THE 20th BUDAPEST NEPHROLOGY SCHOOL

NEPHROLOGY, HYPERTENSION, DIALYSIS, TRANSPLANTATION

DIABETIC NEPHROPATHY REVISITED

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Austria

G.M. 2013

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TYPE I DIABETES MELLITUS NEPHROPATHY

A SLOWLY PROGRESSING DISEASE AND THUS HARD TO STUDY

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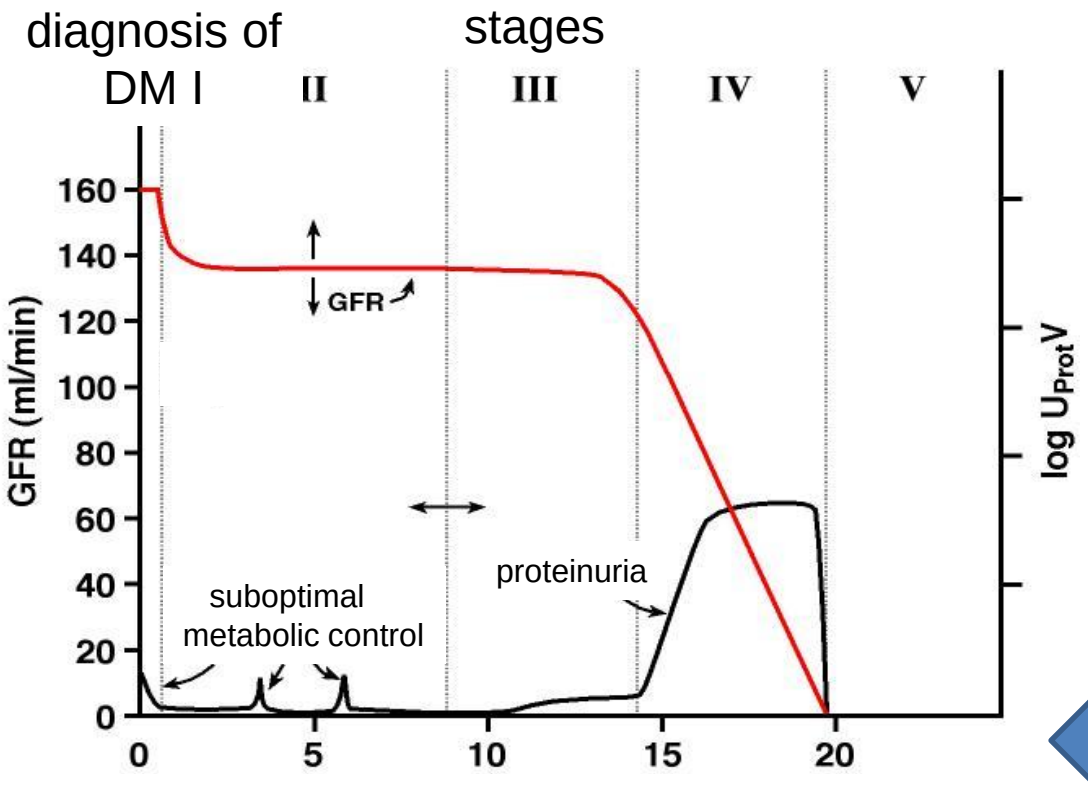

blood pressure ⊥⊥ - mildly ↑ moderately ↑ ↑ ↑

histology glom hypertrophy — GBM ↑ Hyper trophy — V_V Mes ↑ — V_V Mes ↑ glom closure — glom closure — hypertrophy

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"The problem with studying kidney disease is, that no man lives long enough."

-Thomas Addis

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TYPE I DIABETES MELLITUS
NEPHROPATHY
A SEQUENCE OF STAGES

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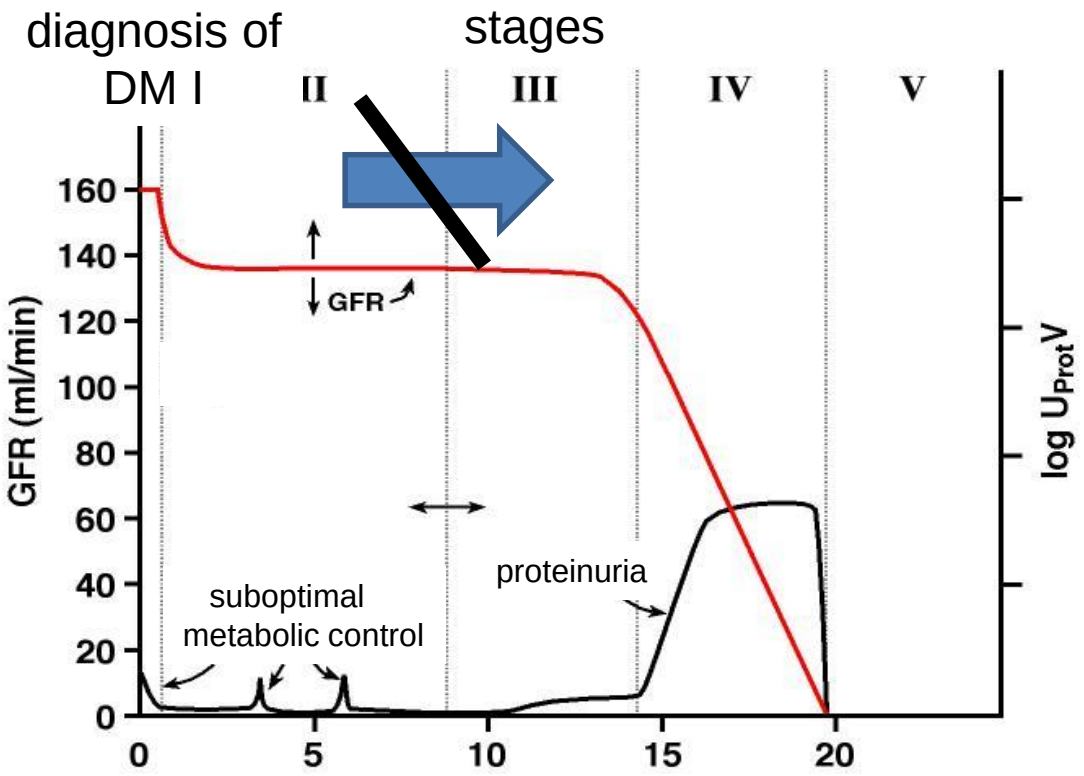

blood pressure ⊥⊥ - mildly ↑ moderately ↑ ↑ ↑

histology	glom Hyper trophy	GBM ↑ V_V Mes ↑	V_V Mes ↑ glom closure	glom closure hypertrophy

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STRICT METABOLIC CONTROL AND RENAL FUNCTION IN TYPE 1 DIABETES

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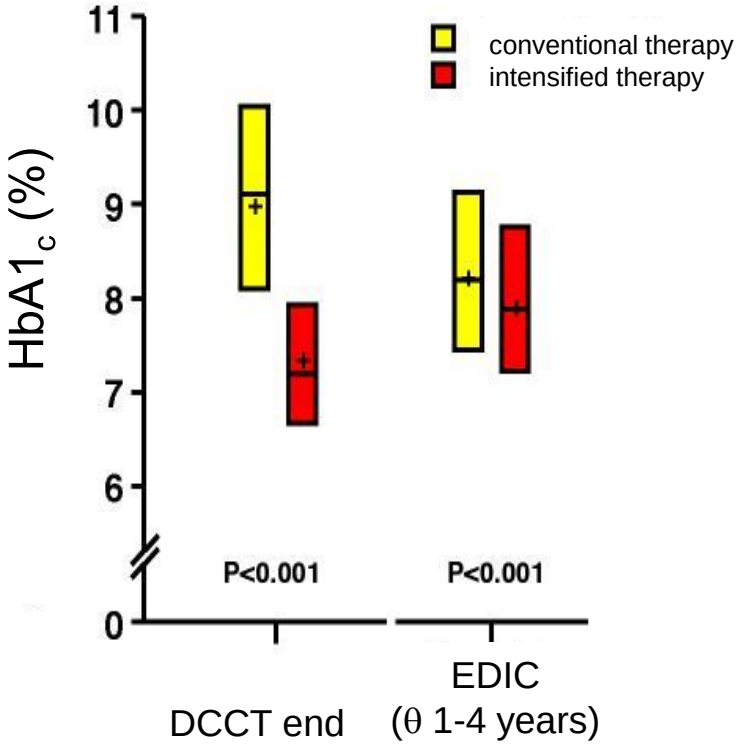

renal complications during EDIC (%)

	conventional	intensified
de novo microalbuminuria	11	5*
de novo albuminuria in case of		
normoalbuminuria	2	0*
microalbuminuria	31	8*

at the end of the DCCT

DCCT Group N Engl J Med 2000

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	intensive diabetes therapy		conventional diabetes therapy		risk reduction with intensive therapy	p value
	nb of events	incidence rate / 1000 person -yr	nb of events	incidence rate / 1000 person-yr	% (95% CI)	
eGFR <60 ml/min/1.73m^2	24	1.6	46	3.0	50 (18-69)	0.006
onset during DCCT	1		3			
onset during EDIC	23		43			
eGFR <45 ml/min/1.73m^2	24	1.6	39	2.5	40 (1-64)	0.045
eGFR <30 ml/min/1.73m^2	13	0.8	23	1.5	44 (−9-72)	0.09
ESRD	**8**	0.5	**16**	1.1	51 (−14-79)	0.10
eGFR <60 ml/min/1.73m^2 or death	53	3.4	80	5.2	37 (10-55)	0.01

DCCT/EDIC Research Group N Engl J Med 2011

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covariate	risk associated with the covariate		effect of DCCT intensive diabetes therapy, adjusted for the covariate	
	Hazard Ratio (95% CI)	p value	risk reduction *% (95% CI)*	p value
none			50 (18-69)	0.006
HBA1c	2.73 (2.31-3.23)	<0.001	−23 (−106-27)	0.44
albumin excretion (mean)	1.11 (1.09-1.13)	<0.001	10 (−63-50)	0.73
mean arterial blood pressure	2.52 (2.06-3.08)	<0.001	51 (20-70)	0.004
body mass index	1.16 (0.74-1.82)	0.51	50 (19-70)	0.005
use of RAAS inhibitors	7.60 (3.8-15.1)	<0.001	44 (8-66)	0.02
use of antihypertensives	13.90 (6.3-30.7)	<0.001	42 (5-65)	0.03

DCCT/EDIC Research Group N Engl J Med 2011

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A SEQUENCE OF STAGES

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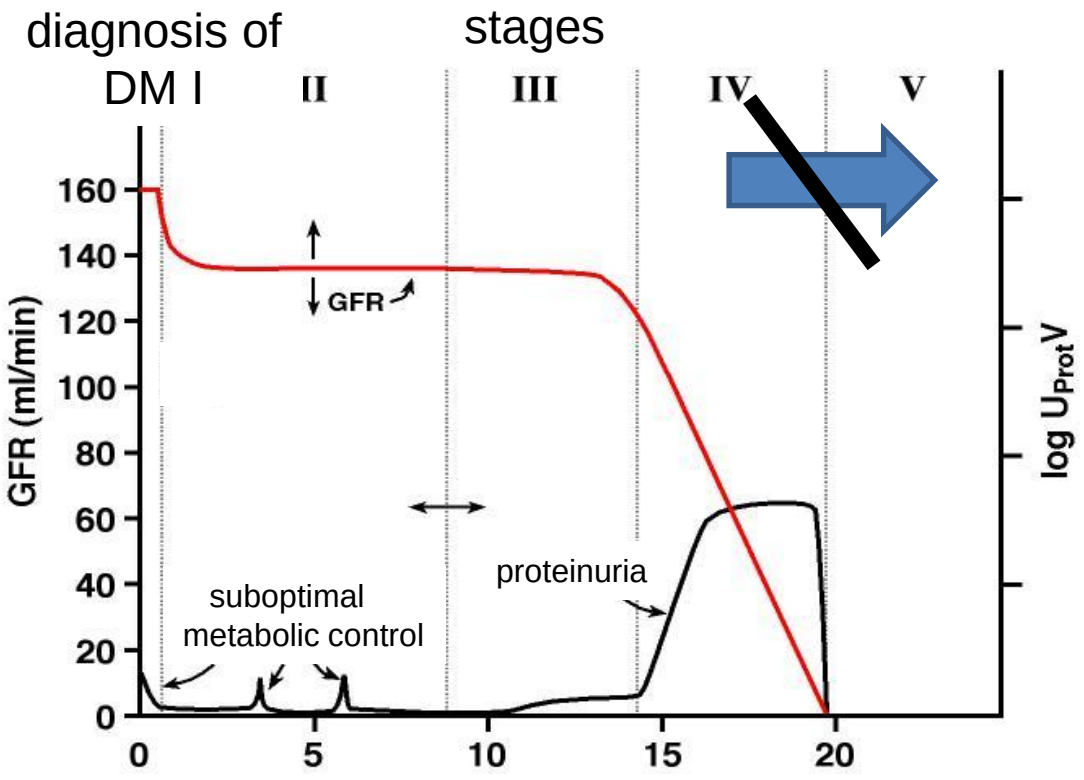

blood pressure ⊥ ⊥ - mildly ↑ moderately ↑ ↑ ↑

histology	glom Hyper trophy	GBM ↑ V_V Mes ↑	V_V Mes ↑ glom closure	glom closure hypertrophy

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CAPTOPRIL IN PATIENTS WITH TYPE 1 DIABETES AND NEPHROPATHY

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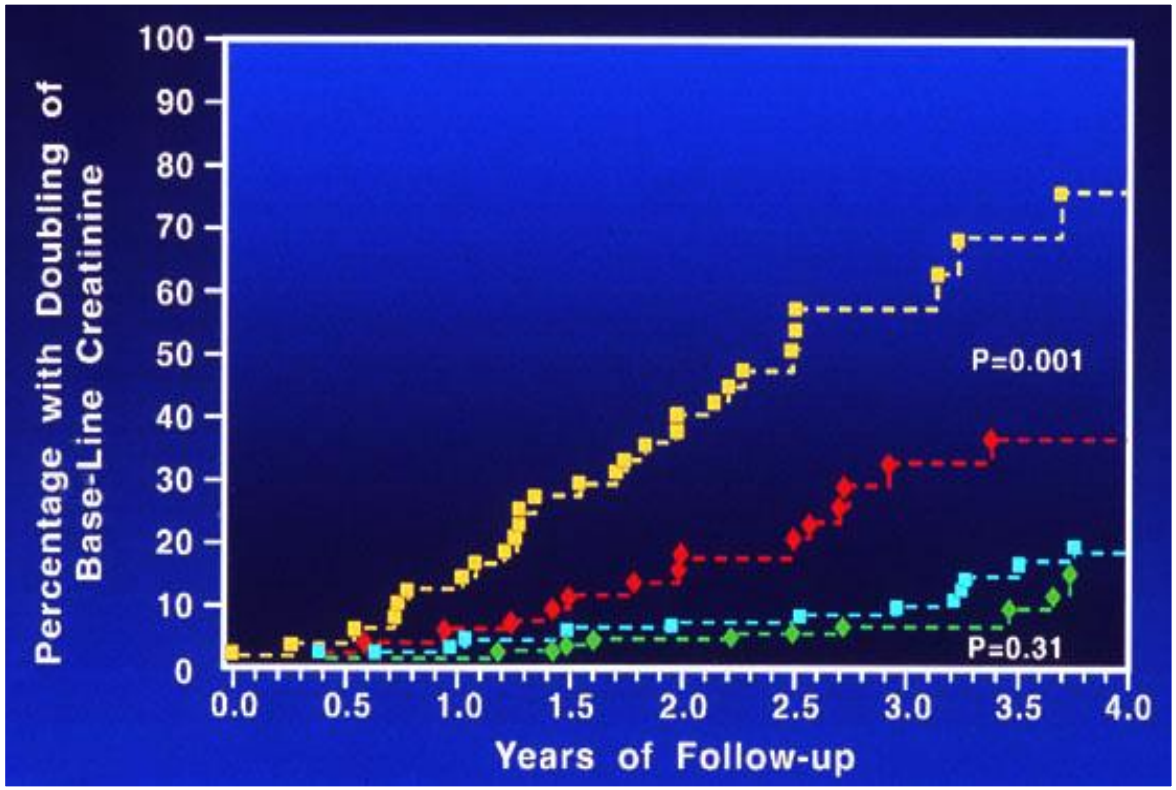

baseline creatinine

increased (control group)

increased (Captopril group)

normal

Lewis EJ et al. N Engl J Med 1993

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EFFECT OF ANTIHYPERTENSIVE THERAPY ON CHANGE IN ALBUMINURIA AND CHANGE IN GFR IN TYPE 1 DIBETES MELLITUS

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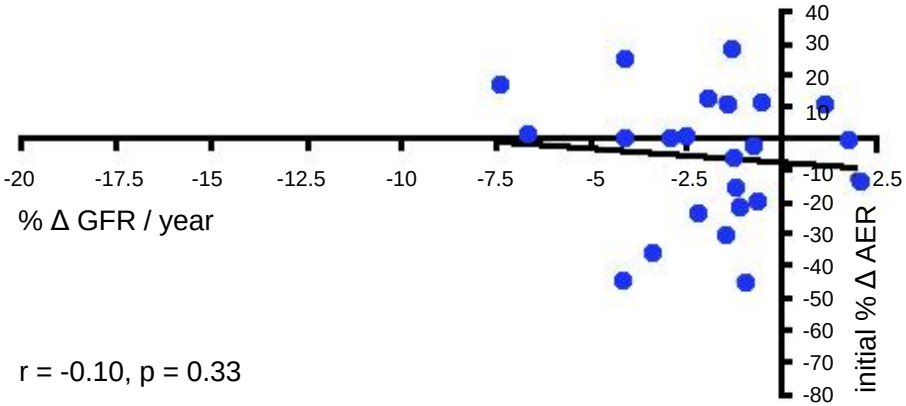
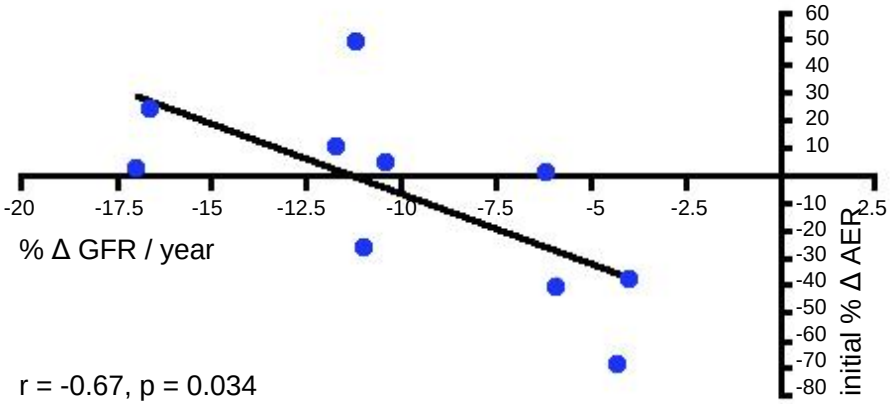


early nephropathy



late nephropathy

Jerums G et al. Am J Nephrol 2008

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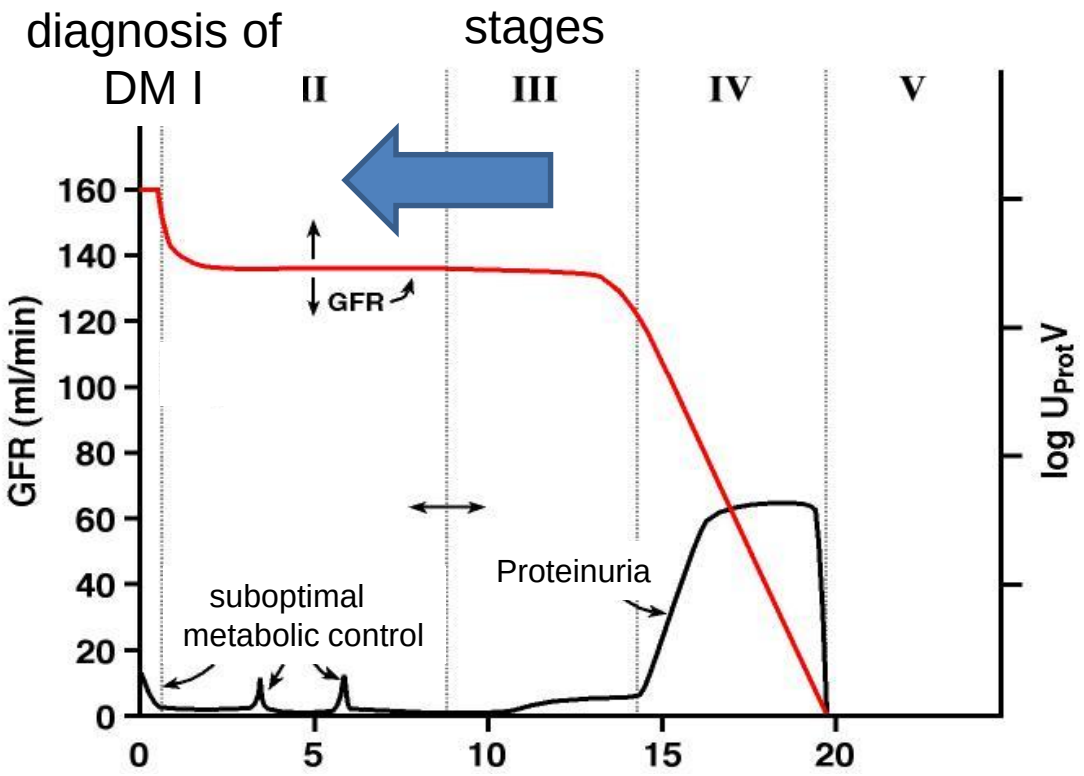

Blood pressure ⊥⊥ - mildly ↑ moderately ↑ ↑ ↑

Histology glom hypertrophy GBM ↑ Hyper trophy V_V Mes ↑ V_V Mes ↑ glom closure glom closure hypertrophy

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RENAL PROGNOSIS IN TYPE 1 DIABETICS

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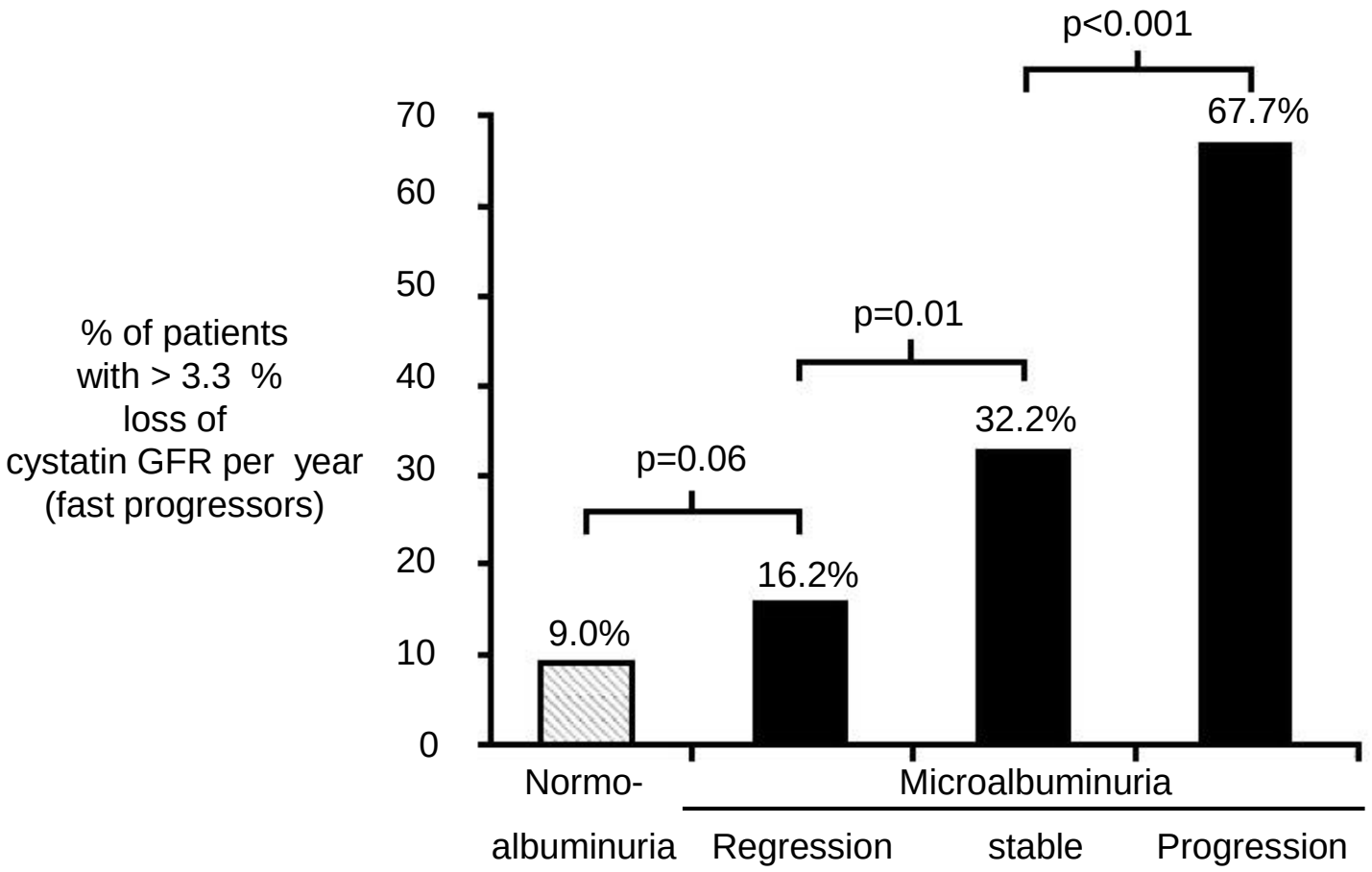

Perkins BA et al. J Am Soc Nephrol 2007

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PROGRESSION OF DIABETIC NEPHROPATHY IN PIMA INDIANS

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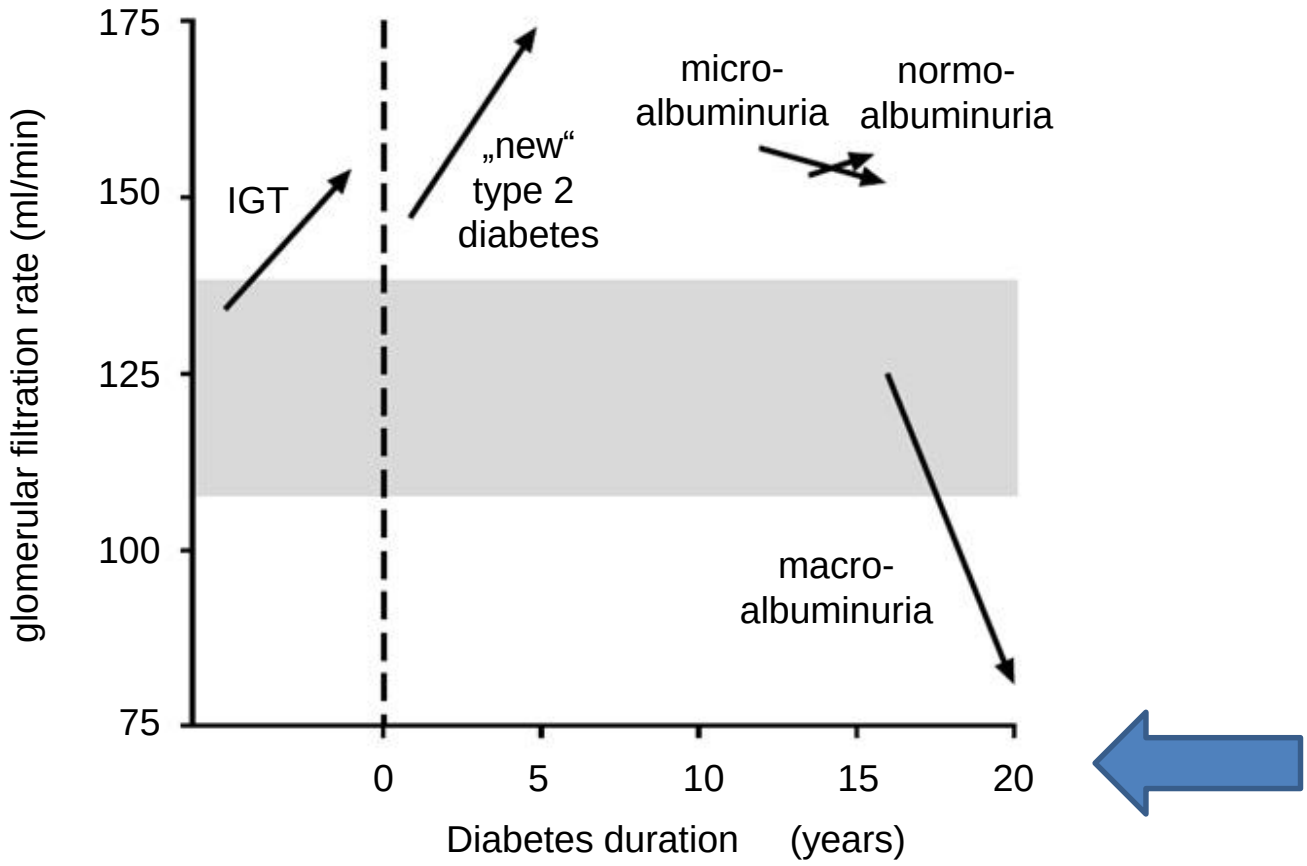

Nelson RG et al. N Engl J Med 1996

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STENO 2

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	conventional therapy (n = 63)	intensified therapy (n = 67)	p value
Δ albuminuria (mg/24 hr)			
median	+ 30	- 20	0.007
range	-251 to 4729	-230 to 5474	
Δ glomerular filtration rate (ml/min/1.73 m²)	-32 ± 3	-30 ± 3	0.68

incidence of „diabetic nephropathy *: RR 0.39 (95% CI 0.17-0.87)

* defined as incidence of macroalbuminuria

Gaede P et al. New Engl J Med 2003

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PROGRESSION OF DIABETIC NEPHROPATHY IN PIMA INDIANS

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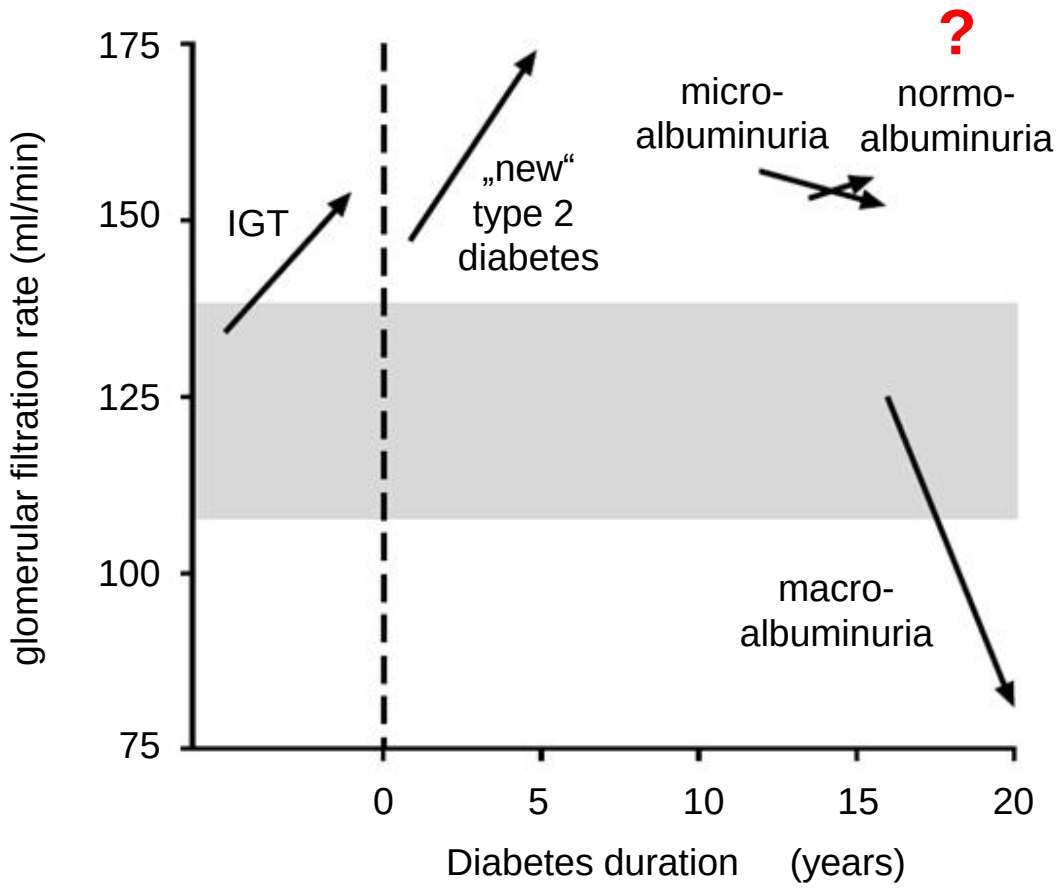

Nelson RG et al. N Engl J Med 1996

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NEPHROPATHY IN PATIENTS WITH TYPE II DIABETES IS NOT A UNIFORM DISEASE

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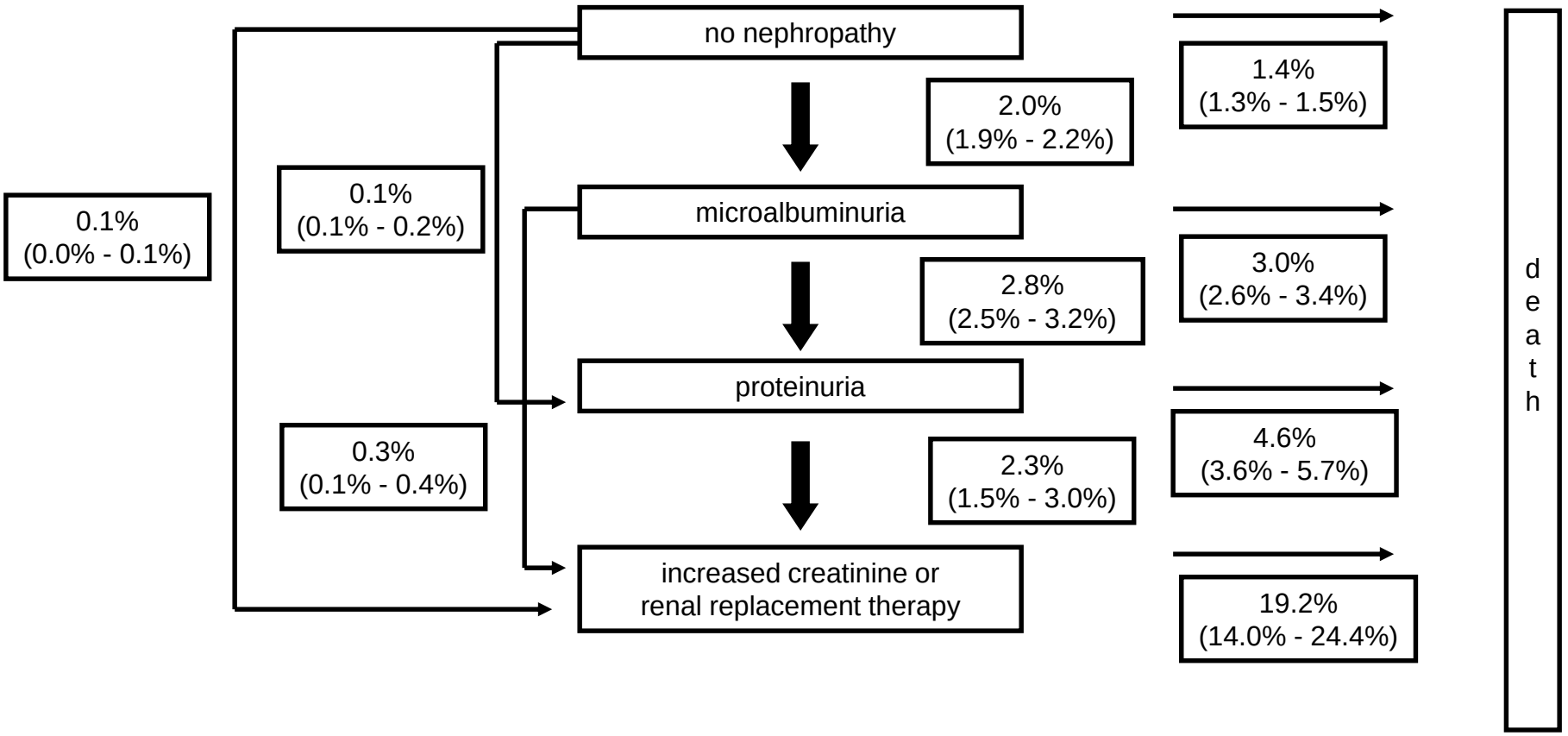

Adler A et al. Kidney Int 2003

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HOW VALID ARE SURROGATES LIKE PROTEINURIA IN PATIENTS WITH TYPE II DIABETES AND NEPHROPATHY ?

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1544 of 4.031 (38%) patients develop albuminuria within 15 years of follow up

1.449 of 5.032 (29%) patients develop CKD (C+G Clearance < 60 ml/min) during 15 years of follow up

51% of the patients with incident CKD never had prior albuminuria

Retnakaran R et al. UKPDS Diabetes 2006

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NEPHROPATHY IN PATIENTS WITH TYPE II DIABETES IS NOT A UNIFORM DISEASE

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AER (ug/min)	**45**	**50**	**39**
		histology	
	(almost) normal	diab. nephropathy	atypical lesions
n	10	10	14
age (years)	54	60	61
Diabetes duration (years)	8	14*	10
HbA1c (%)	7.5	9.6*	8.5
RRs (mmHg)	142	154	155
RRd (mmHg)	91	92	90
GFR (ml/min)	111	91	101
retinopathy			
background	5/10	5/10	8/14
proliferativ	0/10	5/10*	0/14

Fioretto P et al. Diabetes 1996

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"The problem with studying kidney disease is, that no man lives long enough."

-Thomas Addis

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NKF Teams Up with FDA to Set Targets for Clinical Trials

The FDA is now considering new endpoints for clinical trials in CKD patients as a result of a special scientific workshop convened by the NKF and the FDA on December 3-4 in Baltimore. After extensive analysis of data from observational cohorts and interventional trials, the workshop planning committee and attendees recommended a 30 or 40% decline in GFR as new surrogate endpoints for some clinical trials in chronic kidney disease used for regulatory approval

www.kidney.org/professionals/

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TREATMENT OF OVERT DIABETIC NEPHROPATHY

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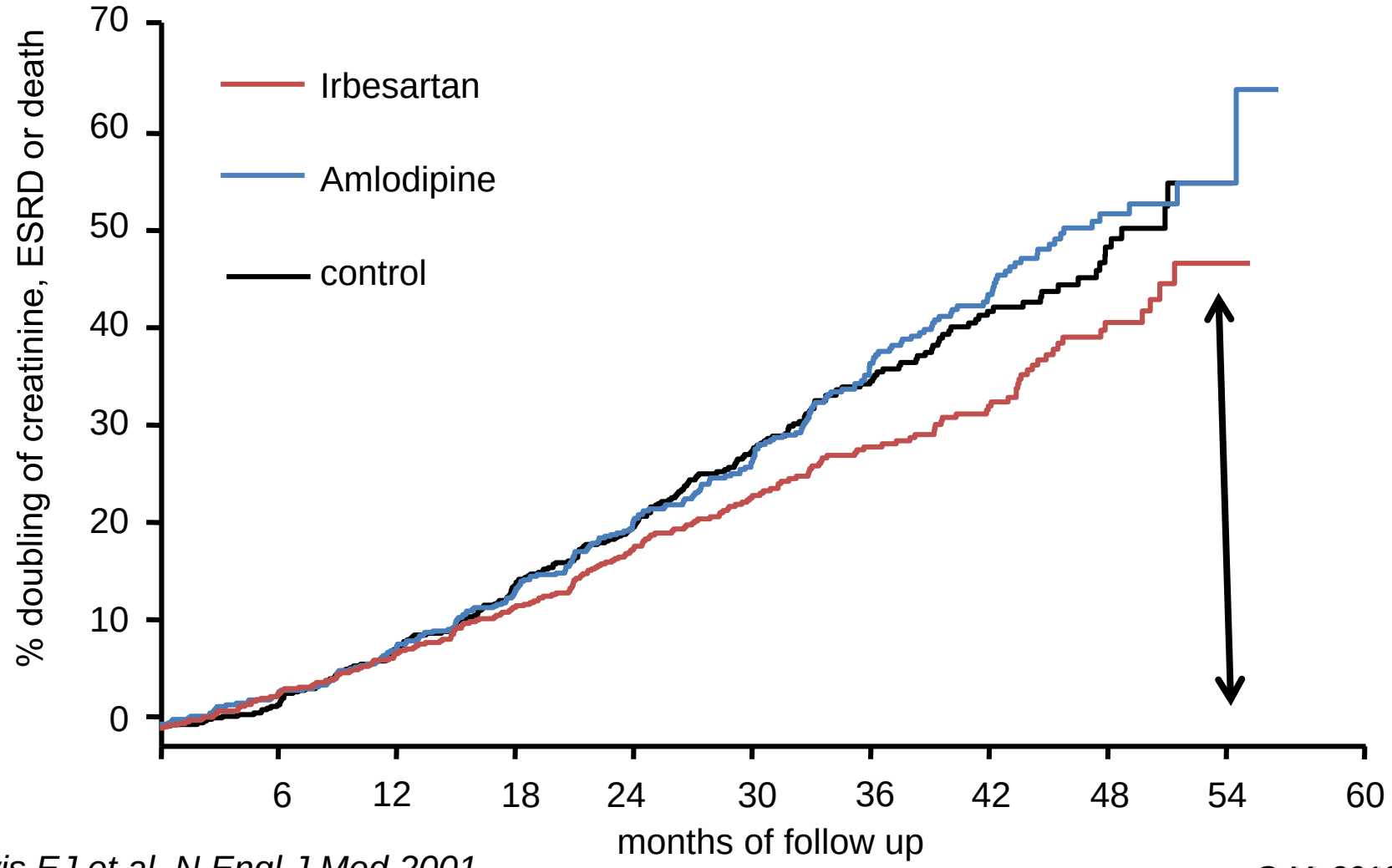

Lewis EJ et al. N Engl J Med 2001

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TREATMENT OF DIABETIC NEPHROPATHY WITH PARICALCITOL

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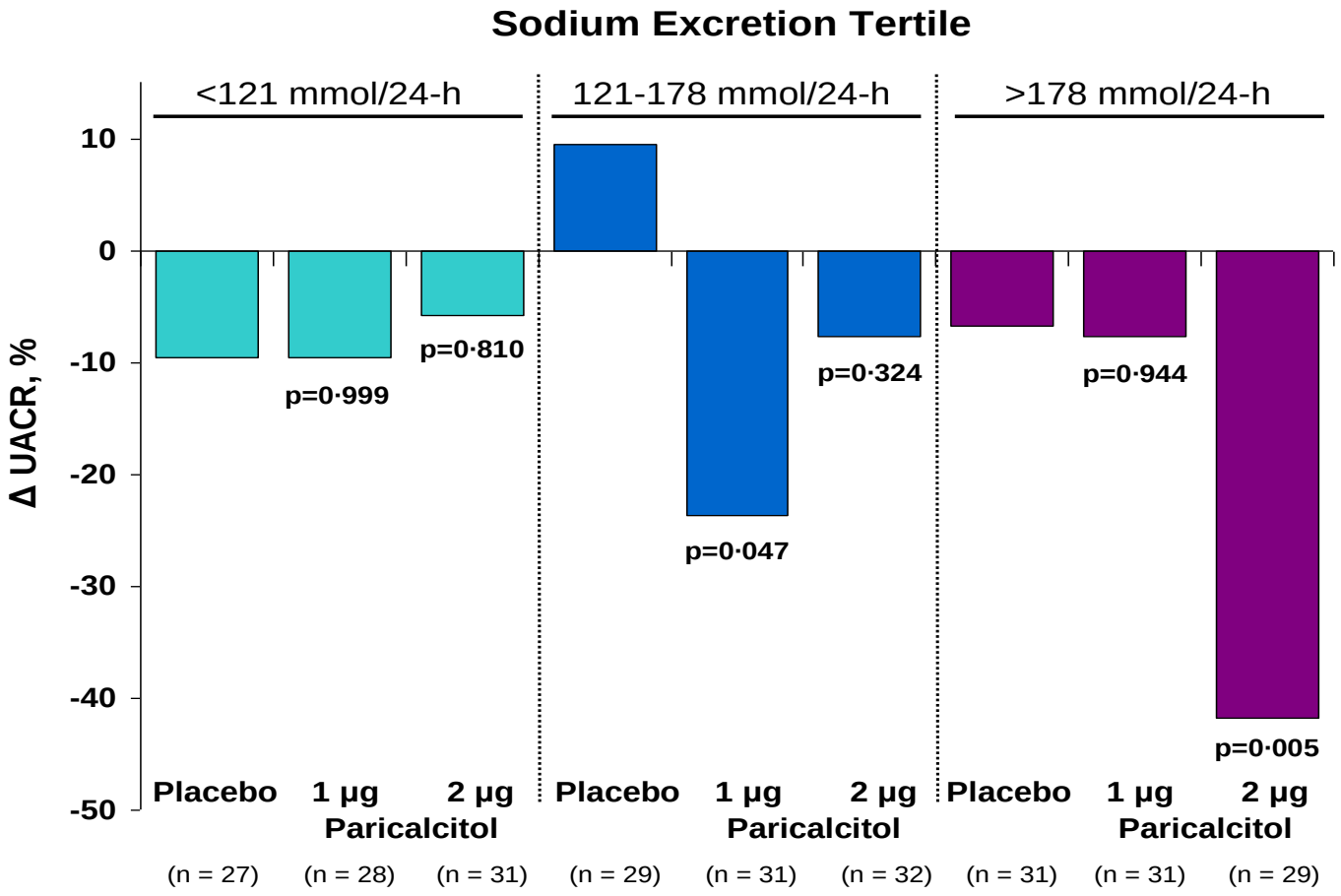

De Zeeuw D et al. Lancet 2010

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CYTOKINE MILIEU IN FIBROGENESIS

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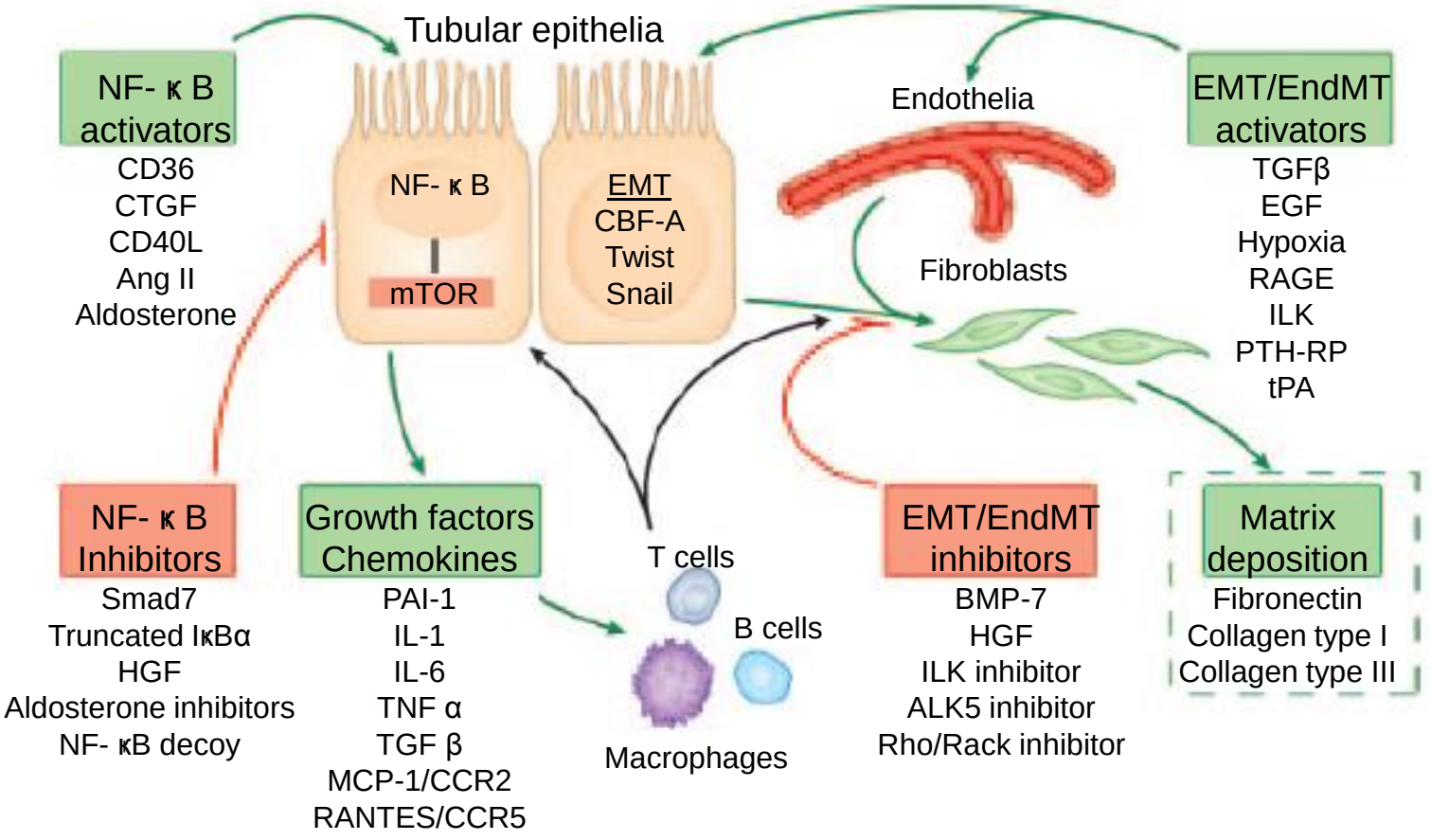

Zeisberg M et al. J Am Soc Nephrol 2010

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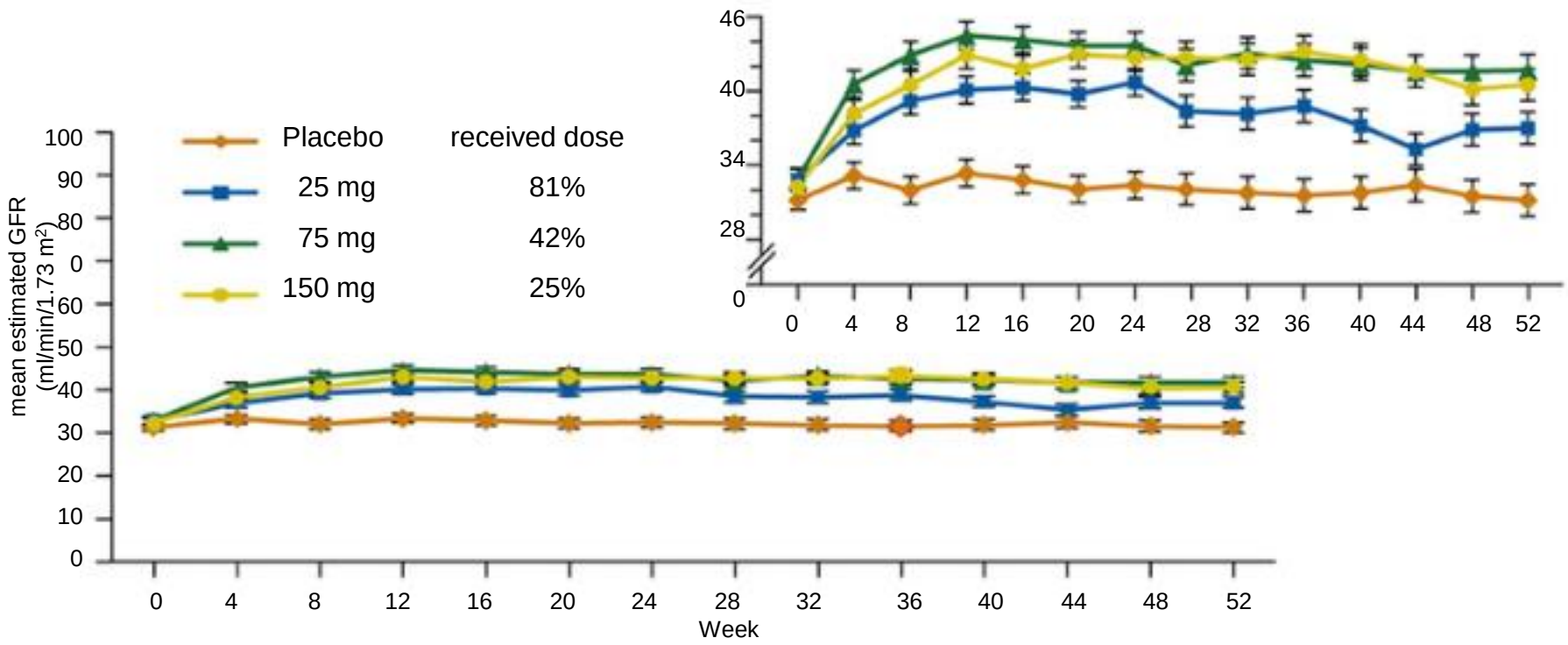

Pergola PE et al. N Engl J Med 2011

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CYNOMOLGUS MONKEY

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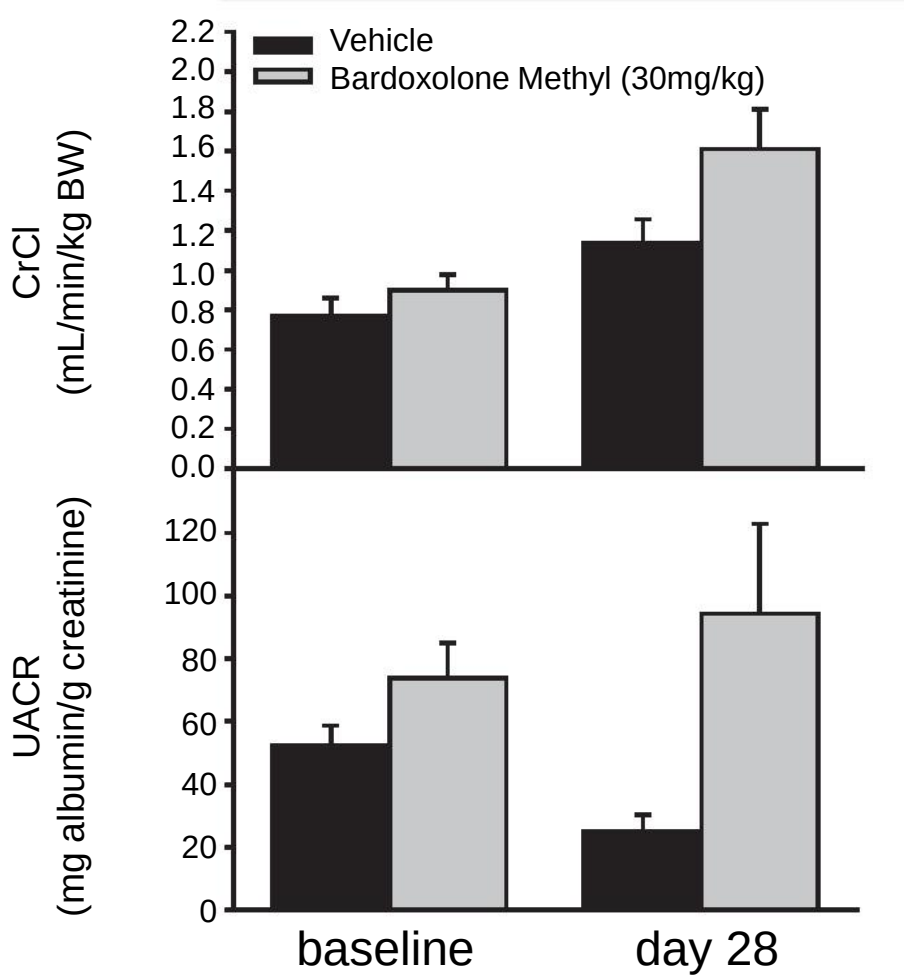

Reismann SA et al J Am Soc Nephrol 2012

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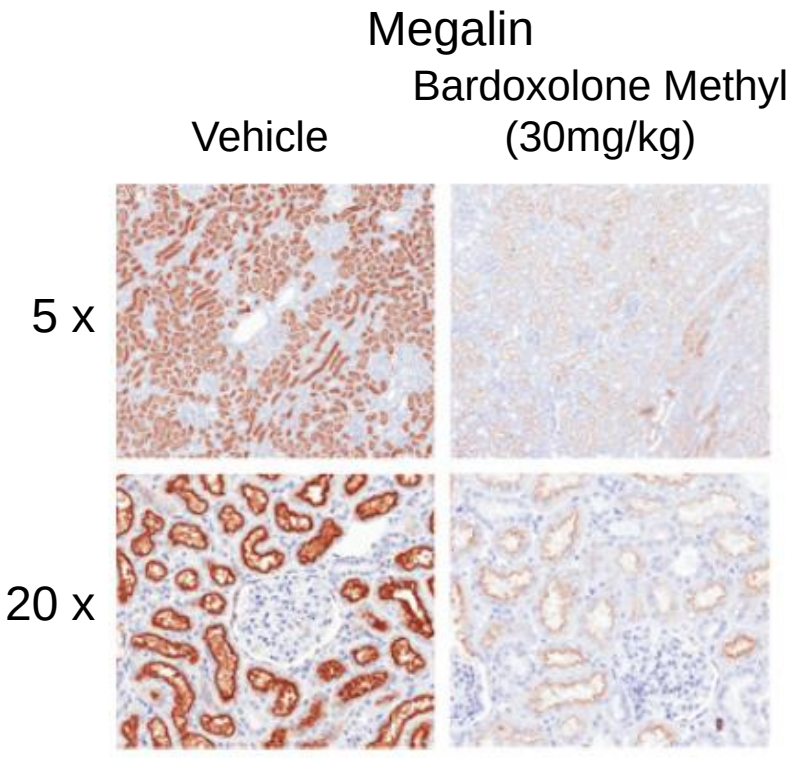

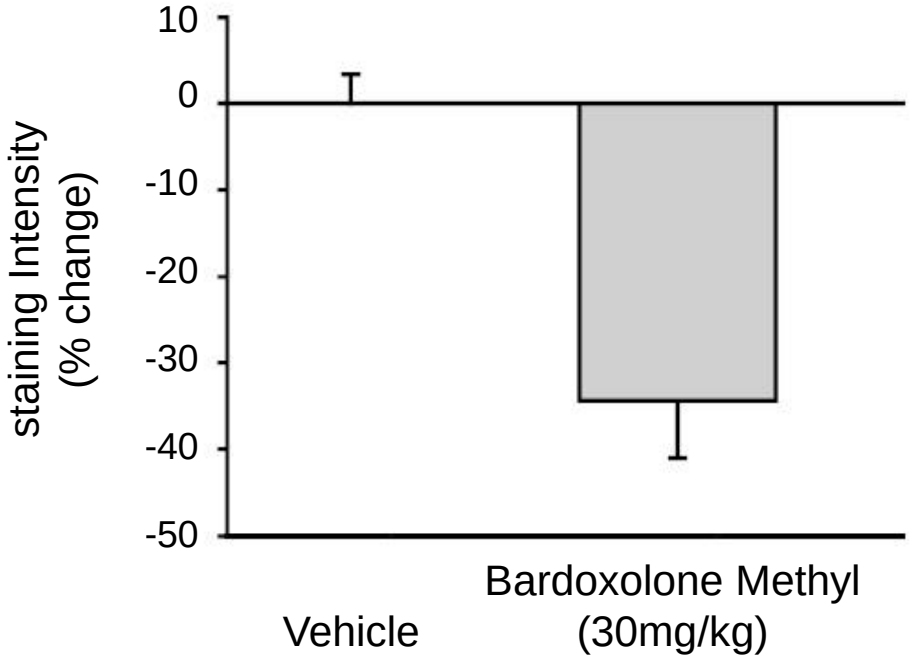

Reismann SA et al J Am Soc Nephrol 2012

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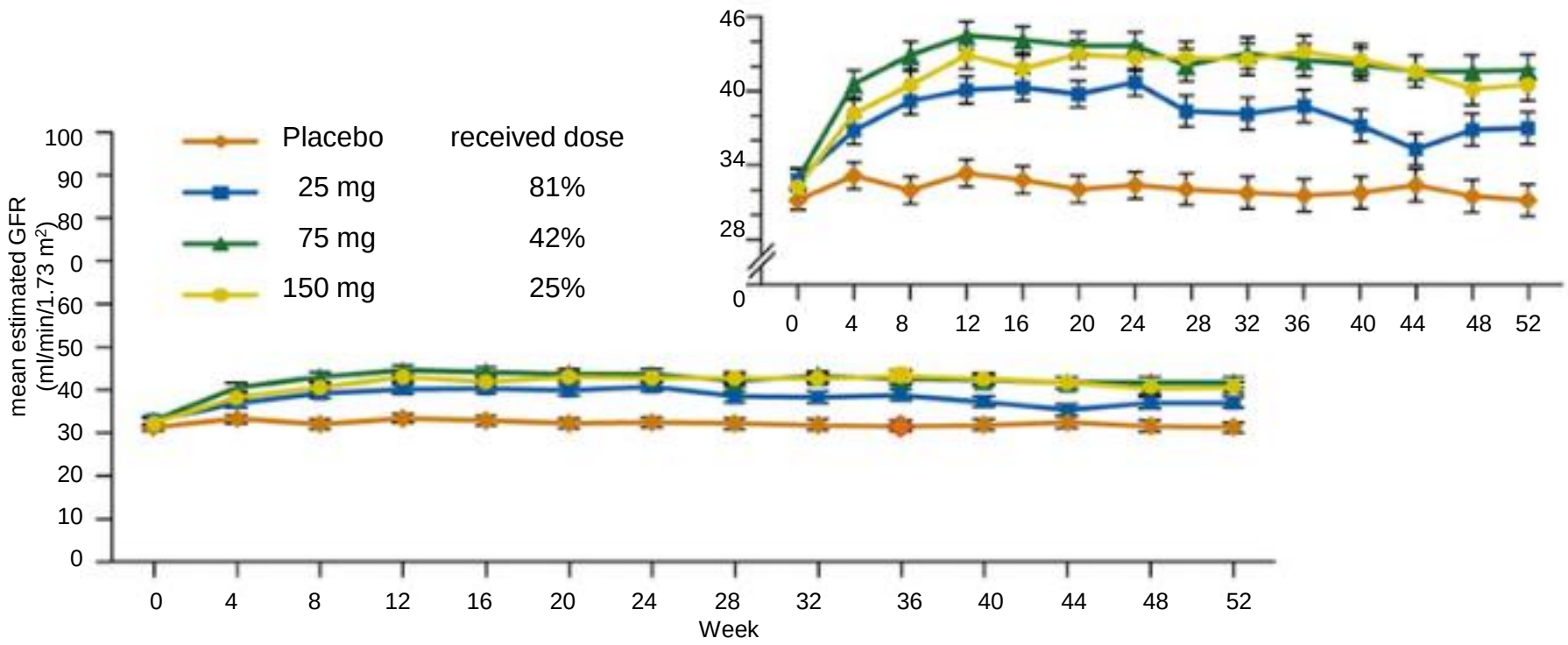

Pergola PE et al. N Engl J Med 2011

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A SYNTHETIC TRITERPENOID IN SPRAGUE DAWLEY RATS

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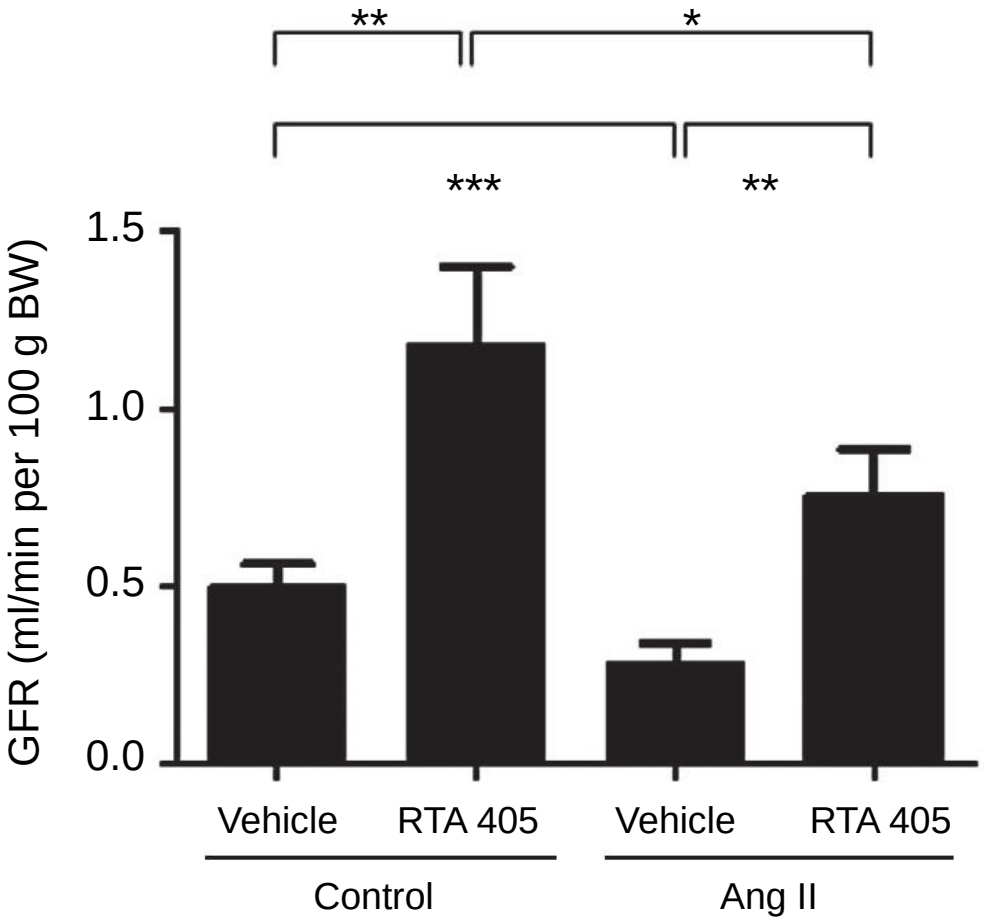

Ding Y et al. Kidney Int 2012

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A SYNTHETIC TRITERPENOID IN HUMAN MESANGIAL CELLS

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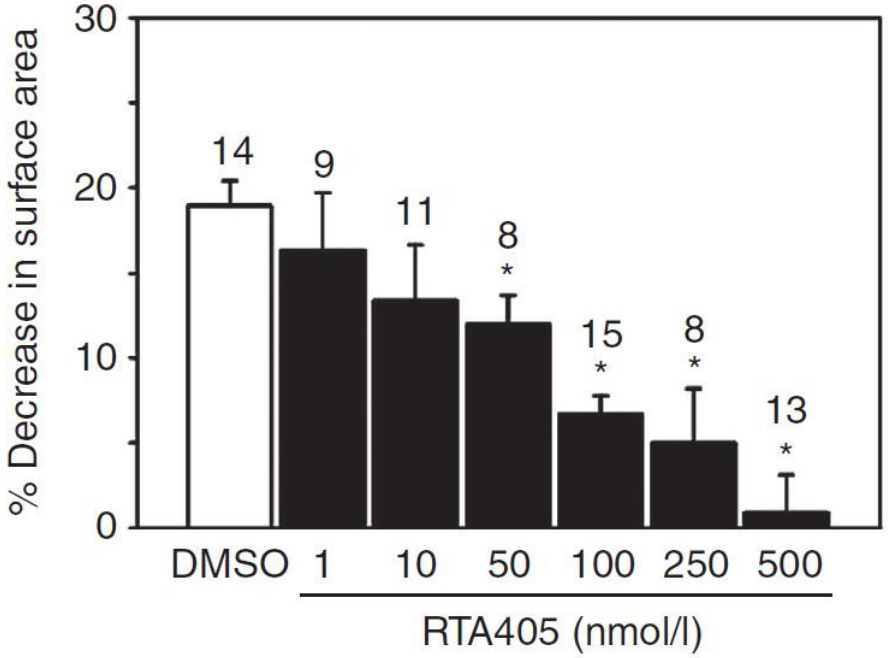

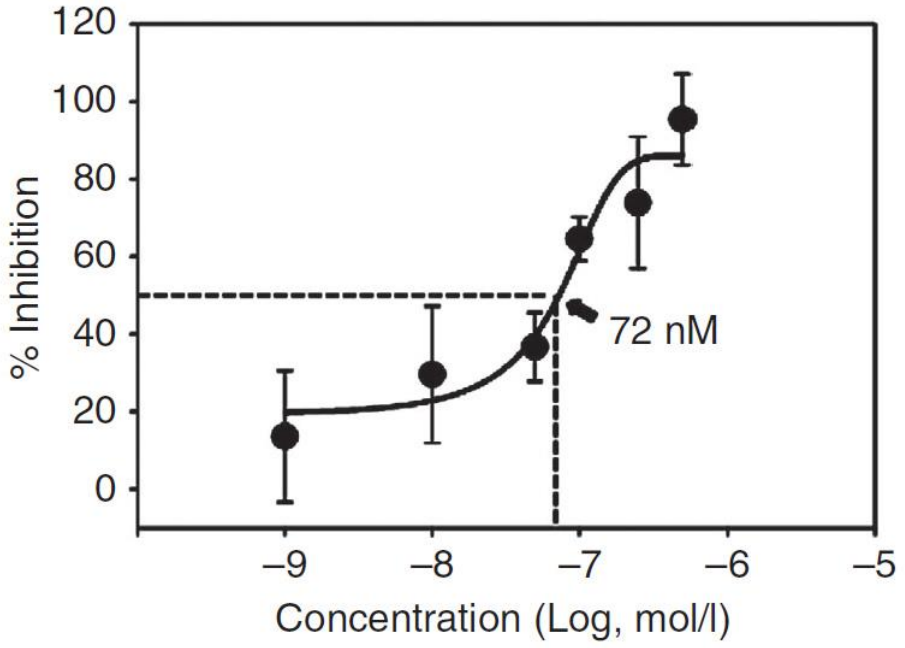

Ding Y et al. Kidney International 2012

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PIRFENIDONE IN DIABETIC NEPHROPATHY

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Treatment	eGFR Change (ml/min per 1.73 m²)	eGFR Change with imputation (ml/min per 1.73 m²)
Placebo	-2.2 ± 4.8	-3.7 ± 5.7
1200 mg Pirfenidone per day	3.3 ± 8.5	3.3 ± 8.5
2400 mg Pirfenidone per day	-1.9 ± 6.7	-2.1 ± 6.4
total	-0.3 ± 7.0	-0.7 ± 9.1

Sharma K et al. J Am Soc Nephrol 2011

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THE KIDNEY AS A TARGET ORGAN IN PHARMACEUTICAL RESEARCH

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Relevant targets in CKD.

Target(s)	Approach	Drug development status	Refs
RAAS, Aldo	Control of systemic blood pressure	In clinical practice	[69–72,74–77,79,80,82,83]
Endothelin receptor A	Inflammation	In clinical practice	[53,64,196,197]
Endothelin receptor B	Inflammation	In clinical practice	[53,64,196,197]
M1/M2 switch	Inflammation	Preclinical level	[117–119]
HIF-1	Hypoxia	Preclinical level	[122–125]
Actin polymerization	Direct inhibition of fibrotic cells	Phase I	[21,155,156]
Myofibroblast viability	Direct inhibition of fibrotic cells	Preclinical level	[162]
MMPs	ECM remodeling	Preclinical level	[167,168]
PAI-1	ECM remodeling	Phase I, II	[169–174]
LOXL2	ECM remodeling	Phase I	[169,175]
DDRs	ECM remodeling	Preclinical level	[169,176–178]
Snail, Twist and Slug	Phenotypical modulation	Preclinical level	[126]
Wnt/β-catenin signaling	Phenotypical modulation	Phase I	[127–130]
TGF-β1	Phenotypical modulation	Phase I, II	[131,132]
Smads	Phenotypical modulation	Phase I	[131,135–137]
αvβ6 integrin	Phenotypical modulation	Phase II	[138,139]
BMP-7	Phenotypical modulation	Phase I	[140–143]
Kielin/chordin-like protein	Phenotypical modulation	Preclinical level	[144]
USAG-1	Phenotypical modulation	Preclinical level	[145,146]
Gremlin	Phenotypical modulation	Preclinical level	[147,148]
ALK-3	Phenotypical modulation	Preclinical level	[149–151]
HGF	Phenotypical modulation	Phase I	[152–154]
Cannabinoid receptors	Phenotypical modulation	Preclinical level	[157,158]
MeCP2	Phenotypical modulation	Preclinical level	[159,161]
PPAR-γ	Phenotypical modulation	In clinical practice	[160]

Prunotto M et al. Drug Dis Today 2011

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FOLIC ACID AND VITAMIN B IN DIABETES MELLITUS

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	Baseline mean (SE) (n=238)	mean change (SE) 18 mo (n=104) (n=101)	24 mo (n=88) (n=83)	36 mo (n=61) (n=57)	difference at 36 months between groups (95% CI)	p value
isotope GFR						
Placebo	54.7 (1.9)	-8.1 (1.4)		-10.7 (1.7)	-5.8 (-10.6 to -1.1)	.02
B Vitamine		-10.2 (1.4)		-16.5 (1.7)		
proteinuria						
Placebo	1.47 (0.11)	0.33 (0.13)	0.21 (0.14)	0.17 (0.16)	0.05 (-0.39 to 0.50)	.82
B Vitamine		0.11 (0.13)	0.08 (0.14)	0.22 (0.16)		

House AA et al. JAMA 2010

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