Aldosterone and Kidney Disease

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Nephrology Dialysis Transplantation

Full Review

Aldosterone and kidney: a rapidly moving frontier (an update)

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Keywords:

NDT (2013) e-pub Nov.4th

*Aldosterone **beyond** the classical concept*

The postclassical concept

Treatment targets <u>beyond epithelial issues</u>
and synthesis <u>beyond adrenal gland</u>

Treatment targets

- **Heart** *(LV hypertrophy, fibrosis in right and left ventricle)*
- **Brain** *(hypothalamus - hypertension, salt appetite)*
- **Vessel wall**
- **<u>Kidney:</u> *structures beyond distal tubulus*** →
  glomerulus, interstitium, epithelial tubular cells

Synthesis

- **Aldosterone <u>- Synthesis</u>**
  *# **adrenal gland** (endocrine)*
  # local synthesis in gut, skin, CNS, heart, renal cortex …

Subtotal Nephrectomy *(SNX)*

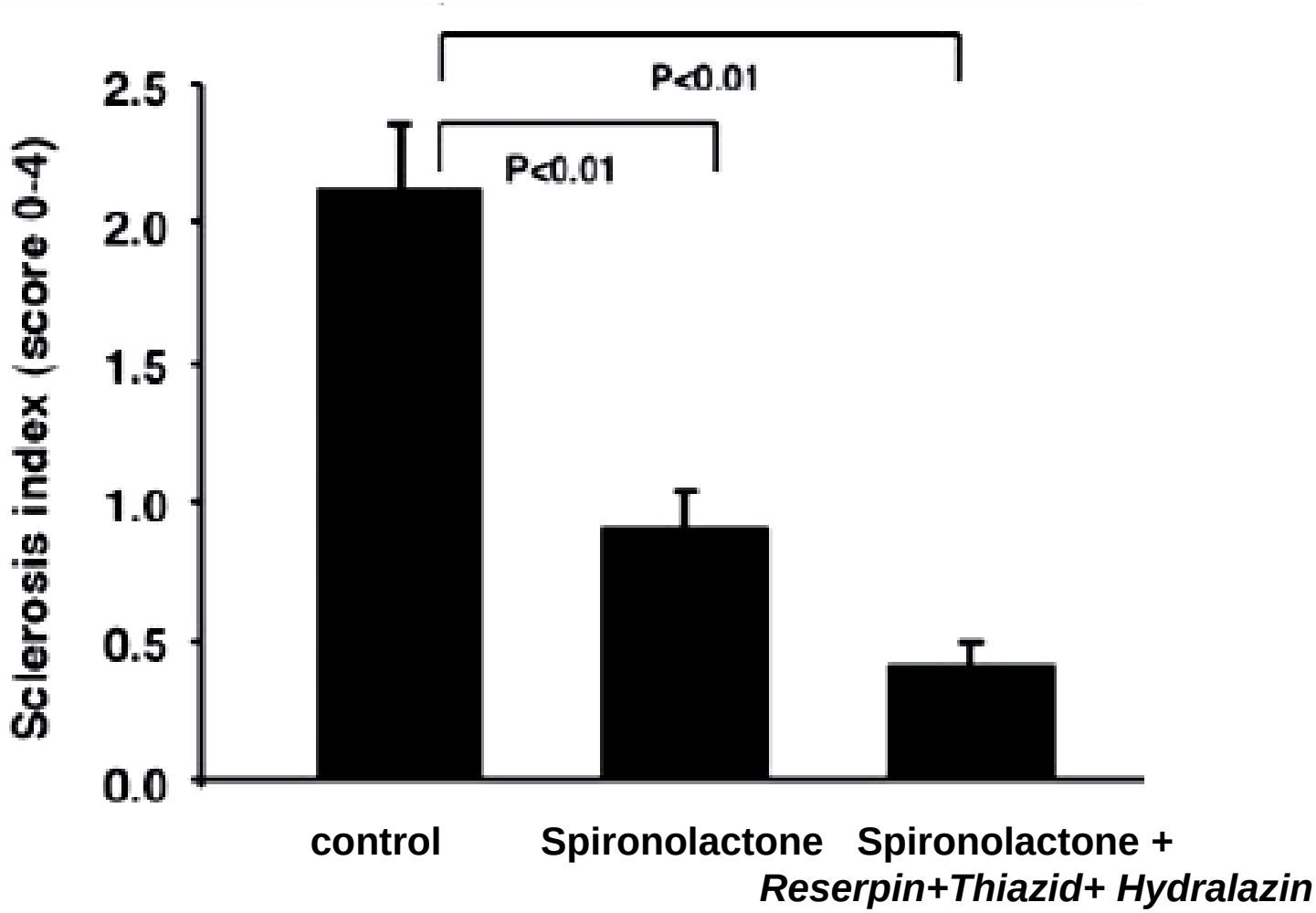
Aldosterone overcomes the effect of RAS blockade (ACEi+ARB)

	p-Aldosterone (pg/ml)	Heartweight (g)	Proteinuria (mg/day)
- **Sham-op**	50±12	1.03±0.05	19±6
- **SNX**	526±250	1.33±0.19	203±103
- **SNX + ACEi+ARB**	181±124	0.88±0.11	30±15
- **SNX + ACEi+ARB+ Aldosterone**	487±114	1.28±0.12	217±71

true for exogenous and endogenous aldosterone

Greene,J.Clin.Invest,(1996) 98:1063

Spironolactone :
in the rat model after subtotal nephrectomy :
regression of established glomerulosclerosis



Aldigier, J.Am.Soc.Nephrol.(2005) 16:3306

“High salt” antagonizes the beneficial effect of aldosterone blockade on the development of:

 # thrombotic and/or proliferative lesions in glomeruli

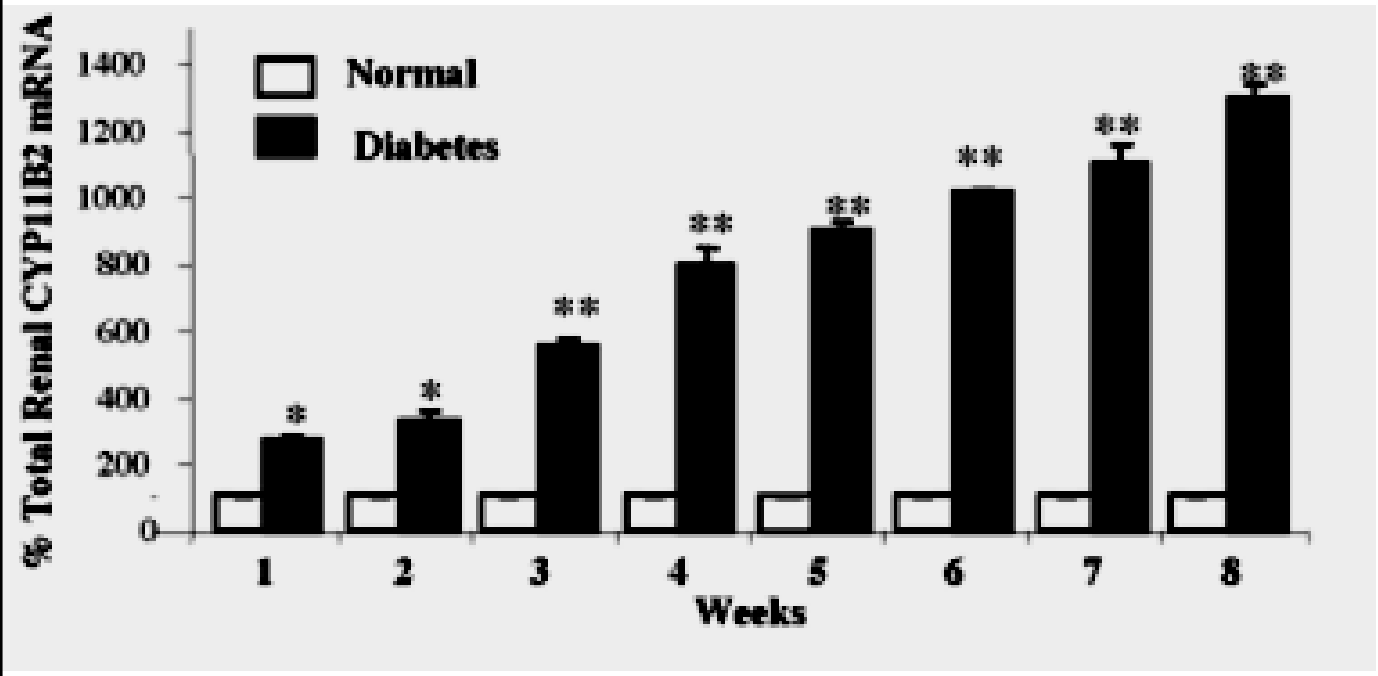
 # lesions of renal vessels

Rocha, Hypertension (1999) 33:232

Rocha, Endocrinology (2000) 141:3871

Terada, Clin.Exp.Nephrol.(2012) 16:81

Beyond synthesis of aldosterone in the adrenal gland
local (!) synthesis of aldosterone occurs in damaged organs
e.g. the kidney in diabetes



Aldosterone synthase
(CYP11B2)

in the renal cortex
of adrenalectomised diabetic rats
local production of aldosterone

Xue,
Hypertension (2005) 46:584

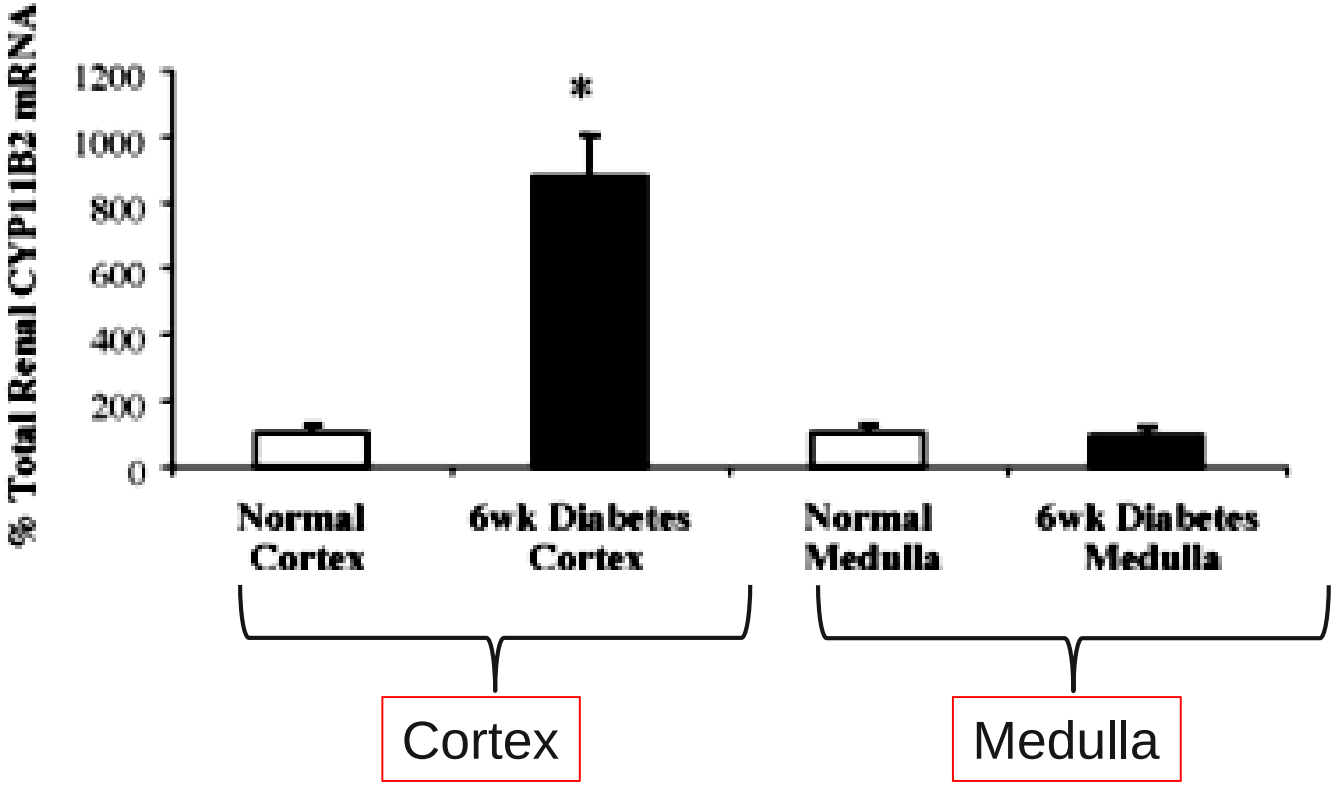
Because there is local synthesis of aldosterone :
the plasma concentration of aldosterone is
not necessarily the only relevant indication for aldosterone blockade

In adrenalectomised diabetic rats

local production of Aldosterone restricted to the renal cortex,

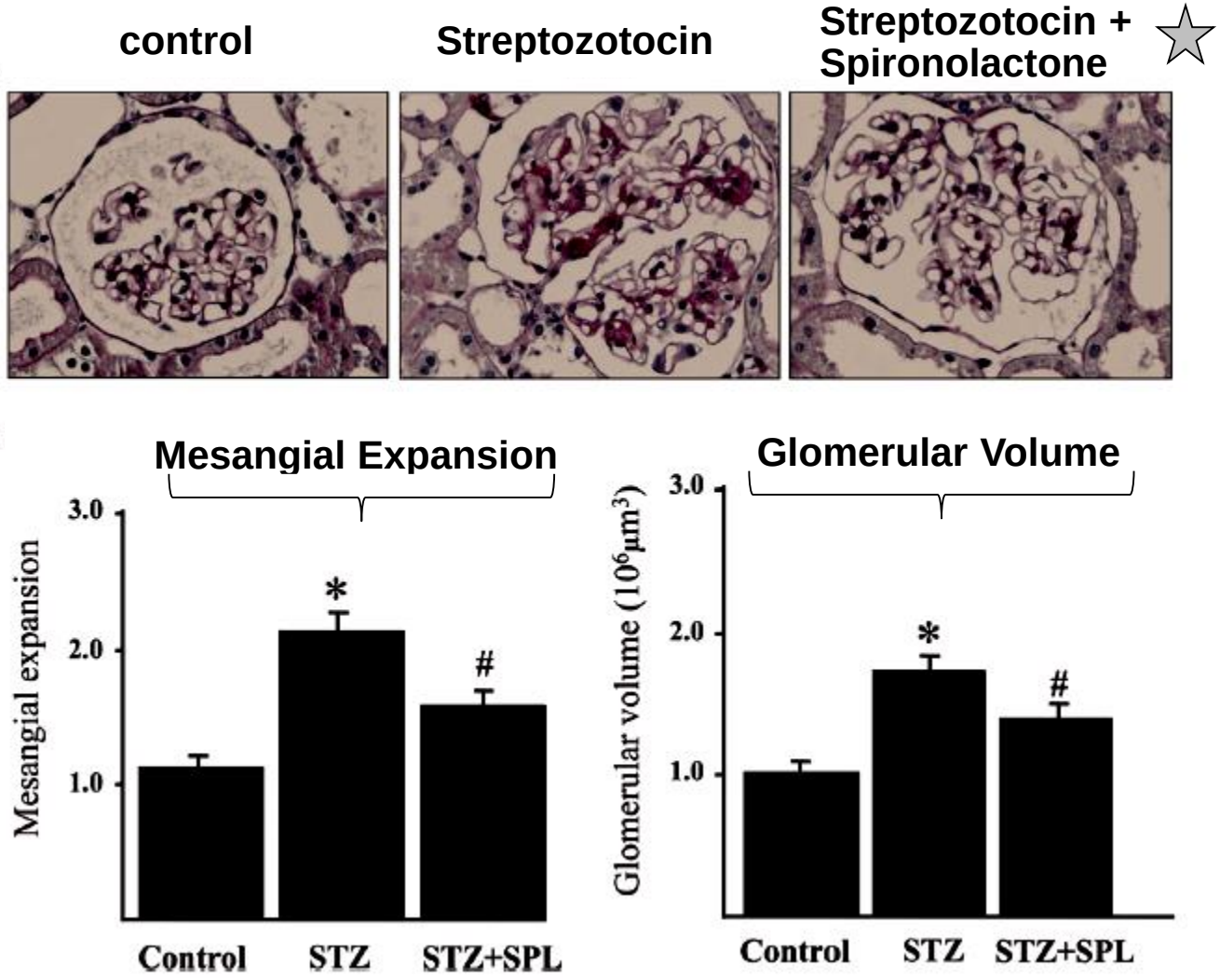
but not does not occur in the renal medulla

Aldosterone-Synthase (CYP11B2)



Xue, Hypertension (2005) 46:584

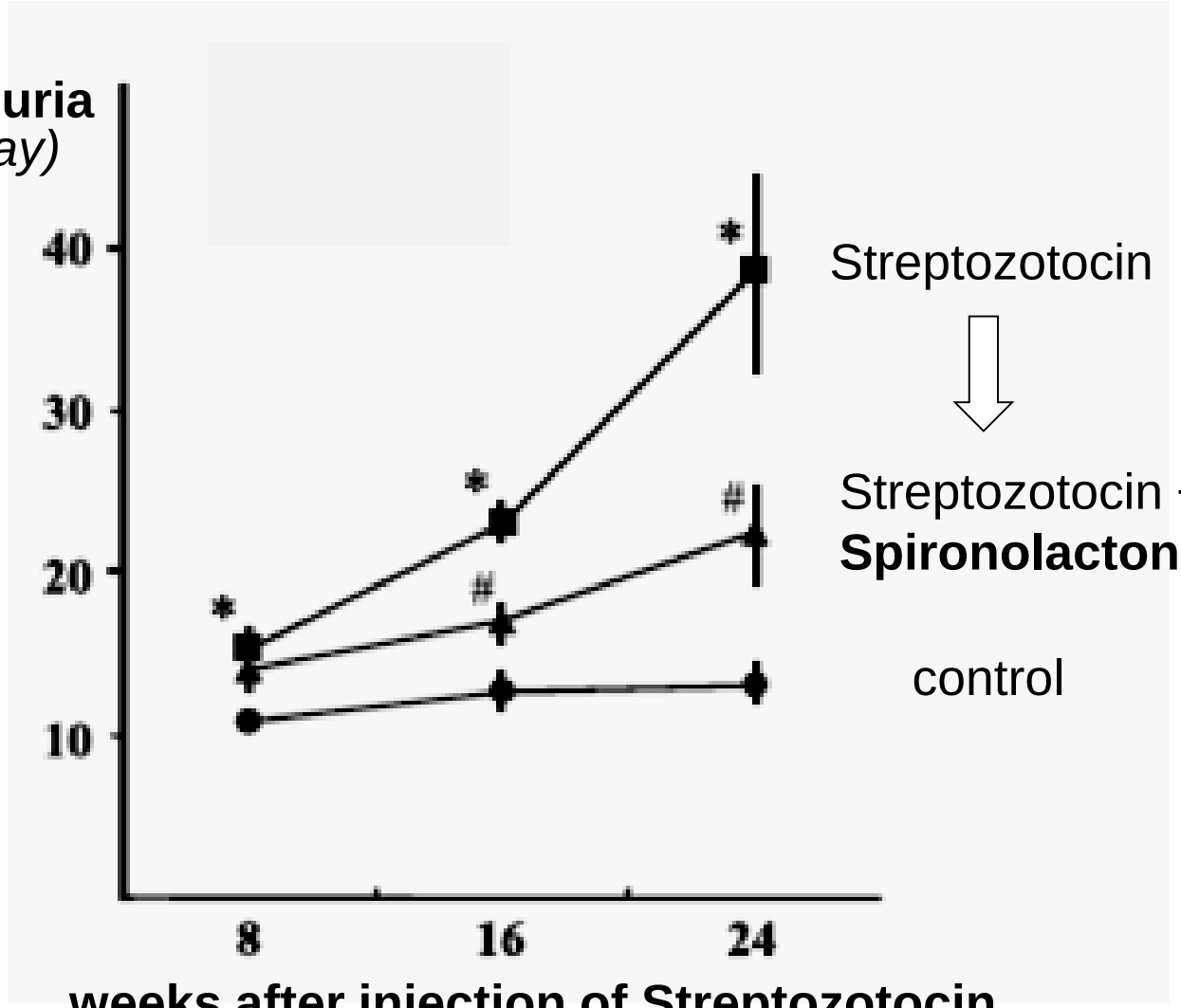
Spironolactone mitigates ☆ glomerular damage from hyperglycemia:
i.e. podocyte damage, mesangial expansion and *glomerulomegaly*



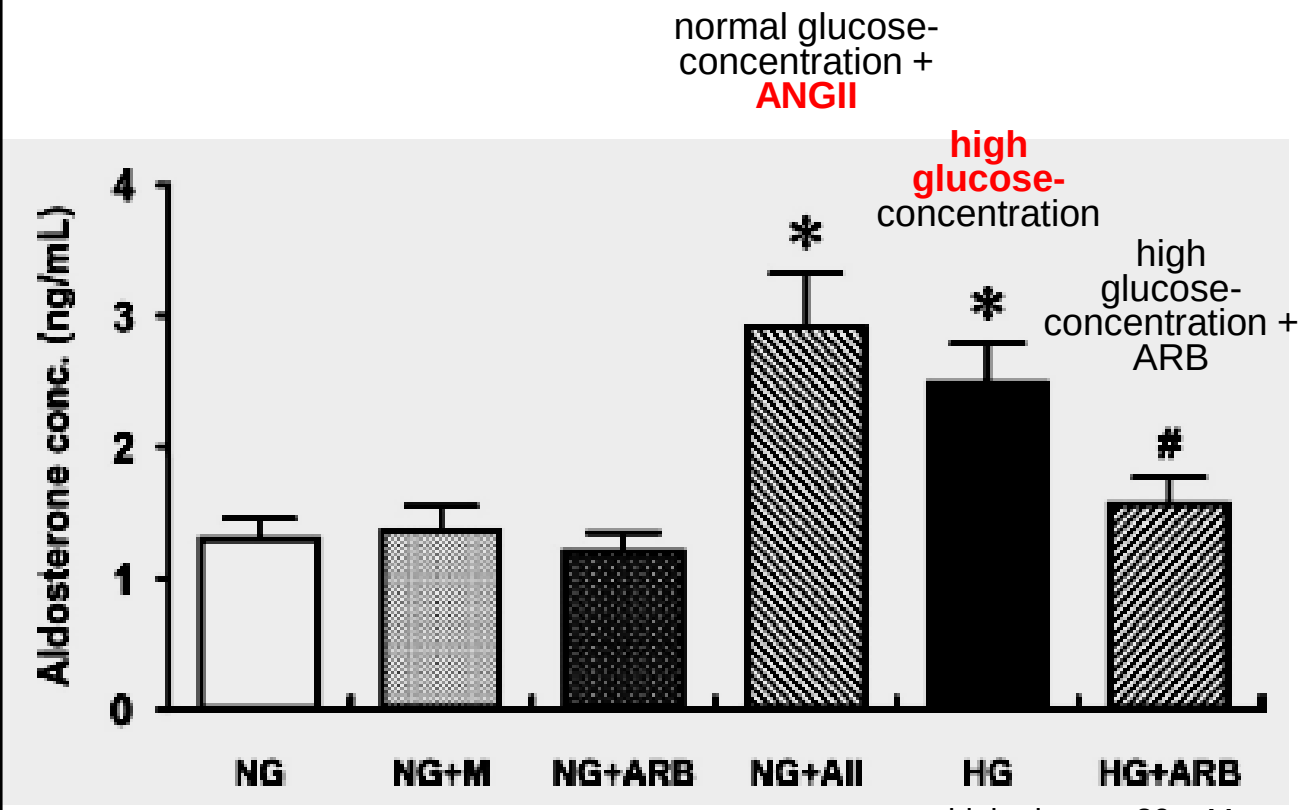
Toyonaga, Nephrol.Dial.Transplant.(2011) 26:2475

Spironolactone reduces podocyte damage caused by hyperglycemia :

⇨ **Spironolactone thus lowers proteinuria in diabetic rats**



Toyonaga, Nephrol.Dial.Transplant.(2011) 26:2475



Angiotensin receptor blocker antagonises glucose-induced aldosterone synthesis

Aldosterone synthesised by podocytes in vitro

stimulated by :

 # ANG II

 # high glucose concentration

reduced by :

Angiotensin-receptor-blocker

Lee, Am.J.Physiol.Renal (2009) 297:F1381

In humans :

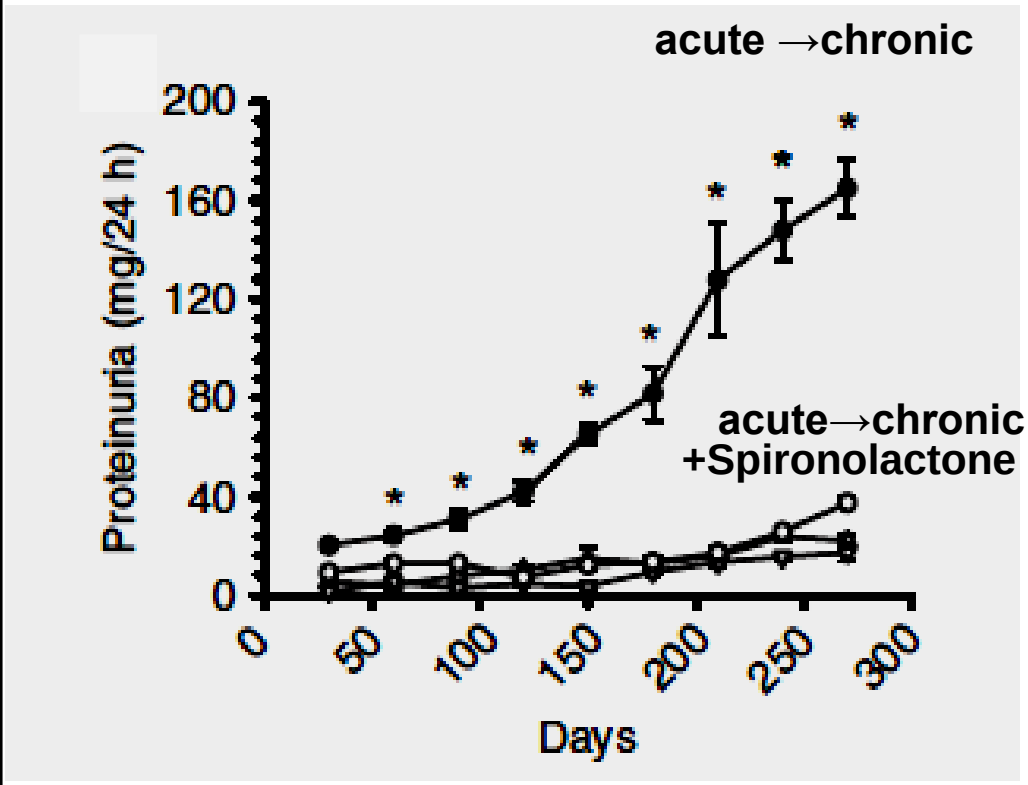
Aldosterone predicts incident CKD and microalbuminuria

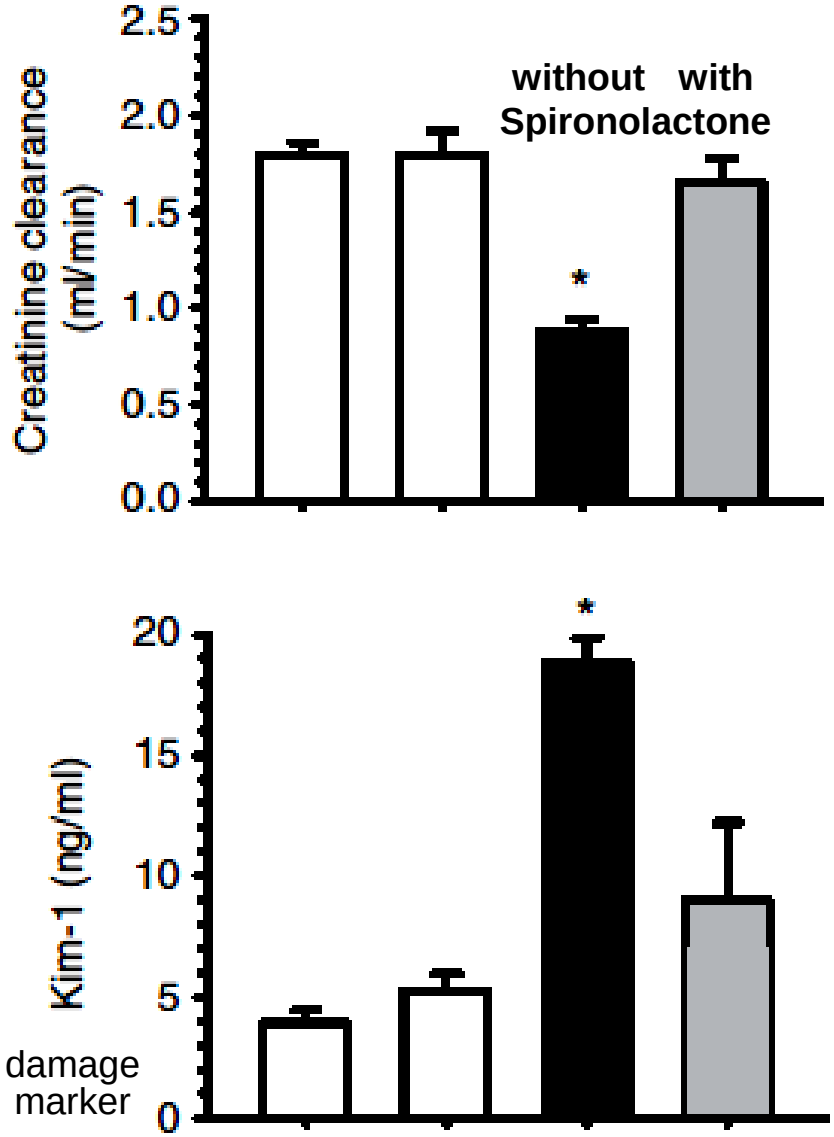
(Framingham offspring study)

Biomarkers	*P*	Odds Ratio	95% Confidence Interval
Incident CKD			
entire panel	0.0005		
specific markers			
homocysteine	<0.0001	1.41	1.20 to 1.65
aldosterone	0.047	1.17	1.002 to 1.36
Incident microalbuminuria			
entire panel	0.003		
specific markers			
aldosterone	0.017	1.23	1.04 to 1.46
BNP	0.0037	1.30	1.09 to 1.54
homocysteine	0.04	1.20	1.01 to 1.42

Fox, J.Am.Soc.Nephrol.(2010) 21: 2143

In rats spironolactone prevents secondary chronic renal insufficiency after recovery from ischemic acute renal failure





Barrera-Chimal, Kidney Internat.(2013) 83-93

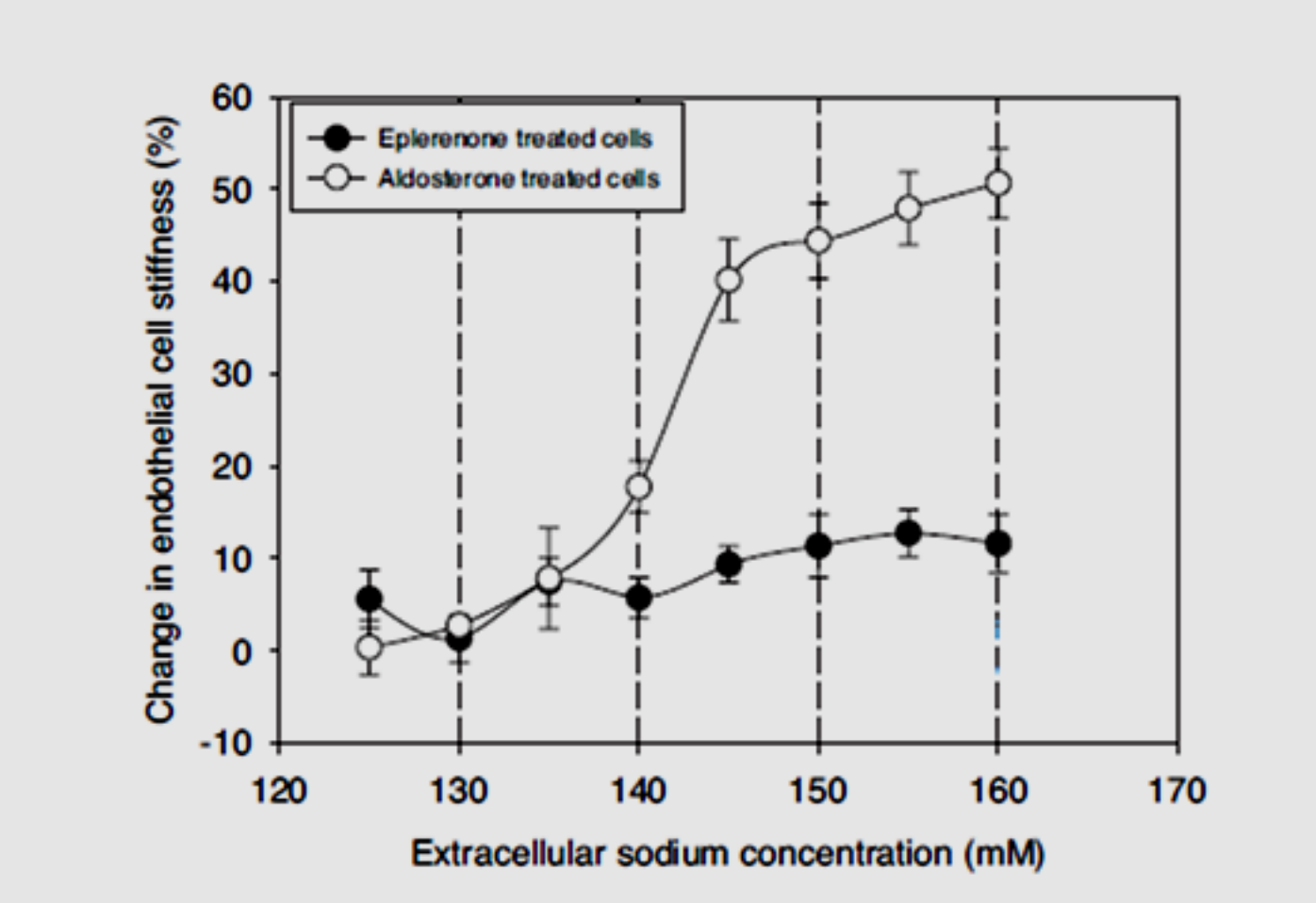
[Na^+] causes stiffening of human vascular endothelial cells in vitro

endothelial cell stiffness

stiffening by Aldosterone ○

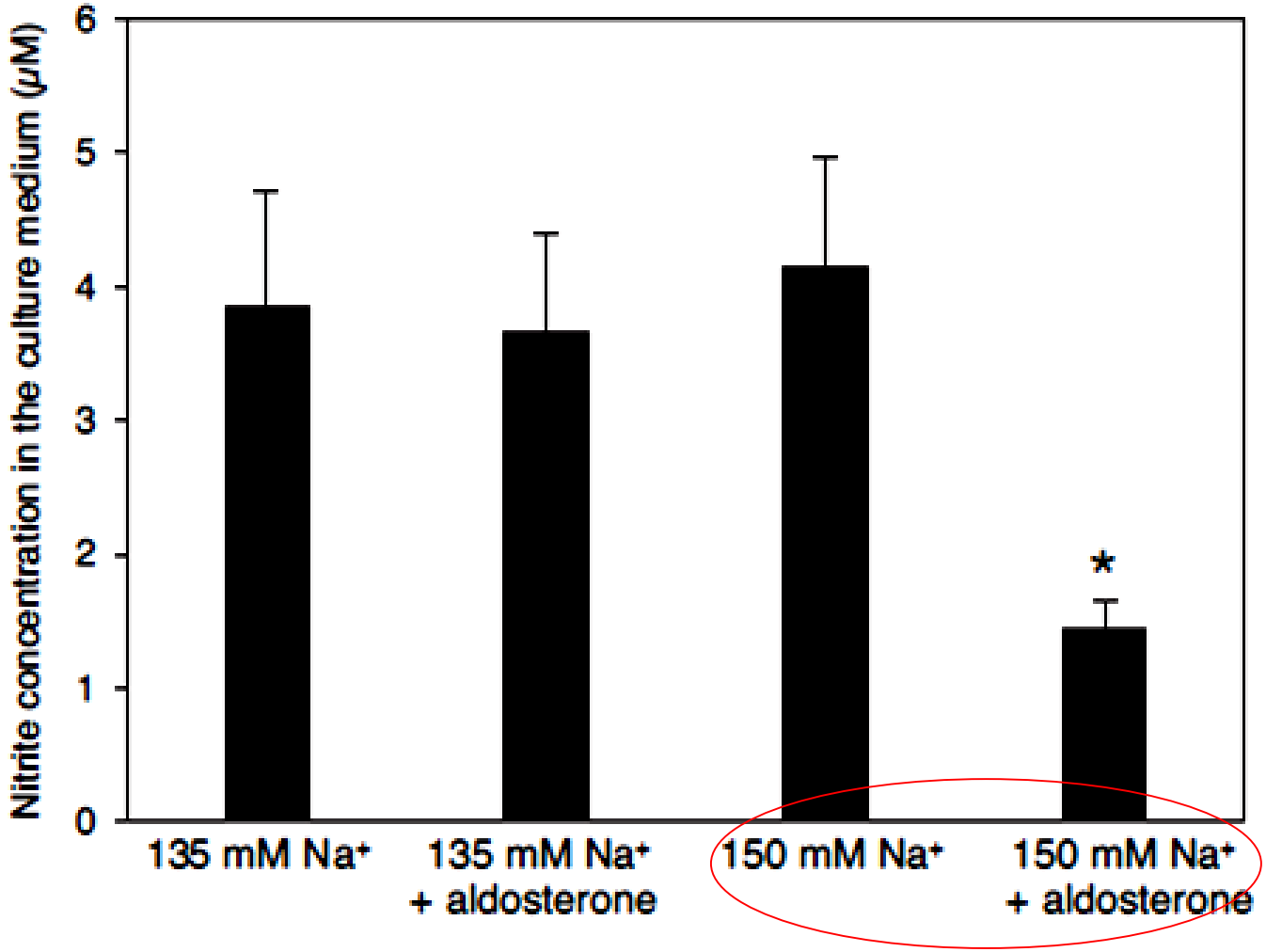
no stiffening by Eplerenone ●

presumably also relevant for renal vessels !



Oberleithner, Proc.Natl.Acad Sci USA (2007) 104:16281

Human endothelial cells : high [Na^+] concentration plus aldosterone : inhibition of nitrite *(dilatory)* synthesis *(permissive effect)*



Oberleithner, Proc.Natl.Acad Sci USA (2007) 104:16281

Hyperfiltration in primary hyperaldosteronism

beneficial renal effect of Spironolacton/Eplerenon

prospective multicentric study in Germany :
29 patients with newly diagnosed hyperaldosteronism
overall cohort of 119 patients

1° aldosteronism :
 # increased GFR and increased albumin/creatinin ratio
 # after start of treatment with Spironolactone/Eplerenone
⇨ GFR and albuminuria declined

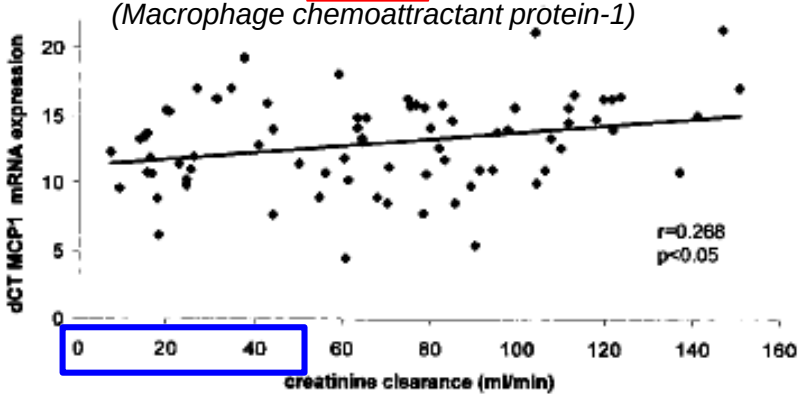
Aldosterone causes glomerular hyperfiltration and albuminuria

Patients treated with well regulated blood pressure
→ renal parameters not altered

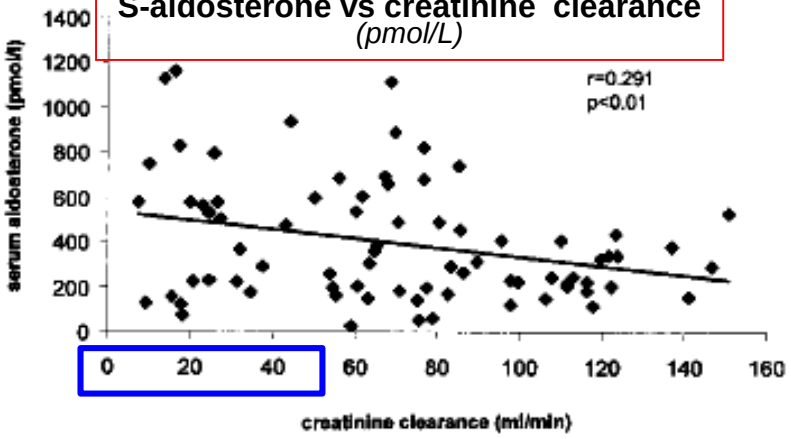
Fourkiotis, Europ.J.Endocrinol.(2013)169:75

Arbeit macht kaputt *(work kills)*
Karl Marx
~ hyperfiltration damages the glomerulus

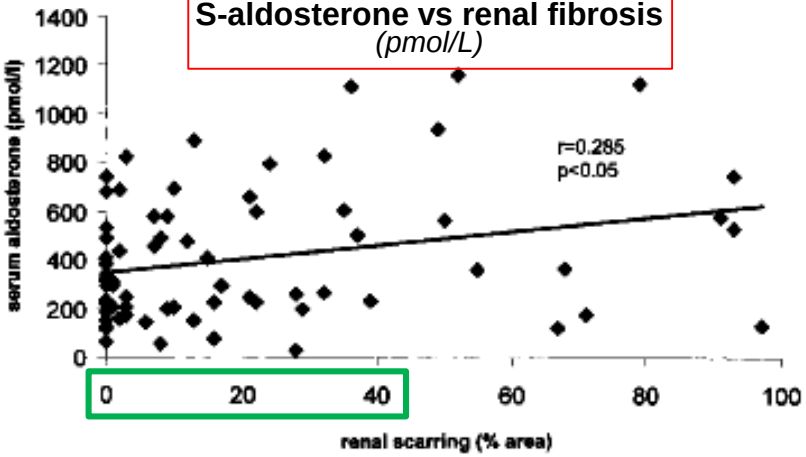
MCP-1
(Macrophage chemoattractant protein-1)



S-aldosterone vs creatinine clearance
(pmol/L)



S-aldosterone vs renal fibrosis
(pmol/L)



CKD patients

Serum aldosterone concentration and renal findings

Renal biopsy in
CKD patients with pronounced proteinuria
at different creatinine clearances

at decreased creatinine clearance :

 # MCP1mRNA in kidney ↓

 # serum aldosterone ↑

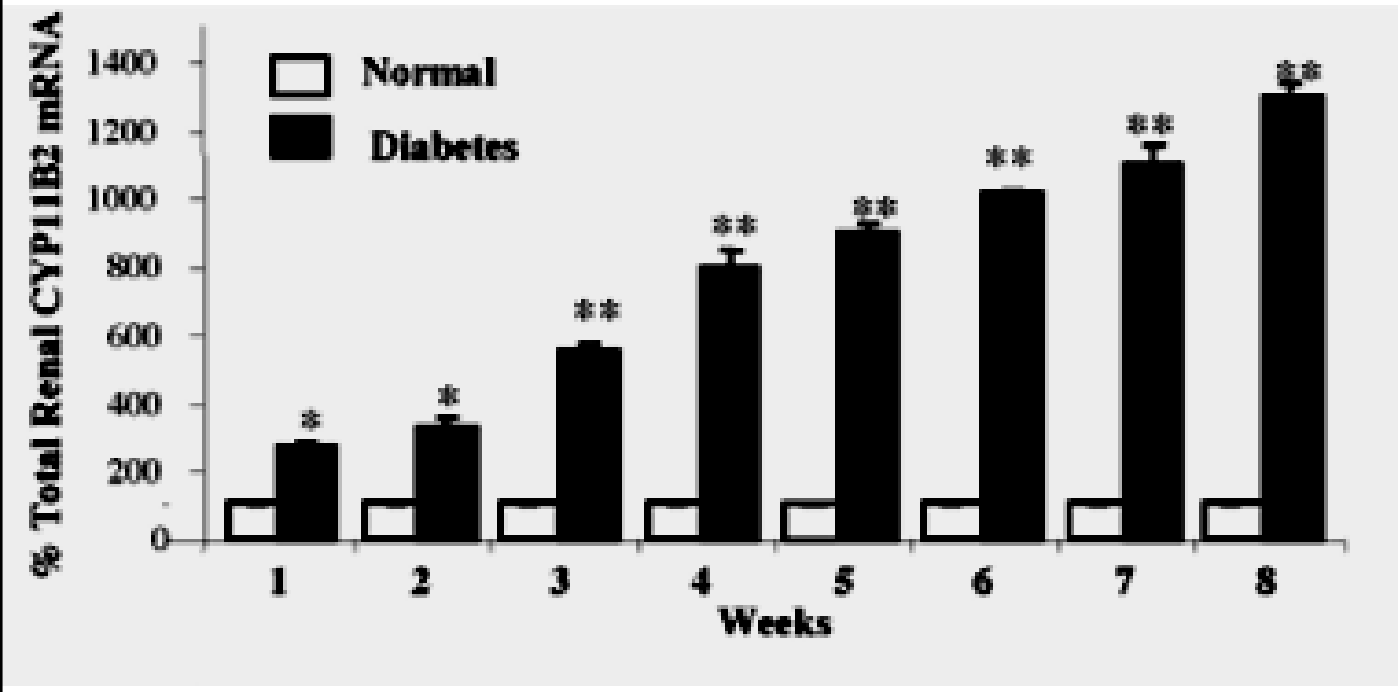
 # renal fibrosis no (significant) correlation ~

Quinkler,
Circulation (2005) 112:1435

Are only plasma aldosterone values relevant ?

They may underestimate the role of local aldosterone synthesis

and the therapeutic potential of aldosterone blockade

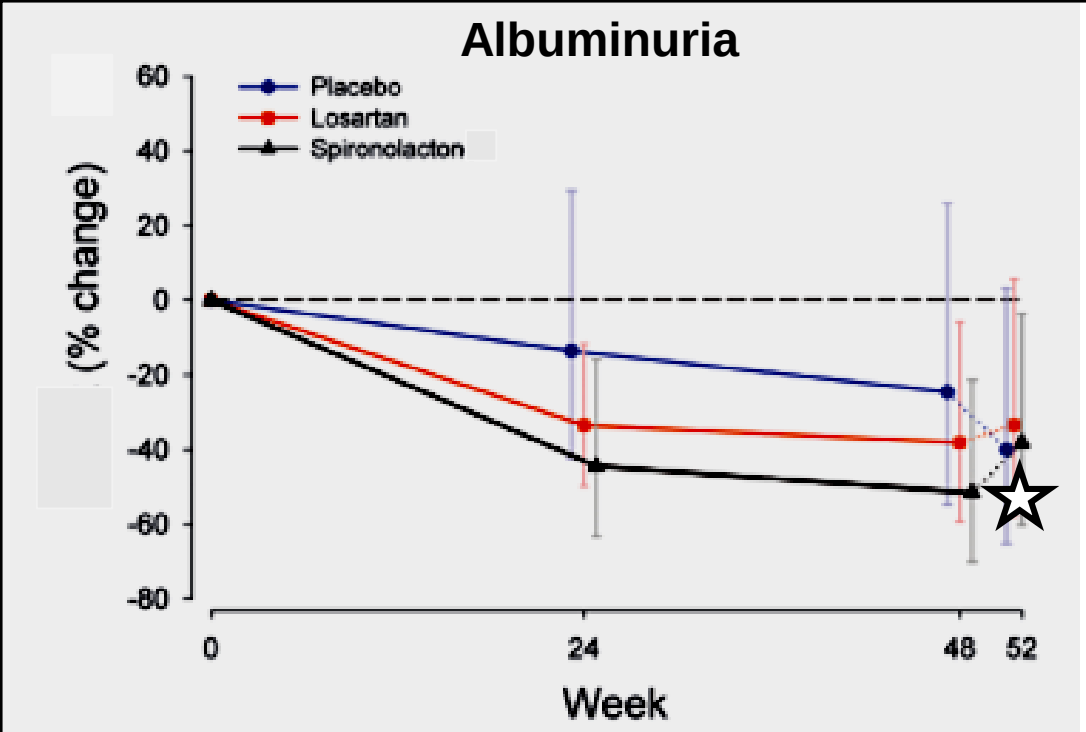


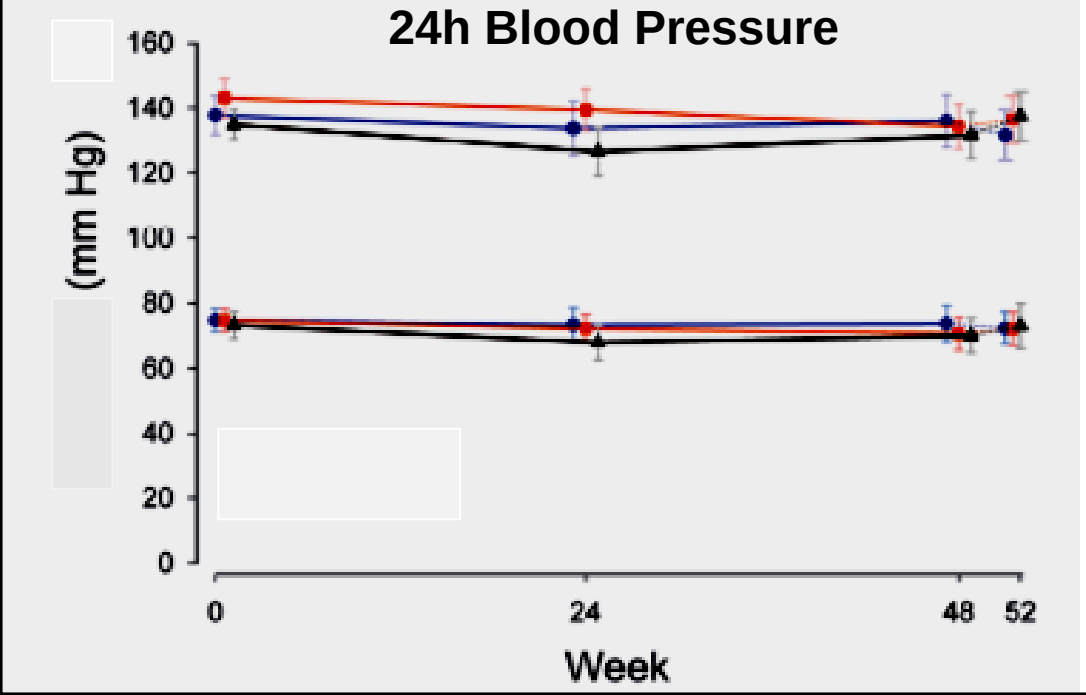
cortex

Potential role of local aldosterone synthesis:

Progressive expression of CYP11B2mRNA in the renal cortex of diabetic rats

Xue, Hypertension (2005) 46:584





Diabetic Nephropathy

aldosterone blockade effective even after maximal inhibition of ACE :

additional inhibition by mineralocorticoid antagonist :

— **Placebo**

— **Angiotensinreceptor blocker**

— **Mineralocorticoid-antagonist** ☆

Mineralocorticoid-blockade

additional renoprotection (albuminuria ↓)

despite

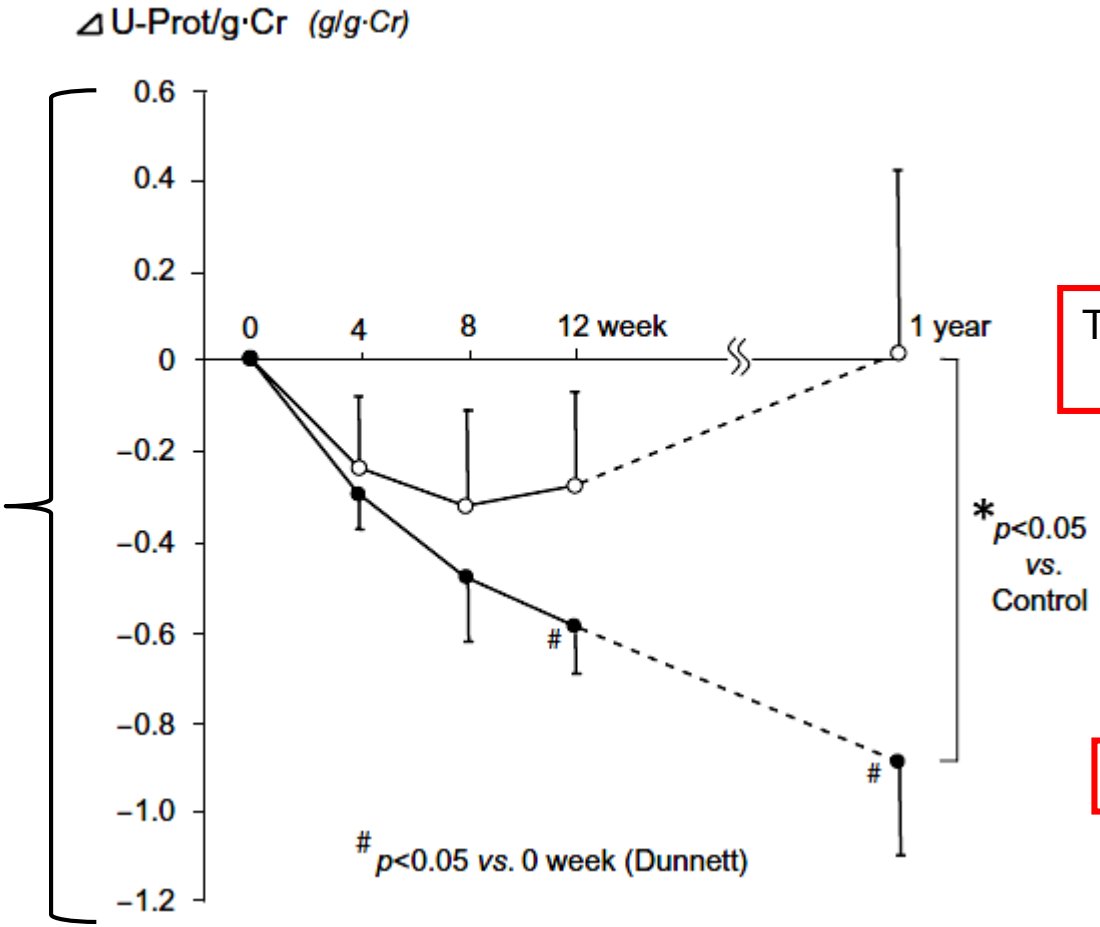
no further decrease of blood pressure

Mehdi,
J.Am.Soc.Nephrol.(2009) 20:2641

Nephrotic patients treated with ACEi plus ARB :
when Spironolactone *(but not Furosemide)* is added
⇨ further decrease of proteinuria unrelated to blood pressure

baseline

Enalapril 5 mg+
Losartan 50mg



intervention

Trichloromethazide 1mg
or Furosemide 10mg

Spironolactone 25mg

"benefit from Spironolactone not explained by its diuretic effect, but by abrogation of mineralocorticoid effect"

Furumatsu, Hypertens.Res.(2008) 31:59

Spironolactone on top of RAS blockade – further evidence of reduction of albuminuria and GFR

Doppel-blind randomised placebo-controlled cross-over study

21 type 1 **diabetics** with microalbuminuria

Spironolactone 25 mg/day or Placebo for 60 days

R_x Spironolactone:

 # albuminuria ↓ : from **90** mg/day to **35** mg/day (*p=0.01*)

 # GFR ↓ : from 78±6 to 72±6 mL/min/1.73m^2 *(p=0.003)* *(reversal of hyperfiltration?)*

 # blood pressure : unchanged

well tolerated, but in 2 patients S-K^+ rose to 5.7 mmol/L

Nielsen, Diabet.Med.(2012) 29:e184

In healthy individuals the serum-aldosterone concentration predicts future microalbuminuria and GFR decrease

Framingham population

2345 individuals

9.5 years follow-up

endpoints: eGFR < 60 ml/min/1.73m^2

urine albumin/creatinin > 25 (♀) or 17 (♂) mg/g creatinin

Predictors :

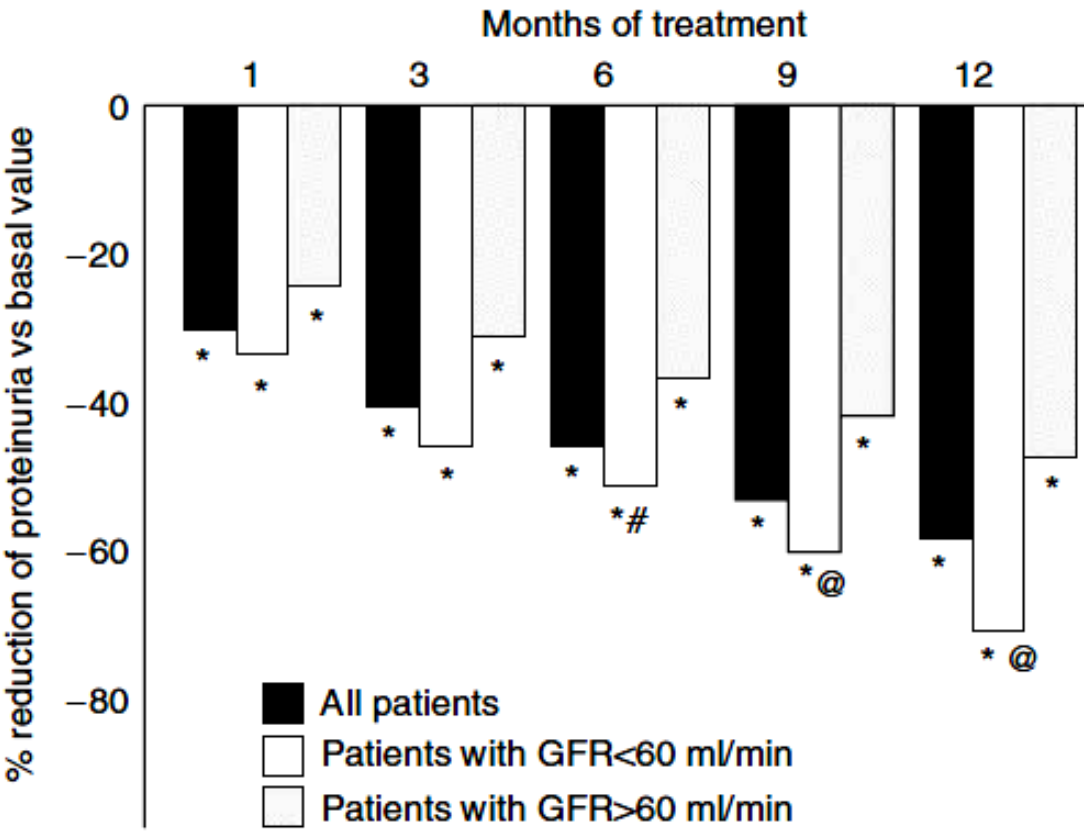
microalbuminuria : log serum aldosterone, BNP, homocystein

GFR < 60 ml/min/1.73m^2 : serum aldosterone and homocystein

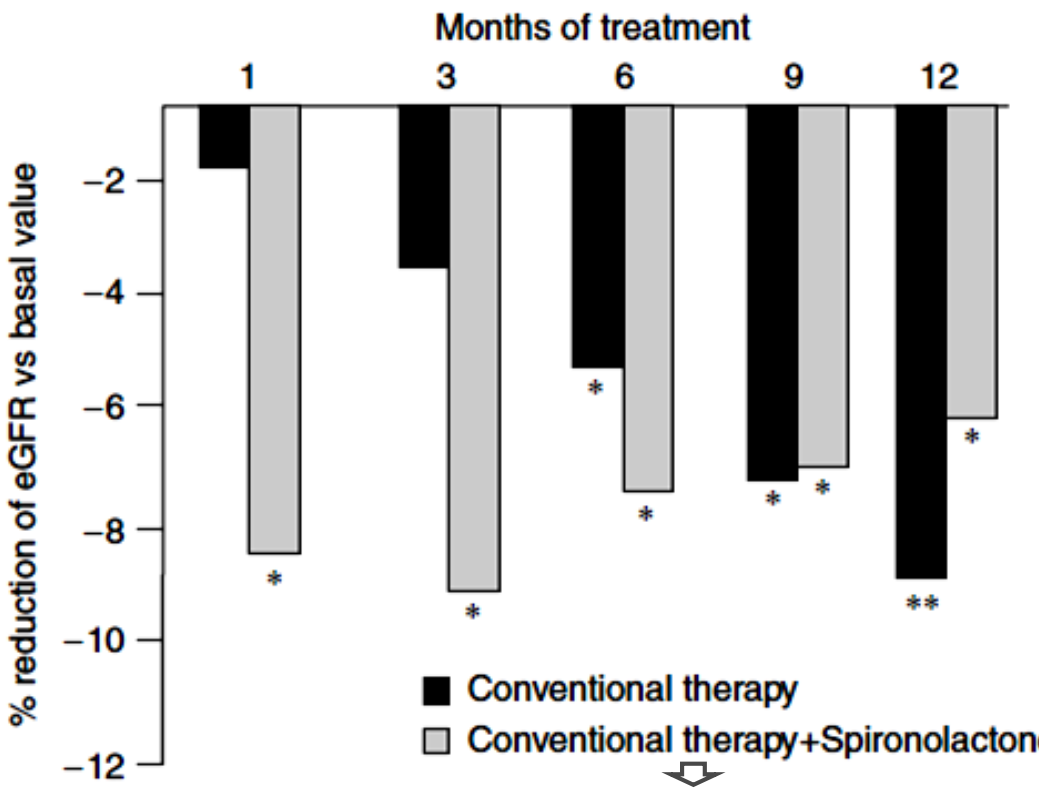
Fox, J.Am.Soc.Nephrol.(2010) 21:2143

Spironolactone *(25mg/day)* –
in <u>CKD patients</u> : progressive lowering of proteinuria and eGFR

Δ proteinuria



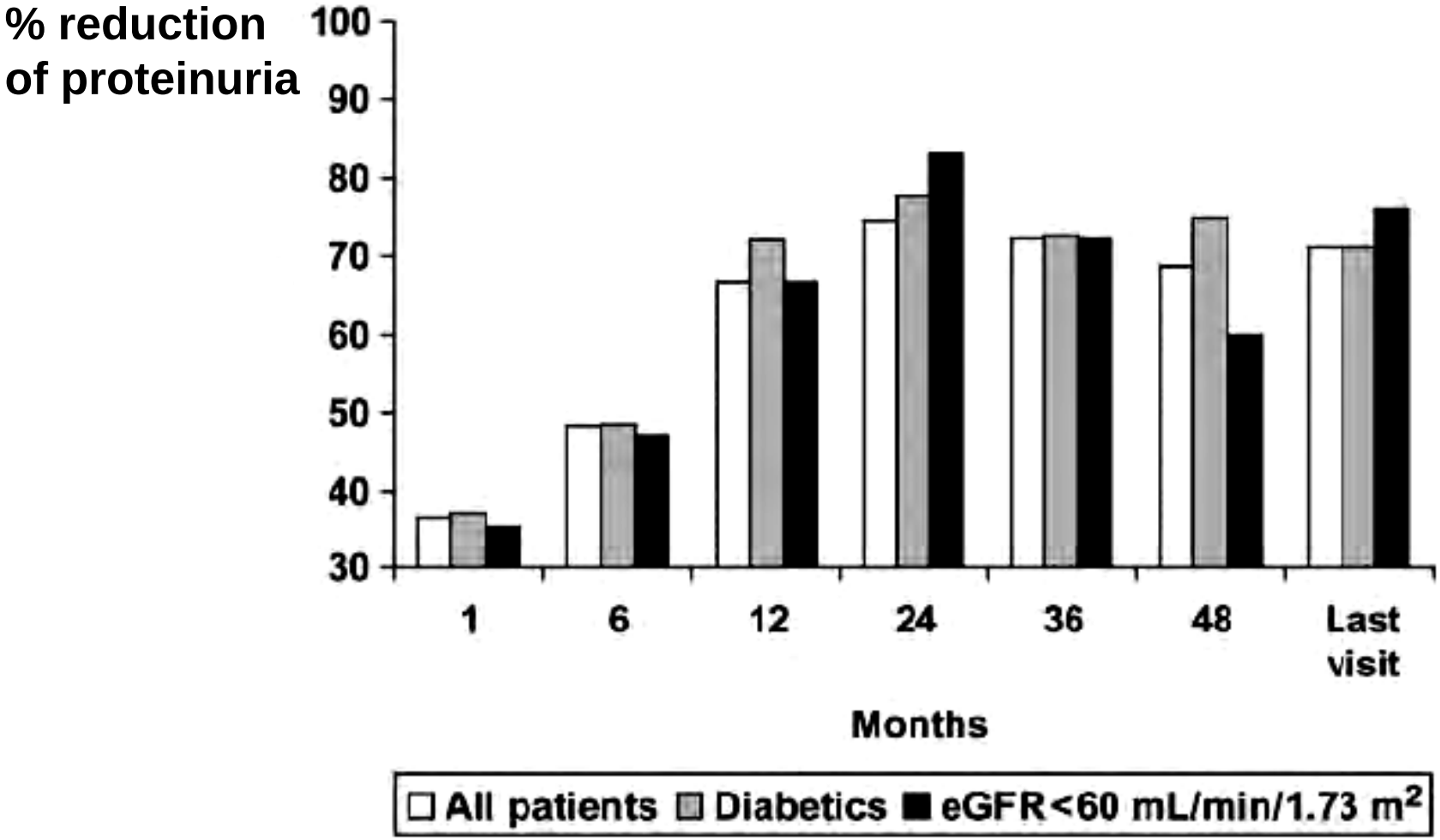
Δ eGFR



<u>early</u> : GFR decrease
(reversal of hyperfiltration)
<u>late :</u> less eGFR loss

Bianchi, Kidn.Internat.(2006) 70:2116

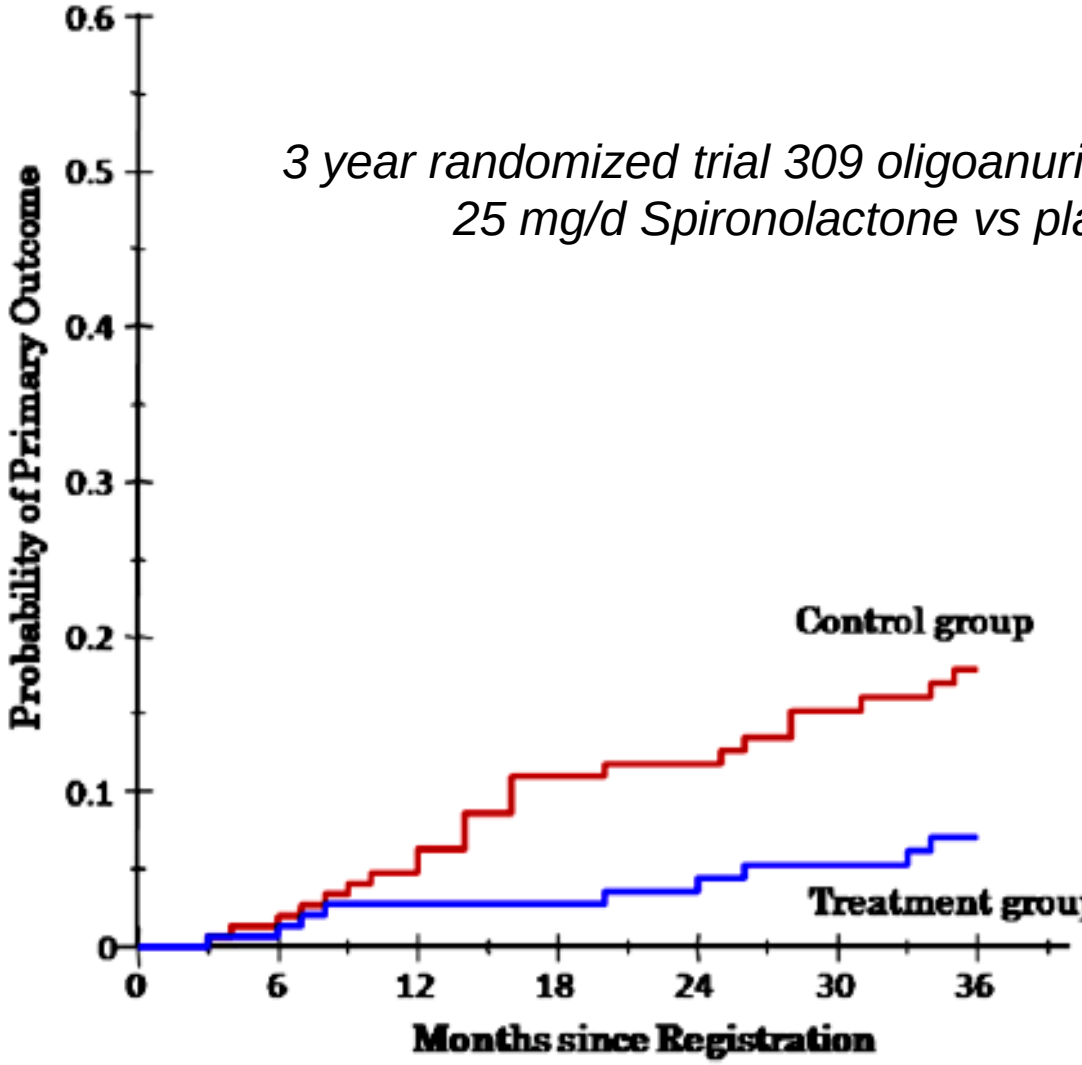
Spironolactone (25mg/d) on top of RAS blockade – again added benefit :progressive reduction of proteinuria by 61% *(43-77%)*



Morales, Nephrol.Dial.Transplant.(2013) 28:405

CKD: Spironolactone beyond the kidney :
less cardiovascular /cerebrovascular morbidity / mortality in <u>hemodialysed</u> patients

3 year randomized trial 309 oligoanuric HD patients
25 mg/d Spironolactone vs placebo



12.5% in controls
HR p <0.404 *(95% 0.202-0.809)*
p=0.017

5.7%
HR p<0.379 *(95% 0.173-0.832*
p=0.016

Matsumoto, JACC (2014) 63:528

Limitation of RAS Blockade

Aldosterone "escape"

first communication

Patients with renal failure (n=10) and treated with Captopril

	p-Aldosterone (pg/ml)
before Captopril	266 ± 30
Captopril 6 months	105 ± 16
Captopril 12 months	234 ± 31

Ruilope, Am.J.Kid.Dis.(1989) 13:120

“Aldosteron escape“ -

~ half of the patients with diabetic nephropathy ⇨

secondary increase of serum - aldosterone during RAS blockade

63 type 1 diabetic patients, Losartan 100 mg/day
36 months follow-up

	Escape *n=26*			**No Escape** *n=37*		
	start	2 months	end of study	start	2 months	end of study
p-aldosterone *(pg/ml)*	88 *62-125*	57 *43-76*	102 *78-134*	70 *54-92*	83 *69-102*	49 *40-60*
GFR-decrease		**5** ml/min/year *0.4 - 15.9*			**2.4** ml/min/year *-1.6 - 11.0*	

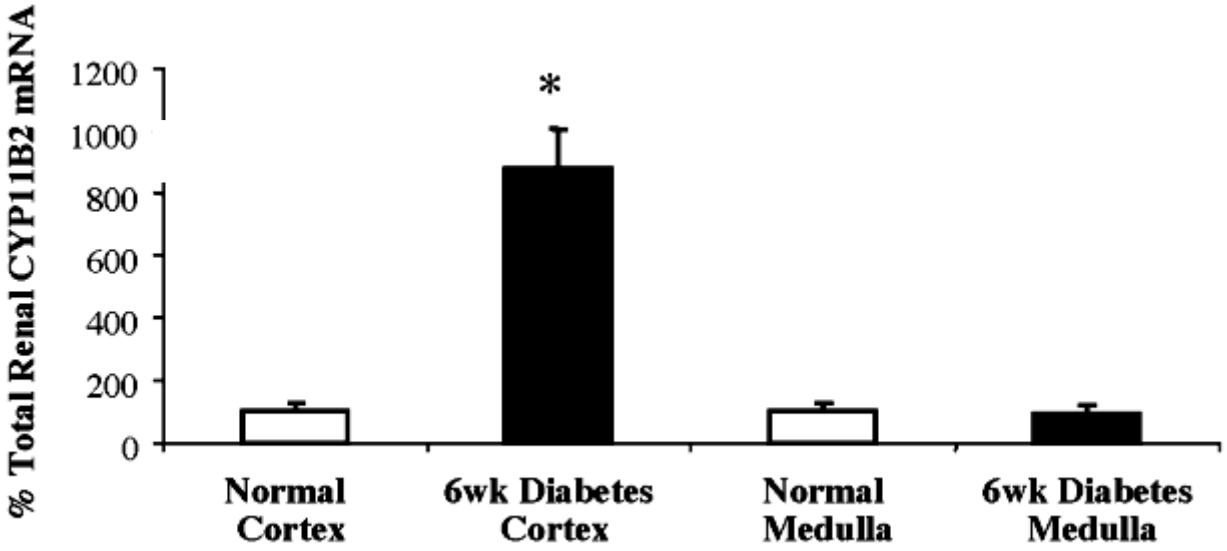
Escape : *more rapid loss of GFR*

Schjoedt, Diabetologia (2004) 47:1936

Why do we see less progression with aldosterone blockade even in (a proportion of) CKD patients without elevated p-aldosterone?

⇨ **Local synthesis of aldosterone in kidney cortex ?**

e.g. high salt, diabetes …



Xue, Hypertension (2005) 46:584

Aldosterone and allograft function

153 transplant recipients

5 year follow-up; yearly s-aldosterone

Higher serum plasma aldosterone ⇨

significantly higher risk of ESRD

HR 1.01 *(95% CI 1.00-1.02)*

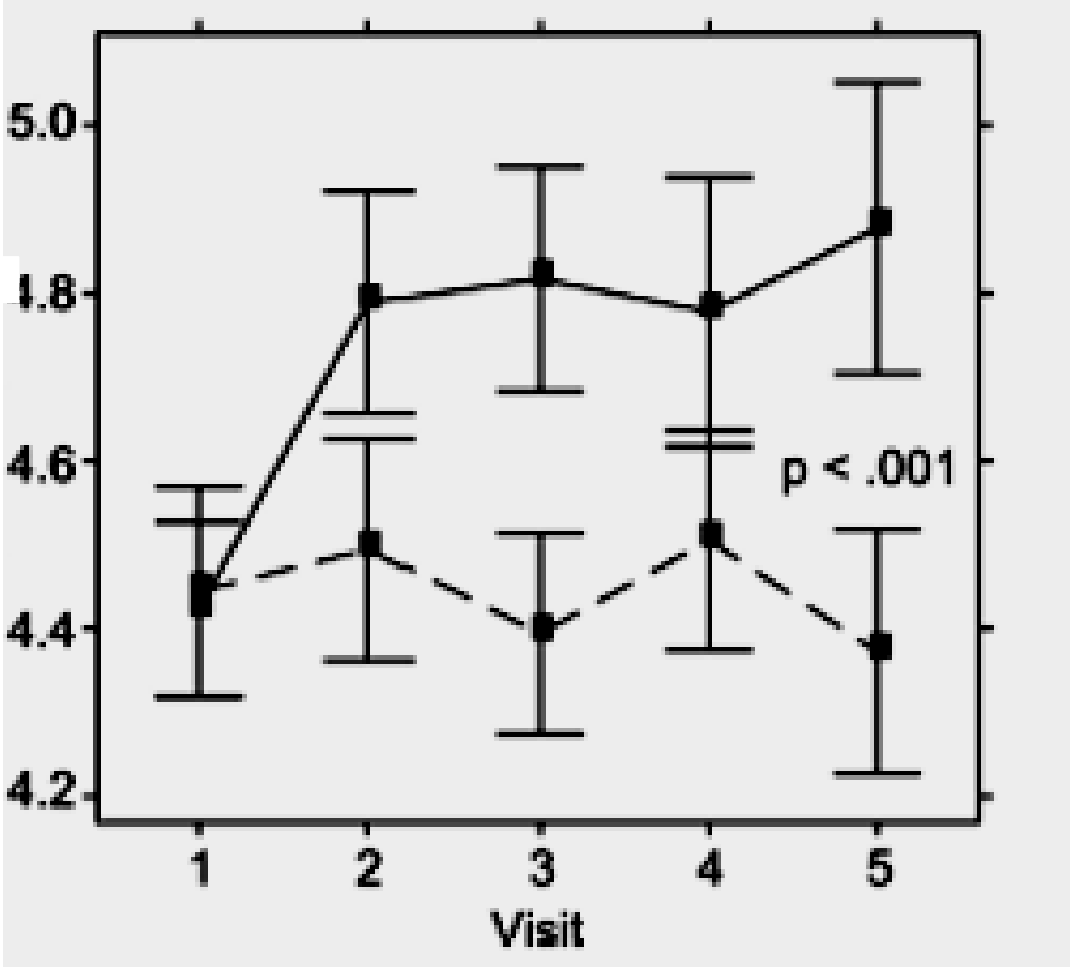
even though systemic aldosterone
does not reflect the intrarenal system

Issa, Kidn.Internat.(2014) 85:404

Why had we been in the past so hesitant to use RAS plus aldosterone blockade in advanced CKD? Justified concern of hyperkalemia !

Serum K^+ of CKD patients on ACE inhibitors with or without Spironolactone

Out-patients serum K^+ *(mmol/L)*



Lisinopril + Spironolacton

~Δ 0.45 mmol/L
but wide scatter !!

Lisinopril + Placebo

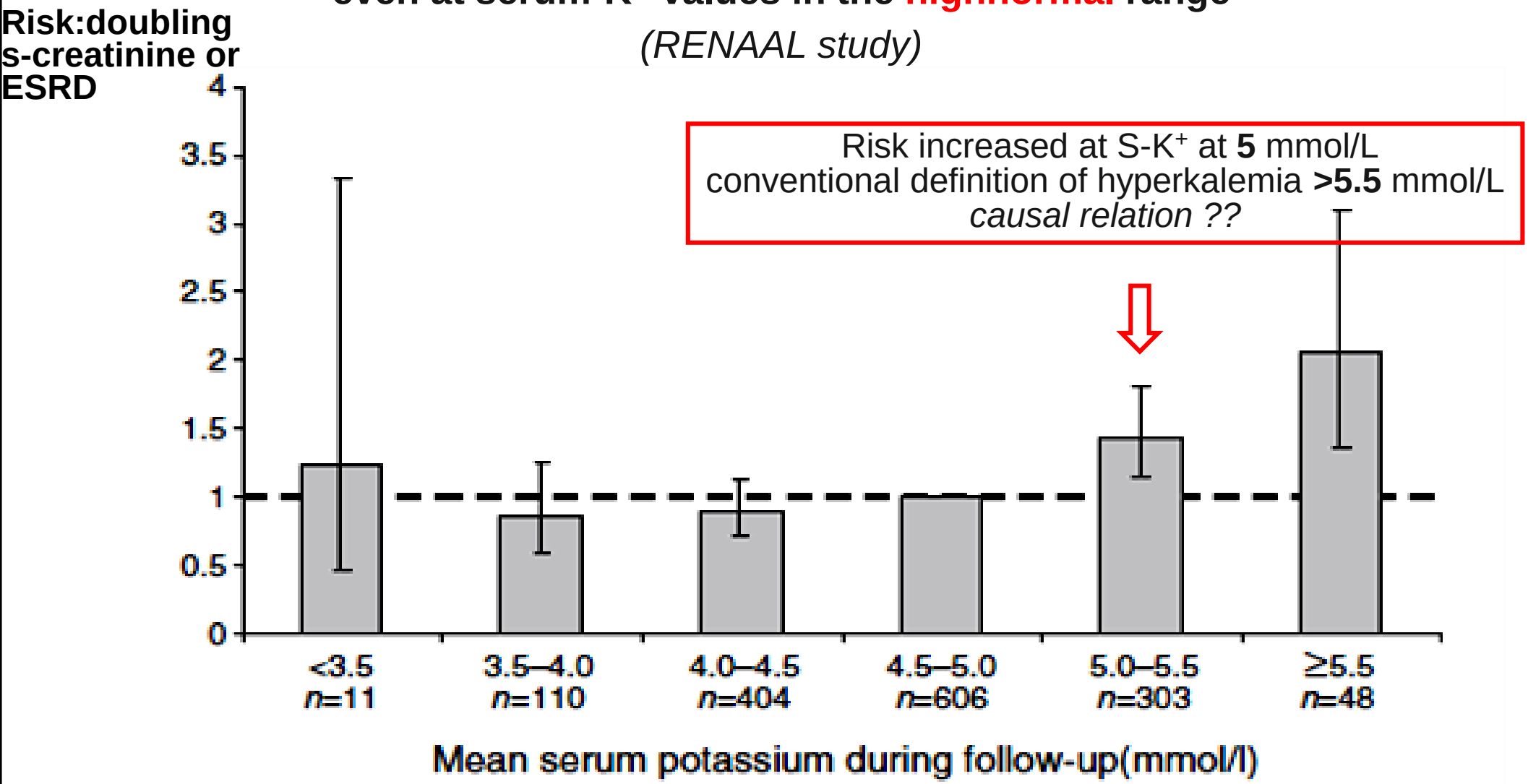
Preston, Hypertension (2009) 53:754

Type 2 diabetic patients with nephropathy :

increased risk of endstage renal disease or doubling of S-creatinine

even at serum-K^+ values in the highnormal range

(RENAAL study)



Miao, Diabetologia (2011) 54:44

K^+ handling in CKD patients treated with ARB blockade plus Aldosterone blockade

safety ?

randomized cross-over 4 week trial
40 mg Lisinopril + 25mg Spironolactone vs placebo
18 participants GFR 25.7 ml/min

at 4 week (study end) 35 mmol oral K^+ challenge :
S-K^+ **4.87** mmol/l (L/S) vs **4.37** (controls);*p<0.001*

after oral K^+ :
only modest 0.44 mmol/h increase of K^+ excretion,
but 0.67 mmol/L increase in serum K^+
:

Preston, Hypertension (2009) 53:754

Beneficial effect and safety of Spironolactone

added on top of recommended antihypertensive treatment

in diabetic nephropathy

22 patients type 2 diabetes with nephropathy
randomized double-masked cross-over study

in randomized order :
Spironolactone 25 mg/d vs matched placebo for 8 weeks

during addition of **Spironolactone** :

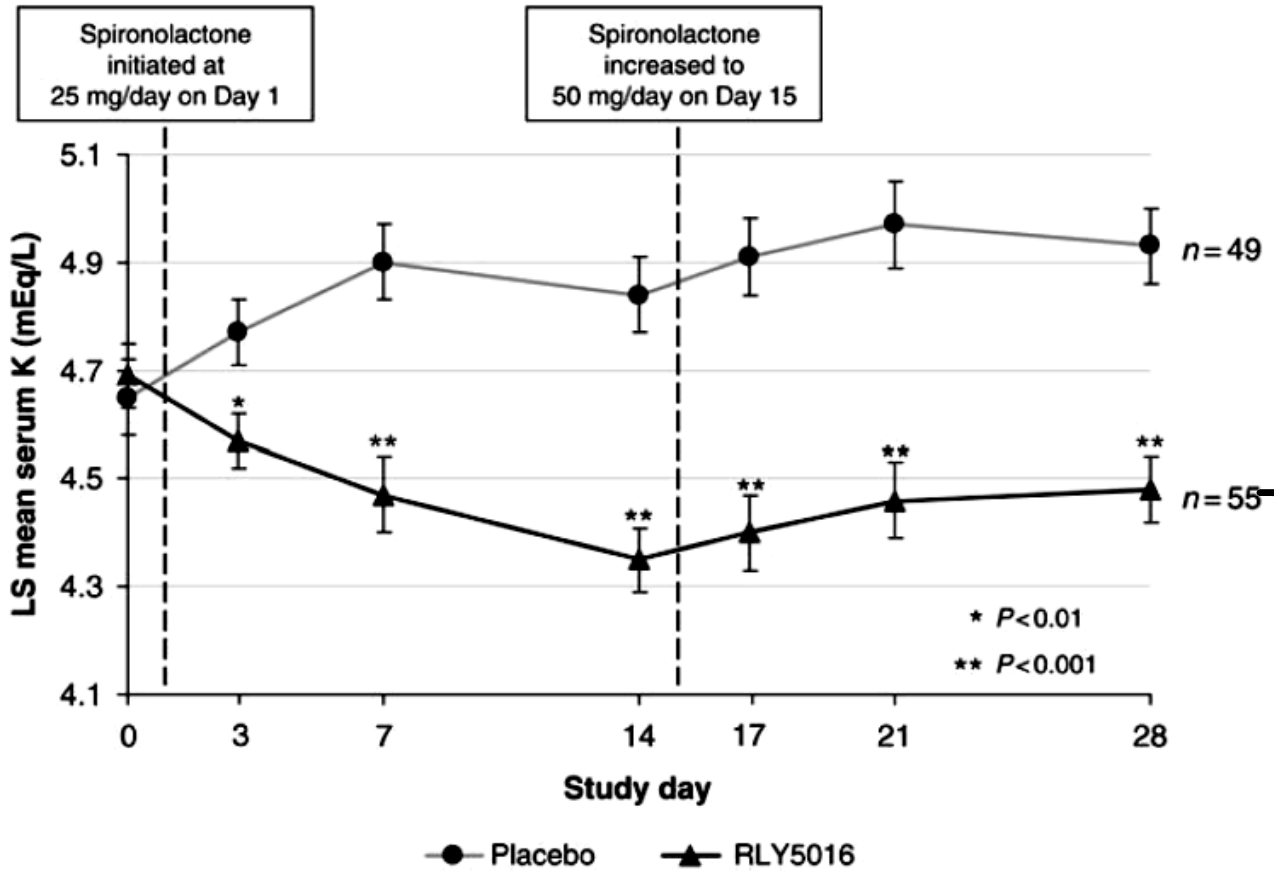
albuminuria - 33%
24h ambulatory BP : - 6 mmHg systolic; - 4mmHg diastolic

only 1/22 patients had to be excluded because of hyperkalemia

Rossing, Diabetes Care (2005) 28:2106

Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial

Bertram Pitt[1*], Stefan D. Anker[2,3], David A. Bushinsky[4], Dalane W. Kitzman[5], Faiez Zannad[6], and I-Zu Huang[7], on behalf of the PEARL-HF Investigators



K^+ bound in the gut by **RLY5016**

Pitt, Eur.Heart J. (2011) 32:820

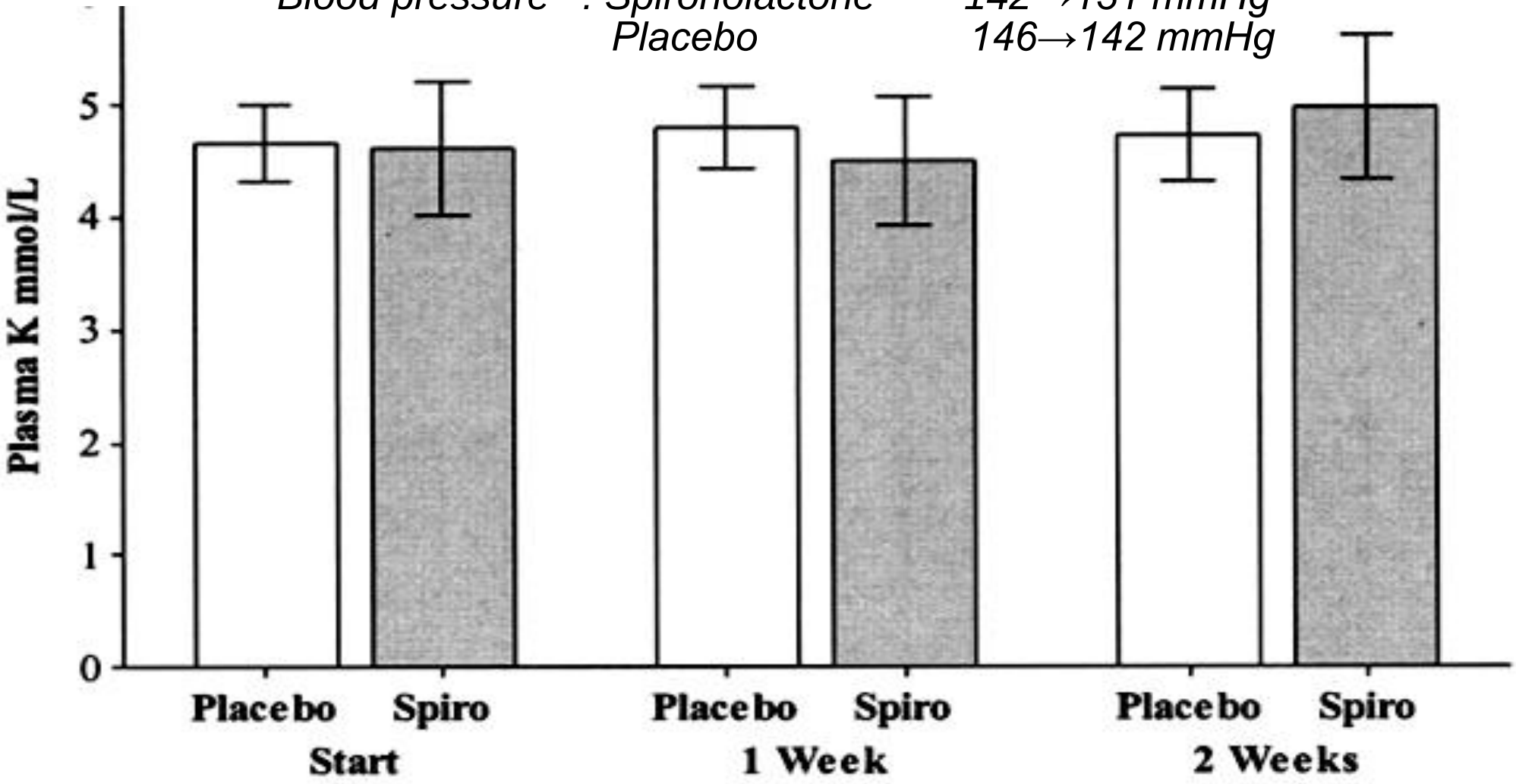
50 mg Spironolactone lowers blood pressure

even in anuric (!) hemodialysis patients

without significant change of S-K⁺

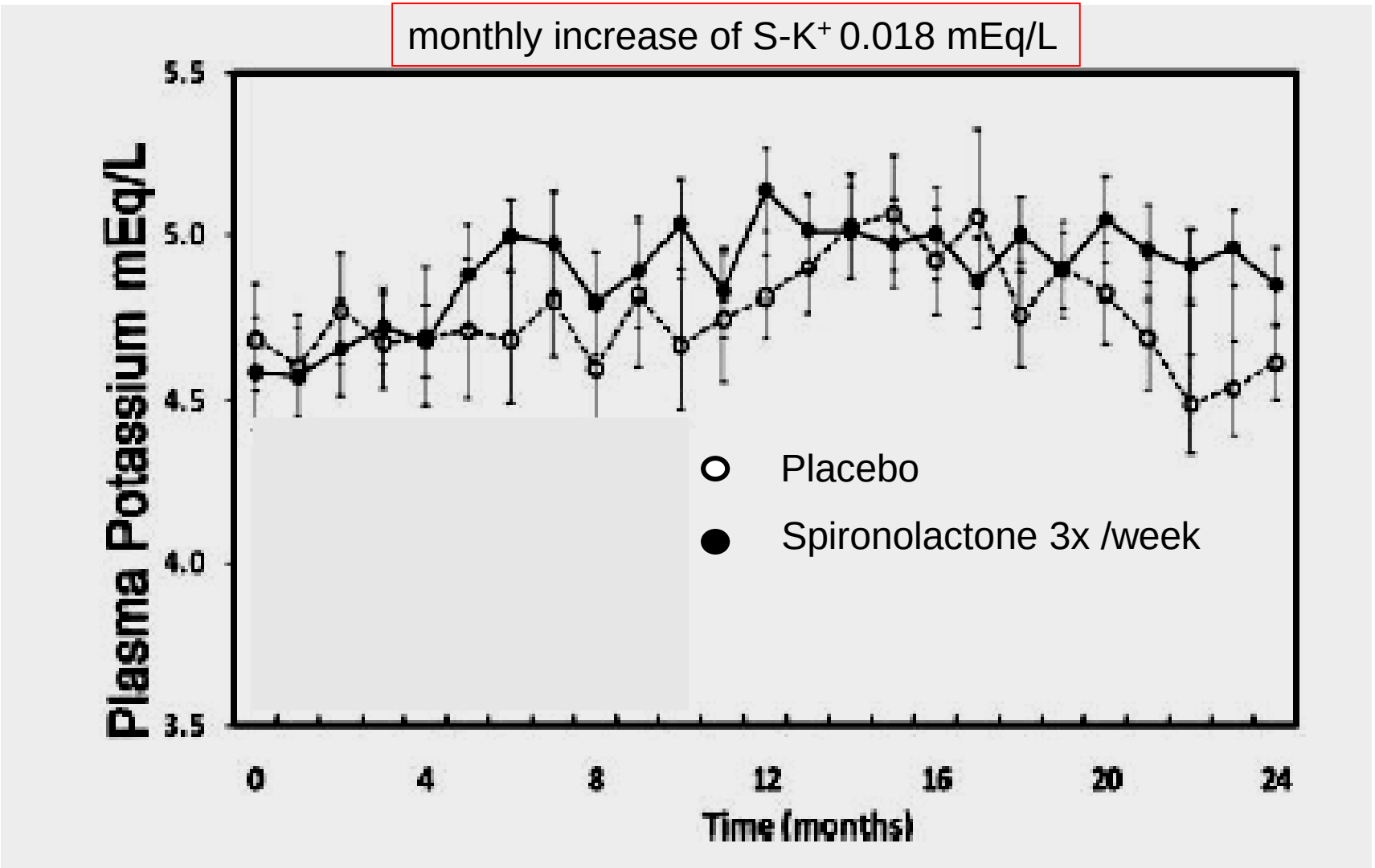
Blood pressure : Spironolactone 142→131 mmHg

Placebo 146→142 mmHg



Gross, Am.J.Kidn.Dis (2005) 46:94

Spironolactone 50mg 3x / week : impact on predialytic S-K^+ in hemodialysed patients



Vukusich, CJASN (2010) 5:1380

Renal aspirin: will all patients with chronic kidney disease one day take spironolactone?

Andrew S Bomback*, Abhijit V Kshirsagar and Philip J Klemmer

Nature Clin.Practice Nephrol. (2009) 5: 74

Proposal appears rational :

but in view of experimental and scarce controlled clinical data better documentation of safety is still necessary

Aldosteron

in renal patients :
primary treatment target
kidney

but in renal patients
also treatment targets of Aldosterone
beyond the kidney

Patients with modest reduction of eGFR : cardiovascular mortality correlated to plasma aldosterone

(LURIC study)

3,153 patients, age 62.7 ±10.6 years, no primary kidney disease
follow-up 7.75 years

Pat. with eGFR **< 60** ml/min/1.73m^2

cardiovascular mortality
HR 1.08
(95%CI 1.02-1.13)
p=0.004

"sudden death"
HR 1.18
(95%CI 1.08-1.29)
p=0.001

higher P-aldosterone aggravates CV risk even in CKD patients

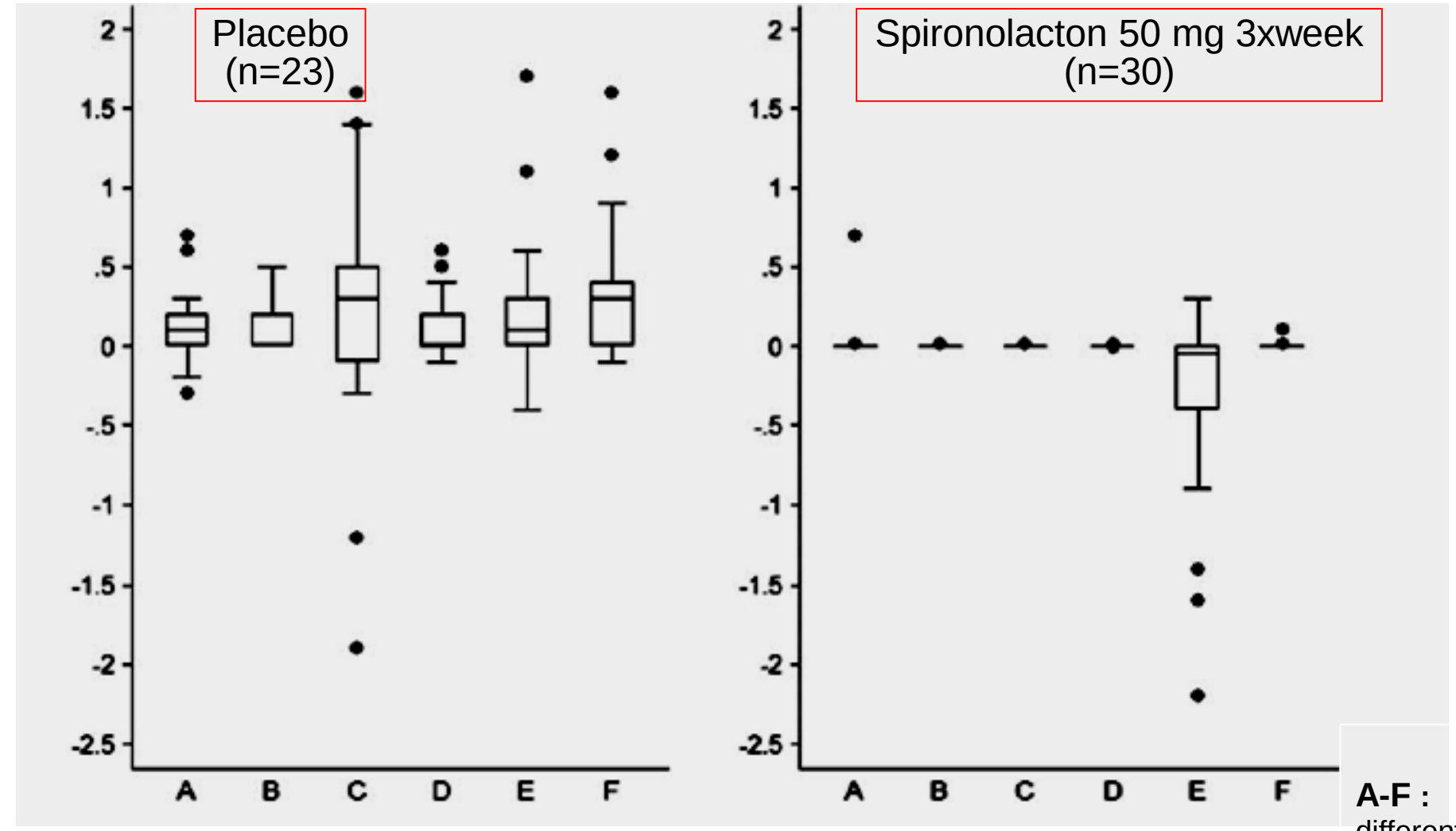
eGFR **> 60** ml/min/1.73m^2

higher aldosterone : CV events not significantly higher

Tomaschitz, AJKD (2011) 57:403

Spironolacton :
less thickening of carotid- intima/media in hemodialysis-patients

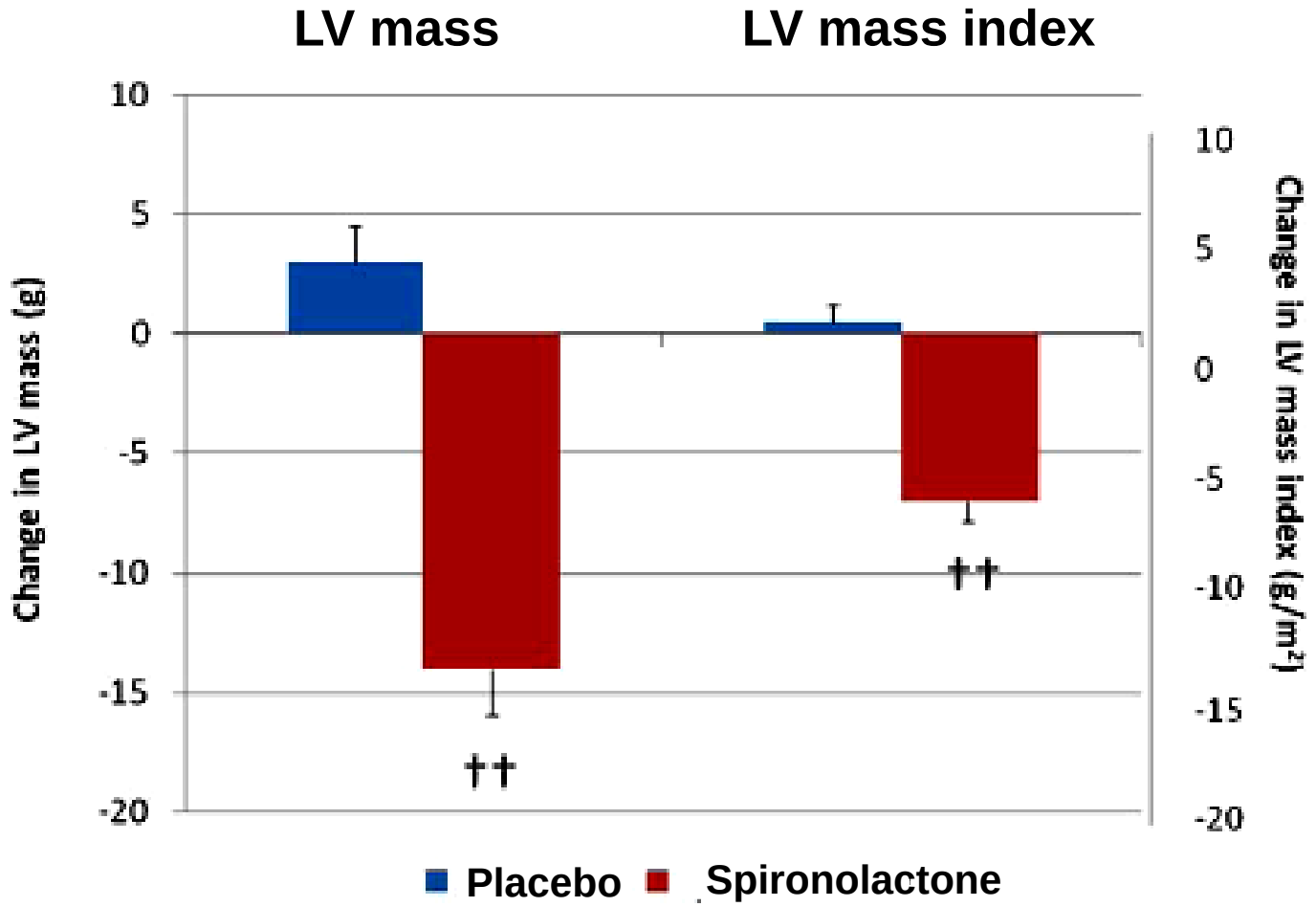
randomised doubleblind Placebo-controlled study



Vukusich, CJASN (2010) 5:1380

Spironolactone reduces LVM in patients with CKD 2-3

112 pat. CKD 2,3 and *ABPM* < 130/85 mmHg on *RAS blockade*
Spironolactone 25 mg/day or Placebo

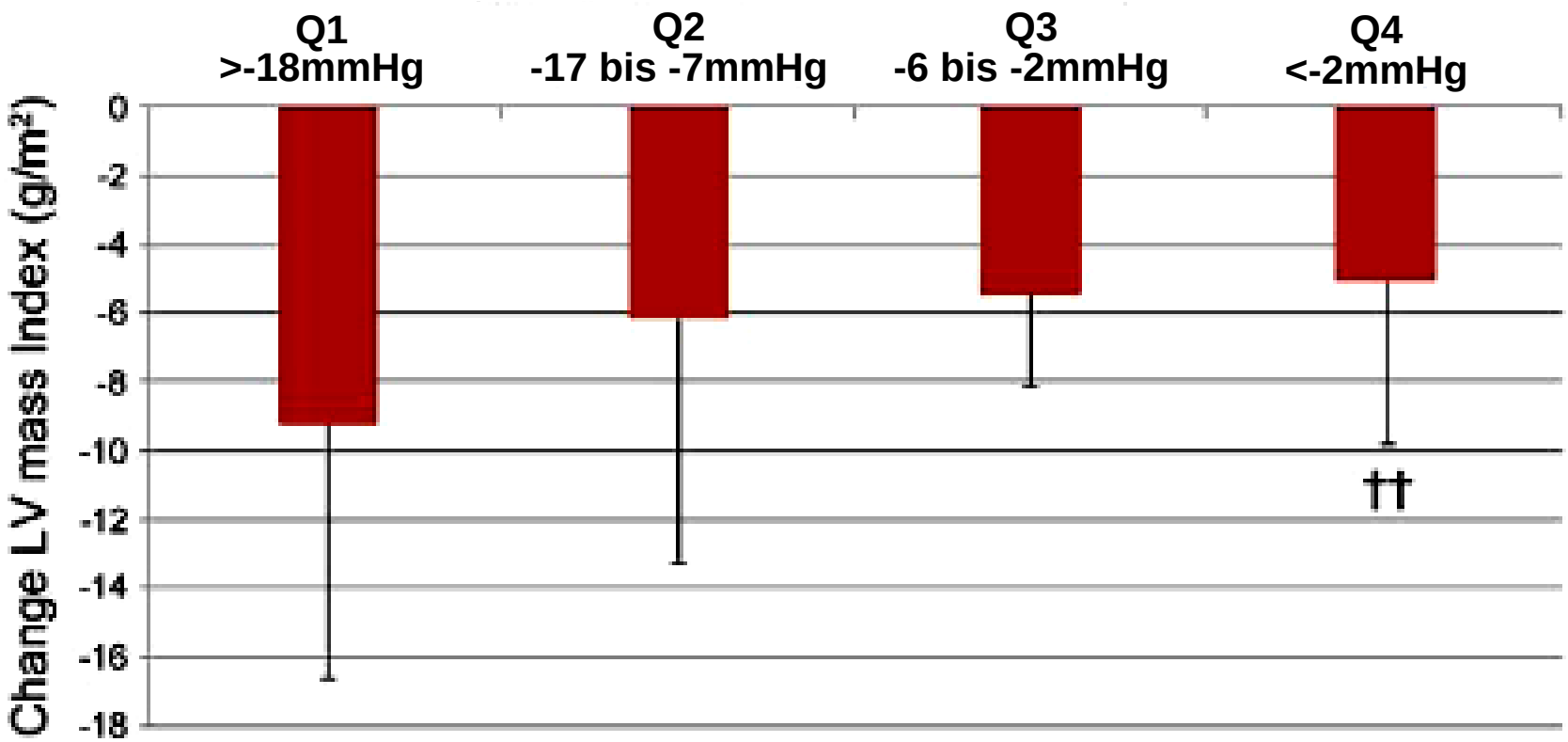


Edwards, J.Am.Coll.Cardiol.(2009) 54: 505

Spironolactone reduces LVM in patients with CKD 2-3 – in all quartiles of central blood pressure changes

112 pat. CKD 2,3 and daytime ABPM < 130/85 mmHg on RAS blockade addition of Spironolactone 25 mg/day or Placebo

Quartiles of reduction of central blood pressure



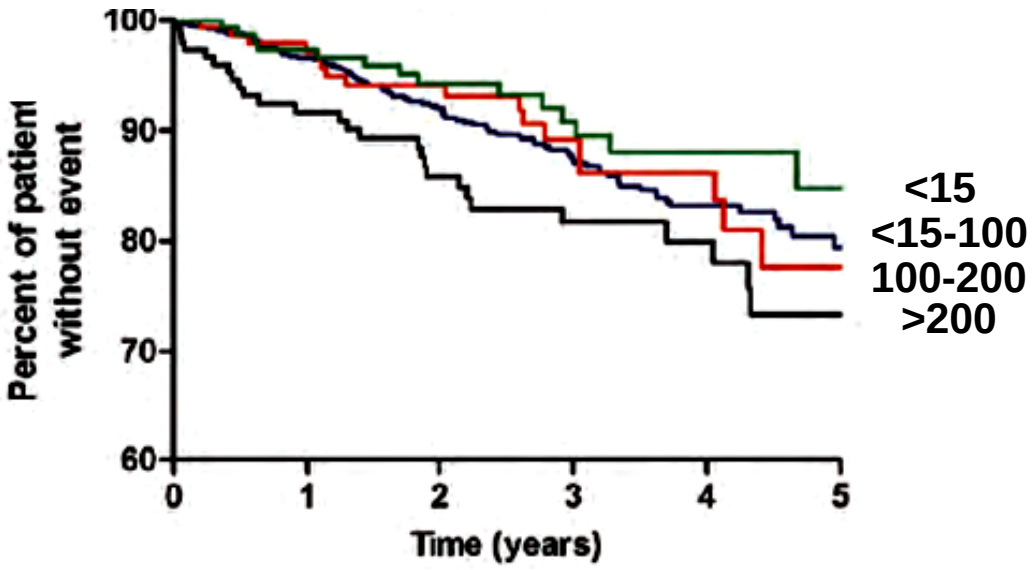
Edwards, J.Am.Coll.Cardiol.(2009) 54: 505

Plasma aldosterone plus cortisol

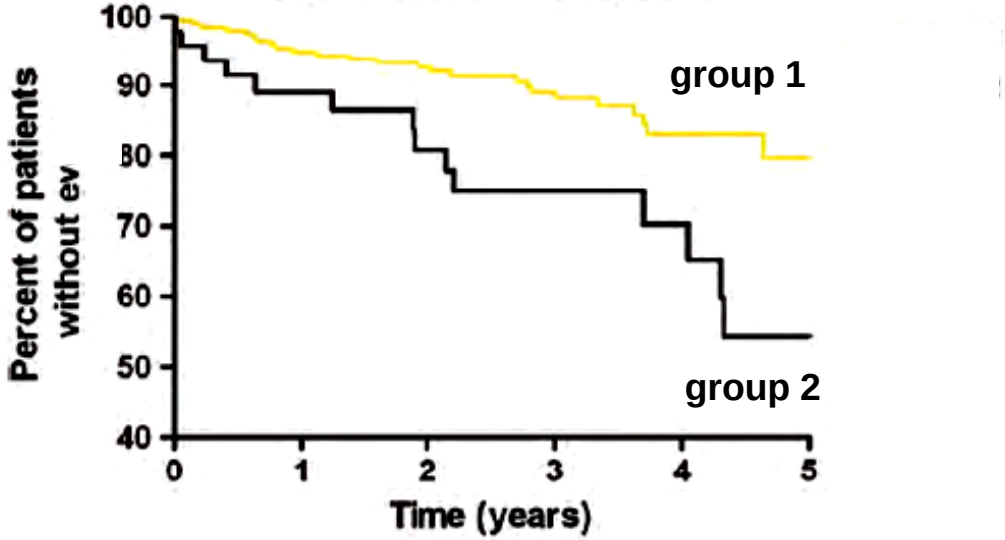
Interaction :
increased risk of sudden death in type 2 diabetics on hemodialysis
(4D study)

Drechsler , Eur.Heart J.,(2013) 34:578

Aldosterone
(pg/ml)

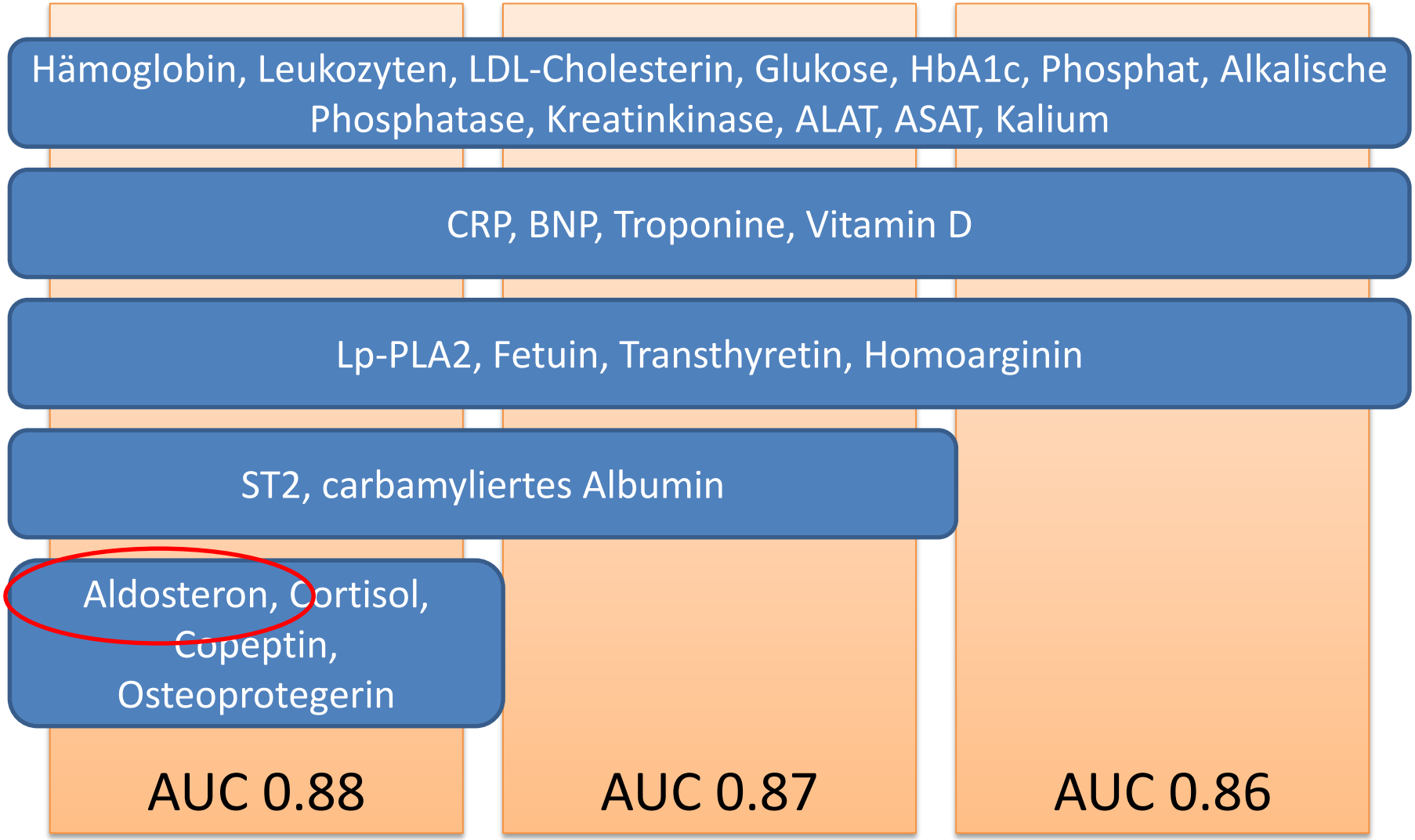


high Aldosterone plus high Cortisol particularly high CV risk



group 1 : Aldosteron < 15 pg/ml; Cortisol < 13.2 mg/dl
group 2 : Aldosteron > 200 pg/ml; Cortisol > 21.1 µg/dL

Aldosterone (*in the normal range*)
one of the factors **predicting** 1 year **mortality**
(4D study, hemodialysed diabetic patients)



courtesy Prof.Maerz

New consideration !

Spironolactone :
Prevention of vascular calcification in early renal failure ?

in smooth muscle cells of the human aorta :

Aldosterone increases :
phosphate transporter PiT-1, as well as TnFα, Cbfa1/Runx2, alkal.phosphatase
⇨ vascular calcification

this is prevented by :
Spironolactone

Voelkl et al,
Spironolactone ameliorates PIT1-dependent vascular osteoinduction in klotho -/- mice
J.Clin.Invest .(2013) 123. 812

Lang,Ritz,Voelkl,Alesutan
Vascular calcification – is aldosterone the culprit ?
Nephrol.Dial.Transplant. (2013) 28:1080

Aldosterone synthase inhibition in humans

Michel Azizi[1,2,3], Laurence Amar[1,2,3] and Joël Menard[1,2,3]

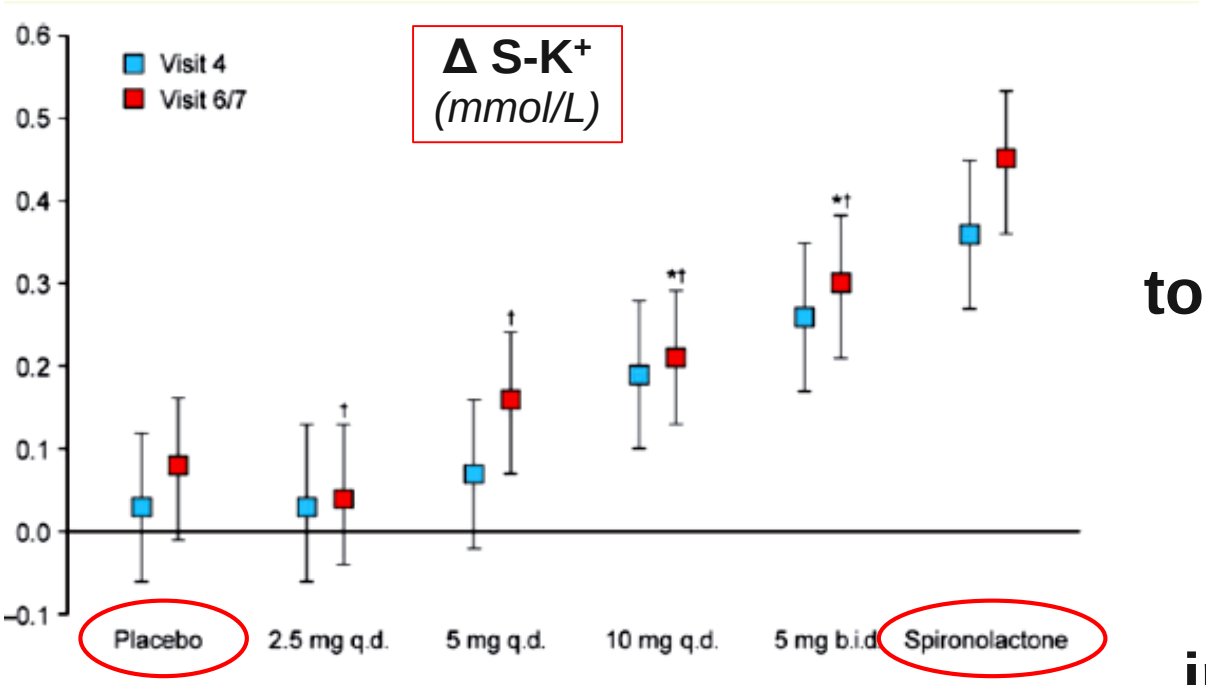
Nephrol.Dial.Transplant.(2013) 28:36

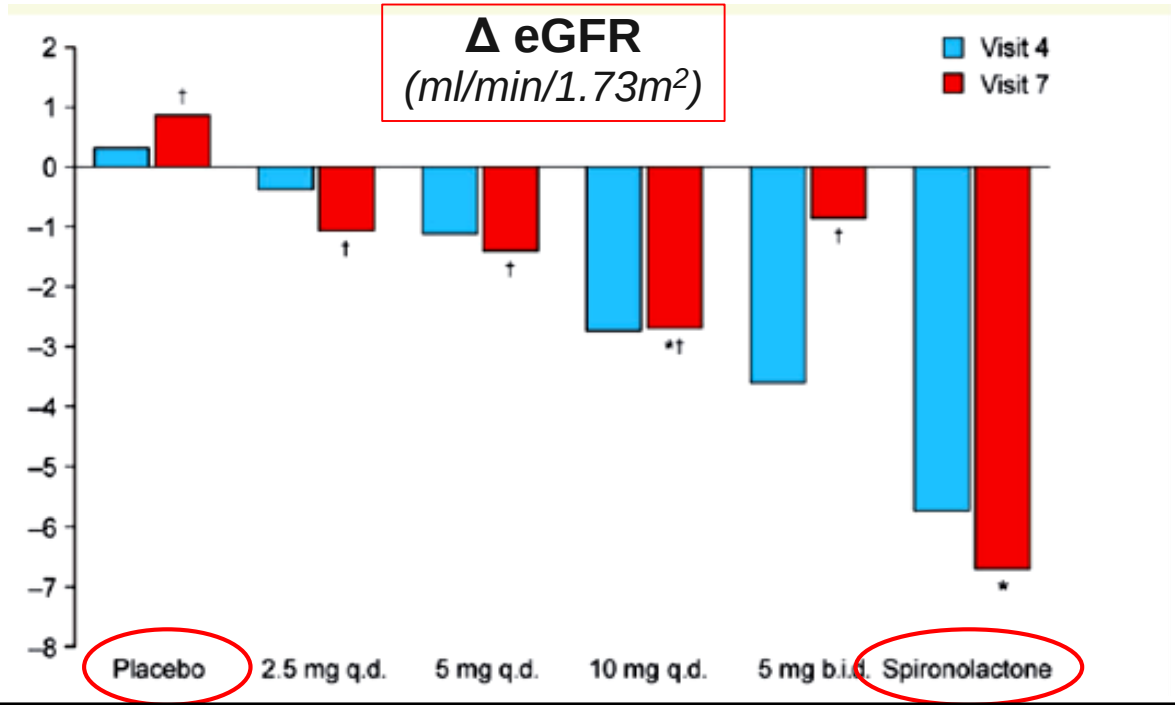
Inhibition of Aldosterone effects*:*

 # not only with ***Spironolactone****,*
but also with
 # aldosterone ***synthase inhibitors***
or
***nonsteroidal receptor antagonists***

Discovery of BAY 94-8862: A Nonsteroidal Antagonist of the Mineralocorticoid Receptor for the Treatment of Cardiorenal Diseases

Bärfacker, Chem.Med.Chem.(2012) 7:1385





Safety *(S-K⁺)* **and tolerability** *(ΔeGFR)* **of the novel nonsteroidal mineralocorticoid receptor antagonist** *(BAY94-8862)* **in patients with heart failure**

note: also more moderate reduction of eGFR

(perhaps reversal of hyperfiltration)

Pitt, Eur.Heart J. (2013) 34:2453

What did he say ?

new insights into the role of aldosterone in kidney damage :

renal damage caused not only via systemic aldosterone ,
but also via local aldosterone production

aldosterone : crucial role in the “escape phenomenon“ of kidney disease
(incl.secondary increase of proteinuria)

aldosterone induced tissue damage is aggravated by salt

novel role of aldosterone in vascular calcification

novel drugs to block aldosterone effects
(nonsteroidal mineralocorticoid antagonists; mineralocorticoid receptor blockers)

Old bridge in Heidelberg

The aldosterone/kidney interaction has become a new frontier in nephrology

Thank you for your attention

Aldosteron "escape" during RAS Blockade

⇨ *higher risk of progression (loss of GFR)*

63 hypertensive patients; type 1 diabetes and diabetic nephropathy

Losartan 100 mg/day, 35 months follow-up

p- Aldosteron concentration

increase 26 Pat. (57 → 102 pg/ml) – "escape"

decrease 37 Pat. (83 → 49 pg/ml)

Decrease of GFR

aldosterone	escape	5.0 ml/min/year *(0.4-15.9)*
no aldosteron	escape	2.4 ml/min/year *(-2-11.0)*

Correlation *: the higher aldosterone – the greater GFR loss*

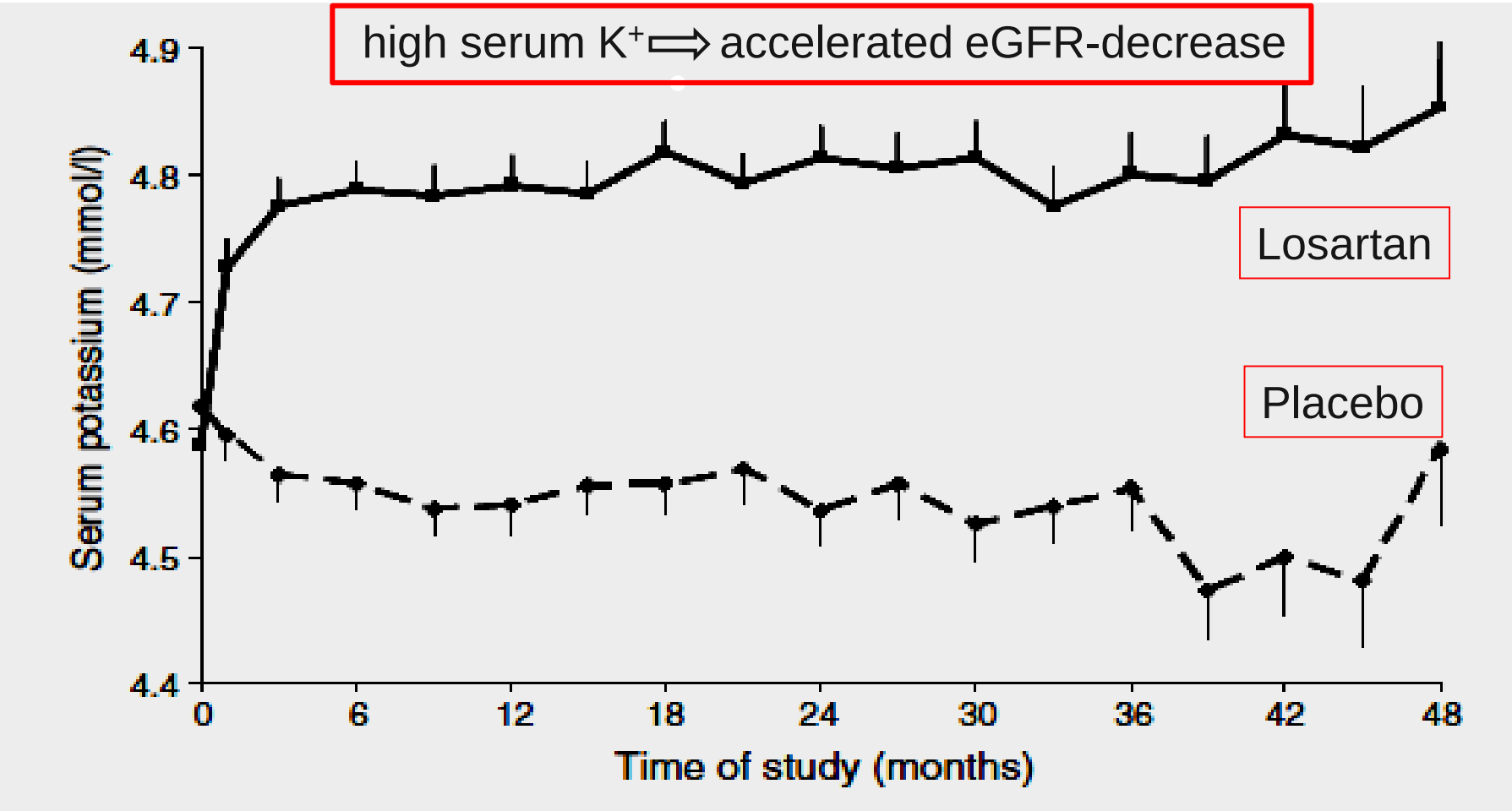
Δ plasma-aldosteron ↑ / Δ GFR- decrease ↓

Schjoedt,Diabetologia (2004) 47:1936

Limiting side effect :
increased plasma K^+ in patients with RAS blockade plus Aldosteron blockade

Losartan increases serum- K^+ in Type 2 diabetic patients with reduced renal function

(RENAAL study)



Miao, Diabetologia (2011) 54:44

Spironolactone
in mild to moderate chronic kidney disease : safety and tolerability

115 patients with non-diabetic early stage CKD
(eGFR 30-89 ml/min/1.73m^2)

Spironolactone 25 mg/day for 4 weeks,
subsequently randomization to :
placebo or # continuing treatment for 36 weeks

serious hyperkalemia (>6mmol/L) was < 1%
S-K^+ 5.5-5.9 mmol/L in 9 pat on Spironolactone

⇨ Spironolactone reasonably tolerated in selected patients with early stage CKD

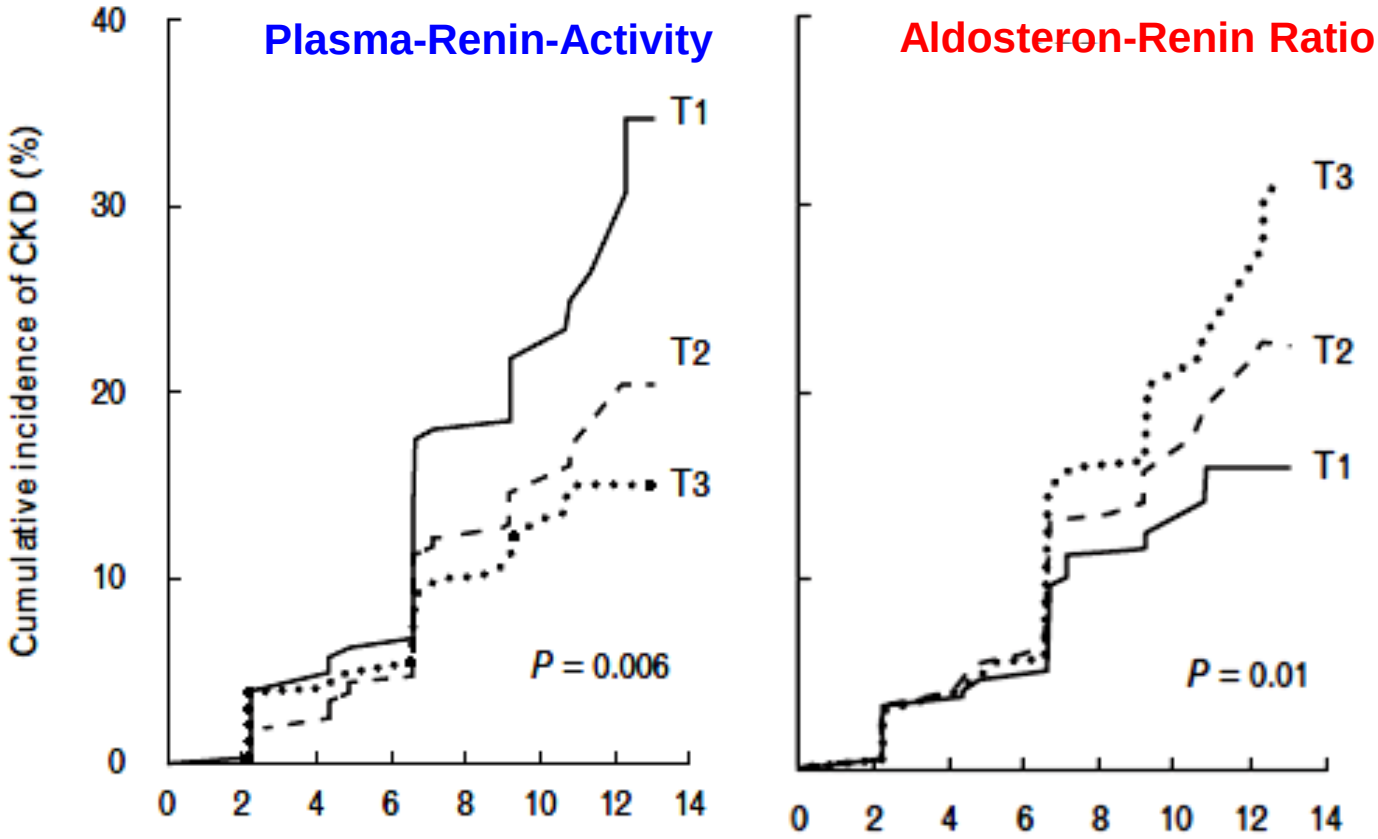
Edwards, Brit.J.Clin.Pharmacol.(2011) 73:447

Plasma-Renin-Activity *(PRA)* **and** **Aldosteron-Renin Ratio** *(ARR)* **:**

both correlated with **new onset CKD**

Ohasama study

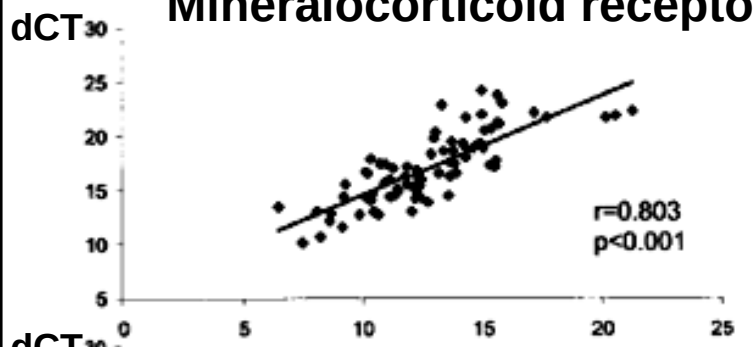
689 participants in Japanese population, mean age 58 years,
*no medication at start;of study; duration of study **9.1 years** :*
118 participants with new onset of CKD



Kaplan-Meier survival-function for cumulative onset of CKD
in tertiles of PRA and ARR

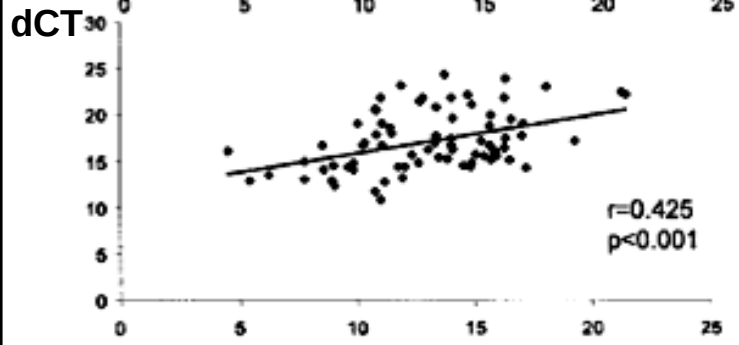
Terata, J.Hypertens. (2012) 30:1632

Mineralocorticoid receptor mRNA



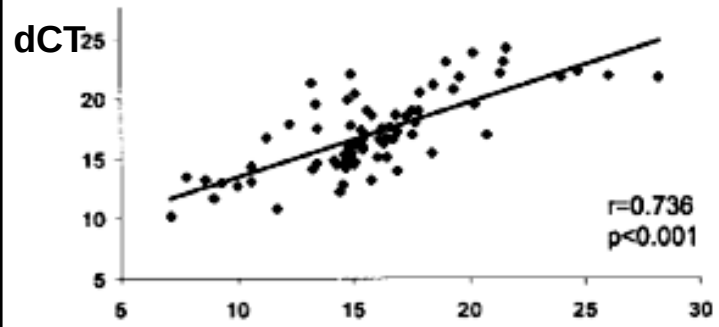
 # sgk-1

(serum-and glucocorticoid regulated kinase)

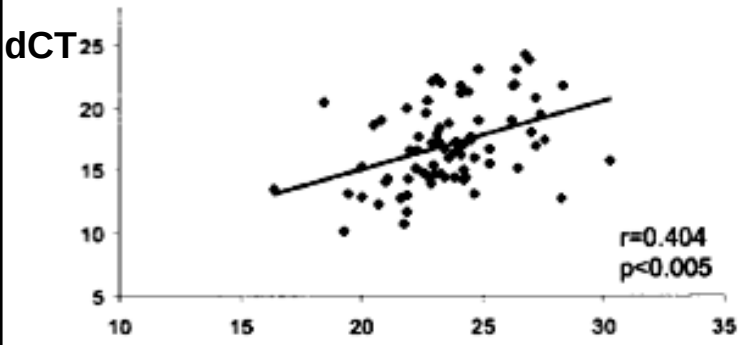


 # MCP-1

(monocyte chemoattractant protein-1)



 # TGFβ1



 # Interleukin 6

In renal biopsies
mineralocorticoid - receptor mRNA

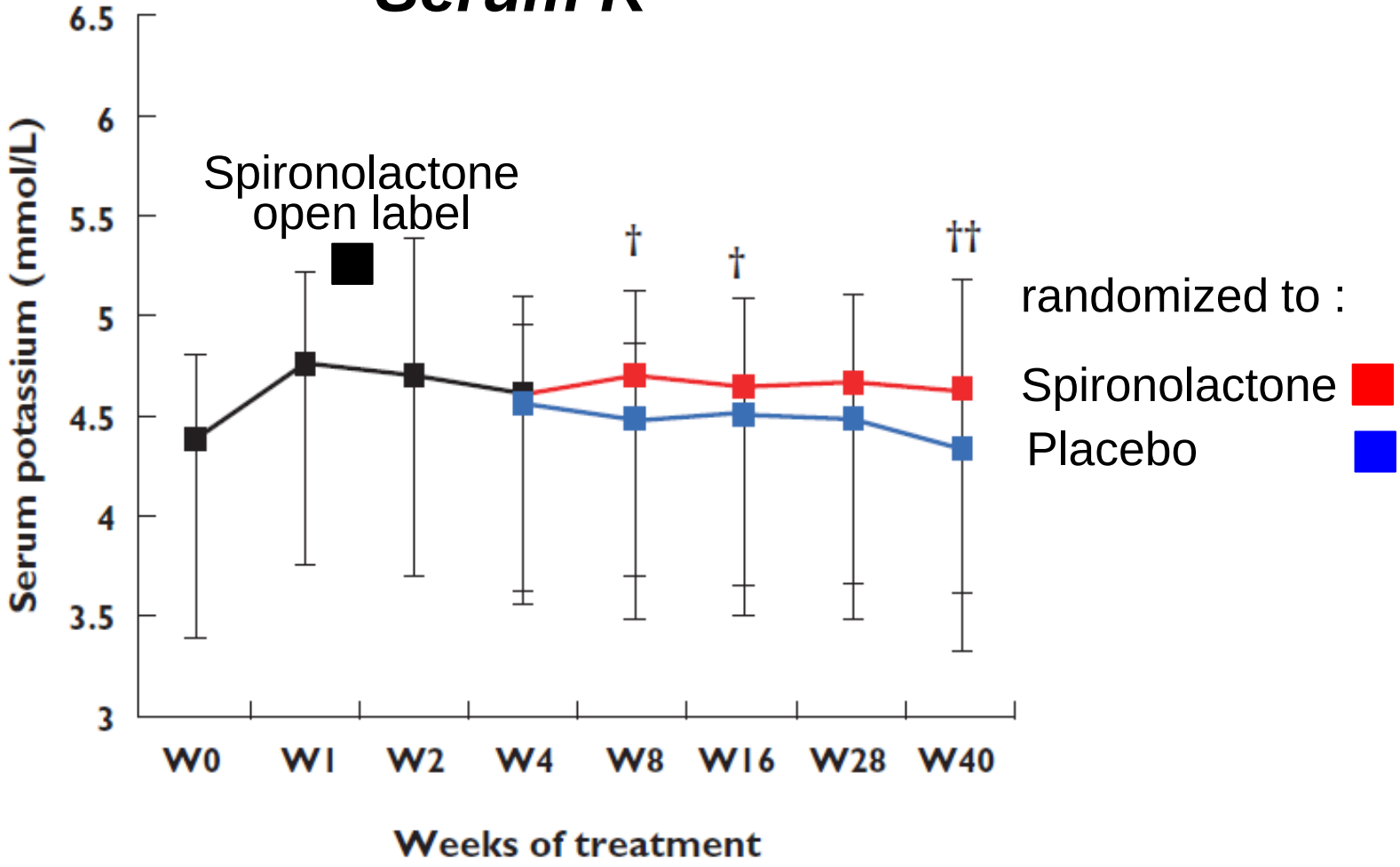
correlated with
sgk-1
and with mRNA of
mediators of kidney injury
(MCP-1; TGFβ1; interleukin 6)

Quinkler, Circulation (2005) 112:1435

numbers of necessary cycles (=low concentration – higher number of cycles necessary)

Spironolactone in mild to moderate chronic kidney disease on top of ACEi or ARB

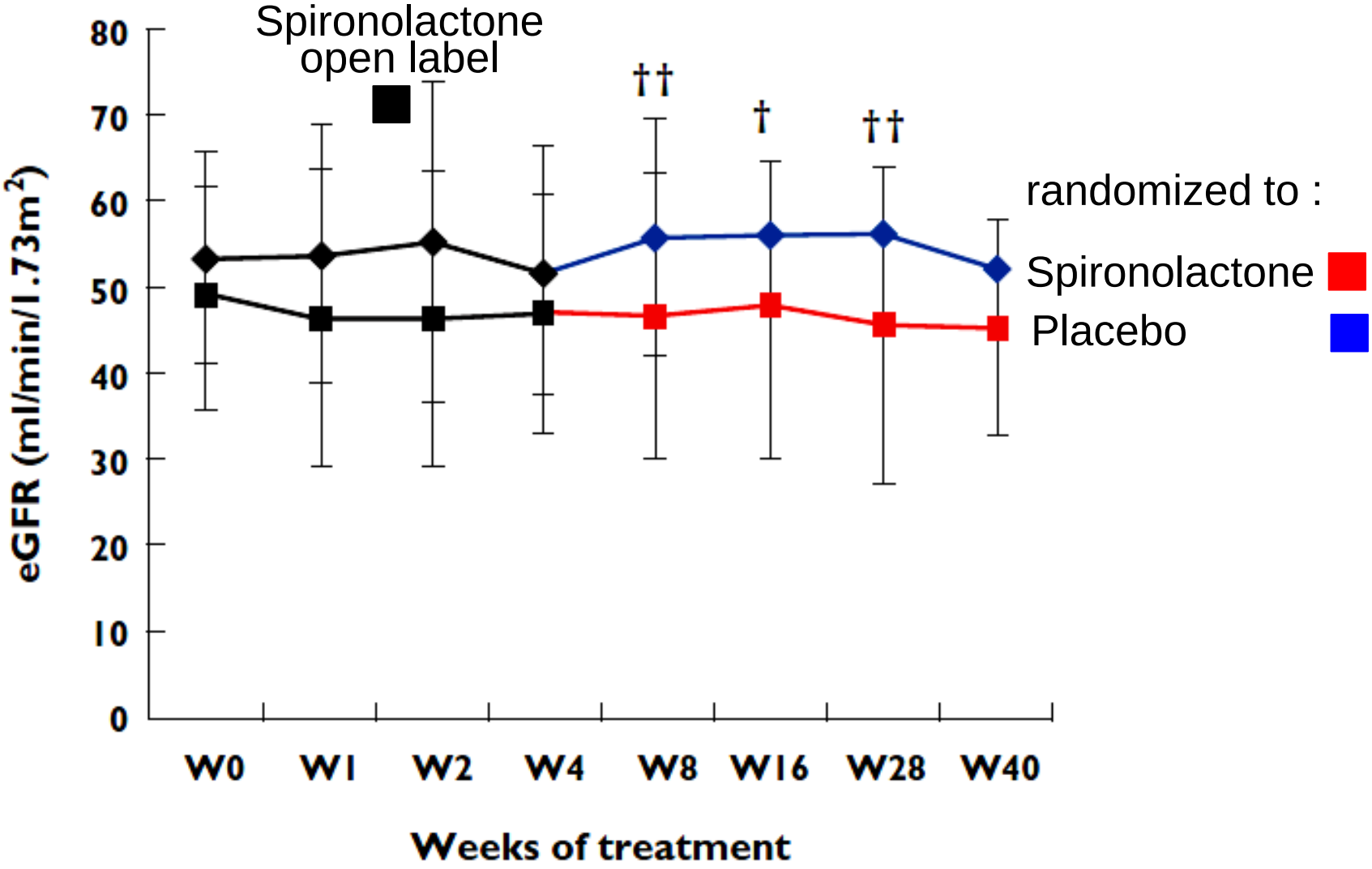
Serum K^+



Edwards, Brit.J.Clin.Pharmacol.(2012) 73:447

Spironolactone in mild to moderate chronic kidney disease on top of ACEi or ARB

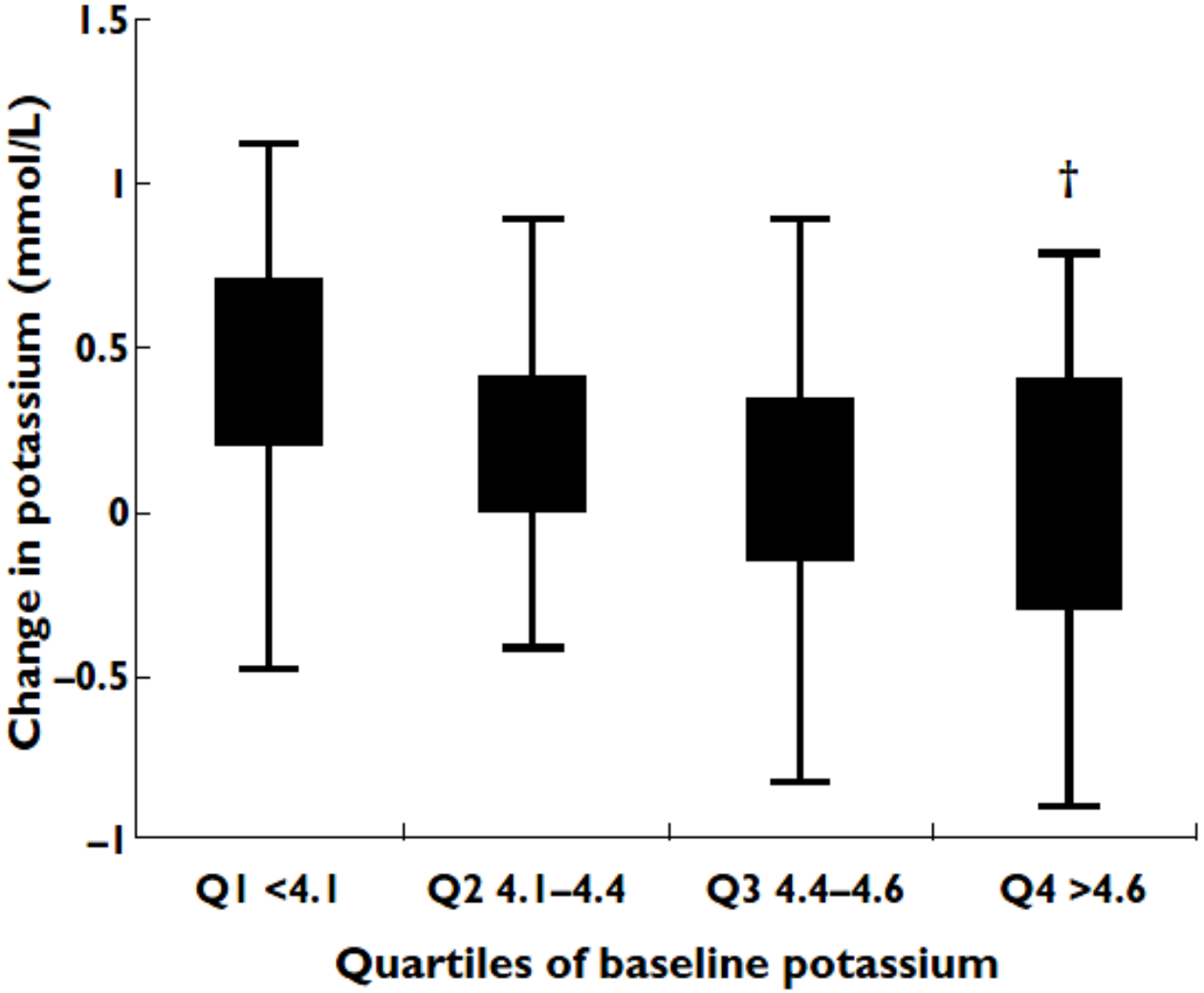
eGFR



Edwards, Brit.J.Clin.Pharmacol.(2012) 73:447

Spironolactone in mild to moderate chronic kidney disease

change in S-K^+ according to baseline S-K^+



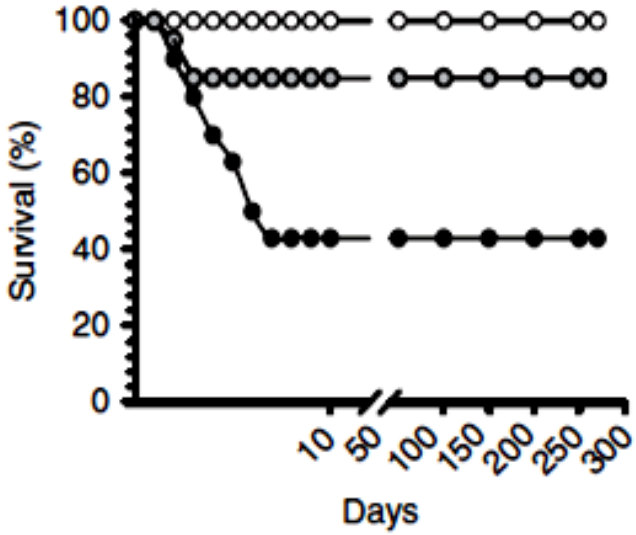
Edwards, Brit.J.Clin.Pharmacol.(2012) 73:447

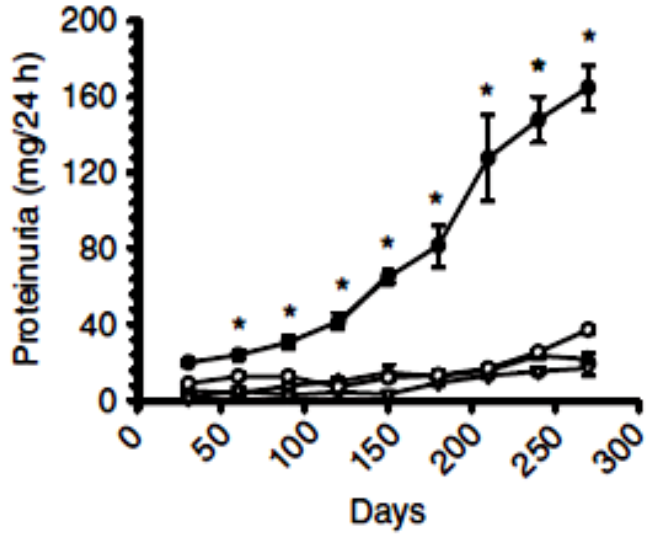
Acute kidney injury
prevented by Spironolactone in rats

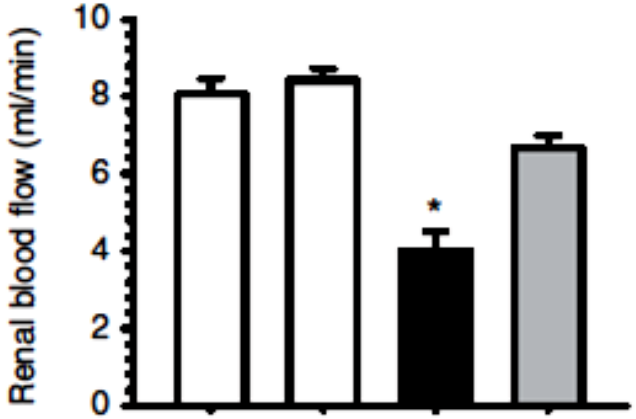
sham

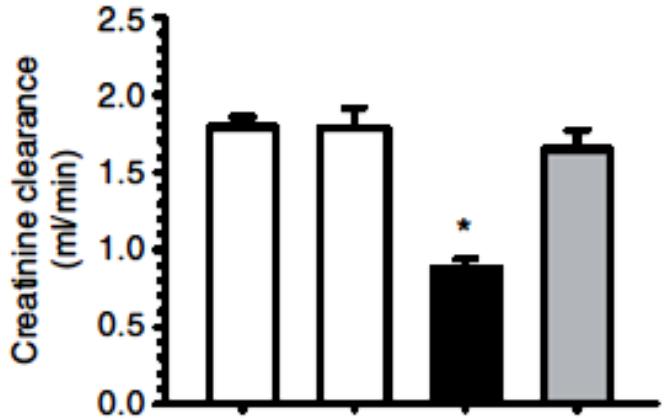
ischemia

ischemia + Spironolactone







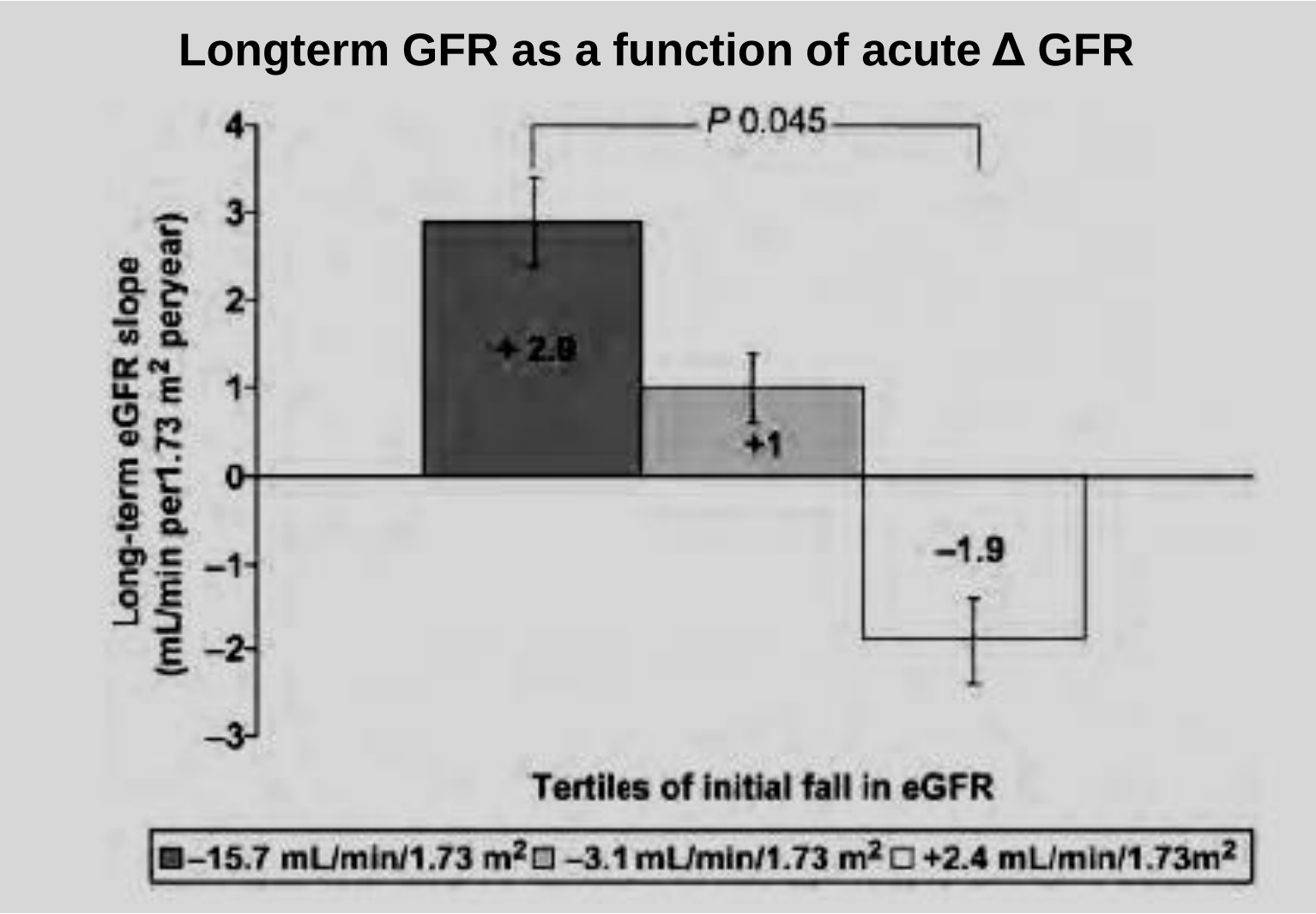


Barrera-Chimal, Kidn.Internat.(2013) 83:93

Spironolactone *(25 mg/day)*

Renoprotection in 87 patients with proteinuric kidney disease (>1g/day)
follow-up 25 months

the higher the initial eGFR fall, the better longterm evolution of eGFR



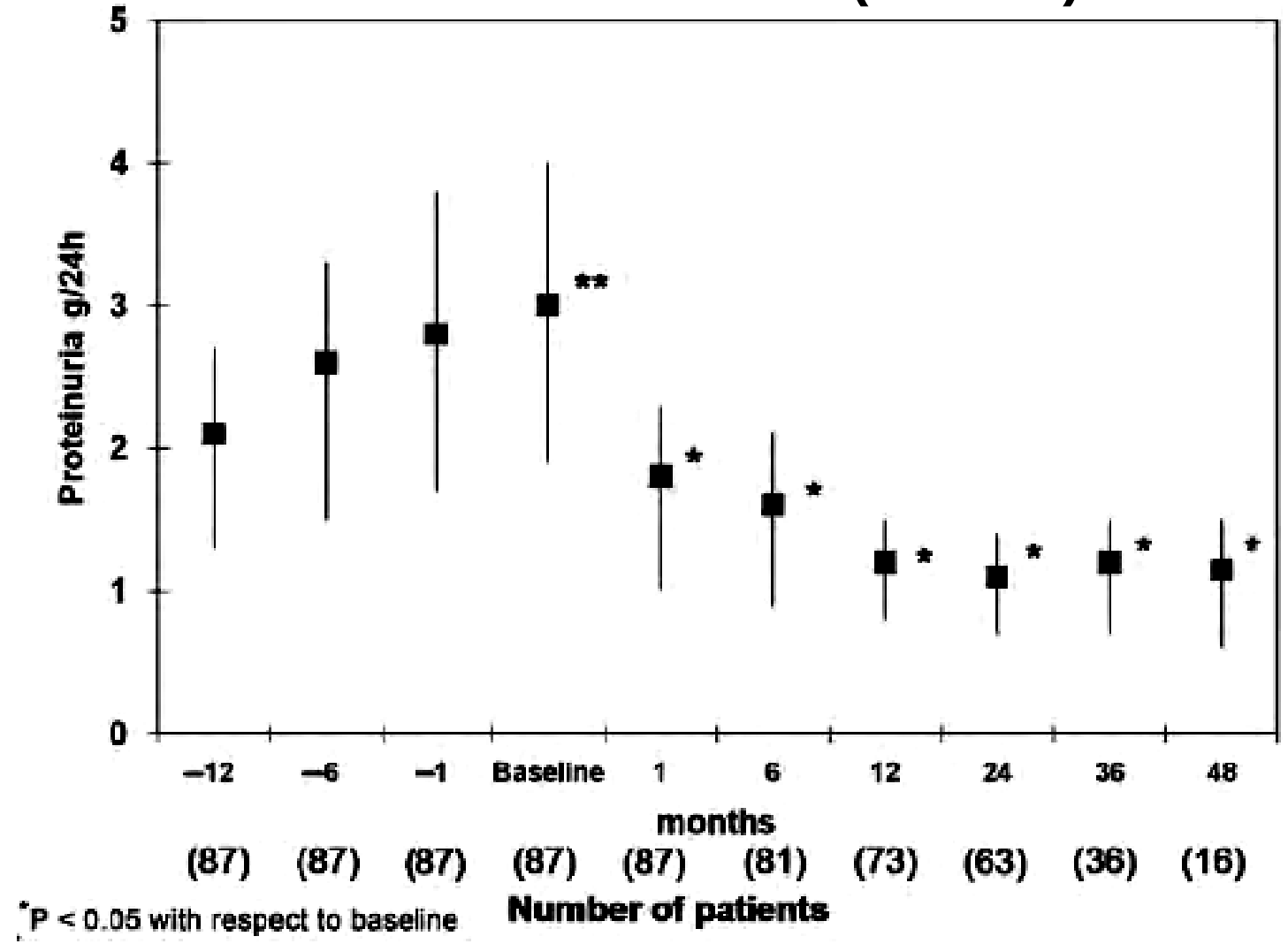
Morales, NDT (2013) 28:405

Spironolactone *(25 mg/day)*

Renoprotection in 87 patients with proteinuric kidney disease (>1g/day)

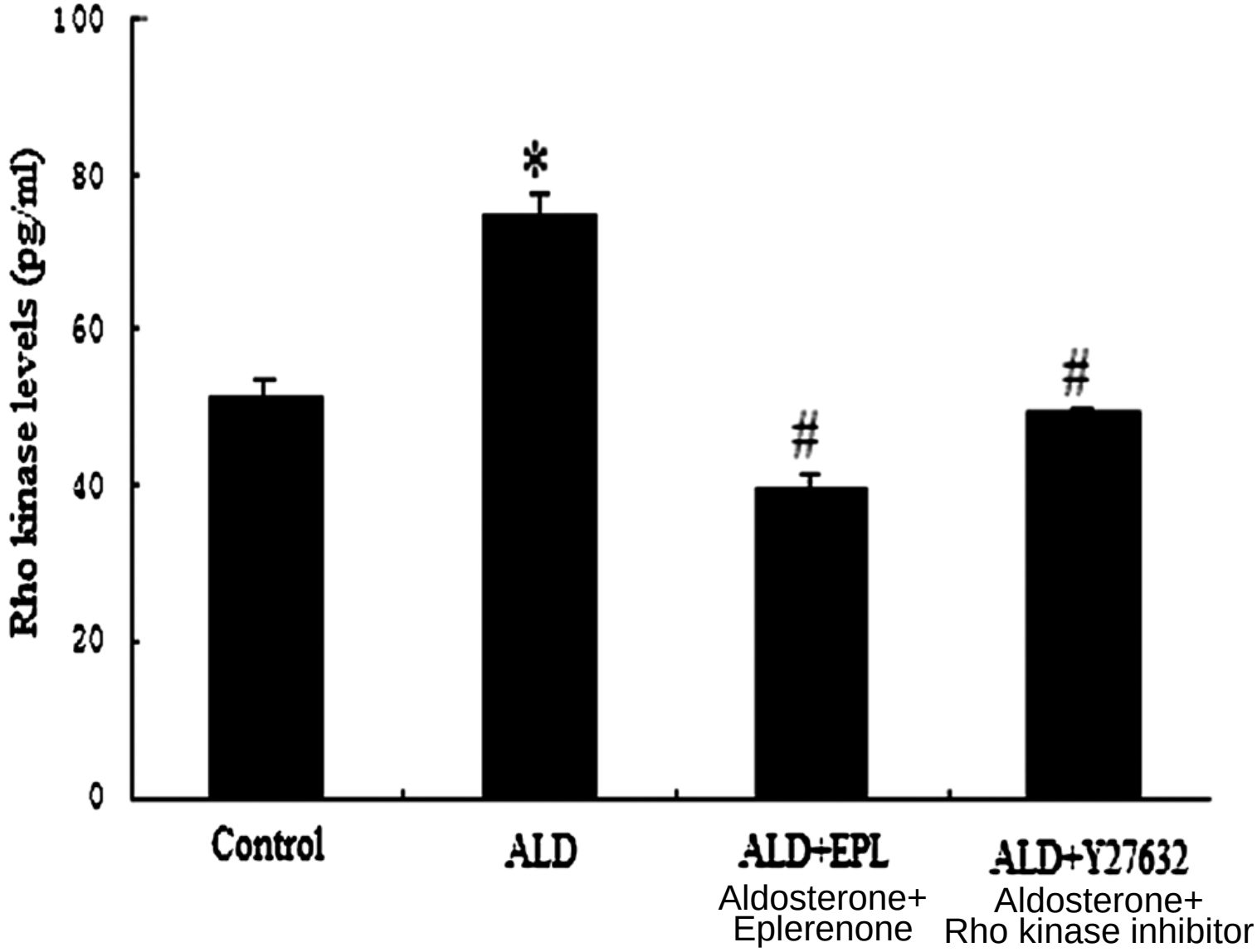
follow-up 25 months

Proteinuria – 61% (43-77%)



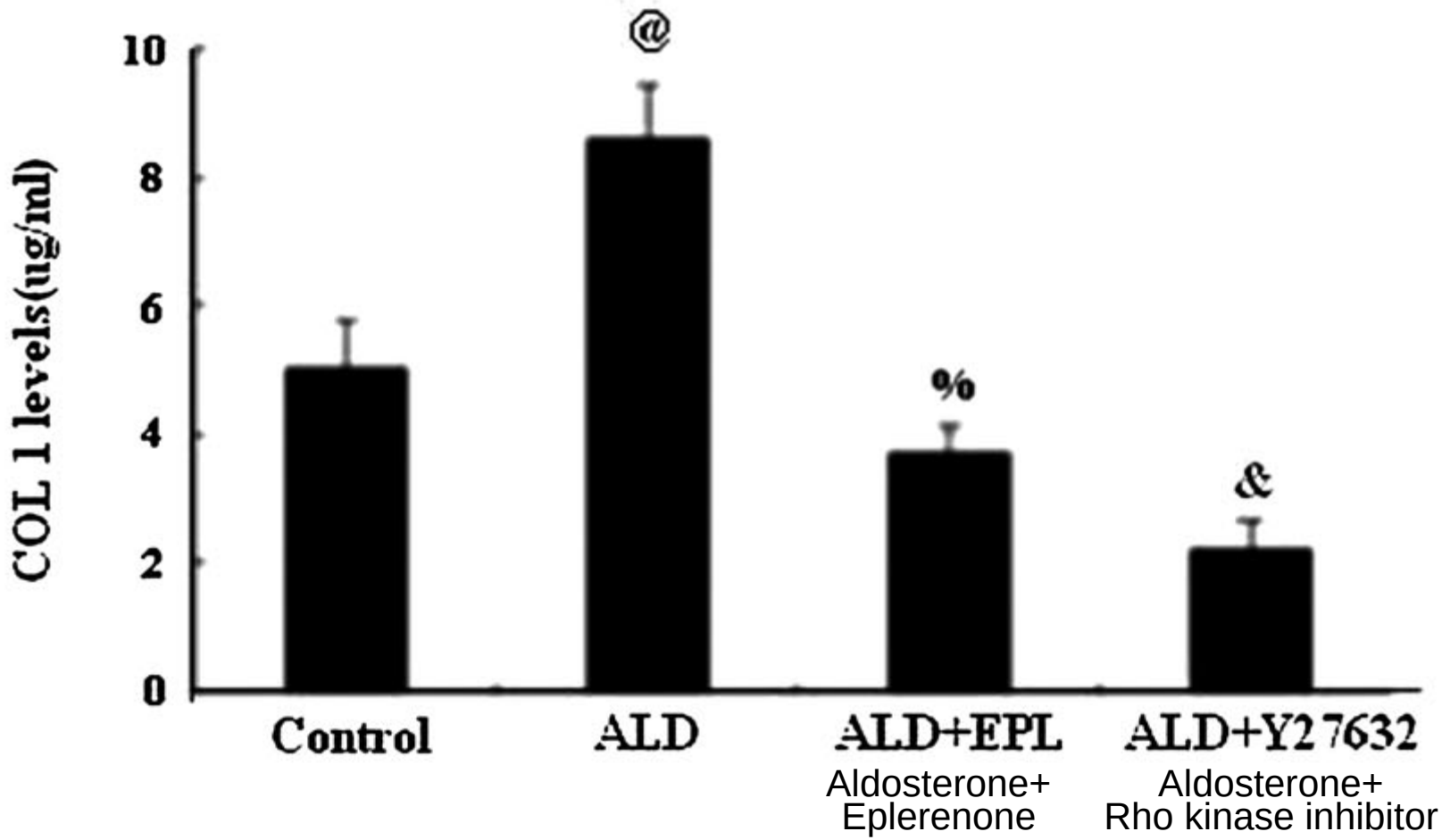
Morales, NDT (2013) 28:405

The role of Rho-kinase pathway for profibrotic differentiation of renal epithelial cells by EMT *(epithelial-mesenchymal transition)*



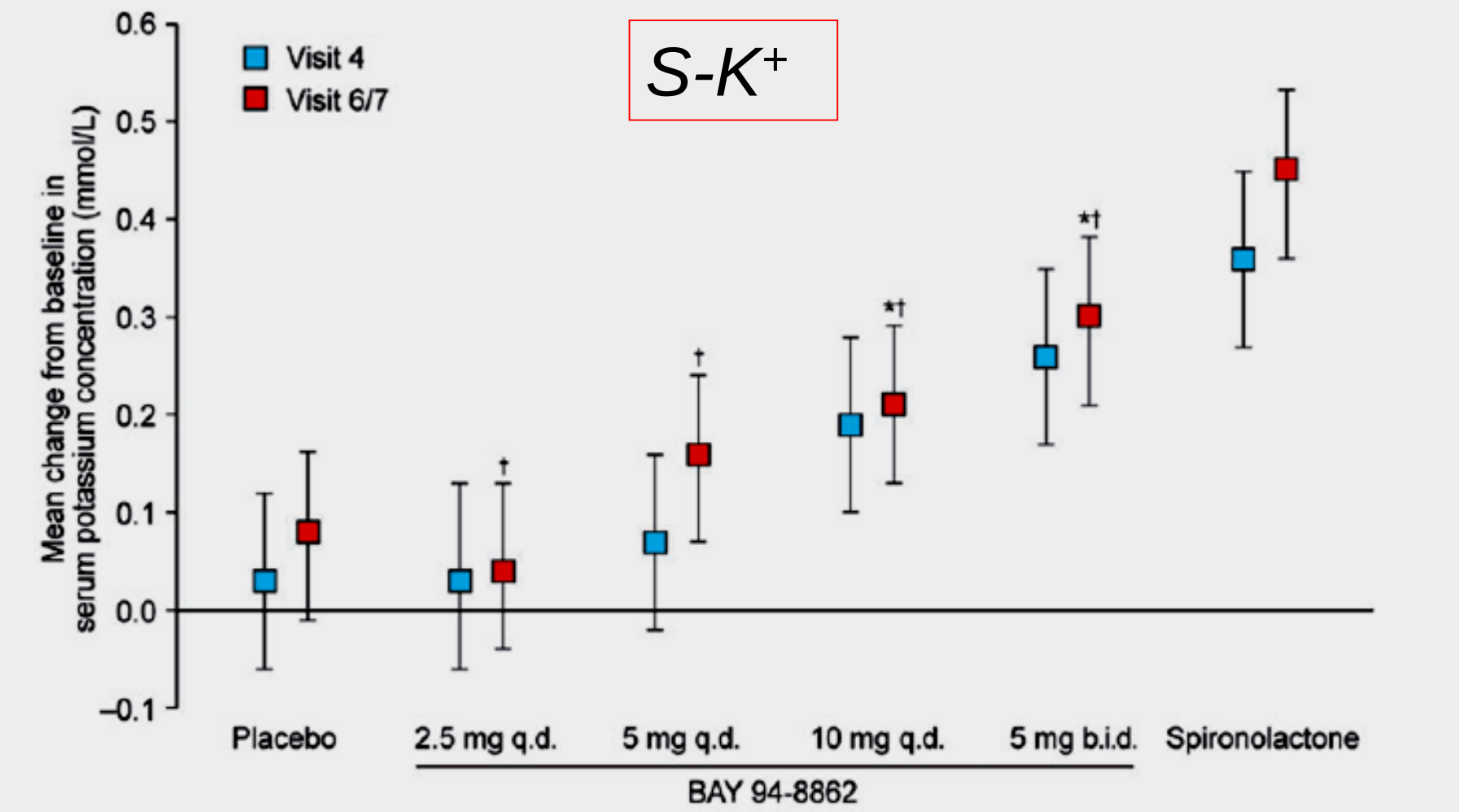
Wei, Cell.Biol.Int.(2013) 37:725

The role of Rho-kinase pathway for profibrotic differentiation of renal epithelial cells by EMT *(epithelial-mesenchymal transition)*



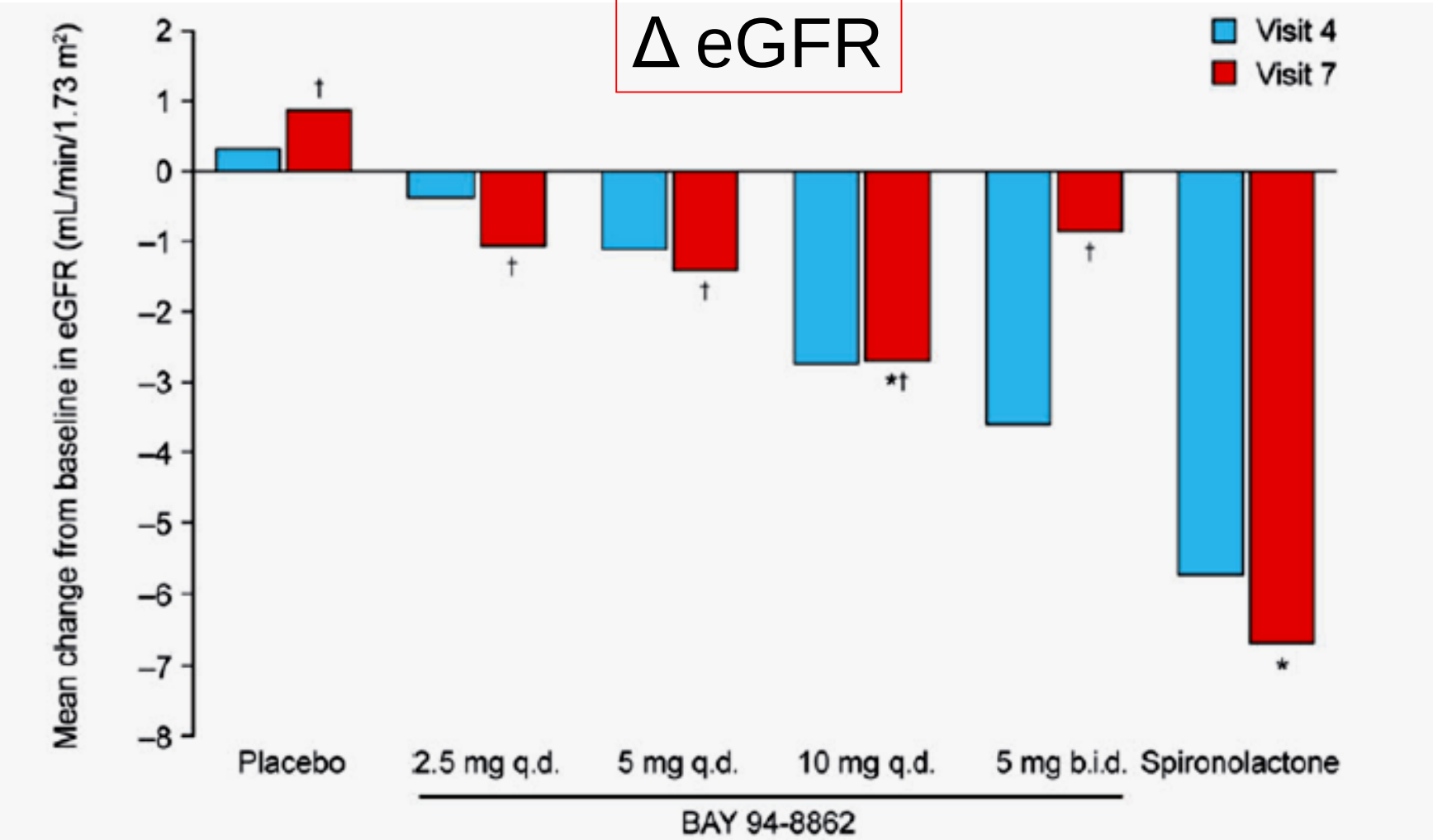
Wei, Cell.Biol.Int.(2013) 37:725

The novel non-steroidal mineral receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild/moderate CKD



Pitt, Eur.Heart J.(2013) 34:2453

The novel non-steroidal mineral receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild/moderate CKD



Pitt, Eur.Heart J.(2013) 34:2453

Spironolactone + ACE inhibitors or ARB in chronic glomerular disease

221 patients with chronic glomerular disease

Spironolactone 20 mg/day on top of ACEi or ARB

proteinuria,S-creatinine, S-K^+,plasma aldosterone,BP

4 weekly for 16 weeks :

significant reduction of proteinuria,

no significant differences :

eGFR,S-K^+ ,plasma aldosterone and BP

Wang, Exp.Ther.Med.(2013) 6:1527

S-K^+ with RAS blockade and with Spironolactone in diabetic nephropathy

Blinded, 3 arm, placebo controlled clinical trial
80 participants with diabetic nephropathy
randomized to :
Spironolactone (25mg/d), to Losartan (100mg/d) or Placebo
VII 2003-XII 2006

S-K^+ (mEq/L)
on Spironolactone 5.0;
on Losartan 4.7;
on Placebo 4.5
despite similar renal Na^+ and K^+ excretion
⇨ Role of <u>extrarenal</u> K^+ homeostasis

van Buren, CJASN (2014) 9:205

Safety of Mineralocorticoid Receptor Antagonists in Patients Receiving Hemodialysis

- in studies with Spironolactone doses ranging from 25mg 3 times/week after dialysis to 300 mg/day … have shown little increases in serum K^+ particularly with the lower doses.

- the literature base is limited by methodological weaknesses, low patient numbers, short follow-up and lack of blinded control group.

- Mineralocorticoid receptor antagonists may be used safely in patients with ESRD receiving hemodialysis, although additional large controlled trials are needed before definitive treatment recommendations can be made

Baker, Annals Pharmacotherapy (2012) 46:889

Beneficial impact of Spironolactone on nephrotic range proteinuria in diabetic nephropathy

20 Caucasian diabetic patients with nephrotic range proteinuria (>2500 mg/d) despite recommended antihypertensive treatment (incl.ACEi or ARB)

in random order on top of Rx :
Spironolactone 25 mg/day or placebo for 2 months
Spironolactone : reduction of albuminuria 32% (CI 21-42%) from 3718 (2910-4749) mg/24h on placebo

Schjoedt, Kidn.Internat.(2006) 70:536

Spironolactone diminishes albuminuria in type 1 diabetics with microalbuminuria

(double-blind, randomized placebo-controlled crossover trial)

21 type 1 diabetic patients with microalbuminuria
25 mg or placebo once daily for 60 days
on top of standard antihypertensive Rx

Spironolactone treatment :
ablbuminuria reduced 60% (*range 21-80%) p=0.01*
no change in blood pressure
GFR decrease from 78 to 71 ml/min/1.73m^2 *p=0.003*

Rx well tolerated, but 2 patients S-K 5.7 mmol/L

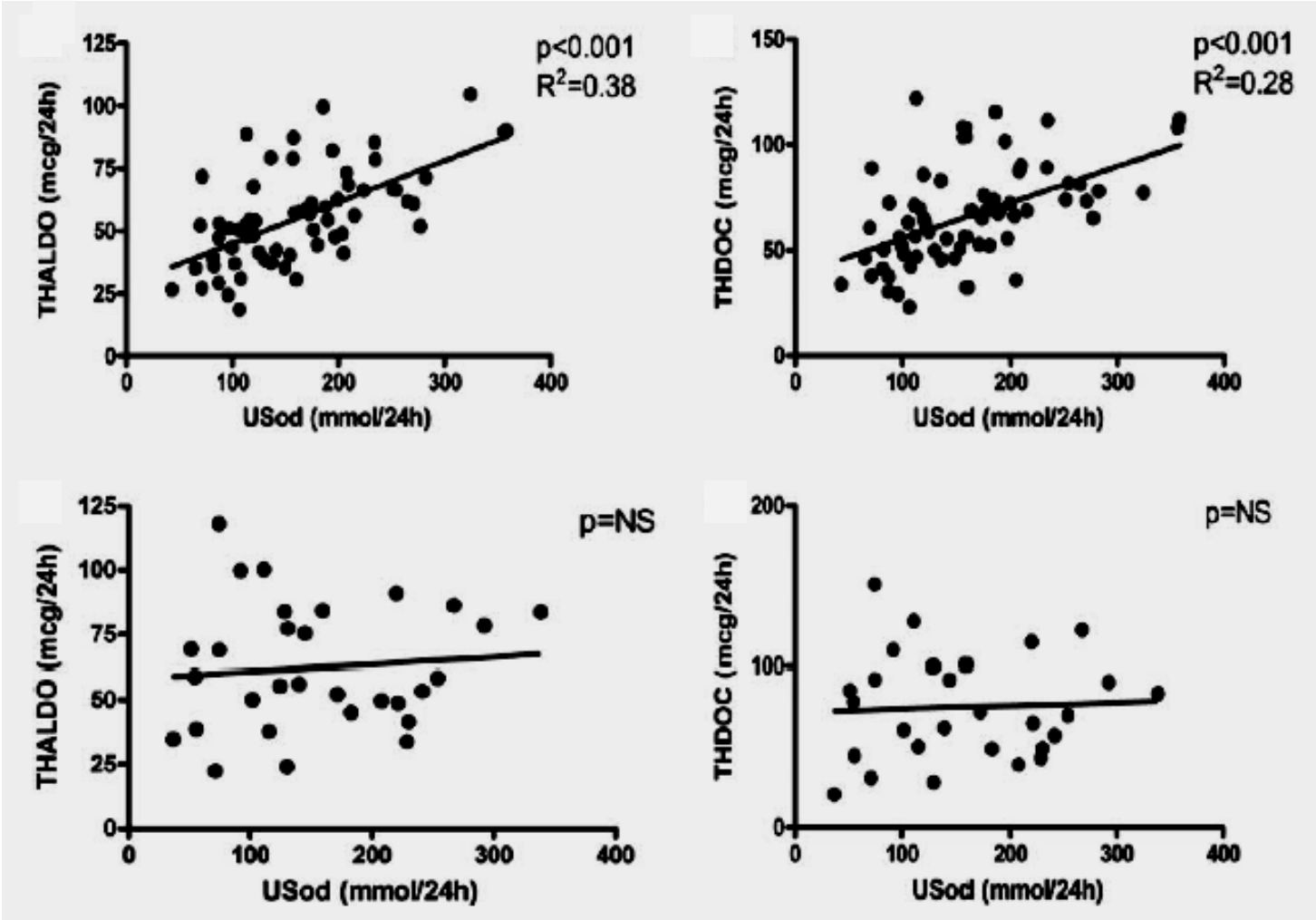
Nielsen, Diabet.Medicine (2012) 29:e184

In CKD *(but not in primary hypertension)* **:**
urinary-sodium-excretion determines excretion of mineralocorticoid-metabolites :

Thaldo *(tetrahydroaldosterone)* **THDOC** *(tetrahydrocorticosterone)*

CKD 3/4

primary hypertension



McQuarrie, Nephrol.Dial.Transplant.(2013) 29:1526