RAAS blockade in diabetic kidney disease

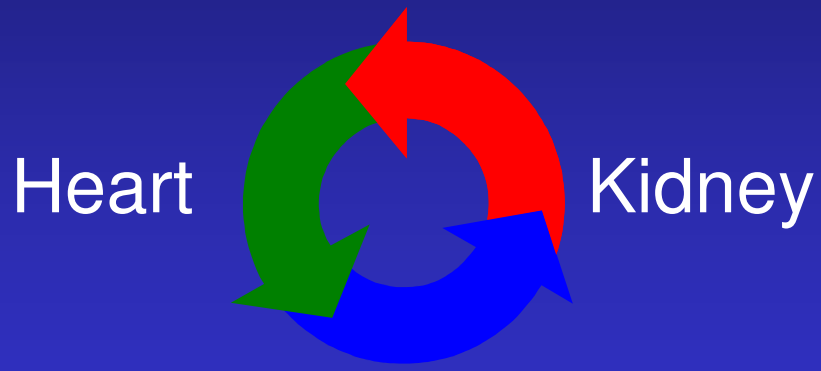
ACEi vs ARB

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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Editorial group: Cochrane Renal Group.
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Review content assessed as up-to-date: 15 August 2006.

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Effects of ARB on mortality

Analysis 2.1. Comparison 2 AIIRA versus placebo/no treatment, Outcome 1 All-cause mortality.

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

Comparison: 2 AIIRA versus placebo/no treatment

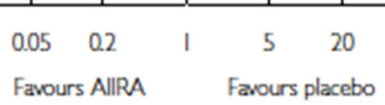
Outcome: 1 All-cause mortality

Study or subgroup	AIIRA n/N	Placebo/no treatment n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
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 (AIIRA), 249 (Placebo/no treatment)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.63$, df = 2 (P = 0.73); $I^2 = 0.0\%$

Test for overall effect: Z = 0.07 (P = 0.95)



Effects of ACEI on mortality

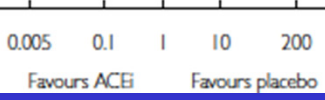
Analysis 1.1. Comparison 1 ACEi versus placebo/no treatment, Outcome 1 All-cause mortality.

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

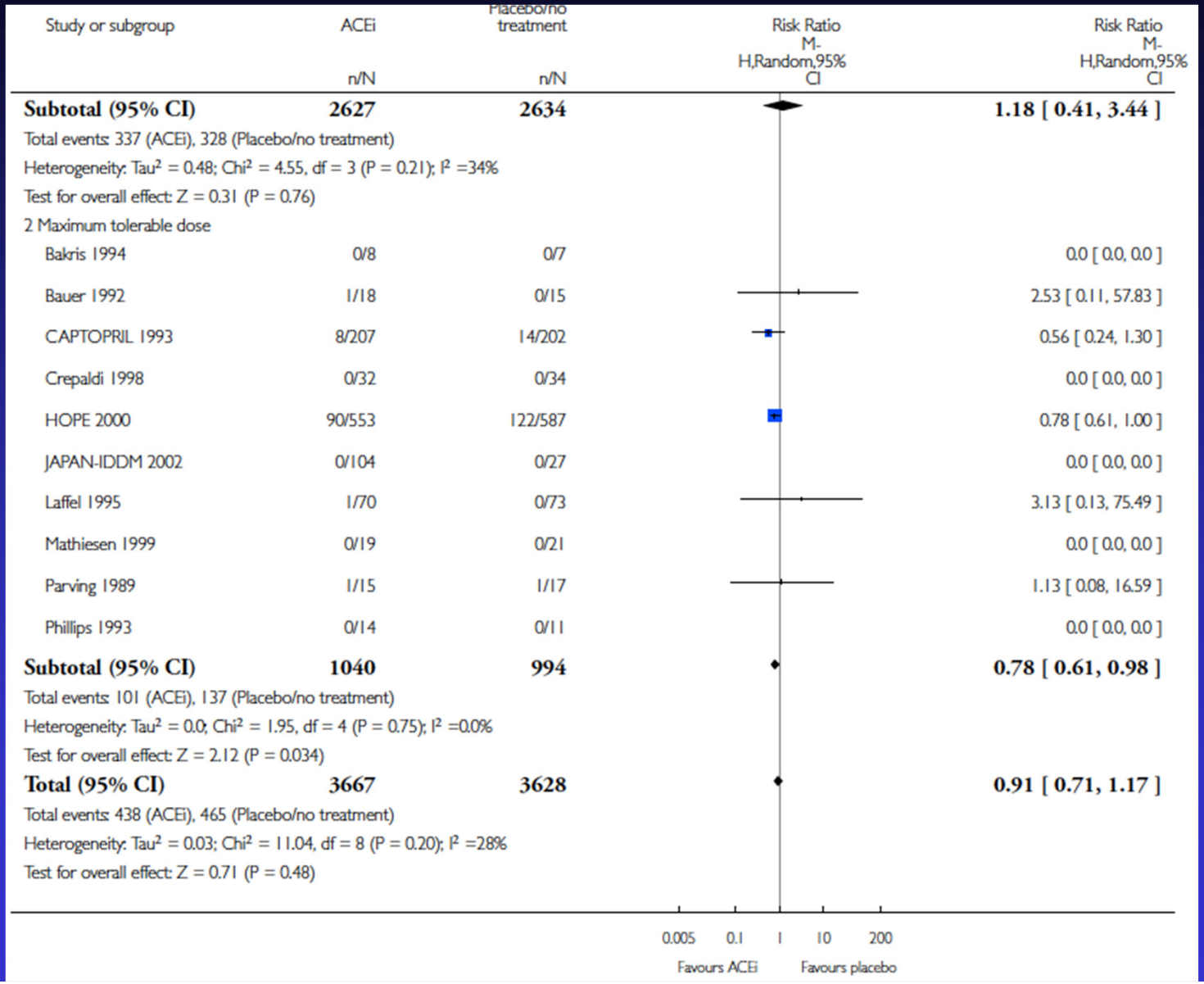
Comparison: 1 ACEi versus placebo/no treatment

Outcome: 1 All-cause mortality

Study or subgroup	ACEi n/N	Placebo/no treatment n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Half or less maximum tolerable dose				
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]



Effects of ACEI on mortality



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 AIIRA versus placebo/no treatment

Outcome: 4 End-stage kidney disease

Study or subgroup	AIIRA n/N	Placebo/no treatment n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
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), 295 (Placebo/no treatment)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0.0\%$

Test for overall effect: Z = 3.18 (P = 0.0015)

Effects of ACEI on ESRD

Analysis 1.4. Comparison 1 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: 1 ACEi versus placebo/no treatment

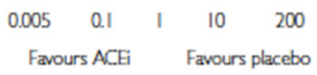
Outcome: 4 End-stage kidney disease

Study or subgroup	ACEi n/N	Placebo/no treatment n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
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 (Placebo/no treatment)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.71$, df = 3 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 2.28 (P = 0.023)



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

Comparison: 2 AIIRA versus placebo/no treatment

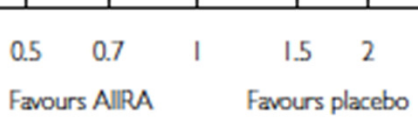
Outcome: 3 Doubling of serum creatinine

Study or subgroup	AIIRA n/N	Placebo/no treatment n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
IDNT 2001	98/579	135/569		0.71 [0.57, 0.90]
Parving 2001a	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: $Tau^2 = 0.00$; $Chi^2 = 1.22$, df = 1 (P = 0.27); $I^2 = 18\%$

Test for overall effect: Z = 2.91 (P = 0.0036)



Analysis 1.3. Comparison 1 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: 1 ACEi versus placebo/no treatment

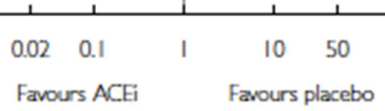
Outcome: 3 Doubling of serum creatinine

Study or subgroup	ACEi n/N	Placebo/no treatment n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
AIPRI 1996	1/6	7/15		0.36 [0.06, 2.32]
Capek 1994	0/9	0/6		0.0 [0.0, 0.0]
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		0.0 [0.0, 0.0]
Total (95% CI)	**3399**	**3381**		**0.68 [0.47, 1.00]**

Total events: 103 (ACEi), 145 (Placebo/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)



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.

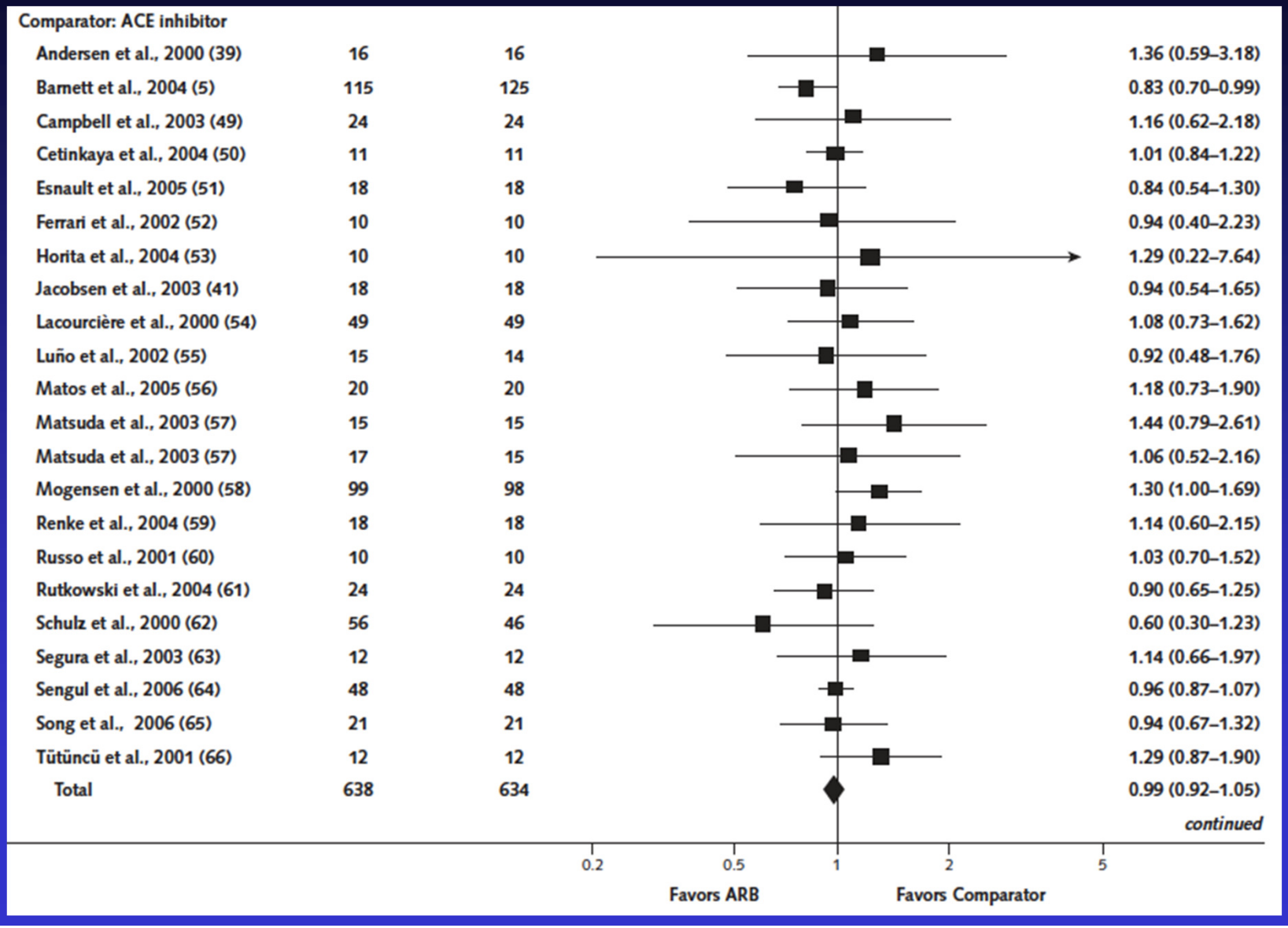
Limitations: Most studies were small, varied in quality, and did not provide reliable data on adverse drug reactions. Proteinuria reduction is only a surrogate for important progression of renal failure.

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. www.annals.org

For author affiliations, see end of text.

Effects of ARB vs ACEi on proteinuria



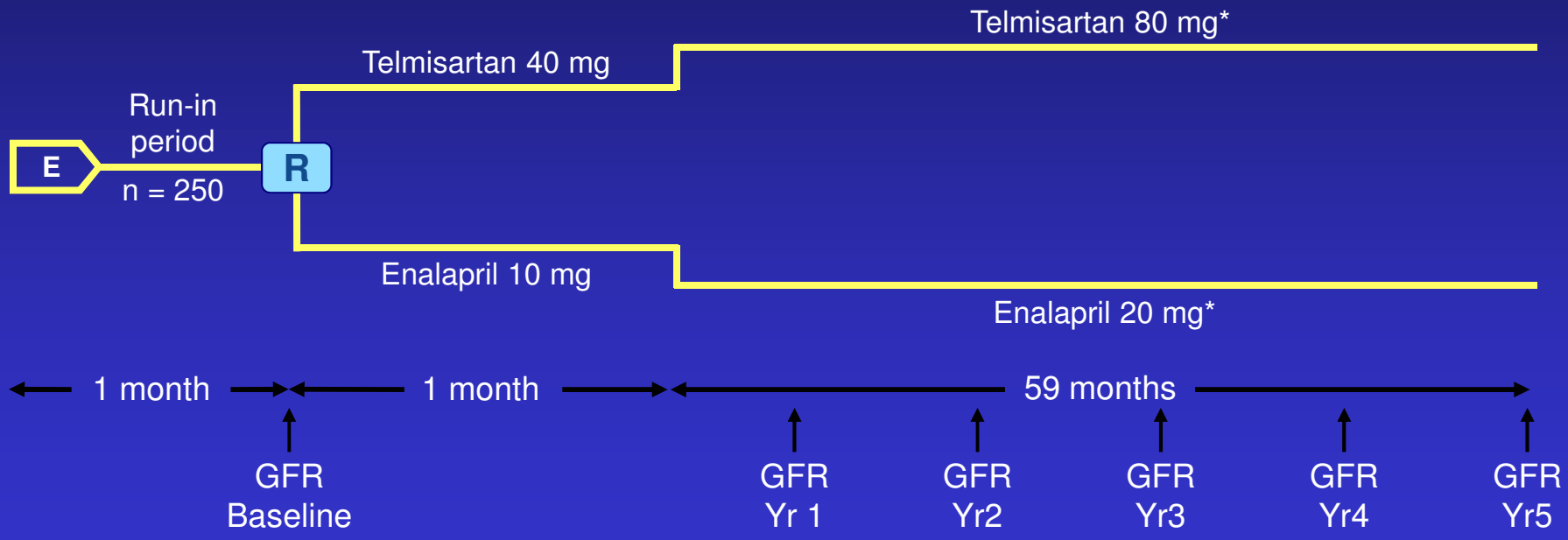
Agenda

- How?
  - Separate studies of ACEi and ARB on the same outcomes (many studies, metaanalyses)
  - **head-to-head comparisons of ACEi vs ARB (few studies)**

DETAIL

Telmisartan vs enalapril in diabetic nephropathy

Prospective, randomized, double-blind,
forced-titration, multicentre, parallel-group, 5-year treatment

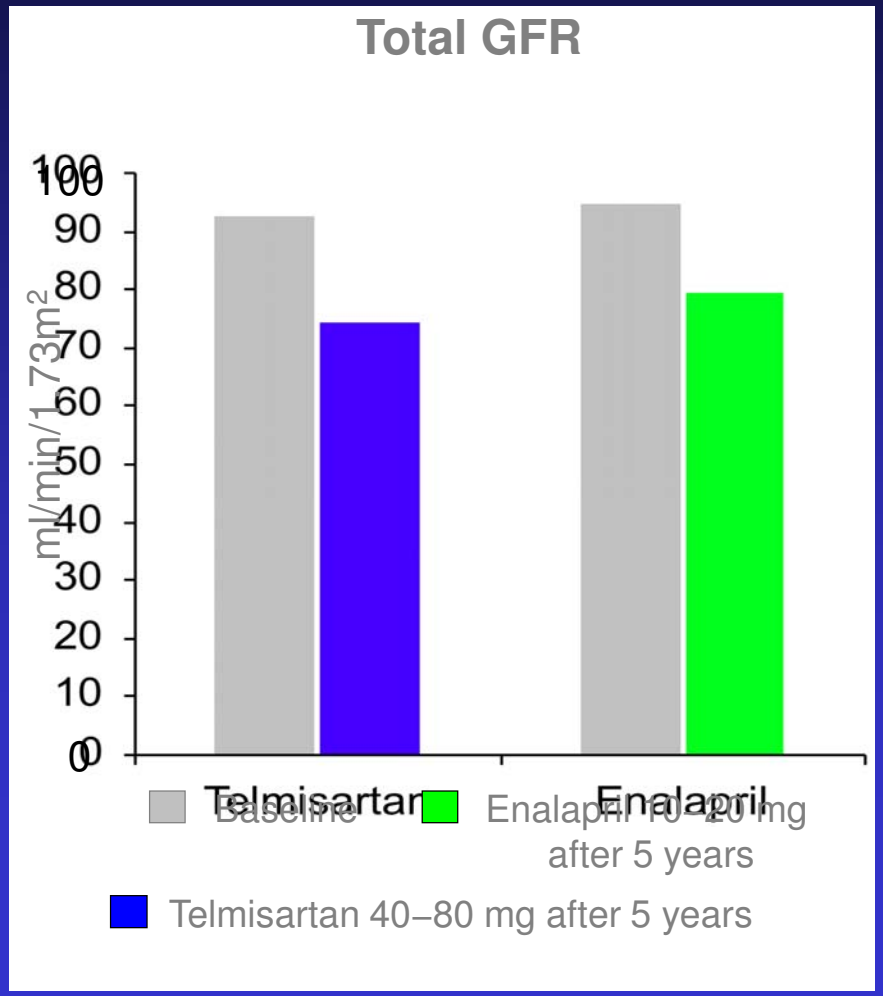


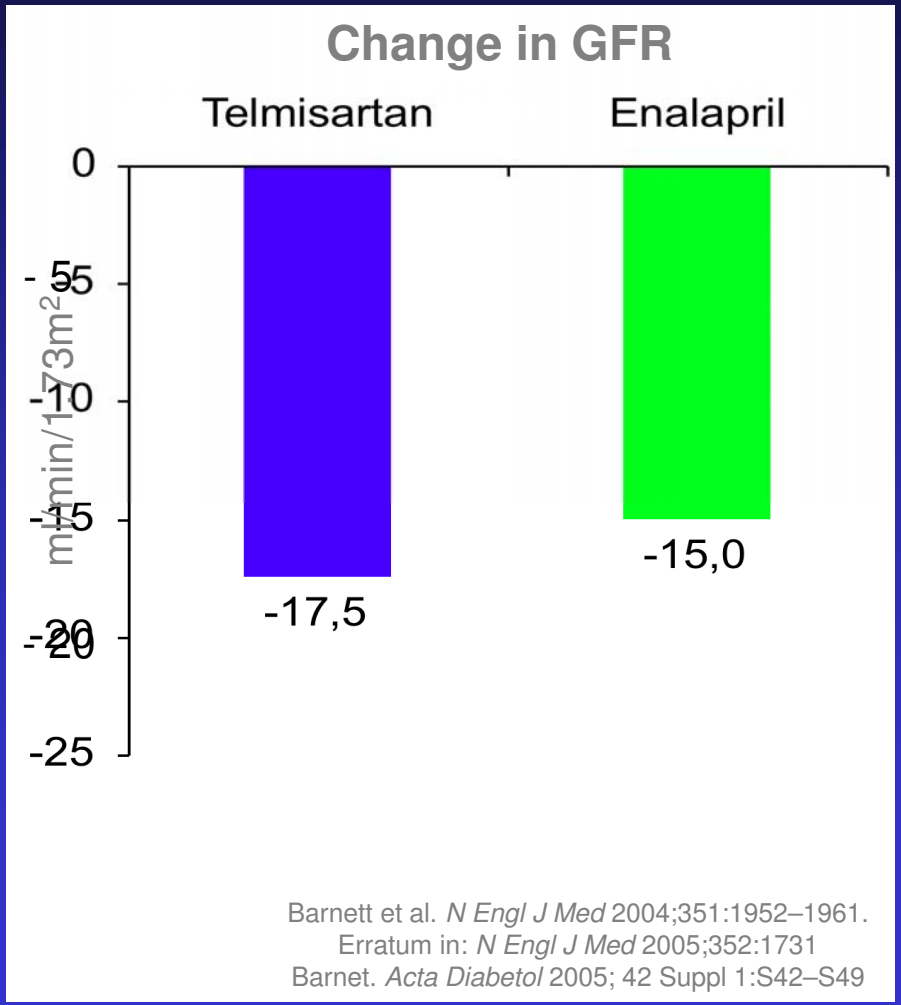
*Optional dose-reduction to telmisartan 40 mg or Enalapril 10 mg after 2 months

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

DETAIL

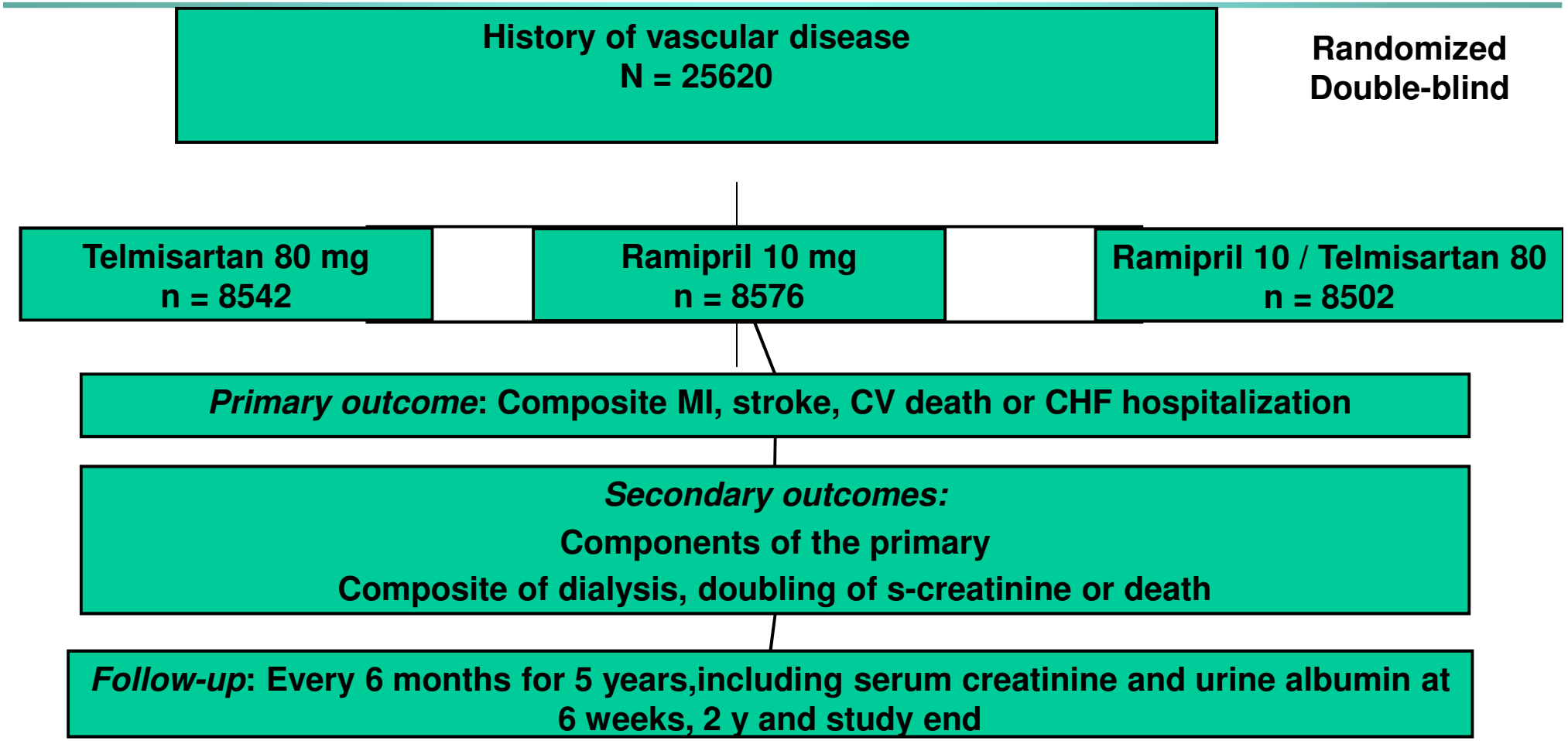
Primary endpoint: GFR after 5 years





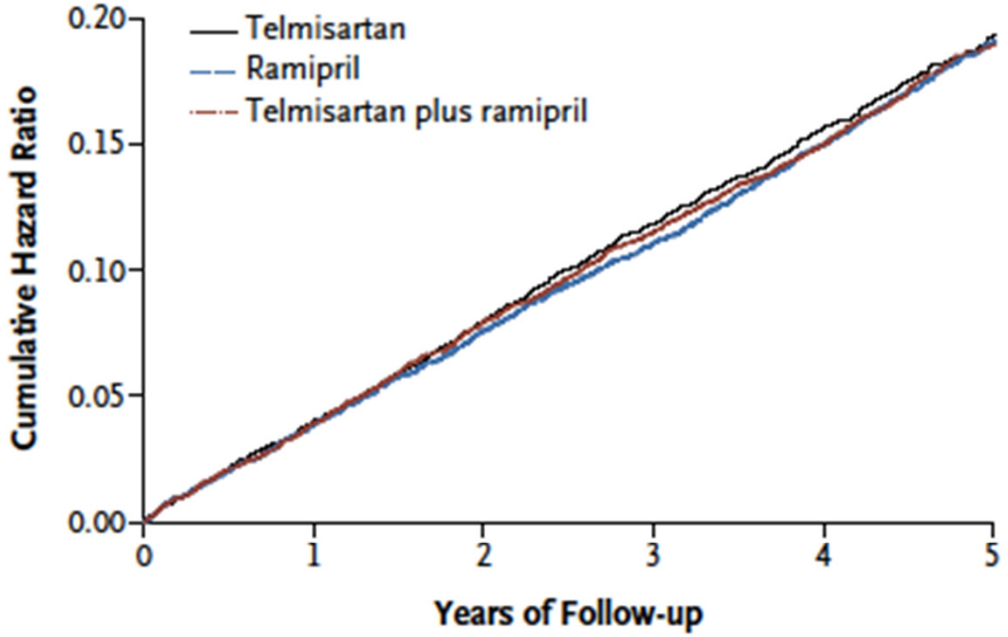
Barnett et al. *N Engl J Med* 2004;351:1952–1961.
Erratum in: *N Engl J Med* 2005;352:1731
Barnet. *Acta Diabetol* 2005; 42 Suppl 1:S42–S49

ONTARGET: Design



Ontarget Investigators *NEJM 2008;358: 1547;* Mann et al., *Lancet 2008;372:547*

ONTARGET: Results, prim. outcome



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

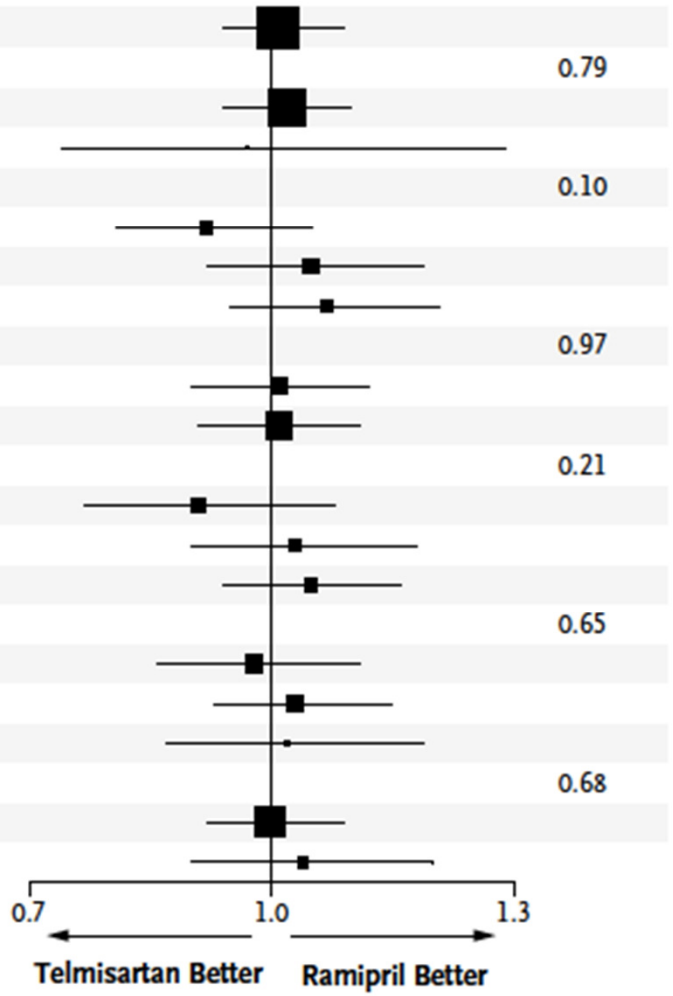
Figure 1. Kaplan–Meier Curves for the Primary Outcome in the Three Study Groups.

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

ONT: Results, prim. outcome, subgroups

A

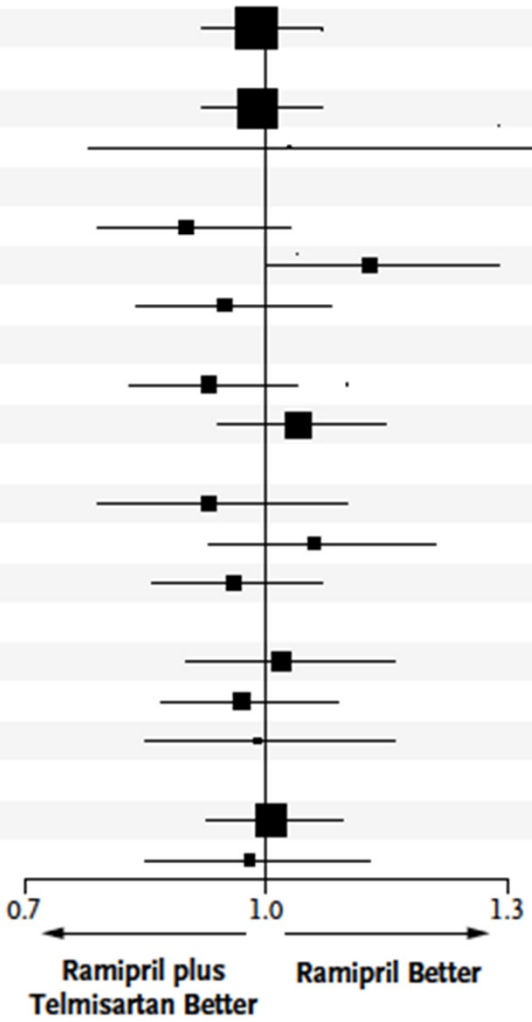
Subgroup	No. of Patients	Incidence of Primary Outcome in Ramipril Group (%)	P Value for Interaction
Primary composite	17,118	16.5	
Cardiovascular disease			0.79
Yes	15,627	16.8	
No	1,486	13.1	
Systolic blood pressure			0.10
≤134 mm Hg	5,704	16.2	
>134 to ≤150 mm Hg	6,042	14.9	
>150 mm Hg	5,352	18.4	
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	



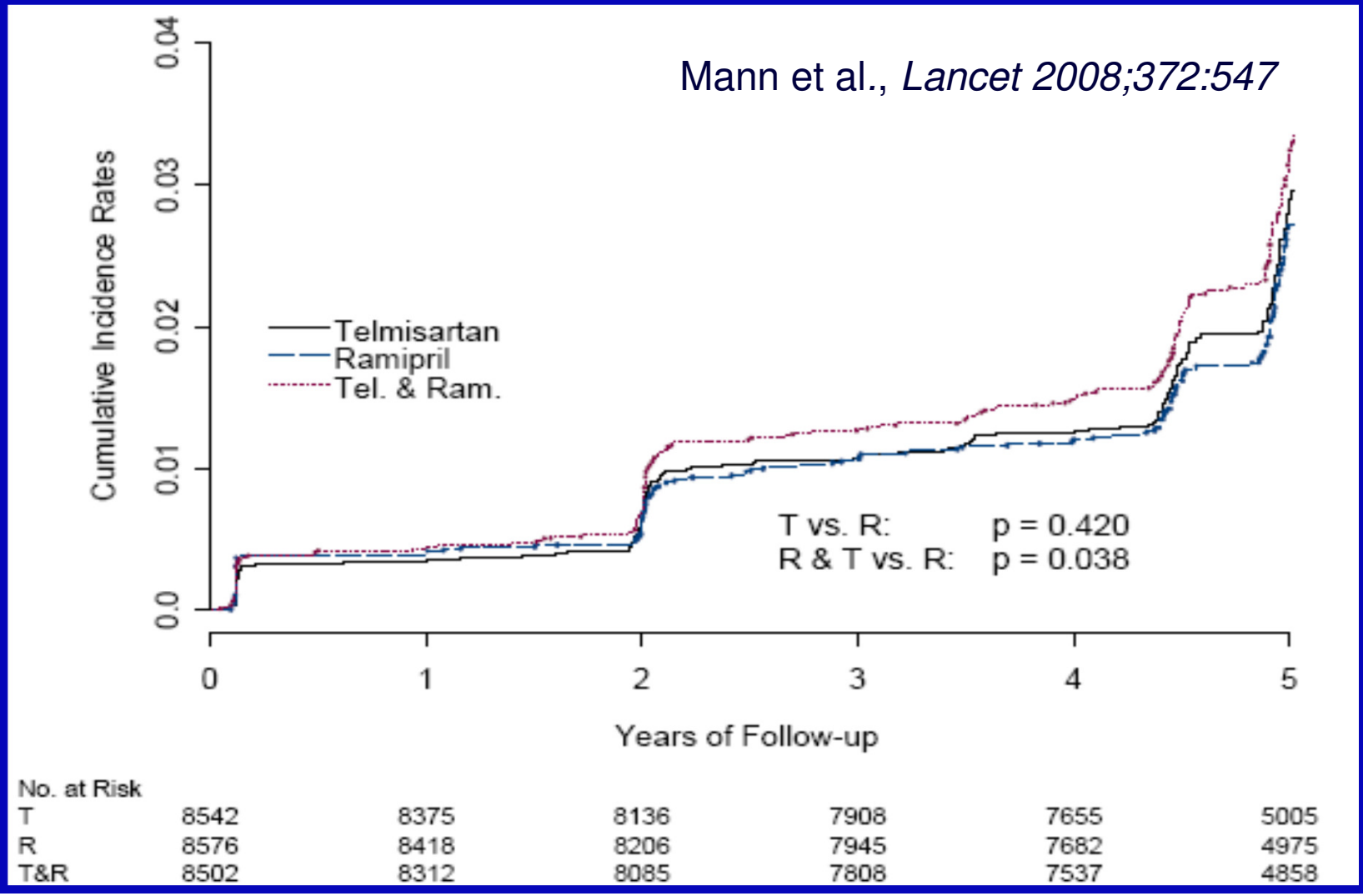
ONT: Results, prim. outcome, subgroups

B

Subgroup	No. of Patients	Incidence of Primary Outcome in Ramipril Group (%)	P Value for Interaction
Primary composite	17,078	16.5	
Cardiovascular disease			0.82
Yes	15,589	16.8	
No	1,484	13.1	
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	



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



ORIENT trial: ACEi + ARB in diabet. NP

comparison: **- Olmesartan**
- Placebo

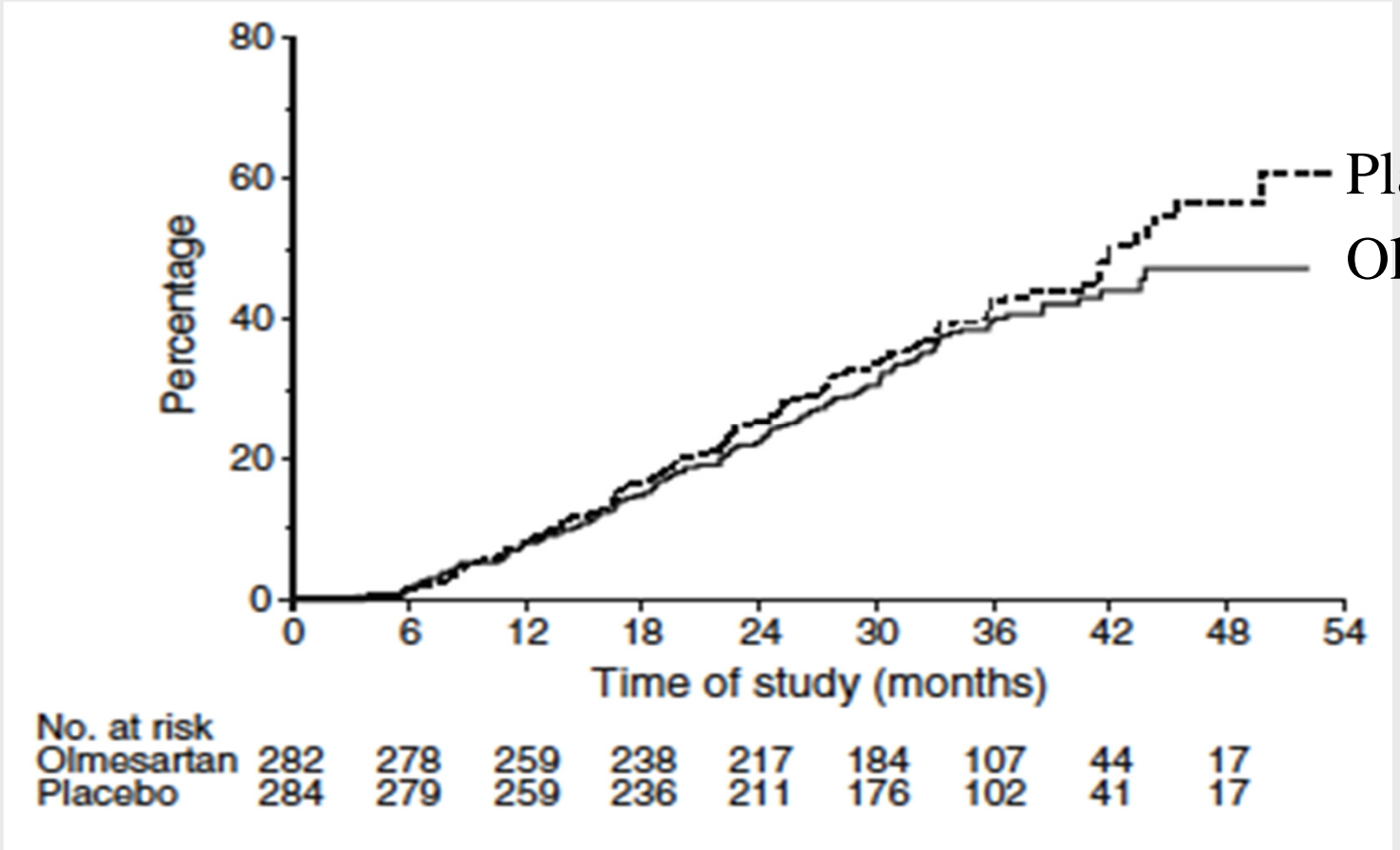
- 600 Pat with type 2 DM, hypertension, macroalbuminuria and serum-creatinine 1.2 - 2.5 mg/dl
- 75% treated with ACEi
- mean follow-up 3.2 years

- **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

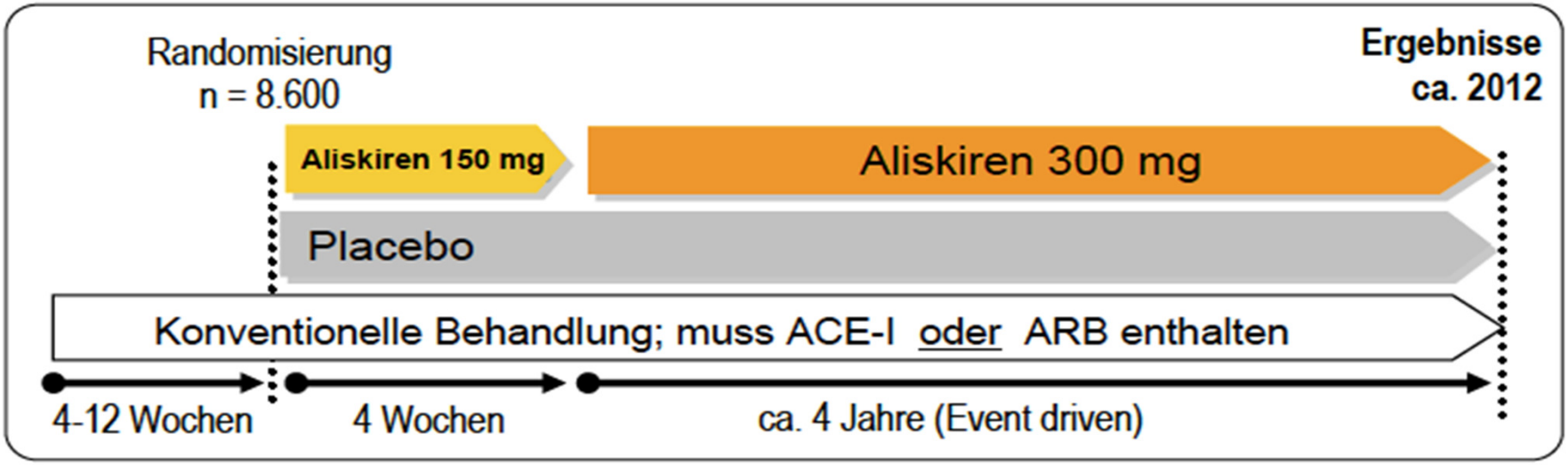


Imai et al Diabetologia (2011) 54:2978–2986

Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE): rationale and study design

Hans-Henrik Parving[1,2], Barry M. Brenner[3], John. J. V. McMurray[4], Dick de Zeeuw[5], Steven M. Haffner[6], Scott D. Solomon[3], Nish Chaturvedi[7], Mathieu Ghadanfar[8], Nicole Weissbach[8], Zhihua Xiang[8], Juergen Armbrecht[8] and Marc A. Pfeffer[3]

- 8.600 randomisierte Patienten mit Typ II-DM und Albuminurie > 0,2 g/g oder Mikroalbuminurie plus eGFR < 30-60 ml/min oder kardiovaskuläre Erkrankung



Parving et al. Nephrol Dial Transplant. 24:1663, 2009

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 …..

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

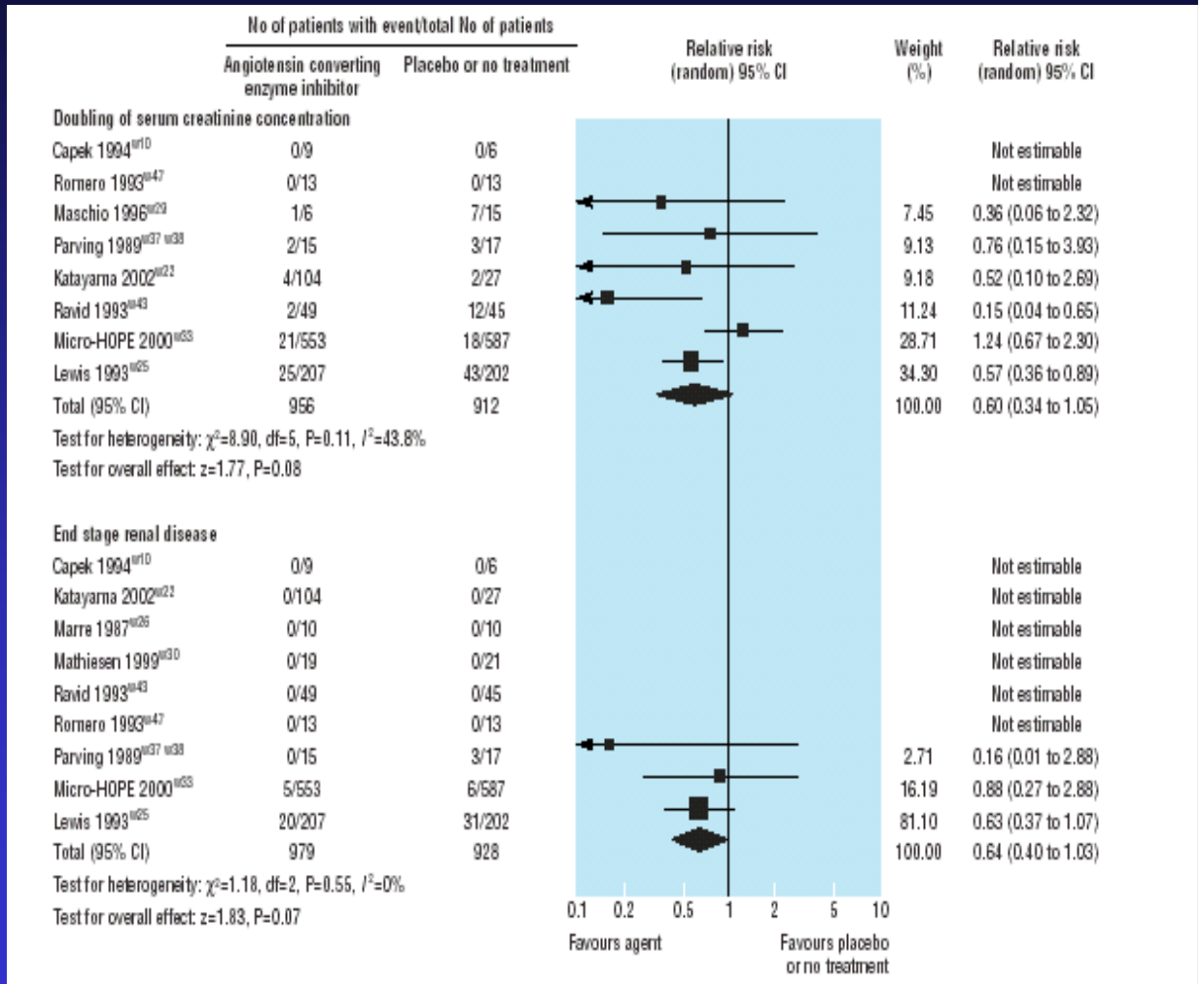
  Evidence for harm

E N D

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



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

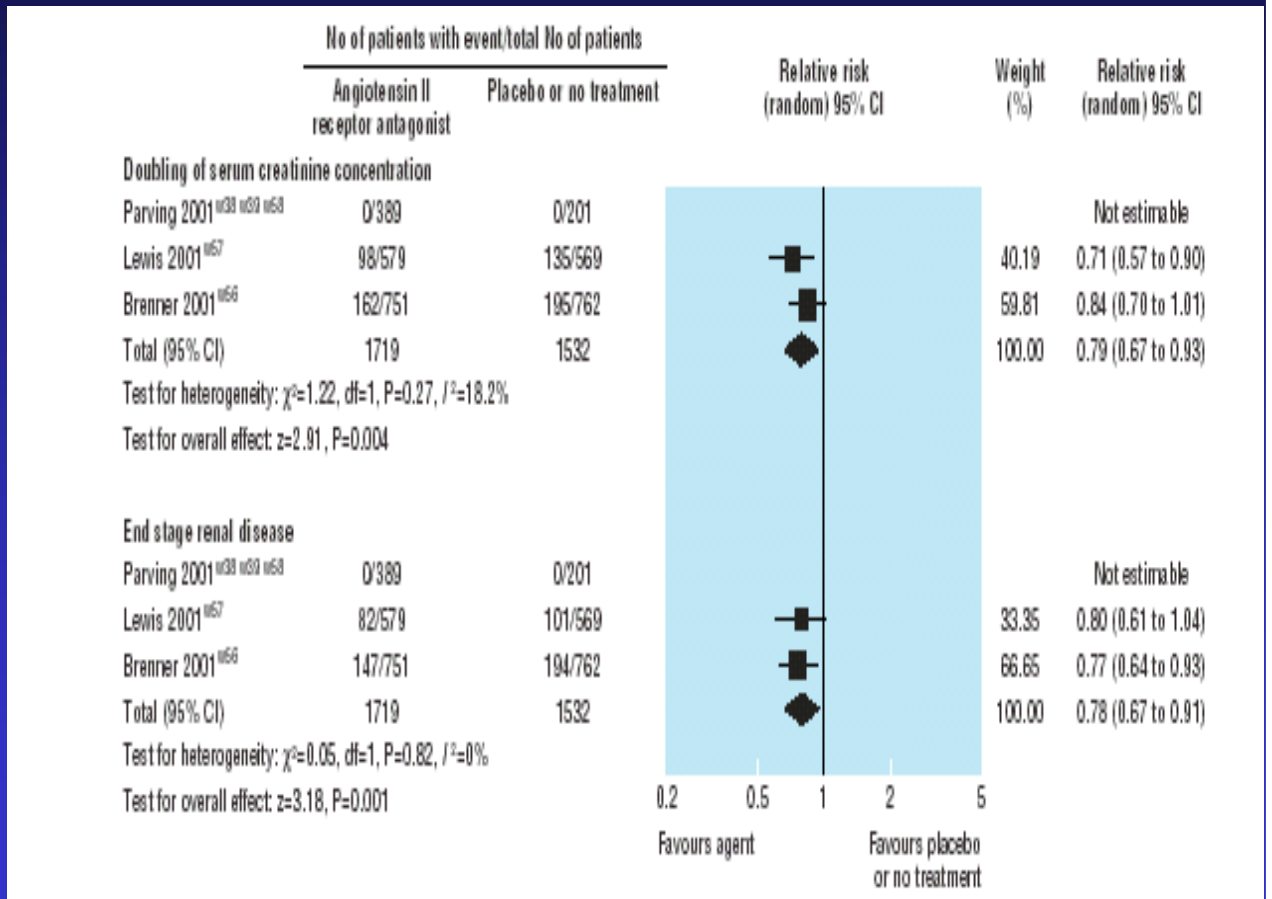


Fig 6 Effect of angiotensin II receptor antagonists compared with placebo or no treatment on renal function (doubling of serum creatinine concentration and end stage renal disease)

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

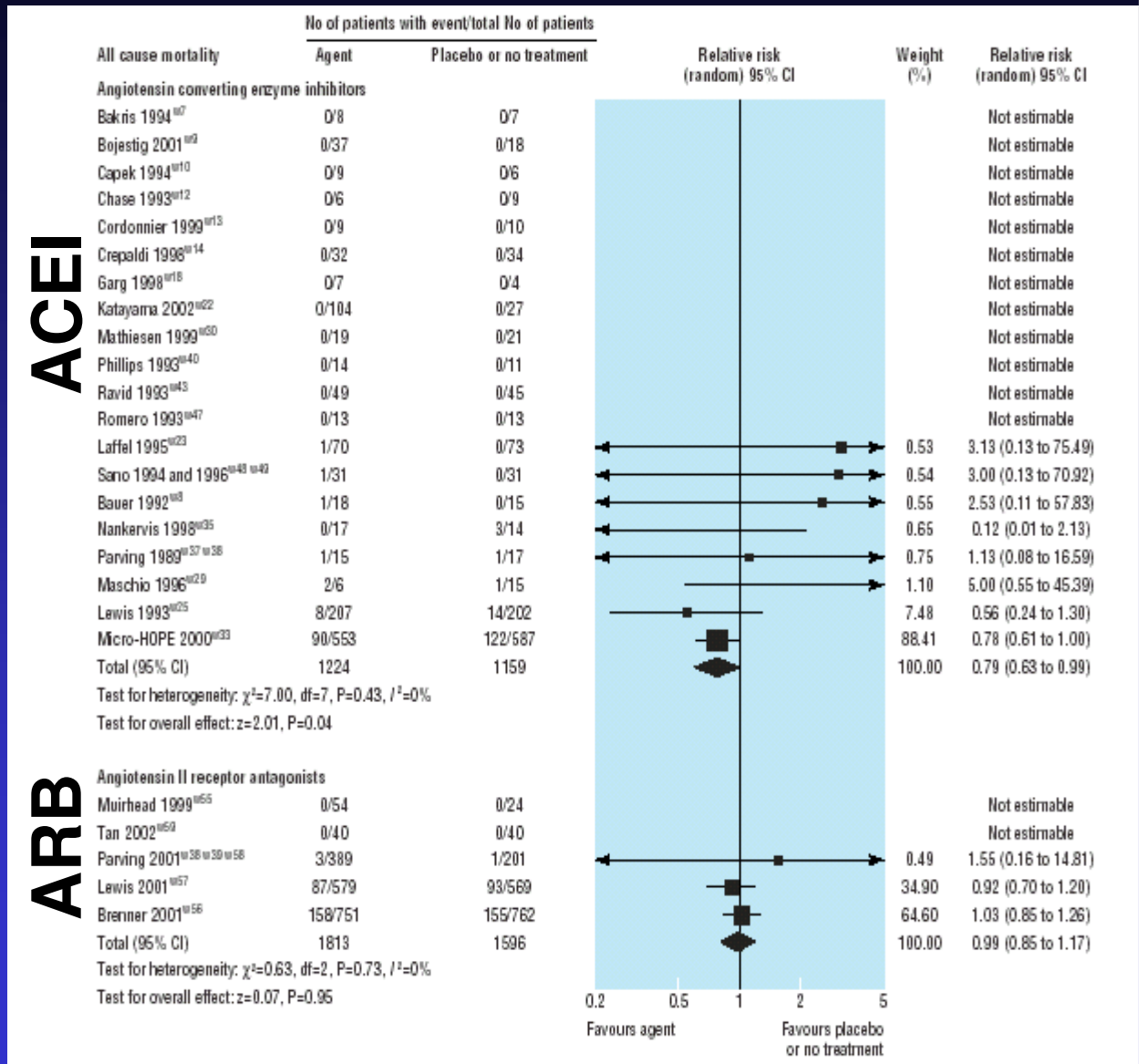


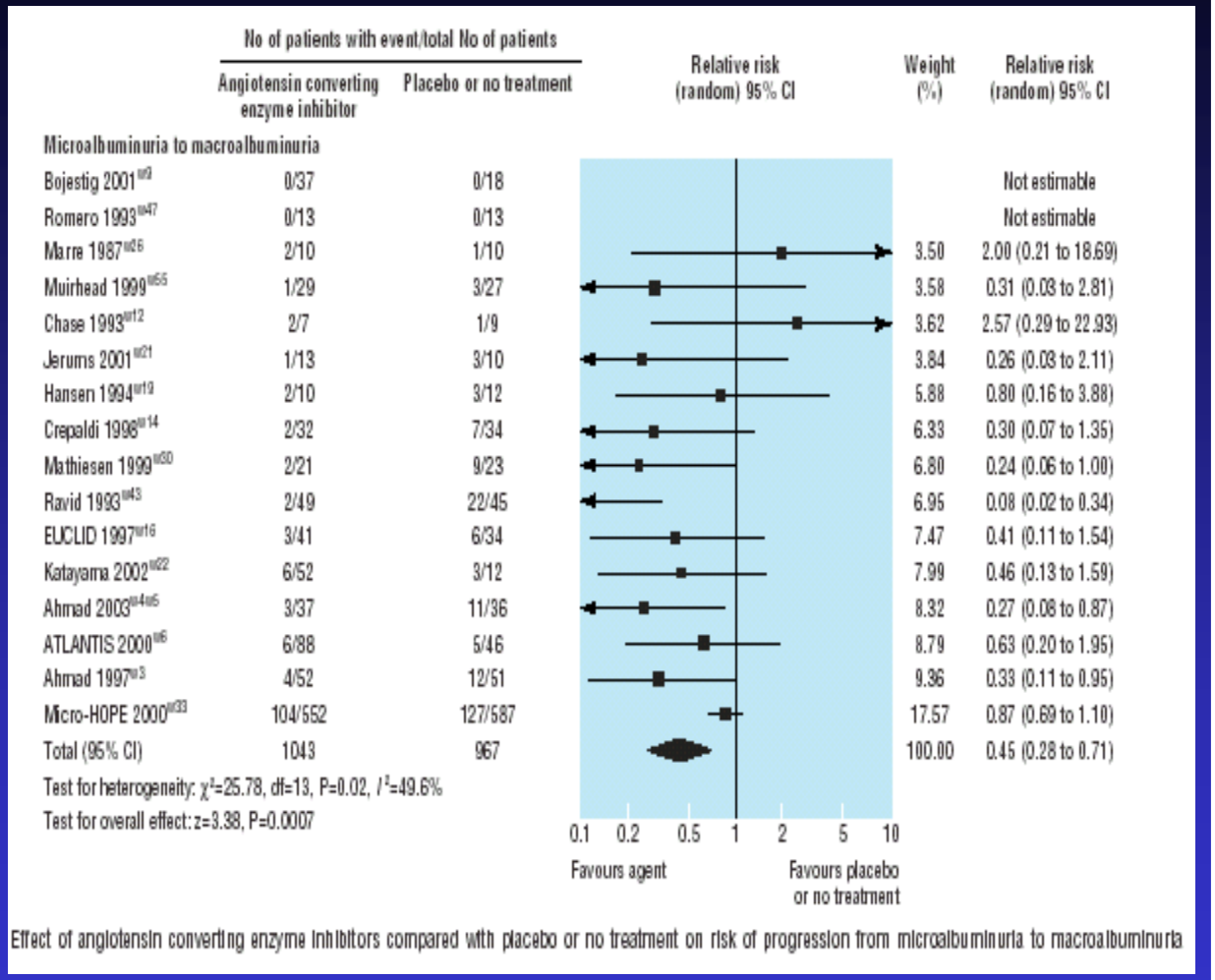
Fig 2 Effect of angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists compared with placebo or no treatment on overall mortality

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



Effect of angiotensin converting enzyme inhibitors compared with placebo or no treatment on risk of progression from microalbuminuria to macroalbuminuria

Renal outcomes* & ACEI

* 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

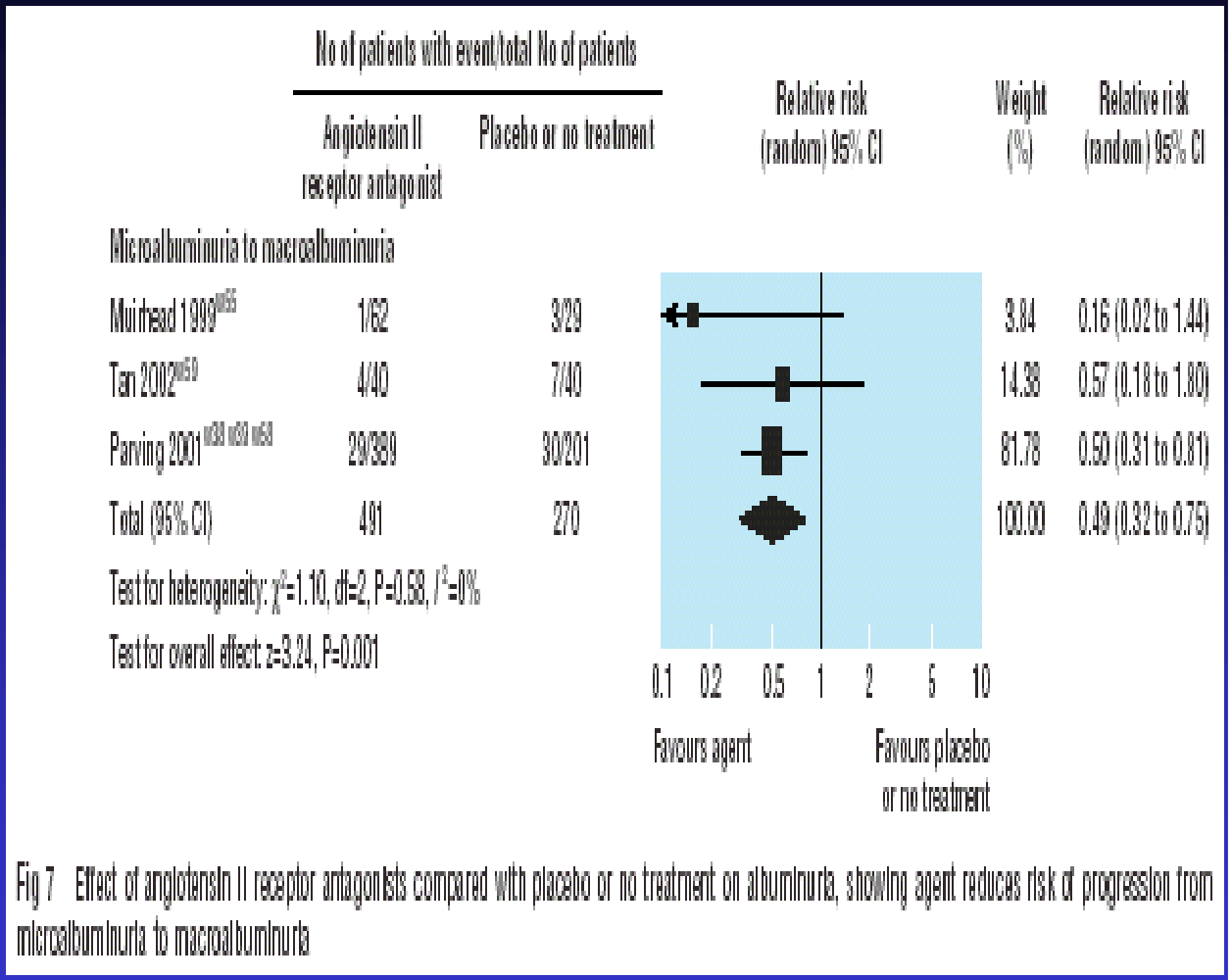


Fig 7 Effect of angiotensin II receptor antagonists compared with placebo or no treatment on albuminuria, showing agent reduces risk of progression from microalbuminuria to macroalbuminuria

Renal outcomes* & ARB

* Progression from micro - to macroalbuminuria

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

NDT
Nephrology Dialysis Transplantation

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 Maione[1], Sankar D Navaneethan[2,3], Giusi Graziano[1], Ruth Mitchell[3], David Johnson[4], Johannes F.E. Mann[5,6], Peggy Gao[5], Jonathan C Craig[3,7,8], Giovanni Tognoni[9], Vlado Perkovic[10], Antonio Nicolucci[1], Salvatore De Cosmo[11], Antonio Sasso[12], Olga Lamacchia[13], Mauro Cignarelli[13], Valeria Maria Manfreda[14], Giorgio Gentile[15,16] and Giovanni FM Strippoli[1,3,7,16,17]

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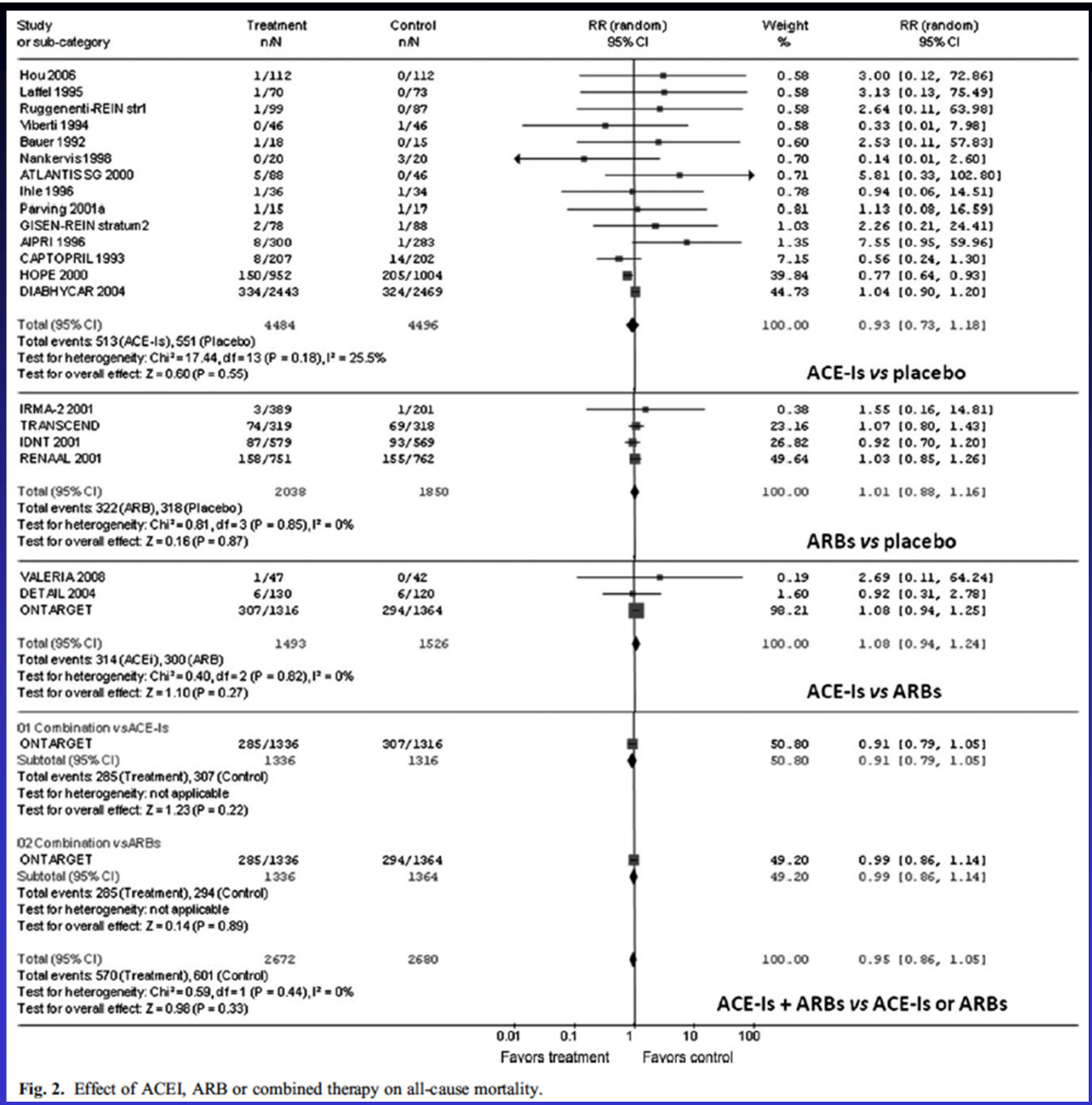

Fig. 2. Effect of ACEI, ARB or combined therapy on all-cause mortality.

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

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			
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			
Fatal events[a]	2	2930	0.80 (0.61–1.04)
Nonfatal events[b]	3	3290	1.00 (0.93–1.07)
Renal			
Doubling of creatinine	3	3269	1.03 (0.77–1.38)
Microalbuminuria → macroalbuminuria	3	2856	1.20 (0.99–1.46)
Microalbuminuria → normoalbuminuria	3	131	1.00 (0.62–1.61)
ACEI + ARB versus ACEI			
Cardiovascular			
Fatal events[a]	1	2652	0.95 (0.71–1.27)
Nonfatal events[b]	1	2652	1.03 (0.96–1.10)
Renal			
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			
Cardiovascular			
Fatal events[a]	1	2700	0.77 (0.58–1.01)
Nonfatal events[b]	1	2700	1.03 (0.96–1.11)
Renal			
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)

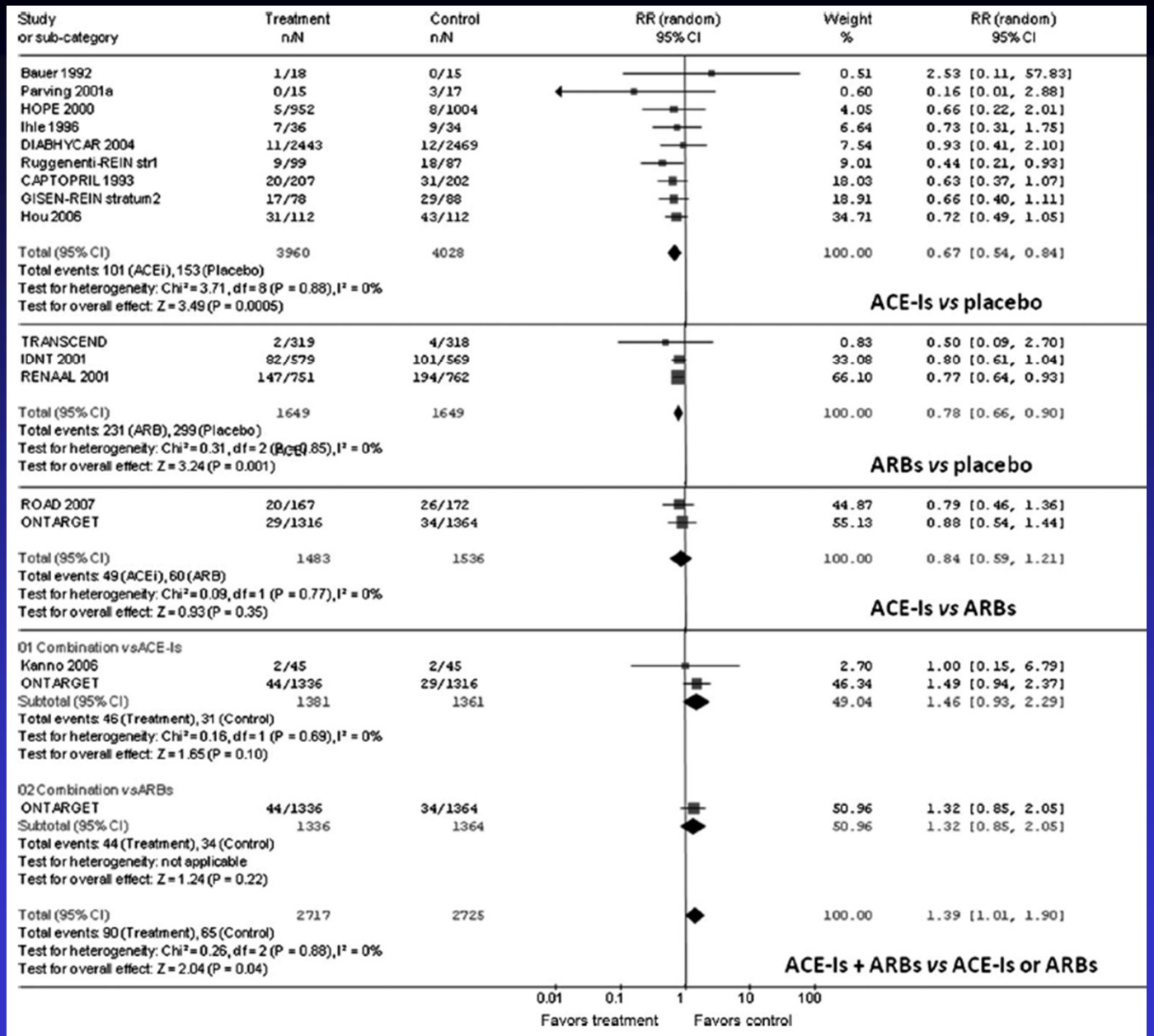

Fig. 3. Effect of ACEI, ARB or combined therapy on ESKD.