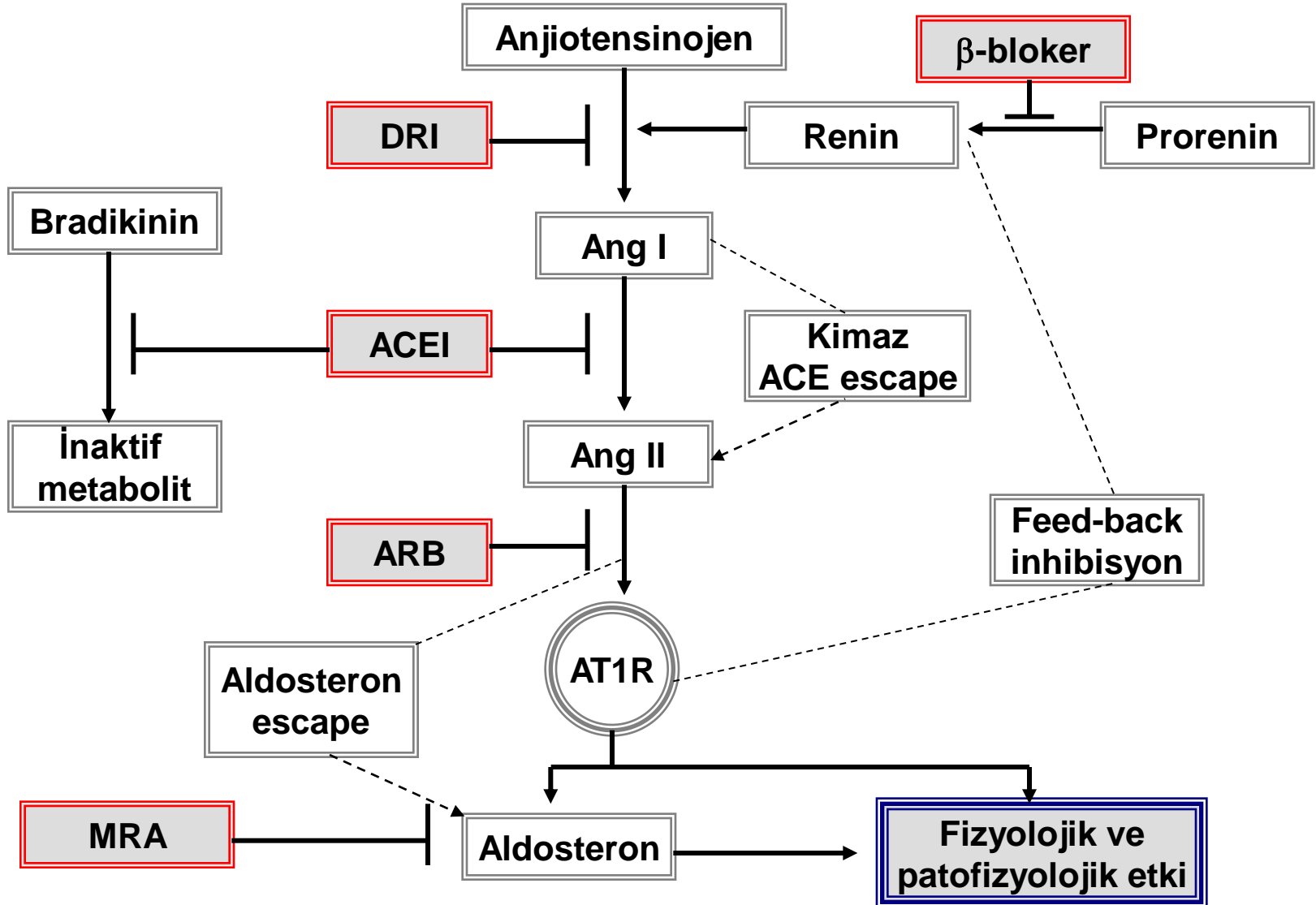


Optimal vasküler koruma
Mineralokortikoid reseptör antagonistleri

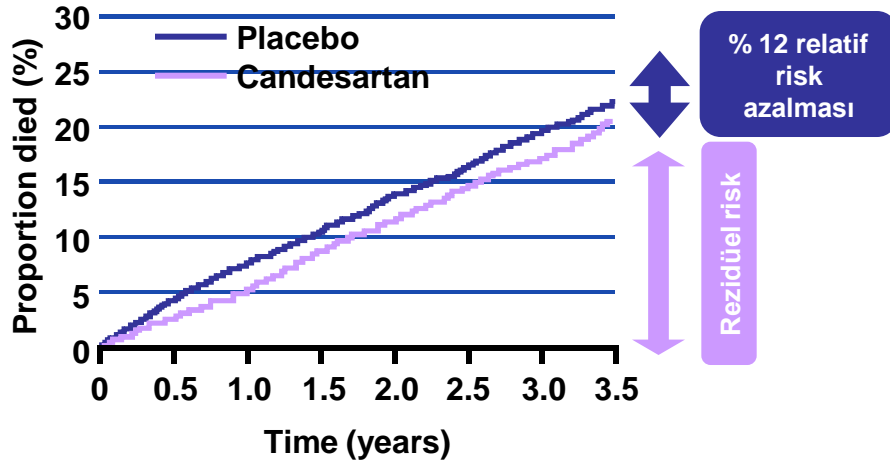
Dr. Celalettin USALAN

Renin anjiotensin aldosteron sistemi ve inhibisyonu

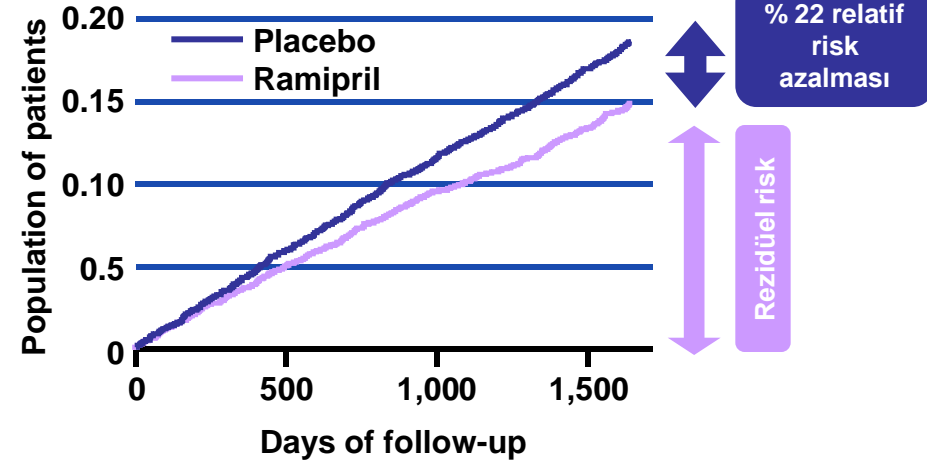


Rezidüel risk: ACE-i ve ARB ile tedaviye rağmen morbidite ve mortalite halen yüksek

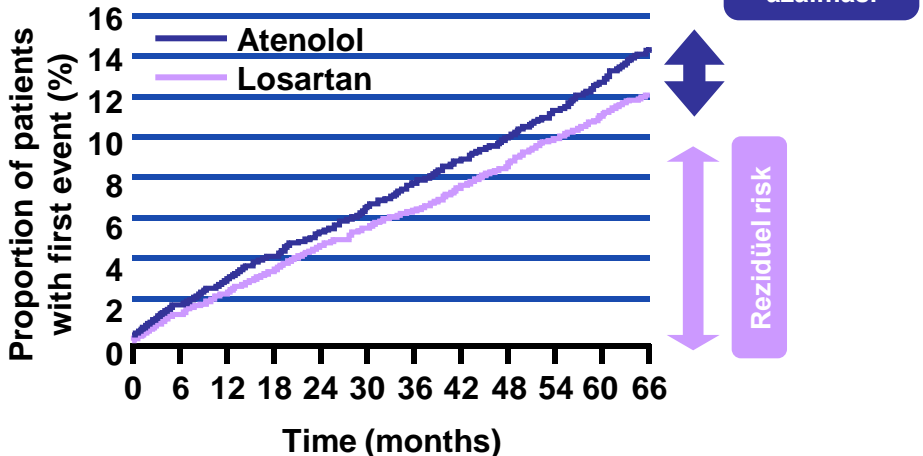
CHARM-Overall¹: CV death



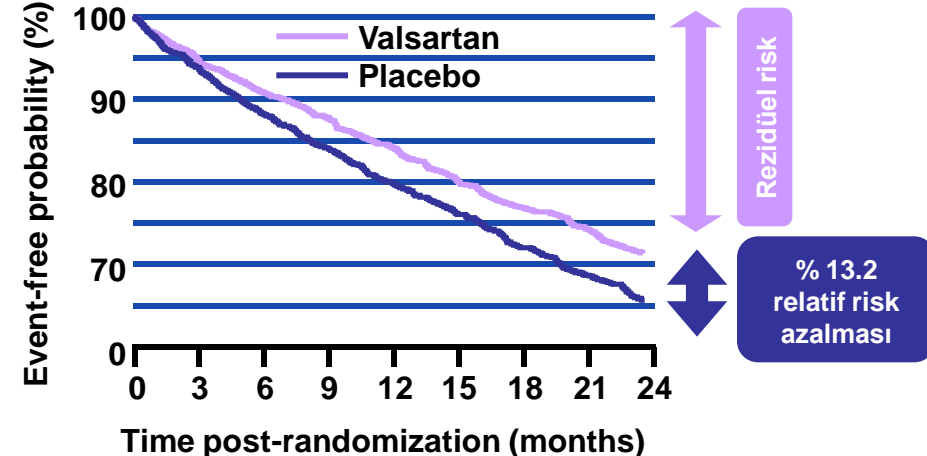
HOPE²: CV death, stroke and MI



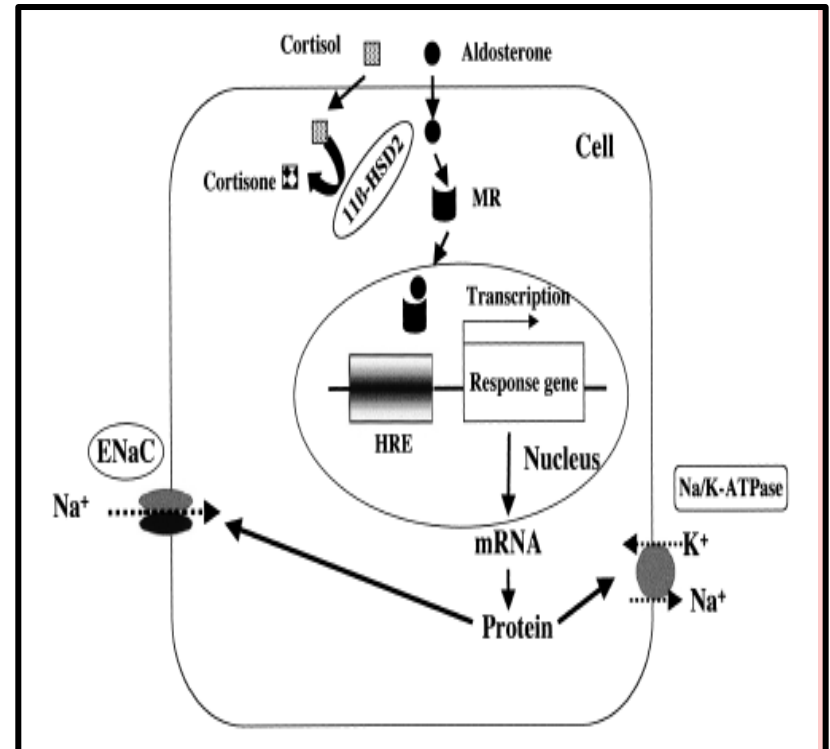
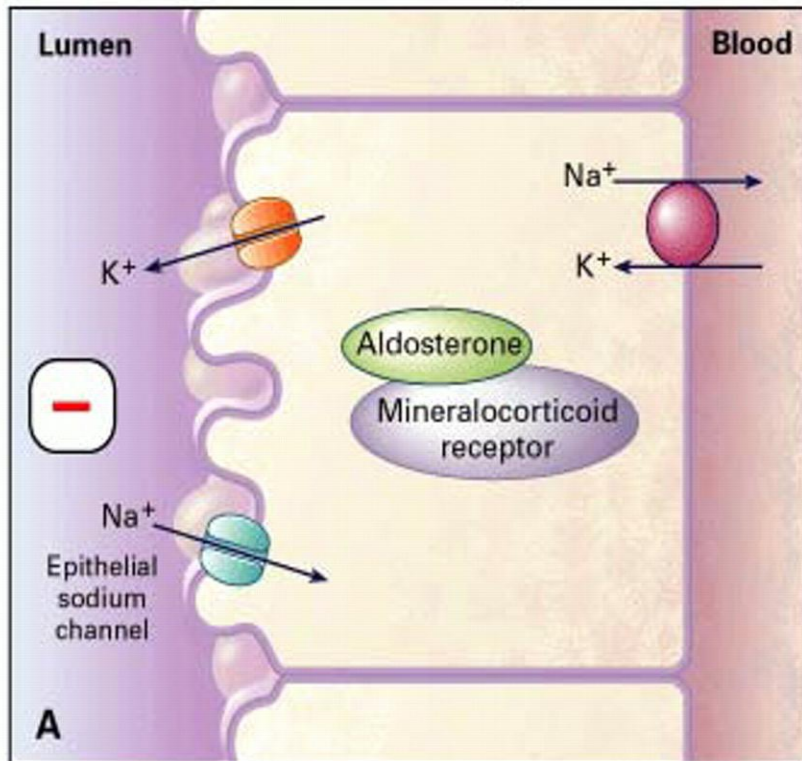
LIFE³: CV death, stroke and MI



Val-HeFT⁴: freedom from combined endpoint



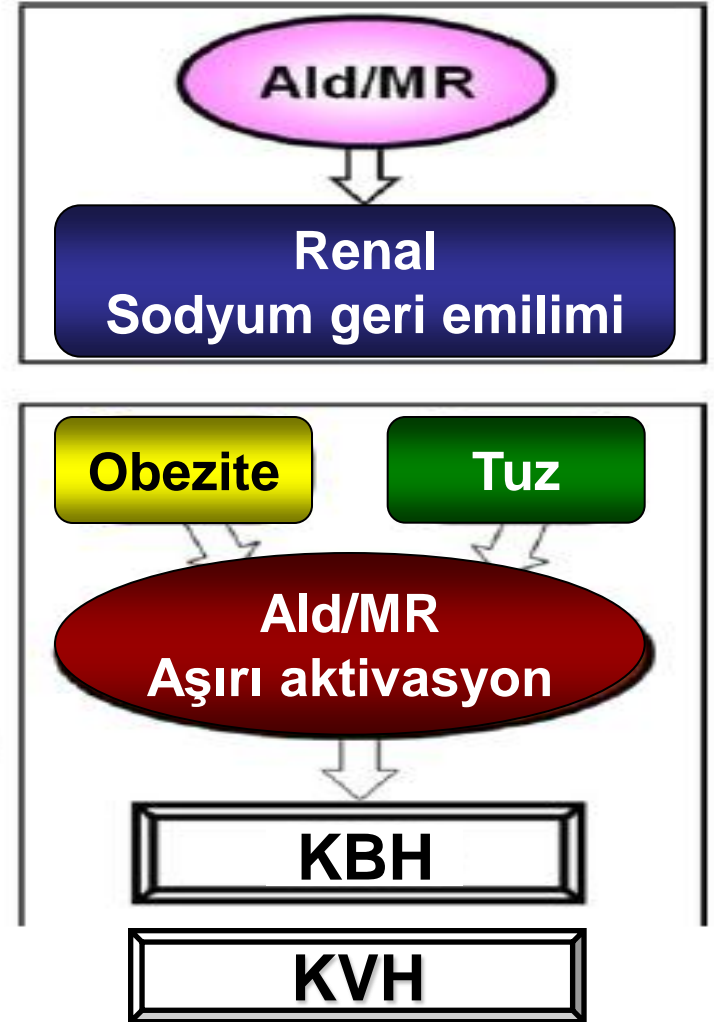
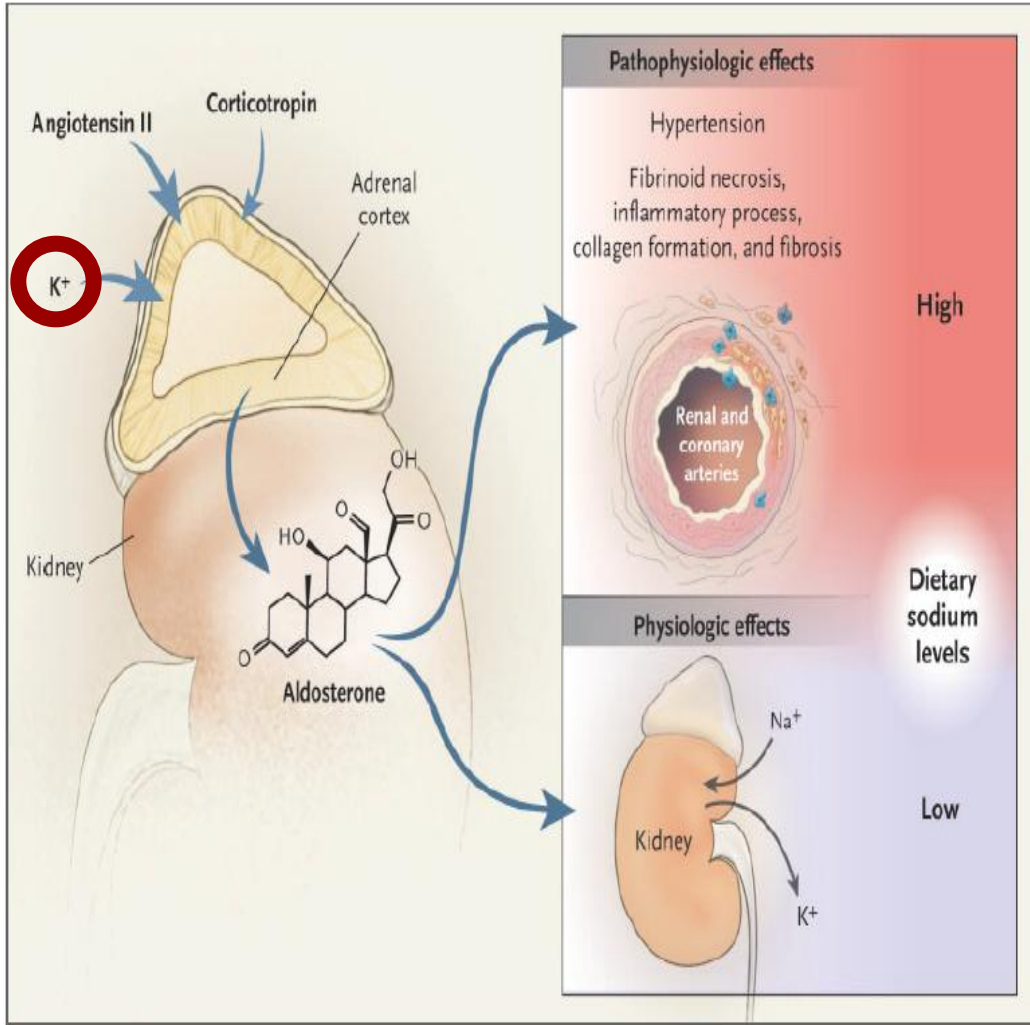
Mineralokortikoid reseptör (aldosteron) etki mekanizması



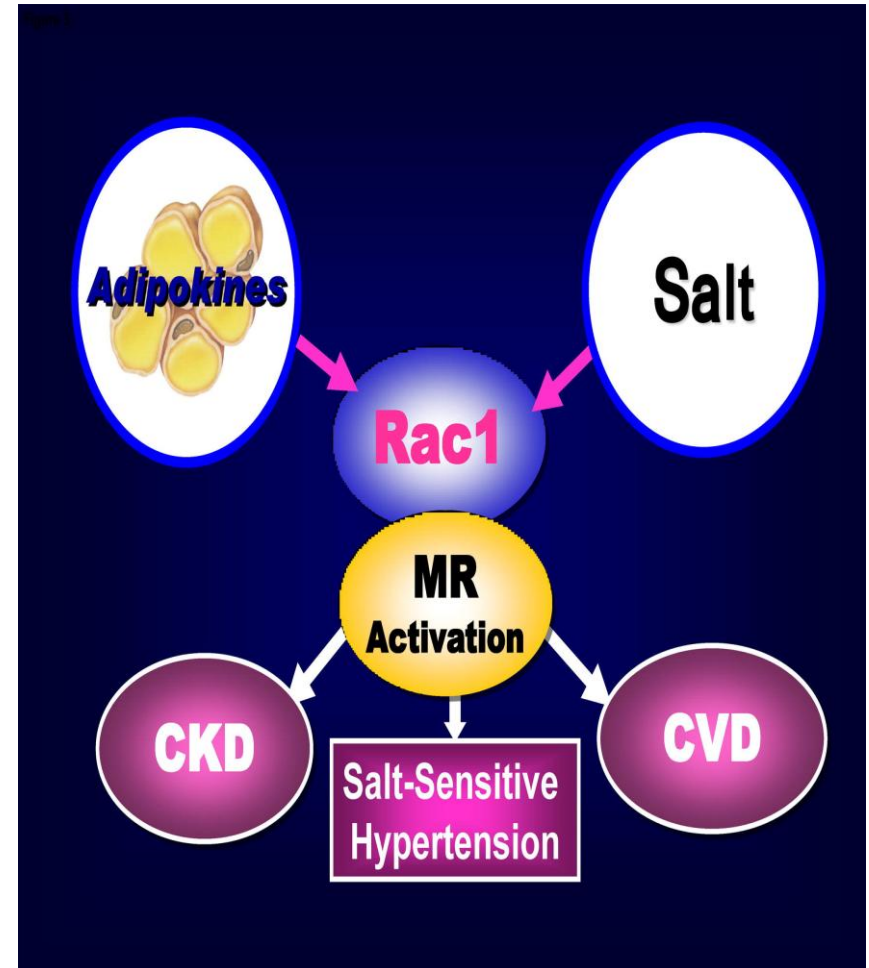
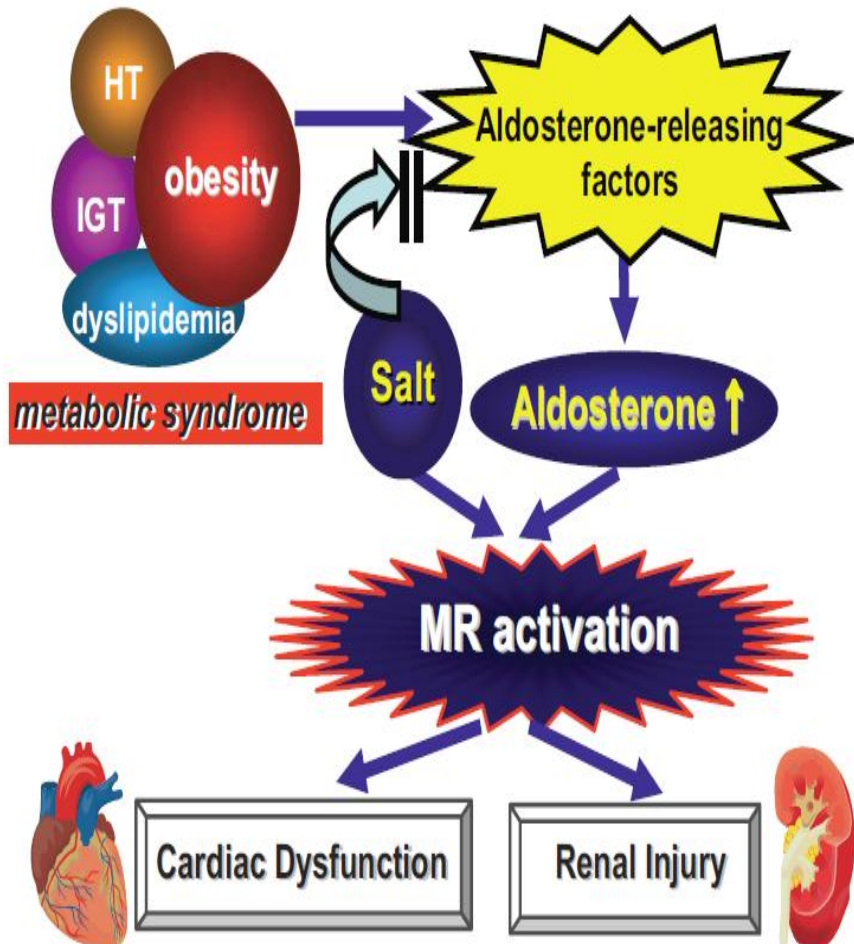
Artmış mineralokortikoid reseptör aktivasyonu

- Uygunsuz mineralokortikoid reseptör aktivasyonu
 - Patofizyolojik, non-genomik etki
 - Epitalyal dokular dışında etkili (kalp, böbrek vasküler yapı vb.)
 - Aşırı tuz tüketimi ve obezite ile ilişkili

Mineralokortikoid reseptör (aldosteron) aktivasyonu



Obezite, metabolik sendrom/tip II DM & Mineralokortikoid reseptör (aldosteron) aktivasyonu

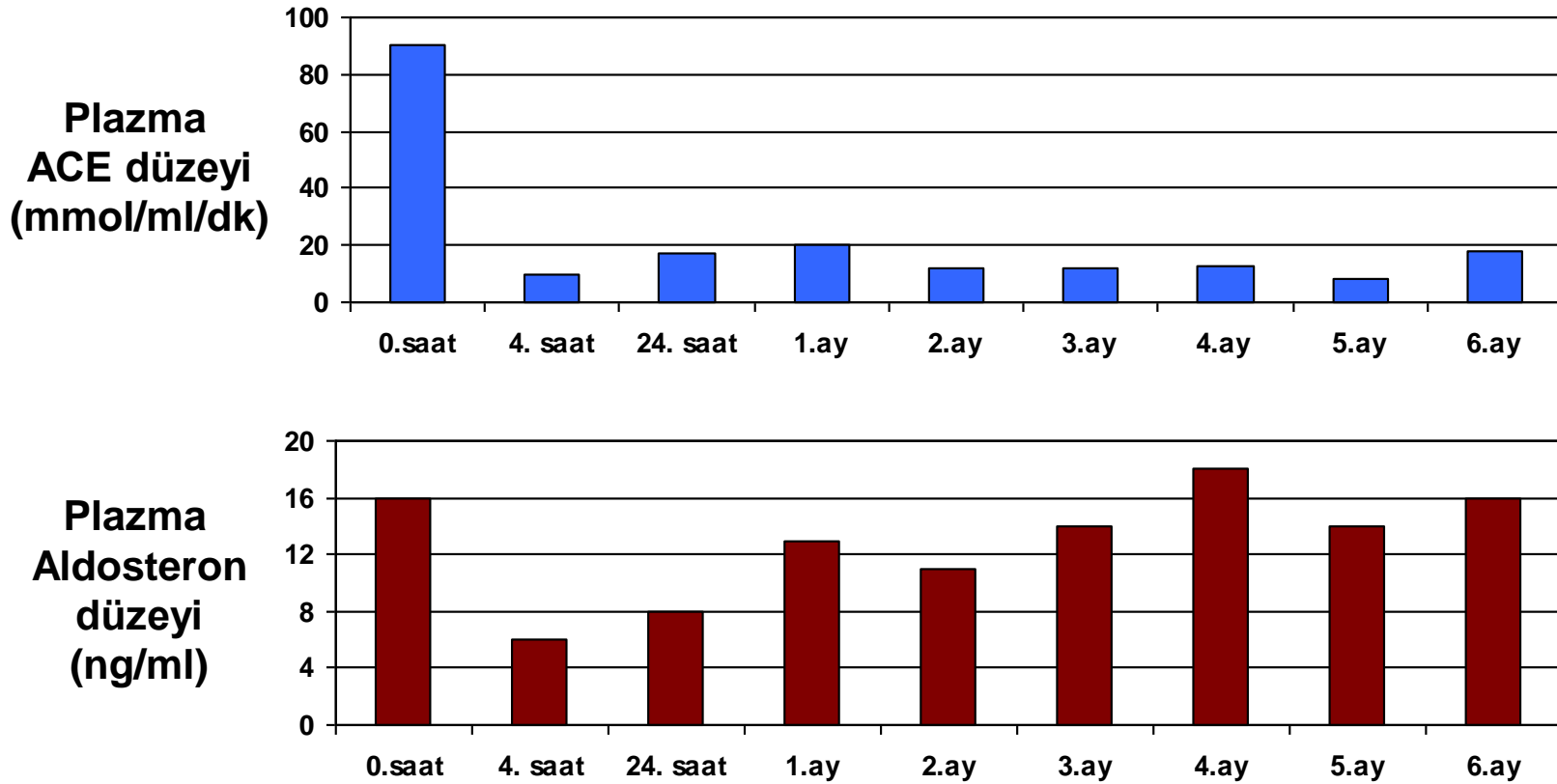


Artmış mineralokortikoid reseptör aktivasyonu

- Uygunsuz mineralokortikoid reseptör aktivasyonu
 - Patofizyolojik etki, non-genomik etki
 - Epitalyal dokular dışında etkili (kalp, böbrek vb.)
 - Aşırı tuz tüketimi ve obezite ile ilişkili
- **Aldosteron “kaçış” fenomeni**
 - ACE-i veya ARB alan hastalarda süreçte plazma aldosteron düzeyinde artış

ACE-i kullanımında aldosteron “Kaçış” fenomeni

MI sonrası; Enalapril 20 mg, günde iki kez



The incidence and implications of aldosterone breakthrough

Andrew S Bombback* and Philip J Klemmer

SUMMARY

Interruption of the renin–angiotensin–aldosterone system has become a leading therapeutic strategy in the treatment of chronic heart and kidney disease. Angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers do not, however, uniformly suppress the renin–angiotensin–aldosterone system. Plasma aldosterone levels are elevated in a subset of patients despite therapy. This phenomenon, known as ‘aldosterone escape’ or ‘aldosterone breakthrough’, has only been directly examined in small numbers of patients. The key questions of how often breakthrough occurs and whether breakthrough leads to worse outcomes have yet to be definitively answered. In this Review, we summarize the reported data on the incidence and clinical implications of aldosterone breakthrough, and highlight areas of uncertainty that have yet to be adequately addressed in the literature. Although the available evidence is not strong enough to support widespread screening for aldosterone breakthrough, our findings should prompt physicians to consider the phenomenon in select patients as well as guide future research efforts.

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Define aldosterone breakthrough in the context of angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) use.

The incidence and implications of aldosterone breakthrough

Andrew S Bombback* and Philip J Klemmer

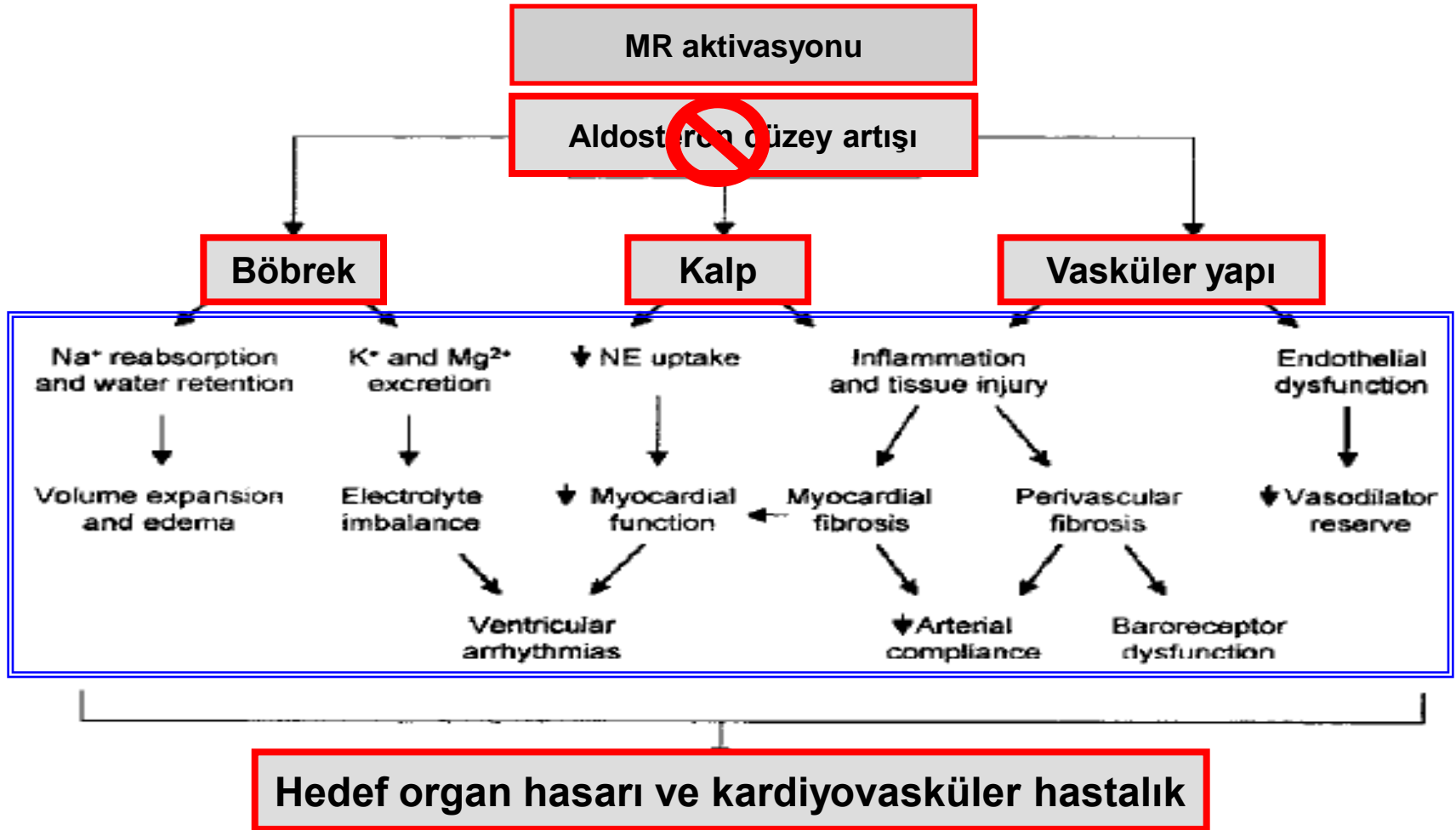
Aldosteron kaçıışı “escape” bazal değere göre aldosteron artışı; 6. ayda % 10, 1. yılda % 53

Table 1 Overview of studies reviewed during preparation of this article.

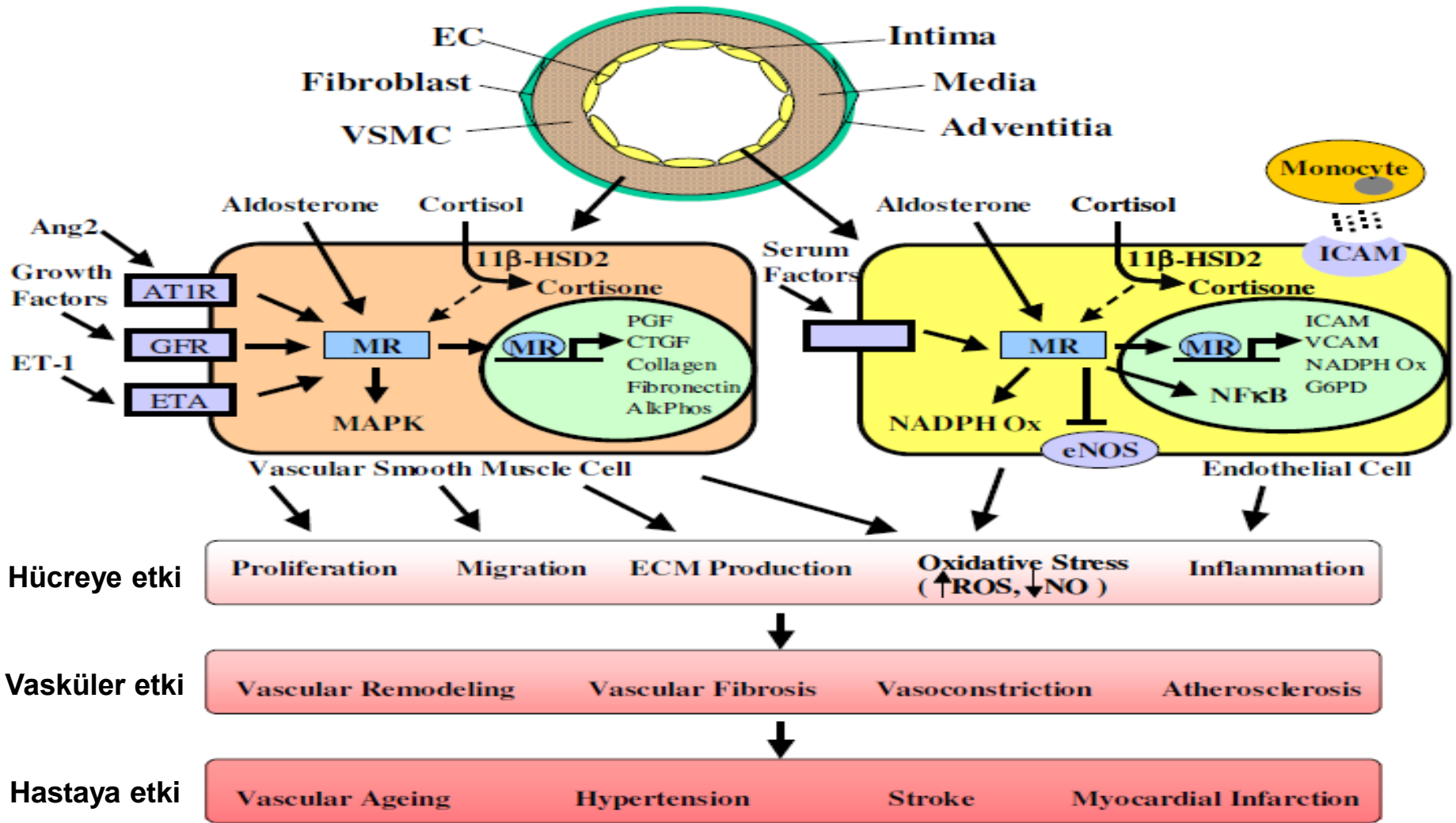
Study	Subjects	Congestive heart failure	Chronic kidney disease	Renin-angiotensin-aldosterone system blockade	Definition of aldosterone breakthrough	Incidence of aldosterone breakthrough
Lee <i>et al.</i> (1999) ²⁷	22	Yes	No	ACE inhibitor titrated to maximum tolerated dose for 18 months	Aldosterone >80 pg/ml ^a after 18 months	23% (5/22)
MacFadyen <i>et al.</i> (1999) ⁶	91	Yes	No	“Stable ACE inhibitor therapy” for at least 4 weeks	Aldosterone >144 pg/ml ^a after at least 4 weeks	38% (35/91)
Sato and Saruta (2001) ³²	75	No	No	ACE inhibitor for 40 weeks	Aldosterone ≥baseline levels after 40 weeks	51% (38/75)
Cicoira <i>et al.</i> (2002) ²⁸	141	Yes	No	ACE inhibitor for at least 6 months	Aldosterone >0.42 nmol/l ^a after at least 6 months	10% (14/141)
Tang <i>et al.</i> (2002) ²⁹	75	Yes	No	Enalapril 2.5 mg twice per day or 20 mg twice per day for 6 months	Aldosterone ≥160 pg/ml ^a after 6 months	35% (26/75)
Sato <i>et al.</i> (2003) ³⁰	45	No	Yes	Trandolapril titrated to goal blood pressure of 130/85 mmHg for 40 weeks	Aldosterone ≥baseline levels after 40 weeks	40% (18/45)
Schjoedt <i>et al.</i> (2004) ⁴	63	No	Yes	Losartan 100 mg per day for 24–42 months	Aldosterone ≥baseline levels after 24–42 months	41% (26/63)
Horita <i>et al.</i> (2006) ³¹	43	No	Yes	Temocapril 1 mg per day, losartan 12.5 mg per day, or both, for 12 months	Aldosterone ≥baseline levels after 12 months	53% (23/43)

^aIn normal subjects with normal sodium intake, values for plasma aldosterone range from 50 to 150 pg/ml (0.139 to 0.416 nmol/l). Abbreviation: ACE, angiotensin-converting enzyme.

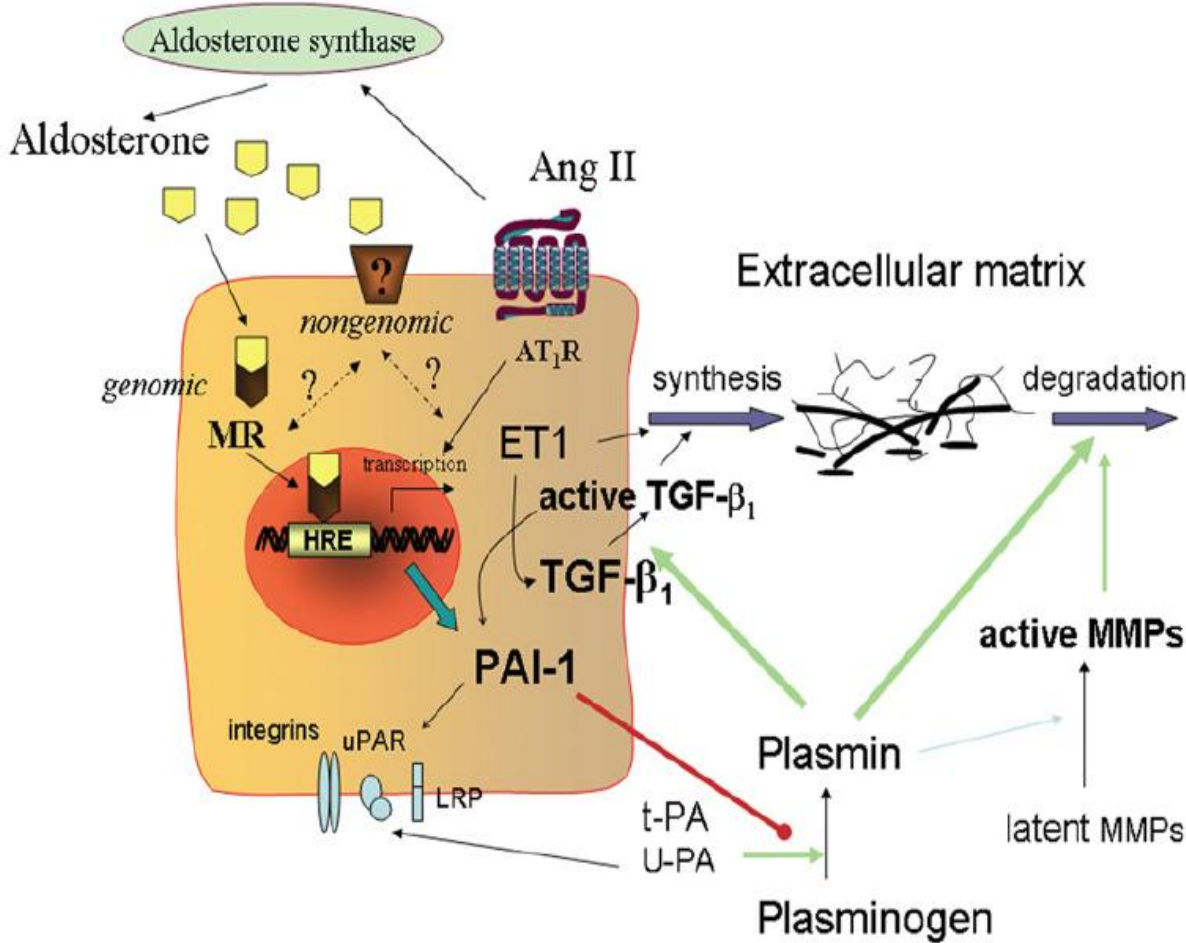
Mineralokortikoid reseptör (aldosteron) aktivasyonu & Vasküler hastalık



Mineralokortikoid reseptör (aldosteron) aktivasyonu & Vasküler hastalık



Mineralokortikoid reseptör (aldosteron) aktivasyonu & trombotik, inflammatuar ve fibrotik etki



Clinical Science (2007) 113, 267–278.
 Molecular and Cellular Endocrinology 350 (2012) 248–255.

Aldosteron & Kardiyovasküler risk-1

- **HT gelişimi ve şiddeti ile ilişkili**
 - Normotensiflerde plazma aldosteron düzey yüksekliğinin HT gelişimi açısından prediktif değeri var
 - Framingham çalışması ¹
 - Plazma aldosteron düzeyi 24 saatlik ambulator KB düzey ölçümleri ile ilişkili ^{2, 3}
 - Dirençli HT'da plazma aldosteron düzeyi yüksek
 - Hiperaldosteronizm sıklığı % 5-10 ⁴, % 20 ⁵
 - HT şiddeti artıkça hiperaldosteronizm sıklığı artar ⁶
 - <160/100 mmHg; sıklık % 2
 - 160-180/100-109 mmHg; sıklık % 8
 - >180/110 mmHg mmHg; sıklık % 13

1. Vasan R, N Eng J Med, 2004, 2. El-Gharbawy AH, Hypertension, 2001, 3. Grion CE, Hypertension, 2005
4. Gordon RD, Clin Exp Pharmacol Physiol, 1994, 5. Calhoun DA, Hypertension 2002, 6. Mosso L, Hypertension 2003.

Aldosteron & Kardivasküler risk-2

- **HT'da hedef organ hasarı gelişimi ile ilişkili** ⁷
 - İnme sıklığı 4 kat yüksek
 - MI sıklığı 6.5 kat yüksek
 - Atriyal fibrilasyon sıklığı 12 kat yüksek
- **Plazma aldosteron düzeyi ile KV anormallikler ilişkili** ⁸
 - Sol ventrikül hipertrofisi
 - Diyastolik disfonksiyon
 - Endotel disfonksiyonu
 - Artmış aritmi sıklığı (atriyal fibrilasyon) ¹³
- **KKY'de plazma aldosteron düzeyi ile mortalite ilişkili** ^{9, 10}
- **KBH'da proteinüri ve KBH progresyonu ile ilişkili** ^{11, 12}
- **Obezite, metabolik sendrom ve de tip II DM'ta plazma aldosteron düzeyi yüksek** ⁸

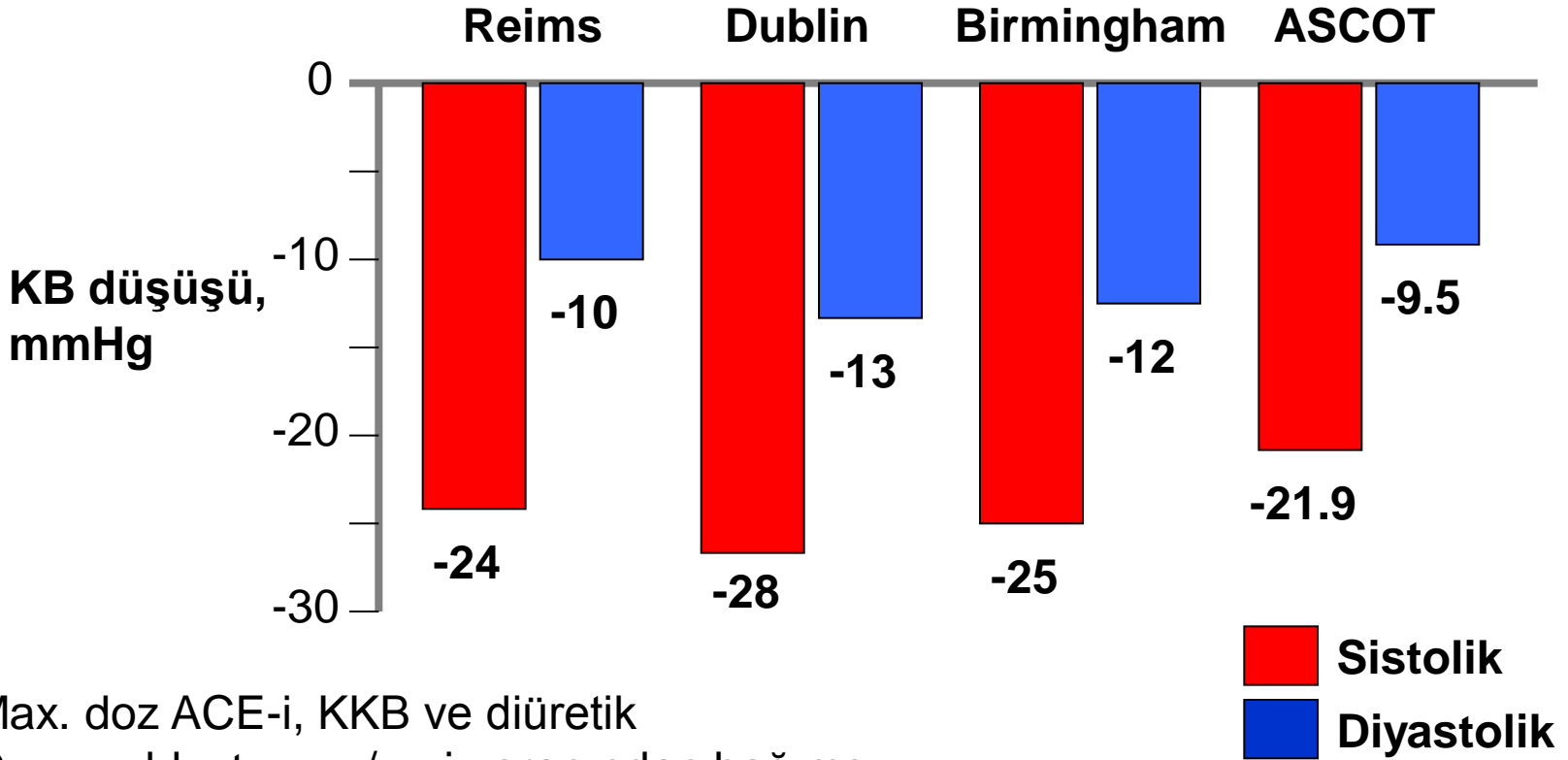
Mineralokortikoid reseptör antagonistlerinin klinik kullanımı

- **Hipertansiyon**
 - **Dirençli hipertansiyon**
- **Kardiyovasküler hastalık**
 - **Konjestif kalp yetmezliği**
- **Kronik böbrek hastalığı**

MR antagonisti & Hipertansiyon

- Hafif-orta şiddette HT'da etkili
- Düşük renin HT, siyah ırk, yaşlı ve diyabetiklerde etkin KB düşüşü ¹⁻³
- Metabolik sendrom, diyabet ve de SVH olan hastalarda etkin KB düşüşü ve SV kitle indeksinde belirgin gerileme ⁴

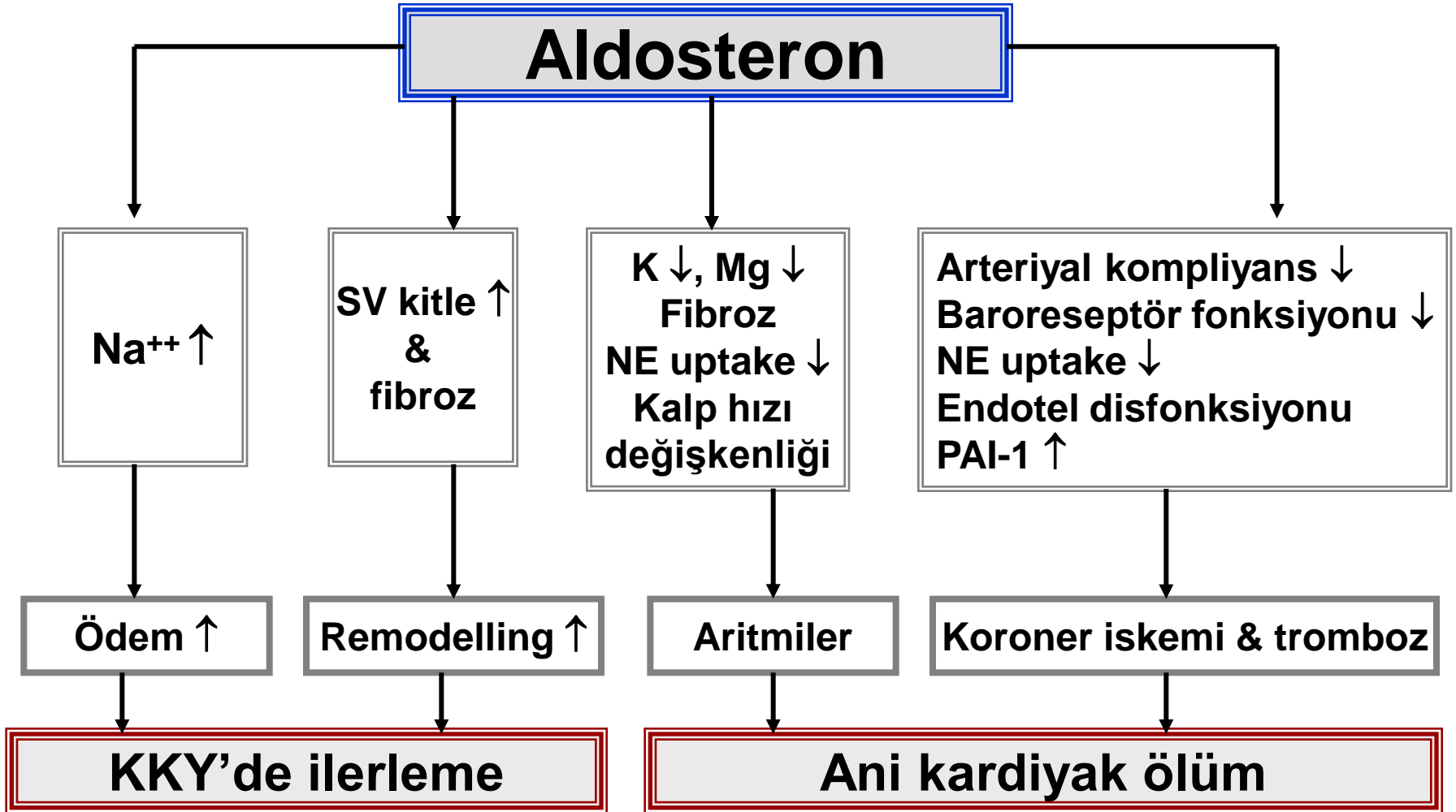
Dirençli hipertansiyonda spirinolakton ile anlamlı kan basıncı düşüşü



Max. doz ACE-i, KKB ve diüretik
Cevap aldosterone/renin oranından bağımsız

Adapted from Pimenta et al, 2007

Kalp yetersizliğinde aldosteron



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NUMBER 10



THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

BERTRAM PITT, M.D., FAIEZ ZANNAD, M.D., WILLEM J. REMME, M.D., ROBERT CODY, M.D., ALAIN CASTAIGNE, M.D.,
ALFONSO PEREZ, M.D., JOLIE PALENSKY, M.S., AND JANET WITTES, PH.D.,
FOR THE RANDOMIZED ALDACTONE EVALUATION STUDY INVESTIGATORS*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

APRIL 3, 2003

VOL. 348 NO. 14

Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction

Bertram Pitt, M.D., Willem Remme, M.D., Faiez Zannad, M.D.,
James Neaton, Ph.D., Felipe Martinez, M.D., Barbara Roniker, M.D., Richard Bittman, Ph.D.,
Steve Hurley, B.S., Jay Kleiman, M.D., and Marjorie Gatlin, M.D., for the Eplerenone Post-Acute Myocardial
Infarction Heart Failure Efficacy and Survival Study Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JANUARY 6, 2011

VOL. 364 NO. 1

Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

Faiez Zannad, M.D., Ph.D., John J.V. McMurray, M.D., Henry Krum, M.B., Ph.D., Dirk J. van Veldhuisen, M.D., Ph.D.,
Karl Swedberg, M.D., Ph.D., Harry Shi, M.S., John Vincent, M.B., Ph.D., Stuart J. Pocock, Ph.D.,
and Bertram Pitt, M.D., for the EMPHASIS-HF Study Group*

Mineralokortikoid reseptör (aldosteron) antagonistisi & Kalp yetmezliği

Table 1 Comparison of major trial of aldosterone antagonists

Study	Patients, <i>n</i>	Start and end dates of enrollment	Inclusion criteria	Baseline characteristics	Mean EF	Exclusion	Baseline medications	Outcomes	
								All-cause mortality	CV death or HF hosp
RALES [5]	1663	1995–1996	NYHA IV in last 6 mo (III/IV @ enrollment) + EF ≤35%	65 years old; women 27%; ICM 55% (USA excluded)	25%	Cr >2.5, K ⁺ >5	ACEI (94%); loop diuretic (100%); BB (10%)	35% vs 46% ^a ; RR 0.70 (0.6–0.82)	Death: RR 0.69; HF hosp: RR 0.65
EPHESUS [6]	6632	1999–2001	3–14 days post-MI + EF ≤40% + HF (rales, edema on CXR, S3) OR DM	64 years old; women 28%; all post-MI; 45% had reperfusion therapy	33%	Cr >2.5, K ⁺ >5	ACEI/ARB (86%); diuretic (60%); BB (75%)	14.4% vs 16.7% ^a ; RR 0.85 (0.75–0.96 [21% RRR of SCD])	26.7% vs 30% ^a ; RR 0.87, <i>P</i> =0.002
EMPHASIS-HF [7**]	2737	2006–2010	NYHA II + EF ≤30% (30%–35% + QRS >130) + HF hosp in 6 mo OR elevated BNP	68 years old; women 22%; ICM 70%	26%	GFR <30, K ⁺ >5	ACEI/ARB (94%); diuretic (85%); BB (86%)	12.5% vs 15.5%; HR 0.76 (0.62–0.93)	18.3% vs 25.9% ^a ; HR 0.63 (0.54–0.74)

Table 1 Trials of aldosterone receptor blockade in MI and heart failure: main characteristics and outcomes

Study Year	RALES 1999	EPHESUS 2003	EMPHASIS-HF 2011	TOPCAT 2013*	REMINDER 2012*	ALBATROSS 2013*
Primary end point	Mortality	Mortality, CV death, or hospitalisation for HF	CV death, or hospitalisation for HF	CV death, or hospitalisation for HF	Mortality, or hospitalisation for HF	Death, or worsened HF, or arrhythmias
No. of patients	1663	6642	2737	3515 [†]	612 [†]	1600 [†]
Inclusion criteria						
Injury disease	Severe HF	Post-MI (within 3–14 days), HF or diabetes	Mild HF, ≥ 55 years	Clinical HF, ≥ 55 years	STEMI, within 24 hours	STEMI or high-risk non-STEMI, within 72 hours
NYHA	III–IV	I–IV	II	I–IV	n. a.	n. a.
EF (%)	< 35	< 40	< 35	> 45	> 40	n. a.
Major exclusion criteria	P-creatinine > 220 μM, P-K > 5.0	P-creatinine > 220 μM, P-K > 5.0	eGFR < 30 mL/min/m ² , P-K > 5.0	eGFR < 30 mL/min/m ² , P-K > 5.5	eGFR < 30 mL/min/m ² , P-creatinine ≥ 220 μM, history of HF	P-creatinine > 220 μM and/or Creatinine clearance < 30 mL/min/m ²
Mean age, (years ± SD)	65 ± 12	64 ± 12	68.7 ± 7.7	Ongoing study	Ongoing study	Ongoing study
Medical therapy	ACE-I, diuretic	ACE-I/ARB, β-blocker, diuretic	ACE-I/ARB, β-blocker, diuretic	ACE-I/ARB, β-blocker, diuretic	ACE-I/ARB, β-blocker	ACE-I/ARB, β-blocker
MR antagonist	Spironolactone	Eplerenone	Eplerenone	Spironolactone	Eplerenone	Acute bolus of canrenoate, then spironolactone
Dose (mg/day)	25–50	25–50	25–50	15–45	Up to 50	25
Mean daily dose (mg)	26	43	39	Ongoing study	Ongoing study	25
Mean follow-up	24 months	16 months	21 months	3.45 years	18 months	6 months
Mortality						
All cause	–30%	–15%	–34%	Primer sonlanım Fark yok	Primer sonlanım %42.9 RR azalması	Ongoing study
Cardiovascular	–31%	–17%	–37%			
Hospitalisation for HF	–33%	–23%	–42%			
P-K > 6 mM (placebo %/active %)	1%/2%	3.9%/5.5%	1.9%/2.5%			

The Effect of Aldosterone Antagonists for Ventricular Arrhythmia: A Meta-Analysis

Jiafu Wei MD, PhD, Juan Ni PhD, Dejie Huang MD,
Mao Chen MD, PhD, Shaodi Yan PhD and Yong Peng PhD

Abstract

Background

Sudden cardiac death (SCD) from cardiac arrest, one of the most common types of cardiac-related death, is most often triggered by ventricular arrhythmia (VA). It has been reported that aldosterone antagonists (AAs) have the benefit of reducing SCD in patients with heart failure (HF). It also has been indicated in animal experiments and clinical trials that AAs may have an antiarrhythmic effect.

Hypothesis

AAs have an effect on VA in patients with HF or coronary artery disease.

Methods

We searched the Cochrane Central Register of Controlled Trials, PubMed, Current Controlled Trials, and the National Research Register, and identified randomized controlled trials on the effect of AAs on VA.

Results

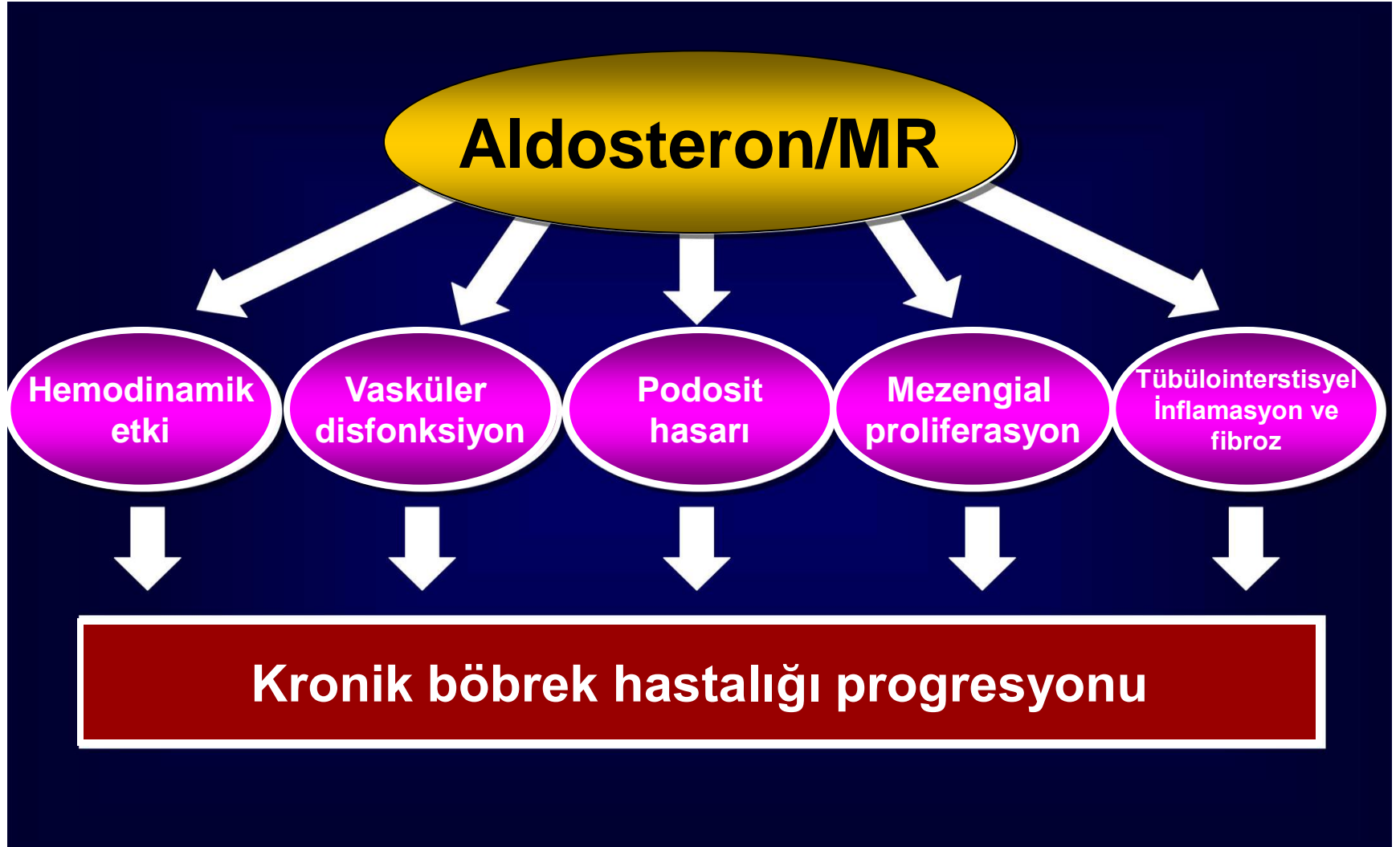
All together in patients significantly reducing the risk of SCD (RR: 0.77).

Conclusion The addition of AAs significantly reducing the risk of SCD and ventricular premature complexes.

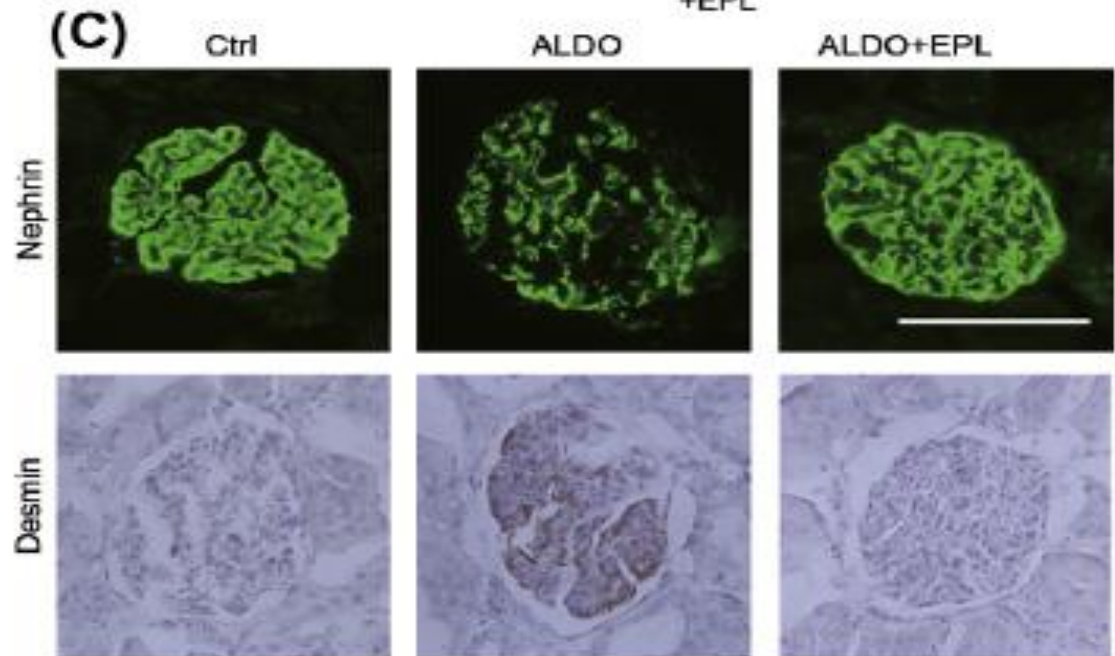
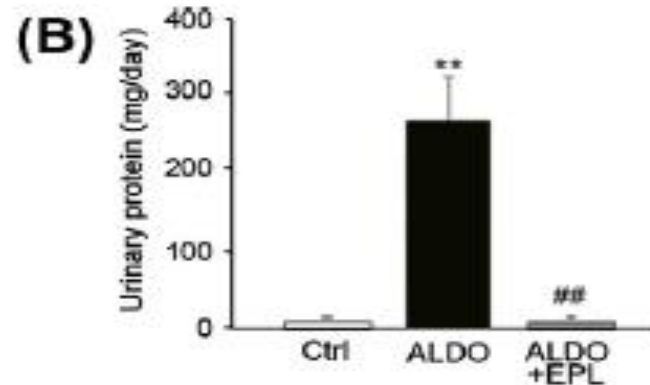
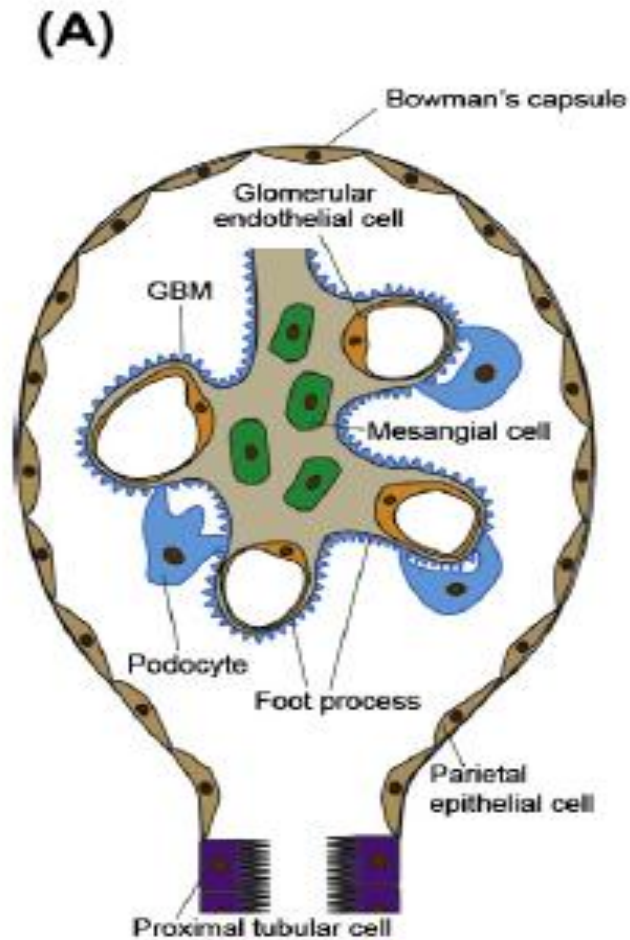
Results

All together, **7 trials with a total of 8635 patients** were identified and extracted. **AAs reduced the risk of SCD in patients with HF by 21%** (relative risk [RR]: 0.79, 95% confidence interval [CI]: 0.67–0.93). AAs significantly reduced the episodes of ventricular premature complexes (mean difference 705 ± 646 episodes per 24 hours). **Risk of ventricular tachycardia was reduced by 72%** (RR: 0.28, 95% CI: 0.10–0.77).

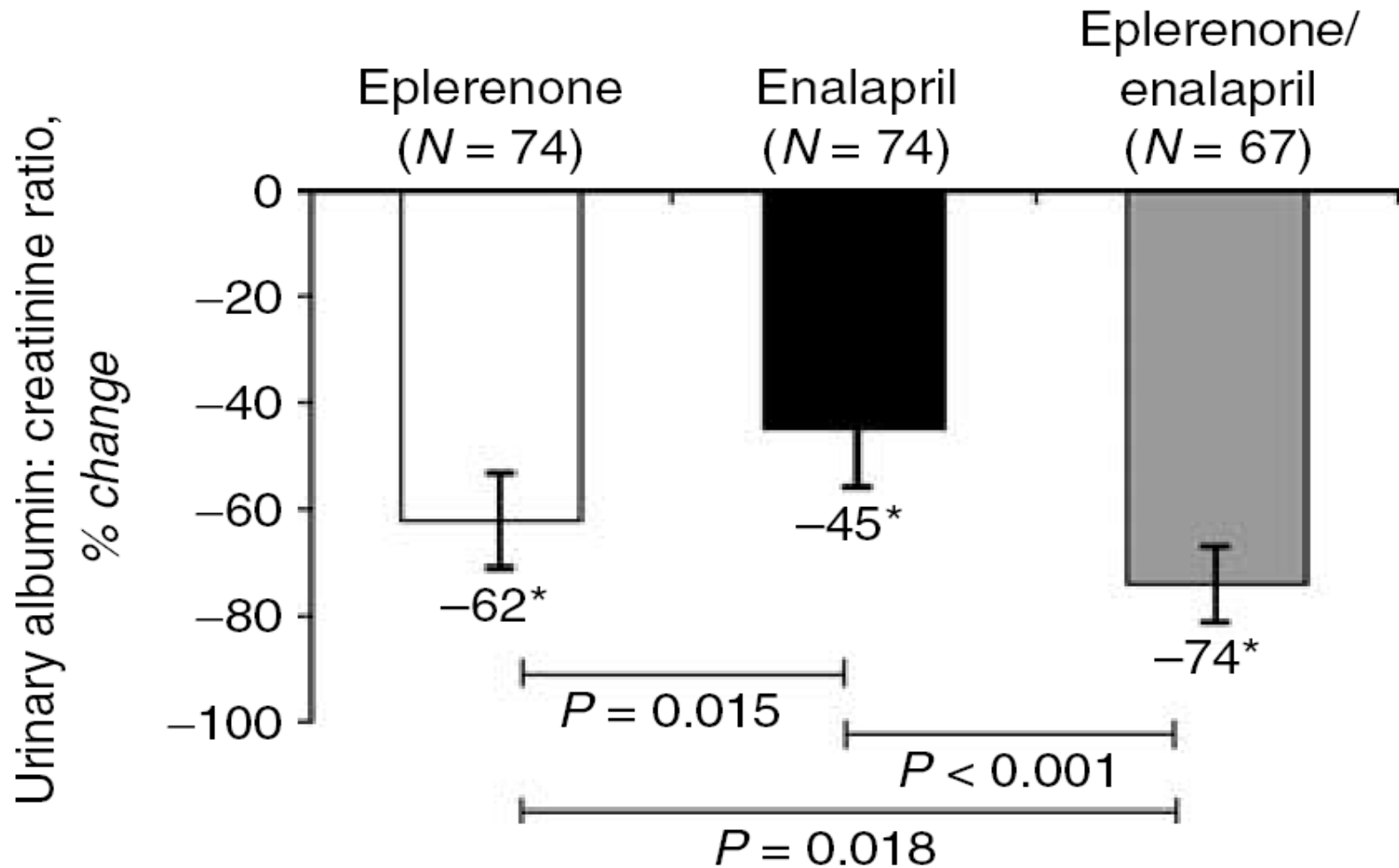
Mineralokortikoid reseptör (aldosteron) aktivasyonu & Kronik böbrek hastalığı



Mineralokortikoid reseptör (aldosteron) aktivasyonu/antagonizm & Kronik böbrek hastalığı



MR (aldosteron) antagonisti & proteinüri



ORIGINAL ARTICLE

Efficacy and Safety of Combined vs. Single Renin–Angiotensin–Aldosterone System Blockade in Chronic Kidney Disease: A Meta-Analysis

Paweena Susantitaphong,^{1–3} Kamal Sewaralthahab,¹ Ethan M. Balk,^{2,4} Somchai Eiam-ong,³ Nicolaos E. Madias,^{1,2} and Bertrand L. Jaber^{1,2}

Curr Hypertens Rep (2011) 13:282–288
DOI 10.1007/s11906-011-0202-2

Mineralocorticoid Receptor Blockade in Chronic Kidney Disease

Matthew J. Volk · Andrew S. Bomback · Philip J. Klemmer

Mini-Review

Aldosterone Antagonism in Chronic Kidney Disease

Manish P. Ponda and Thomas H. Hostetter

Division of Nephrology, Department of Medicine, Albert Einstein College of Medicine, Bronx, New York

Clin J Am Soc Nephrol 1: 668–677, 2006. doi: 10.2215/CJN.00120106

Blood
Purification

Blood Purif 2012;33:119–124
DOI: [10.1159/000334161](https://doi.org/10.1159/000334161)

Published online: January 20, 2012

Mineralocorticoid Receptor Blockade in Chronic Kidney Disease

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Aldosterone Antagonism in Chronic Kidney Disease

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Division of Nephrology, Department of Medicine, Albert Einstein College of Medicine, Bronx, New York

Clin J Am Soc Nephrol 1: 668–677, 2006. doi: 10.2215/CJN.00120106

Table 1. Studies of aldosterone antagonists in CKD^a

Patient Characteristics	n	Intervention	Outcome		Reference
			Δ Proteinuria	Δ SBP/DBP (mmHg)	
Type II DM	215	ACEI vs Epl vs Epl+ACEI	-45% -62% -74%	-20/-15 -20/-13 -22/-16	94
HTN Nondiabetic +MA ^b	494	ACEI vs Epl		-13/-11 -15/-11	96
Type II DM	64	ACEI vs Epl	-26% -62%		
	46	β-blocker and HCTZ			
Nondiabetic chronic GN	42	Ex			
Proteinuria (>1.5 g/d), majority DM	41	AC			
HTN +MA ^b	269	CCB			
	35	CCB vs Epl	-10% -50%		
Nondiabetic chronic GN	22	Existing ARB + Spiro	-13%	-9/-7	93
Type II DM	20	ACEI/ARB and diuretic + Spiro vs placebo	-33%	-6/-4 (24-hour)	86
Type I DM	20	ACEI/ARB and diuretic + Spiro vs placebo	-30%	NS (24-hour)	92
Type II DM 'aldosterone escape'	13	Existing ACEI + Spiro	-28%	NS	91

KB düşürücü etkiden bağımsız proteinüride % 15-54 azalma

^aSBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; ACEI, ACE inhibitor; Epl, eplerenone; Spiro, spironolactone, MA, microalbuminuria; GN, glomerulonephritis; CCB, calcium channel blocker; NS, not significant; NA, not applicable.

^bSubgroup analysis.

Nat Clin Pract Nephrol. 2009 February ; 5(2): 74–75. doi:10.1038/ncpneph1004.

Renal aspirin: will all patients with chronic kidney disease one day take spironolactone?

Andrew S Bomback^{*}, **Abhijit V Kshirsagar**, and **Philip J Klemmer**

AS Bomback is the Doc J Thurston III Fellow, AV Kshirsagar is Associate Professor of Medicine and PJ Klemmer is Professor of Medicine in the Department of Medicine, Division of Nephrology and Hypertension, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.

ORIGINAL ARTICLE

Efficacy and Safety of Combined vs. Single Renin–Angiotensin–Aldosterone System Blockade in Chronic Kidney Disease: A Meta-Analysis

Paweena Susantitaphong,¹⁻³ Kamal Sewaralthahab,¹ Ethan M. Balk,^{2,4} Somchai Eiam-ong,³ Nicolaos E. Madias,^{1,2} and Bertrand L. Jaber^{1,2}

- 59 klinik çalışma, toplam hasta sayısı=4975
- Albuminüri (p=0.001) ve proteinüride azalma (p=0.03)
- % 9.4 normoalbuminüriye dönüş
- Scre ikiye katlanması, hastaneye yatış, mortaliteye etkisi yok
- Analizde aldosteron içeren grupta GFH'a etki yok
- ACE-i + ARB kombinasyonunda GFH'da anlamlı azalma var (p=0.001)
- % 3.4 daha fazla hiperkalemi ve % 4.6 hipotansiyon sıklığı

Mineralokortikoid reseptör (aldosteron) antagonistisi klinik endikasyonları

MR (aldosteron) antagonistisi

KESİN

- Kalp yetmezliği
- Post MI disfonksiyon
- Dirençli HT

MUHTEMEL

- Sol ventrikül hipertrofisi
- Diyabetik ve diyabet dışı proteinüri
- Atriyal fibrilasyon ve post MI aritmi

ZAYIF (veri az)

- Erken KBH progresyon
- KBH (Diyaliz)'da KV koruma ?
- Serebrovasküler hast. hasarın azaltılması ?