

Diabetic Nephropathy: Treatment Updates

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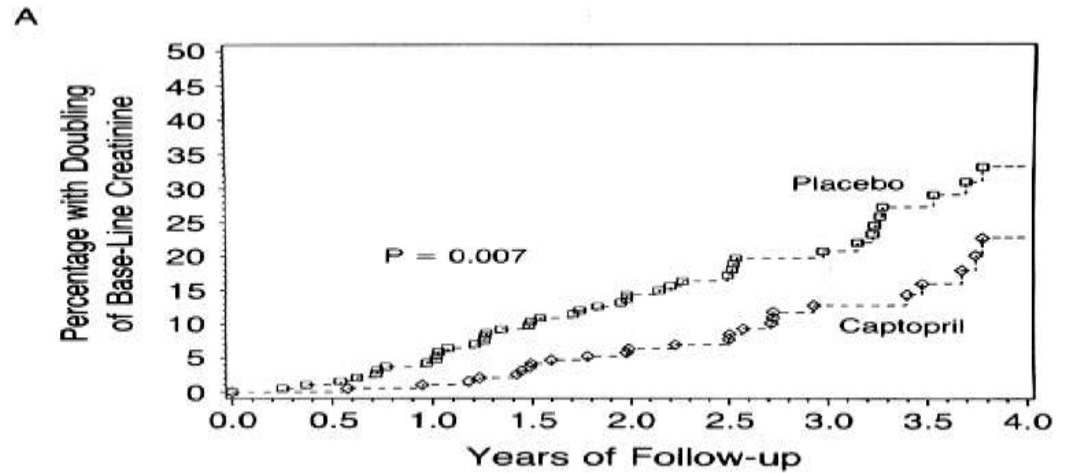
Objectives

- Review pathogenesis of diabetic nephropathy to identify targets for novel therapies
- Review novel therapies of diabetic nephropathy
- Look again at the current standard therapeutic options

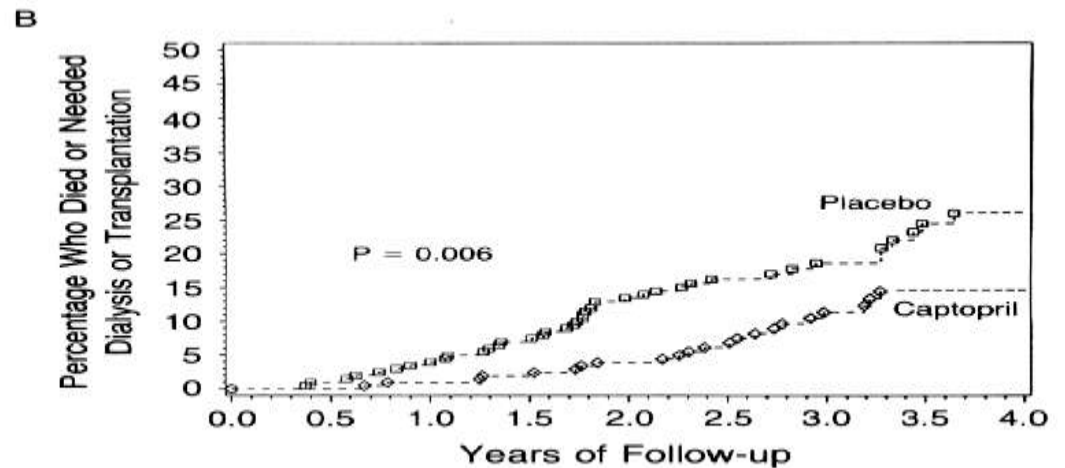
Introduction

- Despite advances in the control of hyperglycemia and hypertension, the development and progression of diabetic nephropathy remain major healthcare problems
- Diabetic nephropathy is the leading cause of ESRD in the USA and world-wide

Since the landmark Lewis study which showed captopril *reduced proteinuria* and lowered decline of GFR by 50%, RAS inhibition has been the standard of therapy in DN



Placebo	202	184	173	161	142	99	75	45	22
Captopril	207	199	190	180	167	120	82	50	24



Placebo	202	198	192	186	171	121	100	59	26
Captopril	207	207	204	201	195	140	103	64	37

Cumulative Incidence of Events in Patients with Diabetic Nephropathy in the Captopril and Placebo Groups.

- Current therapies proven to slow the progression of DN include blockade of the RAAS with ACEi or ARBs in both type 1 and type 2 DM
- Given better understanding of pathogenesis, newer therapies are slowly emerging

- Pathophysiology: interaction of hemodynamic and metabolic abnormalities and genetics

LOCATION	ABNORMALITY	MECHANISM
Mesangial Cell	Expansion Matrix overproduction Hypertrophy	Altered metabolism Collagen deposition Mesangial cell AII synthesis Mechanical stress
Glomerular Basement Membrane	Thickening Matrix deposition Decreased charge	Collagen deposition Protein crosslinking AGEs Loss of heparan sulfate proteoglycans
Pedocyte	Effacement Detachment from GBM Reduced number Apoptosis	Nephrin down regulation Mechanical stress
Glomerular Endothelial Cell	Defective autoregulation Microvascular changes Increased permeability Reduced glycocalyx	Afferent vasodilatation Efferent vasoconstriction AII actions VEGF expression Endothelin Reactive oxygen species
Tubulo-Interstitium	Interstitial fibrosis Tubular hypertrophy TBM thickening Inflammation Ischemia	Collagen production Extracellular matrix synthesis Fibroblast proliferation

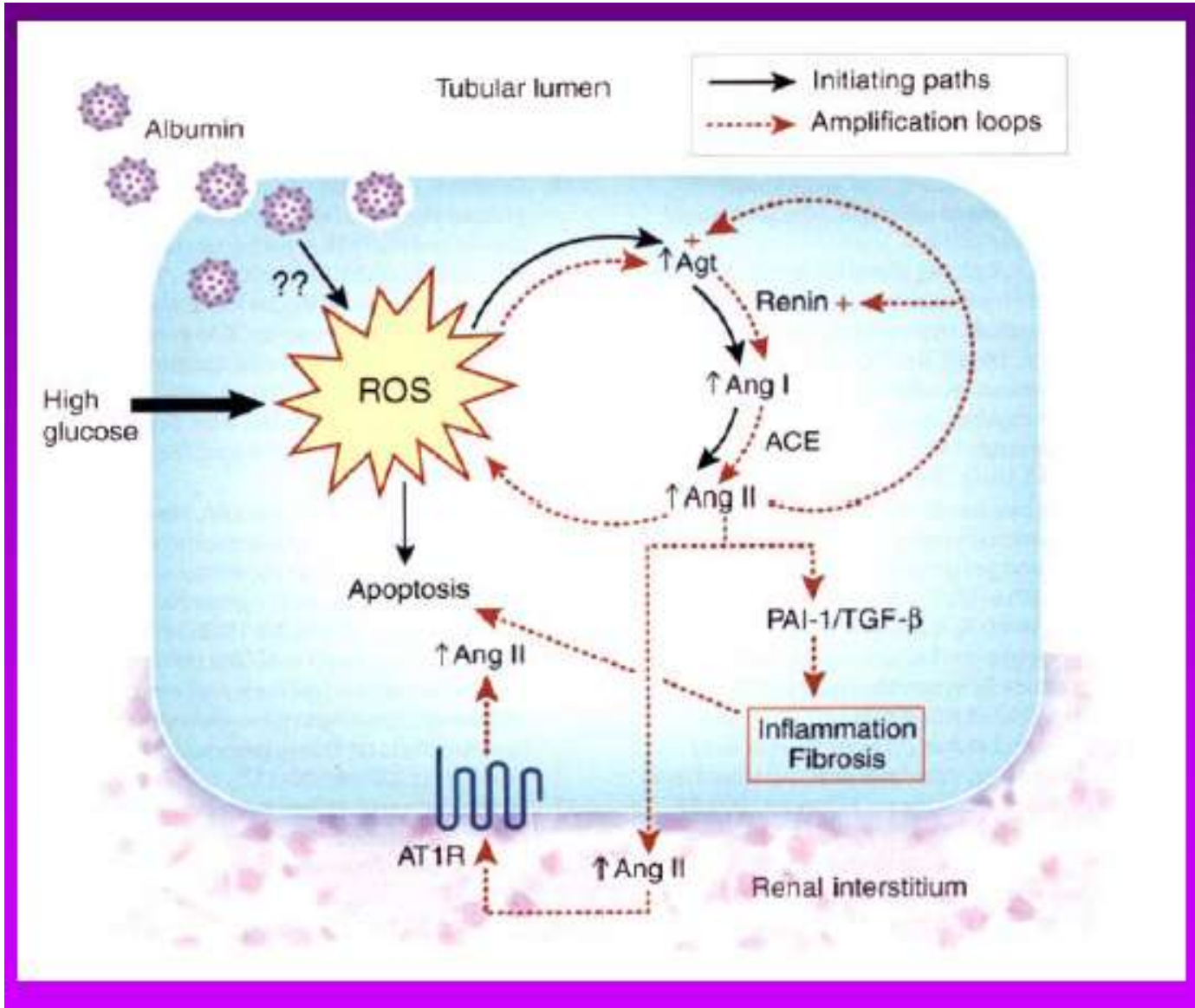
Hemodynamic abnormalities

- Systemic hypertension
- Hyperfiltration and intraglomerular hypertension
- Activation of RAAS
- Activation of endothelin
- Ischemia

Metabolic abnormalities

- Extracellular:
 - AGE
 - production of matrix
- Intracellular:
 - AGE
 - secretion of pro-fibrotic cytokines ie TGF-B
 - increased protein kinase C (PKC)
 - abnormal polyol metabolism
 - increased oxidative stress
 - secretion of pro-inflammatory cytokines
 - growth factors
 - abnormal metalloproteinases

Hemodynamic and Metabolic insults in DN



Clinical Trials

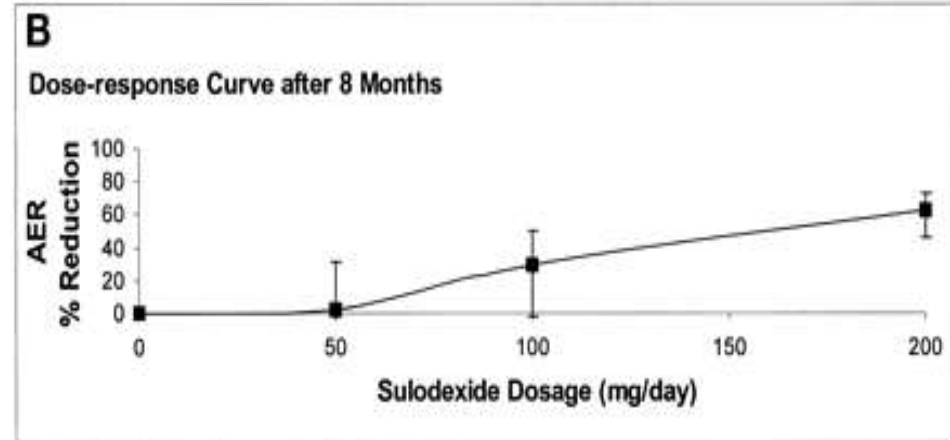
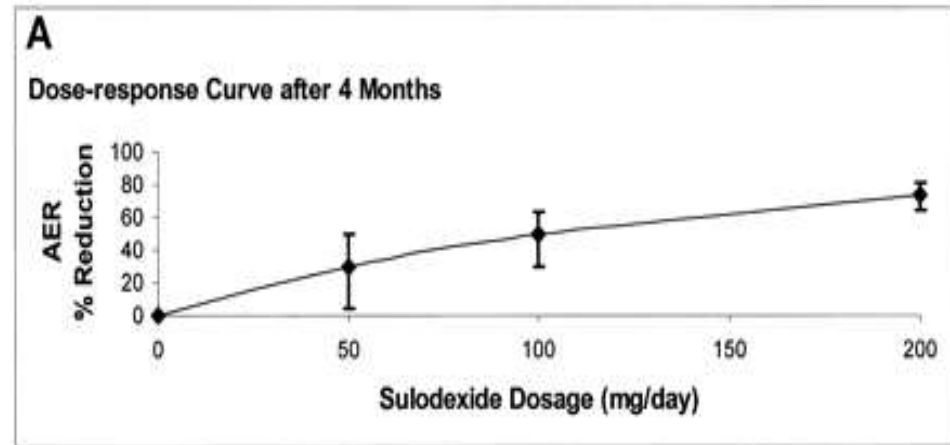
- Search for diabetic nephropathy in clinicaltrials.gov yields 230 studies
- Agents used include: [sulodexide](#), sevelamer, rosiglitazone, pioglitazone, [ruboxistaurin](#), n-acetyl-cysteine, [pyridoxamine](#), colchicine, [bardoxolone](#), benfotiamine, the antifibrotic agent pirfenidone, metalloproteinase inhibitors, ACTH, [paricalcitol](#), [vitD](#), [aliskiren](#)

Sulodexide

- Oral formulation of purified glycosaminoglycans, 80% heparin sulfate and 20% dermatan sulfate
- Similar to heparin with no anticoagulation properties when given orally
- Mechanisms of action:
 - inhibits heparinase which is upregulated in hyperglycemia and decreases the proteoglycan content of GBM.
 - Restores anionic heparin sulfate charge on GBM.
 - Suppresses TGF- β

Di.N.A.S. Trial JASN 13:1615, 2002

- Randomized, control trial in 223 micro- and macroalbuminuric Type 1 and Type 2 DM with Cr 150 $\mu\text{mol/L}$ (1.69 mg/dl), stable BP and metabolic control.
- Treated for 4 months with 50 mg, 100 mg or 200 mg of sulodexide
- Very well tolerated



Albuminuria decreased by 30, 49 and 74% compared with placebo

Sulodexide

- Recent pilot study of 149 Type 2 DM with microalbuminuria. A 50% reduction in ACR was seen in 25.3% of sulodexide treated vs. 15.4% given placebo ($p=0.26$) (NDT 0:1-9, 2007).
- ***SUN-Micro-Trial***, 1000 microalbuminuric DM on max RAAS inhibition treated with sulodexide failed to show reduction of albumin excretion in adequately powered study. Phase 4 study was cancelled by Keryx Biopharmaceutical

Ruboxistaurin

- RBT is an oral PKC- β inhibitor
- PKC is a family of at least 12 isoforms, play role in signal transduction
- PKC activated in response to diacylglycerol, which is increased by hyperglycemia
- Activated PKC causes kidney damage through generation of NADPH oxidase leading to oxidative stress and signaling TGF- β to induce matrix production

Ruboxistaurin

- In animal studies normalized hyperfiltration and reduced matrix, TGF-B and albuminuria
- Pilot study of 123 diabetics with macroalbuminuria treated for 1 yr had 24% reduction in albuminuria and stable eGFR. Effect seen at 1 month but did not reach statistical significance (Diabetes Care 28 (11) 2686-90, 2005)

Table 3—Change from baseline in urinary ACR and eGFR, blood pressure, and A1C at follow-up visits

Treatment	n	1 month	3 months	6 months	12 months
Urinary ACR change (%)*					
Placebo	63	-16 ± 7†	-9 ± 8	-9 ± 10	-9 ± 11
RBX	39	-24 ± 7†	-28 ± 6†	-29 ± 8†	-24 ± 9†
Urinary ACR change (mg/d)					
Placebo	63	17 (424)	-37 (413)†	21 (661)	26 (896)†
RBX	39	-60 (363)††	-130 (417)††	-136 (398)	-121 (481)
eGFR change (ml/min per 1.73 m²)					
Placebo	62	—	—	-2.7 ± 1.8	-4.8 ± 1.8†
RBX	37	—	—	-0.2 ± 1.9	-2.5 ± 1.9
Systolic blood pressure (mmHg)					
Placebo	62	133 ± 16	135 ± 15	136 ± 16	138 ± 19
RBX	39	135 ± 15	136 ± 15	134 ± 16	134 ± 18
Diastolic blood pressure (mmHg)					
Placebo	62	77 ± 12	76 ± 8	76 ± 10	76 ± 10
RBX	39	74 ± 10	74 ± 9	73 ± 11	74 ± 10
A1C (%)					
Placebo	62	—	—	7.7 ± 1.1	7.7 ± 1.2
RBX	36	—	—	8.0 ± 1.3	7.9 ± 1.3

Ruboxistaurin and Diabetic Retinopathy

- Identified concern re increased incidence of nephropathy and CAD
- A long-term evaluation of 3 DR trials of RBT showed no difference in rate of elevated AER or eGFR (Expert Opin Drug Saf 5: 835-45, 2006)
- FDA did not give approval for retinopathy and Eli Lilly failed to develop the product further

	Placebo	RBT 4/8mg	RBT 16mg	RBT 32mg	<i>p</i>
n	237	228	238	235	
Nephropathy	1 (0.4%)	2 (0.9%)	7 (2.9%)	1 (0.4%)	0.031
Proteinuria	2 (0.8%)	3 (1.3%)	9 (3.8%)	2 (0.9%)	0.038
CAD	16(6.8%)	8(3.5%)	31(13.0%)	1 (4.7%)	<0.001

Pyridoxamine

- Active inhibitor of of AGEs, likely through inhibition of glycated proteins (Amadori products) breakdown,
- Reduces in toxic effects of reactive oxygen species
- Scavenging of reactive carbonyl compounds

Pyridoxamine

- In animal models of Type 1 Type 2 DM, pyridoxamine (pyridorin[®]) preserved kidney function

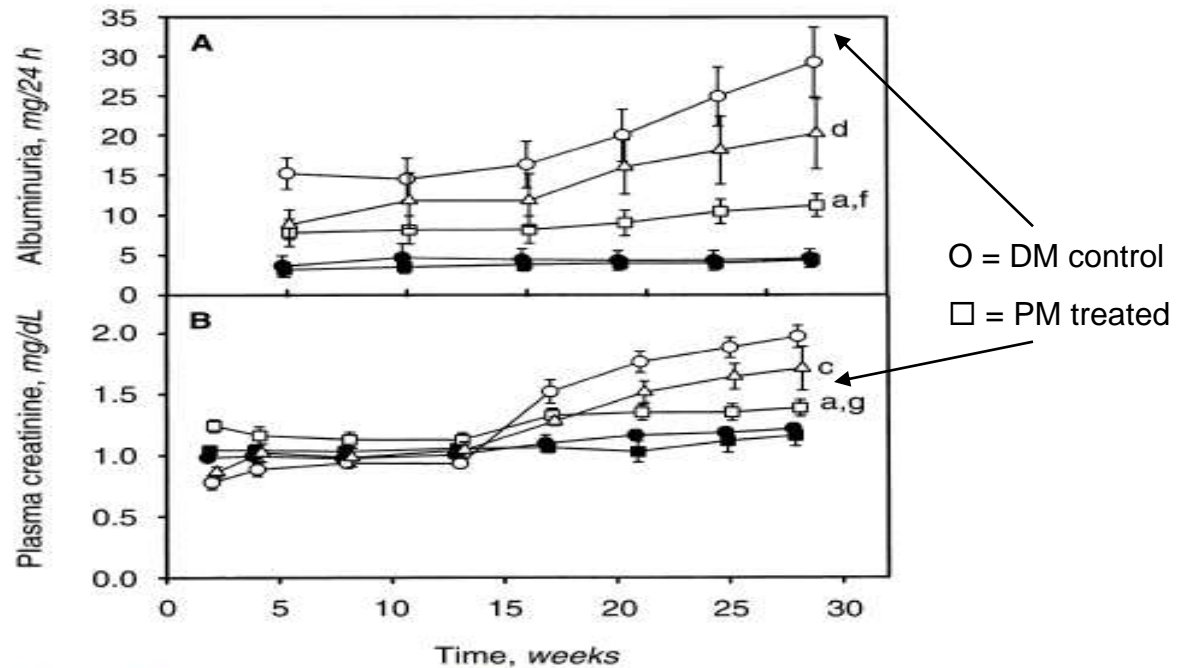


Fig. 1. Effect of pyridoxamine (PM) and aminoguanidine (AG) on development of nephropathy in streptozotocin (STZ)-diabetic rats. Urine (24-hour samples) and blood were collected at 4-week intervals for measurement of urinary albumin (A) and plasma creatinine (B) concentrations. Symbols are: (●) untreated, non-diabetic control; (■) PM-treated, non-diabetic control; (○) diabetic control; (△) AG-treated diabetic; and (□) PM-treated diabetic rats. All diabetic groups vs. non-diabetic controls in A and B, $P \leq 0.001$. For this and subsequent graphs: ^{a,b,c,d,e} $P < 0.0001$, < 0.001 , < 0.01 , < 0.05 , and NS vs. D; ^{f,g} $P < 0.01$, $P < 0.05$ vs. D + AG; ^h $P > 0.05$ vs. C.

Two Phase 2 trials in type 1 and type 2 DM, 212 patients treated with 250 mg of pyridoxamine for 6 mo had 48% reduction of Cr, reduction of urinary TGF-B, but no change in UAE and was well tolerated. Phase 2b trial ongoing

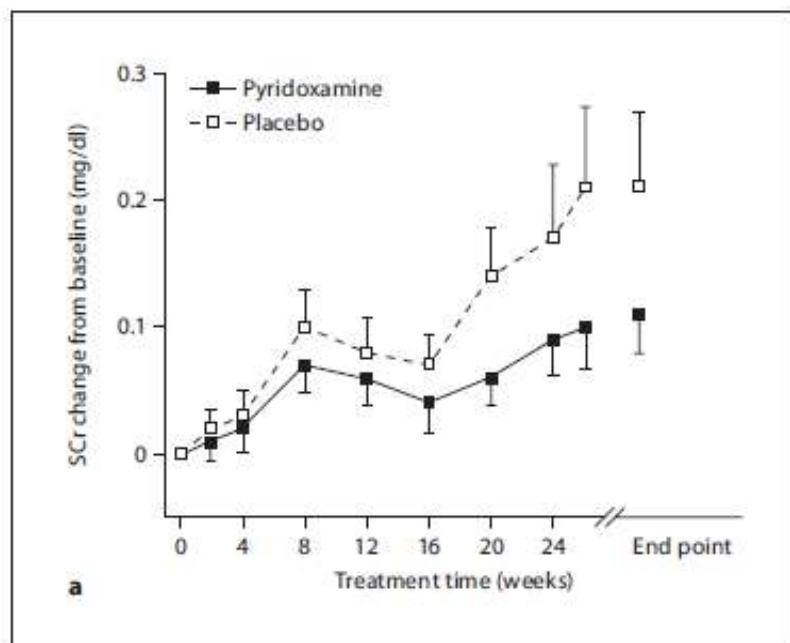
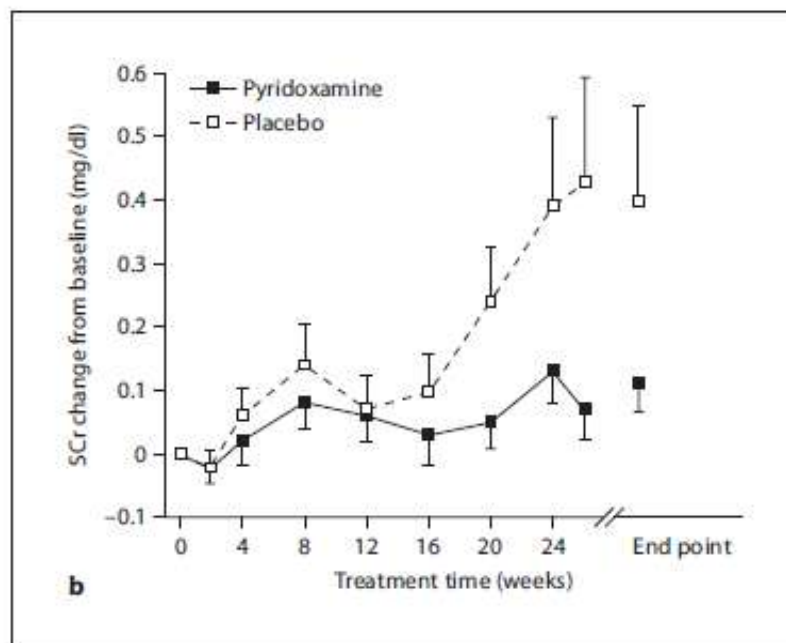


Fig. 1. a SCr change from baseline in all patients, as analyzed from the merged data set. Data are given as mean \pm SEM. $p = 0.028$ for the change from baseline measurement to week 26, as calculated by repeated measures, mixed model analysis with baseline SCr as a fixed covariate. Values at 'end point' refer to the last on-treatment SCr measurements for individual patients. **b** SCr change from baseline in patients with type 2 diabetes having a baseline



SCr value ≥ 1.3 mg/dl, from the merged data set. The data are given as mean \pm SEM. $p = 0.0033$ for the change from baseline measurement to week 26, as calculated by repeated measures, mixed model analysis with baseline SCr as a fixed covariate. Values at 'end point' refer to the last on-treatment SCr measurements for individual patients.

The Effect of Pyridorin on the Progressive Renal Dysfunction of Overt Type 2 Diabetic Nephropathy.

Edmund J Lewis MD, Julia Lewis MD, Tom H Greene PhD, Robert C Atkins MD, Itamar Raz MD, and Lawrence G Hunsicker MD. For the Collaborative Study Group, Chicago, IL, United States.

Pyridorin (Pyr) inhibits formation of advanced glycosylation end products and scavenges reactive oxygen species and toxic carbonyls. We report a double-blind, randomized, placebo-controlled Phase 2b trial of 307 subjects with type 2 diabetic nephropathy with serum creatinine (Scr) [1.3-3.3 mg/dl in females; 1.5-3.5 mg/dl in males] and urine protein:creatinine ratio (PCR) \geq 1200 mg/g. Subjects were randomized to oral twice daily placebo, Pyr 150 mg or Pyr 300 mg for 52 weeks. Stable ACE/ARB dosage and stable blood pressure with concomitant antihypertensive therapy were maintained. The primary endpoint was change in Scr from baseline to 52 weeks. To determine the effect of Pyr according to severity of kidney disease, prespecified analyses were employed to study baseline Scr subgroups. Patient demographics included: age 63.9 ± 9.5 (SD) BMI 33.6 ± 6.5 ; diabetes duration 17.6 ± 8.5 yrs; nephropathy duration 5.3 ± 4.5 yrs, systolic BP 138.4 ± 13.9 ; Scr 2.2 ± 0.57 mg/dl; PCR 3030 ± 1971 mg/G and were balanced among the 3 groups. Primary results revealed the mean change in Scr at week 52 was: placebo (n=103) 0.36 mg/dl; Pyr 150 (n=99) 0.43 mg/dl; Pyr 300 (n=105) 0.35 mg/dl (both Pyr groups vs placebo $p=0.651$). Analysis of covariance for treatment interaction with baseline Scr as a continuous variable revealed Pyr 150 vs placebo ($p=0.006$); Pyr 300 vs placebo ($p=0.012$); Pyr (both groups) vs placebo ($p=0.002$). Examination of baseline Scr tertiles revealed the change in Scr at 52 wks in the lowest Scr tertile (Scr 1.3 – 1.86 mg/dl): placebo (n=33) 0.28 ± 0.62 mg/dl; Pyr 150 (n=33) 0.06 ± 0.22 mg/dl; Pyr 300 (n=36) 0.14 ± 0.2 mg/dl (Pyr both groups vs placebo $p=0.046$). There was no significant treatment effect in the middle (Scr 1.86-2.44) ($p=0.573$) or upper (Scr >2.44) ($p=0.097$) tertiles. There were no significant adverse events associated with Pyr. **We conclude that Pyr failed to significantly alter the progression of Scr at one year follow-up in the total patient population studied. However slowing of progression in that subgroup with the most intact renal function (Scr 1.3-1.86 mg/dl) reached statistical significance.**

Bardoxolone

- oral antioxidant inflammation modulator used initially in oncology, induces Nrf2 a major regulator of anti-oxidant genes
- mimics the activities of prostaglandins that play a key role in the resolution of inflammation and oxidative stress
- Phase 2a studies in type 2 DM (presented at NKF 'spring clinicals' 2009) revealed a 36% increase in eGFR in CKD 4 after 1-2mo.
- A 12-month Phase 2b clinical study has been initiated

Vitamin D/analogues

- inhibit renin, angiotensin expression and have anti-proliferative, anti-fibrotic effects
- In animal models of DN have been shown to be renoprotective in combination with RAS blockade
- A small study with paricalcitol showed reductions in albuminuria
- The **VITAL** study tests the hypothesis whether paricalcitol persistently reduces albuminuria in Type 2 DM with micro- and macroalbuminuria treated with an ACEI and/or ARB

Aliskiren

- Renin inhibitor with anti-hypertensive properties approved by FDA in 2007
- reduces angiotensin I, angiotensin II and aldosterone levels
- reduces TGF- β

Aliskiren

- Animal models: reduces albuminuria, BP and normalises Cr in transgenic rats with human renin/angiotensin genes
- Shown to be renoprotective with reduced tubulointerstitial fibrosis vs. perindopril in rats (Diabetologica 50:2398-2404; 2007)

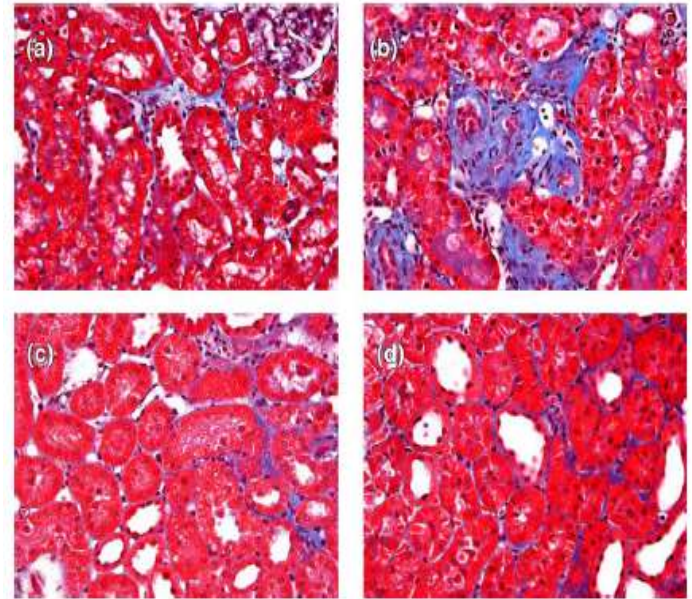
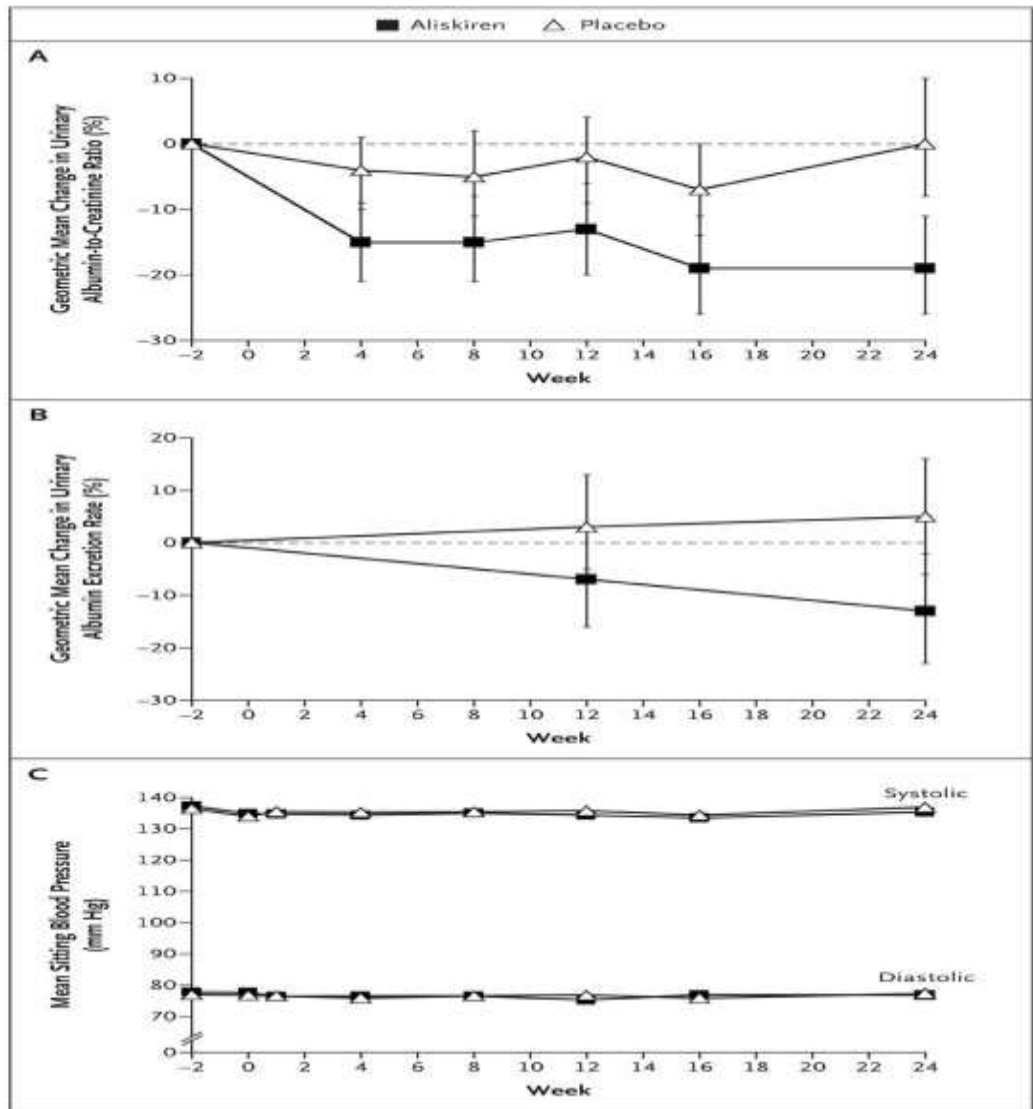


Fig. 5 Representative Masson's trichrome-stained sections from control and diabetic *Ren-2* rats treated or not with aliskiren or perindopril. In control (a) rats, very little collagen (blue staining) is present within the interstitium, while extensive interstitial fibrosis was noted in diabetic animals (b). Interstitial fibrosis in diabetic rats was reduced by perindopril (c) and to a greater extent by aliskiren (d). Original magnification $\times 350$

AVOID trial (NEJM 358:2433-2446, 2008)

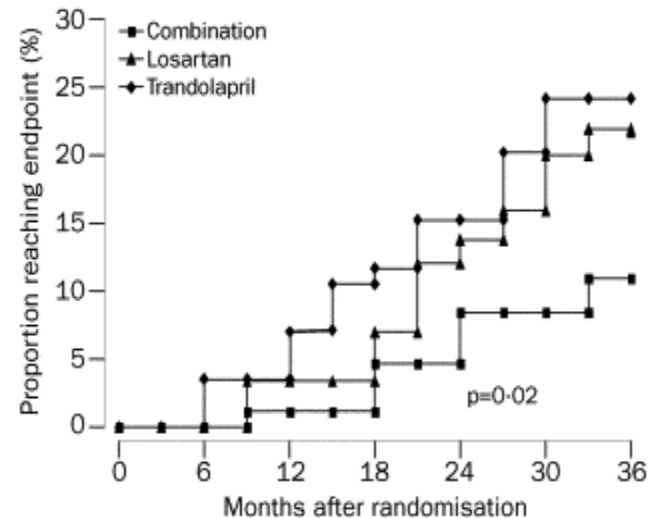
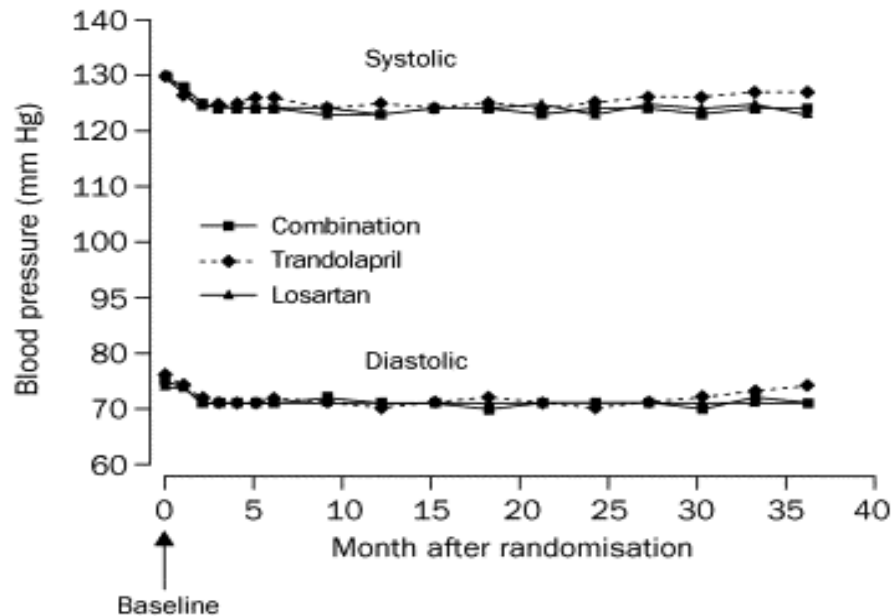
- 599 Type 2 DM treated with 100 mg of losartan randomized to aliskiren vs. placebo
- 20% reduction of UACR
- Results of ***ALTITUDE*** trial (with doubling Cr, ESRD) awaited



Multiple drug treatment: maximized inhibition of RAAS

- COOPERATE:** combination treatment of ARB (losartan) and ACEi (trandolapril) in **non-diabetic** nephropathy provided better renoprotection than either drug alone.

Primary outcome: doubling Cr/ESRD; proteinuria at baseline 2.4-2.5 g/day



	0	6	12	18	24	30	36
Number at risk							
Losartan	89	88	84	79	65	59	47
Trandolapril	86	85	83	75	72	63	58
Combination	88	87	86	83	76	73	67

Multiple drug treatment: maximized inhibition of RAAS

- **CALM Study:** Randomized, DM2 with HTN, microalbuminuria, 12 wks follow up. Primary outcome: albuminuria and BP
- Results: candesartan same as lisinopril, combination well tolerated and better at reducing BP
- No significant changes in CrCl in any of the treatment groups. CrCl was slightly decreased over 24 weeks in lisinopril (adjusted mean decrease 0.0835 ml/sec, $P=0.04$) and the combination treatment (0.0735 ml/sec, $P=0.05$) but not in candesartan.

Combined ACEi and ARB in DM

- Multiple small trials suggest combination therapy provides additive benefit in DN
- Meta analysis: 10 trials, 156 ACE + ARB, 159 ACE, duration 8-12 weeks ([Diabet Med 2007, 24\(5\):486](#))
 - Proteinuria reduced with combination, BP lower, but reduced GFR (3.9 ml/min), increased K⁺ (by 0.2)
- VA NEPHRON-D: ongoing randomized controlled study, losartan and lisinopril vs. losartan alone, endpoints reduction GFR, ESRD, death

OnTARGET: Concerns about ACE + ARB Combinations

- Approximately 25,000 patients with vascular disease or high-risk DM
- Double-blind randomization: telmisartan 80mg/day or ramipril 10 mg/day or both for mean 56 mo.
- Outcomes; death, MI, CVA, hospitalization for CHF
- Result: the two drugs were 'therapeutically equivalent' and ARB/ACE combination was associated with more adverse events without increased benefit
- Renal outcomes published separately
- Primary outcome: composite of doubling of Cr, dialysis, death. Secondary outcome included albuminuria

	Primary Outcome	eGFR decline
Ramipril	13.5%	-2.82
Telmisartan	13.4%	-4.12
Both	14.5%	-6.11

- But...UAE was less with combination therapy

NEJM 358(15):1547-59, 2008

Lancet 372(9638):547-53, 2008

Recommendations

- Maximize BP control to reach target values
- Titrate doses of ACEi or ARB to reduce UAE
- Some recommend combination with ACE/ARB be avoided in those with proteinuria < 1 g/day [\(Nat Clin Pract Nephrol 5\(1\): 12-3, 2009\)](#)