36th Autumn Congress of Korean Diabetes Association

Combination therapy of diabetic nephropathy

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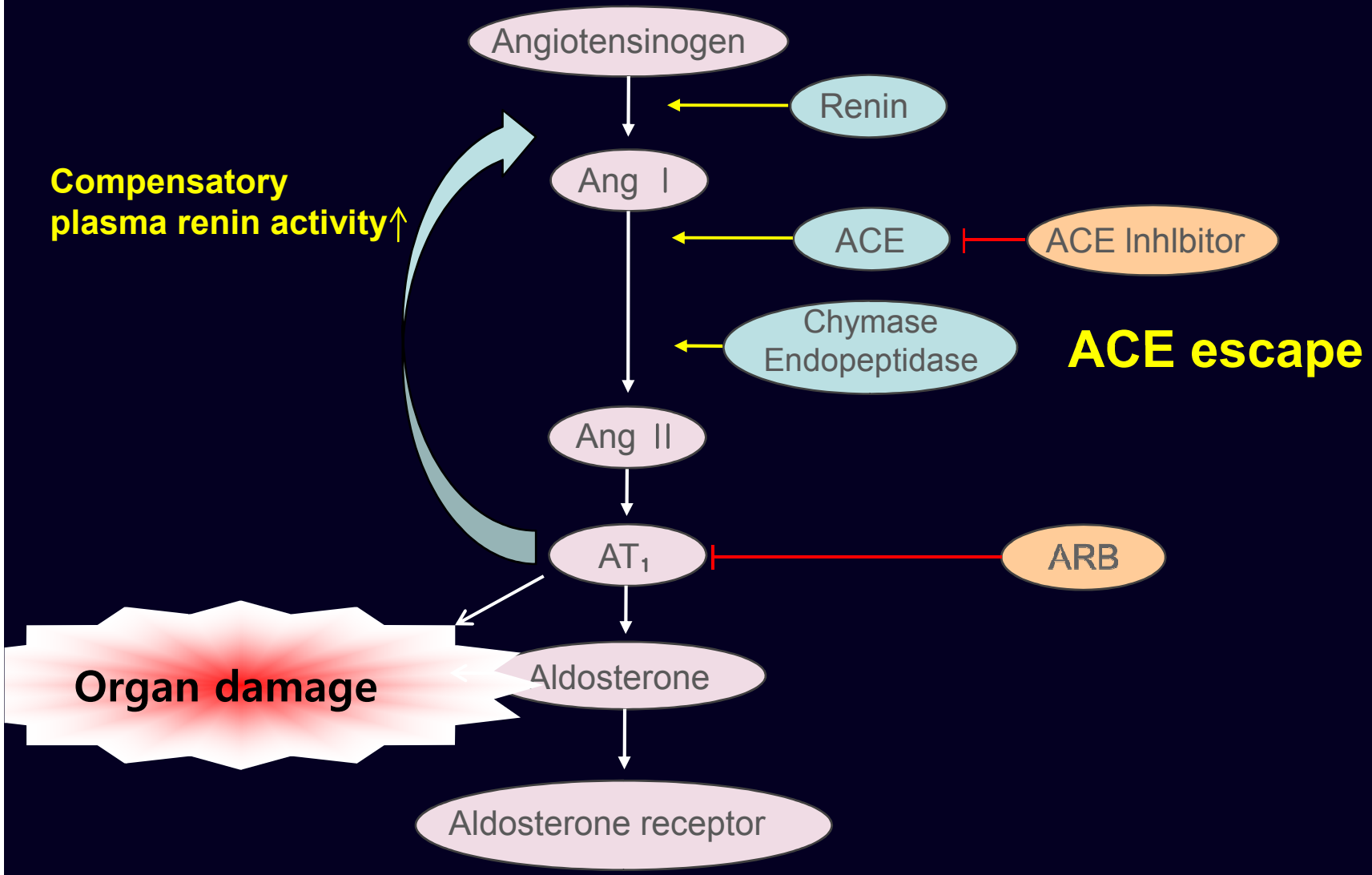
Progression of diabetic nephropathy in spite of RAAS blockade

- Many patients continues to lose renal function and progress to ESRD, despite the treatment of Angiotensin converting enzyme inhibitors (ACEIs) or Angiotensin II receptor blockers (ARBs)

- This may be due to failure to reach optimal BP goals, changes in salt intake, genetic polymorphism, and incomplete blocking of renin angiotensin aldosterone system (RAAS)

Reasons for suboptimal effects of ACEIs or ARBs



Maximizing RAAS inhibition

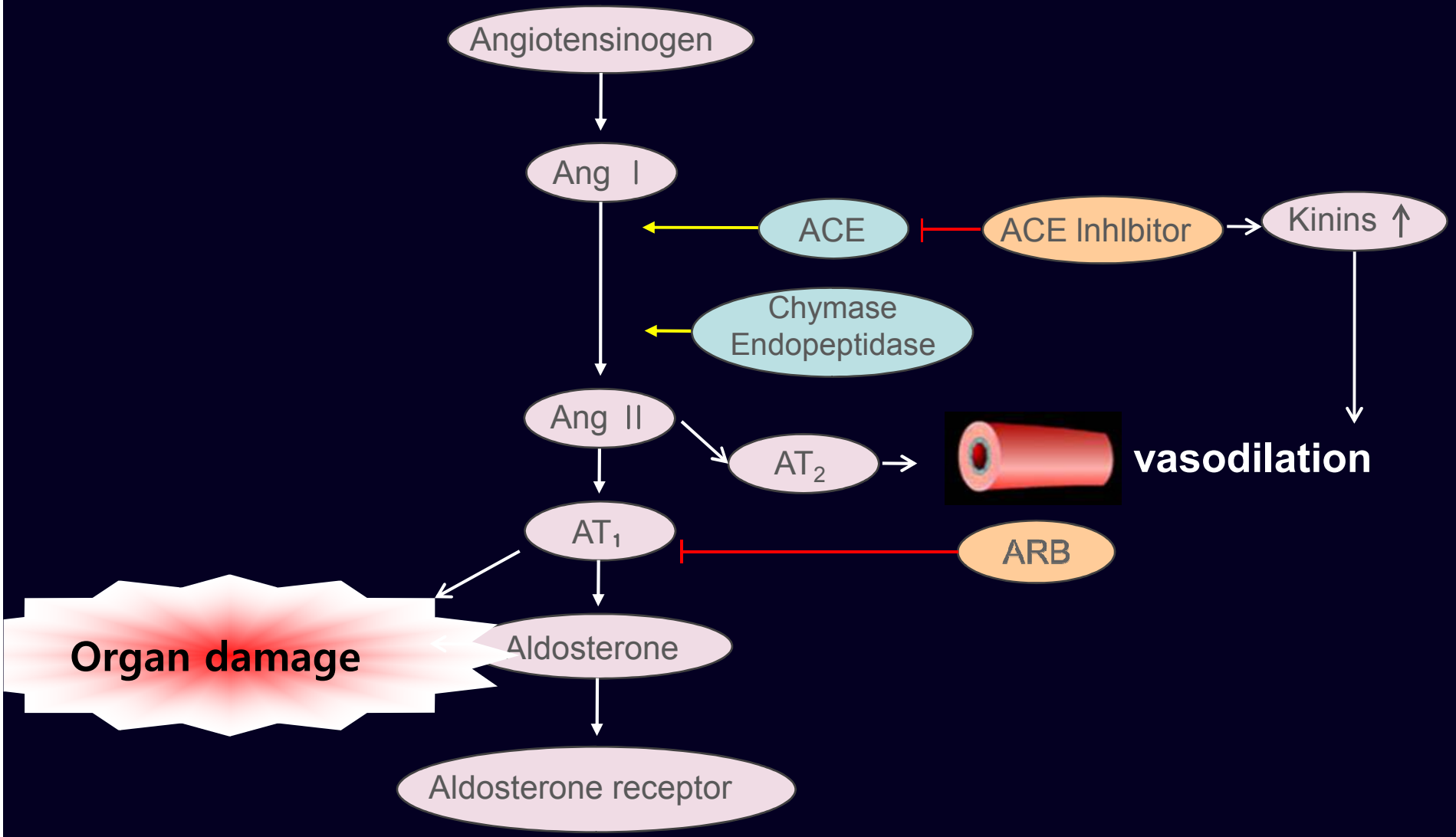
- Increasing the dosage of ARB
- ACEI + ARB
- ACEI (ARB) + aldosterone antagonist
- ACEI (ARB) + renin inhibitor
- Triple combination (ACEI + ARB + aldosterone antagonist)

Debate and issue of current status about combined RAAS blockade in diabetic nephropathy

- Is there evidence that BP independent effect of RAAS combination therapy?
- What do important studies suggest to us including ONTARGET study?
- Can we select the subgroup who will be benefitted by the combination therapy?
- What is the ideal dual blockade therapy?

ACEI+ARB combination trials

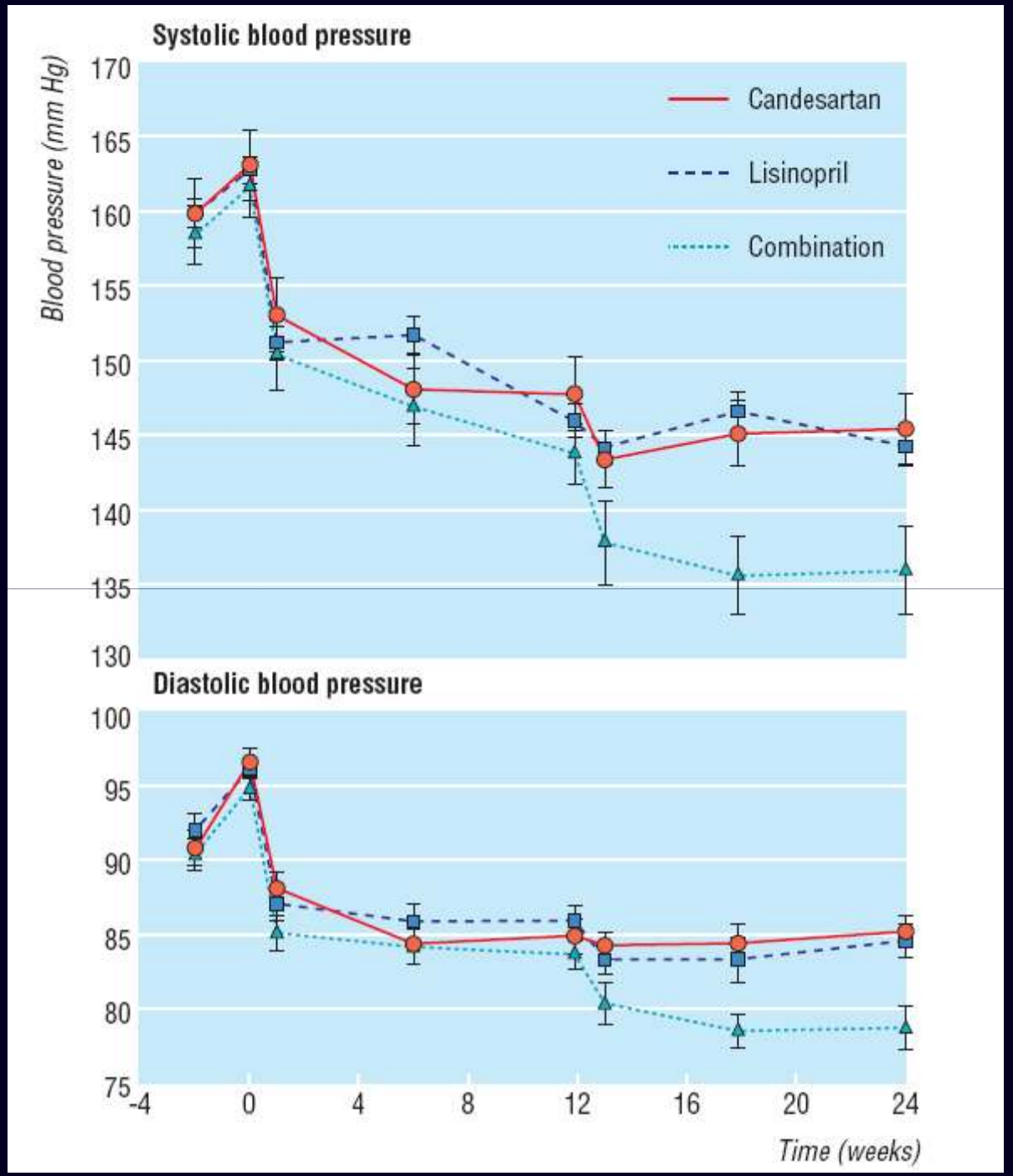
Rationale for a combination therapy with ACEI+ARB



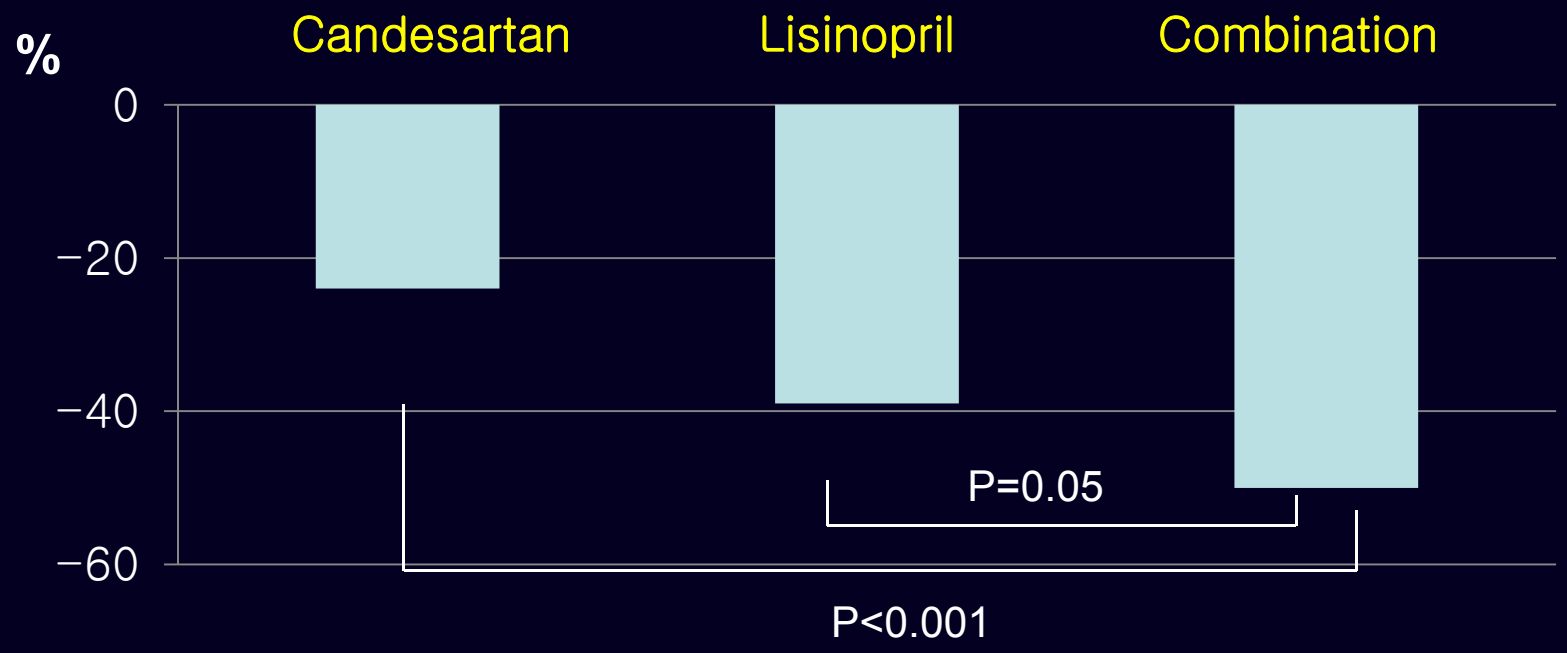
ACEIs plus ARBs in T2DM (CALM study)

- Candesartan and Lisinopril Microalbuminuria (CALM) study
- 12-week randomized, prospective study in 199 microalbuminuric diabetic patients
- Candesartan (16mg) + lisinopril (20mg) vs. either monotherapy

Motensen CE, BMJ 2000


Systolic blood pressure
Blood pressure (mm Hg)
170
165
160
155
150
145
140
135
130
Candesartan
Lisinopril
Combination
Diastolic blood pressure
100
95
90
85
80
75
-4
0
4
8
12
16
20
24
Time (weeks)

Change of urinary albumin creatinine ratio (ACR)



- Greater reductions in urinary ACR with combination therapy than with candesartan or lisinopril

- Reductions in microalbuminuria were accompanied by BP reductions

ACEIs + ARBs

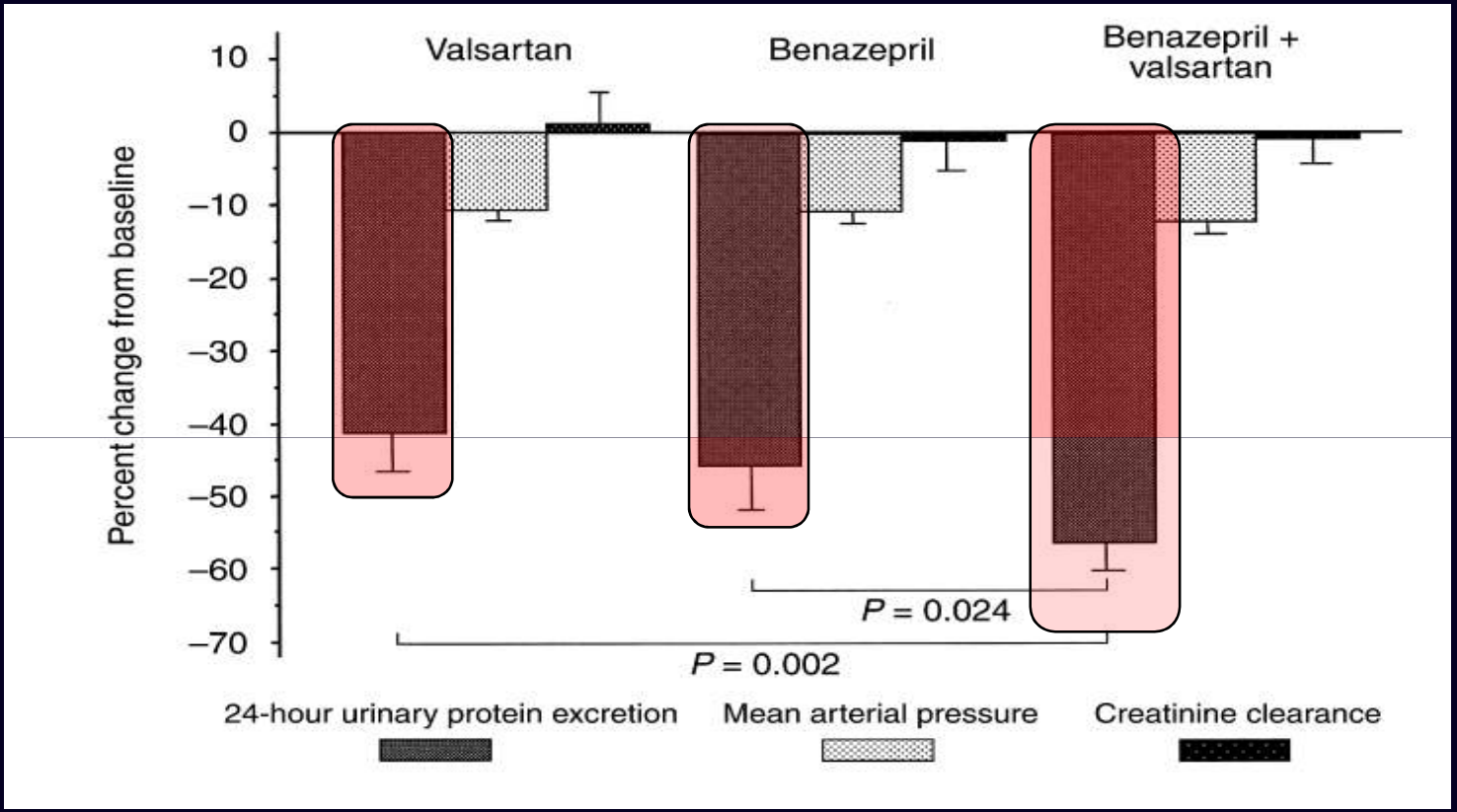
- The superior antiproteinuric effect was the result of more-effective RAAS inhibition or the result of greater reductions in BP???

Effect of combined ACEI and ARB in nondiabetic CKD

- 2-month randomized, cross-over study of 24 pts with nondiabetic, chronic nephropathies
- benazapril (20mg) vs. valsartan (160mg) vs. benazapril (10mg) + valsartan (80mg)
- Comparable BP control

Campbell R, Kidney International 2003

Changes of proteinuria, BP, and creatinine clearance



Superior antiproteinuric effect of dual blockade is not due to increased antihypertensive effect, but due to more effective RAAS inhibition.

Campbell R, Kidney International 2003

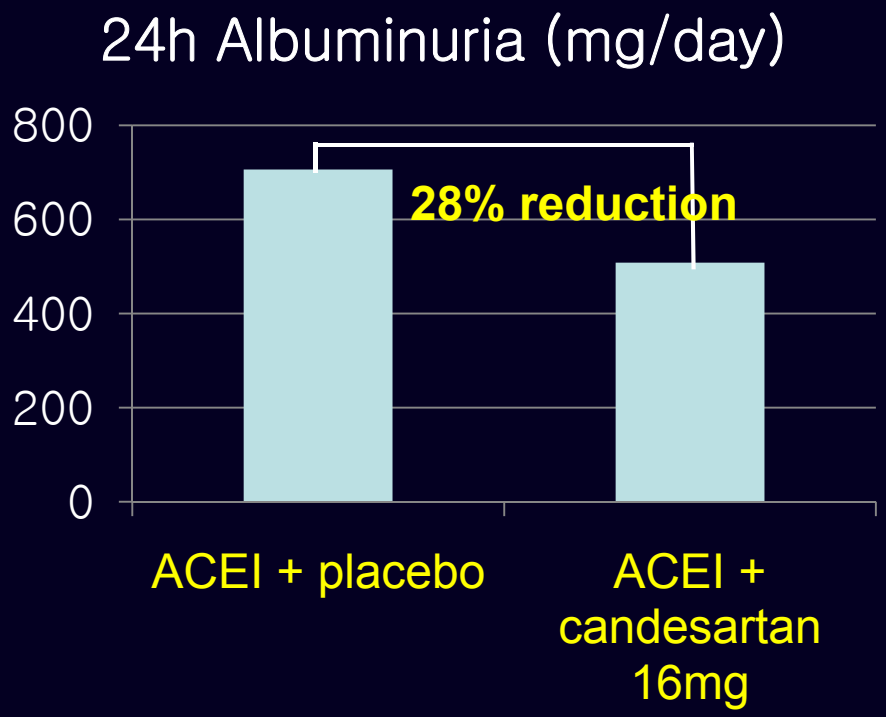
Add-on ARB with maximized ACEI in T2DM

- In the previous studies, the full renoprotective potential of RAAS blocking agents may not have been reached because either the ACEI or ARB was not given in maximal recommended doses

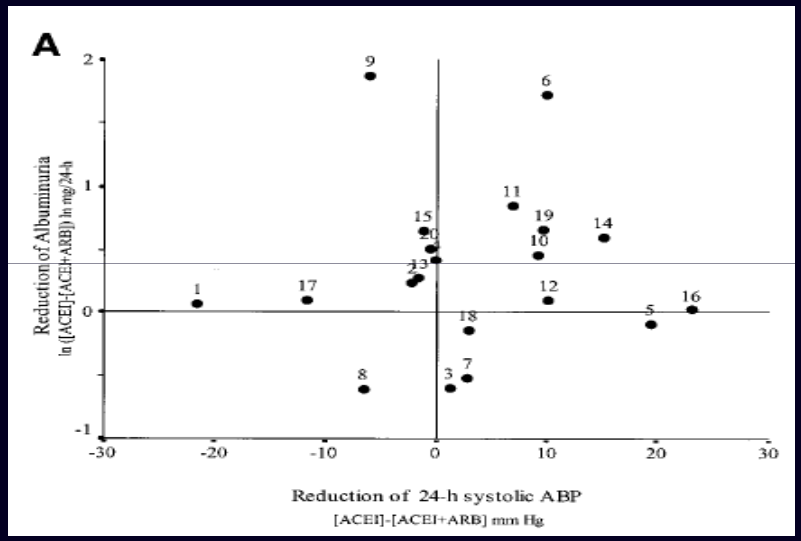
- 2-month crossover study in 20 pts with T2DM
- Previous antihypertensive tx [Lisinopril or enalapril (40mg) or captopril 150mg]
- Candesartan (16mg) vs. placebo on previous medication

Rossing K, Diabetes Care 2003

Add-on ARB with maximized ACEI in T2DM



No association between change in BP and albuminuria



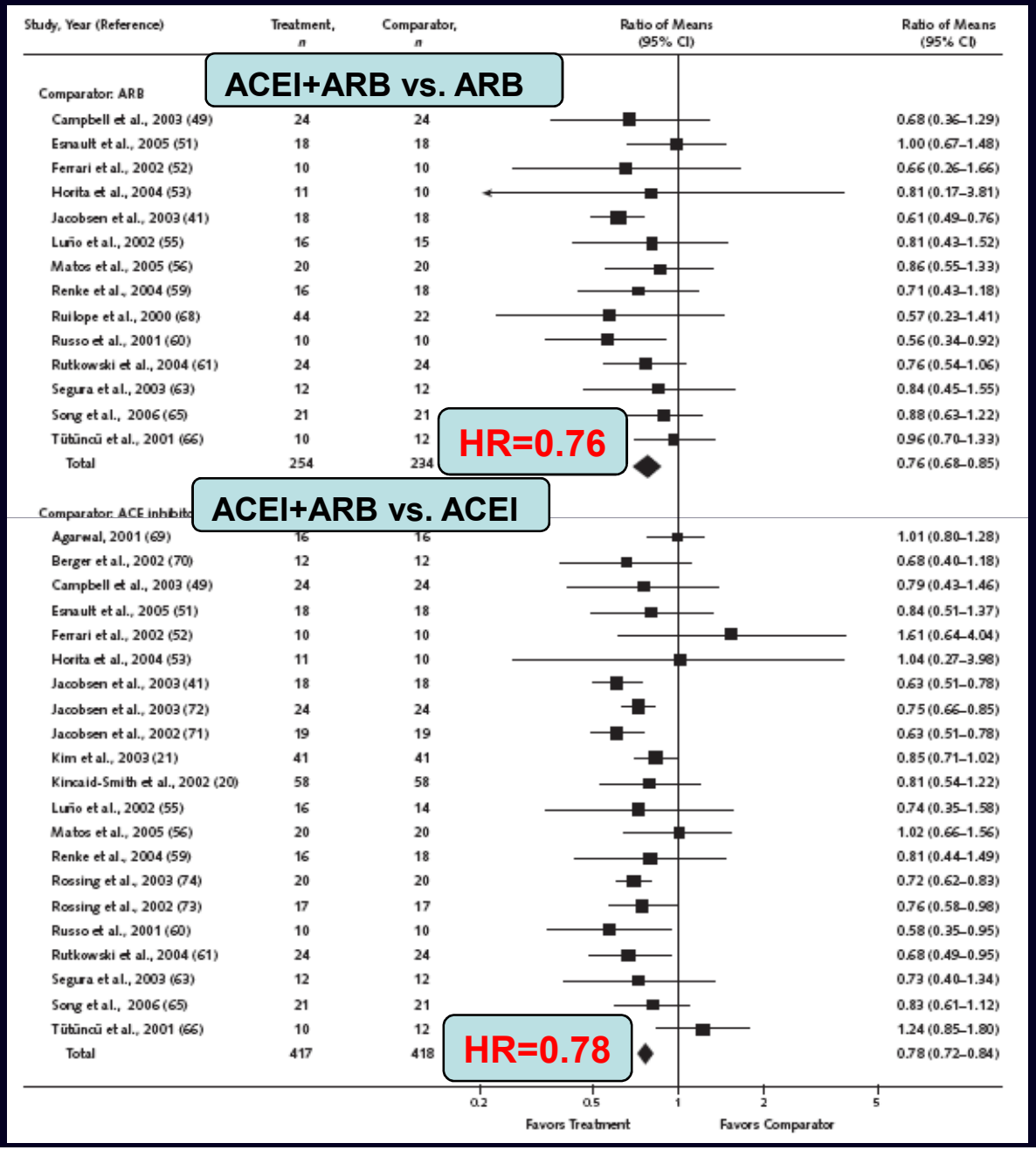
- Dual RAAS blockade provides superior renoprotection independent of BP changes in comparison with maximally recommended doses of ACEI

The previous studies

- Small sized
- Duration of therapy was short
- The surrogate marker of renal disease (albuminuria) was observed rather than hard outcome (ESRD, mortality..)

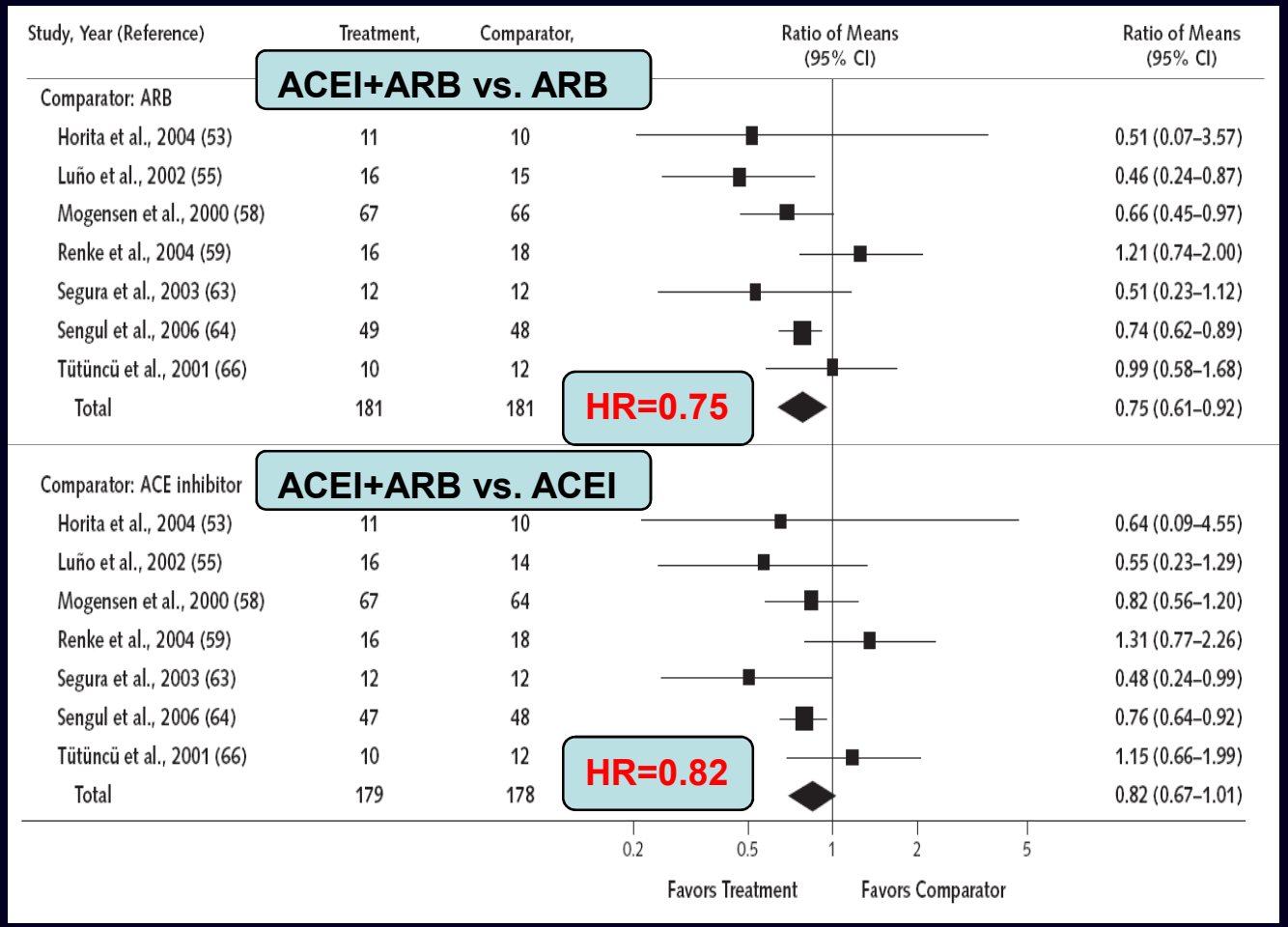
Meta-analysis: Reduction in proteinuria in renal disease at 1 to 4 months

- 49 RCTs
- 6181 subjects
- Diabetic, nondiabetic renal disease
- Microalbuminuria or proteinuria



Ann Intern Med. 2008;148:30-48.

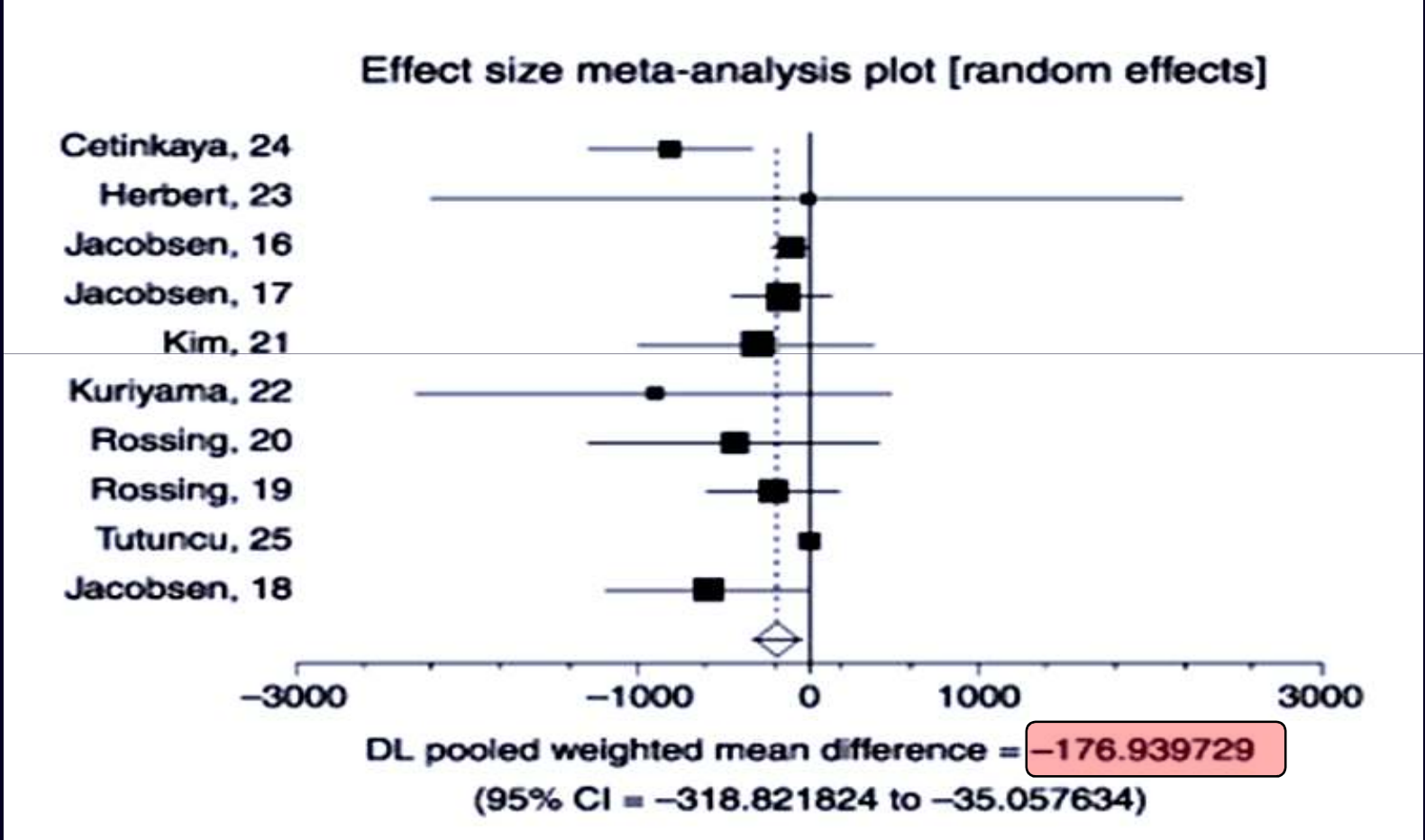
Meta-analysis: Reduction in proteinuria at 5 to 12 months



Ann Intern Med. 2008;148:30-48.

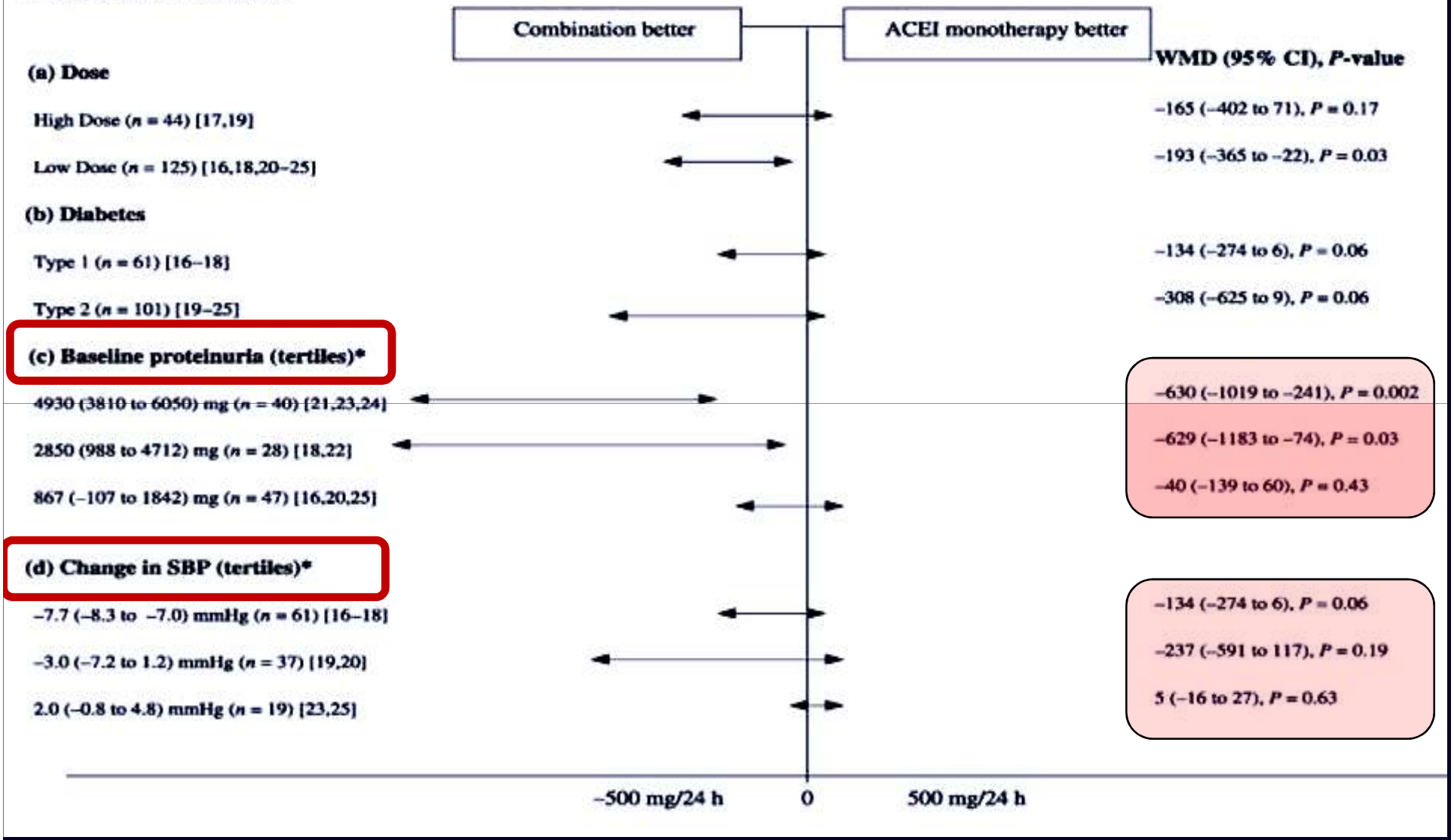
Meta-analysis of ACEI + ARB combination in DN

- 10 RCTs (N=156), microalbuminuria or proteinuria



Jennings DL, Diabetic Medicine, 2007

Subgroup analyses



ONTARGET study

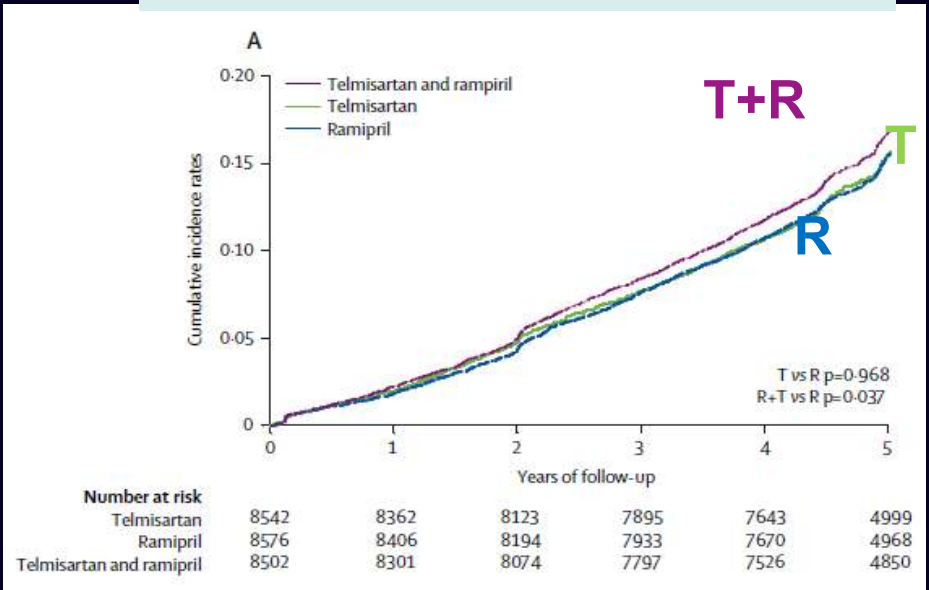
- Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial
- 25620 pts with established atherosclerotic vascular disease, including 6982 individuals with diabetes and end organ damage, to ramipril (10mg), telmisartan (80mg), or a combination of the two for median 56 months of follow-up
- Despite an additional reduction in SBP of 2-3mmHg, combination therapy showed no significant benefit on the primary outcome (death from CVD, MI, stroke, hospitalization for HF)

Baseline characteristics of the study subjects

- Mean age: 66 yr
- DM: 38%
- eGFR: 73.6 mL/min/1.73m^2
- Microalbuminuria: N=3356,13.2% of all, 30% of DM
- Proteinuria: N=1025, 4% of all, 12% of DM
- eGFR <30 mL/min/1.73m$^{2:}$ 1% of all

Low renal risk patients!

Primary renal outcome



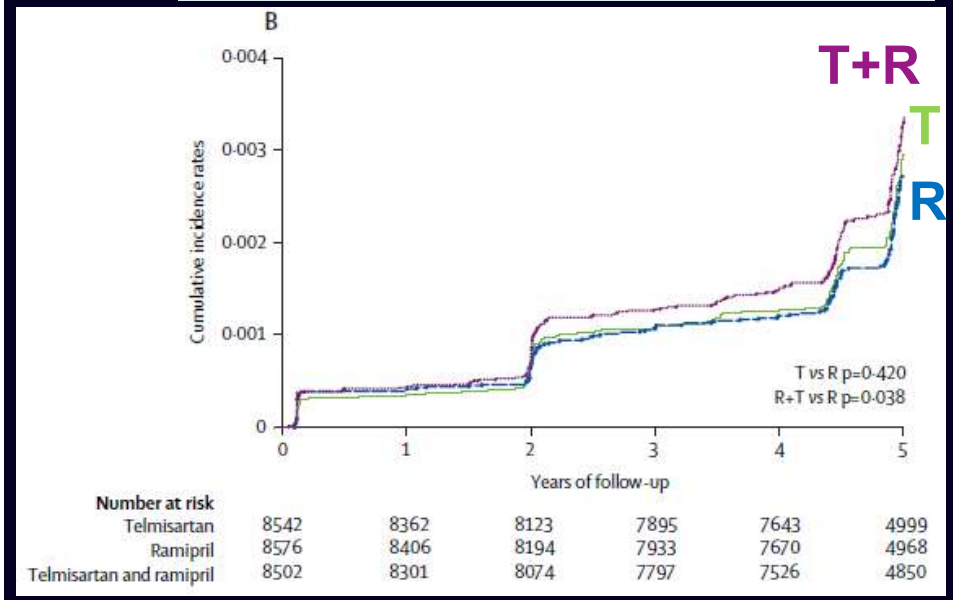
Primary renal outcome

- dialysis, doubling of serum Cr, death

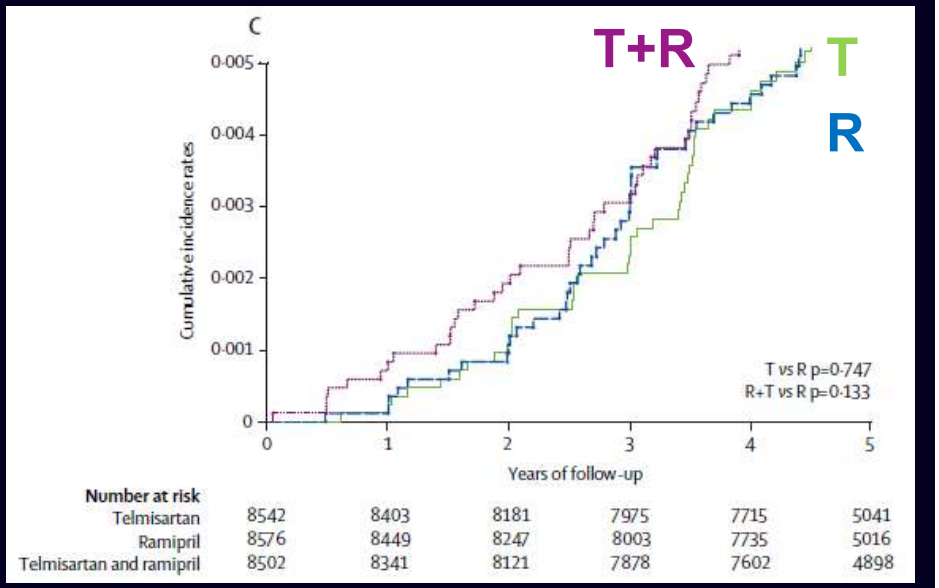
Secondary renal outcome

- dialysis, doubling of serum Cr

Secondary renal outcome



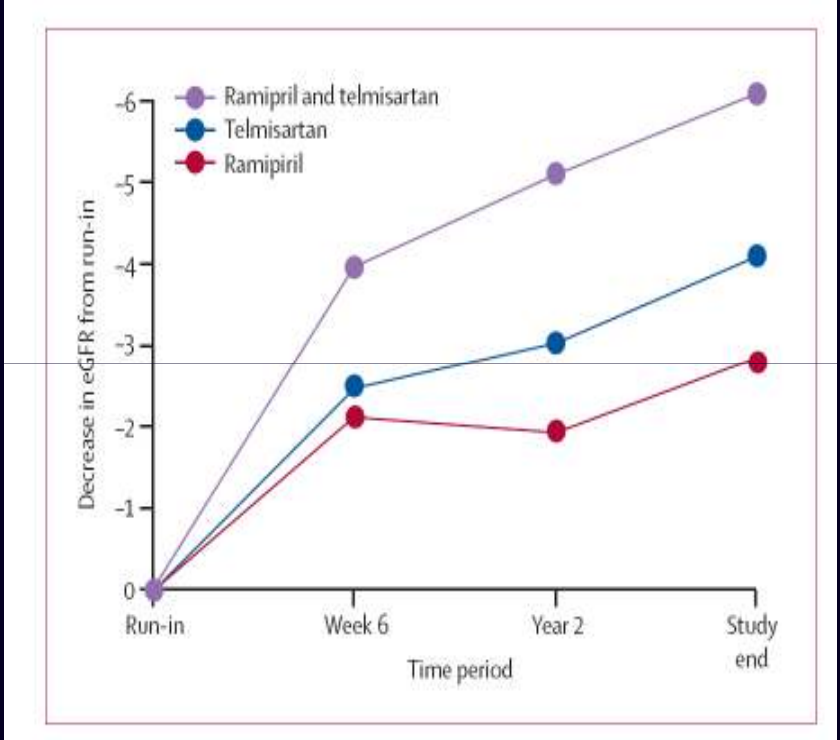
Dialysis



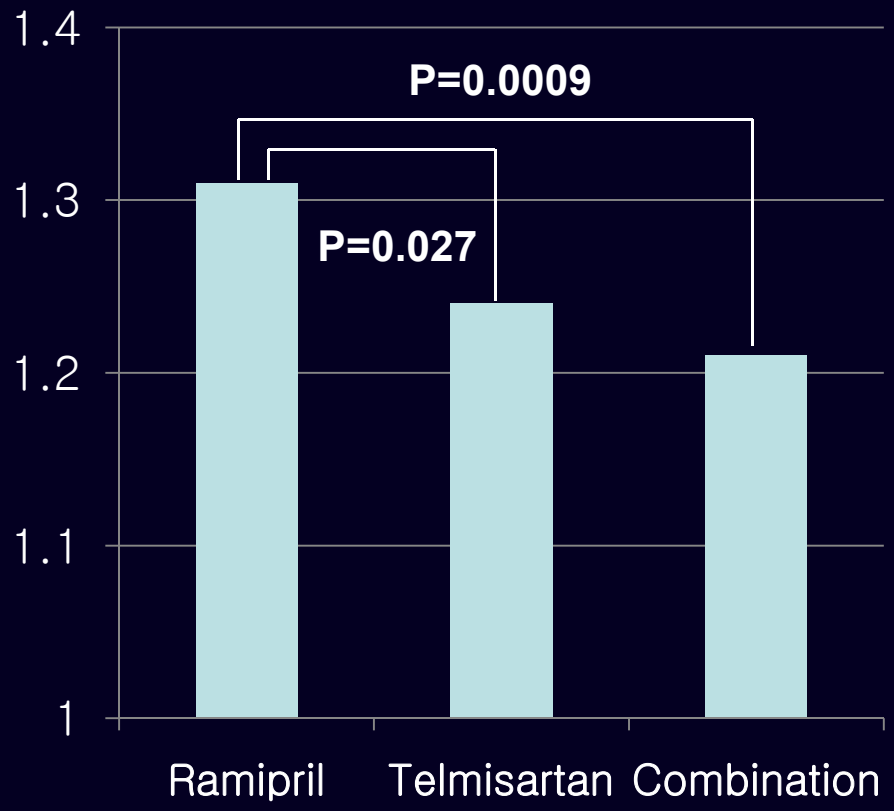
	Ramipril n (%)	Telmisartan n (%)	Ramipril+ telmisartan n (%)	Telmisartan *vs* ramipril HR (95% CI)	p	Ramipril+ telmisartan *vs* ramipril HR (95% CI)	p
All death	1014 (11·8)	989 (11·6)	1065 (12·5)	0·98 (0·90–1·07)	0·641	1·07 (0·98–1·16)	0·144
Doubling	140 (1·63)	155 (1·81)	166 (1·95)	1·11 (0·88–1·39)	0·378	1·20 (0·96–1·50)	0·110
Acute dialysis	13 (0·15)	20 (0·23)	28 (0·33)	1·55 (0·77–3·11)	0·221	2·19 (1·13–4·22)	0·020
Chronic dialysis	33 (0·39)	31 (0·36)	34 (0·40)	0·94 (0·58–1·54)	0·817	1·05 (0·65–1·69)	0·854

In macroalbuminuric diabetic patients, primary renal outcome was reduced by 8% (nonsignificant)

Decrease in eGFR



Last observation/baseline ACR ratio



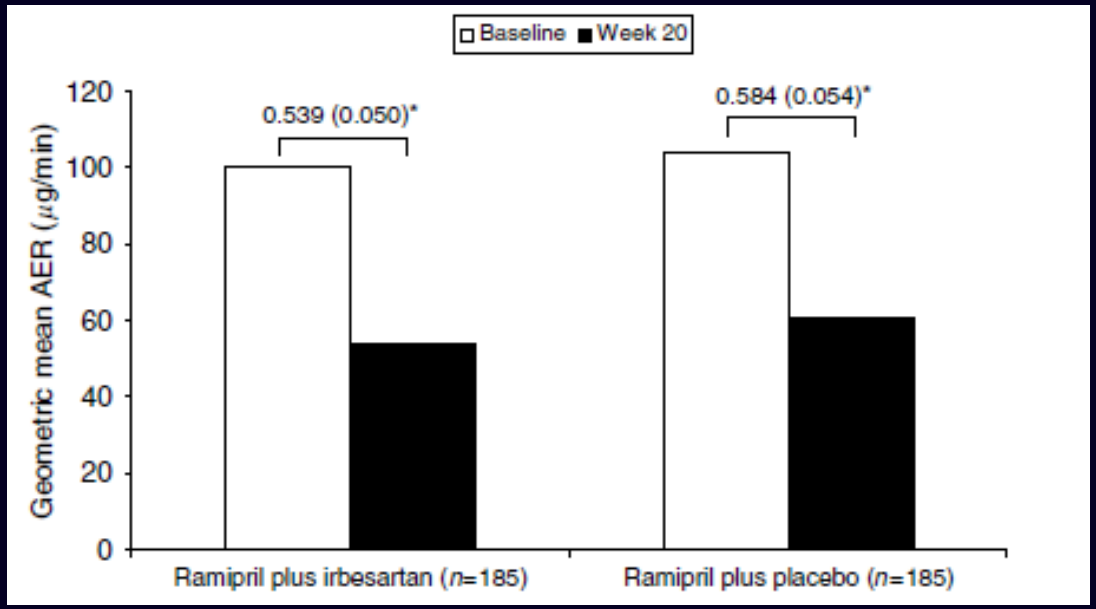
Lancet 2008; 372: 547–53

Lessons from ONTARGET study

- In patients at increased CV risk but without significant proteinuria, maximal RAAS inhibition does not improve renal and CV outcomes and is associated with an increased risk of adverse events
- Combination therapy may be effective in subgroups of participants who had macroalbuminruia at entry
- Decreasing proteinuria does not necessarily translate into improved renal outcomes

IMPROVE study

- 20-week RCT of 414 pts with hypertension and microalbuminuria
- ramipril (10mg) vs. ramipril (10mg) + irbesartan (300mg)
- BP was lower in the combination group



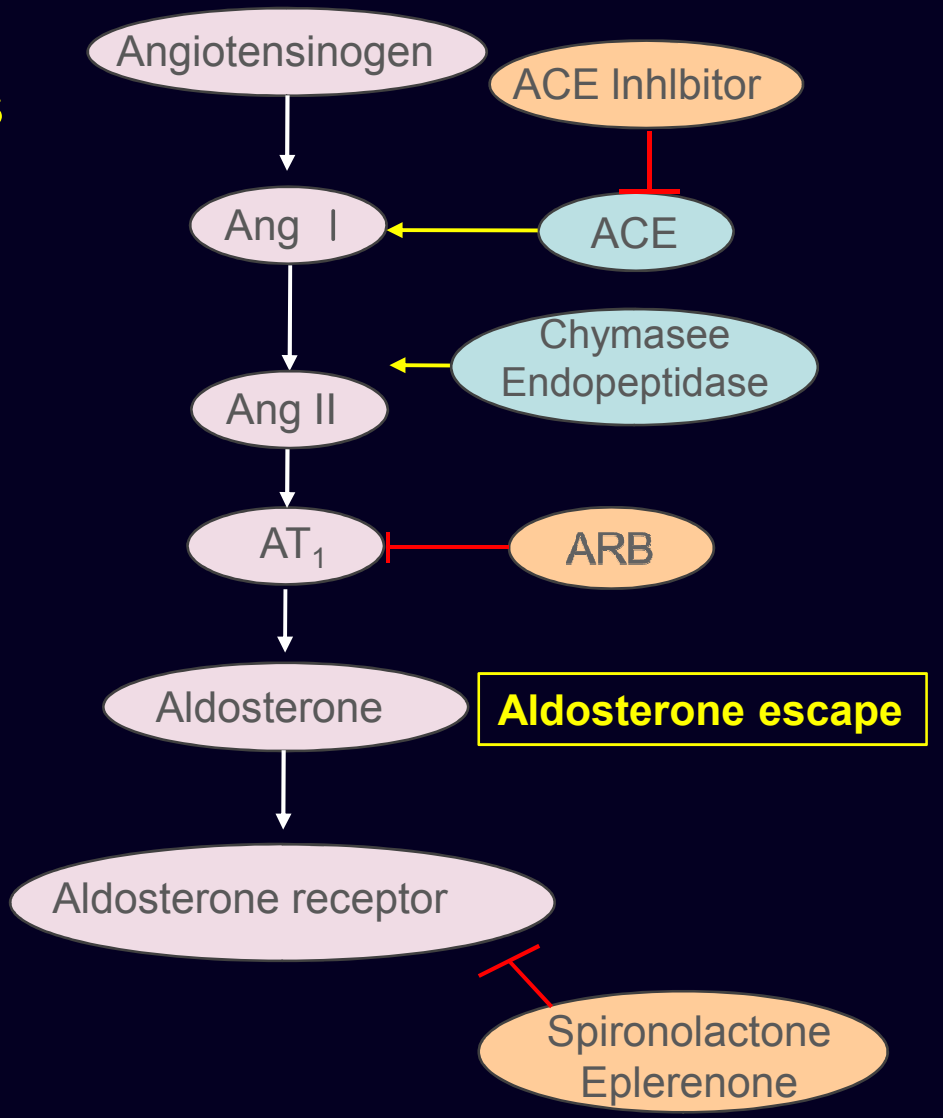
Summary of ACEI+ARB combinations

- Many small studies showed greater reductions in proteinuria and microalbuminuria with ACEI+ ARB combinations than monotherapies, although most studies used sub-maximal doses of each agent
- In larger studies, the benefit of combination on renal protection was not demonstrated.
- Combination treatment had safety and tolerability issues than monotherapy

ACEI(ARB) + aldosterone receptor antagonist combination trials

Rationale of add on aldosterone antagonism

- ACEI or ARB fail to suppress aldosterone synthesis effectively
- Aldosterone synthesis is regulated out of RAS via potassium and ACTH level
- Aldosterone escape

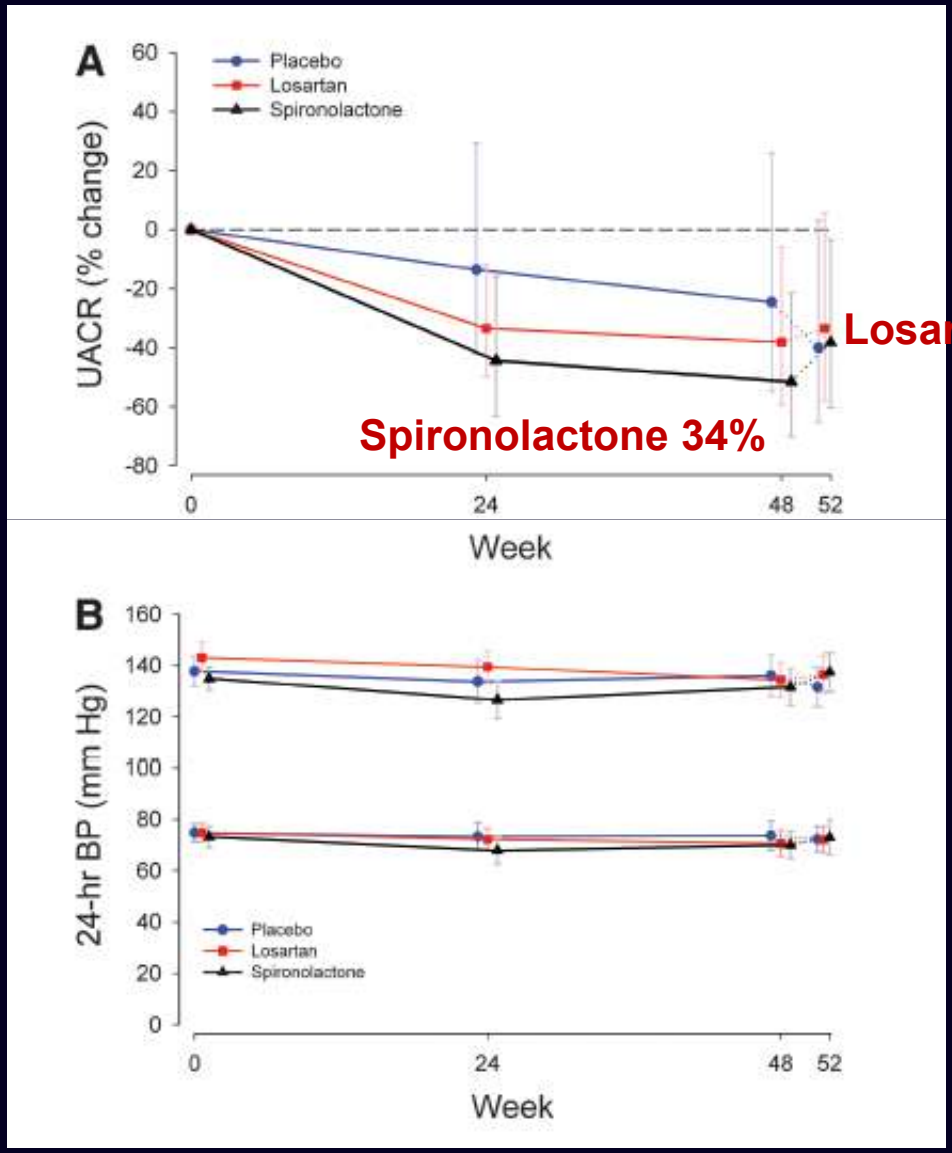


Effect of aldosterone antagonism

- 12-month randomized, double-blind trial in 81 patients with T2DM, hypertension, albuminuria (≥300mg/g)
- Baseline treatment: maximal dose of ACEI: lisinopril (80mg)
- Add on Spironolactone (25mg) vs. losartan (100mg) vs. placebo
- Maintain equal BP control among study groups

Mehdi UF, J Am Soc Nephrol 2009

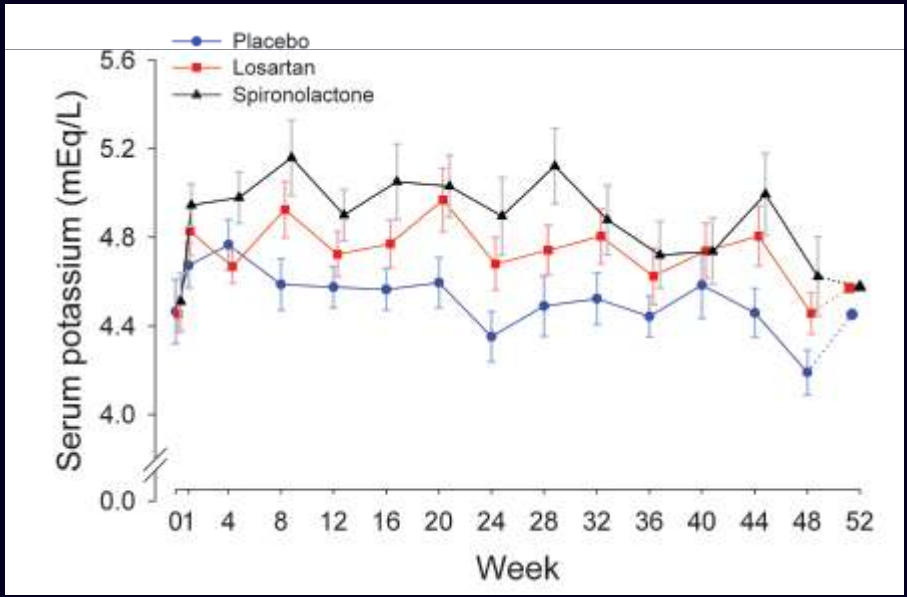
Change in urinary ACR and BP



Losartan 17%

Spironolactone 34%

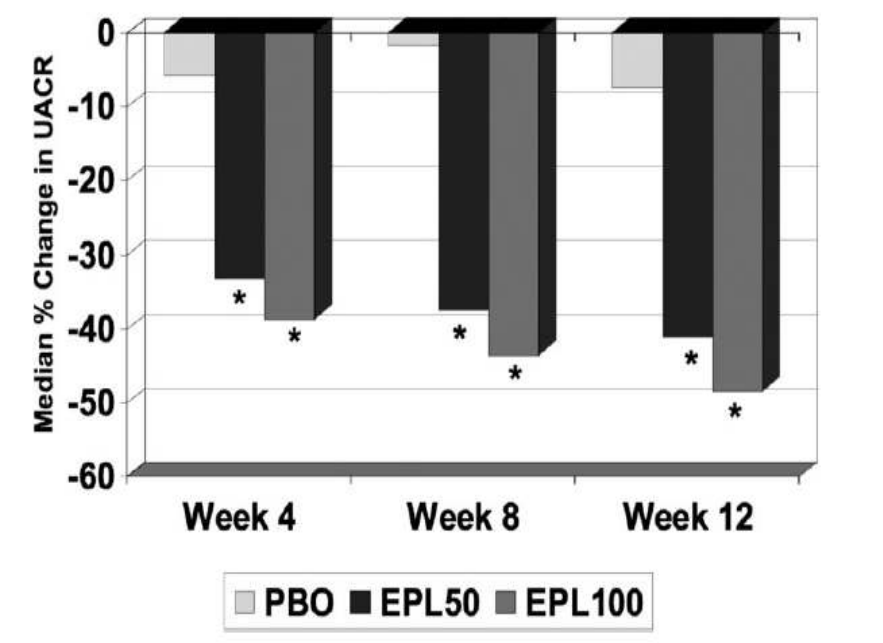
Change in serum K



Mehdi UF, J Am Soc Nephrol 2009

Effect of Eplerenone

- Eplerenone, a specific aldosterone antagonist that is devoid of non-selective mineralocorticoid effects of spironolactone
- RCT of 286 T2DM with microalbuminuria despite ACEI, add on therapy with 50mg or 100mg epelerenone



Combination of ACEI and Eplerenone 50 or 100mg Sinigificantly reduces albuminuria without significant increases in hyperkalemia

Epstein M, Clin J Am Soc Nephrol 2006

Summary of add-on aldosterone antagonism

- Several studies showed albuminuria reduction with aldosterone antagonist regardless of BP change
- Long-term renoprotective effect of epelerenone?
- Improved renal outcomes may offset adverse effects such as hyperkalemia, particularly in patients with DM and renal insufficiency?

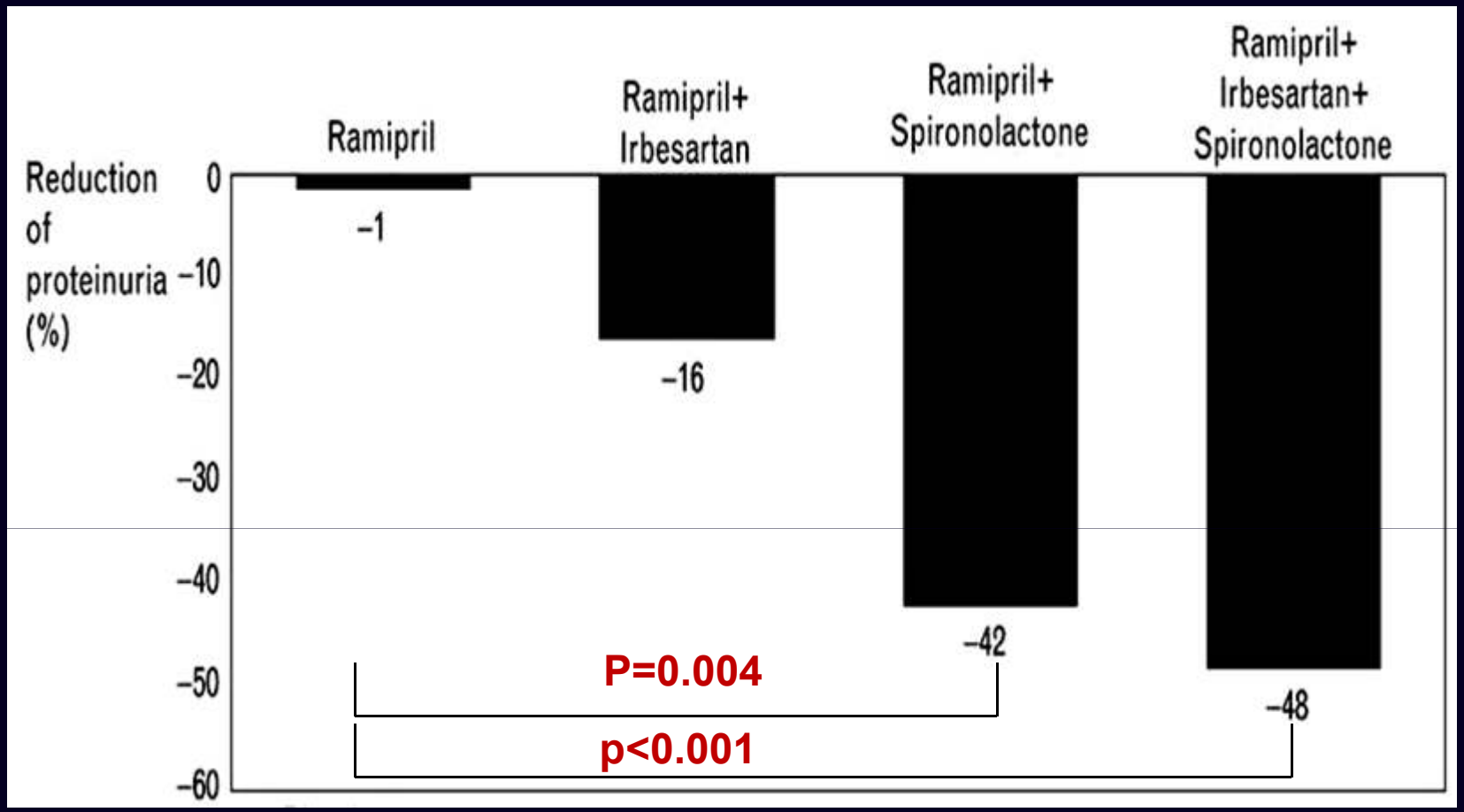
Triple blockade
: ACEI+ARB+aldosterone antagonist combination trials in nondiabetic kidney disease

Which combination is effective in reducing albuminuria in non-diabetic CKD?

- 3-month RCT of 46 patients with nondiabetic nephropathies (proteinuria >1.5g/day)

Groups	Ramipril (5mg)	Irbesartan (150mg)	Spironolactone (25mg)
1	O	placebo	placebo
2	O	O	placebo
3	O	placebo	O
4	O	O	O

Chrysostomou A, Clin J Am Soc Nephrol, 2006



- Aldosterone blockade offers a valuable adjuvant treatment with ACEI
- No advantage of triple blockade

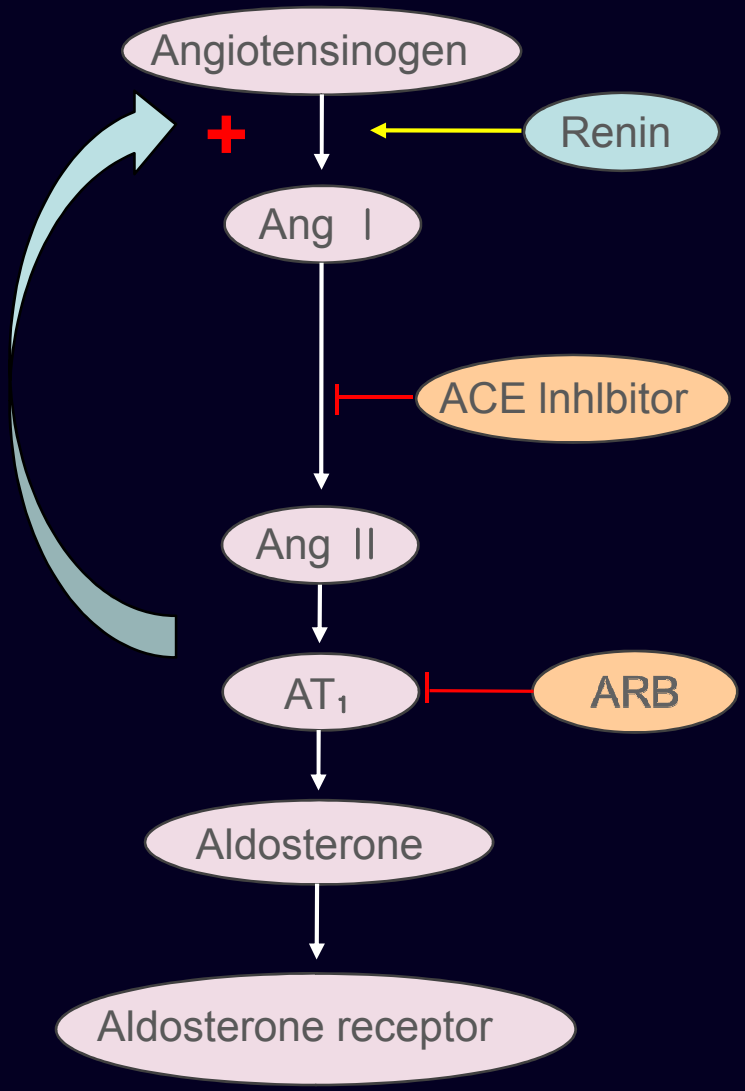
Chrysostomou A, Clin J Am Soc Nephrol, 2006

ARB+direct renin inhibitor combination trials

Direct renin inhibition

- The equivocal effects of ACEI+ARB combination therapy may be due to increased plasma renin activity (PRA) as a result of compensatory feedback mechanism

- Renin inhibitor: block initial and rate limiting step in the formation of AngI

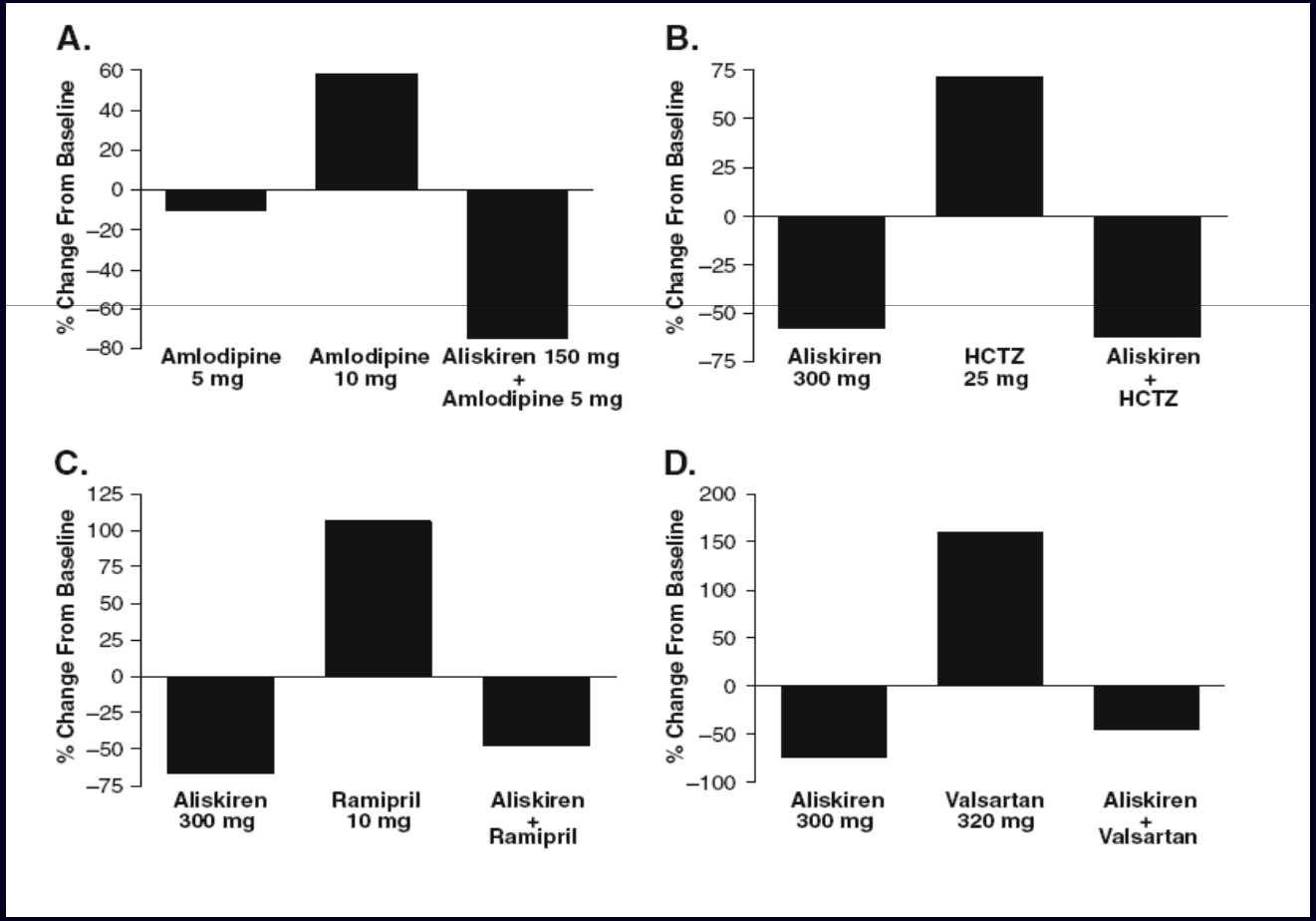


Changes of RAAS system by RAAS blockade

Class	Renin Concentration	PRA	Ang I	Ang II
ACEI	↑	↑	↑	↓
ARB	↑	↑	↑	↑
Direct renin inhibitor	↑	↓	↓	↓

Effect of aliskiren alone or in combination with other antihypertensives on PRA

Aliskiren: first FDA-approved, orally active direct renin inhibitor (DRI)



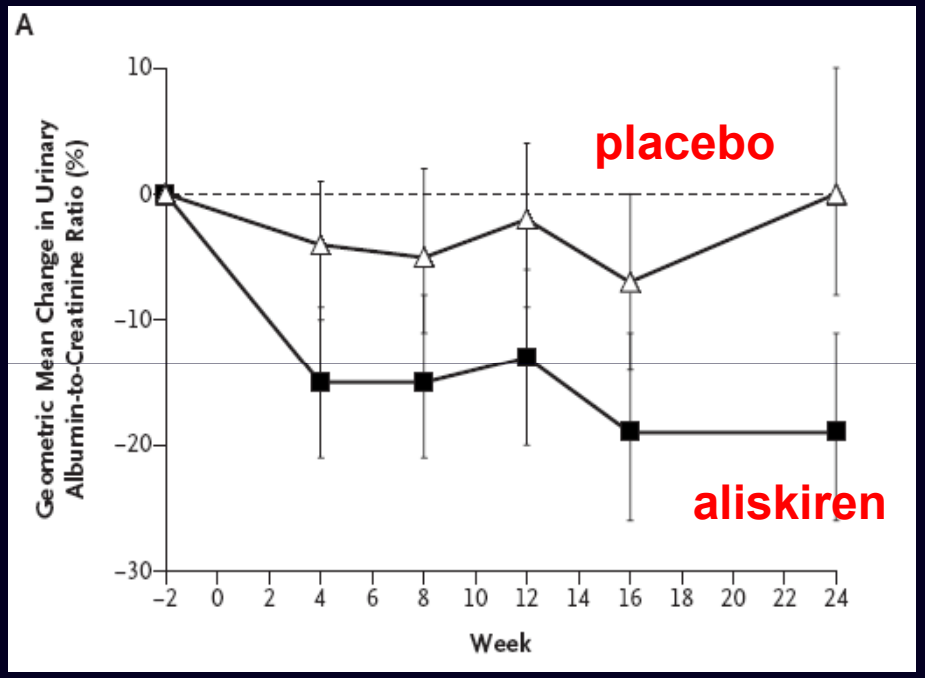
Mende W, Cardiovas Drugs Ther 2010

Aliskiren combined with losartan in T2DM and nephropathy (AVOID study)

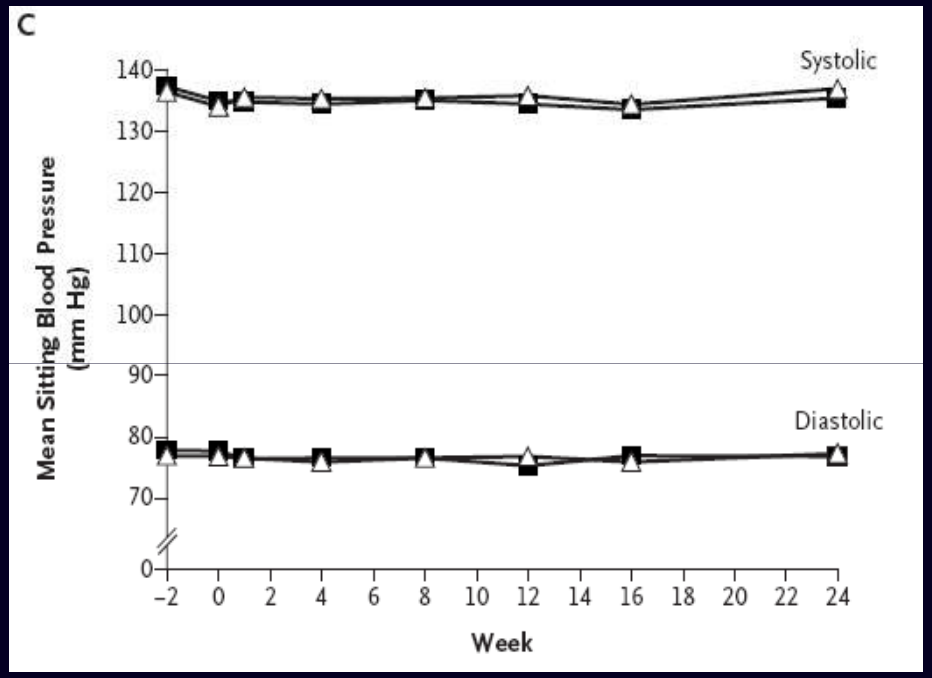
- 6-month multicenter, randomized, double-blind study in 599 pts with diabetic nephropathy
- Urinary ACR >300mg/g or >200mg/g with RAAS blockade
- Add aliskiren or placebo to patients who received 100mg of losartan
- Aliskiren (150mg*3mon -> 300mg*3mon)
- Primary outcome: reduction in the ratio of albumin to creatinine at 6 months

Parving HH, N Engl J Med 2008

Change in urinary ACR



Change in BP



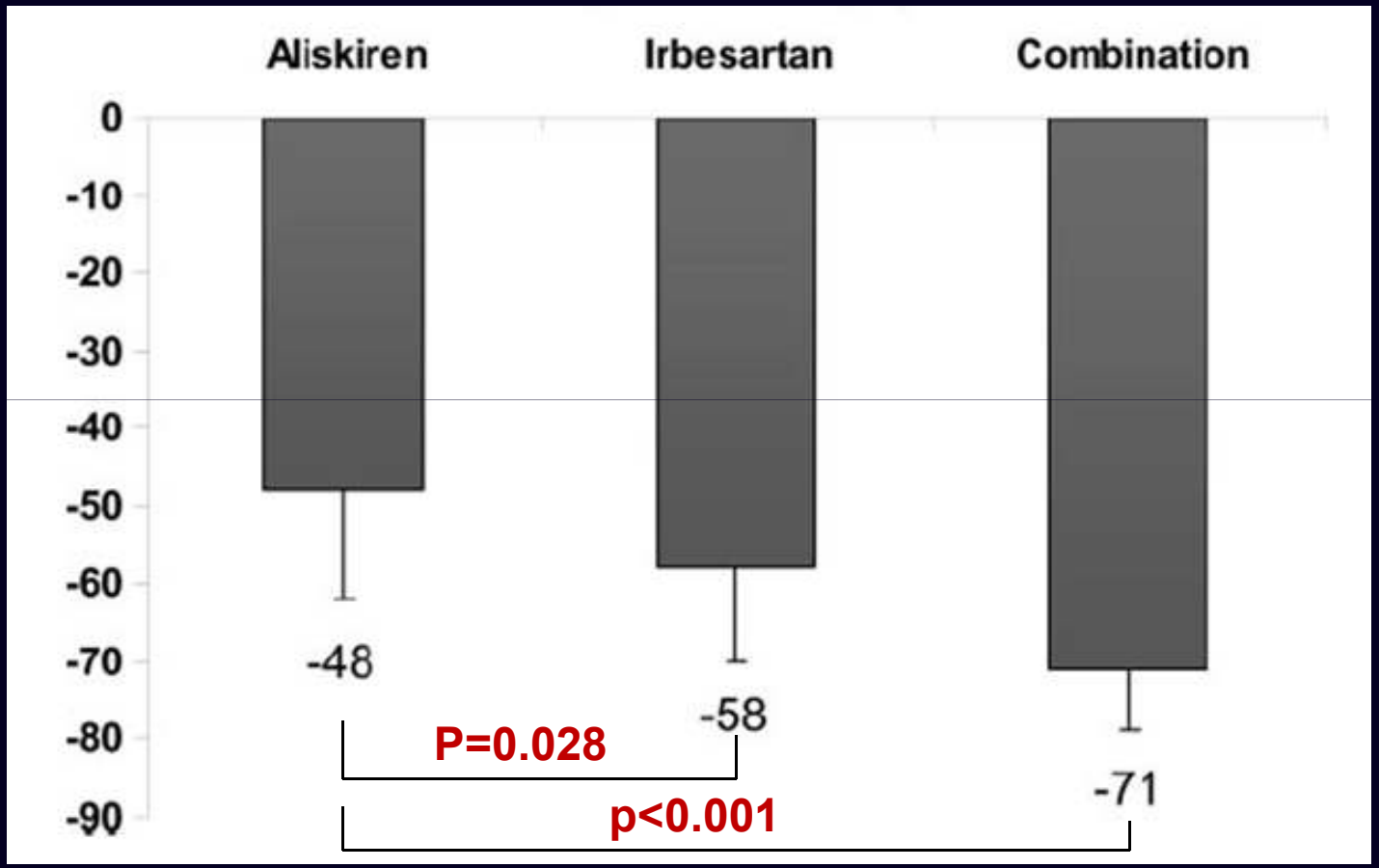
Parving HH, N Engl J Med 2008

Renal effects of aliskiren compared with and in combination with Irbesartan in T2DM

- 2-month randomized, double-blind cross-over trial in 26 pts with T2DM, hypertension, albuminuria (>100mg/day)
- Placebo, Aliskiren (300mg), irbesartan (300mg), Aliskiren+irbesartan (300mg each)
- Primary outcome: change in albuminuria
- Secondary outcome: 24-h BP, GFR

Persson F, Dibetes Care 2009

Changes in urinary albumin excretion rate (%)



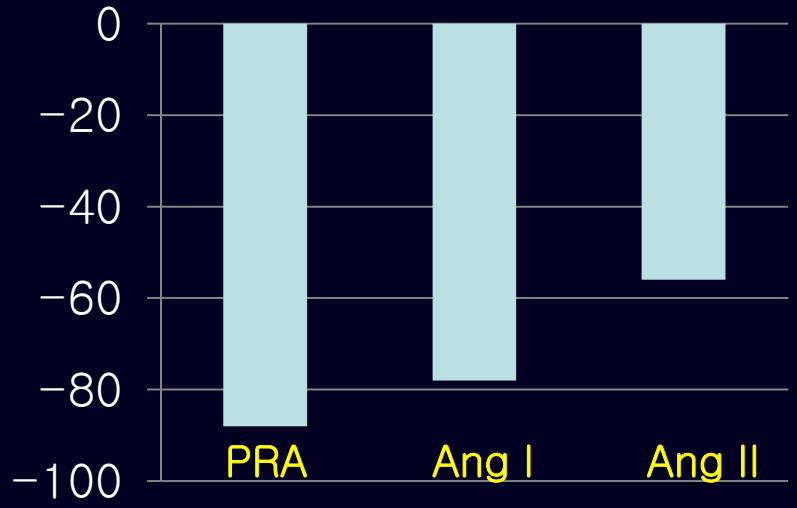
Persson F, Dibetes Care 2009

Changes in GFR and RAAS

- 24-h BP: reduced 3/4mmHg by aliskiren, 12/5 by irbesartan, 10/6 by combination
- Plasma renin concentration increased 11fold in the combination group: more effective blockade of RAAS

Change of GFR

Change of RAAS in combination group



Persson F, Dibetes Care 2009

Safety and tolerability of ACEI+aliskiren or ARB+aliskiren combinations

- In a pooled analysis of data from over 7000 patients with hypertension treated with aliskiren for 6 to 8 weeks, overall incidence of adverse events was similar to placebo (39.8 vs. 40.2%)
- Incidence of hyperkalmeia was similar to placebo (1 vs. 0.6%)
- Hyperkalemia was higher in those receiving aliskiren/ramipril compared with ramipril alone (5.5 vs. 2.6%)

Summary of ARB+aliskiren trials

- Aliskiren apprears to have a renoprotective effect by more complete inhibition of RAAS

- Long-term outcome trial of aliskiren
  : The Aliskiren Trial In Type 2 diabetes Using Cardio-renal Disease Endpoints (ALTITUDE) study

- To determine whether the addition of aliskiren once daily for 4 years to therapy with ACEI or ARBs reduces renal and CV events in 8600 T2DM pts and microalbuminuria, macroalbuminuria and CVD

Conclusion

- Is there evidence that BP independent effect of RAAS combination therapy?

  -- May be yes

- What do important studies suggest to us including ONTARGET study?

  -- Individualize treatment modality by patients characteristics

- Can we select the subgroup who will be benefitted by the combination therapy?

  -- Overt protenuria despite the use of maximal recommended dosage of ACEI or ARB may be beneficial from their combination therapy

Conclusion

- What is the ideal dual blockade therapy?

-- ACEI(ARB) + aldosterone antagonist, especially ACEI(ARB) + DRI may be better options because of more complete blocking RAAS.

Whether these new regimens confer better outcomes await the result from ongoing clinical trials.

Thank you for your attention!