Estrategias Antiproteinúricas

Montevideo, Uruguay

14-15 Septiembre 2015

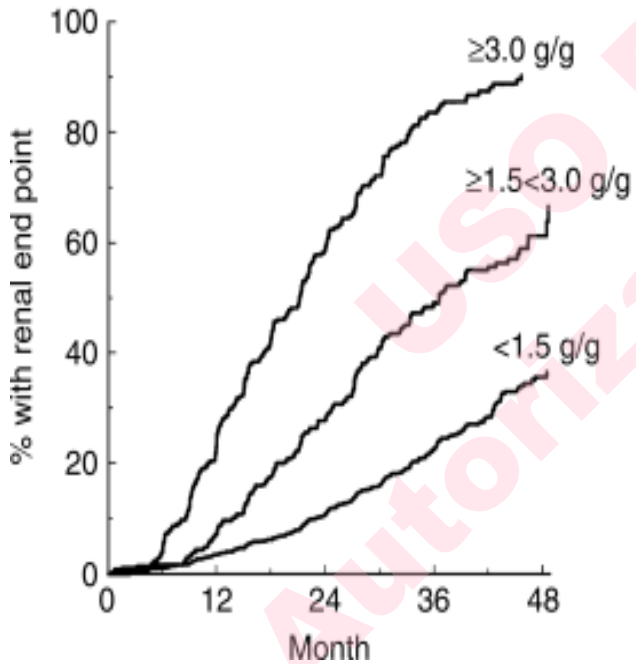
DOUBLING OF BASELINE SCR OR END-STAGE RENAL FAILURE

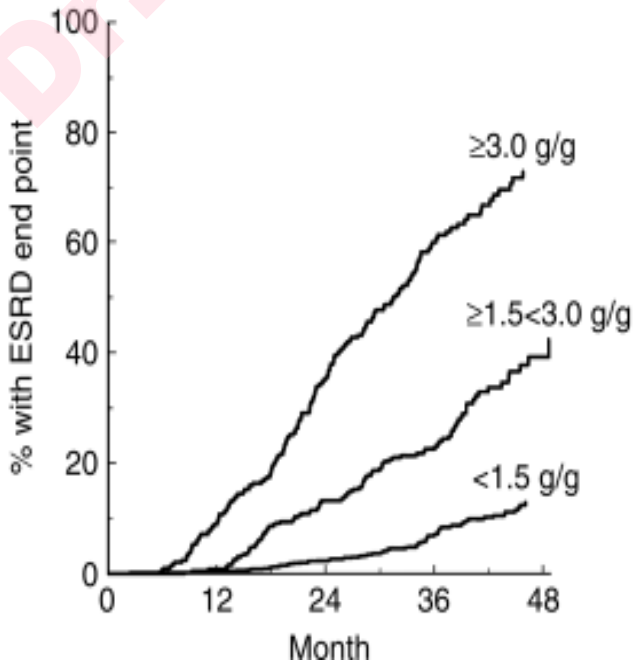
	Treatment with ACEI/ARA	Placebo
Benazepril in Non-diabetic Nephropathies 1996 (3 y.) (AIPRI)	31/300 (10%)	57/283 (20%)
Ramipril in non-diabetic nephropathies 1997 (2 y.) (REIN)	18/56 (32%)	40/61 (65%)
Captopril in type 1 diabetes 1993 (3y)	45/207 (21%)	74/202 (36%)
Irbersartan in type 2 diabetes 2001(2.6 y.) (IDNT)	180/579 (31%)	236/569 (41%)
Losartan in Type 2 diabetes 2001 (3.4 y) (RENAAL)	309/751 (41%)	392/762 (51%)

De Zeeuw D et al. Proteinuria, a target for renoprotection in patients with Type 2 diabetic nephropathy: lessons from RENAAL.Kidney Int 65: 2309-2320, 2004

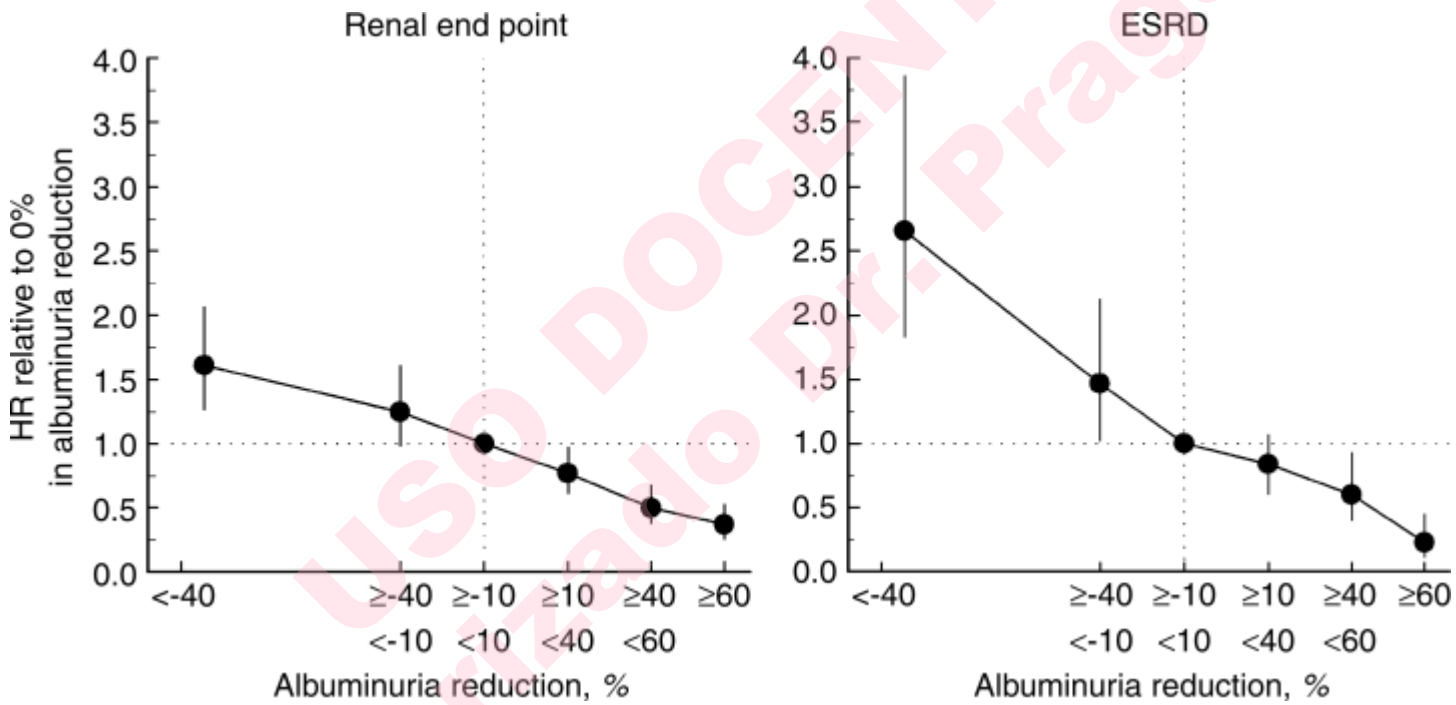
Renal end point			Adjusted	
	HR	*P* values	HR	*P* values
Alb: ≥1.5<3.0 vs. <1.5 g/g	2.47	<.0001	2.22	<.0001
Alb: ≥3.0 vs. <1.5 g/g	6.52	<.0001	5.18	<.0001
Alb: ≥3.0 vs. ≥1.5<3.0 g/g	2.64	<.0001	2.33	<.0001

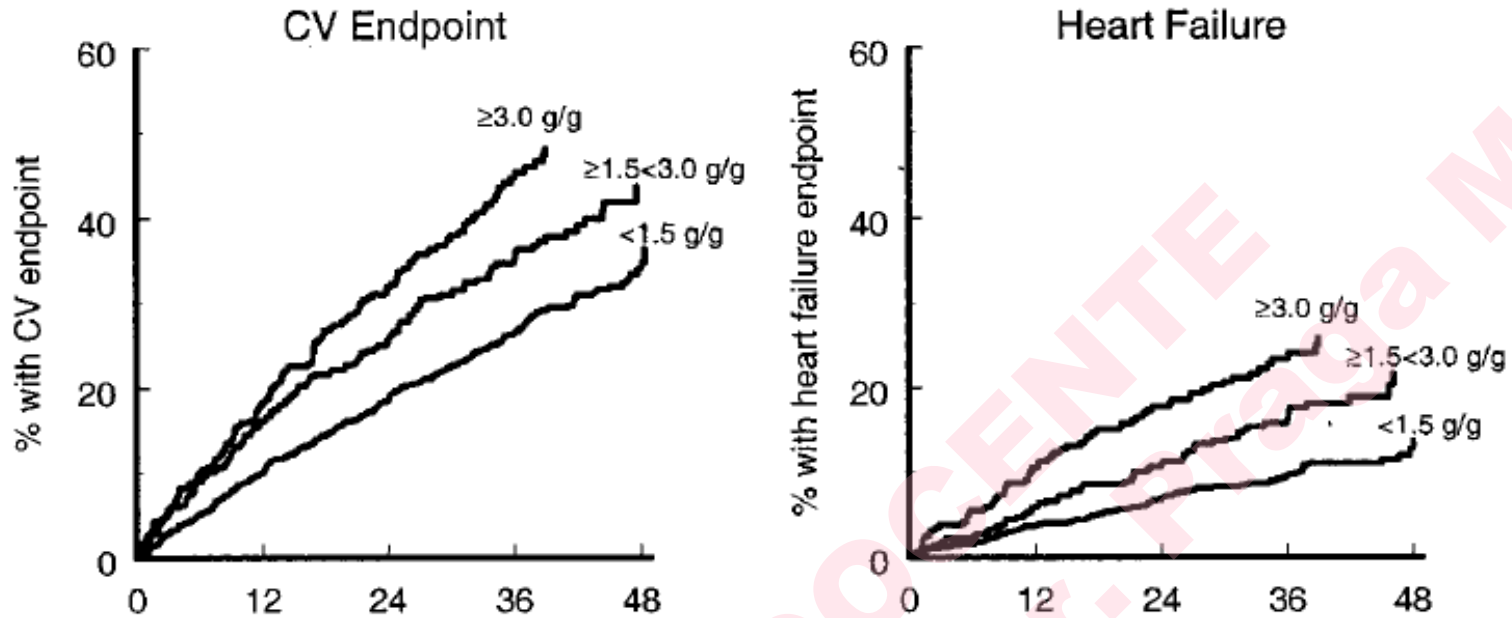
ESRD			Adjusted	
	HR	*P* values	HR	*P* values
Alb: ≥1.5<3.0 vs. <1.5 g/g	4.01	<.0001	3.23	<.0001
Alb: ≥3.0 vs. <1.5 g/g	11.49	<.0001	8.10	<.0001
Alb: ≥3.0 vs. ≥1.5<3.0 g/g	2.86	<.0001	2.51	<.0001

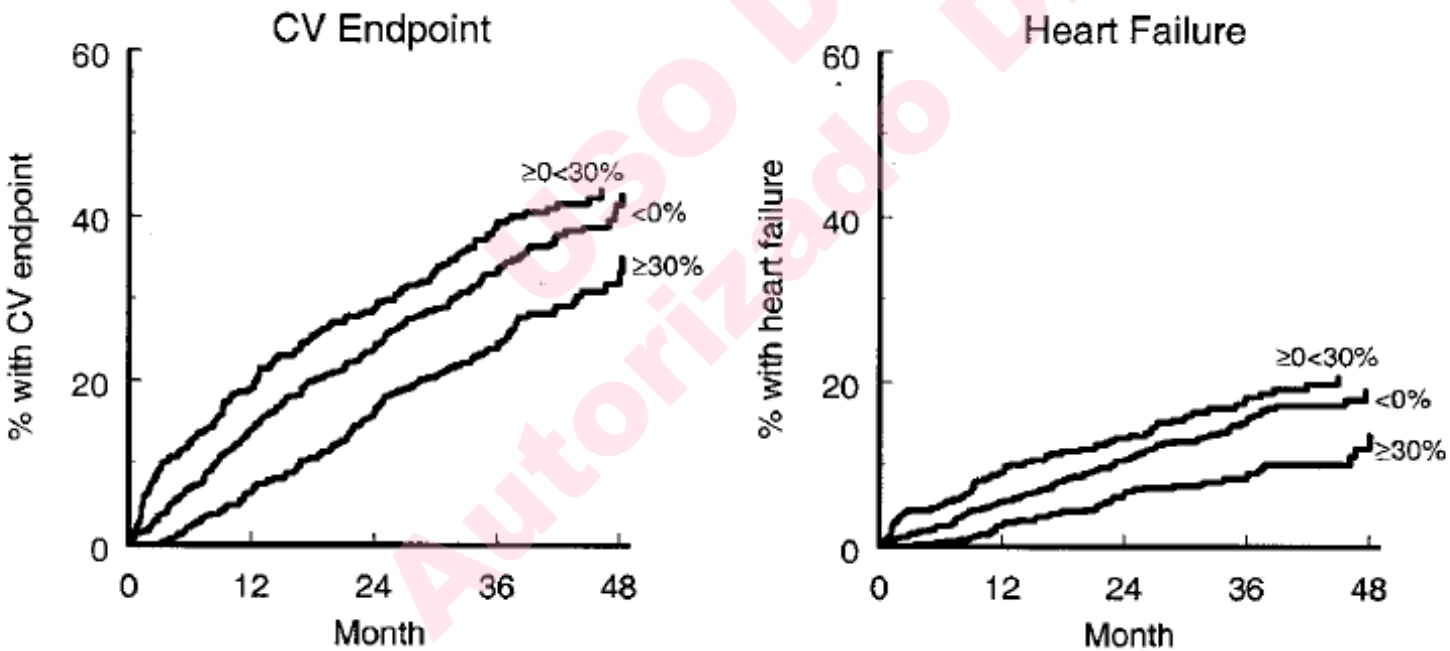




De Zeeuw D et al. Proteinuria, a target for renoprotection in patients with Type 2 diabetic nephropathy: lessons from RENAAL
Kidney Int 65: 2309-2320, 2004







RENAAL
Circulation 2004

2013 KDIGO CKD RECOMMENDATIONS

HYPERTENSION

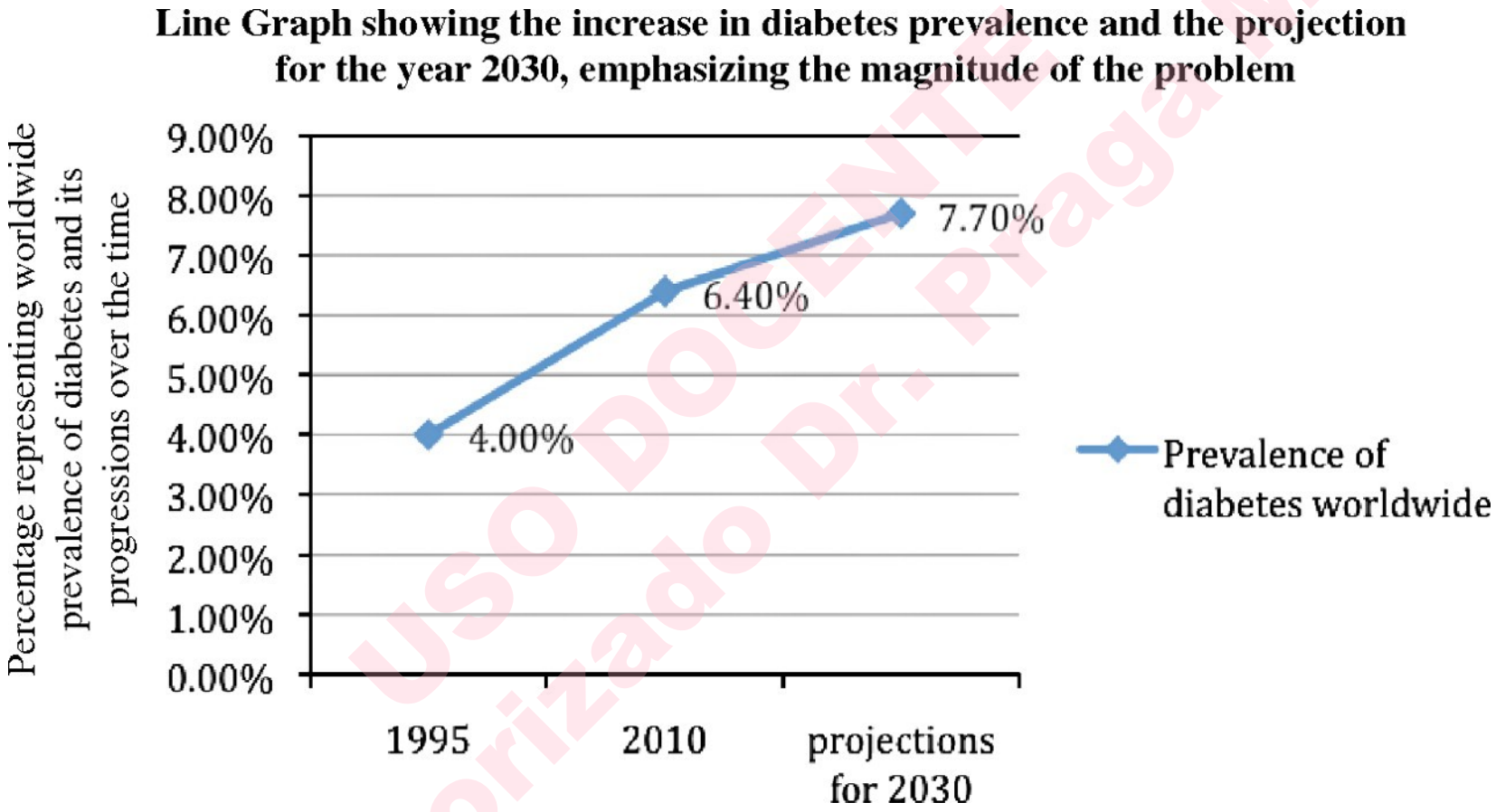
-Target BP ≤ 140/90 mmHg if albuminuria < 30 mg/d.

-Target BP ≤ 130/80 mmHg if albuminuria ≥ 30 mg/d.

-Diabetes: use ACEI or ARB if albuminuria ≥ 30 mg/d.

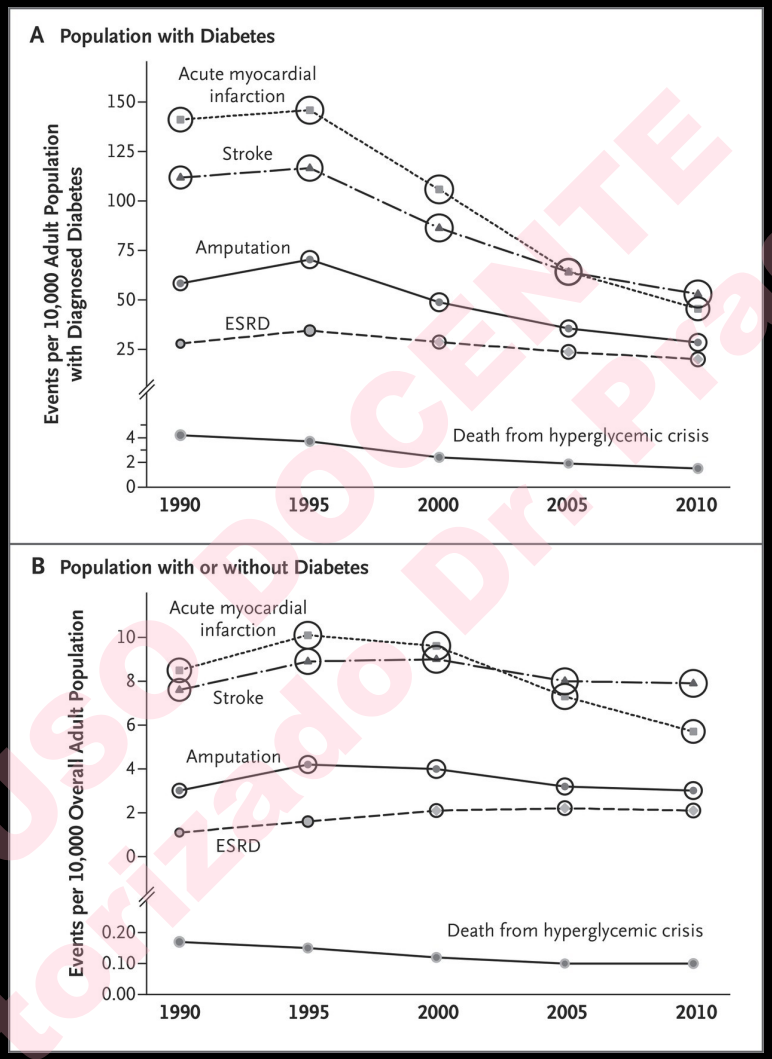
-Nondiabetes: use ACEI or ARB if albuminuria ≥ 300 mg/d

Prevalence of diabetes worldwide in the years 1995, 2010 and projections for 2030, as reported by King et al. [24], Rathmann and Giani [79] and Shaw et al. [13].



Farag Y M , and Gaballa M R Nephrol. Dial. Transplant. 2011;26:28-35

NDT
Nephrology Dialysis Transplantation



The NEW ENGLAND JOURNAL of MEDICINE

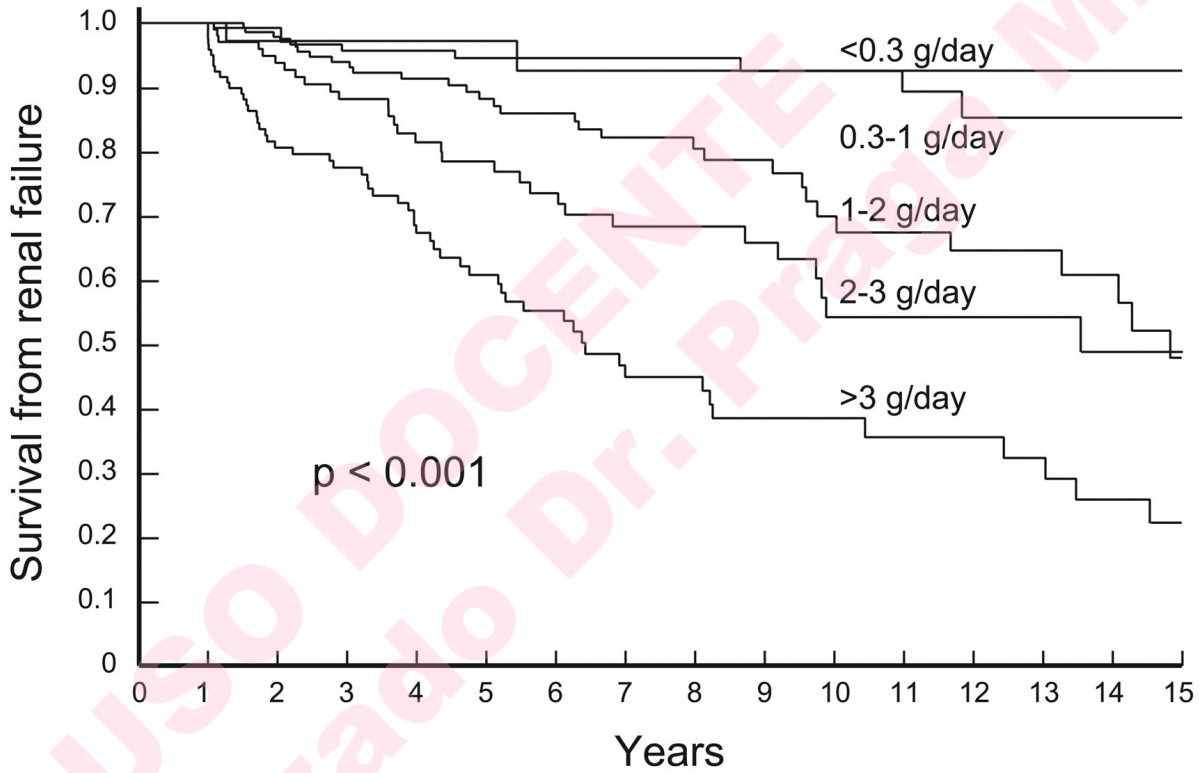
PROTEINURIA TARGET FOR RENAL OUTCOMES

PROTEINURIA <0.5 g/24h

ALBUMINURIA (ACR) <300 mg/g

Different proteinuria targets in different kidney diseases?

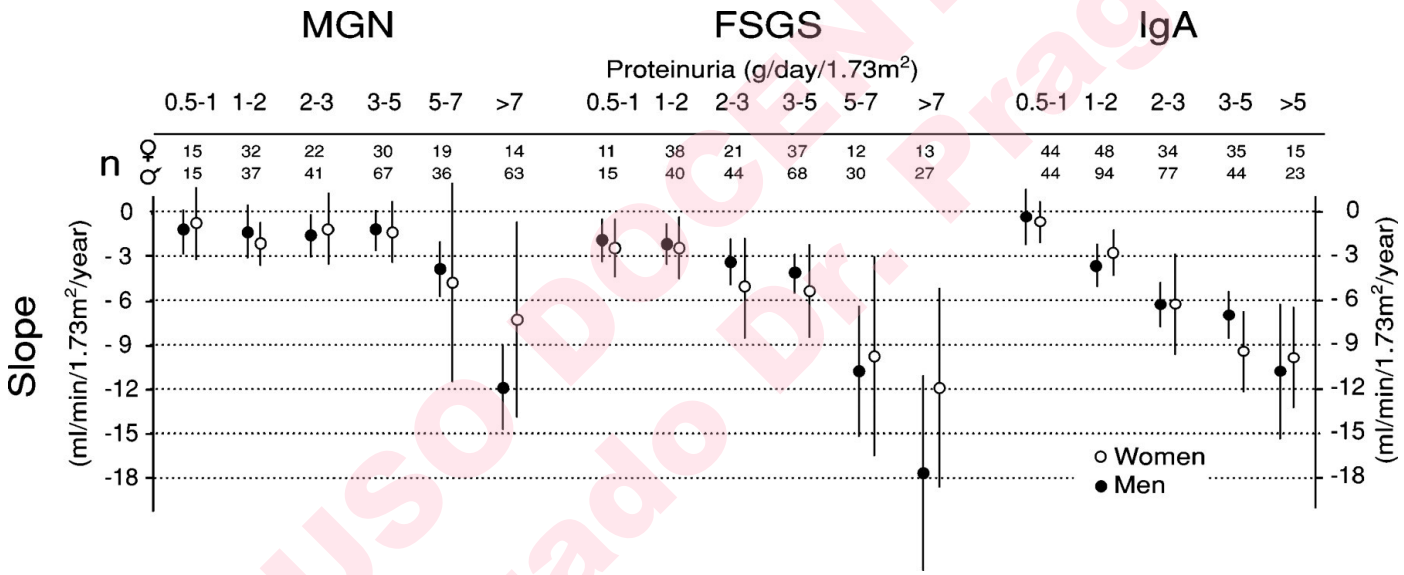
Reich, H. N. et al. J Am Soc Nephrol 2007;18:3177-3183
Renal survival by category of TA-proteinuria



<0.3 g/day	37	22	8	1
0.3-1 g/day	134	79	35	11
1-2 g/day	145	79	28	10
2-3 g/day	105	50	18	4
>3 g/day	120	44	13	6

JASN

Interaction between time average proteinuria and sex in relation to the rate of renal function decline in MGN, FSGS and IgA nephropathy



Cattran, D. C. et al. Nephrol. Dial. Transplant. 2008 23:2247-2253; doi:10.1093/ndt/gfm919

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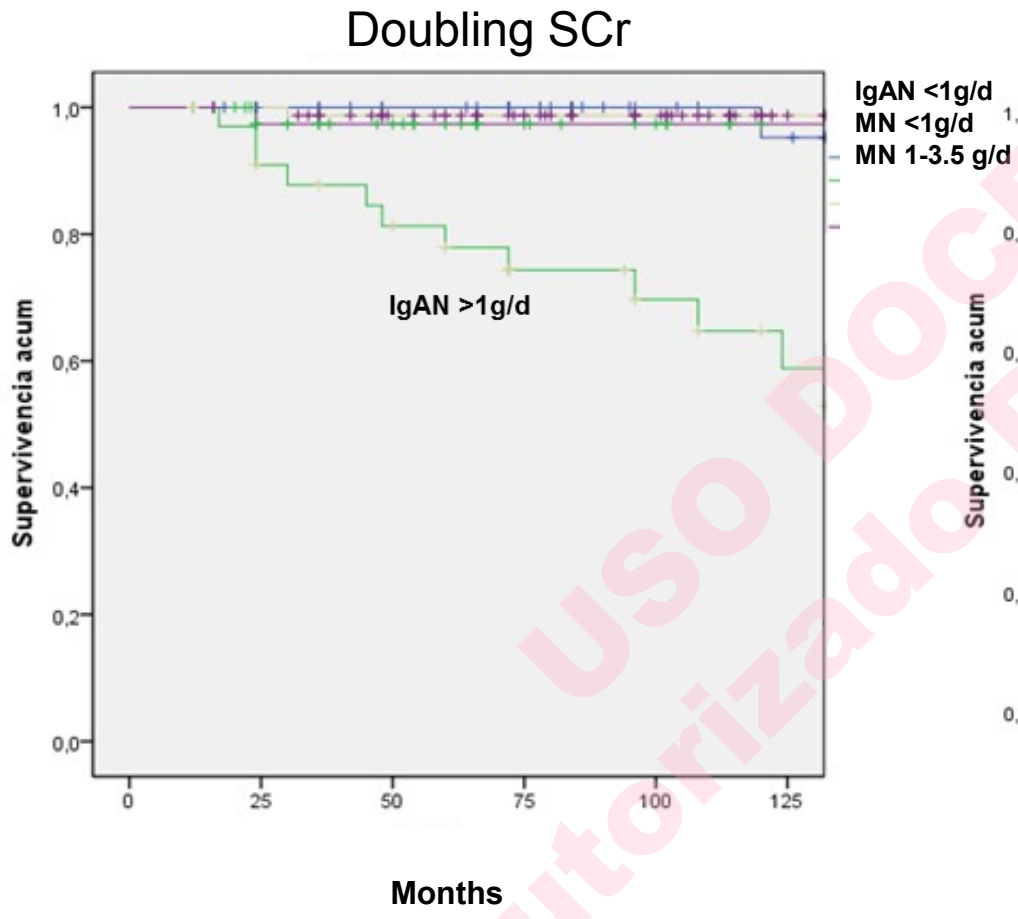
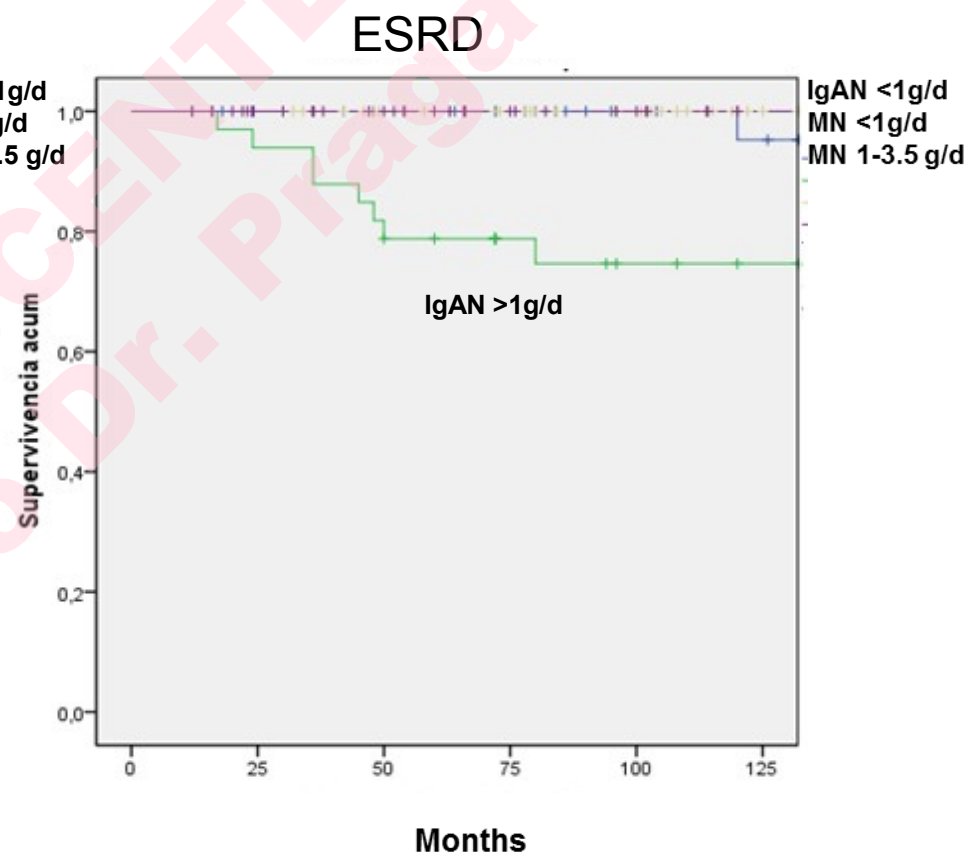
Renal survival in IgAN and MN according to mean proteinuria during follow-up





Clinical Case

- 45 yr-old man, HIV infection on antiretroviral treatment.
- Slowly increasing proteinuria (0.6 g/24h). S. Creatinine 0.9 mg/dl, normal urine sediment, BP 140/90 mmHg, BMI 28 Kg/m2.
- Enalapril 5-10 mg/d. Proteinuria decreased to <0.2-0.3 g/d.
- 8 yr later, normal renal function, good BP control

PROTEINURIA TARGET <0.5 g/24h

Clinical Case

- **Male, 60-years-old. Obese (BMI >35 Kg/m2) for > 20 yr**
- **Right nephrectomy at age 48 because tumor**
- **Submitted with Serum Creatinine 1.4 mg/dl, proteinuria 3.2 g/24h, BP 135/90 mmHg**
- **Enalapril, increasing doses (40 mg/d) : initial proteinuria decrease (2-2.5 g/24 h), but it tended to increase again (>3 g/24h) after the first year, in parallel with further weight gain**

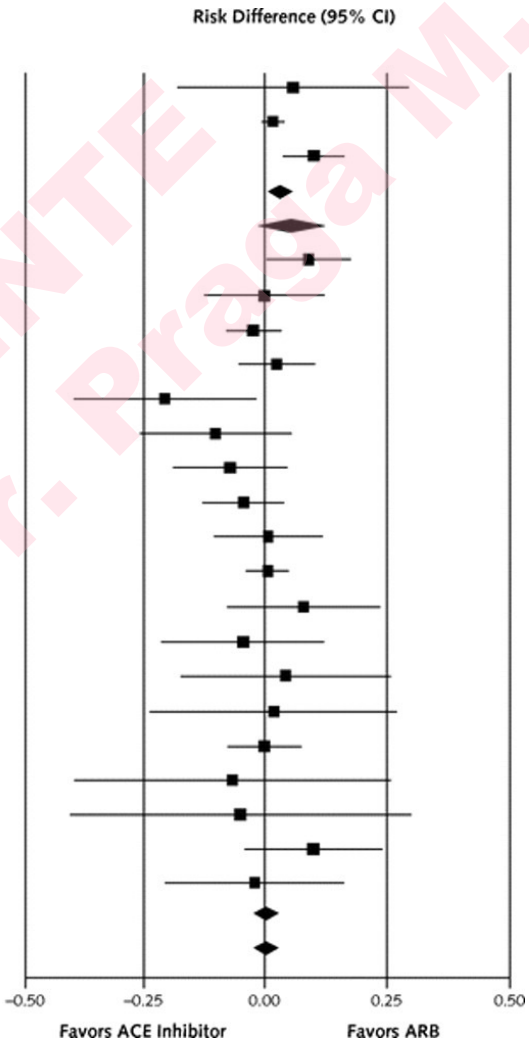
PROTEINURIA TARGET <0.5 g/24h

Antiproteinuric therapies

- Combination ACEI+ARB……..>40%
- (ACEI/ARB)+Antialdosteronics….>40%
- (ACEI/ARB)+Aliskiren……..20%
- (ACEI/ARB)+ Paricalcitol……15-20%
- (ACEI/ARB)+ Pentoxyfillin…… 15-17%

Successful monotherapy: angiotensin-converting enzyme (ACE) inhibitors versus angiotensin II receptor blockers (ARBs)

Study, Year (Reference)	Time Point, *wk*	Events/Total, *n/n*	
		ARB	ACE Inhibitor
Verdecchia et al., 2000 (68)	172	12/22	32/66
Mazzaglia et al., 2005 (83)	52	348/1382	1072/4602
Hasford et al., 2002 (80)	52	394/754	140/333
Fixed			
Random			
Saito et al., 2004 (60)	26	66/200	51/214
Cuspidi et al., 2002 (34)	48	53/115	57/124
Ruilope et al., 2001 (59)	12	153/168	152/163
Larochelle et al., 1997 (47)	12	11/121	4/61
Lacourcière et al., 2000 (46)	52	20/52	30/51
Ruff et al., 1996 (69)	12	3/50	4/25
Townsend et al., 1995 (66)	12	62/132	72/136
Neutel et al., 1999 (55)	48	169/385	93/193
Karlberg et al., 1999 (43)	26	89/139	88/139
Malacco et al., 2004 (49)	16	479/604	479/609
Fogari et al., 2004 (73)	16	45/75	39/75
Rosei et al., 2005 (58)	24	39/66	40/63
Ghiadoni et al., 2003 (42)	26	23/29	21/28
Uchiyama-Tanaka et al., 2005 (67)	52	14/18	19/25
Argenziano and Trimarco, 1999 (27)	26	182/264	182/264
Robles et al., 2004 (82)	12	10/15	11/15
Kavgaci et al., 2002 (44)	26	13/20	7/10
Mogensen et al., 2000 (53)	24	54/66	46/64
Eguchi et al., 2003 (37)	12	29/37	29/36
Fixed			
Random			



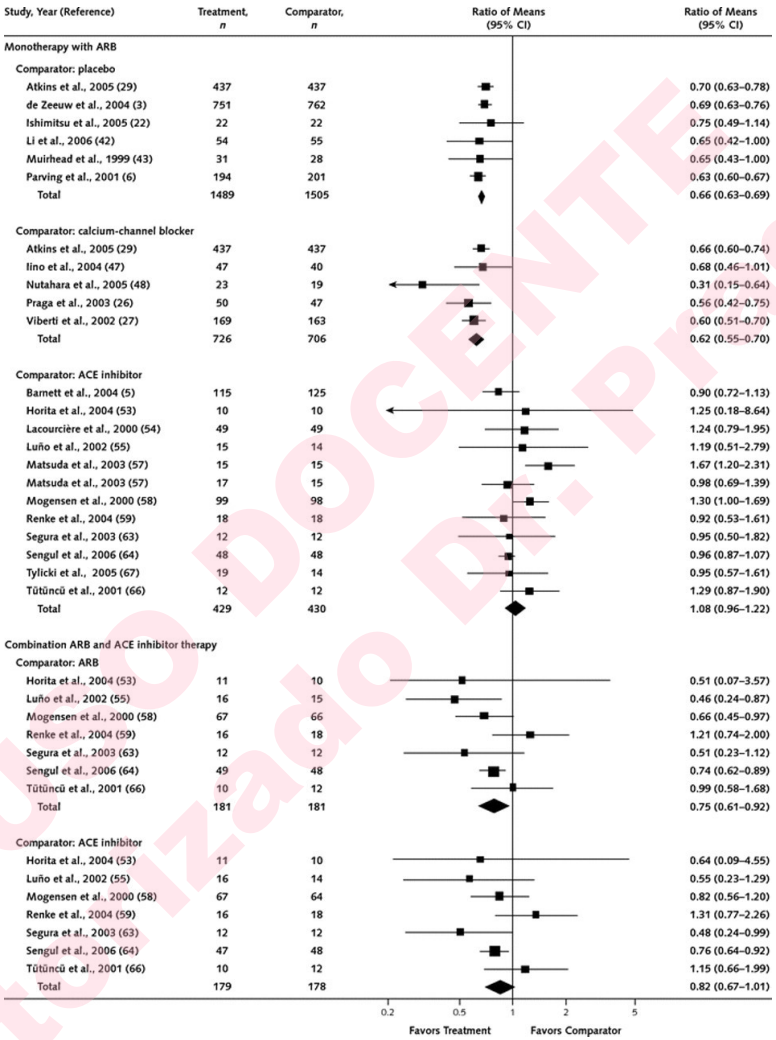
Matchar, D. B. et. al. Ann Intern Med 2008;148:16-29

Conclusion.Available evidence shows that ACE inhibitors and ARBs have similar effects on blood pressure control.

Annals of Internal Medicine

Reduction in proteinuria at 5 to 12 months

Conclusion.
Reduction in proteinuria from ARBs and ACE inhibitors is similar, but their combination is more effective than either drug alone.



Kunz, R. et. al. Ann Intern Med 2008;148:30-48

Annals of Internal Medicine

Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial
Lancet 2008

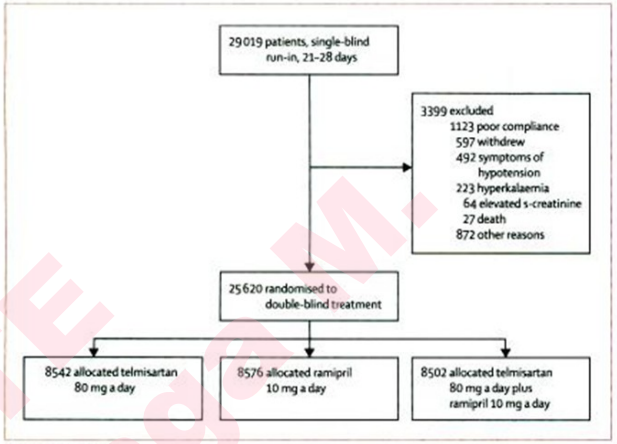


Figure 1: **Trial profile**
All participants received randomised therapy except 43 lost to follow-up, so 99·8% were followed-up until end of study or until a primary event.[4]

	Ramipril gMean (95% CI)	Telmisartan gMean (95% CI)	Ramipril+telmisartan gMean (95% CI)	Telmisartan vs ramipril p	Telmisartan+ramipril vs ramipril p
UACR, Baseline	0·81 (0·78–0·84)	0·83 (0·80–0·86)	0·81 (0·78–0·84)	0·246	0·923
2-year ratio to baseline	1·17 (1·13–1·20)	1·08 (1·05–1·12)	1·05 (1·02–1·08)	0·0013	<0·0001
Final ratio to baseline	1·32 (1·27–1·37)	1·25 (1·20–1·29)	1·22 (1·17–1·26)	0·033	0·0028
LO ratio to baseline	1·31 (1·26–1·35)	1·24 (1·20–1·28)	1·21 (1·17–1·25)	0·027	0·0009

UACR=urine albumin to creatinine ratio (mg/mmol); Final=study end. gMean=geometric mean. LO=last observation value; for patients with at least one follow-up value, changes from baseline to last observation were compared between groups. All UACR values were log-transformed before analyses; gMean-values are back-transformed. Differences were calculated using an ANOVA model adjusted for baseline values. Number of participants with measurements=21 076 at baseline, 19 397 at 2 years, 16 098 at study end.

Table 3: **Changes in log urine albumin to creatinine ratio**

Although combination therapy reduces proteinuria to a greater extent than monotherapy, overall it worsens major renal outcomes (dialysis, doubling of serum creatinine, death)

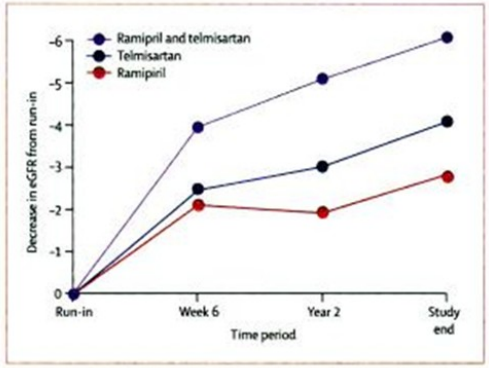


Figure 2: **Decrease in estimated glomerular filtration rate (eGFR) during the trial, from baseline to study end**

Proteinuria: Is the ONTARGET renal substudy actually off target?
Ruggenenti P, Remuzzi G.
Nat Rev Nephrol 2009

Have we fallen off target with concerns surrounding dual RAAS blockade?
Lattanzio, Weir MR.
Kidney Int. 2010

- Non-proteinuric CKD patients at low risk of progression
- Inadequate power of the study to assess renal outcomes,
- High number of AKI because of inadequate design

Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy. The VA NEPHRON-D trial

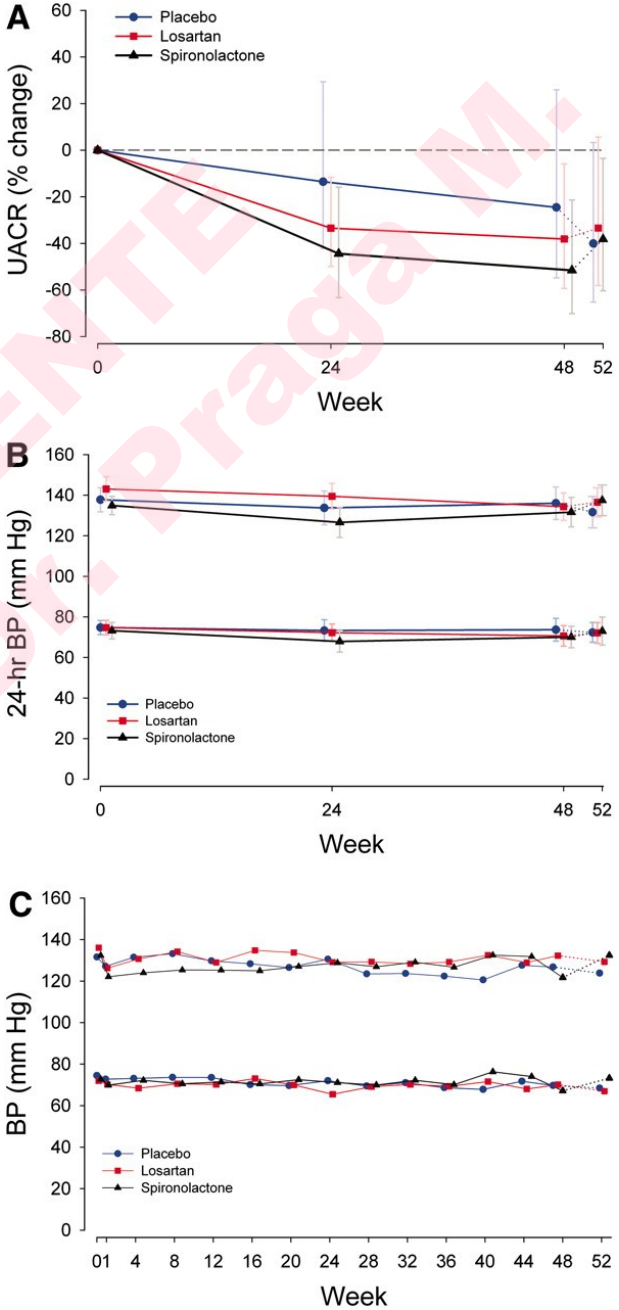
Fried L et al. N Engl J Med 2013
Combination therapy with an ACE inhibitor and an ARB was associated with an increased risk of adverse events among patients with diabetic nephropathy.

Effect of dual blockade of the renin-angiotensin system on the progression of type 2 diabetic nephropathy: a randomized trial. The PRONEDI trial

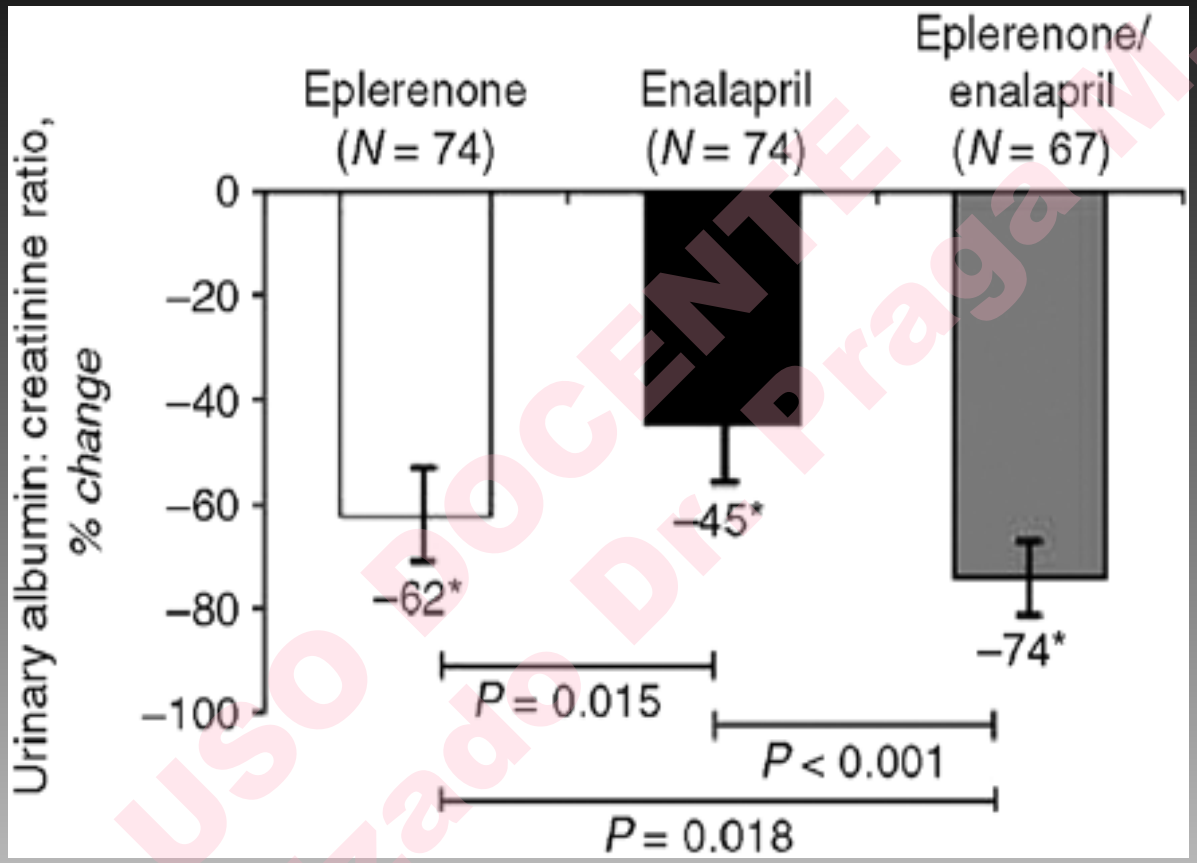
Fernández-Juárez G et al, AJKD 2013
We were unable to show a benefit of the combination of lisinopril and irbesartan compared to either agent alone at optimal high doses on the risk of progression of type 2 diabetic nephropathy.

Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy

Reduction in Albuminuria
After adding Spironolactone: >40%

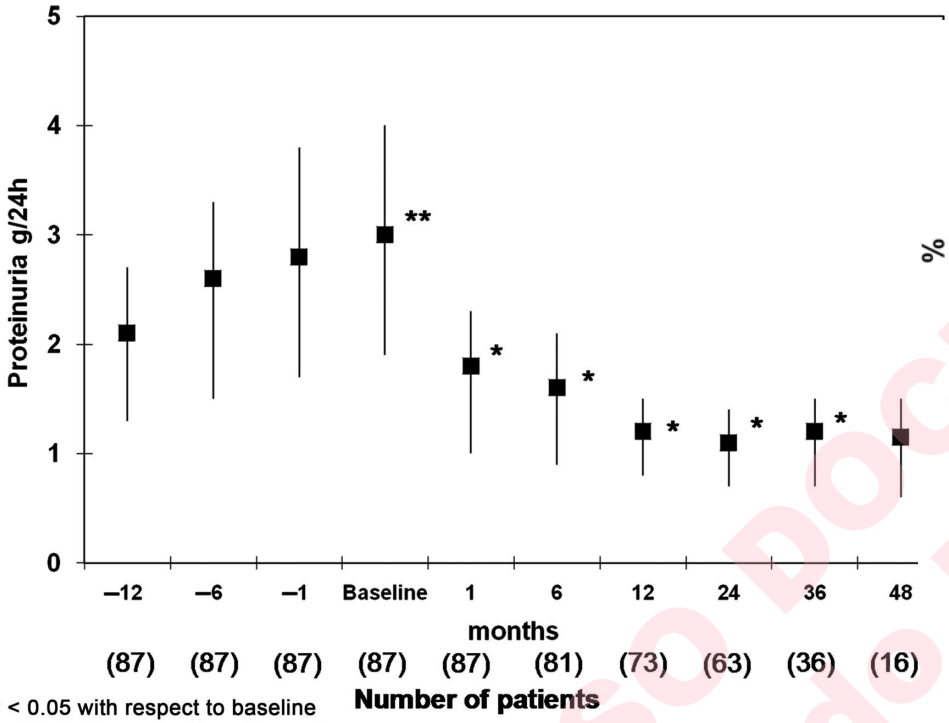


Mehdi, U. F. et al. J Am Soc Nephrol 2009



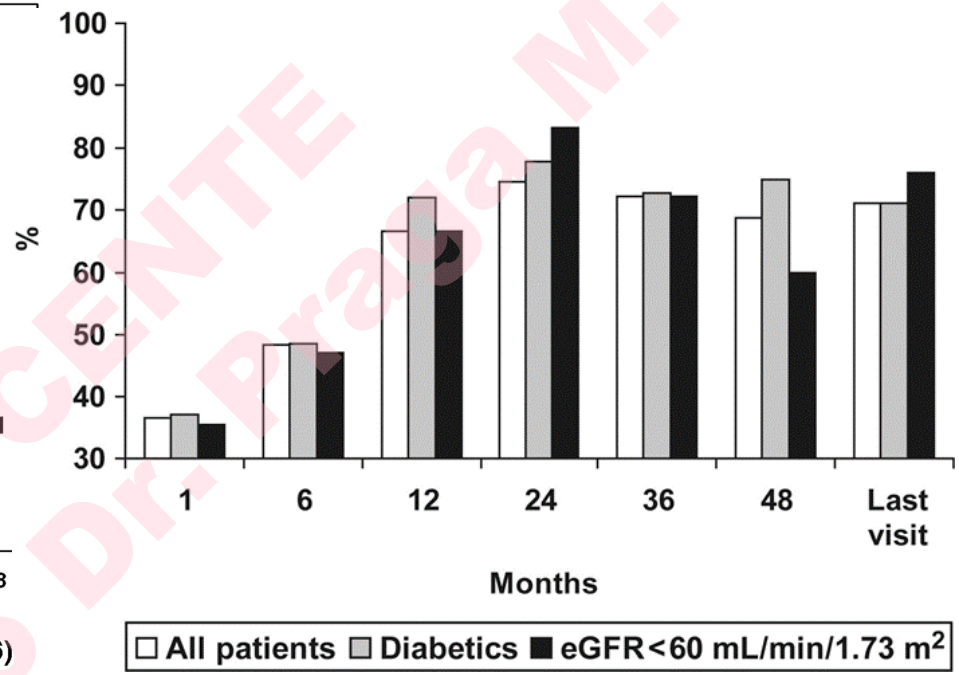
Epstein M . Antiproteinuric efficacy of eplerenone enalapril, and eplerenone/enalapril combination in diabetic hypertensives with microalbuminuria.
***Am J Hypertens* 2002; 15: 24A**

Evolution of proteinuria during follow-up.



*P < 0.05 with respect to baseline
**P < 0.05 with respect to –12 month

Percentage of patients with proteinuria reductio
>50% of baseline values during follow-up.



Renoprotective effects of mineralocorticoid receptor blockers in patients with proteinuric kidney diseases. Morales E et al, NDT 2013

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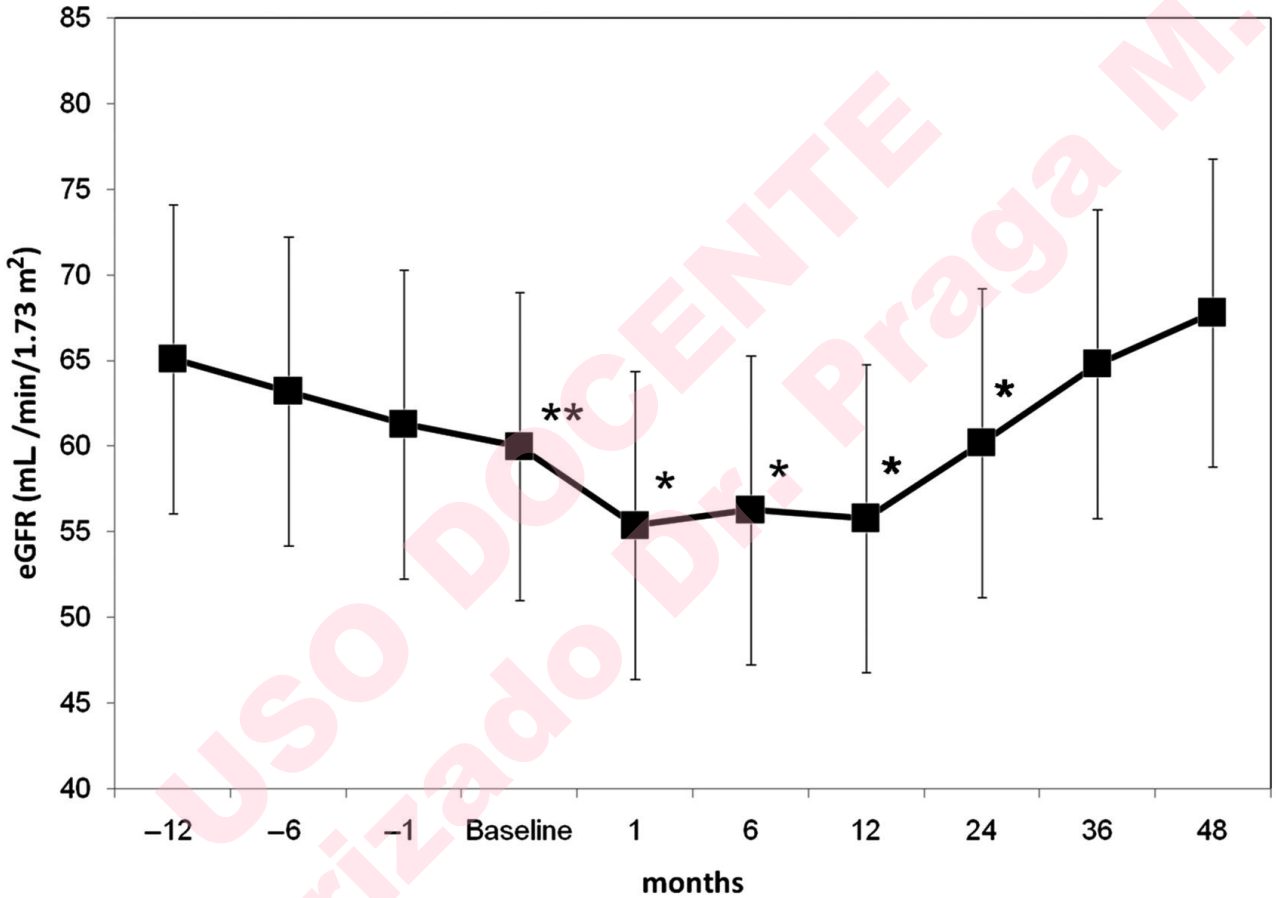
Evolution of eGFR during follow-up.



(87) (87) (87) (87) (87) (81) (73) (63) (36) (16)

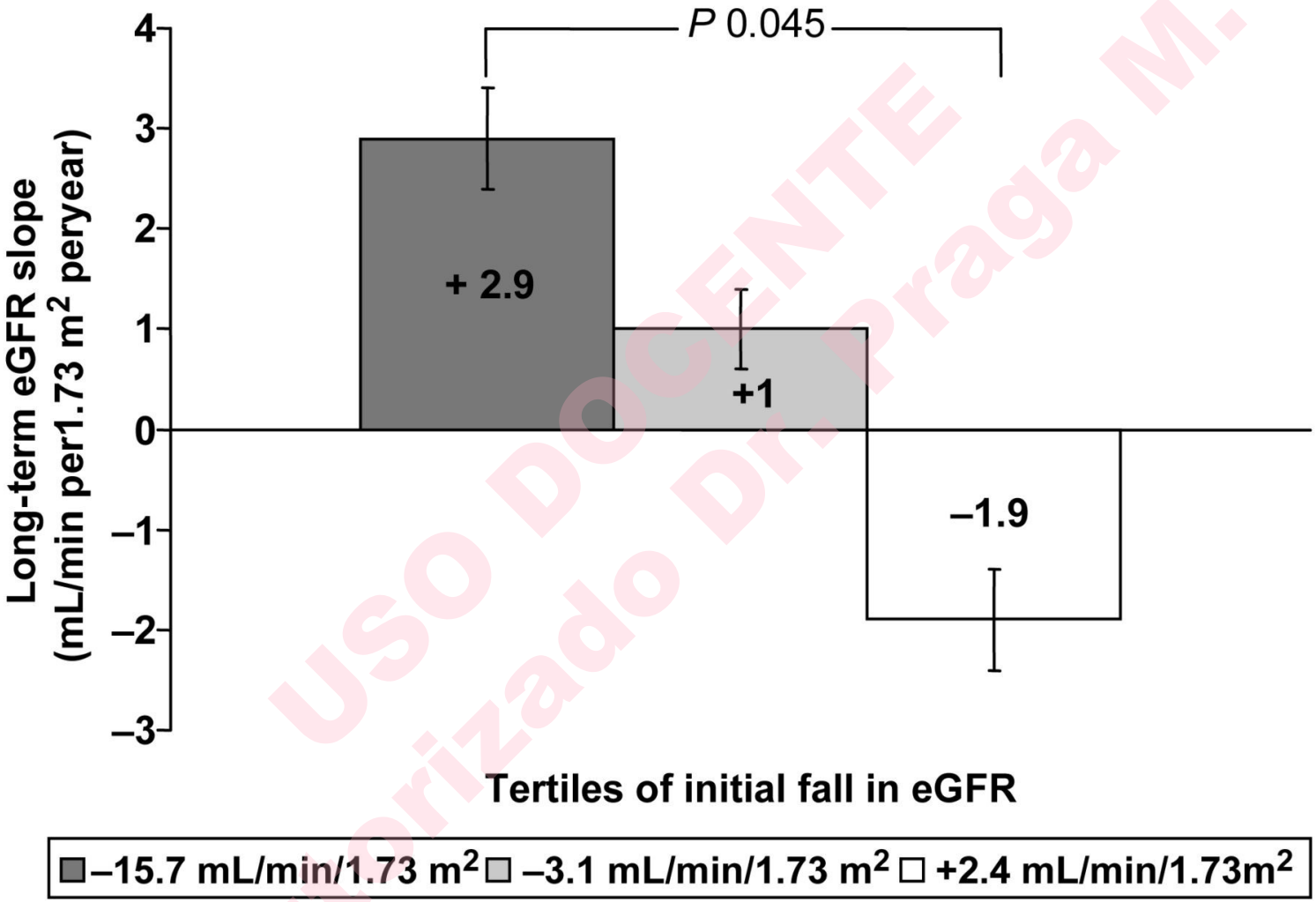
Number of patients

*P < 0.05 with respect to baseline
**P < 0.05 with respect to –12 month

Enrique Morales et al. Nephrol. Dial. Transplant. 2013;28:405-412

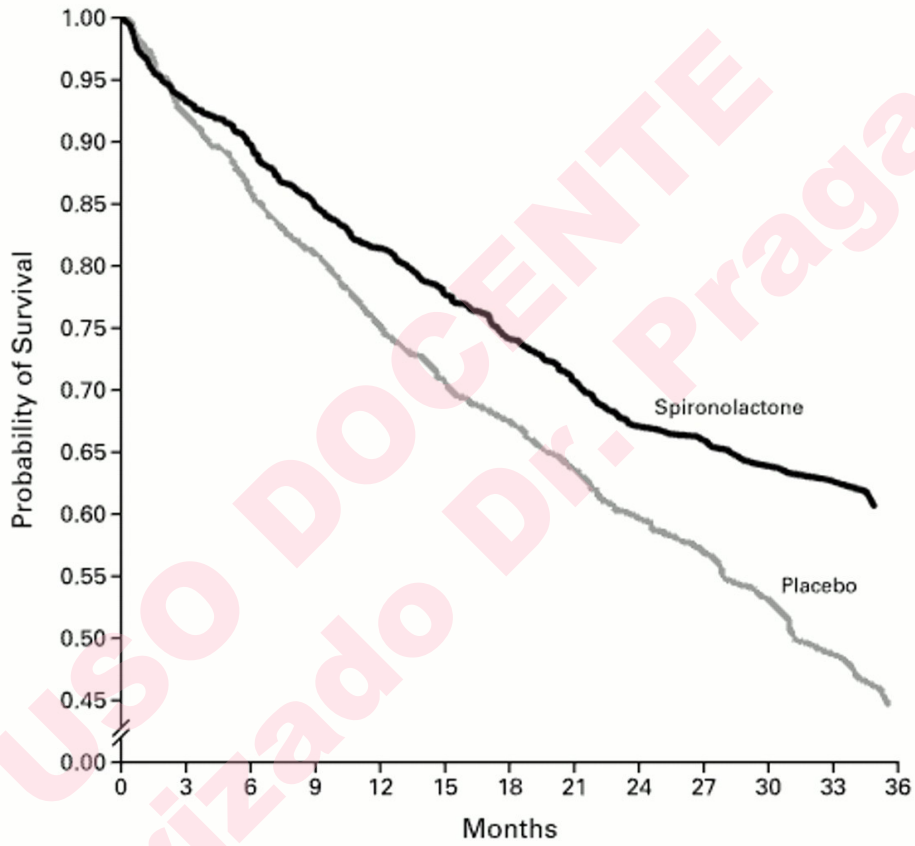
NDT Nephrology Dialysis Transplantation

Long-term eGFR slope stratified by acute decline in eGFR during the first month of MRB treatment.



Morales E et al. Nephrol. Dial. Transplant. 2013;28:405-412

NDT Nephrology Dialysis Transplantation



No. at Risk													
Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

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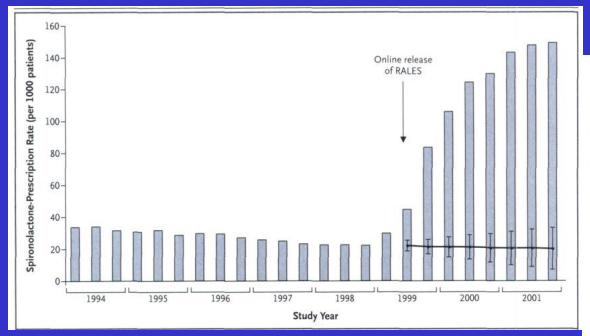
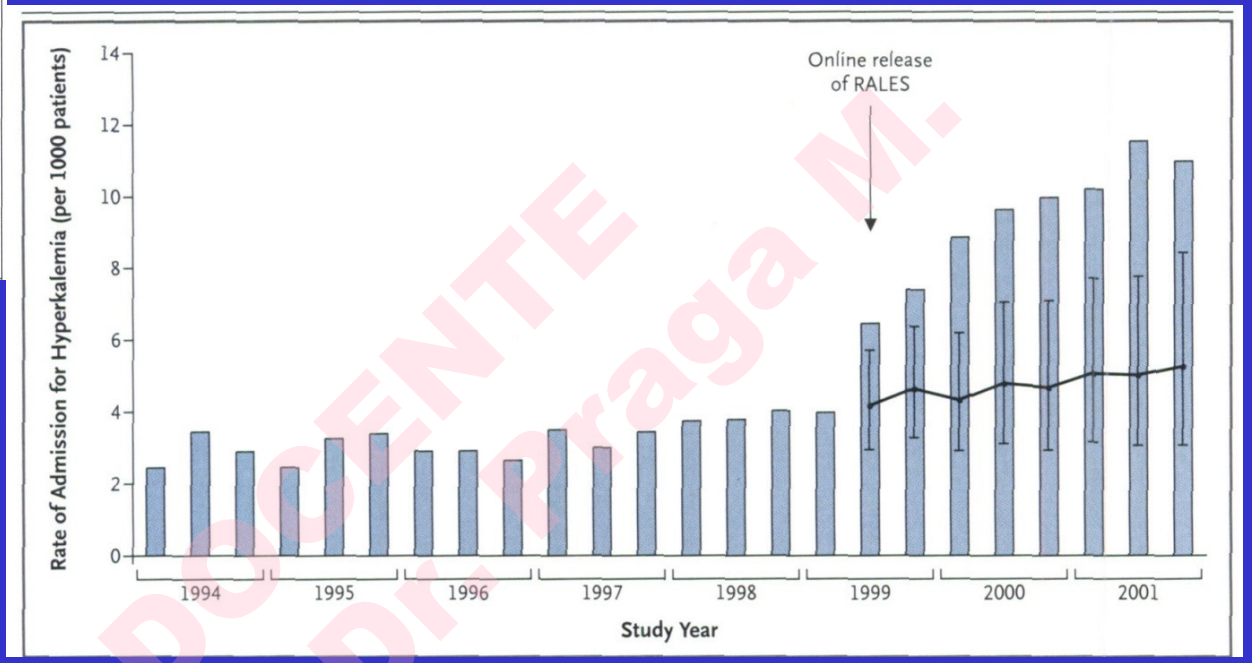




Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study (RALES)

Juurlink DN et al
NEJM 351: 543, 2004

Finerenone: less hyperkalaemia, worsening renal function, and blood pressure decrease than Spironolactone
Pitt B et al. Eur Heart J. 2013

Effect of Finerenone on Albuminuria in Patients With Diabetic Nephropathy

A Randomized Clinical Trial

JAMA. 2015;314(9):884-894.

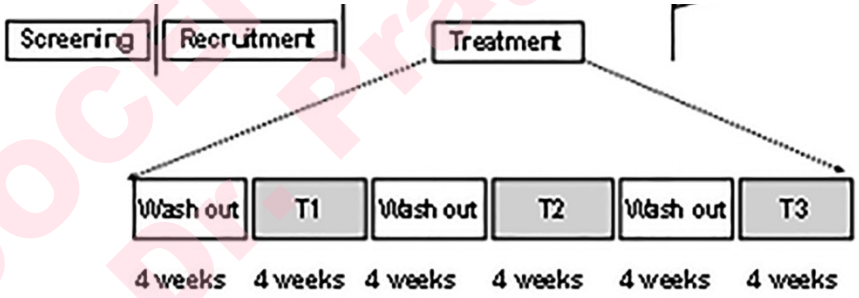
MAIN OUTCOMES AND MEASURES The primary outcome was the ratio of the urinary albumin-creatinine ratio (UACR) at day 90 vs at baseline. Safety end points were changes from baseline in serum potassium and estimated glomerular filtration rate.

CONCLUSIONS AND RELEVANCE Among patients with diabetic nephropathy, most receiving an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, the addition of finerenone compared with placebo resulted in improvement in the urinary albumin-creatinine ratio. Further trials are needed to compare finerenone with other active medications.

Diverse diuretics regimens differentially enhance the antialbuminuric effect of renin–angiotensin blockers in patients with chronic kidney disease

Enrique Morales[1], Jara Caro[1], Eduardo Gutierrez[1], Angel Sevillano[1], Pilar Auñón[1], Cristina Fernandez[2] and Manuel Praga[1,3]

Kidney International advance online publication, 26 August 2015;
doi:10.1038/ki.2015.249



21 patients:
UACR >300 mg/g
eGFR >30 ml/min/1.73 m2

Prospective Randomized,
Crossover Trial

T1: Spironolactone 25 mg/d
T2: Hydrochlorothiazide 50 mg/d
T3: Hydrochlorothiazide 50 mg/d + Amiloride 5 mg/d

On top of Enalapril 40 mg/d

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Table 2 | Effects of diuretics on albuminuria and proteinuria

	Spironolactone		Hydrochlorothiazide		Hydrochlorothiazide+amiloride	
	Baseline	4 Weeks	Baseline	4 Weeks	Baseline	4 weeks
UACR (mg/g)	810 (601–1020)	742* (241–1244)	1011 (803–1218)	566*+ (205–927)	1135 (926–1344)	398*+ (212–584)
% UACR reduction		34 (21–47)		42 (28–56)		56 (44–67)
Patients with >30% UACR reduction (%)		12 (57)		17 (81)		17 (81)
Patients with >50% UACR reduction (%)		6 (28)		12 (57)		14 (66)
24-H Albuminuria (mg)	1600 (1047–2152)	1125.2* (500–1750)	1417 (868–1965)	935* (266–1603)	1882 (1325–2440)	577* (300–855)
24-H Proteinuria (g)	1.7 (1.3–2.2)	1.5* (0.8–2.3)	1.7 (1.3–2.1)	1.3* (0.6–2)	2.4 (1.9–2.8)	0.9* (0.6–1.2)

Abbreviation: UACR, urinary albumin-to-creatinine ratio.
*$P<0.05$ for intragroup comparison; +$P<0.05$ for between-group comparison.

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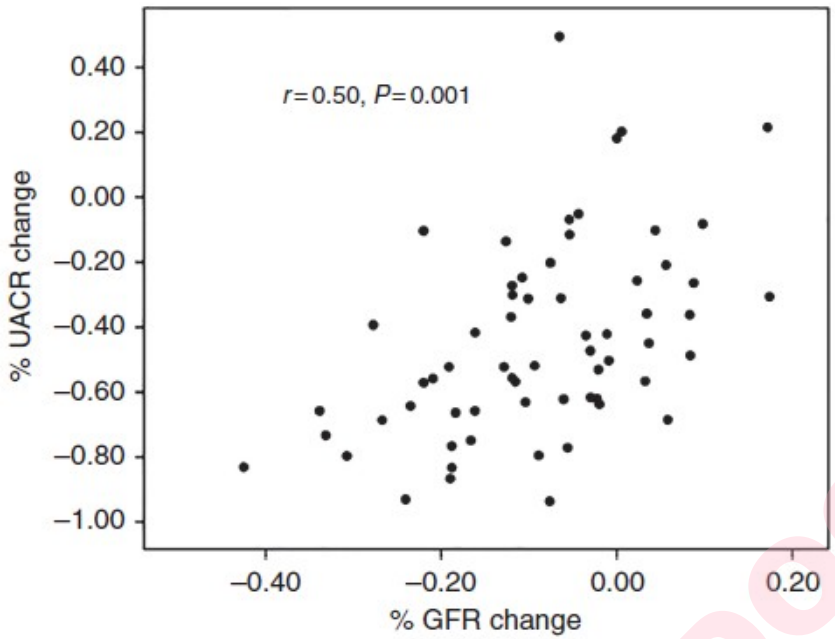
24-H Albuminuria (mg)	1600 (1047–2152)	1125.2* (500–1750)	1417 (868–1965)	935* (266–1603)	1882 (1325–2440)	577* (300–855)
24-H Proteinuria (g)	1.7 (1.3–2.2)	1.5* (0.8–2.3)	1.7 (1.3–2.1)	1.3* (0.6–2)	2.4 (1.9–2.8)	0.9* (0.6–1.2)

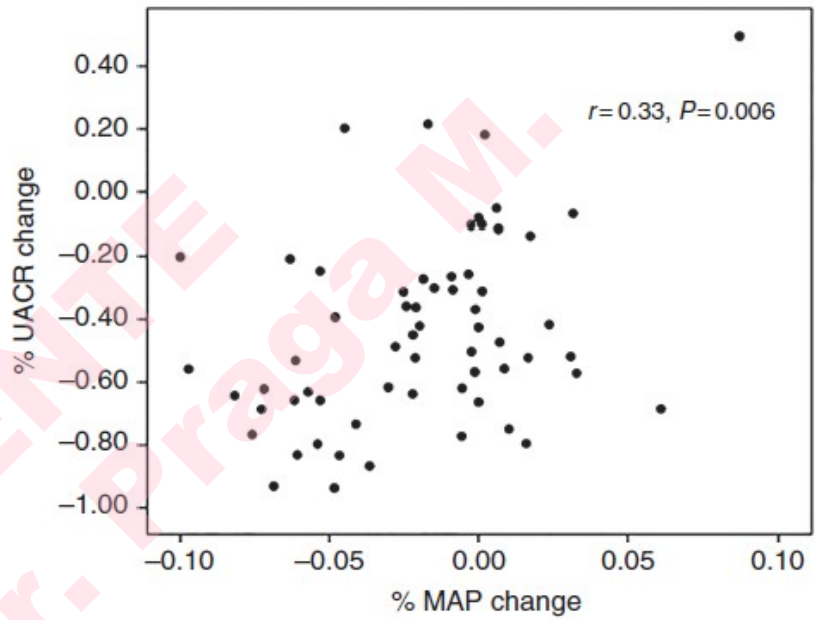
Abbreviation: UACR, urinary albumin-to-creatinine ratio.
*$P<0.05$ for intragroup comparison; +$P<0.05$ for between-group comparison.

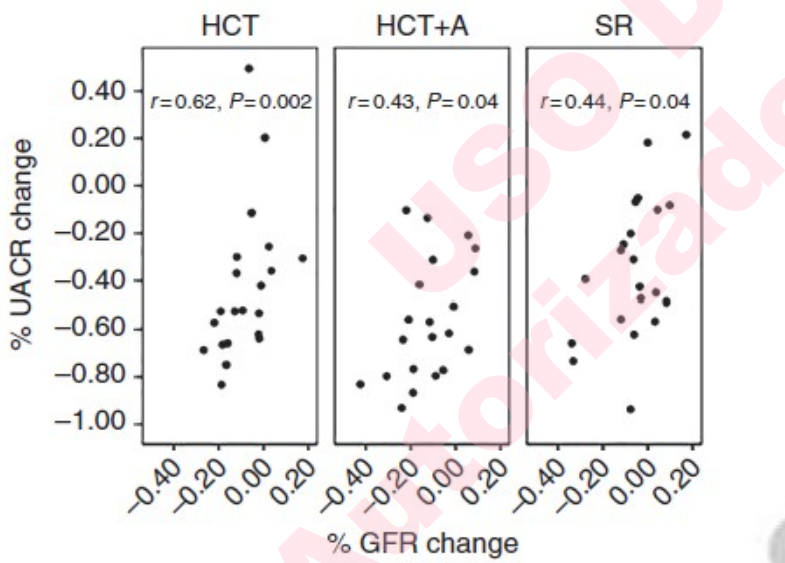
Table 4 | Effects of diuretics on other biochemical parameters

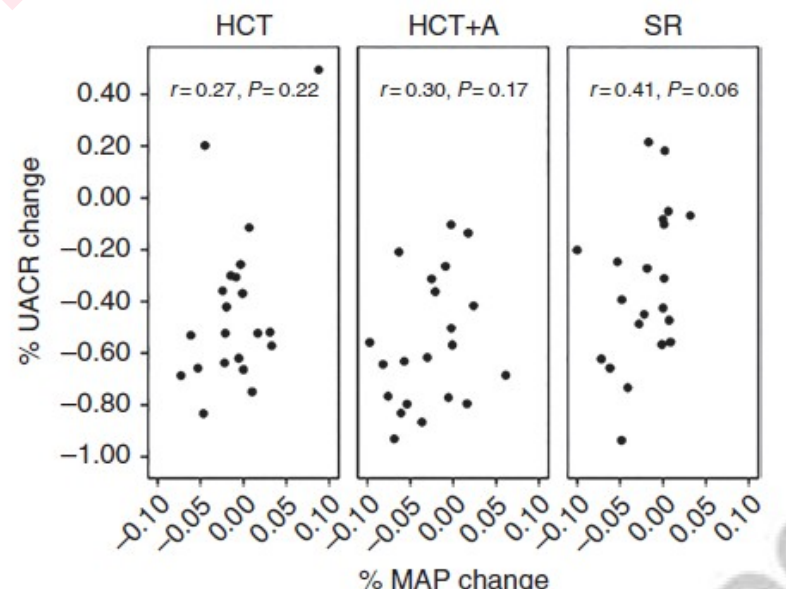
	Spironolactone		Hydrochlorothiazide		Hydrochlorothiazide+amiloride	
	Baseline	4 Weeks	Baseline	4 Weeks	Baseline	4 Weeks
Sodium (mEq/l)	141 (2.8)	140 (1.8)	140 (3.4)	140 (2.3)	141 (1.9)	140 (2.7)
Potassium (mEq/l)	4.7 (0.4)	5 (0.6)*	4.6 (0.4)	4.5 (0.4)	4.6 (0.5)	5 (0.6)*
Urinary sodium (mEq/24 h)	184 (152–261)	227 (183–271)	216 (175–256)	240 (146–333)	194 (160–227)	208 (164–253)
Urinary potassium (mEq/24 h)	73 (59–87)	79 (67–91)	77 (67–88)	80 (56–105)	80 (66–94)	76 (67–91)
Uric acid (mg/dl)	6.3 (1.4)	6.8 (1.8)*	6.5 (1.5)	7.3 (1.6)*	6.4 (1.5)	7.6 (1.7)*
Renin (pg/ml)	47 (28–66)	82* (37–126)	46 (27–65)	106* (50–163)	34 (13–54)	168* (95–241)
Aldosterone (pg/ml)	150 (110–198)	203* (162–244)	166 (127–205)	182 (142–222)	119 (80–158)	298* (198–398)

*$P<0.05$ for intragroup comparisons.



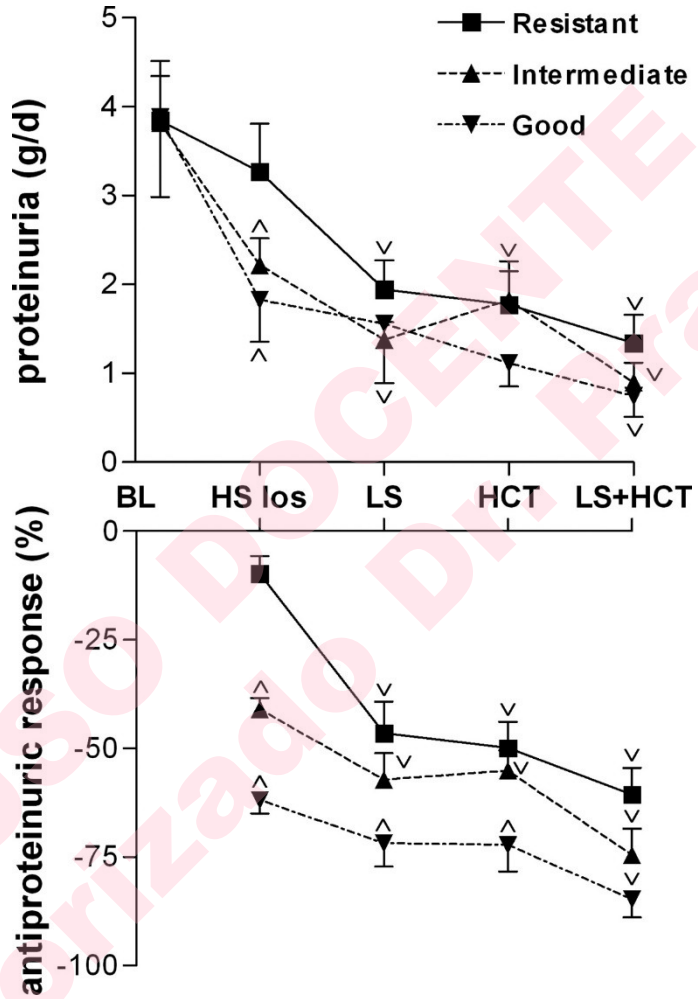






Morales et al, Kidney Int

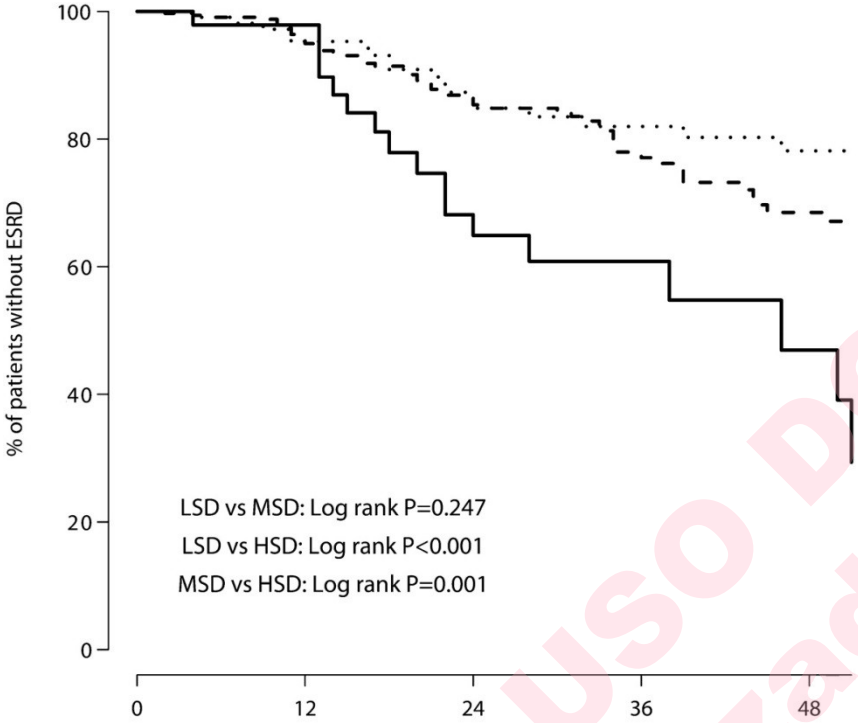
Figure 4. In proteinuric patients without diabetes, sodium depletion by LS or a diuretic is specifically beneficial in those who are resistant to RAAS blockade

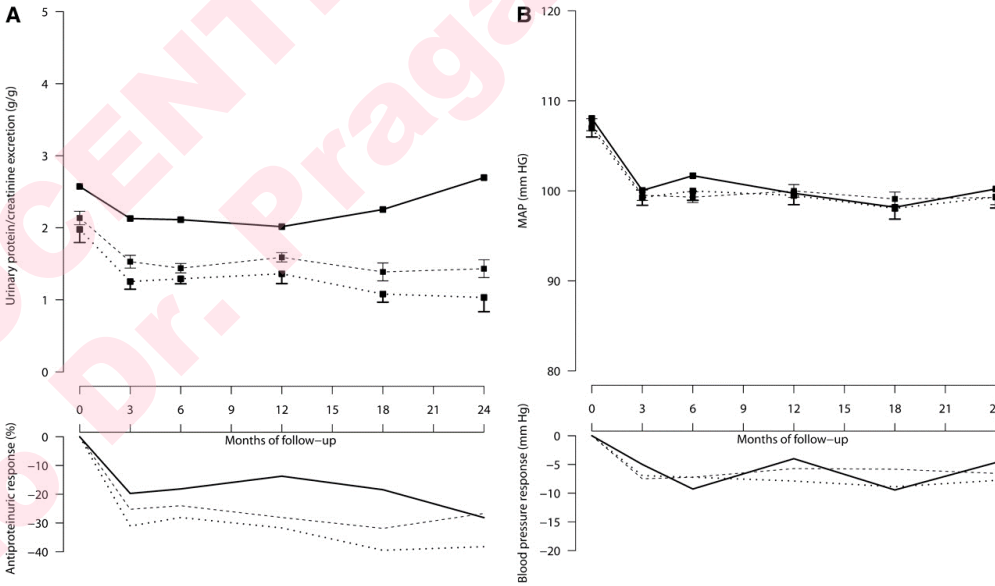


Vogt, L. et al. J Am Soc Nephrol 2008;19:999-1007

Sodium intake, ACE inhibition, and progression to ESRD

Stefan Vegter et al. JASN 2012;23:165-173

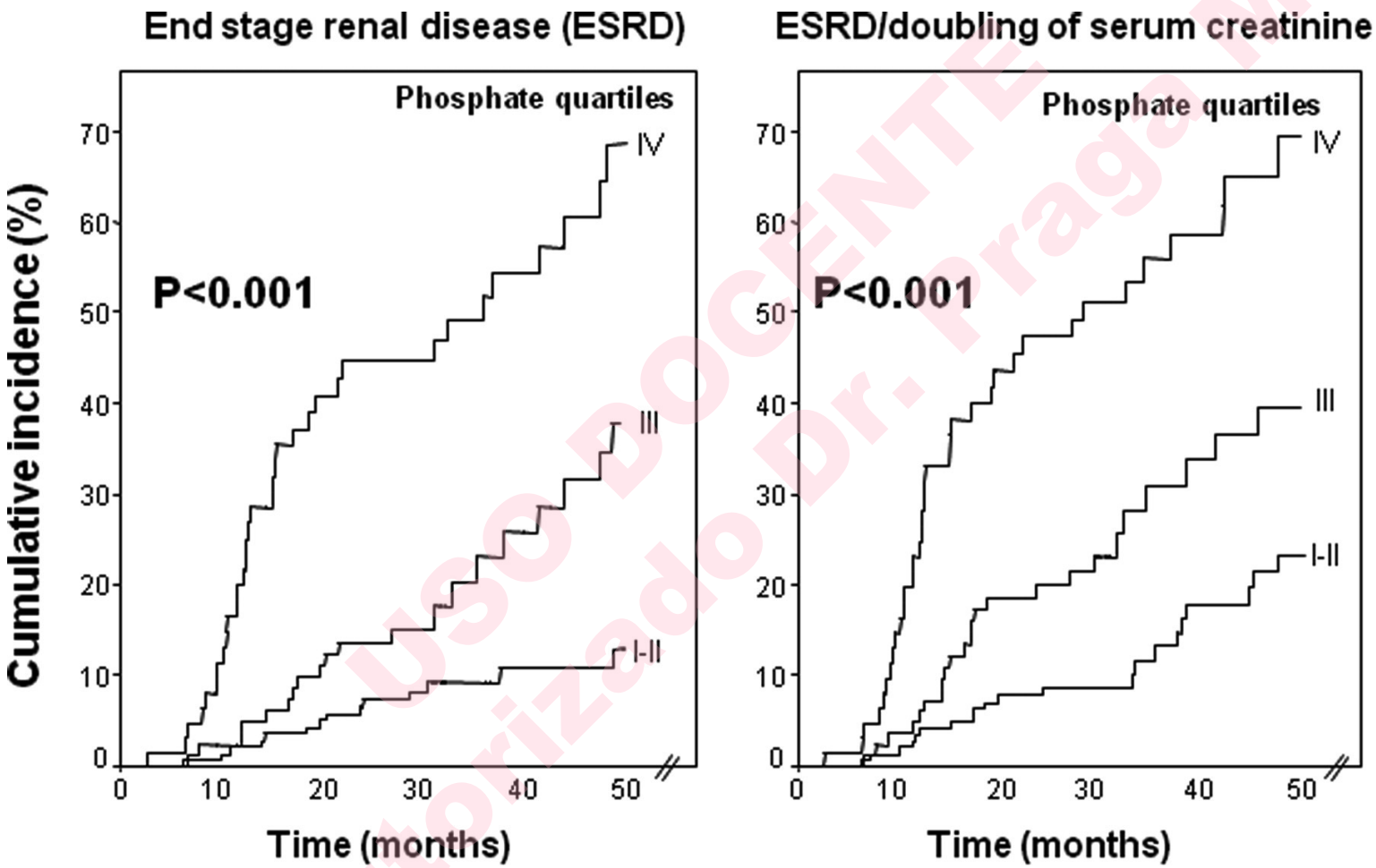




In 500 patients with proteinuric chronic nephropathies, higher salt intake is associated with an increased risk of progression to ESRD, more proteinuria at baseline and less proteinuria reduction on follow-up, but does not appear to appreciably affect BP control

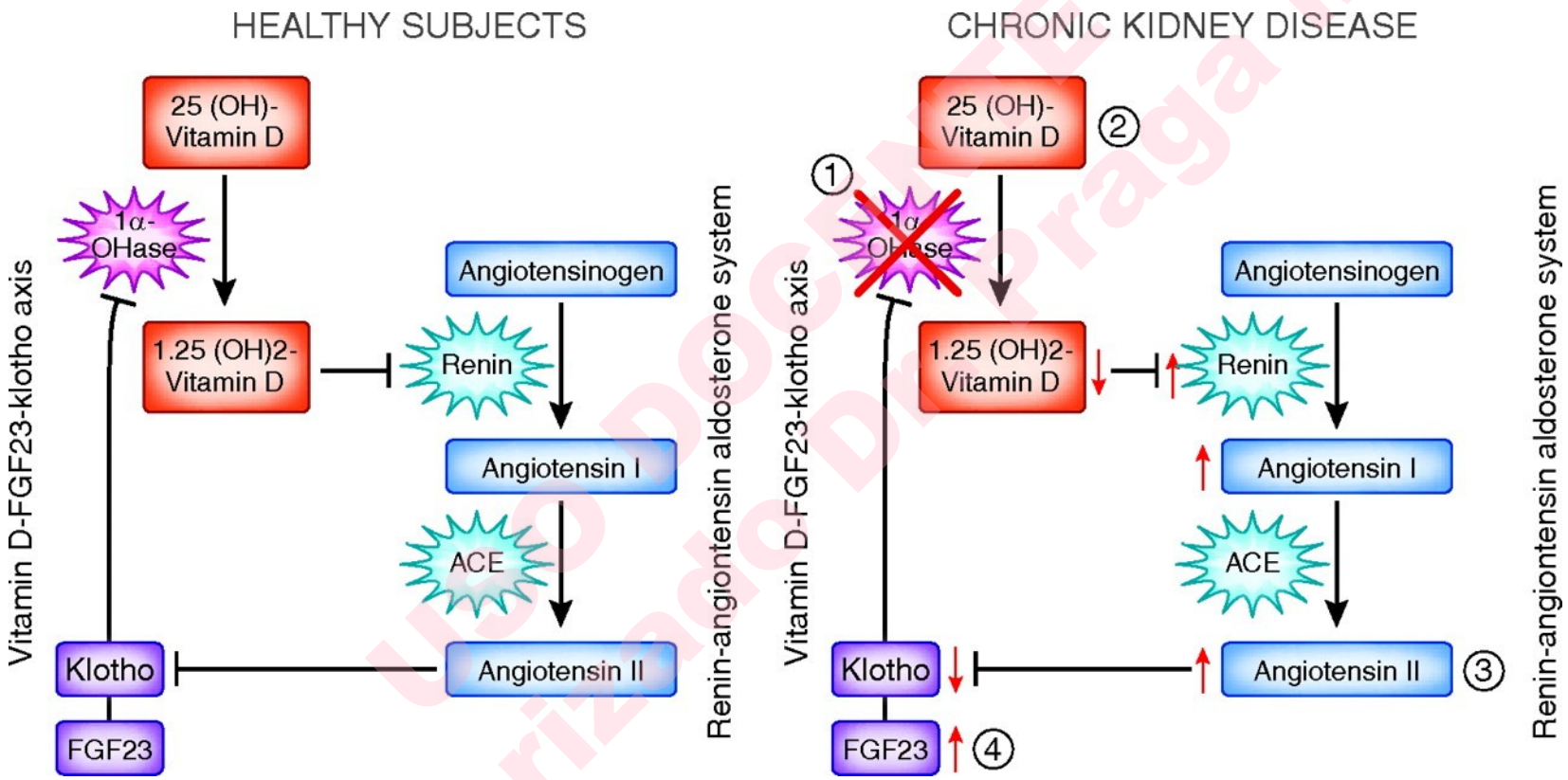
Phosphate may promote CKD progression and attenuate renoprotective effect of ACE inhibition

Carmine Zoccali et al. JASN 2011;22:1923-1930



Cumulative incidence of ESRD alone and in combination with doubling serum creatinine in patients stratified according to serum phosphate quartiles.

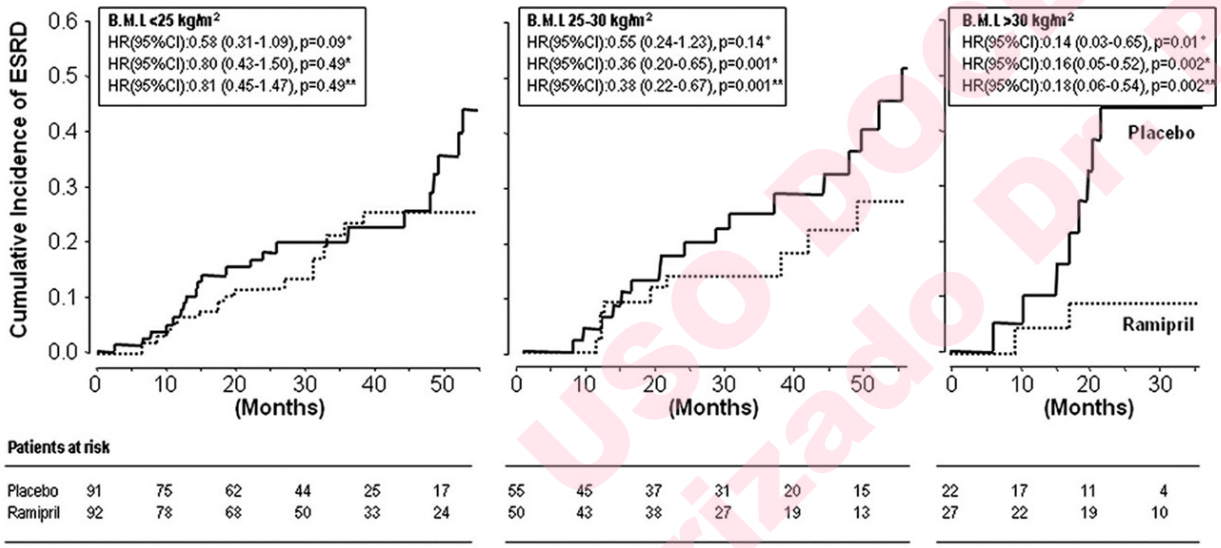
Cross talk between vitamin D (red), FGF-23-Klotho (yellow), and the RAAS (blue) in healthy subjects and patients with chronic kidney disease.



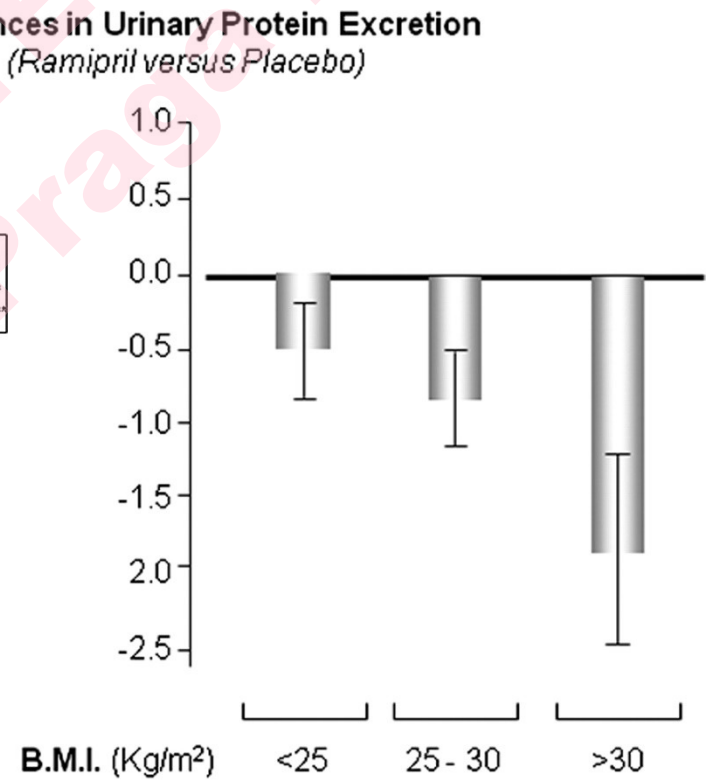
de Borst M H et al. JASN 2011;22:1603-1609

ACE inhibition is renoprotective among obese patients with proteinuria.

Mallamaci F et al. JASN 2011;22:1122-1128

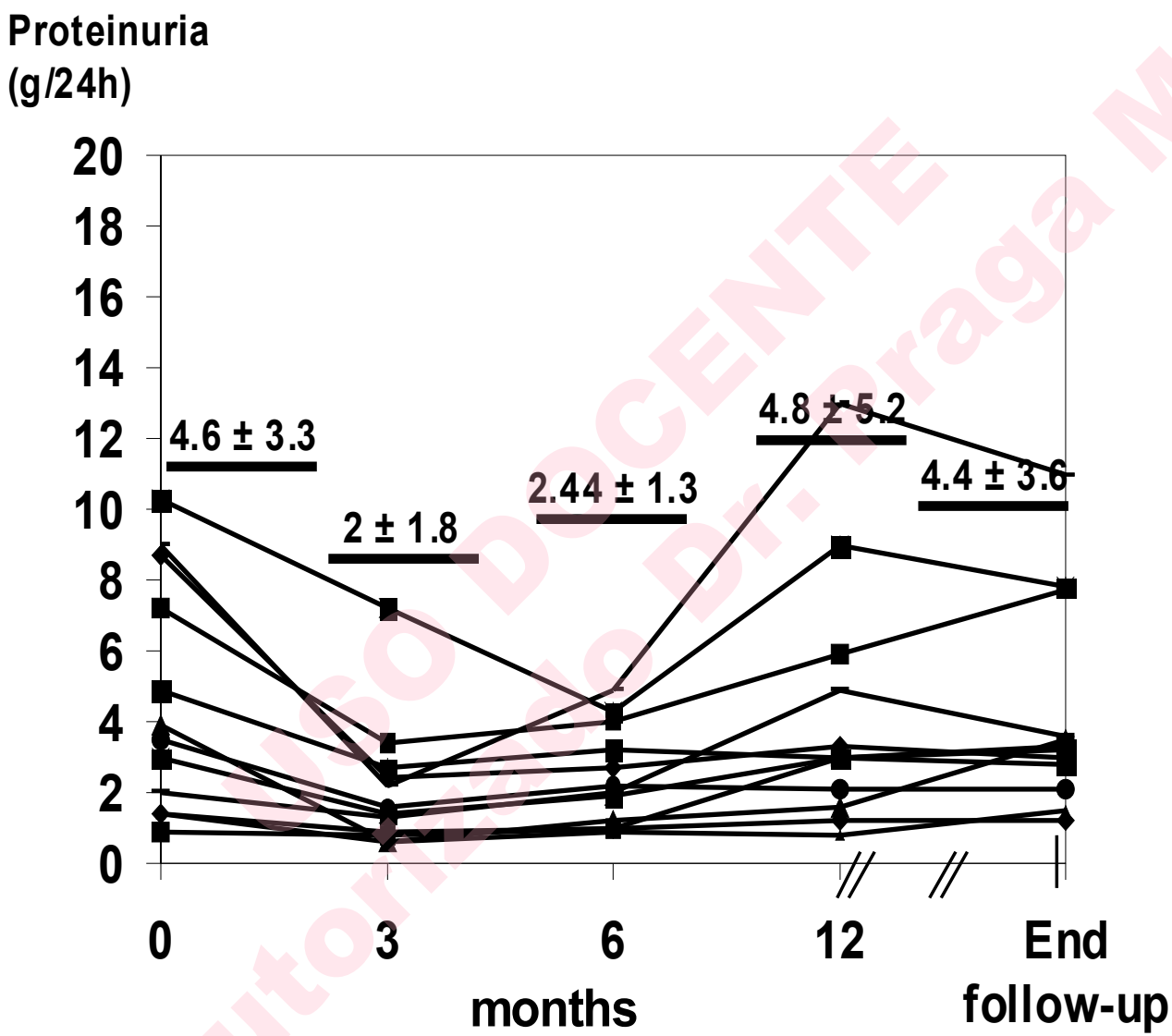


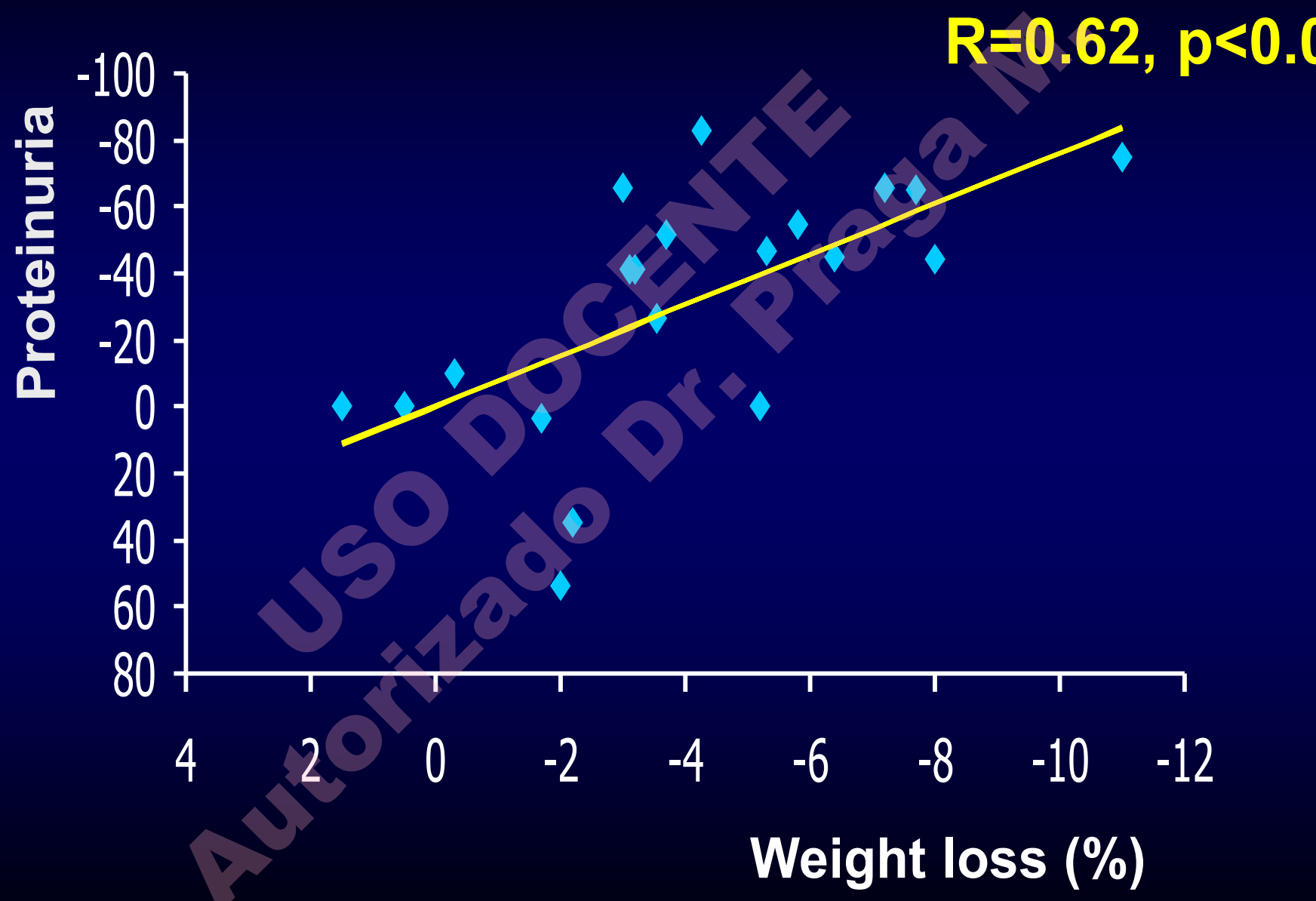
°Crude.
*Calculated in a model including treatment (Ramipril versus placebo), BMI classes, BMI*treatment interaction term, gender, baseline systolic blood pressure, albumin, hemoglobin, urinary protein and GFR.
**Shrinkage corrected.

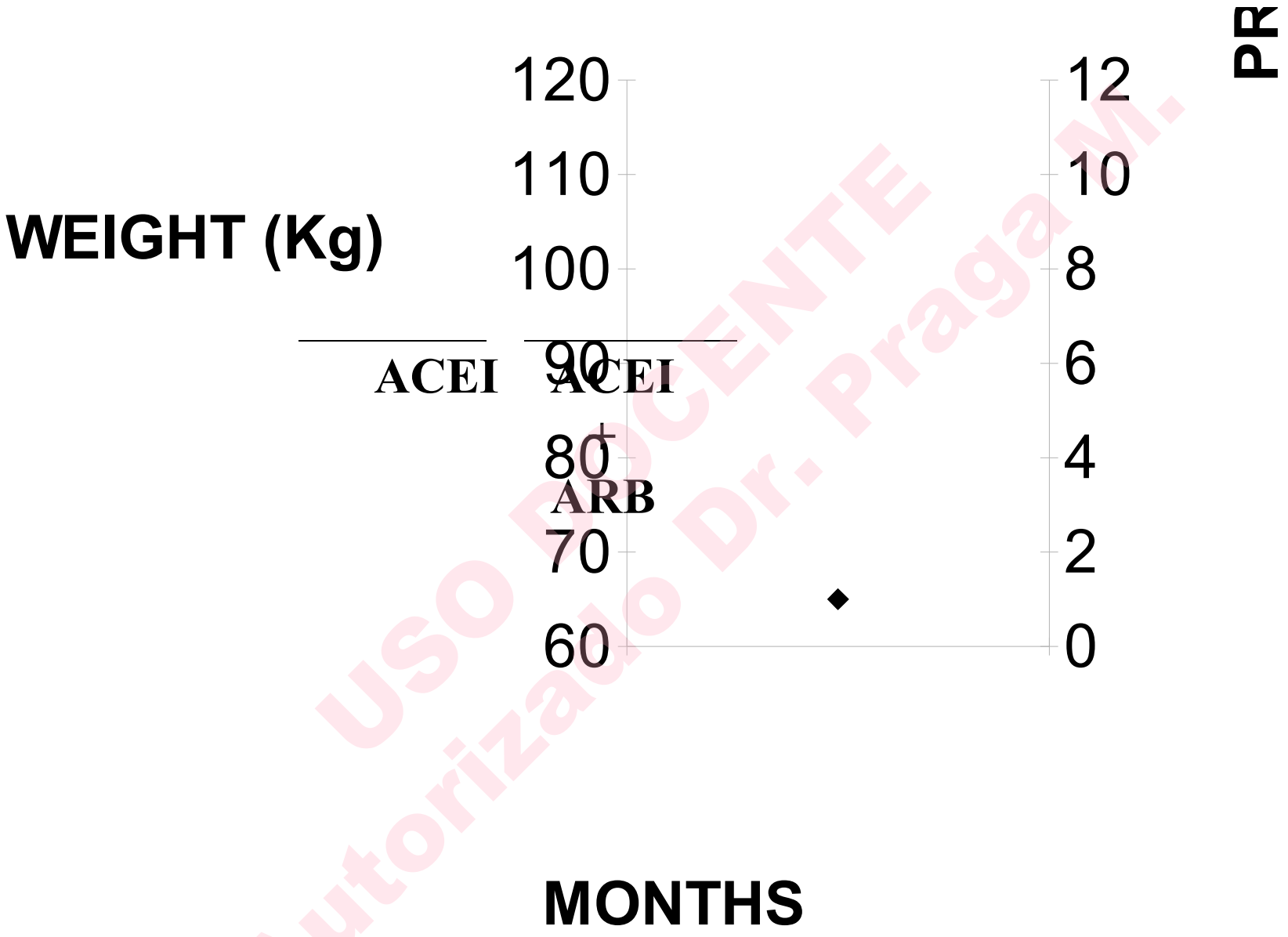


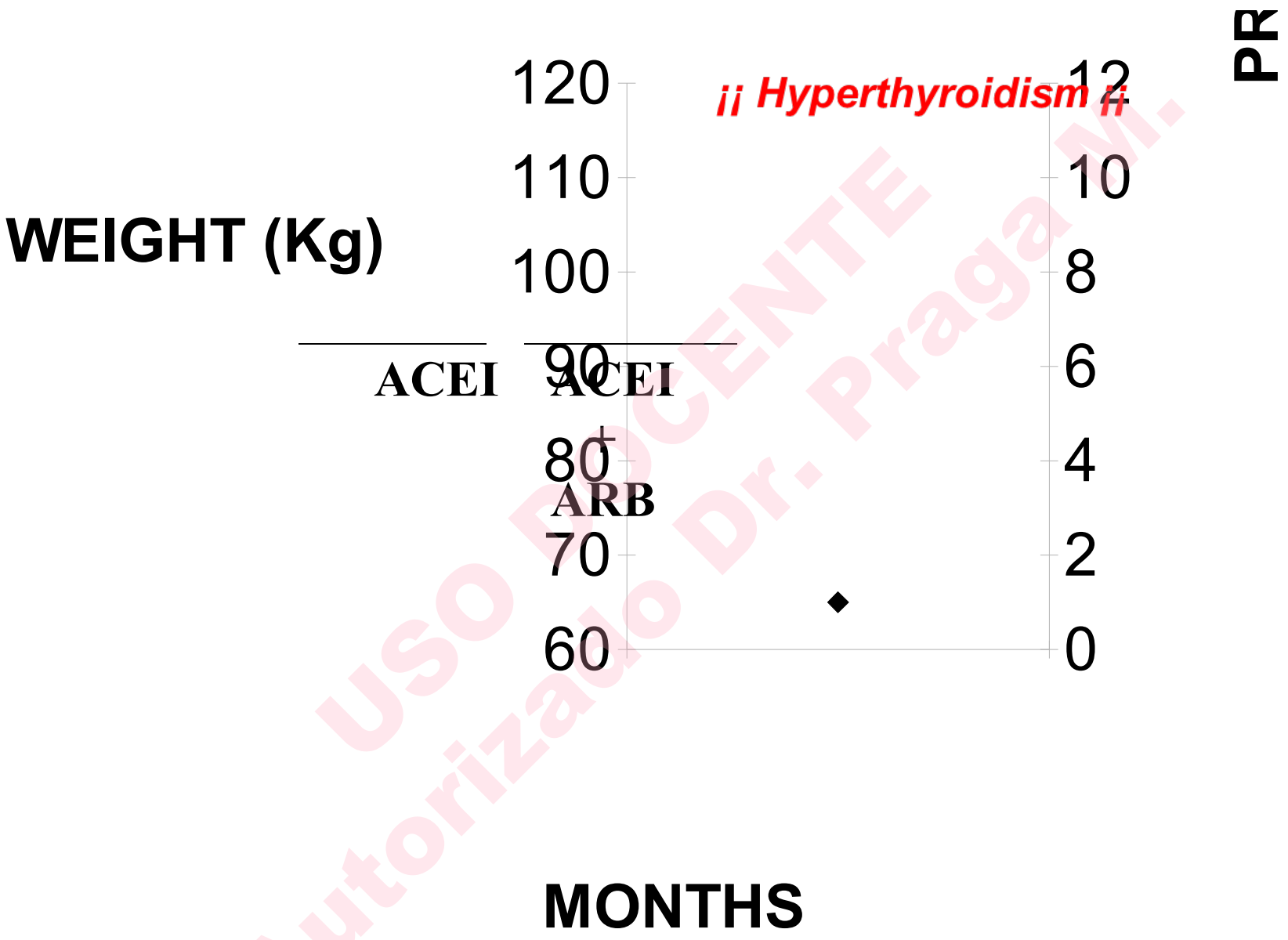
The anti-proteinuric effect of ramipril is maximal on obese patients and minimal in patients with normal BMI.

FSGS associated with obesity. Evolution









Weight loss and proteinuria: a systematic review of clinical trials and comparative chorts

Afshinnia et al, NDT 2010

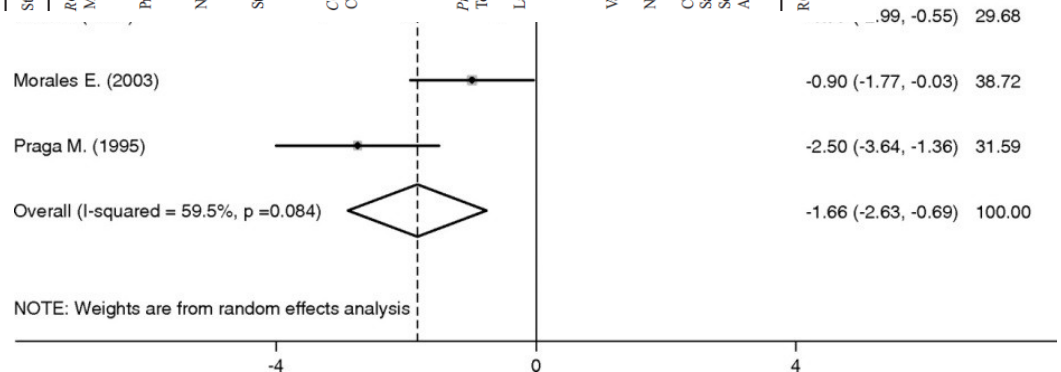
Change in overt proteinuria with weight lo by diet caloric restriction.

Conclusions. Weight loss is associated with decreased proteinuria and microalbuminuria. There were no data evaluating the durability of this decrease or the effect of weight loss on CKD progression.

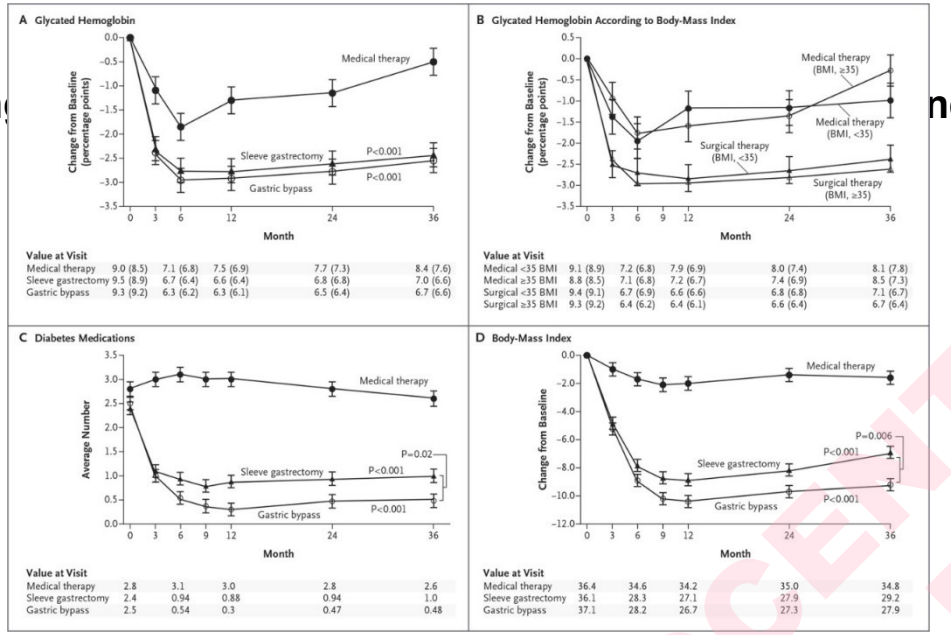
Table 1. Characteristics of the interventional studies

Study	Group	n	Age ± SD (years)	Intervention, dose and definition	Comparison with	Outcome measured in each study
RCT						
Morales E. (2003)	Case	20	56.1 ± 10.1	Low caloric diet, 150% of basal energy expenditure	Before vs after intervention, case vs control	Weight, BMI, proteinuria, crcl
	Control	10	56.5 ± 15.2	Regular diet		
Praga M. (1995)	Case	9	47.3 ± 8.0	Low caloric diet, 1000–1400 kcal/day	Before vs after intervention, case vs control	BMI, proteinuria, crcl
	Control	8	49.5 ± 12.7	Regular diet captopril 25–50 mg/day		
Nicholson AS. (1999)	Case	7	51.0 ± 4.7	Low caloric diet, 1409 kcal/day	Before vs after intervention, case vs control	Weight, albuminuria
	Control	4	60.0 ± 3.8	Regular diet		
Stenlof K. (2006)	Case	42	53.0 ± 11.8	Topiramate, 192 mg/day	Before vs after intervention, case vs control	Weight, albuminuria
	Control	51	54.0 ± 9.8	Placebo		
CCT						
Cubeddu LX. (2008)	UAE <10	23	48.1 ± 11.6	Low caloric diet, 1800–2000 kcal/day (men), 1600–1800 kcal/day (women) exercise (brisk walking, 150 min/week) metformin 500 mg PO TID	Before vs after intervention	Weight, BMI, albuminuria
	UAE 10–29	18	41.0 ± 9.4			
Prospective cohorts						
Tong PC. (2002)	Diabetes	33	18 to 50	Orlistat 120 mg PO TID in diabetics	Before vs after intervention	Weight, BMI, albuminuria
	No diabetes	27		Orlistat 120 mg PO TID in diabetics		
Lazarevic G. (2002)	Case	30	54.8 ± 7.3	Exercise, three to five sessions per week, including 45–60 min of warm-up, brisk walking and cool-down at a work load corresponding to 50–75% of maximal heart rate	Before vs after intervention	BMI, ACR
Vasquez B. (1984)	Diabetes	24	38.4 ± 10.3	Low caloric diet 500 kcal/day	Before vs after intervention	Weight, proteinuria, albuminuria
	No diabetes	7	31.4 ± 6.9	Low caloric diet 500 kcal/day		
Navarro-Diaz M (2006)	Case	61	41.1 ± 9.1	Gastric bypass	Before vs after intervention	Weight, BMI, proteinuria, crcl, albuminuria
Chagnac A. (2003)	Case	8	36.0 ± 2.0	Gastroplasty	Before vs after intervention	Weight, BMI, GFR, albuminuria
Saiki A. (2005)	Case	22	53.6 ± 8.4	Low caloric diet, 11–19 kcal/kg/day	Before vs after intervention	Weight, BMI, crcl, proteinuria
Solerte SB. (1989)	Case	24	49.2 ± 4.0	Low caloric diet, 1410 kcal/day	Before vs after intervention	BMI, crcl, GFR, proteinuria
Agrawal V. (2008)	Case	94	45.6 ± 10.5	Gastric bypass	Before vs after intervention	Weight, BMI, albuminuria–creatinine ratio

RCT, randomized controlled trial; CCT, controlled clinical trial; crcl, creatinine clearance; UEA, urinary excretion of albumin.



Mean Chan ne to 3



Schauer PR et al.
N Engl J Med 2014;370:2002-2013

S14 Diabetes Care Volume 37, Supplement 1, January 2014

Standards of Medical Care in Diabetes—2014

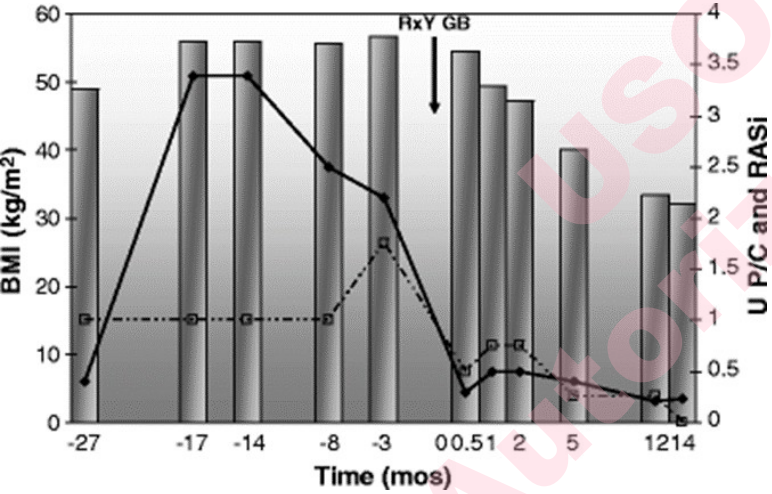
American Diabetes Association

L. Bariatric Surgery

Recommendations

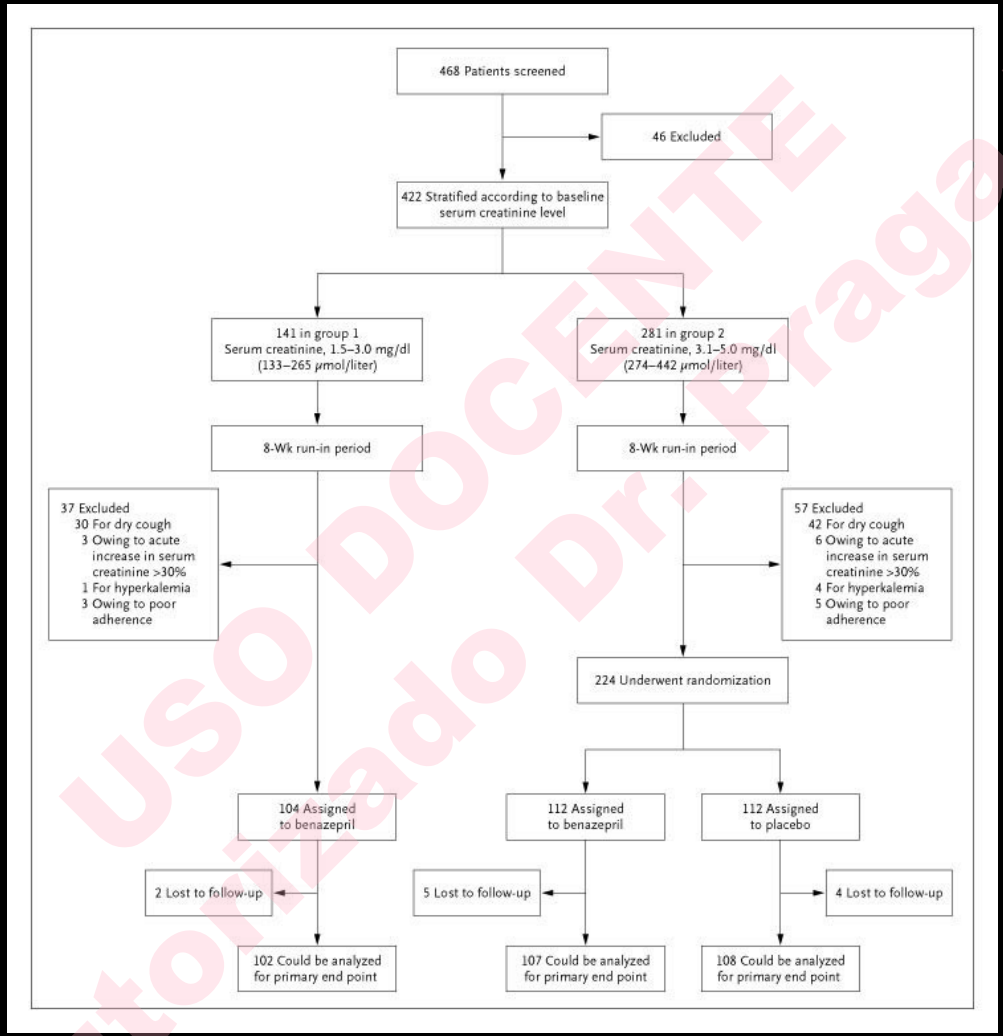
- Bariatric surgery may be considered for adults with BMI >35 kg/m^2 and type 2 diabetes, especially if diabetes or associated comorbidities are difficult to control with lifestyle and pharmacological therapy. B
- Patients with type 2 diabetes who have undergone bariatric surgery need lifelong lifestyle support and medical monitoring. B
- Although small trials have shown glycemic benefit of bariatric surgery in patients with type 2 diabetes and BMI 30–35 kg/m^2, there is currently insufficient evidence to generally recommend surgery in patients with BMI <35 kg/m^2 outside of a research protocol. E
- The long-term benefits, cost-effectiveness, and risks of bariatric surgery in individuals with type 2 diabetes should be studied in well-designed controlled trials with optimal medical and lifestyle therapy as the comparator. E

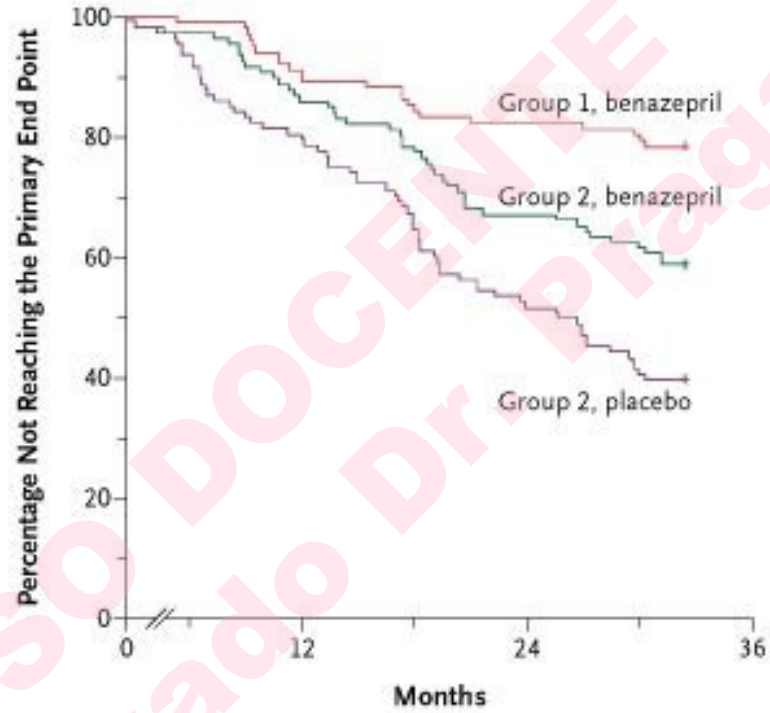
Bariatric surgery in ORG
Need of prospective controlled studies



Obesity-related focal and segmental glomerulosclerosis: normalization of proteinuria in an adolescent after bariatric surgery. Fowler SM, Pediatr Nephrol 2009

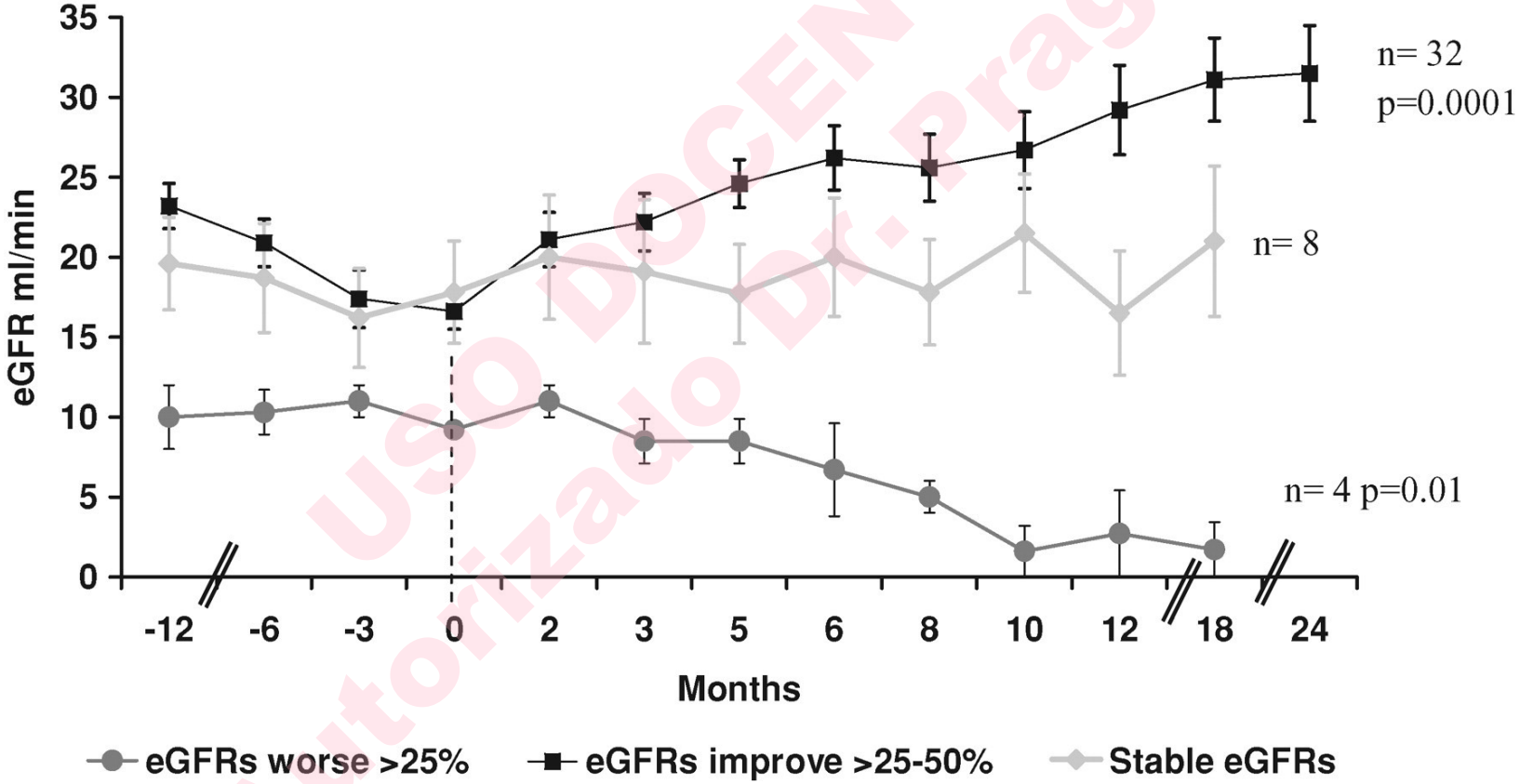
Should RAS blockade be maintained throughout the entire clinical course of CKD patients?





No. at Risk				
Group 1, benazepril	102	96	84	40
Group 2, benazepril	107	96	73	32
Group 2, placebo	108	88	59	22

Changes in eGFR after stopping ACEi/ARB in patients with advanced CKD. Data presents changes as mean eGFR ± SEM in patients with advanced CKD up to 24 months after stopping ACEi/ARB.



Nephrol. Dial. Transplant. 2010;25:3977-3982

NDT
Nephrology Dialysis Transplantation

Clinical Case

- A 28 yr-old-man with type 1 diabetes started at 18 yr. Referred in 1990 because of renal function derangement.
- BP 133/78 mmHg.
- Serum creatinine 1.4 mg/dl,(CKD-EPI: 69 ml/m/1.73m2)
- Proteinuria 1.7 g/24 h.
- Enalapril treatment was started. Mean Enalapril doses during follow-up: 25 mg/day
- Mean Proteinuria during follow-up: 0.3 g/day
- …..**<u>And twenty-three years later</u> (2013): Serum creatinine 1.3 mg/dl, CKD-EPI: 65 ml/min/1.73 m2)**

Clinical Case

BUT……

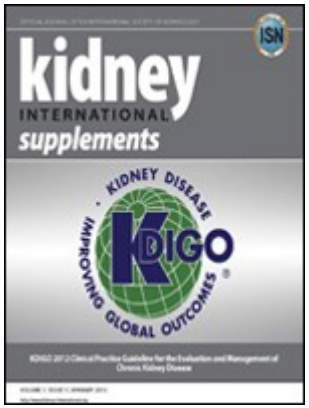
Severe ischemic cardiopathy,

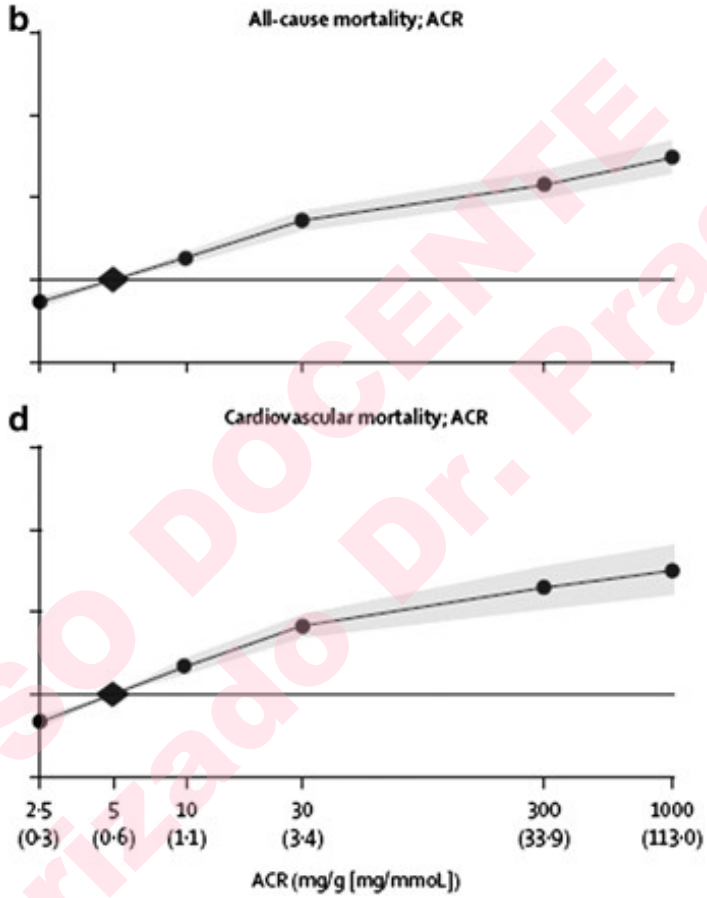
Two Myocardial infarctions,

Peripheral vascular disease….

Could cardiovascular events in CKD patients be decreased by further proteinuria/albuminuria reduction?

All-Cause and Cardiovascular mortality according with albuminuria





Conclusions

RAS blockade continues to be the central antiproteinuric and renoprotective therapy in CKD

MEASURES TO ENHANCE REDUCTION IN PROTEINURIA BY ACEI/ARBs

- Antialdosteronic diuretics (eplerenone, spironolactone)
- Other diuretics (hydrochlorothiazide, amiloride)
- Combination ACEI+ARB
- Paricalcitol
- Pentoxyfillin
- Low-sal intake
- Dietary phosphate restriction
- Weight loss (low-calorie diets, drugs, bariatric surgery)
- Lifestyle changes (physiscal exercise, stop smoking)