RAAS blockade in diabetic kidney disease

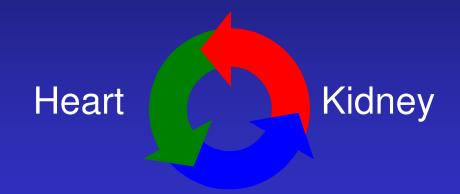
ACEi vs ARB

Johannes Mann

KIDIGO meeting, New Delhi march 2012

RAAS blockade in diabetic kidney disease

ACEi vs ARB



KIDIGO meeting, New Delhi march 2012

Agenda

- Peter Rossing covered RAS in general
- I will cover:
 - ACEi vs ARB vs combo's ...
 - on outcomes:
 - albuminuria, GFR, ESRD
 - CV events
 - mortality

Agenda

• How?

 Separate studies of ACEi and ARB on the same outcomes (many studies, metaanalyses)

head-to-head comparisons of ACEi vs
ARB (few studies)

Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease

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Effects of ARB on mortality

Analysis 2.1. Comparison 2 AIIRA versus placebo/no treatment, Outcome I All-cause mortality.

Review: Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease

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Comparison: 2 AlIRA versus placebo/no treatment

Outcome: I All-cause mortality

Study or subgroup	AIIRA	Placebo/no treatment	Risk Ratio M-	Risk Ratio M-
	n/N	n/N	H,Random,95%	H,Random,95%
IDNT 2001	87/579	93/569		0.92 [0.70, 1.20]
IRMA-2 2001	3/389	1/201		1.55 [0.16, 14.81]
Muirhead 1999	0/54	0/24		0.0 [0.0, 0.0]
RENAAL 2001	158/751	155/762	-	1.03 [0.85, 1.26]
Tan 2002	0/40	0/40		0.0 [0.0, 0.0]
Total (95% CI)	1813	1596	+	0.99 [0.85, 1.17]
Total events: 248 (AlIRA), 24	9 (Placebo/no treatment)			
Heterogeneity: $Tau^2 = 0.0$; C	$Chi^2 = 0.63, df = 2 (P = 0.7)$	3); l ² =0.0%		
Test for overall effect: $Z = 0.$	07 (P = 0.95)			
			0.05 0.2 1 5 20	
			Favours AIIRA Favours placebo	

Effects of ACEI on mortality

Analysis I.I. Comparison I ACEi versus placebo/no treatment, Outcome I All-cause mortality.

Review: Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease

Comparison: I ACEi versus placebo/no treatment

Outcome: I All-cause mortality

Study or subgroup	ACEi	Placebo/no treatment	Risk Ratio	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl	H,Random,95% Cl
I Half or less maximum tolerable (lose			
AIPRI 1996	2/6	1/15	+	5.00 [0.55, 45.39]
Bojestig 2001	0/37	0/18		0.0 [0.0, 0.0]
Capek 1994	0/9	0/6		0.0 [0.0, 0.0]
Chase 1993	0/6	0/9		0.0 [0.0, 0.0]
Cordonnier 1999	0/9	0/10		0.0 [0.0, 0.0]
DIABHYCAR 2004	334/2443	324/2469	•	1.04 [0.90, 1.20]
Garg 1998	0/7	0/4		0.0 [0.0, 0.0]
Nankervis 1998	0/17	3/14		0.12 [0.01, 2.13]
Ravid 1993	0/49	0/45		0.0 [0.0, 0.0]
Romero 1993	0/13	0/13		0.0 [0.0, 0.0]
Sano 1994	1/31	0/31		3.00 [0.13, 70.92]
			0.005 0.1 1 10 200	
			Favours ACEi Favours placebo	

Effects of ACEI on mortality

Study or subgroup	ACEi	Placebo/no treatment	Risk Ratio	Risk Ratio
study of subgroup	ACEI	ueauneni	M-	M-
	n/N	n/N	H,Random,95% Cl	H,Random,95% Cl
Subtotal (95% CI)	2627	2634	+	1.18 [0.41, 3.44]
Total events: 337 (ACEi), 328 (Pla	cebo/no treatment)			
Heterogeneity: Tau ² = 0.48; Chi ²		l ² =34%		
Test for overall effect: $Z = 0.31$ (P	= 0.76)			
2 Maximum tolerable dose				
Bakris 1994	0/8	0/7		0.0 [0.0, 0.0]
Bauer 1992	1/18	0/15		2.53 [0.11, 57.83]
CAPTOPRIL 1993	8/207	14/202	-	0.56 [0.24, 1.30]
Crepaldi 1998	0/32	0/34		0.0 [0.0, 0.0]
HOPE 2000	90/553	122/587	-	0.78 [0.61, 1.00]
JAPAN-IDDM 2002	0/104	0/27		0.0 [0.0, 0.0]
Laffel 1995	1/70	0/73		3.13 [0.13, 75.49]
Mathiesen 1999	0/19	0/21		0.0 [0.0, 0.0]
Parving 1989	1/15	1/17		1.13 [0.08, 16.59]
Phillips 1993	0/14	0/11		0.0 [0.0, 0.0]
Subtotal (95% CI)	1040	994	•	0.78 [0.61, 0.98]
Total events: 101 (ACEi), 137 (Pla	cebo/no treatment)			
Heterogeneity: Tau ² = 0.0; Chi ² =		=0.0%		
Test for overall effect: $Z = 2.12$ (P				
Total (95% CI)	3667	3628	•	0.91 [0.71, 1.17]
Total events: 438 (ACEi), 465 (Pla	-			
Heterogeneity: Tau ² = 0.03; Chi ²		; I² =28%		
Test for overall effect: $Z = 0.71$ (P	= 0.48)			
			0.005 0.1 1 10 200	
			Favours ACEi Favours placebo	

Effects of ARB on ESRD

Analysis 2.4. Comparison 2 AIIRA versus placebo/no treatment, Outcome 4 End-stage kidney disease.

Review: Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease

Comparison: 2 AlIRA versus placebo/no treatment

Outcome: 4 End-stage kidney disease

Study or subgroup	AIIRA	Placebo/no treatment	Risk Ratio	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl	H,Random,95% Cl
IDNT 2001	82/579	101/569		0.80 [0.61, 1.04]
Parving 2001a	0/389	0/201		0.0 [0.0, 0.0]
RENAAL 2001	147/751	194/762		0.77 [0.64, 0.93]
Total (95% CI)	1719	1532	-	0.78 [0.67, 0.91]
Total events: 229 (AIIRA), 29	5 (Placebo/no treatment)			
Heterogeneity: Tau ² = 0.0; Cl	$hi^2 = 0.05, df = 1 (P = 0.8)$	2); I ² =0.0%		
Test for overall effect: $Z = 3.1$	8 (P = 0.0015)			
			0.5 0.7 I I.5 2	
			Favours AlIRA Favours placebo	

Effects of ACEI on ESRD

Analysis I.4. Comparison I ACEi versus placebo/no treatment, Outcome 4 End-stage kidney disease.

Review: Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease

Comparison: I ACEi versus placebo/no treatment

Outcome: 4 End-stage kidney disease

Study or subgroup	ACEi	Placebo/no treatment	Risk Ratio M-	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl	H,Random,95%
Capek 1994	0/9	0/6		0.0 [0.0, 0.0]
CAPTOPRIL 1993	20/207	31/202	-	0.63 [0.37, 1.07]
DIABHYCAR 2004	4/2443	10/2469		0.40 [0.13, 1.29]
HOPE 2000	5/553	6/587	-	0.88 [0.27, 2.88]
JAPAN-IDDM 2002	0/104	0/27		0.0 [0.0, 0.0]
Marre 1987	0/10	0/10		0.0 [0.0, 0.0]
Mathiesen 1999	0/19	0/21		0.0 [0.0, 0.0]
Parving 1989	0/15	3/17	— · —	0.16 [0.01, 2.88]
Ravid 1993	0/49	0/45		0.0 [0.0, 0.0]
Romero 1993	0/13	0/13		0.0 [0.0, 0.0]
Total (95% CI)	3422	3397	•	0.60 [0.39, 0.93]
Total events: 29 (ACEi), 50 (Plac	cebo/no treatment)			
Heterogeneity: Tau ² = 0.0; Chi ²	= 1.71, df = 3 (P = 0.64); l ² =0.0%		
Test for overall effect: $Z = 2.28$	(P = 0.023)			
			0.005 0.1 1 10 200	
			Favours ACEi Favours placebo	

Effects of ARB on DSC

Analysis 2.3. Comparison 2 AIIRA versus placebo/no treatment, Outcome 3 Doubling of serum creatinine.

Review: Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease

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Comparison: 2 AlIRA versus placebo/no treatment

Outcome: 3 Doubling of serum creatinine

Study or subgroup	Alira	Placebo/no treatment	Risk Ratio M-	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl	H,Random,95% Cl
IDNT 2001	98/579	135/569		0.71 [0.57, 0.90]
Parving 2001 a	0/389	0/201		0.0 [0.0, 0.0]
RENAAL 2001	162/751	195/762		0.84 [0.70, 1.01]
Total (95% CI)	1719	1532	-	0.79 [0.67, 0.93]
Total events: 260 (AIIRA), 330) (Placebo/no treatment)			
Heterogeneity: $Tau^2 = 0.00$; C	$2hi^2 = 1.22, df = 1 (P = 0.2)$	27); l ² =18%		
Test for overall effect: $Z = 2.9$	I (P = 0.0036)			
			0.5 0.7 I I.5 2	
			Favours AlIRA Favours placebo	

Analysis I.3. Comparison I ACEi versus placebo/no treatment, Outcome 3 Doubling of serum creatinine.

Review: Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease

Comparison: I ACEi versus placebo/no treatment

Outcome: 3 Doubling of serum creatinine

Study or subgroup	ACEi	Placebo/no treatment	Risk Ratio	Risk Ratio
	n/N	n/N	M- H,Random,95% Cl	M- H,Random,95% Cl
AIPRI 1996	1/6	7/15		0.36 [0.06, 2.32]
Capek 1994	0/9	0/6		۵٥ [۵۵, ۵۵]
CAPTOPRIL 1993	25/207	43/202	+	0.57 [0.36, 0.89]
DIABHYCAR 2004	48/2443	60/2469	-	0.81 [0.56, 1.18]
HOPE 2000	21/553	18/587	-	1.24 [0.67, 2.30]
JAPAN-IDDM 2002	4/104	2/27		0.52 [0.10, 2.69]
Parving 1989	2/15	3/17		0.76 [0.15, 3.93]
Ravid 1993	2/49	12/45		0.15 [0.04, 0.65]
Romero 1993	0/13	0/13	1	0.0 [0.0, 0.0] ·
Total (95% CI)	3399	3381	•	0.68 [0.47, 1.00]
Total events: 103 (ACEi), 145 (P	lacebo/no treatment)			
Heterogeneity: $Tau^2 = 0.08$; Chi	² = 9.52, df = 6 (P = 0.15)	; I ² =37%		
Test for overall effect: $Z = 1.95$ ((P = 0.051)			
	-			
			0.02 0.1 1 10 50	
			Favours ACEi Favours placebo	

Effects of ARB vs ACEi on proteinuria

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

Background: Reduction of proteinuria is associated with delayed progression of chronic kidney disease. Reports suggest that angiotensin-receptor blockers (ARBs) reduce proteinuria, but results are variable. The relative effect of ARBs and angiotensin-converting enzyme (ACE) inhibitors, and their combined administration, remains uncertain.

Purpose: To establish the effect of ARBs versus placebo and alternative treatments, and the effect of combined treatment with ARBs and ACE inhibitors, on proteinuria.

Data Sources: English-language studies in MEDLINE and the Cochrane Library Central Register of Controlled Trials (January 1990 to September 2006), reference lists, and expert contacts.

Study Selection: Randomized trials of ARBs versus placebo, ACE Inhibitors, calcium-channel blockers, or the combination of ARBs and ACE inhibitors in patients with or without diabetes and with microalbuminuria or proteinuria for whom data were available on urinary protein excretion at baseline and at 1 to 12 months.

Data Extraction: Two Investigators Independently searched and abstracted studies.

Data Synthesis: Forty-nine studies involving 6181 participants reported results of 72 comparisons with 1 to 4 months of follow-up and 38 comparisons with 5 to 12 months of follow-up. The ARBs reduced proteinuria compared with placebo or calcium-channel blockers over 1 to 4 months (ratio of means, 0.57 [95% CI, 0.47 to 0.68] and 0.69 [CI, 0.62 to 0.77], respectively) and 5 to 12 months (ratio of means, 0.66 [CI, 0.63 to 0.69] and 0.62 [CI, 0.55 to 0.70], respectively). The ARBs and ACE inhibitors reduced proteinuria to a similar degree. The combination of ARBs and ACE inhibitors further reduced proteinuria more than either agent alone: The ratio of means for combination therapy versus ARBs was 0.76 (CI, 0.68 to 0.85) over 1 to 4 months and 0.75 (CI, 0.61 to 0.92) over 5 to 12 months; for combination therapy versus ACE inhibitors, the ratio of means was 0.78 (CI, 0.72 to 0.84) over 1 to 4 months and 0.82 (CI, 0.67 to 1.01) over 5 to 12 months. The antiproteinuric effect was consistent across subgroups.

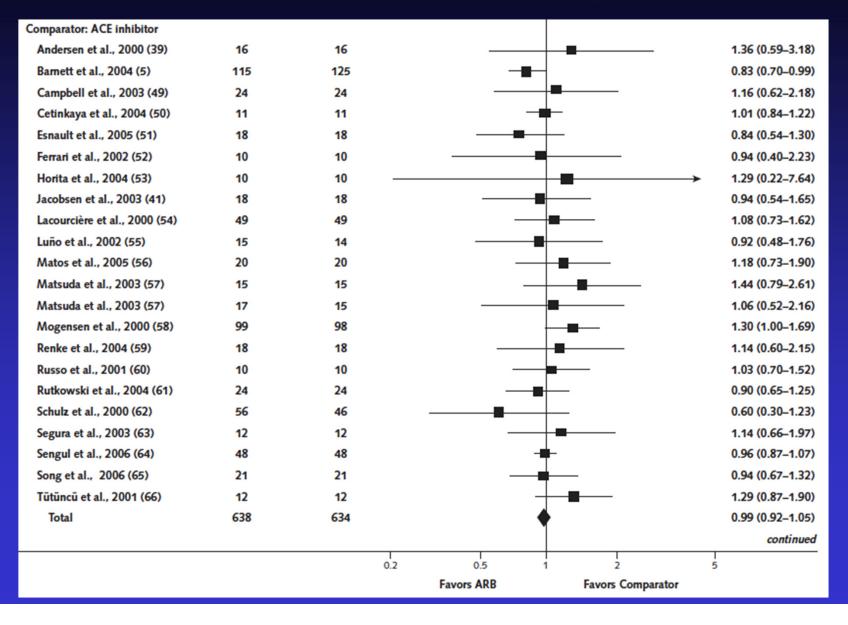
Limitations: Most studies were small, varied in quality, and did not provide reliable data on adverse drug reactions. Proteinuria reduction is only a surrogate for important progression of renal failure.

Conclusion: The ARBs reduce proteinuria, independent of the degree of proteinuria and of underlying disease. The magnitude of effect is similar regardless of whether the comparator is placebo or calcium-channel blocker. Reduction in proteinuria from ARBs and ACE inhibitors is similar, but their combination is more effective than either drug alone. Uncertainty concerning adverse effects and outcomes that are important to patients limits applicability of findings to clinical practice.

Ann Intern Med. 2008;148:30-48. For author affiliations, see end of text.

www.annais.org

Effects of ARB vs ACEi on proteinuria

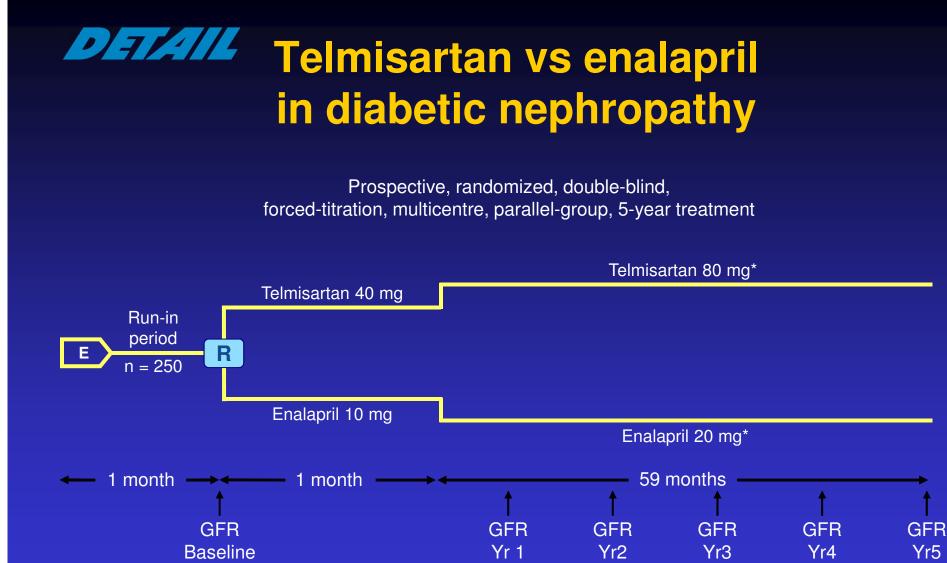


Agenda

• How?

Separate studies of ACEi and ARB on the same outcomes (many studies, metaanalyses)

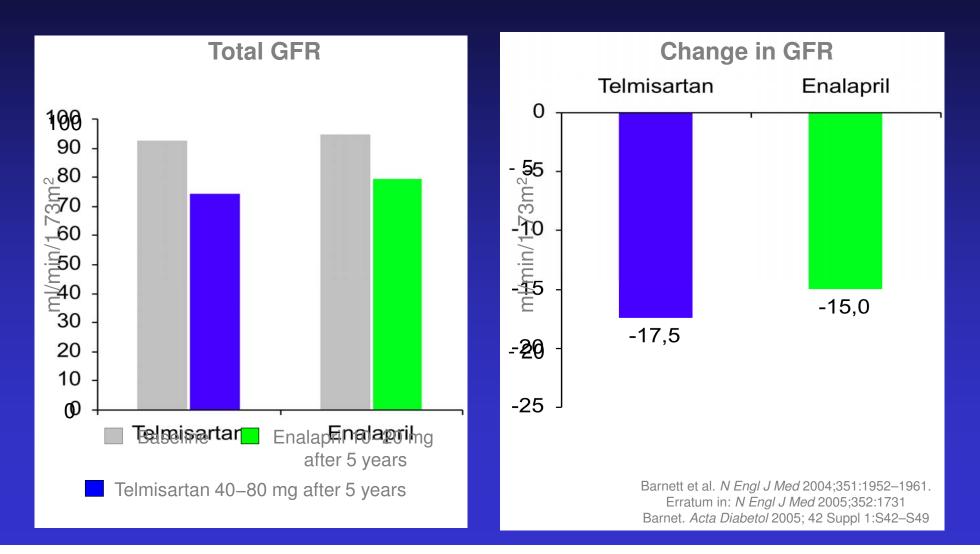
 head-to-head comparisons of ACEi vs ARB (few studies)



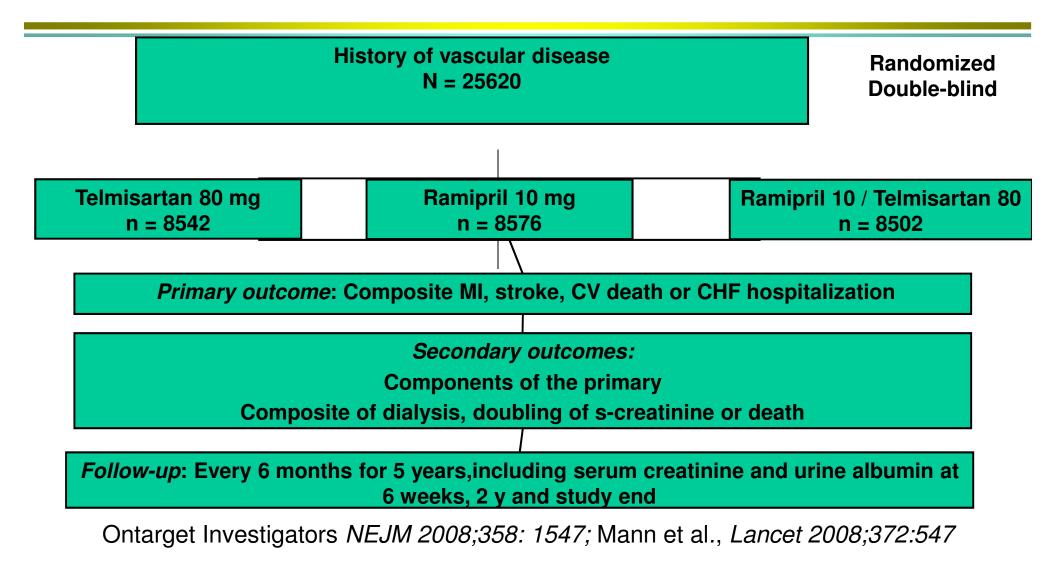
*Optional dose-reduction to telmisartan 40 mg or Enalapril 10 mg after 2 months

Barnett et al. N Engl J Med 2004;351:1952-1961

Primary endpoint: GFR after 5 years



ONTARGET: Design



ONTARGET: Results, prim. outcome

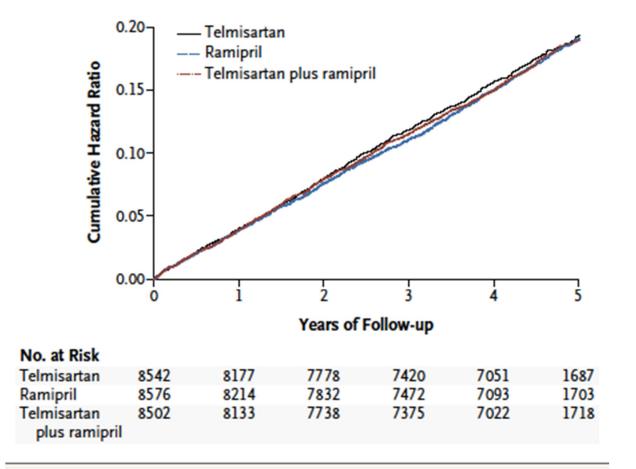


Figure 1. Kaplan–Meier Curves for the Primary Outcome in the Three Study Groups.

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

ONT: Results, prim. outcome, subgroups

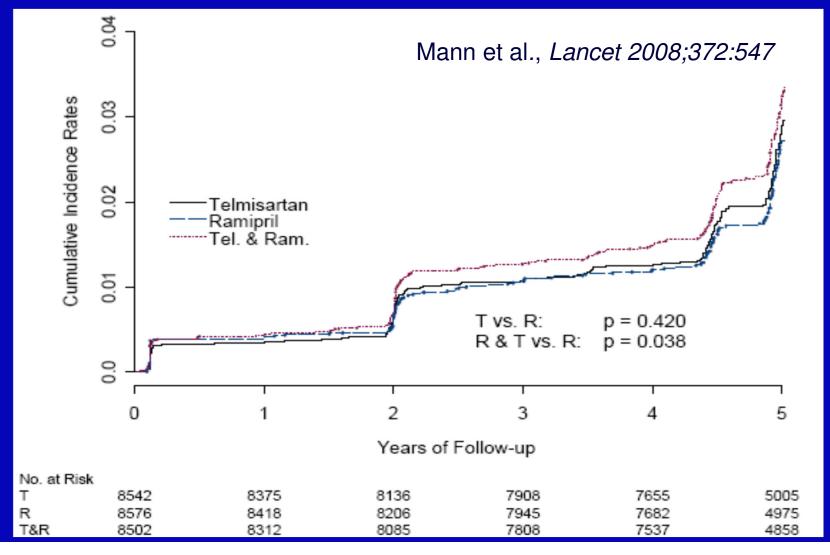
Subgroup	No. of Patients	Incidence of Primary Outcome in Ramipril Group (%)	Relative Risk (95% CI)	P Value for Interaction
Primary composite	17,118	16.5		
Cardiovascular disease			T	0.79
Yes	15,627	16.8		
No	1,486	13.1	· · · · ·	
Systolic blood pressure				0.10
≤134 mm Hg	5,704	16.2		
>134 to ≤150 mm Hg	6,042	14.9		
>150 mm Hg	5,352	18.4		
Diabetes				0.97
Yes	6,391	20.7		
No	10,722	14.0	_	
HOPE risk score				0.21
≤3.677	5,751	10.1		
>3.677 to ≤4.090	5,620	15.0		
>4.090	5,747	24.4		
Age				0.65
<65 yr	7,319	13.0		
≥65 to <75 yr	7,310	17.3		
≥75 yr	2,489	24.2		
Sex				0.68
Male	12,537	16.7		
Female	4,581	15.8		
		0.7	1.0	1.3
		1	Telmisartan Better Ramipril Be	tter

ONT: Results, prim. outcome, subgroups

Subgroup	No. of Patients	Incidence of Primary Outcome in Ramipril Group (%)	Relative Risk (95% CI)	P Value for Interaction
Primary composite	17,078	16.5		
Cardiovascular disease				0.82
Yes	15,589	16.8		
No	1,484	13.1	Ţ	
Systolic blood pressure				0.64
≤134 mm Hg	5,714	16.2		
>134 to ≤150 mm Hg	6,019	14.9	· •	
>150 mm Hg	5,329	18.4		
Diabetes				0.15
Yes	6,365	20.7	_ ·	
No	10,708	14.0		
HOPE risk score				0.97
≤3.677	5,676	10.1		
>3.677 to ≤4.090	5,570	15.0		
>4.090	5,832	24.4		
Age				0.75
<65 yr	7,362	13.0		
≥65 to <75 yr	7,177	17.3		
≥75 yr	2,539	24.2		
Sex				0.82
Male	12,497	16.7		
Female	4,581	15.8	1.0	1.3
		0.7	Ramipril plus Ramipril Be	→ […]

Telmisartan Better

Renal-ONTARGET: Dialysis or doubling of screatinine (n= 613 outcomes in 25,620 participants)



ORIENT trial: ACEi + ARB in diabet. NP

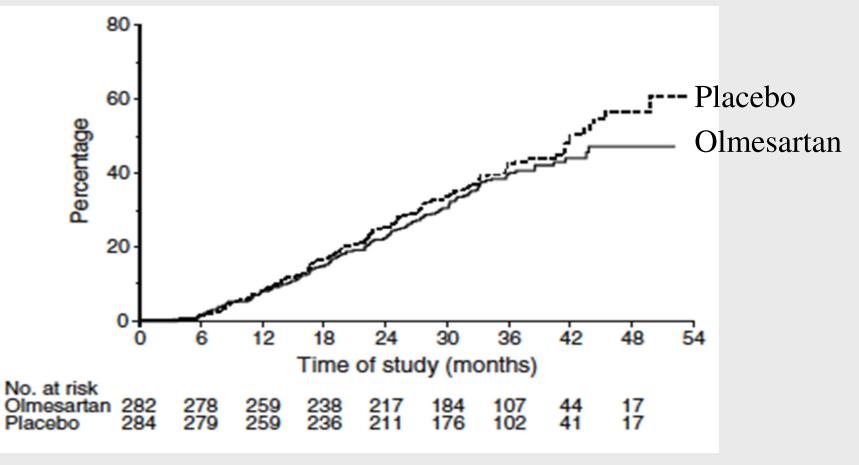
comparison:- Olmesartan- Placebo

- 600 Pat with type 2 DM, hypertension, macroalbuminuria and serum-creatinine 1.2 2.5 mg/dl
- 75% treated with ACEi
- mean follow-up 3.2 years
- Prim. outcomes: Dialysis, doubling of serum creatinine or
- death in 41% vs 45%, p=0.78
- CV outcomes: 18 vs 21 Pat.

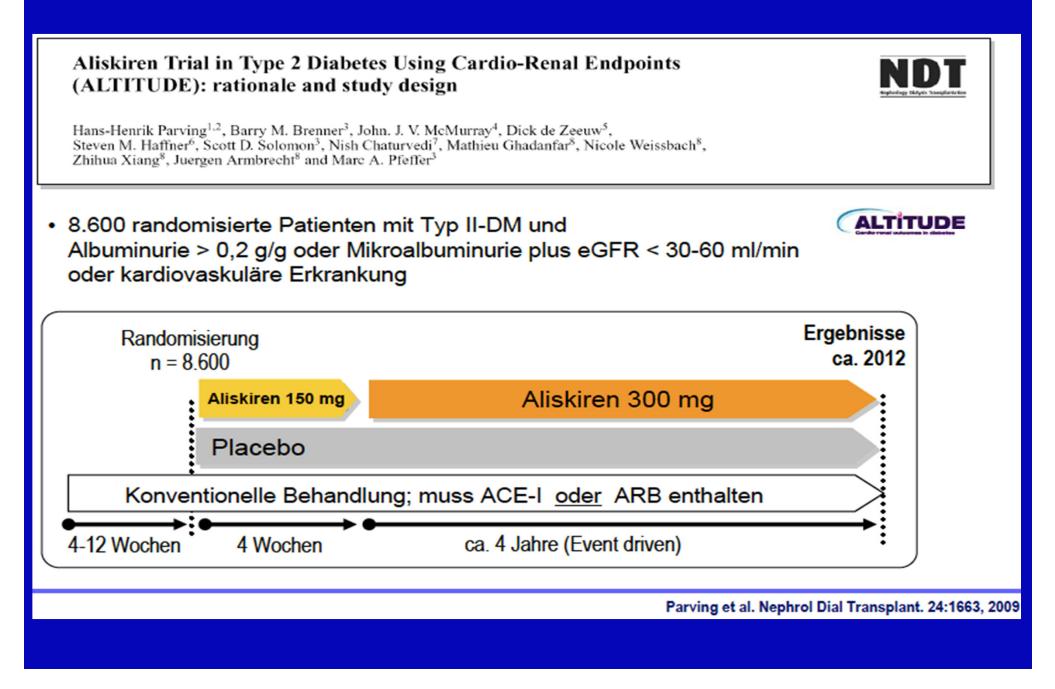
Imai et al Diabetologia (2011) 54:2978–2986

ORIENT trial: ACEi + ARB in diabet. NP

Dialysis, creatinine x2 or death



Imai et al Diabetologia (2011) 54:2978–2986



ALTITUDE TRIAL, preliminary results

Variable	Aliskiren (N=4283)	Placebo (N=4296)	Total (N=8579)	HR	95% CI	P-value
Primary composite outcome	581 (13.6%)	542 (12.6%)	1123 (13.1%)	1.09	(0.97, 1.22)	0.1663
Secondary composite outcome - CV	444 (10.4%)	396 (9.2%)	840 (9.8%)	1.14	(0.99, 1.30)	0.0664
Secondary composite outcome - renal	166 (3.9%)	180 (4.2%)	346 (4.0%)	0.93	(0.76, 1.15)	0.5178
Component event:						
CV death	179 (4.2%)	162 (3.8%)	341 (4.0%)	1.12	(0.90, 1.38)	0.3110
Resuscitated sudden death	13 (0.3%)	8 (0.2%)	21 (0.2%)	1.64	(0.68, 3.95)	0.2737
Non-fatal MI	90 (2.1%)	88 (2.0%)	178 (2.1%)	1.03	(0.77, 1.39)	0.8302
Non-fatal stroke	112 (2.6%)	85 (2.0%)	197 (2.3%)	1.34	(1.01, 1.77)	0.0439
Unplanned hospitalization for heart failure	150 (3.5%)	155 (3.6%)	305 (3.6%)	0.98	(0.78, 1.23)	0.8716
Onset of ESRD/renal death	72 (1.7%)	60 (1.4%)	132 (1.5%)	1.22	(0.87, 1.72)	0.2518
Doubling of baseline serum creatinine	141 (3.3%)	159 (3.7%)	300 (3.5%)	0.90	(0.71, 1.12)	0.3431
Death from any cause	297 (6.9%)	277 (6.4%)	574 (6.7%)	1.08	(0.92, 1.27)	0.3661

In people with diabetic nephropathy

- <u>Mortality</u>: Evidence for reduction by ACEI, no such evidence for ARB
- <u>Major renal & CV outcomes</u>: Evidence for **no** difference of ACEi and ARB
- <u>Proteinuria</u>: Evidence for **no** difference of ACEi and ARB

 <u>Cough</u>: Evidence for ARB causing less cough than ACEi, evidence for no other major differences in harm

In people with diabetic nephropathy

Combo of ACEi & ARB or ACEi/ARB & DRI :

Evidence for no benefit

Evidence for harm

END

Effects of ACEI on renal outcomes, doubling of serum creatinine & dialysis

Strippoli et al BMJ 2004;329:828-39

Meta-analysis of ACEI & ARB trials in people with *diabetic nephropathy* on renal outcomes and on mortality

	No of patients with event/total No of patients					D.L.C.
	Angiotensin converting enzyme inhibitor	Placebo or no treatment	Relative risk (random) 95% Cl		Weight (%)	Relative risk (random) 95% Cl
Doubling of serum crea	tinine concentration					
Capek 1994 ^{w10}	0/9	0/6				Not estimable
Romero 1993 ⁰⁴⁷	0/13	0/13				Not estimable
Maschio 1996 ^{w29}	1/6	7/15	* *		7.45	0.36 (0.06 to 2.32)
Parving 1989 ^{w37 w38}	2/15	3/17			9.13	0.76 (0.15 to 3.93)
Katayarna 2002 ^{w22}	4/104	2/27			9.18	0.52 (0.10 to 2.69)
Ravid 1993 ⁰⁴³	2/49	12/45			11.24	0.15 (0.04 to 0.65)
Micro-HOPE 2000 ^{w63}	21/553	18/587		-	28.71	1.24 (0.67 to 2.30)
Lewis 1993 ^{w25}	25/207	43/202			34.30	0.57 (0.36 to 0.89)
Total (95% CI)	956	912		•	100.00	0.60 (0.34 to 1.05)
Test for heterogeneity: ;	£=8.90, df=5, P=0.11, /2=4	3.8%				
Test for overall effect: z:	=1.77, P=0.08					
End stage renal diseas	9					
Capek 1994 ^{w10}	0/9	0/6				Not estimable
Katayarna 2002 ^{w22}	0/104	0/27				Not estimable
Marre 1987 ^{er26}	0/10	0/10				Not estimable
Mathiesen 1999 ^{w30}	0/19	0/21				Not estimable
Ravid 1993 ⁶⁴³	0/49	0/45				Not estimable
Romero 1993 ^{a47}	0/13	0/13				Not estimable
Parving 1989 ^{w37 w38}	0/15	3/17	-		2.71	0.16 (0.01 to 2.88)
Micro-HOPE 2000 ^{#33}	5/553	6/587			16.19	0.88 (0.27 to 2.88)
Lewis 1993 ^{w25}	20/207	31/202		-	81.10	0.63 (0.37 to 1.07)
Total (95% CI)	979	928	-		100.00	0.64 (0.40 to 1.03)
Test for heterogeneity: 🤉	@=1.18, df=2, P=0.55, /²=0					
Test for overall effect: z:	=1.83, P=0.07	0	.1 0.2 0.5		10	
		F	avours agent	Favours place		
				or no treatme	III.	

Effect of angiotensin converting enzyme inhibitors compared with placebo or no treatment on renal function (doubling of serum creatinine concentration and age renai disease)

Effects of ARB on renal outcomes, doubling of serum creatinine & dialysis

Strippoli et al BMJ 2004;329:828-39

Meta-analysis of ACEI & ARB trials in people with *diabetic nephropathy* on renal outcomes and on mortality

	No of patients with event/total No of patients							
	Angiotensin II receptor antagonist	Placebo or no treatment	-		elative dom) 99		Weight (%)	Relative risk (random) 95% Cl
Doubling of serum creati	nine concentration							
Parving 2001 #38 #59 #58	D'389	0/201						Not estimable
Lewis 2001 ^{w57}	98/579	135/569		-	F.		40.19	0.71 (0.57 to 0.90)
Brenner 2001 ^{#56}	162/751	195/762		-			59.81	0.84 (0.70 to 1.01)
Total (95% CI)	1719	1532			•		100.00	0.79 (0.67 to 0.93)
Test for heterogeneity: χ^2	=1.22, df=1, P=0.27, / ² =1	18.2%						
Test for overall effect: z=2	.91, P=0.004							
End stage renal disease								
Parving 2001 038 039 058	D'389	0/201						Not estimable
Lewis 2001 ^{#67}	82/579	101/569		-			33.35	0.80 (0.61 to 1.04)
Brenner 2001 ^{w56}	147/751	194/762		-			66.65	0.77 (0.64 to 0.93)
Total (95% CI)	1719	1532					100.00	0.78 (0.67 to 0.91)
Test for heterogeneity: χ	=0.05, df=1, P=0.82, / ² =1	0%						
Test for overall effect: z=3	.18, P=0.001	().2	0.5	1	2	5	
		I	Favours	agerit		Favours placeb or no treatme		

Fig 6 Effect of anglotensin II receptor antagonists compared with placebo or no treatment on renal function (doubling of serum creatinine concentration and end stage renal disease)

Effects of ACEI & ARB on mortality

Strippoli et al BMJ 2004;329:828-39

Meta-analysis of ACEI & ARB trials in people with *diabetic nephropathy* on renal outcomes and on mortality

	No of patients (with event/total No of patien	ts					
All cause mortality	Agent	Placebo or no treatmen	t		elative risk	N.	Weight	Relative risk
Angiotensin converting enzyr	ne inhibitors			(ran	dom) 95% (a	(%)	(random) 95% C
Bakris 1994 ^{w?}	D'8	0/7						Not estimable
Bojestig 2001 ^{∞9}	0/37	0/18						Not estimable
Capek 1994 ^{wt0}	D'9	0/6						Not estimable
Chase 1993 ^{ut2}	0/6	D/9						Not estimable
Cordonnier 1999 ^{urts}	D/9	0/10						Not estimable
Crepaldi 1998 ^{w 14}	0/32	0/34						Not estimable
Garg 1998 ^{w18}	0/7	0/4						Not estimable
Katayama 2002 ^{w22}	0/104	0/27						Not estimable
Mathiesen 1999 ^{∞SD}	0/19	0/21						Not estimable
Phillips 1993 ⁰⁴⁰	0/14	0/11						Not estimable
Ravid 1993 ^{#43}	0/49	0/45						Not estimable
Romero 1993⊪47	0/13	0/13						Not estimable
Laffel 1995 ^{w23}	1/70	0/73	-				0.53	3.13 (0.13 to 75.4
Sano 1994 and 1996 ^{048 049}	1/31	0/31	-				0.54	3.00 (0.13 to 70.9
Bauer 1992 ^{w8}	1/18	0/15	-				0.55	2.53 (0.11 to 57.8
Nankervis 1998 ^{u35}	0/17	3/14	-			_	0.65	0.12 (0.01 to 2.1)
Parving 1989 ^{w37 w38}	1/15	1/17	-				0.75	1.13 (0.08 to 16.5
Maschio 1996 ^{w29}	2/6	1/15					1.10	5.00 (0.55 to 45.3
Lewis 1993 ^{w25}	8/207	14/202		-			7.48	0.56 (0.24 to 1.3)
Micro-HOPE 2000 ^{w33}	90/553	122/587		-			88.41	0.78 (0.61 to 1.0)
Total (95% CI)	1224	1159					100.00	0.79 (0.63 to 0.9
Test for heterogeneity: x ² =7.0	0, df=7, P=0.43, / 2	=0%			-			
Test for overall effect: z=2.01,	P=0.04							
Angiotensin II receptor antag	onists							
Muirhead 1999 ^{w65}	0/54	0/24						Not estimable
Tan 2002 ^{w59}	0/40	0/40						Not estimable
Parving 2001 ^{w38 w39 w58}	3/389	1/201	-		-		0.49	1.55 (0.16 to 14.8
Lewis 2001 ^{w57}	87/579	93/569		-	-		34.90	0.92 (0.70 to 1.2)
Brenner 2001 ^{w56}	158/751	155/762			-		64.60	1.03 (0.85 to 1.26
Total (95% CI)	1813	1596			-		100.00	0.99 (0.85 to 1.17
Test for heterogeneity: x2=0.6	3, df=2, P=0.73, /2				T			,
Test for overall effect: z=0.07,			0.2	0.5	1	2	5	
			Favours		·	avours placeb or no treatmen)	

Fig 2 Effect of anglotensin converting enzyme inhibitors or anglotensin II receptor antagonists compared with placebo or no treatment on overall mortality

Strippoli et al BMJ 2004;329:828-39

Meta-analysis of ACEI & ARB trials in people with diabetic nephropathy on

- all cause mortality

- renal outcomes

Renal outcomes* & ACEI

	No of patients with event/total No of patients			Belative risk					B.1.2	
	Angiotensin converting enzyme inhibitor	Placebo or no treatmen	t	(random) 95% Cl		Weight (%)	Relative risk (random) 95% Cl			
Microalbuminuria to ma	ocroalbuminuria									
Bojestig 2001 ^{w2}	0/37	0/18								Not estimable
Romero 1993 ⁸⁴⁷	0/13	0/13								Not estimable
Marre 1987 ^{w26}	2/10	1/10				-	-		3.50	2.00 (0.21 to 18.69)
Muirhead 1999 ⁰⁵⁵	1/29	3/27	+	-		-			3.58	0.31 (0.03 to 2.81)
Chase 1993 ^{w12}	2/7	1/9		-		-	-		✤ 3.62	2.57 (0.29 to 22.93)
Jerums 2001 ^{ar21}	1/13	3/10	+	-		-			3.84	0.26 (0.03 to 2.11)
Hansen 1994 ^{utg}	2/10	3/12				-		-	5.88	0.80 (0.16 to 3.88)
Crepaldi 1998 ^{w 14}	2/32	7/34	-	-		+			6.33	0.30 (0.07 to 1.35)
Mathiesen 1999 ^{nSD}	2/21	9/23	-	-		-			6.80	0.24 (0.06 to 1.00)
Ravid 1993 ¹⁰⁴³	2/49	22/45	+						6.95	0.08 (0.02 to 0.34)
EUCLID 1997 ^{w16}	3/41	6/34	_			_	-		7.47	0.41 (0.11 to 1.54)
Katayama 2002 ^{w22}	6/52	3/12	-		-	-	-		7.99	0.46 (0.13 to 1.59)
Ahmad 2003 ^{t04u5}	3/37	11/36	+	-		-			8.32	0.27 (0.08 to 0.87)
ATLANTIS 2000 ¹⁰⁶	6/88	5/46			-	-	_		8.79	0.63 (0.20 to 1.95)
Ahmad 1997 ^{u 3}	4/52	12/51	_	_	-	-			9.36	0.33 (0.11 to 0.95)
Micro-HOPE 2000 ^{#33}	104/552	127/587			-	-			17.57	0.87 (0.69 to 1.10)
Total (95% CI)	1043	967		-	-				100.00	0.45 (0.28 to 0.71)
Test for heterogeneity: χ	2=25.78, df=13, P=0.02, /2	=49.6%								
Test for overall effect: z=			0.1	0.2	0.5	1	2	5	10	
						I				
			ravou	irs agen	L			ours plac		

Effect of anglotensin converting enzyme inhibitors compared with placebo or no treatment on risk of progress

* Progression from micro - to macroalbuminuria

Strippoli et al BMJ 2004;329:828-39

Meta-analysis of ACEI & ARB trials in people with *diabetic nephropathy* on

- all cause mortality

- renal outcomes

Renal outcomes* & ARB microalbunhurla to macroalbunhurla

	No of palients with event/total No of patients			B10 11						w · 1.	N17 11
	Angiotensin II receptor antagonist	Placebo or no treatment	-	Relative risk (random) 95% Cl			Weight (%)	Relative risk (random) 95% Cl			
Microalbuminuria to mac											
Muirhead 1999 ^{er55}	1/62	3/29	H				-			3.84	0.16 (0.02 to 1.44)
Tan 2002 ⁰⁵⁹	4/40	7/40		-			-			14.38	0.57 (0.18 to 1.80)
Parving 2001 ^{e38 e69 e68}	29/389	30/201				-				81.78	0.50 (0.31 to 0.81)
Total (95% CI)	491	270			•	•				100.00	0.49 (0.32 to 0.75)
Test for heterogeneity: x²=1.10, df=2, P=0.58, /²=0%											
Testfor overall effect: z=3	3.24. P=0.001										
		ĺ).1	02	0.5	1	2	6	10		
		Favou	irs ager	t			ours pla no trear				

Fig 7 Effect of anglotensin II receptor antagonists compared with placebo or no treatment on albuminuria, showing agent reduces risk of progression from microalbuminuria to macroalbuminuria

* Progression from micro - to macroalbuminuria

Nephrol Dial Transplant (2011) 0: 1–20 doi: 10.1093/ndt/gfq792



Original Article

Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and combined therapy in patients with micro- and macroalbuminuria and other cardiovascular risk factors: a systematic review of randomized controlled trials

Ausilia Maione¹, Sankar D Navaneethan^{2,3}, Giusi Graziano¹, Ruth Mitchell³, David Johnson⁴, Johannes F.E. Mann^{5,6}, Peggy Gao⁵, Jonathan C Craig^{3,7,8}, Giovanni Tognoni⁹, Vlado Perkovic¹⁰, Antonio Nicolucci¹, Salvatore De Cosmo¹¹, Antonio Sasso¹², Olga Lamacchia¹³, Mauro Cignarelli¹³, Valeria Maria Manfreda¹⁴, Giorgio Gentile^{15,16} and Giovanni FM Strippoli^{1,3,7,16,17}

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Study	Treatment	Control	RR (random)	Weight	RR (random)
or sub-category	n/N	n/N	95% CI	%	95% CI
Hou 2006	1/112	0/112	-	0.58	0.00.10.10.00.000
Laffel 1995	1/112	0/112		0.58	3.00 [0.12, 72.86]
Ruggenenti-REIN strl	1/99	0/87		0.58	3.13 [0.13, 75.49] 2.64 [0.11, 63.98]
Viberti 1994	0/46	1/46		0.58	0.33 (0.01, 7.98)
Bauer 1992	1/18	0/15		- 0.60	2.53 [0.11, 57.83]
Nankervis1998	0/20	3/20		0.70	0.14 (0.01, 2.60)
ATLANTIS SG 2000	5/88	0/46			5.81 [0.33, 102.80]
Ihle 1996	1/36	1/34		0.78	0.94 [0.06, 14.51]
Parving 2001a	1/15	1/17	1	0.81	1.13 (0.08, 16.59)
GISEN-REIN stratum2	2/78	1/88		1.03	2.26 [0.21, 24.41]
AIPRI 1996	8/300	1/283		- 1.35	7.55 [0.95, 59.96]
CAPTOPRIL 1993	8/207	14/202		7.15	0.56 [0.24, 1.30]
HOPE 2000	150/952	205/1004		39.84	0.77 [0.64, 0.93]
DIABHYCAR 2004	334/2443	324/2469	-1	44.73	1.04 [0.90, 1.20]
DIADITICAL 2004	001/2110	524/2405	T	11.70	1.04 (0.50, 1.20)
Total (95% CI)	4484	4496	4	100.00	0.93 [0.73, 1.18]
Total events 513 (ACE-Is), 551 (Ĭ		
Test for heterogeneity: Chi ² =17.4		25.5%	I		
Test for overall effect: Z = 0.60 (P				AC	E-Is vs placebo
IRMA-2 2001	3/389	1/201		0.38	1.55 (0.16, 14.81)
TRANSCEND	74/319	69/318	+	23.16	1.07 [0.80, 1.43]
IDNT 2001	87/579	93/569	+	26.82	0.92 [0.70, 1.20]
RENAAL 2001	158/751	155/762	1	49.64	1.03 [0.85, 1.26]
			T		
Total (95% CI)	2038	1850	+	100.00	1.01 [0.88, 1.16]
Total events 322 (ARB), 318 (Pla	(cebo)		T T		
Test for heterogeneity: Chi2=0.81		6			
Test for overall effect: Z = 0.16 (P				AR	Bs vs placebo
VALERIA 2008	1/47	0/42		0.19	2.69 [0.11, 64.24]
DETAIL 2004	6/130	6/120		1.60	0.92 [0.31, 2.78]
ONTARGET	307/1316	294/1364	<u>i</u>	98.21	1.08 [0.94, 1.25]
			Т		
Total (95% CI)	1493	1526	•	100.00	1.08 [0.94, 1.24]
Total events: 314 (ACEi), 300 (AF	RB)		ſ		
Test for heterogeneity: Chi2=0.40		%			
Test for overall effect: Z = 1.10 (P	= 0.27)			AC	E-Is <i>vs</i> ARBs
01 Combination vsACE-Is					
ONTARGET	285/1336	307/1316		50.80	0.91 [0.79, 1.05]
Subtotal (95% CI)	1336	1316	•	50.80	0.91 [0.79, 1.05]
Total events: 285 (Treatment), 30					
Test for heterogeneity: not applic					
Test for overall effect: Z = 1.23 (P	= 0.22)				
02 Combination vsARBs	1000 00000	1000000000	1		
ONTARGET	285/1336	294/1364	7	49.20	0.99 [0.86, 1.14]
Subtotal (95% CI)	1336	1364	•	49.20	0.99 [0.86, 1.14]
Total events: 285(Treatment), 29					
Test for heterogeneity: not applic					
Test for overall effect: Z = 0.14 (P	= 0.89)		I		
Tatal (050) CIN	0.000		1	100.00	
Total (95% CI)	2672	2680	1	100.00	0.95 [0.86, 1.05]
Total events 570 (Treatment), 60		v.	I		
Test for heterogeneity: Chi ² =0.59		Ao.		ACE-IS + ARB	s vs ACE-Is or ARBs
Test for overall effect: Z = 0.98 (P	= 0.33)			ACC IS T AND	
			0.01 0.1 1 10	100	
			Favors treatment Favors contr		
			Tavela requirent ravels contr	wi	
Fig. 2. Effect of ACEI, A	RB or combined the	rapy on all-cause	mortality.		
- B. B. LINCE OF HOLL, H	tas of comonica the	mapy on an eause			

outcomes and renal outcomes; Significant results have been reported in bold								
Outcomes	No. of trials	No. of patients	RR (95% CI)					
ACEI versus placebo/no treatment								
Cardiovascular								
Fatal events ^a	6	7873	0.94 (0.65-1.37)					
Nonfatal events ^b	9	8231	0.88 (0.82-0.94)					
Renal								
Doubling of creatinine	9	8460	0.62 (0.46-0.84)					
Microalbuminuria → macroalbuminuria	18	2888	0.49 (0.36-0.65)					
Microalbuminuria → normoalbuminuria	15	1860	2.99 (1.82-4.91)					
ARB versus placebo/no treatment								
Cardiovascular			Max Room and American Maximum					
Fatal events ^a	2	1785	1.10 (0.81-1.50)					
Nonfatal events ^b	4	3888	0.77 (0.61-0.98)					
Renal	~							
Doubling of creatinine	3	3298	0.78 (0.68-0.90)					
Microalbuminuria → macroalbuminuria	5	1907	0.45 (0.37-0.54)					
Microalbuminuria → normoalbuminuria	4	1211	2.83 (1.14-7.07)					
ACEI versus ARB								
Cardiovascular	2	2020	0.00 (0 (1 1 0 0)					
Fatal events ^a	2	2930	0.80 (0.61-1.04)					
Nonfatal events ^b	3	3290	1.00 (0.93-1.07)					
Renal	2	2260	1.02 (0.77, 1.29)					
Doubling of creatinine	3	3269	1.03 (0.77–1.38)					
Microalbuminuria → macroalbuminuria Microalbuminuria → normoalbuminuria	3	2856	1.20 (0.99–1.46)					
ACEI + ARB versus ACEI	3	131	1.00 (0.62–1.61)					
Cardiovascular								
Fatal events ^a	1	2652	0.05 (0.71 1.27)					
Nonfatal events ^b	1	2652	0.95 (0.71–1.27) 1.03 (0.96–1.10)					
Renal	1	2032	1.05 (0.90-1.10)					
Doubling of creatinine	2	2742	0.40 (0.02-6.61)					
Microalbuminuria → macroalbuminuria	2	2739	0.73 (0.59–0.89)					
Microalbuminuria → normoalbuminuria	4	156	1.25 (0.61-2.59)					
ACEI + ARB versus ARB	-	150	1.25 (0.01-2.55)					
Cardiovascular								
Fatal events ^a	1	2700	0.77 (0.58-1.01)					
Nonfatal events ^b	î	2700	1.03 (0.96–1.11)					
Renal		2700						
Doubling of creatinine	1	2700	1.09 (0.77-1.54)					
Microalbuminuria → macroalbuminuria	2	2782	0.87 (0.71–1.08)					
Microalbuminuria → normoalbuminuria	4	151	1.09 (0.78–1.53)					

Table 2. Effects of ACEI, ARB and combined therapy with ACEI + ARB on cardiovascular outcomes and renal outcomes; Significant results have been reported in bold

Study or sub-category	Treatment n/N	Control n <i>i</i> N	RR (random) 95% Cl	Weight %	RR (random) 95% Cl	
Bauer 1992	1/18	0/15		0.51	2.53 [0.11, 57.83]	
Parving 2001a	0/15	3/17	• • • · · · · · · · · · · · · · · · · ·	0.60	0.16 [0.01, 2.88]	
HOPE 2000	5/952	8/1004		4.05	0.66 [0.22, 2.01]	
Ihle 1996	7/36	9/34		6.64	0.73 [0.31, 1.75]	
DIABHYCAR 2004	11/2443	12/2469		7.54	0.93 [0.41, 2.10]	
Ruggenenti-REIN str1	9/99	18/87		9.01	0.44 [0.21, 0.93]	
CAPTOPRIL 1993	20/207	31/202		18.03	0.63 [0.37, 1.07]	
GISEN-REIN stratum2	17/78	29/88		18.91	0.66 [0.40, 1.11]	
Hou 2006	31/112	43/112	-=-	34.71	0.72 [0.49, 1.05]	
Total (95% CI)	3960	4028	•	100.00	0.67 [0.54, 0.84]	
Total events 101 (ACEi), 153 (Pla	acebo)		•			
Test for heterogeneity: Chi ² = 3.71 Test for overall effect: Z = 3.49 (P		6		AC	E-Is vs placebo	
TRANSCEND	2/319	4/318		0.83	0.50 [0.09, 2.70]	
IDNT 2001	82/579	101/569	-	33.08	0.80 [0.61, 1.04]	
RENAAL 2001	147/751	194/762	-	66.10	0.77 [0.64, 0.93]	
Total (95% CI)	1649	1649	•	100.00	0.78 [0.66, 0.90]	
Total events: 231 (ARB), 299 (Pla	icebo)					
Test for heterogeneity: Chi2=0.31	1, df = 2 (Bc=0.85), 12 = 09	6				
Test for overall effect: Z = 3.24 (P	= 0.001)			AR	Bs vs placebo	
ROAD 2007	00.020	04/100		44.00		-
	20/167	26/172		44.87	0.79 [0.46, 1.36]	
ONTARGET	29/1316	34/1364	-	55.13	0.88 [0.54, 1.44]	
Total (95% CI)	1483	1536	+	100.00	0.84 [0.59, 1.21]	
Total events 49 (ACEi), 60 (ARB))					
Test for heterogeneity: Chi2=0.09	9, df=1 (P=0.77), I ² =09	6				
Test for overall effect: Z = 0.93 (P	= 0.35)			AC	E-Is <i>vs</i> ARBs	
01 Combination vsACE-Is						-
Kanno 2006	2/45	2/45	·	2.70	1.00 [0.15, 6.79]	
ONTARGET	44/1336	29/1316		46.34	1.49 [0.94, 2.37]	
Subtotal (95% CI)	1381	1361	-	49.04	1.46 [0.93, 2.29]	
Total events 46 (Treatment), 31 (-		,,	
Test for heterogeneity: Chi2=0.16		6				
Test for overall effect: Z = 1.65 (P						
02 Combination vsARBs	10.000		_	100000		
ONTARGET	44/1336	34/1364		50.96	1.32 [0.85, 2.05]	
Subtotal (95% CI)	1336	1364	+	50.96	1.32 [0.85, 2.05]	
Total events: 44 (Treatment), 34 (
Test for heterogeneity: not application						
Test for overall effect: Z = 1.24 (P	= 0.22)					
Total (95% CI)	2717	2725		100.00	1.39 [1.01, 1.90]	
Total events 90 (Treatment), 65 (6169	•	200.00	2.05 [2.04, 2.50]	
Test for heterogeneity: Chi ² =0.26		5				
Test for overall effect: Z = 2.04 (P				ACE-Is + AR	Bs vs ACE-Is or ARBs	
				100		-
			0.01 0.1 1 10	100		
			Favors treatment Favors cor	ntrol		
Fig. 3. Effect of ACEL A	RB or combined the	many on FSKD				

Fig. 3. Effect of ACEI, ARB or combined therapy on ESKD.