Effective Treatment Strategies to Delay the Progression of Renal Disease and Vascular Disease in CKD

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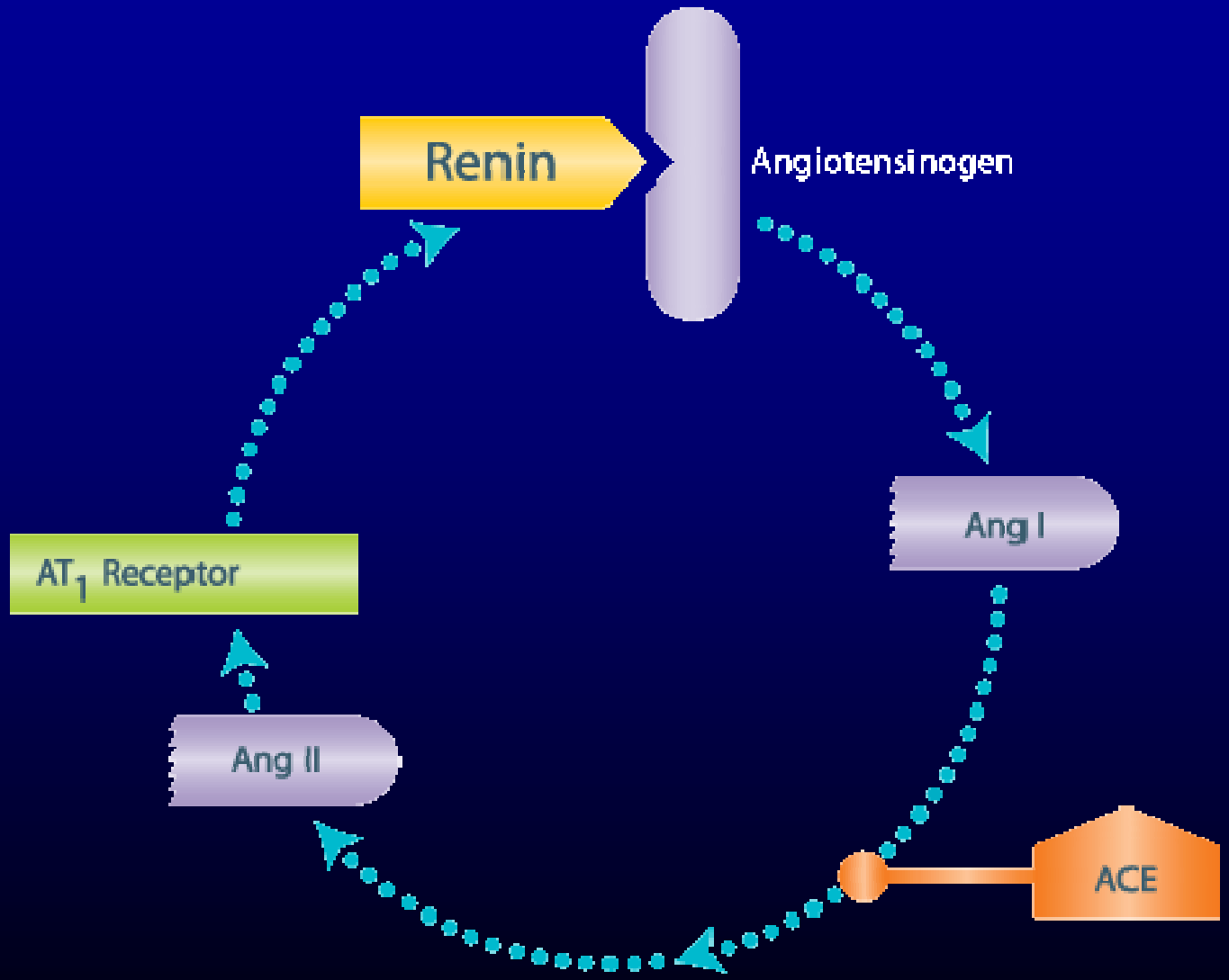
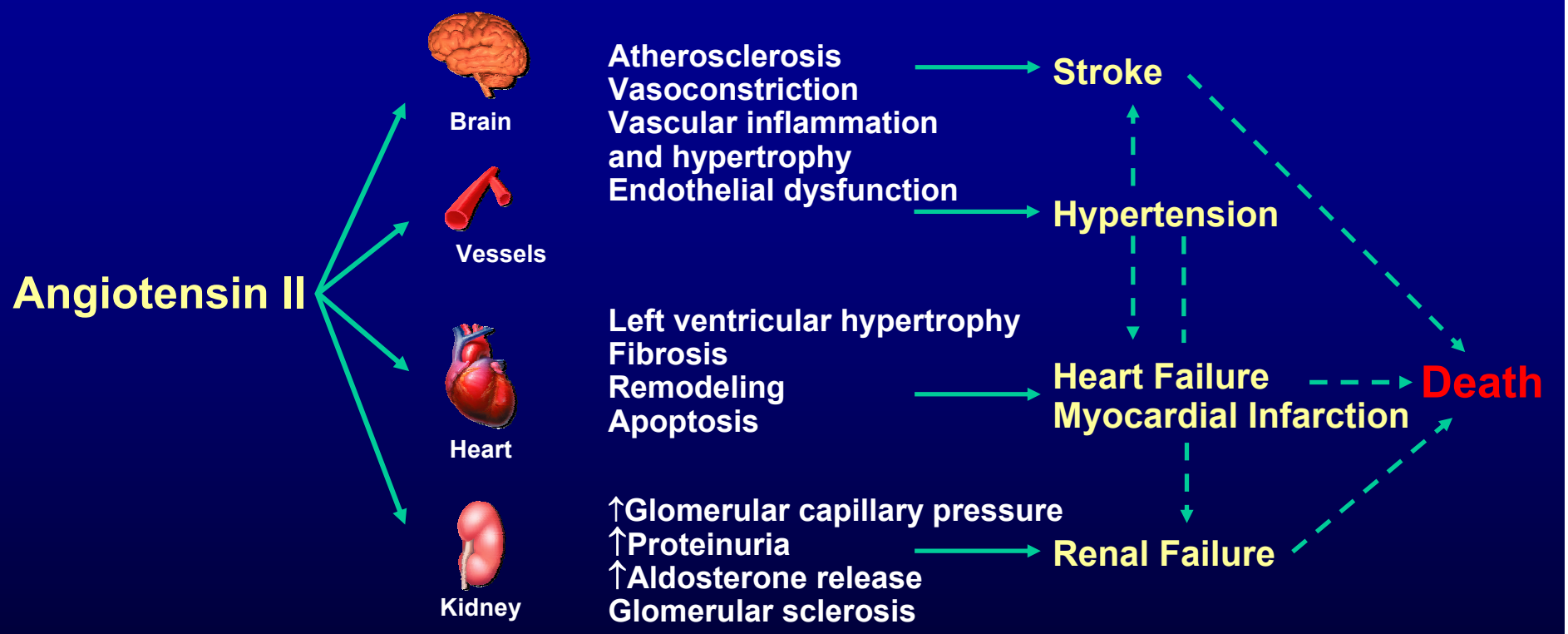
Renin Angiotensin Aldosterone System



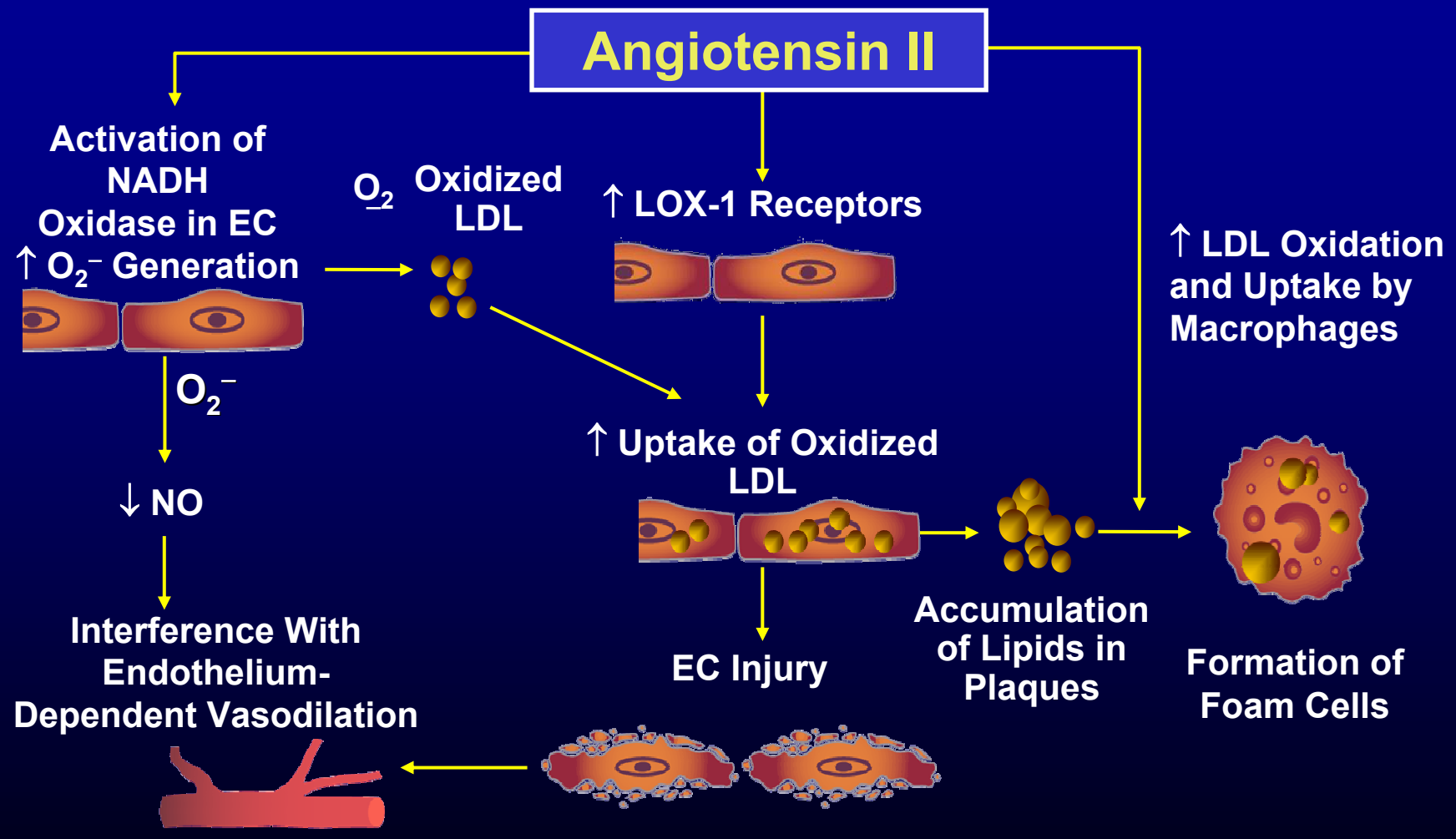
Jackson EK. In: Brunton LL, et al, eds. *The Pharmacological Basis of Therapeutics*. 11th ed. 2006: 789-821.

Renin Angiotensin System and End-Organ Damage

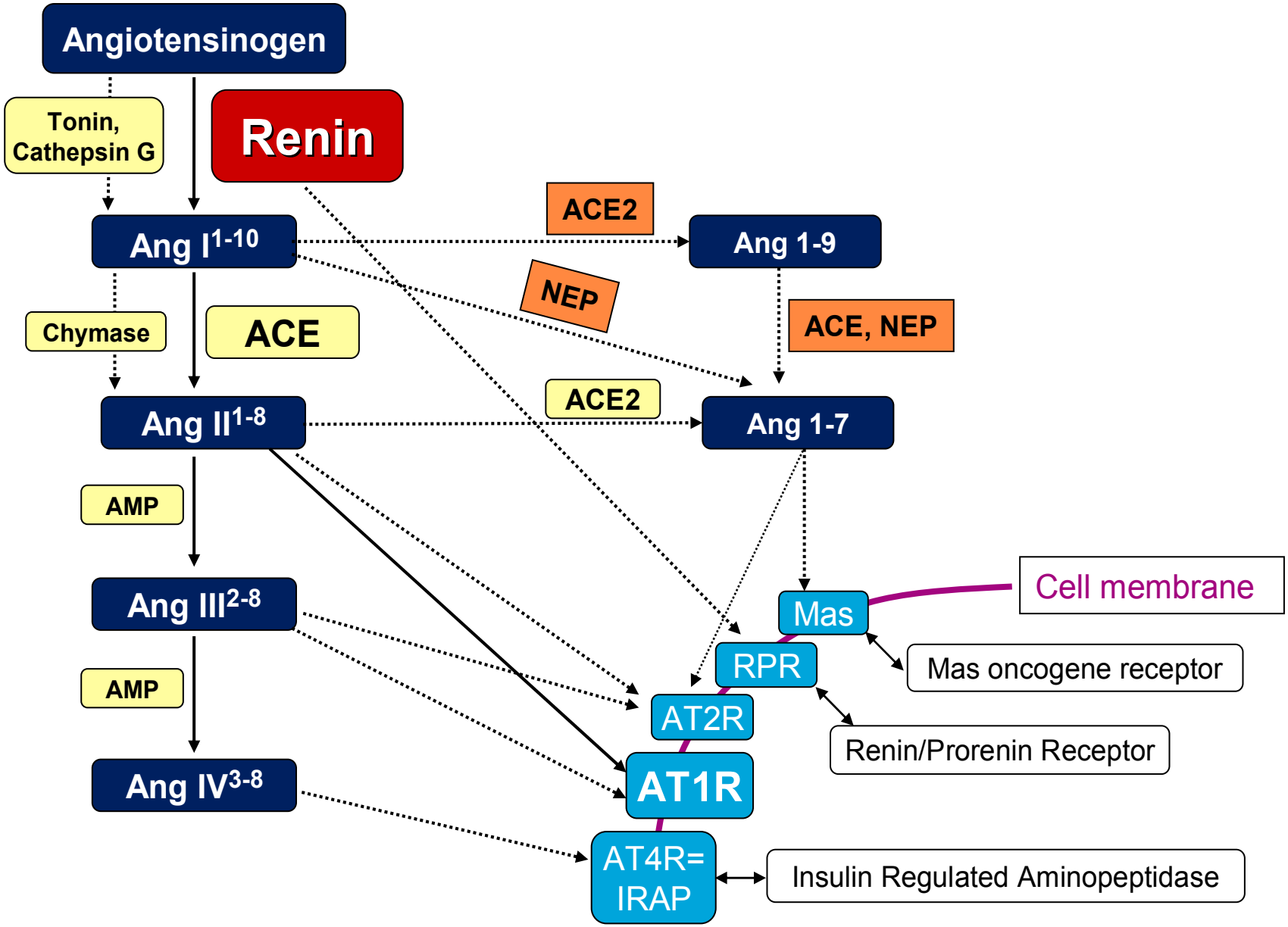


Willenheimer et al, Eur Heart J 1999
Dahlof B, J Hum Hypertens 1995
Fyhrquist F, J Hum Hypertens 1995
Anderson S, Exp Nephrol 1996
Booz GW et al, Heart Fail Rev 1998

The Role of Angiotensin II in Endothelial Dysfunction and Atherosclerosis

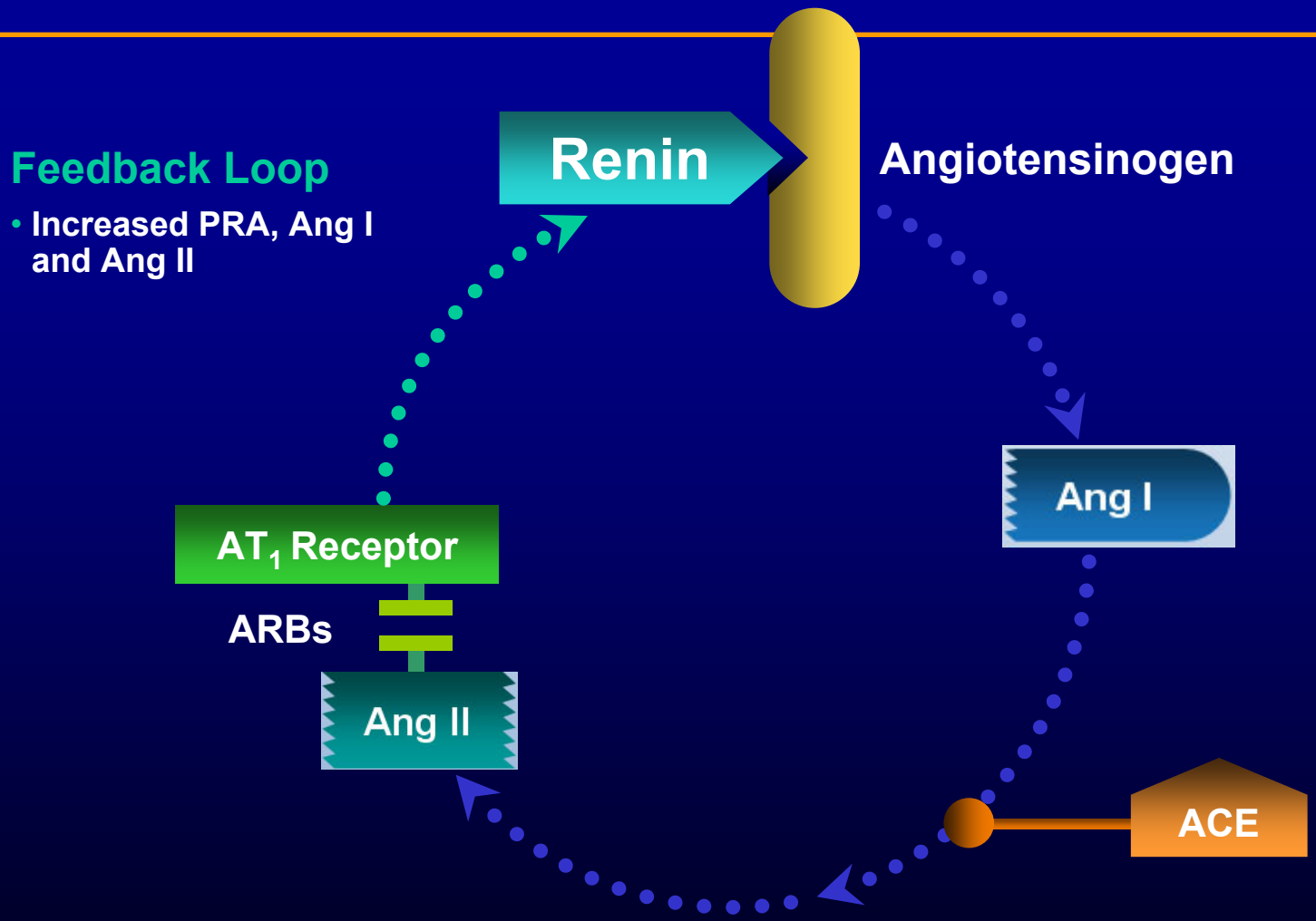


NADH = nicotinamide adenine dinucleotide; EC = endothelial cell.



Modified from Fyhrquist and Saijonmaa. J Intern Med 2008;264:224–236
Jones ES, et al. Pharmacol Ther 2008;120:292–316

Blockade of the Renin Angiotensin System



Feedback Loop

- Increased PRA, Ang I and Ang II

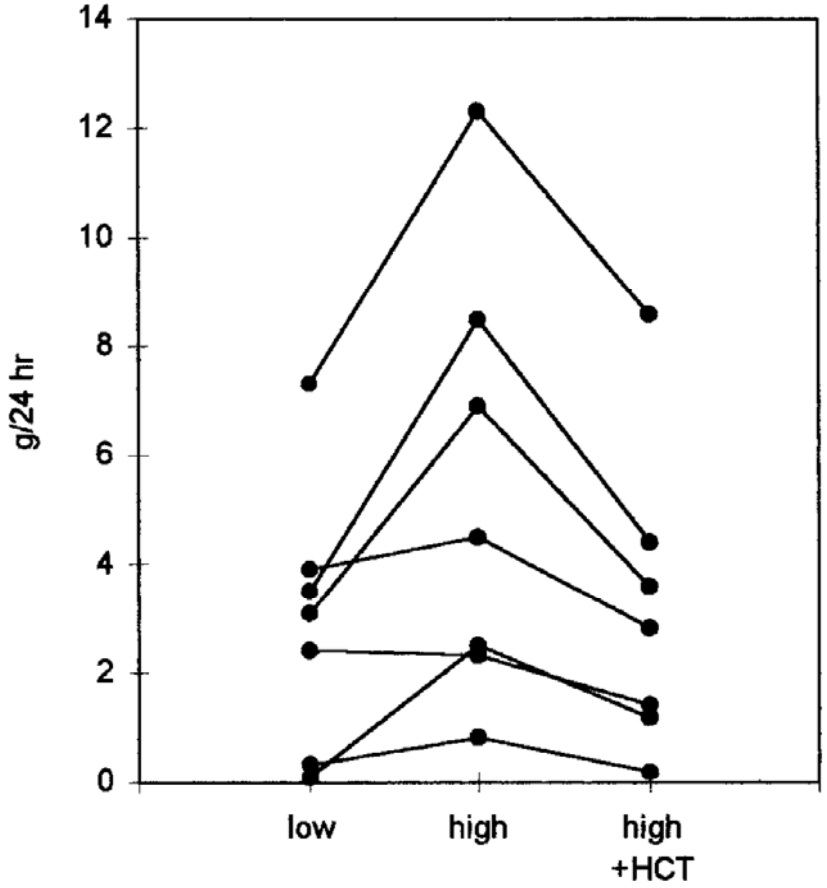
Strategies to achieve RAAS inhibition

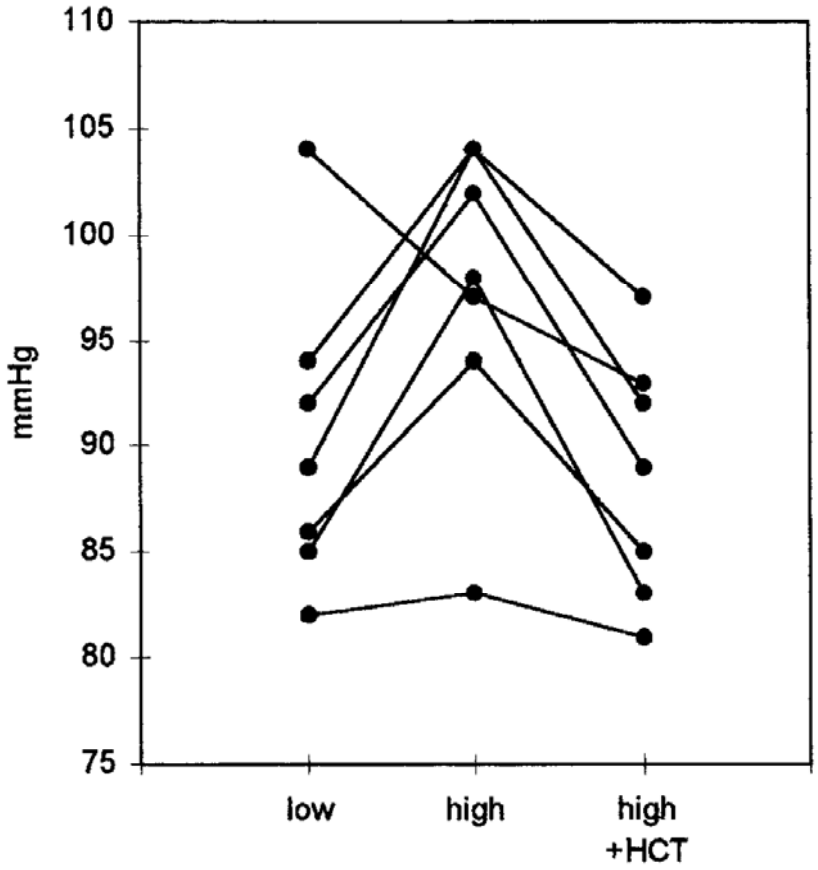
- Sodium restriction and/or diuretics to enhance RAAS blockade
- ACEI vs. ARB?
- Supramaximal doses of ACEI/ARB
- Combination of therapy for RAAS blockade
- Vitamin D receptor activation

Sodium restriction and/or diuretics

- Effect of RAAS blockade is blunted by a high salt diet
- Sodium restriction or diuretic therapy may restore the efficacy of ACEI/ARB and contribute to renoprotection through BP control and proteinuria reduction

Heeg JE, et al. *Kidney Int* 1989; 36: 272–279
Jerums G, et al. *Kidney Int* 1992; 41: 904–911

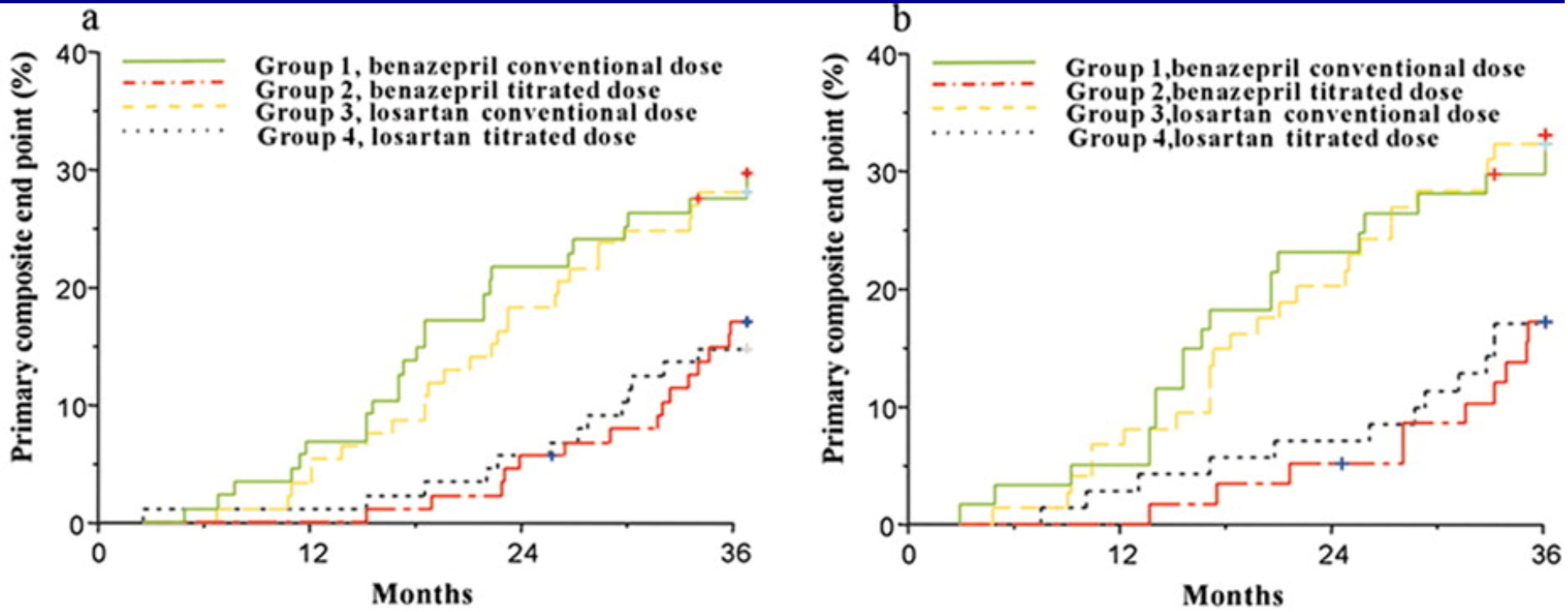




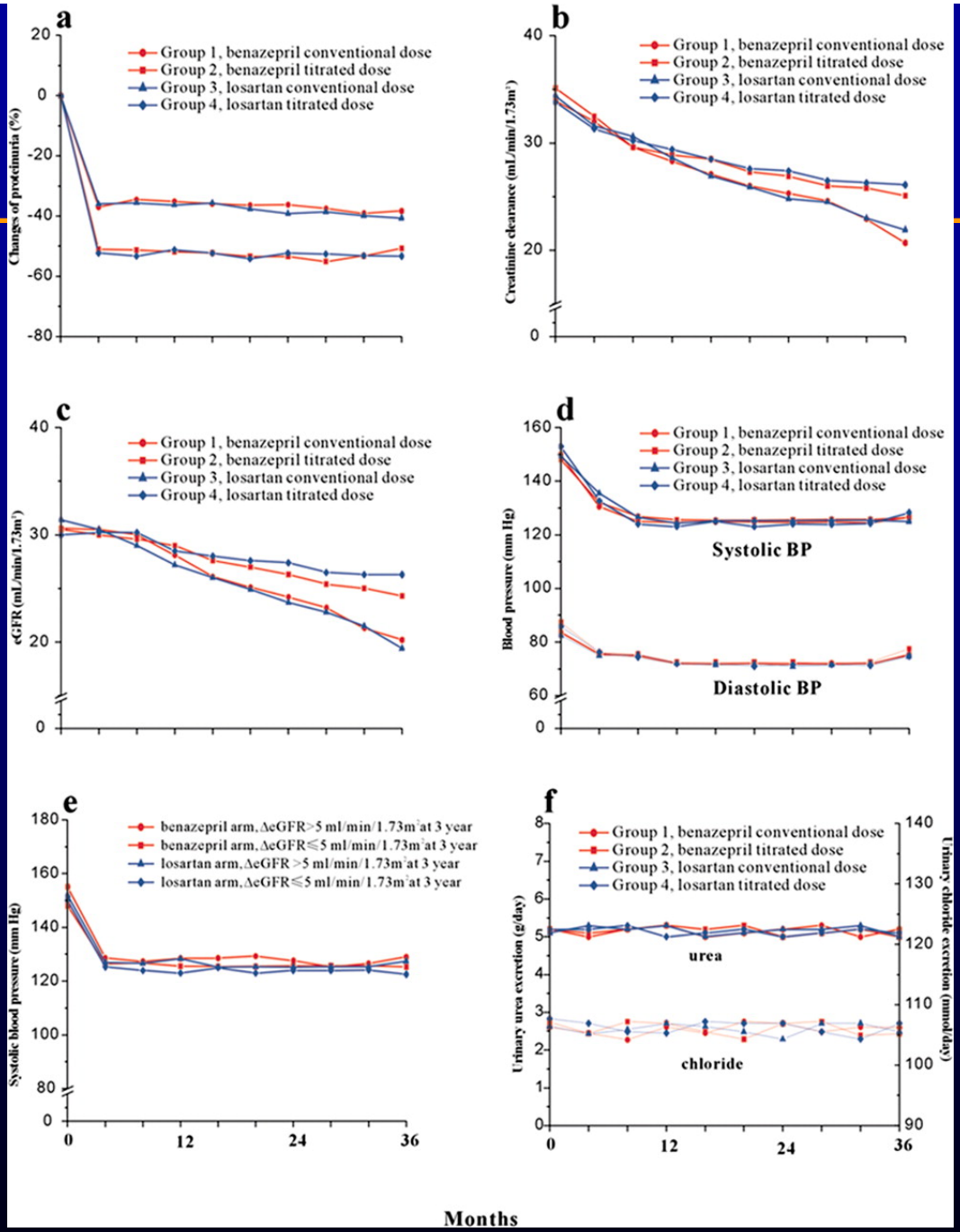
Buter H, et al. Nephrol Dial Transplant 1998;13:1682–5

ACEI vs. ARB

- Are ARBs more effective at suppressing RAAS?
- Are any theoretical differences clinically relevant?



Hou FF, et al. J Am Soc Nephrol 2007;18:1889–98

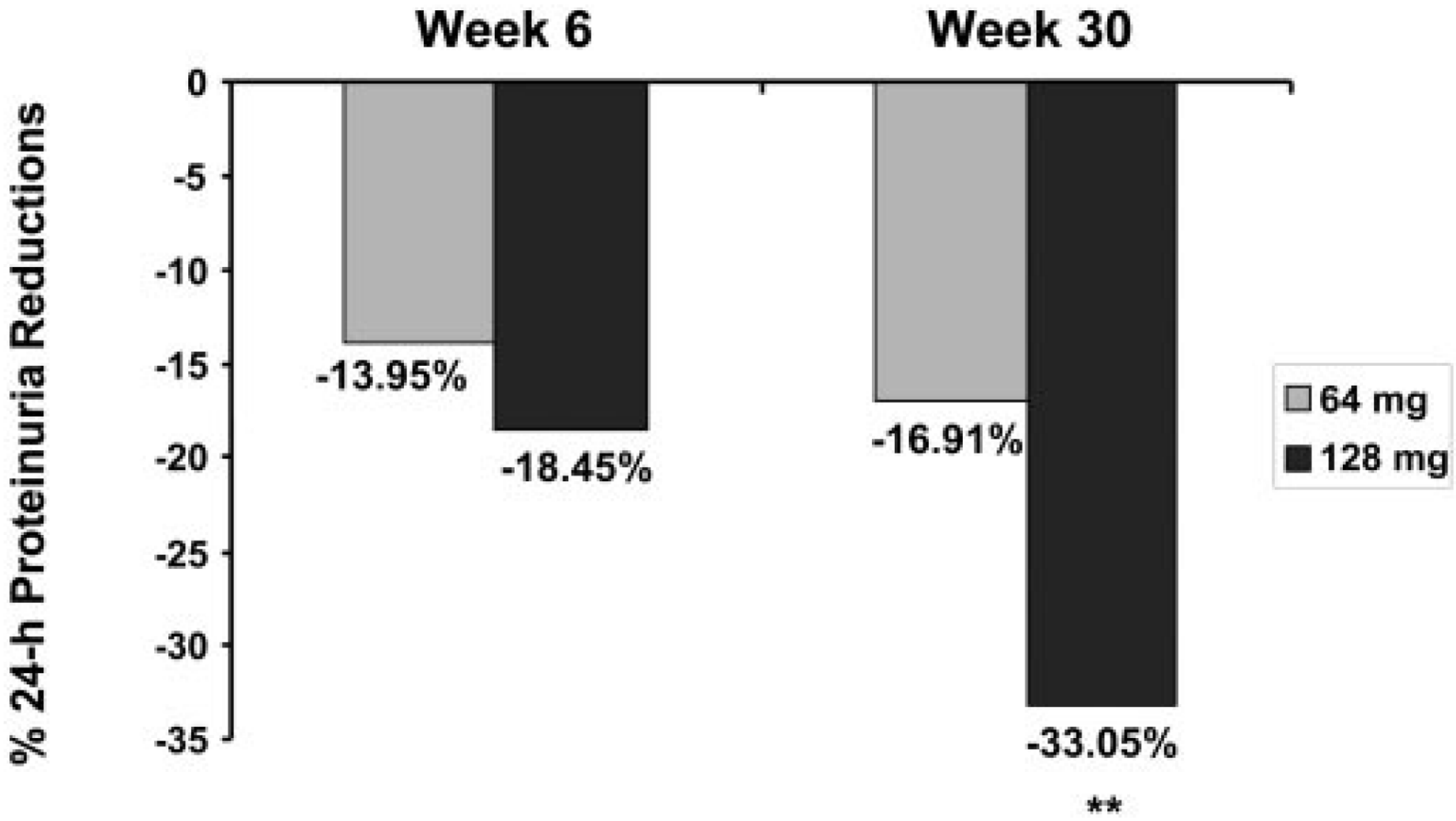


Hou FF, et al. J Am Soc Nephrol 2007;18:1889–98

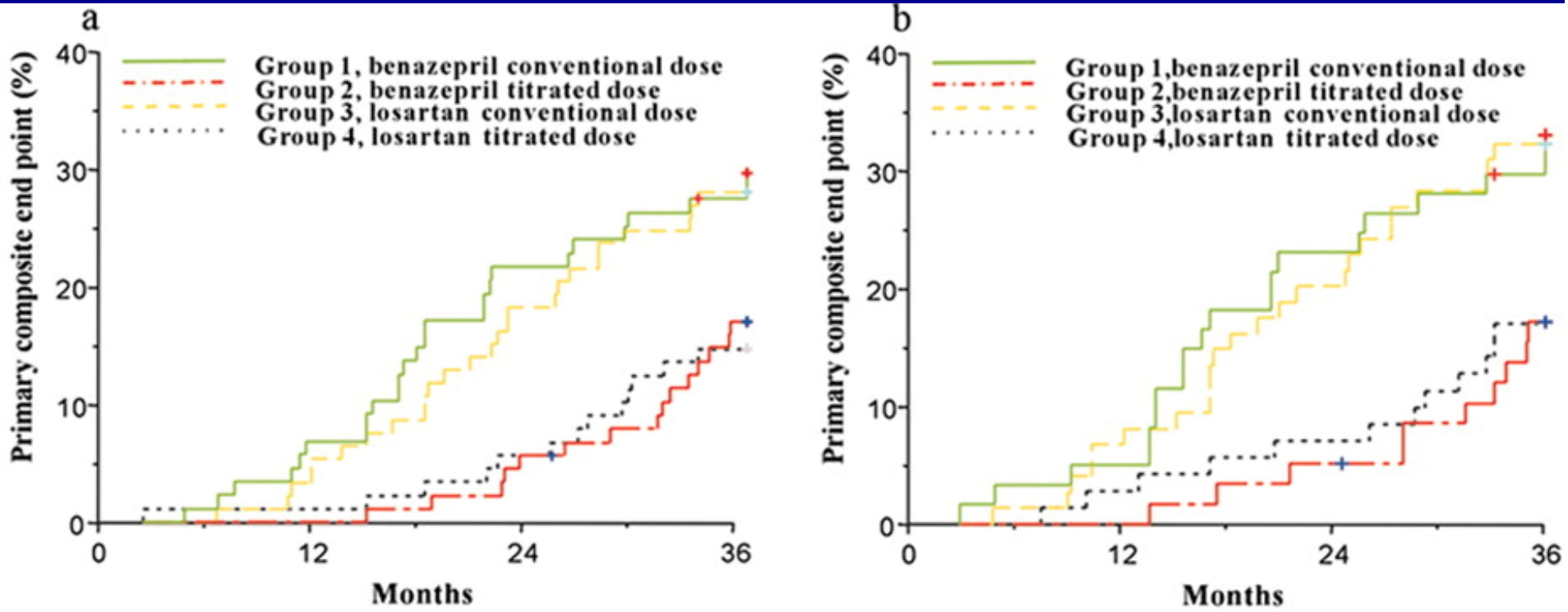
Increase the dose of ACEI/ARB

- Maximal renal benefit from ACEI/ARB may require higher dosages than those needed to normalize BP
- Clinical trials showed better proteinuria reduction with supramaximal doses of ACEI/ARB
- Few studies examined clinical end points

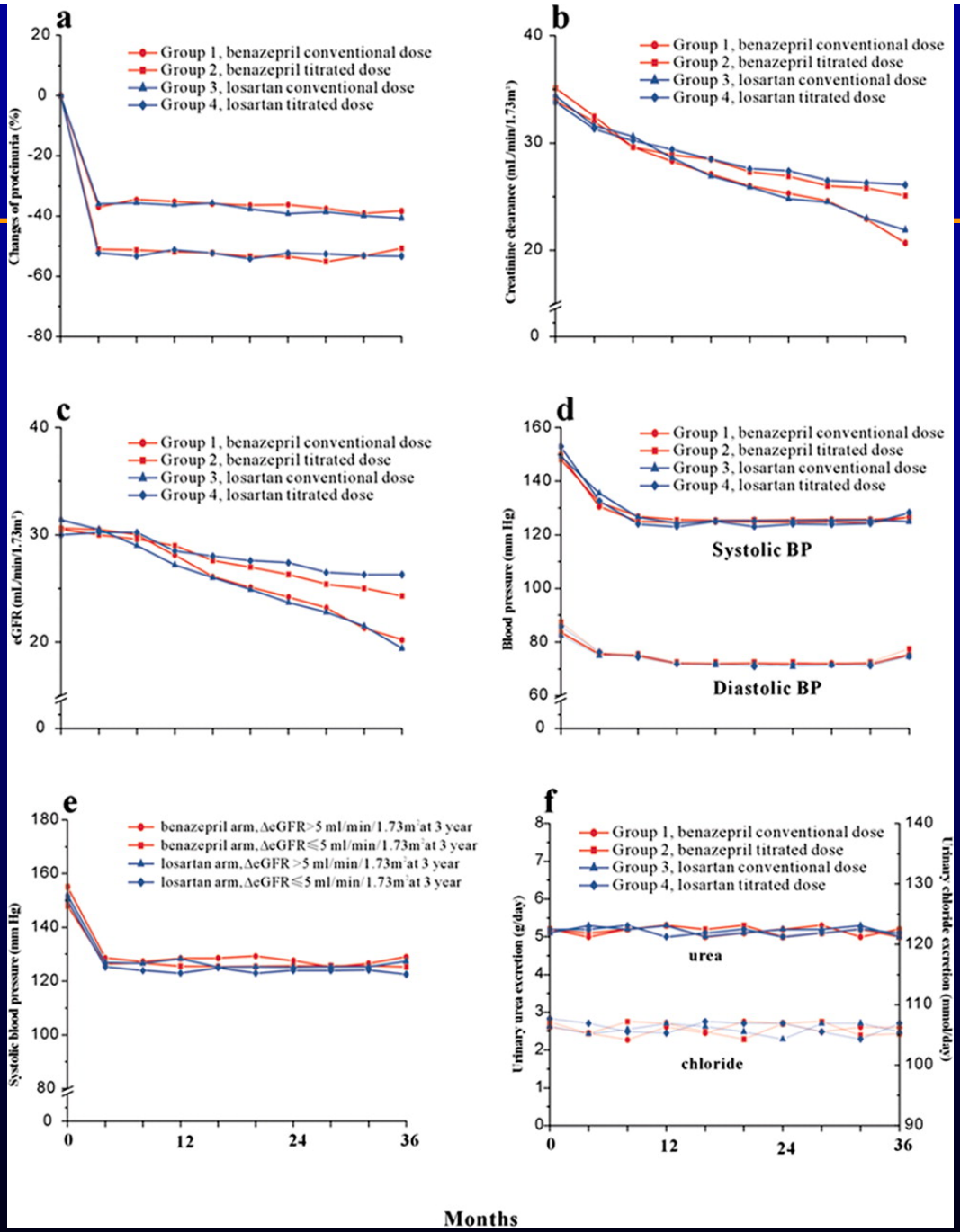
Peters H , et al. *Kidney Int* 54 : 1570 –1580, 1998
Fogo AB. *Kidney Int* 59 : 804 –819, 2001
Laverman GD, et al. *Am J Kidney Dis* 38 : 1381 –1384, 2001
Aranda P, et al. *Am J Kidney Dis* 46 : 1074 –1079, 2005
Andersen S, et al. *Nephrol Dial Transplant* 17 : 1413 –1418, 2002
Burgess E, et al. J Am Soc Nephrol 2009;20:893–900



Burgess E, et al. J Am Soc Nephrol 2009;20:893–900



Hou FF, et al. J Am Soc Nephrol 2007;18:1889–98



Hou FF, et al. J Am Soc Nephrol 2007;18:1889–98

Combination therapy for RAAS blockade

- The redundancy of the RAAS makes suppression difficult
- Combining agents acting at different sites of the RAAS may result in more complete suppression
- The addition of candesartan 16 mg daily to maximal recommended doses of ACEI in patients with Type 2 diabetes and nephropathy enhanced the reduction in albuminuria independent of changes in BP (Rossing 2003).

Rossing K, et al. Diabetes Care 2003;26:2268–74

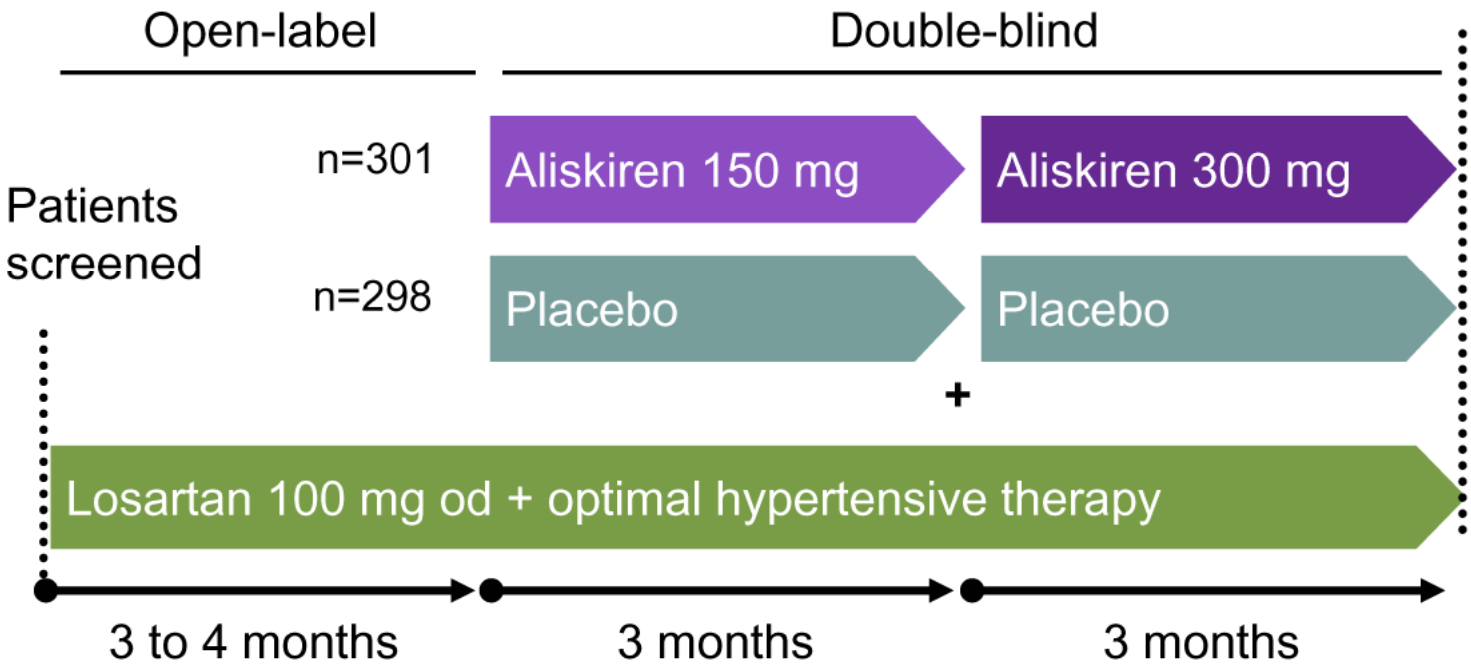
Combination therapy for RAAS blockade

- Direct renin inhibitors (DRI) may provide superior blockade of RAAS
- Aliskiren has been shown to have equivalent BP lowering effects compared to ARB and ACEI
- The AVOID study showed reduction in proteinuria after adding aliskiren to maximal recommended dose of losartan in patients with hypertension and type 2 diabetes with nephropathy
- Clinical trials examining the effects of aliskiren added to ACEI/ARB on hard clinical end points are underway

Parving HH, et al. N Engl J Med 2008;358:2433–46

Study Design: Aliskiren Combined with Losartan in Type 2 Diabetes and Nephropathy

N=599 patients with HTN/type 2 DM/albuminuria*

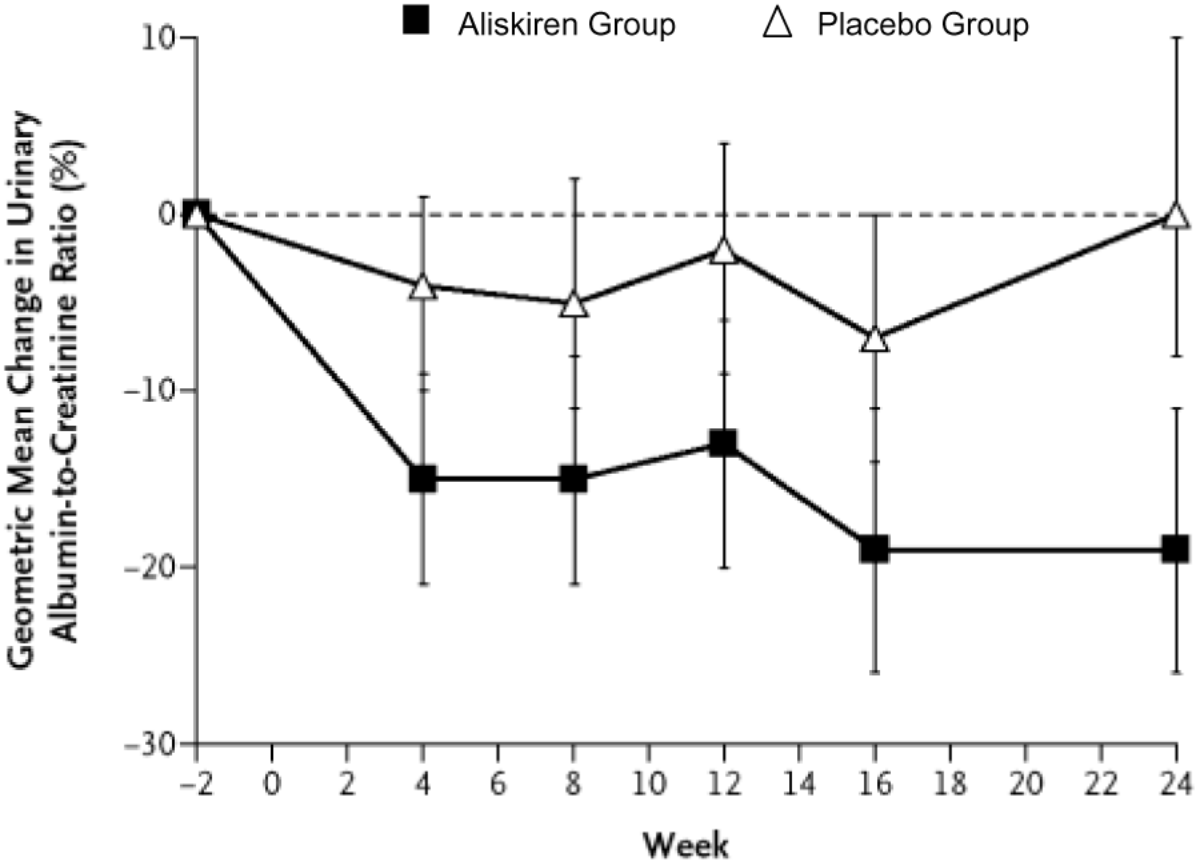


Primary endpoint: difference in proteinuria between treatment groups at 24 weeks.

*UACR >300 mg/g; or UACR >200 mg/g in patients receiving therapy targeted at blockade of the RAAS. All patients must have had a urinary albumin to creatinine ratio ≤3500 mg/g.

Parving H-H et al. *N Engl J Med.* 2008;358:2433-2446.

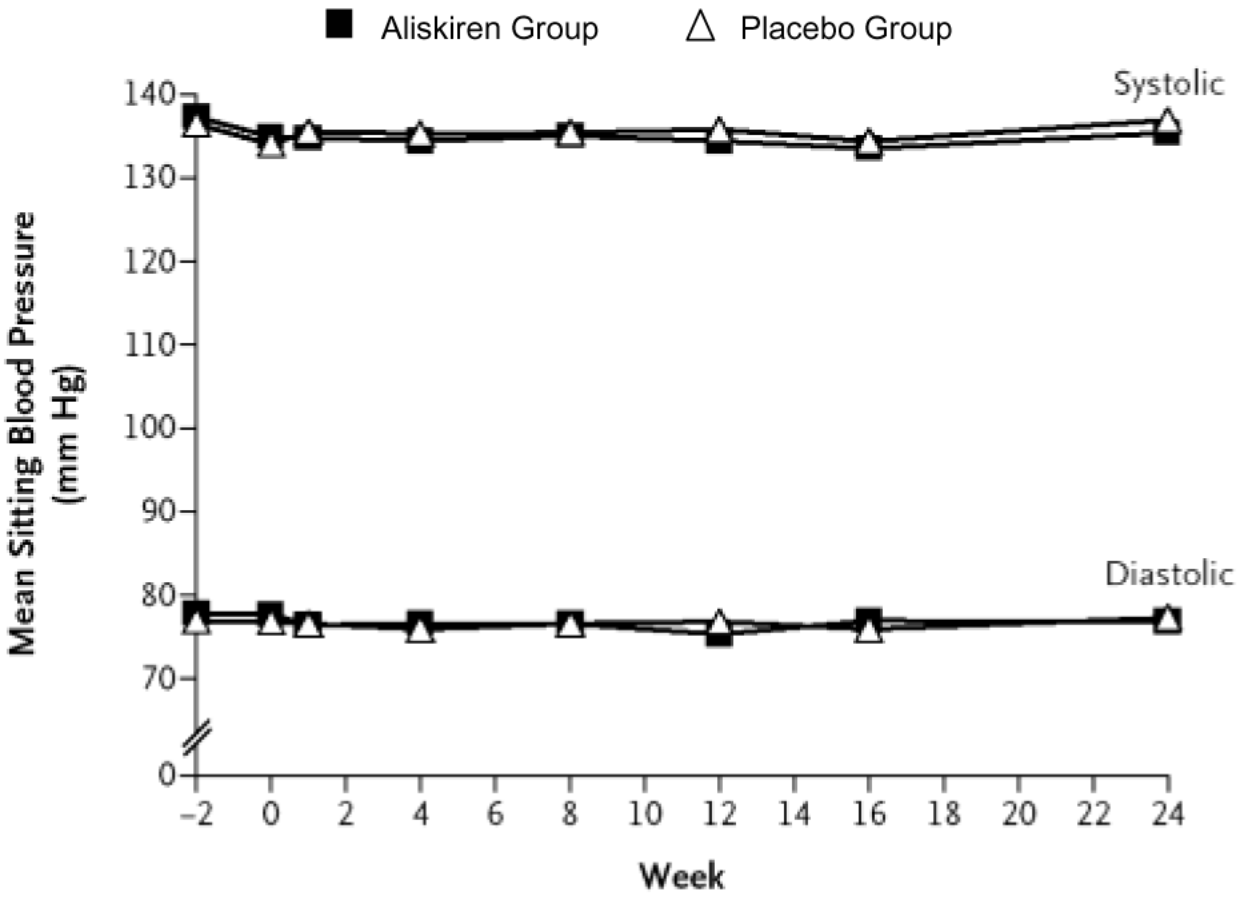
Primary Endpoint: Difference in UACR at 24 weeks



- At week 24, the difference in proteinuria between the groups was 20%.

Parving H-H et al. *N Engl J Med.* 2008;358:2433-2446.

Mean Blood Pressure at Baseline and End of Study



- No difference in mean BP was seen between aliskiren and placebo.

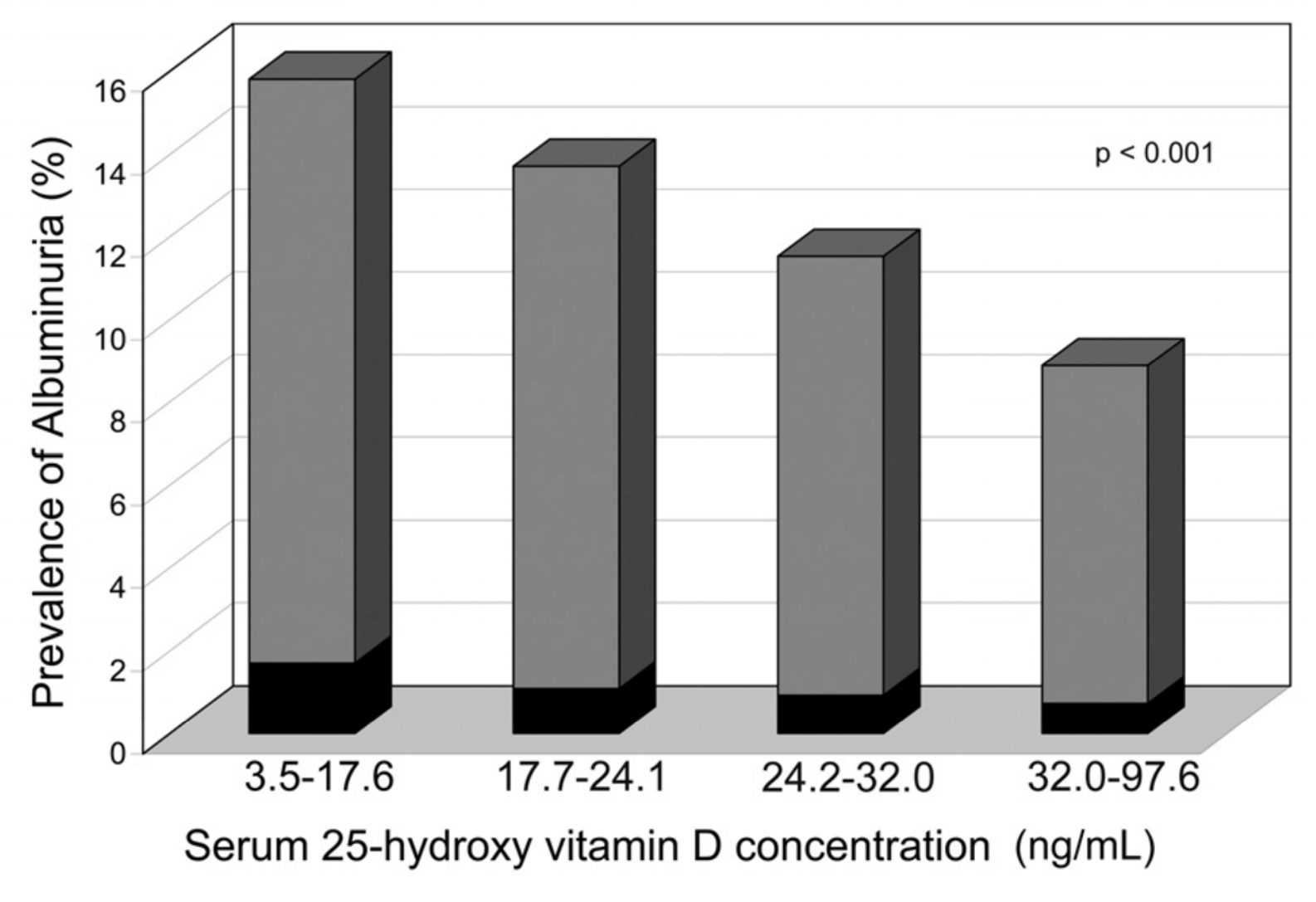
Parving H-H et al. *N Engl J Med.* 2008;358:2433-2446.

Vitamin D receptor activation

- Observational studies have suggested an association between lower 25OHD levels and higher proteinuria/higher incidence of ESRD
- Treatment with active vitamin D has been associated with a trend towards lower incidence of ESRD

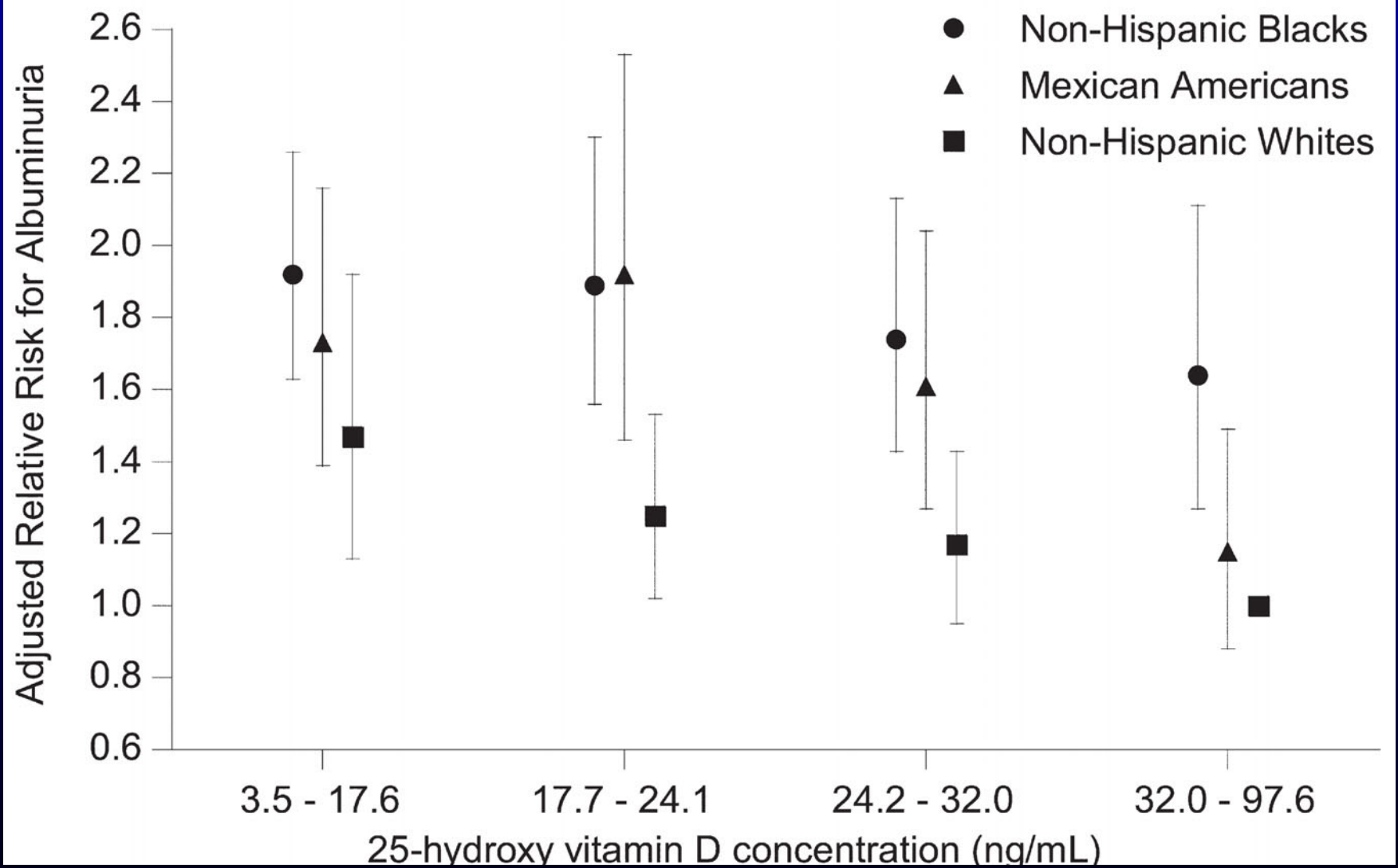
De Boer et al, *Am J Kidney Dis 2007;* 50:69-77
Ravani et al, *Kidney International* 2009; 75:88–95
Kovesdy et al, *Arch Intern Med* 2008;168:397-403

25OH vitamin D levels and albuminuria



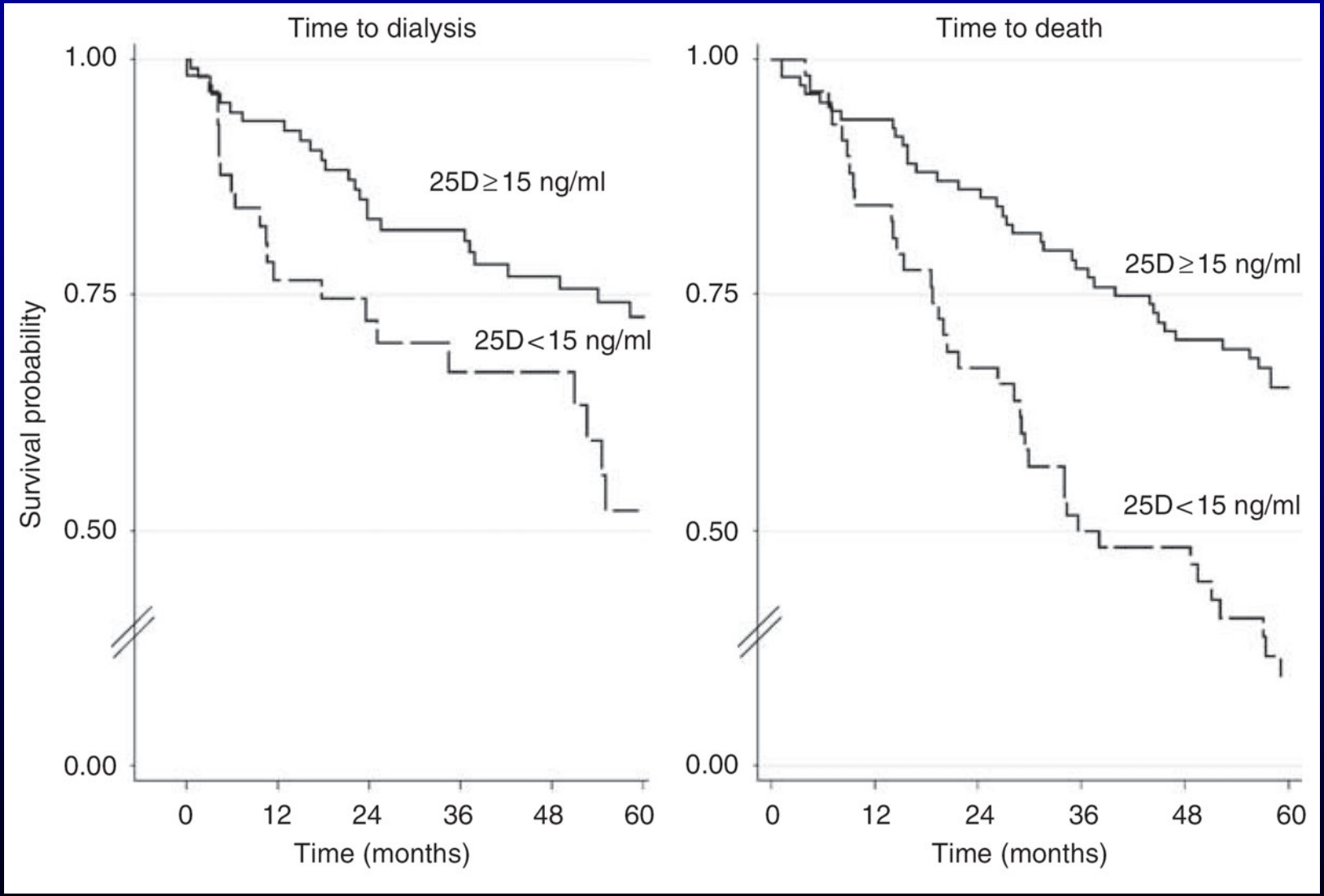
De Boer et al, *Am J Kidney Dis 2007;* 50:69-77.

25OH vitamin D levels and albuminuria



De Boer et al, *Am J Kidney Dis 2007;* 50:69-77.

25OHD levels and outcomes in CKD



Ravani et al, *Kidney International* 2009; 75:88–95.

Risk of various end points for calcitriol treated vs. non-treated CKD patients

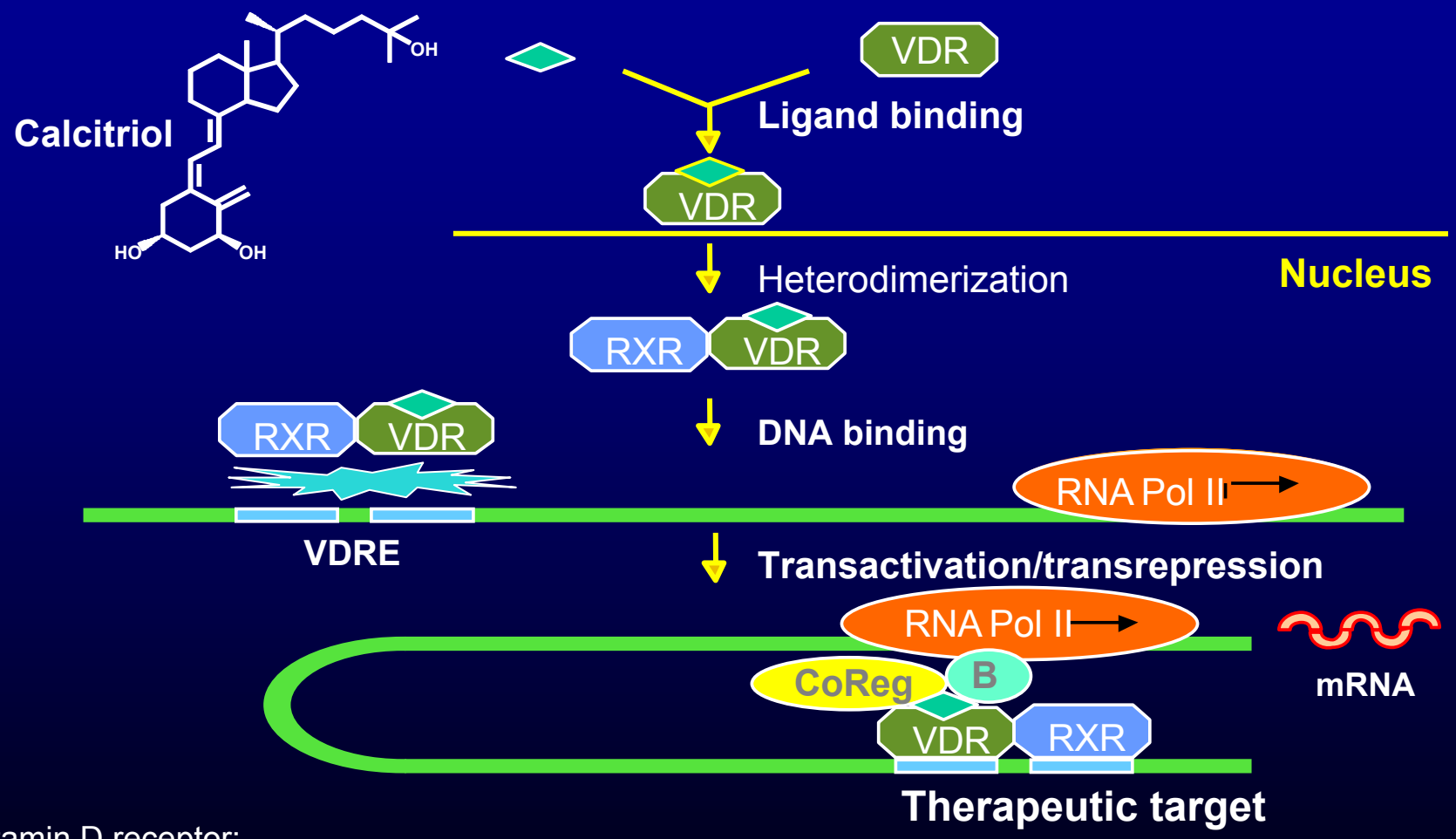
Level of adjustment	Death before ESRD	Composite of Death before ESRD or ESRD	ESRD
Unadjusted	0.53 (0.37-0.77)	0.72 (0.56-0.92)	0.95 (0.67-1.34)
Age, race, BMI, SBP, DBP, smoking status, comorbidity index, diabetes mellitus, use of calcium containing phosphate binders and use of sevelamer	0.47 (0.32-0.69)	0.55 (0.42-0.72)	0.67 (0.46-0.97)
Model 2 plus PTH, estimated GFR, calcium, phosphorus, albumin, cholesterol, hemoglobin, WBC count, percent lymphocytes in WBC and 24 hour urine protein	0.35 (0.23-0.54)	0.46 (0.35-0.61)	0.75 (0.50-1.12)

Kovesdy et al, *Arch Intern Med* 2008;168:397-403

Vitamin D receptor activation

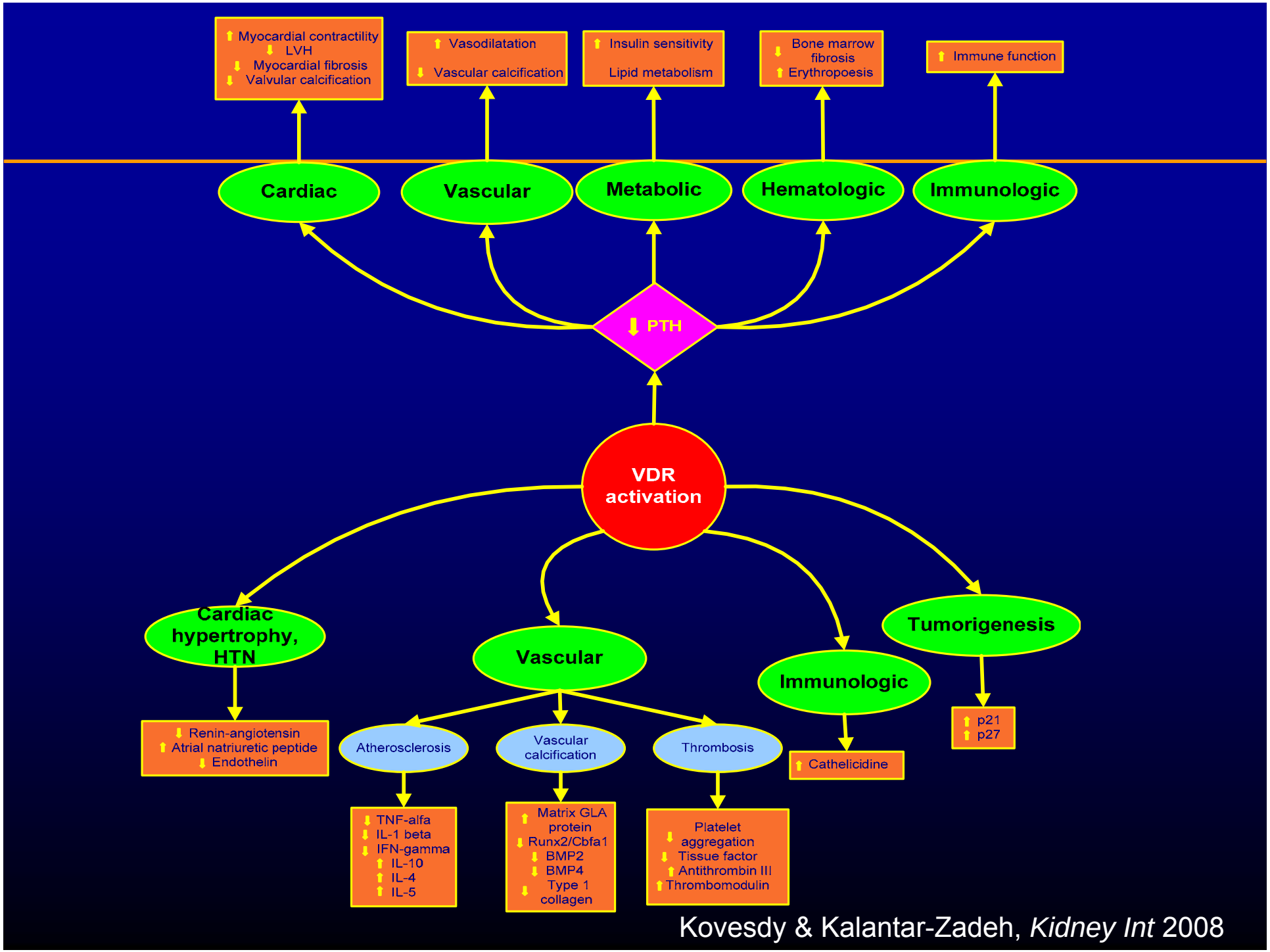
- The biological actions of vitamin D receptor activation provided plausible explanations for the observed associations

Cellular action of calcitriol and the vitamin D receptor (VDR)

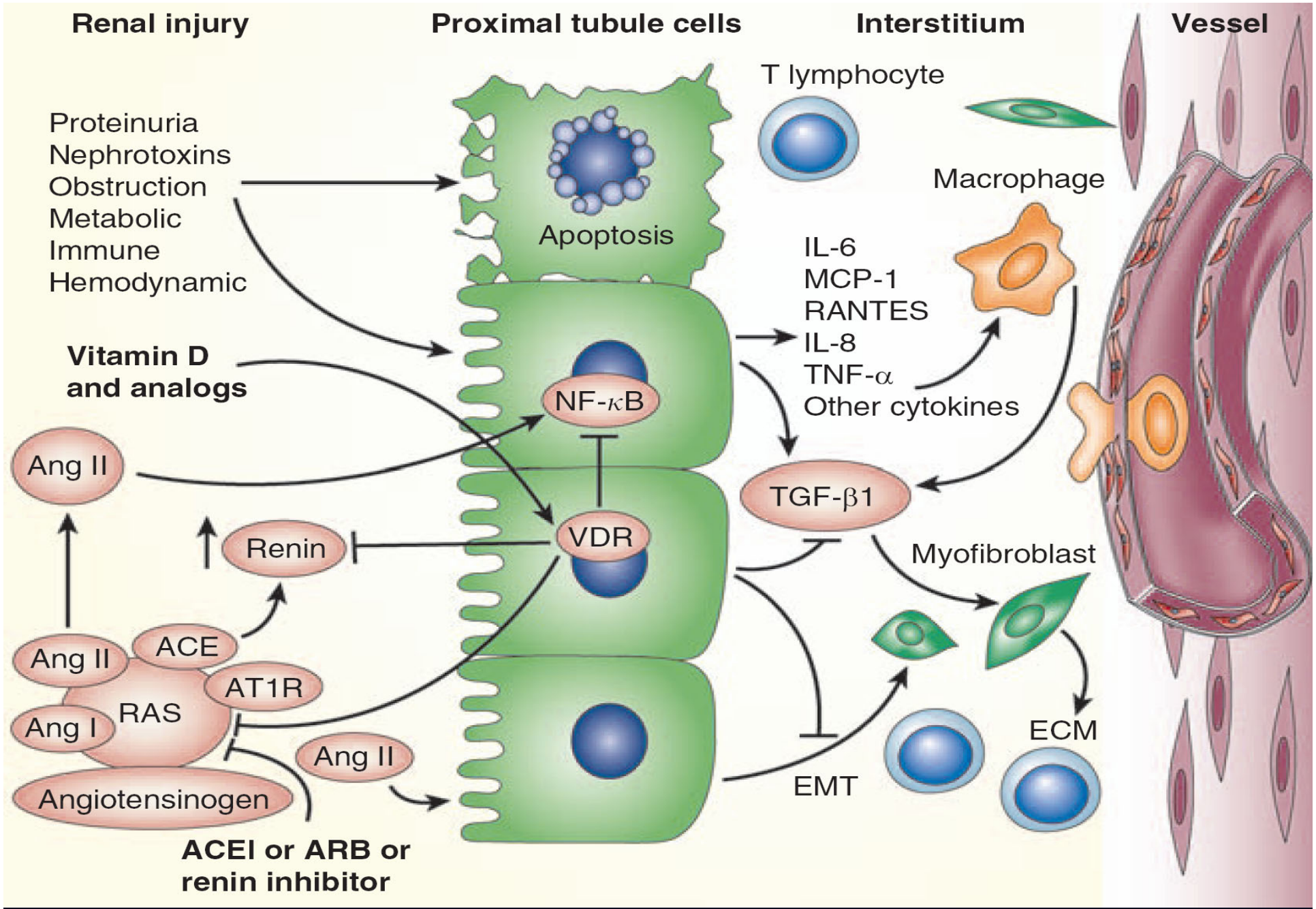


VDR, vitamin D receptor;
VDRE, vitamin D response element;
RXR, retinoid x receptor.

Dusso AS, et al. Semin Nephrol 2004;24:10–16



Kovesdy & Kalantar-Zadeh, *Kidney Int* 2008



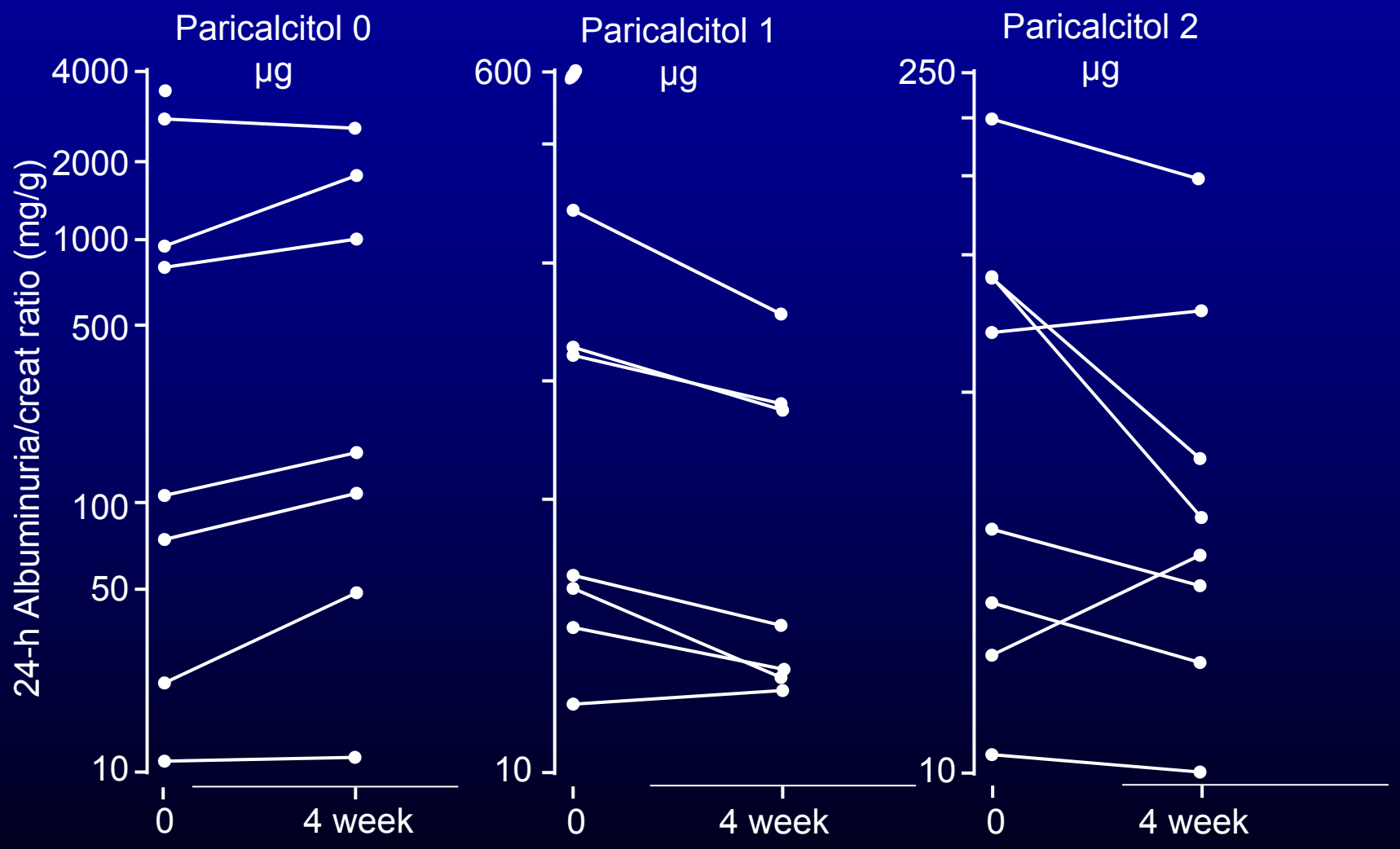
Li and Batuman, Kidney Int 2009;76:2019-2021

Vitamin D receptor activation

- Observational studies and biologic plausibility cannot prove cause-and-effect
- A number of small clinical trials suggested that active vitamin D therapy alone or in combination can induce lowering of proteinuria

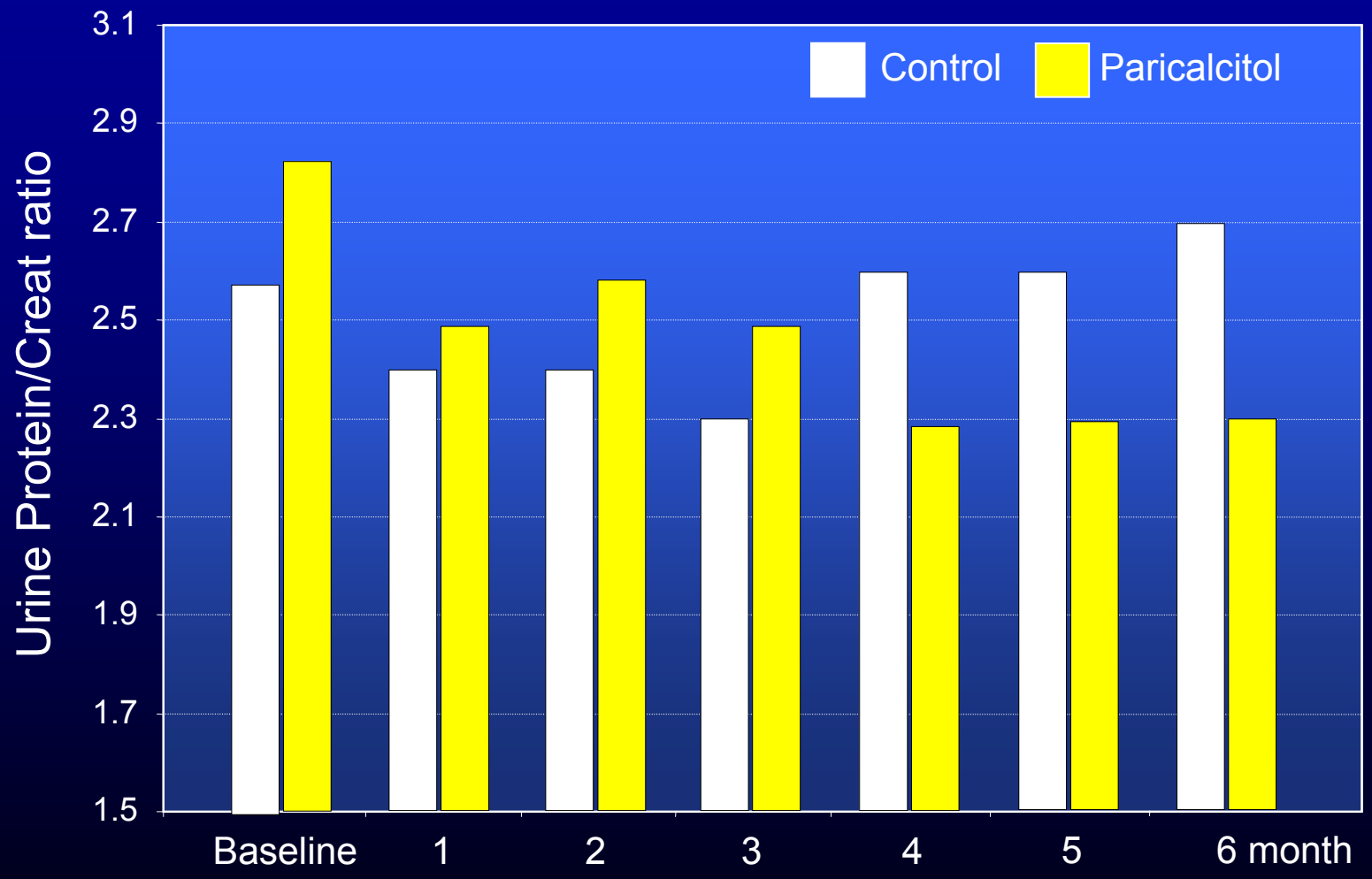
Alborzi P, et al. Hypertension 2008;52:249–55
Fishbane S, et al. Am J Kidney Dis 2009;54:647–52
Agarwal R, et al. Kidney Int 2005;68:2823–8
Szeto CC, et al. Am J Kidney Dis 2008;51:724–31

Effect of Paricalcitol on albuminuria in CKD stage 3 patients



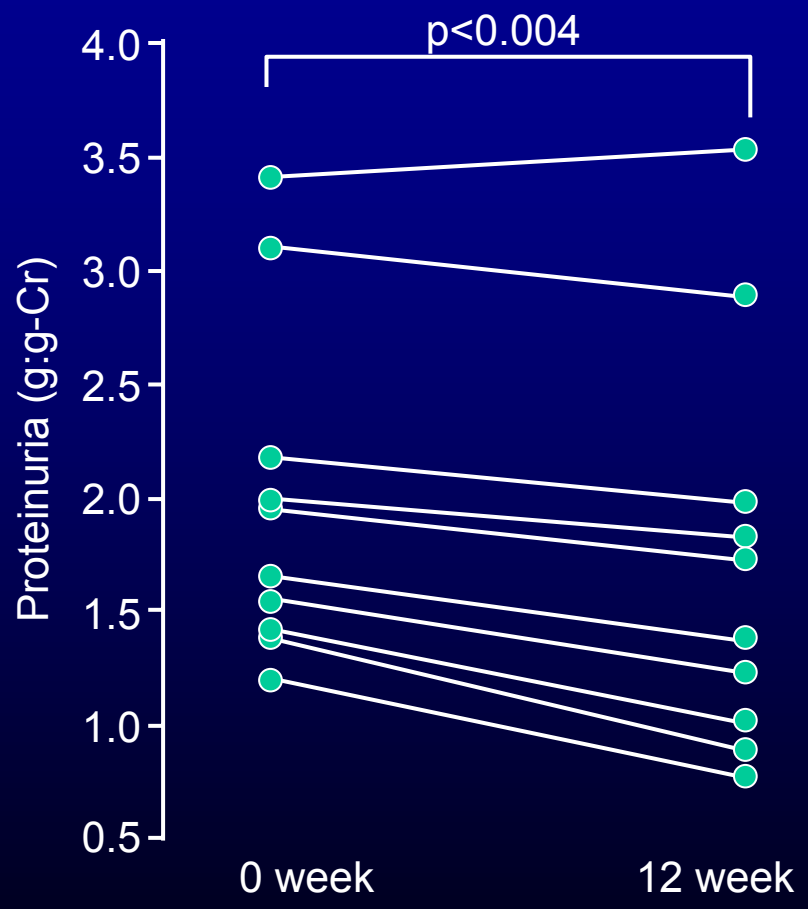
Alborzi P, et al. Hypertension 2008;52:249–55

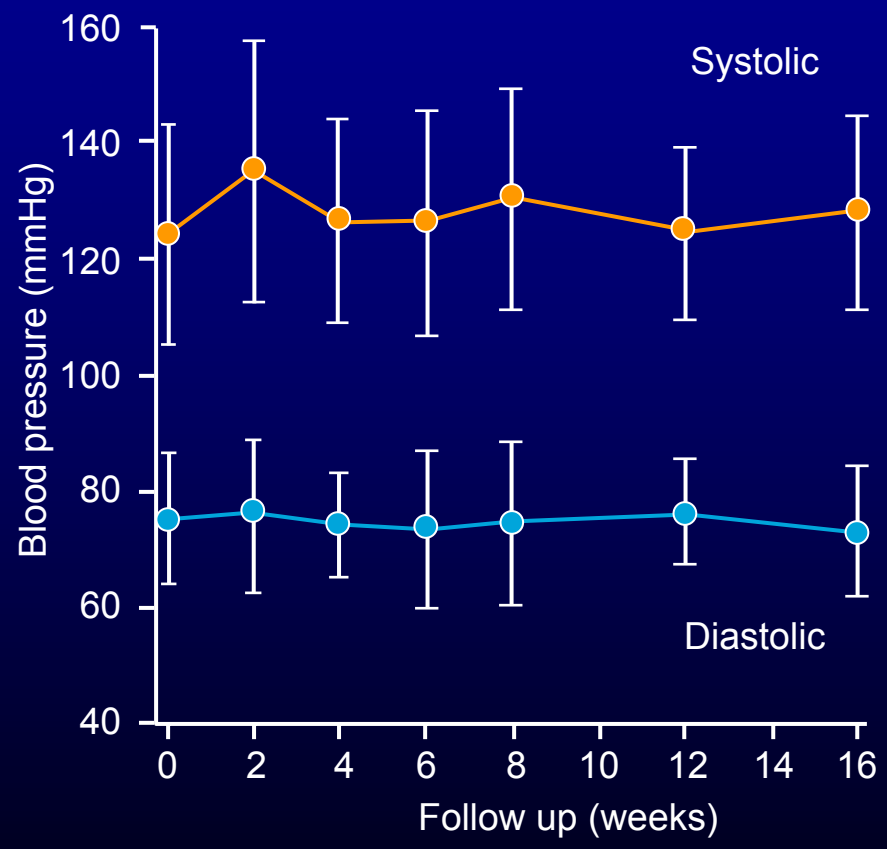
Effect of paricalcitol on spot UProt/creat in nondiabetic proteinuric patients



Fishbane S, et al. Am J Kidney Dis 2009;54:647–52

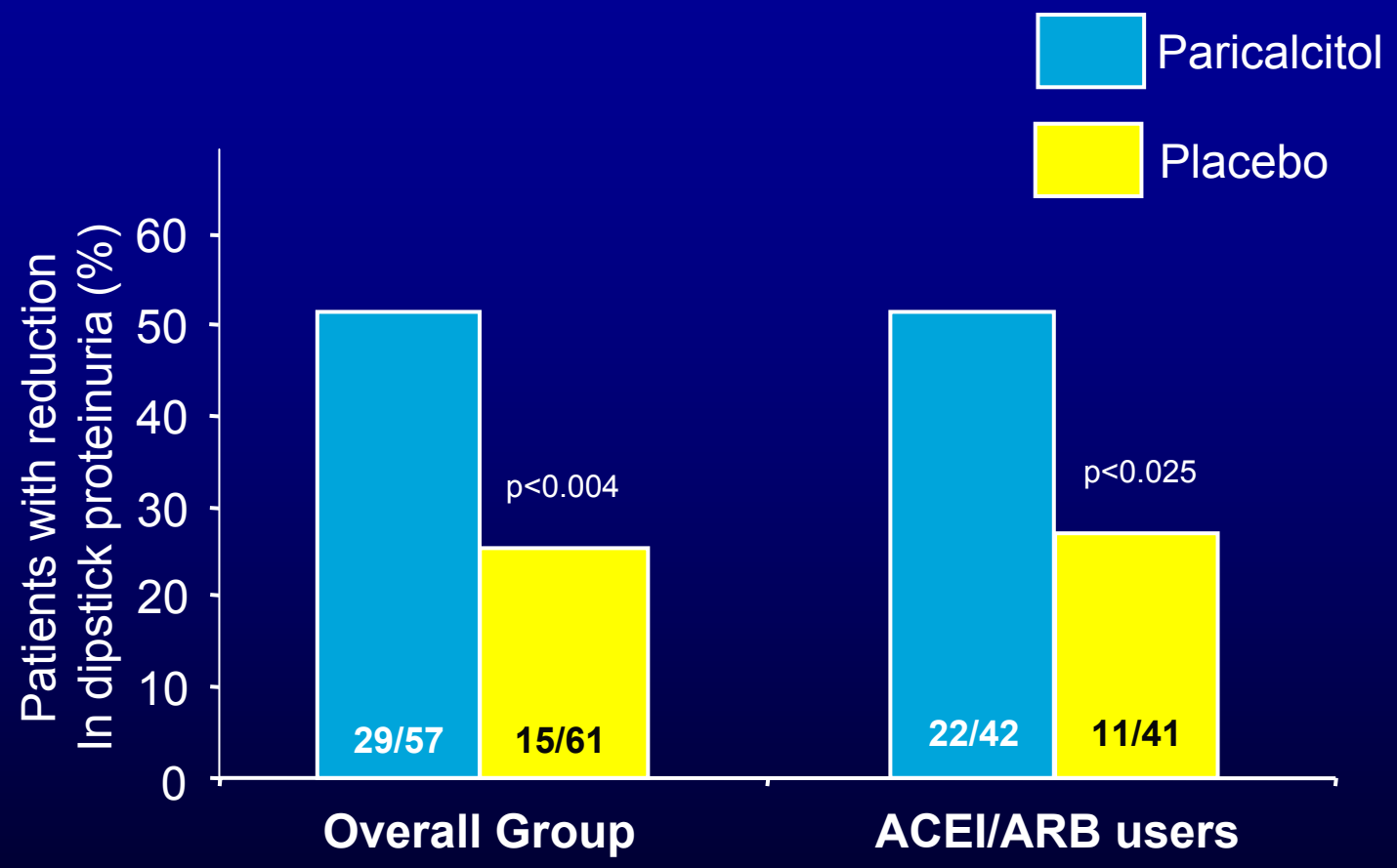
Effect of oral calcitriol on proteinuria and blood pressure in IgA nephropathy on top of ACEi/ARB treatment





Szeto CC, et al. Am J Kidney Dis 2008;51:724–31

Additive antiproteinuric effect of paricalcitol on top of ACEI/ARB



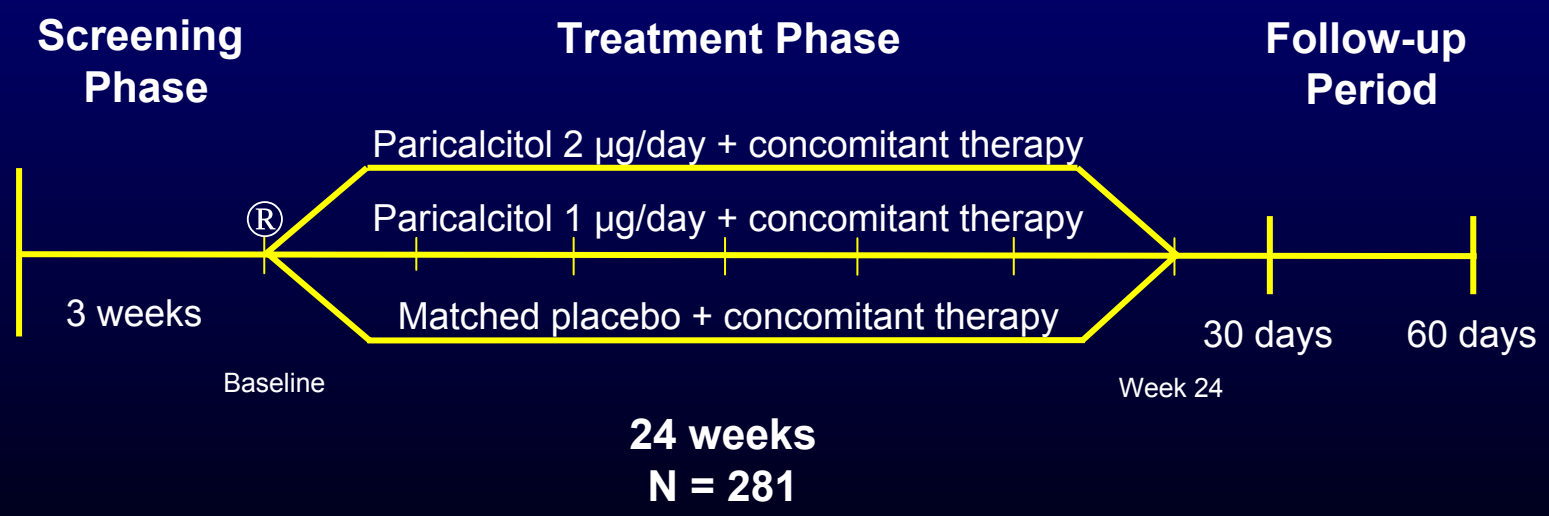
Independent of a number of factors, including age, sex, race, DM, HTN
Adjustment for urine specific gravity increased the adjusted odds of reduction of protein from 3.2 to 4.0

Agarwal R, et al. Kidney Int 2005;68:2823–8

VITAL Study Question and Design

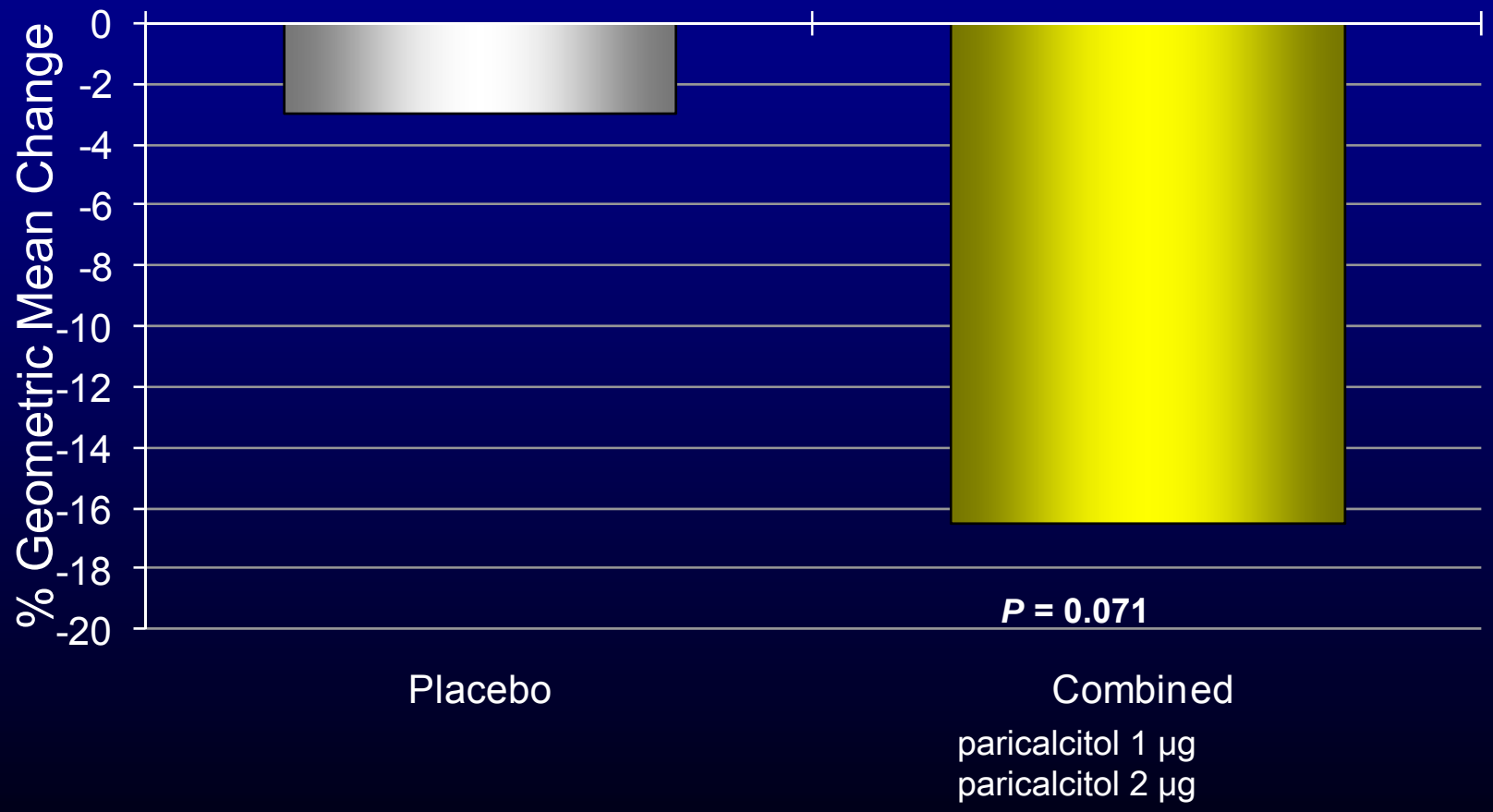
Does treatment with paricalcitol capsules reduce albuminuria in subjects with type 2 diabetic nephropathy receiving treatment with ACE inhibitors and/or ARBs?

Double-blind, placebo controlled, multicenter study



Primary Endpoint: Effect of paricalcitol on UACR

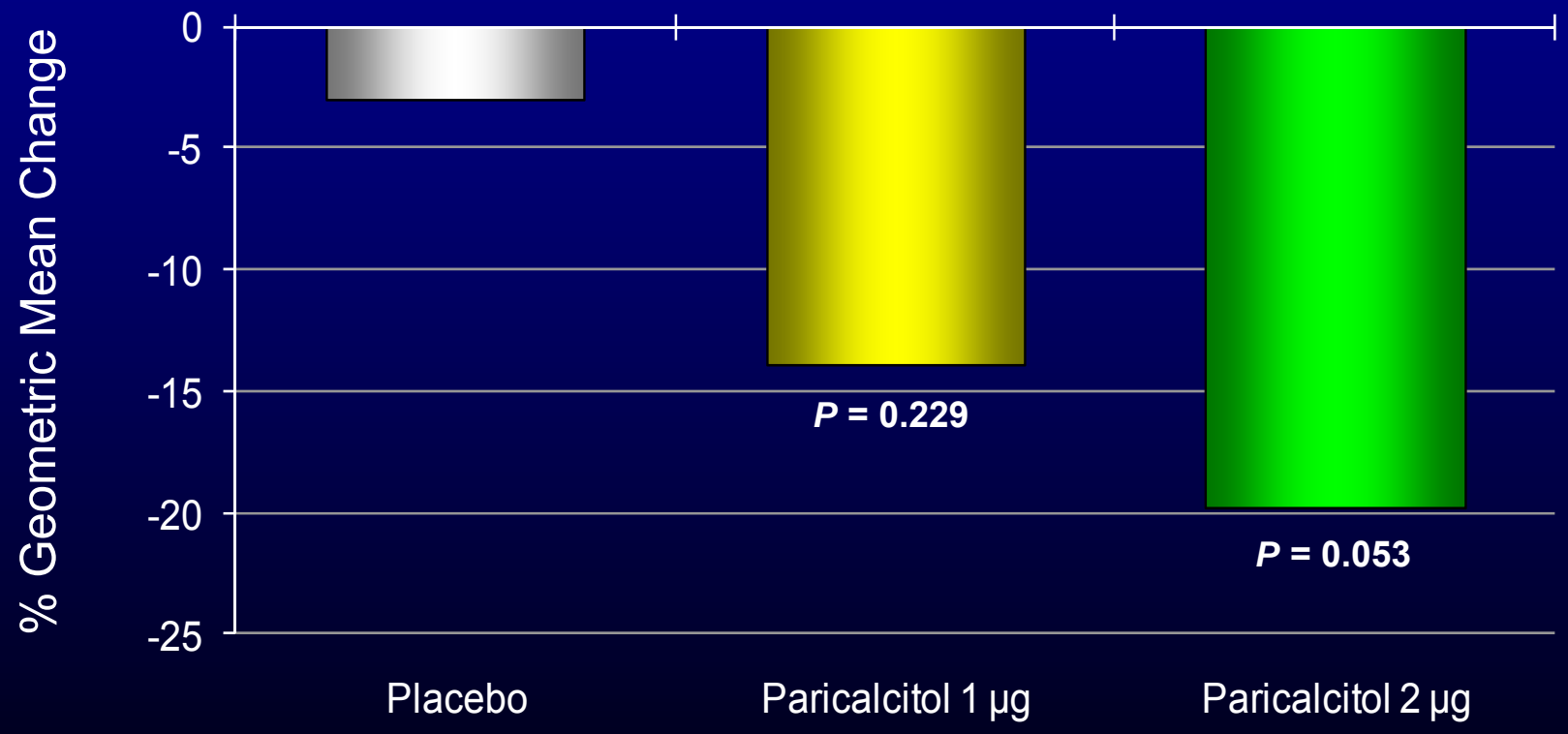
Percent geometric mean change from baseline to the last on-treatment UACR for combined doses compared to placebo



De Zeeuw et al; submitted

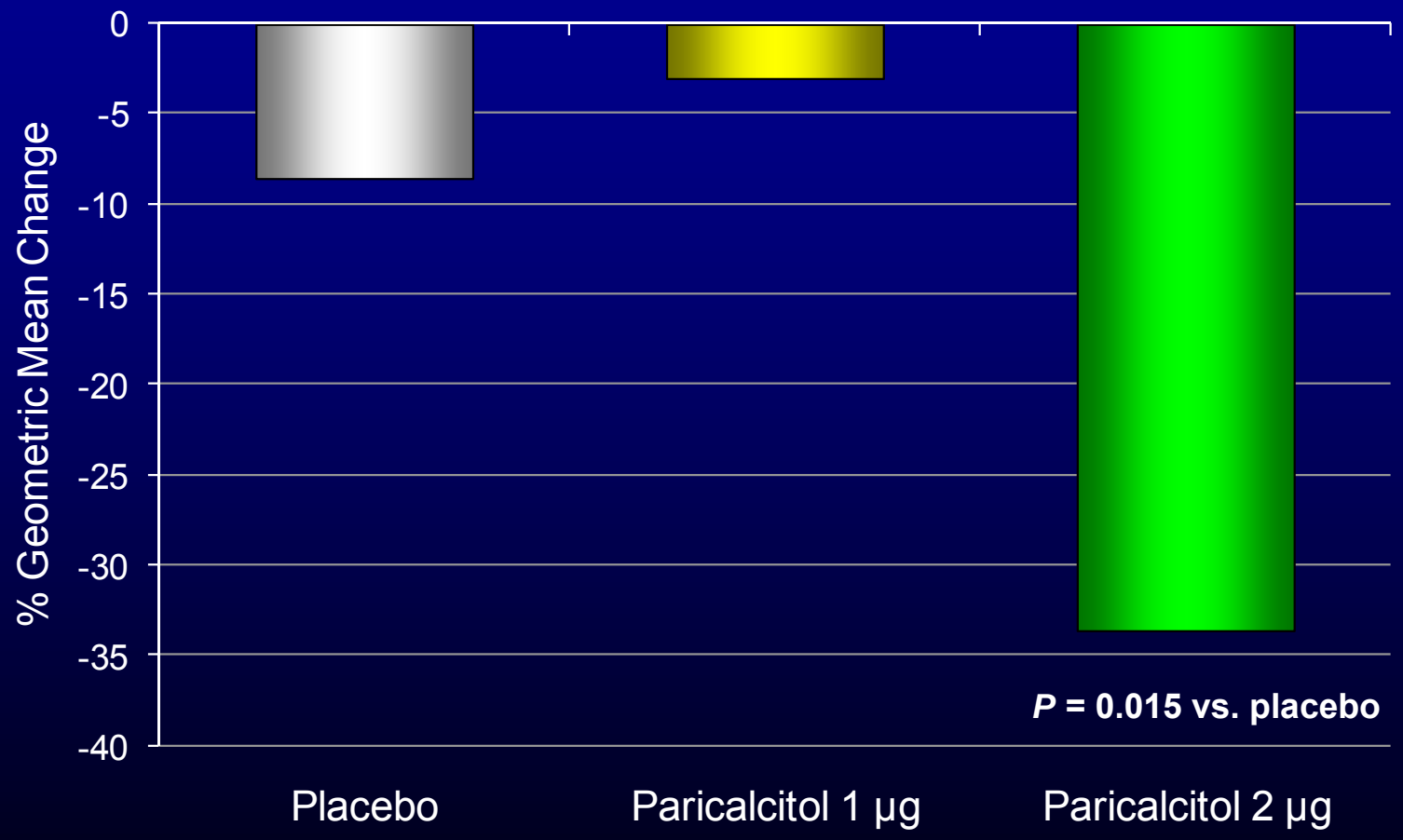
Secondary Endpoint: Effect of paricalcitol doses on UACR

Percent geometric mean change from baseline to the last on-treatment UACR for individual dose groups compared to placebo



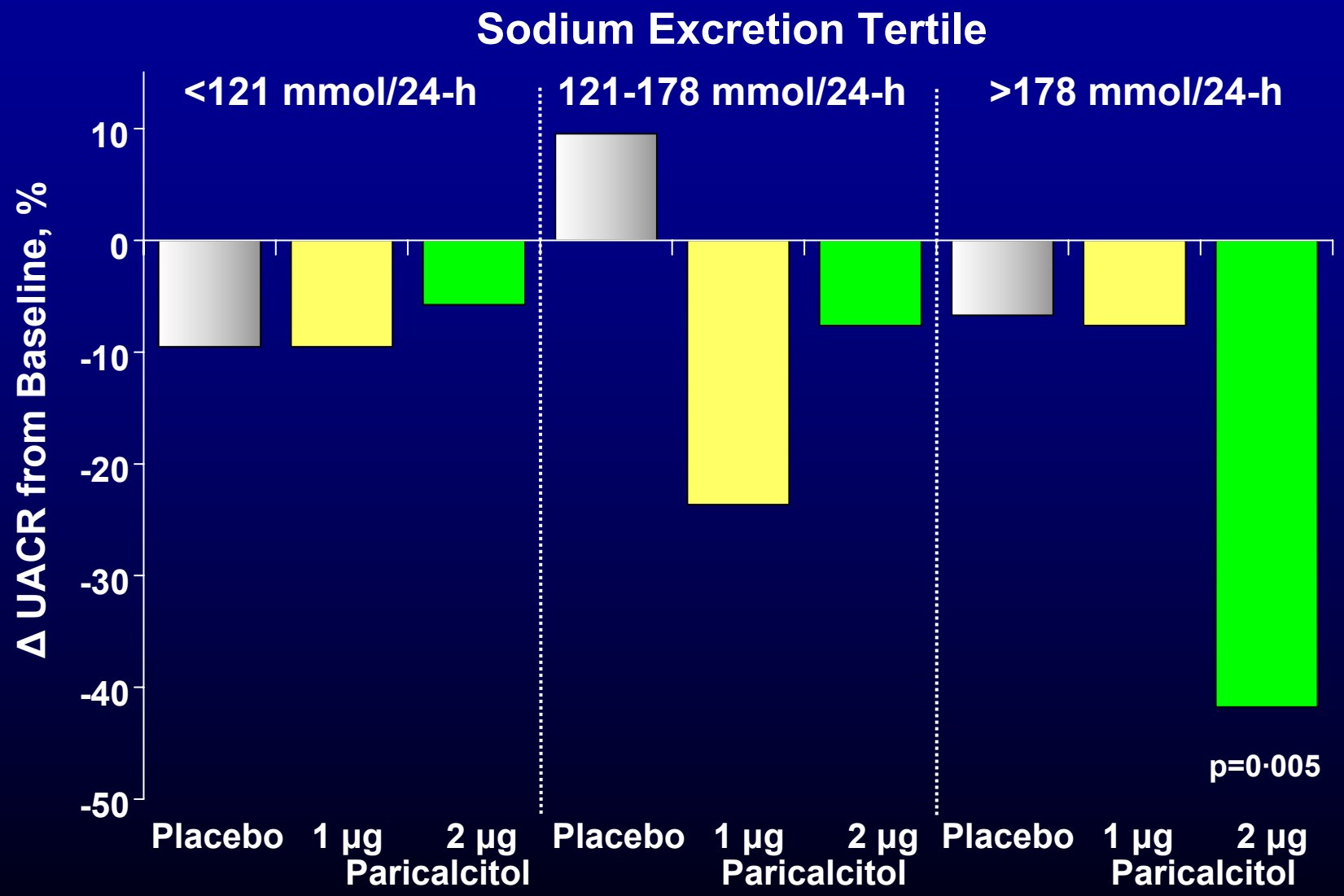
De Zeeuw et al; submitted

Secondary Endpoint: Paricalcitol 2 µg/day reduces 24-hour urinary albumin excretion



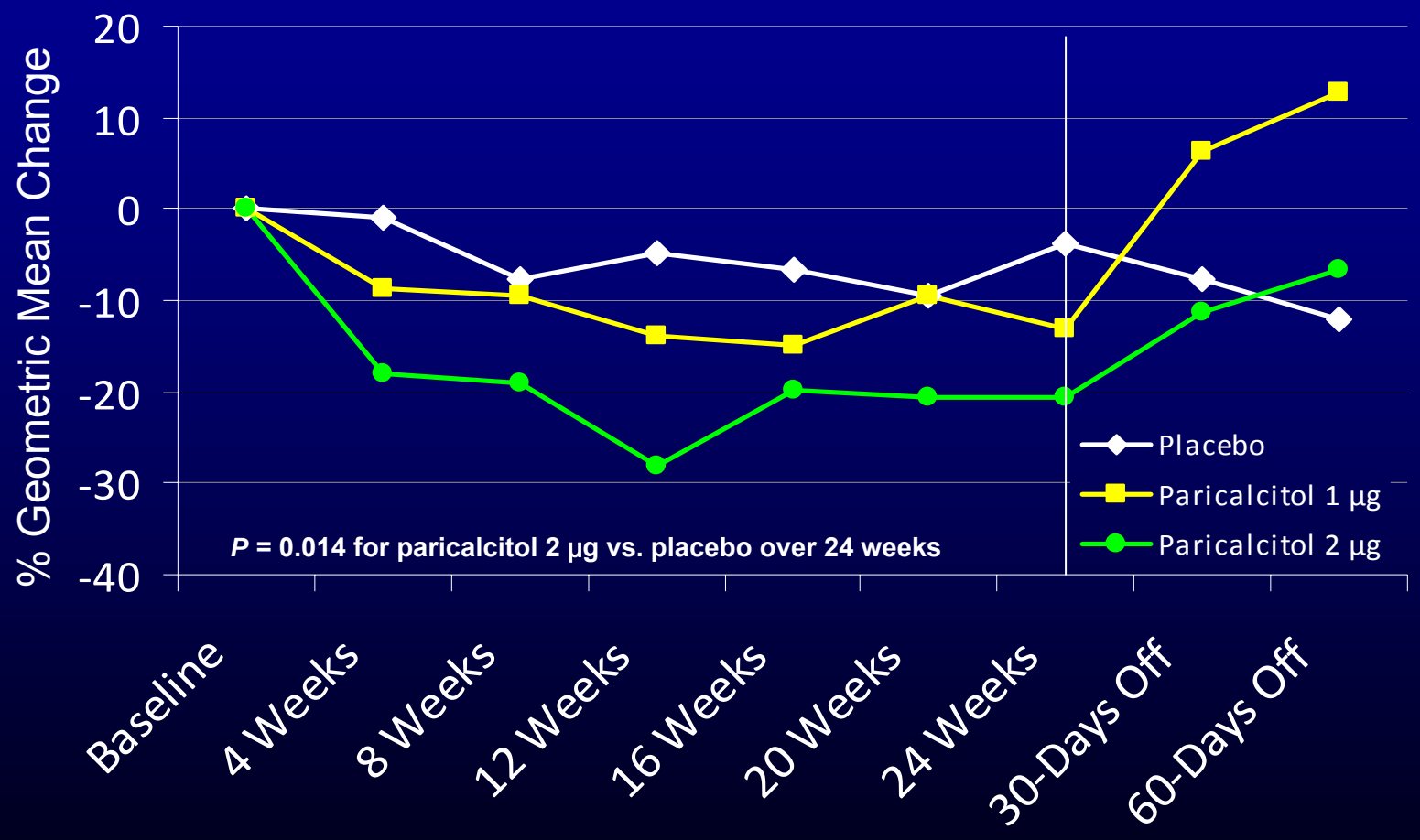
De Zeeuw et al; submitted

Post-hoc Endpoint: Dietary sodium intake modulates the UACR effect of paricalcitol 2 µg/day



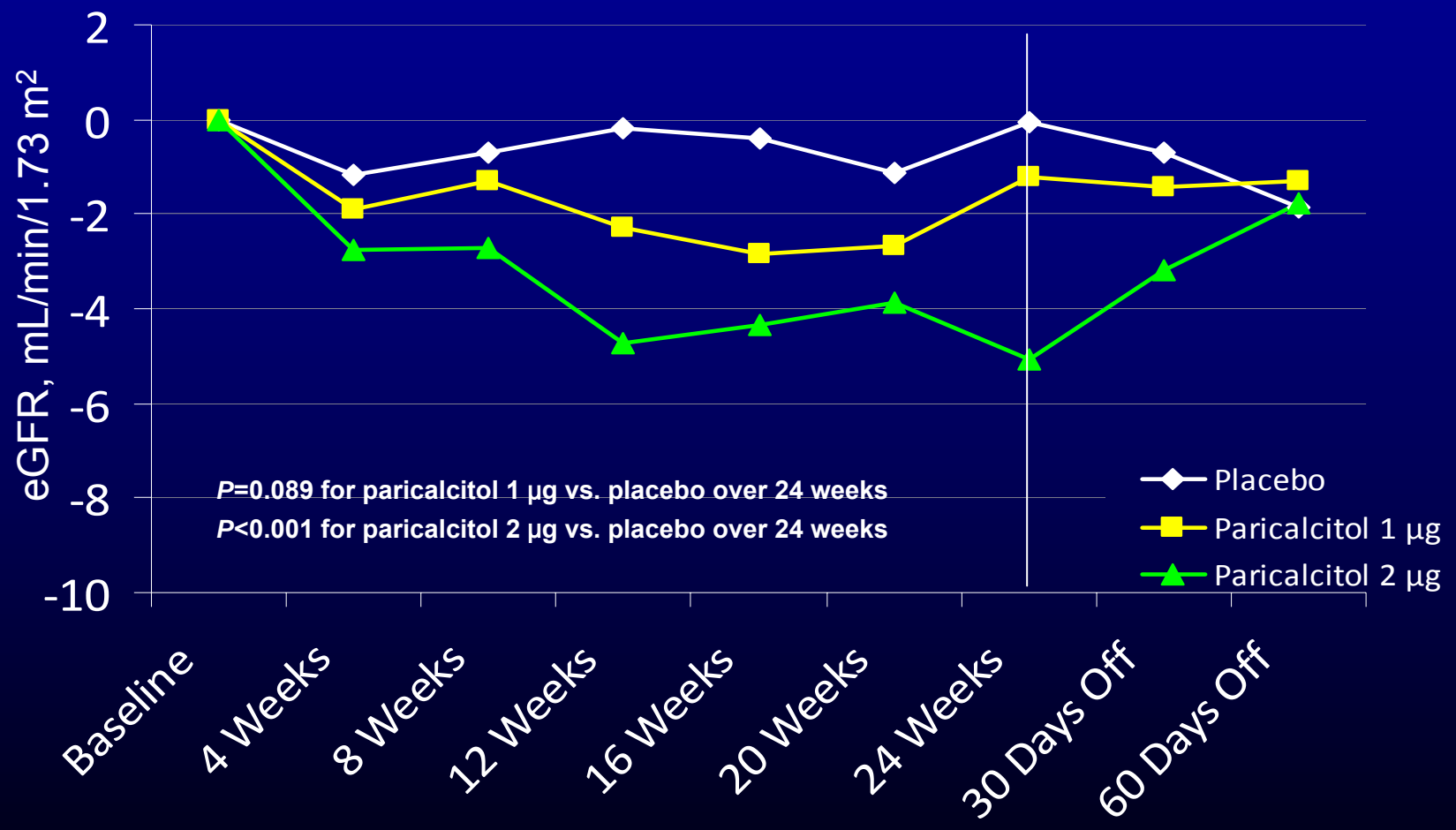
De Zeeuw et al; submitted

Tertiary Endpoint: paricalcitol 2 µg/day reversibly reduces UACR over time (repeated measures 24 wks)



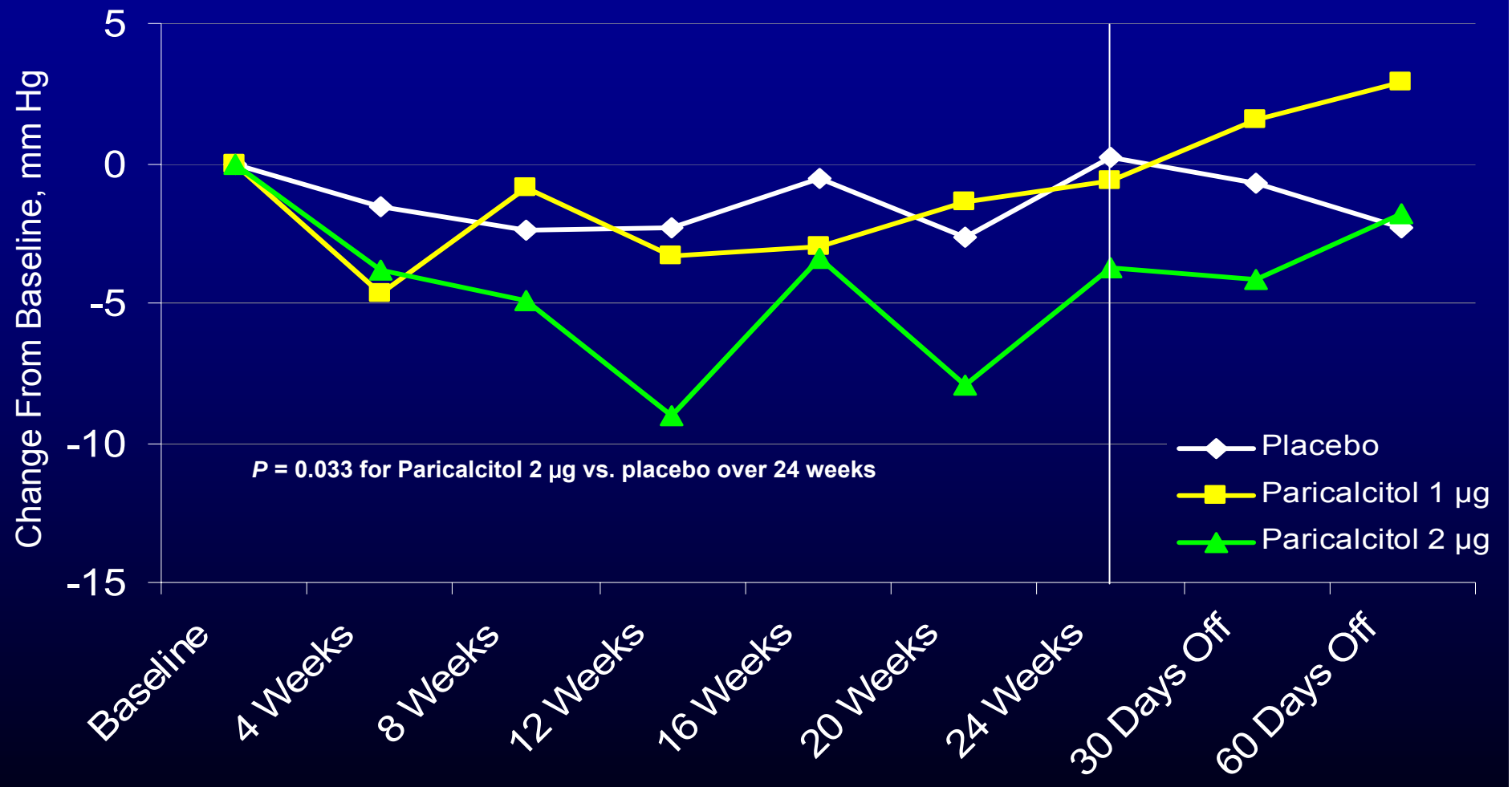
De Zeeuw et al; submitted

Tertiary Endpoint: paricalcitol 2 µg/day reversibly reduces eGFR over time (repeated measures 24 wks)



De Zeeuw et al; submitted

Safety measure: paricalcitol 2 µg/day reversibly reduces systolic BP over time (repeated measures 24 wks)

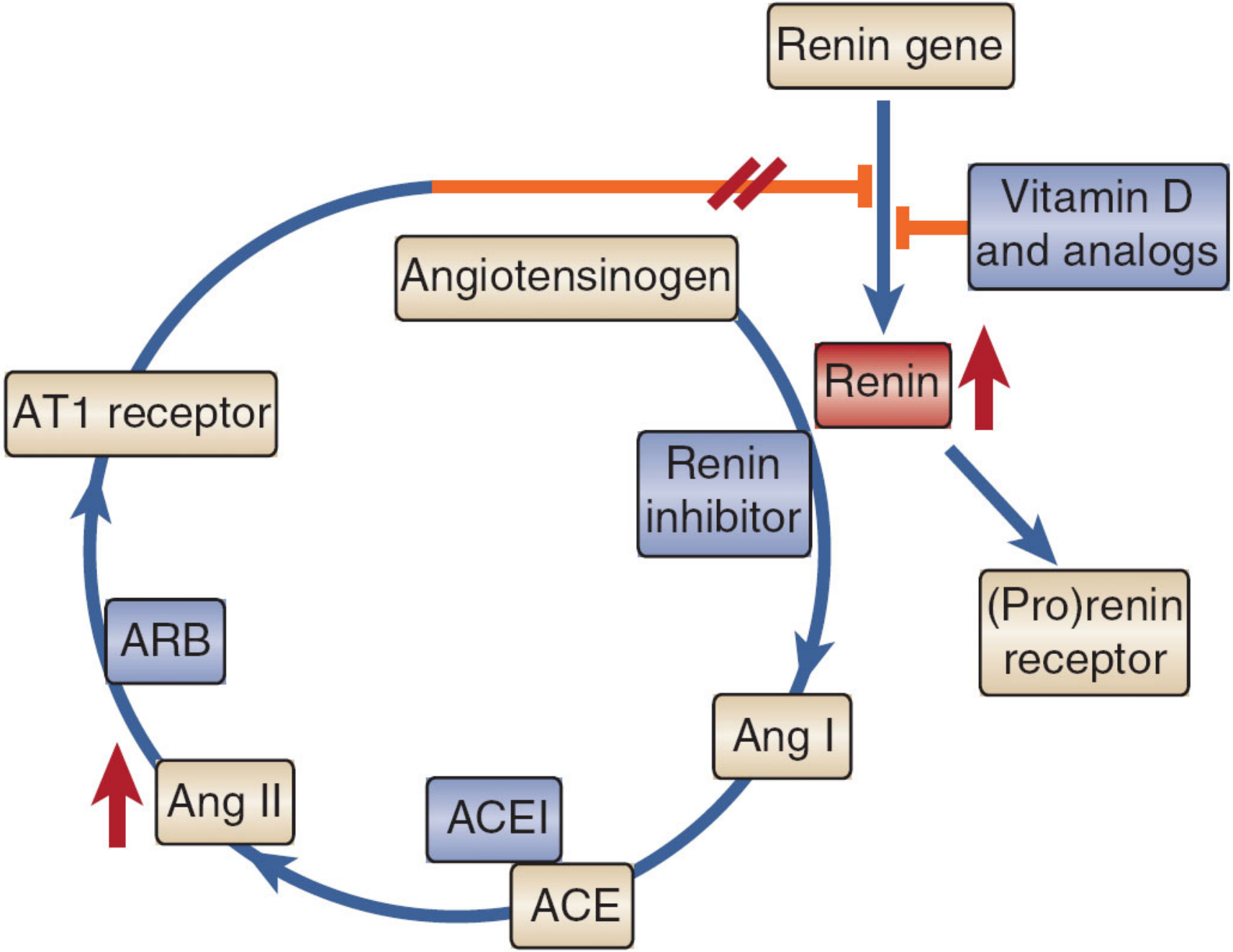


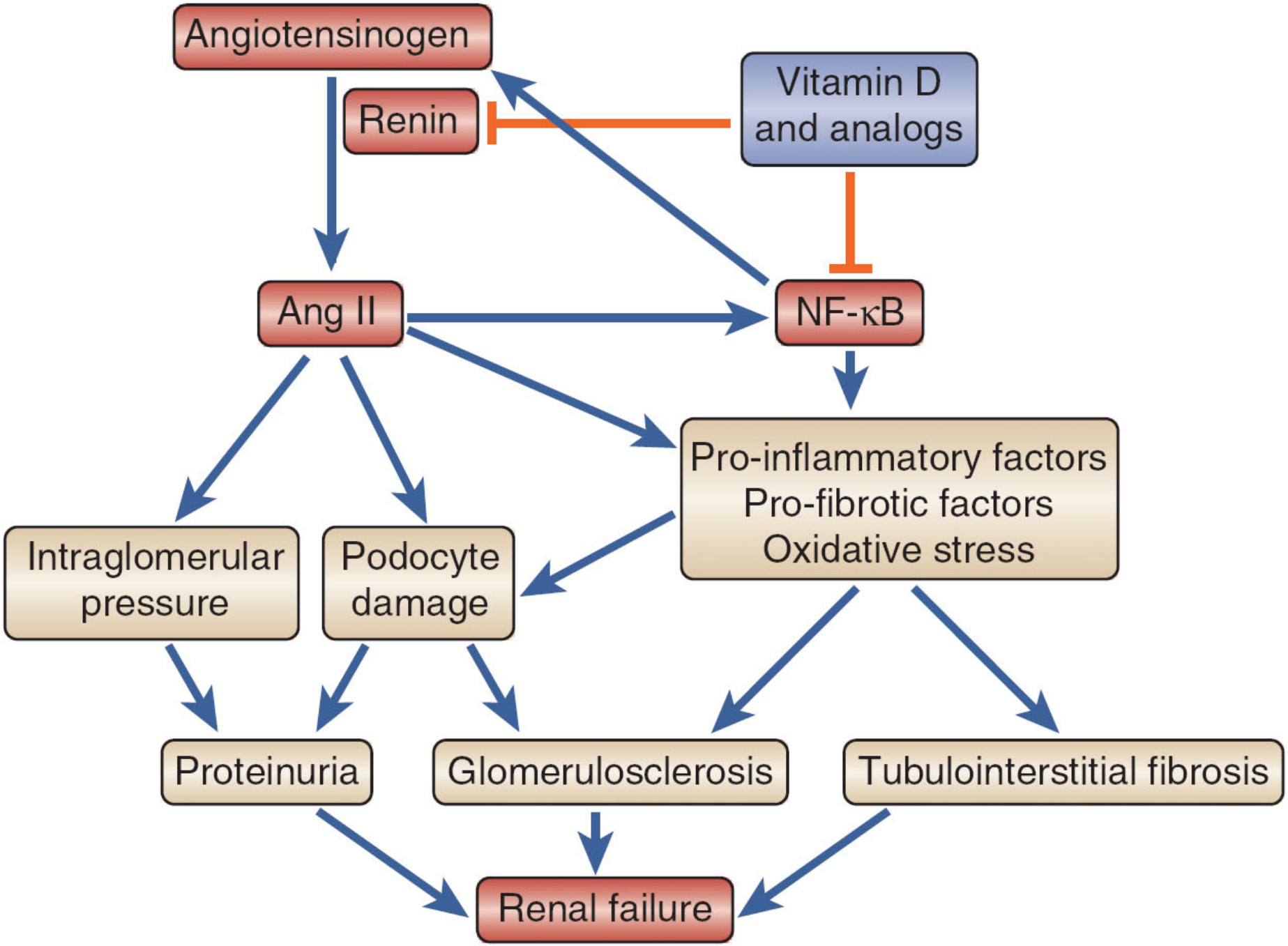
De Zeeuw et al; submitted

Conclusions

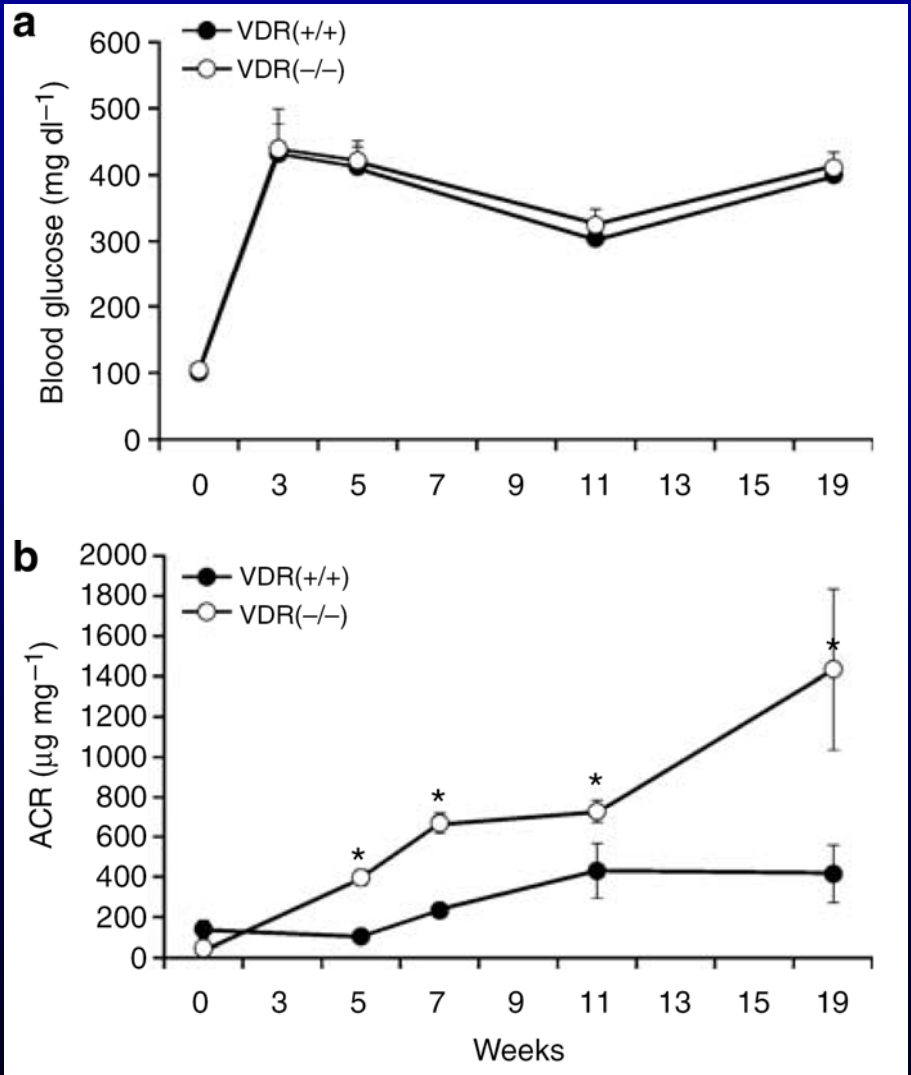
- RAAS inhibition continues to be the cornerstone of reno- and vascular protection
- Various strategies can be used to enhance RAAS inhibition, but the clinical utility of these approaches has not been thoroughly tested
- Vitamin D therapy can emerge as a novel treatment fro RAAS inhibition that is devoid of the sided effects that may inhibit the use of ACEI/ARB

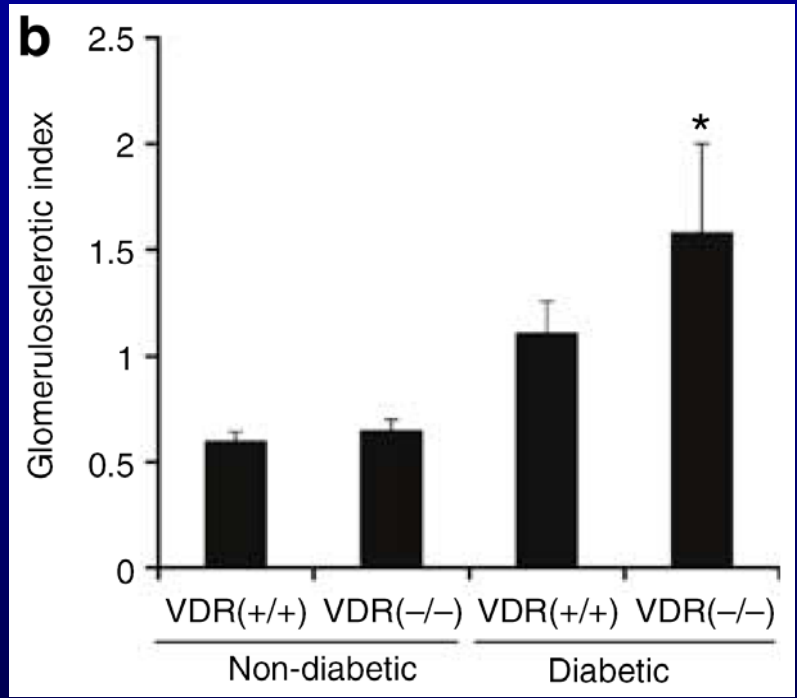
BACKUP SLIDES


Renin gene
Vitamin D and analogs
Angiotensinogen
Renin
AT1 receptor
Renin inhibitor
(Pro)renin receptor
ARB
Ang I
Ang II
ACEI
ACE


Angiotensinogen
Renin
Vitamin D
and analogs
Ang II
NF-κB
Pro-inflammatory factors
Pro-fibrotic factors
Oxidative stress
Intraglomerular
pressure
Podocyte
damage
Proteinuria
Glomerulosclerosis
Tubulointerstitial fibrosis
Renal failure

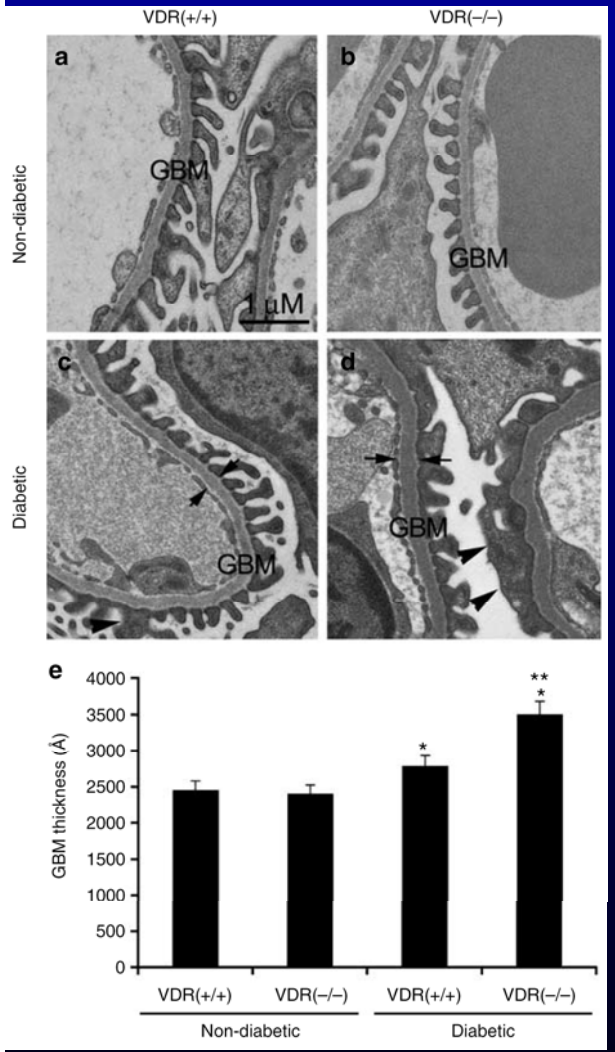
Role of VDR in albuminuria, glomerulosclerosis

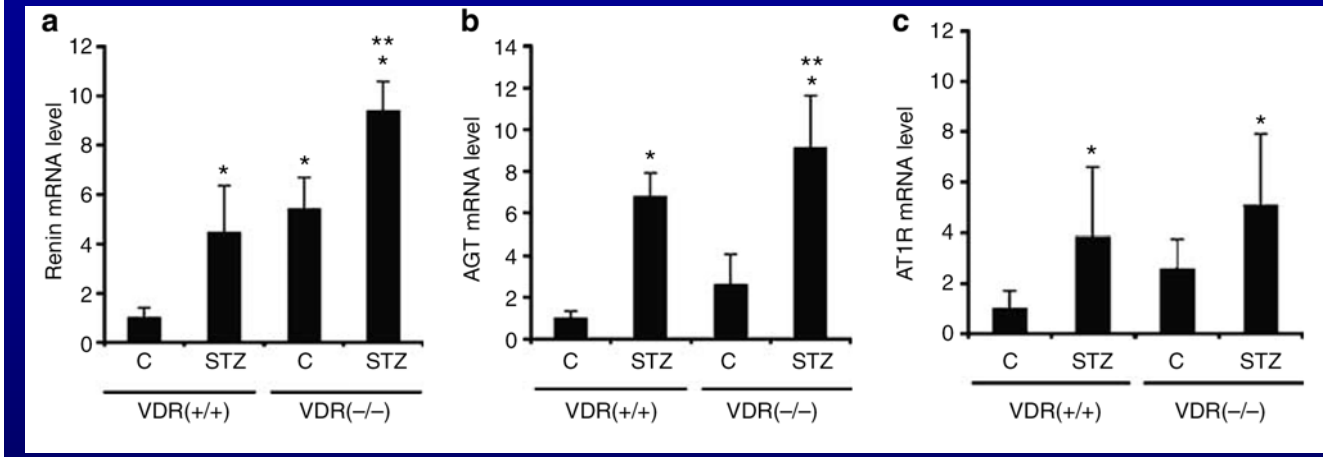




Zhang et al,
Kidney International 2008;73: 163–171

VDR and renal morphology, RAS activation





Zhang et al,
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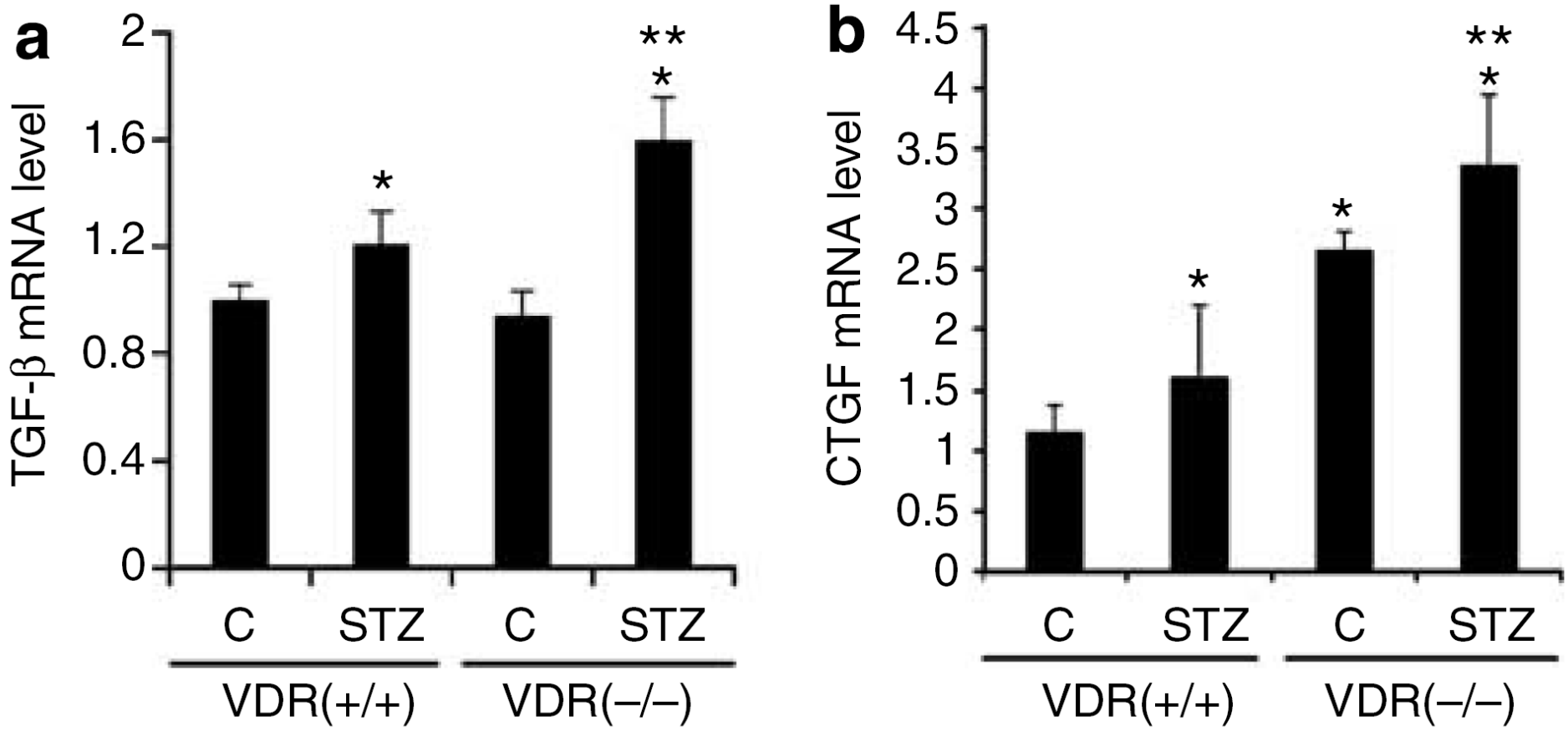
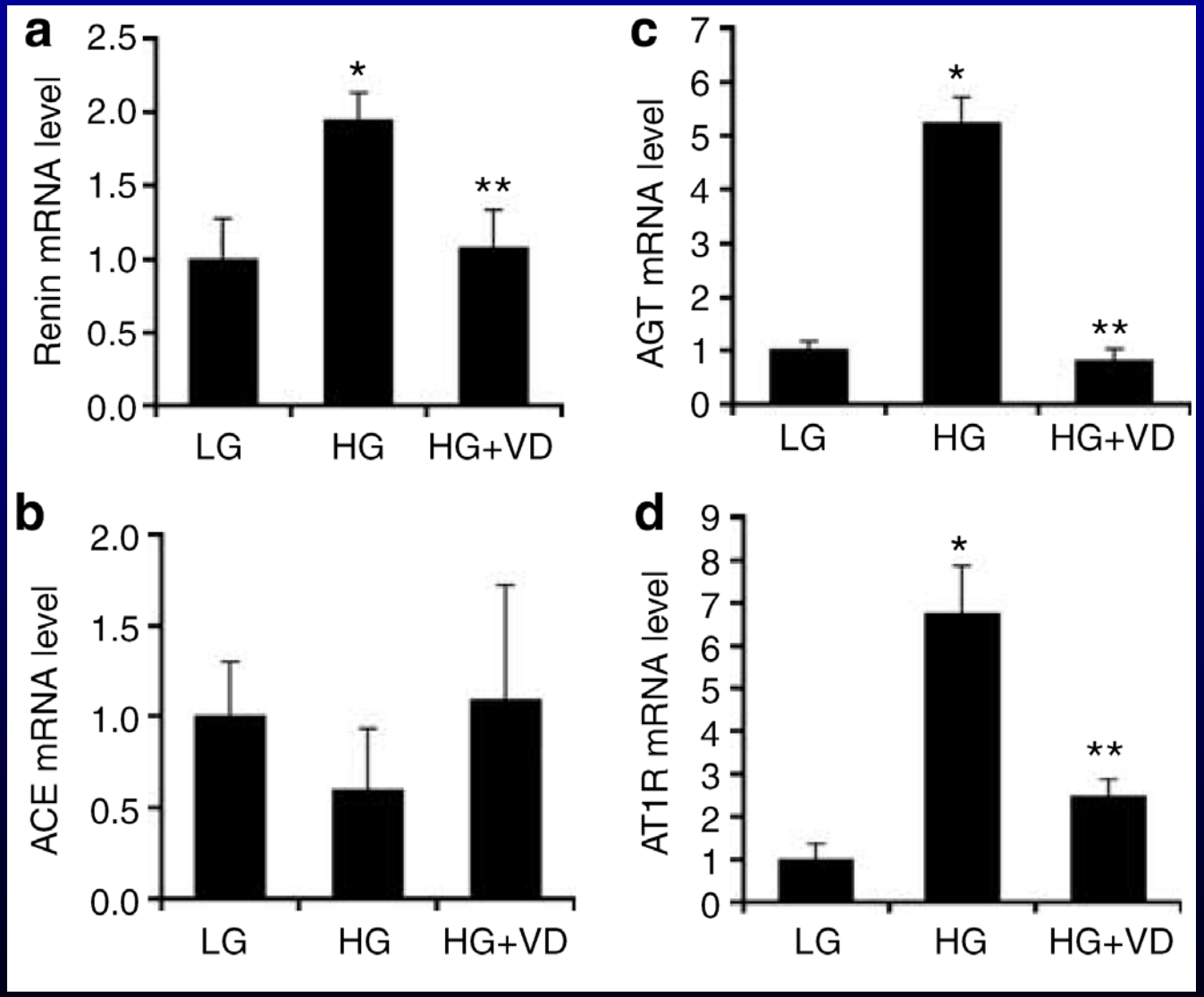
VDR and intrarenal inflammation



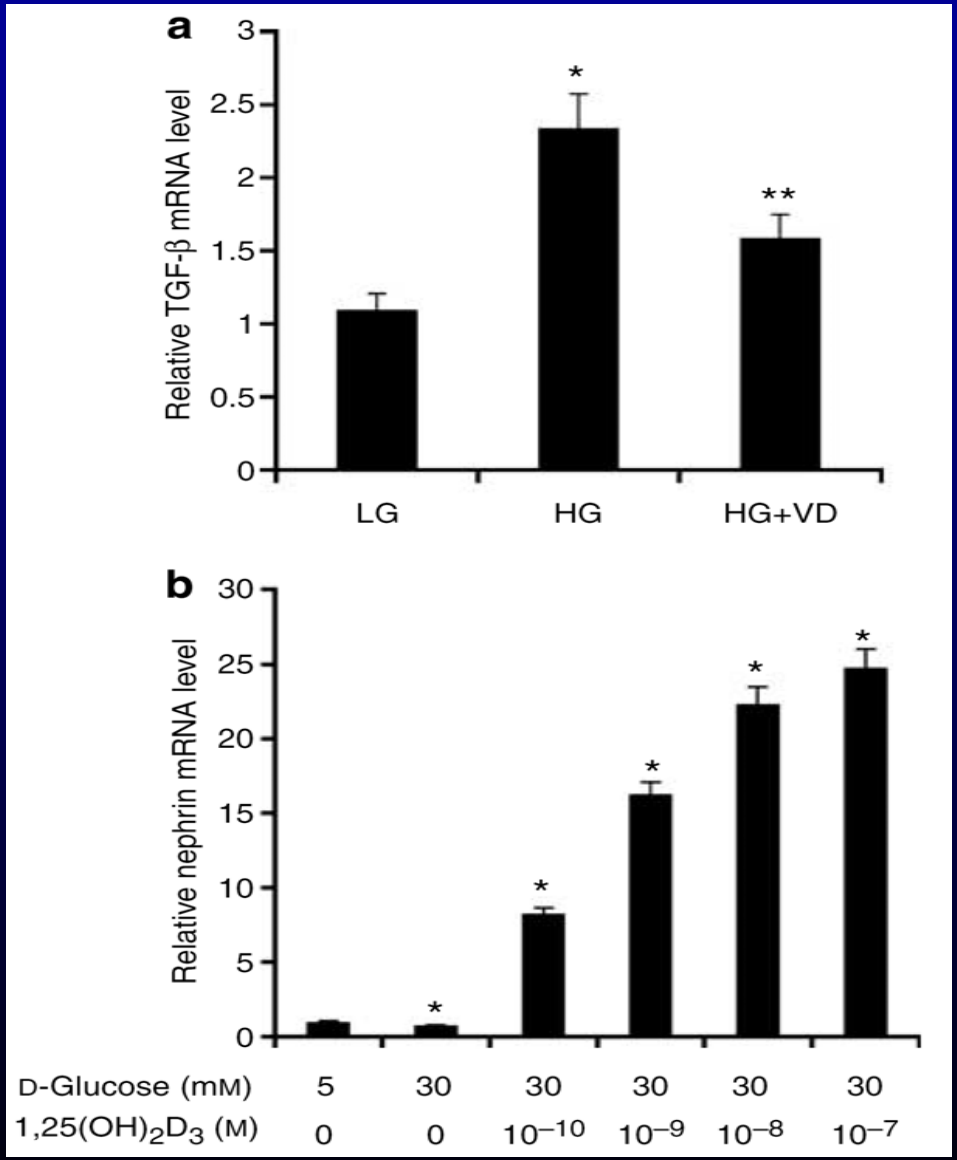
Zhang et al, *Kidney International* 2008;73: 163–171

VDRA and intrarenal RAS expression



Zhang et al, *Kidney International* 2008;73: 163–171

VDRA and TGFβ, nephrin



Zhang et al,
Kidney International 2008;73: 163–171

Selective Vitamin D Receptor (VDR) Activator for Albuminuria Lowering (VITAL) Study in Type 2 Diabetic Nephropathy

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Eligibility Criteria

Key Inclusion Criteria

- Diagnosed with type 2 diabetes on medication for at least 12 months
- Received a stable dose of ACE-inhibitor or ARB for ≥3 months
- eGFR (simplified MDRD) between 15 to 90 mL/min/1.73m^2
- Urinary albumin creatinine ratio (UACR) between 100 to 3000 mg/g creatinine on 3 consecutive first morning void urine samples
- PTH between 35 to 500 pg/mL

Key Exclusion Criteria

- VDR activator therapy within 6 months of screening
- Poorly controlled hypertension (SBP ≥160 mm Hg and/or DBP ≥100 mm Hg)
- History of allergic reaction to paricalcitol or similar drugs
- Primary glomerulonephritis or secondary nephritis
- Acute renal failure within 12 weeks of the Screening Phase

VITAL Study Endpoints

Primary Endpoint (ITT population)

- Percent geometric mean change from baseline to the last on-treatment UACR, comparing the combined paricalcitol dose groups (1 µg/day and 2 µg/day) with placebo

Secondary Endpoints (ITT population)

For the individual paricalcitol doses:

- Percent geometric mean change from baseline to the last on-treatment measurement in 24 hour urine albumin
- Proportion of subjects achieving at least a 15% reduction in the last on-treatment UACR from baseline

Tertiary Endpoints (ITT population)

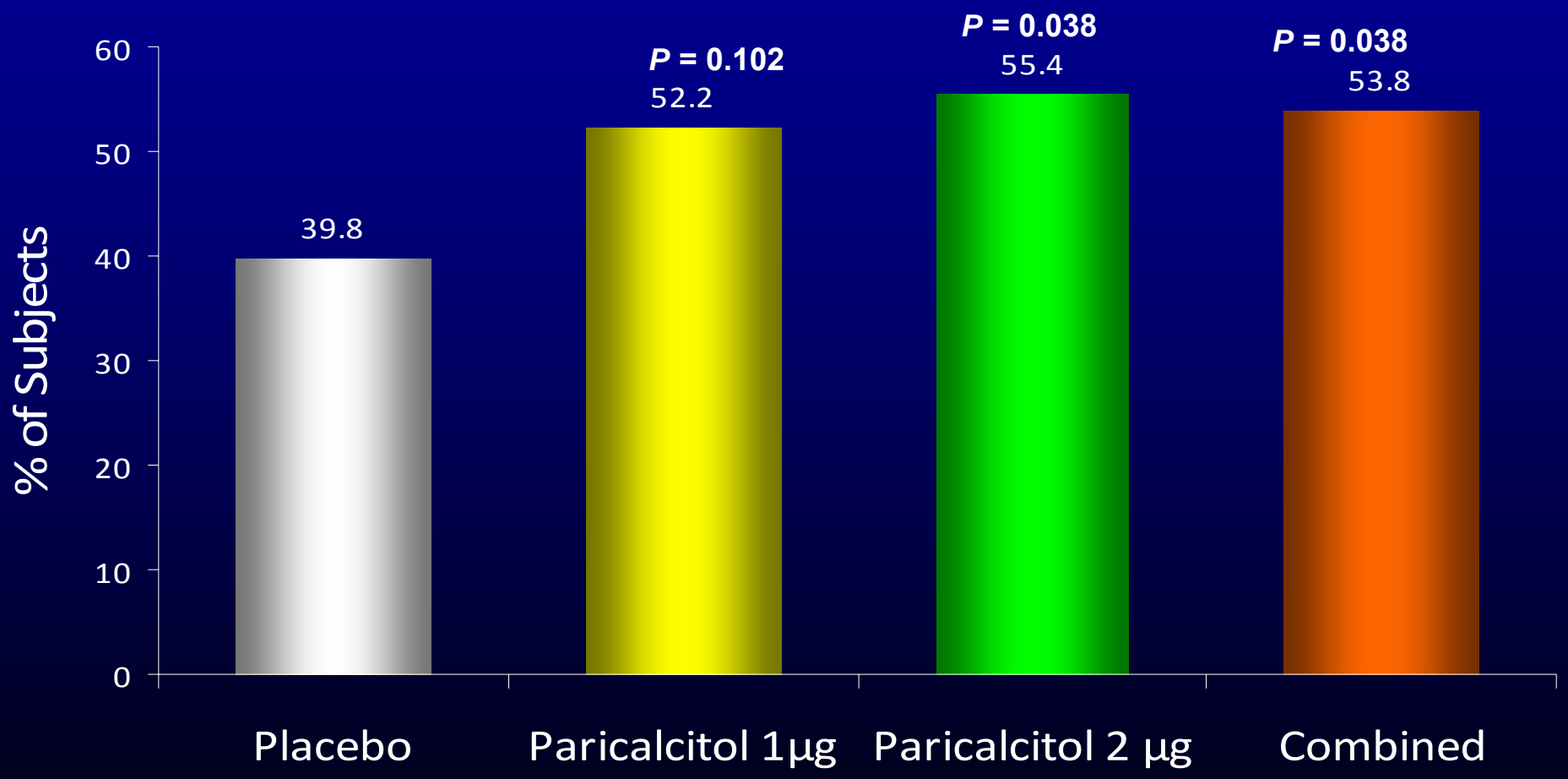
- Change in UACR and eGFR repeated measures analysis
- Change in UACR and eGFR to the 30-day and 60-day post-treatment

VITAL Baseline Characteristics (N=281)

	Placebo (n = 93)	Paricalcitol 1 µg (n = 93)	Paricalcitol 2 µg (n = 95)
Age (years), mean ± SD	64 ± 11	64 ± 10	65 ± 10
Female, n (%)	33 (35)	27 (29)	26 (27)
Race, n (%)			
White	72 (77)	63 (68)	66 (70)
Black	11 (12)	15 (16)	14 (15)
Asian	10 (11)	14 (15)	15 (16)
Other	0 (0)	1 (1)	0 (0)
Blood pressure, mean ± SD			
Systolic blood pressure, (mm Hg)	142 ± 17	142 ±18	141 ± 16
Diastolic blood pressure, (mmHg)	73 ± 12	73 ± 12	73 ± 9
Urinary Indices			
UACR[a], (mg/g creatinine), median [Q1,Q3]	642 [263,1128]	626 [288,1225]	597 [246,1172]
24-hour urinary albumin, (mg/d), median [Q1,Q3]	705 [238,1534]	564 [307,1724]	819 [290,1447]
Serum creat. (mg/dL), mean ±SD	2.0 ± 1	1.9 ± 1	1.9 ± 1
eGFR[b] (ml/min/1.73 m), mean ±SD	39 ± 17	40 ± 15	42 ± 18

[a]UACR=urinary albumin:creatinine ratio
[b]eGFR=estimated glomerular filtration rate

Secondary Endpoint: paricalcitol 2 µg/day increases the percentage of subjects with > 15% reduction in UACR



De Zeeuw et al; submitted

Safety

	Placebo (n = 93)	Paricalcitol 1 µg (n = 93)	Paricalcitol 2 µg (n = 95)
Hypercalcemia (2 consecutive Ca >10.5 mg/dL)	1 (1%)	1 (1%)	3 (3%)
Any Adverse Event	58 (62%)	59 (63%)	63 (66%)
Any Serious Adverse Event	12 (13%)	13 (14%)	19 (20%)
Any Adverse Event Leading to Discontinuation of Study	2 (2%)	4 (4%)	11 (12%)*
Deaths	0 (0%)	0 (0%)	3 (3%)

*P-value = 0.018

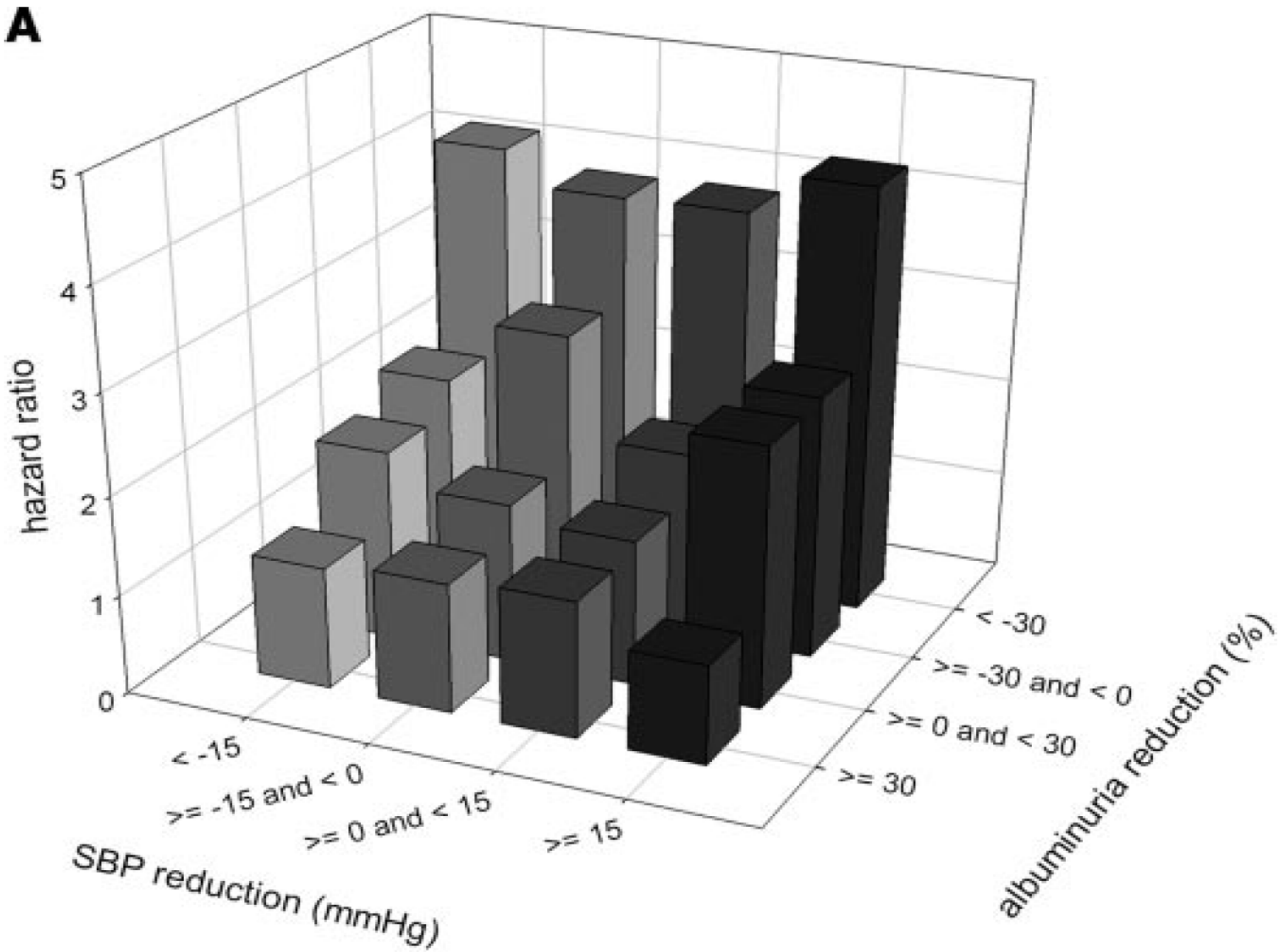
De Zeeuw et al; submitted

Conclusions

- Paricalcitol 2 µg/day lowers albuminuria in patients with diabetic nephropathy who are on stable RAAS blockade.
- Paricalcitol 2 µg/day is most effective during high sodium intake (thus complementing the effect of RAAS blockade which is maximal during low sodium intake)
- Paricalcitol was found to be generally safe and tolerable and was associated with a low incidence of hypercalcemia in this study.
- The albuminuria-lowering effect of paricalcitol 2 µg/day was associated with a reversible fall in eGFR and systolic blood pressure (renoprotective?)
- Selective VDR activation with paricalcitol may be a novel approach to lowering the risk of kidney disease progression when used on top of ACE inhibitor or ARB therapy.

- A post-hoc analysis of RENAAL showed that the risk of ESRD depended on albuminuria reduction and also showed dependence on the residual level of albuminuria, even in patients who reached the current SBP target.

Eijkelkamp WB, et al. J Am Soc Nephrol 2007;18:1540–6



Eijkelkamp WB, et al. J Am Soc Nephrol 2007;18:1540–6