RAS and diabetic nephropathy

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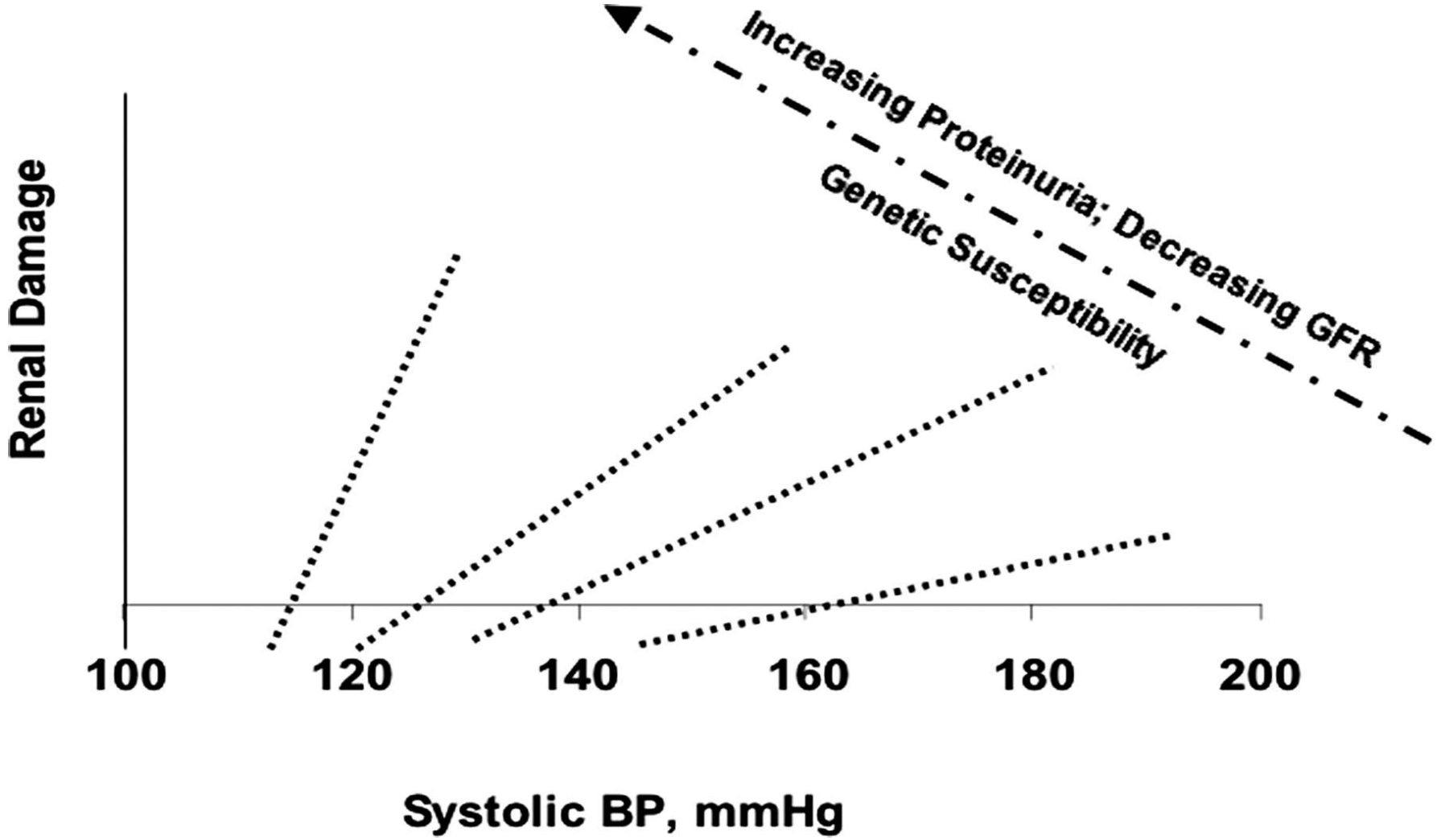
Debate and Issue of current status about RAS blockade in patients with diabetic nephropathy

- The more , the better in CKD patients ?
- What do important studies suggest to us including On-Target Study ?
- What is the ideal dual blockade therapy in CKD ?

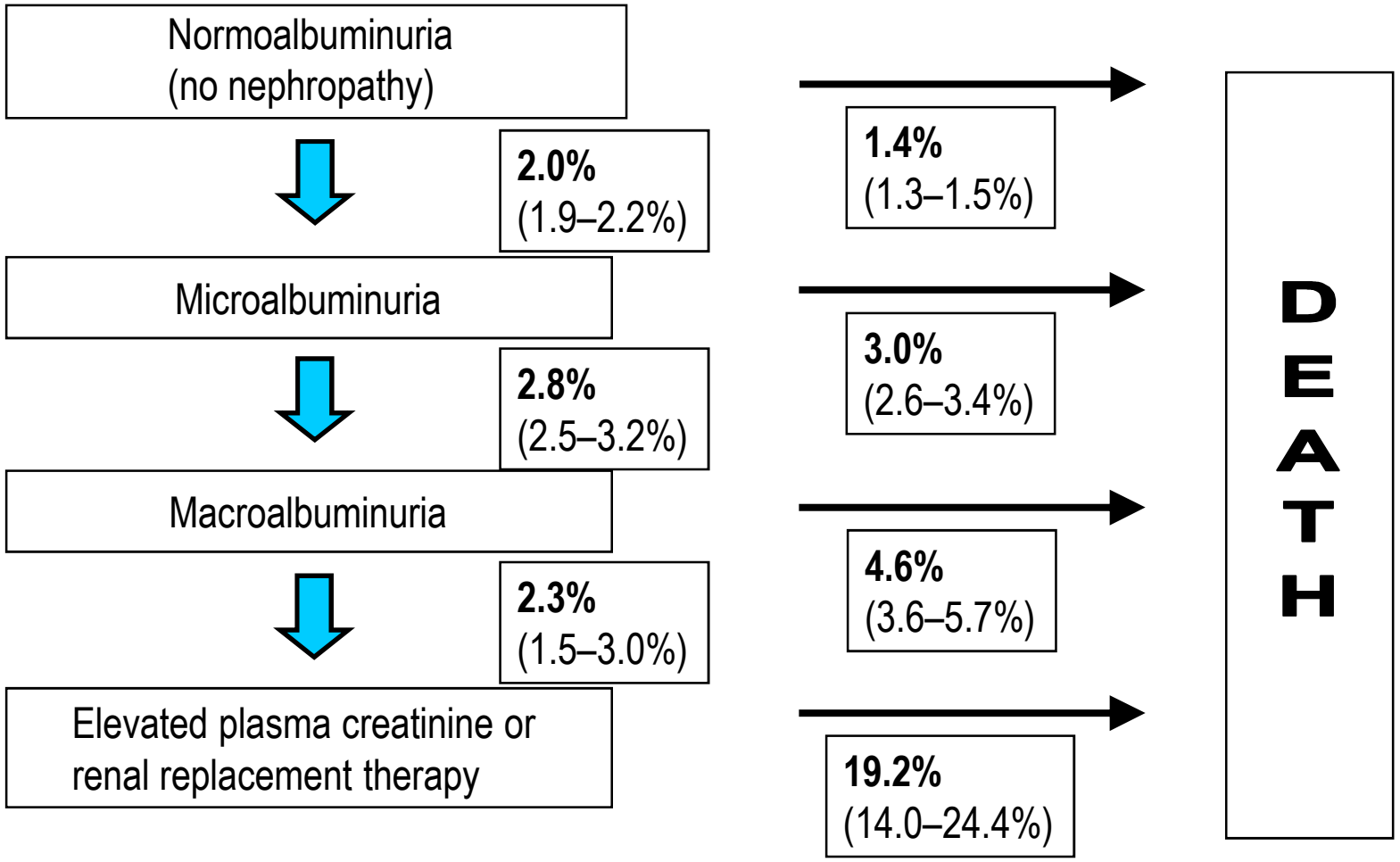
  AECI+ARB vs. ACEI(ARB)+aldosterone inhibitor vs. AECI(ARB)+DRI
- What is the role of triple blockade ?
- Can we select the subgroup which expect the ideal combination?
- Do we have the ideal primary outcome study ?
- Is there any difference between diabetic and non-diabetic patients ?
- Is there any difference based on the stage of diabetic nephropathy ?

Potential difference in susceptibility to hypertensive renal damage



(Clin J Am Soc Nephrol, 2006)

Annual transition rates through stages of diabetic nephropathy



(Kidney Int. 2003; 63: 225–2)

Interpretation of albuminuria results

DKD is often present if:

- Macroalbuminuria
- Microalbuminuria

  Presence of retinopathy

  in type 1 diabetes, duration at least 10years

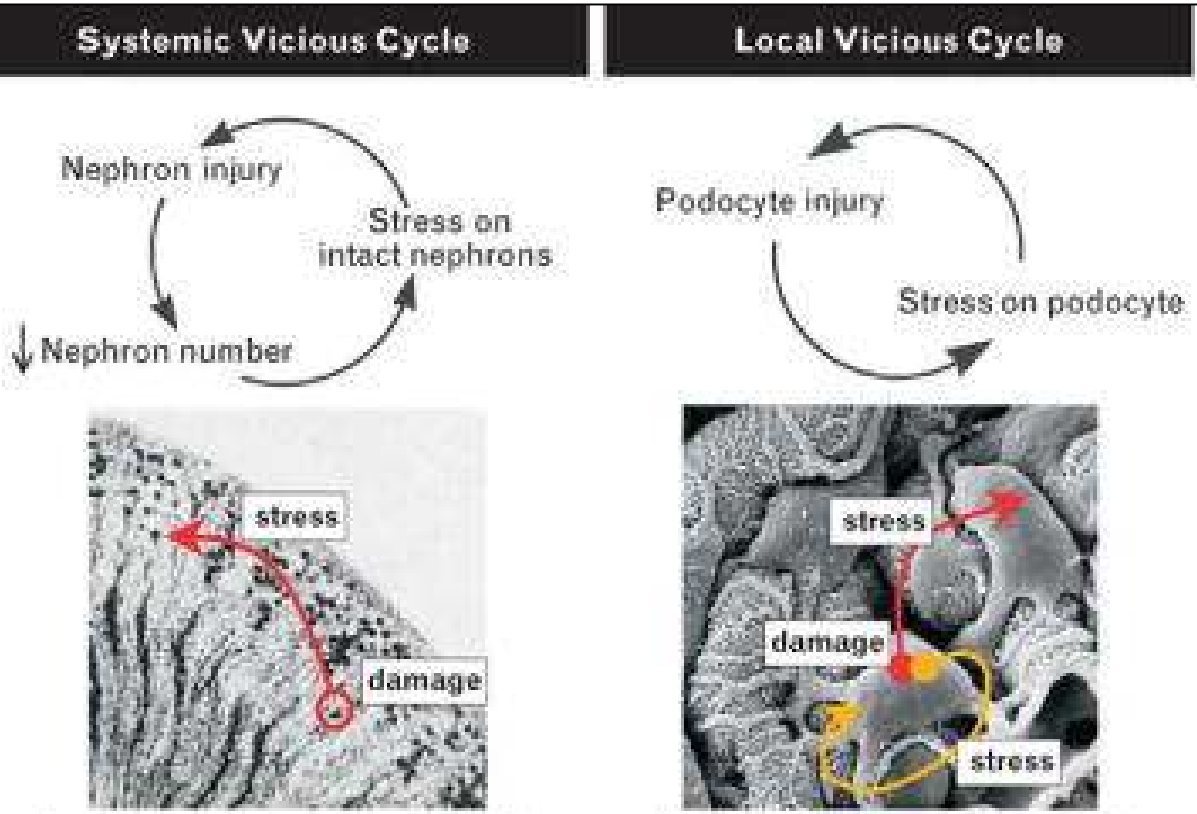
DKD may not be present if:

- Absence of diabetic retinopathy
- Rapid decline in GFR (1>ml/min per month)
- Sudden onset of nephrotic syndrome
- Refractory hypertension
- Active urinary sediment (hematuria)
- Signs or symptoms of systemic disease
- >30% reduction in GFR after starting RAS blockade

Marker of progression of diabetic nephropathy

Method	Advantage	Disadvantage	Comments
AER (immunoassay)	• Sensitive	• Not specific for CKD	Initial response to antihypertensive treatment predicts long-term GFR progression in late nephropathy
	• Specific for albumin	• High intra-individual variability	
ACR (immunoassay)	Does not require timed collection	Needs gender specific reference range	Suitable for screening and assessing progression in same individual
HPLC	Similar sensitivity to immunoassay	Not specific for albumin	Overestimates normal range historically based on immunoassay
Proteomics	Documents full nephropathy phenotype	Complex to perform and interpret	Potential to assess progression
CTGF, TGF-β	More specific for CKD than AER	Expensive	Potential to assess progression

The systemic and local vicious cycles during progression of glomerular sclerosis: Urinary podocyte marker ?



late stage	When	*early-late stages*
distant glomerulus	Where	*inside glomerulus*
glomerulus to glomerulus	How	*podocyte to podocyte*

Whereas the classic vicious cycle is a phenomenon relevant only at late stages, the newly proposed vicious cycle operates from early stages of glomerular sclerosis. Whereas the classic theory explains the spread of lesion from glomerulus to distant glomerulus, the new theory explains podocyte to podocyte spread within the glomerulus. Thus, the classic vicious cycle is a systemic phenomenon, and contrastingly, the new vicious cycle is a local phenomenon.

Table 3. Presence of Microalbuminuria and Macroalbuminuria and Retinopathy in Subjects With Type 2 Diabetes Mellitus With Chronic Renal Insufficiency*

	Subjects With Type 2 Diabetes Mellitus, % (95% Confidence Interval)†	Population Estimate in Millions (95% Confidence Interval)
Microalbuminuria (sampled n = 64)	45 (31-59)	0.6 (0.3-0.7)
Macroalbuminuria (sampled n = 47)	19 (10-28)	0.2 (0.1-0.3)
Retinopathy (sampled n = 58)	28 (21-36)	0.3 (0.2-0.4)
No retinopathy or albuminuria (sampled n = 51)‡	30 (21-39)	0.3 (0.2-0.4)

*Includes angiotensin-converting enzyme users. Chronic renal insufficiency defined as glomerular filtration rate less than 60 mL/min per 1.73 m^2 body surface area calculated with the Modification of Diet in Renal Disease Study formula.[19]

†Newly diagnosed type 2 diabetes mellitus defined by American Diabetes Association criteria.[13] Percentages are based on weighted data.

‡Albuminuria includes microalbuminuria or macroalbuminuria.

(JAMA, 2003)

The role of AER/GFR relationships in assessment of progression of diabetic nephropathy

❖ In the pooled analysis of studies in type 1 diabetes, there was a similar correlation between initial change in AER and overall rate of change in GFR in late nephropathy but no significant relationship in early nephropathy.

❖ In type 2 diabetes there was also a significant correlation in late nephropathy, but no significant relationship was again demonstrated in studies of early nephropathy.

❖ This pooled analysis indicates that initial changes in AER during antihypertensive therapy at CKD stages 1 and 2 do not predict long-term changes in GFR on an intention to treat basis.

❖ This suggests that measurement of changes in GFR at CKD stages 1 and 2 may be of equal or greater clinical importance than measurement of changes in AER

Estimates of GFR as markers of progression of nephropathy

Method	Advantage	Disadvantage	Comments
Creatinine clearance	24-h urinary creatinine excretion allows check on completeness of urinary collection	Underestimates hyperfiltration, overestimates GFR at CKD stages 3 and 4 • Time consuming and training required for patients to perform accurate urine collections	Underestimates GFR progression
Cockcroft-Gault	Requires weight for calculating eGFR	Underestimates GFR at CKD stages 1 and 2	Underestimates GFR progression at CKD stages 1 and 2
MDRD-4	• Suitable for automated reporting • Accurate at CKD stages 3 and 4	• Influenced by body weight, muscle mass • Underestimates GFR at CKD stages 1 and 2	Underestimates GFR progression at CKD stages 1 and 2
Cystatin C	• Independent of weight or muscle mass	• More expensive than creatinine • False low GFR with inflammation, steroid therapy, hyperthyroidism	Accurate marker of GFR progression at CKD stages 1 and 2

Treatment guidelines for patients with hypertension, diabetes and nephropathy

- Annually check for proteinuria, albuminuria, serum creatinine and calculate the estimated glomerular filtration rate (eGFR)[1,2]
- In patients with proteinuria, albuminuria or reduced eGFR:
  - **use angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) titrated to the maximum tolerated dose[1,2]**
  - **intensify management of blood pressure (BP) to achieve target of <130/80 mmHg[1,2]**
  - monitor progression of nephropathy[1,2]
  - advise limiting protein intake to 0.8 g/kg daily in patients with proteinuria[1]
  - intensify other renal and cardiovascular protection measures (e.g. smoking cessation, aspirin therapy and lipid-lowering therapy)[1]

(1. IDF 2005; 2. ADA 2006)

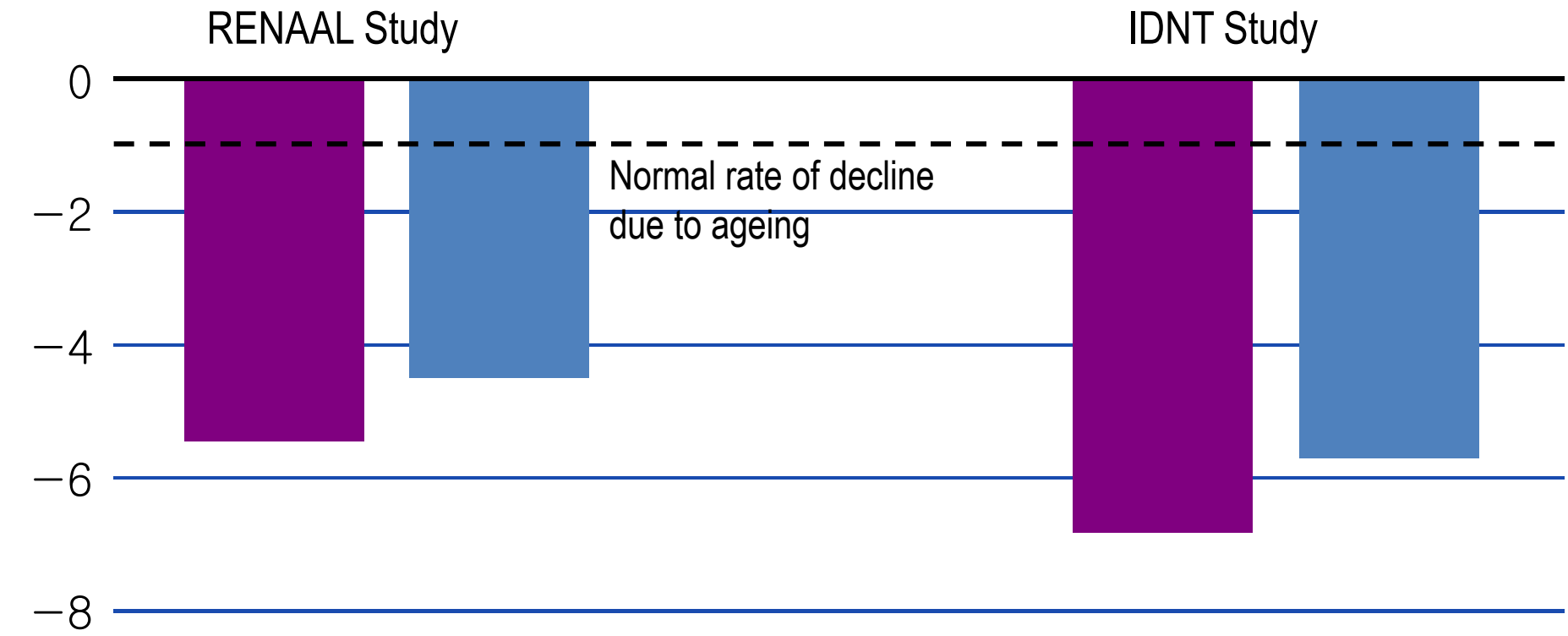
Evidence for use of antihypertensive agents (UKPDS data)

- Intensive control of BP using a target BP <150/85 mmHg in patients with diabetes significantly reduced* the risk of:
  - all diabetes complications by 24%
  - diabetes-related deaths by 32%
  - stroke by 44%
  - heart failure by 56%
  - microvascular complications by 37%

- **Agents targeting the Renin System may offer additional renal protection beyond BP-lowering efficacy**
  - **the ARBs irbesartan and losartan are approved for the treatment of nephropathy in patients with Type 2 diabetes and hypertension**

*Compared with less intensive control (target BP <180/105 mmHg)

Existing antihypertensives have limitations: Despite treatment with ARBs, the rate of decline in renal function is still higher than expected due to ageing



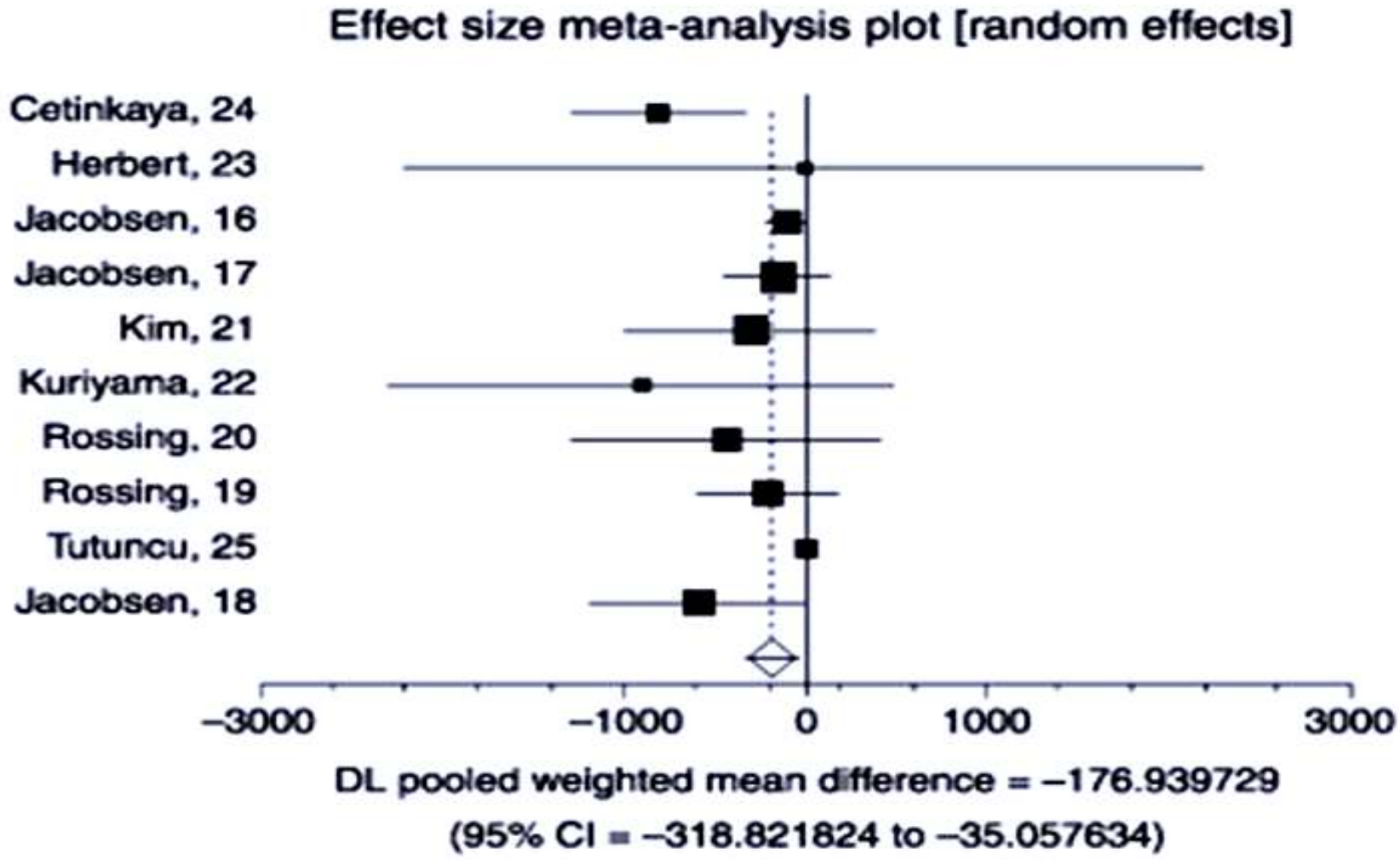
(Weber & Giles, Rev. Card. Vasc. Med. 2006)

Rationale for a combination therapy with ACEI+ARB

- Beneficial aspect
  - Non-classical pathway produced Ang II is blocked by ARB
  - ACEI additionally increase kinins
  - Synergistically increase Ang I : vasodilator

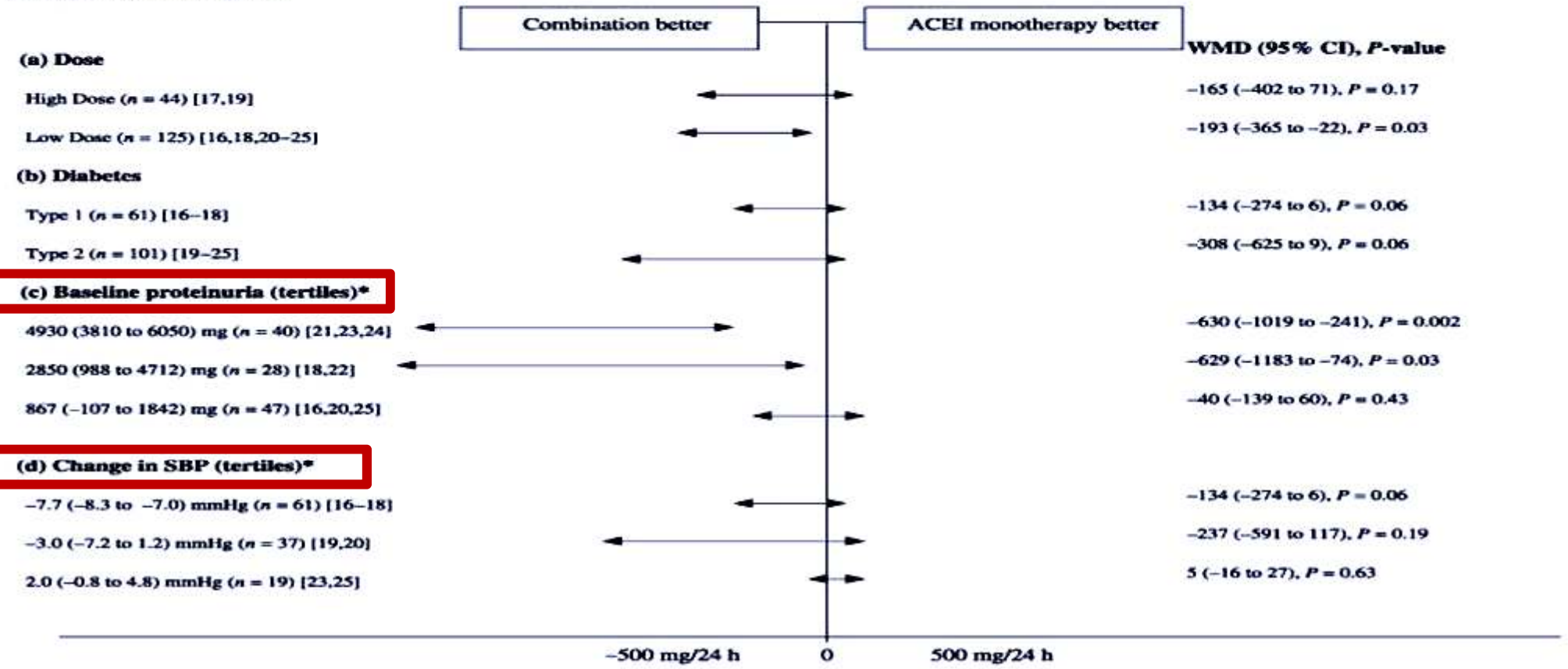
- Detrimental aspect
  - Role of AT2 stimulation by ARB is blocked by ACEI
  - Simply provide higher degree of blockade of RAS
  - Rare fatal complication of combinations

Efficacy of ACEi and ARB combination

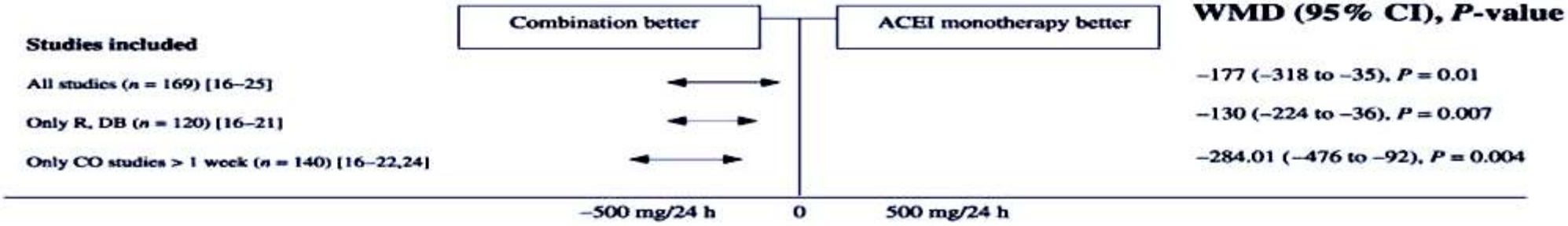


(Diabetic Med, 2007)

Subgroup analyses



Sensitivity analyses

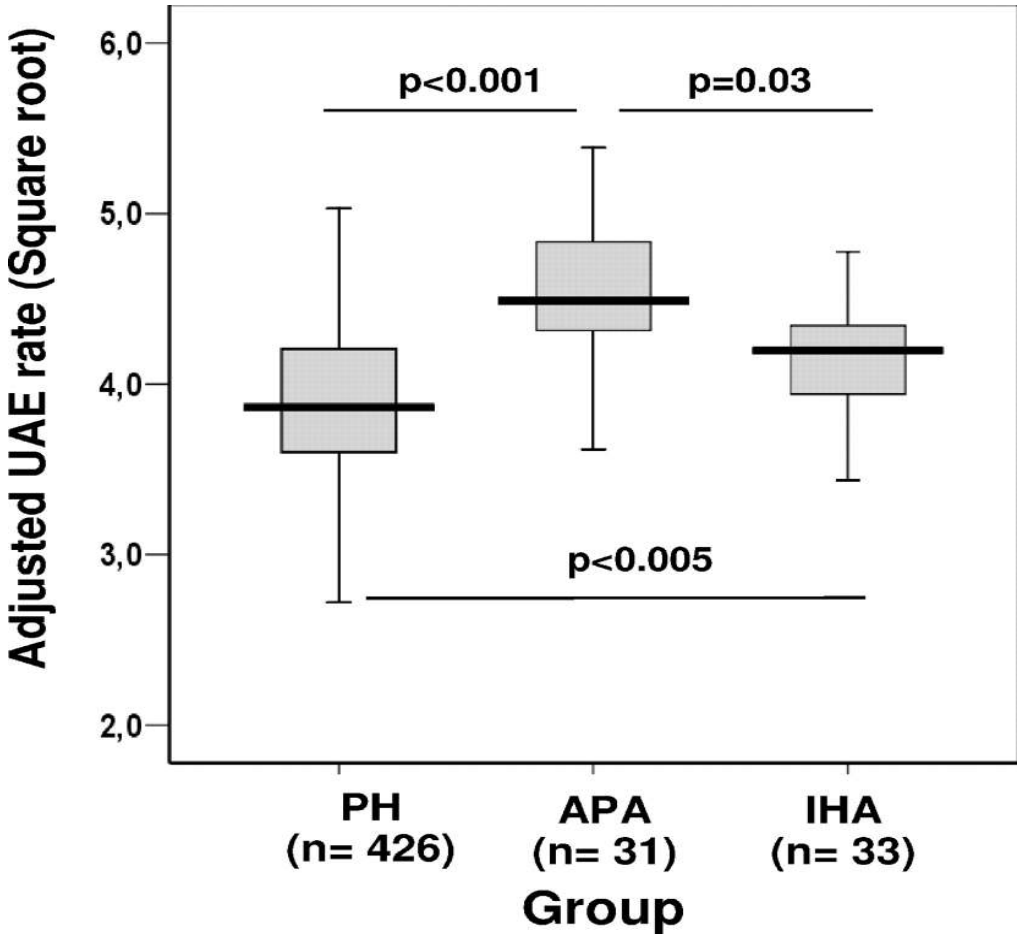


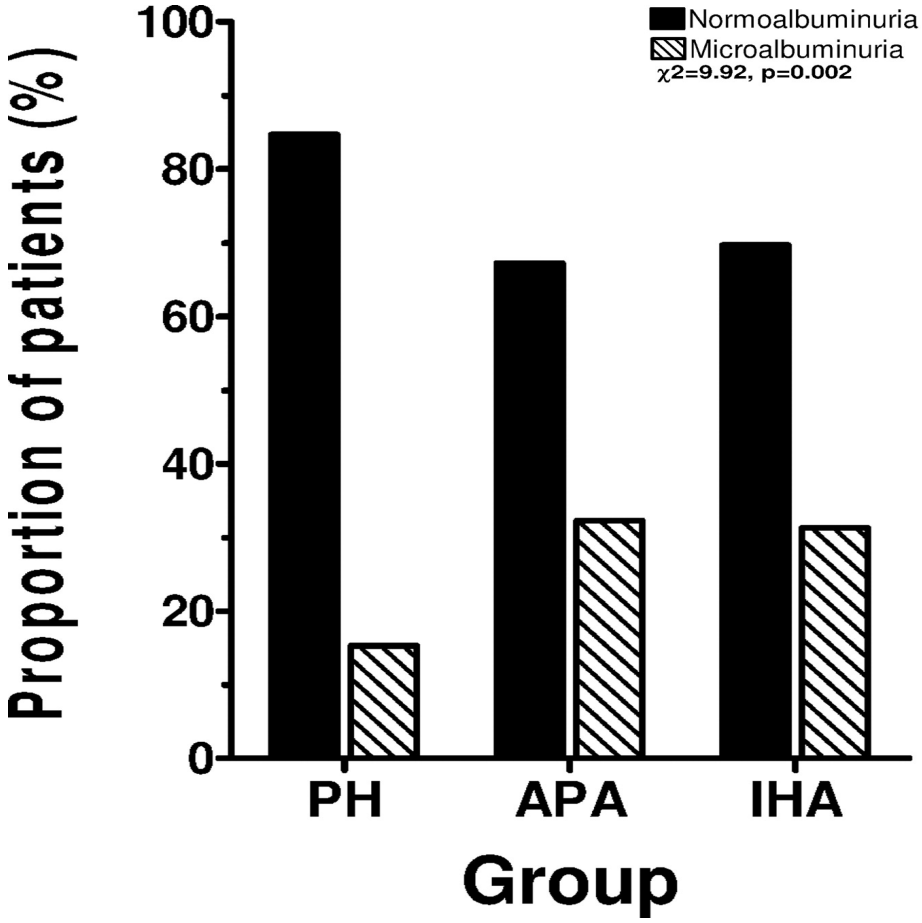
Emerging new agents in diabetic nephropathy

- PPAR agonist
- Aldosterone antagonist
- PKC beta specific inhibitor (Ruboxistaurin)
- Pentoxifylline
- Sulodexide
- ACE2 activator
- DRI (direct renin inhibitor)
- Vitamin D analogue

Role of aldosterone and its inhibition in the progression of diabetic nephropathy

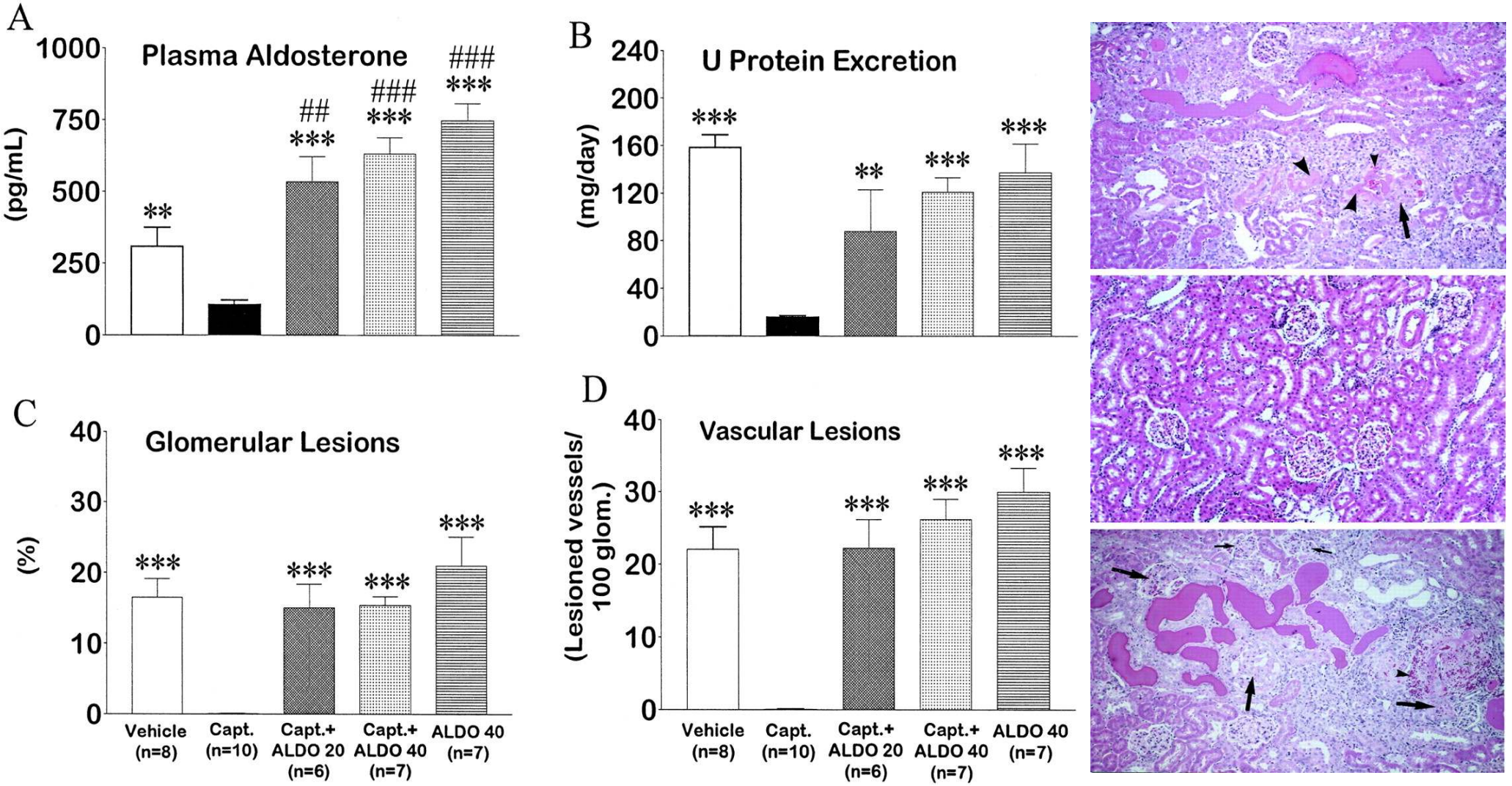
PAPY study : Primary Aldosteronism Prevalence in Italy





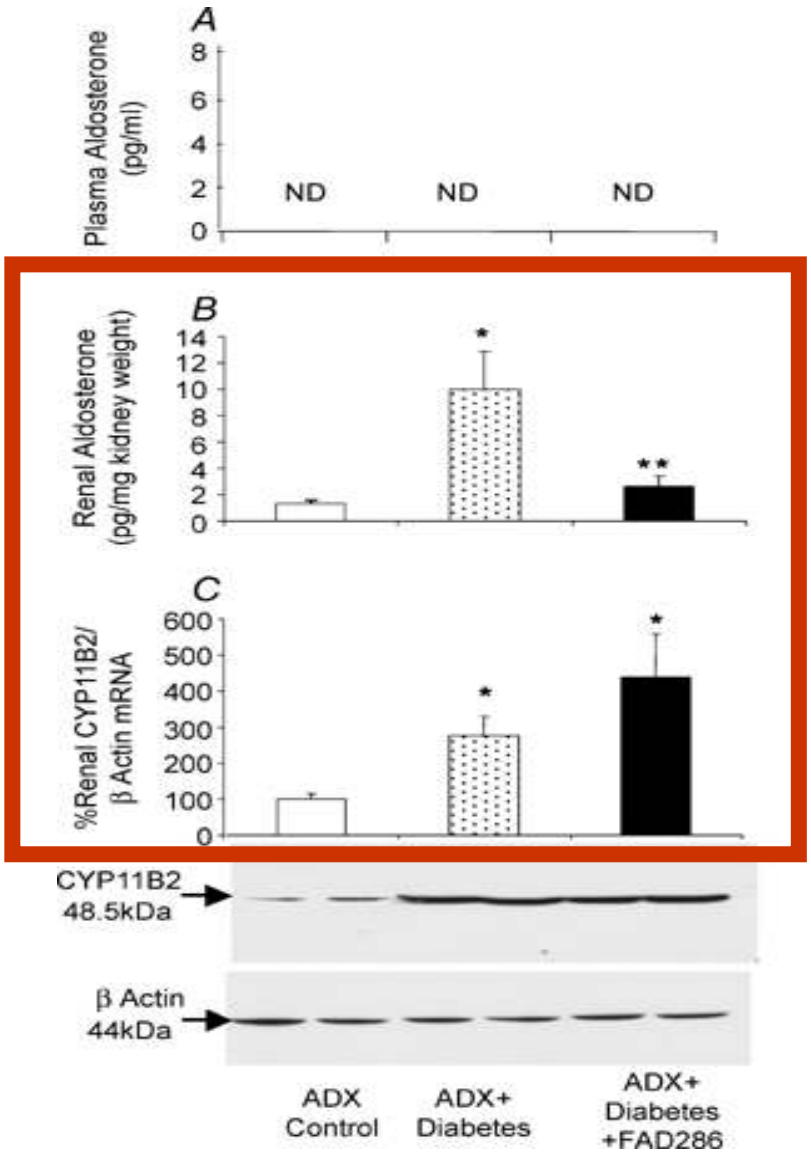
(Hypertension, 2006)

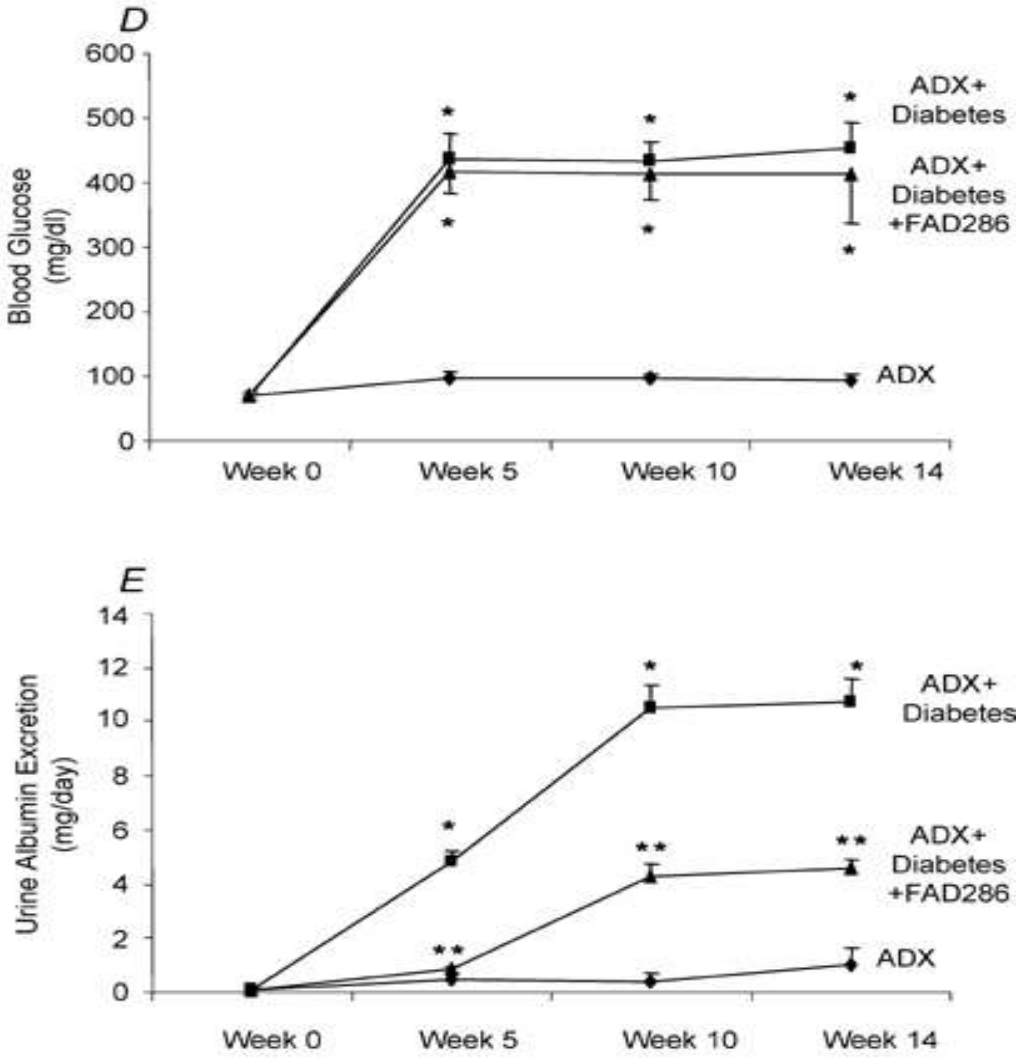
Effect of aldosterone on renal function in SHRSP rats



(Hypertension, 1999)

Renal aldosterone synthesis is increased in diabetic kidney





(Exp Physiol, 2008)

GFR decline rate : aldosterone escaper 5ml/min/yr vs. non-escaper 2.4ml/min/yr
Correlation : plasma aldosterone level and decline in GFR (r^2=0.19, p<0.001)
Two fold increase in aldosterone level – decrease in GFR 1.5ml/min/yr

	Escape group (*n*=26)			Non-escape group (*n*=37)		
	Baseline	2 months	End of study[b]	Baseline	2 months	End of study[b]
P-aldosterone[a] (pg/ml)	88 (62–125)	57[c] (43–76)	102[d] (78–134)	70 (54–92)	83[e] (69–102)	49[c, d] (40–60)
P-renin[a] (μU/ml)	29 (20–40)	52[f] (36–75)	137[f, g] (92–204)	48[e] (33–69)	64[f] (47–86)	112[f, g] (78–161)
P-angiotensin II[a,h] (pmol/l)	10 (6–16)	16[f] (8–31)	35[f, g] (20–63)	9 (7–13)	15[f] (9–26)	23[f, g] (15–35)
S-potassium (mmol/l)	4.2±0.1	4.1±0.1	4.0±0.1	4.2±0.1	4.3±0.1	4.0±0.1
24-h systolic BP (mm Hg)	154±3	145±3[f]	134±3[c, g]	150±3	142±3[f]	132±2[c, d]
24-h diastolic BP (mmHg)	79±2	76±2[f]	72±2[c, g]	80±2	75±2[c]	72±1[c]
Albuminuria[a] (mg/24 h)	1347 (973–1865)	970[f] (672–1401)	390[f, g] (214–711)	1016 (776–1329)	676[f] (477–958)	301[f, g] (184–492)
U-potassium (mmol/24 h)	62±5	63±6	67±8	69±4	67±4	58±5
U-sodium (mmol/24 h)	145±12	132±12	134±18	133±9	145±13	115±12
U-K : Na ratio	0.46±0.04	0.53±0.07	0.63±0.09[f]	0.59±0.05	0.56±0.04	0.68±0.13

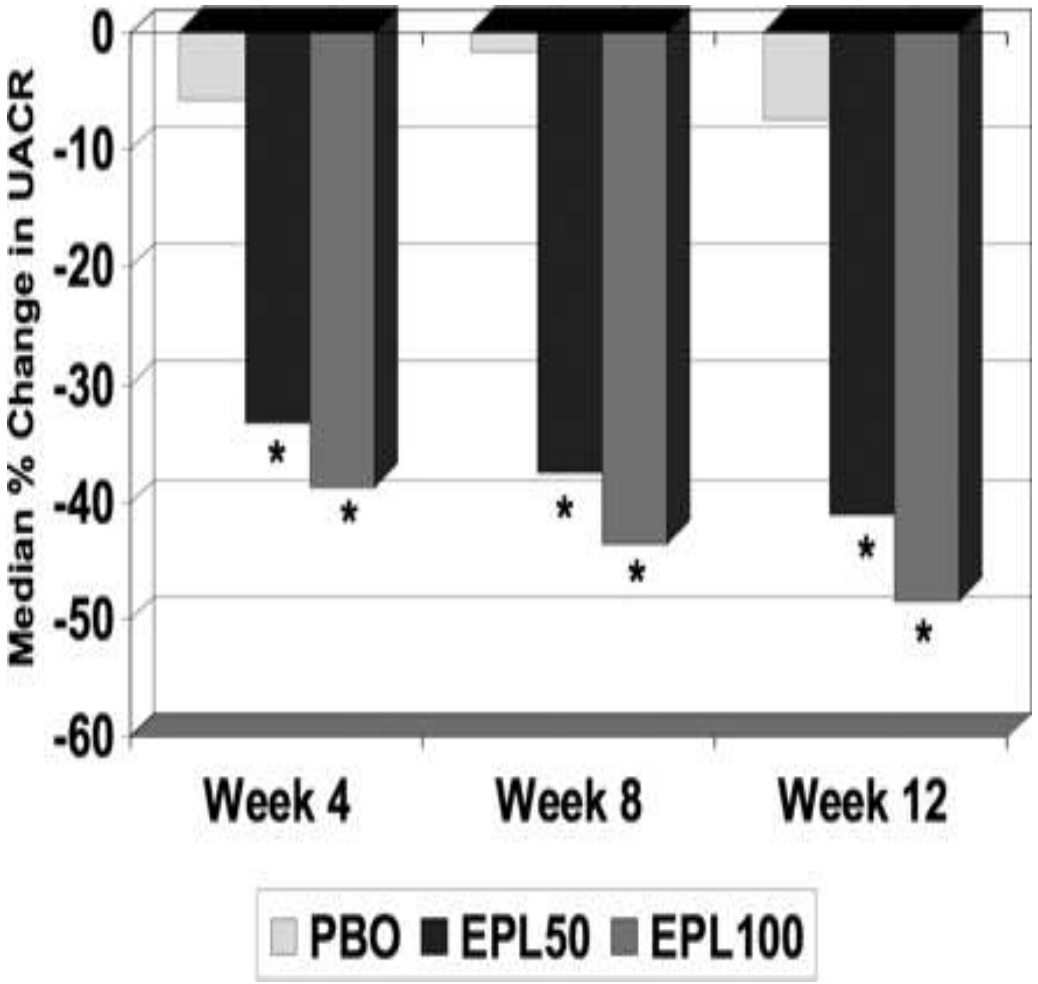
(Diabetologia,2004)

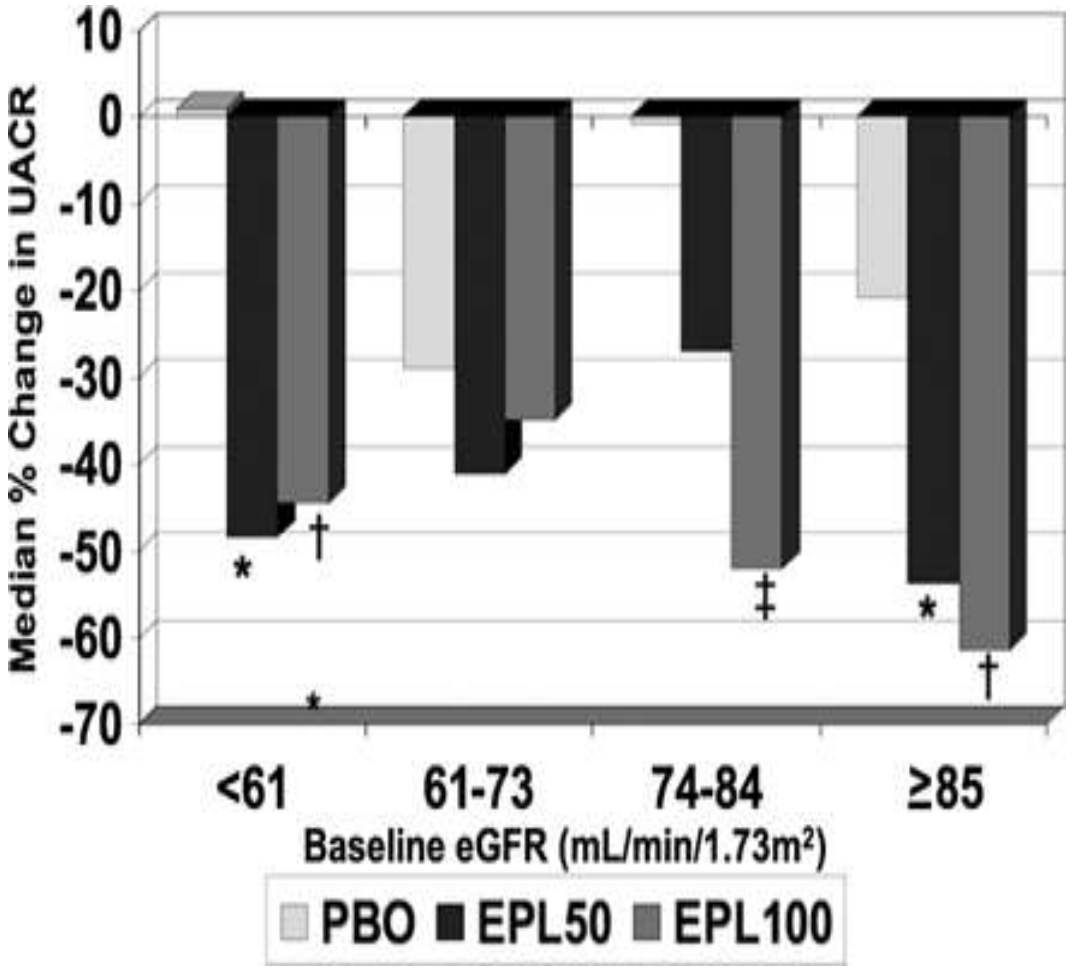
Add on spironolactone upon maximal RAS inhibition in diabetic nephropathy

	Conventional antihypertensive treatment		Mean difference (95% CI)	*P*-value
	+Placebo	+Spironolactone 25 mg		
Albuminuria (mg/24 h)[a]	3718 (2910–4749)	2510 (1831–3441)	−32% (−42 to −21)	<0.001
Systolic blood pressure (mm Hg)				
Office	146 (4)	142 (4)	−4 (−11 to 4)	0.32
24-h[b]	143 (3)	137 (3)	−6 (−10 to −2)	0.004
Day (7–23)[b]	147 (3)	140 (4)	−7 (−12 to −3)	0.002
Night (23–7)[c]	135 (3)	133 (4)	−2 (−7 to 2)	0.32
Diastolic blood pressure (mm Hg)				
Office	76 (2)	73 (2)	−3 (−6 to 0.4)	0.08
24-h[b]	81 (2)	77 (2)	−4 (−6 to −2)	0.001
Day (7–23)[b]	84 (2)	80 (2)	−5 (−7 to −3)	<0.001
Night (23–7)[c]	74 (2)	73 (2)	−1 (−4 to 2)	0.44
GFR (ml/min/1.73 m^2)	64 (2)	62 (2)	−3 (−6 to 1)	0.13
Fractional albumin clearance (θ_{alb}) ($\times 10^{-6}$)[a]	1.79 (1.25–2.56)	1.24 (0.82 to1.87)	−31% (−40 to −20)	<0.001
Urinary sodium excretion (mmol/24 h)	239 (36)	210 (19)	−29 (−84 to 26)	0.28
Urinary K/Na ratio	0.43 (0.05)	0.43 (0.04)	0.01 (−0.06 to 0.07)	0.78
Bodyweight (kg)	93.8 (5.7)	92.6 (5.6)	1.1 (−0.1 to 2.4)	0.07
Plasma renin activity (ng AI/ml/h)[a]	8.9 (5.8–13.5)	16.1 (9.2–28.1)	81% (25–162)	0.003
Plasma aldosterone (pg/ml)[a]	38 (25–56)	68 (50–93)	80% (23–163)	0.004
Plasma creatinine (μmol/l)	141 (15)	149 (15)	8 (−4 to 20)	0.17
Plasma potassium (mmol/l)	4.1 (0.1)	4.3 (0.1)	0.2 (−0.004 to 0.5)	0.054
Plasma sodium (mmol/l)	139 (1)	138 (1)	−1 (−3 to 1)	0.28
Hemoglobin (mmol/l)	7.6 (0.2)	7.3 (0.2)	−0.2 (−0.5 to 0.01)	0.057
Hemoglobin A_{1c} (%)	8.2 (0.3)	8.4 (0.3)	0.2 (−0.1 to 0.5)	0.20
Plasma cholesterol (mmol/l)	4.7 (0.3)	4.6 (0.2)	−0.1 (−0.4 to 0.3)	0.74
Plasma LDL cholesterol (mmol/l)	2.3 (0.2)	2.3 (0.2)	0.0 (−0.3 to 0.3)	0.88
Plasma HDL cholesterol (mmol/l)	1.5 (0.2)	1.5 (0.1)	−0.07 (−0.2 to 0.04)	0.20

(Kidney Int, 2006)

Effect of eplerenone combined with enalapril in type 2 diabetic nephropathy

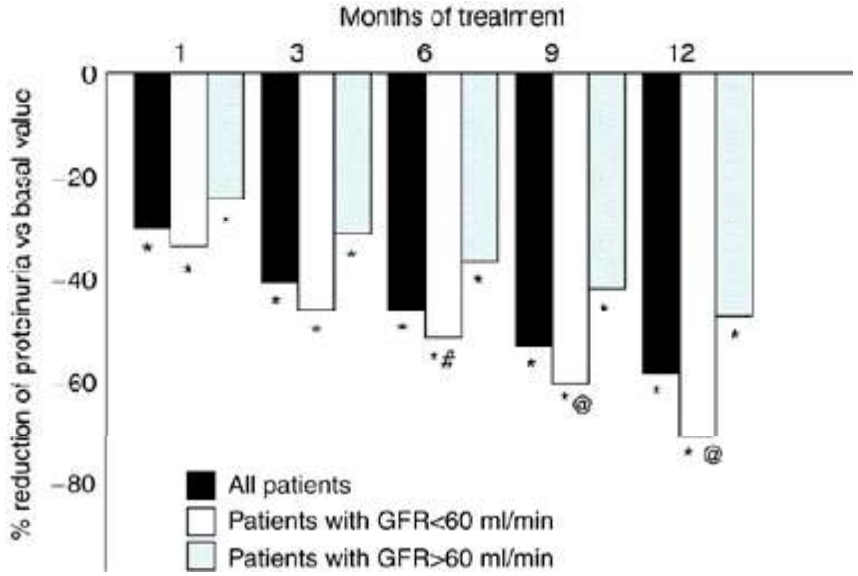


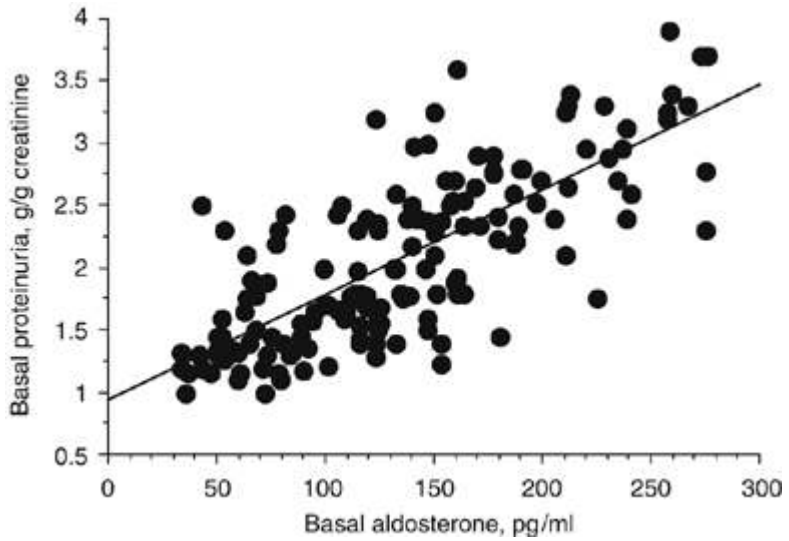


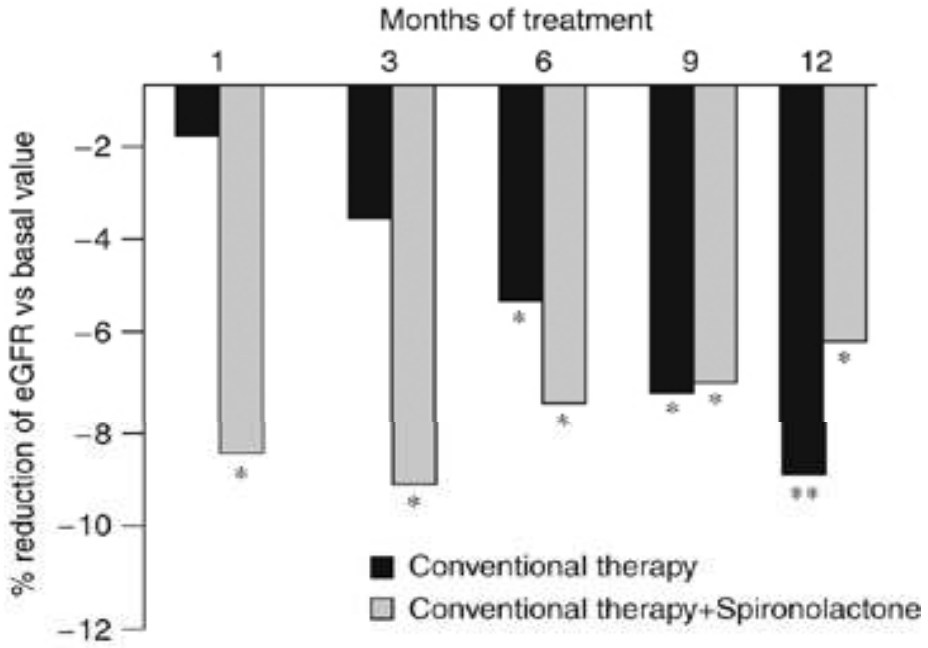
Overall percentage change of UAER from baseline in type 2 diabetic patients

(J Am Soc Nephrol, 2006)

Predictor of spironolactone response in CKD patients







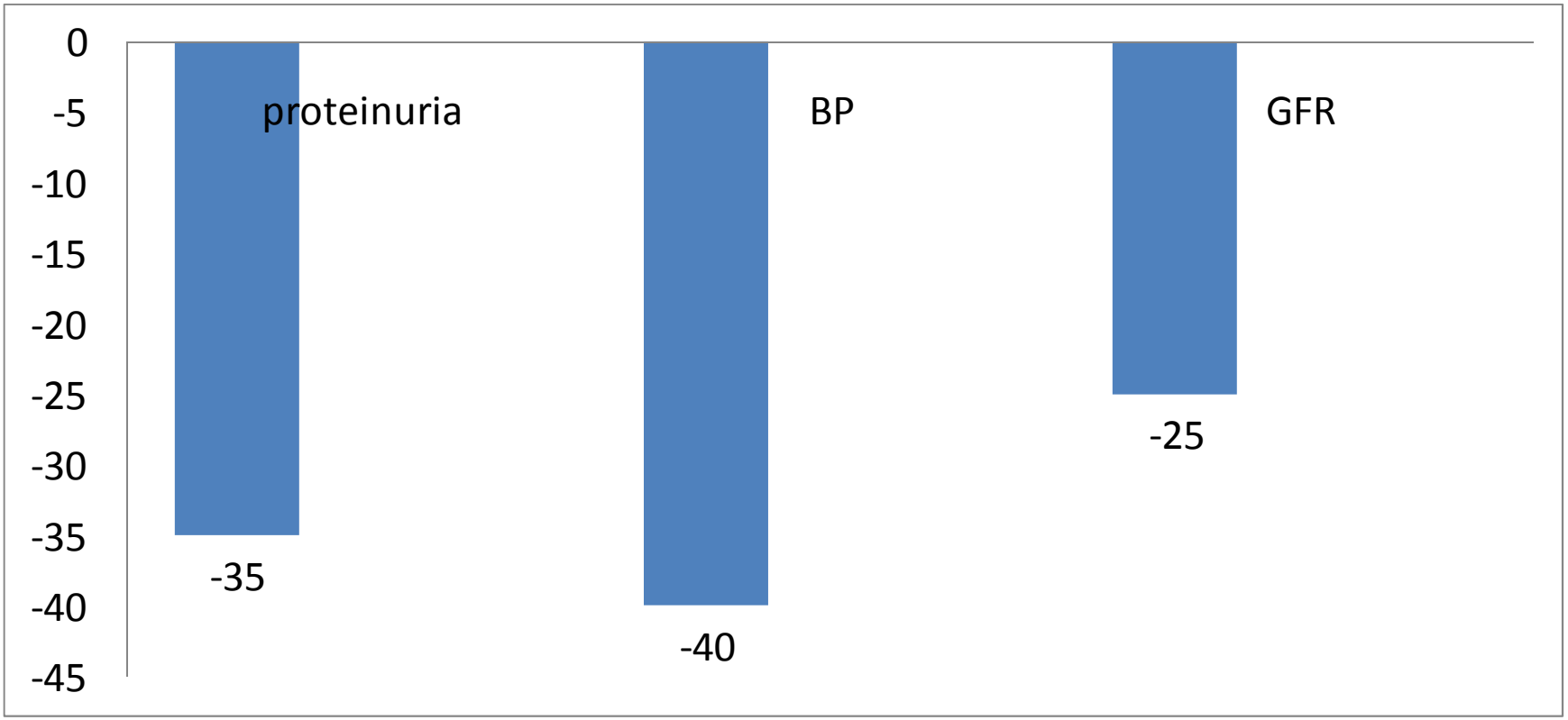
SBP

Basal aldosterone levels

Change in 1month GFR

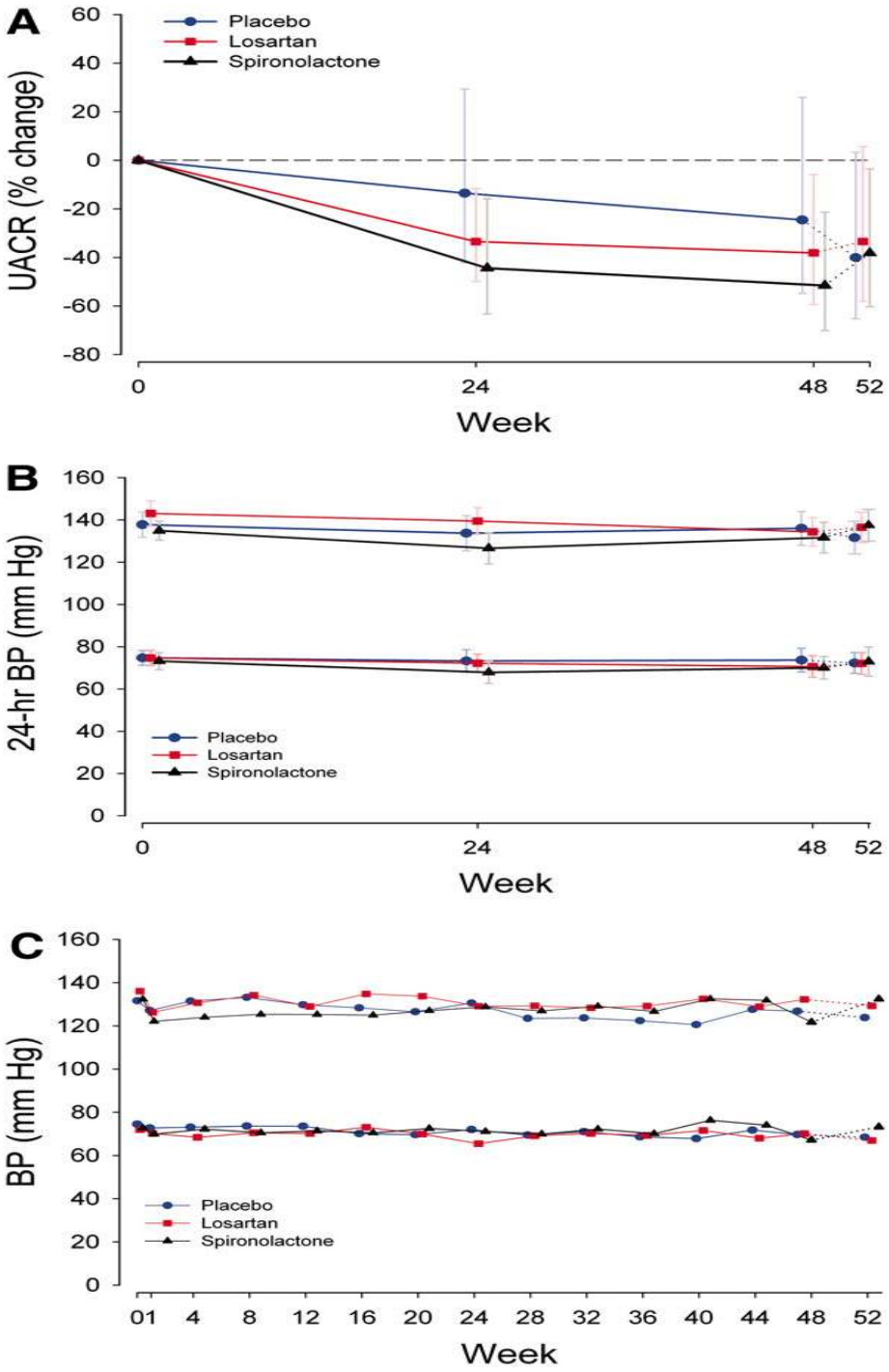
(Kidney Int, 2006)

Overview of effect of adding aldosterone antagonist to RAS blockade in CKD: Meta-analysis results



(Am J Kidney Dis, 2008)

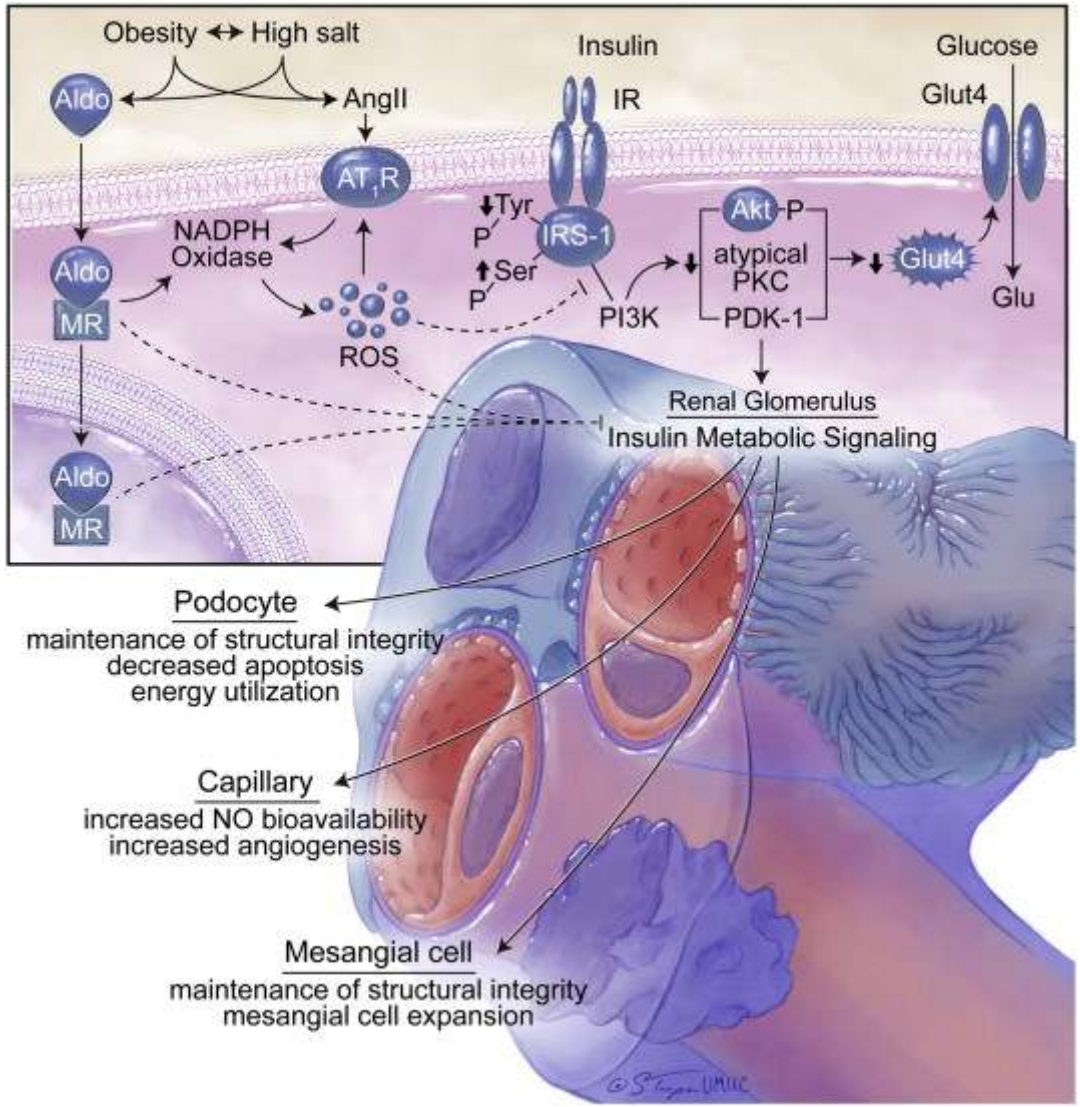
Double-blind, placebo-controlled trial in 81 patients with diabetes, hypertension, and albuminuria, who received lisinopril (80 mg once daily)



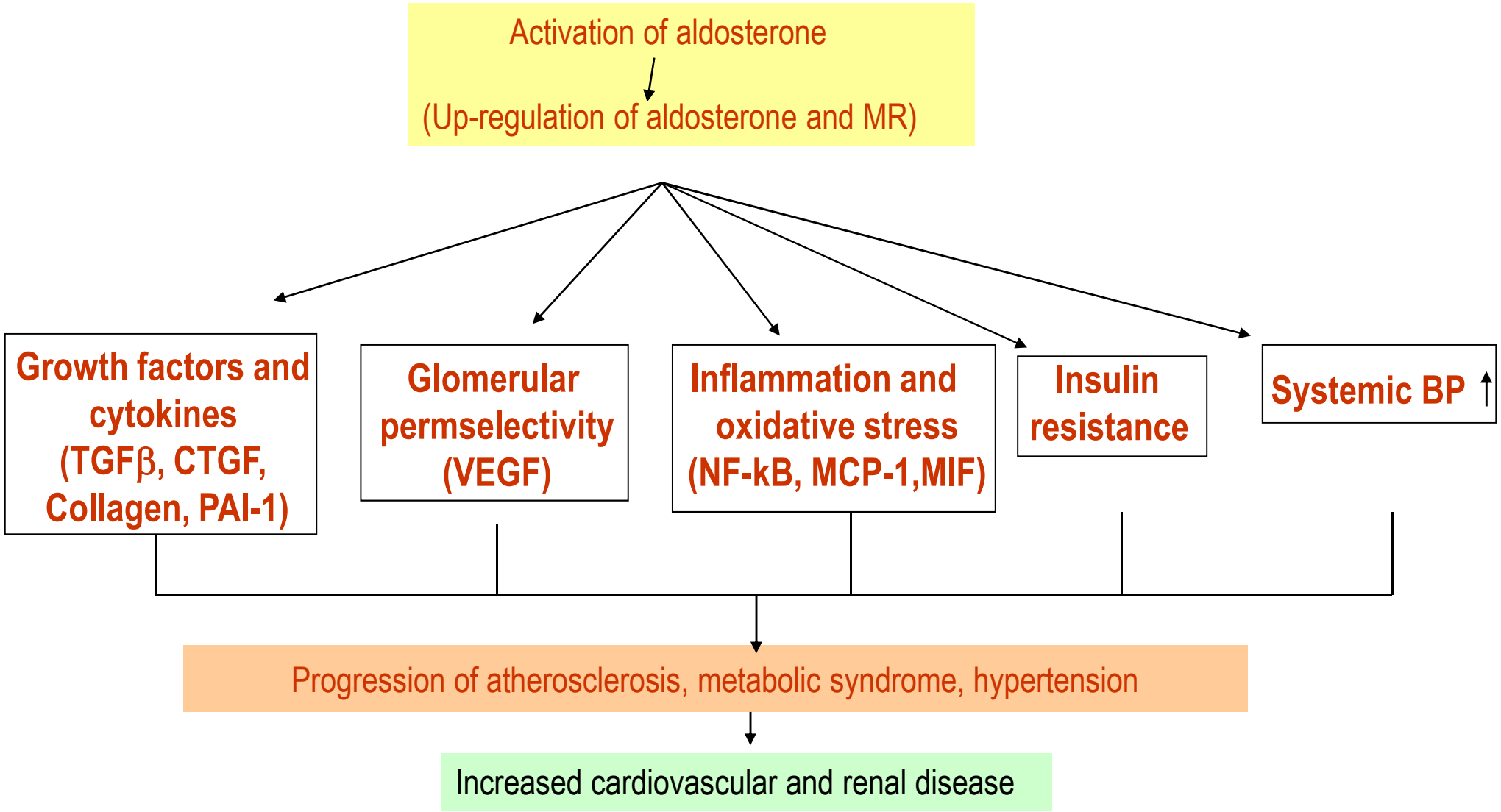
16.8% reduction: ACEi+ARB
34.0% reduction: ACEi+SPR

(J Am Soc Nephrol, 2009)

Aldosterone (Aldo) and Angiotensin II (Ang II) actions on Glomerular Insulin Metabolic Signaling

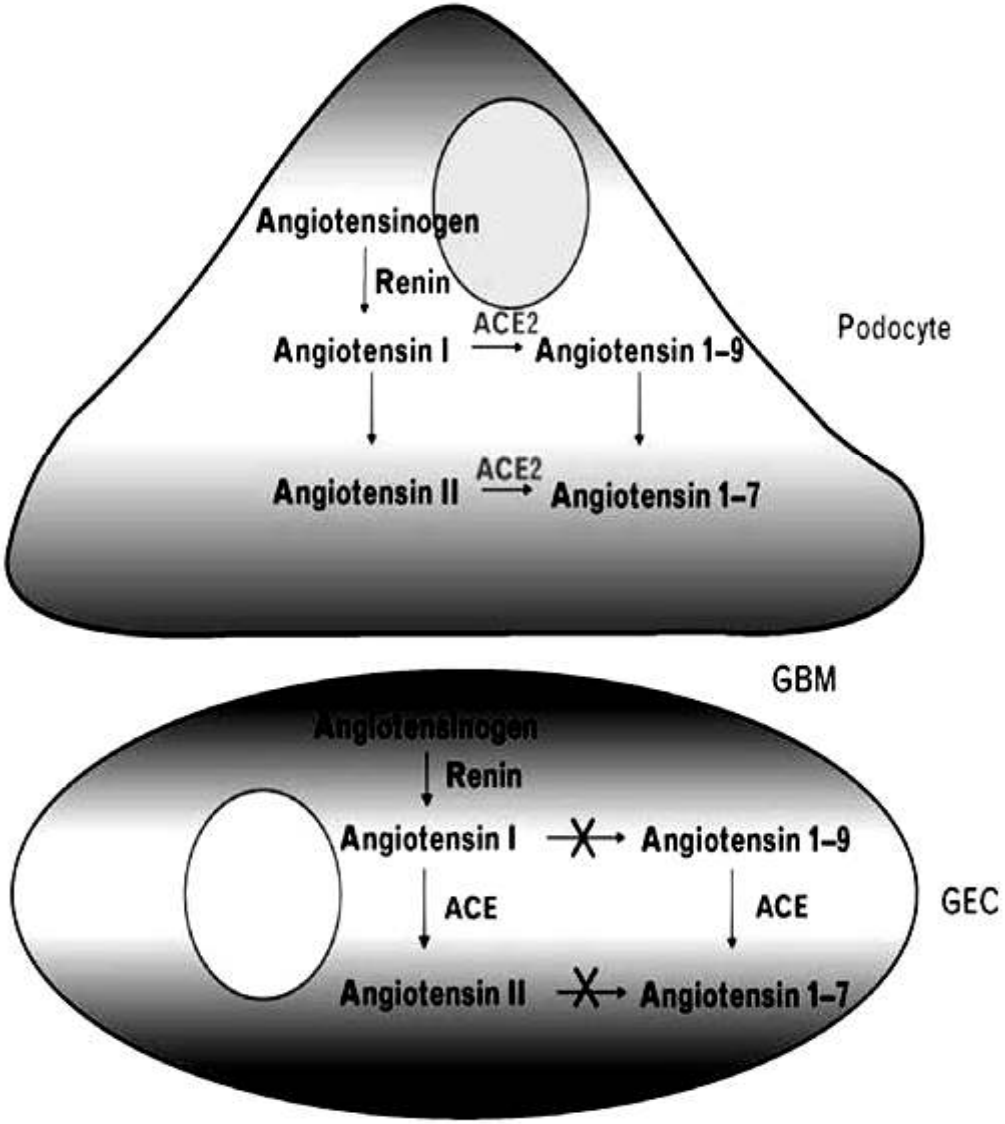


New aspect of aldosterone in diabetic nephropathy

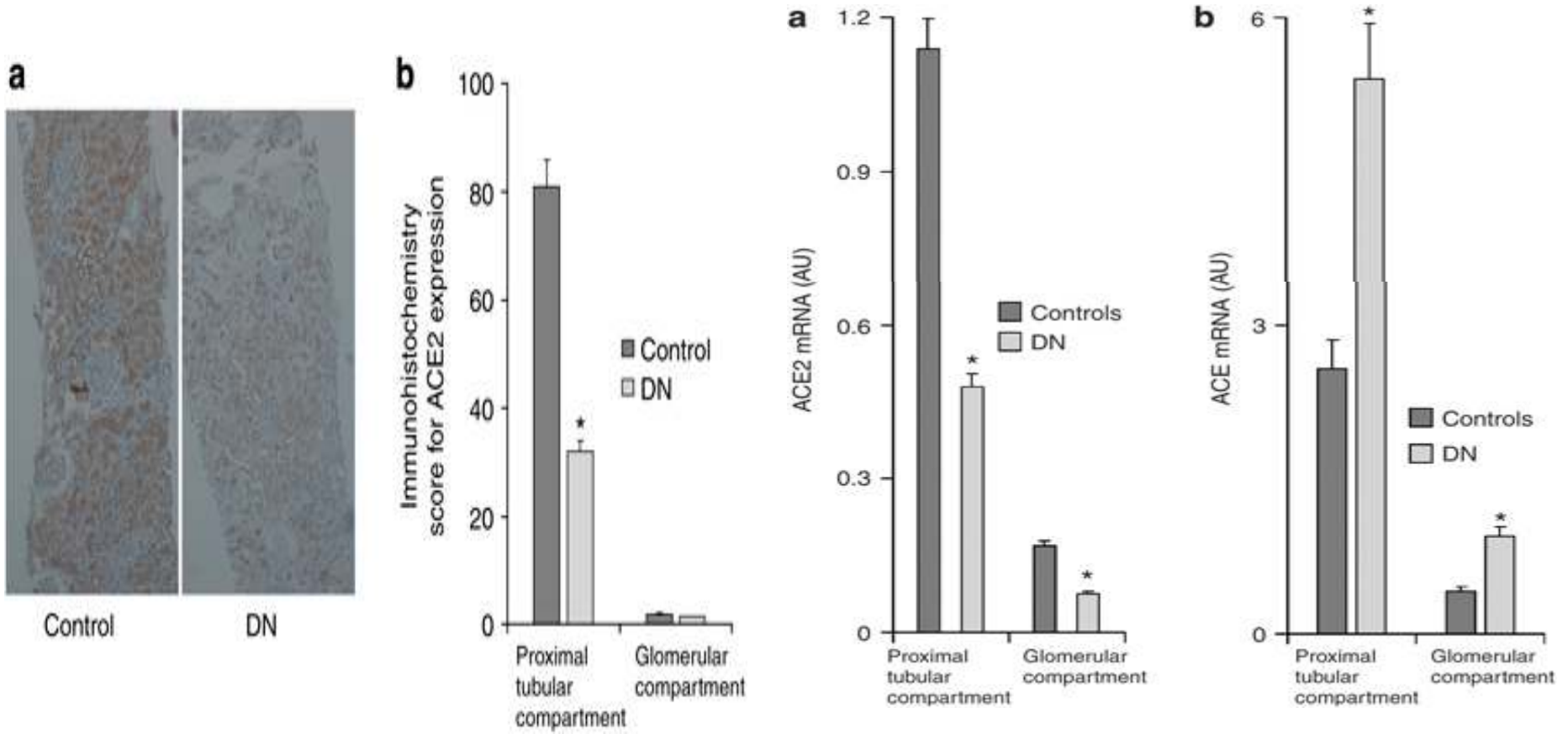


New aspects of the renin-angiotensin system: angiotensin-converting enzyme 2 - a potential target for treatment of hypertension and diabetic nephropathy

Proposed mechanism of ACE2 role in diabetic nephropathy

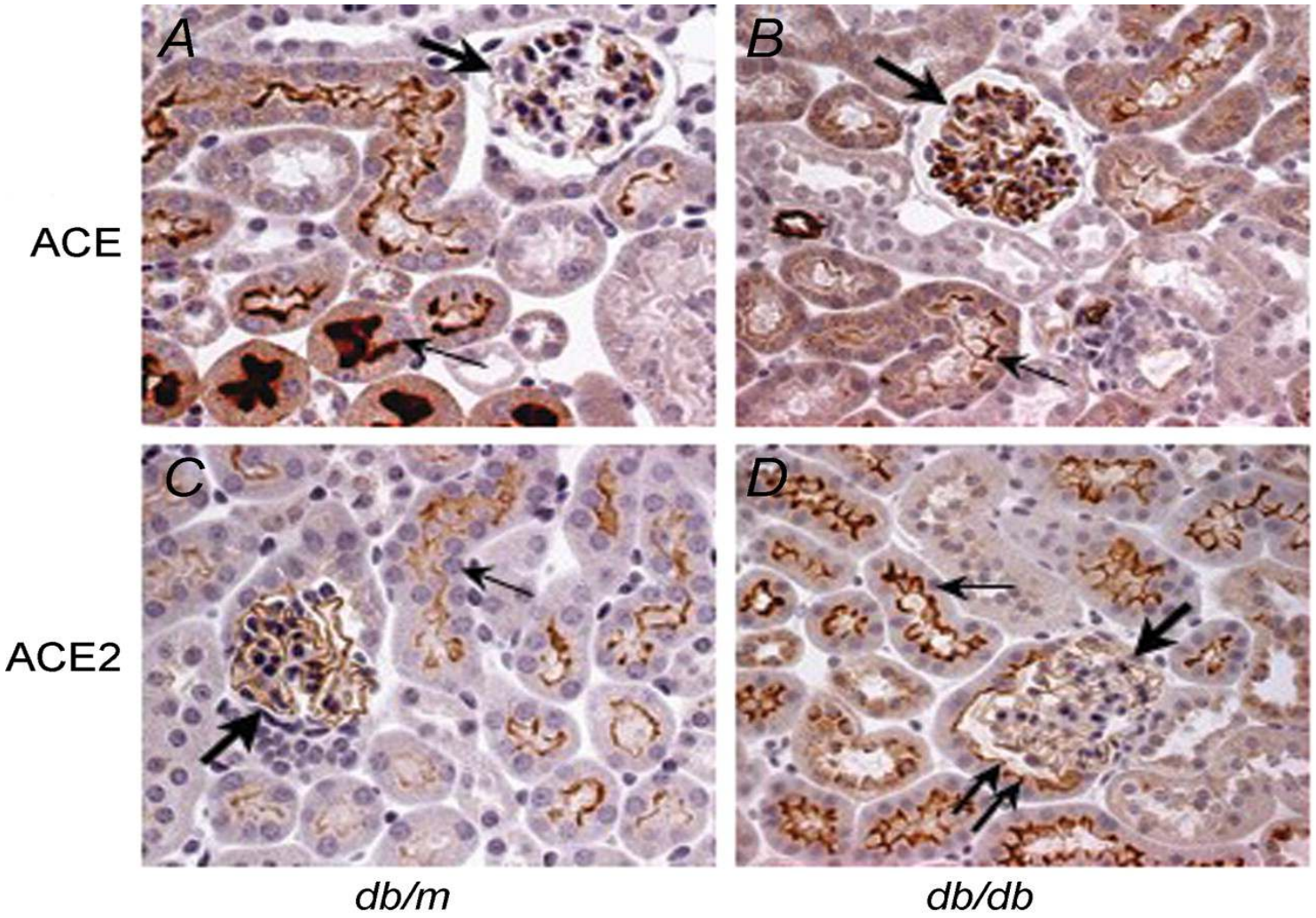


Decreased glomerular and tubular expression of ACE2 in patients with type 2 diabetes and kidney disease



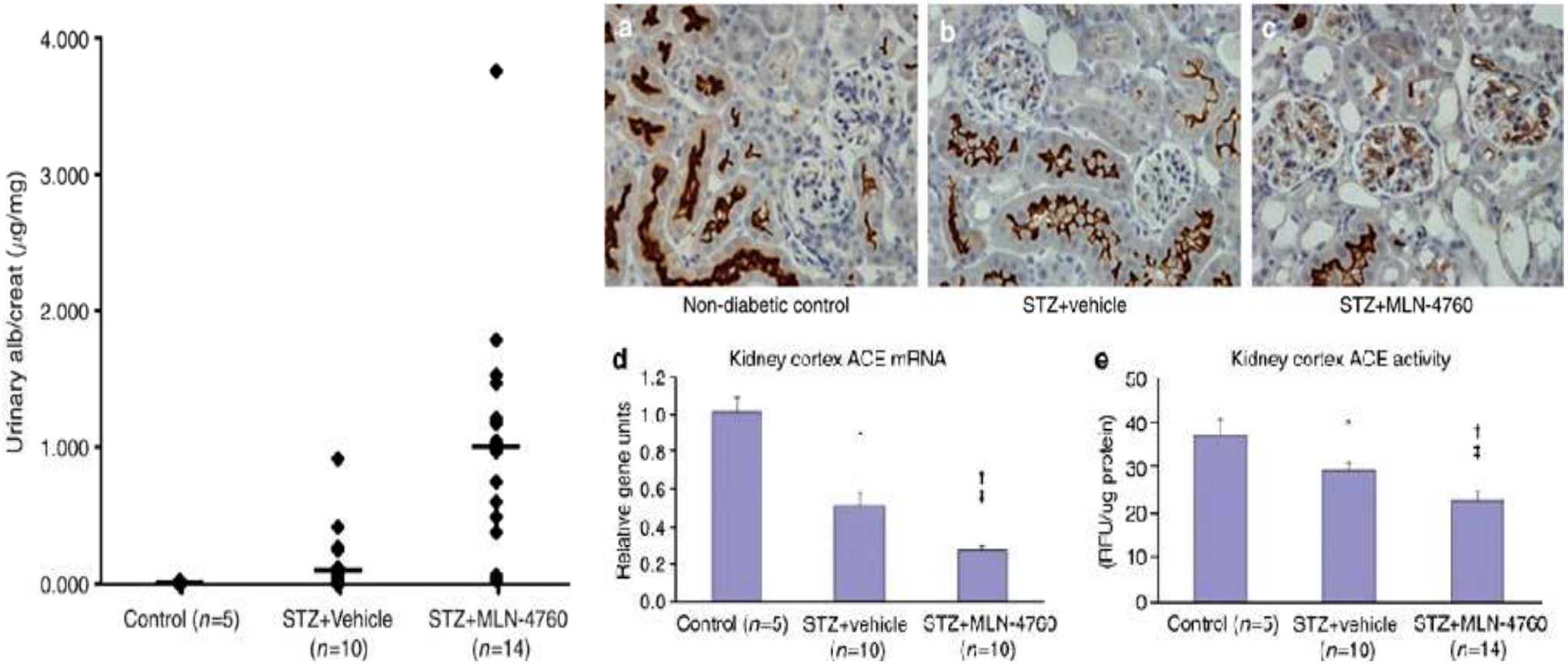
(Kidney Int, 2008)

Immunohistochemistry of ACE and ACE2 in Diabetic Kidney



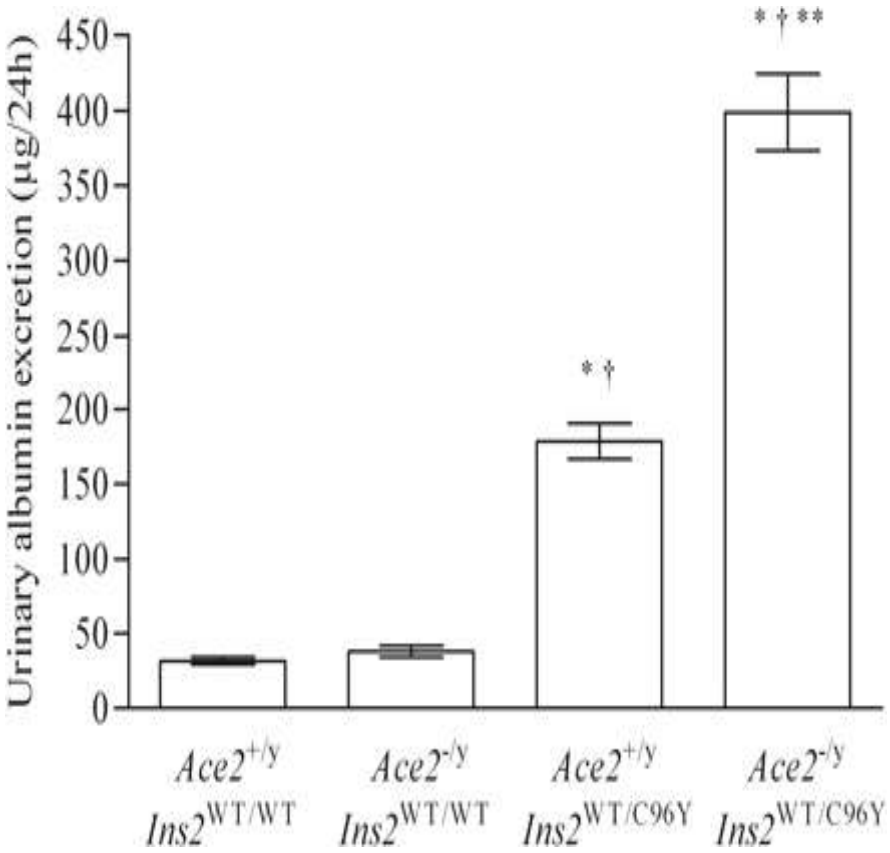
(Exp Physiol, 2008)

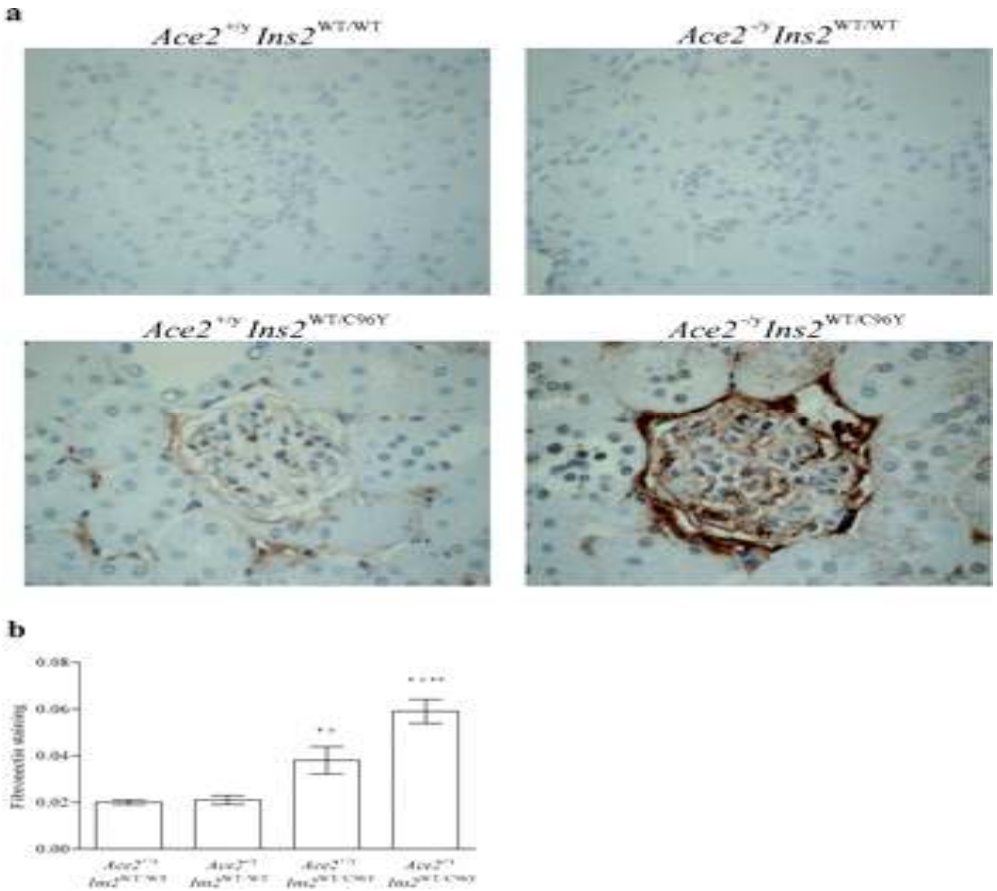
ACE2 inhibition worsens glomerular injury in association with increased ACE expression in streptozotocin-induced diabetic mice



(Kidney Int, 2007)

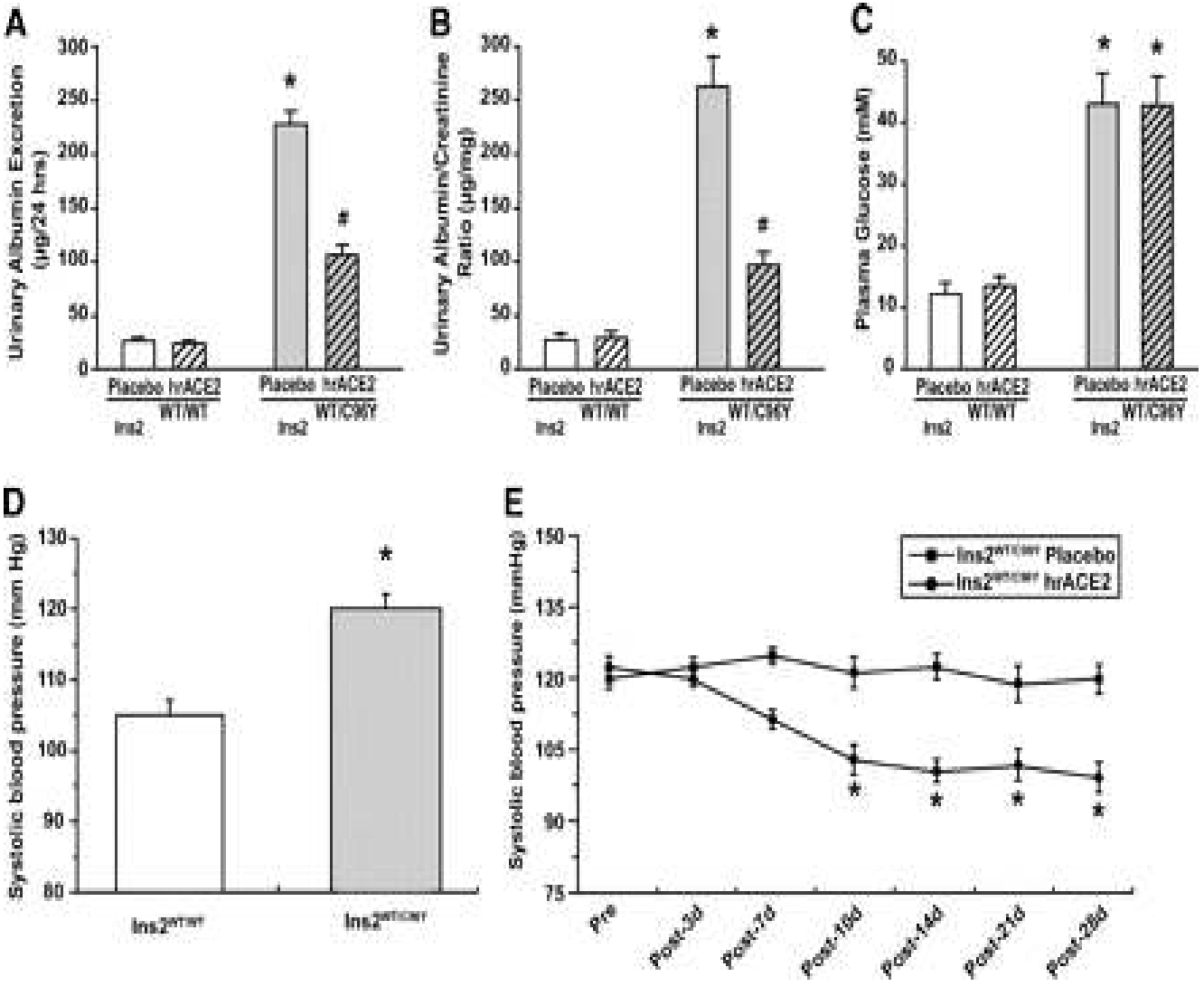
Development of increased urinary AERs and glomerular fibronectin expresison in the diabetic mice





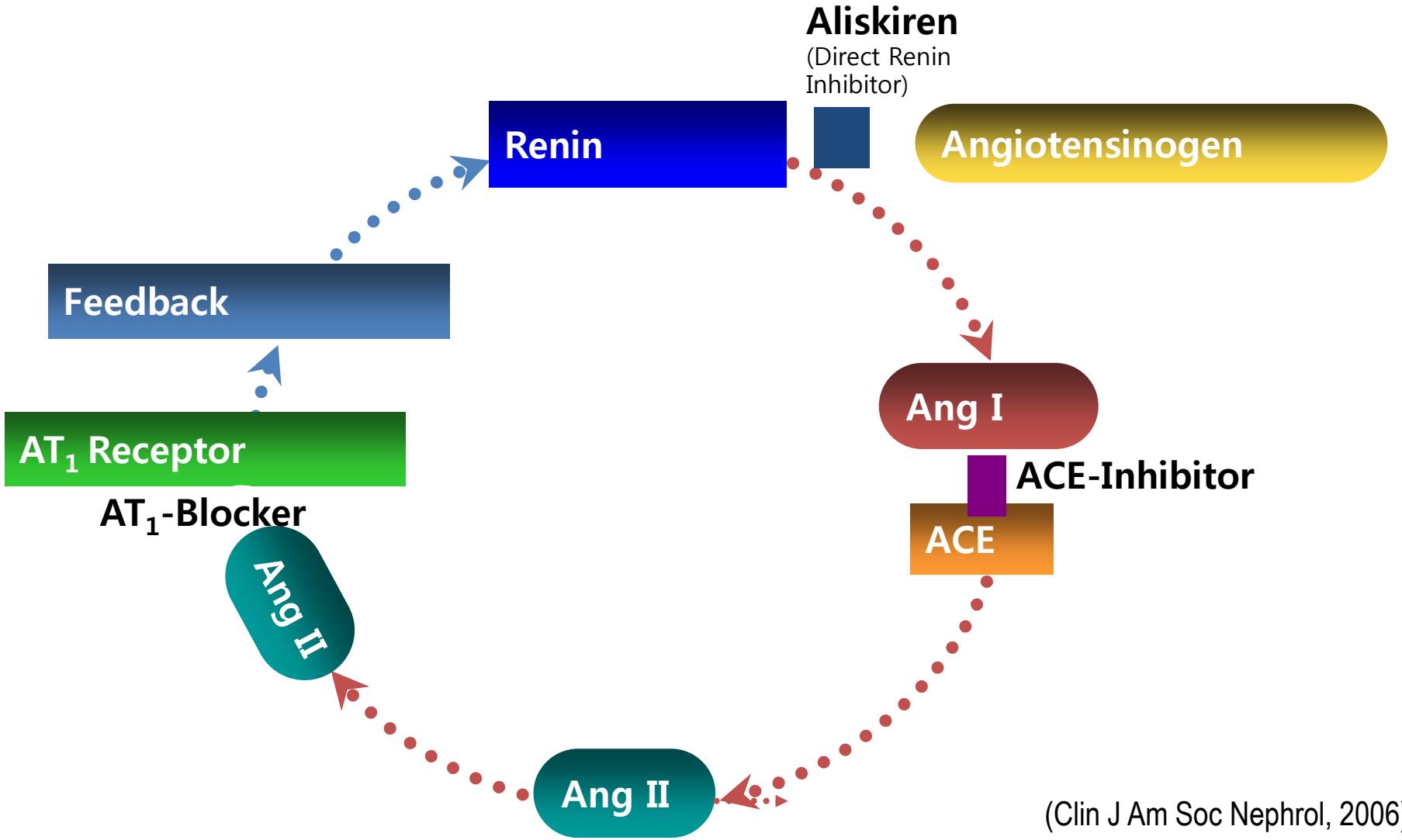
(Am J Pathol, 2007)

Human recombinant ACE2 reduces the progression of DN



(Diabetes, 2010)

Aliskiren controls the Renin-System at the rate-limiting Step

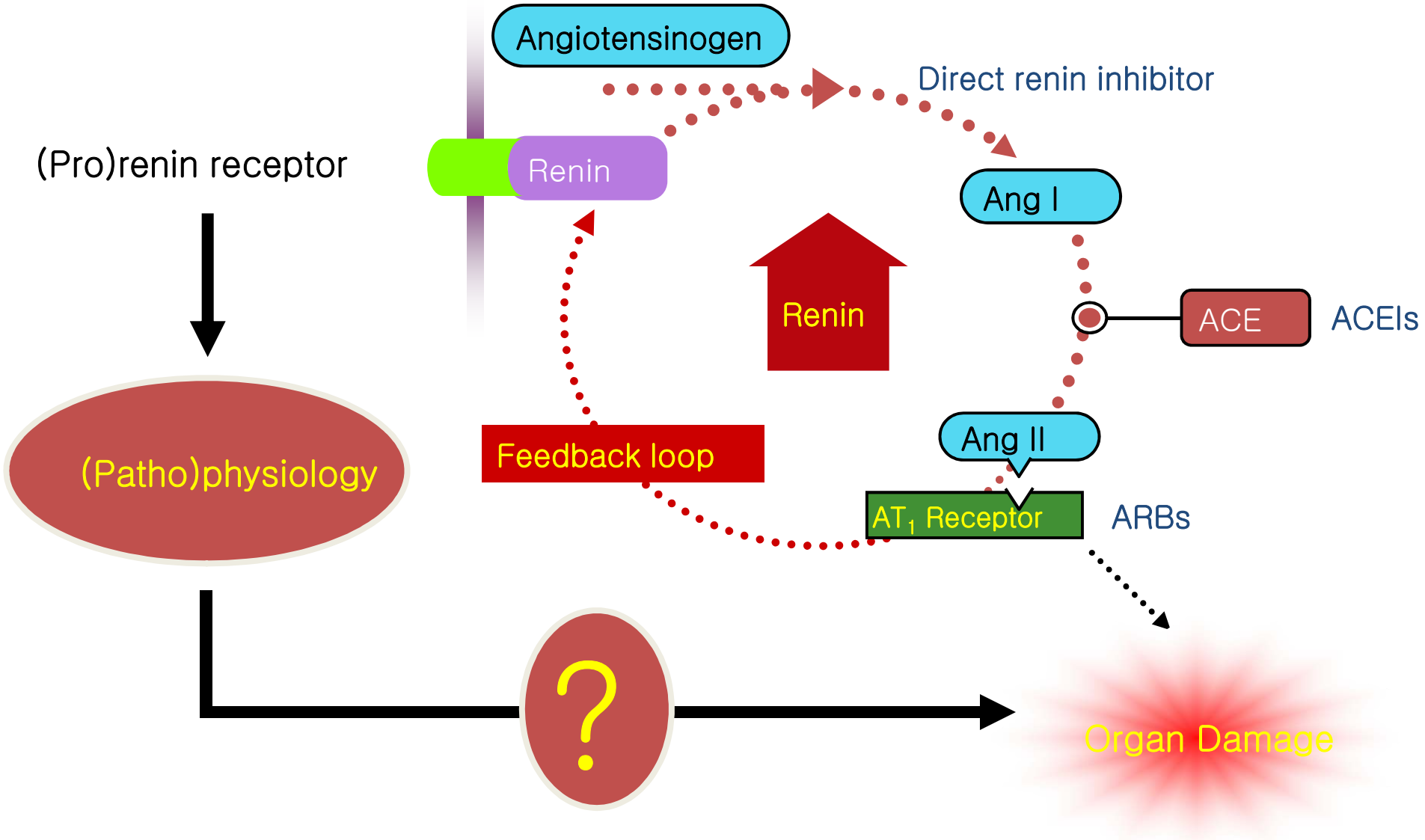


(Clin J Am Soc Nephrol, 2006)

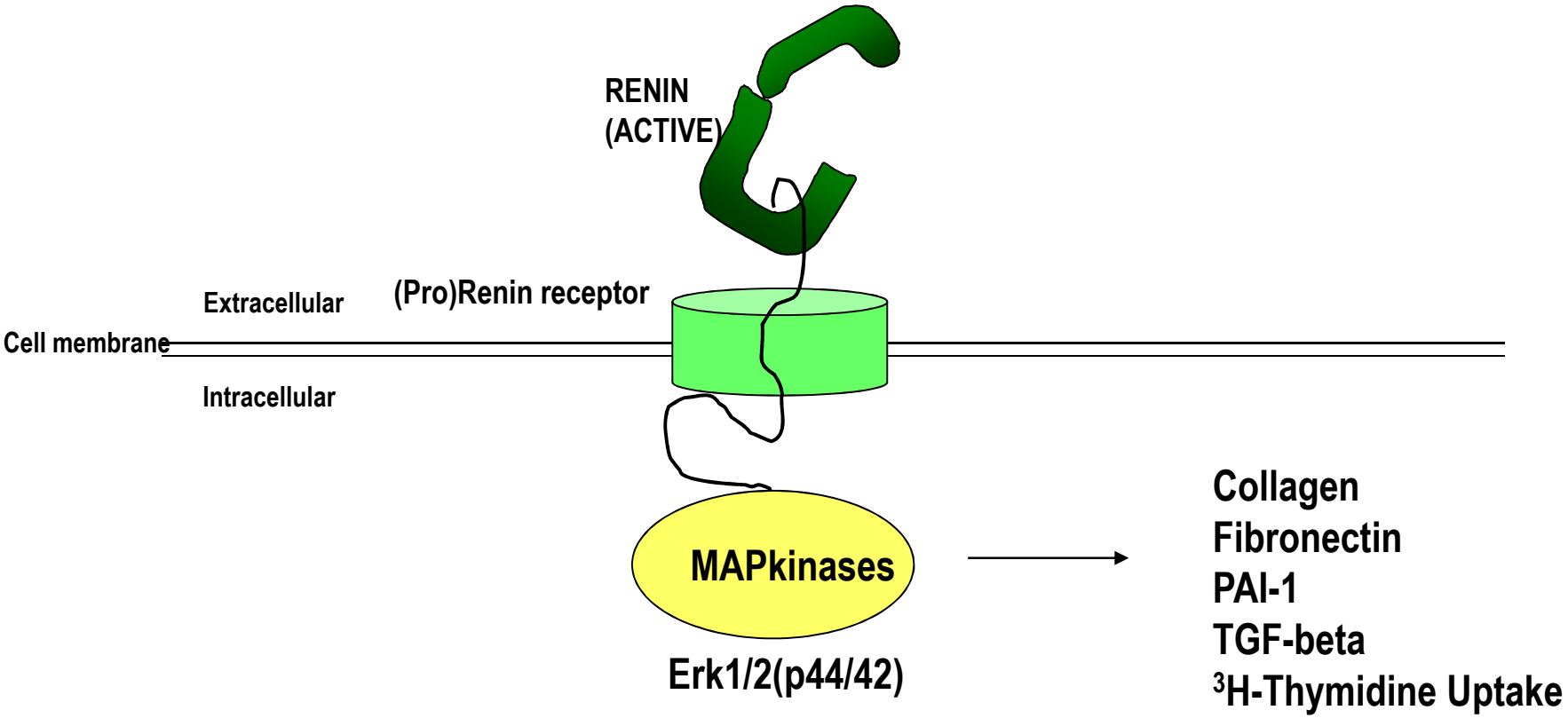
Unlike ACEIs and ARBs, aliskiren reduces Ang I, Ang II and PRA

Class	Renin Concentration	PRA	Ang I	Ang II
ACEI				
ARB				
DRI (Aliskiren)				

The new renin angiotensin system?

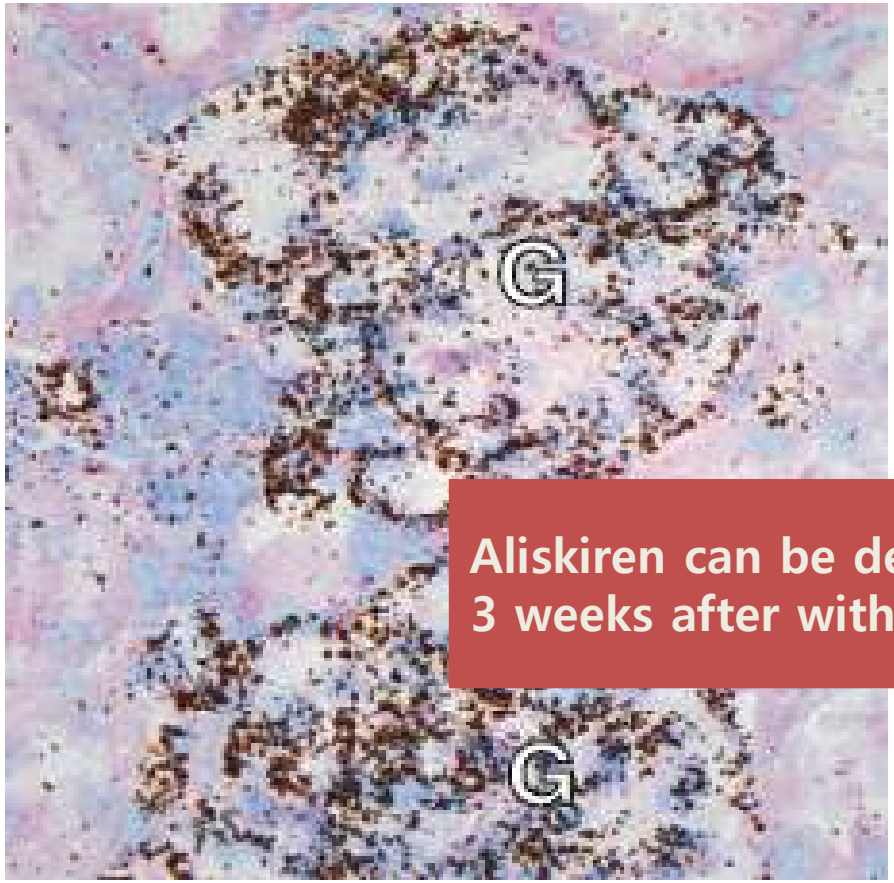


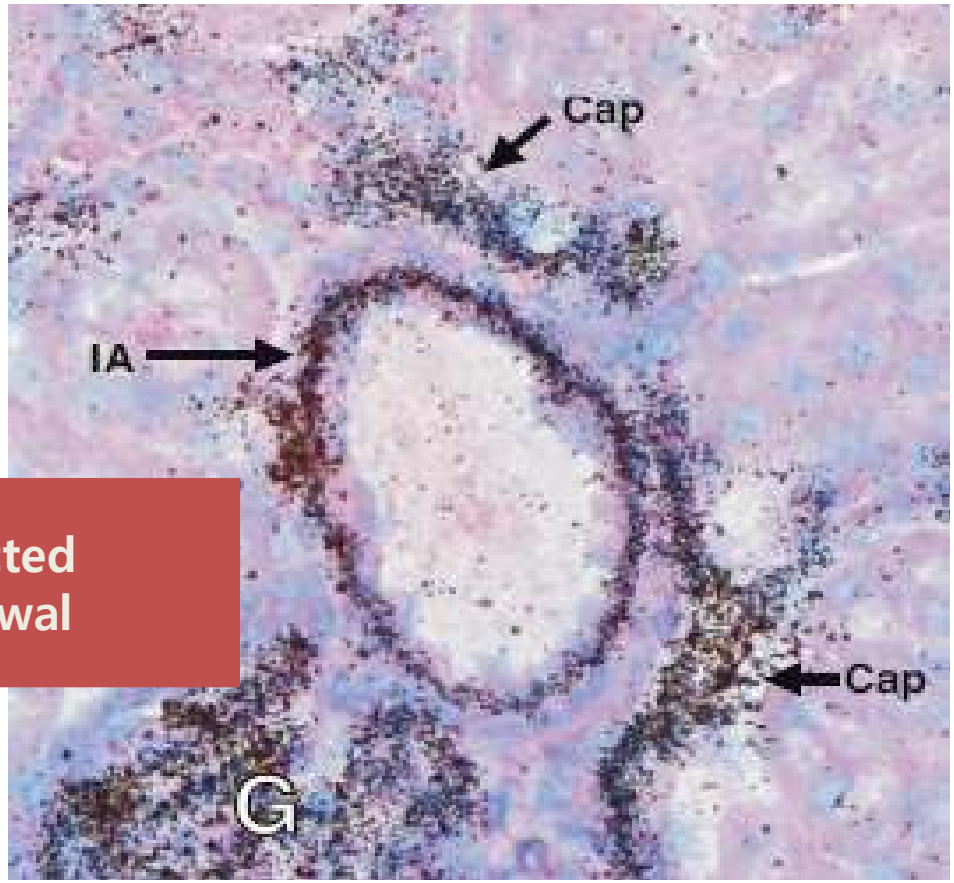
(Pro) renin Receptor Binding



Modified from James L. Pool, JMCP, 2007 Oct 13(8): S21-S33

Aliskiren localizes in the kidney



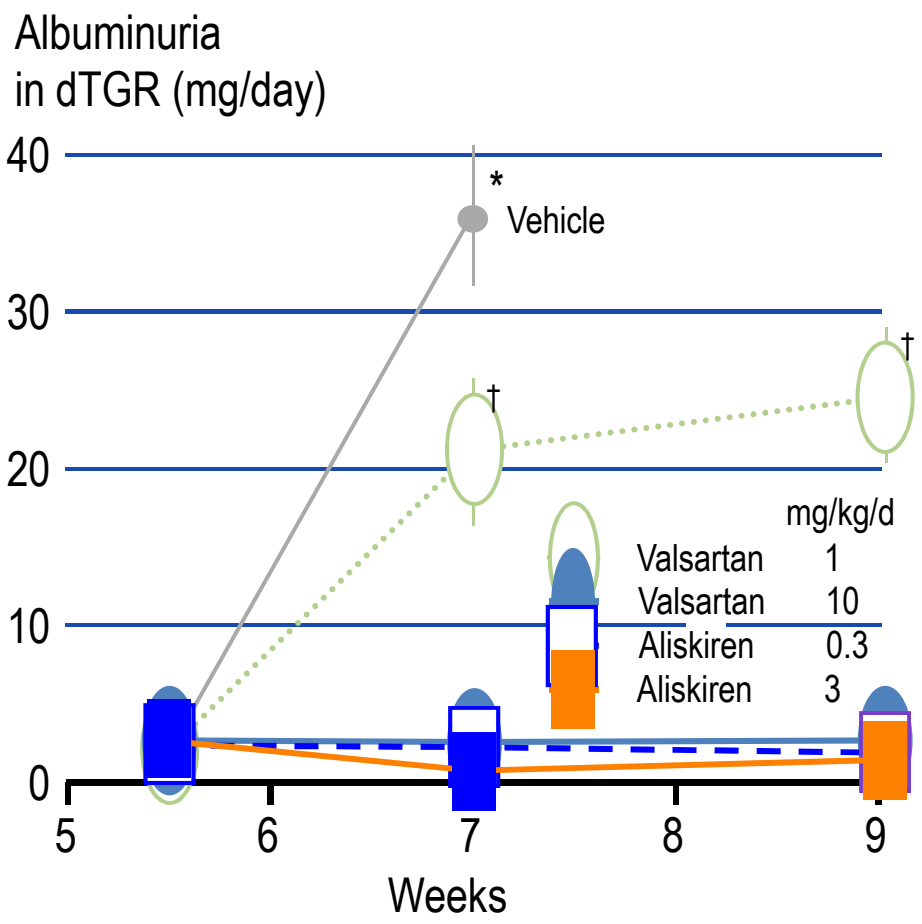


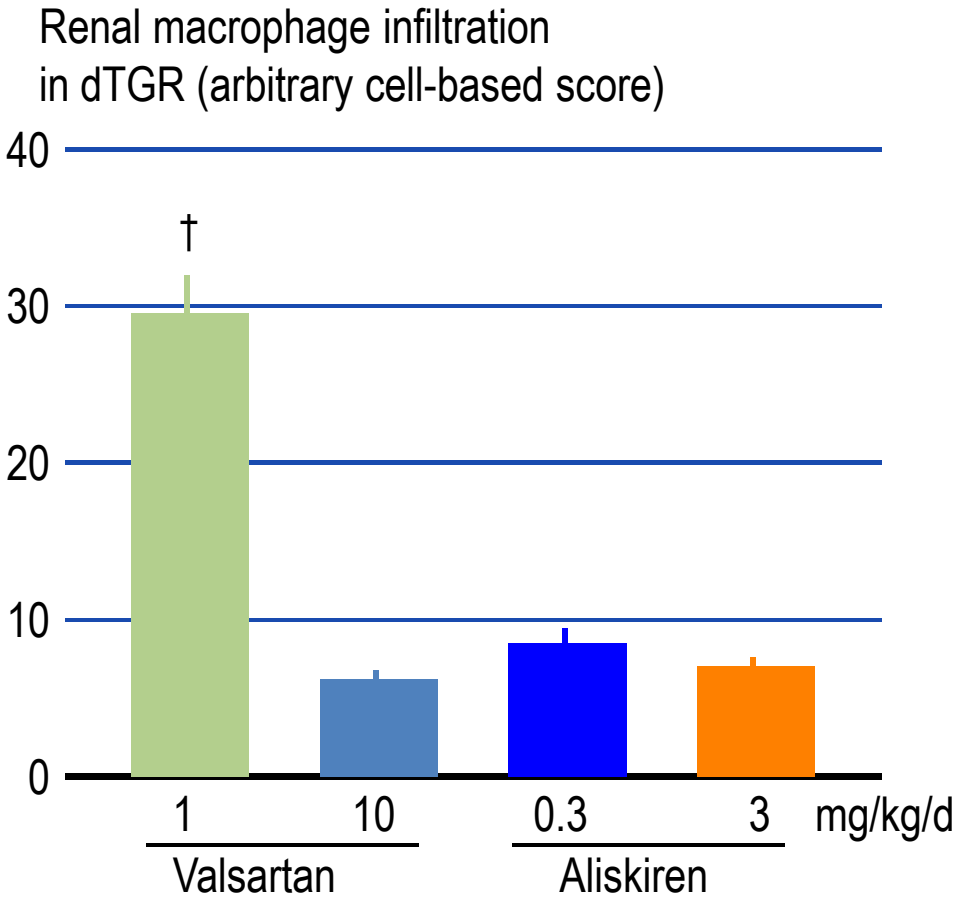
Aliskiren can be detected 3 weeks after withdrawal

G = glomerulus
IA = interlobular artery
Cap = Capillaries

(J Clin Hypertens, 2006)

Aliskiren prevents albuminuria and inhibits renal inflammation in dTGR



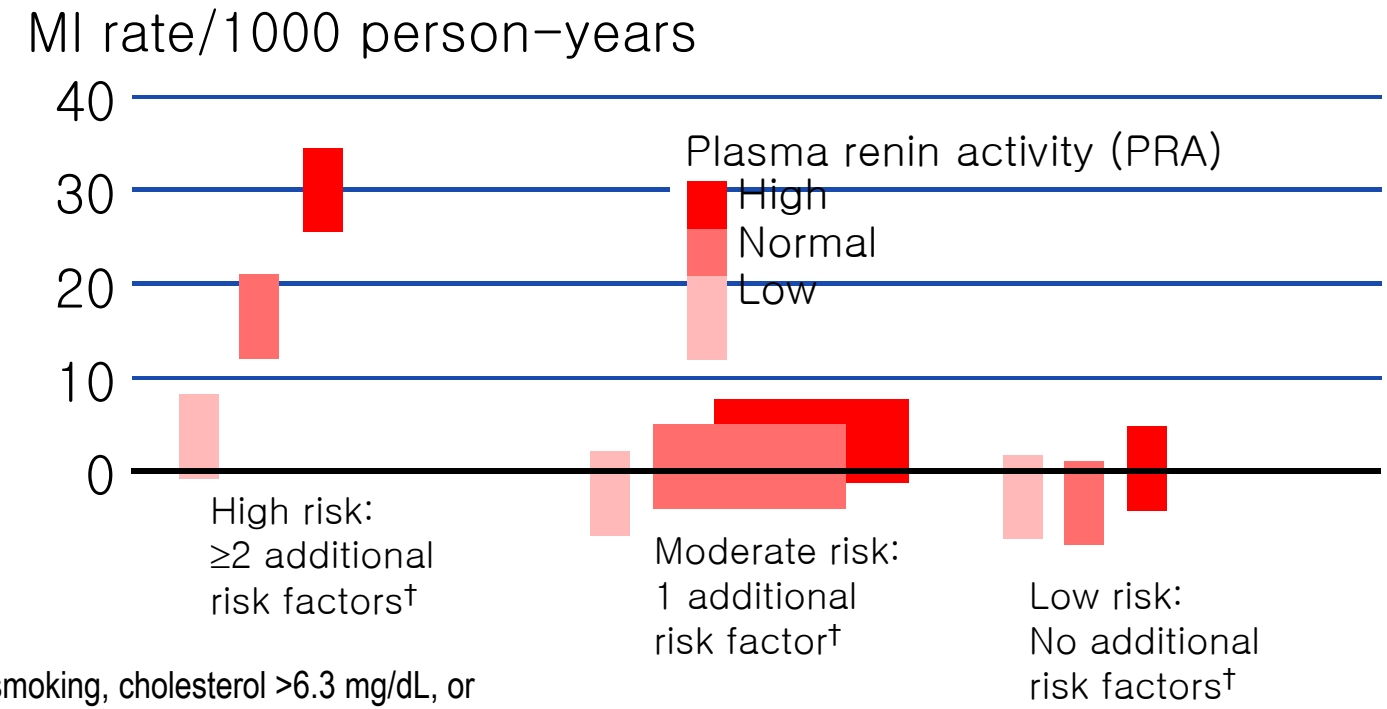


*p<0.05 vs all other groups; †p<0.05 vs other groups
Untreated rats died by Week 8

Pilz B, *et al*. 2005

Elevated PRA may be associated with increased risk of myocardial infarction

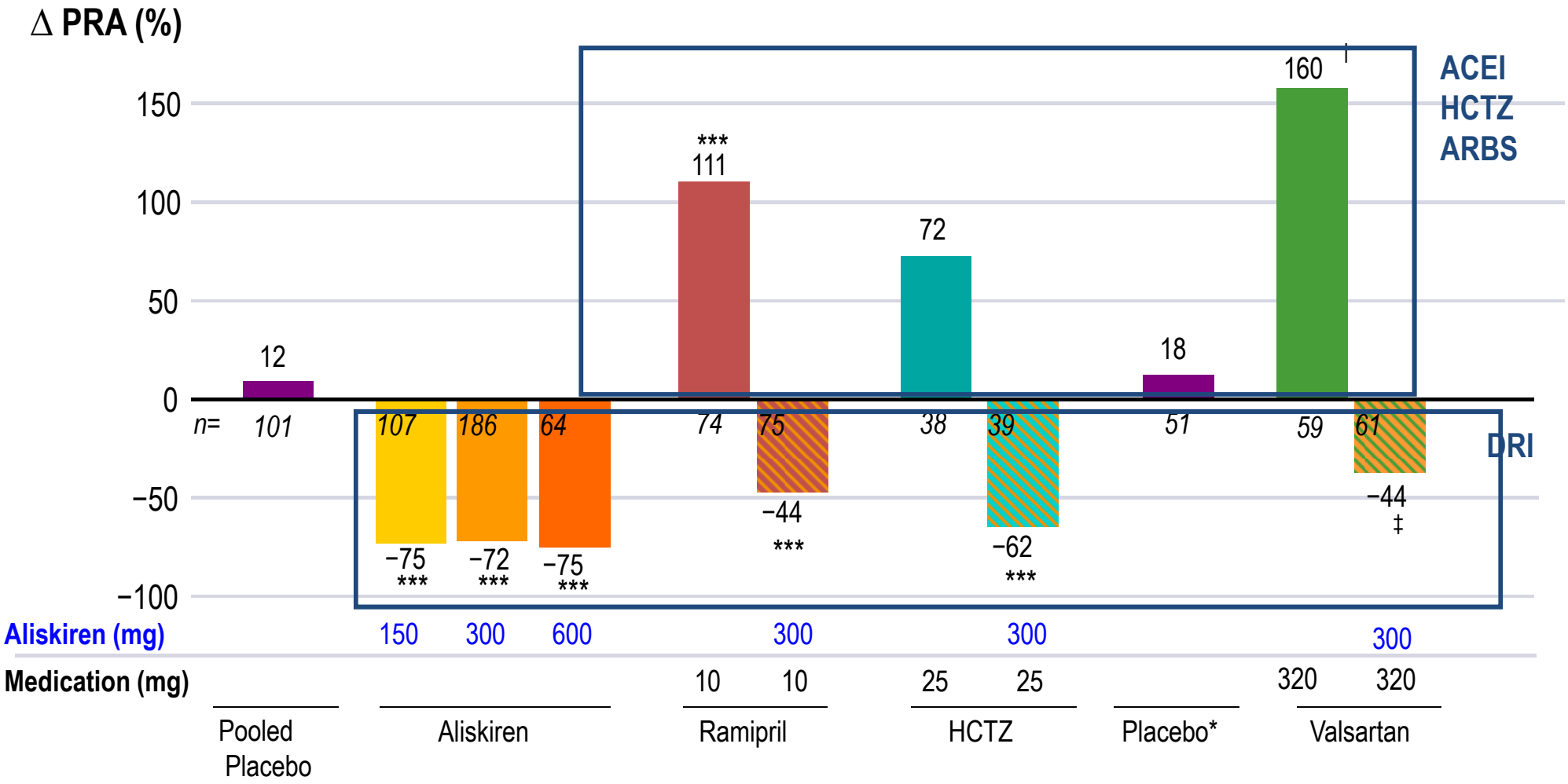
- Existing treatments do not provide optimal suppression of the renin system
  - Increased PRA levels and additional cardiovascular risk factors increase risk of myocardial infarction (MI)



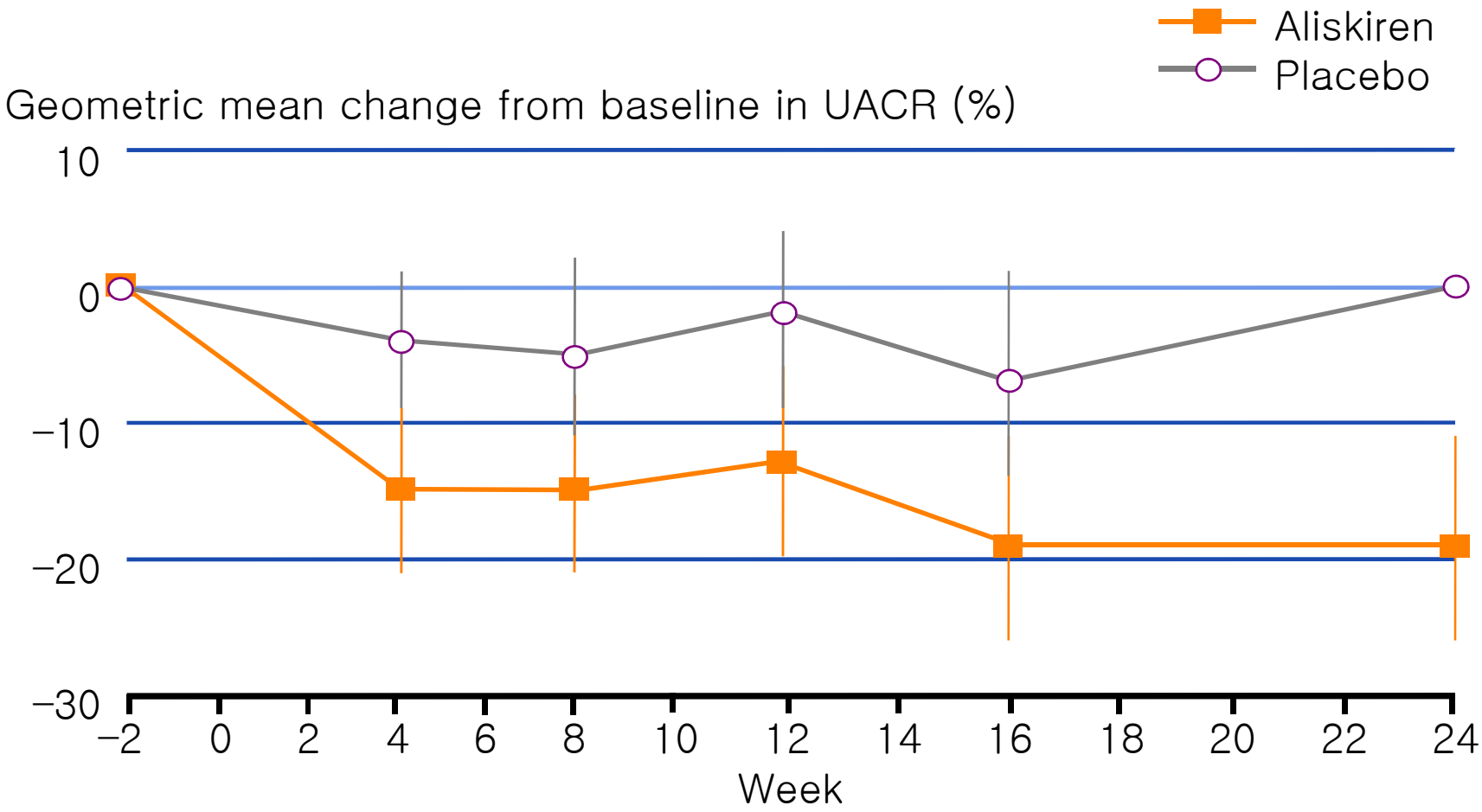
†Risk factors defined as: smoking, cholesterol >6.3 mg/dL, or left ventricular hypertrophy

(Alderman *et al*. 1997)

Aliskiren inhibits PRA Rise



Changes in UACR with aliskiren and placebo throughout the course of the study

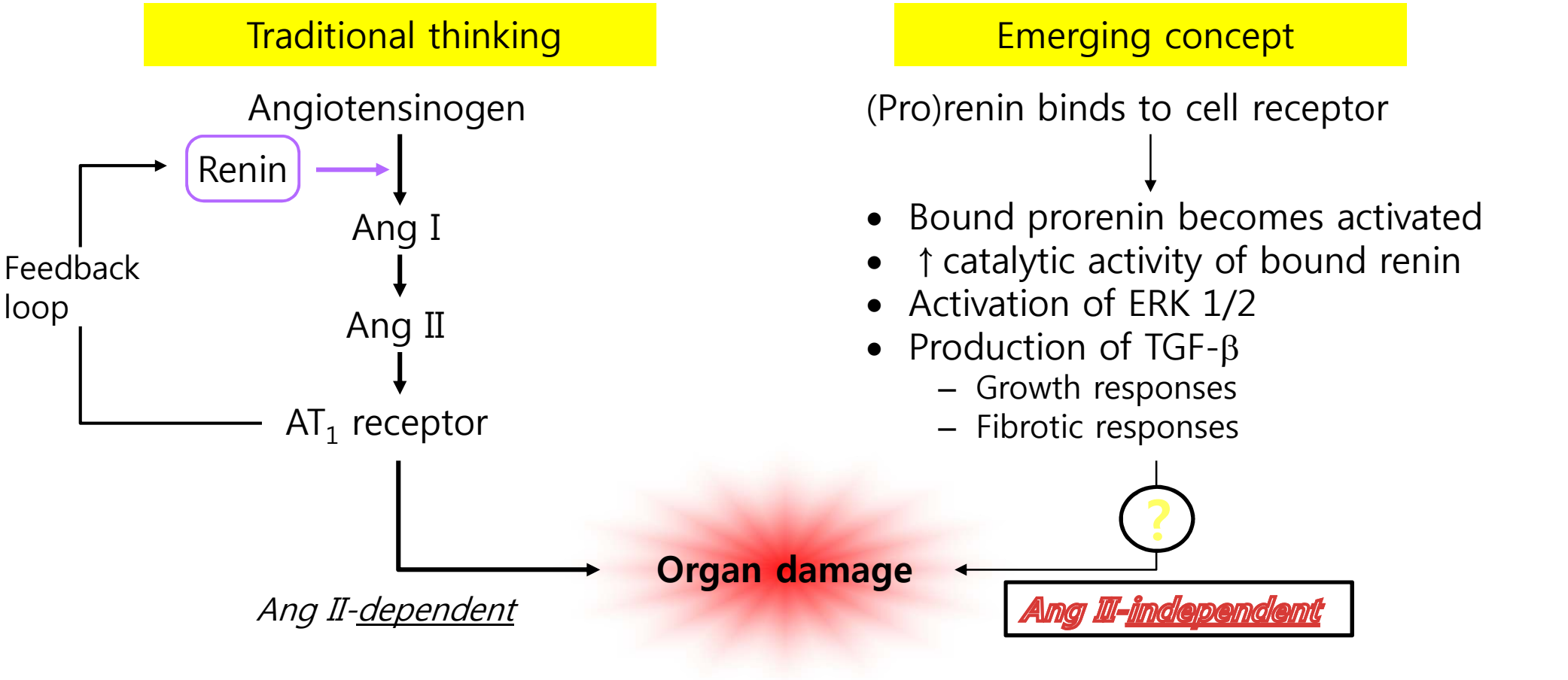


Data are shown as change from baseline in geometric mean (95% CI)
Baseline was the week –2 value
UACR, urinary albumin:creatinine ratio

(NEJM, 2008)

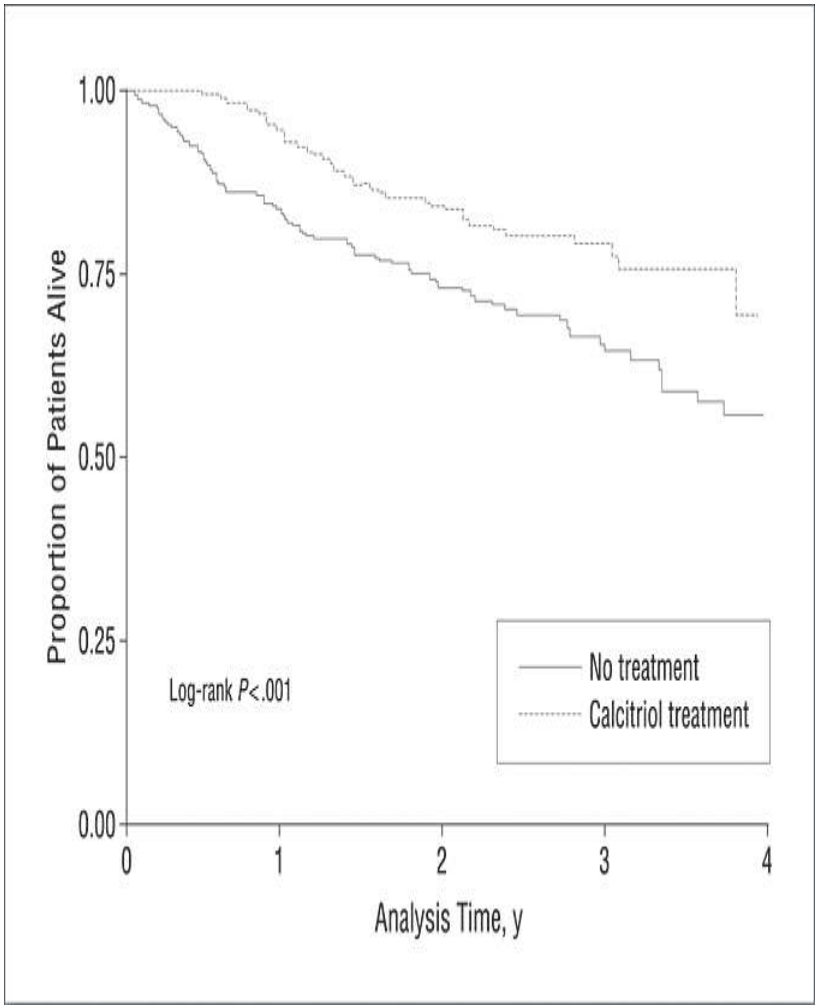
Emerging concept: (Pro)renin receptor

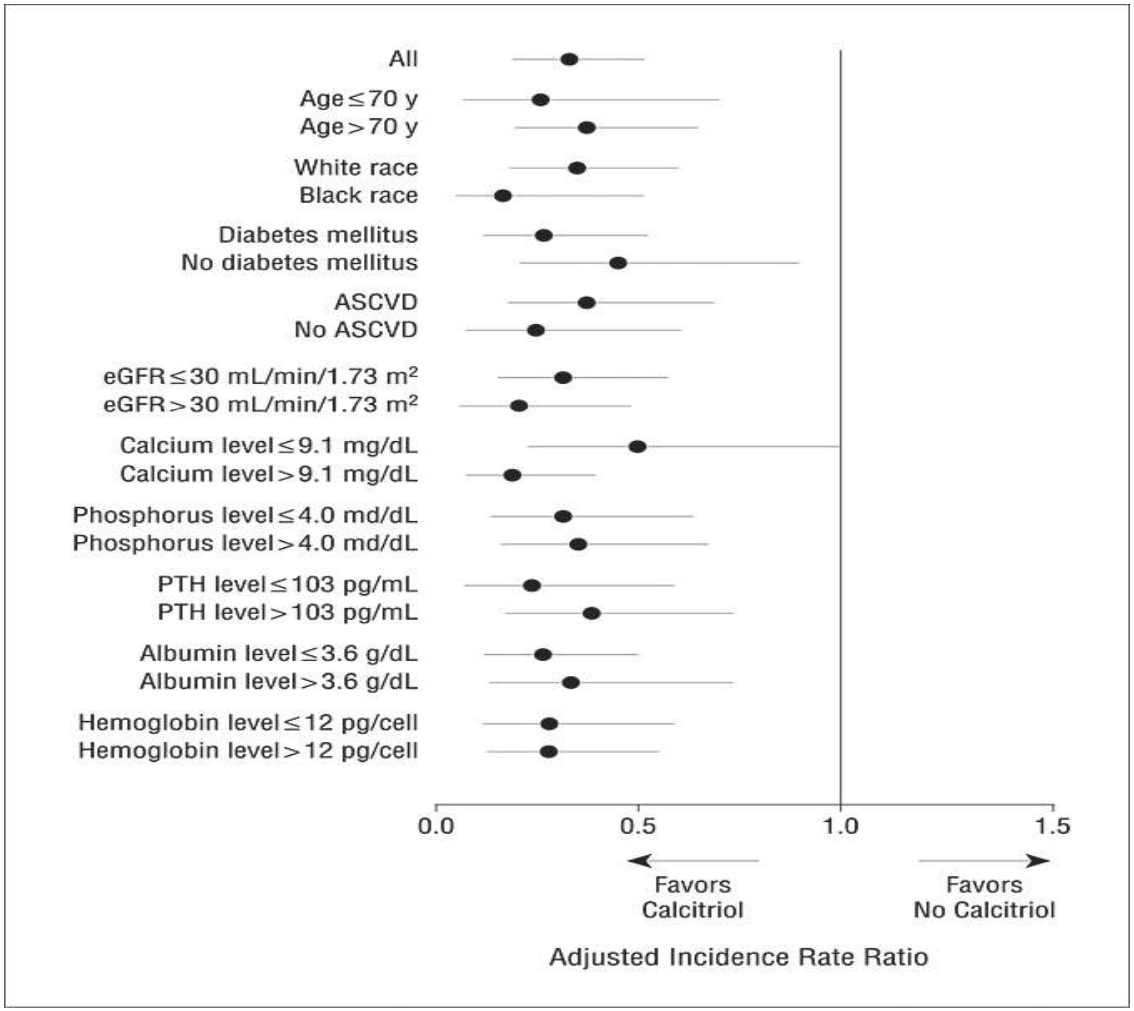
Renin may cause organ damage independent of Ang II



(Nguyen G *et al.*, J Clin Invest. 2002;109:1417–1427)
(Guo C *et al.*, J Clin Invest. 2001;107:703–715)
(Huang Y *et al.*, Kidney Int. 2006;69:105–113)

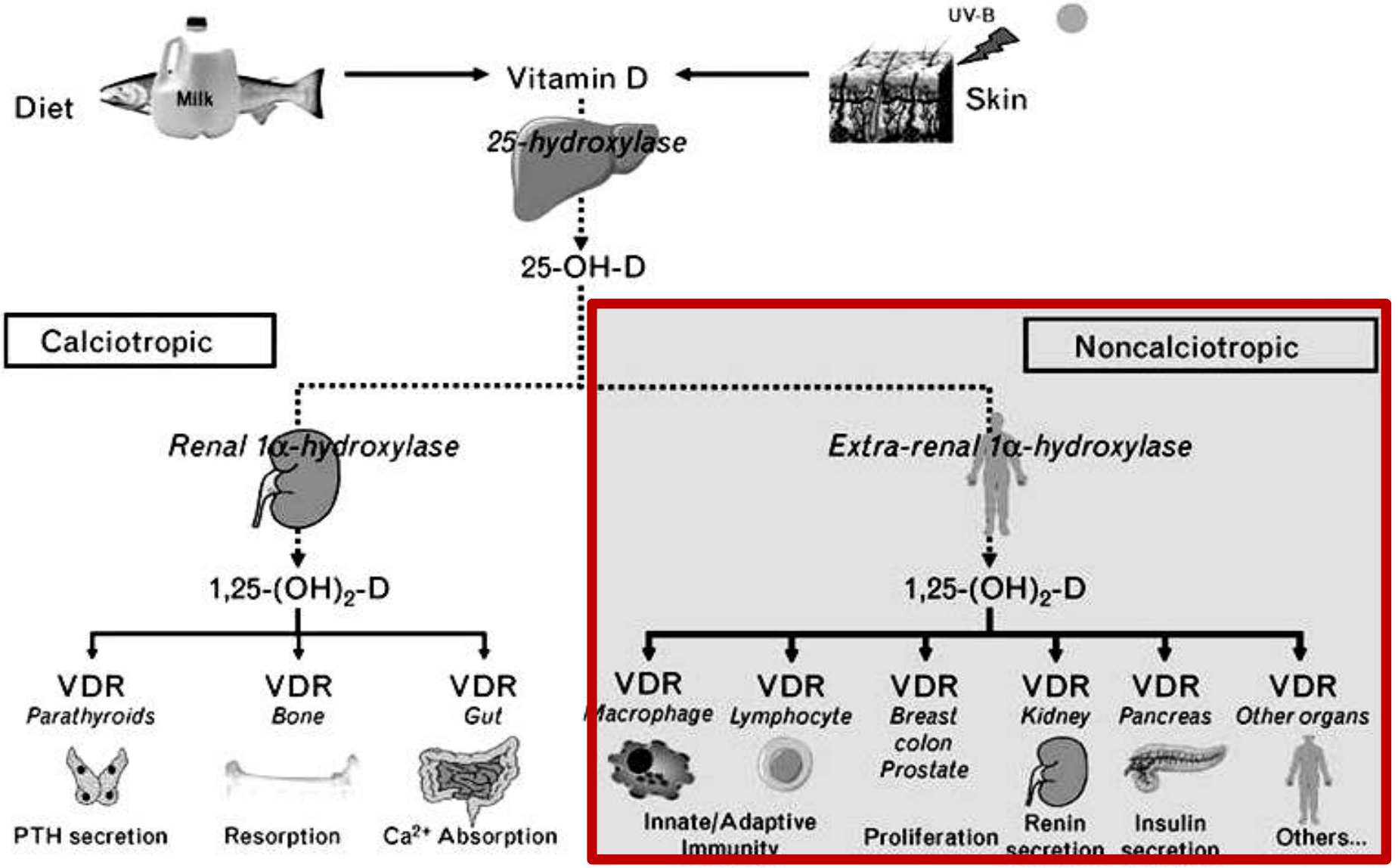
Association of Activated Vitamin D Treatment and Mortality in Chronic Kidney Disease



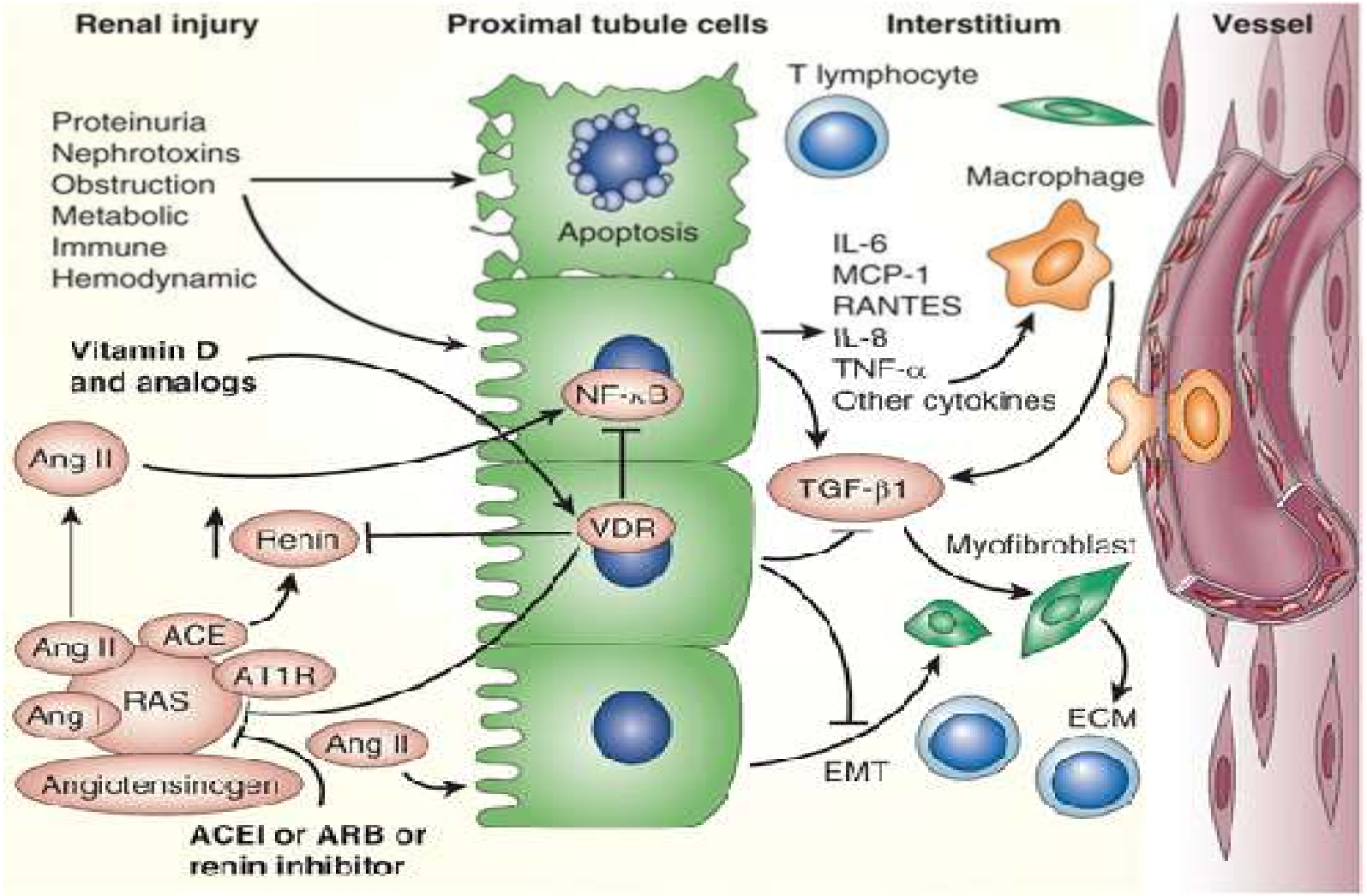


(Arch Intern Med, 2008)

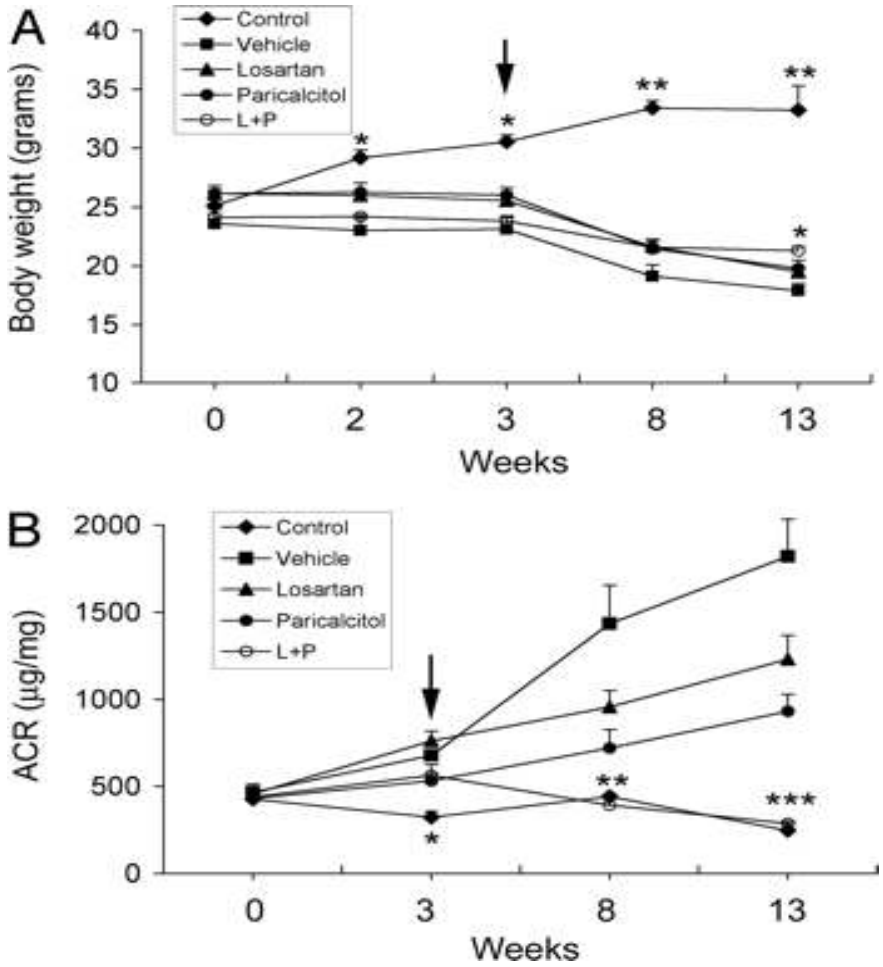
Noncalciotropic physiologic effect of Vitamin D activation

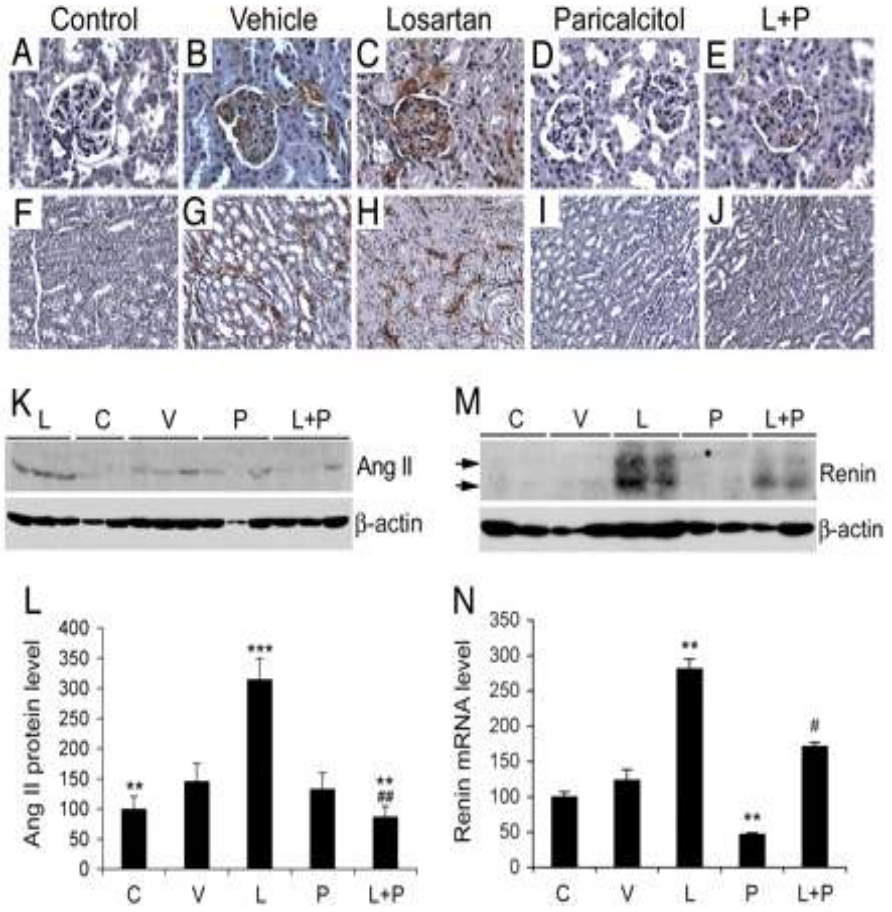


Renoprotective effects of combination therapy with renin–angiotensin system inhibitors and vitamin D receptor activators in chronic kidney disease



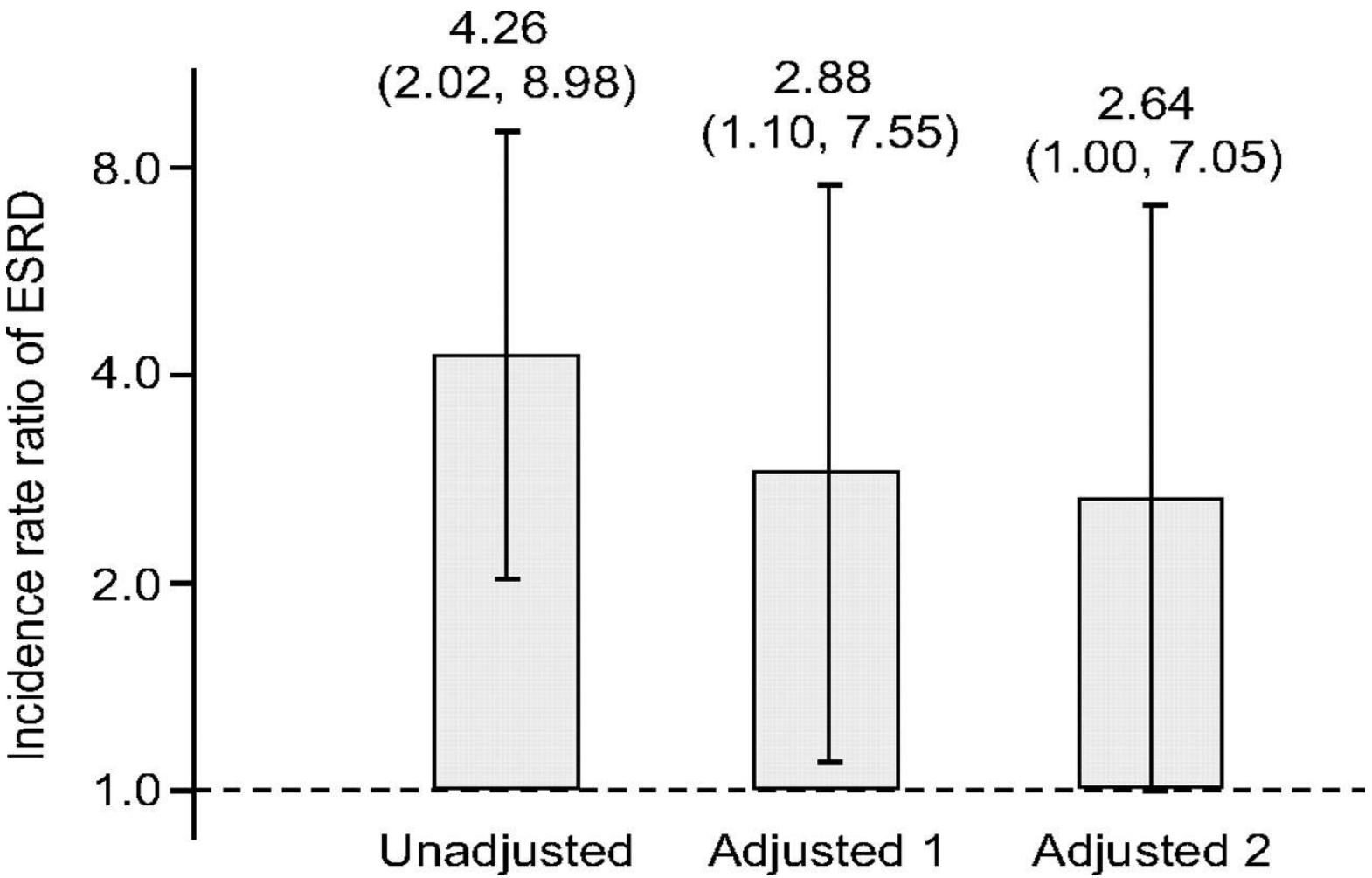
Combination therapy with AT1 blocker and vitamin D analog markedly ameliorates diabetic nephropathy: Blockade of compensatory renin increase





(Proc Natl Acad Sci USA, 2008)

Relative Risk for ESRD in pts with 25(OH)D levels <15 ng/ml



(J Am Soc Nephrol, 2009)

Management Strategies in diabetic nephropathy

- **Early screening** and diagnosis of diabetic kidney disease
- **Careful interpretation of microalbuminuria** in type 2 DM
- Multi-faceted approach to care of DKD patients
- Contoversial issue of ACEi and ARB combination
- Effect of **aldosterone antagonist**: selected patients
- Role of **PPAR agonist** in CVD mortality and renoprotection
- Effect of **direct renin inhibitor** in diabetic nephropathy
- **New marker** for early detection and progression in DKD
- Monitoring of progression of DKD: **UAE and GFR**
- Role of **vitamin D therapy, ACE2 agonist** in diabetic nephropathy
- **Combination therapy** with different RAS blockade: ideal group ?