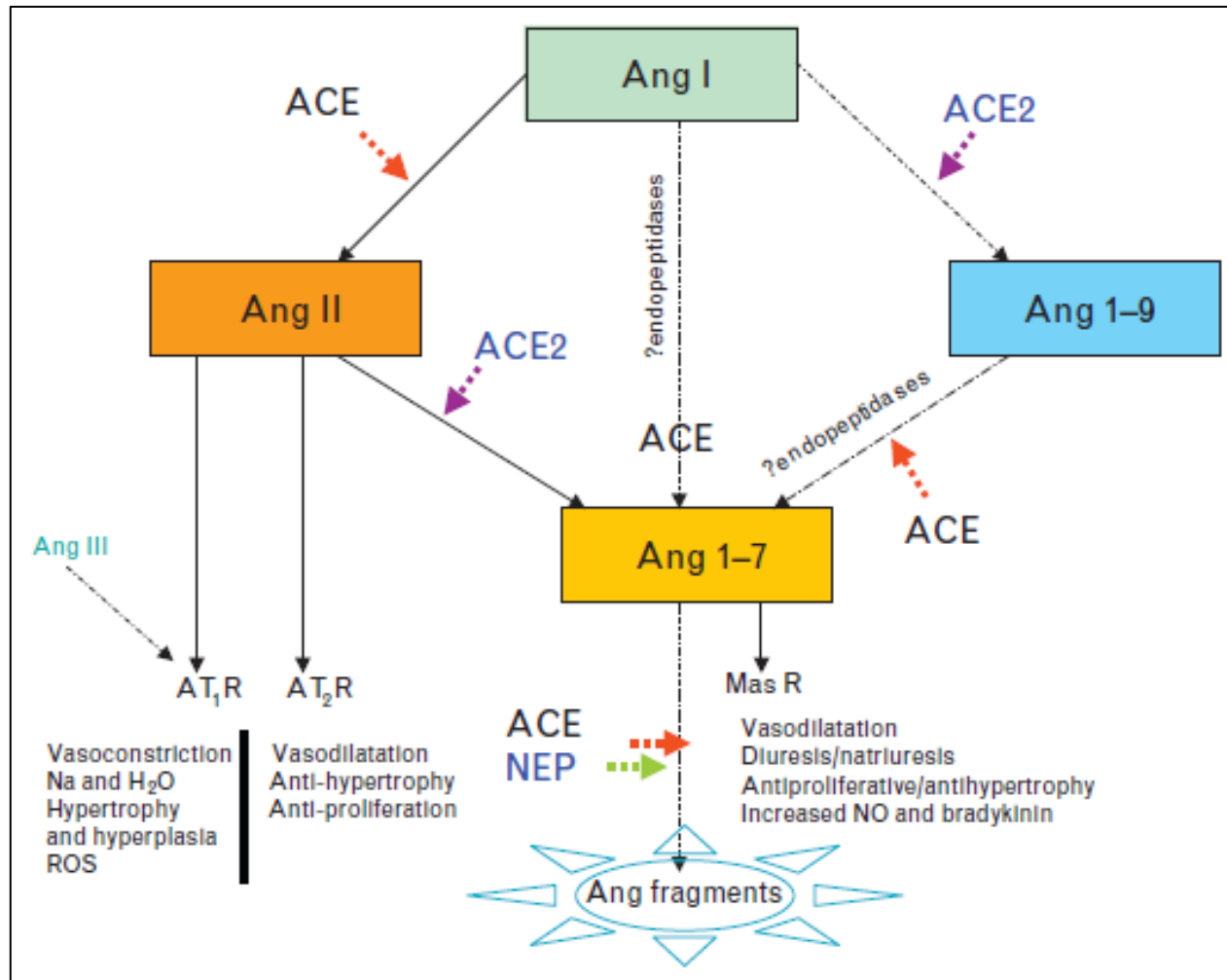
Bu tartiřma burda biter mi ?





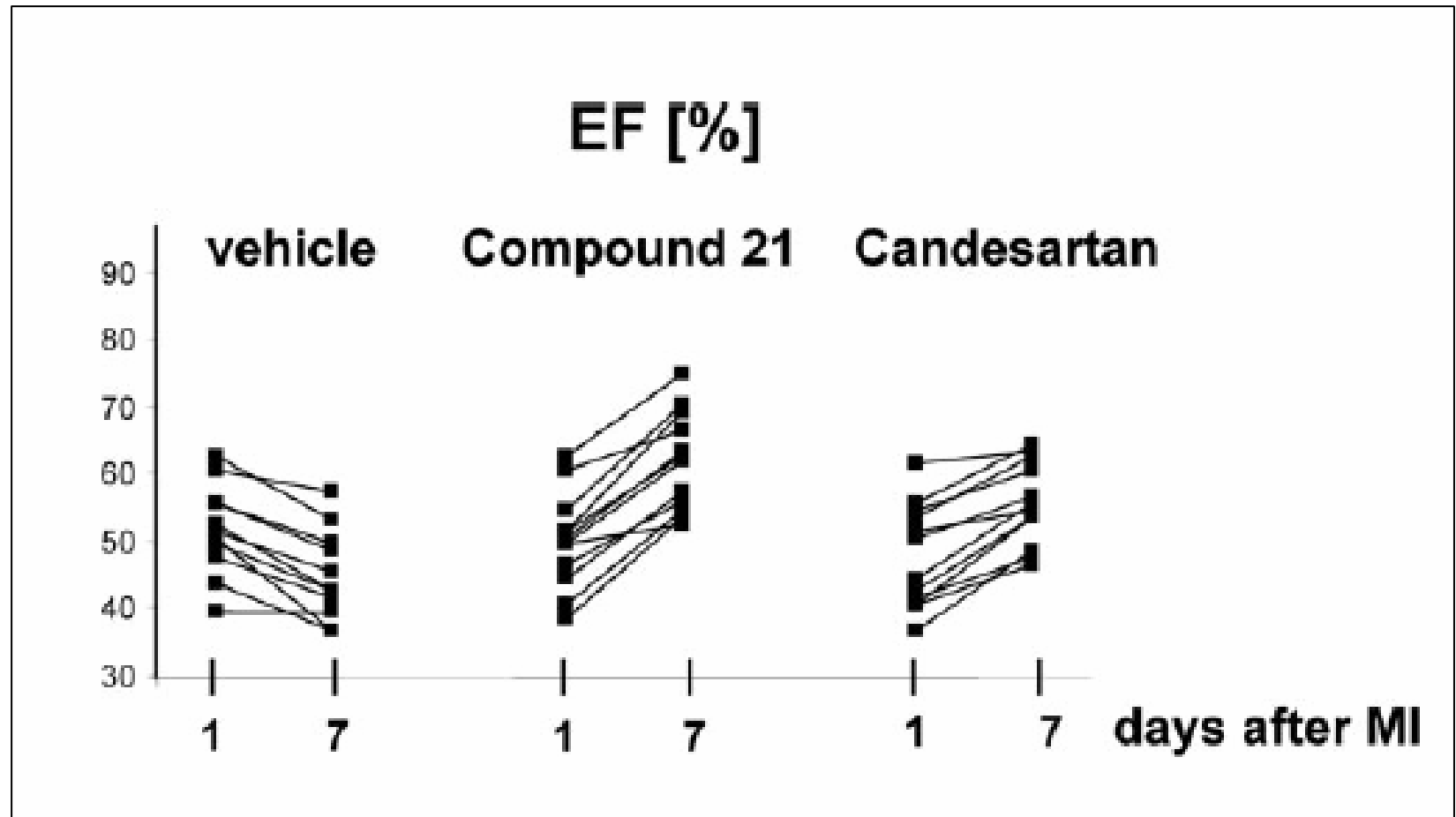
Julie R. Ingelfinger

Current Opinion in Nephrology and Hypertension 2009, 18:79–84



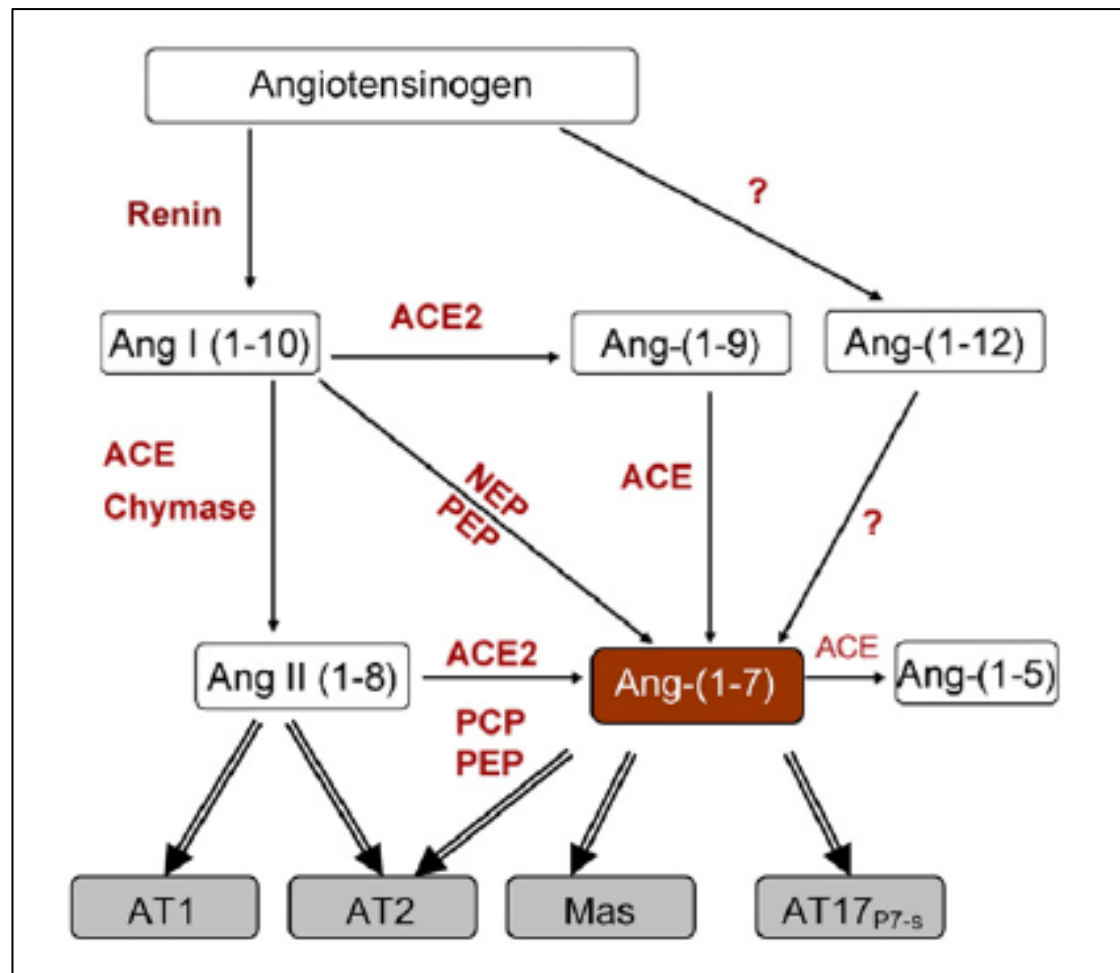
Angiotensin II Type 2 Receptor Stimulation

A Novel Option of Therapeutic Interference With the Renin-Angiotensin System in Myocardial Infarction?



Angiotensin-(1-7): Pharmacological properties and pharmacotherapeutic perspectives

European Journal of Pharmacology 585 (2008) 303–312



Kan Basıncında Nereye Kadar ?

A. SYSTOLIC BLOOD PRESSURE



STROKE MORTALITY
(Floating abscissa)

115

USUAL SYSTOLIC BLOOD PRESSURE
(mmHg)

B. DIASTOLIC BLOOD PRESSURE



STROKE MORTALITY
(Floating abscissa)

75

USUAL DIASTOLIC BLOOD PRESSURE
(mmHg)

AGE AT RISK

80-89 YEARS

70-79 YEARS

60-69 YEARS

50-59 YEARS

Hedef Kan Basıncı ?



Hypertension

New ONTARGET analysis shows lower not necessarily better when it comes to BP

SEPTEMBER 3, 2008 | [Lisa Nainggolan](#)

- A new observational analysis of the **ONTARGET** study shows that **lower is not necessarily better when it comes to blood pressure in this patient population**, with coronary heart disease or diabetes plus additional risk factors.
- Although there was evidence that lower was better in terms of stroke, there was a suggestion of harm when **BP was reduced below 130 mm Hg systolic** for the outcome of cardiovascular death in diabetics.

Clinical cardiology

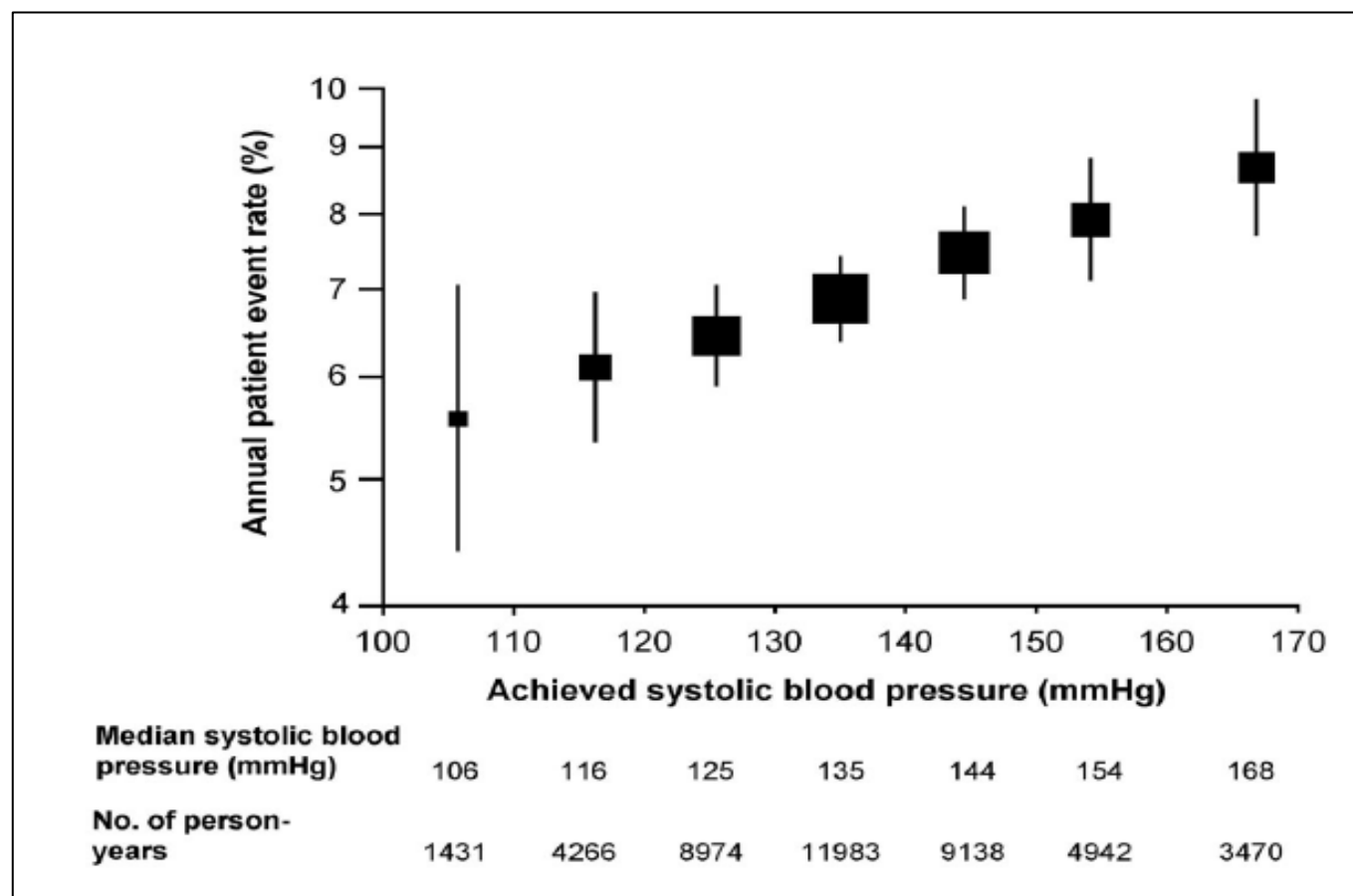
Return of the J-curve: TNT analysis shows that BP can be too low in CAD patients

MAY 8, 2009 | [Michael O'Riordan](#)

- An analysis of one of the major "lower-is-better" cholesterol trials has shown that **lower might not be best when it comes to blood pressure**. In fact, in this group of patients with coronary artery disease, despite substantial lowering of LDL-cholesterol levels, a J-curve relationship exists between systolic and diastolic blood pressure and cardiovascular events.
- Compared with the reference blood pressures, systolic >130 to 140 mm Hg and diastolic >70 to 80 mm Hg, patients with **systolic blood pressure $\leq$ 110 mm Hg** had a threefold increased risk of cardiovascular events, whereas those with **diastolic blood pressure $\leq$ 60 mm Hg** had a 3.3-fold increased risk of events.

Lowering Blood Pressure Reduces Renal Events in Type 2 Diabetes

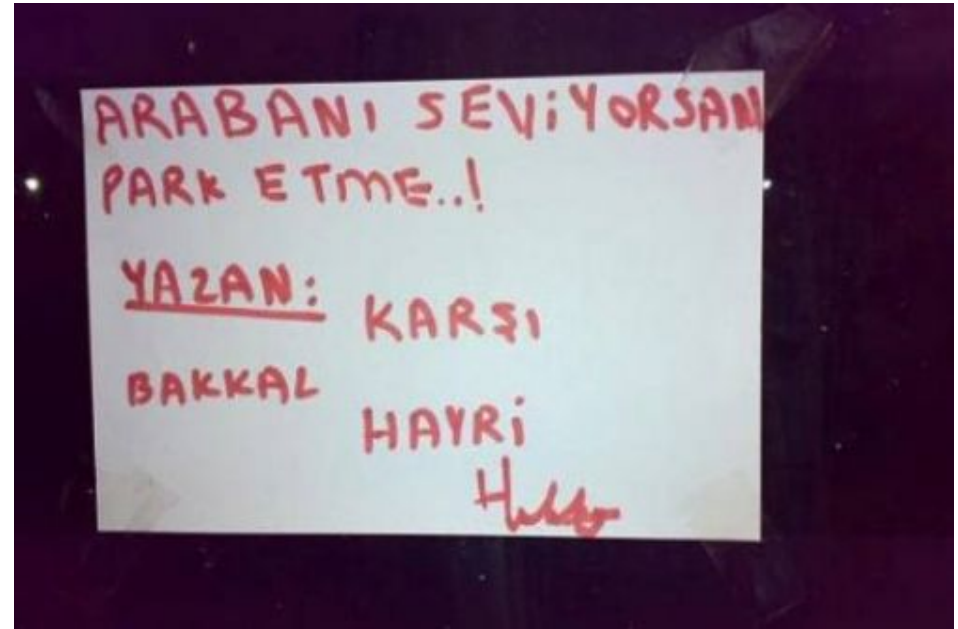
Bastiaan E. de Galan,^{*,†} Vlado Perkovic,^{*} Toshiharu Ninomiya,^{*} Avinesh Pillai,^{*} Anushka Patel,^{*} Alan Cass,^{*} Bruce Neal,^{*} Neil Poulter,[‡] Stephen Harrap,[§] Carl-Erik Mogensen,^{||} Mark Cooper,[¶] Michel Marre,^{**} Bryan Williams,^{††} Pavel Hamet,^{‡‡} Giuseppe Mancia,^{§§} Mark Woodward,^{*} Paul Glasziou,^{|||} Diederick E. Grobbee,^{¶¶} Stephen MacMahon,^{*} and John Chalmers,^{*}
on behalf of the ADVANCE Collaborative Group



Sonuç Olarak....

- Kan basıncının hem bireysel, hem toplumsal kontrolü önemlidir.
- Hedef toplum için olabildiğince düşük, birey için bireyin tolere edebildiği en düşük değer olmalıdır.
- Renin anjiyotensin sisteminin baskılanması önemlidir.
- Bugün için ACE inhibitörleri ile ARB'ler, RAS'ı baskılamakta eş değerdir.
- Renin-anjiyotensin sisteminin bilinmeyenleri, bilinenleri yanında çok çok büyüktür.

Sonuç Olarak....Neyi Koruyacađız ?



Sonuç Olarak....Nasıl Koruyacağız ?



...ama mutlaka koruyalım



