Hangi İlaç Renin Anjiyotensin Aldosteron Sistemini Daha İyi Bloke Eder?

Prof. Dr. Tevfik Ecder
İstanbul Bilim Üniversitesi Tıp Fakültesi
İç Hastalıkları Anabilim Dalı
Nefroloji Bilim Dalı

Hangisi Renin-Anjiyotensin Aldosteron Sistemini Daha İyi Bloke Eder?

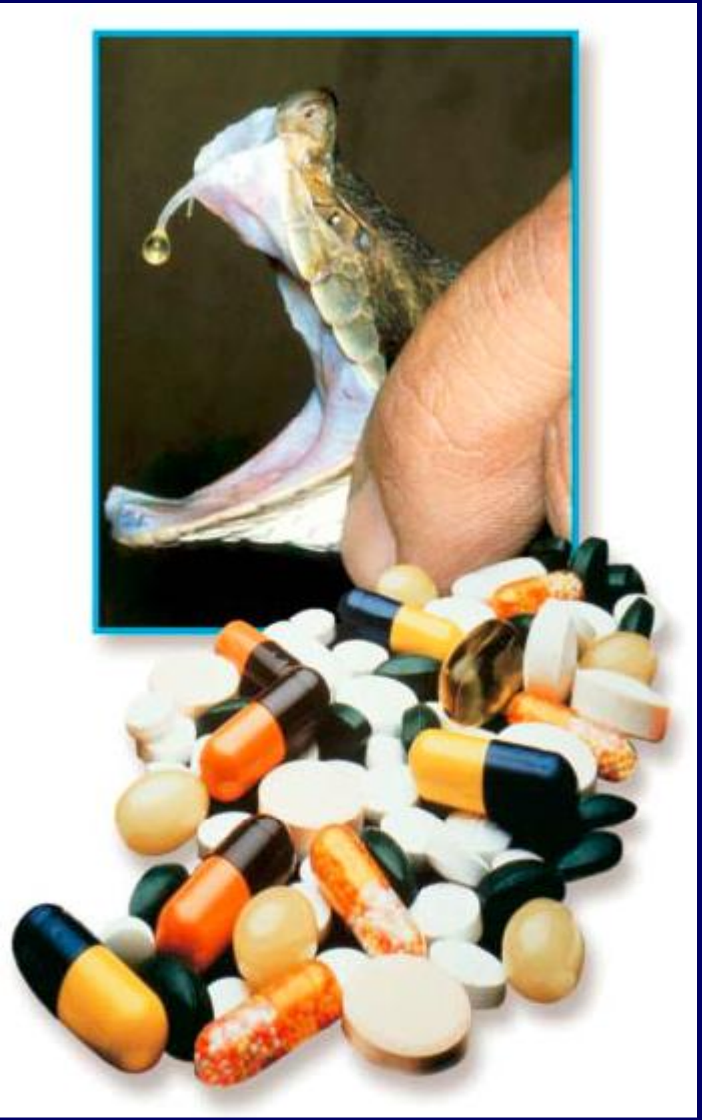
- ACE inhibitörleri
- Anjiyotensin reseptör blokerleri
- Mineralokortikoid reseptör antagonistleri

?

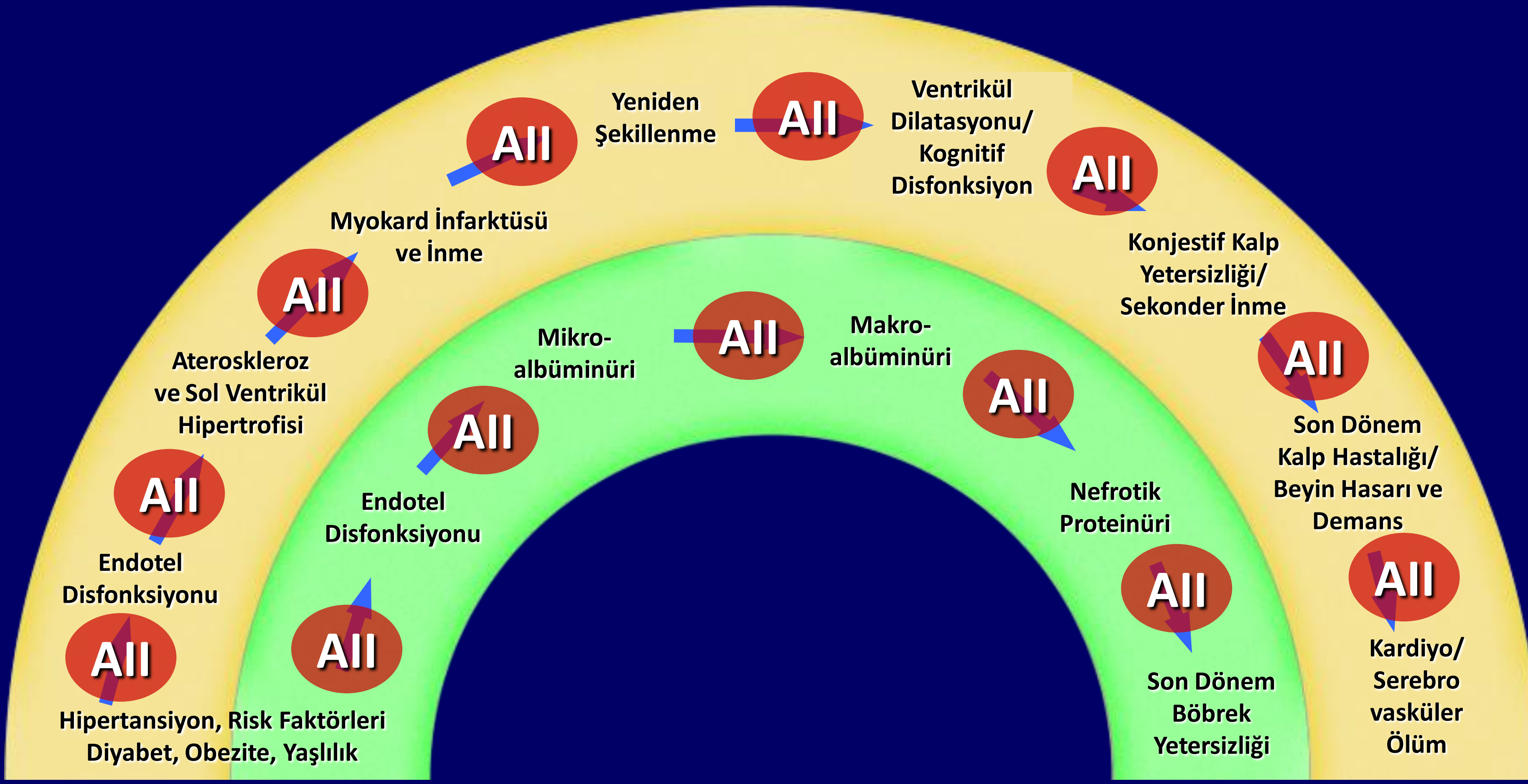

BPF
(Braykinin Potentiating Factor)
Sergio Ferreira
Bothrops jararaca

Yılan Zehirinden Tansiyon Düşürücü İlaç

Sir John Robert Vane (1927-2004)
1982 Nobel Ödülü

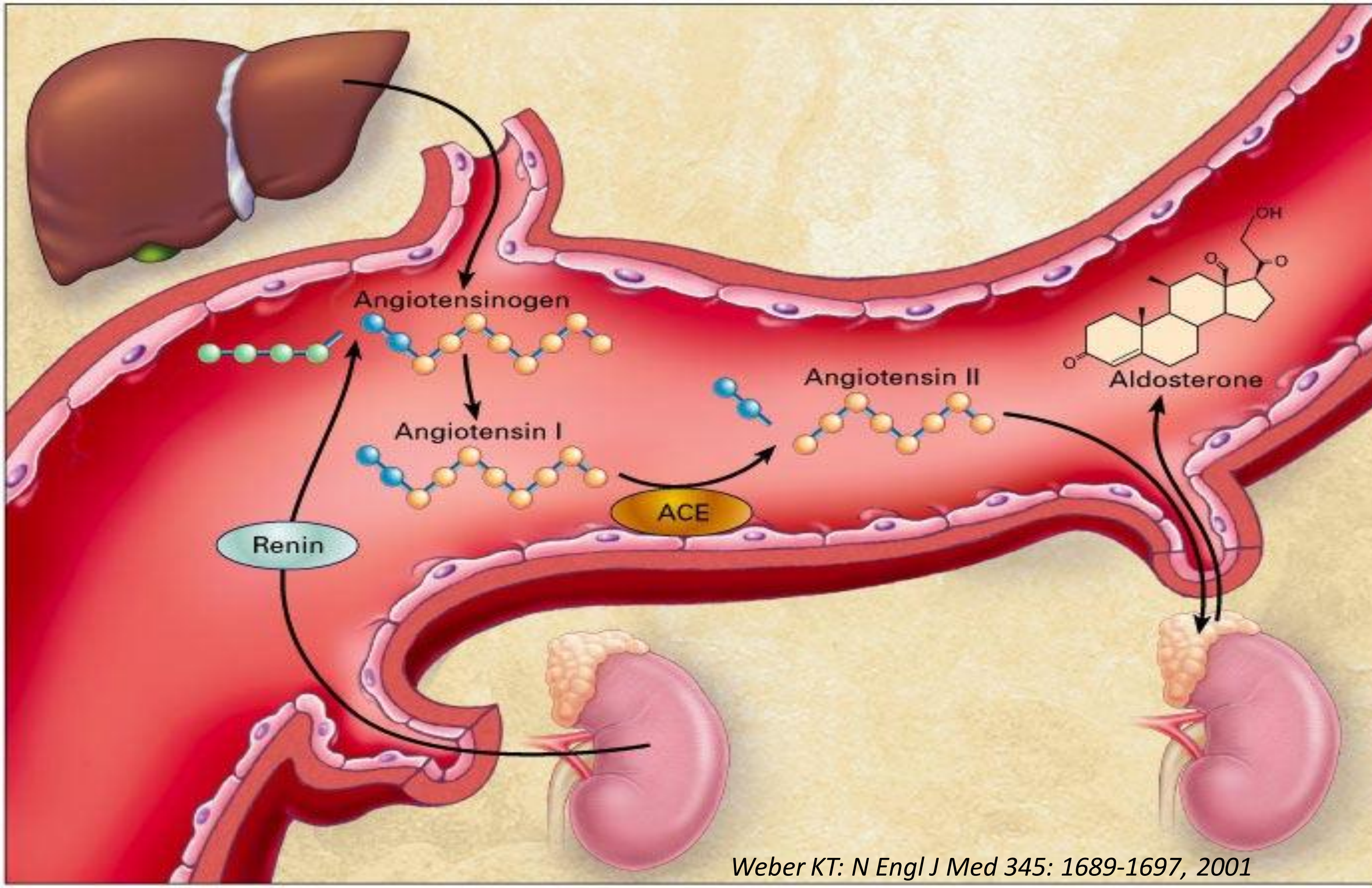


Kardiyorenal Süreç



Dzau, Braunwald. Am Heart J 121:1244–1263, 1991

Renin Anjiyotensin Aldosteron Sistemini Nasıl Baskılayalım?



Weber KT: N Engl J Med 345: 1689-1697, 2001

Renin Anjiyotensin Aldosteron Sistemini Nasıl Baskılayalım?

Pubmed (06.05.2015)

ACE inhibitor: 47622

Angiotensin receptor blocker: 5894

ACE inhibitors: 48818

Angiotensin receptor blockers: 27694

Kalp Yetersizliğinde ACEİ Tedavisi

CONSENSUS *(Cooperative North Scandinavian Enalapril Survival Study) (1987)*	**Enalapril / Plasebo**	**Enalapril, ciddi konjestif kalp yetersizliğinde semptomları düzeltir ve ölüm riskini azaltır.**
SOLVD *(Study of Left Ventricular Dysfunction) (1991)*	**Enalapril / Plasebo**	**Enalapril, sol ventrikül disfonksiyonu olan semptomatik hastalarda hastaneye yatışları ve ölüm riskini azaltır.**
V-HeFT II *(Second Vasodilator-Heart Failure Trial) (1991)*	**Enalapril / Hidralazin ve nitratlar**	**Enalapril, konjestif kalp yetersizliği olan hastalarda ölüm riskini azaltır.**

Miyokard İnfarktüsü Sonrasında ACEİ Tedavisi

SAVE *(Survival and Ventricular Enlargement Trial) (1992)*	**Kaptopril / Plasebo**	**Kaptopril, Mİ sonrasında asemptomatik sol ventrikül disfonksiyonu olan hastalarda ölümü azaltır.**
AIRE *(Acute Infarction Ramipril Efficacy) (1993)*	**Ramipril / Plasebo**	**Ramipril, Mİ sonrasında kalp yetersizliği olan hastalarda ölümü azaltır.**
TRACE *(Trandolapril Cardiac Evaluation) (1995)*	**Trandolapril / Plasebo**	**Trandolapril, Mİ sonrasında sol ventrikül disfonksiyonu olan hastalarda ölümü ve ciddi kalp yetersizliği gelişimini azaltır.**
SMILE *(1995)*	**Zofenopril / Plasebo**	**Zofenopril, Mİ sonrasında ilk 24 saat içinde başlandığında ölümü ve kalp yetersizliği gelişme riskini azaltır.**
FAMIS *(Fosinopril in Acute Myocardial Infarction Study) (1997)*	**Fosinopril / Plasebo**	**Fosinopril, Mİ sonrasında tromboliz tedavisi ile birlikte erken dönemde (<9 saat) verildiğinde ciddi kalp yetersizliği ve ölüm riskini azaltır.**

Kardiyovasküler Riski Yüksek Olan Hastalarda ACEİ Tedavisi

HOPE *(Heart Outcomes Prevention Evaluation) (2000)*	**Ramipril / Plasebo**	**Ramipril, KV riski yüksek olan hastalarda Mİ, inme ve KV nedenlere bağlı ölüm riskini azaltır.**

EUROPA *(European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease and Outcomes Prevention Evaluation) (2003)*	**Perindopril / Plasebo**	**Perindopril, stabil koroner kalp hastalığı olan hastalarda KV ölüm, Mİ veya kardiyak arrest riskini azaltır.**

Kronik Böbrek Hastalığında ACEİ Tedavisi

Lewis *(1993)*	**Kaptopril / Plasebo**	**Kaptopril tedavisi tip 1 diyabete bağlı aşikâr nefropatisi olan hastalarda böbrek yetersizliğinin ilerlemesini yavaşlatır.**
AIPRI *(ACE Inhibition in Progressive Renal Insufficiency) (1993)*	**Benazepril / Plasebo**	**Benazepril tedavisi KBH olan hastalarda böbrek yetersizliğinin ilerlemesini yavaşlatır.**
REIN *(Ramipril Efficacy In Nephropathy) (1998)*	**Ramipril / Plasebo**	**Ramipril tedavisi diyabet dışı nedenlere bağlı nefropatisi olan hastalarda böbrek yetersizliğinin ilerlemesini yavaşlatır.**
MICRO-HOPE *(2000)*	**Ramipril / Plasebo**	**Ramipril tedavisi mikroalbüminürisi olan tip 2 diyabetik hastalarda aşikâr nefropati gelişme riskini azaltır.**
AASK *(African American Study of Kidney Disease) (2001)*	**Ramipril / Amlodipin**	**Ramipril tedavisi hipertansif böbrek hastalığı olan siyahlarda son dönem böbrek yetersizliği veya ölüm riskini azaltır.**
BENEDICT *(2004)*	**Trandolapril / Plasebo**	**Trandolapril tedavisi normoalbüminürisi olan tip 2 diyabetik hastalarda mikroalbüminüri gelişme riskini azaltır.**
Hou *(2006)*	**Benazepril / Plasebo**	**Benazepril tedavisi diyabet dışı nedenlere bağlı ciddi böbrek yetersizliği olan hastalarda (kreatinin 3.1 – 5.0 mg/dl) böbrek yetersizliğinin ilerlemesini yavaşlatır.**

Kardiyorenal Süreçte RAAS Blokajı Tedavisi

Hastalık ve Birincil Sonlanım	ACEİ	ARB	MRA
Kalp yetersizliğinde ölüm	Enalapril (CONSENSUS, SOLVD, V-HeFT II)	Valsartan (Val-HeFT), Kandesartan (CHARM)	Spironolakton (RALES)
Miyokard infarktüsü sonrasında ölüm	Kaptopril (SAVE), Ramipril (AIRE) Trandolapril (TRACE), Zofenopril (SMILE) Fosinopril (FAMIS)	Valsartan (VALIANT)	Eplerenon (EPHESUS)
KV riski yüksek olan hastalarda ölüm	Ramipril (HOPE), Perindopril (EUROPA)	Telmisartan (ONTARGET)	
İnme	Ramipril (HOPE)	Losartan (LIFE)	
Tekrarlayan inme	Perindopril (+ İndapamid) (PROGRESS)	Eprosartan (MOSES)	
Tip 2 diyabetik hastalarda ölüm	Perindopril (+ İndapamid) (ADVANCE)		

Kardiyorenal Süreçte RAAS Blokajı Tedavisi

Hastalık ve Birincil Sonlanım	ACEİ	ARB	MRA
Diyabet dışı KBY'de renal sonlanım	Benazepril (AIPRI, Hou), Ramipril (REIN, AASK)		
Tip 1 diyabete bağlı nefropatide renal sonlanım	Kaptopril (Lewis)		
Tip 2 diyabete bağlı nefropatide renal sonlanım		Losartan (RENAAL), İrbesartan (IDNT)	
Tip 2 diyabete bağlı latent nefropatiden aşikâr nefropati	Ramipril (Micro-HOPE)	İrbesartan (IRMA 2), Valsartan (MARVAL)	
Tip 2 diyabette mikroalbüminüri gelişim	Trandolapril (BENEDICT)	Olmesartan (ROADMAP)	

Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of myocardial infarction, stroke and death: a meta-analysis

Gianpaolo Reboldi[a], Fabio Angeli[b], Claudio Cavallini[b], Giorgio Gentile[a], Giuseppe Mancia[c] and Paolo Verdecchia[b]

Objectives To compare the effects of angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors on the risk of myocardial infarction, stroke, cardiovascular mortality and total mortality.

Methods We conducted a meta-analysis of randomized comparative trials between angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors. Inclusion criteria were publication in peer-reviewed journals indexed in Medline, randomized comparison of angiotensin II receptor blockers vs. angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers + angiotensin-converting enzyme inhibitors vs. angiotensin-converting enzyme inhibitors, report of major complications including myocardial infarction, stroke, cardiovascular mortality or all-cause mortality; average follow-up of at least 1 year in at least 200 patients.

Results Six trials fulfilled the inclusion criteria, for a total of 49 924 patients. In the pooled estimate, there were no significant differences between angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors on the risk of myocardial infarction (odds ratio 1.01; 95% confidence interval 0.95–1.07; $P = 0.75$), cardiovascular mortality (odds ratio 1.03; 95% confidence interval 0.98–1.08; $P = 0.23$) and total mortality (odds ratio 1.03; 95% confidence interval 0.97–1.10; $P = 0.20$). This was the case also when the analysis involved only the comparison between angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. Overall, the risk of stroke was slightly lower with angiotensin II receptor blockers than angiotensin-converting enzyme inhibitors (odds ratio 0.92; 95% confidence interval 0.85–0.99; $P = 0.037$), the direct angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers comparison showing a nonsignificant trend in a similar direction. Statistical heterogeneity among trials was not significant, with a low to null inconsistency statistic, for stroke ($P = 0.67$), myocardial infarction ($P = 0.86$), cardiovascular mortality ($P = 0.14$) and total mortality ($P = 0.12$).

Conclusion This overview suggests that angiotensin II receptor blockers are as effective as angiotensin-converting enzyme inhibitors on the risk of myocardial infarction, cardiovascular mortality and total mortality. Angiotensin II receptor blockers may be slightly more protective than angiotensin-converting enzyme inhibitors on the risk of stroke. *J Hypertens* 26:1282–1289 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Journal of Hypertension 2008, 26:1282–1289

Keywords: hypertension, meta-analysis, mortality, myocardial infarction, prevention, prognosis, stroke, therapy

Abbreviations: ACEIs, Angiotensin converting enzyme inhibitors; ARBs, Angiotensin receptor blockers; AT1, Angiotensyn type I; AT2, Angiotensin type II; BP, Blood Pressure; CHF, Congestive heart failure; CI, Confidence interval; MI, Myocardial infarction; RCTs, Randomised clinical trials

[a]Department of Internal Medicine, University of Perugia, [b]Department of Cardiology, Hospital 'Santa Maria della Misericordia', Perugia and [c]Department of Medicine, University of Milano-Bicocca, Milan, Italy

Correspondence to Paolo Verdecchia, MD, FACC, FAHA, Clinical Research Unit 'Preventive Cardiology', Department of Cardiology, Hospital 'Santa Maria della Misericordia', 06156 Perugia, Italy
E-mail: verdec@tin.it

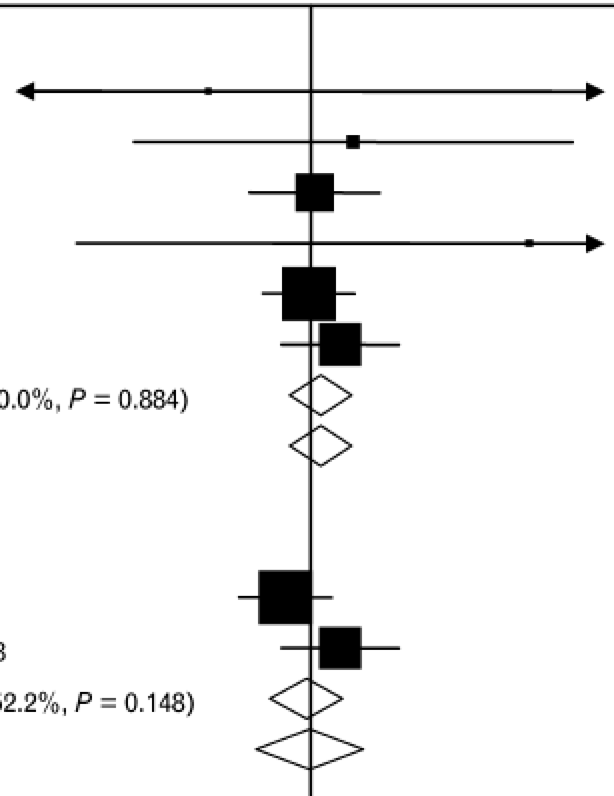
Received 16 April 2008 **Revised** 28 April 2008
Accepted 30 April 2008

Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of myocardial infarction, stroke and death: a meta-analysis

Gianpaolo Reboldi[a], Fabio Angeli[b], Claudio Cavallini[b], Giorgio Gentile[a], Giuseppe Mancia[c] and Paolo Verdecchia[b]

Miyokard İnfarktüsü Riski

Study	Publication year	OR (95% CI)	Events, ARBs	Events, ACEI
ARBs vs. ACEIs				
ELITE	1997	0.79 (0.17, 3.54)	3/352	4/370
ELITE-II	2000	1.11 (0.66, 1.85)	31/1578	28/1574
OPTIMAAL	2002	1.01 (0.87, 1.18)	384/2744	379/2733
DETAIL	2004	1.68 (0.58, 4.86)	9/120	6/130
VALIANT/Val	2003	1.00 (0.90, 1.11)	796/4909	798/4909
ONTARGET/Tel	2008	1.07 (0.94, 1.23)	440/8542	413/8576
Fixed effect model ($I^2 = 0.0\%$, $P = 0.884$)		1.03 (0.95, 1.10)	1663/18245	1628/18292
Random effect model		1.03 (0.95, 1.10)		
ARBs + ACEIs vs. ACEIs				
VALIANT/Val+Cap	2003	0.94 (0.85, 1.05)	756/4885	798/4909
ONTARGET/Tel+Ram	2008	1.07 (0.94, 1.23)	438/8502	413/8576
Fixed effect model ($I^2 = 52.2\%$, $P = 0.148$)		0.99 (0.91, 1.08)	1194/13387	1211/13485
Random effect model		1.00 (0.88, 1.13)		

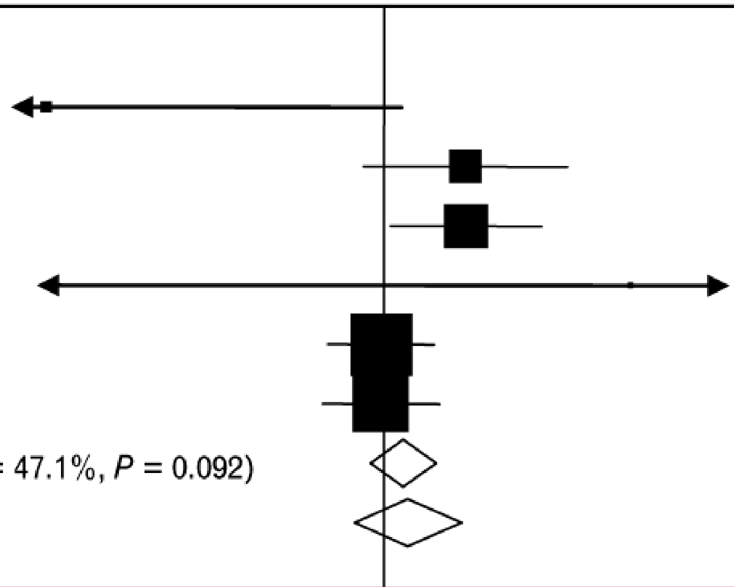


Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of myocardial infarction, stroke and death: a meta-analysis

Gianpaolo Reboldi[a], Fabio Angeli[b], Claudio Cavallini[b], Giorgio Gentile[a], Giuseppe Mancia[c] and Paolo Verdecchia[b]

Kardiyovasküler Ölüm Riski

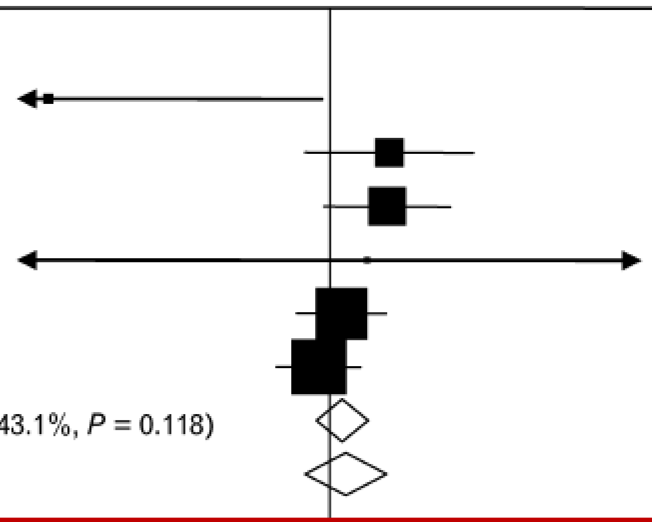
Study	Publication year	OR (95% CI)	Events, ARBs	Events, ACEI
ARBs vs. ACEIs				
ELITE	1997	0.51 (0.25, 1.03)	12/352	24/370
ELITE-II	2000	1.18 (0.96, 1.45)	230/1578	199/1574
OPTIMAAL	2002	1.18 (1.01, 1.37)	420/2744	363/2733
DETAIL	2004	1.64 (0.27, 9.99)	3/120	2/130
VALIANT/Val	2003	1.00 (0.90, 1.11)	827/4909	830/4909
ONTARGET/Tel	2008	1.00 (0.89, 1.12)	598/8542	603/8576
Fixed effect model (I^2 = 47.1%, P = 0.092)		1.04 (0.97, 1.11)	2090/18245	2021/18292
Random effect model		1.05 (0.94, 1.17)		



Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of myocardial infarction, stroke and death: a meta-analysis

Gianpaolo Reboldi[a], Fabio Angeli[b], Claudio Cavallini[b], Giorgio Gentile[a], Giuseppe Mancia[c] and Paolo Verdecchia[b]

Tüm Nedenlere Bağlı Ölüm Riski



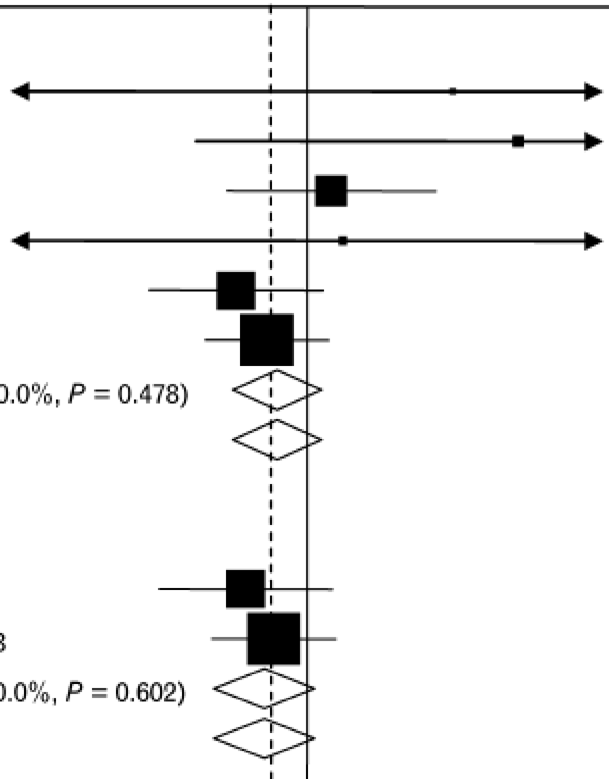
Study	Publication year	OR (95% CI)	Events, ARBs	Events, ACEI
ARBs vs. ACEIs				
ELITE	1997	0.54 (0.29, 0.98)	17/352	32/370
ELITE-II	2000	1.14 (0.95, 1.38)	280/1578	250/1574
OPTIMAAL	2002	1.14 (0.99, 1.31)	499/2744	447/2733
DETAIL	2004	1.09 (0.34, 3.47)	6/120	6/130
VALIANT/Val	2003	1.03 (0.93, 1.13)	979/4909	958/4909
ONTARGET/Tel	2008	0.98 (0.89, 1.07)	989/8542	1014/8576
Fixed effect model (I^2 = 43.1%, P = 0.118)		1.03 (0.97, 1.09)	2770/18245	2707/18292
Random effect model		1.04 (0.95, 1.14)		

Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of myocardial infarction, stroke and death: a meta-analysis

Gianpaolo Reboldi[a], Fabio Angeli[b], Claudio Cavallini[b], Giorgio Gentile[a], Giuseppe Mancia[c] and Paolo Verdecchia[b]

İnme Riski

Study	Publication year	OR (95% CI)	Events, ARBs	Events, ACEI
ARBs vs. ACEIs				
ELITE	1997	1.41 (0.31, 6.33)	4/352	3/370
ELITE-II	2000	1.64 (0.77, 3.48)	18/1578	11/1574
OPTIMAAL	2002	1.06 (0.83, 1.35)	140/2744	132/2733
DETAIL	2004	1.09 (0.34, 3.47)	6/120	6/130
VALIANT/Val	2003	0.85 (0.69, 1.04)	180/4909	211/4909
ONTARGET/Tel	2008	0.91 (0.79, 1.05)	369/8542	405/8576
Fixed effect model ($I^2 = 0.0\%$, $P = 0.478$)		0.93 (0.84, 1.03)	717/18245	768/18292
Random effect model		0.93 (0.84, 1.03)		
ARBs + ACEIs vs. ACEIs				
VALIANT/Val+Cap	2003	0.87 (0.71, 1.06)	183/4885	211/4909
ONTARGET/Tel+Ram	2008	0.93 (0.80, 1.07)	373/8502	405/8576
Fixed effect model ($I^2 = 0.0\%$, $P = 0.602$)		0.91 (0.81, 1.02)	556/13387	616/13485
Random effect model		0.91 (0.81, 1.02)		



Sonuç

- Kardiyorenal süreçte, RAAS'ı bloke eden ilaçlar arasında birinin diğer(ler)ine üstün olduğunu gösteren bir kanıt yoktur.
- Kardiyorenal süreçte ACE inhibitörlerinin yararları ile ilgili kanıtlar daha fazladır.