Diabetic nephropathy

Eberhard Ritz
Heidelberg (Germany)

In order to be a competent nephrologist, one has to be a knowlegeable diabetologist

Eli Friedman

Diabetic nephropathy

Eberhard Ritz
Heidelberg (Germany)

Epidemiology

Renal failure in type 2 diabetes–
“a medical catastrophe of world-wide dimension”

Ritz, Am.J.Kidn.Dis. (1999) 34: 795

-USRDS 2003 **43 % of incident patients**

(www.USRDS.org) **334 ppm *(per million population per year)***

- Heidelberg **49 % of incident patients**

98 ppm

6 % type 1

94 % type 2

Schwenger, Dtsch Med Wschr (2001) 126: 1322

Patients with terminal renal failure and with diabetes as comorbidity

- **classical Kimmelstiel Wilson 70%**
- **ischemic nephropathy 11%**
- **primary kidney disease with superimposed diabetes 19%**

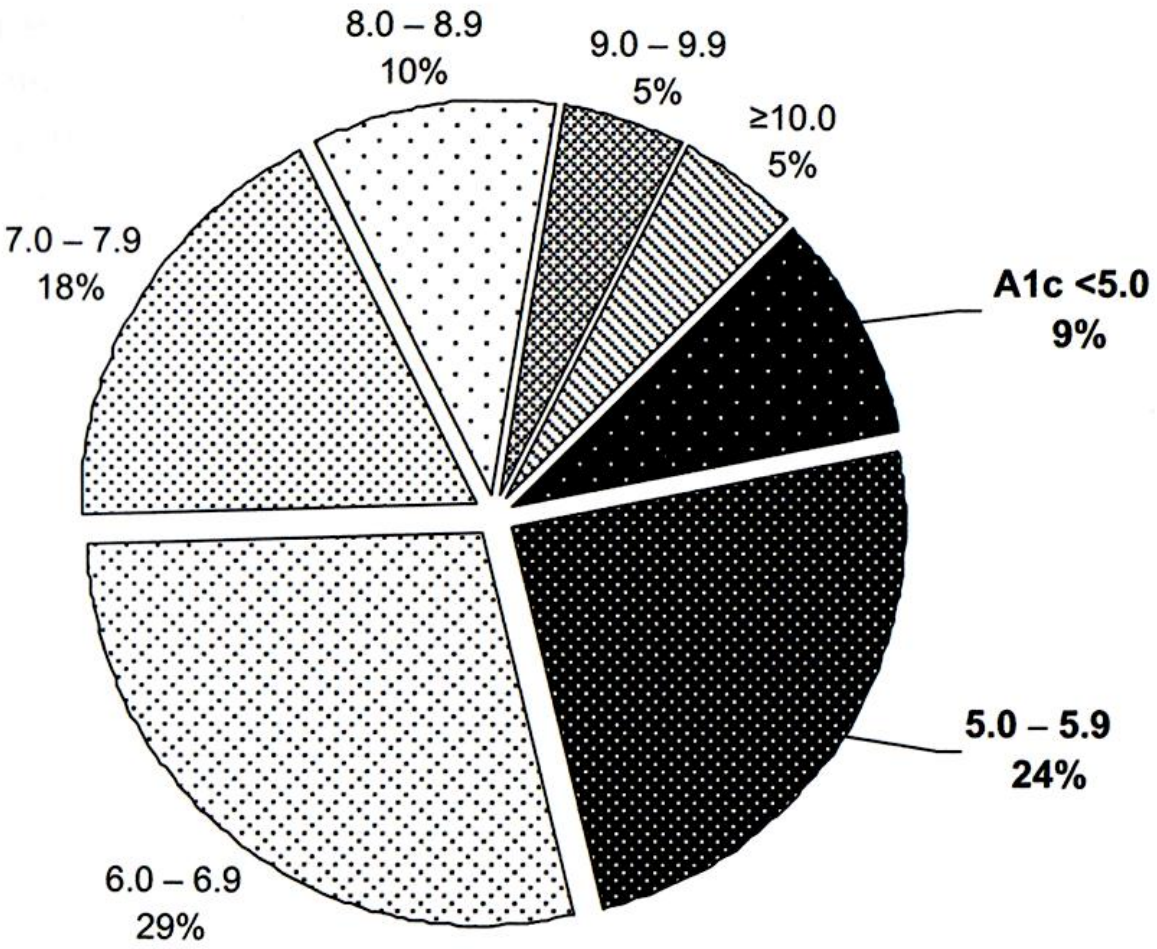
→ **irreversible acute kidney injury** ***(acute on chronic)***
or delayed progression to terminal renal failure after recovery from AKI

→ **diagnosis of diabetes not known to refering physician: 11% ; disappearance of hyperglycemia because of weight loss and anorexia ("burnt-out diabetes")**
(distrust registries !)

Schwenger ,Dtsch.Med.Wschr.(2001) 126: 1322

“Burnt out” diabetes

$HbA1_c$ in 23,618 diabetic patients on hemodialysis in the USA

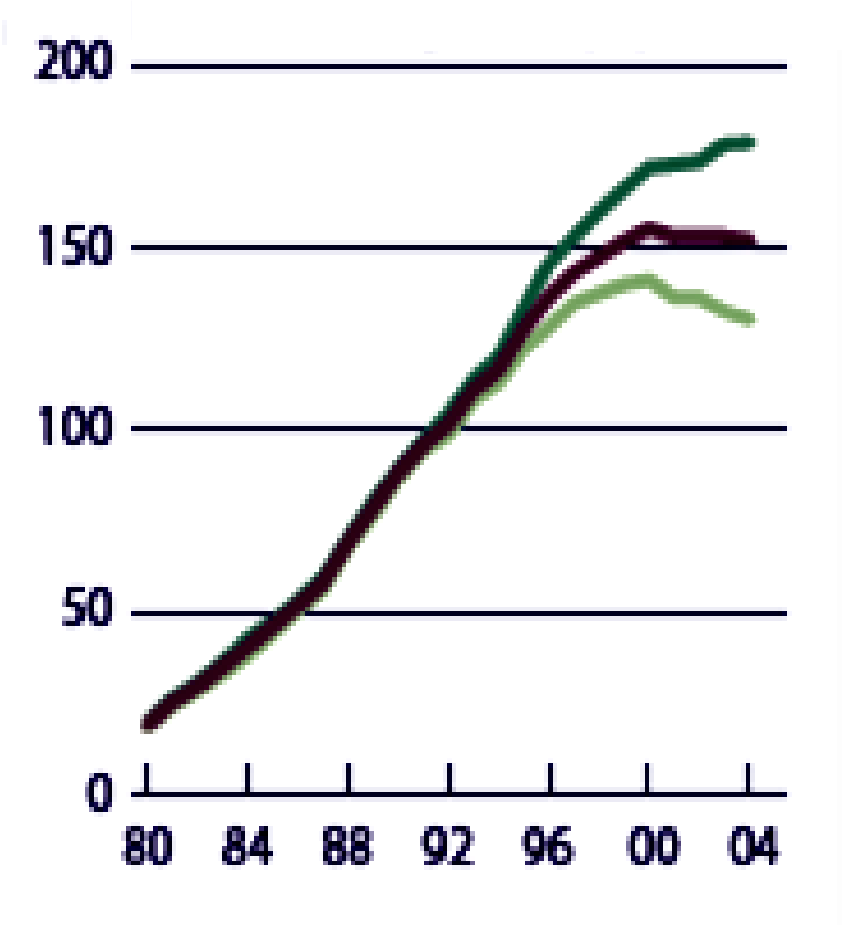


Kalantar-Zadeh,J.Renal Nutr.(2009) 19:33

Continuous increase stopped in USA

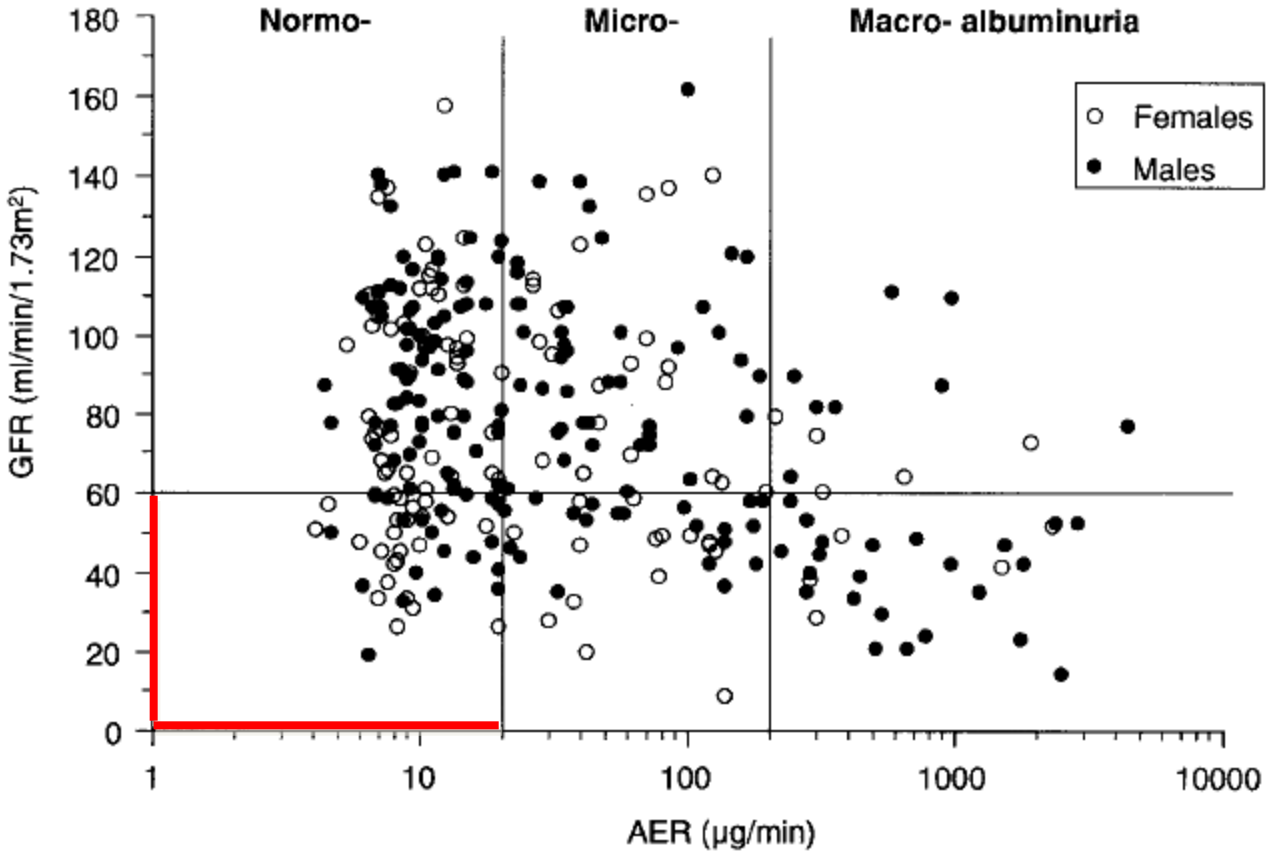
Adjusted incident rates of ESRD with diabetes as the primary diagnosis

per million general population



USRDS 2007

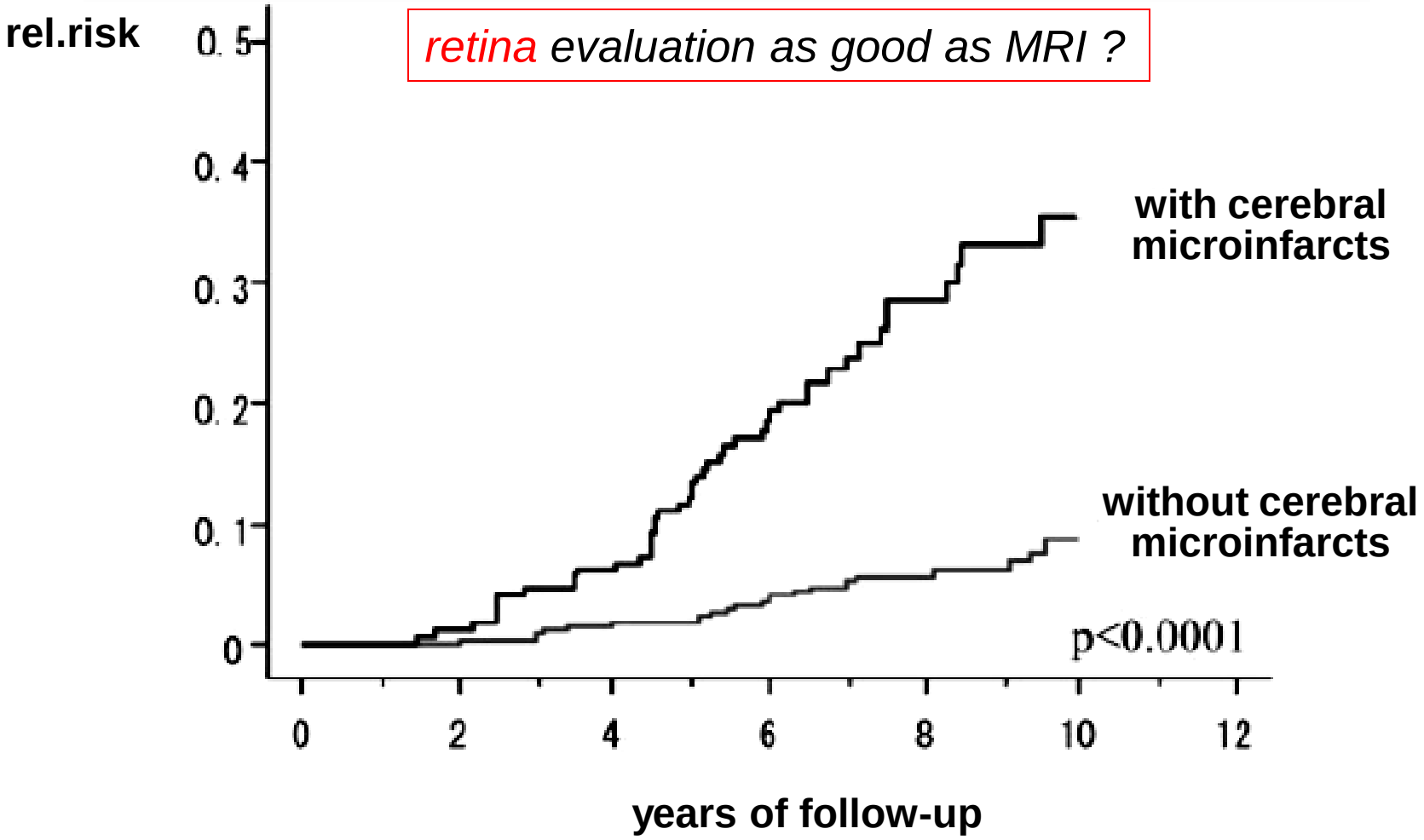
Typ 2 Diabetes with renal failure despite no significant albuminuria



MacIsaac, Diabetes Care (2004) 27:195

Small vessel disease by cerebral MRI

predicts doubling of serum creatinine or dialysis dependency in the absence of microalbuminuria



Uzu, J.Am.Soc,Nephrol.(2010) 20: 520

Past dogma:
Proteinuria is hallmark of diabetic nephropathy

In patients with type 1 diabetes and new-onset microalbuminuria the development of advanced chronic kidney disease may not require progression to proteinuria

Bruce A. Perkins[1], Linda H. Ficociello[2], Bijan Roshan[3], James H. Warram[2] and Andrzej S. Krolewski[2]

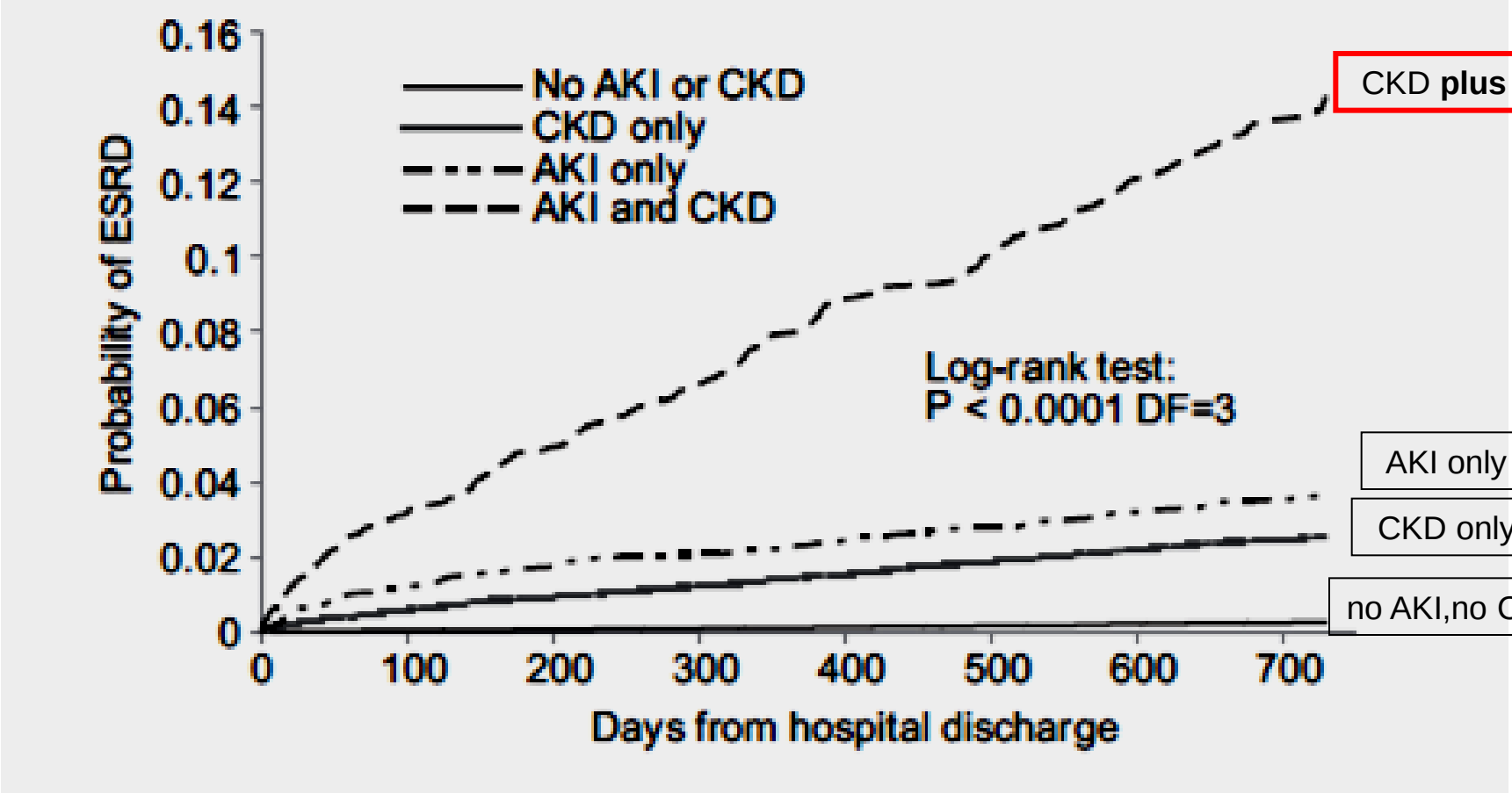
[1]Division of Endocrinology, University of Toronto, Toronto, Ontario, Canada; [2]Section on Genetics and Epidemiology, Joslin Diabetes Center, Boston, Massachusetts, USA and [3]Division of Nephrology, Beth Israel-Deaconess Medical Center and Joslin Diabetes Center, Boston, Massachusetts, USA

Kidney Internat.(2010) 77: 57

Acute kidney injury *(AKI)*

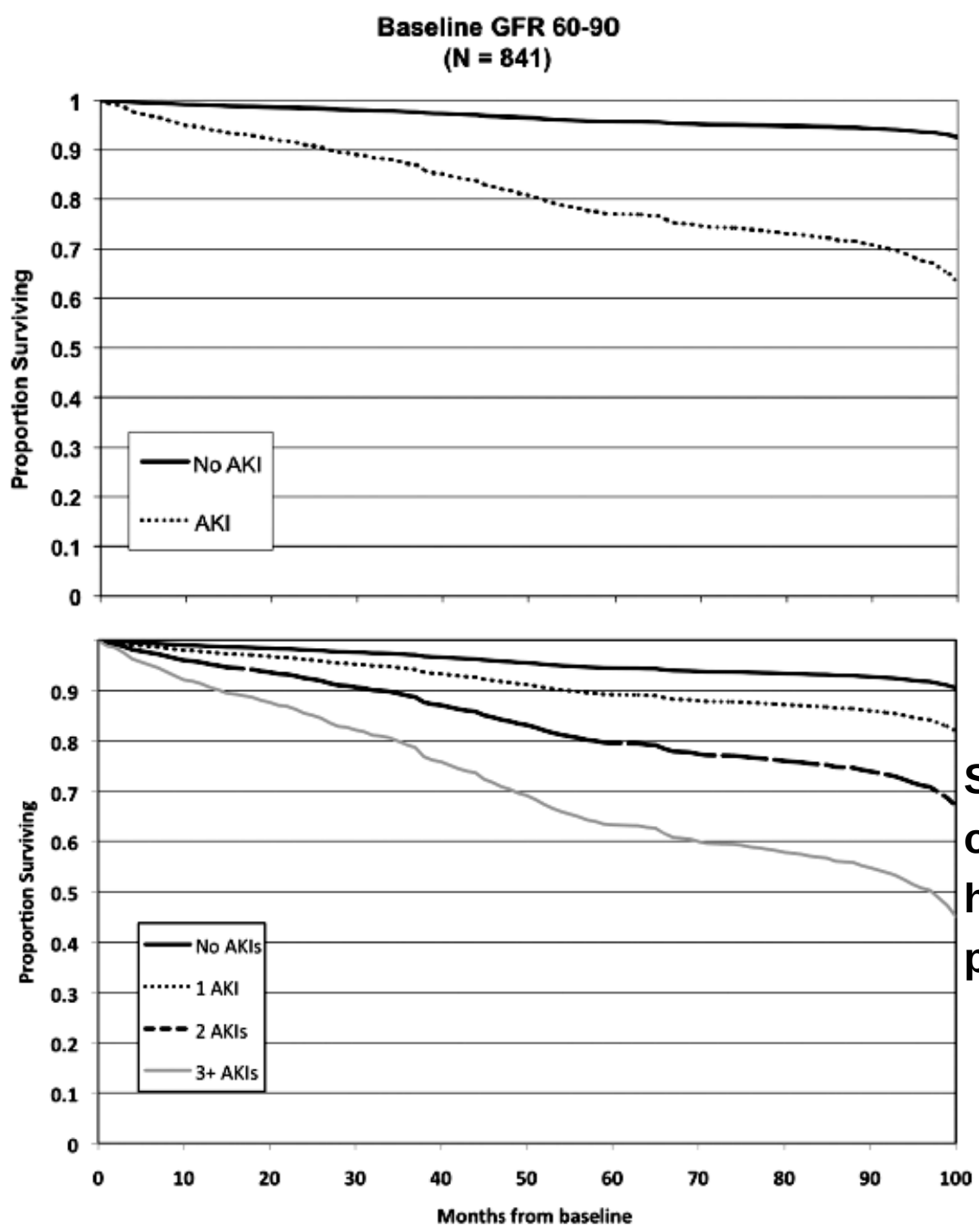
- increases risk of ESRD and

- accelerates progression of preexisting CKD



baseline diabetes : rel.risk of ESRD 2.24 (1.9-2.52)

Ishani, J.Am.Soc.Nephrol.(2009) 20:223



Survival of diabetics hospitalised with AKI episodes to reach CKD 4

(VA healthcare system 1999-2008)

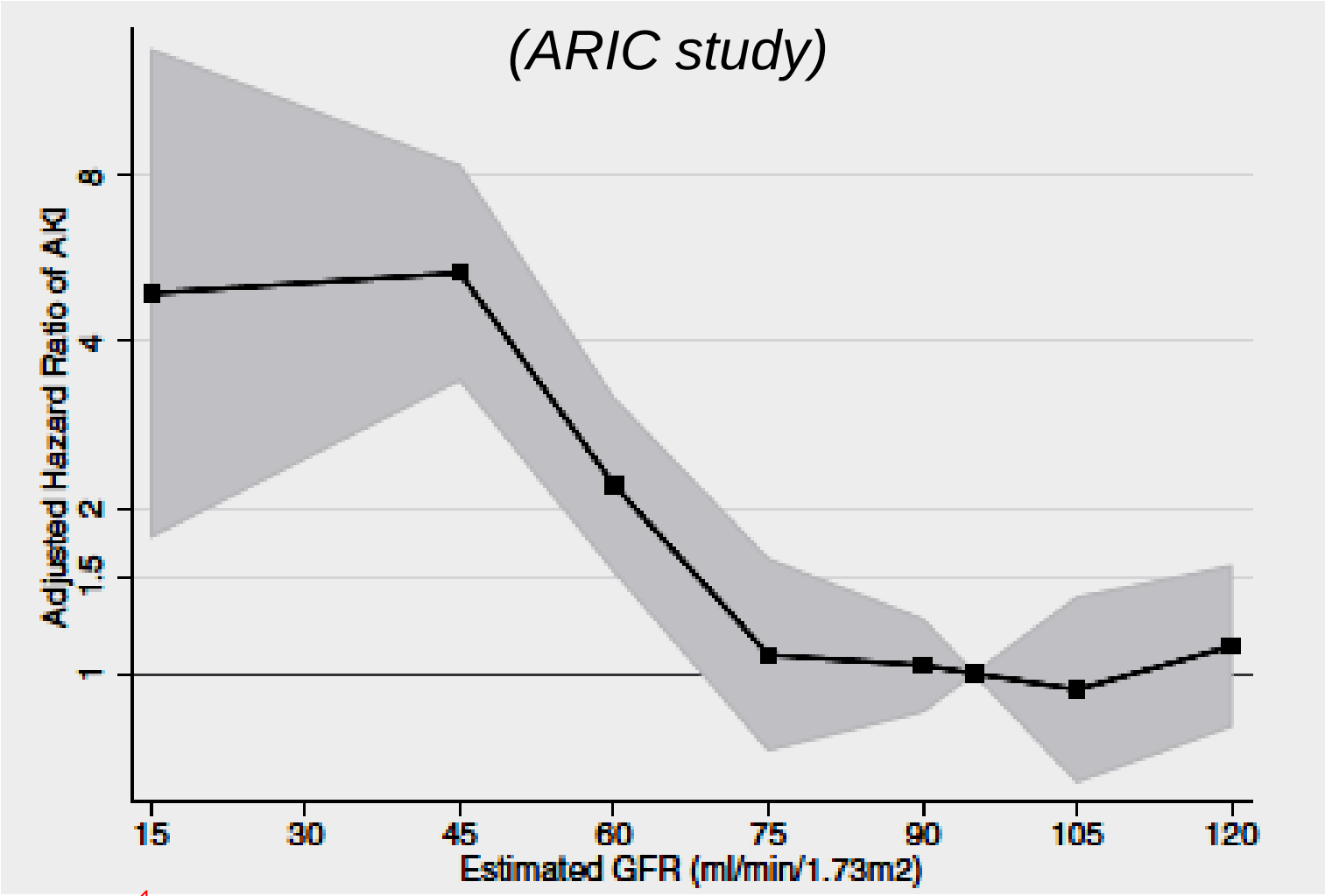
reaching vs not reaching CKD 4

(GFR < 30 ml/min/1.73m²)

S-crea	1.44 *±0.42*	vs 1.05 *±0.26 mg/dl*
obesity	17%	vs 37.9% **!!**
hypertension	41.7%	vs 67.5%
proteinuria	76%	vs 59.8%

Thakar,
CJASN (2011) 6:2567

Low eGFR increases the risk of acute kidney injury (AKI)



Grams J.Am.Soc.Nephrol.(2010) 21:1757

Diabetes after kidney transplantation

US data

- **3 months** **9.1%** *(8.6-9.7)*
- **12 months** **16.0%** **(***15.3-16.7)*
- **36 months** **24.0%** **(***23.1-24.9)*

Predictors : *Africo-Americans, Hispanics*
Males
Hepatitis C
High body mass index
Tacrolimus

Kasiske, Am.J.Transplant.(2003) 3:178

Postinfectious glomerulonephritis in the elderly diabetic

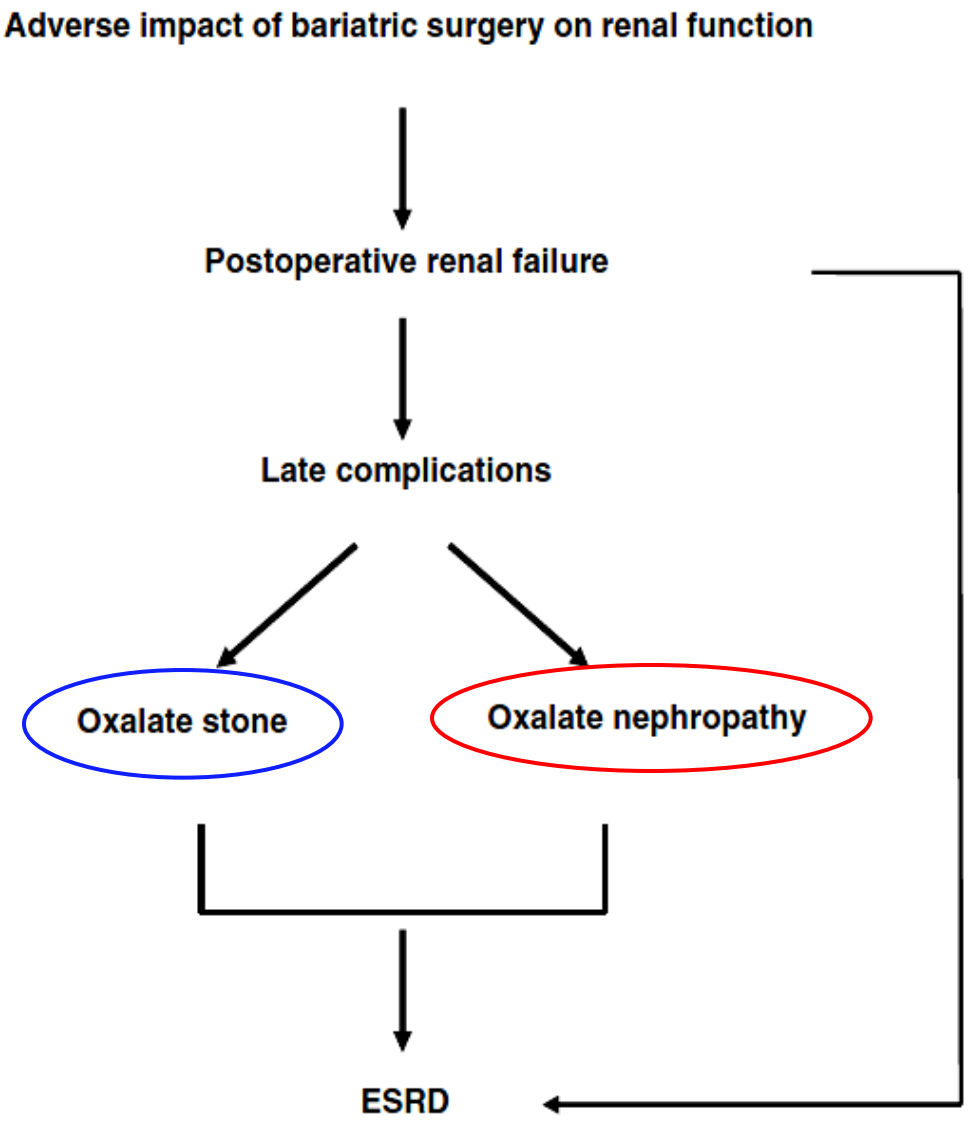
109 patients with postinfectious glomerulonephritis

65-69 years	34%
70-79 “	48%
>80 “	18%

53 % (of all postinfectious GN) **diabetes**
64 % of whom no **diabetic glomerulosclerosis**

82% of diabetic patients **progressed to uremia**

Nasr, J.Am.Soc.Nephrol.(2011) 22: 187



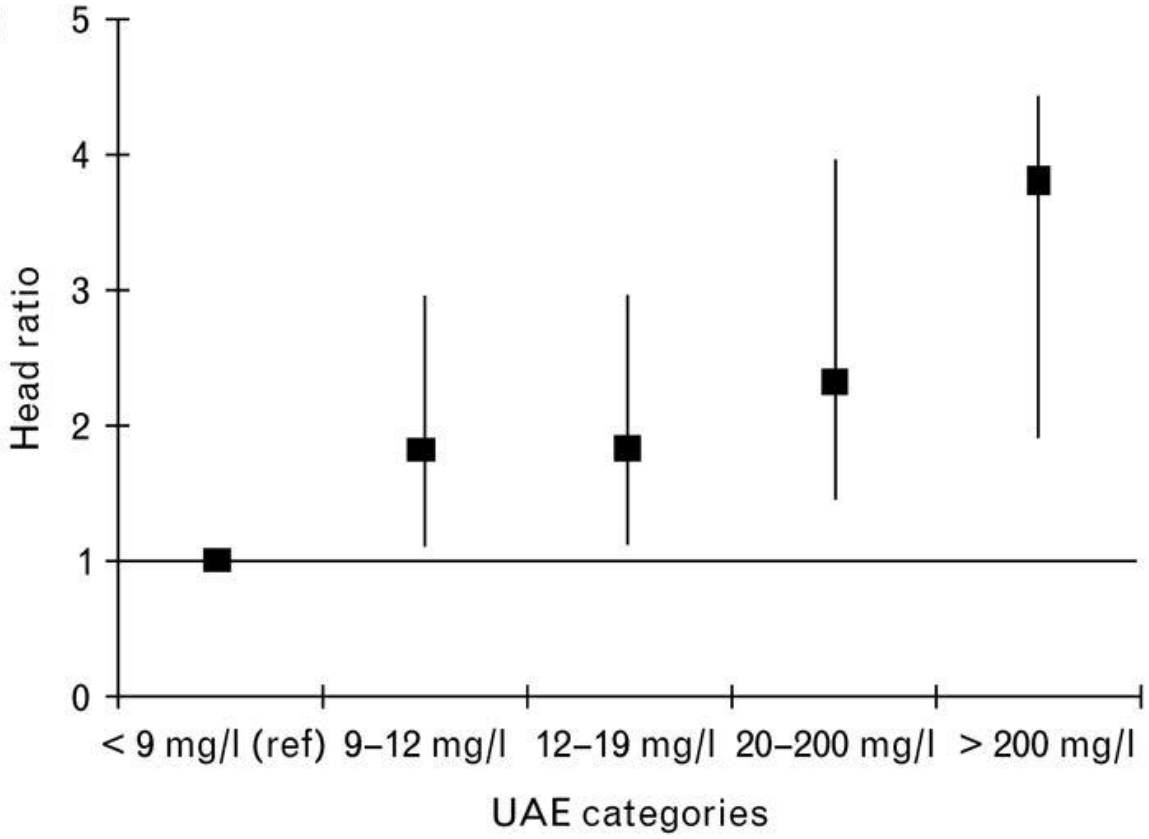
Oxalosis and renal failure after gastric bypass surgery

 # Ahmed, NDT (2010) 25:3142
 # Duffey, J.Am.Coll.Surg. (2010) 211:8
#Montagnac,Nephrol.Ther.(2011) 211:8
 # Moutzouris, Clin.Nephrol.(2011) Suppl.1;p16

Fat malabsorption

Ca^{++} binds free fatty acids
oxalate no longer sufficiently Ca^{++} bound
increased absorption of oxalate
hyperoxaluria and renal oxalosis

Ahmed, Nephrol.Dial.Transplant.(2010) 25:3142



Albuminuria predictor of diabetes

independent of metabolic profile

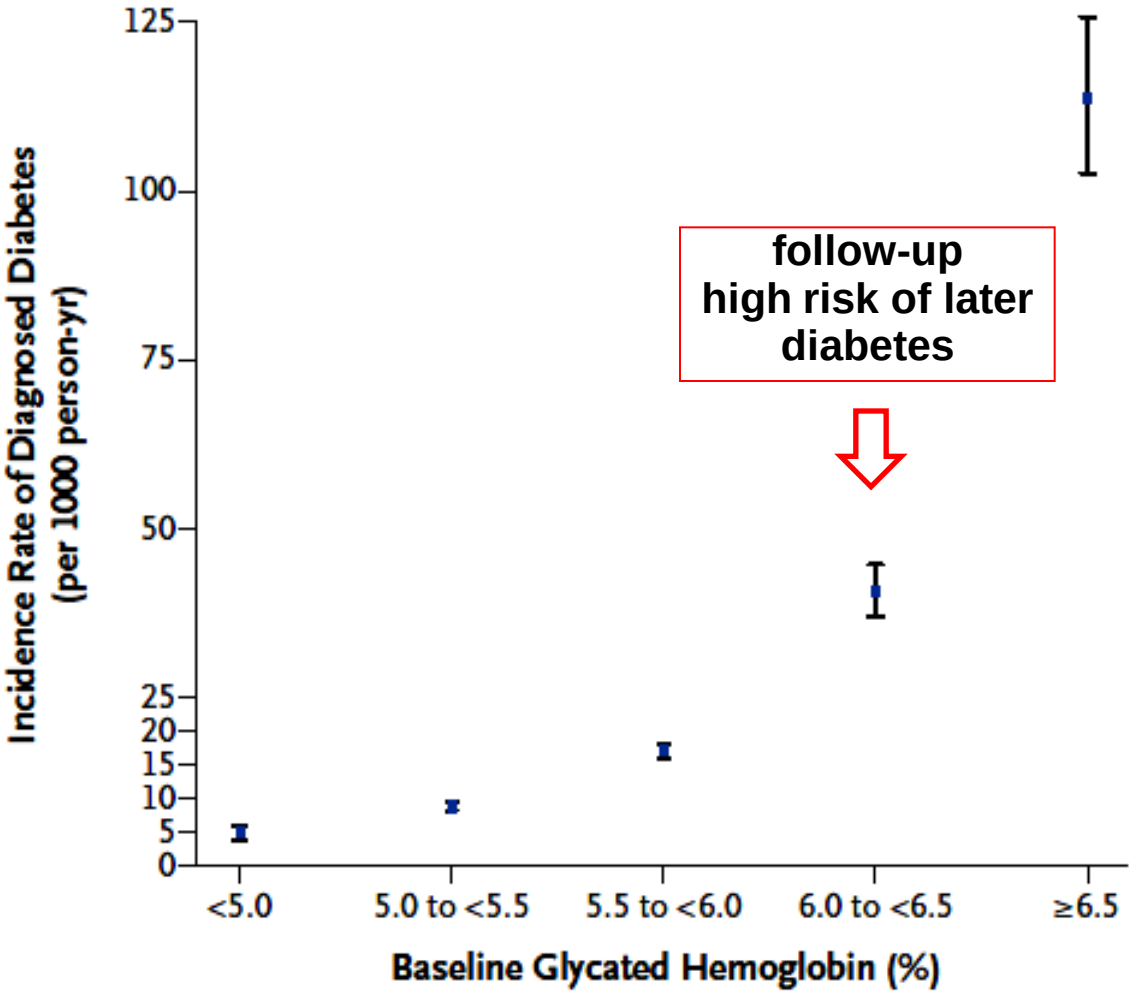
DESIR study

Halimi, J.Hypertens. (2008) 26:2198

ARIC study

11092 individuals, 15 year follow-up

incidence* *of diabetes* *during follow-up according to* *baseline HbA1$_c$



Selvin, New Engl.J.Med. (2010) 362:800

Prediabetic patients with slightly elevated postprandial glycemia

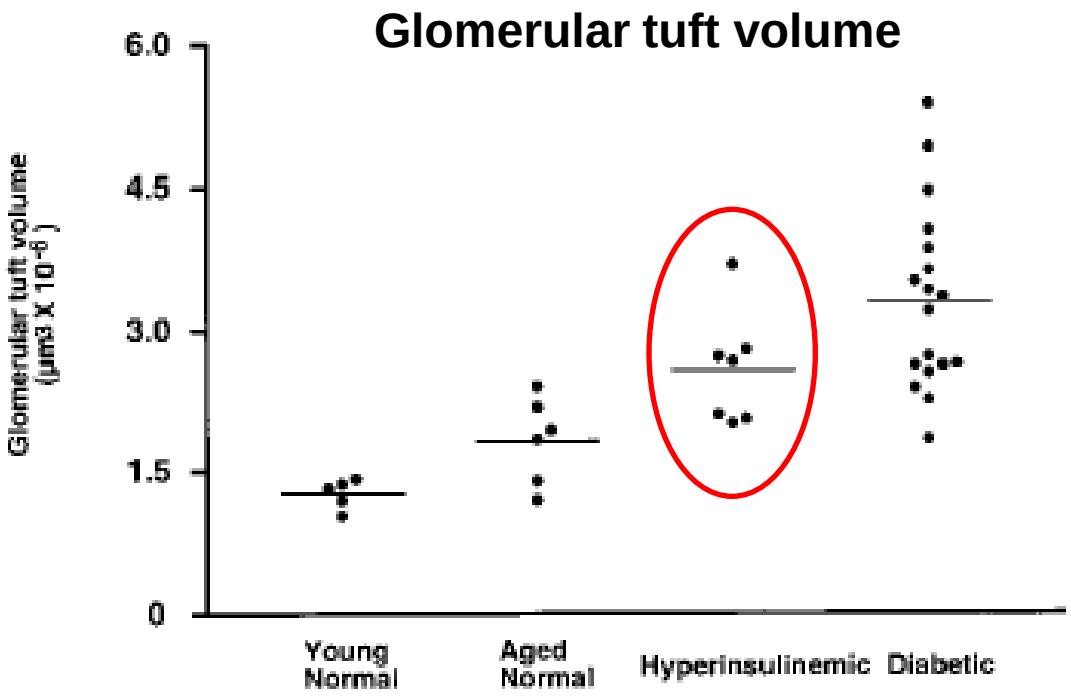
already **reduced kidney function in some patiens**

OGTT

1 h-value

	< 155 mg/dl		**> 155 mg/dl**		
e-GFR (ml/min/1.73m^2)	100	16	95	16	*p<0.0001*
>90 ml/min/1.73m^2	77.2%		69.4%		*p<0.003*
89-69 “	21.7%		27.2%		
59-30 “	1.1%		3.4%		

Succurro, Clin.J.Am.Soc.Nephrol.(2010) 5:1922



Diabetic nephropathy

early treatment – a lesson from rhesus monkeys

Cusumano, Am.J.Kidn.Dis.(2002) 40:1075

Glomerular hypertrophy begins in the **prediabetic hyperinsulinemic phase**. This finding suggests that **early intervention** may be required **in human** patients to preserve normal gomerular structure

Pathologic findings in glomeruli of normoalbuminuric type 1 diabetics

	Nondiabetic controls		type 1 diabetes GFR normal		type 1 diabetes GFR reduced	
thickness of glomerular basal membrane (nm)	332	45.7	469	84.2	545	141
mesangial volume-fraction (% per glomerulus)	8	2	8	2	10	2

Caramori, Diabetes (2003) 52:1036

Diffuse diabetic glomerulosclerosis in a patient with abnormal glucose tolerance –

subsequent development of diabetes mellitus

Altiparmak, Neth.J.Med.(2002) 60: 260

Nodular diabetic glomerulosclerosis in a patient with metabolic syndrome and insulin resistance without diabetes

Souraty, Nature Clin.Pract.Nephrol.(2008) 4:639

issue :

past diabetes remitted or

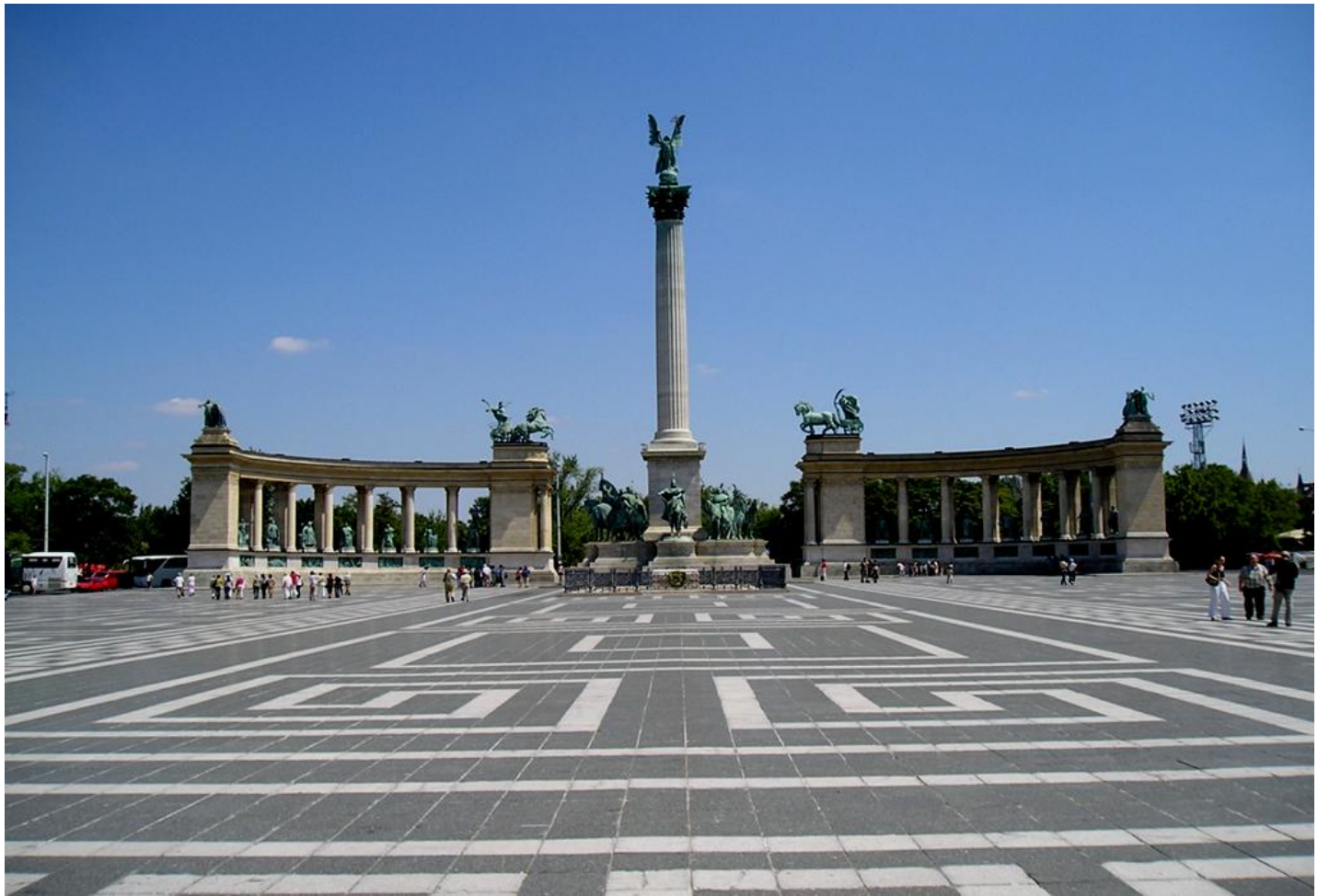
true diabetic nephropathy in prediabetic patient ?

Diabetic nephropathy

Eberhard Ritz
Heidelberg (Germany)

Epidemiology

Prevention and treatment of diabetic nephropathy



Apart from the

management of glycemia

the main treatment targets

in diabetic nephropathy :

- **albuminuria / proteinuria**
- **blood pressure**

http://www.kidney-international.org

Time to abandon microalbuminuria?

P Ruggenenti[1,2] and G Remuzzi[1,2]

[1]*Clinical Research Centre for Rare Diseases 'Aldo e Cele Daccò', Mario Negri Institute for Pharmacological Research, Villa Camozzi, Ranica, Bergamo, Italy and* [2]*Unit of Nephrology, Azienda Ospedaliera, Ospedali Riuniti, Bergamo, Italy*

The term microalbuminuria – a urinary albumin excretion (UAE) between 20 and 200 μg/min – has been introduced to identify subjects at increased risk of renal and cardiovascular disease. However, the relationship between albuminuria and risk is not restricted to the microalbuminuric range and extends to as low as 2–5 μg/min. On the contrary, the increase of UAE above 200 μg/min (macroalbuminuria) heralds the onset of proteinuria (urinary protein excretion above 0.5 g/24 h) and progressive renal and cardiovascular disease. Albuminuria is a component of the metabolic syndrome and

WHY MEASURING ALBUMINURIA?

It is now 40 years since Keen *et al.*[1] had reported an increase in urinary albumin excretion (UAE) in 'newly detected hyperglycemics'. The term microalbuminuria, however, first appeared in the medical literature in 1981, used by Viberti[2] and Svendsen,[3] to describe a UAE below the detection limit of a standard dipstick, but at a level that, as reported by Mogensen *et al.* in 1986,[4] was highly predictive of future overt nephropathy in patients with type I diabetes. Shortly thereafter, it became evident that microalbuminuria pre-

Kidn.Intern.(2006) 70:1214

Urinary albumin concentration :
continuously increasing risk; no threshold;
should be treated as continuous variable like S-cholesterol

Why is albuminuria so predictive of the evolution of diabetic nephropathy?

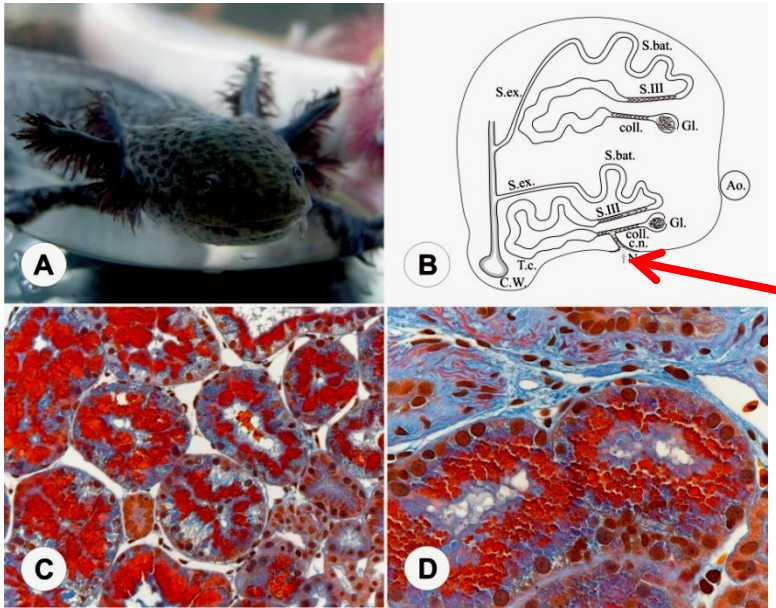
glycated albumin is more nephrotoxic

“not all albumin is created equal”

Glycated albumin
increased nephrotoxicity

Histology scores

	protein droplets		peritubular fibrosis	
NaCl	1.23	0.5	0.40	0.05
albumin	2.74	0.4	2.87	0.7
glycated albumin	3.70	0.4	3.30	0.6



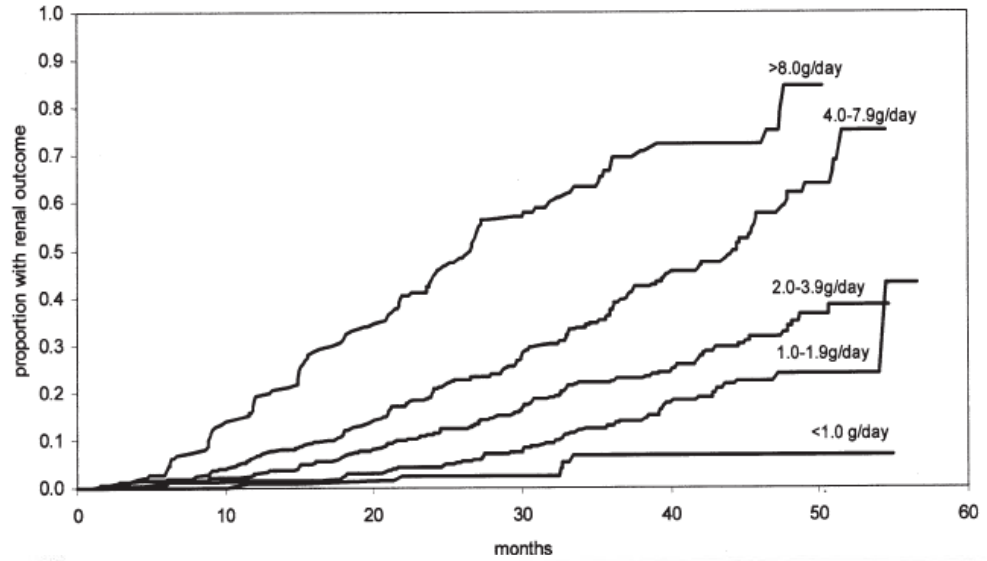
connection between peritoneum and tubule

Gross, Am.J.Physiol.Renal (in press)

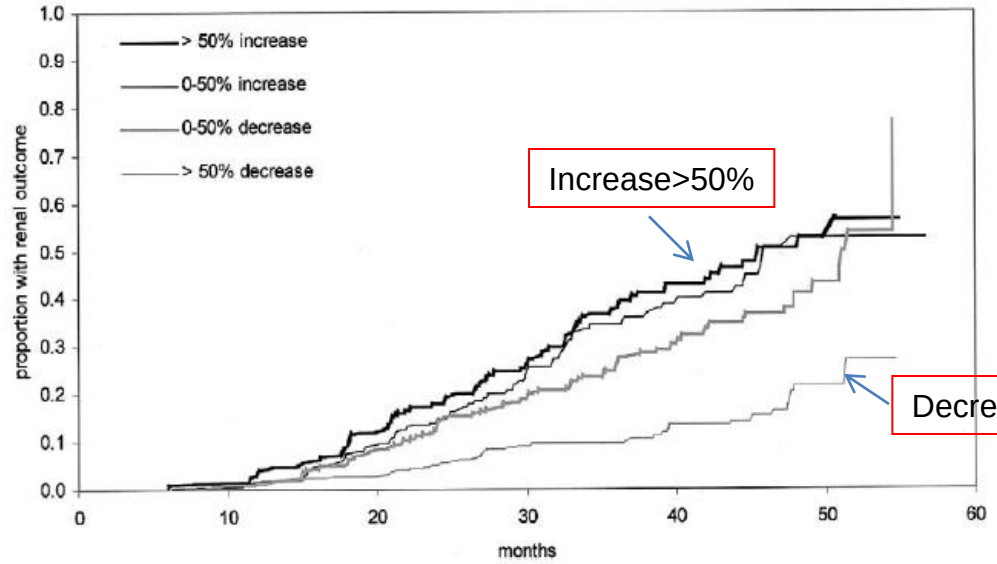
Is proteinuria a valid treatment target in diabetic nephropathy?

What is the evidence ?

renal endpoint



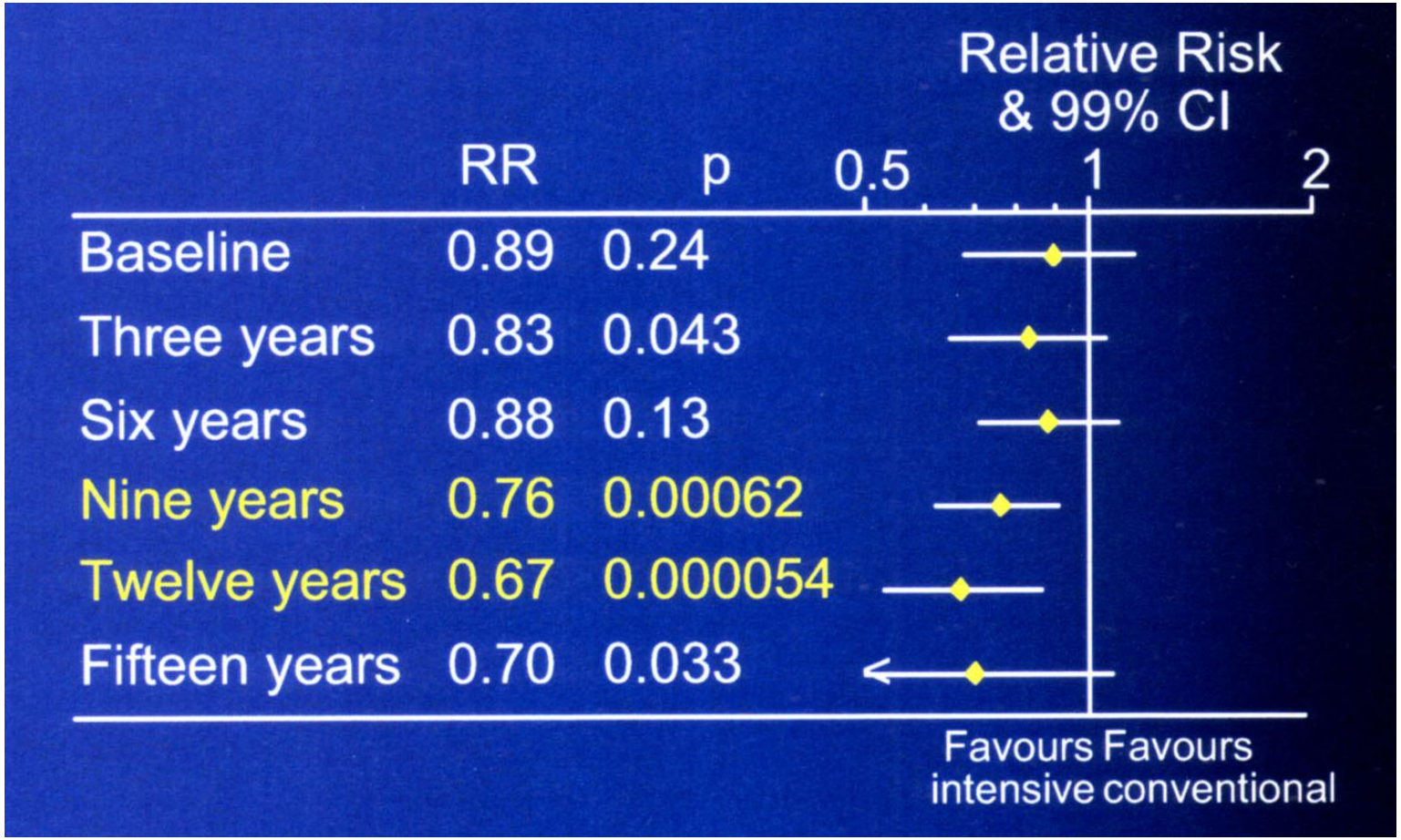
baseline



treatment effect

Atkins, Am.J.Kidn.Dis.(2005) 45:281

Benefit from treating microalbuminuria in type 2 diabetes

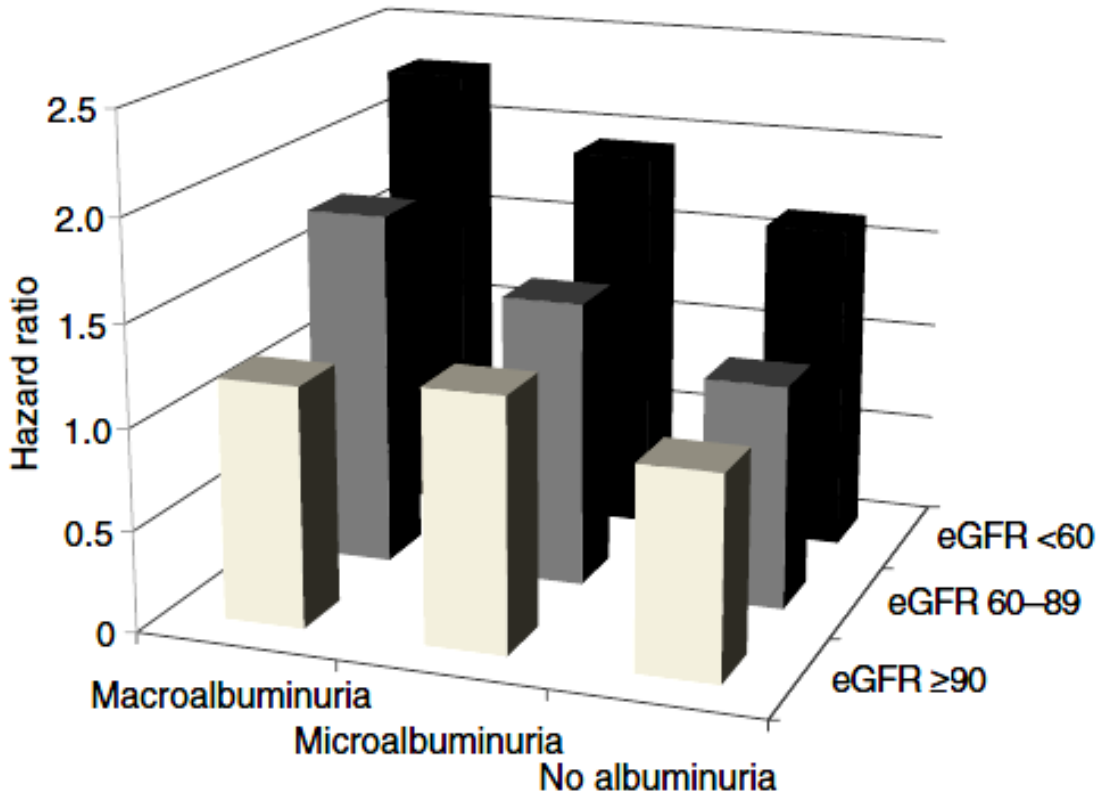


UKPDS study

Both **albuminuria** and **eGFR** are independent and additive predictors of **cardiovascular events** in type 2 diabetes

(FIELD study)

CV events



Drury, Diabetologia (2011) 54:32

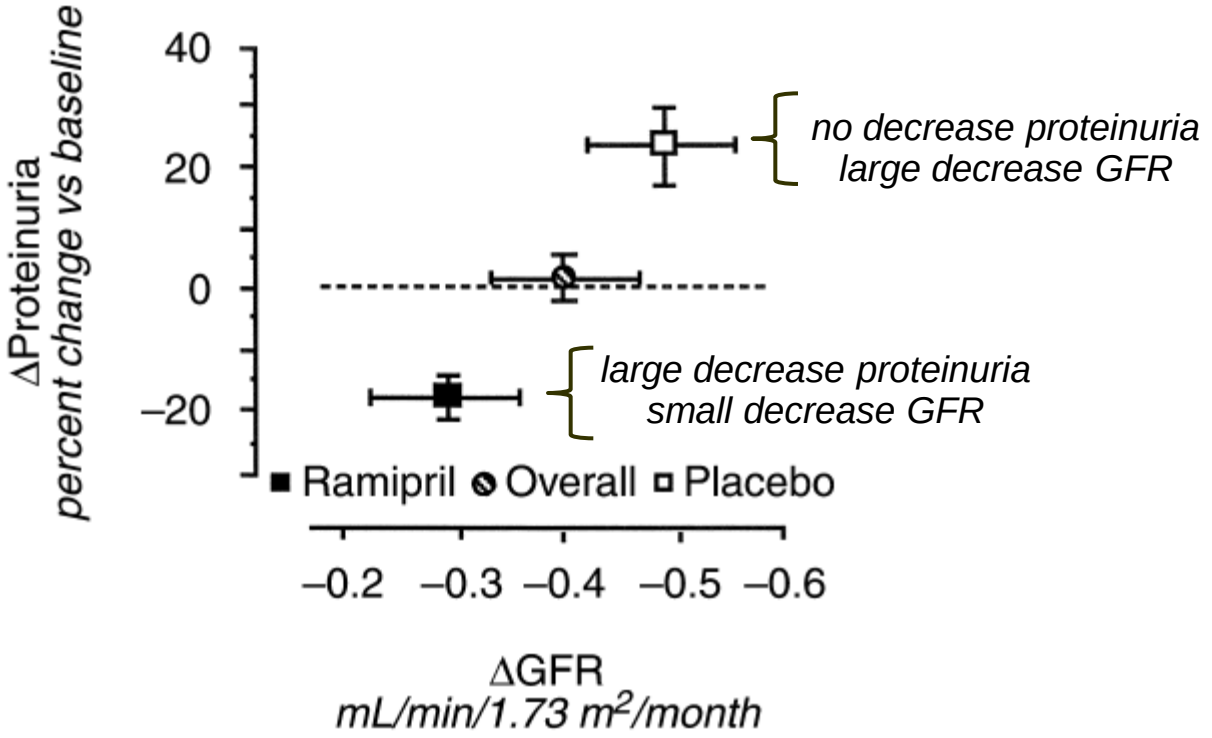
Retarding progression of chronic renal disease :

the neglected issue of residual proteinuria

("fire and forget philosophy")

GISEN study

change in proteinuria after 3 months of treatment predicts longterm evolution of GFR



Ruggenenti, Kidn.Internat.(2003) 63:2254

Intensified glycemic control in type 1 and 2 diabetes ⇨ less incidence of microalbuminuria and macroalbuminuria

relative risk reduction (RRR) by lowering $HbA1_c$ intensified (I) vs conventional (C) treatment:

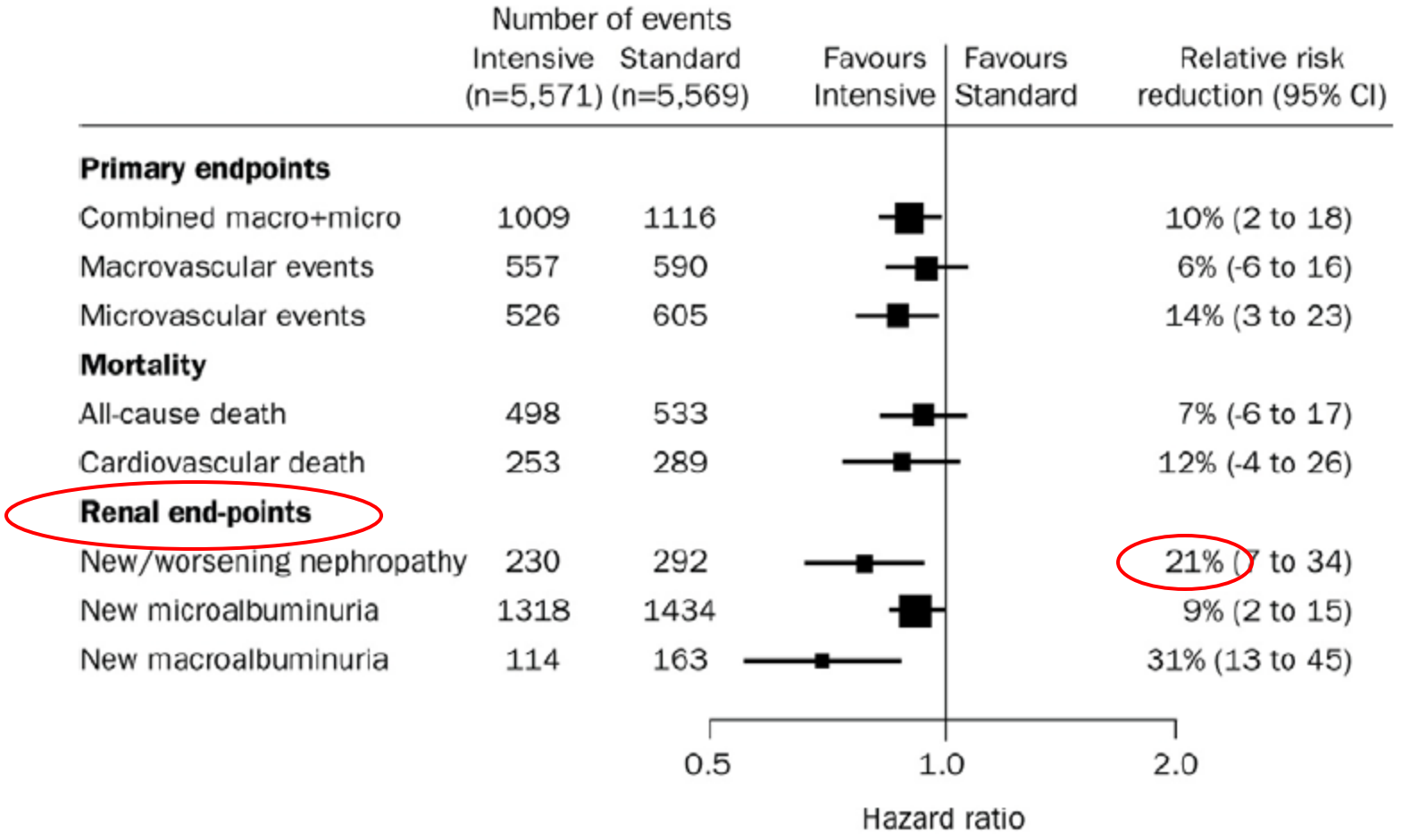
type 1 diabetes *type 2 diabetes*

DCCT	*n*	HbA_{1c}	Microalbuminuria	RRR	*P*	Macroalbuminuria	RRR	*P*
Primary prevention	346 I	7.2% I	16% I	34%	0.04	2.6% I	NS	NS
	378 C	9.2% C	27% C			2.3% C		
Secondary prevention	363 I	7.2% I	26% I	43%	< 0.001	5.2% I	56%	< 0.01
	352 C	9.2% C	42% C			11.3% C		
UKPDS	2408 I	7.0% I	19% I	24%	< 0.001	4.4% I	33%	0.026
	994 C	7.9% C (10-year data)	25% C			6.5% C		

Bilous, Diabetic Medicine (2008)25(Suppl.2)25-29

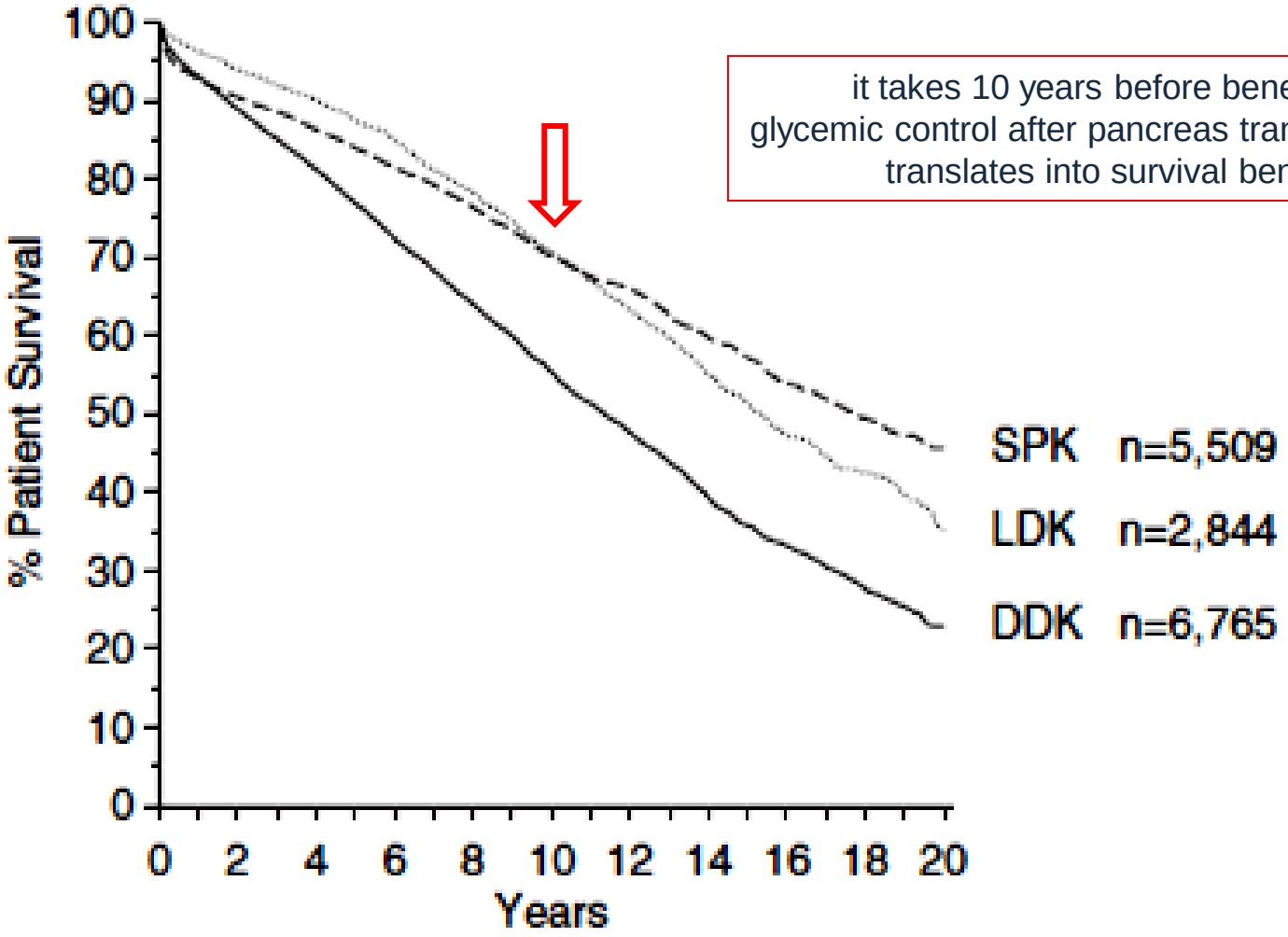
ADVANCE study

11,140 type 2 diabetics, intensivied treatment with Glicazide on top of antidiabetics administered at study entry
achieved $HbA1_c$ value: 6.5% vs 7.3%



1 renal event prevented per 20 patients after 5 years of treatment

Longterm survival of type 1 diabetic patients after simultaneous pancreas-kidney-transplantation (SPK) life donor kidney (LDK) and dead donor kidney transplantation (DDK)

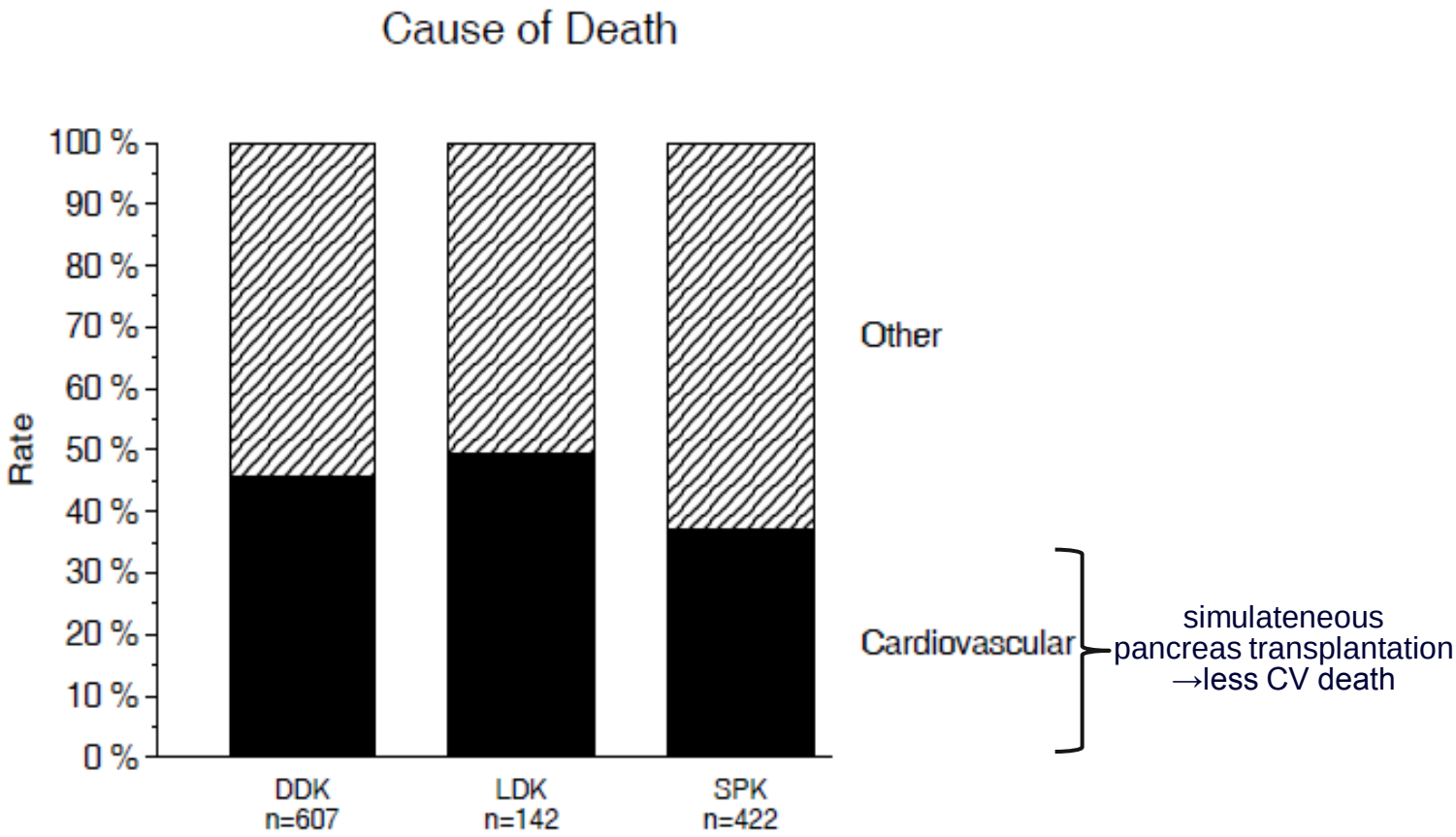


it takes 10 years before benefit of glycemic control after pancreas transplantation translates into survival benefit

Morath, Clin.J.Am.Soc.Nephrol. (2010) 5:549

Causes of death:

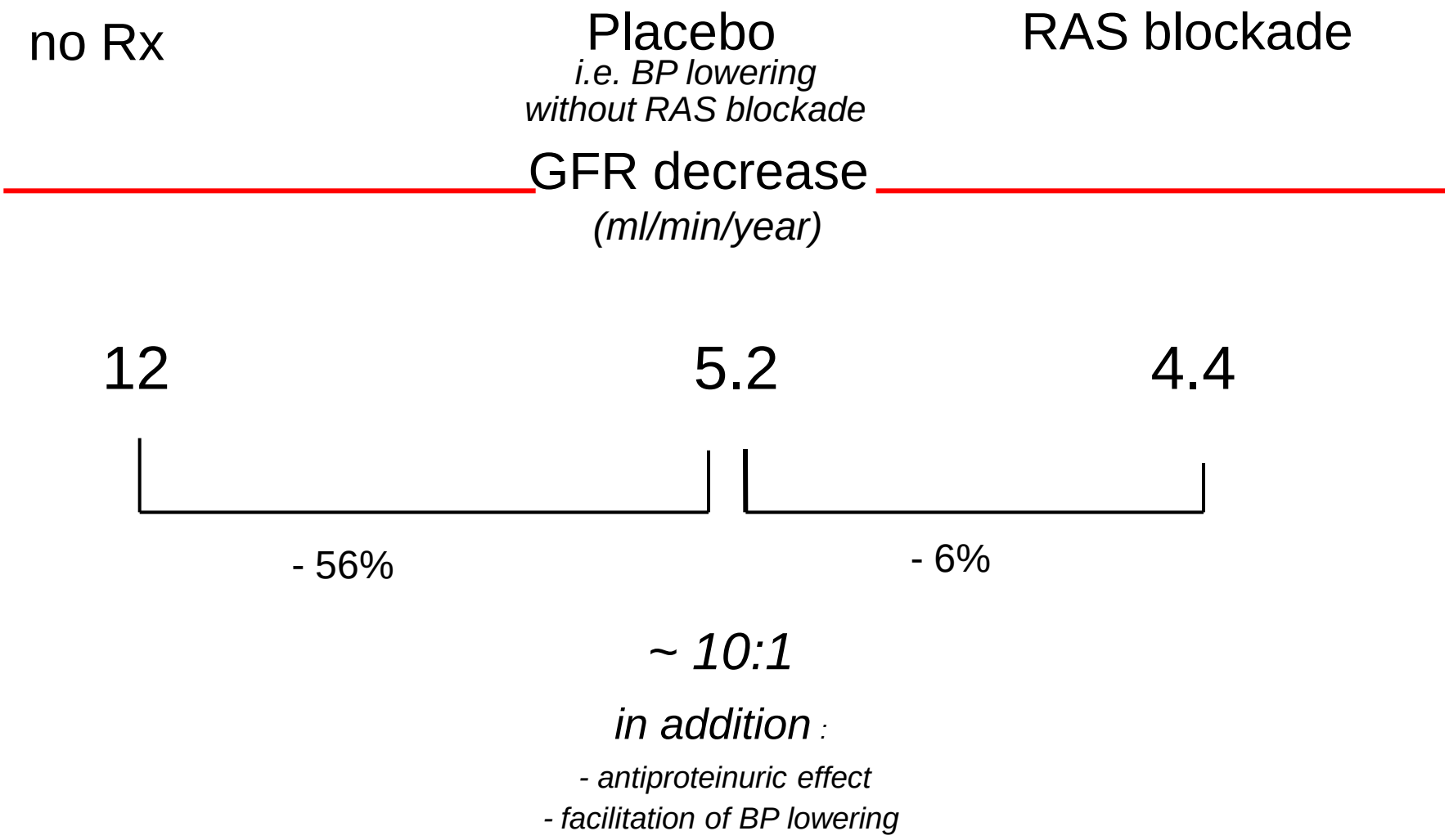
dead donor *- (DDK),* ***life donor*** *- (LDK)* ***or simultaneous*** *(SPK)*
pancreas-kidney transplantation



Morath, J.Am.Soc.Nephrol.(2008) 19:1557

BP lowering vs RAS blockade

RENAAL study



~ 10:1

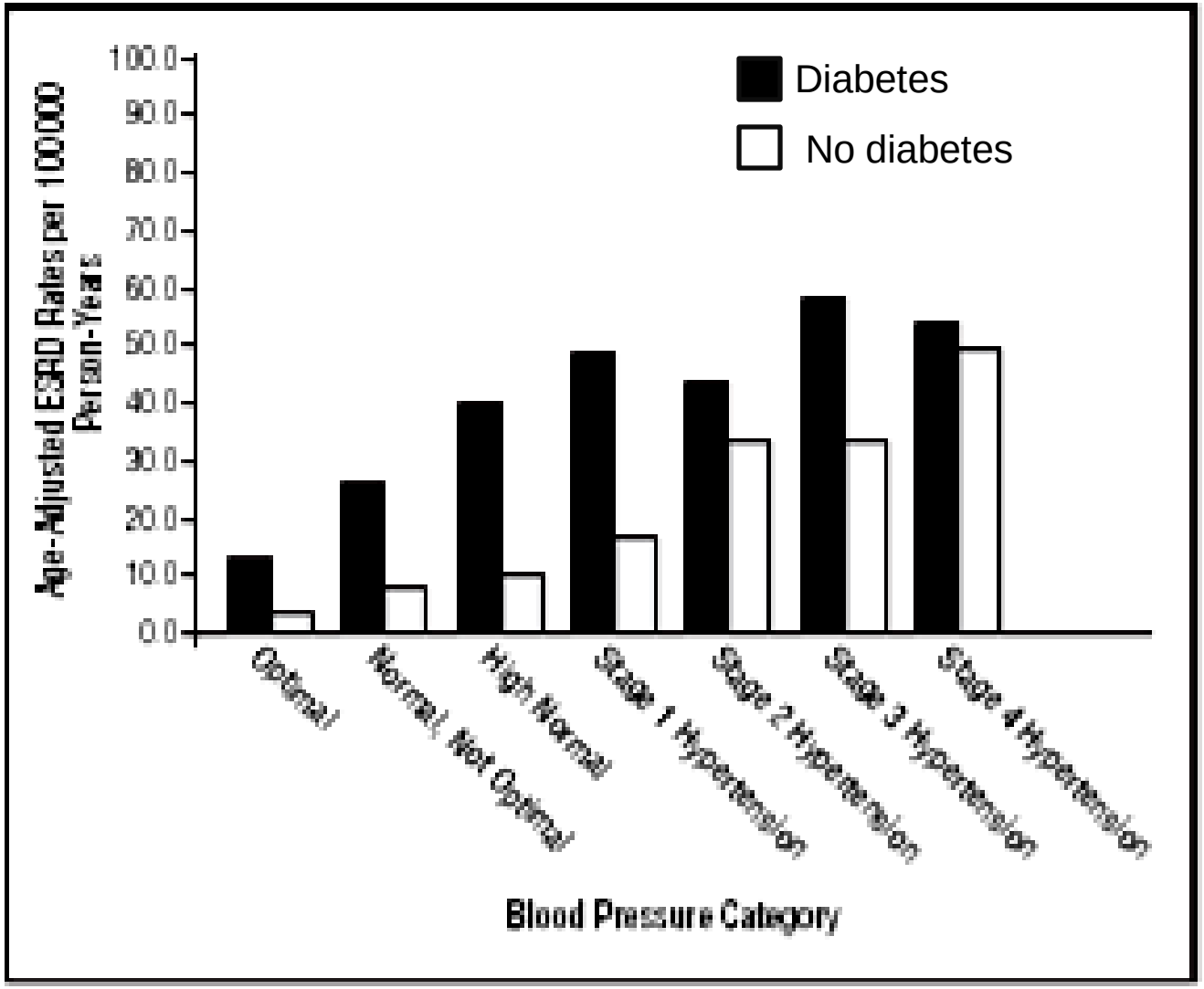
in addition :

- antiproteinuric effect

- facilitation of BP lowering

Blood pressure predicts endstage renal disease in individuals without renal disease at baseline – diabetics vs nondiabetics

(Kaiser Permanente cohort)



Hsu, Arch.Int.Med. (2005) 165:923

Elevated BP and/or abnormal circadian BP profile in newly diagnosed type 2 diabetics

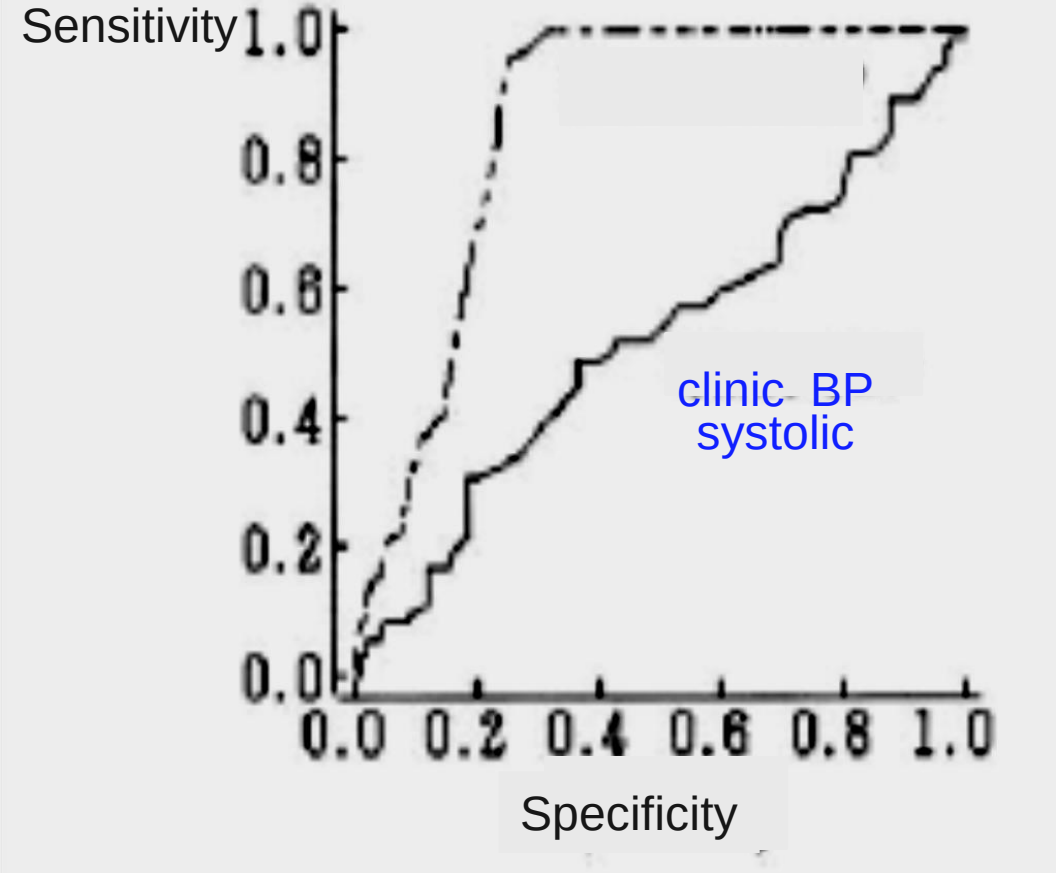
- BP > 130/80 mmHg 60%
- dipping < 15% 79%

Keller, J.Am.Soc.Nephrol. (1996) 7: 2627

Morning BP selfmeasured vs clinic BP better prediction of diabetic complications

(nephropathy, retinopathy, coronary heart disease)

selfmeasured systolic BP
(morning)



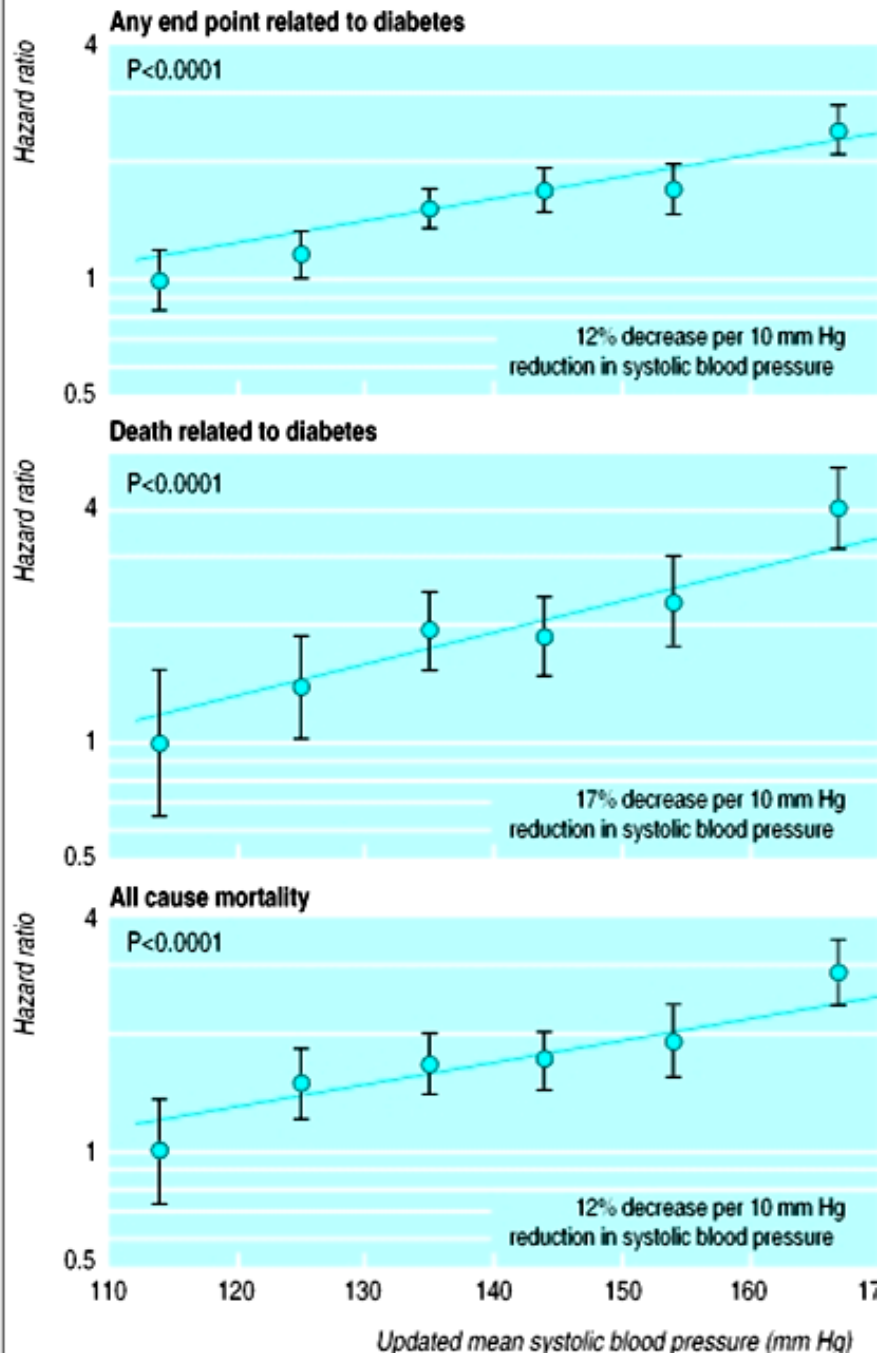
Kamoi, Diabetes Care (2002) 25:2218

Increase of albuminuria in type 2 diabetics

⇨ **nocturnal blood pressure most important predictor**

Blood Pressure Variable	Progression of Albuminuria, %	*P* Value
Office blood pressure[b]		.27
Controlled (n=342)	23.4	
Uncontrolled (n=615)	21.5	
24-h blood pressure[c]		.43
Controlled (n=139)	23.0	
Uncontrolled (n=818)	22.0	
Nocturnal pattern		.011
Dipping (n=295)	17.6	
Flat (n=475)	22.9	
Rising (n=187)	27.3	

Palmas, J.Clin.Hypertens.(2008) 10:12



Target blood pressure

Lower blood pressure at baseline
⇨ **less endpoints and death**
(UKPDS)

The lower the better?

Adler, Brit.Med.J.(2000) 321:412

Treatment of Hypertension in Type 2 Diabetes Mellitus: Blood Pressure

Goals, Choice of Agents, and Setting Priorities in Diabetes Care

Metaanalysis

Treatment of hypertension in type 2 diabetes, with blood pressure goals of 135/80 mm Hg, provides dramatic benefits

Aggressive blood pressure control may be the most important factor in preventing adverse outcomes in patients with type 2 diabetes

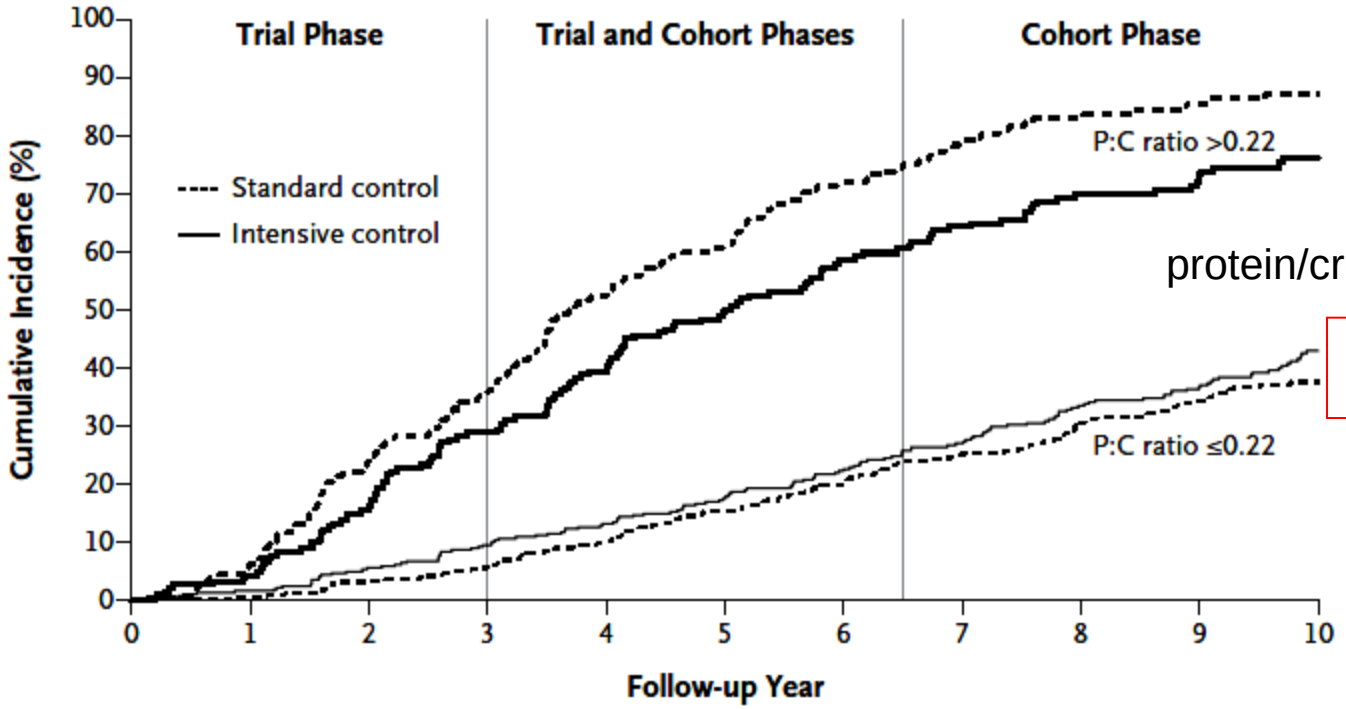
Vijan, Ann.Int.med.(2003)138: 593

Distrust expert opinion, ask for evidence !

Intensive blood pressure lowering and progression : benefit in CKD patients with , but not without, proteinuria

(AASK study)

renal endpoint



P:C elevated

protein/creatinine ratio

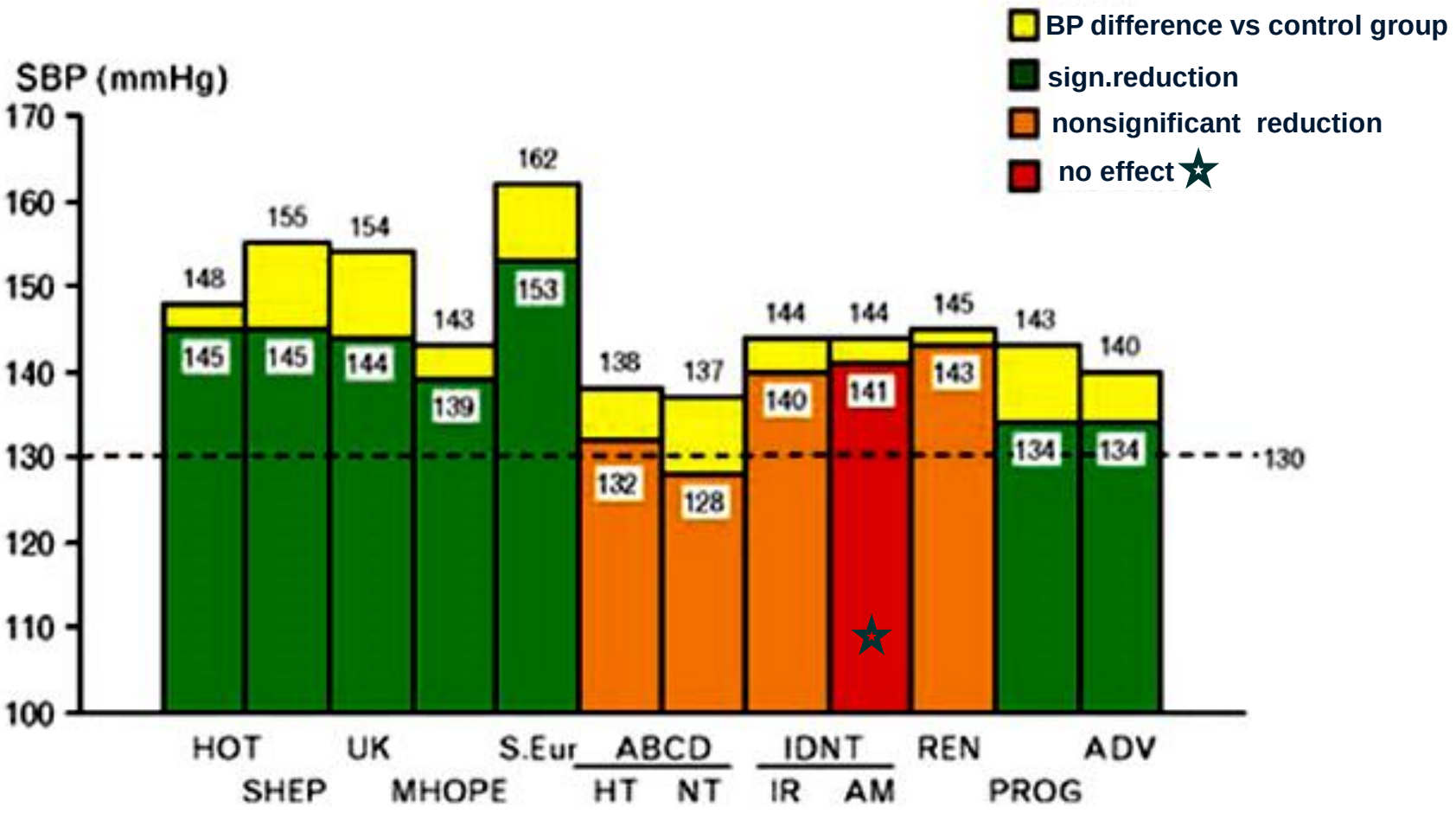
P:C not elevated

Appel, New Engl.J.Med.(2010) 363:918

Achieved systolic blood pressure of diabetic patients

randomised to more active (below) or less active (above) blood pressure lowering

⇨ ***reduction of cardiovascular endpoints***

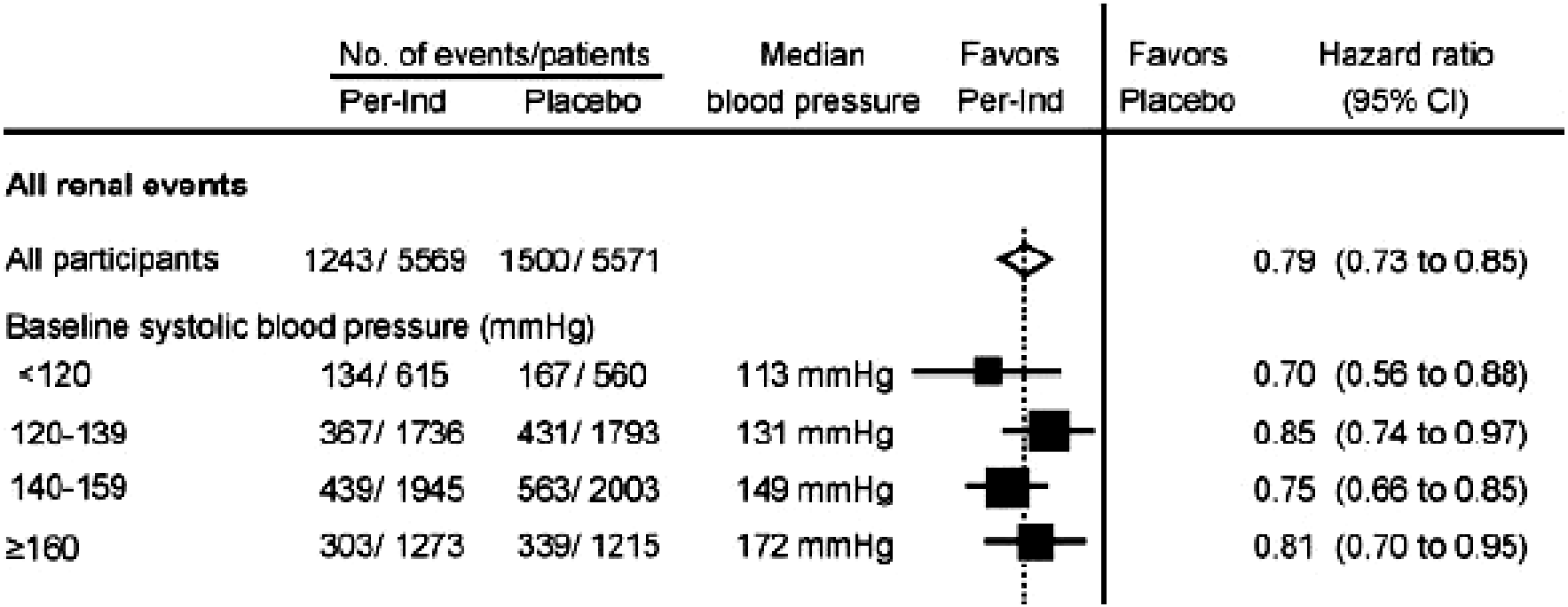


Mancia, J.Hypertens.(2009) 27:2121

Lowering blood pressure reduces renal events in patients with type 2 diabetes –

even if BP is lowered within the normotensive range !

Advance study



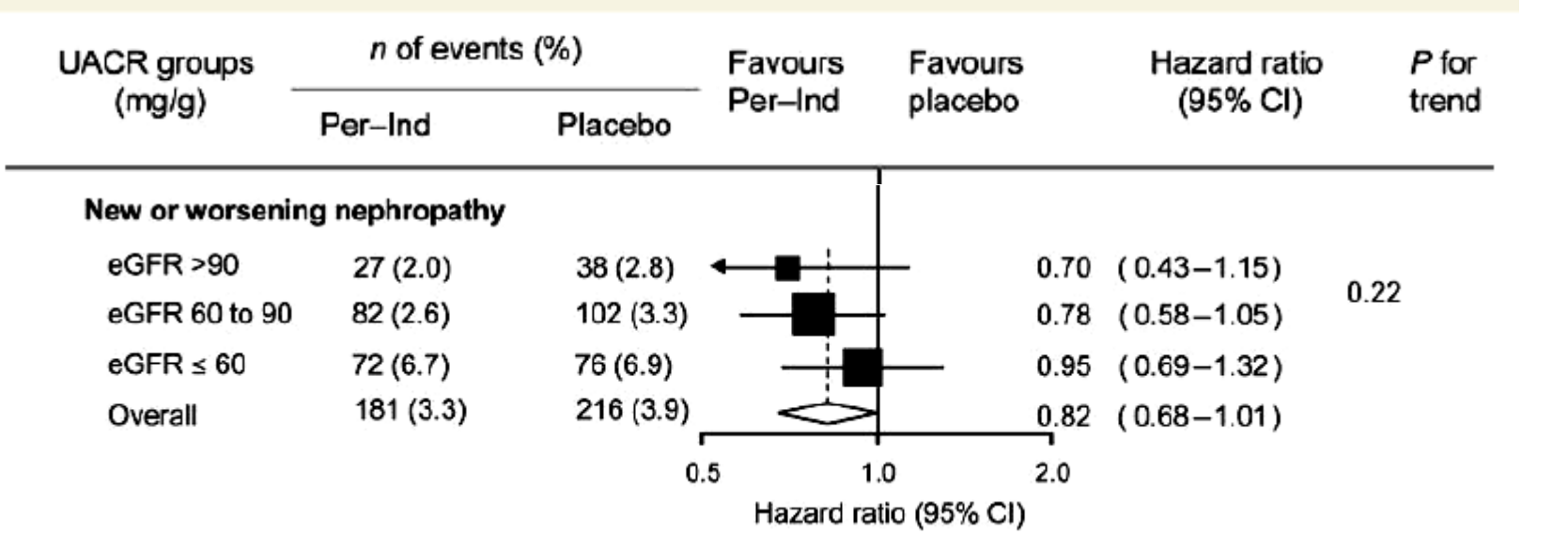
	No. of events/patients		Median	Favors	Favors	Hazard ratio
	Per-Ind	Placebo	blood pressure	Per-Ind	Placebo	(95% CI)
All renal events						
All participants	1243/ 5569	1500/ 5571				0.79 (0.73 to 0.85)
Baseline systolic blood pressure (mmHg)						
! <120	134/ 615	167/ 560	113 mmHg			0.70 (0.56 to 0.88)
120-139	367/ 1736	431/ 1793	131 mmHg			0.85 (0.74 to 0.97)
140-159	439/ 1945	563/ 2003	149 mmHg			0.75 (0.66 to 0.85)
≥160	303/ 1273	339/ 1215	172 mmHg			0.81 (0.70 to 0.95)

de Galan, J.Am.Soc.Nephrol.(2009) 20:883

Effects of a fixed combination of perindopril and indapamide in type 2 diabetes and CKD

The lower eGFR the lesser the effect of treatment

⇨ important to start treatment in early stages of nephropathy



Lambers Heerspink, Europ.Heart J.(2010) 31:2888

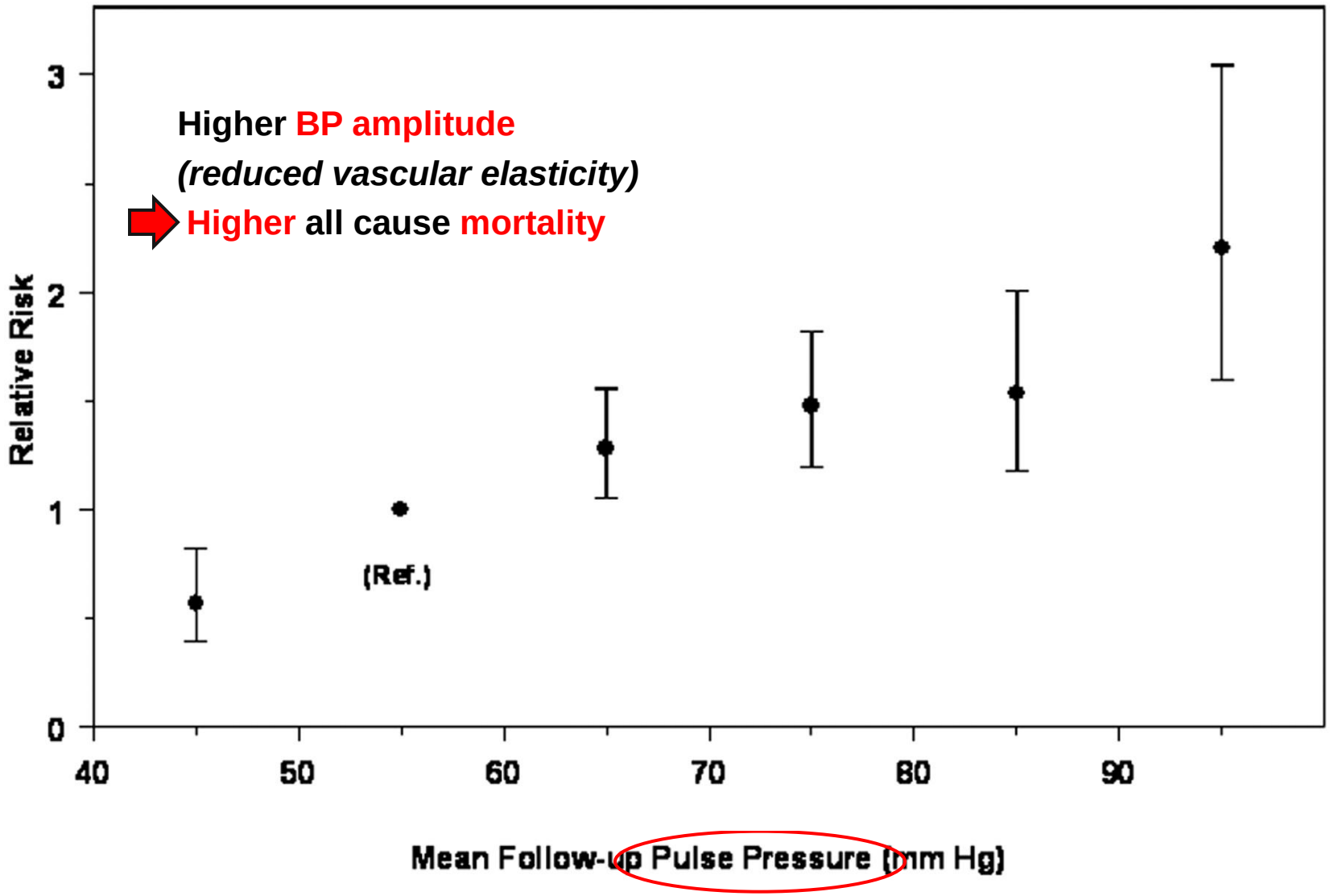
in early phases of diabetic nephropathy : aim for lower systolic BP
(granted that diastolic BP is not < 70 mmHg)

after long duration of diabetes or in presence of cardiovascular damage
avoid aggressive lowering beyond guidelines

personal opinion

BP-amplitude on treatment and total mortality type 2 diabetic patients with nephropathy

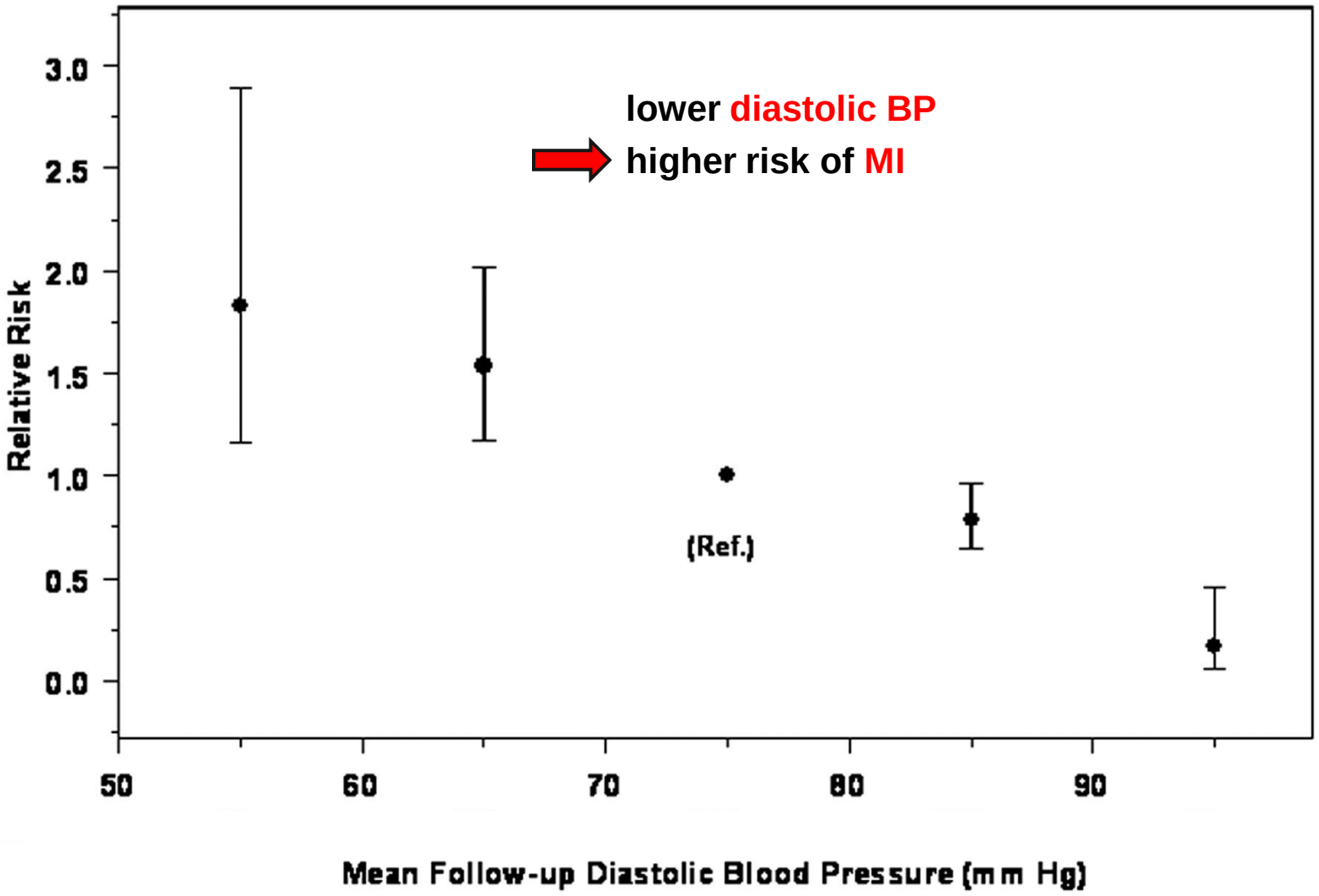
(IDNT study)



Berl, J.Am.Soc.Nephrol.(2005) 16:2170

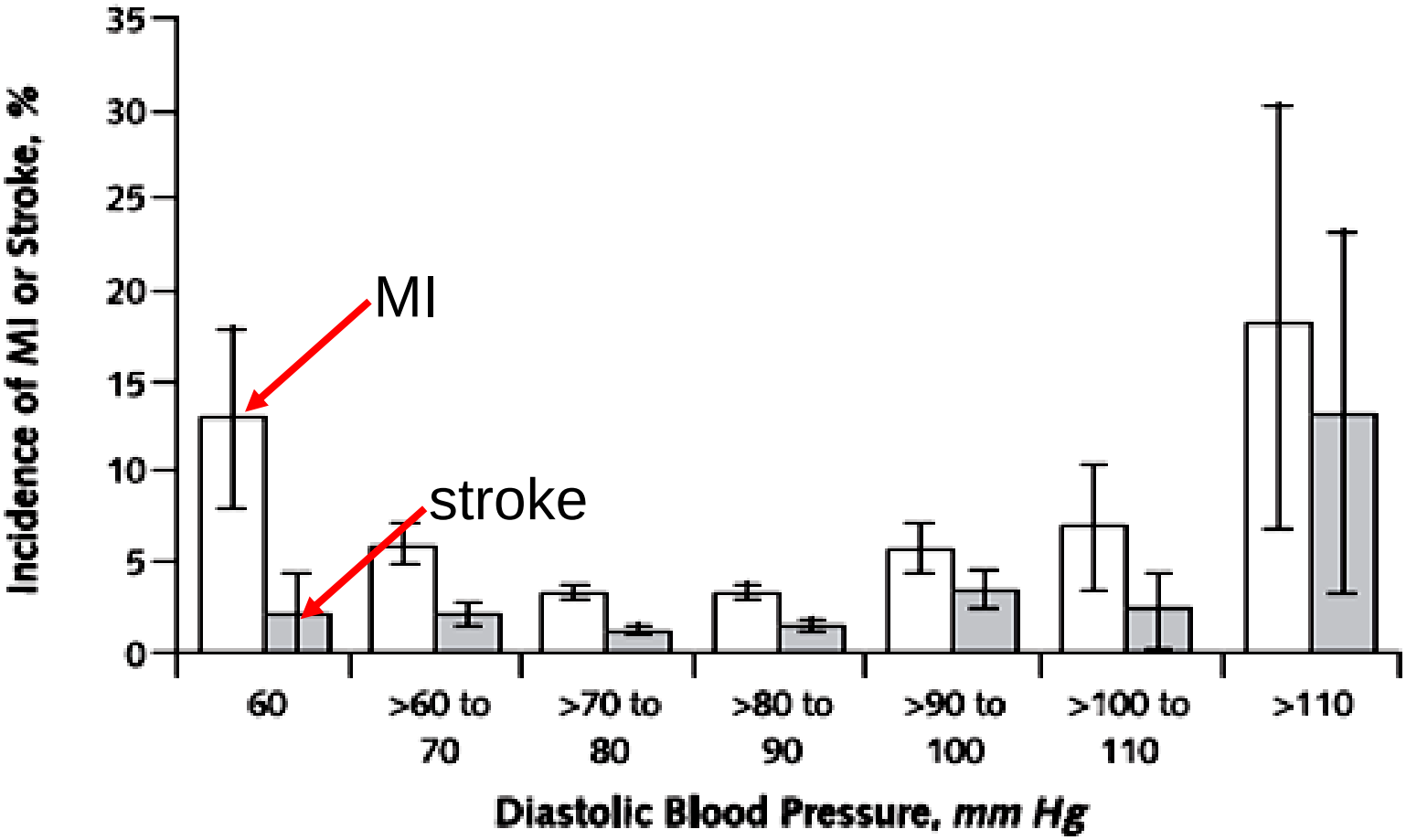
Diastolic BP on treatment and risk of MI – type 2 diabetic patients with nephropathy

(IDNT study)



Berl, J.Am.Soc.Nephrol.(2005) 16:2170

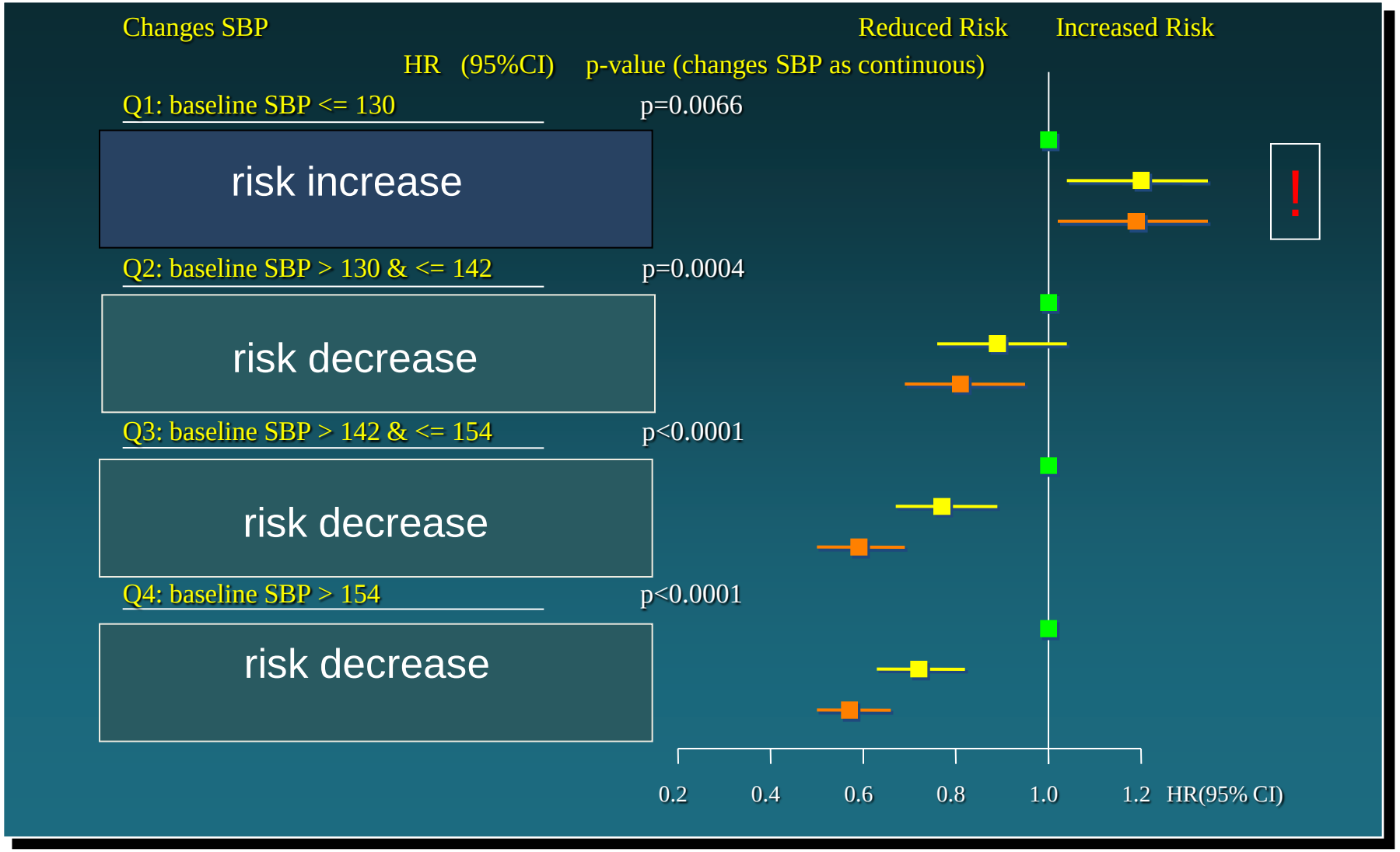
Diastolic BP < 70mmHg :
more frequently de novo MI, but not stroke



Messerli, Ann.Int.Med.(2006) 144:884

Primary endpoint in the ON TARGET study:

adjusted risk according to quartiles of systolic blood pressure at baseline



Sleight , J.Hypertens. (2009) 27:1360

Consequently when aiming for low blood pressures
two caveats

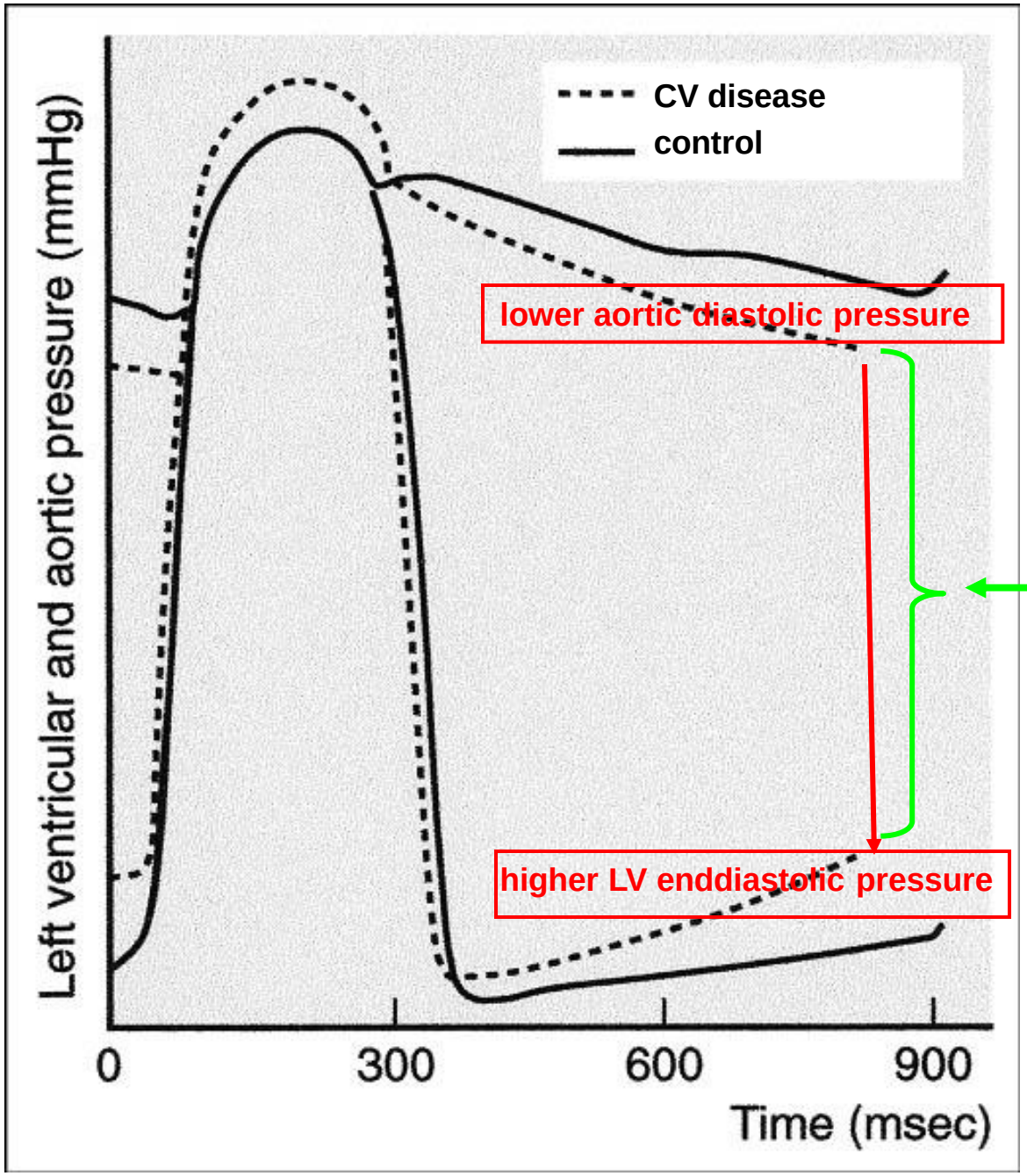
- *do not risk hypotensive episodes*

*(also BP measurement in **upright** position !)*

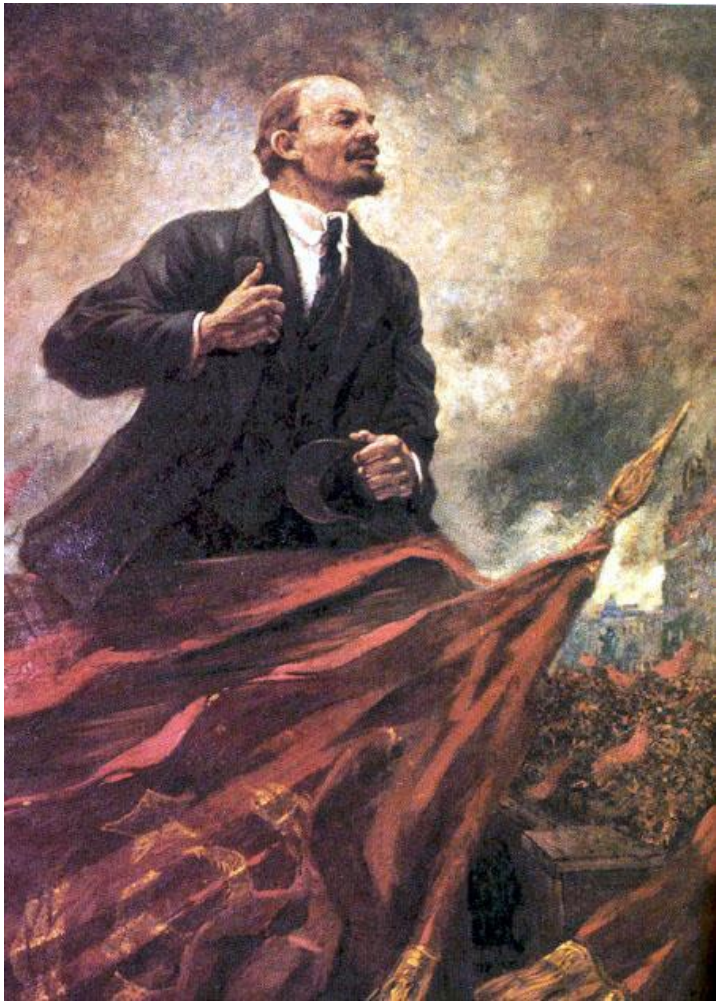
- *do not attempt aggressive lowering*

of systolic blood pressure,

if diastolic blood pressure is very low


CV disease
control
lower aortic diastolic pressure
higher LV enddiastolic pressure
reduced coronary perfusion (in diastole)
Left ventricular and aortic pressure (mmHg)
0
300
600
900
Time (msec)

The communist approach :



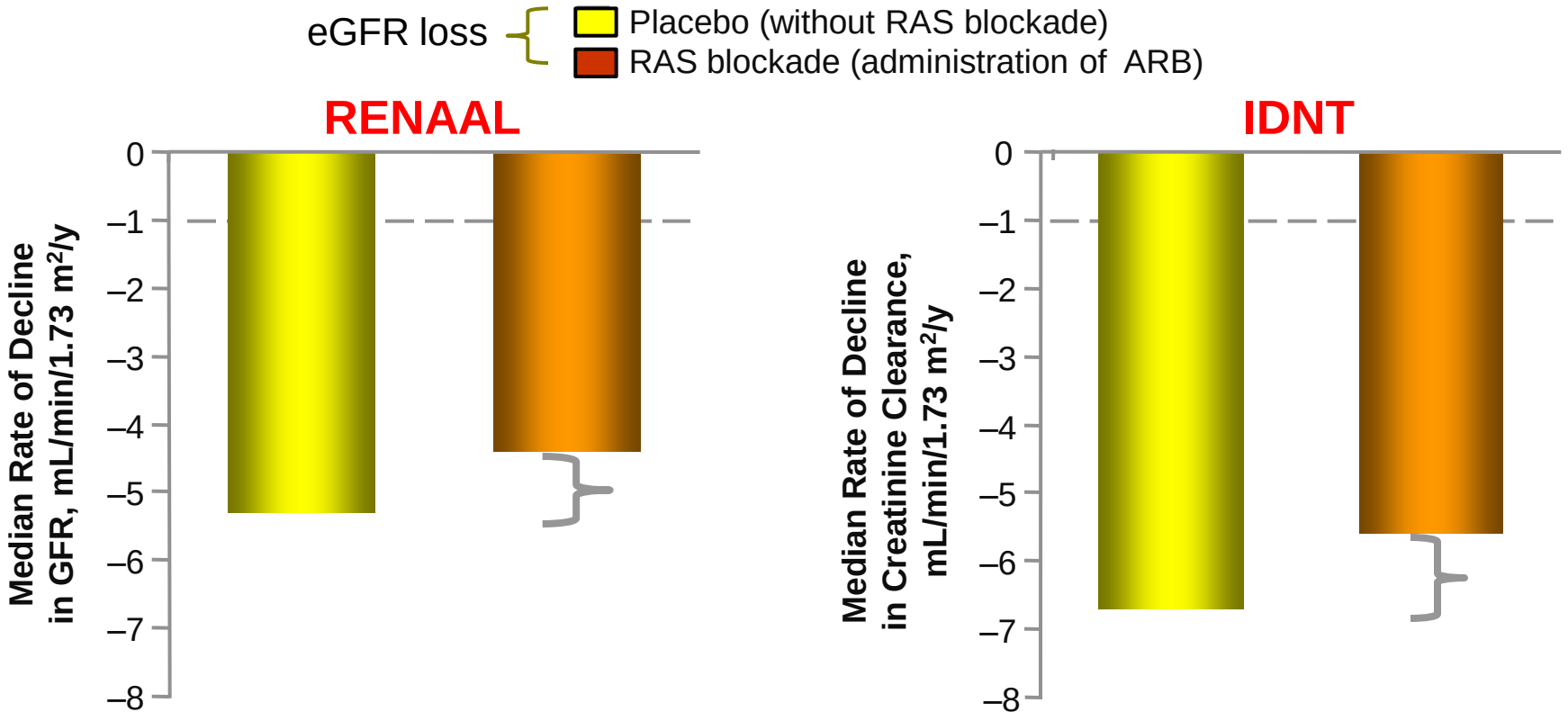
one blood pressure fits all

Roadmap study

Progressive loss of GFR

some diminution of progression by ARB treatment êven in advanced stages, but GFR loss continues

early start of treatment !!

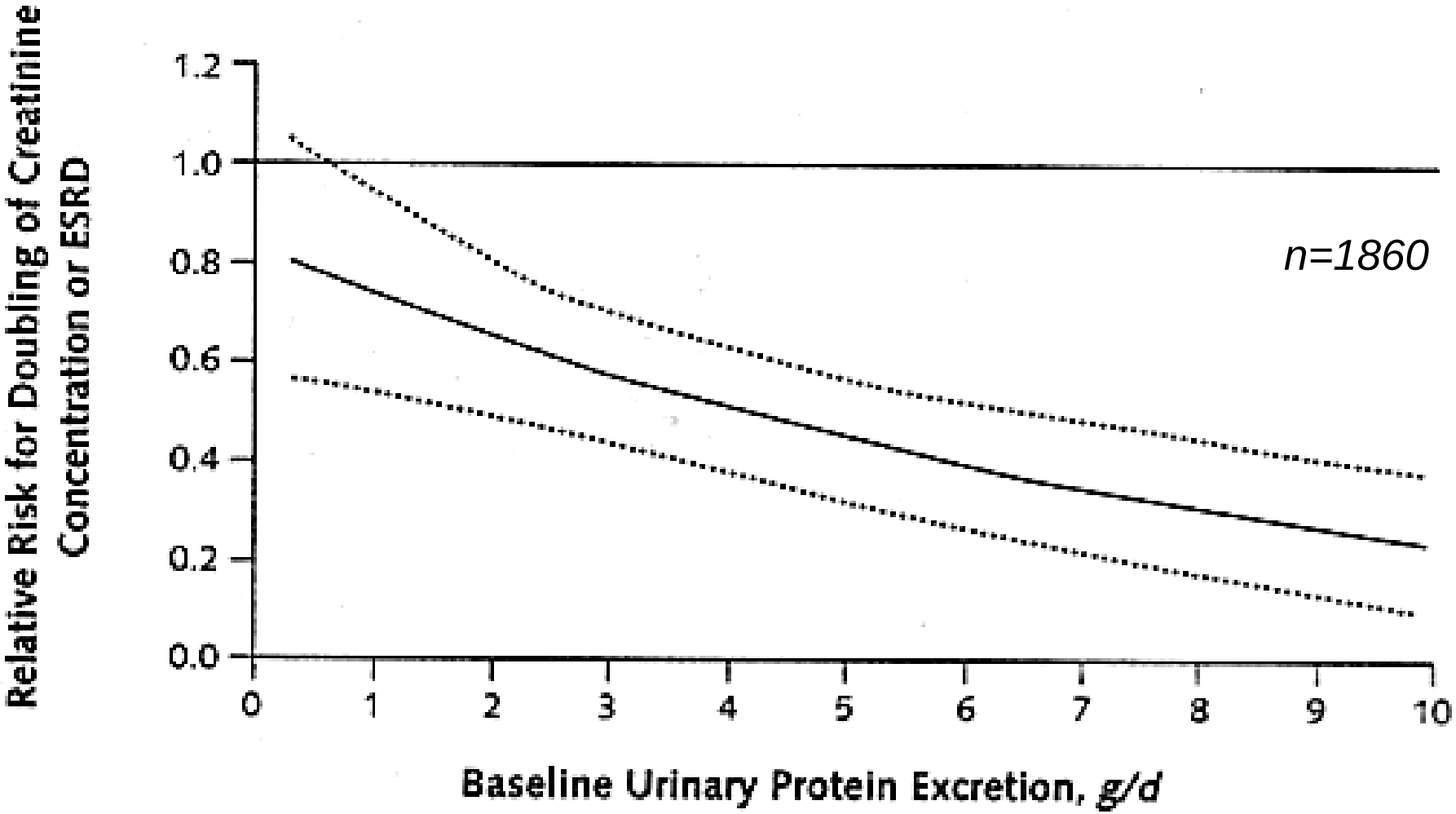


Brenner, N Engl J Med. (2001) 345:861
Lewis, N Engl J Med. (2001) 345:851

Relative risk of progression of CKD and / or ESRD

ACEi vs other antihypertensive agents :

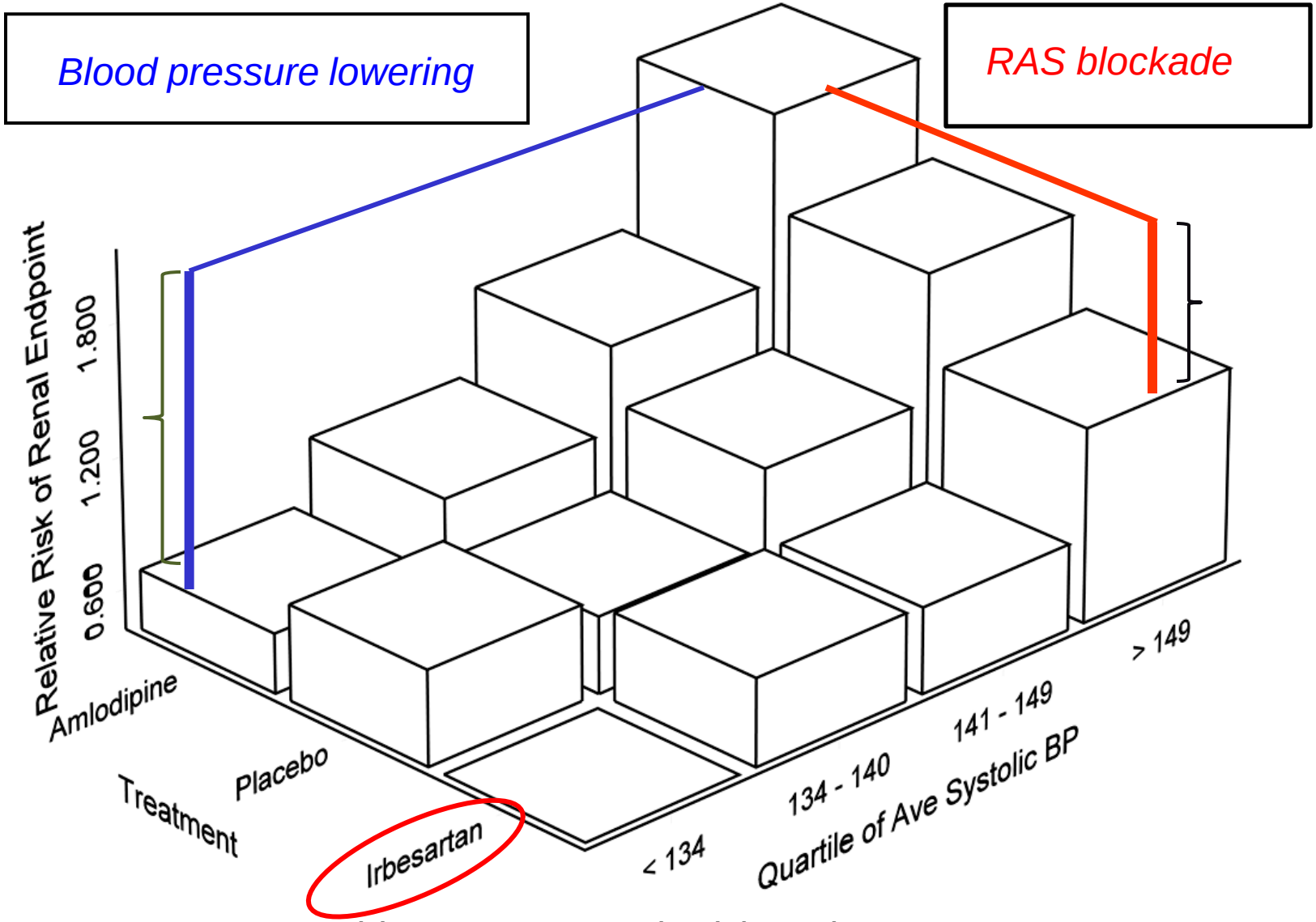
superiority only if proteinuria ≥ 1g / 24h



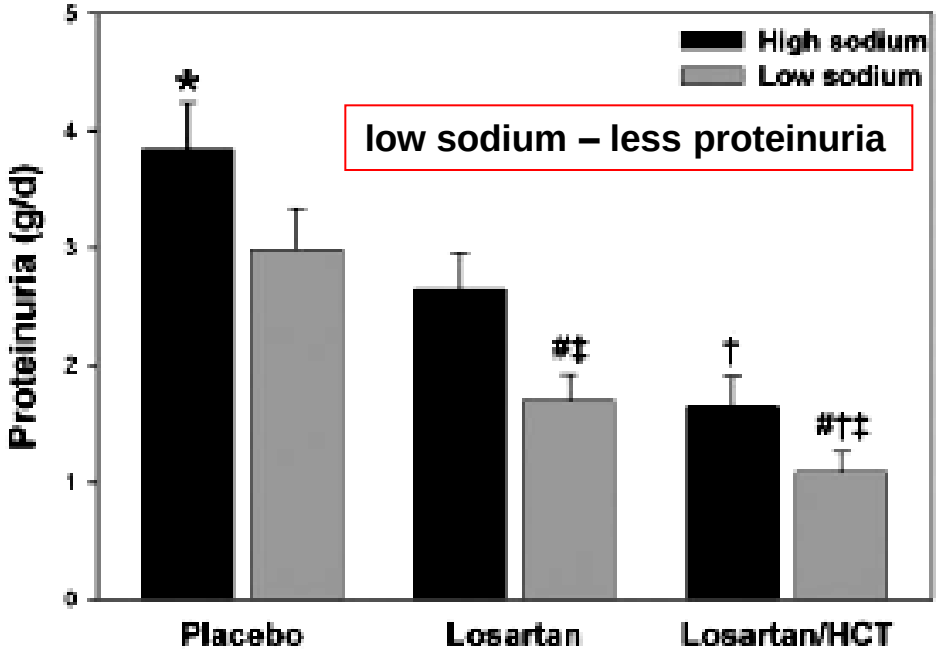
Jafar, Ann Int Med (2001) 135:73

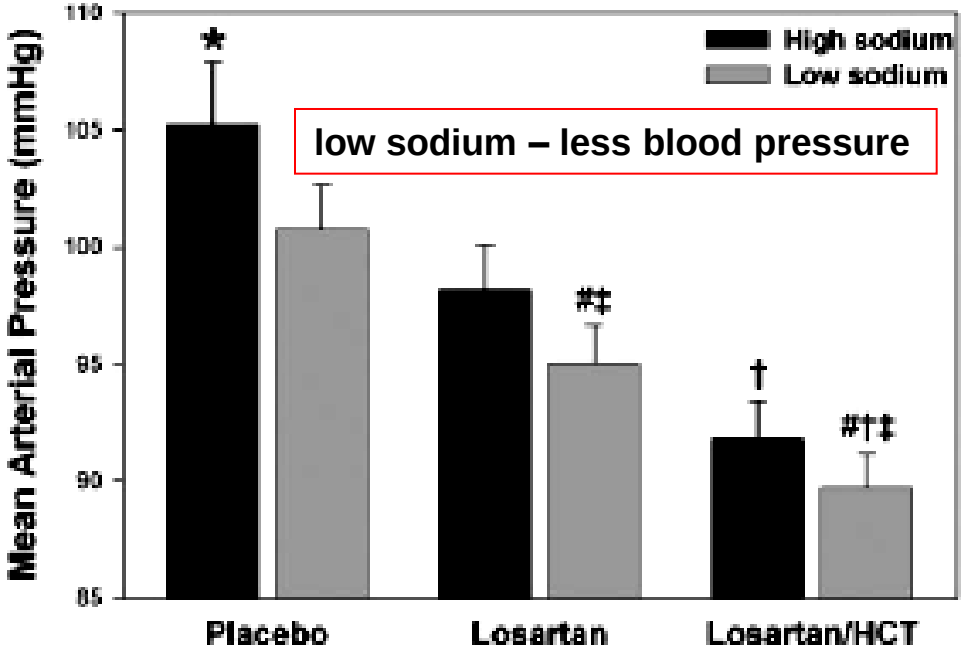
Relative effect of BP lowering and RAS Inhibition to reduce renal endpoint

(IDNT study)



Pohl, J.Am.Soc.Nephrol.(2005)16:3027





RAS blockade :

*the importance of **salt intake***
in diabetic patients
with RAS blockade

Vogt,
J.Am.Soc.Nephrol.(2008) 19:998

Low sodium intake potentiates renal and CV protection by RAS blockade

(RENAAL and IDNT studies)

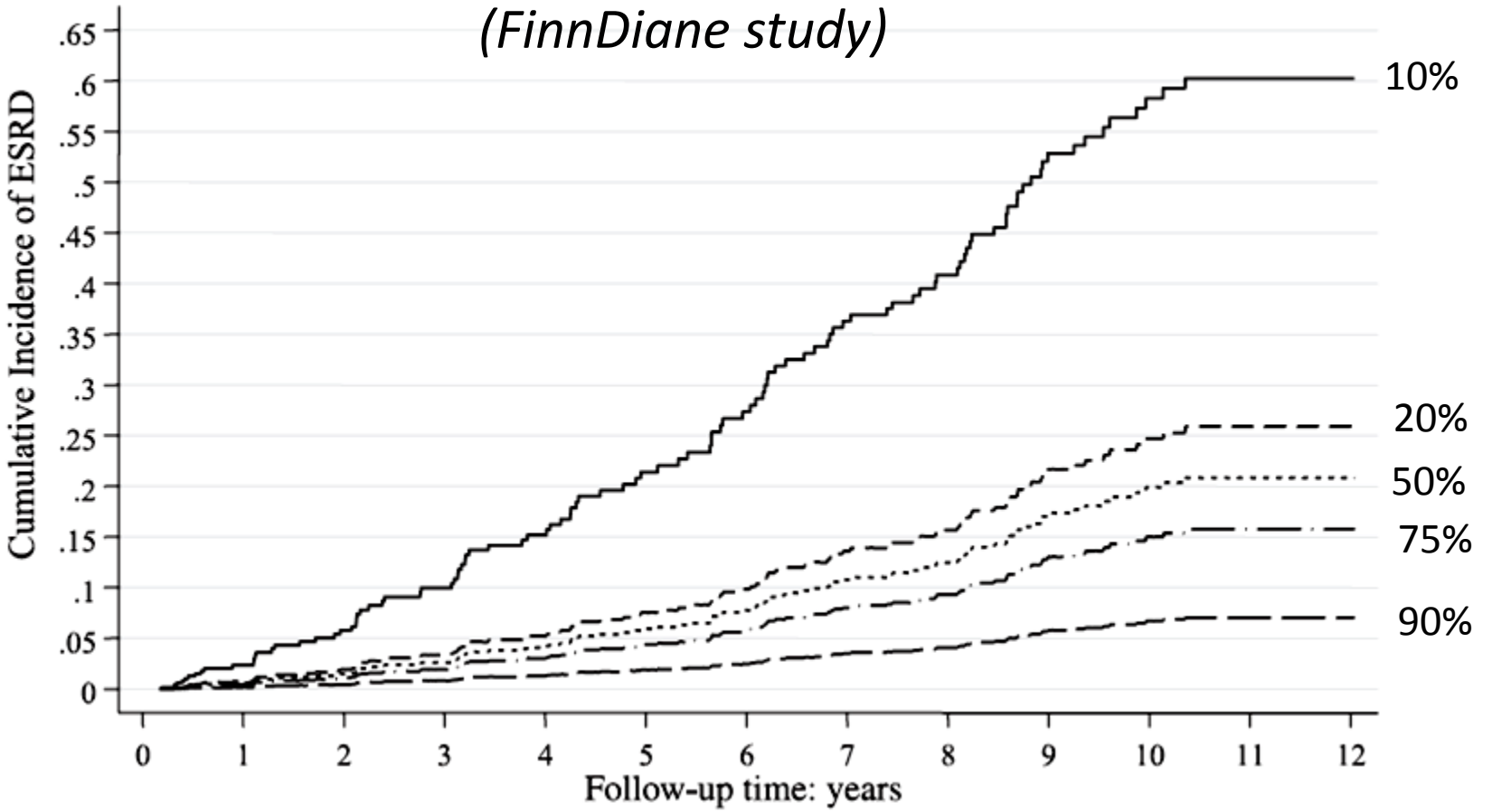
Urinary sodium to creatinine (mmol/g)	6 month response (95% confidence interval)	
	24-hr ACR response *Δ mg albumin/g creatinine*	Systolic BP response *Δ mmHg*
<121	-44 (-55 to -30)	-5.0 (-7.0 to -1.9)
121 – 153	-16 (-32 to +3)	-4.6 (-5.5 to -0.4)
≥ 153	-21 (-35 to -2)	-3.5 (-3.7 to 1.8)

Lambers Heerspink, Nephrol.Dial.Transplant. (submitted)

Is there evidence to the contrary in diabetes ?

24h-sodium-excretion and mortality type 1 diabetic patients

(FinnDiane study)



Thomas, Diabetes Care (2011) 34:861

Diabetic nephropathy

Eberhard Ritz
Heidelberg (Germany)

Epidemiology

Prevention of diabetes

Treatment after "escape" and novel treatments

45 Patients with Type 2 Diabetes

R_x Trandolapril

Albuminuria -40%

18/40 patients ⇩ aldosteron "escape"

➔ 25mg/day Spironolactone

no change of blood pressure

significant reduction of albuminuria

Sato, Hypertension (2003) 41: 64

Aldosterone : “escape” and progression

63 hypertensive patients with type 1 diabetes and diabetic nephropathy

p - Aldosteron :

increased in 26 Pat. (57 → 102 pg/ml) – “escape”

decreased in 37 Pat. (83 → 49 pg/ml)

GFR - loss

aldosterone “escape” 5.0 ml/min/Jahr (*0.4 -15.9*)

no aldosterone “escape” 2.4 ml/min/ Jahr (*-2 - 11.0*)

correlation Δ p-aldosterone / Δ GFR

Schjoedt,Diabetologia (2004) 47:1936

Spironolactone diminishes urinary albumin excretion in type 1 diabetes and microalbuminuria

early stage!

(randomized placebo-controlled cross-over study)

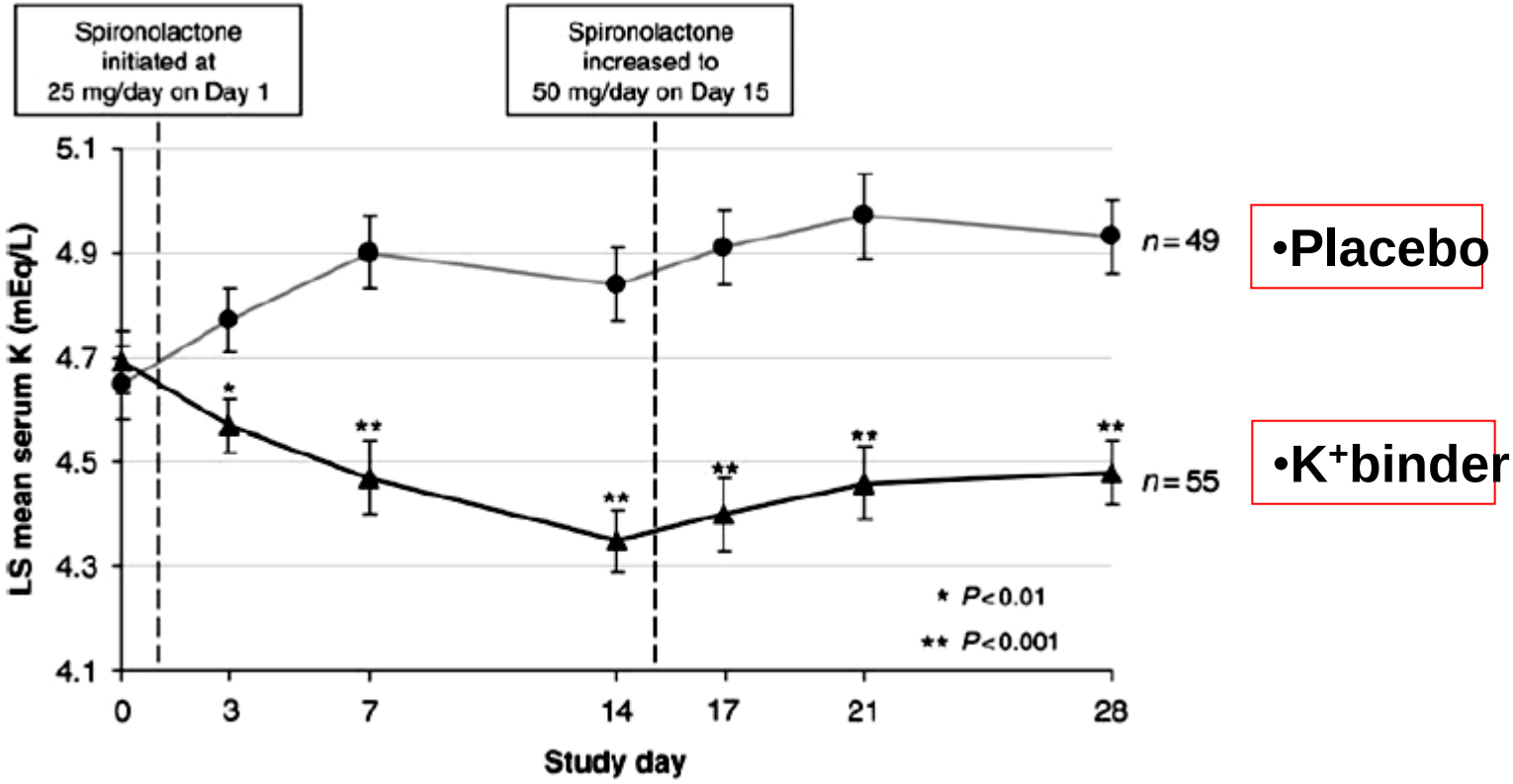
21 patients with **type 1 diabetes** and **microalbuminuria**
60 day periods of Spironolactone 25 mg/day or placebo
added to standard antihypertensive therapy

Spironolactone treatment :
albuminuria decreased by 60% (range 21-80%)
from 90 mg/day to 35 mg/day *(p=0.01)*
Blood pressure did not change
GFR decreased from 78 6 ml/min/1.73m^2 to 72 2 *(p=0.003)*
[reduction of hyperfiltration ?]

Nielsen, Diab.Med.(2012) e-pub Jan 24th

Polymeric K^+ binder RLY5016 in chronic heart failure

(PEARL-HF trial)

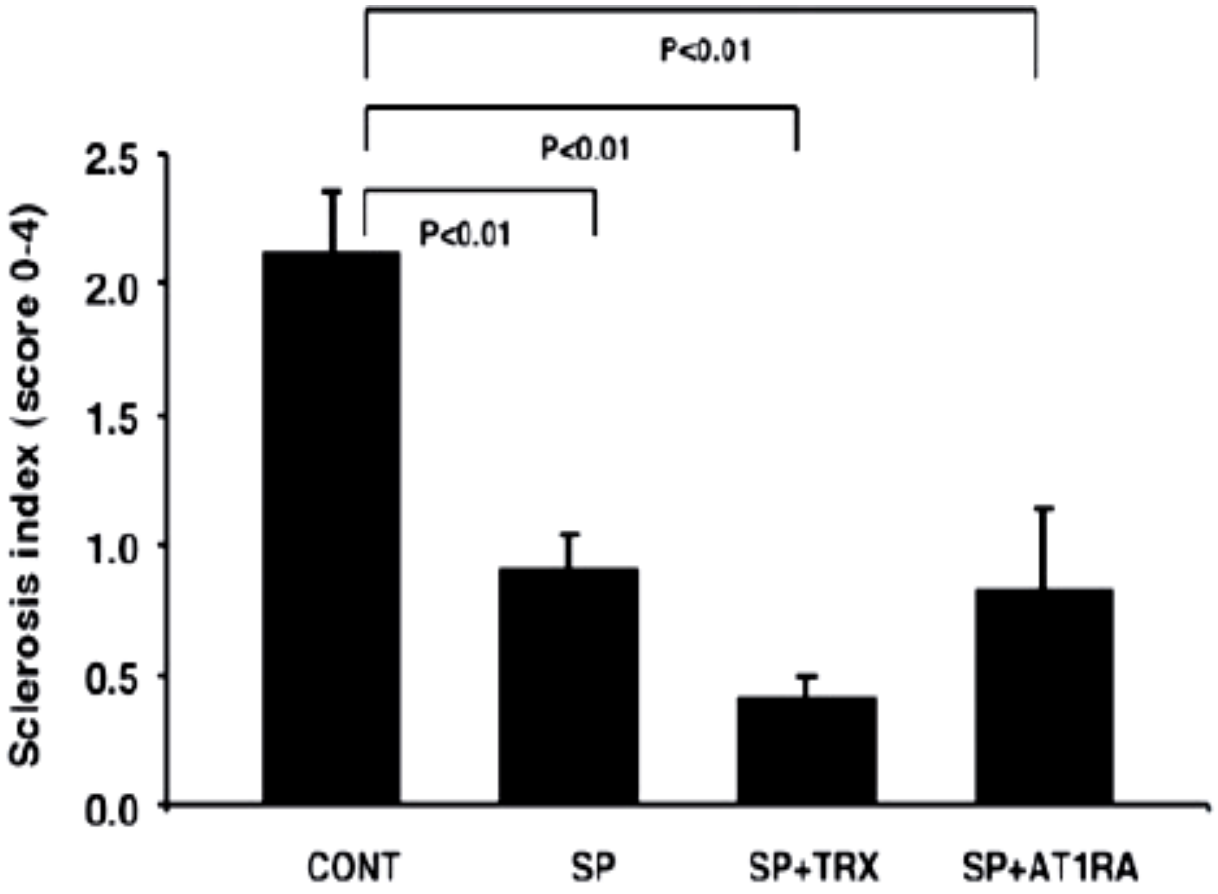


S-K^+ > 5.5 mEq/L : <u>eGFR</u> >60 4/55 on RLY5016 vs 12/49 on placebo

<60 1/15 on RLY5016 vs 5/13 on placebo

Pitt, Europ.Heart J.(2011) 32:820

Spironolactone causes even regression of established glomerulosclerosis after subtotal nephrectomy



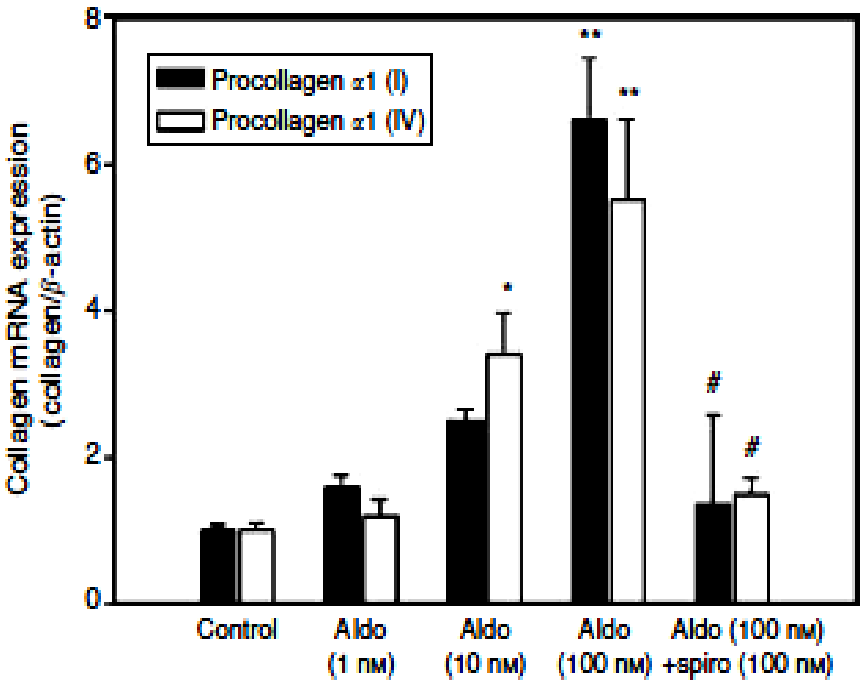
Aldigier, J.Am.Soc.Nephrol.(2005) 16:3306

Aldosterone increases procollagen synthesis in type 2 diabetic rats

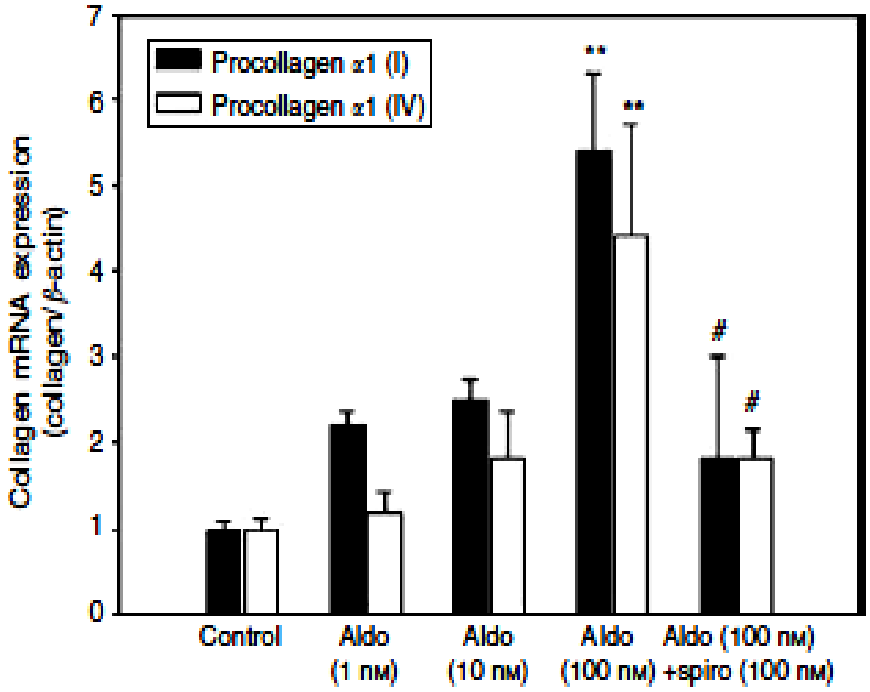
➡ reversal by spironolactone

(glomerulosclerosis, interstitial fibrosis !)

mesangial cells

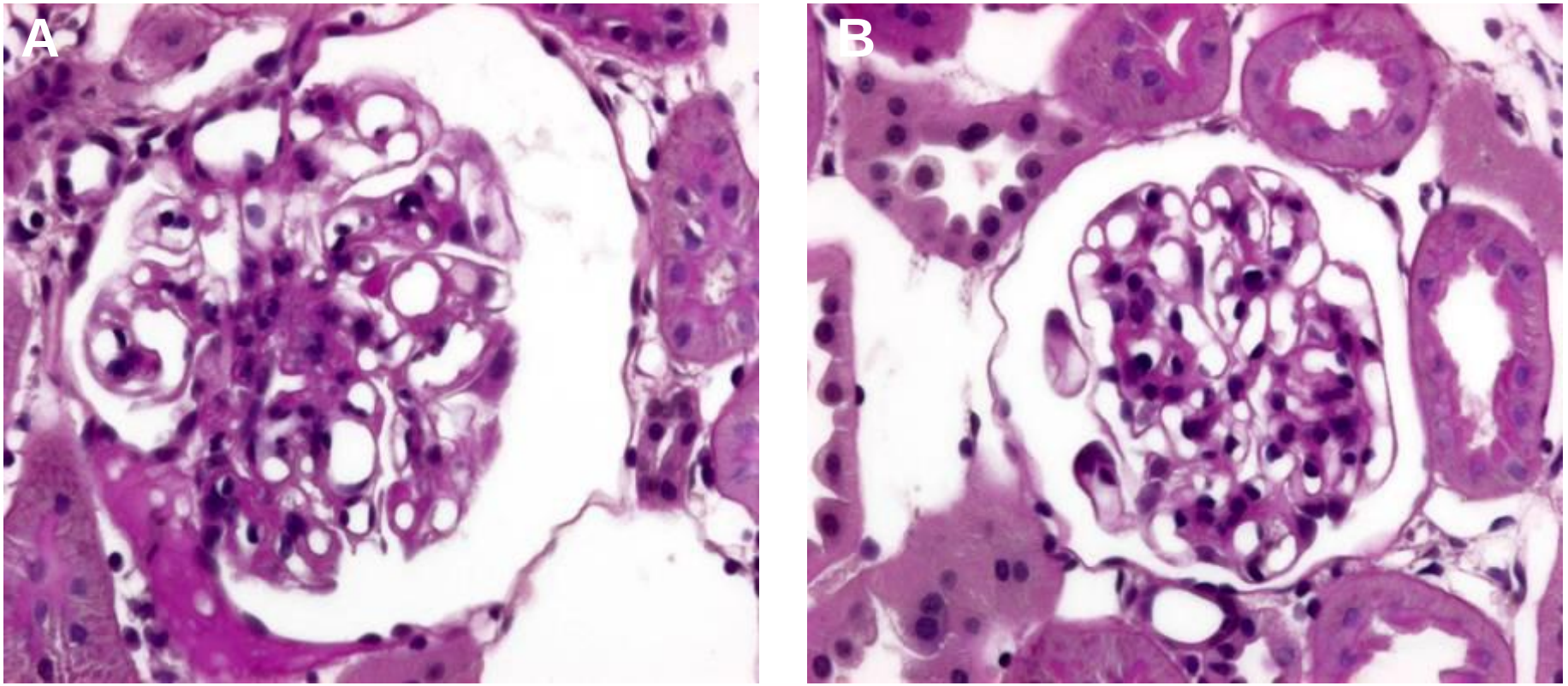


proximal tubular cells



Han, Kidn.Internat.(2006) 70:111

Subtotal nephrectomy
less glomerulosclerosis with administration of $1,25(OH)_2D_3$



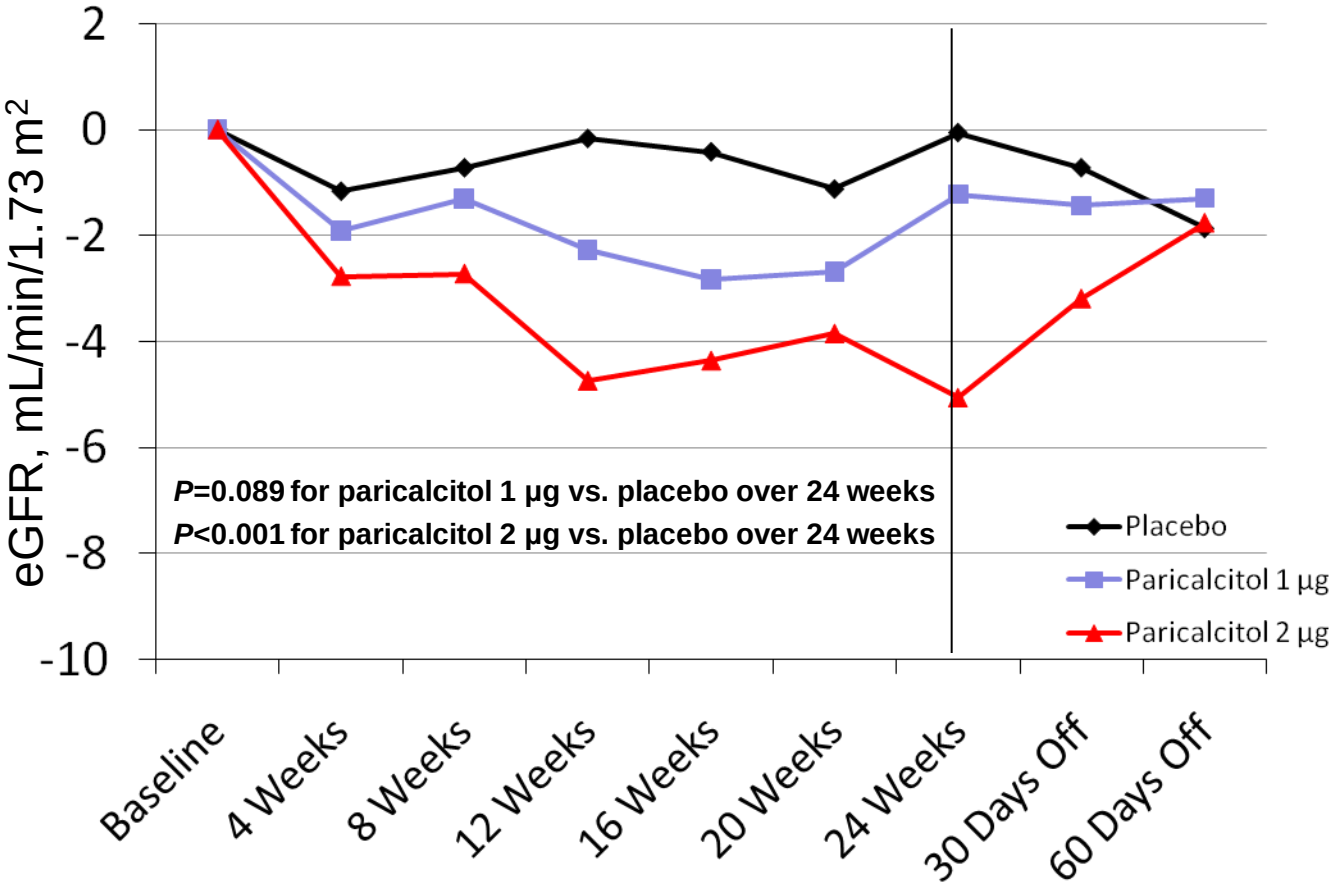
untreated

$1,25(OH)_2D_3$

Schwarz, Kidney Intern (1998) 53: 1690

Time course of eGFR

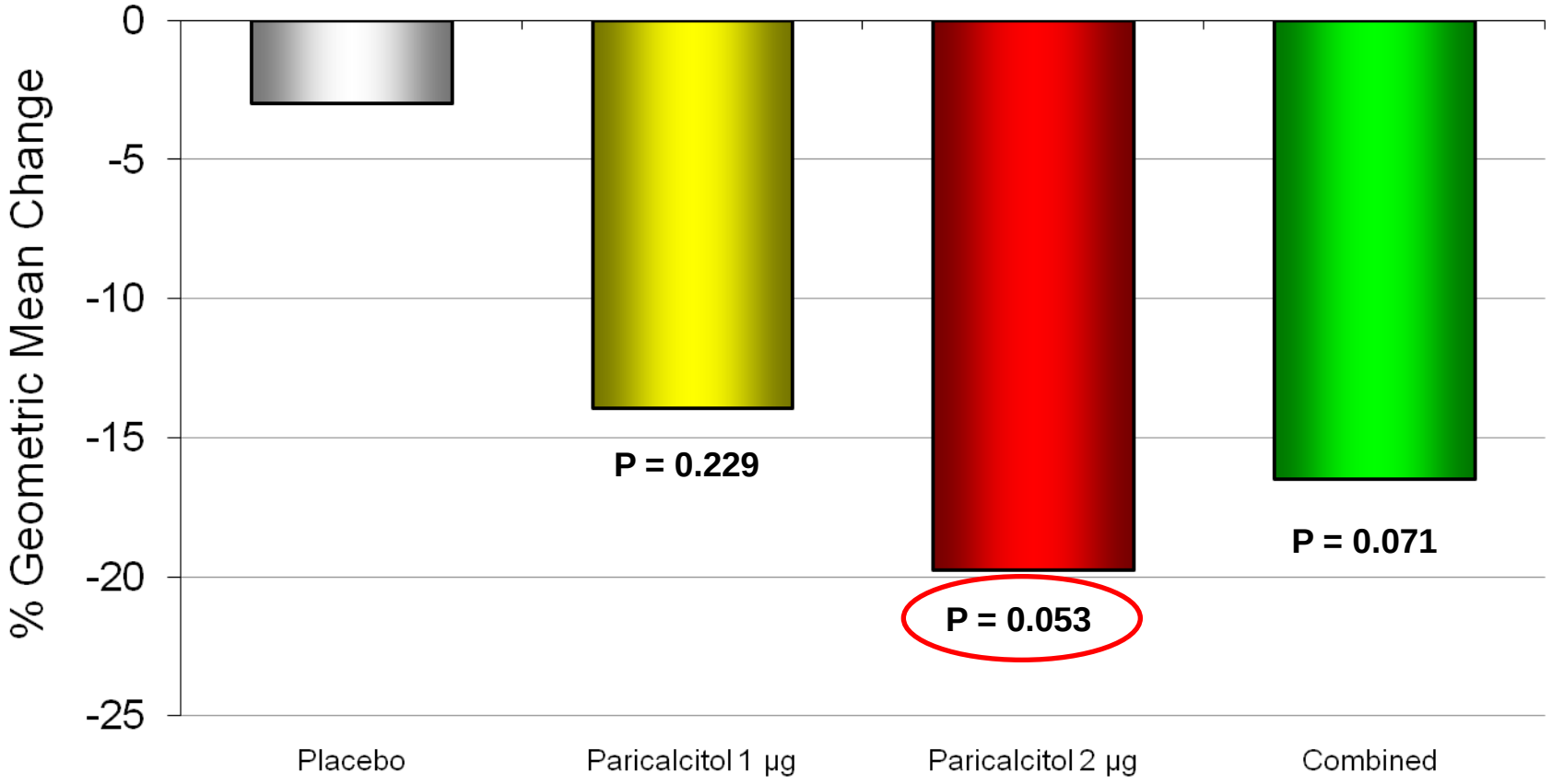
Decrease of eGFR because of suppression of renin ?



de Zeeuw, Lancet (2010) 376:1543

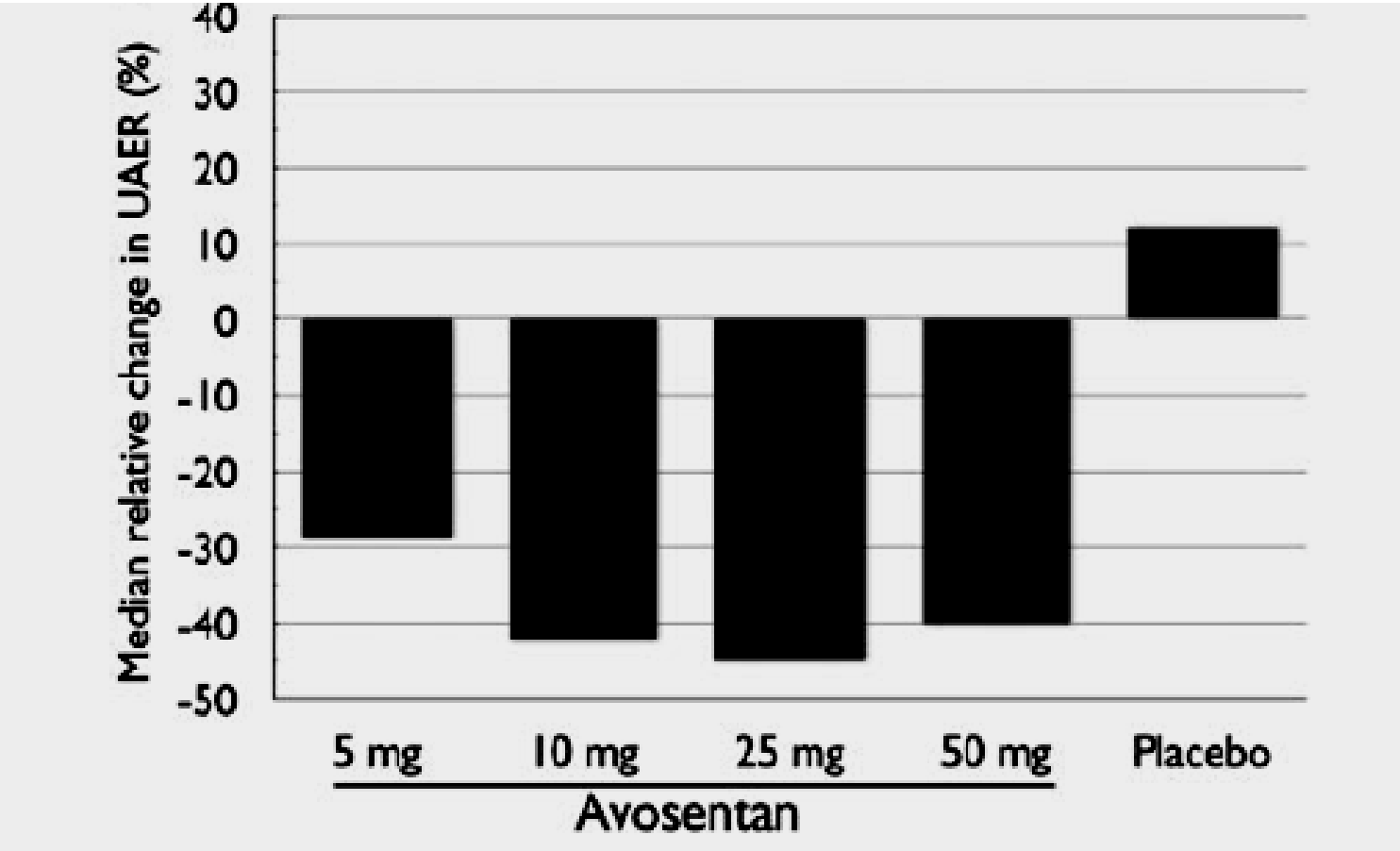
Primary endpoint : effect of Paricalcitol on UACR

(urinary albumin/creatinine ratio)



de Zeeuw, Lancet (2010) 376:1543

Antiproteinuric effect of the Endothelin-receptorA-blocker Avosentan on top of ACEi in proteinuric type 2 diabetic patients

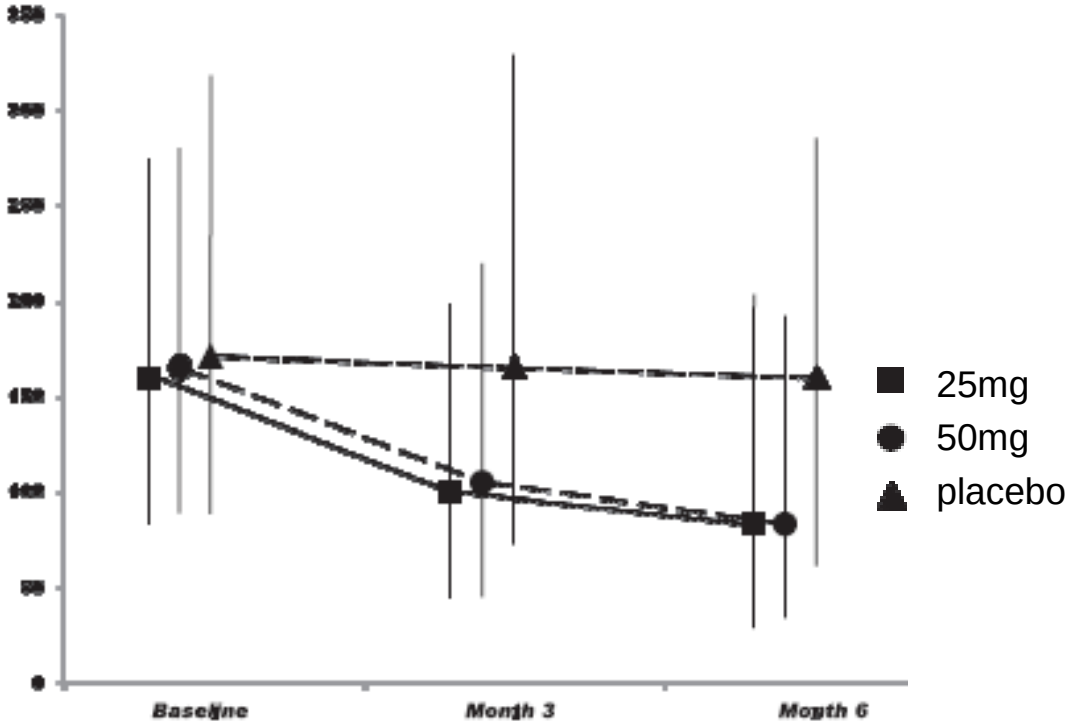


Wenzel, J.Am.Soc.Nephrol.(2009) 20:655

Endothelin receptor blockade

Unacceptable side effects of (high dose) Avosentan in advanced diabetic nephropathy

albumin/creatinine ratio
(mg/mmol)



Major side effect : fluid overload (%)

	Avosentan *(mg)*		***Placebo***
	25	*50*	*0*
fluid overload	28	26	5
dyspnea	31	34	15
pulmonary edema	9	8	4
death		21	7

Mann, J.Am.Soc.Nephrol.(2010) 21:527

What to do if the response to BP lowering is inadequate or if "escape" occurs ?

proven:

- Dose escalation
- Combination ACEi + ARB (???)
- Aliskiren no
- Spironolactone / Eplerenone
- Vitamin D (receptor activator) (Paricalcitol)
- Endothelin receptor blocker

…

preclinical:

- *Renin receptor inhibitors*
- *AT2 receptor agonists*
- *Chymase-inhibitors*

Thank you for your attention

News in diabetes and kidney – which of the answers is correct ?

1. De novo diabetes after start of hemodialysis is due to …

- *high dialysate glucose concentration*
- *co-medication causing insulin resistance*
- *refeeding after patients had lost body weight in the preterminal phase of diabetic nephropathy.*

2. Which of the 3 statements is correct ?

- *Renomegaly (enlarged kidneys) is obligatory for the diagnosis of diabetic nephropathy.*
- *Proteinuria is obligatory for the diagnosis of diabetes associated nephropathy.*
- *Metformin can be given for treatment of type 2 diabetes until stage CKD 3, but not later*.