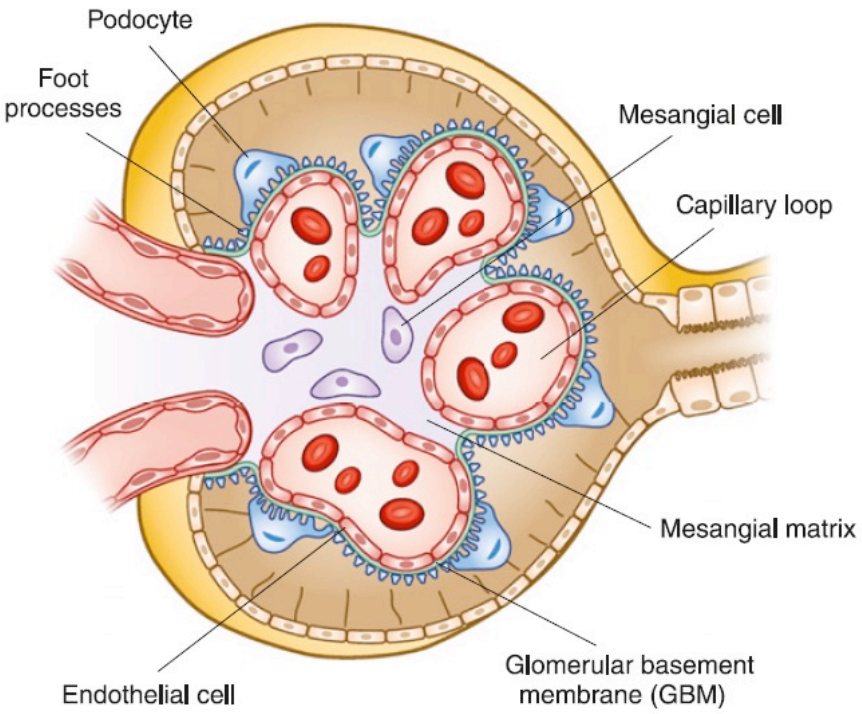
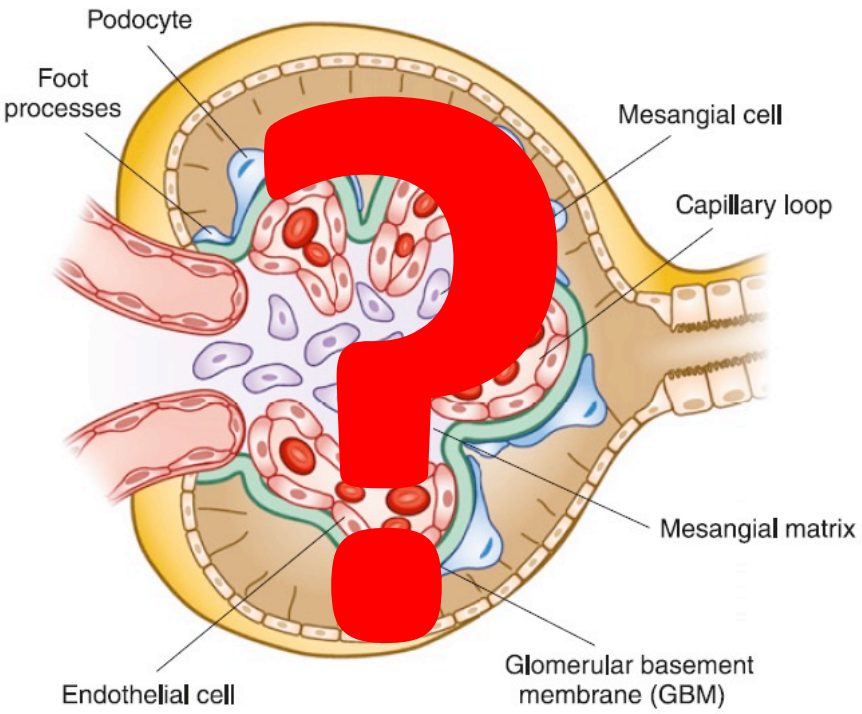
NEFROPATIA DIABETICA
Fattori di progressione e ruolo dei farmaci

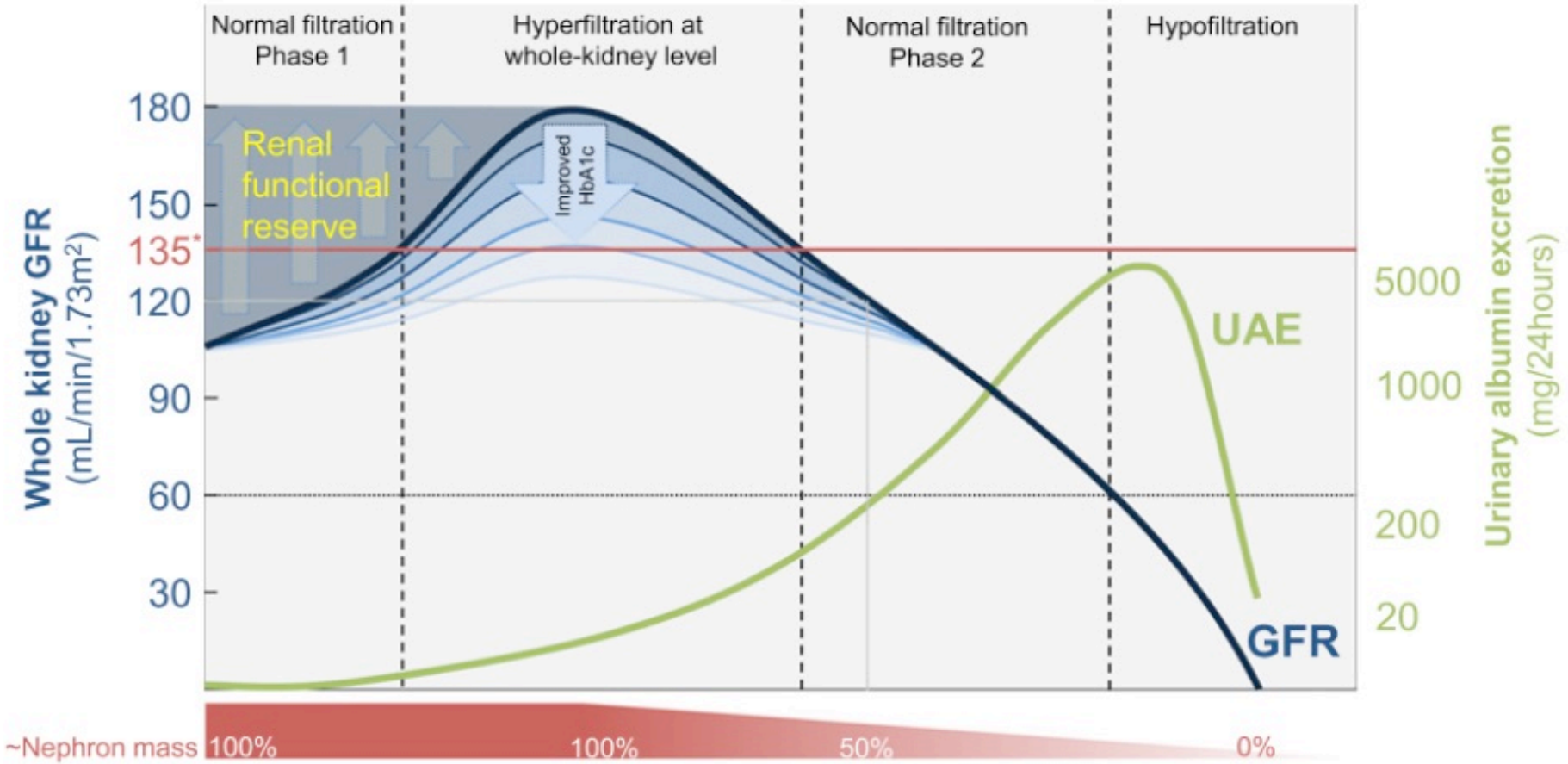
A. Guarnieri
UOC Nefrologia Dialisi e Trapianti
AOU Senese

Normal kidney glomerulus



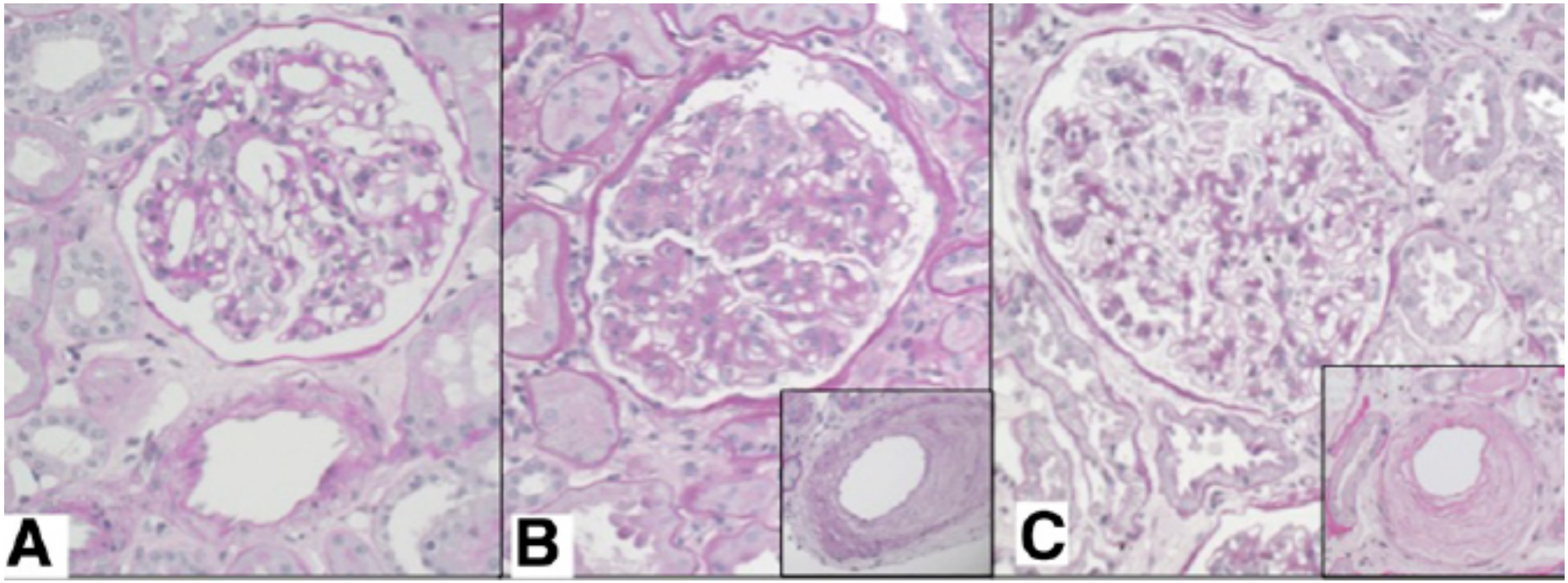
Diabetic kidney glomerulus





UKPDS : 1132 paz. con sviluppo di IRC.
60% no precedente albuminuria. 40% no comparsa di albuminuria

Ridotto GFR e normoalbuminuria

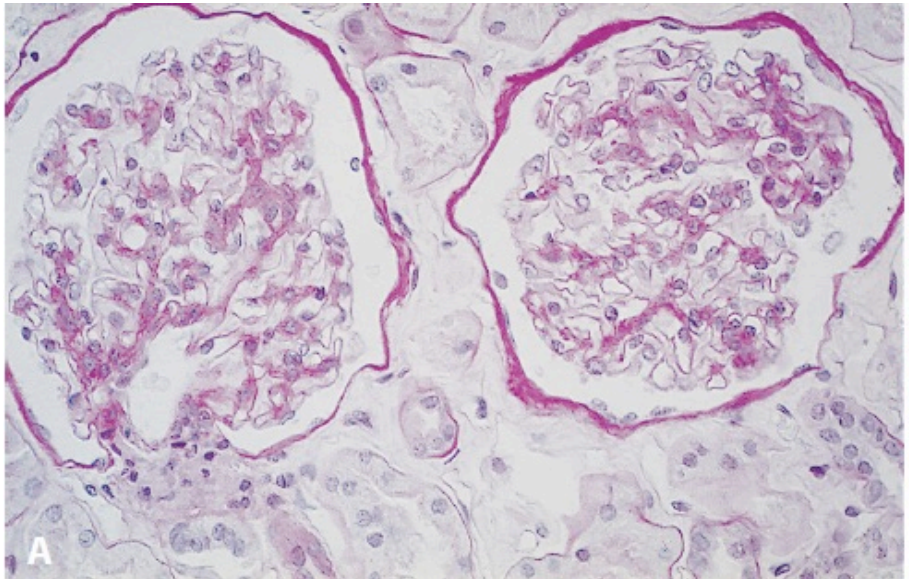


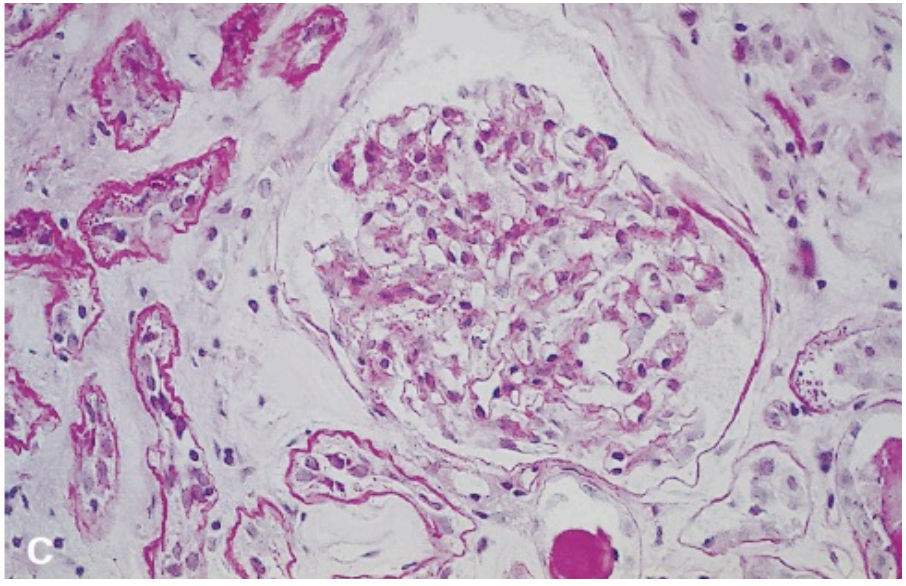
Reperto normale: **2 paz.** Nefropatia diabetica: **3 paz.** Danni vascolari: **3 paz.**

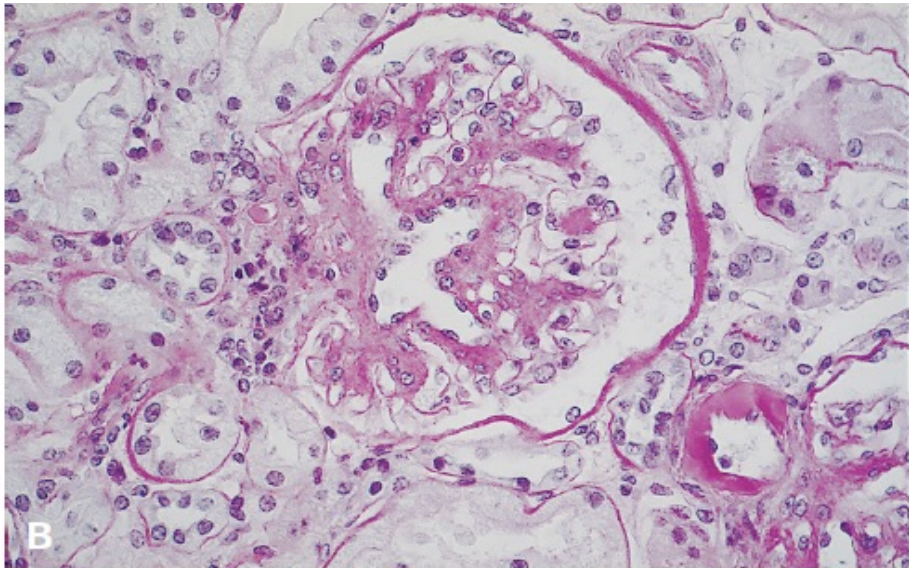
Diabetes Care 36:3620–3626, 2013

Patterns of renal injury in NIDDM patients with microalbuminuria

P. Fioretto[1], M. Mauer[2], E. Brocco[1], M. Velussi[3], F. Frigato[3], B. Muollo[3], M. Sambataro[3], C. Abaterusso[1], B. Baggio[1], G. Crepaldi[1], R. Nosadini[1, 4]







GFR 101 ± 27 mL/min/1.73mq

AER 44 (20-199 µg/min)

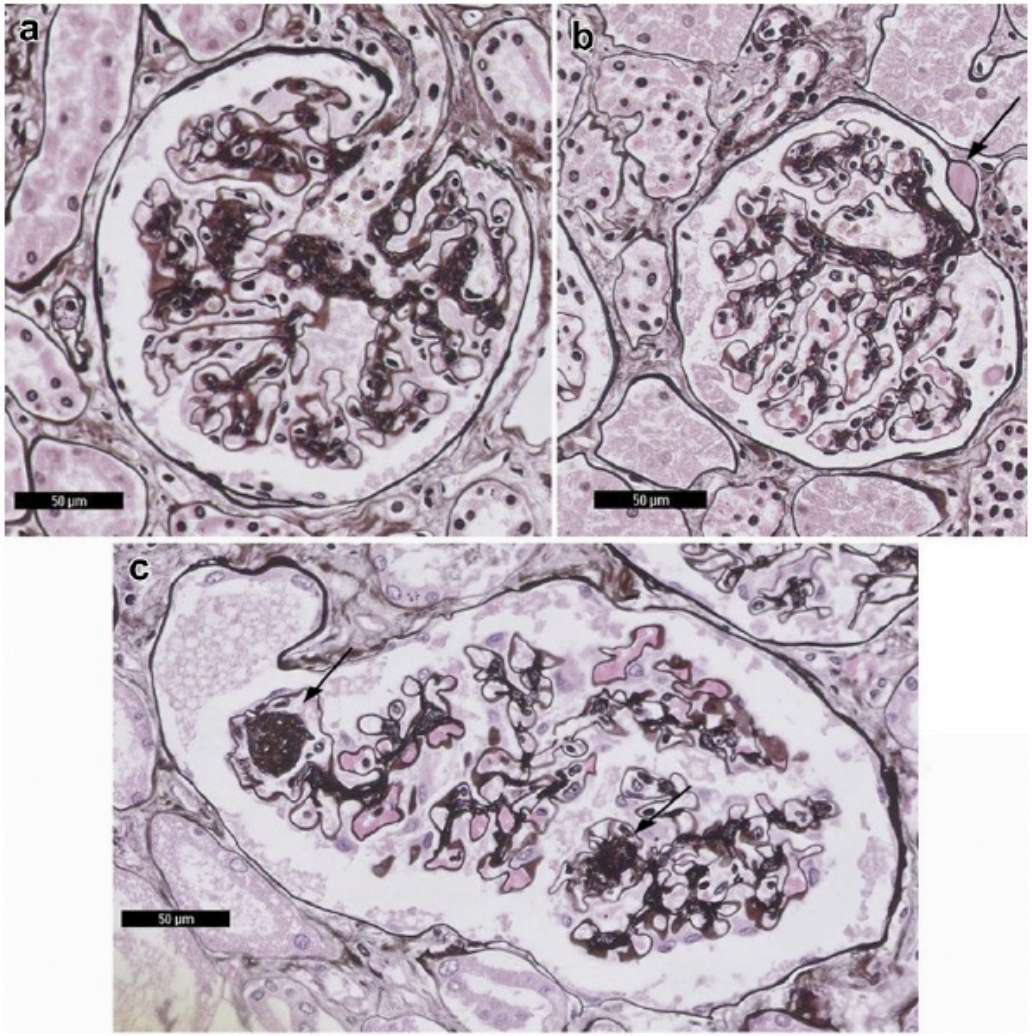
A.Normale (29,4%)

B.Nefropatia diabetica tipica (29,4%)

C.Danno prevalentemente vasculo interstiziale (41,2%)

Diabetologia (1996) 39: 1569–1576

An autopsy study suggests that diabetic nephropathy is underdiagnosed



Kidney International (2016) **90,** 149–156

20/106 diagnosi istologica di nefropatia diabetica in assenza di segni clinici

Predictive factors for non-diabetic nephropathy in diabetic patients. The utility of renal biopsy☆

Table 3 – Predictive factors for non-diabetic nephropathy in diabetic patients.

Parameter	OR	CI (95%)	Lateral significance (*p*)
Creatinine (mg/dL)	1.48	1.01–2.17	0.04
Proteinuria (g/24 h)	0.81	0.68–0.97	0.03
Duration of DM (years)	0.992	0.987–0.998	0.004
Age (years)	1.07	1.01–1.13	0.02
Retinopathy (yes/no)	0.23	0.07–0.81	0.02

Multivariate binary logistic regression analysis. Dependent variable: non-diabetic nephropathy.
95% CI: confidence interval of 95%; OR: odds ratio.

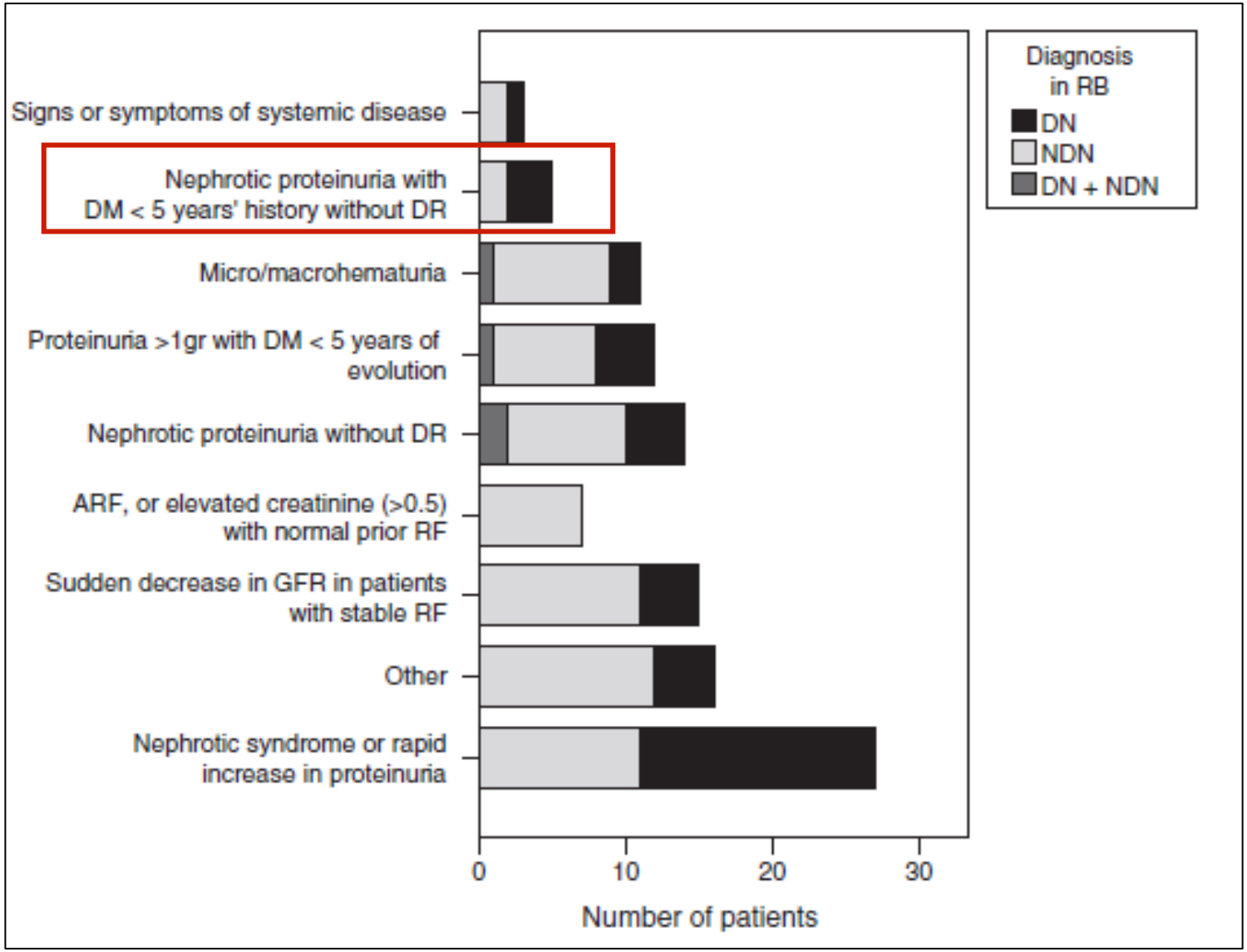

Diagnosis in RB
DN
NDN
DN + NDN
Signs or symptoms of systemic disease
Nephrotic proteinuria with DM < 5 years' history without DR
Micro/macrohematuria
Proteinuria >1gr with DM < 5 years of evolution
Nephrotic proteinuria without DR
ARF, or elevated creatinine (>0.5) with normal prior RF
Sudden decrease in GFR in patients with stable RF
Other
Nephrotic syndrome or rapid increase in proteinuria
0
10
20
30
Number of patients

Table 1. Risk factors for diabetic kidney disease

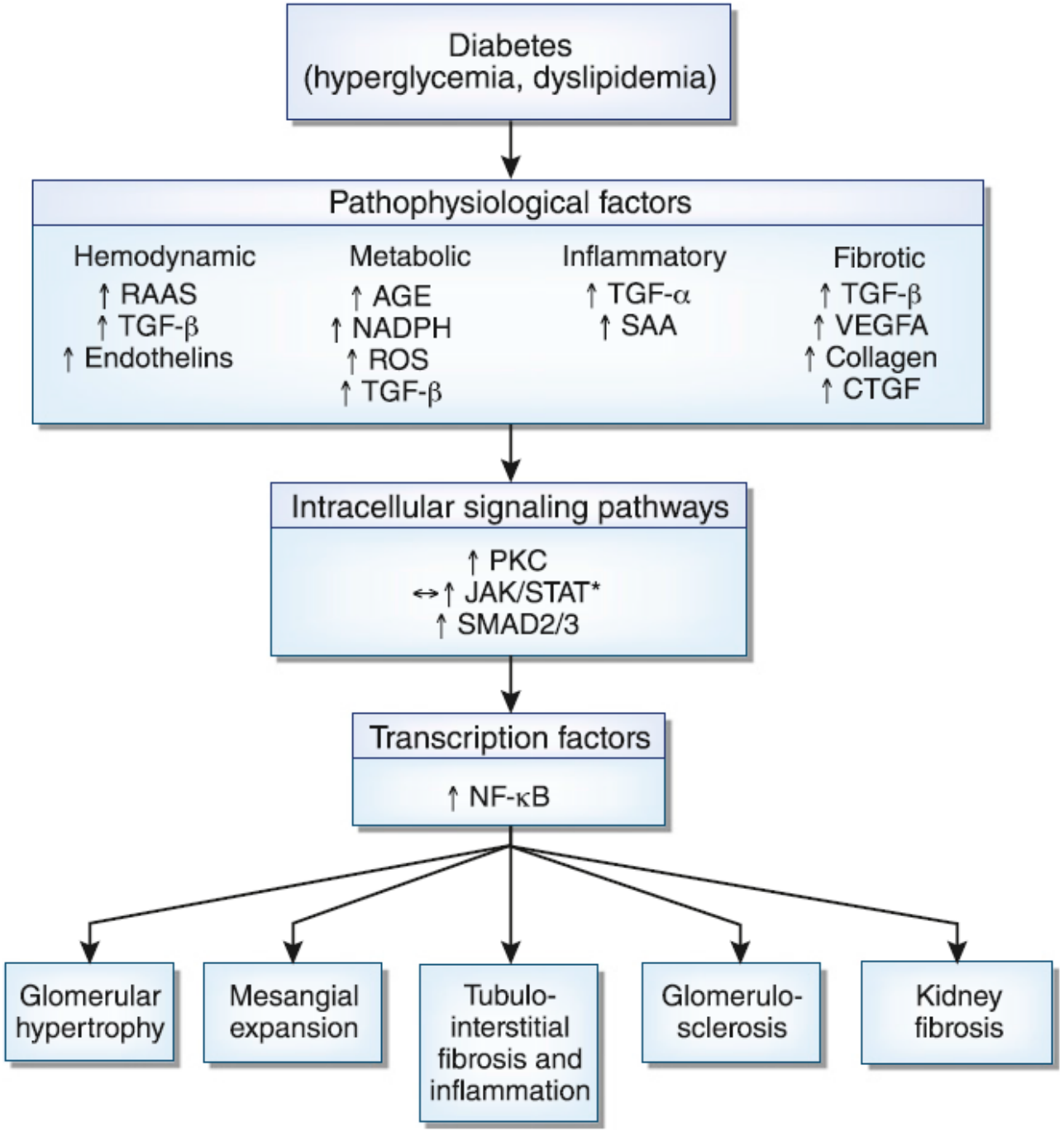
Risk Factor	Susceptibility	Initiation	Progression
Systemic conditions			
Hyperglycemia	+	+	+
Obesity	+	+	+
Hypertension	+		+

DKD, diabetic kidney disease.

Table 1. Risk factors for diabetic kidney disease

Risk Factor	Susceptibility	Initiation	Progression
Demographic			
Older age	+		
Sex (men)	+		
Race/ethnicity (black, American Indian, Hispanic, Asian/Pacific Islanders)	+		+
Hereditary			
Family history of DKD	+		
Genetic kidney disease		+	
Systemic conditions			
Hyperglycemia	+	+	+
Obesity	+	+	+
Hypertension	+		+
Kidney injuries			
AKI		+	+
Toxins		+	+
Smoking	+		+
Dietary factors	+		+
High protein intake	+		+

DKD, diabetic kidney disease.


Diabetes
(hyperglycemia, dyslipidemia)
Pathophysiological factors
Hemodynamic
↑ RAAS
↑ TGF-β
↑ Endothelins
Metabolic
↑ AGE
↑ NADPH
↑ ROS
↑ TGF-β
Inflammatory
↑ TGF-α
↑ SAA
Fibrotic
↑ TGF-β
↑ VEGFA
↑ Collagen
↑ CTGF
Intracellular signaling pathways
↑ PKC
↔↑ JAK/STAT*
↑ SMAD2/3
Transcription factors
↑ NF-κB
Glomerular hypertrophy
Mesangial expansion
Tubulo-interstitial fibrosis and inflammation
Glomerulo-sclerosis
Kidney fibrosis

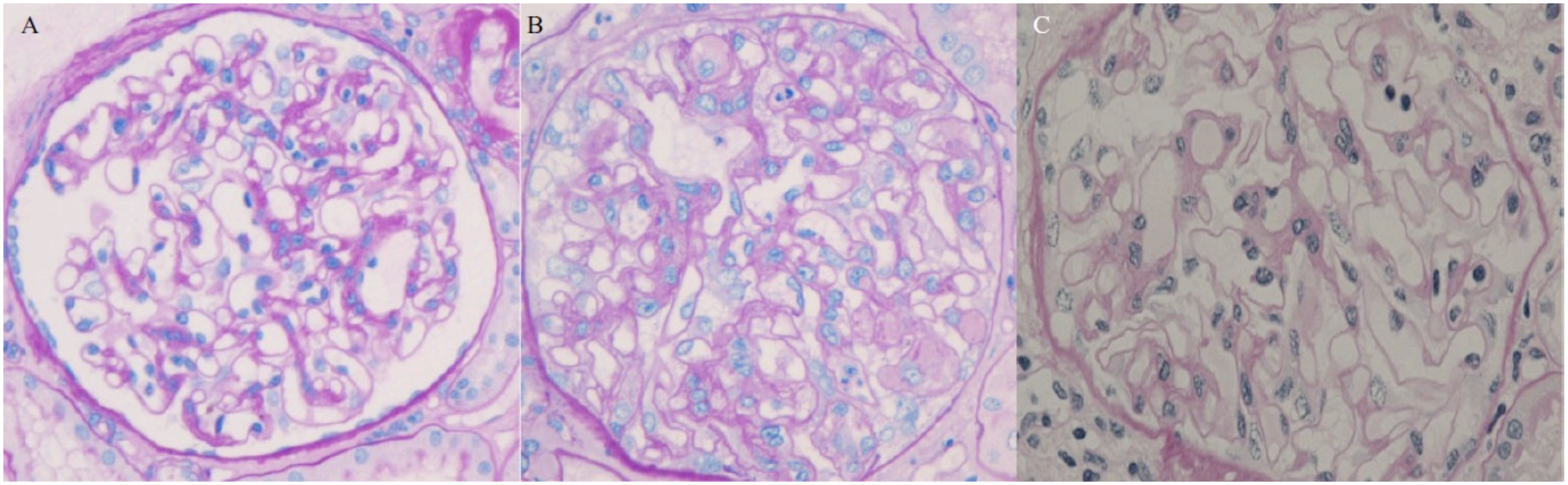
DMT1 normoalbuminurici

	Progressors (n=12)	Nonprogressors (n=59)	P Value
Sex (men/women)	4/8	24/35	NS
Age (yr)	26.7±7.3	35.0±9.9	0.007
Age at onset (yr)	11.1±6.2	15.1±8.7	NS
Diabetes duration (yr)	15.6±7.4	19.8±10.2	NS
Follow-up (yr)	13.9±7.6	12.4±5.4	NS
Albumin excretion rate (μg/min)	7.0±5.2	7.5±4.7	NS
GFR (ml/min per 1.73 m^2)	105.4±25.4	108.7±21.3	NS
Systolic BP (mmHg)	113.0±9.9	114.2±10.8	NS
Diastolic BP (mmHg)	74.2±7.5	70.5±7.8	NS
Hypertension (yes/no)	3/9	12/47	NS
Retinopathy (yes/no/unknown)	5/5/2	14/29/16	NS
A_{1c} (%)	10.4±2.5	8.0±1.2	0.01

Data are mean ± SD or number of subjects with a given characteristic.

J Am Soc Nephrol **24**: 1175–1181, 2013

Histological reversibility of diabetic nephropathy after kidney transplantation from diabetic donor to non-diabetic recipient

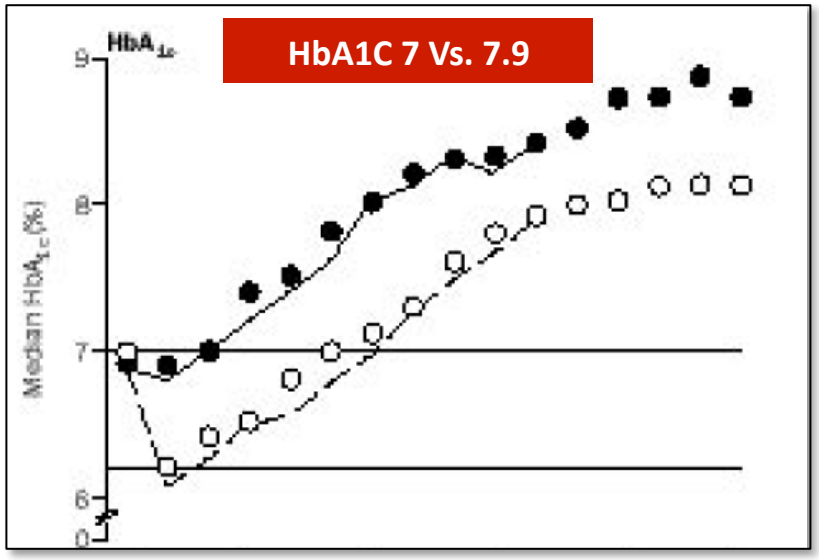


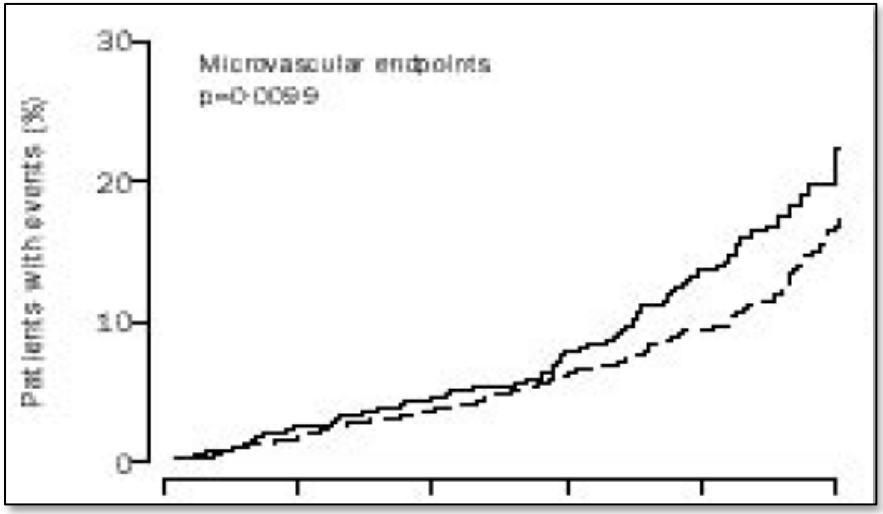
1 ora **1 mese** **1 anno**

Case	Protocol biopsy		
	1 hour	1 month	1 year
1	IIa	IIa	0
2	I	I	0
3	I	I	0

Nephrology **20, Suppl. 2** (2015) 40–44

UKPDS 33





THE LANCET • Vol 352 • September 12, 1998

Legacy Effect of Earlier Glucose Control

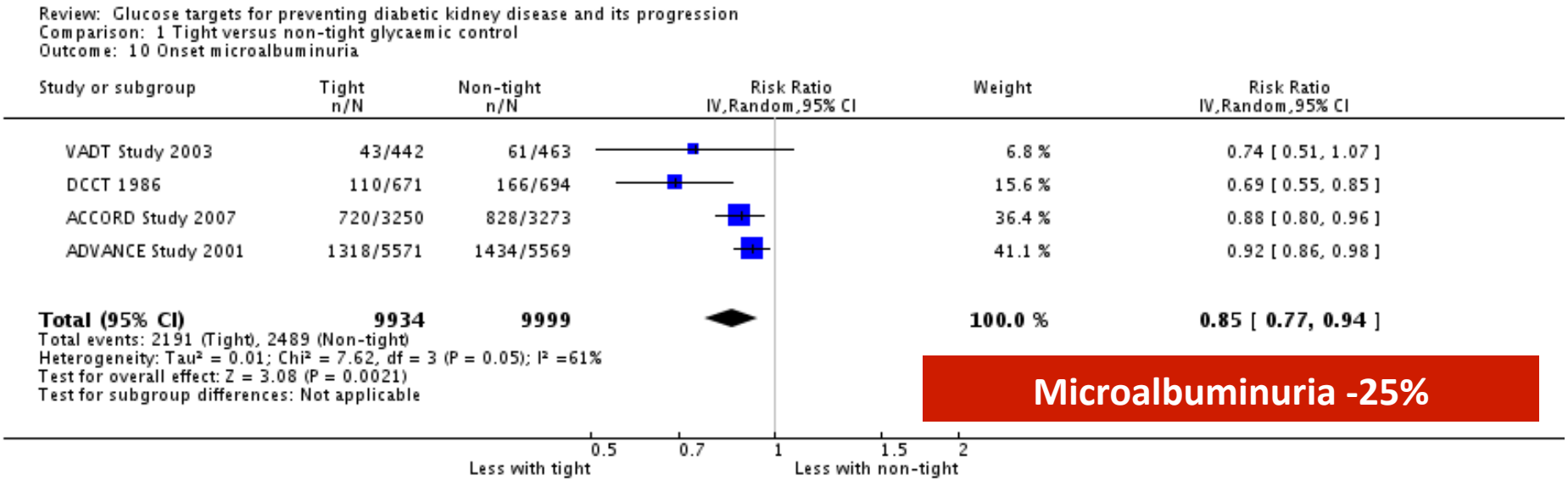
After median 8.5 years post-trial follow-up

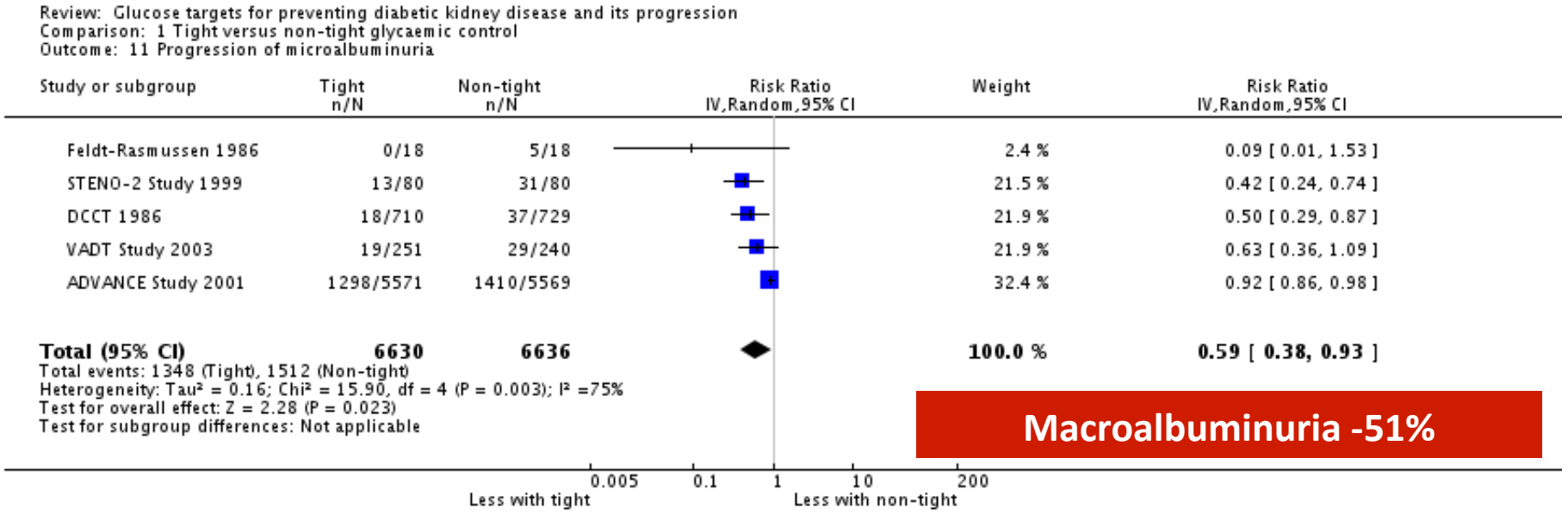
Aggregate Endpoint		1997	2007
Any diabetes related endpoint	*RRR:*	12%	**9%**
	P:	0.029	**0.040**
Microvascular disease	*RRR:*	25%	**24%**
	P:	0.0099	**0.001**
Myocardial infarction	*RRR:*	16%	**15%**
	P:	0.052	**0.014**
All-cause mortality	*RRR:*	6%	**13%**
	P:	0.44	**0.007**

RRR = Relative Risk Reduction, P = Log Rank

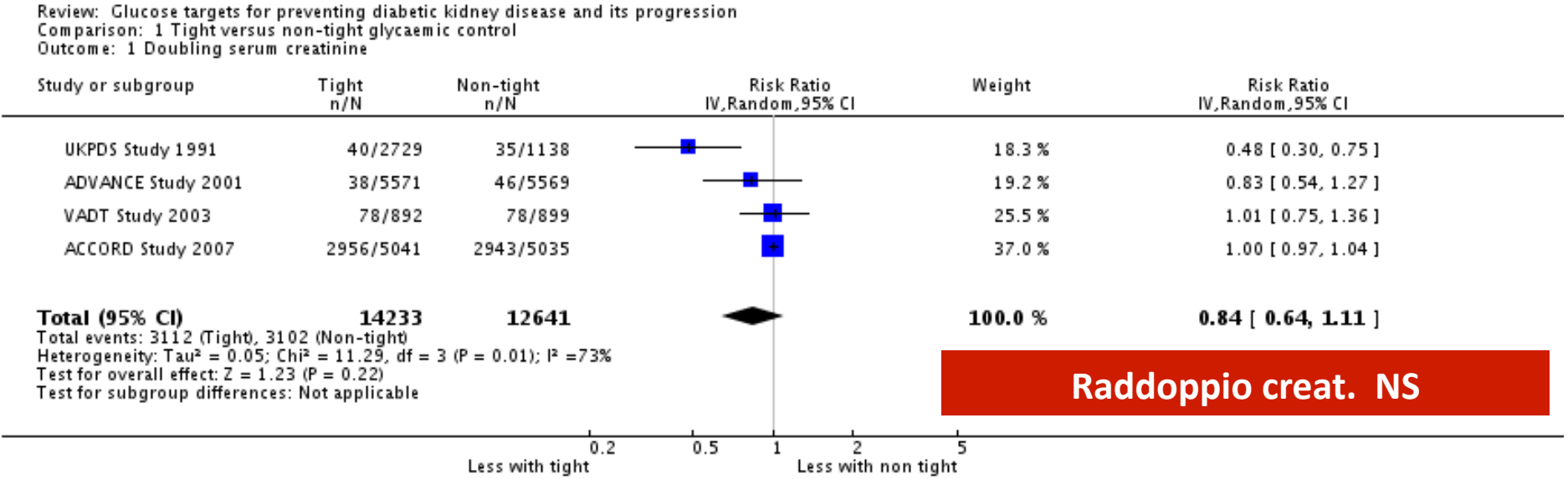
UKPDS 80. N Eng J Med 2008; ***359****:*

ukpds~ptm

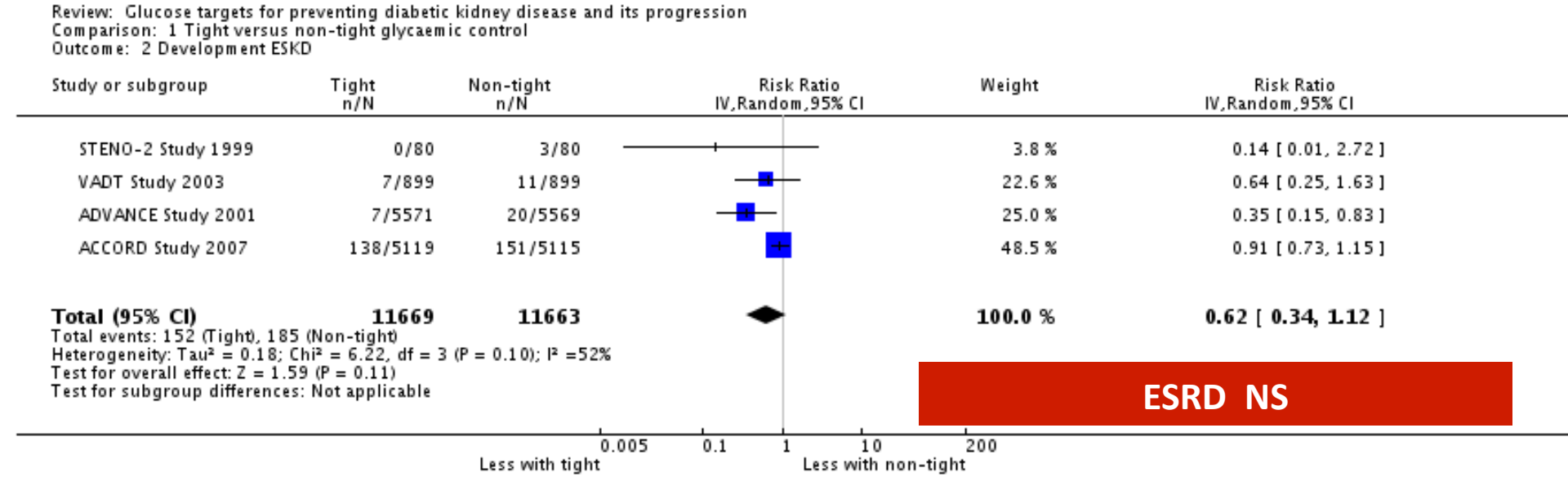




Cochrane Database of Systematic Reviews
8 JUN 2017 DOI: 10.1002/14651858.CD010137.pub2
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010137.pub2/full#CD010137-fig-00110



Raddoppio creat. NS



ESRD NS

Cochrane Database of Systematic Reviews
8 JUN 2017 DOI: 10.1002/14651858.CD010137.pub2
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010137.pub2/full#CD010137-fig-00101

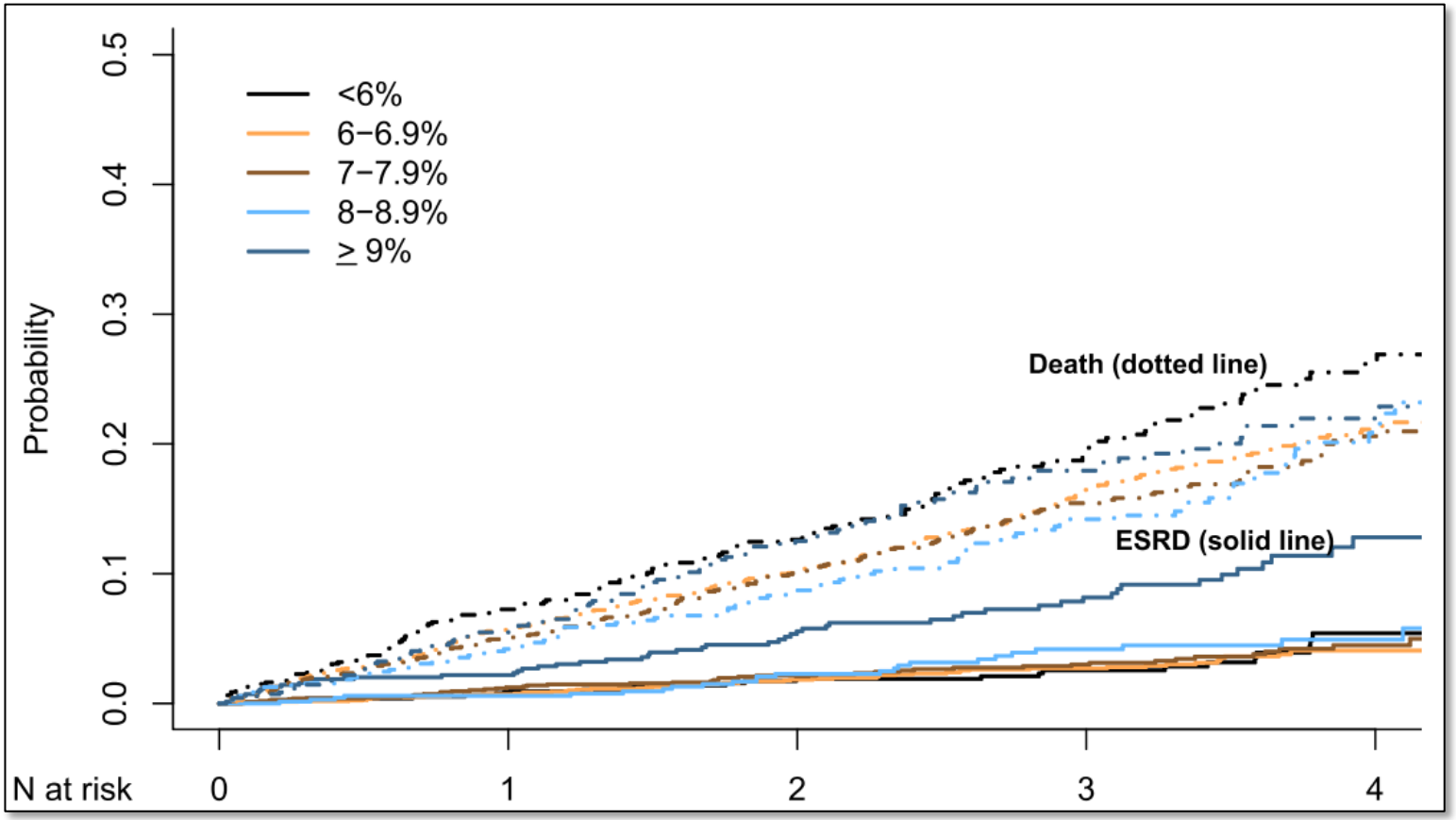
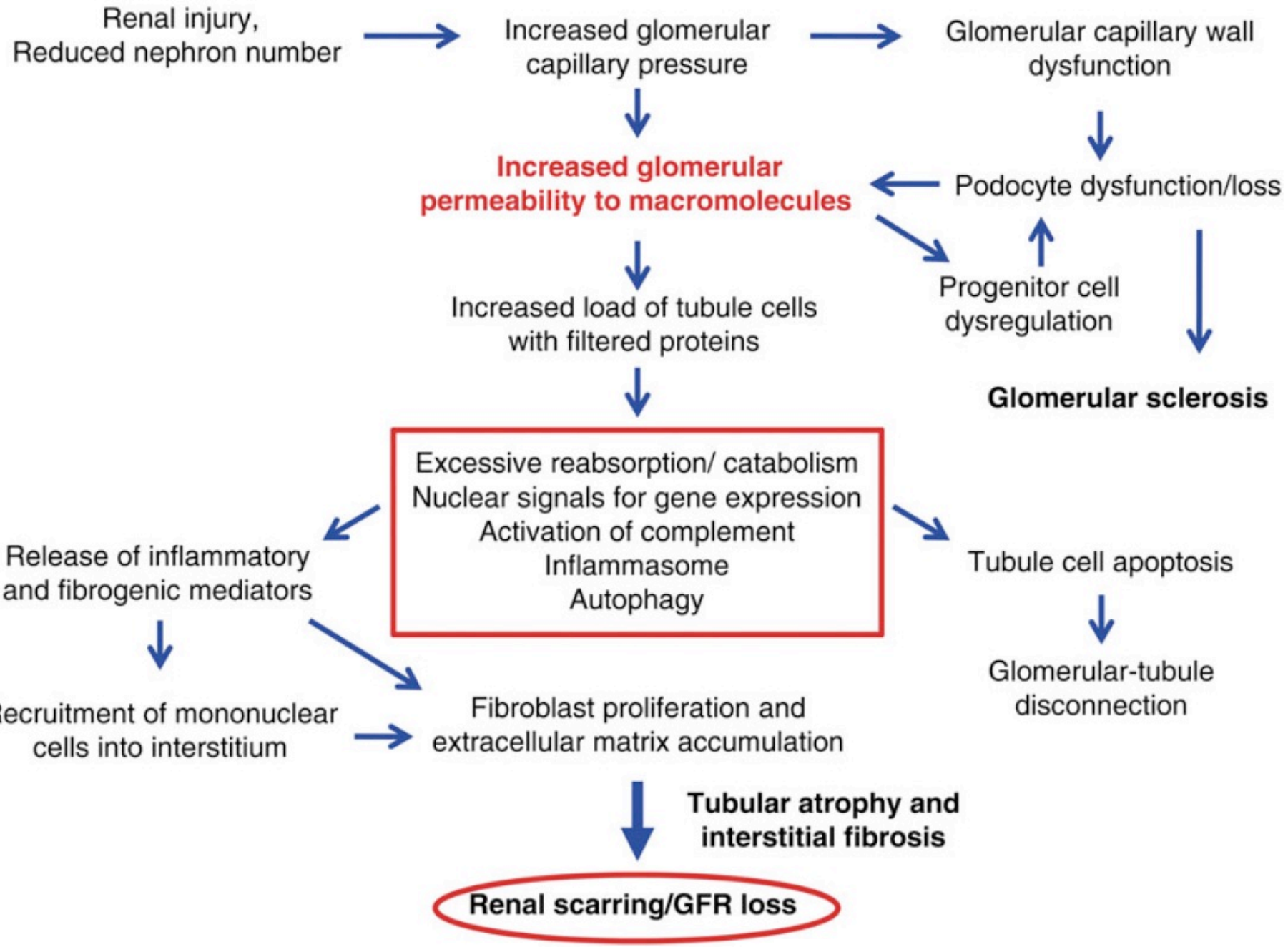
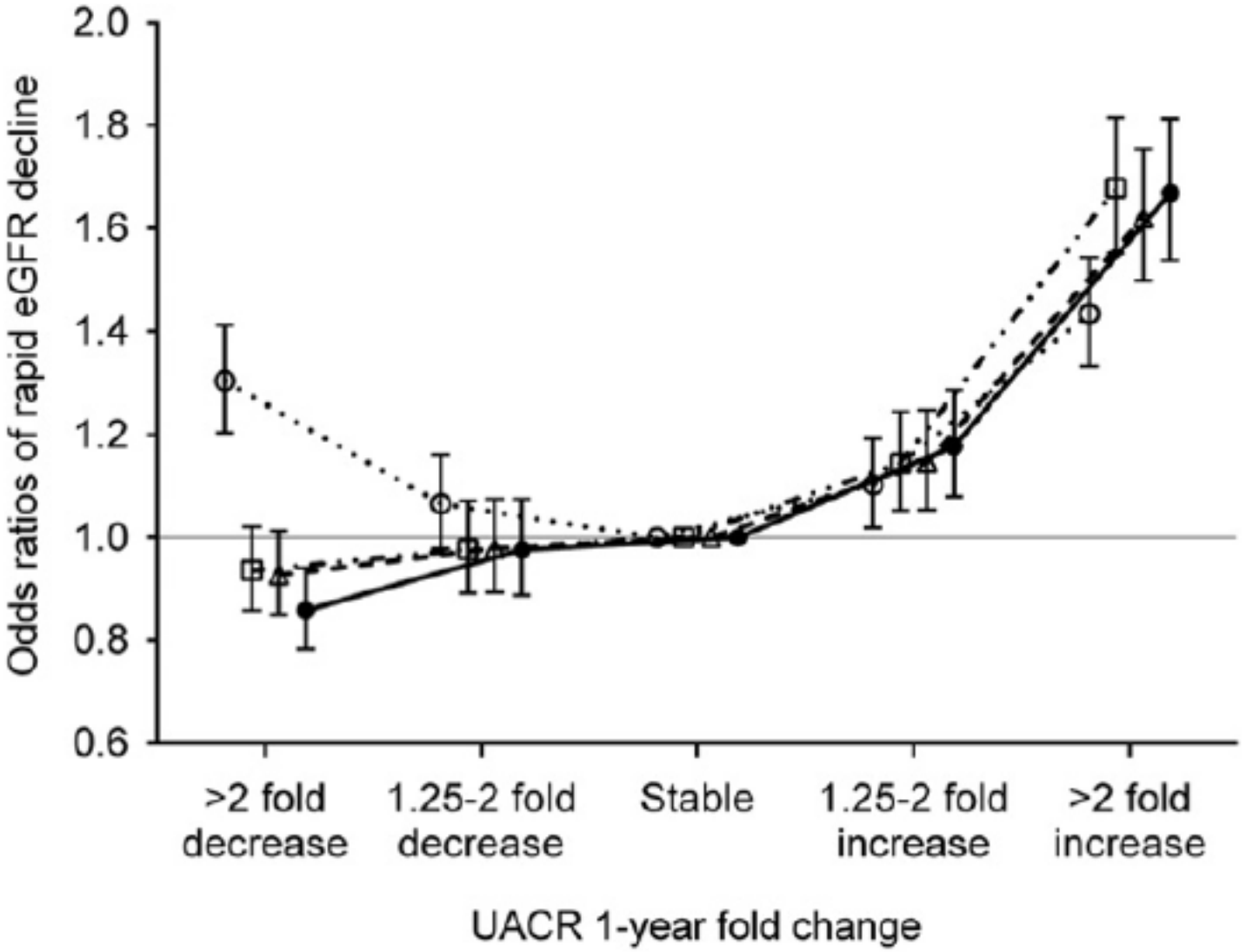


Table 3. Associations of HbA_{1c} With ESRD: Competing-Risk Model With Death as Competing Risk

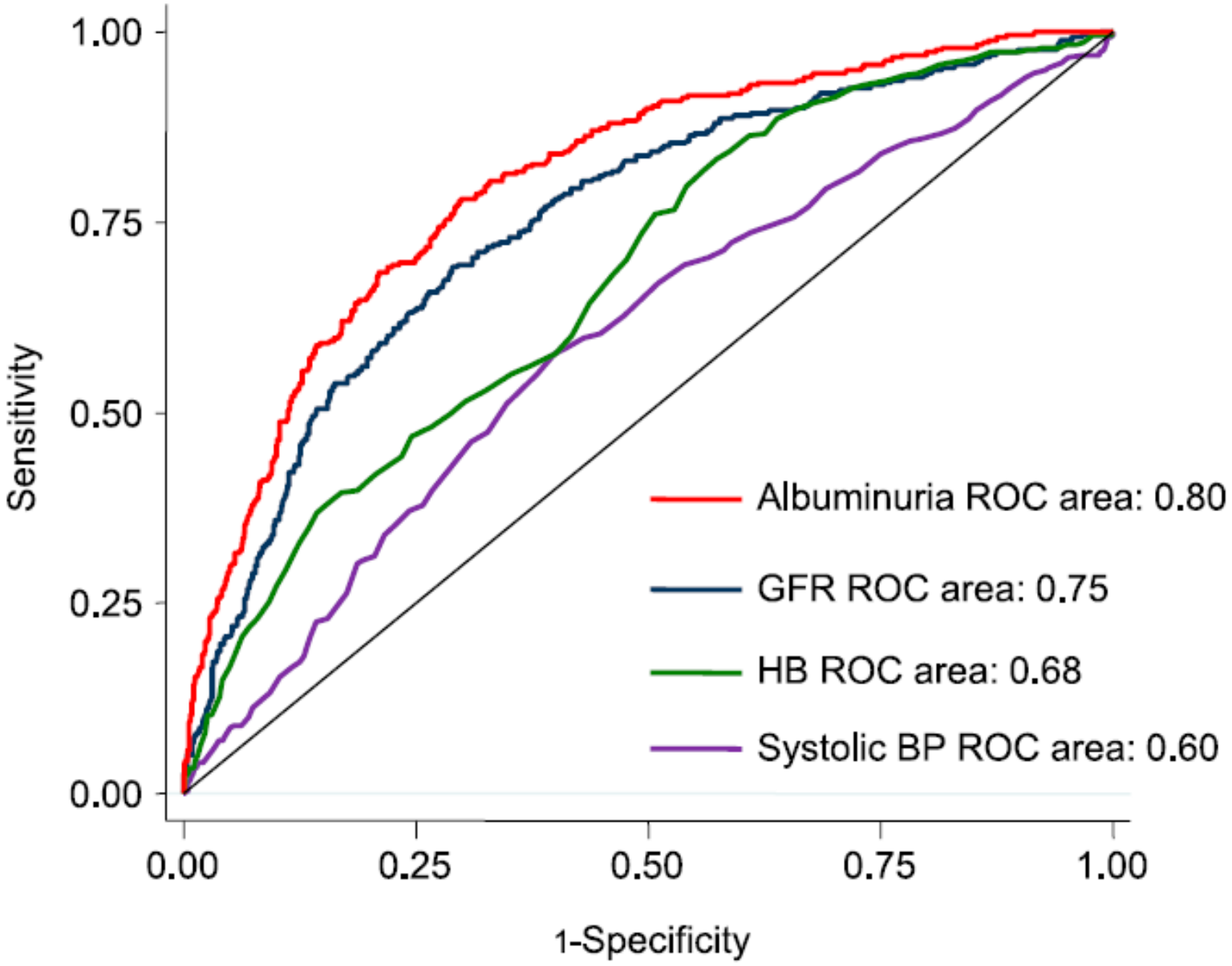
	HbA_{1c} < 6%	HbA_{1c} 7%-7.9%	HbA_{1c} 8%-8.9%	HbA_{1c} ≥ 9%
Unadjusted	1.10 (0.68-1.78)	1.18 (0.80-1.73)	1.31 (0.82-2.11)	3.15 (2.17-4.57)
Adjusted for				
1) Age, race, sex	0.98 (0.61-1.59)	1.05 (0.73-1.55)	1.07 (0.66-1.73)	1.95 (1.32-2.87)
2) 1 + comorbid conditions, BMI group, albumin, hemoglobin, smoking	0.87 (0.53-1.41)	0.99 (0.67-1.47)	1.02 (0.62-1.68)	1.76 (1.15-2.67)
3) 2 + ACEi/ARB, statin, β-blocker, eGFR, proteinuria	0.58 (0.32-1.02)	0.92 (0.62-1.37)	0.65 (0.38-1.12)	1.35 (0.88-2.09)



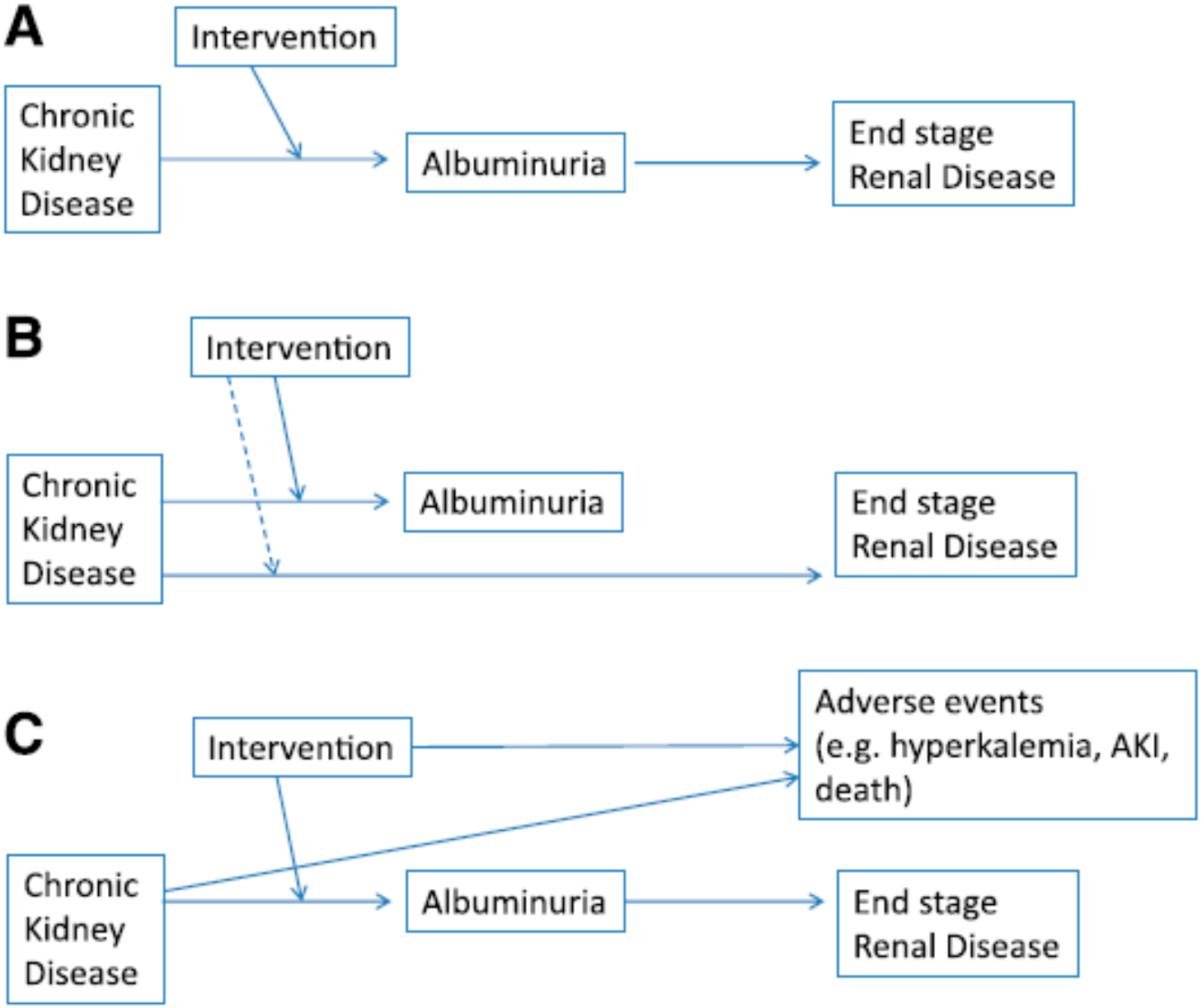
Nephrol Dial Transplant (2015) 30: 706–712

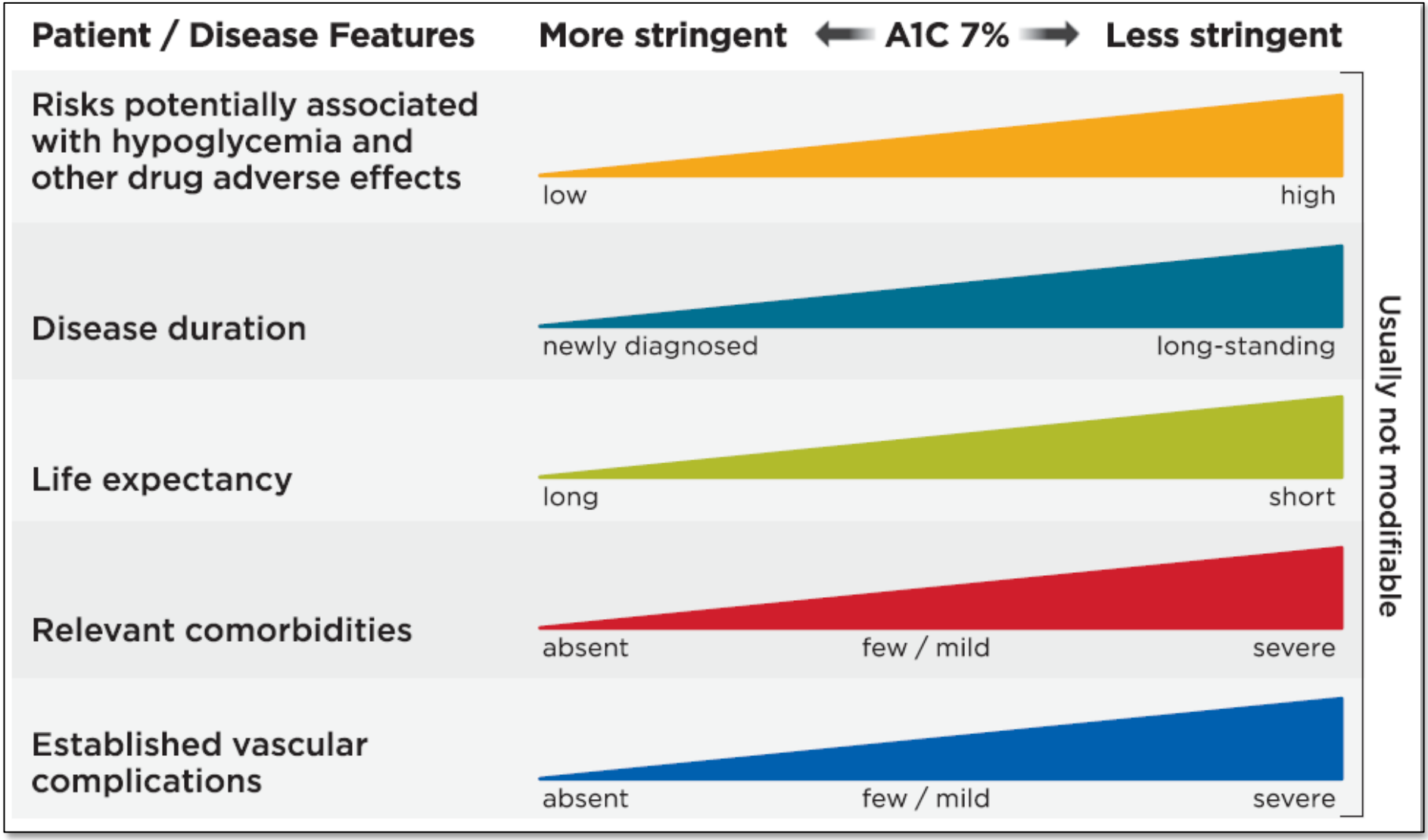

Odds ratios of rapid eGFR decline
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
>2 fold decrease
1.25-2 fold decrease
Stable
1.25-2 fold increase
>2 fold increase
UACR 1-year fold change

RENAAL Trial – predittività sviluppo ESRD

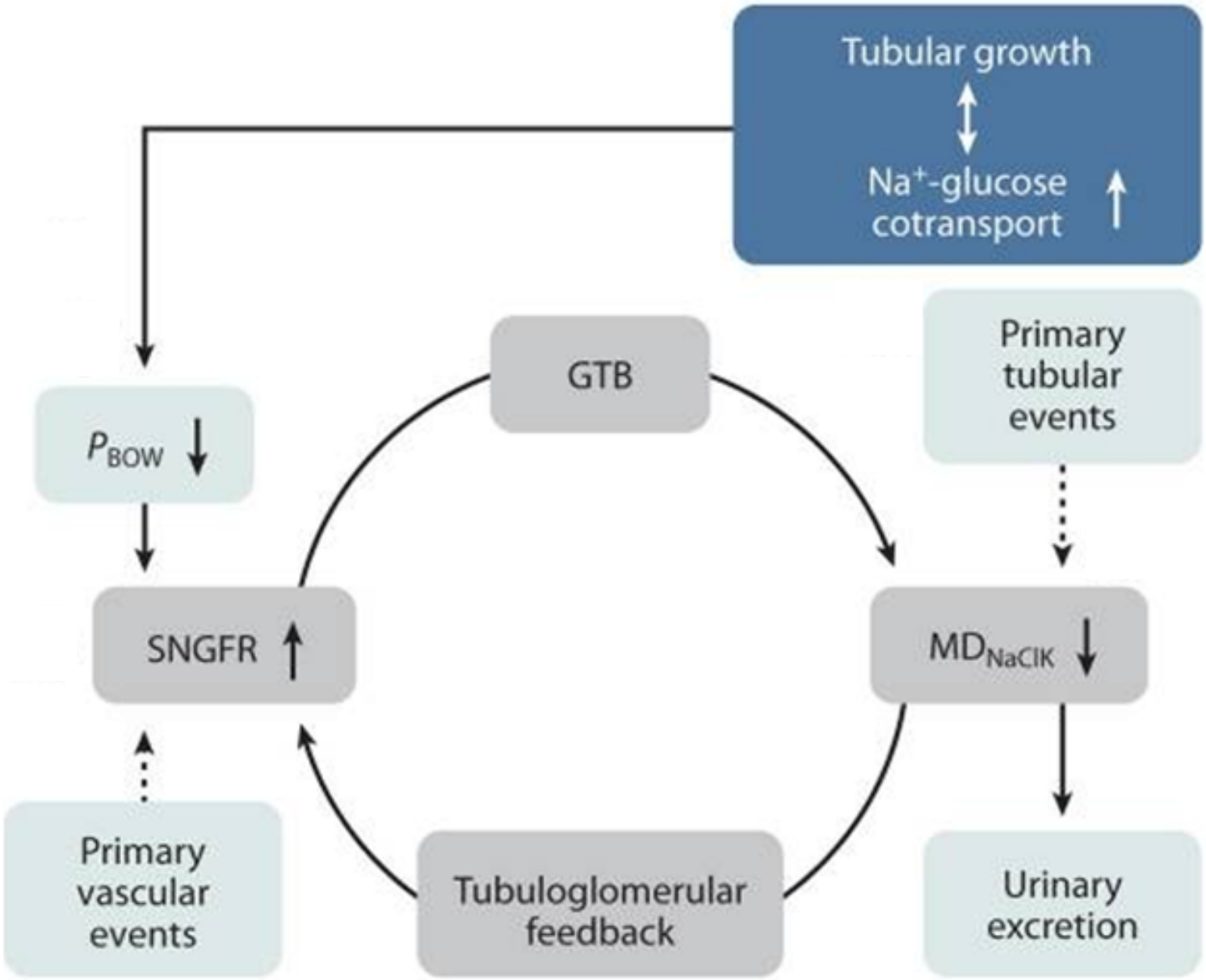


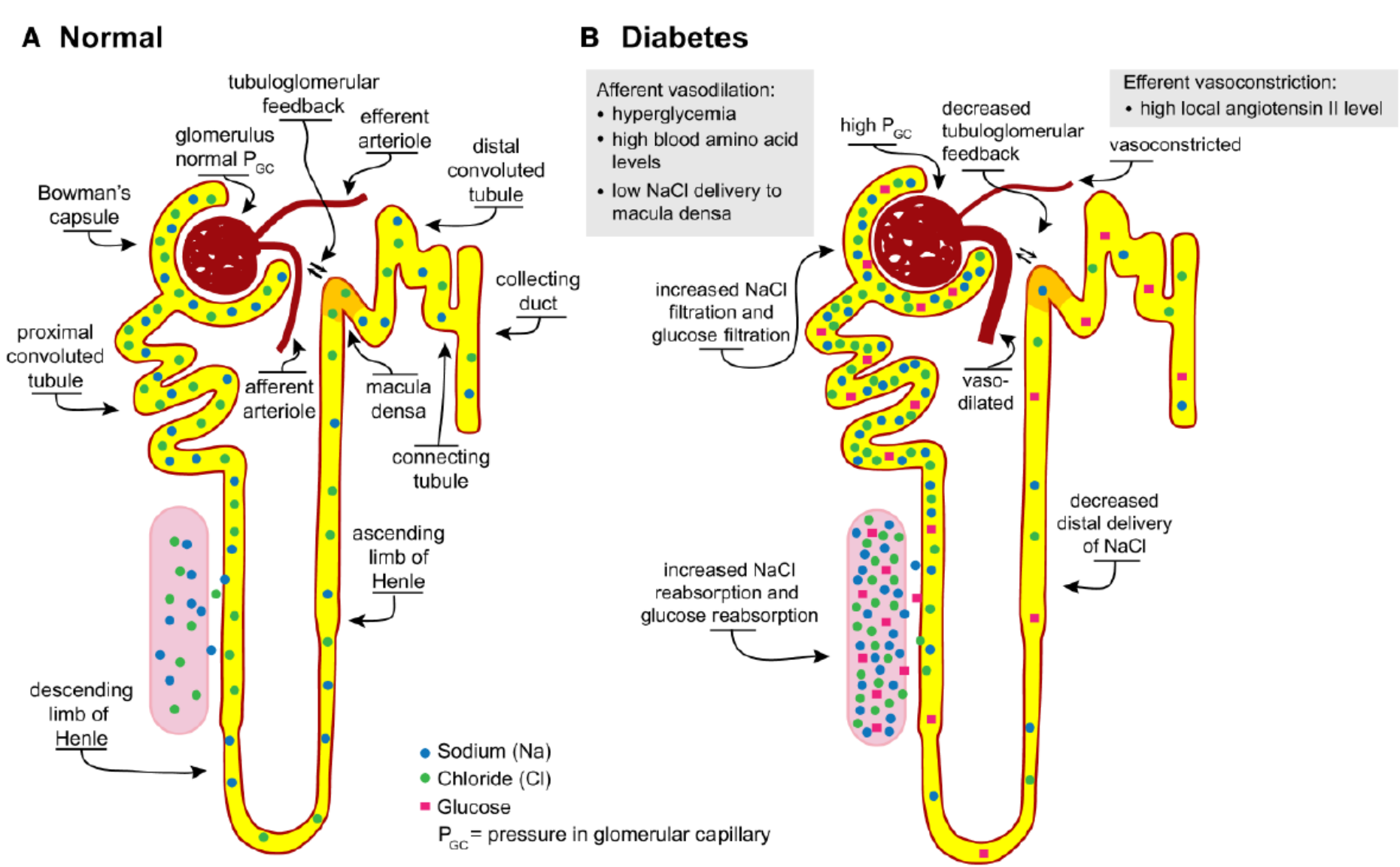
Clin J Am Soc Nephrol ■: ●●●–●●●, 2015


A
Intervention
Chronic Kidney Disease
Albuminuria
End stage Renal Disease
B
Intervention
Chronic Kidney Disease
Albuminuria
End stage Renal Disease
C
Intervention
Adverse events (e.g. hyperkalemia, AKI, death)
Chronic Kidney Disease
Albuminuria
End stage Renal Disease

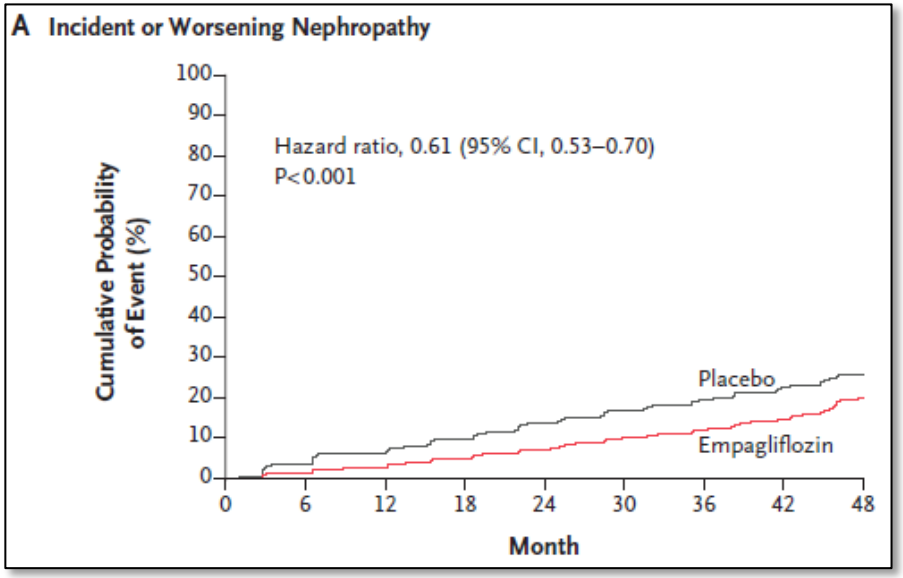

Patient / Disease Features
More stringent
A1C 7%
Less stringent
Risks potentially associated with hypoglycemia and other drug adverse effects
low
high
Disease duration
newly diagnosed
long-standing
Life expectancy
long
short
Relevant comorbidities
absent
few / mild
severe
Established vascular complications
absent
few / mild
severe
Usually not modifiable

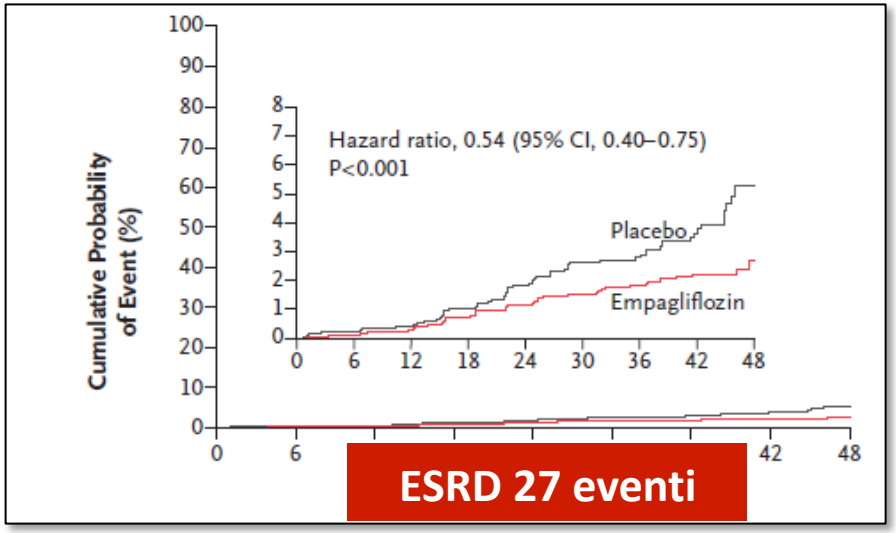
Feedback tubulo-glomerulare e iperfiltrazione




A Normal
tubuloglomerular feedback
efferent arteriole
glomerulus normal P_{GC}
distal convoluted tubule
Bowman's capsule
collecting duct
proximal convoluted tubule
afferent arteriole
macula densa
connecting tubule
ascending limb of Henle
descending limb of Henle
B Diabetes
Afferent vasodilation:
• hyperglycemia
• high blood amino acid levels
• low NaCl delivery to macula densa
Efferent vasoconstriction:
• high local angiotensin II level
high P_{GC}
decreased tubuloglomerular feedback
vasoconstricted
increased NaCl filtration and glucose filtration
vaso-dilated
decreased distal delivery of NaCl
increased NaCl reabsorption and glucose reabsorption
Sodium (Na)
Chloride (Cl)
Glucose
P_{GC} = pressure in glomerular capillary

EMPA-REG OUTCOME

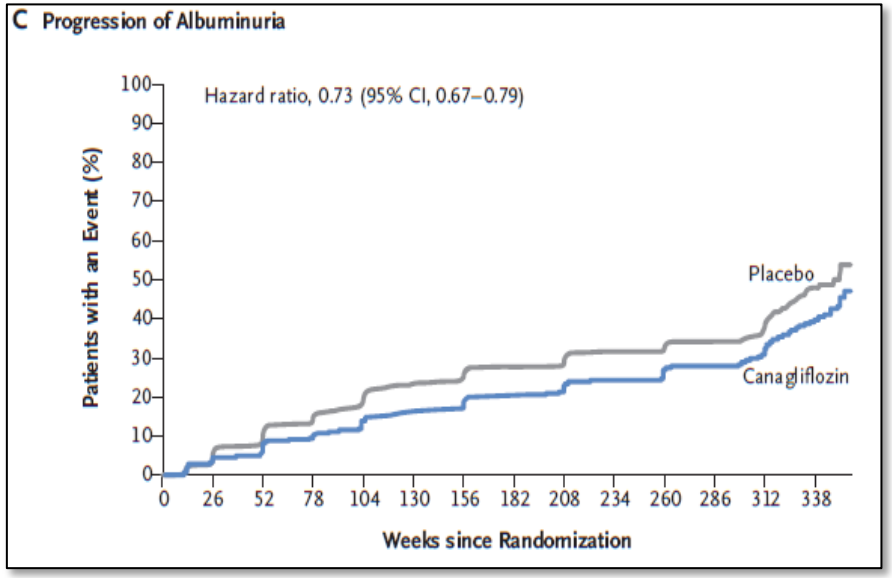


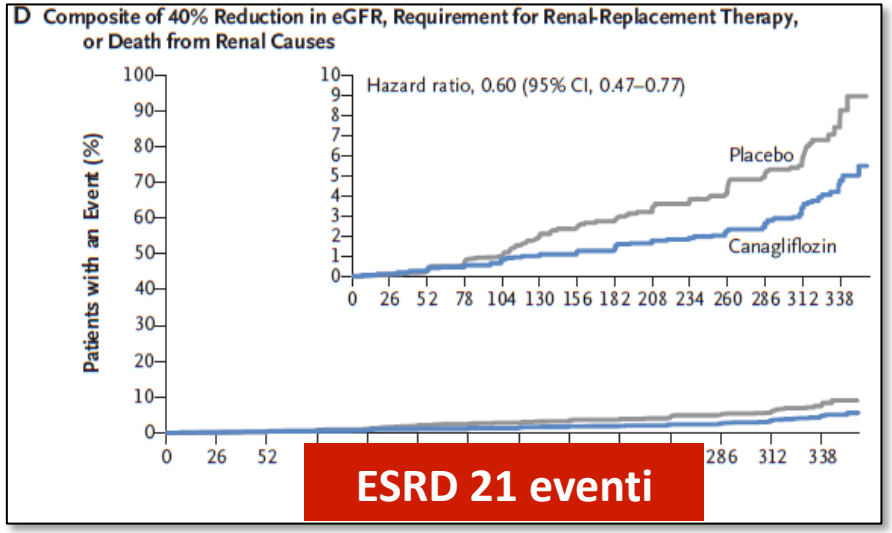


ESRD 27 eventi

N ENGL J MED 375;4 NEJM.ORG JULY 28, 2016

CANVAS





ESRD 21 eventi

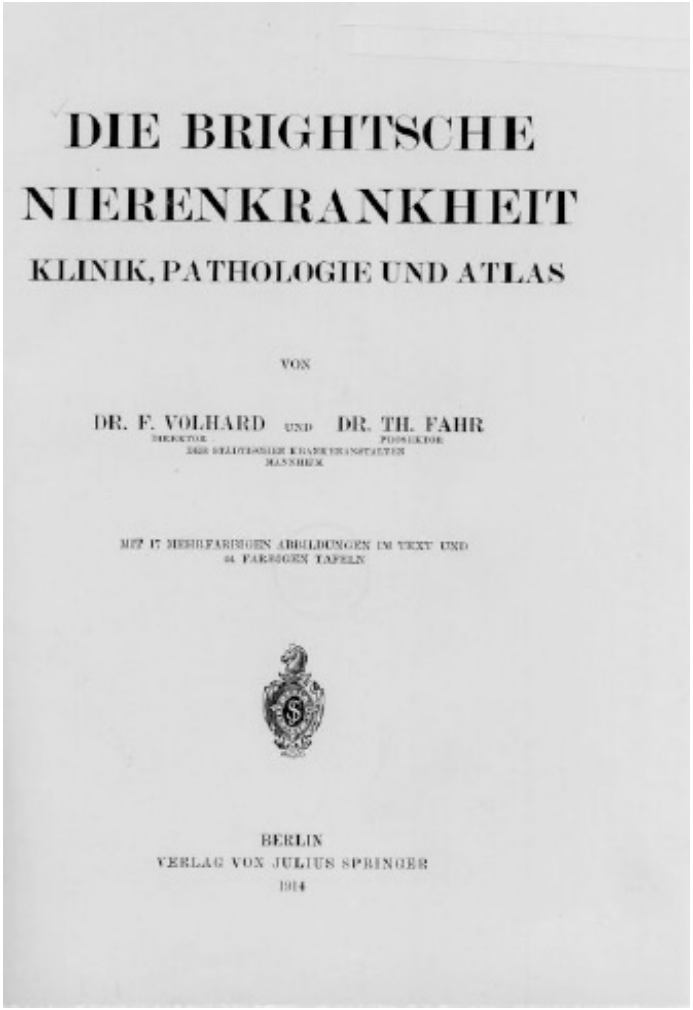
N ENGL J MED NEJM.ORG June 12, 2017,

Table 1. Risk factors for diabetic kidney disease

Risk Factor	Susceptibility	Initiation	Progression
Demographic			
Older age	+		
Sex (men)	+		
Race/ethnicity (black, American Indian, Hispanic, Asian/Pacific Islanders)	+		+
Hereditary			
Family history of DKD	+		
Genetic kidney disease		+	
Systemic conditions			
Hyperglycemia	+	+	+
Obesity	+	+	+
Hypertension	+		+
Kidney injuries			
AKI		+	+
Toxins		+	+
Smoking	+		+
Dietary factors	+		+
High protein intake	+		+

DKD, diabetic kidney disease.

Volhard F, Fahr T. *Die Brightsche Nierenkrankheit. Klinik, Pathologie und Atlas*. Springer: Berlin, 1914.



DIE BRIGHTSCHE
NIERENKRANKHEIT

KLINIK, PATHOLOGIE UND ATLAS

VON

DR. F. VOLHARD UND DR. TH. FAHR

BERLIN
VERLAG VON JULIUS SPRINGER
1914

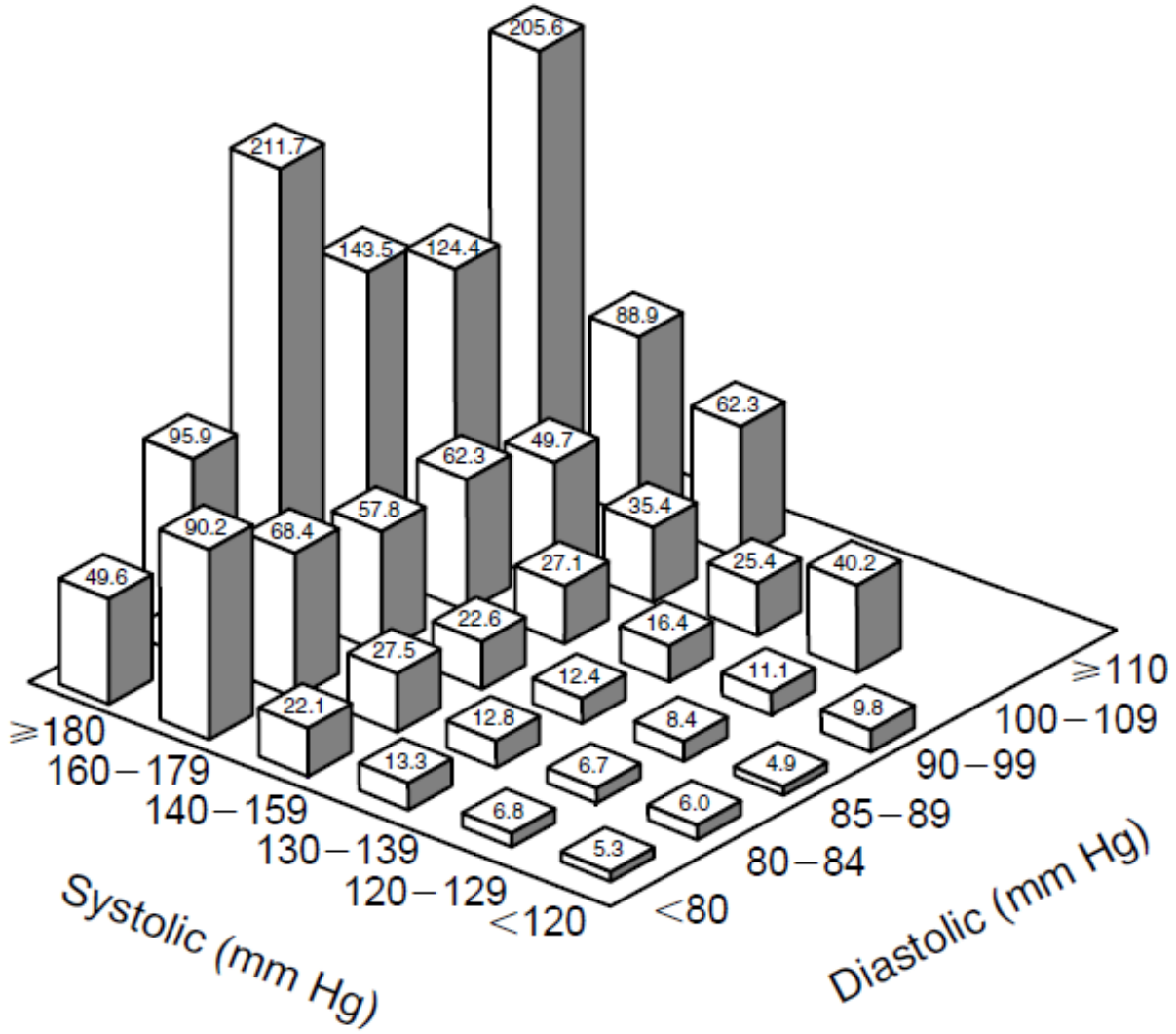
A. Degenerative diseases: Nephrosis, 'genuine' and of known aetiology.
(I) Acute course, chronic course, Final stage: (nephrotic contracted kidney without rise in blood pressure).
Subvariety: Necrotizing nephrosis.

B. Inflammatory diseases: Nephritis.

(1) Diffuse glomerulonephritis with obligatory rise in blood pressure.
Acute stage, chronic stage without and chronic stage with renal impairment
(All 3 stages can run with and without nephrotic component),
(2) Focal nephritis without rise in blood pressure, acute and chronic stage,
septic interstitial focal nephritis, embolic focal nephritis

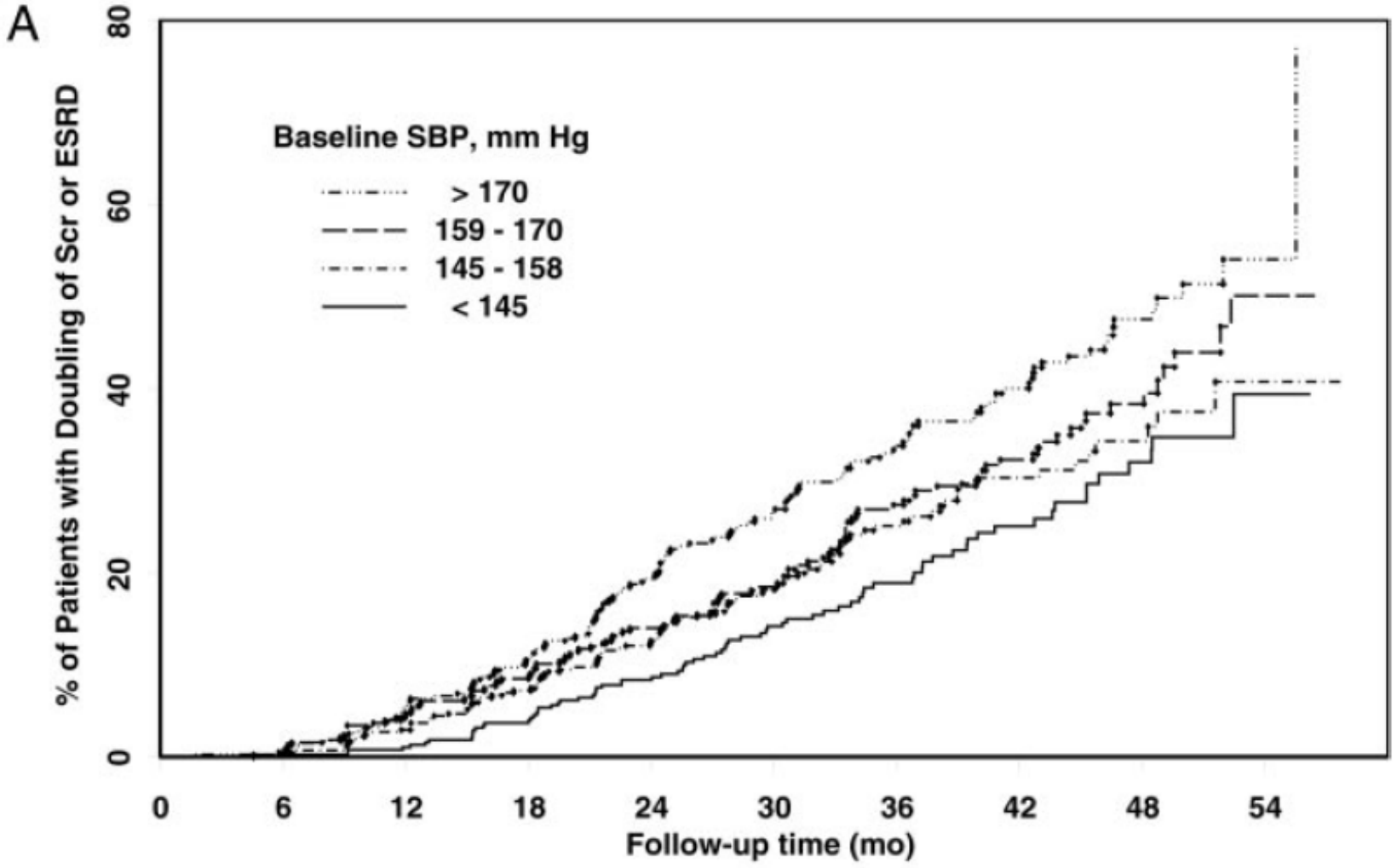
C. Arteriosclerotic diseases: Sclerosis.
(1) Simple benign hypertension, pure sclerosis of the renal vessels.
(2) The combination form: malignant genuine contracted kidney, sclerosis + nephritis.

BLOOD PRESSURE AND END-STAGE RENAL DISEASE IN MEN



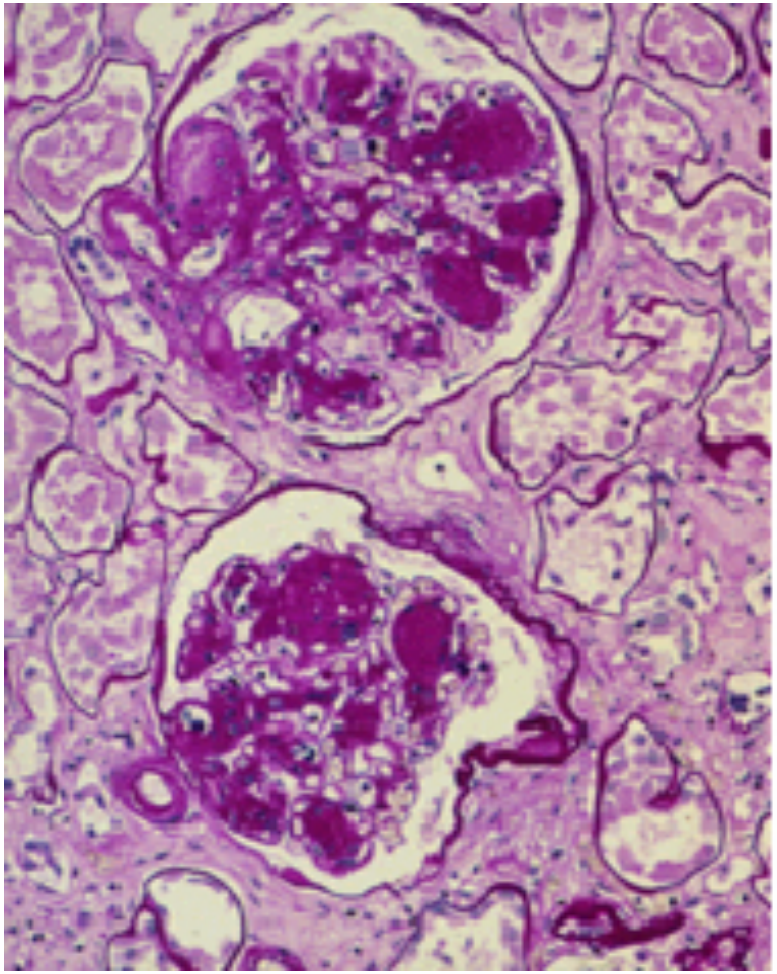
N Engl J Med 1996;334:13-8.

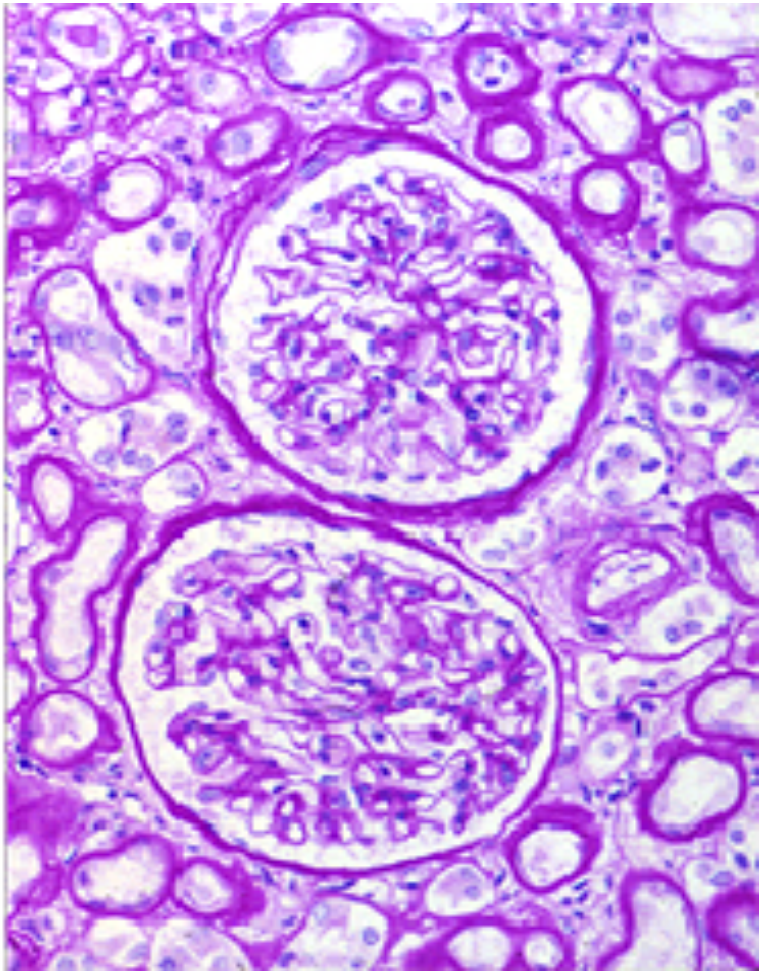
Irbesartan Diabetic Nephropathy Trial



J Am Soc Nephrol 16: 3027–3037, 2005

Unilateral nodular diabetic glomerulosclerosis (Kimmelstiel-Wilson): Report of a case



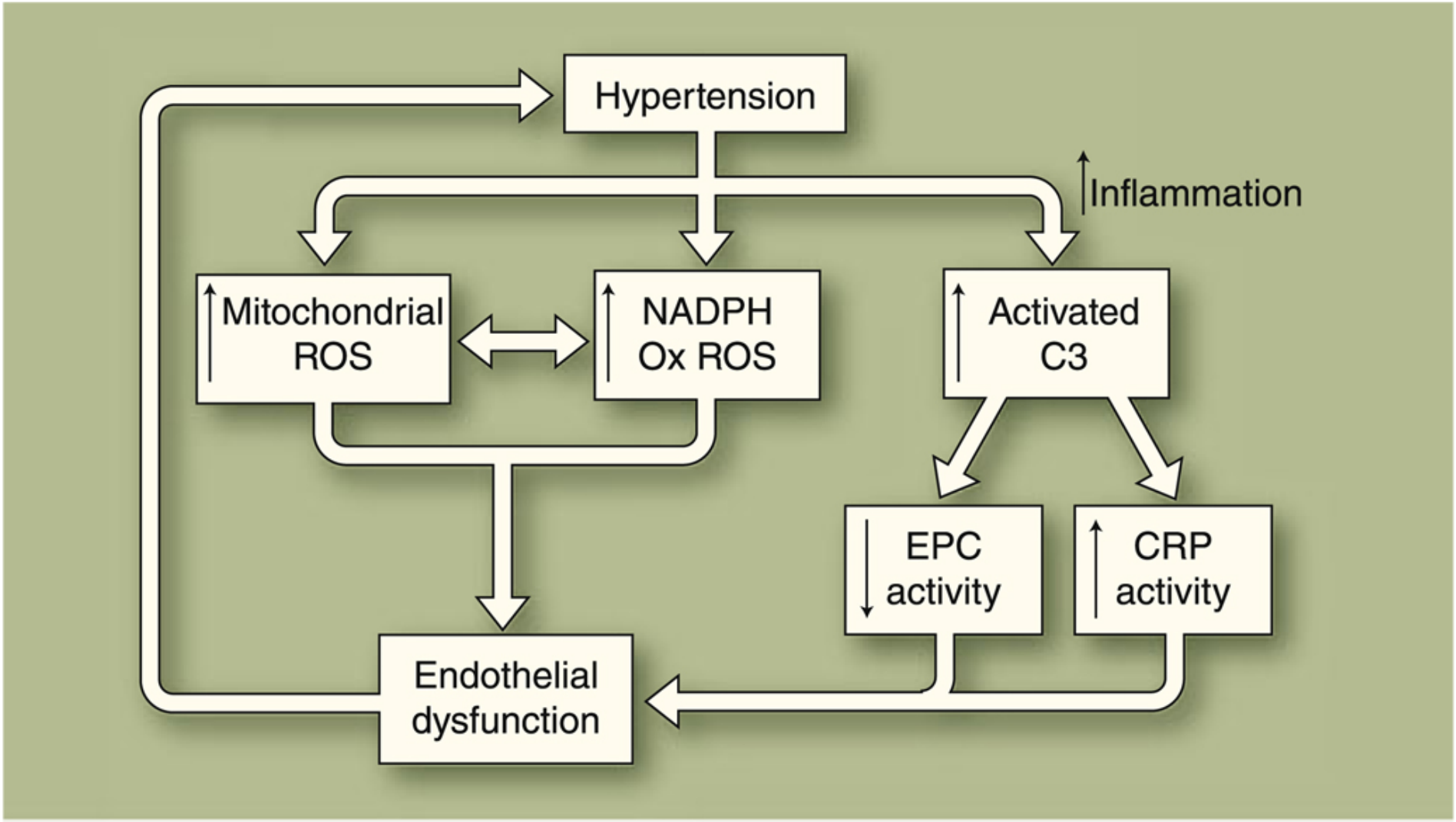


Arteria renale pervia

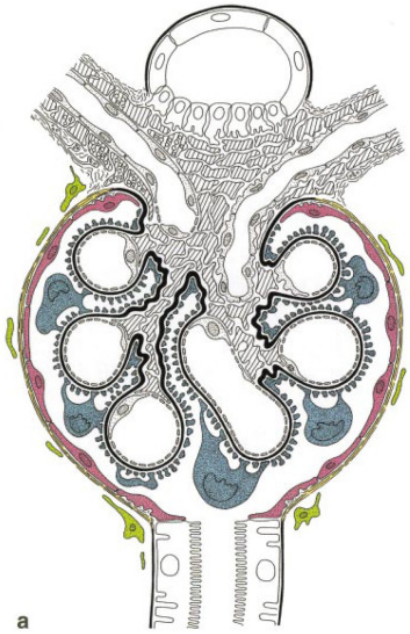
Arteria renale stenotica

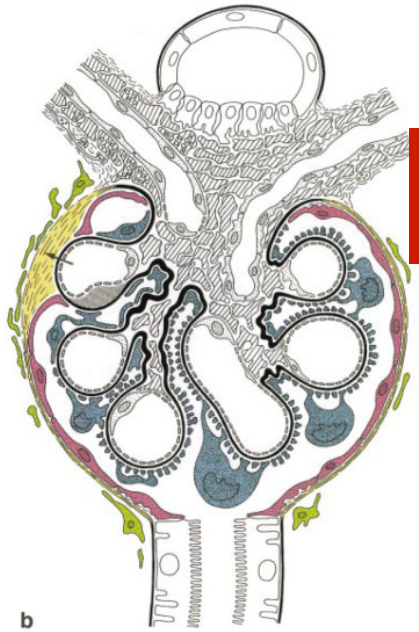
Metabolism. 1973 May;22(5):715-22.

Danno endoteliale diretto



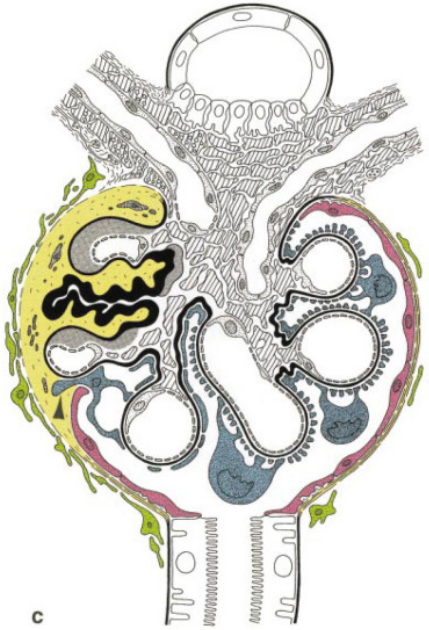
Distacco delle cellule epiteliali glomerulari

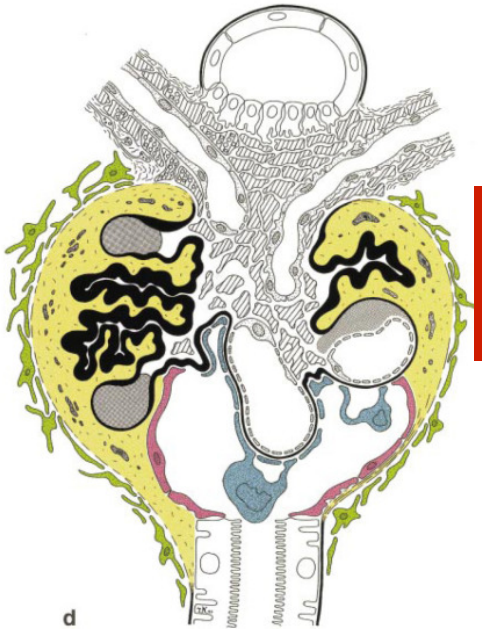




Essudazione acqua e macromolecole

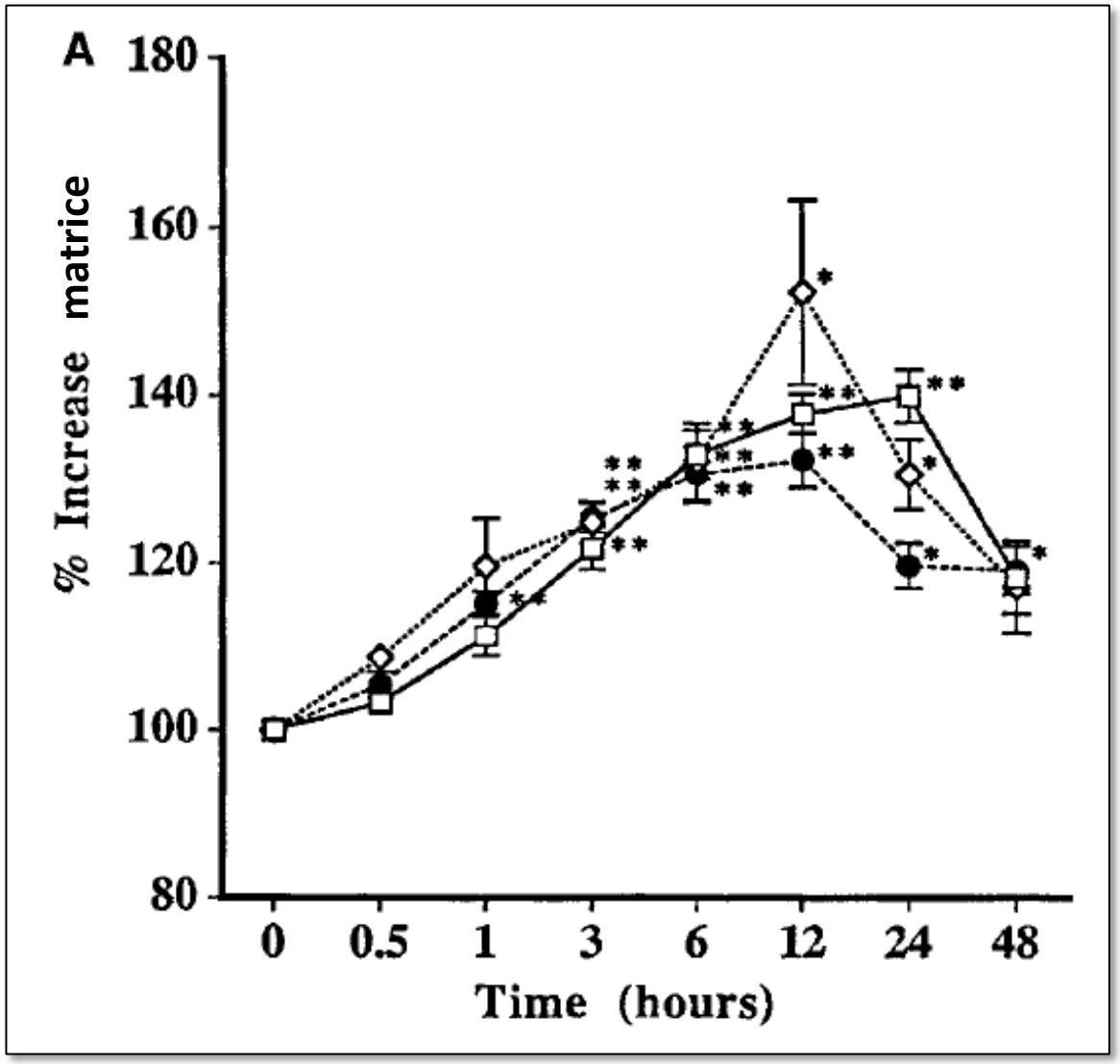
Intrappolamento spazio subendoteliale





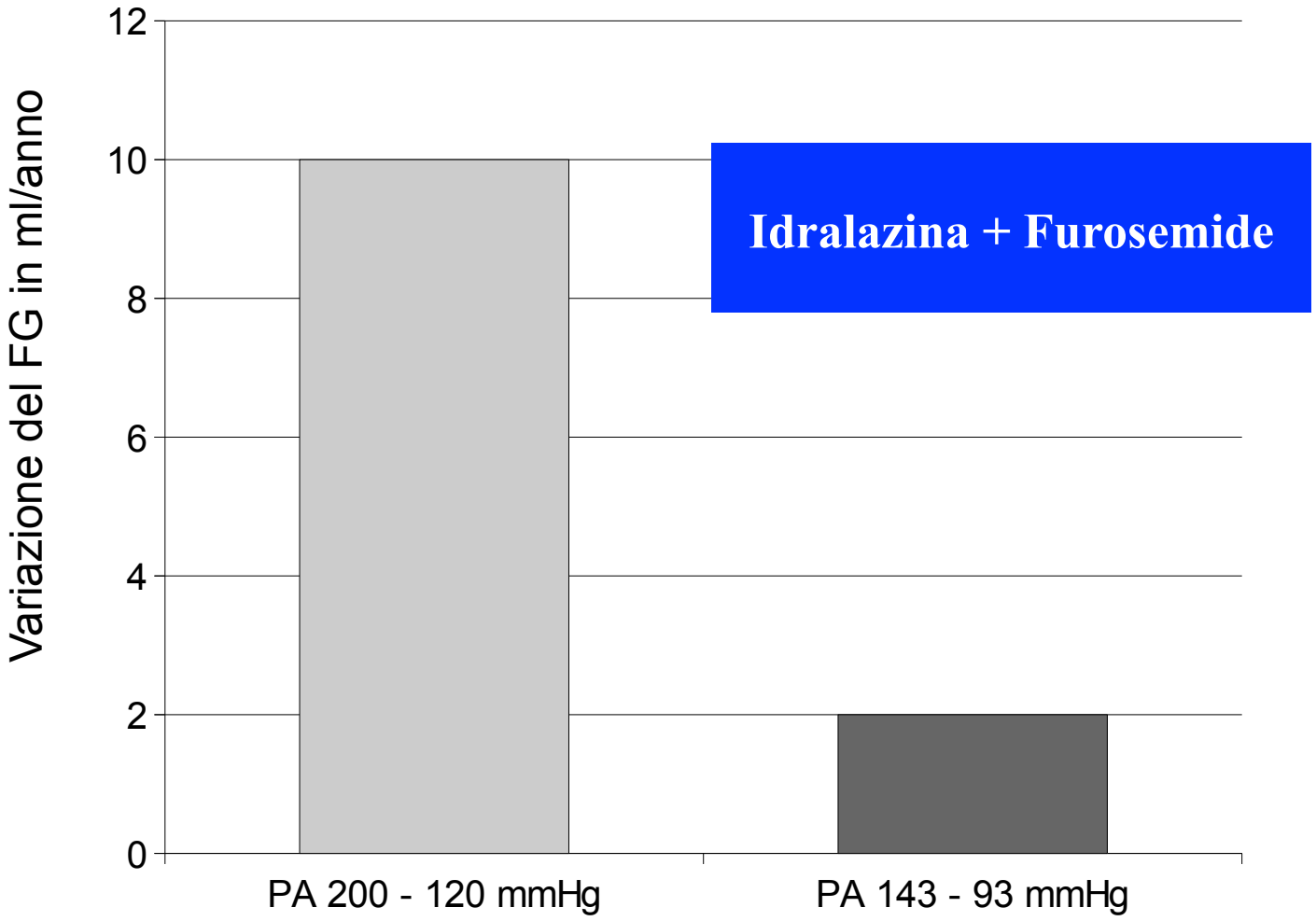
Restringimento lume capillare Riduzione RBF e GFR

«Stiramento» delle cellule mesangiali



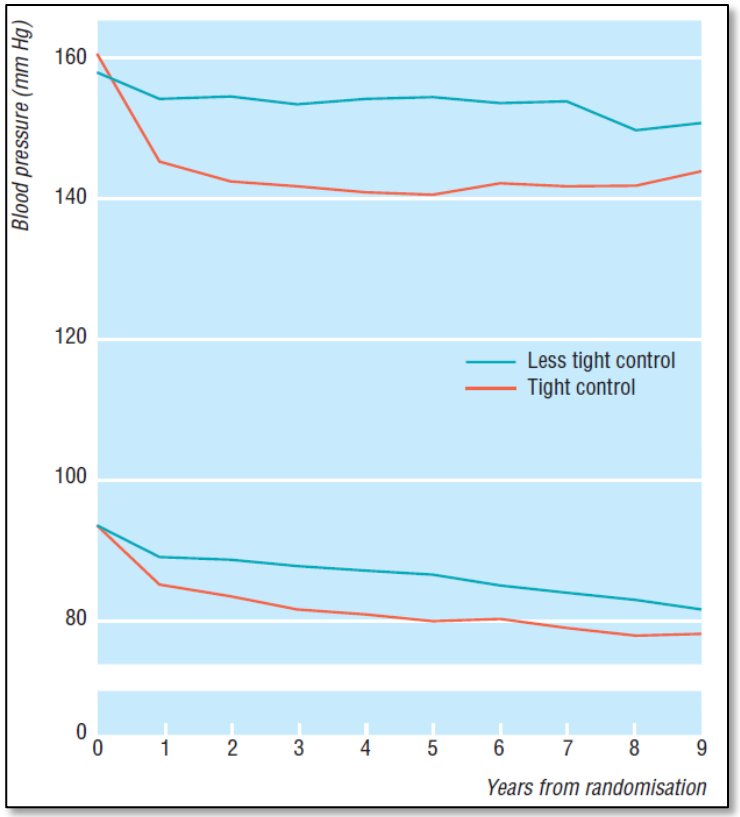
The Journal of Clinical Investigation
Volume 98, Number 9, November 1996, 1991–2000

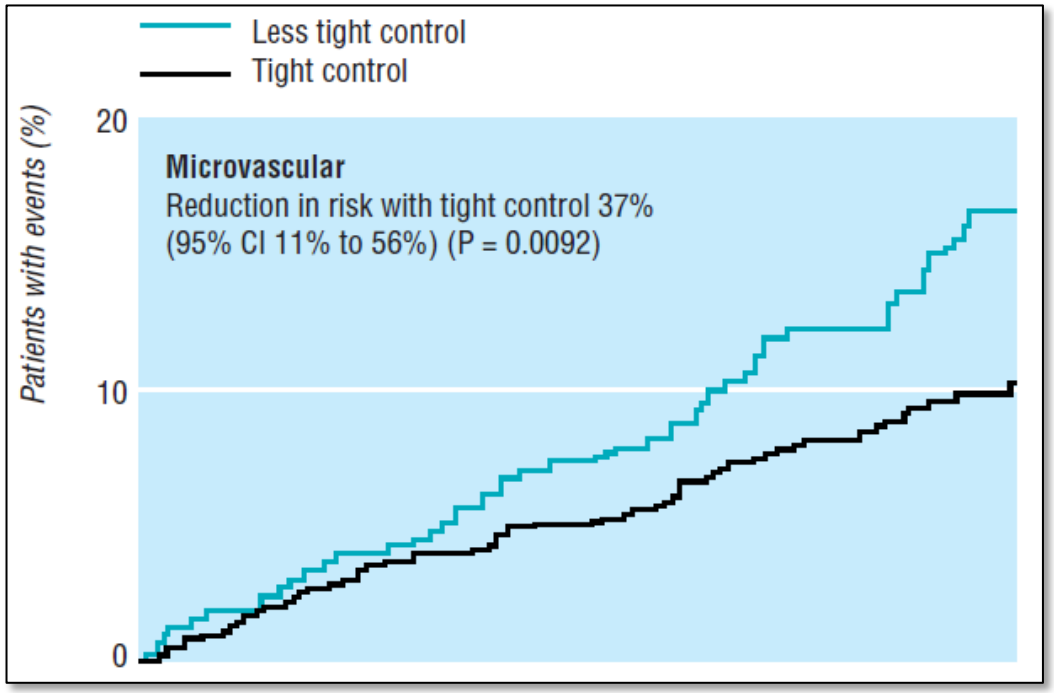
Scandinavian Journal of Clinical & Laboratory Investigation



Mogensen CE. Scand J Clin Lab Invest 1976;36(4):383-8.

UKPDS 38

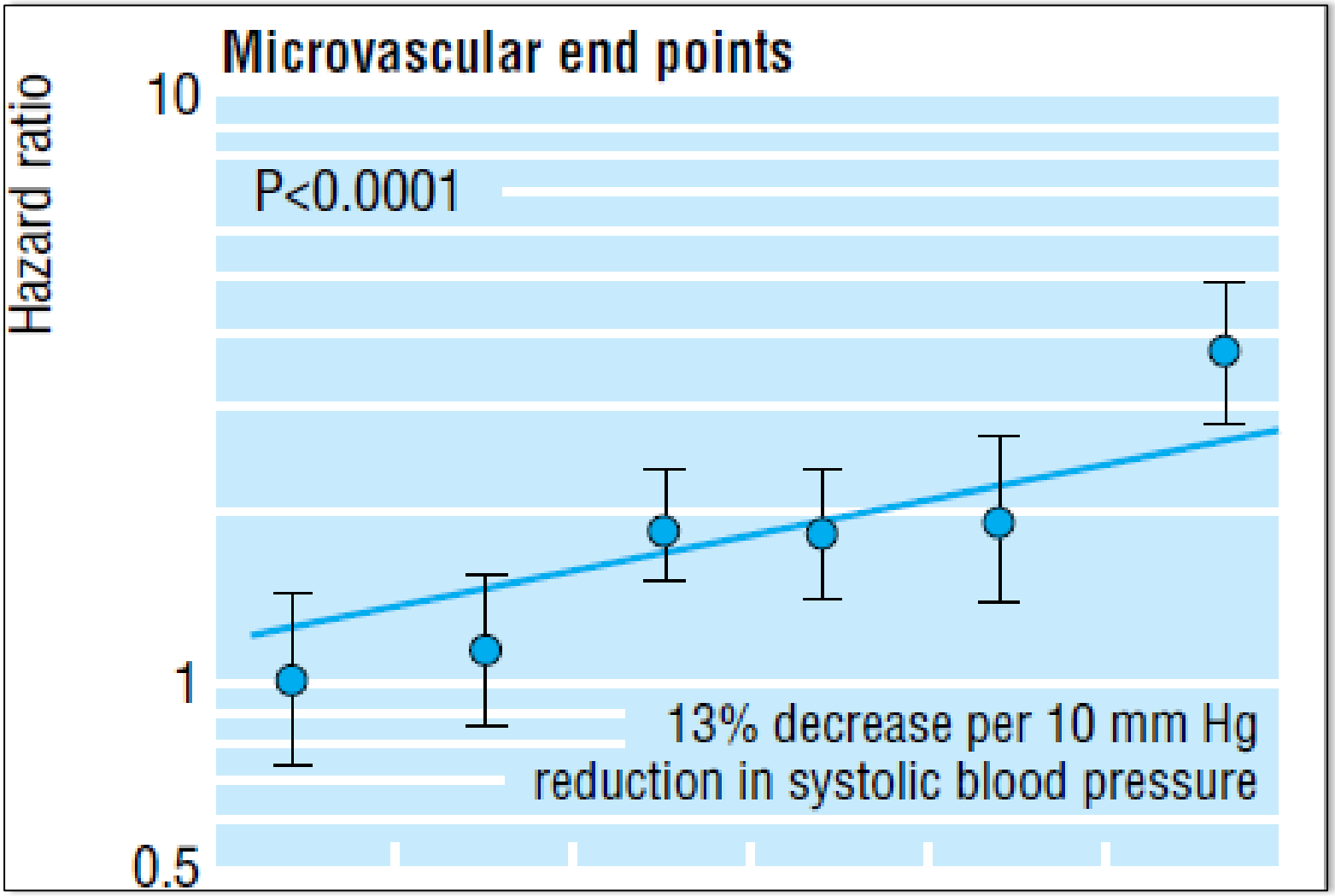




154/87 vs. 144/82 mmHg

BMJ VOLUME 317 12 SEPTEMBER 1998 www.bmj.com

UKPDS 36


Microvascular end points
Hazard ratio
10
1
0.5
P<0.0001
13% decrease per 10 mm Hg
reduction in systolic blood pressure

No Legacy Effect of Earlier BP Control

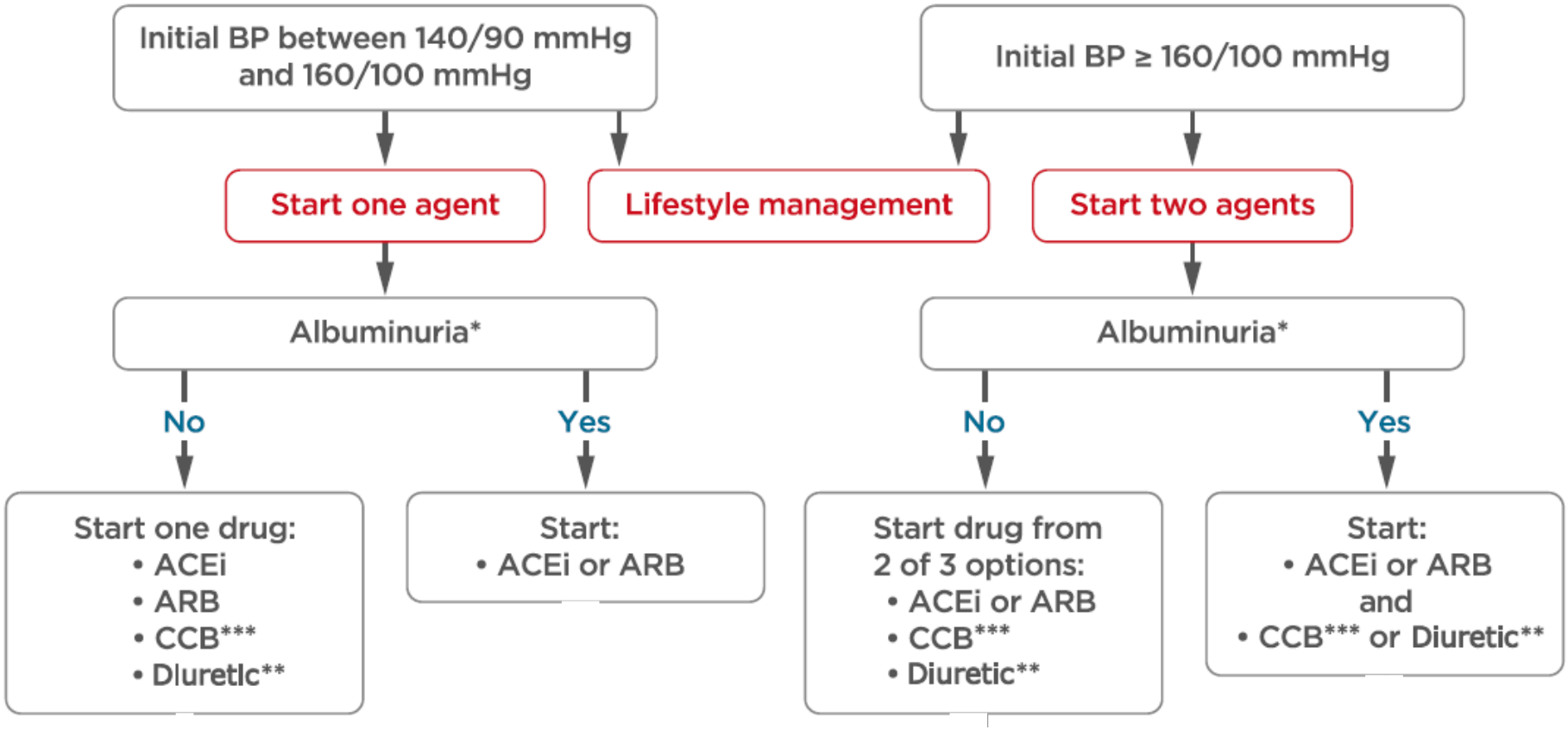
After median 8.0 years post-trial follow-up

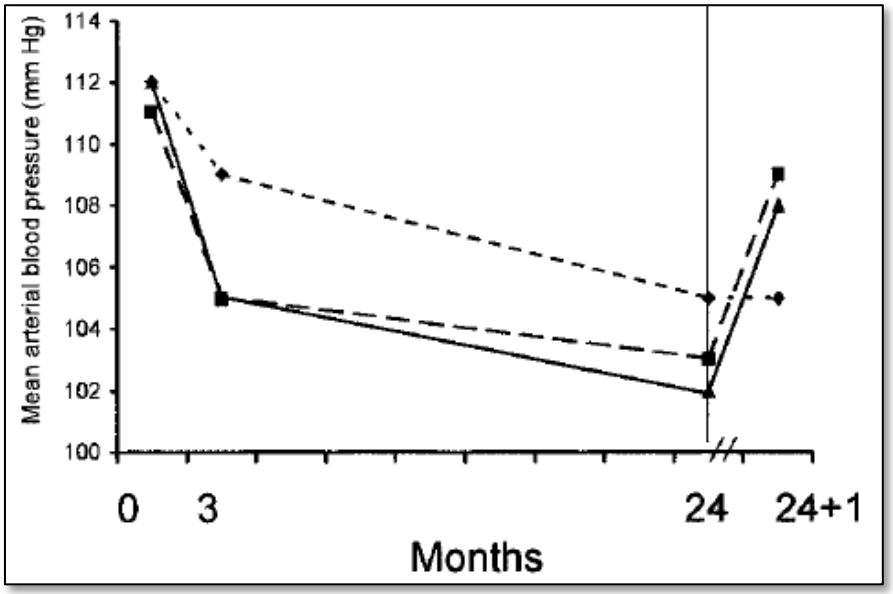
Aggregate Endpoint		1997	2007
Any diabetes related endpoint	*RRR:*	24%	**7%**
	P:	0.0046	**0.31**
Microvascular disease	*RRR:*	37%	**16%**
	P:	0.0092	**0.17**
Myocardial infarction	*RRR:*	21%	**10%**
	P:	0.13	**0.35**
All-cause mortality	*RRR:*	18%	**11%**
	P:	0.17	**0.18**

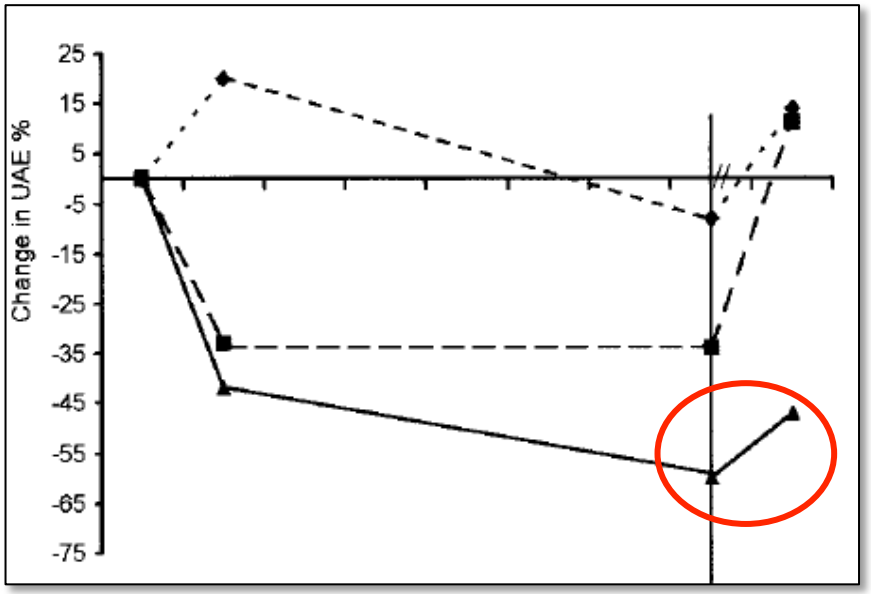
RRR = Relative Risk Reduction, P = Log Rank

UKPDS 81. N Eng J Med 2008; ***359****:*

ukpds~ptm


Initial BP between 140/90 mmHg and 160/100 mmHg
Initial BP ≥ 160/100 mmHg
Start one agent
Lifestyle management
Start two agents
Albuminuria*
Albuminuria*
No
Yes
No
Yes
Start one drug:
• ACEi
• ARB
• CCB***
• Diuretic**
Start:
• ACEi or ARB
Start drug from 2 of 3 options:
• ACEi or ARB
• CCB***
• Diuretic**
Start:
• ACEi or ARB
and
• CCB*** or Diuretic**

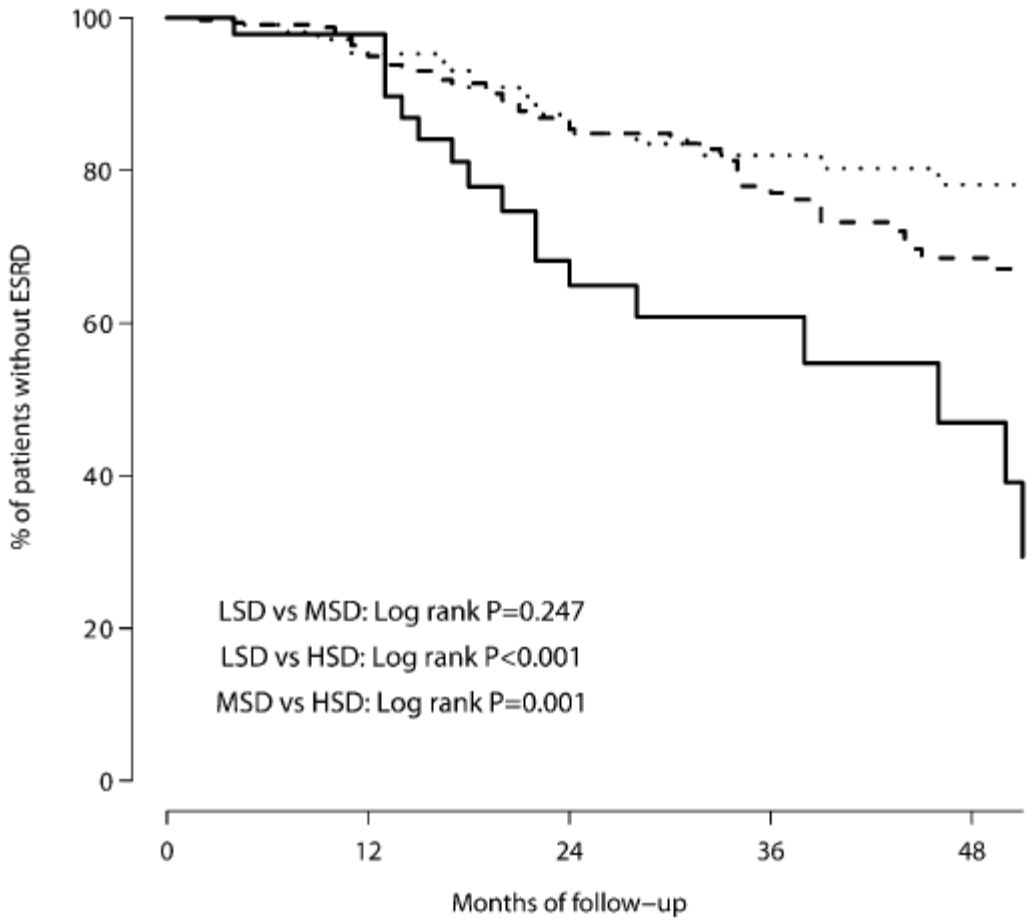

Mean arterial blood pressure (mm Hg)
114
112
110
108
106
104
102
100
0
3
24
24+1
Months


Change in UAE %
25
15
5
-5
-15
-25
-35
-45
-55
-65
-75

Dieta iposodica

Sodium Intake, ACE Inhibition, and Progression to ESRD

Stefan Vegter,*† Annalisa Perna,‡ Maarten J. Postma,*§ Gerjan Navis,† Giuseppe Remuzzi,‡‖ and Piero Ruggenenti‡‖



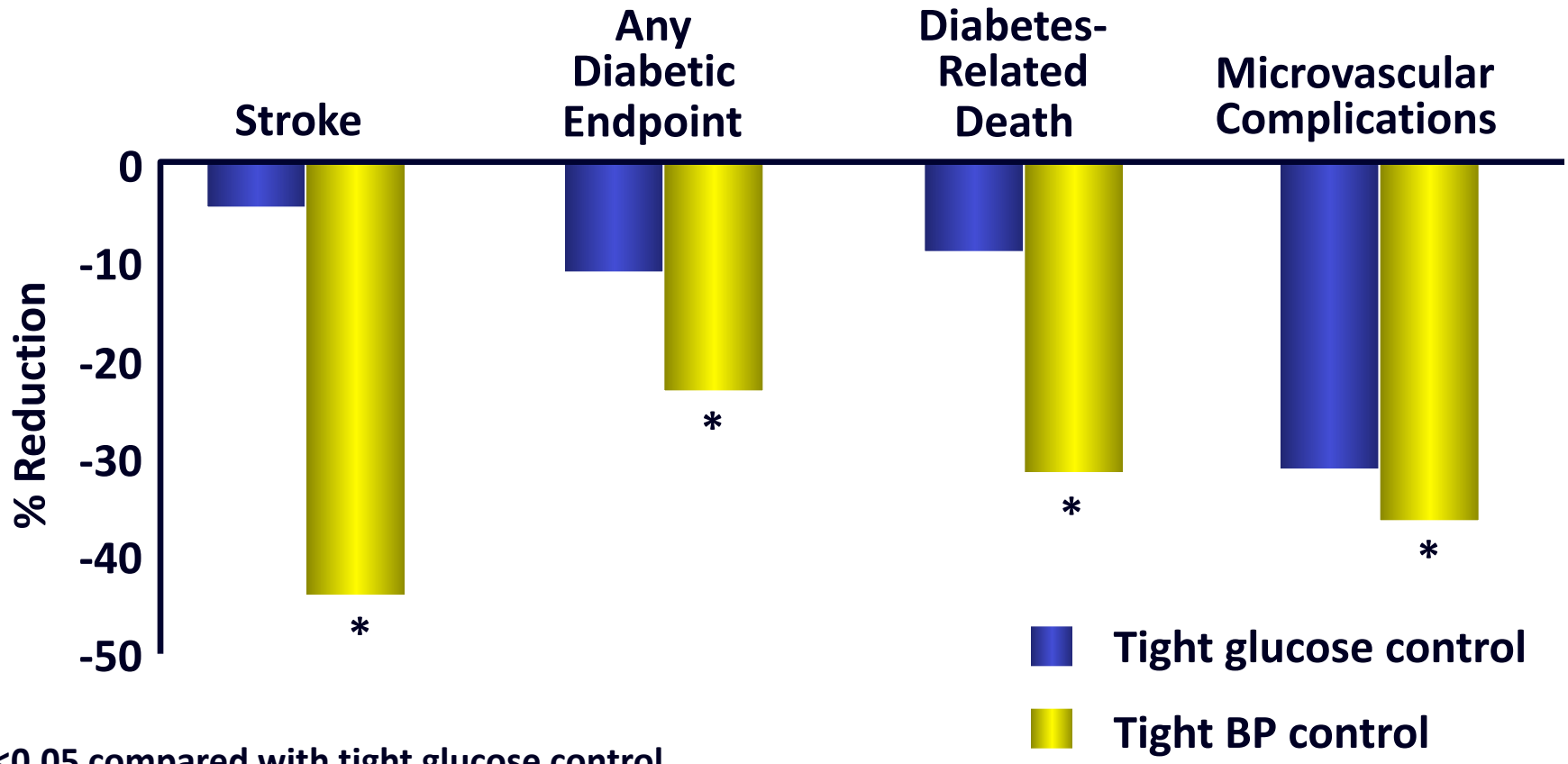
NaU 100 mmol

NaU 100 -200 mmol

NaU > 200 mmol

J Am Soc Nephrol **23:** 165–173, 2012

Effect of Tight Glucose Control vs Tight BP Control on Events: UKPDS



******P*<0.05 compared with tight glucose control.**

Bakris et al. *Am J Kidney Dis*. 2000;36:646-661.

Table 1. Risk factors for diabetic kidney disease

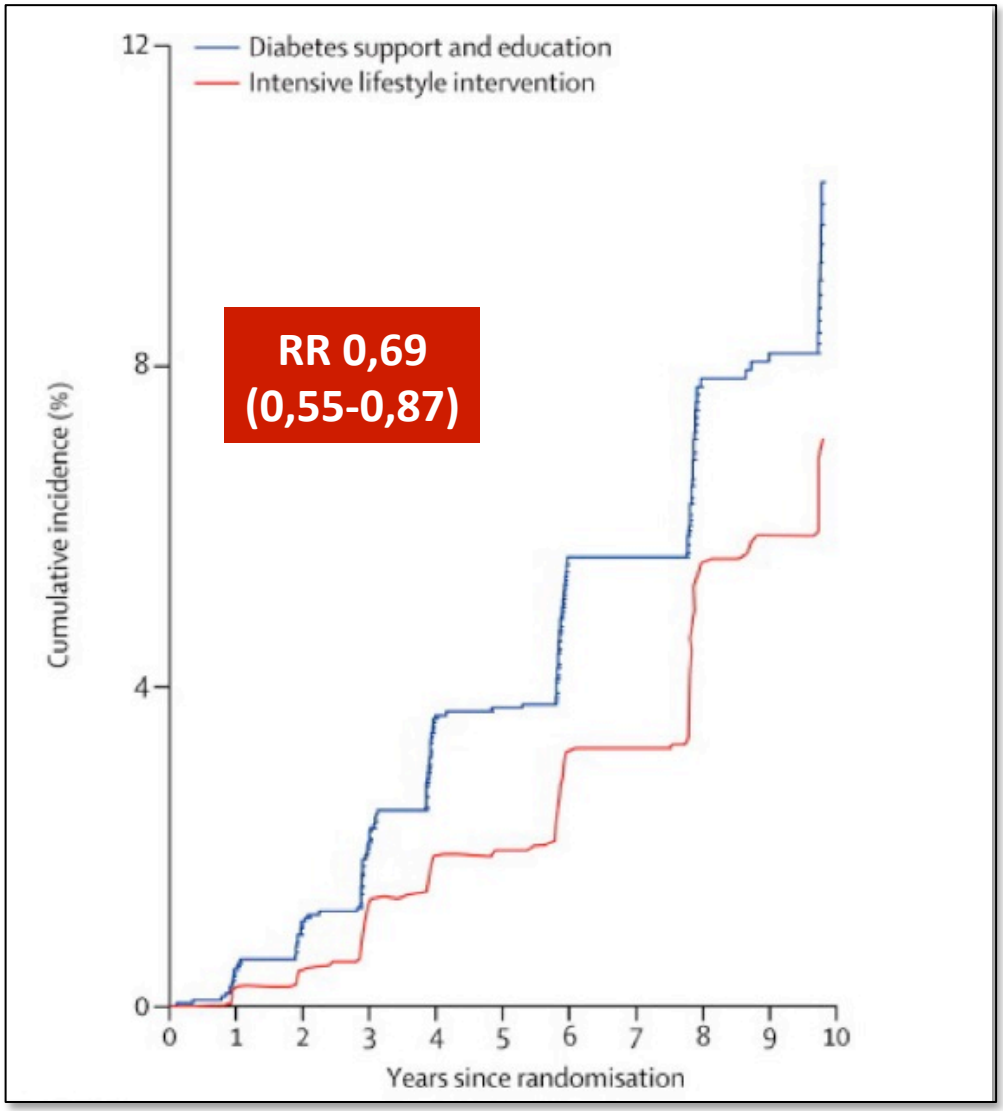
Risk Factor	Susceptibility	Initiation	Progression
Demographic			
Older age	+		
Sex (men)	+		
Race/ethnicity (black, American Indian, Hispanic, Asian/Pacific Islanders)	+		+
Hereditary			
Family history of DKD	+		
Genetic kidney disease		+	
Systemic conditions			
Hyperglycemia	+	+	+
Obesity	+	+	+
Hypertension	+		+
Kidney injuries			
AKI		+	+
Toxins		+	+
Smoking	+		+
Dietary factors	+		+
High protein intake	+		+

DKD, diabetic kidney disease.

Effect of a Long-Term Behavioral Weight Loss Intervention on Nephropathy in Overweight or Obese Adults with Type 2 Diabetes: the Look AHEAD Randomized Clinical Trial

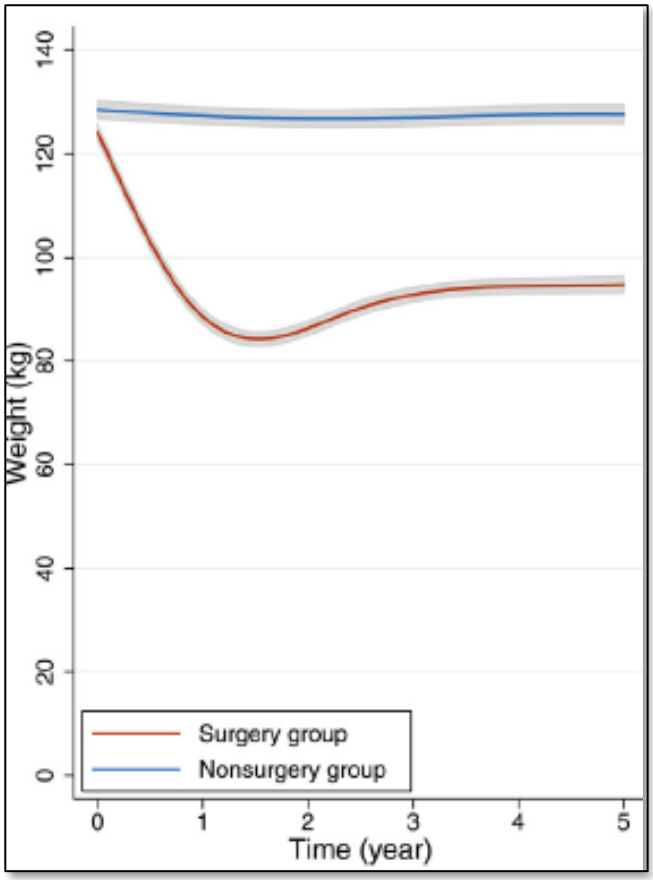
Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

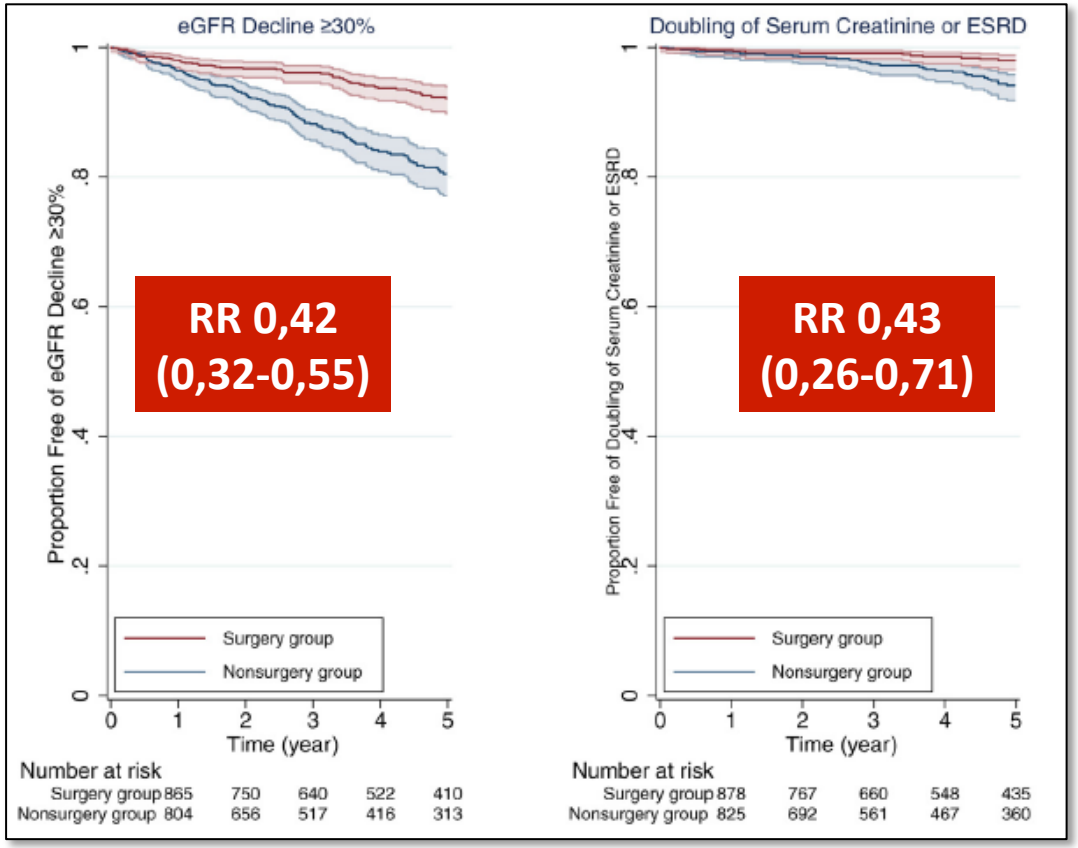
GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			



Lancet Diabetes Endocrinol. 2014 October ; 2(10): 801–809.

Bariatric surgery





Kidney International (2016) **90,** 164–171

- **Ruboxistaurina** (inibitore protein chinasi c-β)

Tuttle KR. Diabetes Care, 2005

- **Pentossifillina** (azione anti-fibrotica e anti-infiammatoria)

Navarro-Gonzales JC. JASN, 2005

Studio in corso (Clinicaltrials.gov NCT01377285)

- **Atrasentan** (antagonista selettivo Endotelina A)

de Zeeuw. JASN, 2014.

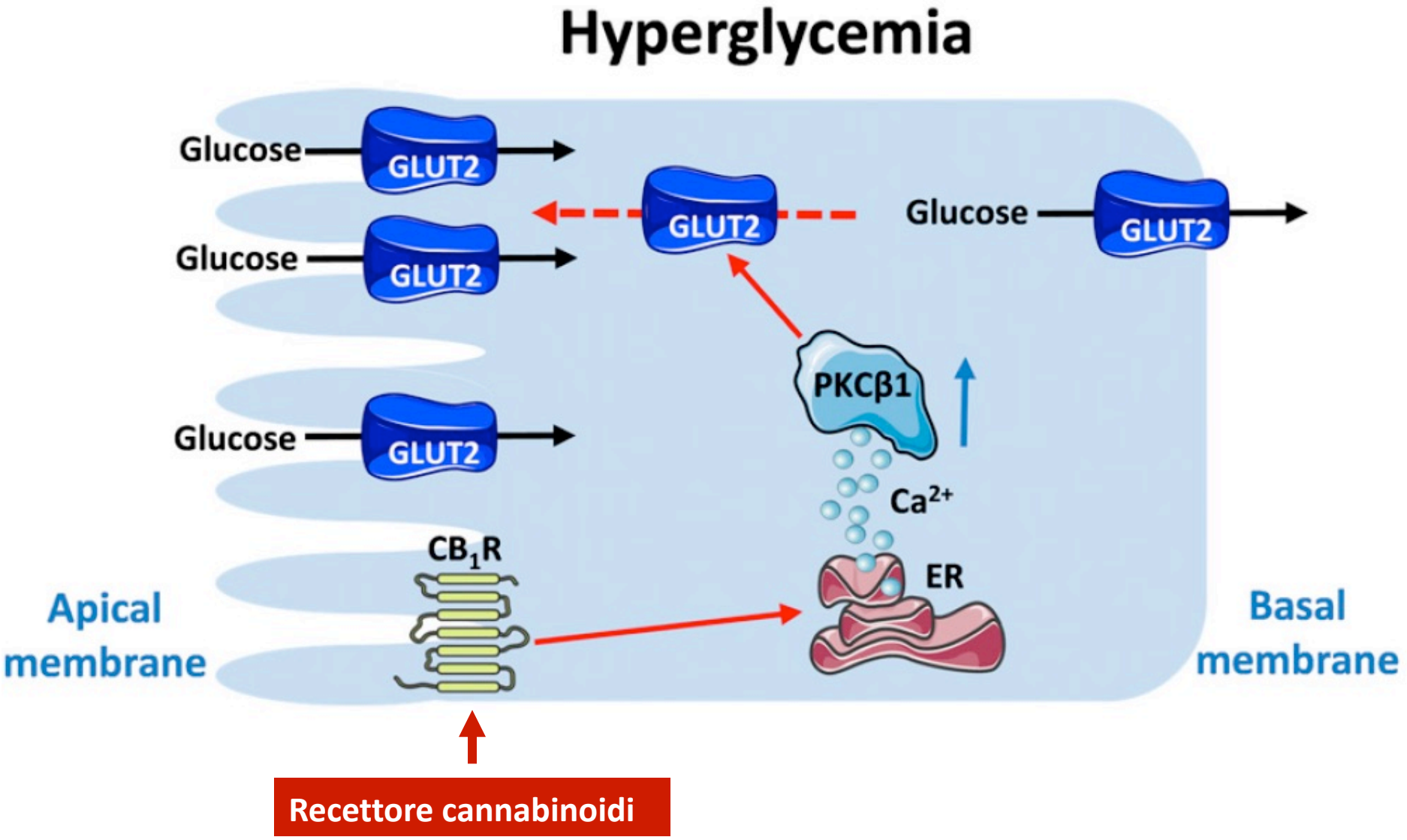
Studio SONAR in corso (Clinicaltrials.gov NCT01858532)

- **Baricitinib** (inibitore selettivo Janus 1 e Janus 2)

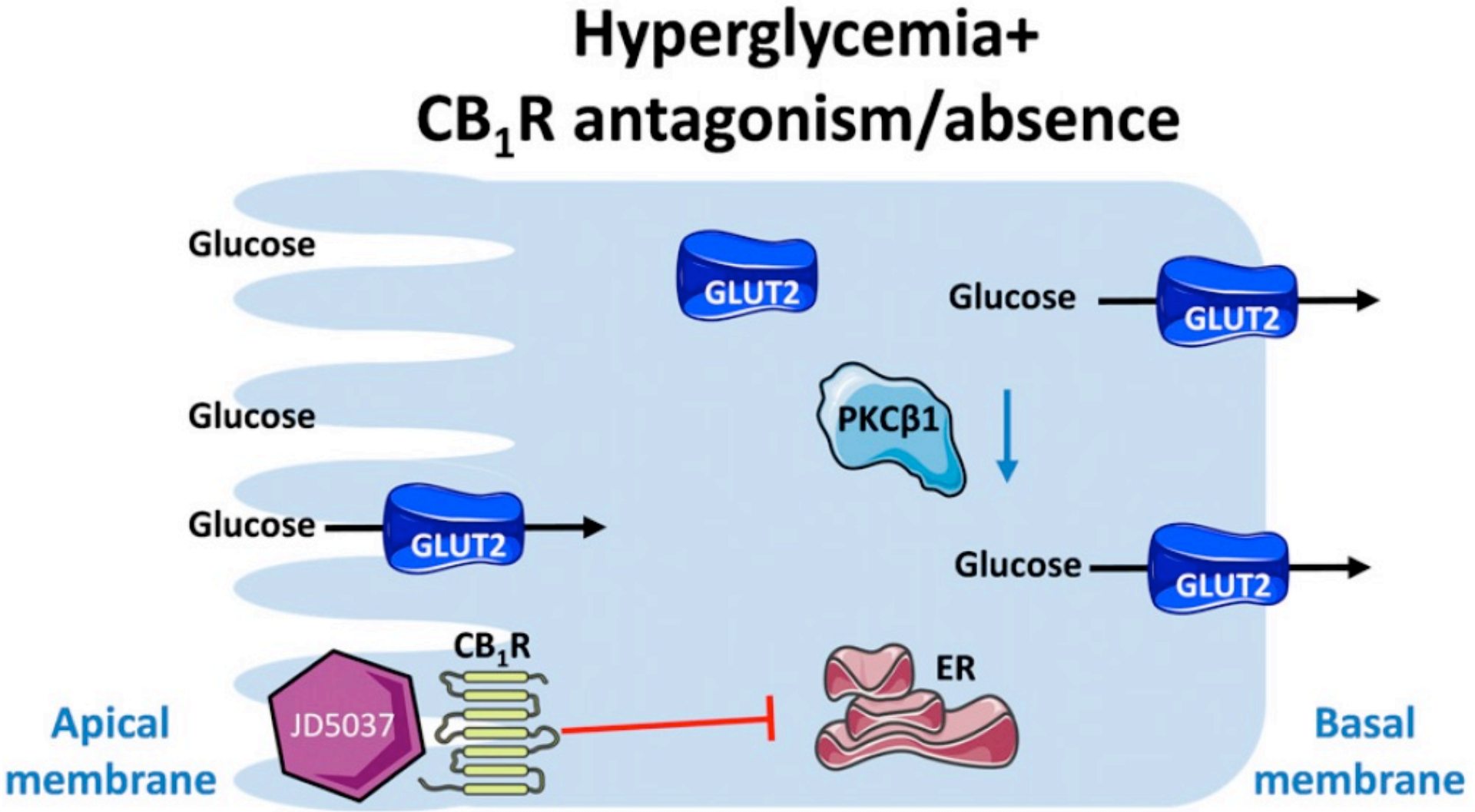
Brosius FC. Diabetologia, 2016

- **Vasohibin-1** (fattore anti-angiogenico endotelio-derivato)

Tanabe K, Biomed Res Int, 2017



J Am Soc Nephrol 29: ccc–ccc, 2017

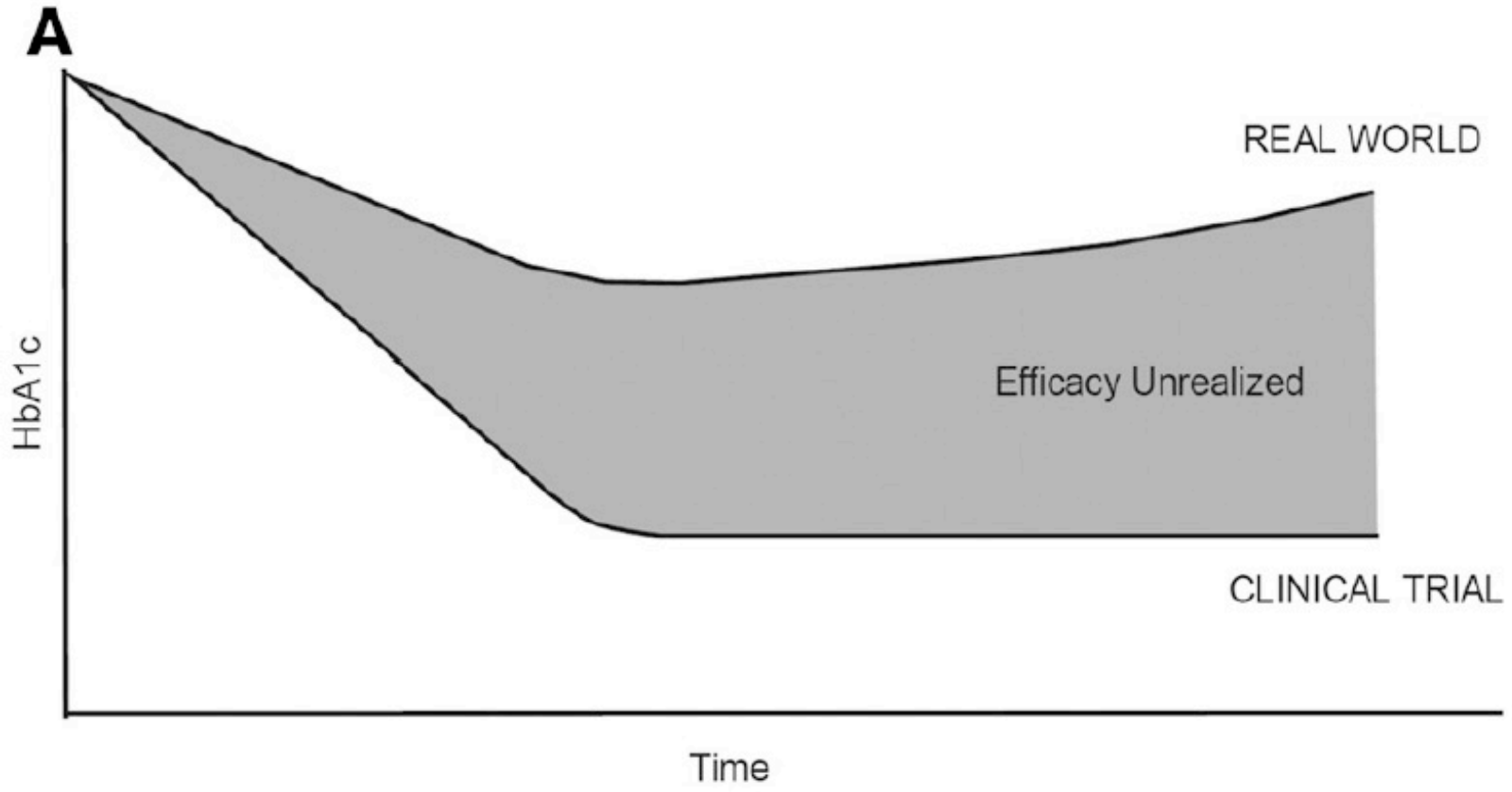


J Am Soc Nephrol 29: ccc–ccc, 2017

Conclusioni

- ✓ Controllo glicemico: un controllo intensivo è protettivo verso micro e macroalbuminuria, i dati sulla progressione del danno sono conflittuali.
- ✓ Controllo PA: indispensabile per rallentare la progressione del danno.
- ✓ Blocco SRAA: maggiori evidenze con ARB. Sicuramente efficaci in presenza di albuminuria.
- ✓ Inibitori SGLT-2: dati promettenti sulla progressione del danno.
- ✓ Perdita di peso: alcuni dati suggeriscono un possibile beneficio.

Diabetes Care Volume 40, November 2017



"Drugs don't work in patients who don't take them."

C. Everett Koop, MD, US Surgeon General, 1985