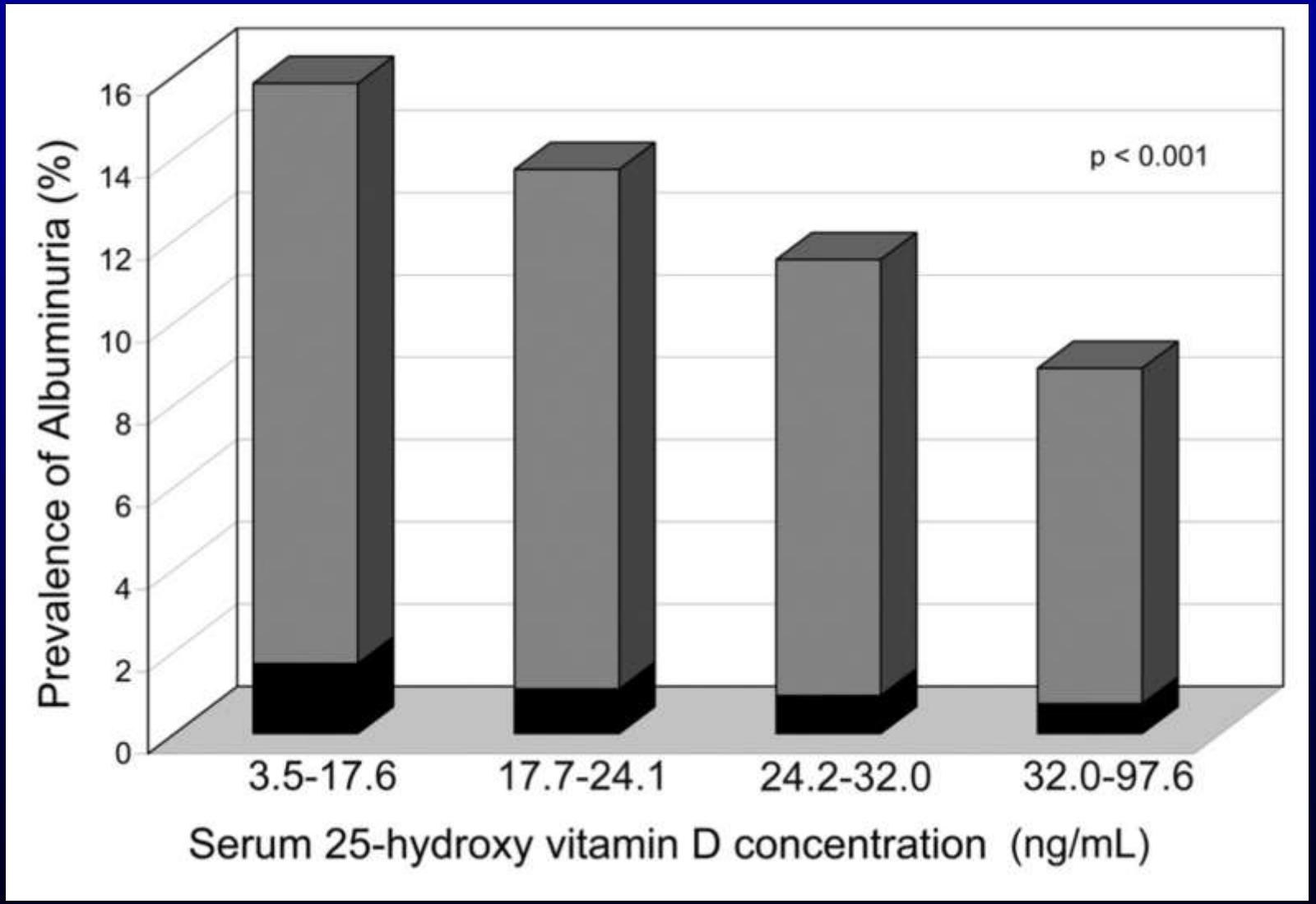
Effective Treatment Strategies to Delay the Progression of Renal Disease in CKD

Csaba P Kovesdy, MD FASN
Salem VA Medical Center, Salem VA
University of Virginia, Charlottesville VA

- Vitamin D
- Metabolic acidosis
- Bardoxolone methyl
- The GI system

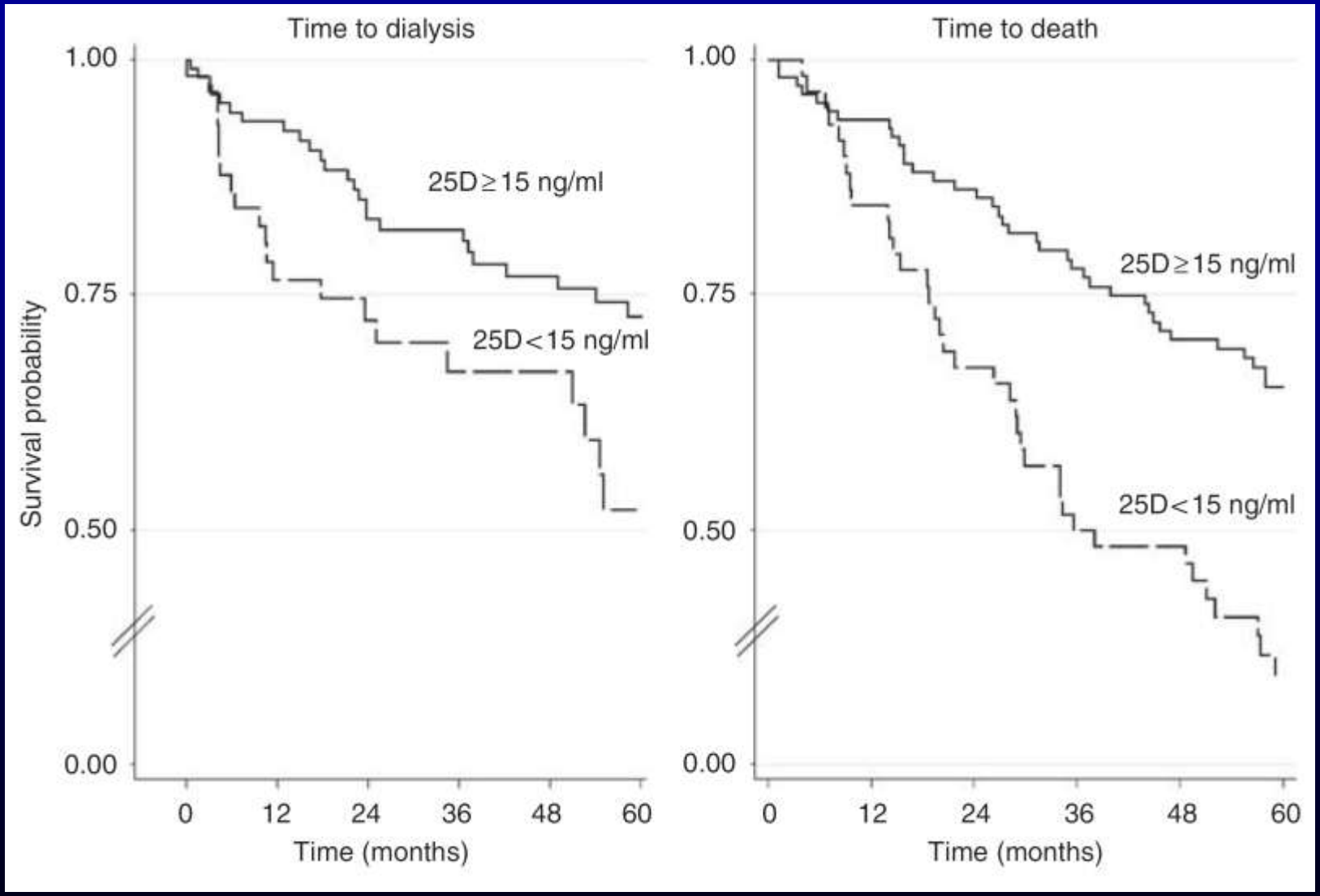
Vitamin D and progression of CKD

25OH vitamin D levels and albuminuria



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

25OHD levels and outcomes in CKD



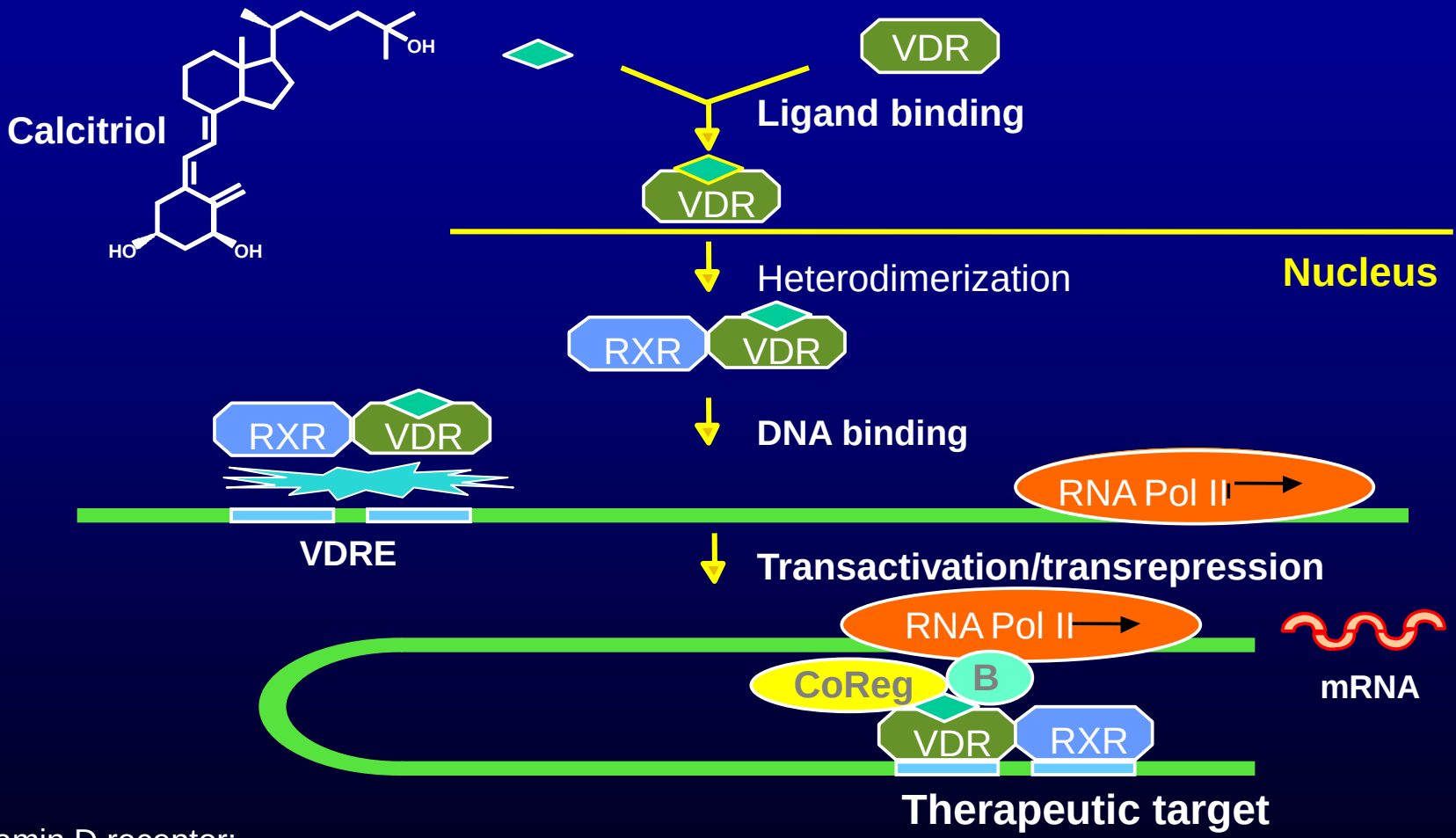
Ravani et al, *Kidney International* 2009; 75:88–95.

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)

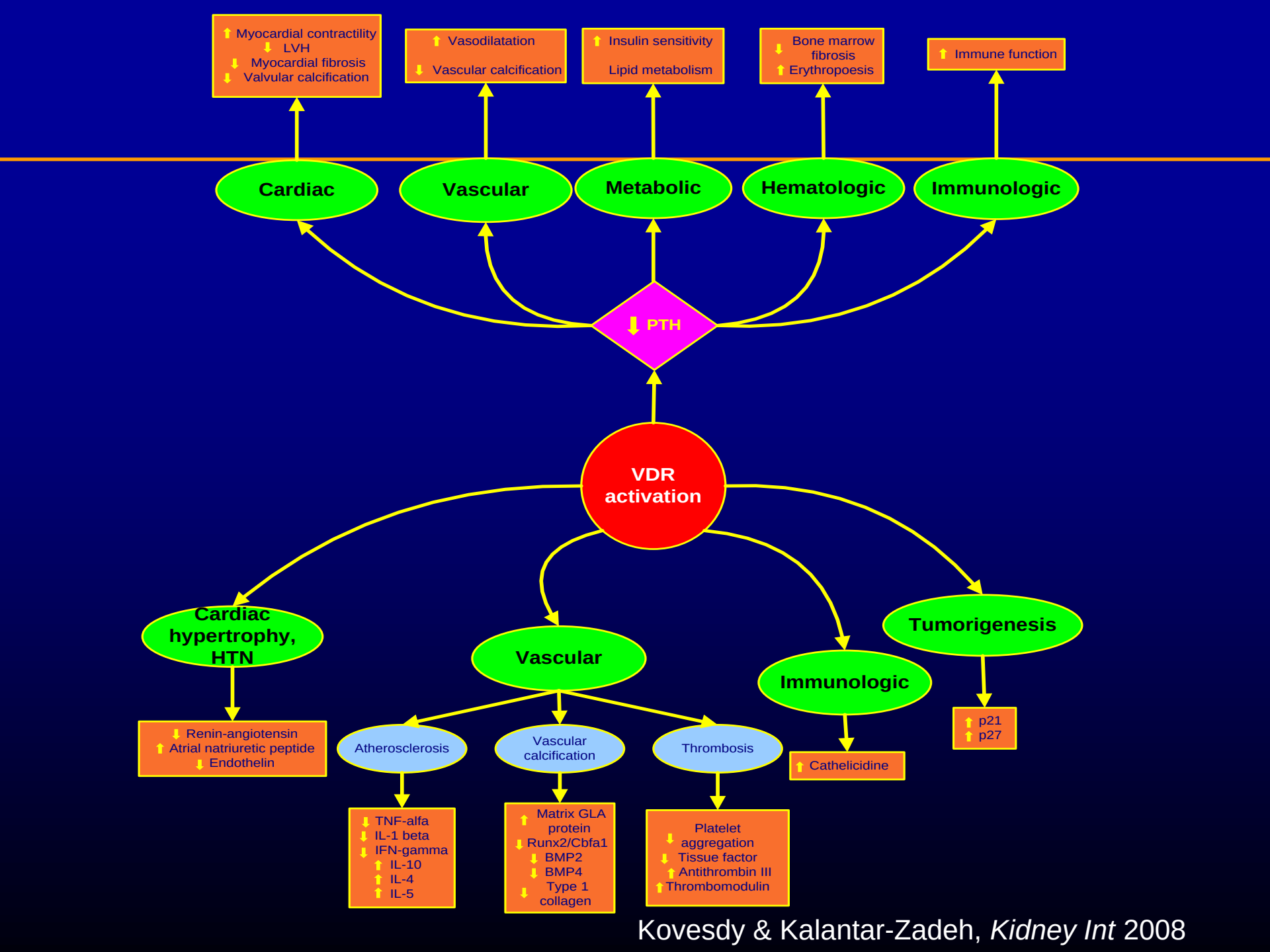
Kovesdy et al, *Arch Intern Med* 2008;168:397-403

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

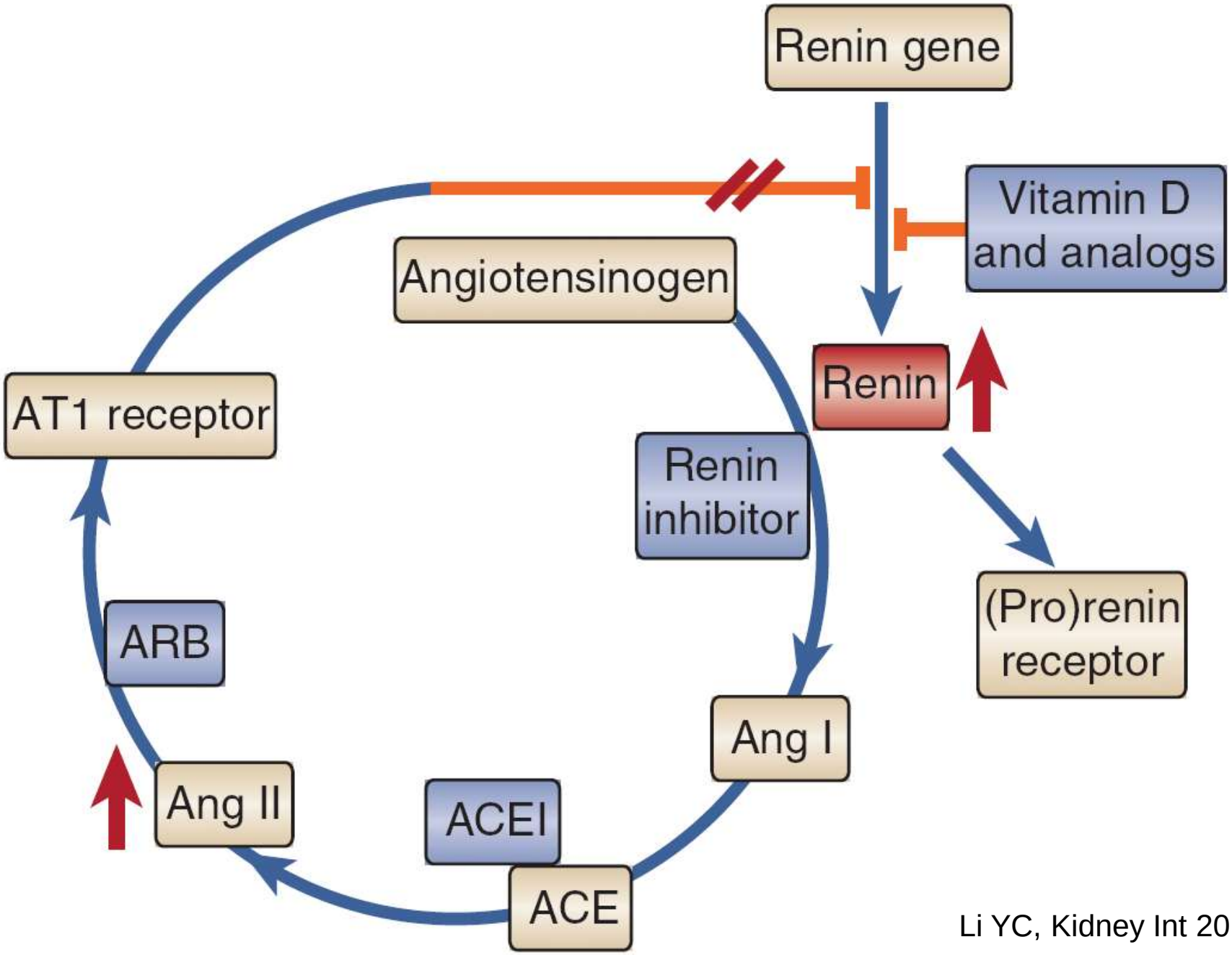


VDR, vitamin D receptor;
VDRE, vitamin D response element;
RXR, retinoid x receptor.

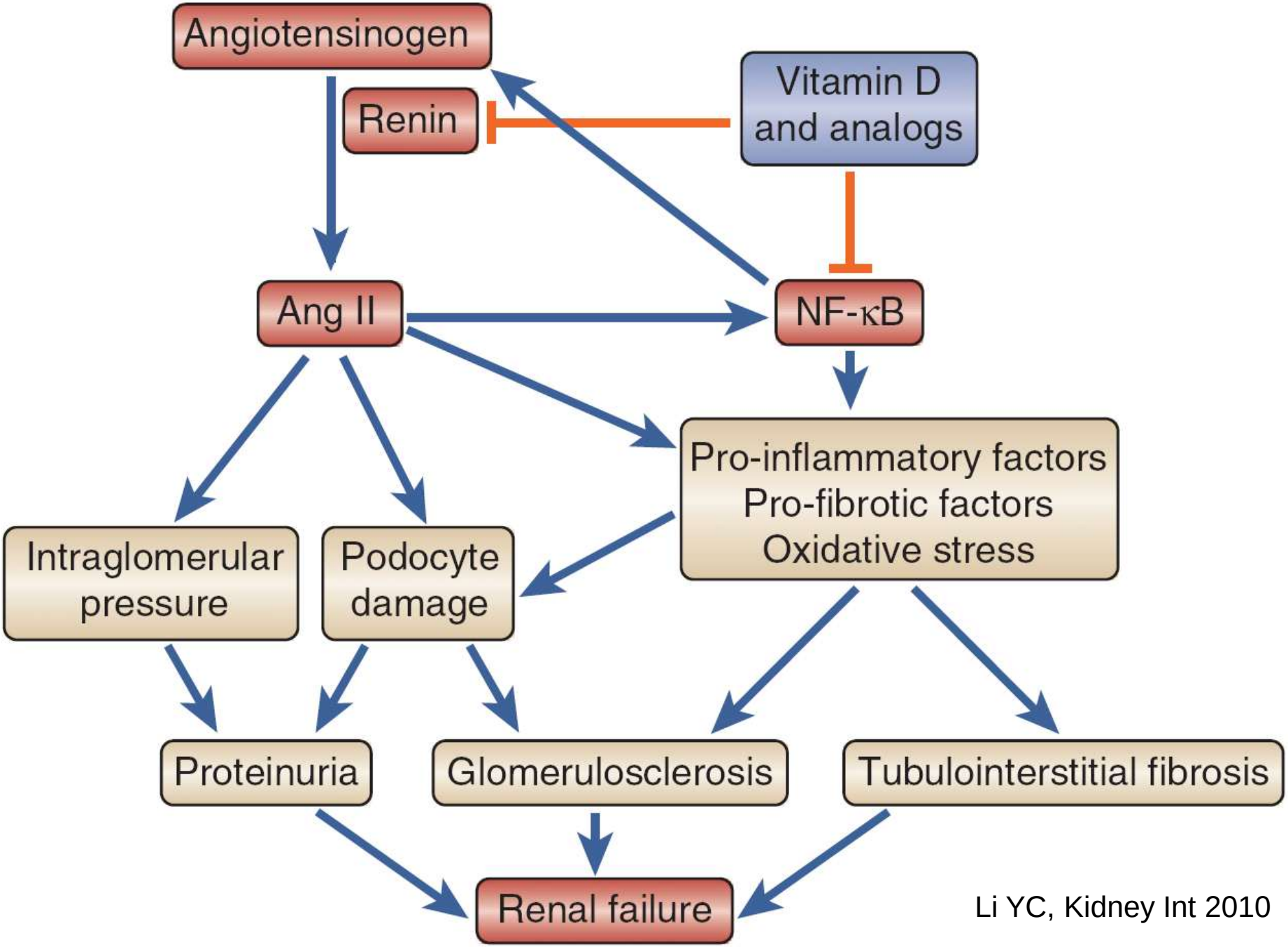
Dusso AS, et al. Semin Nephrol 2004;24:10–16



Kovesdy & Kalantar-Zadeh, *Kidney Int* 2008

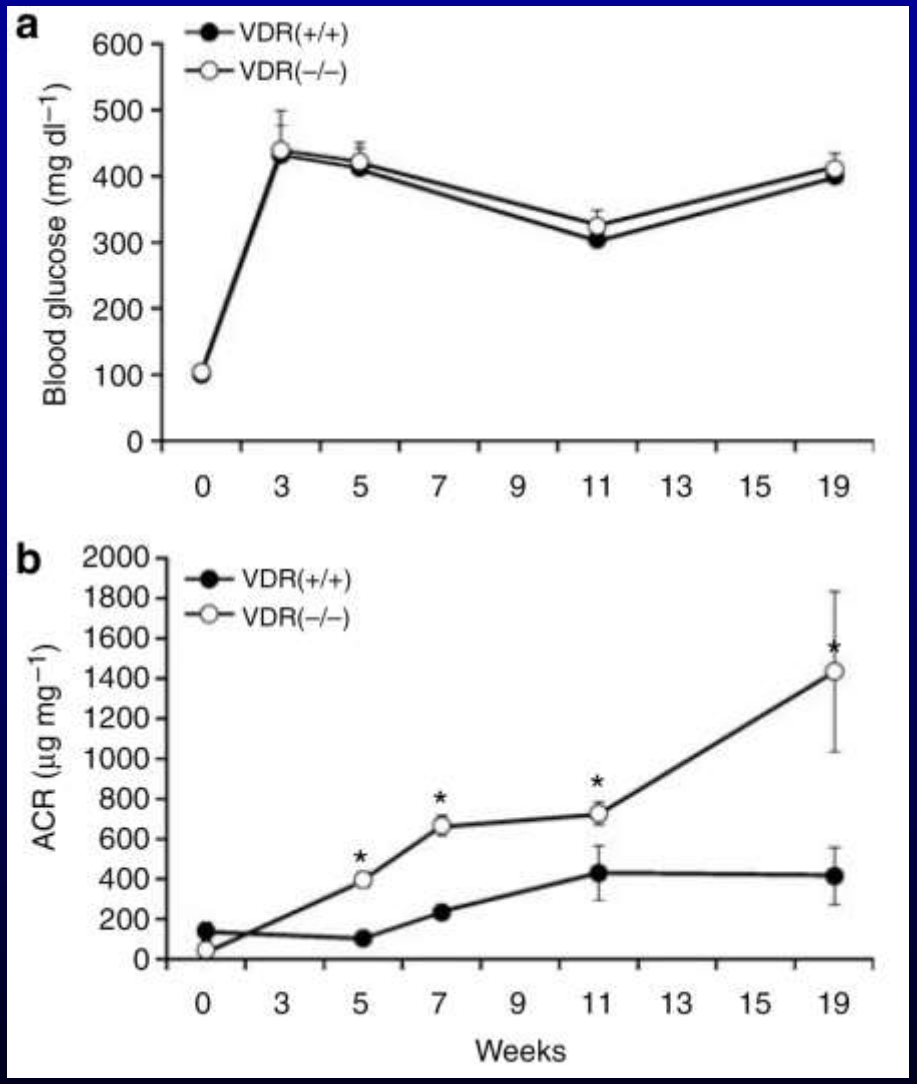


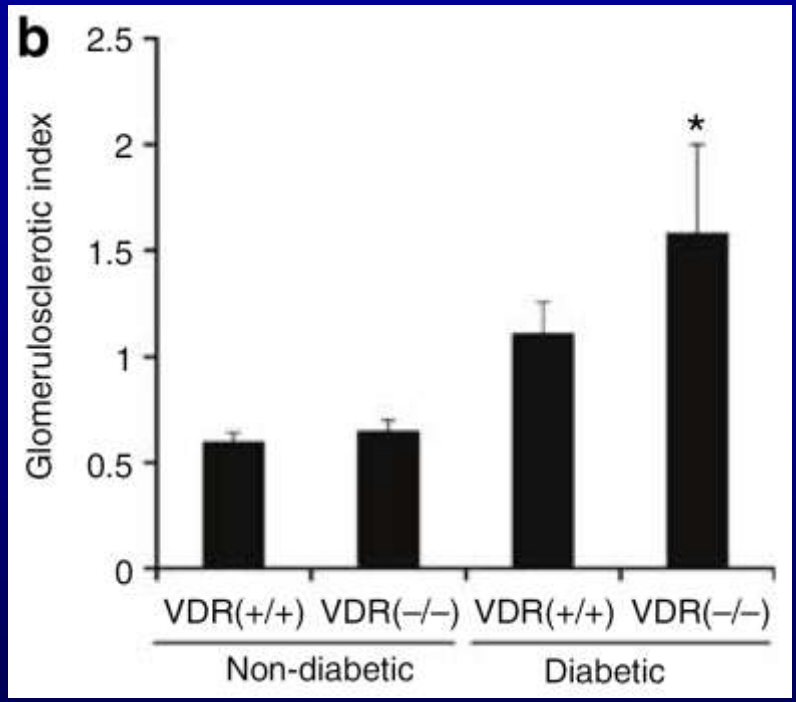
Li YC, Kidney Int 2010



Li YC, Kidney Int 2010

Role of VDR in albuminuria, glomerulosclerosis





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

Clinical trials of VDR for renoprotection

- Small studies using VDR activation show an albuminuria lowering effect

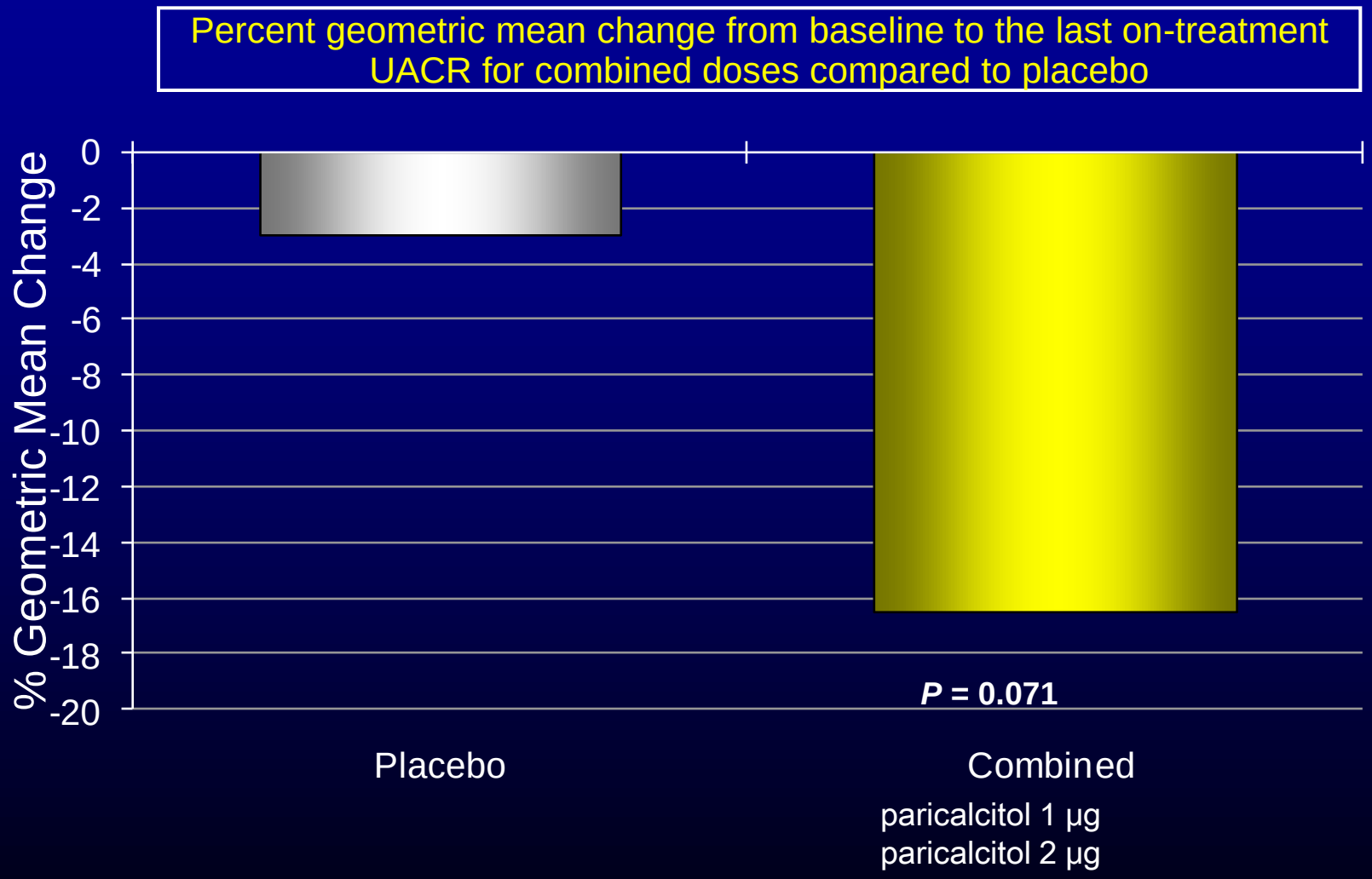
- Paricalcitol may be a therapeutic option for further reduction of albuminuria on top of ACE inhibitor or ARB therapy.

VITAL Study

- Randomized controlled trial
- 281 patients with type 2 DM and albuminuria
- Treated for 24 weeks with
  - Placebo
  - Paricalcitol 1 mg/day
  - Paricalcitol 2 mcg/day
- Primary end point: change in UACR

De Zeeuw et al; Lancet 2010

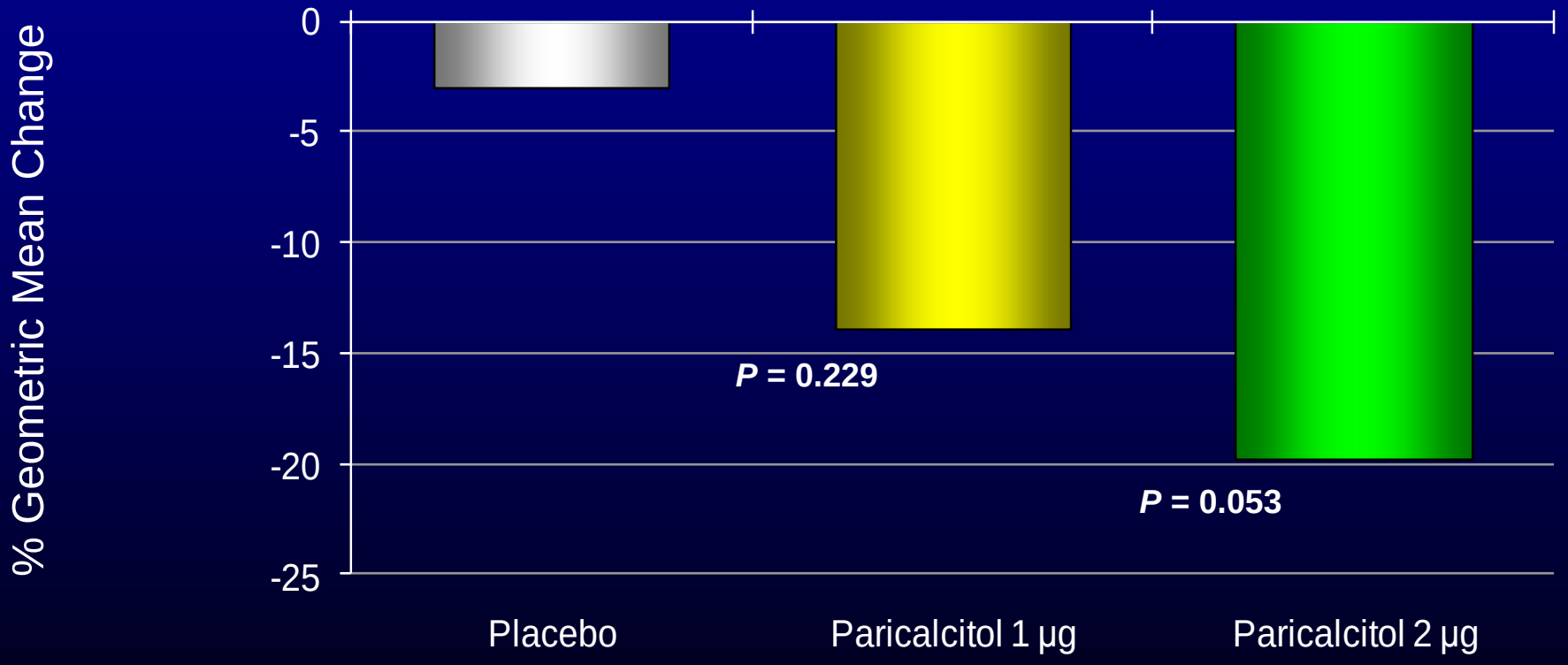
Primary Endpoint: Effect of paricalcitol on UACR



De Zeeuw et al; Lancet 2010

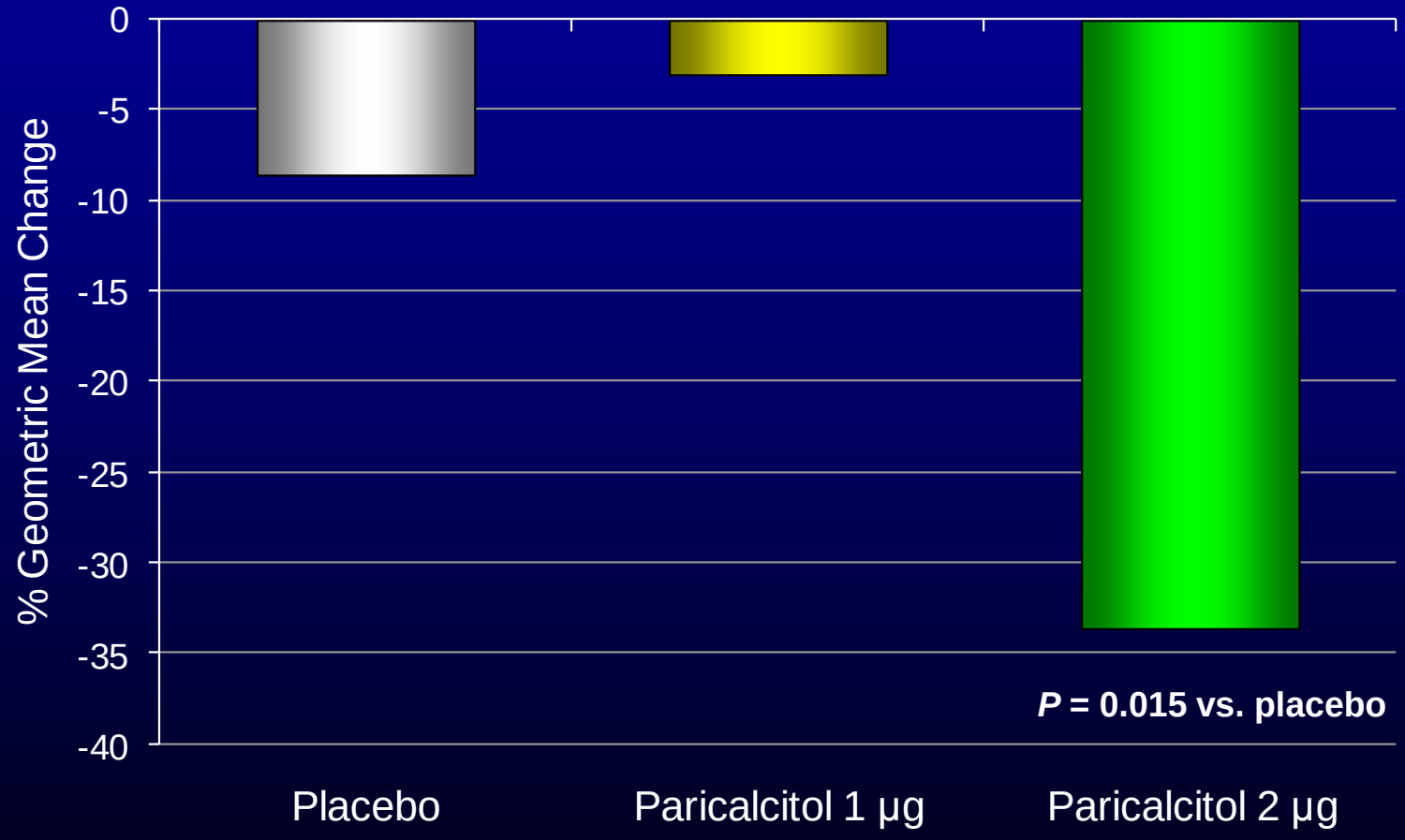
Secondary Endpoint: Effect of paricalcitol doses on UACR

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



De Zeeuw et al; Lancet 2010

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

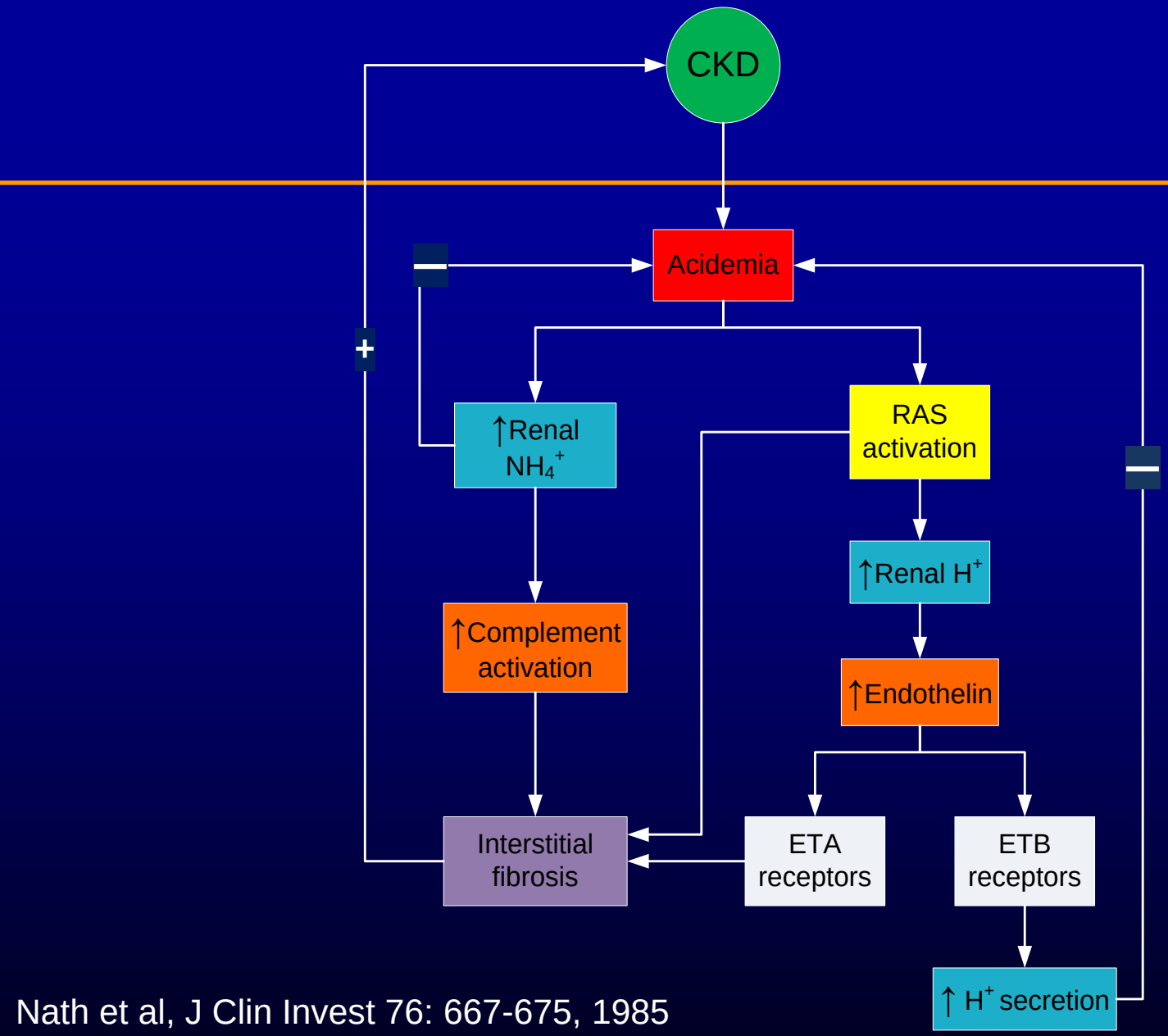


De Zeeuw et al; Lancet 2010

Conclusions – Vitamin D

- Lower vitamin D levels are associated with albuminuria and higher risk of progressive CKD
- Vitamin D receptor activation leads to suppression of RAAS
- Paricalcitol 2 µg/day lowers albuminuria in patients with diabetic nephropathy who are on stable RAAS blockade
- 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

Metabolic acidosis and progression of CKD



Nath et al, J Clin Invest 76: 667-675, 1985
Phisitkul et al, Kidney Int 73: 192–199, 2008
Ng et al, Am J Nephrol 2011;34:55–63
Simon & Hamm, Kidney Int 77: 567 – 569, 2010

W-PO20020

THE EFFECT OF METABOLIC ACIDOSIS ON THE RATE OF DECLINE OF GLOMERULAR FILTRATION RATE IN PATIENTS WITH STAGE 4 CHRONIC KIDNEY DISEASE

IONE DE BRITO ASHURST[1], MIRA VARAGUNAM[2], MARTIN J RAFTERY[2], STAN FAN[2], MOHAMMED MAGDI YAQOOB[2]

Barts and The London NHS Trust[1], Royal London Hospital[2]

- Patients with CKD stage 4:
  - 35 patients with serum bicarbonate 15-20 vs.
  - 55 patients with serum bicarbonate >20
- Followed for 2 years.
- Slope steeper in low bicarbonate group: 20.50 ± 1.09 to 13.92 ± 0.99 ml/min, vs. 19.79 ± 0.93 to 17.13 ± 0.88 ml/min.
- Difference not seen in diabetics.

De Brito-Ashurst et al, *Nephrology 10 (SUPPL.): A248, 2005*

Clinical trials of alkali therapy - 1

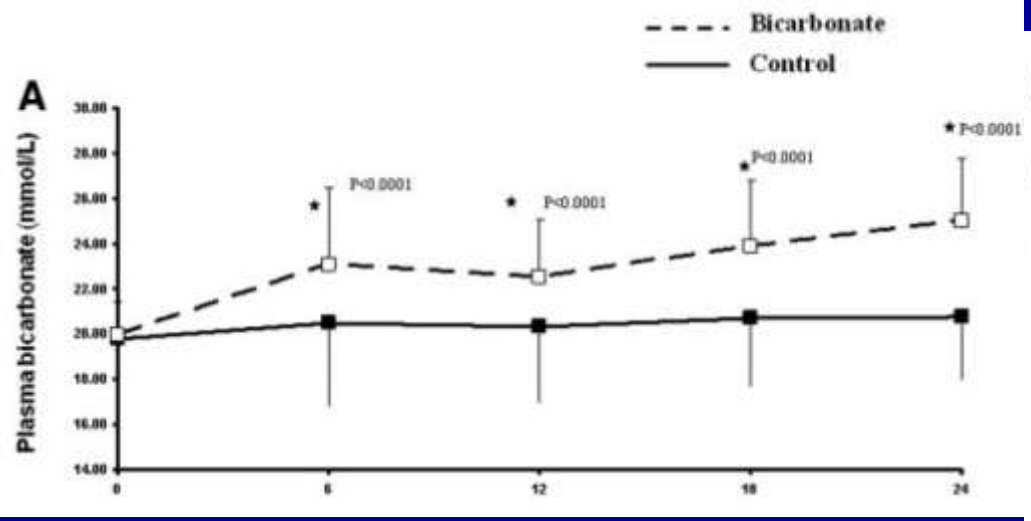
- 134 patients with CKD (CrCl 15 to 30 ml/min) and serum bicarbonate 16 to 20 mmol/L.
- Randomized to oral Na bicarbonate supplementation vs. standard care (open label).
- Intervention: sodium bicarbonate tablets 600 mg 3x/d titrated to achieve and maintain HCO_3 level 23 mmol/L.
- Duration 2 yrs.

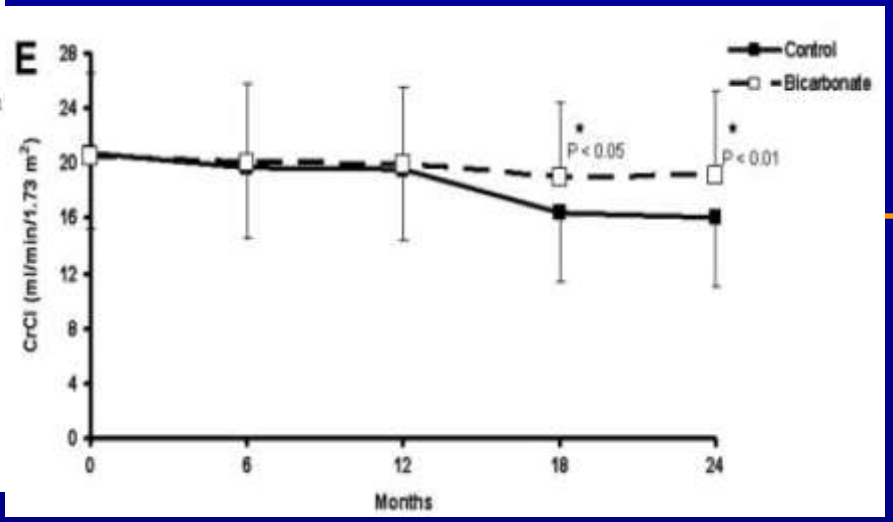
de Brito-Ashurst et al, J Am Soc Nephrol 20: 2075–2084, 2009

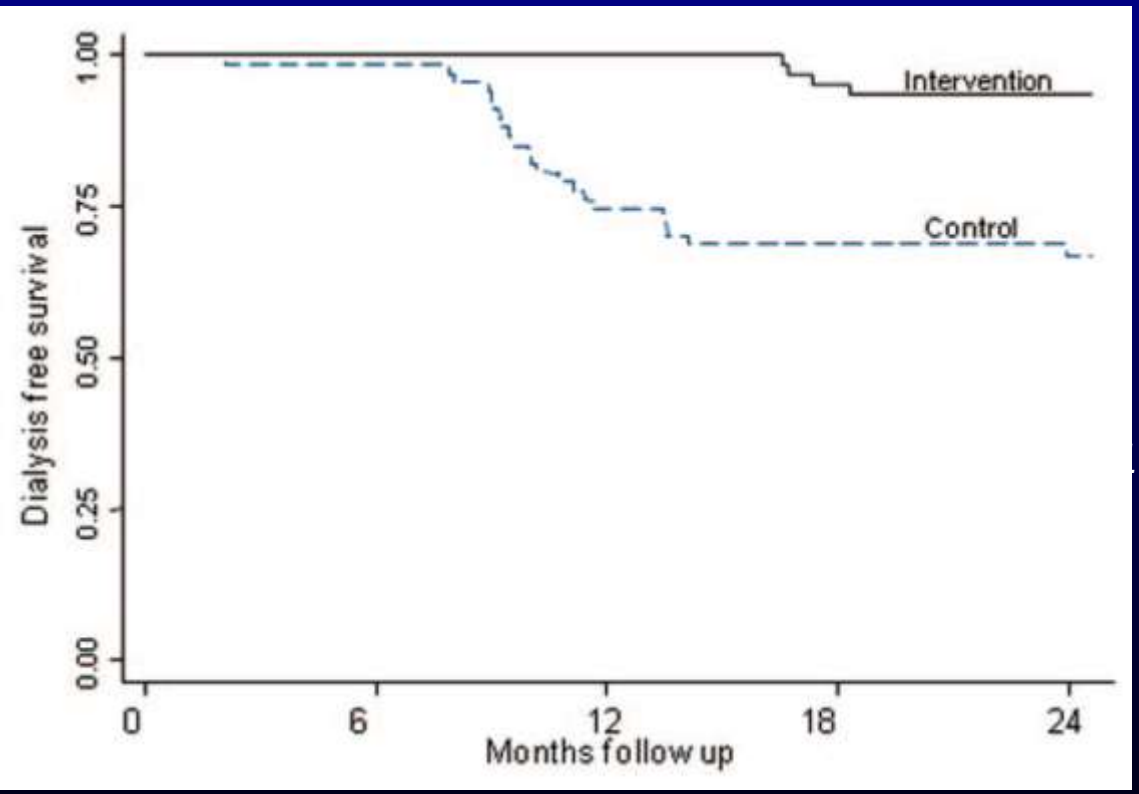
Clinical trials of alkali therapy - 1

- Primary end points
  - rate of CrCl decline
  - proportion of patients with rapid decline of CrCl (3 ml/min/yr)
  - ESRD (CrCl 10 ml/min)
- Secondary end points
  - dietary protein intake
  - normalized protein nitrogen appearance
  - serum albumin
  - mid-arm muscle circumference.

de Brito-Ashurst et al, J Am Soc Nephrol 20: 2075–2084, 2009







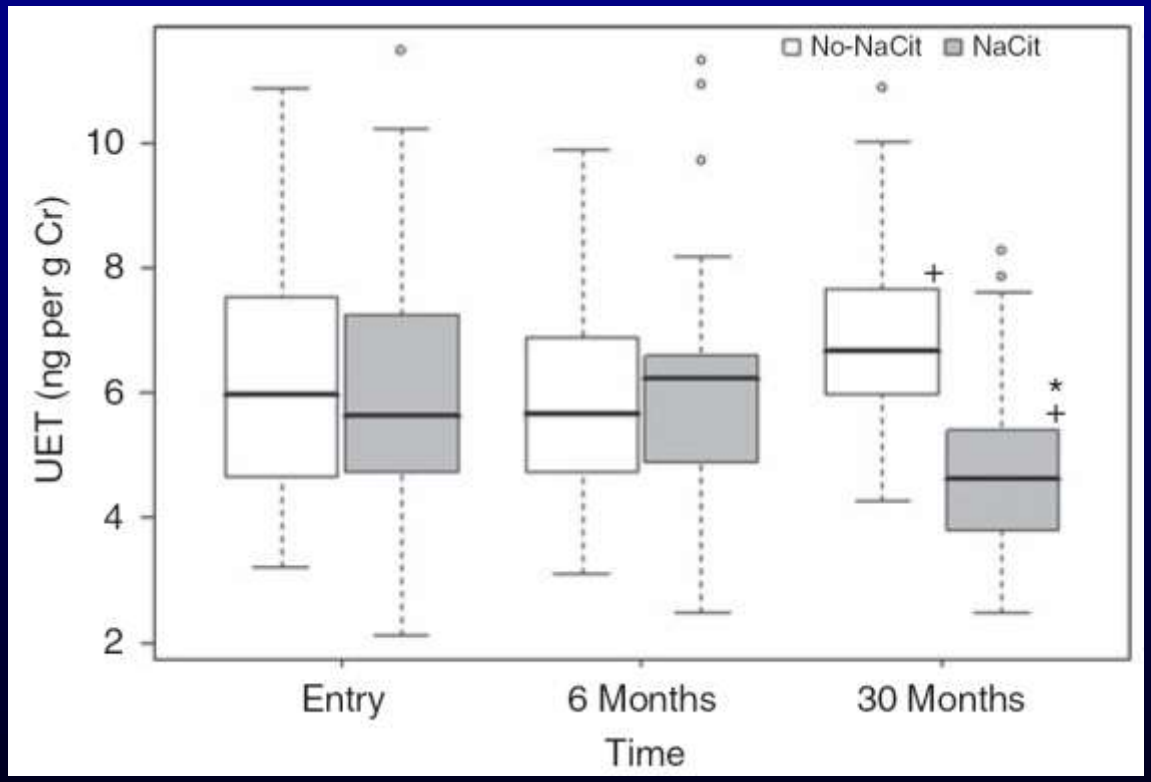
de Brito-Ashurst et al, J Am Soc Nephrol 20: 2075–2084, 2009

Clinical trials of alkali therapy - 2

- 59 patients with hypertensive nephropathy, eGFR 20-60 ml/min and serum bicarbonate <22 mM/l.
- All patients were offered treatment with Na citrate 1 meq of HCO_3 equivalent/kg BW/d in three divided doses
  - 30 accepted treatment: intervention arm
  - 29 did not accept treatment: control arm
- 24 months of therapy
- Primary end point: urine ET-1
- Secondary end points: markers of kidney injury and eGFR

Phisitkul et al, Kidney Int 77: 617–623, 2010

	Month 6	Month 30	*P*-value, 30 vs 6 months	Month 6	Month 30	*P*-value, 30 vs 6 months	Month 6	Month 30
SBP	132.1 ± 6.3	131.9 ± 3.8	0.870	132.4 ± 6.2	132.7 ± 5.7	0.761	0.839	0.490
Pcr (mg/dl)	3.30 ± 0.91	4.24 ± 1.55	<0.0001	3.31 ± 0.69	3.61 ± 0.78	<0.0001	0.954	0.057
eGFRcr (ml/min)	32.5 ± 8.3	24.9 ± 9.7	<0.0001	32.7 ± 8.2	29.5 ± 8.8	<0.0001	0.945	0.066
Pcys (mg/l)	3.94 ± 1.10	5.24 ± 1.41	<0.0001	3.93 ± 0.80	4.33 ± 0.89	<0.0001	0.952	0.005
eGFRcys (ml/min)	31.7 ± 7.9	23.0 ± 6.05	<0.0001	31.4 ± 8.2	27.8 ± 7.4	<0.0001	0.885	0.008



- Rate of eGFR decline lower
- Urine excretion of endothelin lowe
- Urine NAG, urine albumin lower

Phisitkul et al, Kidney Int 77: 617–623, 2010

Clinical trials of alkali therapy - 3

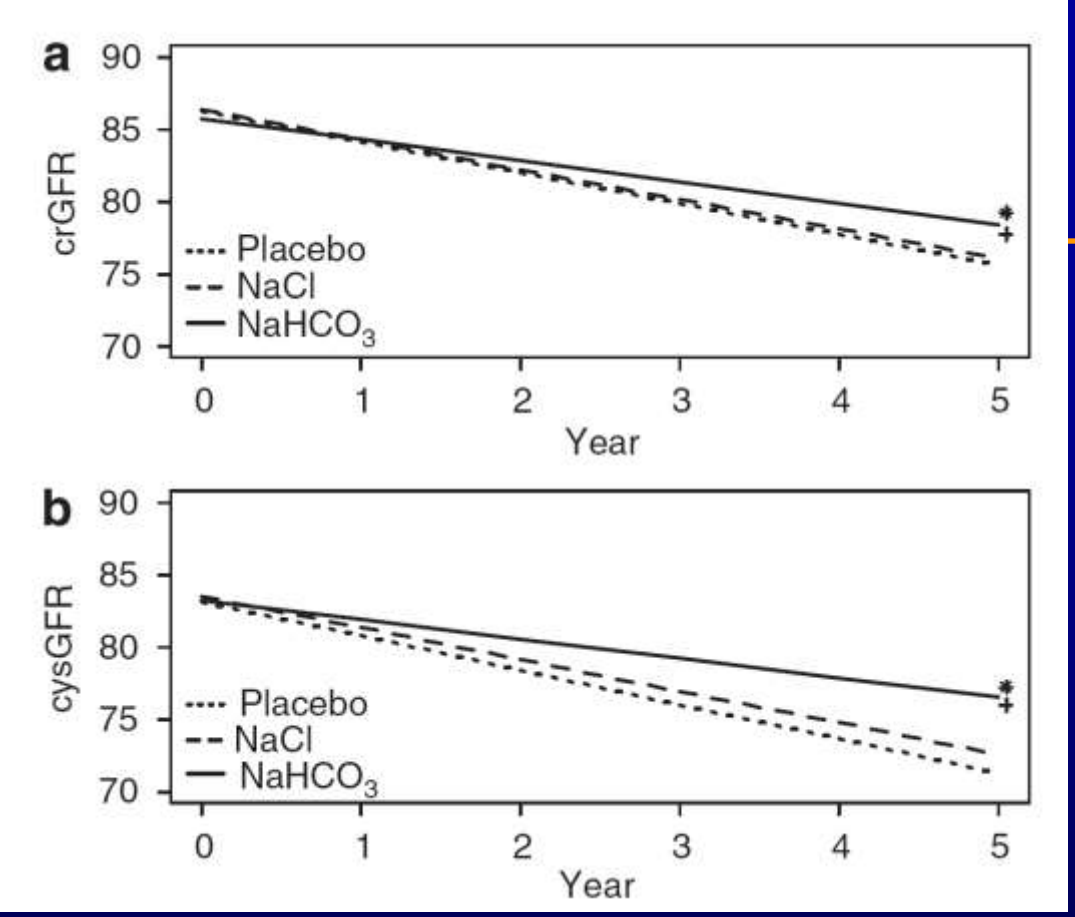
- 120 patients with hypertensive nephropathy (eGFR 75±6 ml/min, CKD stage 2) and macroalbuminuria
- Plasma total carbon dioxide of at least 24.5mM/l.
- Randomized to oral Na bicarbonate (40) vs. oral NaCl (40) vs. placebo (40) after matching for age, eGFR, albuminuria and ethnicity.
- Patients received placebo or 0.5 mEq/kg LBW daily of $NaHCO_3$ or NaCl

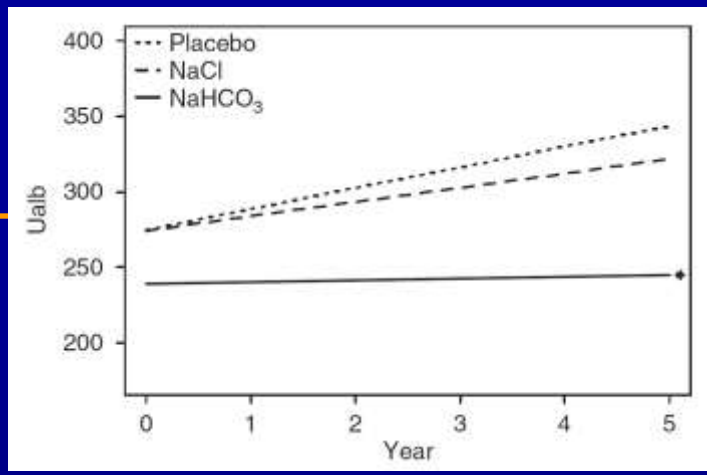
Mahajan et al, Kidney Int 78:303–309, 2010

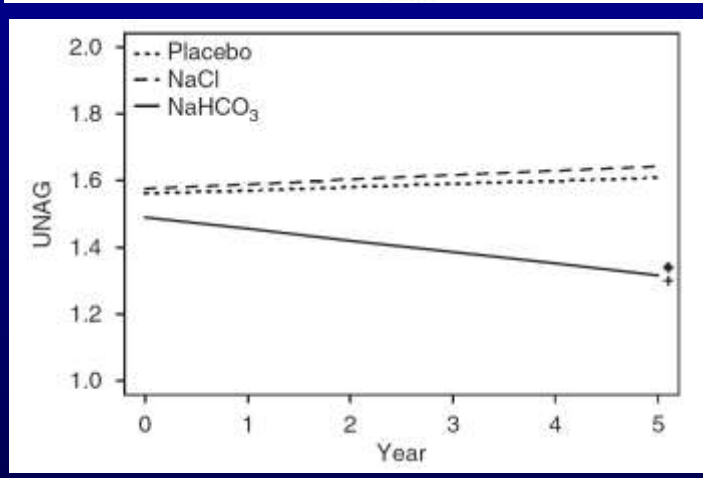
Clinical trials of alkali therapy - 3

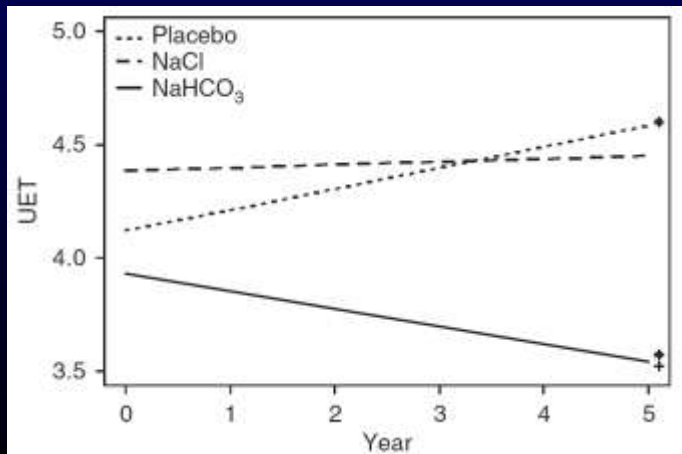
- BP was controlled using primarily ACEI/ARB
- Duration 5 yrs.
- Primary end point: reduction in the rate of eGFR decline in the $NaHCO_3$ group compared with the placebo and NaCl groups.
- Secondary end points: UET, Ualb, and UNAG

Mahajan et al, Kidney Int 78:303–309, 2010









Mahajan et al, Kidney Int 78:303–309, 2010

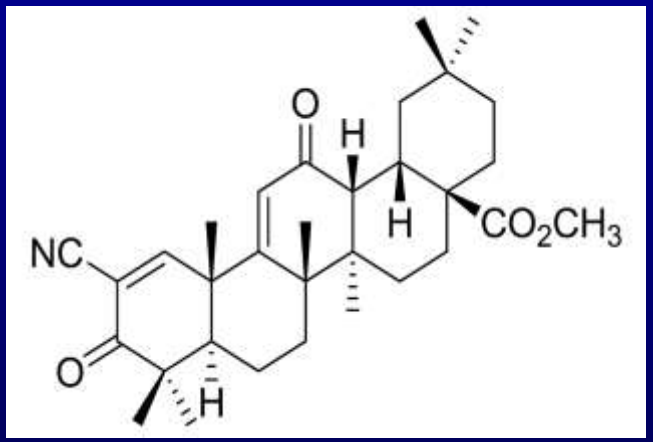
Conclusions – Metabolic acidosis

- Metabolic acidosis causes kidney damage through complex metabolic pathways, which can be abrogated by bicarbonate administration.
- Treatment of metabolic acidosis with bicarbonate supplementation can delay progression of CKD.
- Bicarbonate supplementation could also be used in patients without manifest metabolic acidosis. Further studies are needed to clarify the risks and benefits from the broad application of alkali therapy.

Bardoxolone methyl and progressive CKD

Bardoxolone methyl

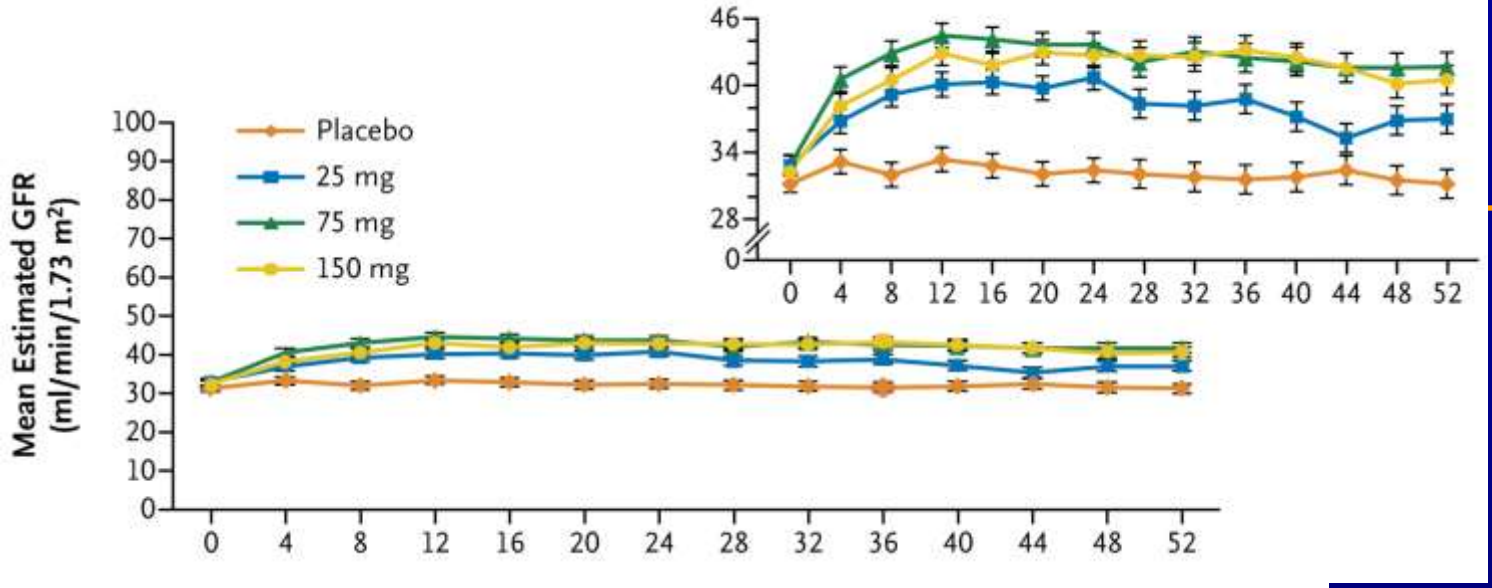
- antioxidant inflammation modulator
- activates the Keap1–Nrf2 pathway
- structure and activity profile of bardoxolone methyl resemble those of the cyclopentenone prostaglandins, endogenous Nrf2 activators that promote the resolution of inflammation
- exerts antiinflammatory effects by inhibiting the proinflammatory nuclear factor κB pathway

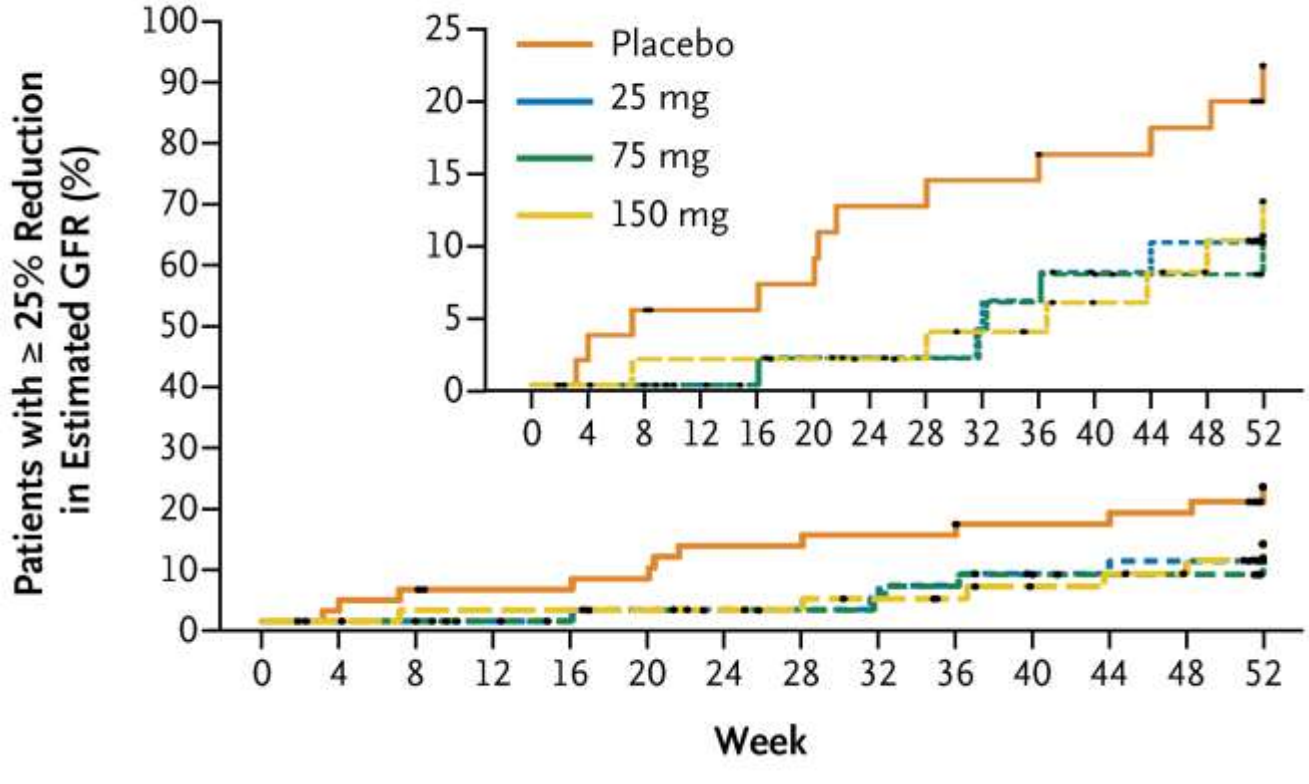


BEAM Study

- 227 patients with diabetic nephropathy (eGFR 20-45)
- Had to be on ACEI/ARB
- Randomized to
  - Placebo
  - 25 mg bardoxolone methyl
  - 75 mg bardoxolone methyl
  - 150 mg bardoxolone methyl
- Primary outcome: change in eGFR in bardoxolone vs. placebo at 24 weeks.

Pergola et al, N Engl J Med 2011; 365:327-336



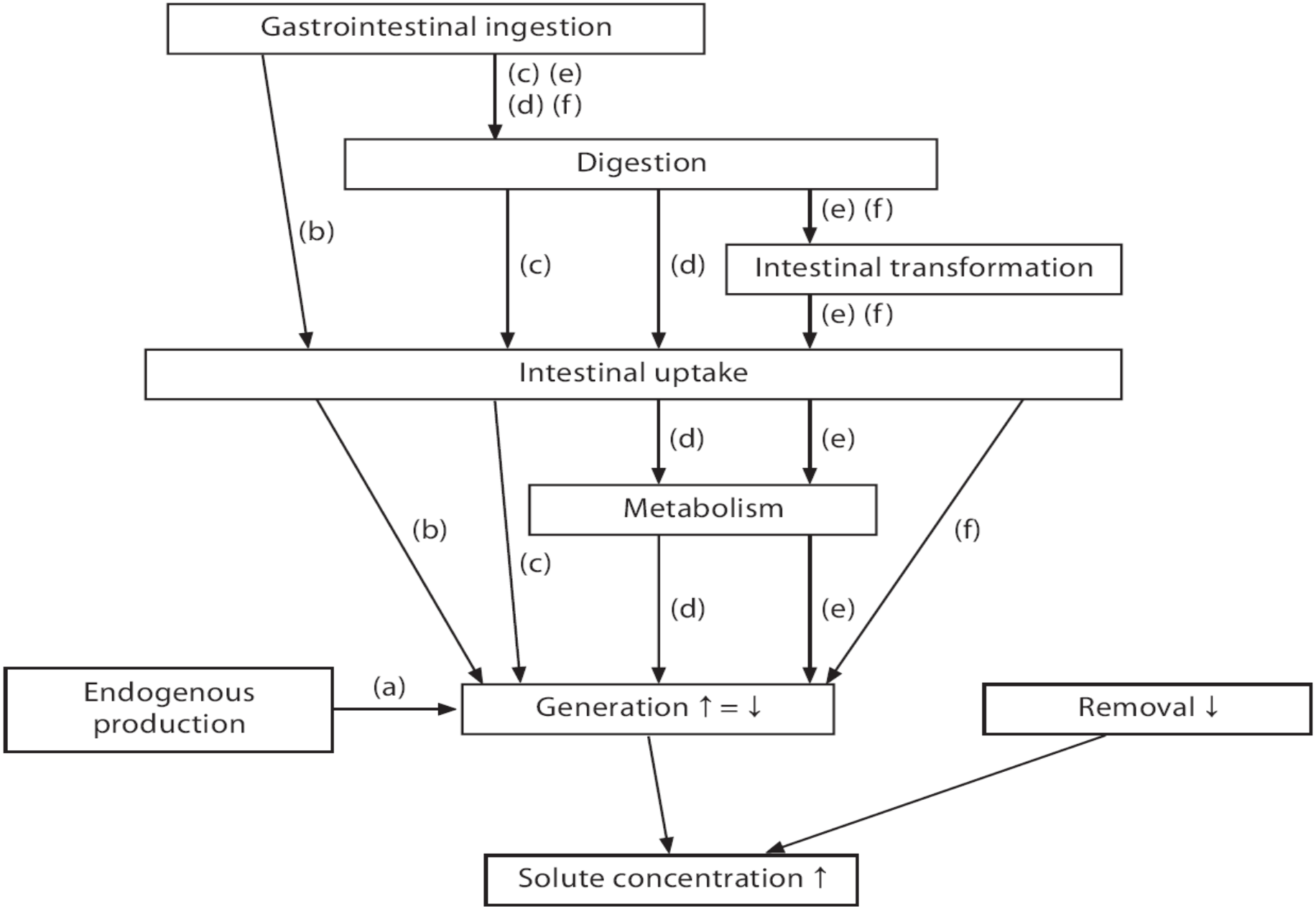


Pergola et al,
N Engl J Med
2011; 365:327-336

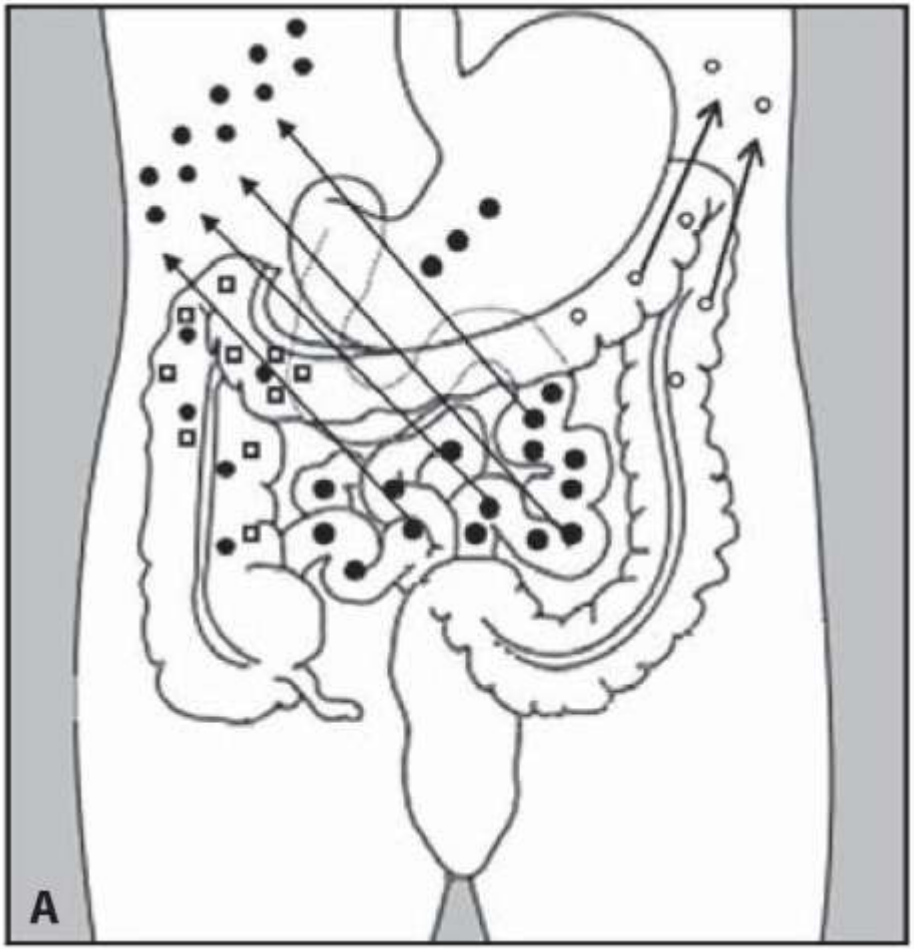
Conclusions – Bardoxolone methyl

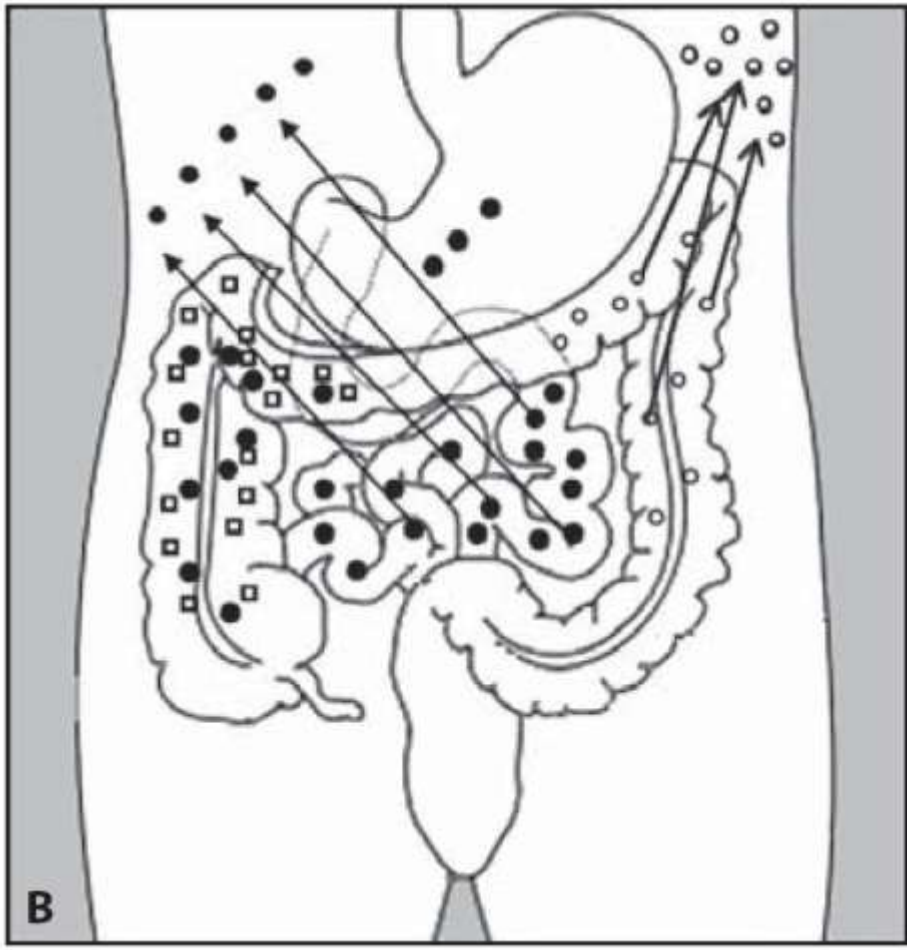
- Treatment with bardoxolone methyl for 52 weeks led to sustained improvement in eGFR among patients receiving standard medical care for CKD
- An ongoing study is examining its effect on ESRD incidence (BEACON)
- Unclear if these results can be extrapolated to non-diabetic patients

The GI system and progression of CKD

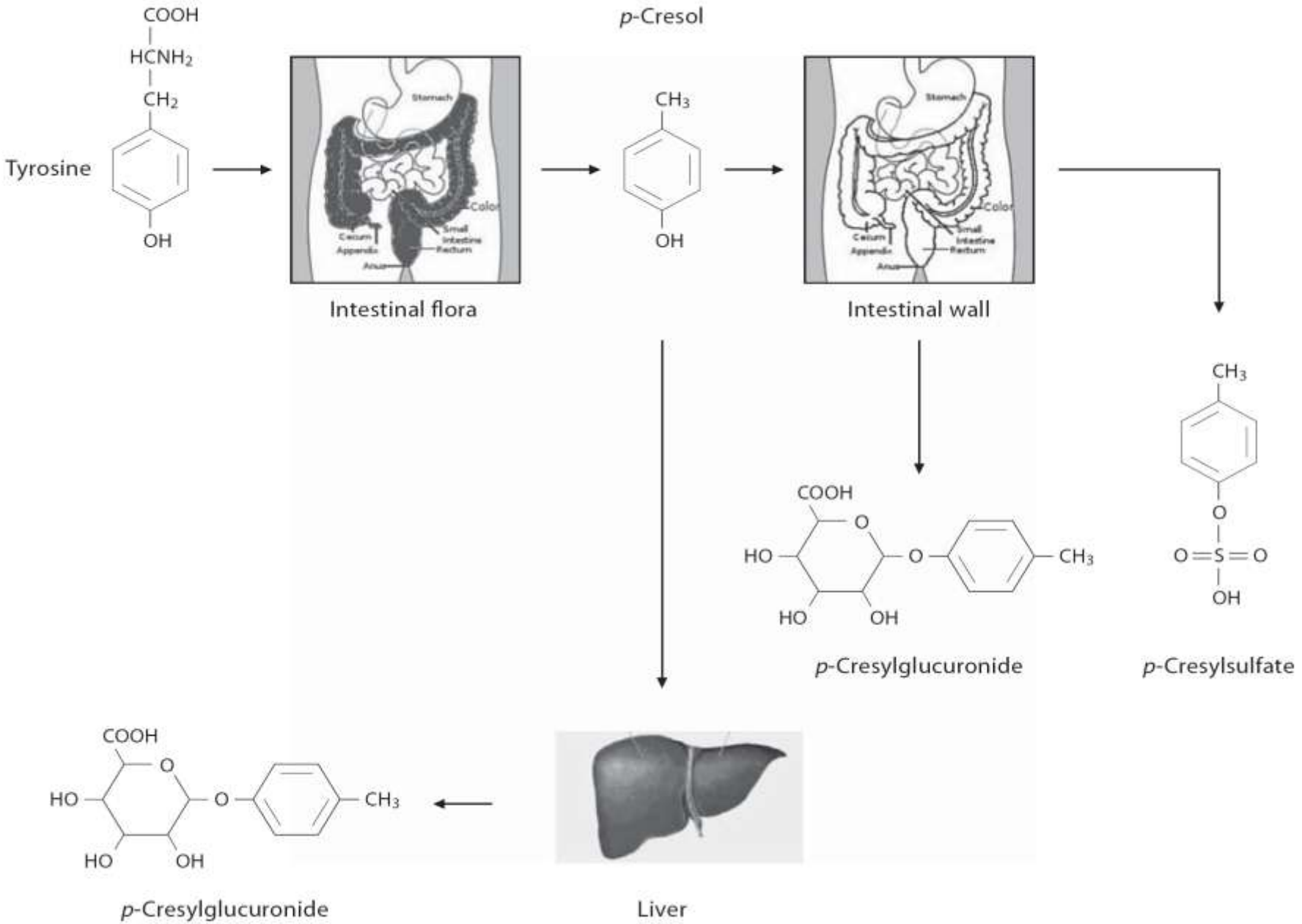


Schepers et al, Blood Purif 2010;29:130–136





Schepers et al, Blood Purif 2010;29:130–136



Schepers et al, Blood Purif 2010;29:130–136

Method	Target molecule	Outcome
Diet	AGEs, phenol, indoles	decrease concentration
Prebiotics		
Gum arabic fiber	urea	decrease concentration
Oligofructose-enriched inulin	*p*-cresol	decrease concentration
Lactulose	*p*-cresol	decrease concentration
Resistant starch	phenol	decrease concentration
Probiotics		
Urease-positive bacteria	urea	decrease concentration
Lactobacillus	urea, *p*-cresol	decrease concentration
Bifidobacterium	*p*-cresol	decrease concentration
Lactic acid bacteria	*p*-cresol, phenols indoles	decrease concentration
Sorbents		
AST-120	*p*-cresol, indoles	survival; preservation of renal function

Schepers et al, Blood Purif 2010;29:130–136

AST-120 (Kremezin; Kureha Chemical Industry Co Ltd, Tokyo, Japan)

- Absorbs small-molecular-weight organic compounds
- In rats and in patients with CKD AST-120 dose-dependently decreases indoxyl-sulfate levels
- In Japan it is approved for treatment of uremic symptoms and delay of ESRD
- AST-120 is being studied in the US for renoprotective indication

Schulman et al, Am J Kidney Dis 2006
Sanaka et al, Am J Kidney Dis 1998

Conclusions - AST-120

- Higher indoxyl sulfate associated with adverse outcomes
- AST-120 lowers levels of indoxyl sulfate
- AST-120 may be an effective renoprotective intervention: ongoing RCTs