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, AJKD (1999) 34: 795

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

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

- Heidelberg **49 % of incident patients**

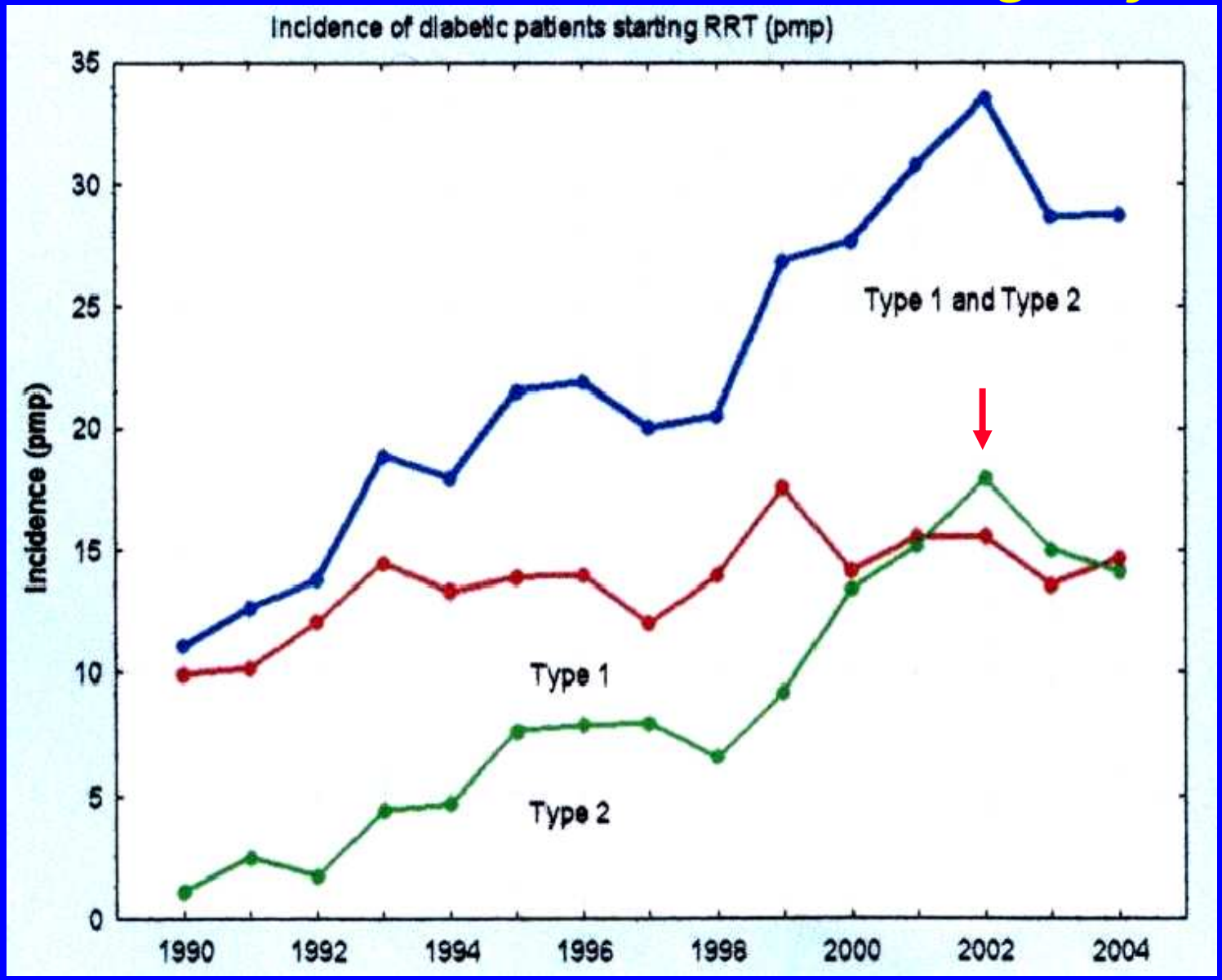
98 ppm

6 % type 1

94 % type 2

Schwenger, Dtsch Med Wschr (2001) 126: 1322

New development :
ESRD in diabetics - *Denmark registry*

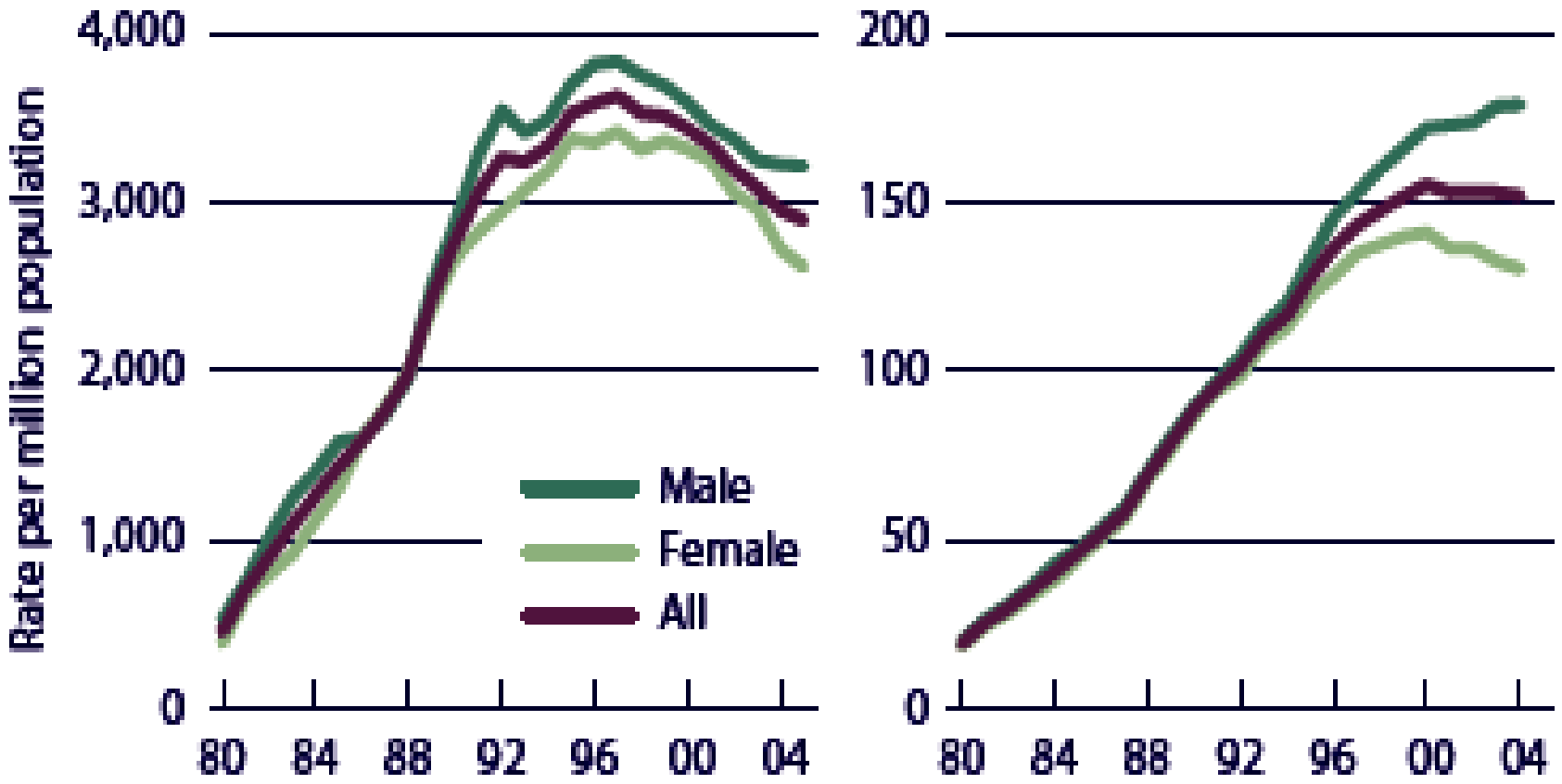


Sorensen, Kidn.Intern.(2006)70:187

Adjusted incident rates of ESRD with diabetes as the primary diagnosis

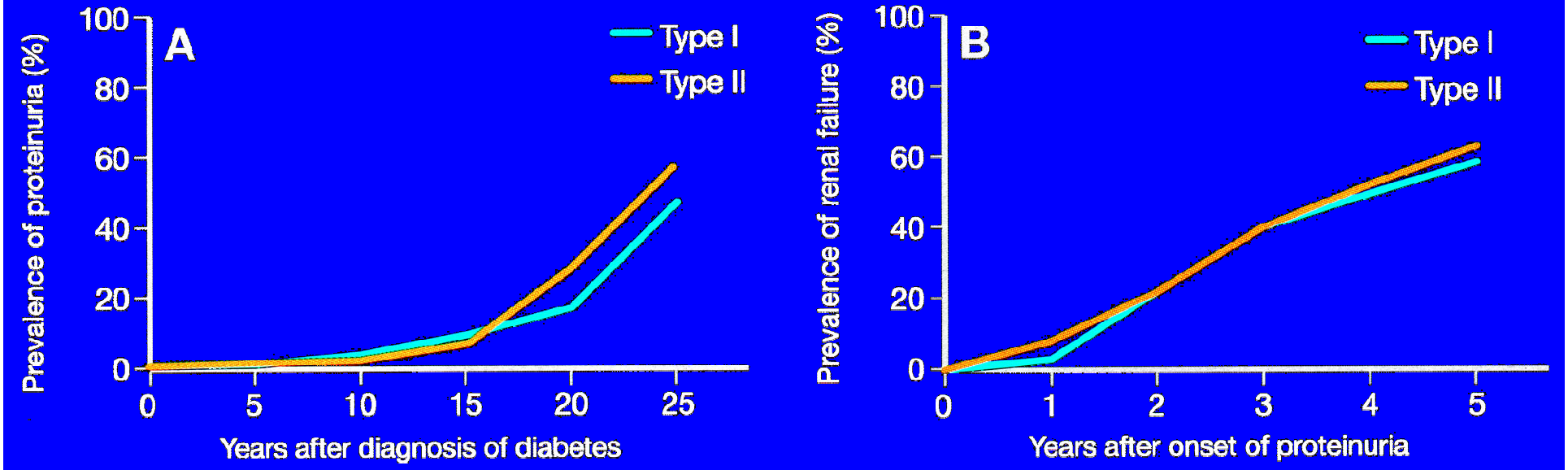
per million diabetics (lead time bias?)

per million general population



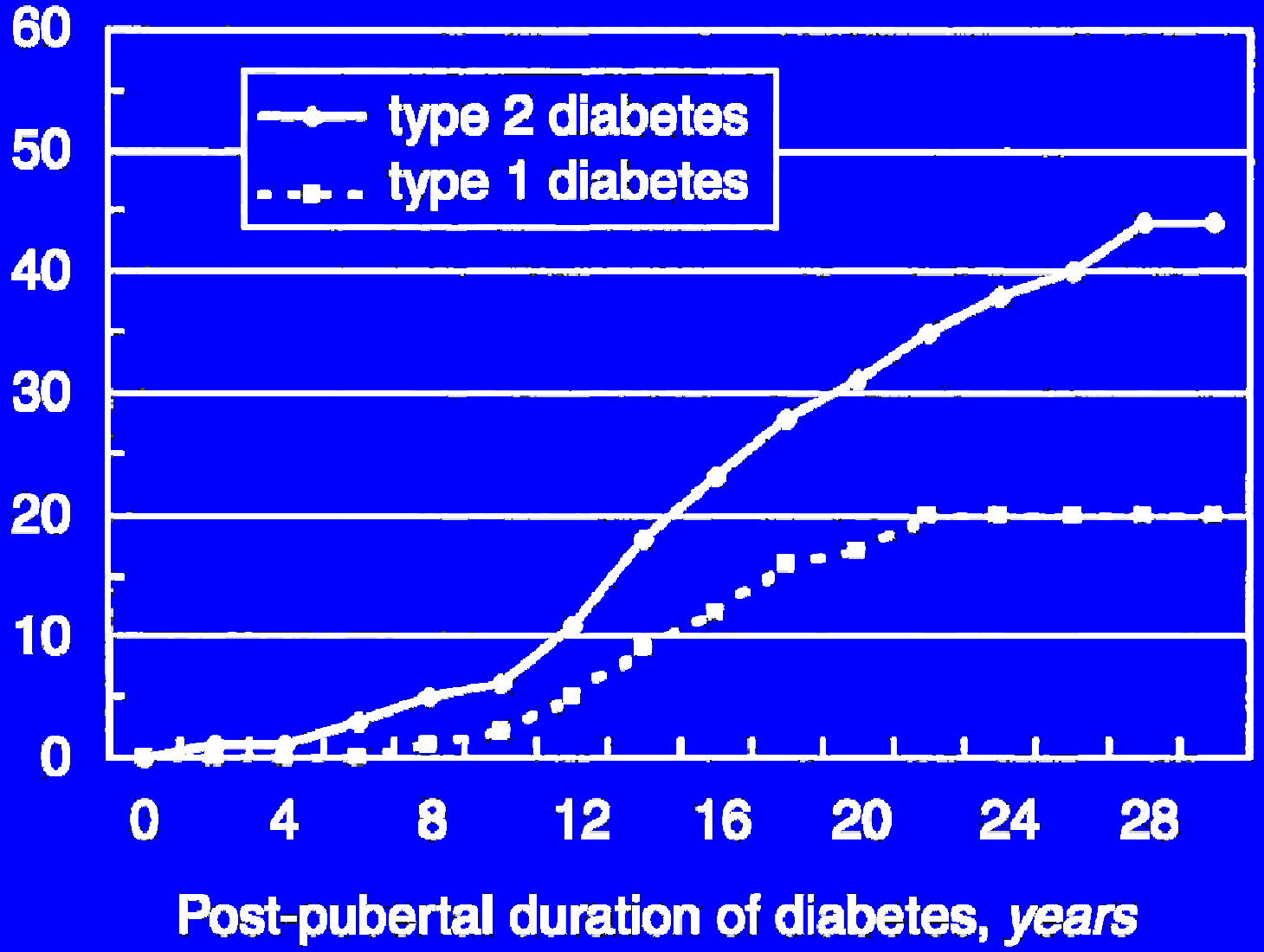
USRDS 2007

Similar renal risk in type 1 and type 2 diabetes



Hasslacher, Nephrol Dial Transpl (1989) 4: 859

Increased renal risk in young Japanese type 2 diabetic patients



Yokoyama, Kidney Intern (2000) 58: 302

Presentation of ESRD patients with diabetes as a co-morbid condition

- typical Kimmelstiel Wilson 70%
- ischemic nephropathy 11%
- other primary renal disease 19%

→ irreversible acute (acute on chronic) renal failure

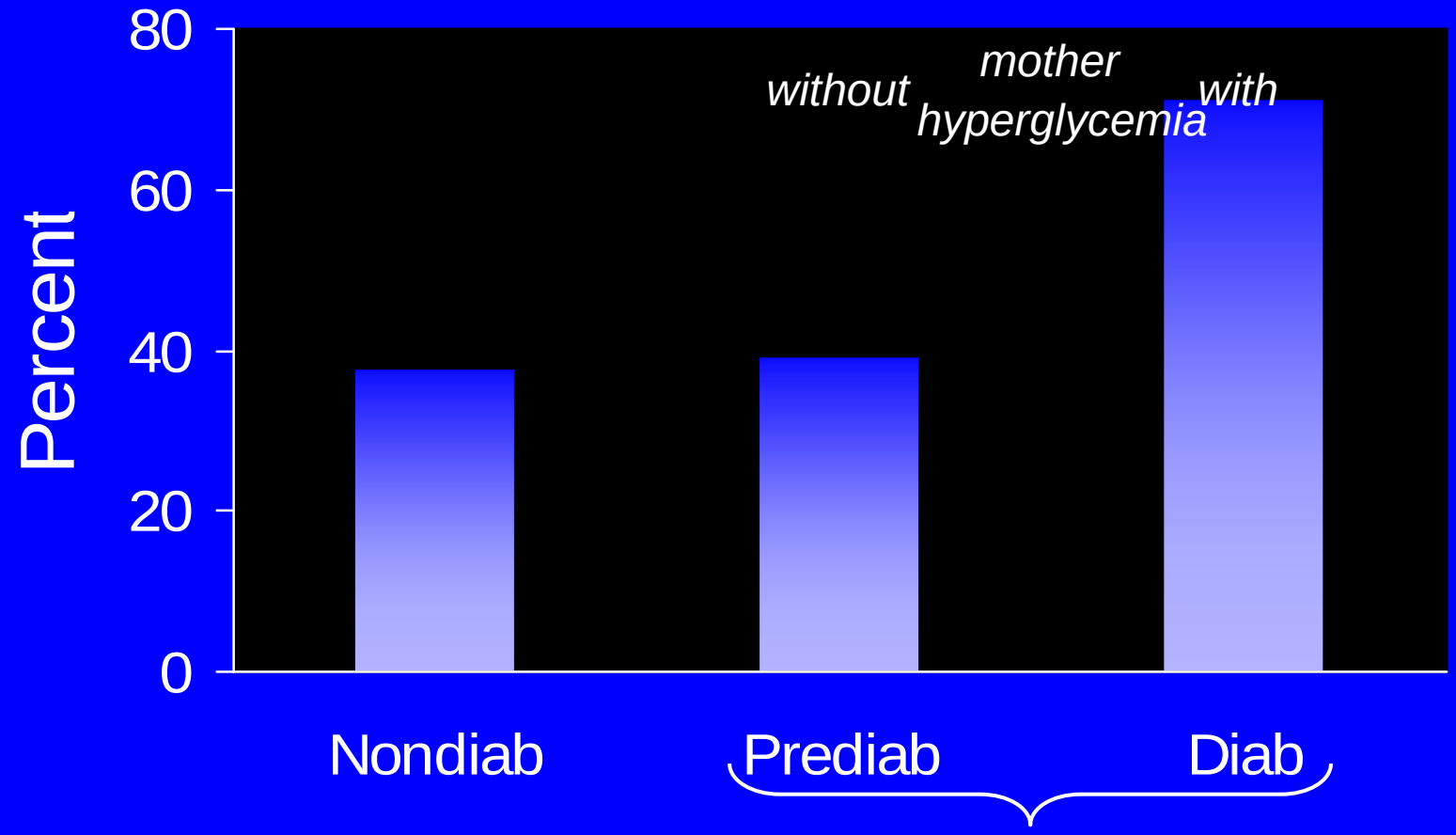
→ diagnosis of diabetes unknown in 11%

(distrust registries)

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

Albuminuria in offspring of prediabetic or hyperglycemic Pima mothers

(Prenatal programming)



Nelson, Diabetes (1998) 47:1489

Diabetic nephropathy

Eberhard Ritz
Heidelberg (Germany)

Epidemiology

Prevention of diabetes

Prevention of (type 2) diabetes – impaired glucose tolerance

 # life style modification

- ***weight loss***
- ***physical exercise***

Tuomilehto, NEJM (2001) 344: 1343

Knowler, NEJM (2002) 346: 393

Hu, NEJM

"Most dinosaurs were vegetarians and they never smoked tobacco or drank alcohol — and where are *they* now?!"

Hypertensive patients – high risk to develop type 2 diabetes

ARIC study *(Atherosclerosis risk in communities)*

→ **De novo diabetes 2.5 times more frequent in hypertensive subjects than in individuals with normal BP**

Gress, New Engl.J.Med.(2000) 342: 905

Prevention of (type 2) diabetes in high risk patients (IGT)

 # life style modification

medications

ACE inhibitors

HOPE, NEJM (2000) 342: 145

ARB

LIFE, Lancet (2002) 359: 995

VALUE, Lancet (2004) 363: 2049

Metformin

New Engl J Med (2002) 346: 1824

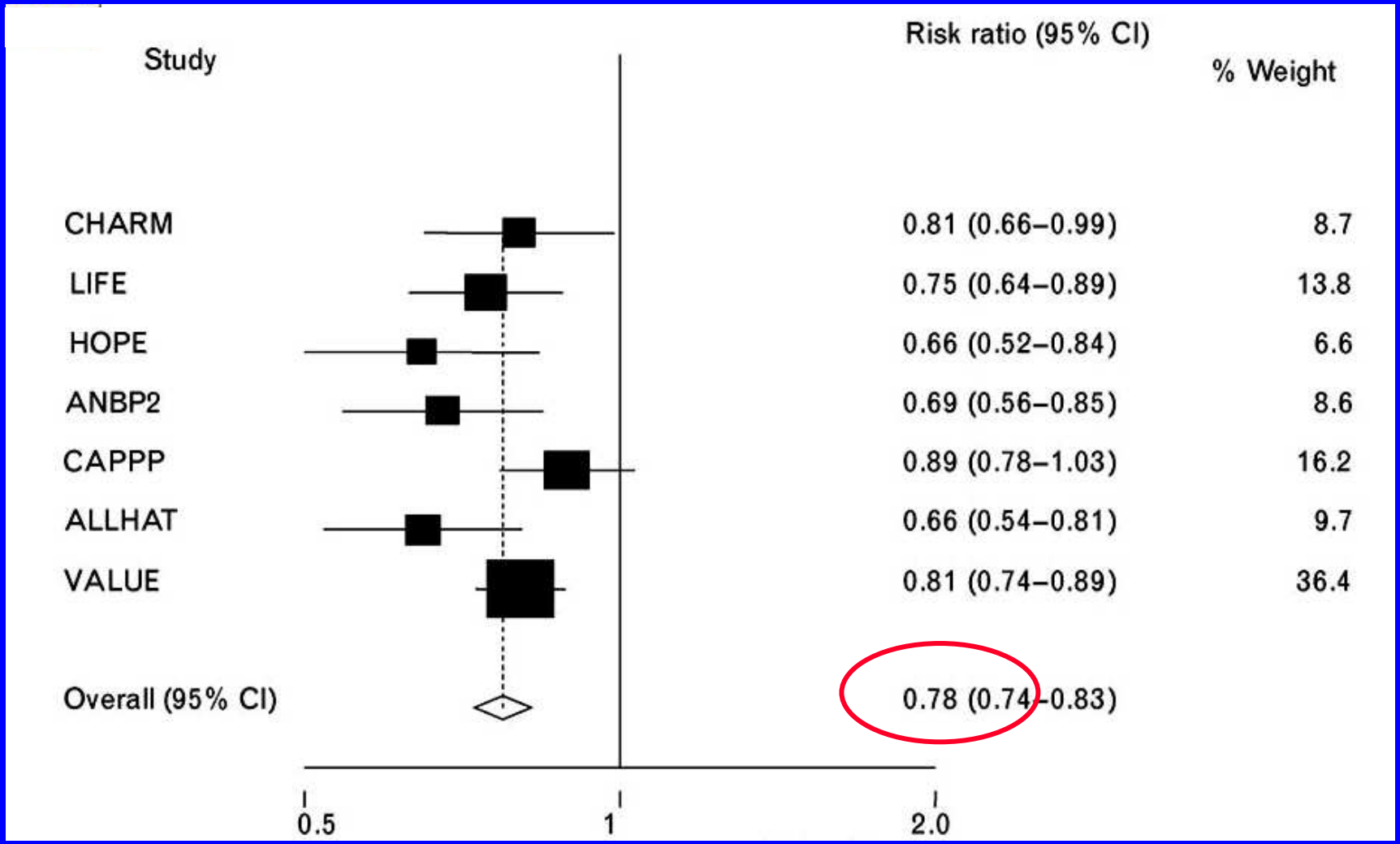
Acarbose

Lancet (2002) 359: 2072

Bezafibrate

Circulation (2004) 109:2197

New onset diabetes
Metaanalysis
RAS blockade vs non-RAS blockade



Jandeleit-Dahm, J.Hypertens (2005) 23:463

Are beta-blockers or diuretics the (major) culprits ?
ARIC - study

→ patients on thiazides no greater risk than individuals on no antihypertensive treatment

→ but betablockers increase risk by 28%

Gress, New Engl J Med (2000) 342:905

Good news for Hungarian wine drinkers **:**

Alcohol and prevention of (type 2) diabetes

***moderate alcohol* consumption –**
***less* de novo *diabetes* vs nondrinkers :**

nurses health study

Hu,New Engl J Med (2001) 345: 790

Hoorn study

de Vegt, Diab Res Clin Pract (2002) 57: 53

one glass a day keeps diabetes away?

Diabetic nephropathy

Eberhard Ritz
Heidelberg (Germany)

Epidemiology

Prevention of diabetes

Diagnosis of diabetic nephropathy

Microalbuminuria

- **30 – 300 mg / day albumin excretion**

  or

- **20 – 200 µg / min or µg/ml respectively**

  (1 day = 1440 min = 1500 ml urine ~ 1 ml/min)

- high day-to-day variability (VC 30%)
diagnosis of MA : 2/3 urine samples positive

⇨**exclude :**

renal causes
(microhematuria,bacteriuria)

comorbidity
(uncontrolled hyperglycemia,hypertension, cardiac failure)

Predictors of microalbuminuria in an inception cohort with type 1 diabetes

during 18 years follow-up:

29% developed persistent microalbuminuria,

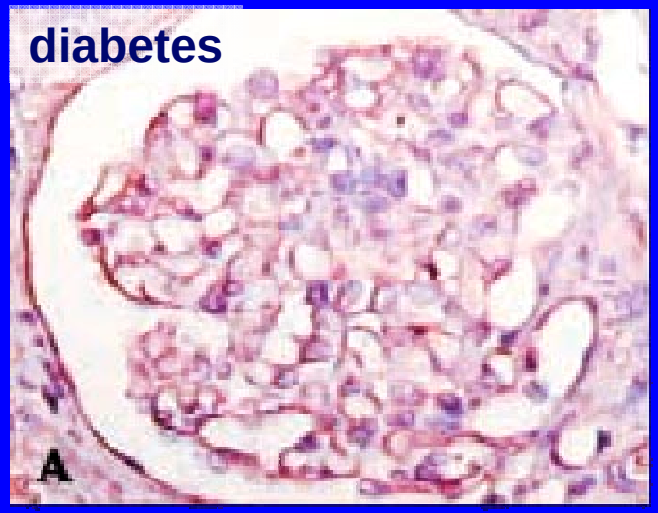
34% of whom progressed to macroalbuminuria

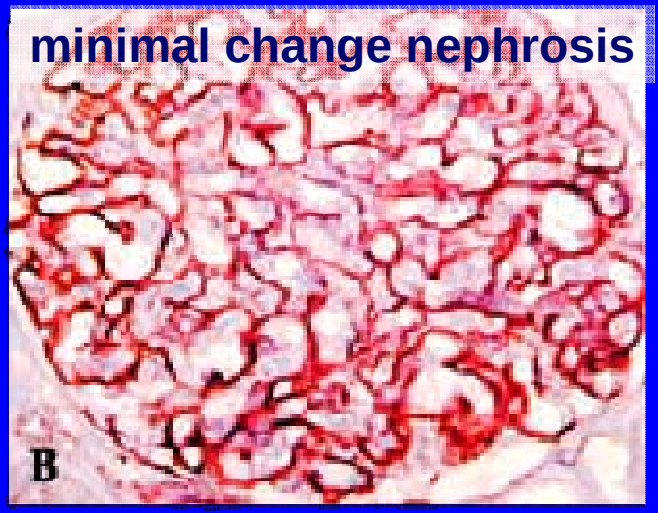
Predictors of the onset of microalbuminuria

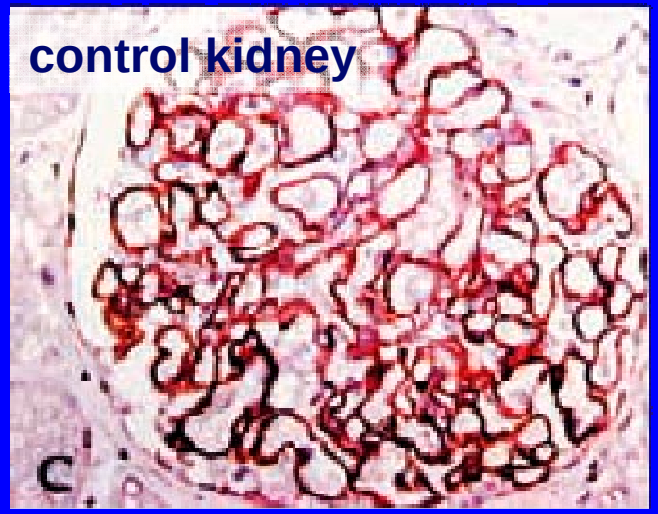
- **10 fold increase of baseline albuminuria**
- **male gender**
- **10 mmHg increase in MAP**
- **1% increase in HbA1c**

Hovind, Brit.med.J.(2004) 328:1105

Nephrin expression is diminished in diabetic nephropathy and preserved by RAS blockade







Benigni, Kidney Inter (2004) 65: 2193

Progressive increase of renal and CV risk with albuminuria within the normal range in type 2 diabetics

albuminuria (mg/day)	relative risk progression to microalbuminuria	relative risk progression to CV endpoint
0-10	1	1
10-20	2.34	1.9
20-30	12.4	9.8

Rachmani, Diab Res (2000) 49: 187

UKPDS – progression of renal disease in type 2 diabetic patients

- **5097 subjects**
- **progression:**

normoalbuminuria – microalbuminuria

2% per year

microalbuminuria – macroalbuminuria

2.8% per year

macroalbuminuria- elevated S_{crea} > 175µmol/l

2.3% per year

Adler, Kidn Intern (2003) 63: 225

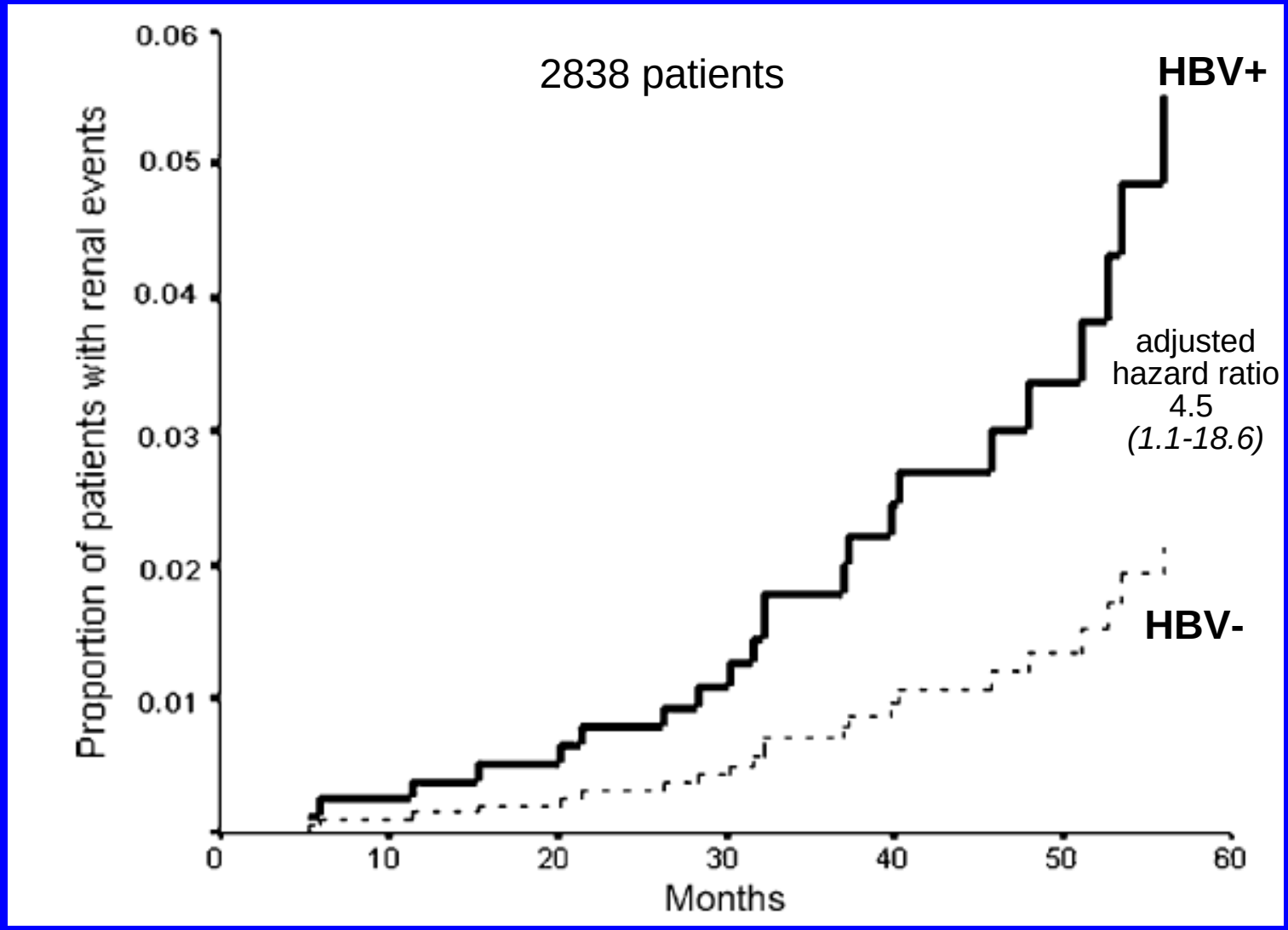
UKPDS – annual death rate

- **normoalbuminuria** **0.7%**
- **microalbuminuria** **2.0%**
- **macroalbuminuria** **3.5%**
- **elevated S_{crea}** **12.1%**

→ **macroalbuminuria:**
more likely to die (CV death) than
to develop renal failure

Adler, Kidn Intern (2003) 63: 225

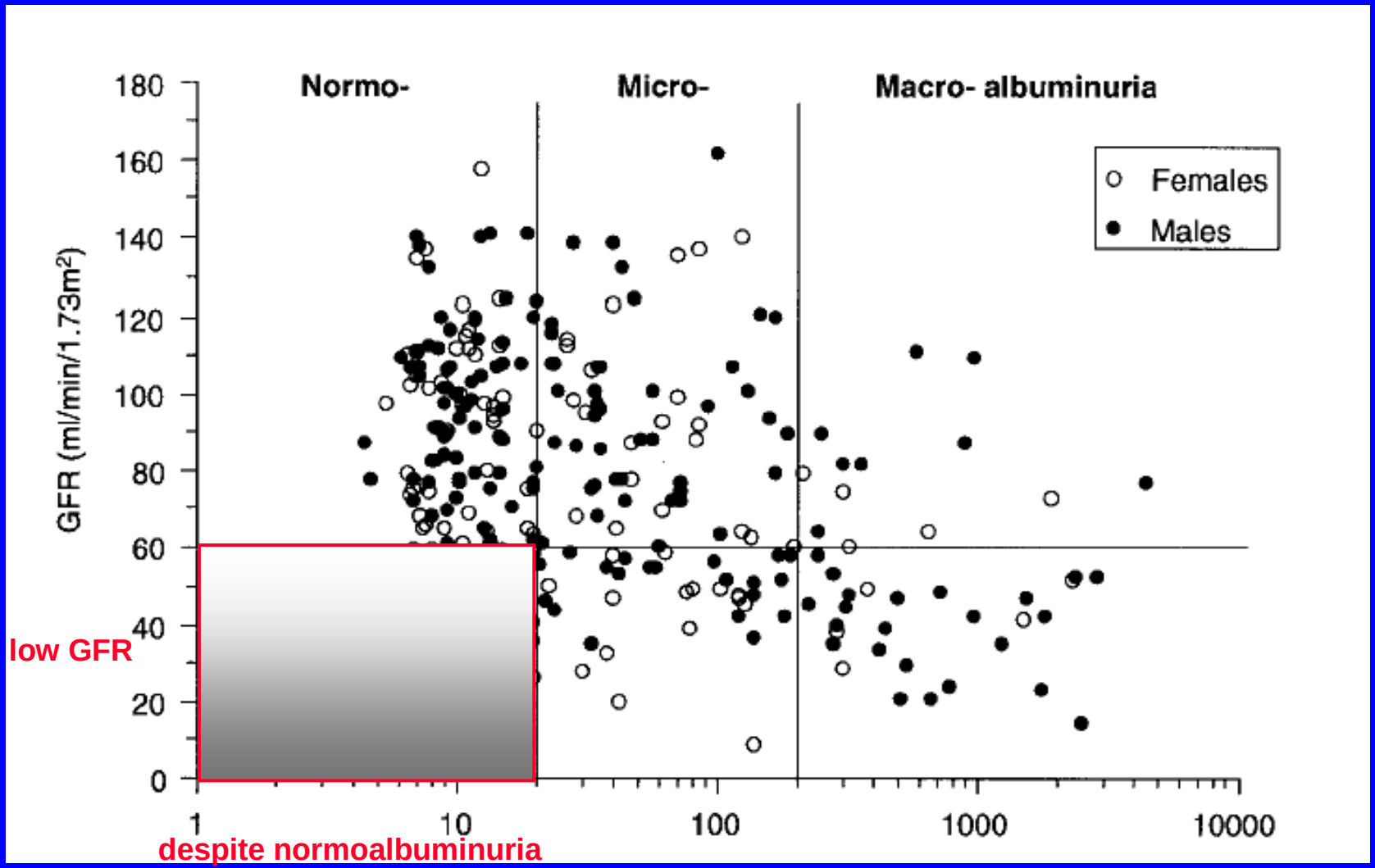
Risk of progression of type 2 diabetic nephropathy in patients with hepatitis B – *adverse effect of inflammation ?*



Cheng, Diabetologia (2006) 49:1777

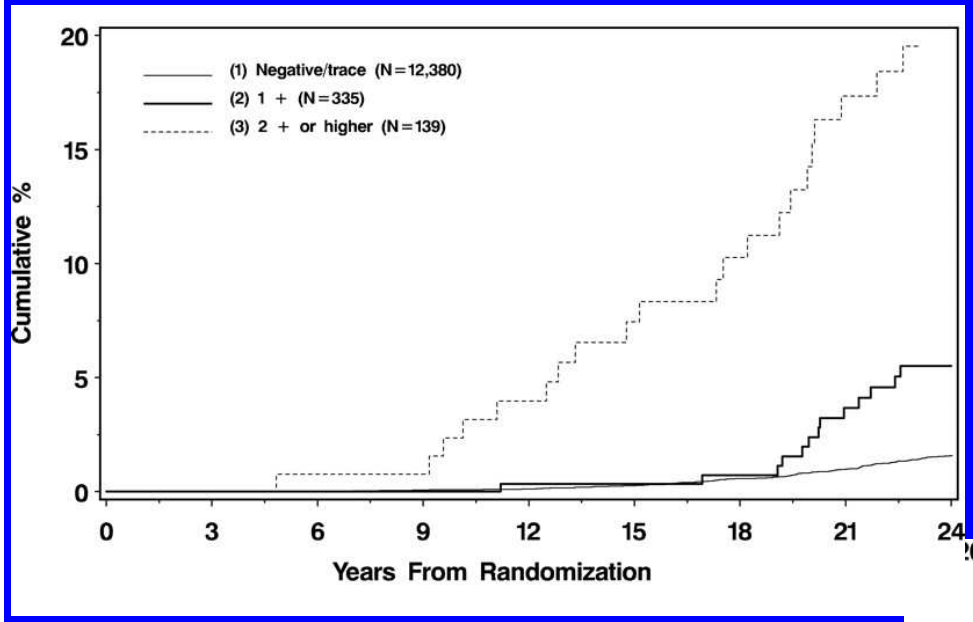
Low GFR despite normoalbuminuria in type 2 diabetes

(ischemic nephropathy)



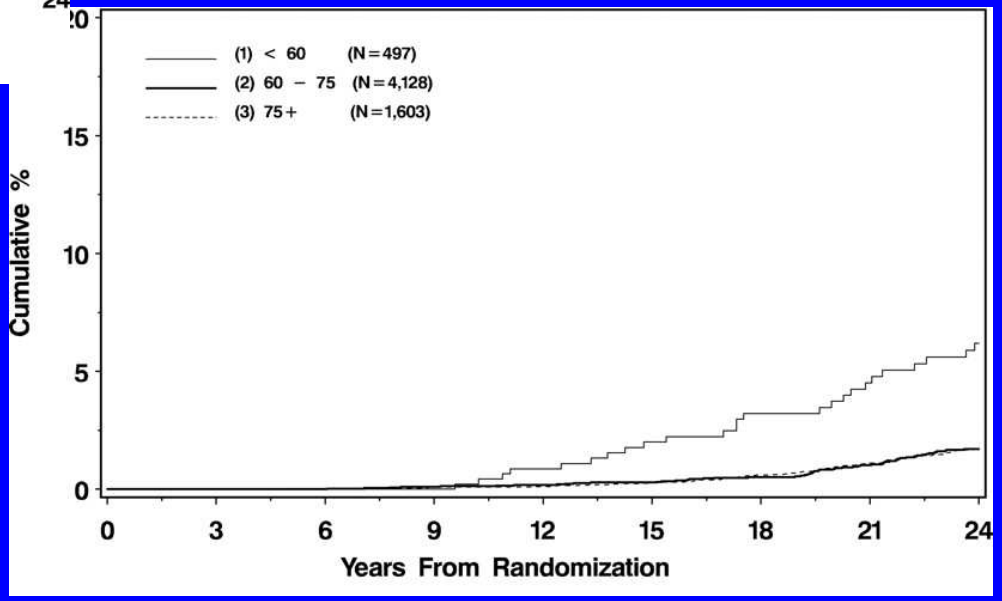
MacIsaac, Diabetes Care (2004) 27:195

Both proteinuria and eGFR predict endstage renal disease within 25 years – but proteinuria is more powerful



baseline proteinuria (Stix)

eGFR



Ishani, J.Am.Soc.Nephrol.(2006) 17:1444

Diabetic nephropathy

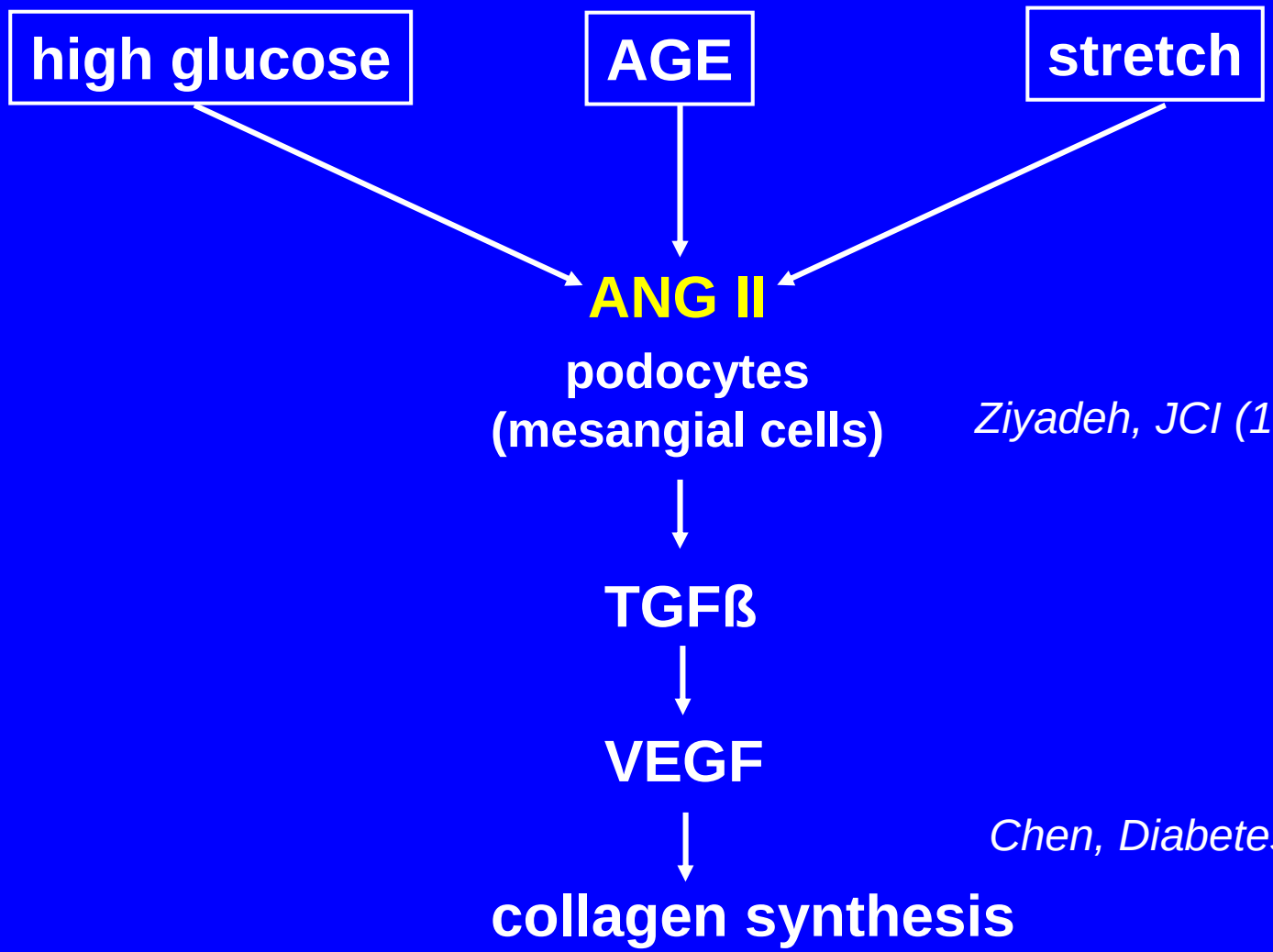
Eberhard Ritz
Heidelberg (Germany)

Epidemiology

Prevention of diabetes

Diagnosis of diabetic nephropathy

Pathogenesis of albuminuria/nephropathy

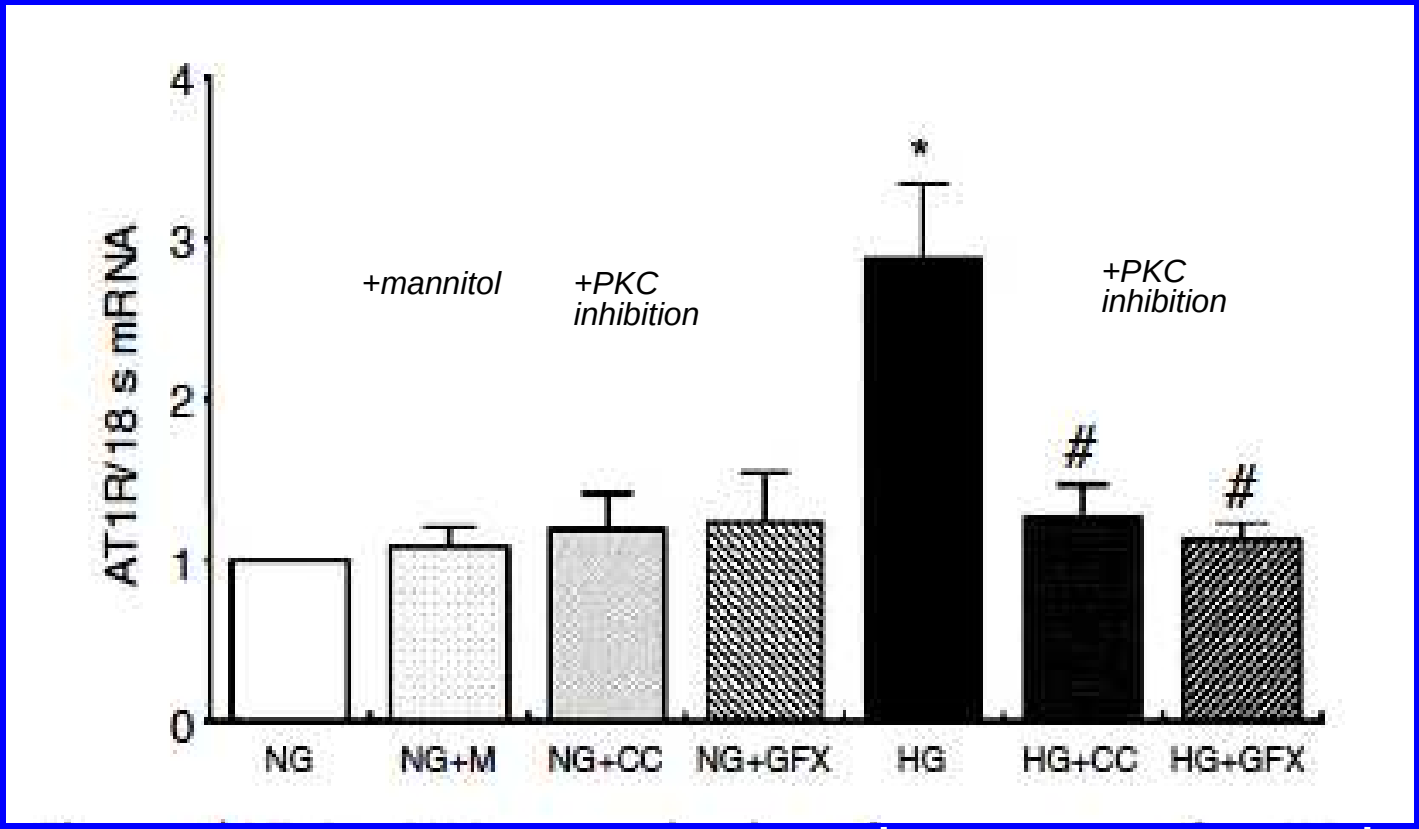


Ziyadeh, JCI (1994) 93:536

Chen, Diabetes (2004)53:2393

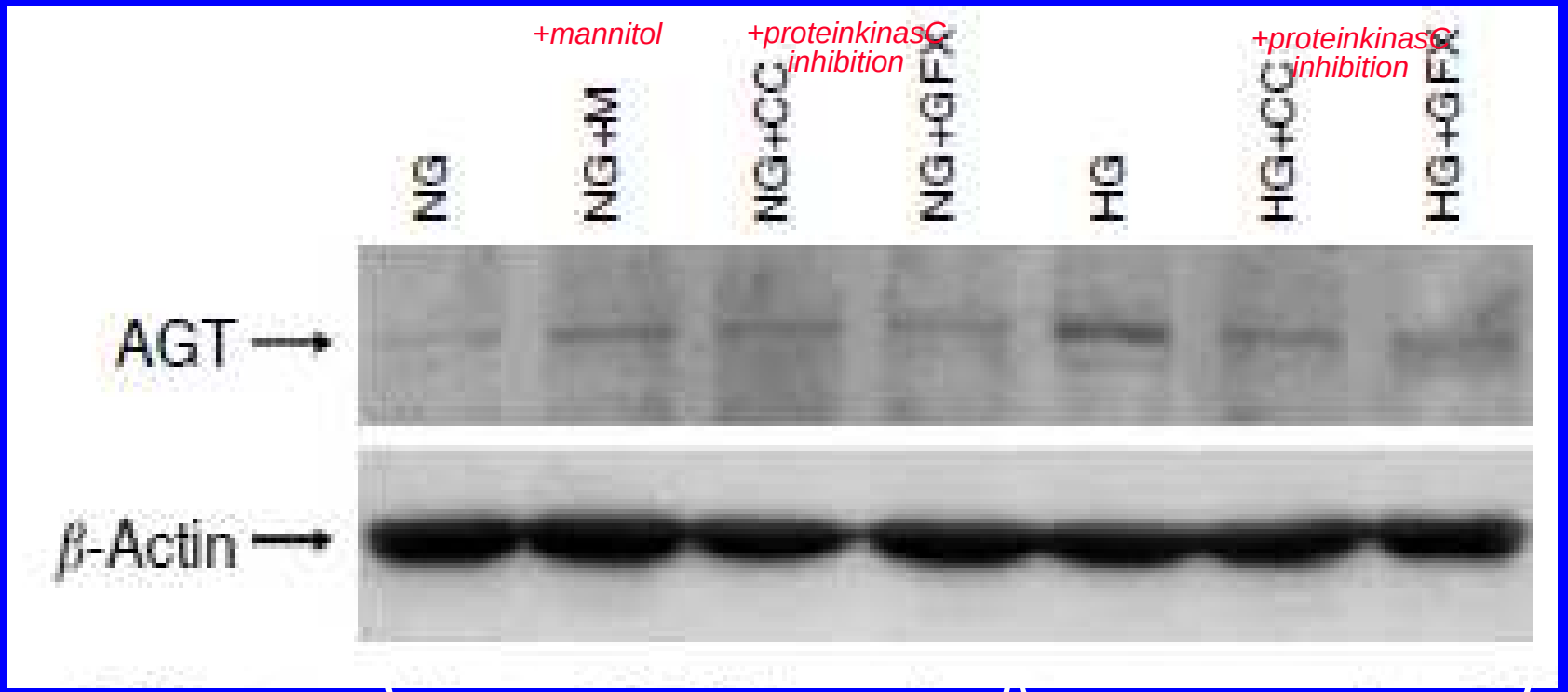
Wolf, Diabetes (2005) 54:1626

High glucose – upregulation of AT1 receptor in podocytes



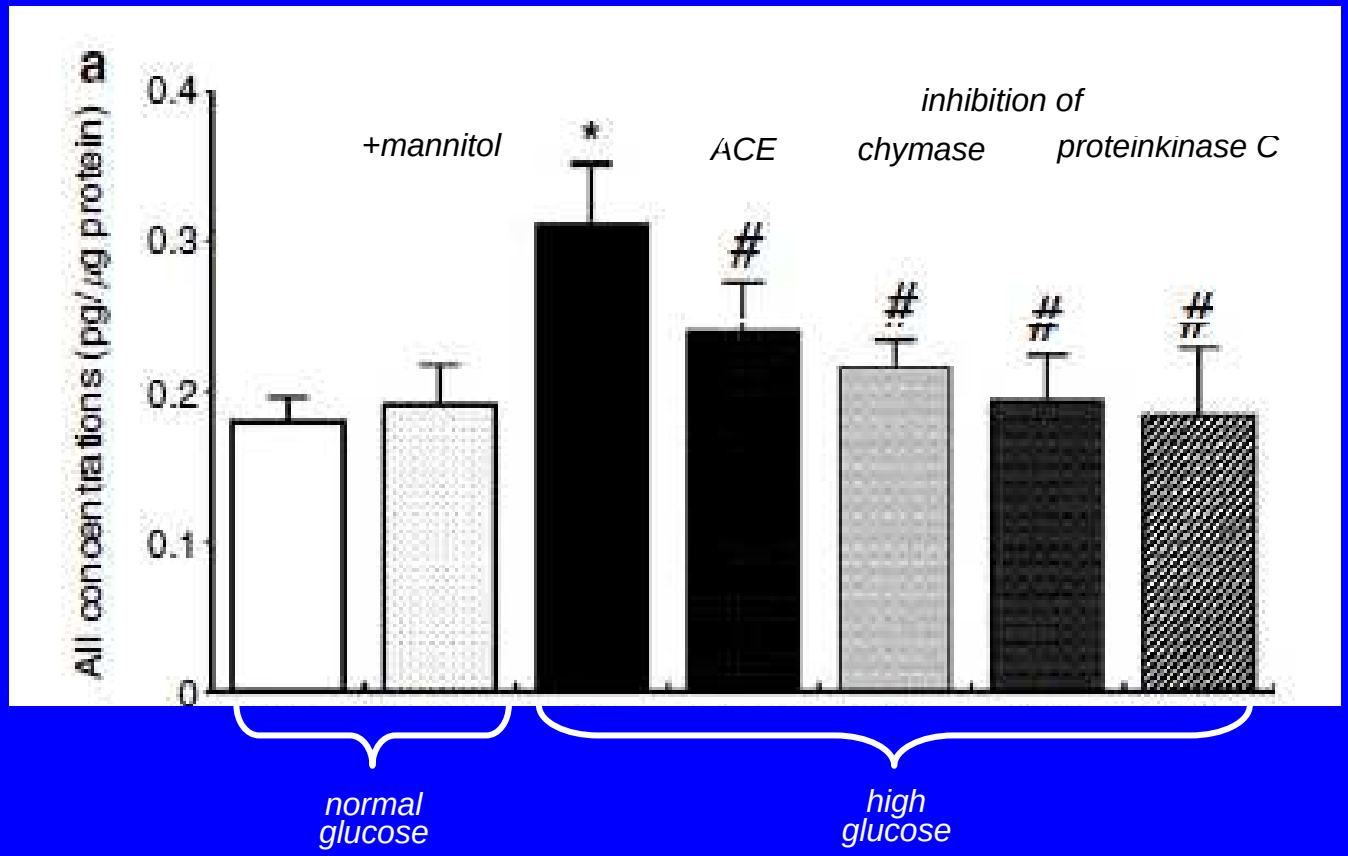
Yoo,Kidn.Intern.(2007)71:1019

High glucose →
increased angiotensinogen (and ANGII)
suppression by PKC inhibitors



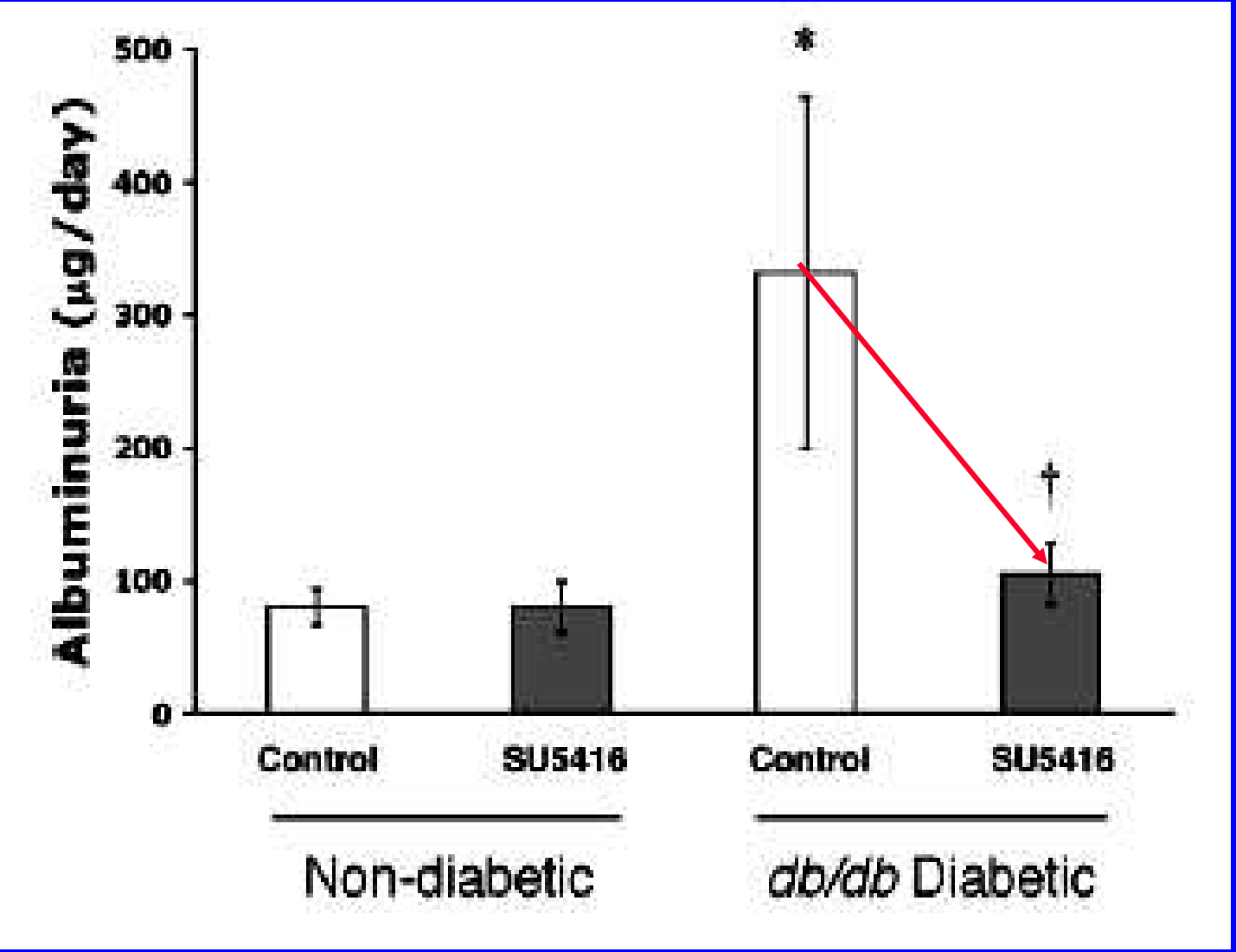
Yoo,Kidn.Intern.(2007)71:1019

ANGII concentration in podocyte lysates – reduced by inhibition of ACE, chymase, PKC



Yoo,Kidn.Intern.(2007)71:1019

The VEGF receptor tyrosine kinase antagonist SU5416 prevents albuminuria in diabetic mice



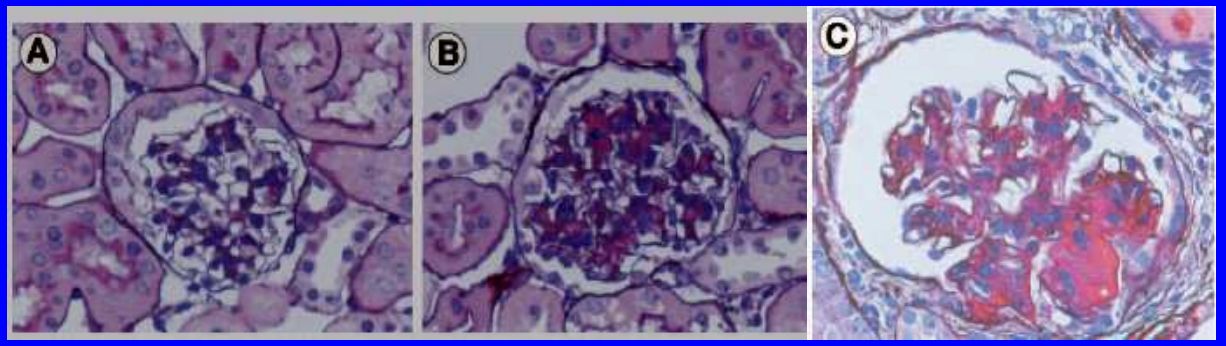
Sung, J.Am.Soc.Nephrol.(2006) 17:3093

Advanced nodular glomerulosclerosis in type 2 diabetic mice triple transgenic for *RAGE, iNOS and megsin (serpin)*

(multiple hits necessary,

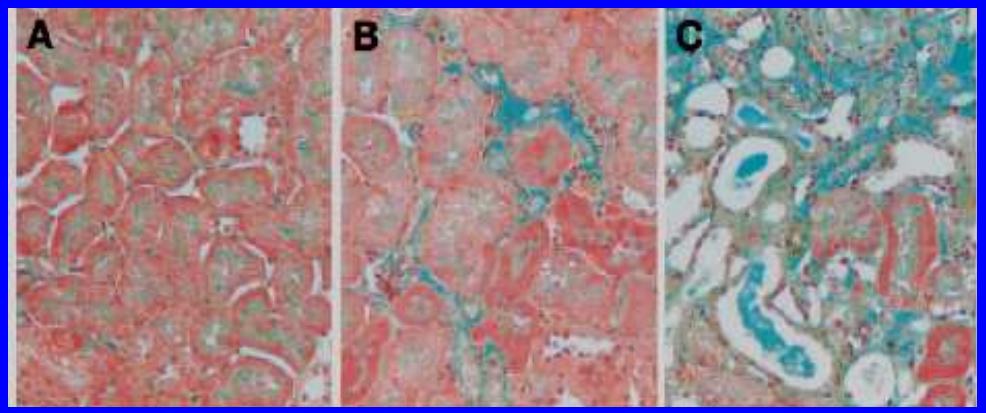
unlikely that one single therapeutic target will be sufficient

in nodular glomerulosclerosis)



Glomerular tuft PAS stain

wild type *RAGE/iNOS ko* *RAGE/iNOS/megsin ko*



tubulointerstitial matrix Masson-Goldner stain

Inagi, Diabetes (2006) 55:356

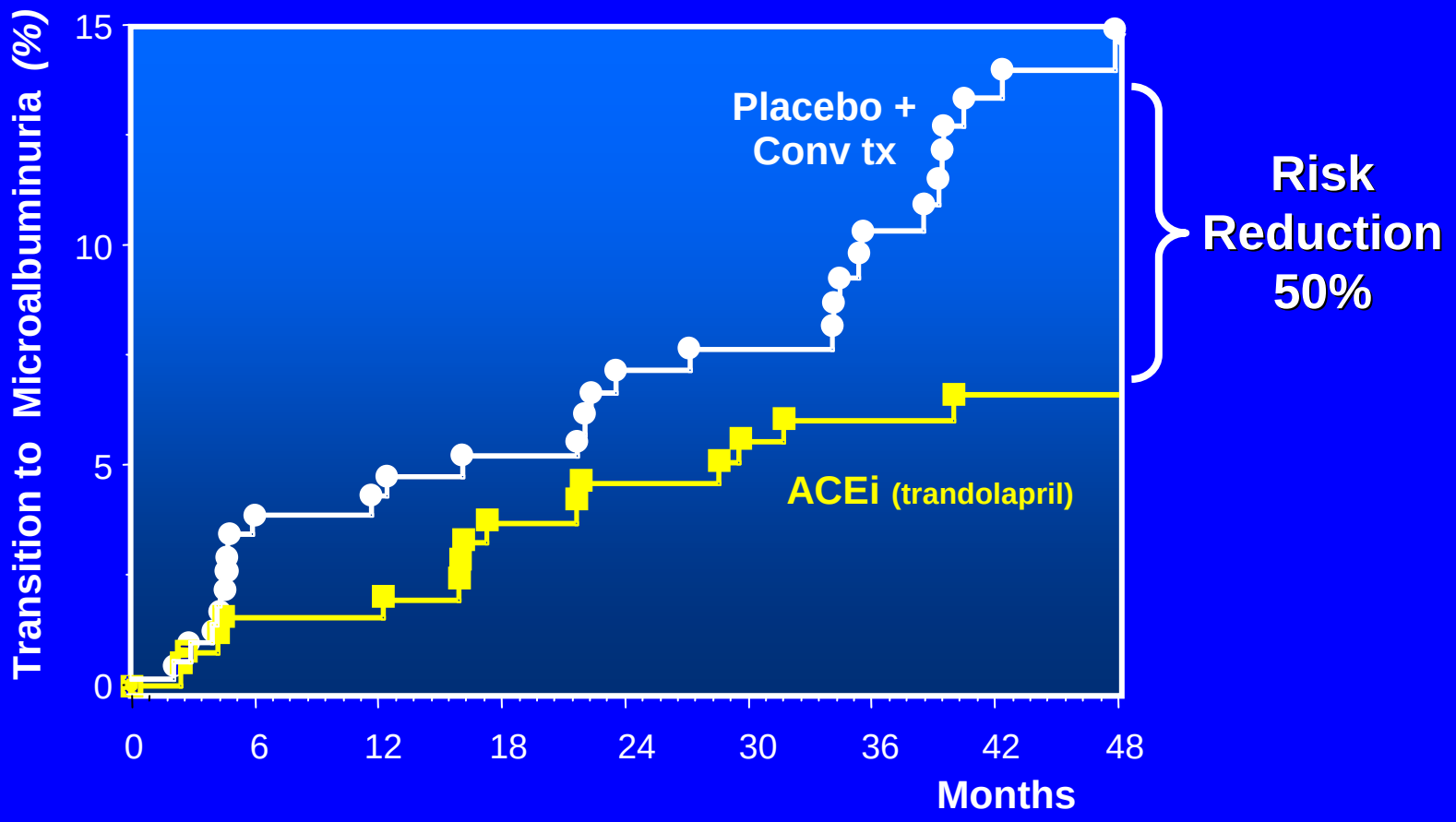
Diabetic nephropathy

Eberhard Ritz
Heidelberg (Germany)

Epidemiology
Prevention of diabetes
Diagnosis of diabetic nephropathy
Pathogenesis of albuminuria/nephropathy
Prevention of diabetic nephropathy

BENEDICT

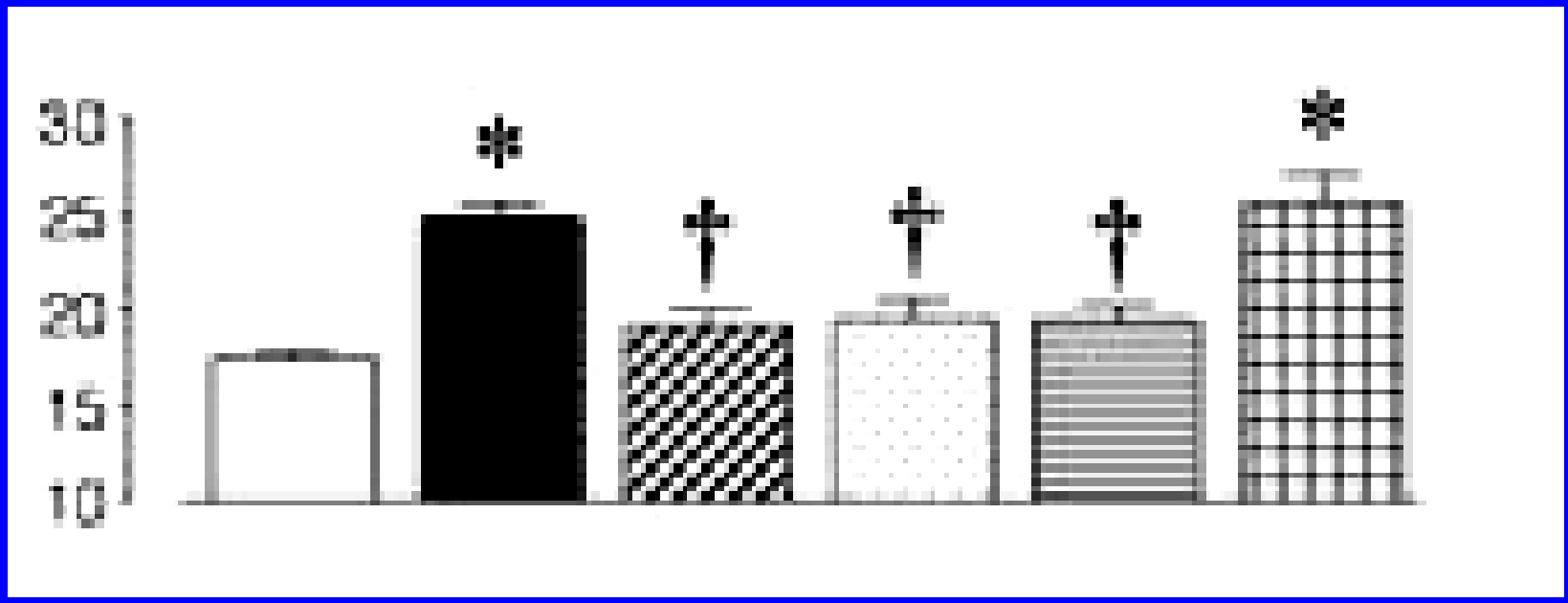
ACE inhibition reduces progression to microalbuminuria in type 2 diabetic patients



Ruggenenti, N Engl J Med (2004) 351:1941

OLETF rats

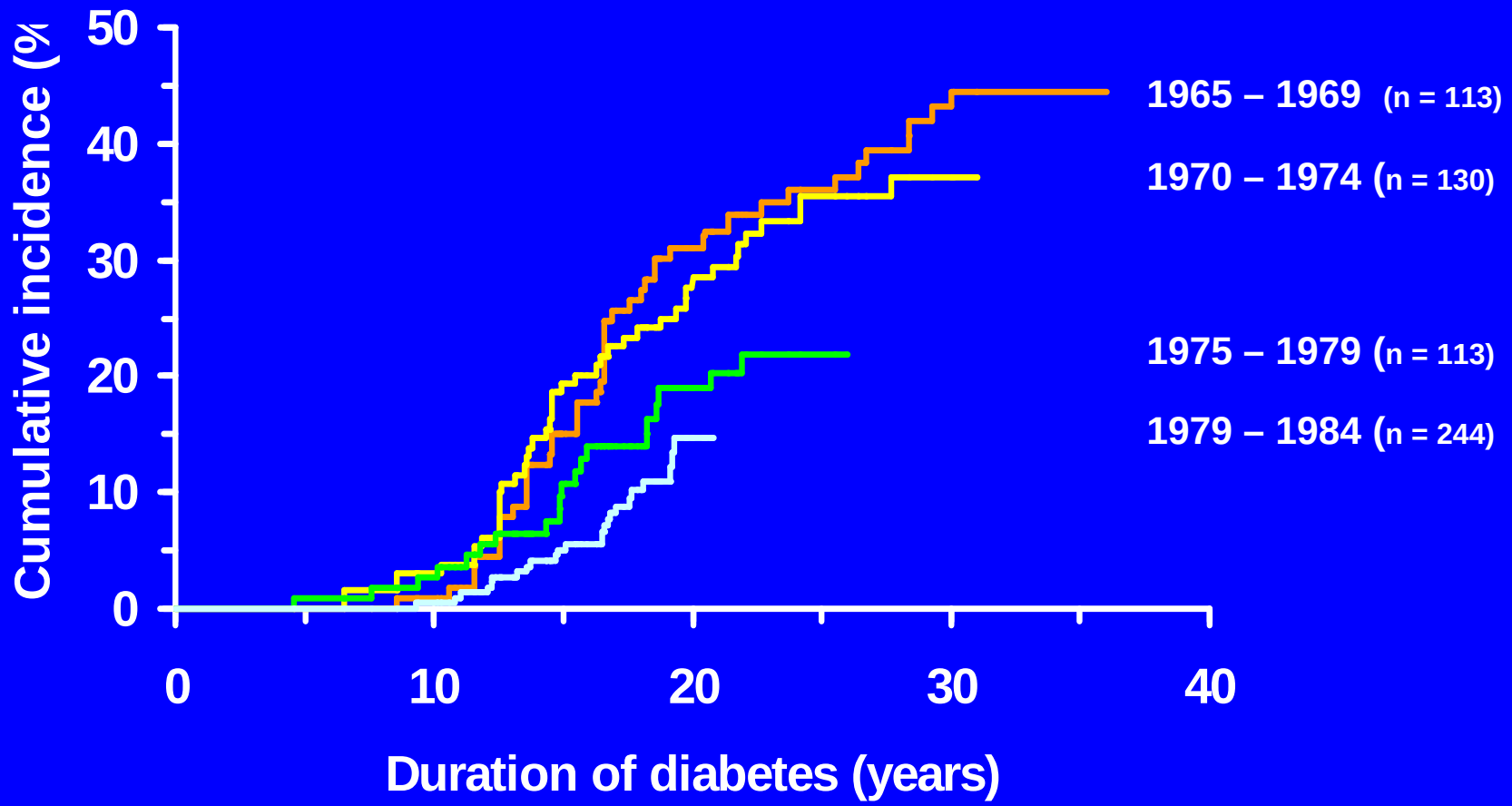
RAS blockade in prediabetic stage →
less renal damage after development of diabetes



Nagai Y.,J.Amer.Soc.Nephrol (2005) 16:703

Decreasing incidence of diabetic nephropathy in type 1 diabetes

Steno Hospital, Kopenhagen



Hovind, Diabetes Care (2003) 26:911

Targets to prevent onset of diabetic nephropathy

- *near-normoglycemia*
- *low blood pressure*
- *blockade of the RAS*
- *cessation of smoking*

Prevention of onset of microalbuminuria

- **glycemic control**

  type 1

  DCCT, NEJM (1993) 329: 977

  type 2

  Kumamoto trial, Diabetes Care (2000) 23: S21
  UKPDS, Lancet (1998) 352: 837

- **ACE inhibitors**

  type 1

  EUCLID, Lancet (1997) 350: 1102
  Lancet (1998) 351: 28

  type 2

  Benedict, New Engl J Med. (2004) 351:1941

- **blood pressure lowering per se**

  ABCD, Kidn Intern (2002) 61: 1086

Diabetic nephropathy

Eberhard Ritz
Heidelberg (Germany)

Epidemiology of diabetes
Prevention of diabetes
Diagnosis of diabetic nephropathy
Prevention of diabetic nephropathy
Management of the diabetic patient with nephropathy

To prevent progression of microalbuminuria / proteinuria

 # cessation of smoking

Sawicki, Diabetes Care (1994) 17: 126

 # blood pressure lowering per se
(125 mmHg seated systolic)

NKF, ADA

 # ACEi; ARB *(blood pressure independent renoprotection)*

Smoking and progression

	rel. risk vs. non-smokers	
smokers, no ACE inhibitors	10	0.001
smokers treated with ACE inhibitors	1.3	N.S.

Orth, Kidn Intern (1998) 54: 926

32 type 2 diabetes with nephropathy

S-creatinine < 1.4 mg/dl

treated with ACE inhibitors

MAP 92 ± 1 mmH

S-creatinine (mg/dl) after

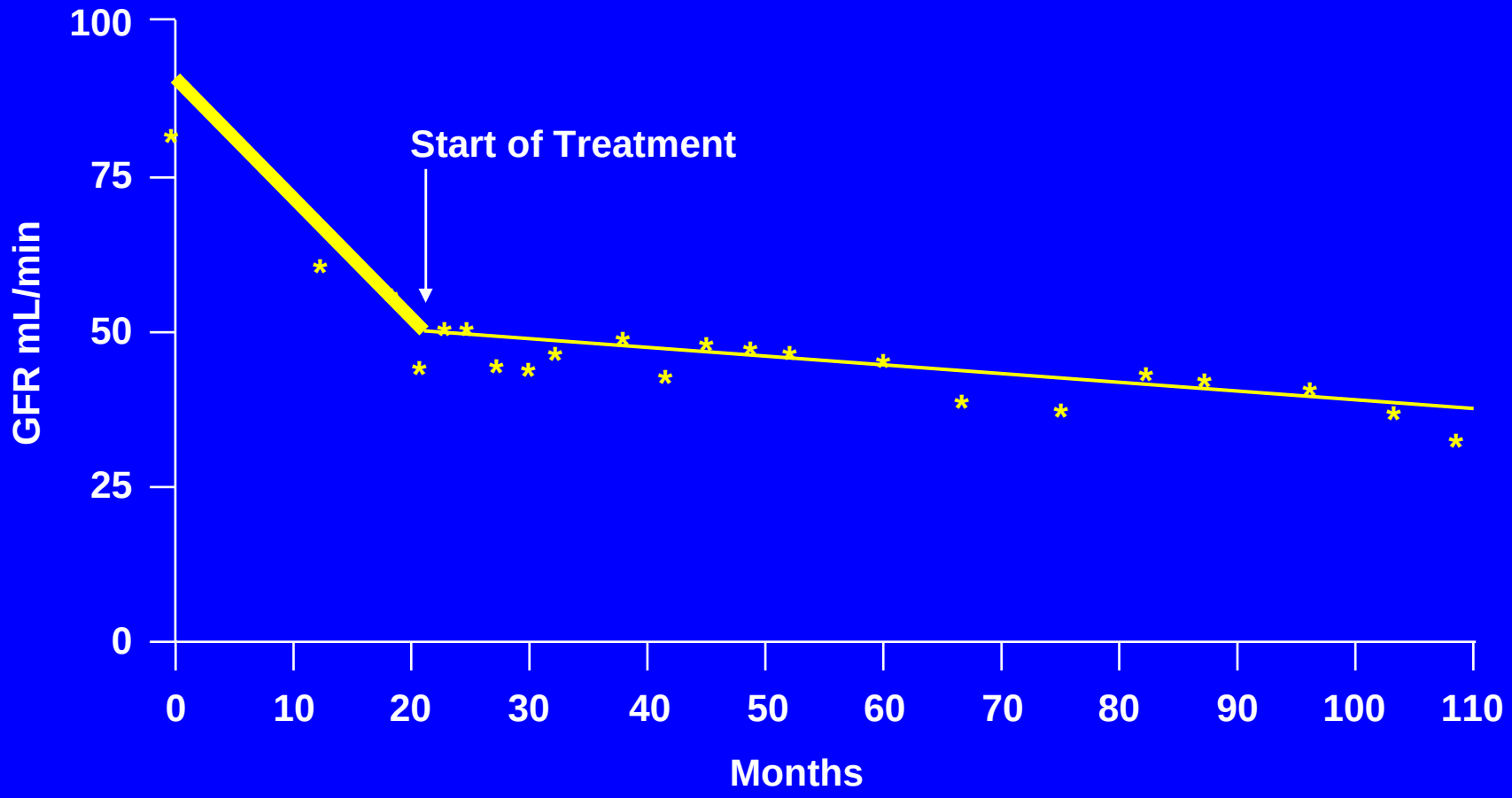
61 months follow-up

smokers	**1.78 ± 0.2**
non-smokers	**1.32 ± 0.01**

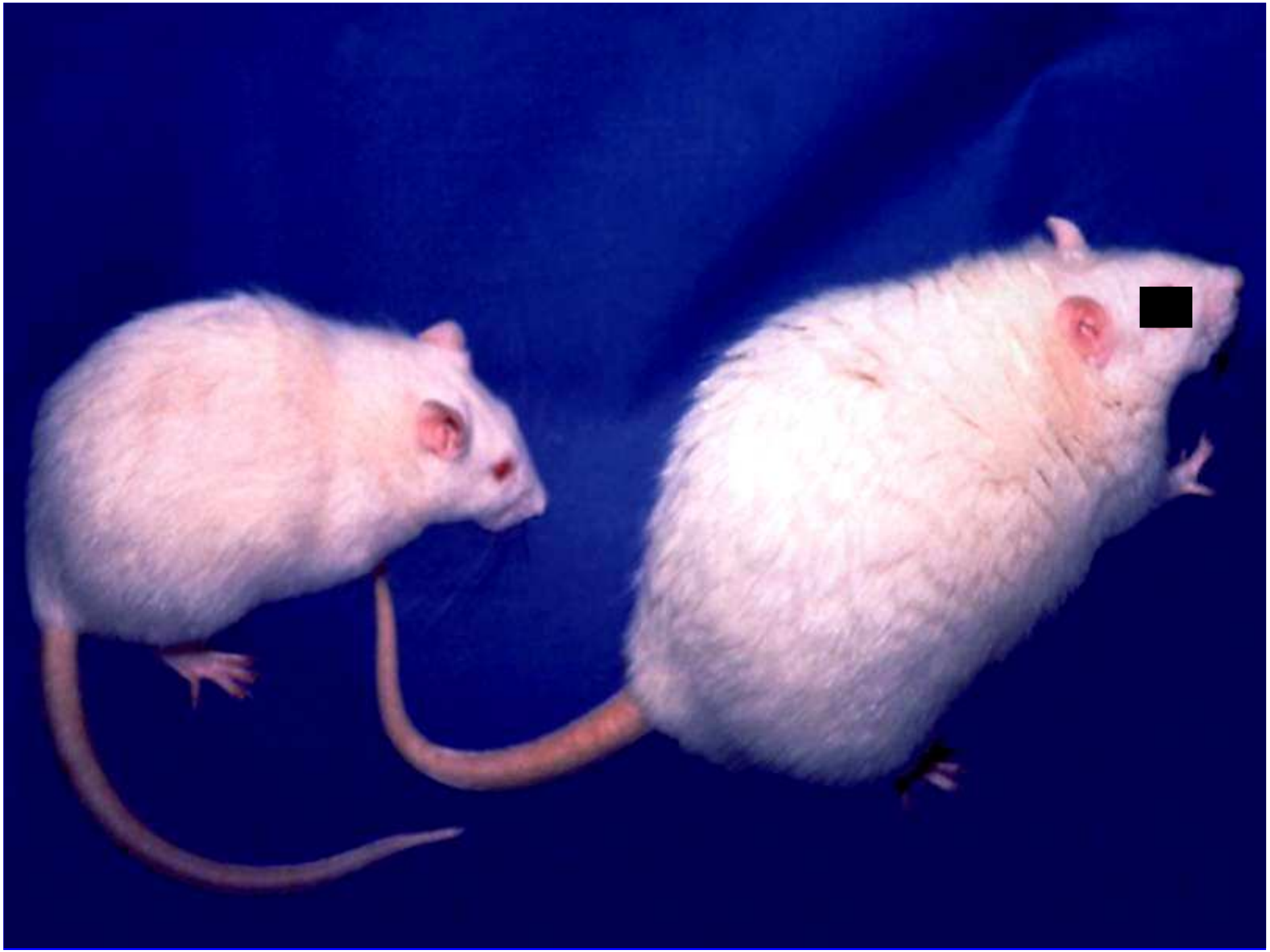
Chuahirun T. , Am J Kidn Dis (2002) 39: 376

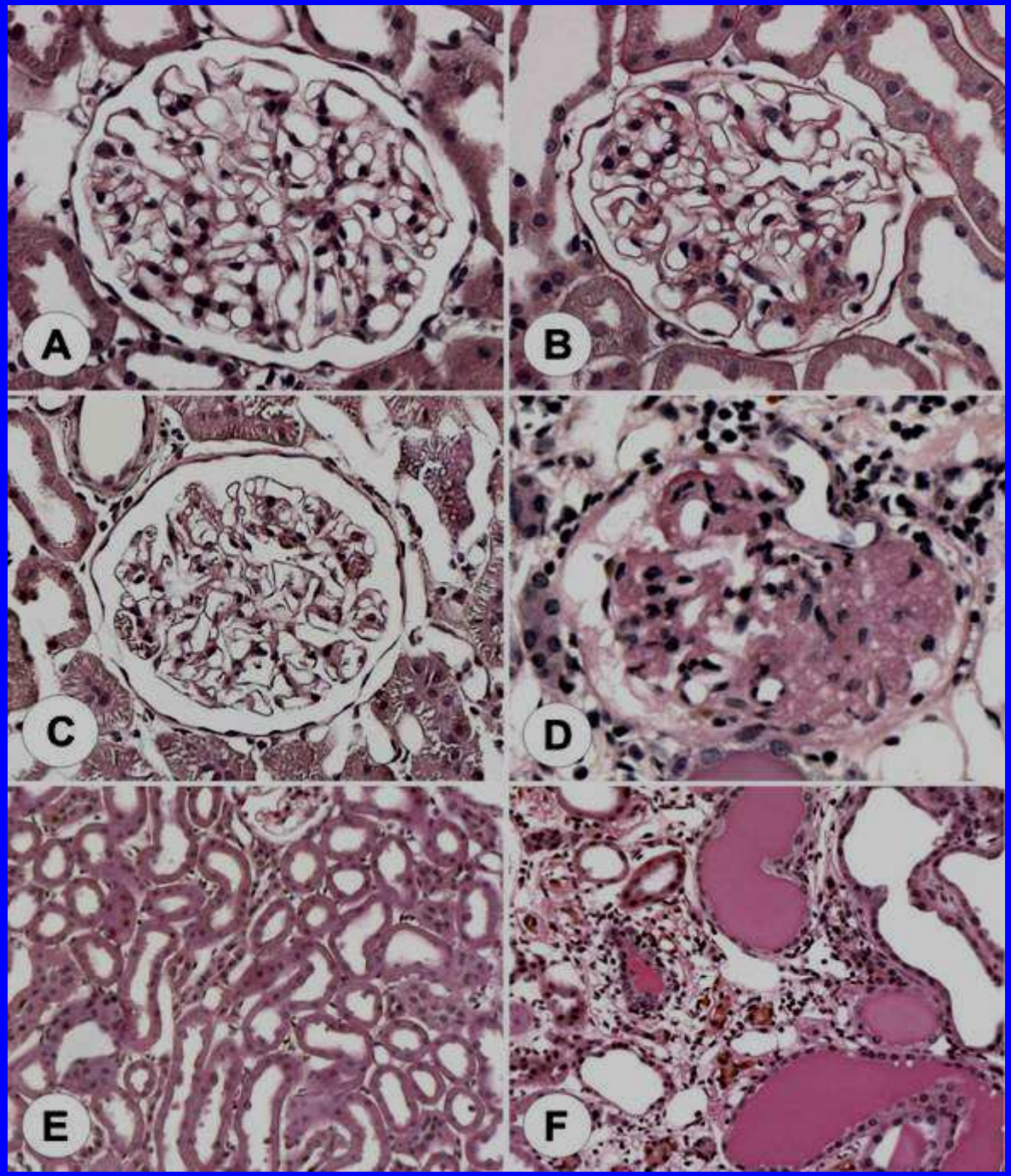
Blood pressure lowering and loss of glomerular filtration rate in diabetic nephropathy

⇨*no evidence that high blood pressure is necessary to "maintain" renal function*



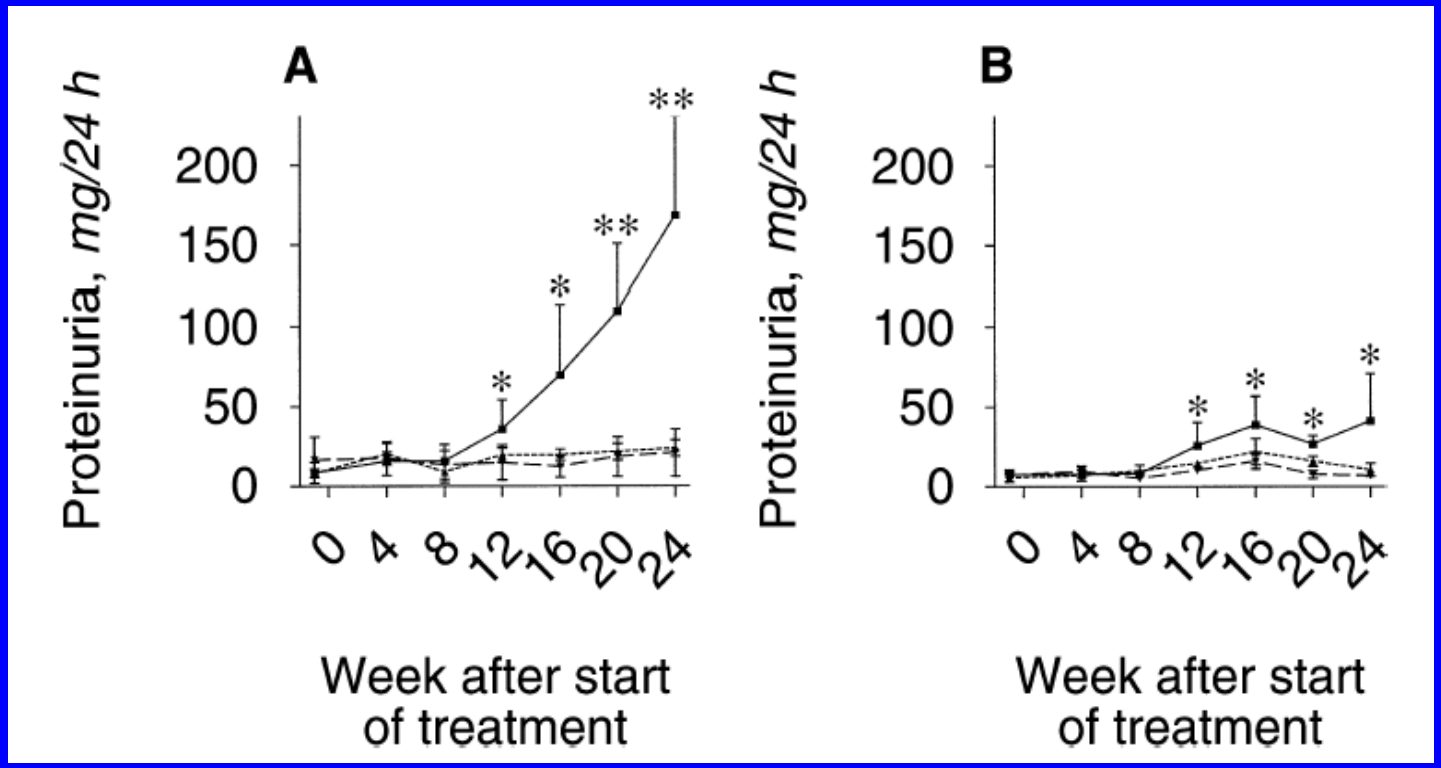
Mogensen CE. *Pract Cardiol.* (1983) 9:156





Gross,Lab Invest (2003)83:1267

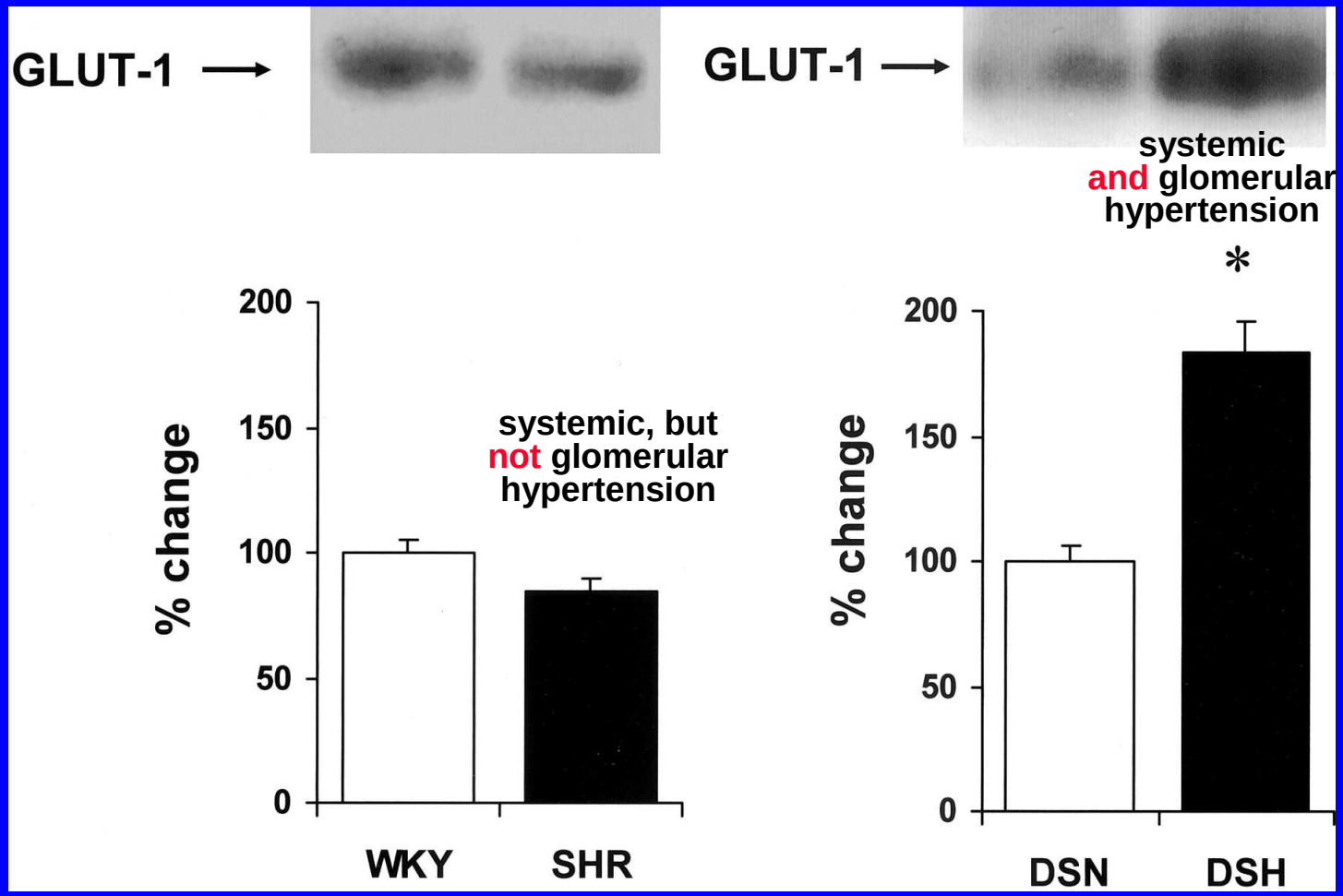
Hypertension superimposed on type II diabetes in Goto Kakizaki rats induces progressive nephropathy



Goto Kakizaki **Wistar**

Janssen, Kidney Intern (2003) 63, 2162

Intraglomerular hypertension → upregulation of GLUT 1 (glucose uptake)



Gnudi,Hypertension (2003) 42:19

Admiral Nelson syndrome :

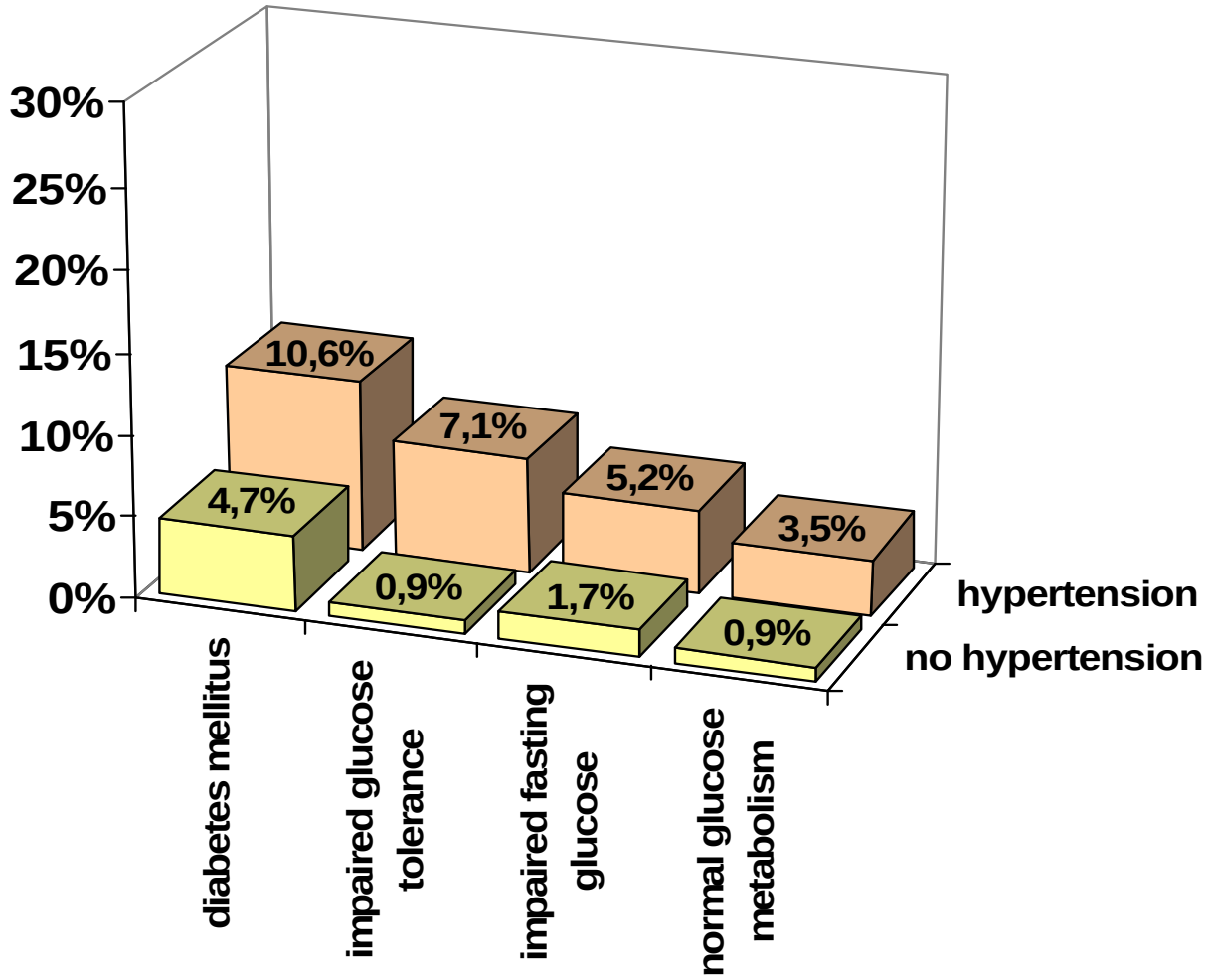
looking with one eye

only at glycemia

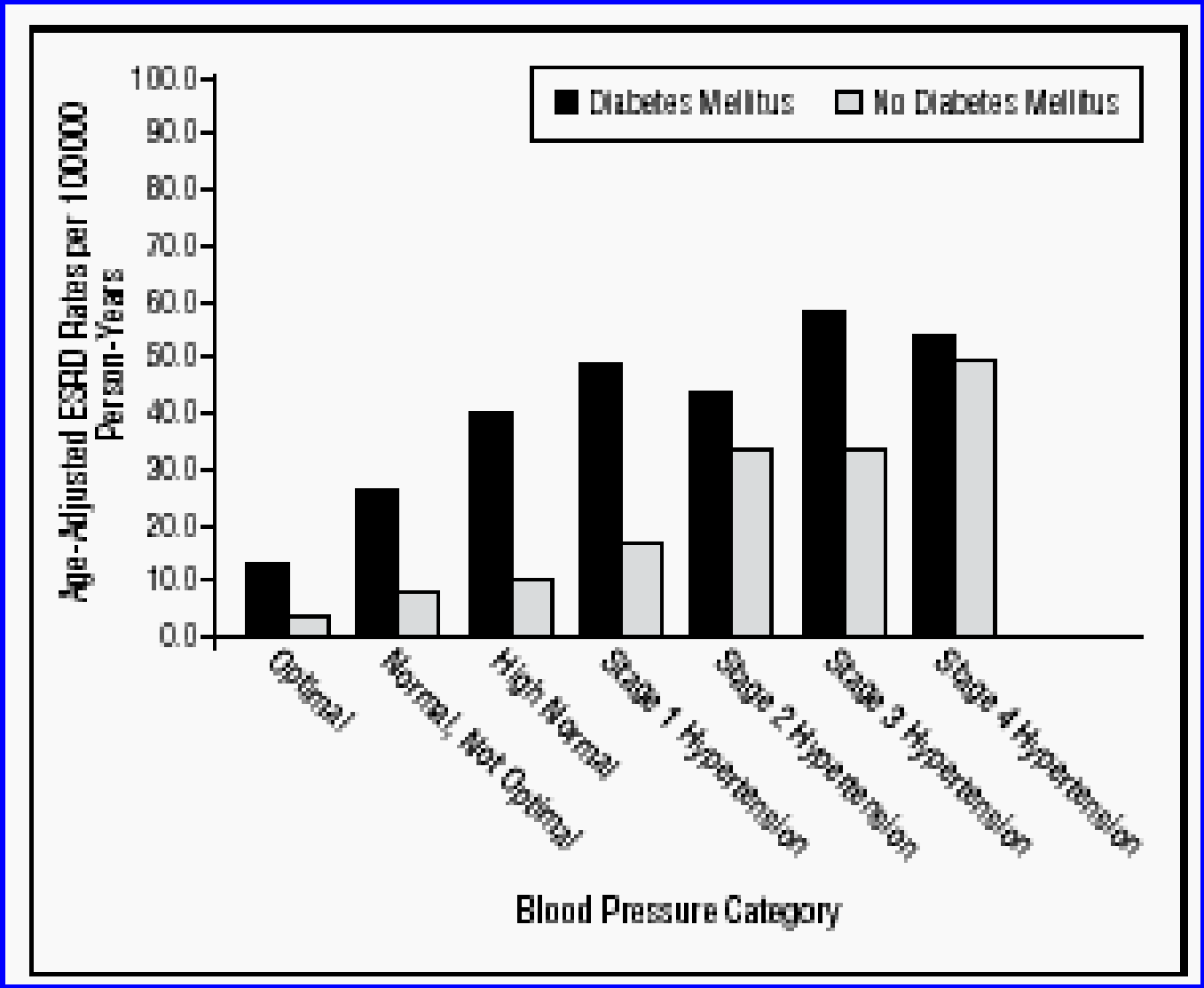
Admiral Horatio Nelson
Victor of Trafalgar
1758-1805

Prevalence of proteinuria

≥0.20 mg/mg urine protein:creatinine



Blood pressure predicts endstage renal disease in individuals without renal disease at baseline – diabetics and nondiabetics (Kaiser Permanente cohort)



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

Elevated BP of abnormal circadian BP profile by ABPM in newly diagnosed type 2 diabetics

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

- hypertensive by 1st or 2nd criterion 80%

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

Independent association of office BP and awake systolic ambulatory BP (ABP) with albuminuria in type 2 diabetics

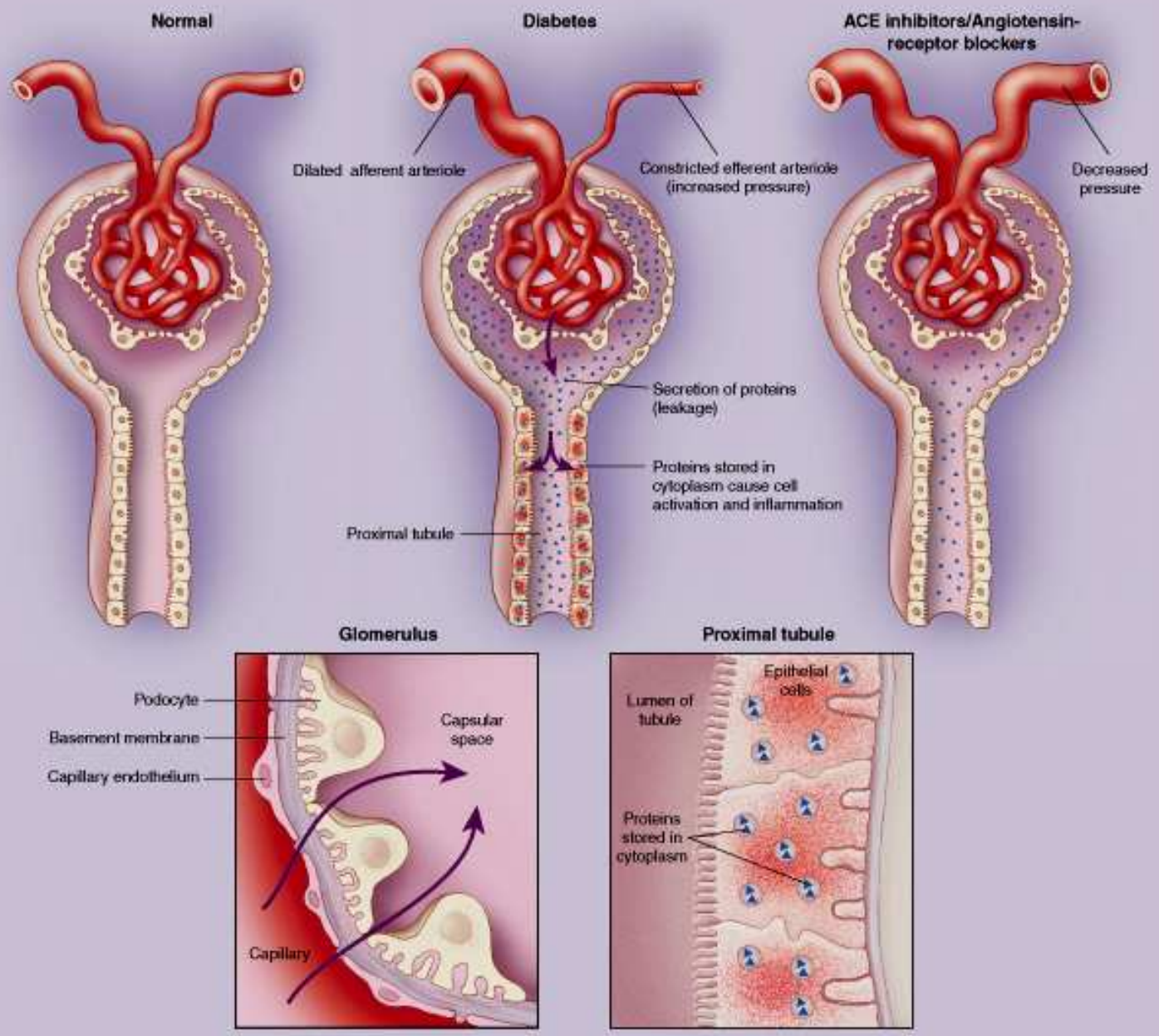
albuminuria :	*controlled office and ABP*	*uncontrolled * office controlled ABP*	*controlled office *uncontrolled ABP*	**uncontrolled office *uncontrolled ABP*
normo	***84.8%***	***71.3%***	***64.0%***	***49.4%***
micro/macro	***15.2%***	***28.8%***	***36.0%***	***50.5%***
odds ratio *(micro-/macroalbuminuria)*	***0.2***	***0.4*** *(white coat HT)*	***0.6*** *(masked HT)*	***1.0***

** >130mmHg*

Moran, Hypertension (2006) 47:955

Treatment goals

1. *BP < 125/75 mmHg*
2. *blockade renin-angiotensin system*
3. *proteinuria < 1g/24h*


Normal
Diabetes
ACE inhibitors/Angiotensin-receptor blockers
Dilated afferent arteriole
Constricted efferent arteriole (increased pressure)
Decreased pressure
Secretion of proteins (leakage)
Proteins stored in cytoplasm cause cell activation and inflammation
Proximal tubule
Glomerulus
Podocyte
Basement membrane
Capillary endothelium
Capsular space
Capillary
Proximal tubule
Epithelial cells
Lumen of tubule
Proteins stored in cytoplasm

Prevention of progression, cardiovascular complications and death in type 2 diabetes – *ADVANCE study*

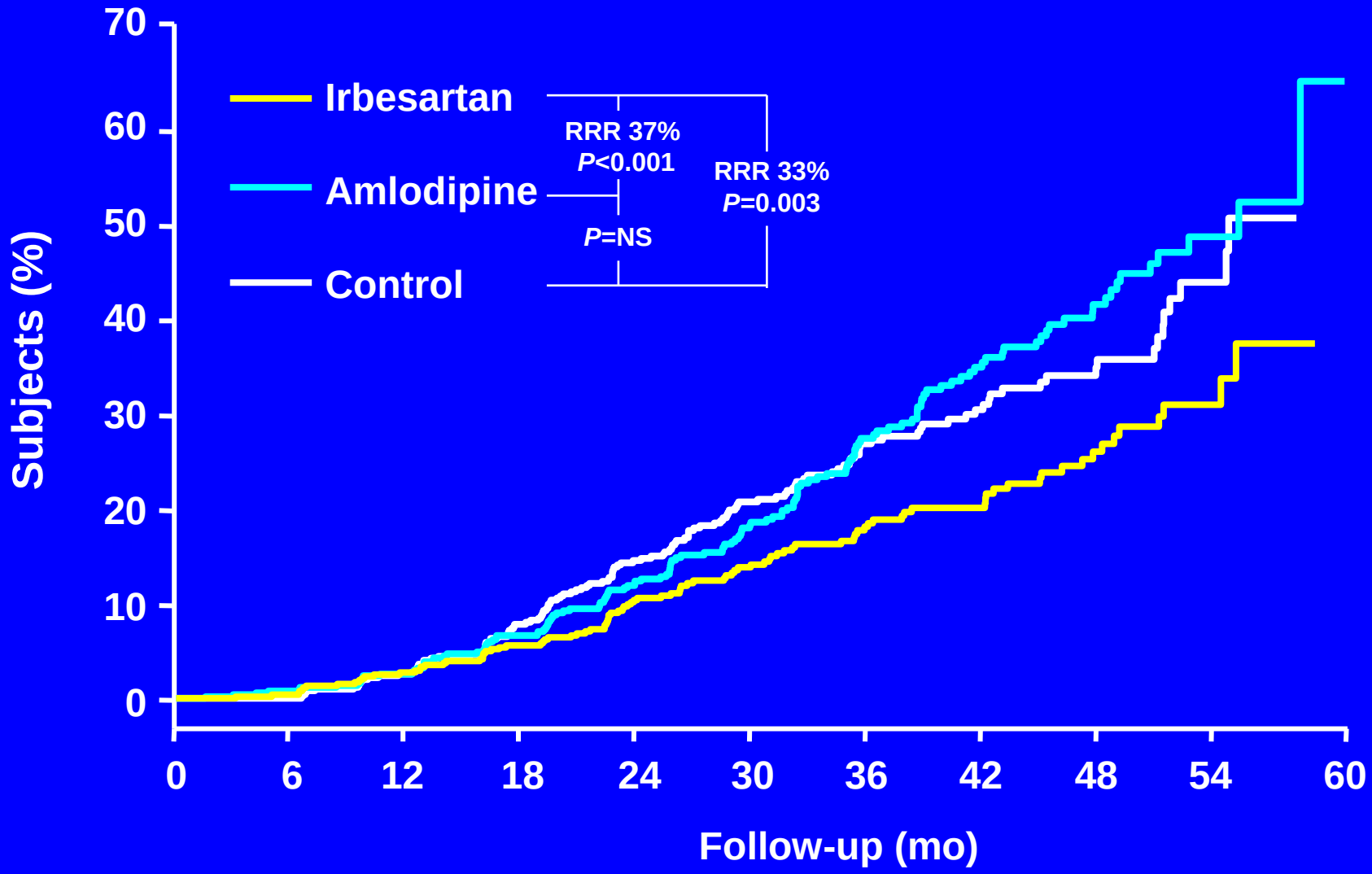
- **on top of current treatment :**
  Perindopril plus Indapamide vs placebo –
  irrespective of blood pressure !

- **after 4.3 years BP reduction no more than 5.6/2.2 mmHg –**
  yet :

- **rel.risk - of macrovascular events ↓ by 9%**
  - of death from CV disease ↓ by 18%
  - renal events ↓ by 21% *(p<0.0001)*

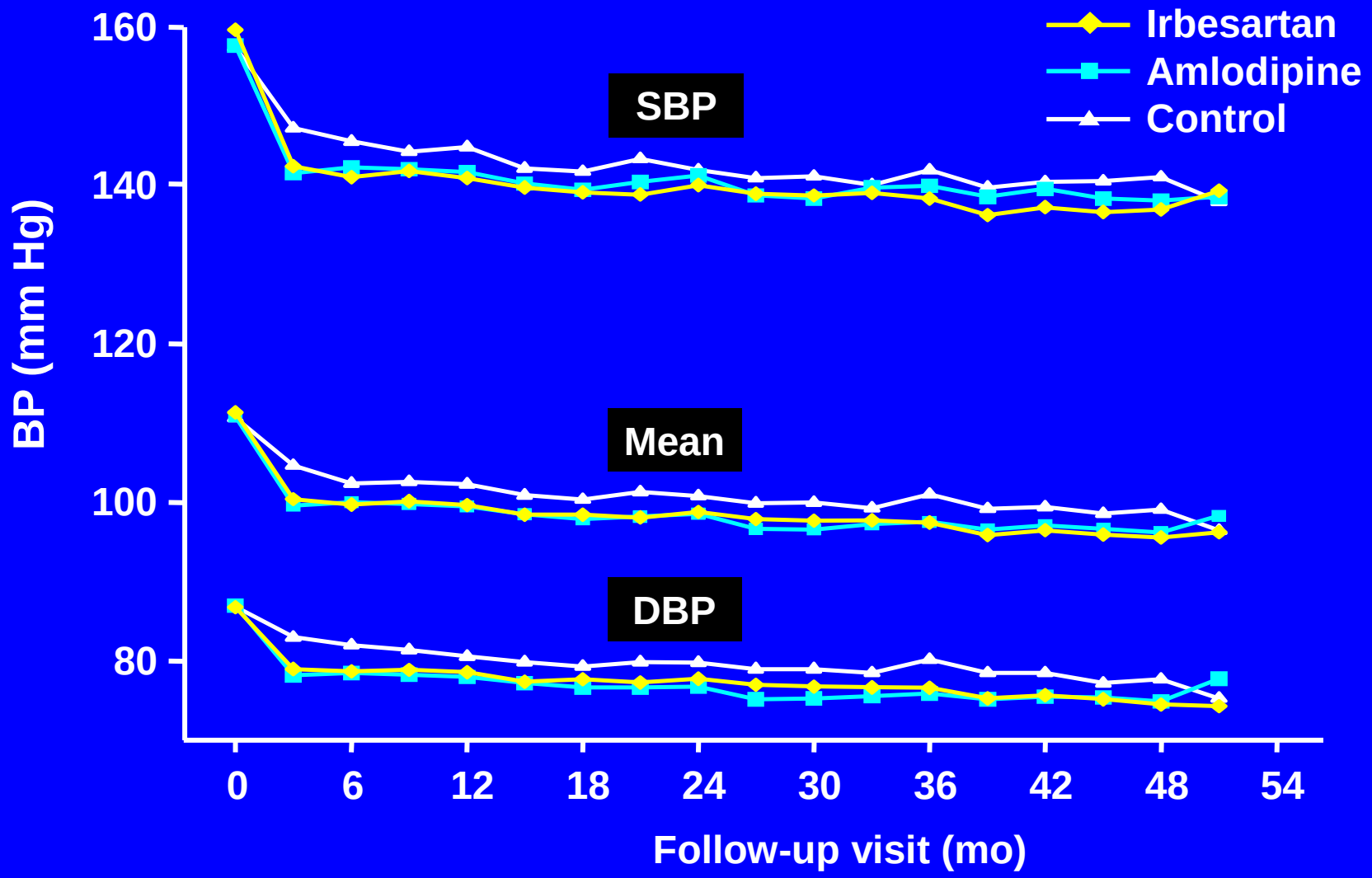
Lancet (2007) 370:829

Time to Doubling of Serum Creatinine



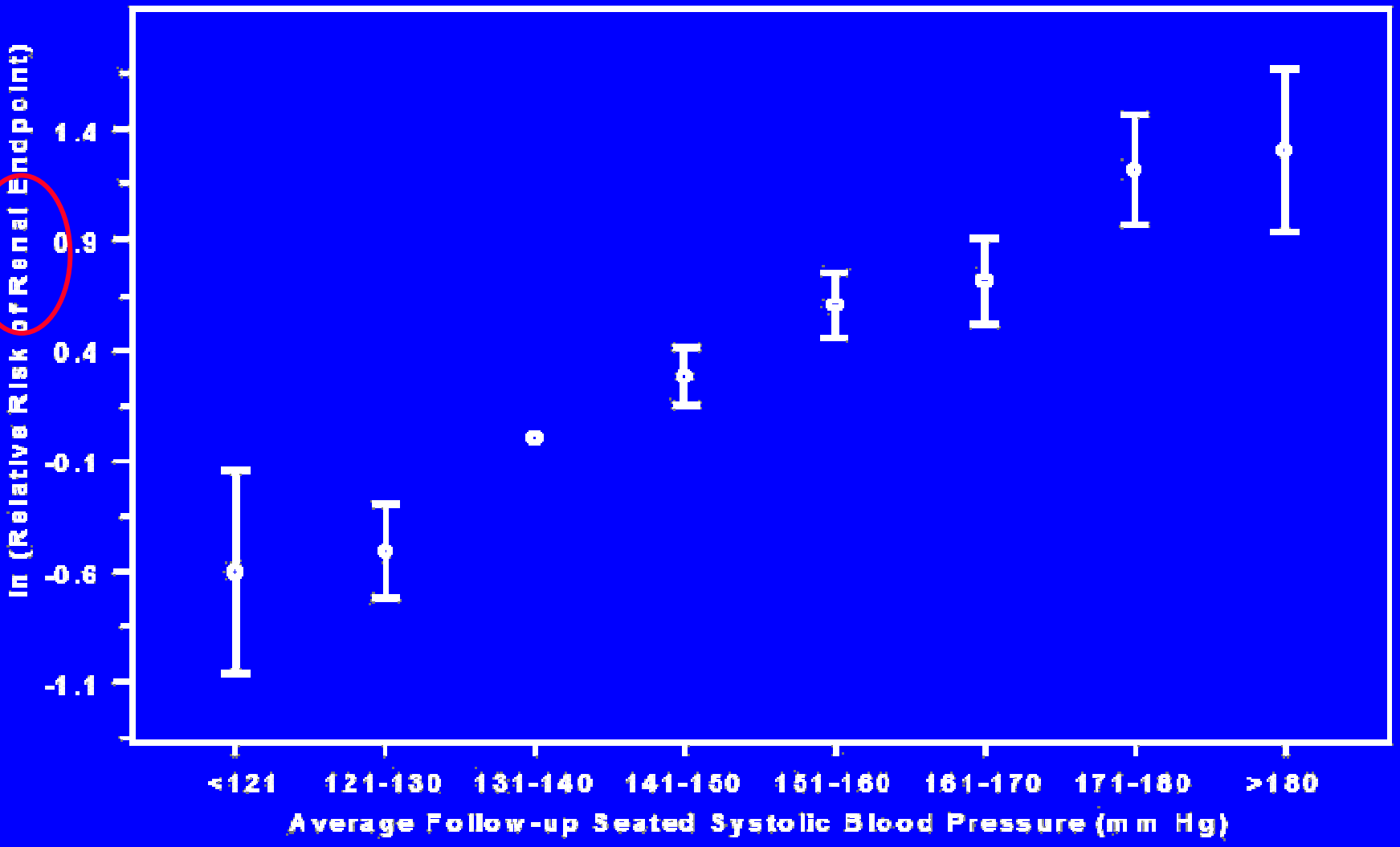
Lewis, New Engl J Med (2001) 345:851

Systolic, Mean, and Diastolic BP



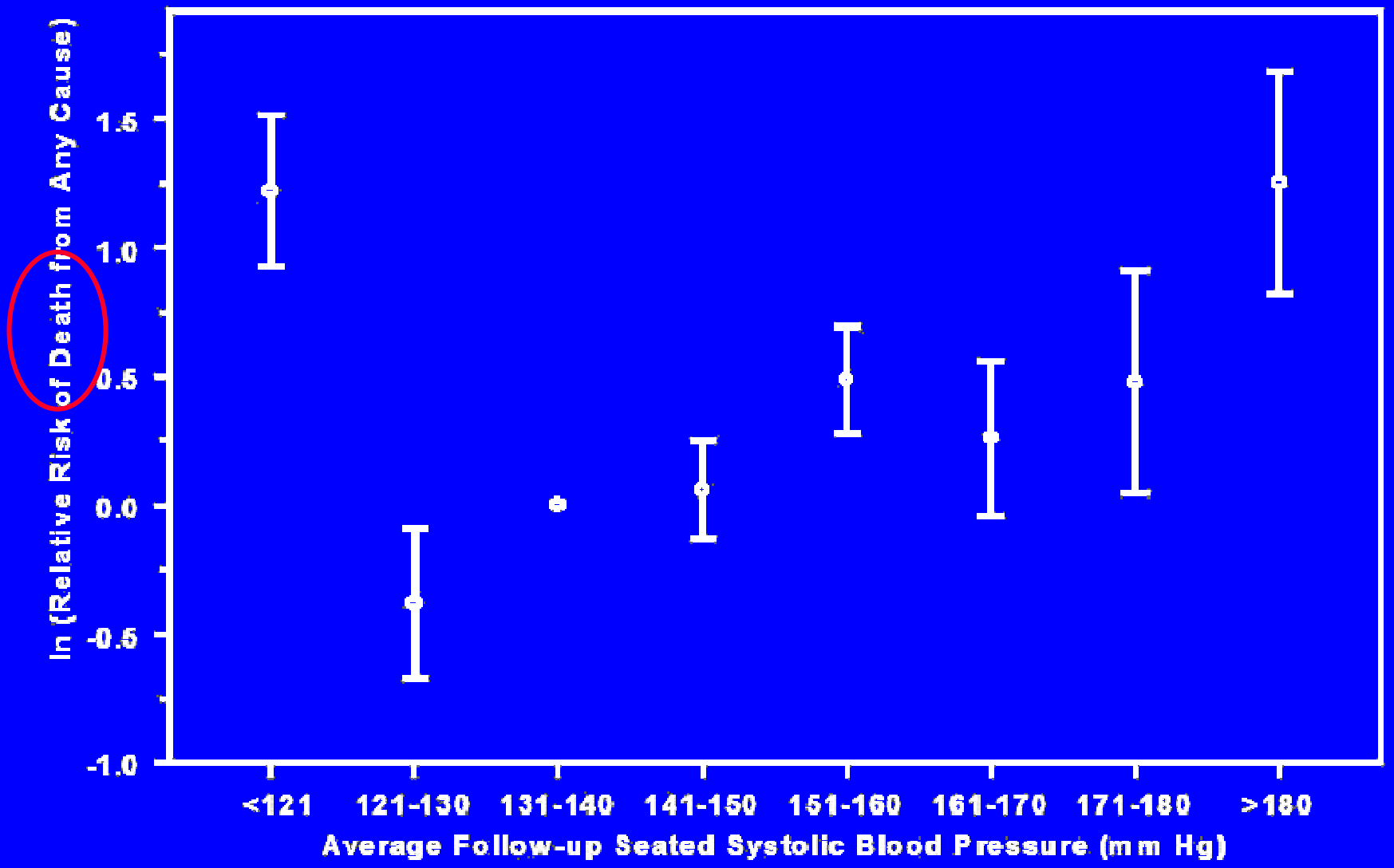
Lewis EJ et al. N Engl J Med 2001;345:851

IDNT: Achieved Systolic Pressure and Renoprotection



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

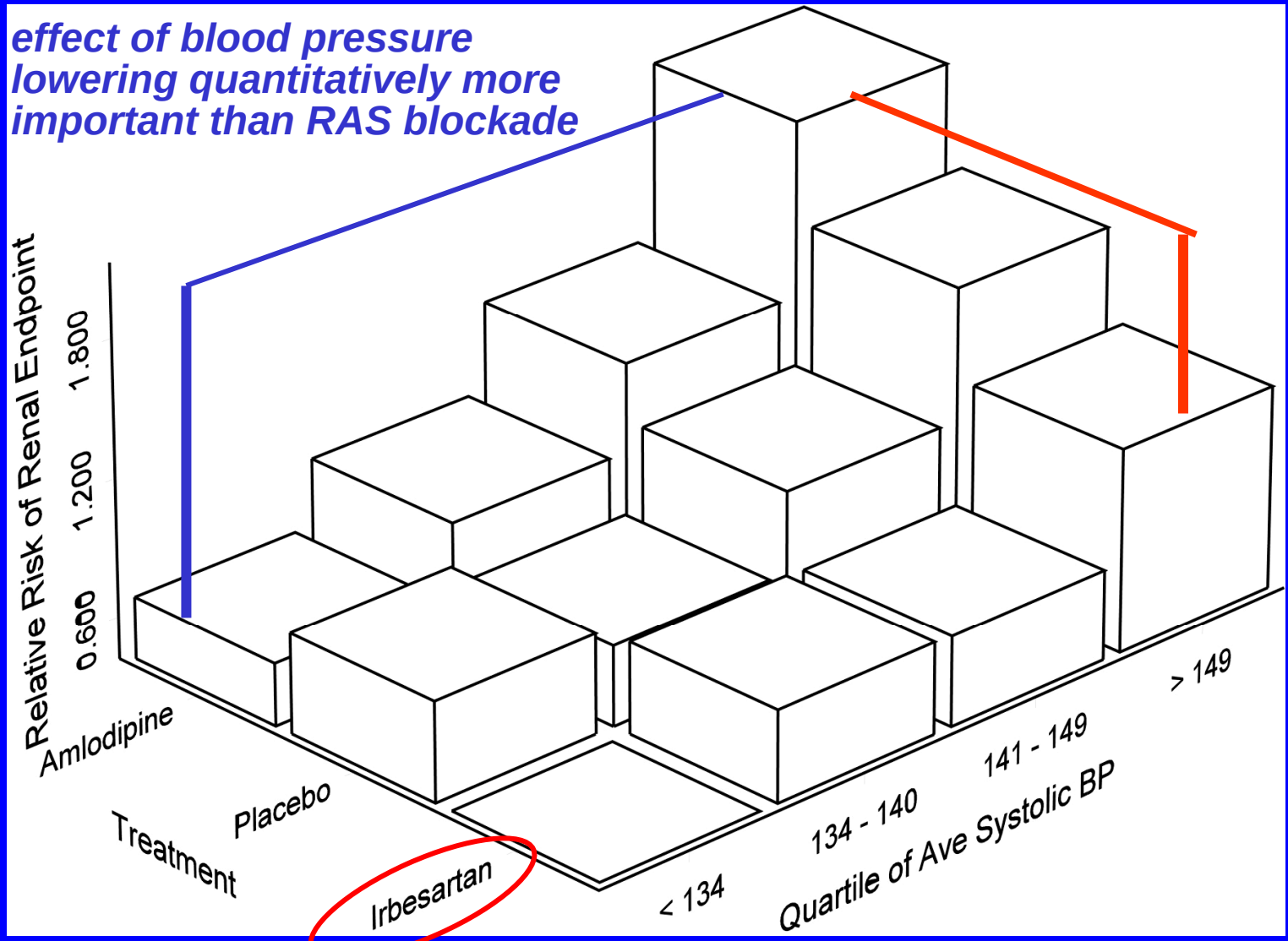
IDNT: Achieved Systolic Pressure and Mortality



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

Relative contribution of achieved BP lowering and RAS inhibition on renal outcome

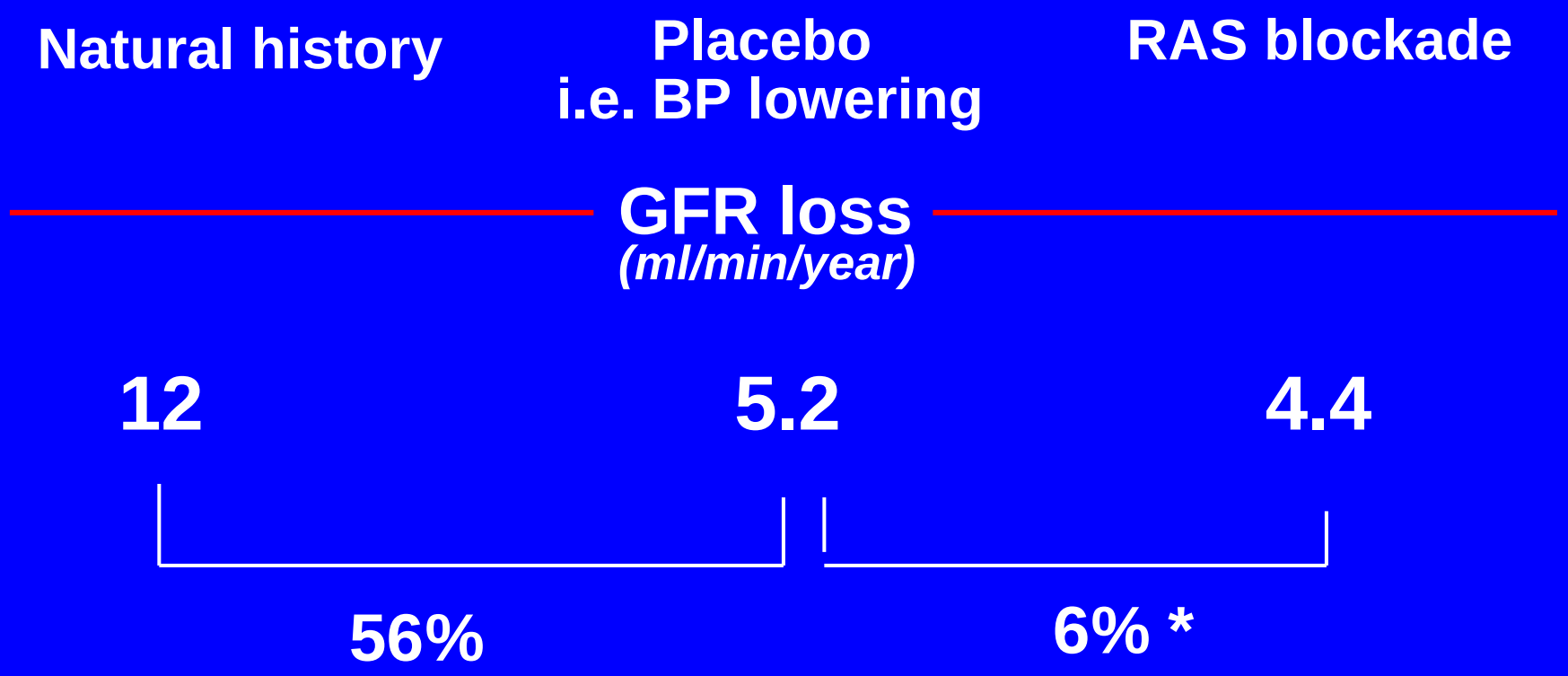
(IDNT study)



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

Blood pressure lowering vs RAS blockade

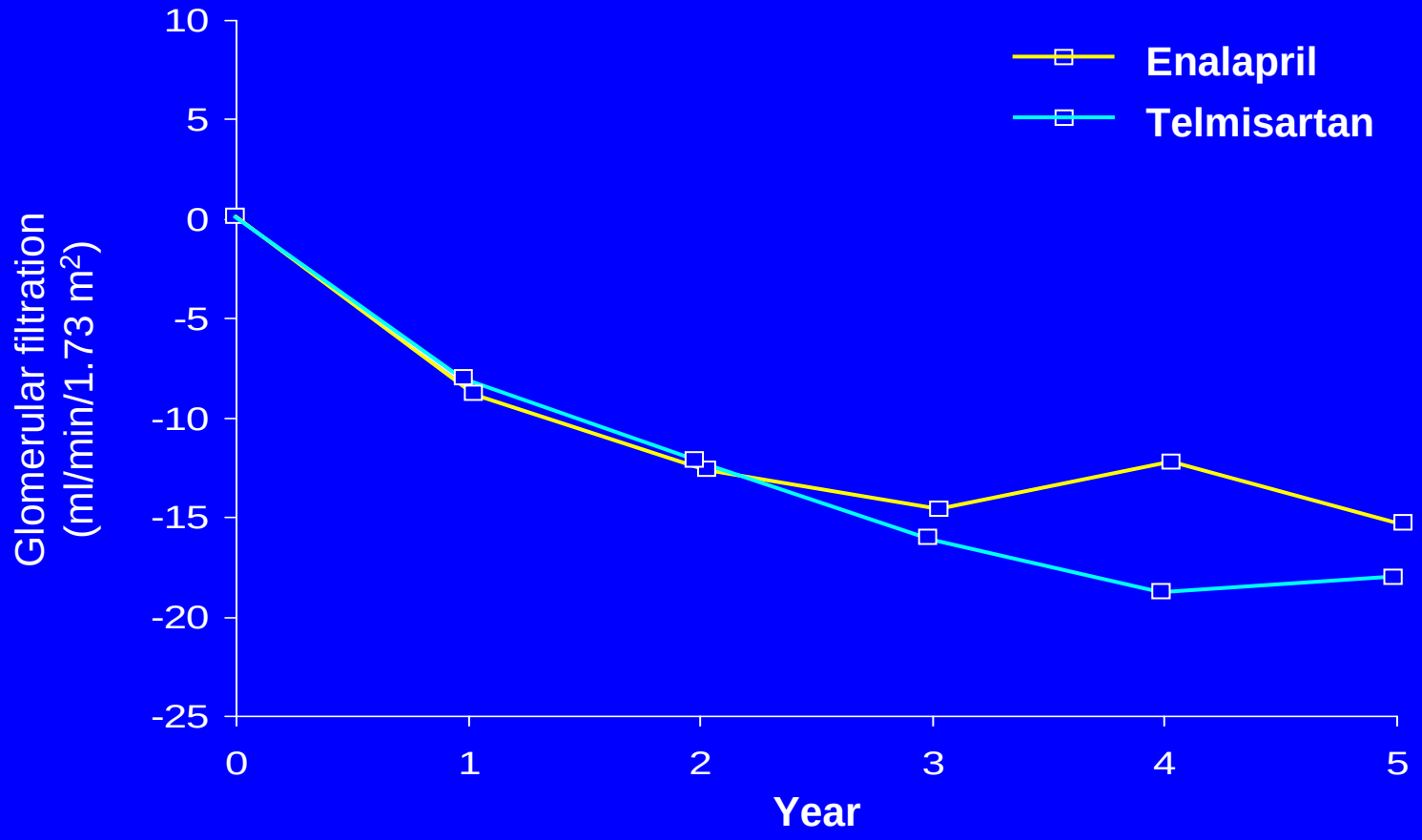
RENAAL study



Brenner, New Engl J Med (2001) 345:861

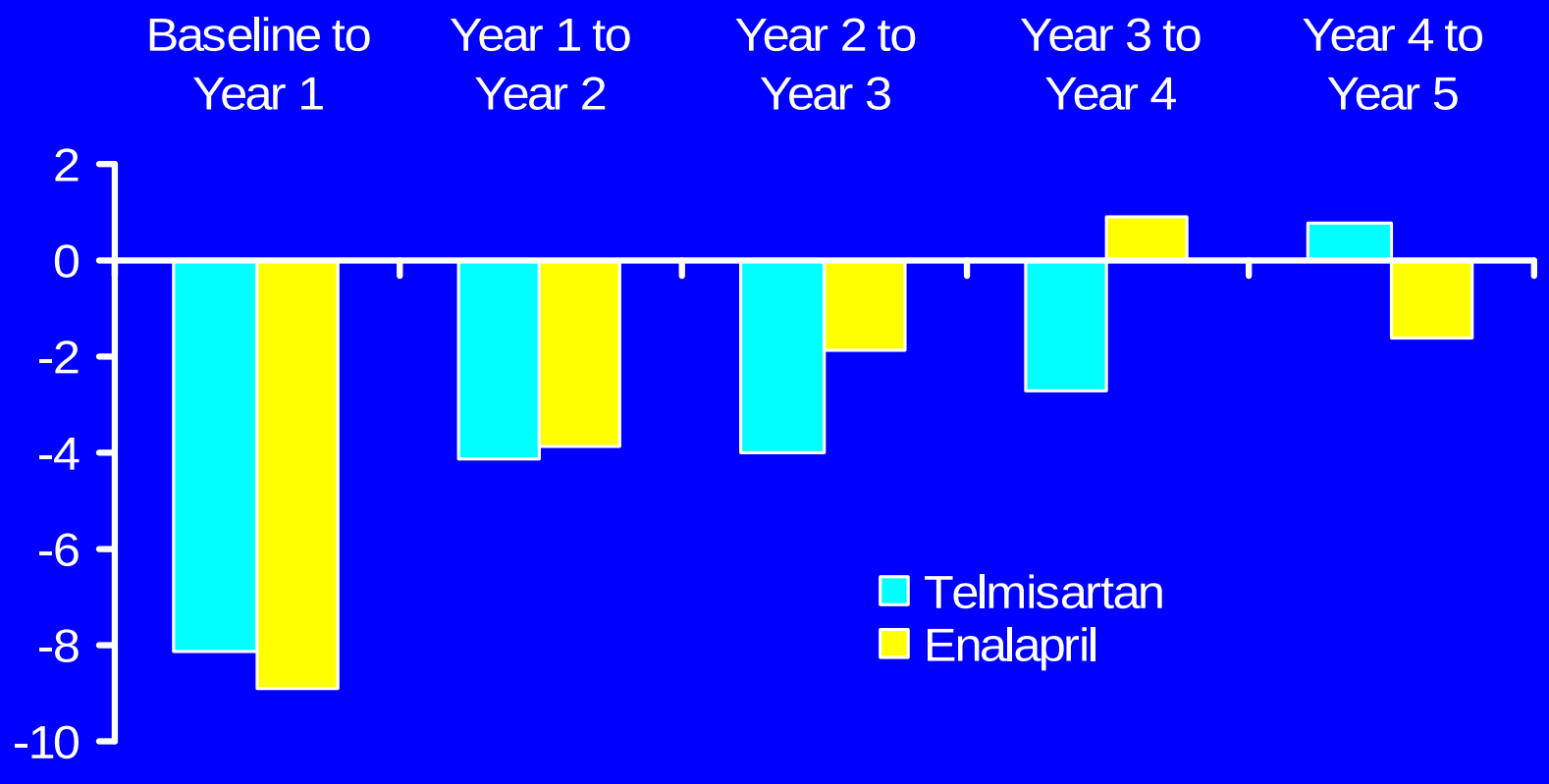
Diabetic nephropathy : start of treatment in early stage

► progressive reduction of GFR loss



Barnett, New Engl J Med (2004) 351:1952

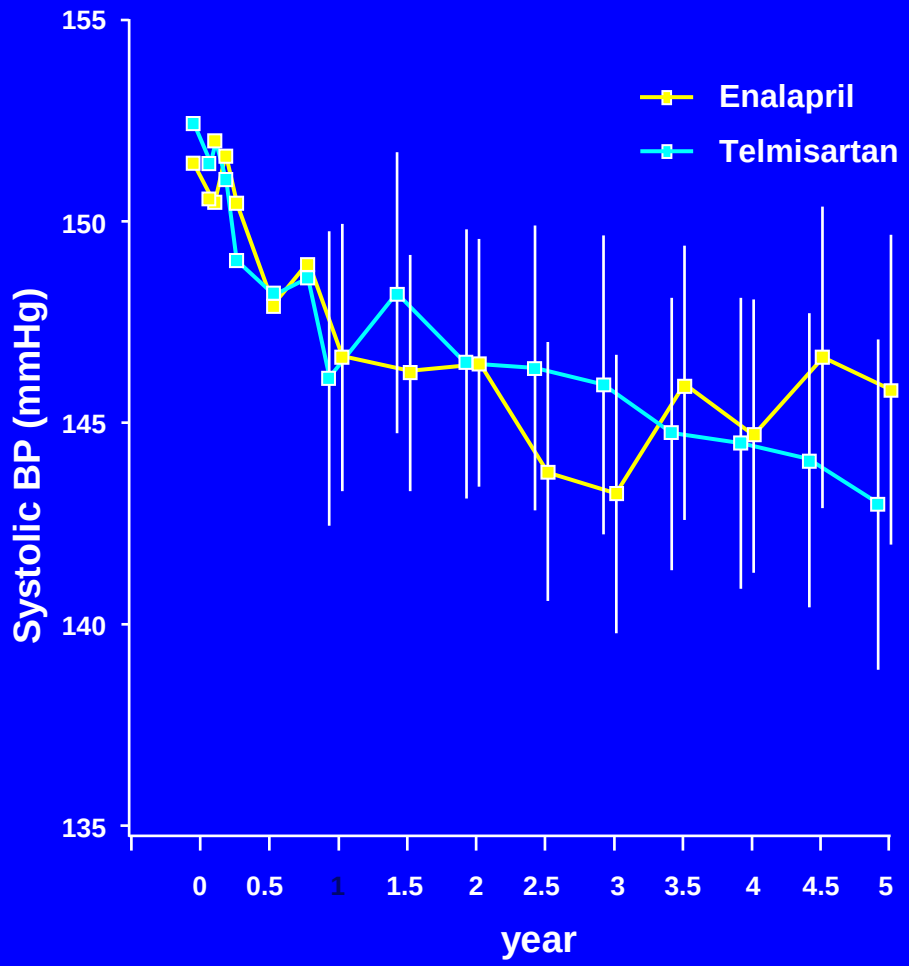
Annual change in GFR

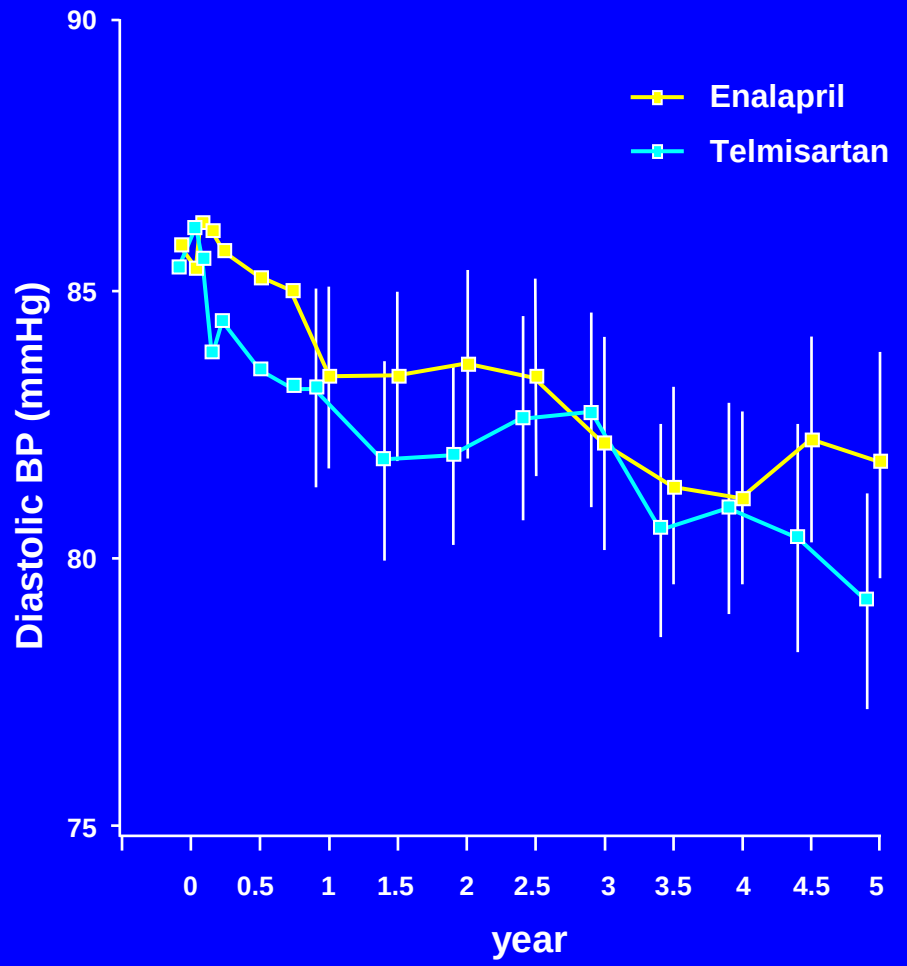


Δ ml/min/year

Barnett, New Engl J Med (2004) 351:1952

Improvement of GFR loss in early diabetic nephropathy – depite substandard blood pressure control

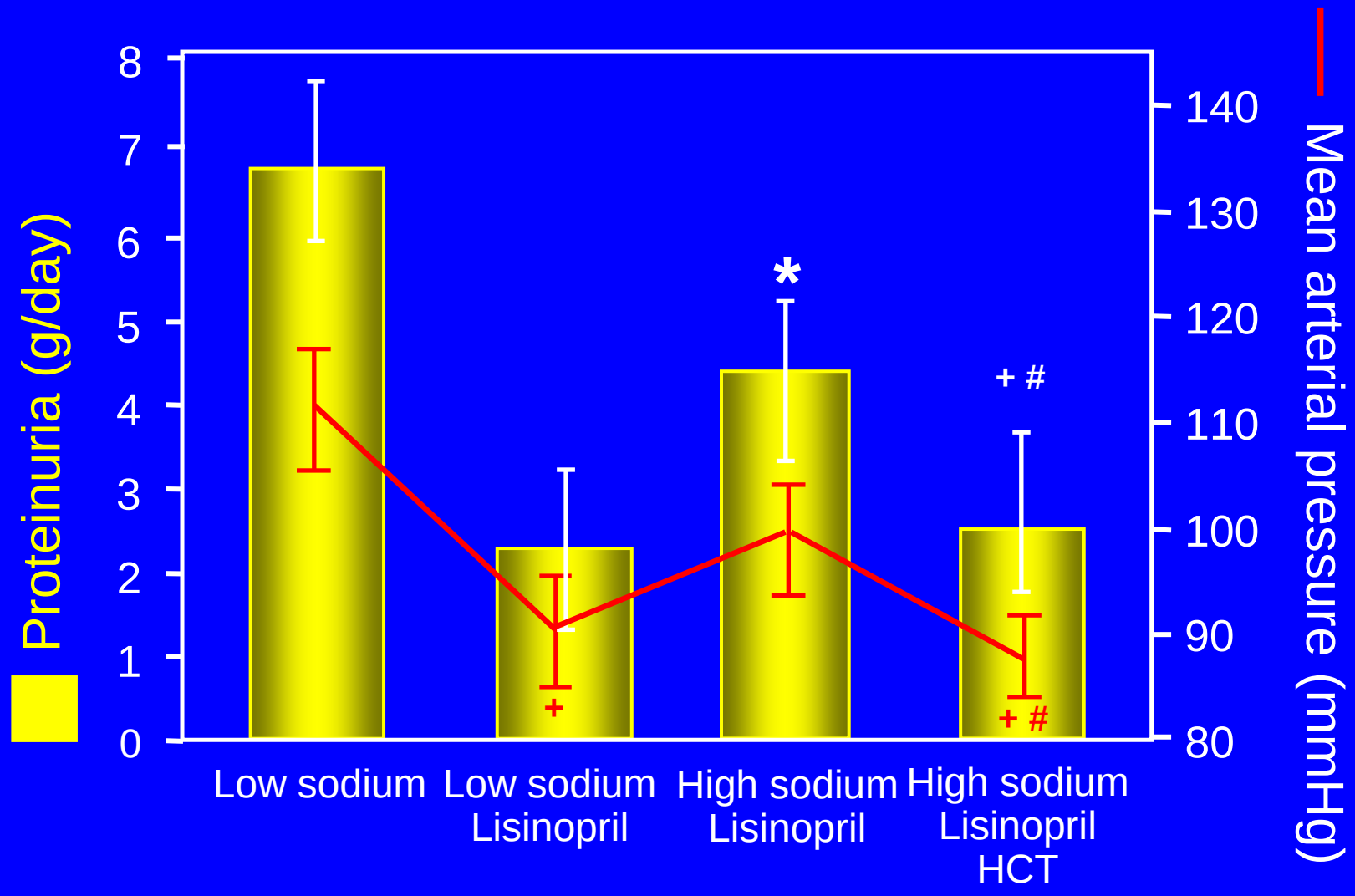




Barnett, New Engl J Med (2004) 351:1952

Antiproteinuric action of ACE inhibition -

effect of low sodium diet and hydrochlorothiazide (HCT)



Buter, Nephrol. Dial. Transpl. (1998) 13:1682

45 patients type 2 diabetes

early nephropathy

40 weeks Trandolapril

urinary albumin -40%

18/40 patients aldosterone escape

→ 25mg/d Spironolactone

no change in blood pressure

significant reduction of albuminuria

Sato, Hypertension (2003) 41: 64

Intensified multifactorial treatment

80 patients randomly assigned

 # conventional treatment (GPs)
in accordance with national guidelines

 # intensified multifactorial intervention

- **targets:** **hyperglycemia**
  hypertension
  dyslipidemia

- **endpoints:** **microalbuminuria**
  CV disease *(secondary prevention)*

Gaede, NEJM (2003) 348, 383

Intensified treatment ⇨ lower risk of:

• CV disease	hazard ratio	0.47 (0.27-0.73)
• nephropathy		0.39 (0.17-0.87)
• retinopathy		0.42 (0.21-0-86)
• autonomic polyneuropathy		0.37 (0.81-0.79)

Gaede, NEJM (2003) 348, 383

Differences between groups at the end of the study

	conventional	intensified
systolic BP (mmHg)	-3	-14
Smoking	-6 pat.	-5 pat.
fasting glucose (mg/dl)	-18	-52
HbA_{1C} (%)	+0.2	-0.5
TG (mg/dl)	+9	-41
LDL-C (mg/dl)	-13	-47
Urinary albumin (mg/24h)	+30	-20

Gaede, NEJM (2003) 348, 383

Thank you for your attention

Diabetic nephropathy

Eberhard Ritz
Heidelberg (Germany)

Epidemiology of diabetes
Prevention of diabetes
Diagnosis of diabetic nephropathy
Prevention of diabetic nephropathy
Management of the diabetic with nephropathy
The uremic diabetic predialysis

Assessment of Patients with Diabetes and Renal Failure

- Rate of progression
- Chronic renal failure, acute renal failure, „acute on chronic“ RF
- Renal problems other than diabetic nephropathy (ischemic nephropathy, cystopathy, urinary tract infection)
- Monitoring for extrarenal complications
  - Microvascular (retinopathy, neuropathy)
  - Macrovascular (coronary heart disease, carotid, lower extremity)

Renal Problems in the Patient with Type 2 Diabetes

- Diabetic nephropathy (Kimmelstiel-Wilson)
- Ischemic nephropathy (atherosclerotic renal artery stenosis, cholesterol microembolism)
- Urinary tract infection (± papillary necrosis)
- Glomerulonephritis (membranous glomerulonephritis)
- Acute renal failure (radiocontrast, nephrotoxic agents, cardiac problems)
- Cystopathy (detrusor paresis) and obstructive uropathy

Differential Diagnosis of Hypertension in Diabetes Mellitus

Type 1

Renoparenchymal hypertension (diabetic nephropathy)

Type 2

Primary hypertension

Renoparenchymal hypertension (diabetic nephropathy)

Renovascular hypertension (atherosclerotic renal artery stenosis)

Isolated systolic hypertension

Pseudohypertension

Secondary hypertension (e.g. Cushing, pheochromocytoma)

Hypertension in the Diabetic Patient With Renal Failure

- Exquisitely volume sensitive
- High ANG II concentration
  further factors:
- Diminished aortic compliance
  (High BP amplitude)
- Disturbed baroreceptor reflex
  (Autonomic polyneuropathy)
  - → Supine hypertension/orthostatic hypotension
- Disturbed autoregulation (cerebral)

Common Problems during Antihypertensive Treatment of Diabetics with Renal Failure

- Deterioration of metabolic control
- Hyperglycemia
- Orthostatic hypotension
- Variable absorption of antihypertensive drugs
  (Gastroparesis)
- Neuropathic edema simulating fluid overload
- Sexual dysfunction
- Claudication
- Deterioration of lipid profile

Cardiac Problems in Diabetic Patients on HD

prospective study, inception cohort

diabetic vs. non-diabetic

more prevalent

- LVH	**(50 vs. 38%)**
- Heart failure	**(58 vs. 24%)**
- IHD	**(32 vs. 18%)**

odds ratio to develop heart failure

- LVH	**5.4**
- LV dilatation	**13.7**
- systolic dysfunction	**26.7**

Foley, Diabetologia, (1997) 40:307
Foley, NDT, (1998) 13:1112

Glycemic Control

Poor glycemic control → poor survival

Wu, Nephrol.Dial.Transplant, (1997) 12: 2105

Glycemia → thirst

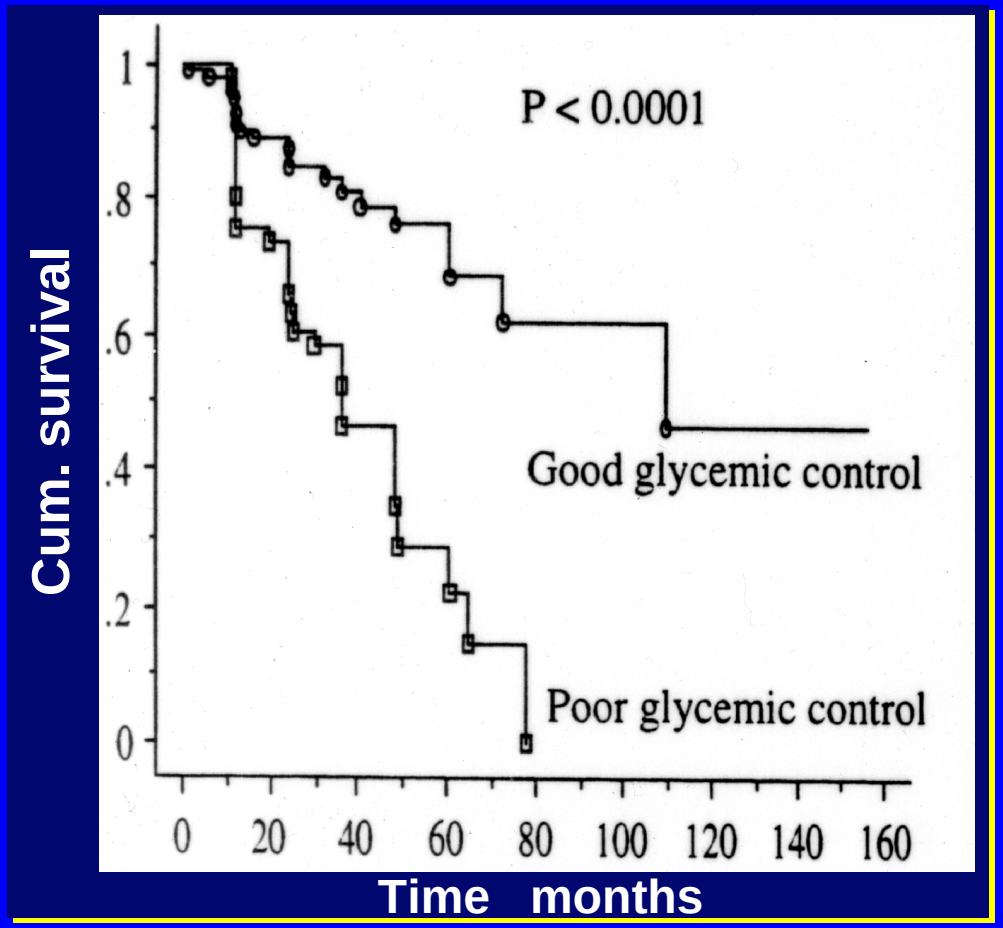
hypervolemia

hyperkalemia

Poor Predialysis Glycemic Control –

Predictor of Mortality on Maintenance Hemodialysis

Type 2 diabetes



Wu, Nephrol.Dial.Transplant, (1997) 12: 2105

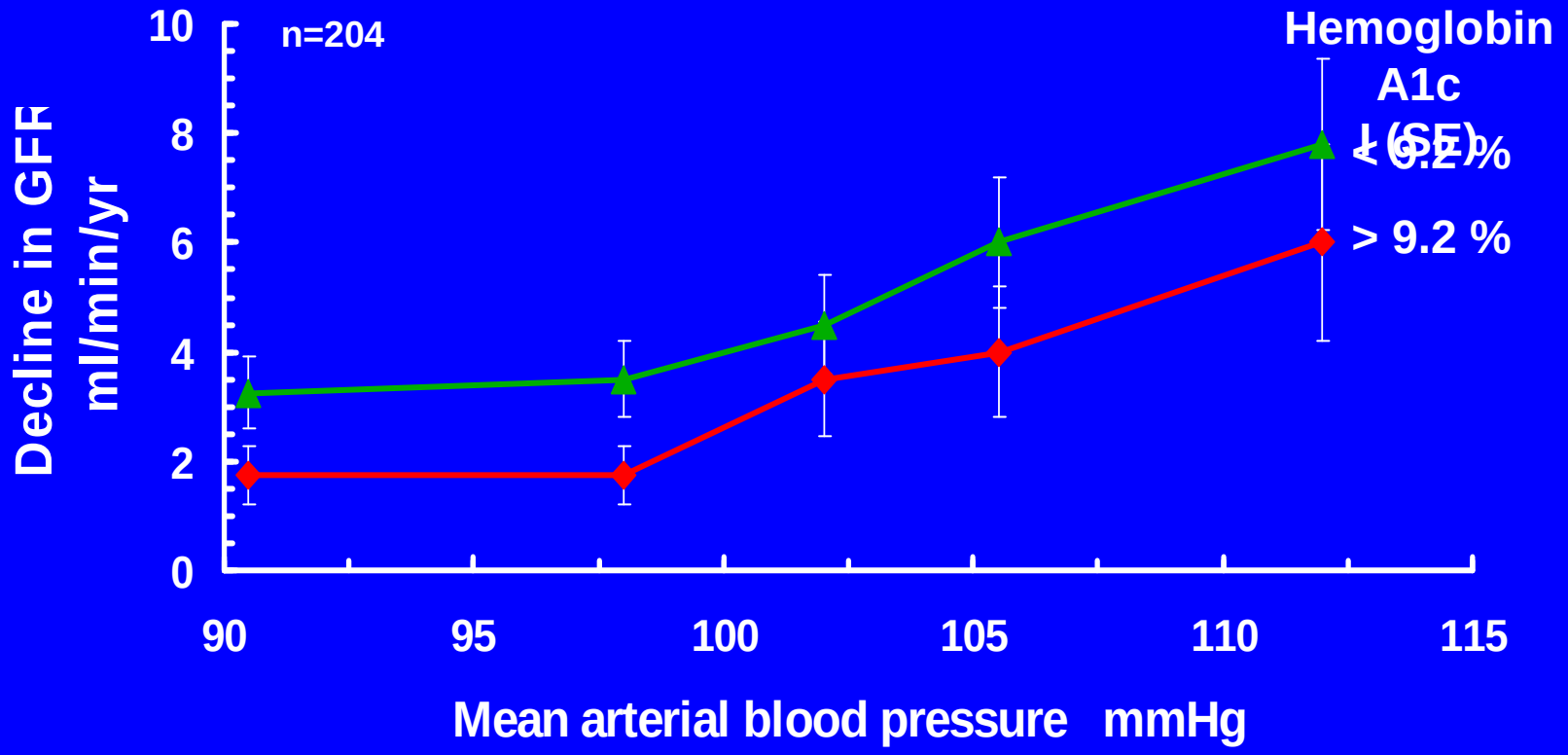
Glycemic Control

- **Insulin half life ↑**
- **Sulfonylurea (metabolites) cumulation**
  Except gliquidone, glimepirid
- **Insulin resistance**
  Circulating inhibitory factors removed by dialysis

→ **Predictibility of net effect on glycemia poor**

→ **Monitor glycemia**

Impact of BP and HbA1c on Decline in GFR in Diabetic Nephropathy



HH Parving, personal communication

Diabetic Neuropathy

- Sensorimotor (glove and stocking)
- Mononeuritis multiplex
  (including monomelic neuropathy after AV fistula)
- Amyotrophy
- Entrapment syndromes

Diabetic Neuropathy - Autonomic Nerve System

- Gastroparesis (vomiting, temporal dissociation insulin/absorption of food)
- Diarrhea/obstipation (± intestinal overgrowth)
- Detrusor paresis (± prostatic obstruction)
- Cardiac (painless MI, absent beat-to-beat variation,anesthesia accidents)
- Supine hypertension/orthostatic hypotension
- (Neuropathic) diabetic foot

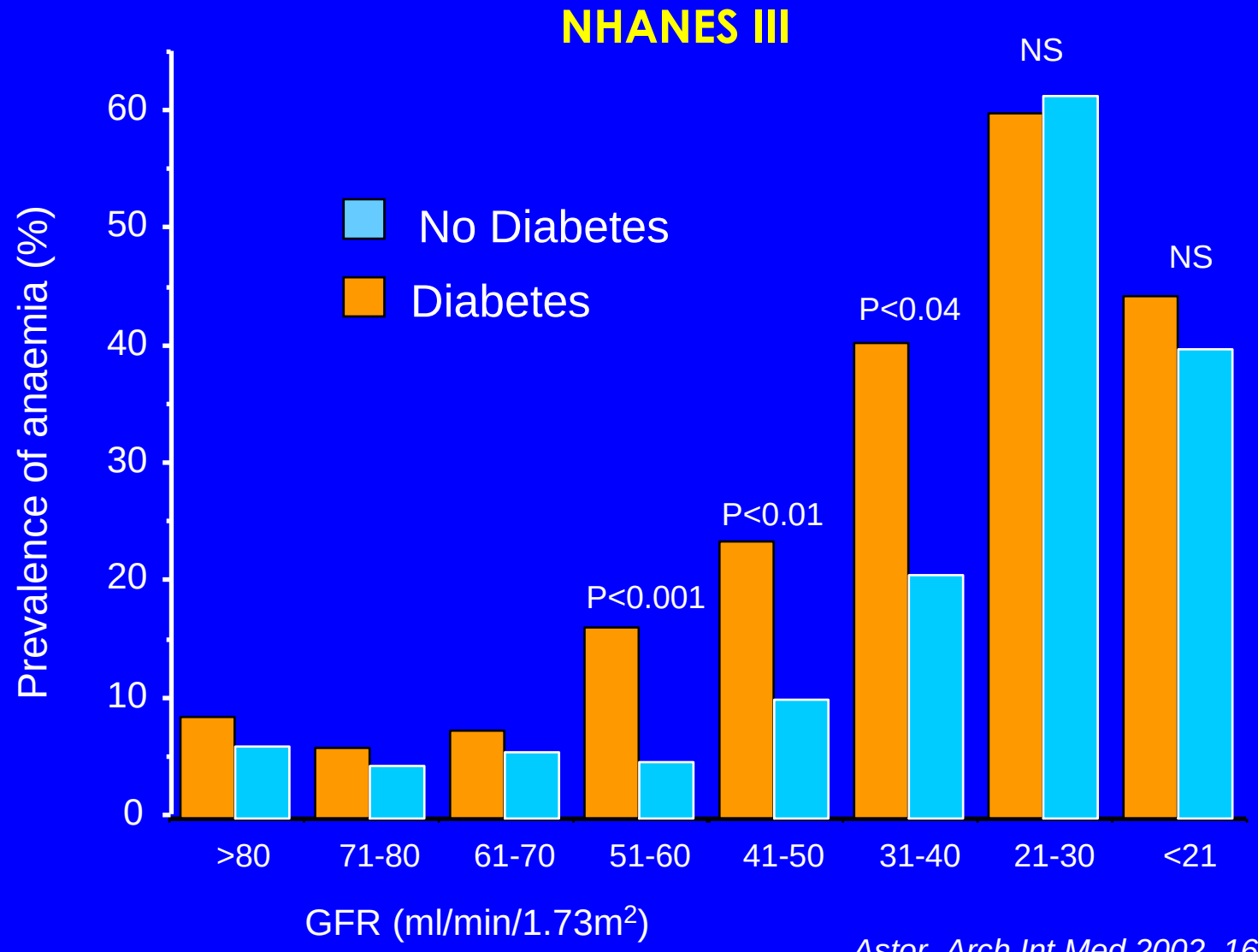
Foot Lesions in Diabetic Patients

Neuropathic	Ischemic
Painless	Painful (intermittent claudication)
Foot warm, pink	Foot cold and livid
Foot pulses ++ (unless severe edema present)	Foot pulses attenuated or absent
Sensation impaired	Sensation unimpaired
Painless metatarsal ulcer	Acral necrosis (tip of toe,heel)
Necrosis below callus	

Neuropathic Foot

- Acute intervention
  - Infection control (mixed aerobic/anaerobic)
  - (Limited!) amputation (patience!)
- Prevention
  - Footwear (shoes)
  - Podiatrist
  - Avoidance of trauma (heat, mechanical)

Prevalence of anaemia according to GFR in patients with and without diabetes



Astor, Arch Int Med 2002, 162, 1401

Diabetic nephropathy

Eberhard Ritz
Heidelberg (Germany)

Epidemiology of diabetes
Prevention of diabetes
Diagnosis of diabetic nephropathy
Prevention of diabetic nephropathy
Management of the diabetic with nephropathy
The uremic diabetic predialysis
Options in terminal uremia :

- ***hemodialysis***
- ***CAPD***
- ***transplantation***
  - ***-isolated kidney***
  - ***-kidney plus pancreas***
  - ***-pancreas after kidney***

The Sad Truth About Hemodialysis in Diabetic Nephropathy

Mehdi Ghavamian, MD; Charley F. Gutch, MD; Klaus F. Kopp, MD; and Willem J. Kolff, MD, PhD

Nine patients with renal failure resulting from diabetic nephropathy were treated by hemodialysis. Average duration of diabetes was 21 years, and mean duration of nephropathy was 26 months. One patient survives after more than three years. Others survived for 9, 20, 19, and 13 months, respectively. Overall mortality was 78% at the end of one year.

All patients had problems with clotting or infection of bloodstream access routes or both. All had further visual deterioration. Neuropathy was not accelerated. Muscle-wasting, hypoproteinemia, and fluid overload were common. Dialysis for such patients may be considered as a palliative measure with little likelihood of long-term survival or improvement in quality of life.

Although it has been assumed that persons with chronic renal failure due to diabetic nephropathy do poorly with long-

al,[1] also in 1971, described 12 diabetics accepted into a home dialysis training program. Nine of these were juvenile diabetics. The authors believed dialy-

25 years, and its duration was from 14 to 30 years (average, 21 years). All had had moderate to severe proteinuria for one to five years prior to terminal renal failure. Peripheral neuropathy, present for two to eight months, was demonstrable in seven patients at the time dialysis was begun. Whether this was diabetic or uremic in origin, or a combination of the two, could not be determined. Advanced retinopathy with hemorrhage was present in all, and seven were blind. A 41-year-old woman had previously undergone bilateral above-knee amputation, and a 33-year-old man had had a toe amputation. Hypertension, severe proteinuria, ane-

Begin of Dialysis

- Earlier than in non-diabetic patients?
- C_{cr} 15 ml/min (S-creatinine underestimates!)
- Dialysis for reasons other than GFR
  - Recurrent pulmonary edema (LV malfunction)
  - Vomiting (gastroparesis + uremia)
  - Cachexia

Diabetes mellitus

“a melting down of the flesh into urine“

Aretaeus, 250 AD

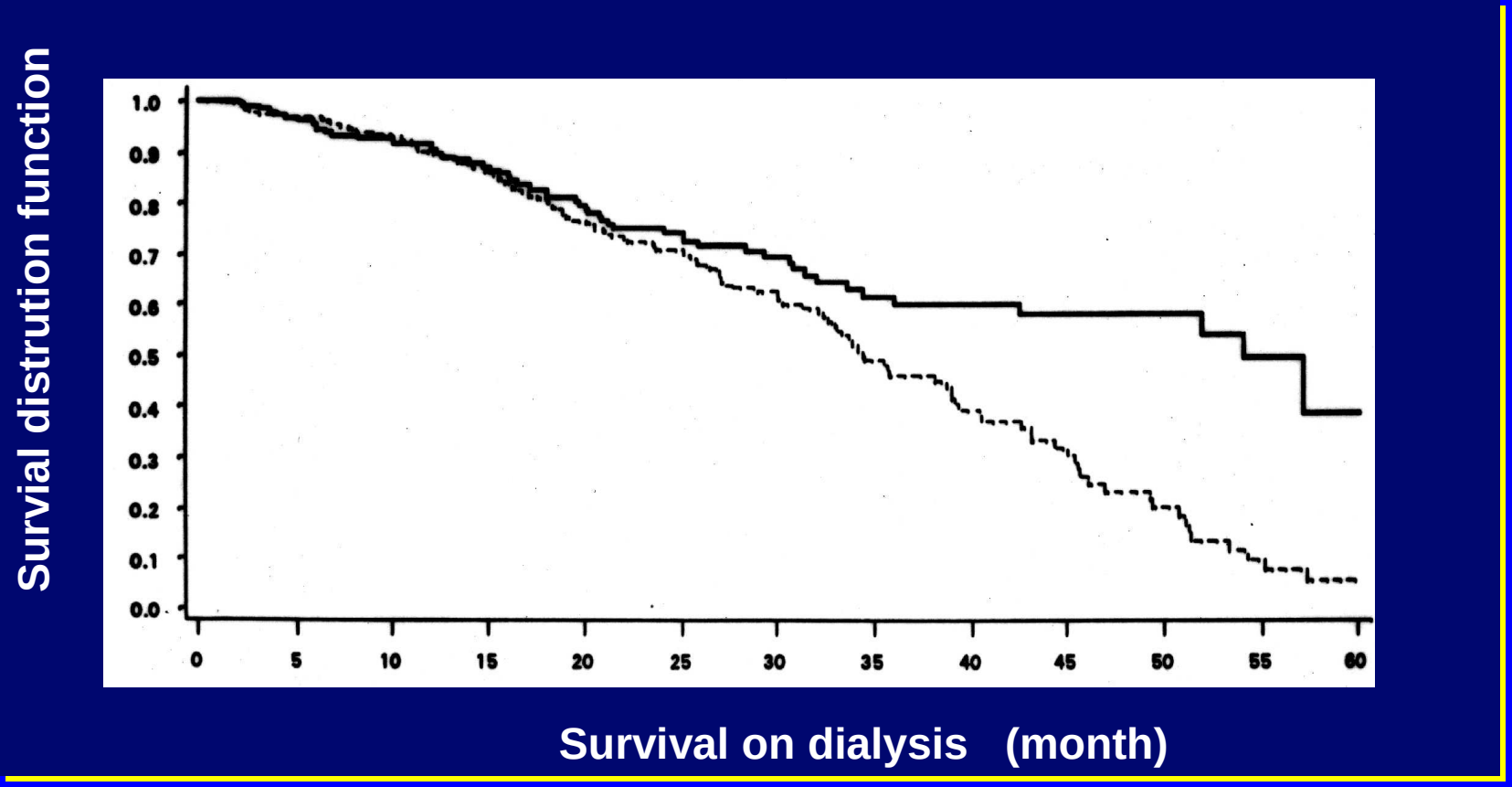
Acute on Chronic Renal Failure

- Radiocontrast
- Antiinflammatory agents, aminoglycosides, (ACE inhibitors)
- Low cardiac output (MI, arrhythmia, hypovolemia)

Options for the Uremic Diabetic Patient

- Hemodialysis
- CAPD
- Renal transplantation
- Combined kidney/pancreasTX
- Pancreas after kidney

Survival of 412 Diabetic Patients with End-Stage Renal Failure



Koch,Nephrol.Dial.Transplant.(1997) 12: 2603

Hypotensive Episodes on Dialysis in Patients with Type 2 Diabetes - Risk of Cardiac Death

1985 - 1994

Prospective study, 35 German dialysis centers

593 diabetic patients admitted

- **181 type I**
- **412 type II**

- **Hypertension 94 %**
- **Smoking 46% (type I), 31% (type II)**
- **Total cholesterol 243 ± 71 mg/dl**
  LDL cholesterol 165 ± 56 mg/dl
  Lp(a) 32 ± 27 mg/dl

Koch,Nephrol.Dial.Transplant.(1997) 12: 2603

Which $HbA1_c$ is optimal on dialysis ?

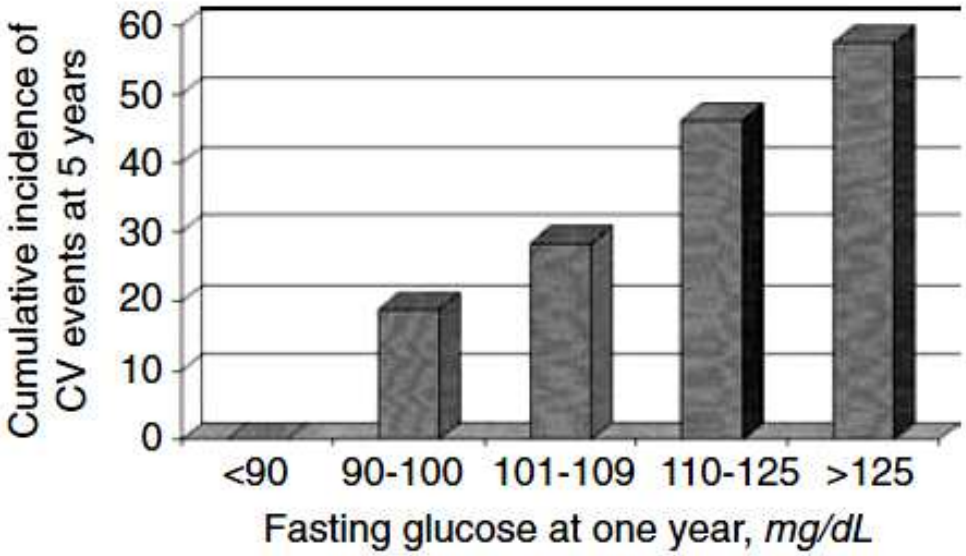
1568 Japanese hemodialysis patients with and 3342 without diabetes
mortality hazard ratio in diabetics 1.37

Quintile	$HbA1_c$	hazard ratio
1	4.5	1
2	5.2	1.23
3	5.9	0.98
4	6.7	1.07
5	8.2 (7.3-19.9)	2.38

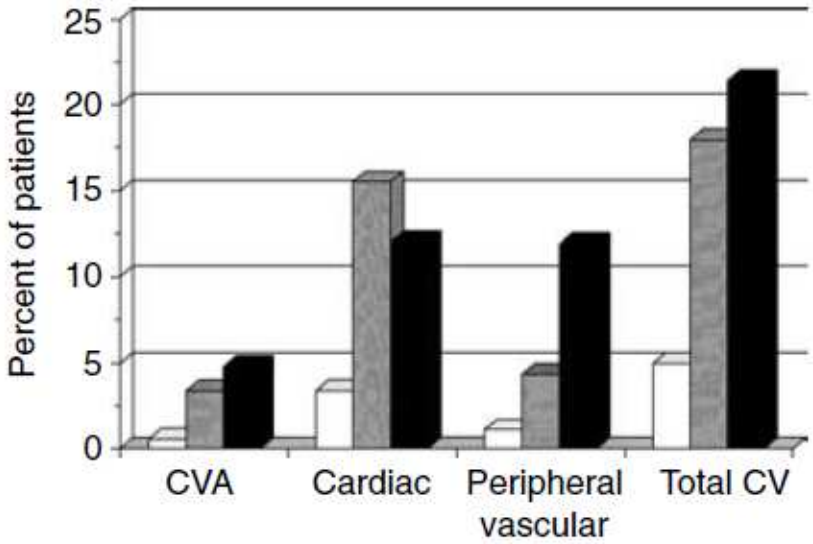
► keep HbA1c below 7.3%

Hayashino, Diabetologia (2007) 50:1170

Type 2 diabetes after transplantation – incidence and type of CV events



cumulative CV events at 5 years according to fasting glucose at 1 year

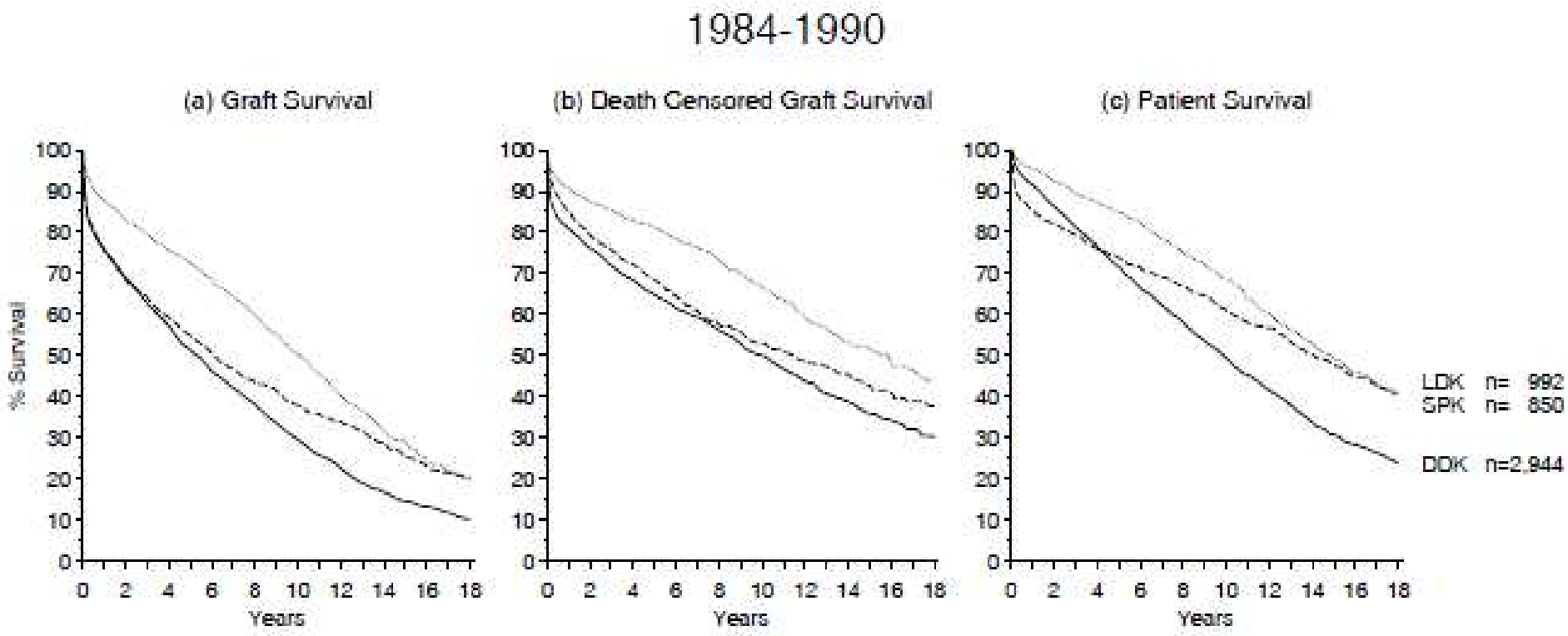


incidence of specific CV events according to fasting glucose at 1 year:
normal
IFG
diabetes

Cosio, Kidn.Intern.(2005)67:2415

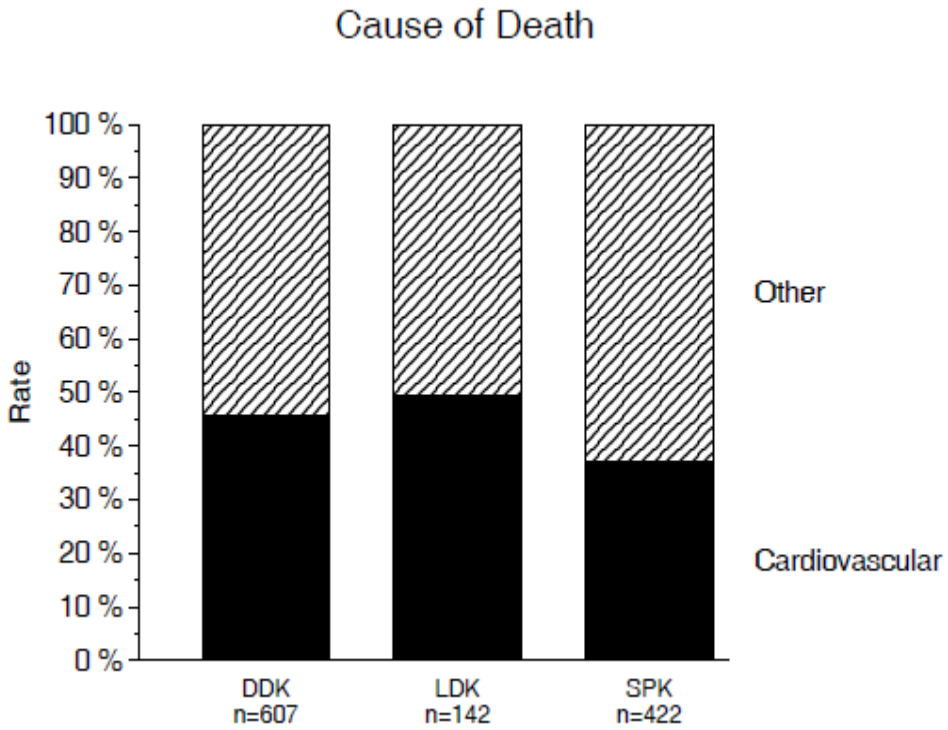
Graft and patient survival

life-donor(LDK) and dead donor (DDK)kidney transplantation vs. simultaneous pancreas-kidney(SPK)



Morath, J.Am.Soc.Nephrol. (in press)

Causes of death in dead donor (DDK), life donor (LDK)and simultaneous pancreas-kidney transplantation (SPK)



Morath, J.Am.Soc.Nephrol. (in press)

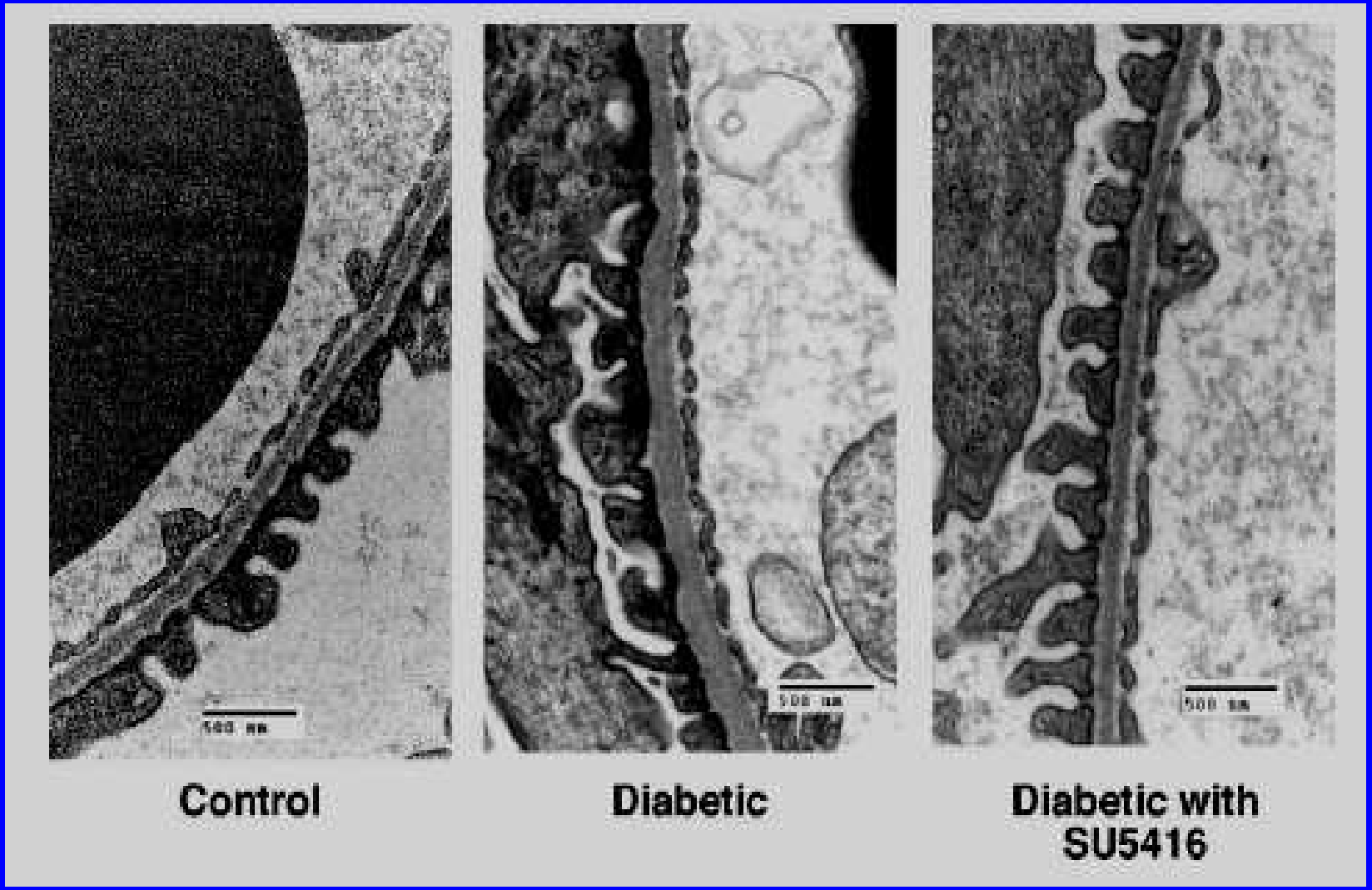
What did he say ?

- Diabetes type 2 rising **prevalence** and partially **preventable**
- Early **diagnosis** of diabetic nephropathy: **microalbuminuria** (MA)
- **Prevention of MA**: near normoglycemia, target blood pressure, RAS inhibition, cessation of smoking
- Diabetic with **renal failure**; main problems hypertension, cardiac disease, diabetic foot (neuropathic, vascular), specific problems of glycemic control, anemia
- Diabetic with uremia; options : hemodialysis, PD, renal TX or renal + pancreas (type 1; type 2?)

Artist : chimpanzee Congo (age 3 years)
Supervisor : Desmond Morris

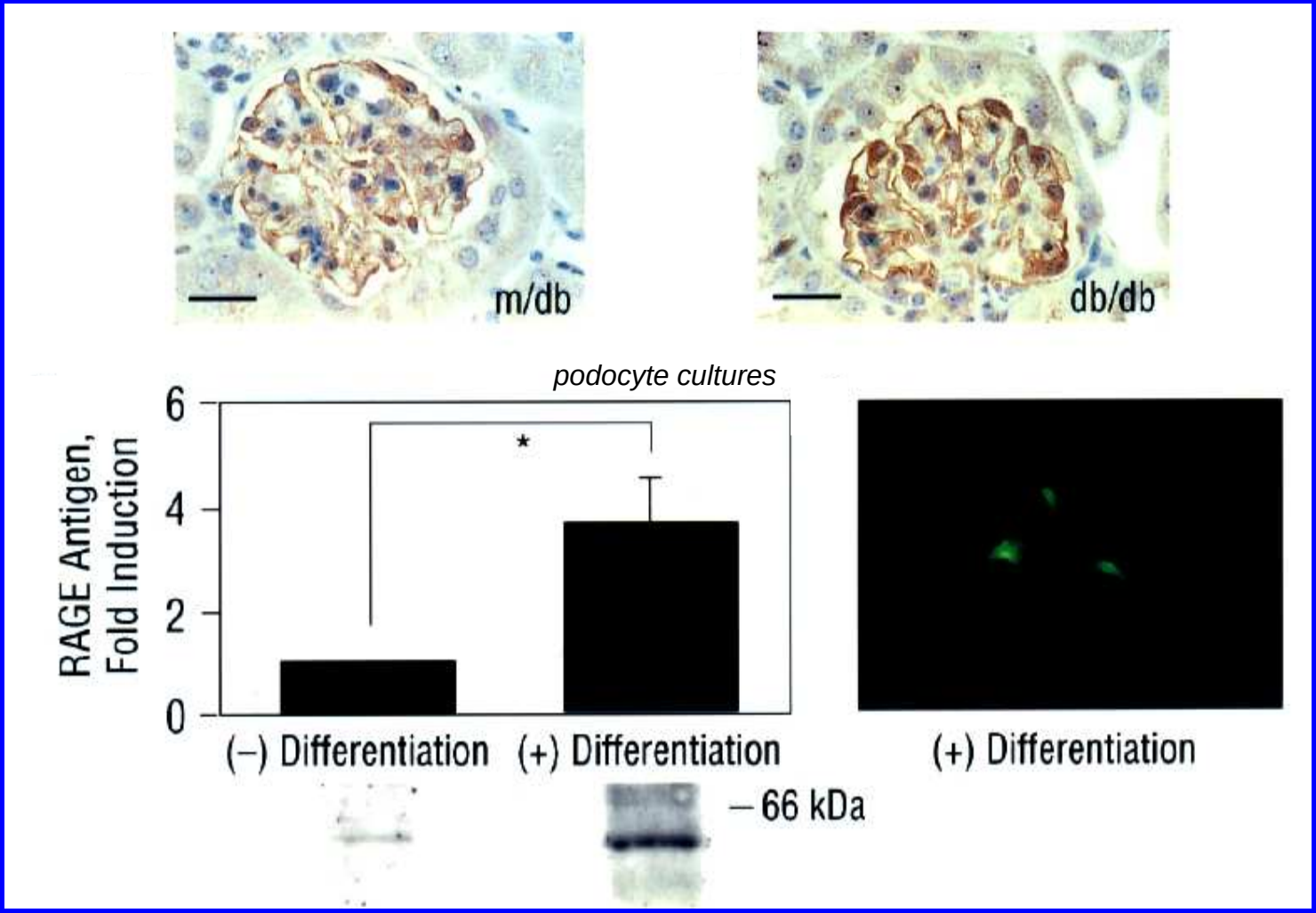
Nature (2005) 435: 1040

The VEGF receptor tyrosine kinaseantagonist SU5416 prevents thickening of the glomerular basement membrane in diabetic mice



Sung, J.Am.Soc.Nephrol.(2006) 17:3093

Expression of RAGE by podocytes in diabetes (db/db mouse)



Wendt, Am.J.pathol.(2003) 162:1123

Prevention of loss of renal function (GFR)

 # BP lowering ~ 120/70 mmHg

 # ACE inhibitors

type 1

Lewis, NEJM (1993) 329: 1456

 # angiotensin receptor blockers

type 2

Irbesartan (IDNT), NEJM (2001) 345: 85
Losartan (RENAAL), New Engl J Med (2001)345: 861

Primary prevention of diabetic nephropathy ? ongoing trials

- **RASS** ***(****renin-angiotensin-system study****) :***

  295 type 1 diabetics, GFR >90 ml/min, BP<

  130/85 mmHg, urinary albumin < 20µg/min

  primary endpoint :

  change of Vv glomerular mesangium over 5 years

- **β-RASS :**

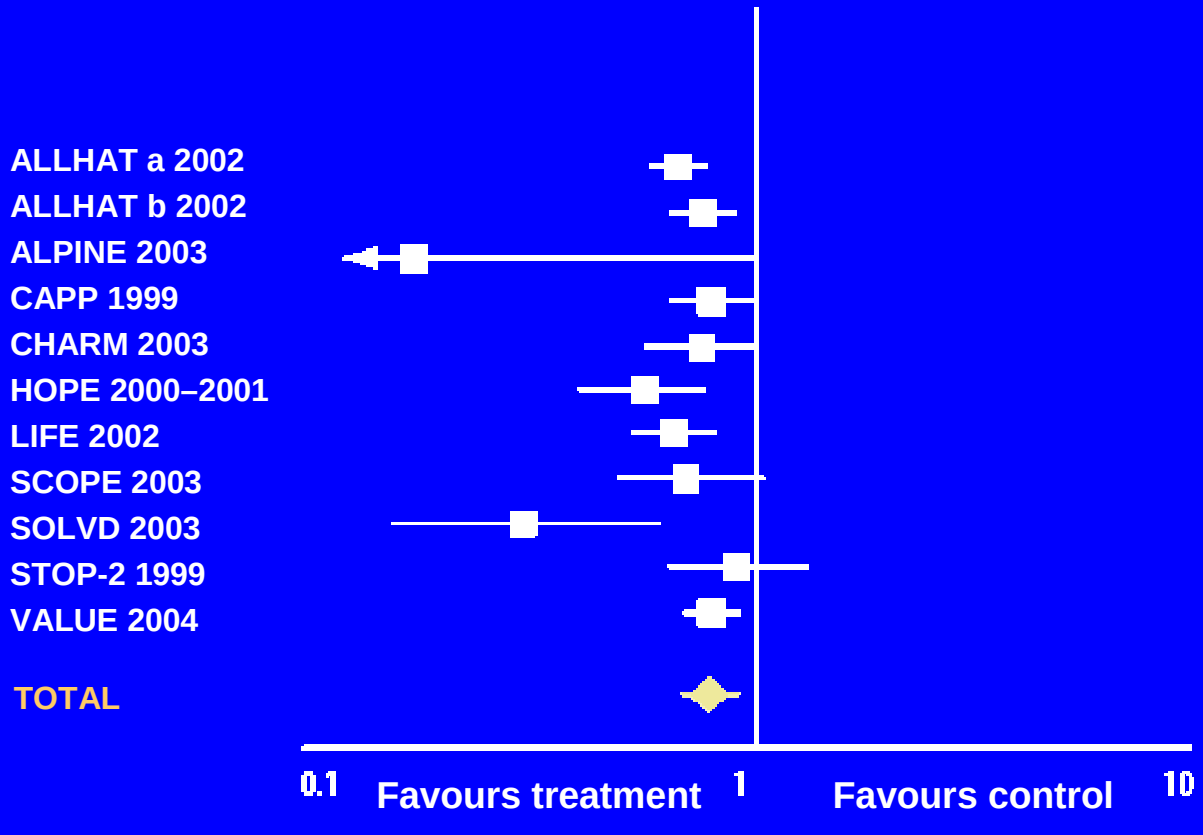
  treatment effects beyond treatment when treatment is discontinued at 10 years

  (~ DCCT/EDIC)

New agents in diabetic kidney disease

- **mineralocorticoid receptor antagonists** *(with maximal RAS inhibition)*
- **[Ruboxistaurin** *(protein C kinase β1 [PKC] inhibitor)]*
- **Pirfedinone** *(antifibrotic TGFβ inhibitor)*
- **Suldeoxide** *(oral chick intestine heparin analogue, heparanase inhibitor, restores electronegative charge of BM, encouraging observational data)*

RAS inhibition reduces risk of new onset diabetes: *Metaanalysis*



Scheen, Diabetes Metab (2004) 30:487

RAS blockade – *improvement of glucose metabolism by multiple mechanisms*

ACE inhibitors and ARBs improve :

- **Insulin signalling**
- **Oxidative stress**
- **Tissue blood flow**
- **Sympathetic activity**
- **Adipogenesis**
- **Potassium balance**
- **β-cell function**
- **Bradykinin and nitric oxide activity**

Control of risk factors in advanced nephropathy of type 2 diabetes –

multicenter cross-sectional analysis :

diabetology, nephrology and primary care

targets	percent patients achieving targets		
	diabetology	*nephrology*	*primary care*
blood pressure <130/80mmHg	13%	14%	10%
total cholesterol < 200 mg/dl	63%	59%	46%
glycemic control HbA1c< 7%	32%	61%	46%
anemia control Hb>12g/dl♂,11g/dl♀	89%	71%	72%

Minutolo, J.Hypertens.(2006) 24:1655

Goal : global cardiovascular risk

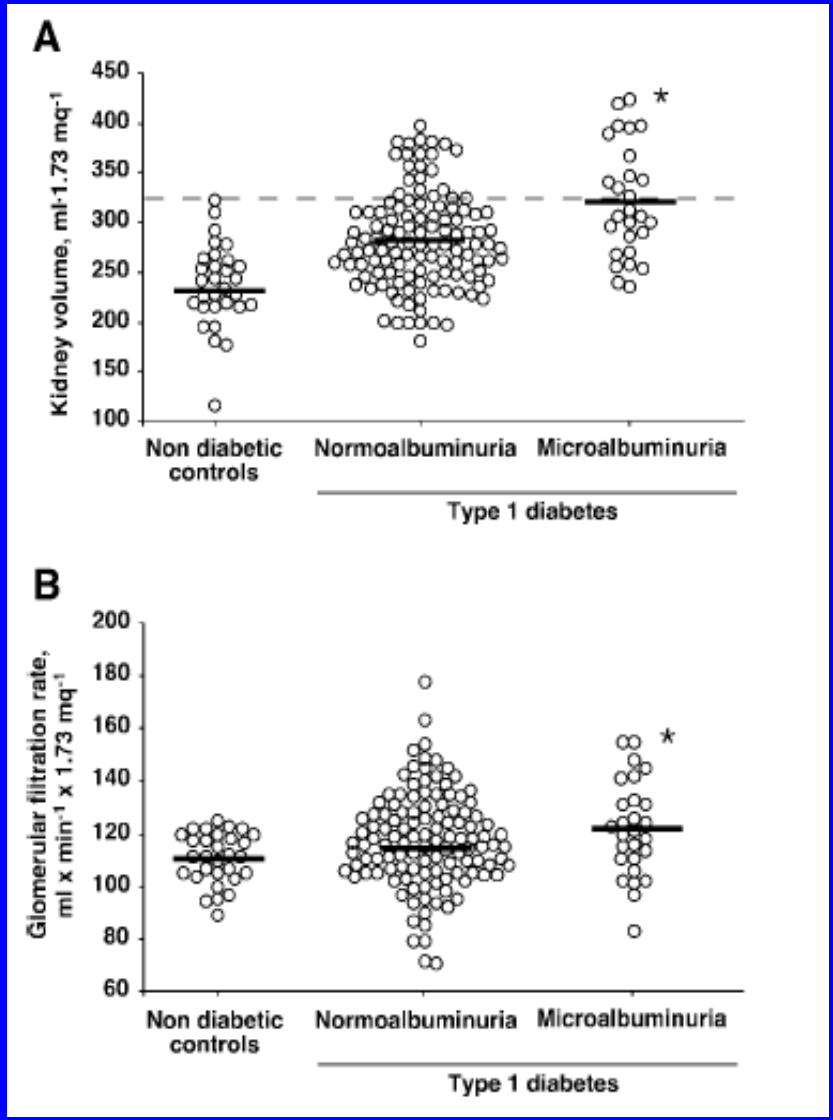
blood pressure + HbA1c + cholesterol

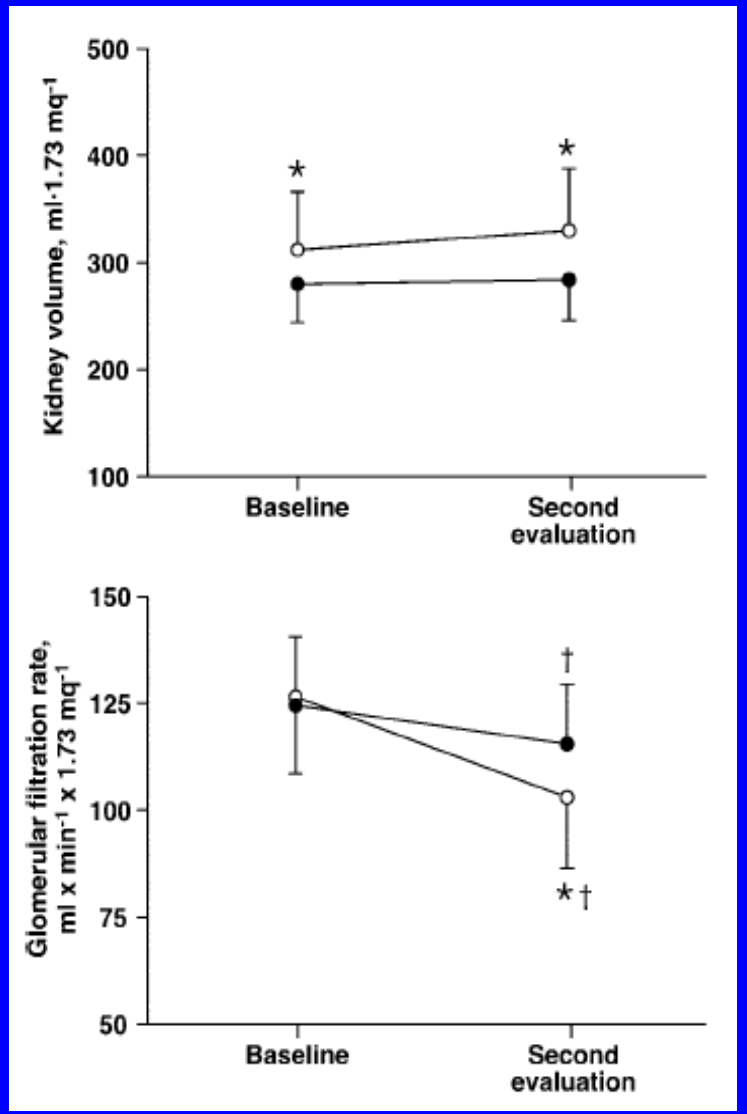
► 4-6 %

Minutolo, J.Hypertens.(2006) 24:1655

Predictor of onset of microalbuminuria in 146 incident type 1 diabetic patients :

greater kidney volume at baseline and more rapid loss of GFR during follow up





Zerbini, Diabetes (2006) 55:2620

Quintiles of plasma 25(OH)D concentration and metabolic syndrome *(NHANES study)*

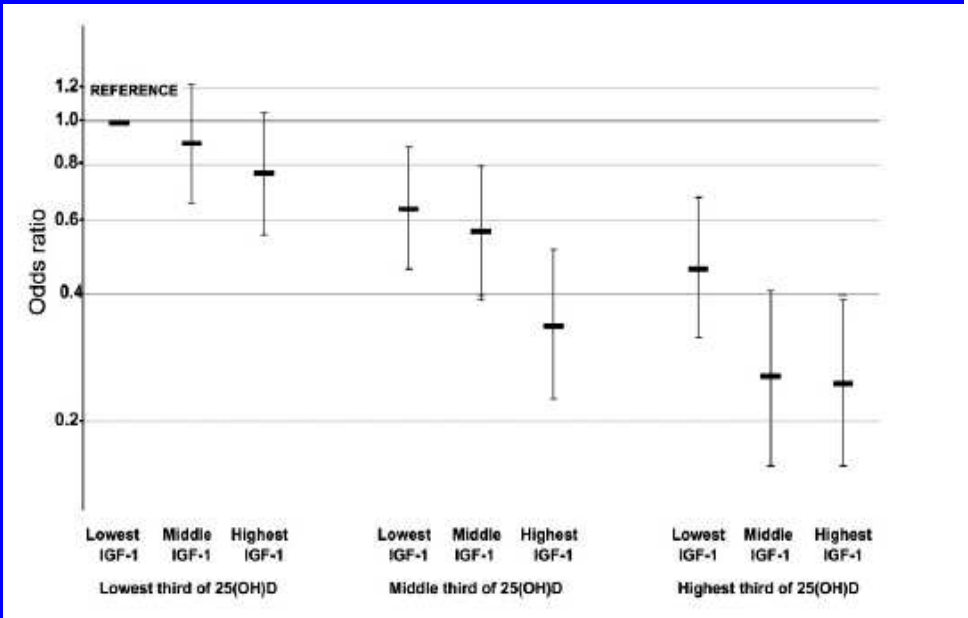
plasma 25(OH)D concentration (nmol/L)				
<48.4	48.5-63.5	63.6-78.2	78.3-96.3	> 96.4
prevalence (%)				
27.5%	26.6%	23.3%	18.7%	13.5%
adjusted odds ratio of metabolic syndrome				
1.0	0.82	0.75	0.6	0.49

p<0.001

Ford, Diabetes Care (2005) 28:1228

25(OH)D and IGF1 – low levels associated with metabolic syndrome in white British adults (45y)

	25(OH)D (tertiles)		
	abdominal obesity	*high HbA1c*	*Hyper-tension*
lowest	**1**	**1**	**1**
middle	**0.63**	**0.43**	**0.72**
highest	**0.39**	**0.14**	**0.57**
	p<0.0001		



Hyppönen, Diabetes (2008) 57:298

Type 2 diabetic patients with low 25(OH)D concentrations – higher frequency of cardiovascular disease

	25(OH)D < 20ng/ml	25(OH)D > 20ng/ml	
	(13.6±9)	*(29.0±9)*	
n	**279**	**180**	
LDL-cholesterol	**3.40**	**3.49**	
(mmol/L)	*± 0.9*	*± 0.9*	
microalbuminuria *(%)*	**18.4**	**18.0**	
macroalbuminuria *(%)*	**6.5**	**5.8**	
Coronary disease *(%)*	**22.9**	**9.5**	*p<0.001*
Cerebrovascular dis *(%)*	**13.5**	**7.8**	*p<0.06*
peripheral vasc.dis. *(%)*	**8.0**	**9.9**	

Cigolini, Diabetes Care (2006) 29:722

Greater intima media thickness in type 2 diabetic patients with low 25(OH)D

	25(OH)D / winter	
	< 37 nmol/L	*> 37nmol/L*
intima-media thickness (mm) *common carotid*	**1.10 ± 0.15**	**0.87 ± 0.14**
	p< 0.01	

Targher, Clin.Endocrinol.(2006)65:593

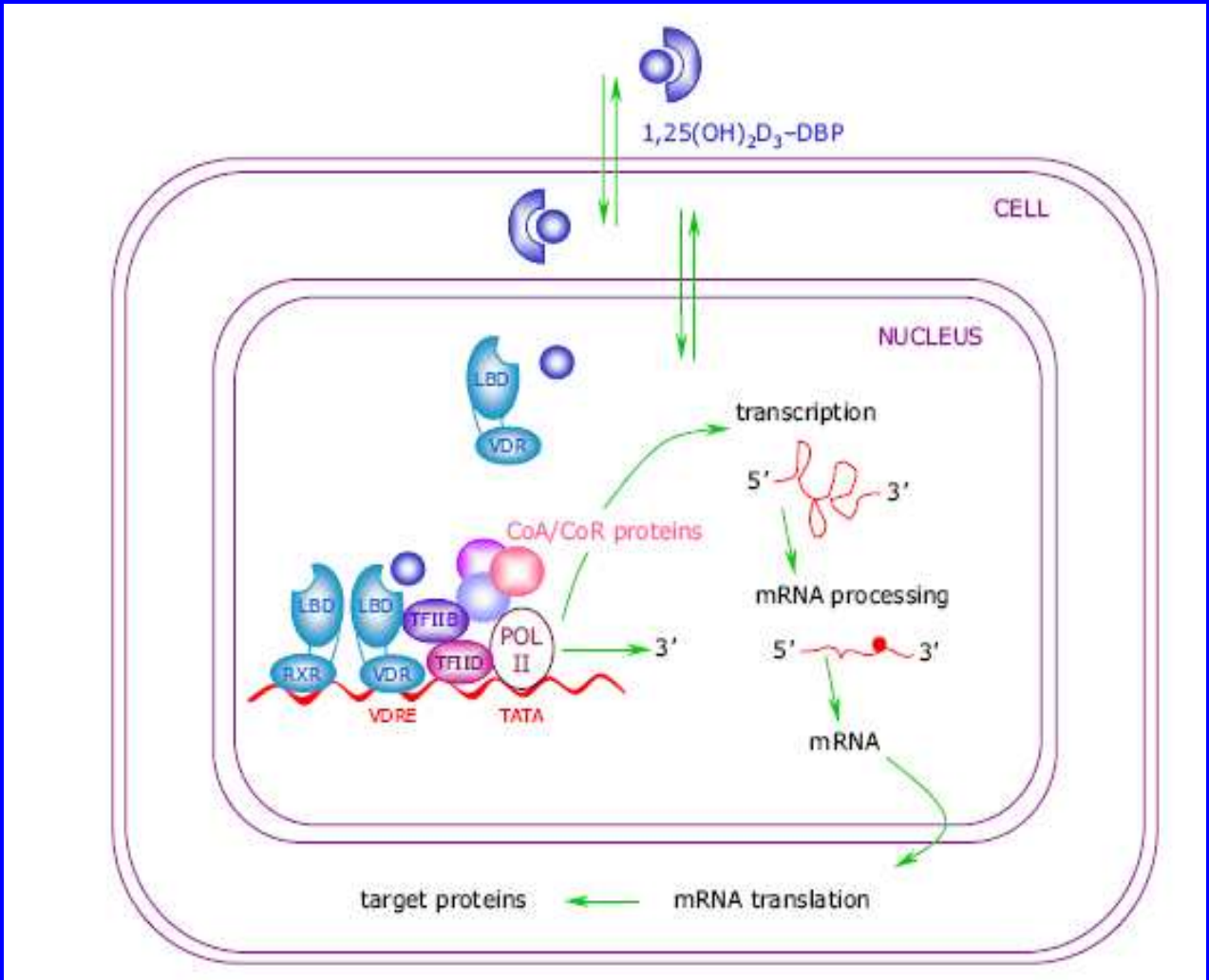
Viatmin D improves endothelial function in type 2 diabetes

49 elderly Scotish patients 25(OH)D < 50nmol/L
single dose 100.000 IU ergocalciferol or placebo

	ergocalciferol	placebo
Δ flow mediated dilatation		
- **hyperemia**	**2.35**	**0.06**
	± 3.12	*± 3.39*
	p < 0.048	
- **glyceryl trinitrate**	**- 1.33**	**- 0.98**
	± 2.72	*± 5.65*
	N.S.	

Sugden, Diabetic Medicine (2008) 25: 320

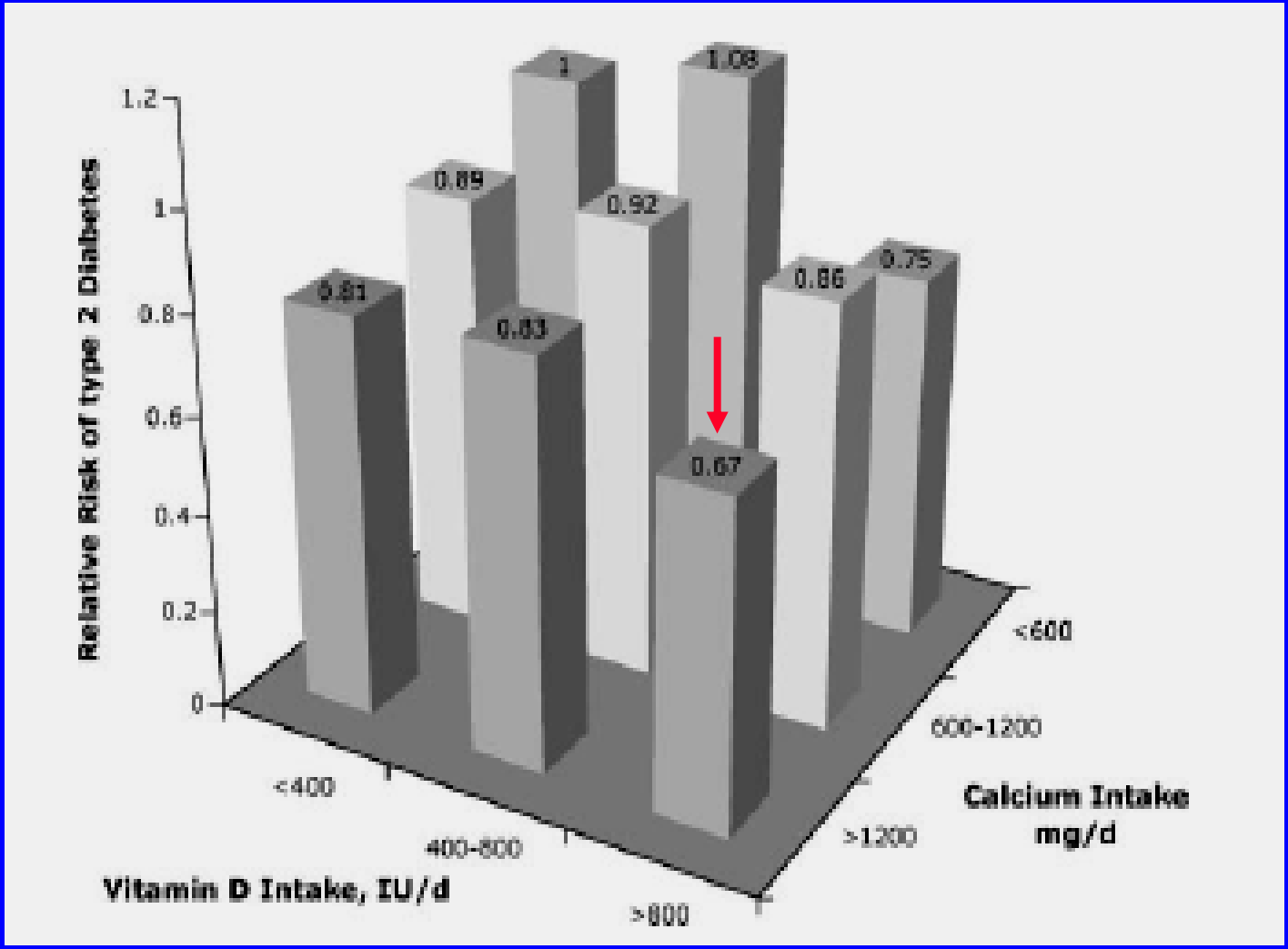
Molecular mechanisms of vitamin D



Matthieu, Diabetologia (2005) 48:1247

Adjusted relative risk of incident type 2 diabetes by vitamin D and calcium intake

(Nurses Health Study)



Pittas, J.Clin.Endocrinol.Metab.(2007) 92:2017

Vitamin D – a modifier of diabetes

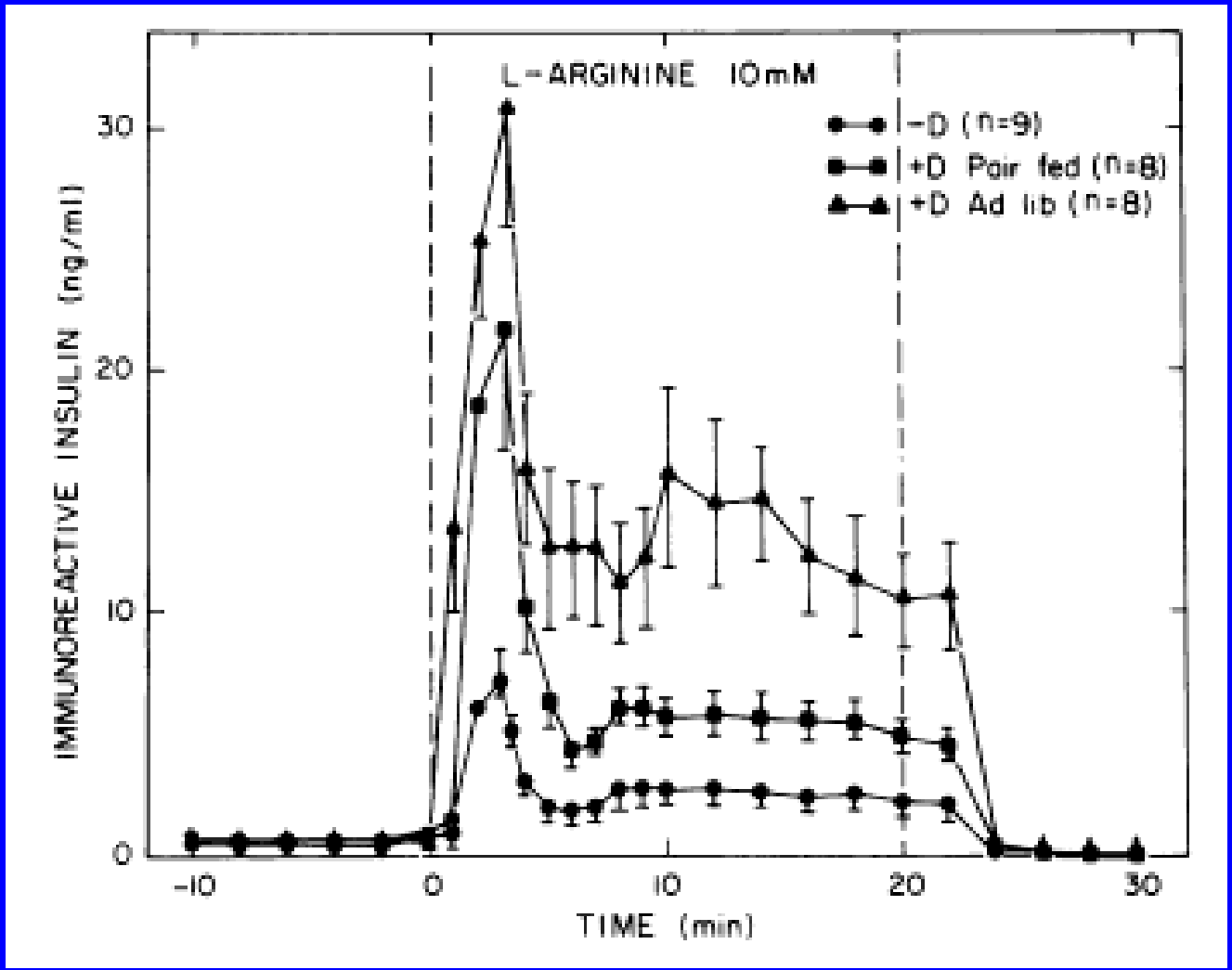
- **risk factor fot type 1 diabetes**

  Mathieu, Trends Endocrinol.Metab.(2005) 16:261

- **plays a role in type 2 diabetes**

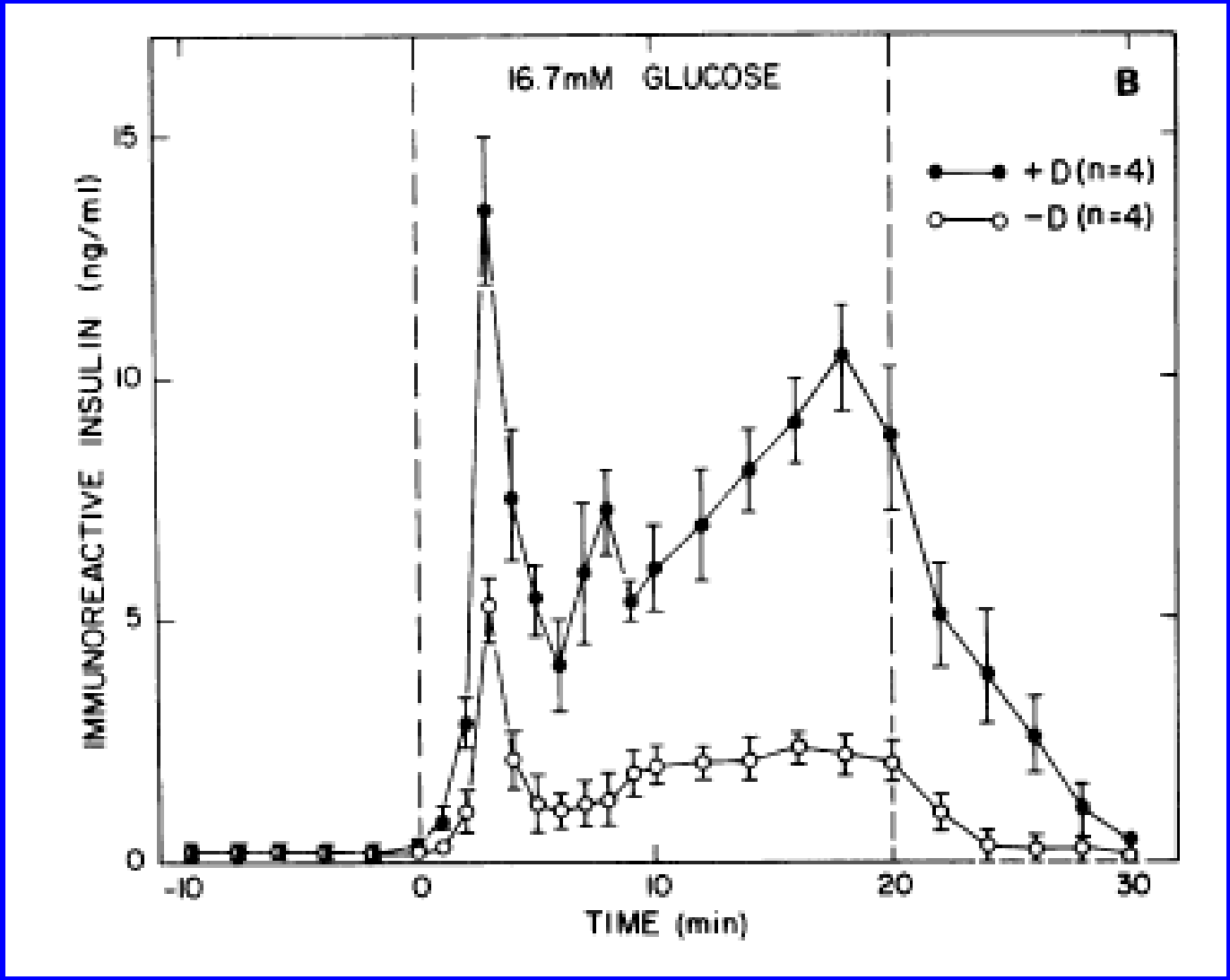
  Pittas, J.Clin.Endocrinol.Metab(2007) 92:2017

Vitamin D potentiates L-arginine induced insulin release



Kadowaki, J.Clin.Invest.(1984) 73: 759

In vitamin D depleted rats : restitution of glucose induced insulin release by vitamin D



Kadowaki, J.Clin.Invest.(1984) 73: 759

Potential mechanisms for the effects of vitamin D on type 2 diabetes

Pittas, J.Clin.Endocrinol.Metab(2007) 92:2017

- **Pancreatic β-cell function**

  active vitamin D affects glucose induced, but not basal insulin secretion

  Bourlon, J.Endocrinol.(1999) 160: 87

  islet has VDR, but also 1α hydroxylase and local synthesis of 1,25(OH)2D3

  Bland, J.Steroid Biochem. (2004) 89-90: 121

  vitamin D supplementation improved insulin release

  Orwoll, Am.J.Clin.Nutr. (1994) 59:1083

Potential mechanisms for the effects of vitamin D on type 2 diabetes

Pittas, J.Clin.Endocrinol.Metab(2007) 92:2017

- **Pancreatic β-cell function → improved**
- **Insulin resistance with reduced glucose uptake reversed, thus increasing glucose uptake**

 # directly by expression of insulin receptor

Maestro, Endocr.J. (2000)47:383

 # indirectly by calcemia, calcium influx and $[Ca^{++}]_i$ ↑ - reverses effect of low intracellular Ca^{++} which :

reduces insulin signal transduction

Zemel,Mol.Cell Biochem. (1998) 188: 129

decreases glucose transporter 4

Reusch, Endocrinology (1991) 129: 3269

Potential mechanisms for the effects of vitamin D on type 2 diabetes

Pittas, J.Clin.Endocrinol.Metab(2007) 92:2017

- **Pancreatic β-cell function → improved**
- **Insulin resistance with reduced glucose uptake reversed, thus increasing glucose uptake**
- **Inflammation → reversed**

Pittas,Diabetes Care (2007) 30:980
Cigolini, Diabetes Care (2006) 30:980
Timms, Quart.J.Med.(2002) 95:787

In type 2 diabetes glycemic control worse in the winter

Behall,Am.J.Clin.Nutr.(1984) 40:1352

39 elderly (mean age 65 years) type 2 diabetic patients

monthly $HbA1_c$ → 0.5% higher during winter

July ***6.42 ± 0.65 %***

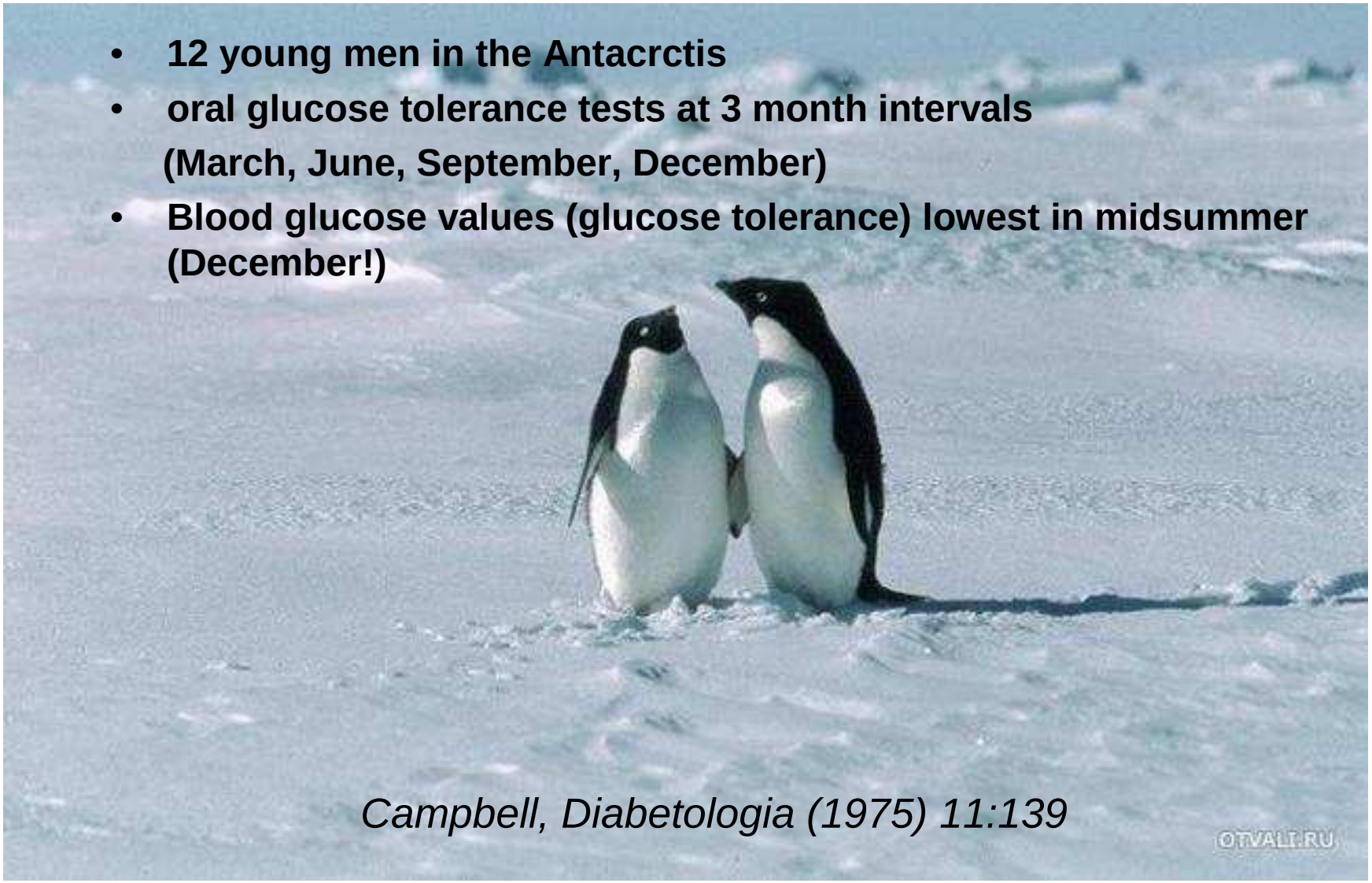
March ***6.96 ± 0.90%***

p< 0.01

- **sunlight (vitamin D) ?**
- **physical inactivity ?**
- **calorie intake ?**

Ishii, Diabetes Care (2001) 24:1503

Glycemic control worse in the dark season



- 12 young men in the Antacrctis
- oral glucose tolerance tests at 3 month intervals
  (March, June, September, December)
- Blood glucose values (glucose tolerance) lowest in midsummer (December!)

Campbell, Diabetologia (1975) 11:139

25(OH)D concentration and prevalent type 2 diabetes –

metaanalysis* – *excluding blacks

25-38 vs 10-23 ng/ml 25(OH)D :

odds ratio: 0.36 *(95%CI 0.16-0.80)*

Pittas,J.Clin.Endocrinol.Metab.(2007) 92:2017

***case- control studies* :**

individuals with glucose intolerance or type 2 diabetes vs controls

→ lower 25(OH)D concentrations

Nyomba, Diabetes (1986) 35:911
Pietschmann, Diabetologia (1988) 31: 892
Aksoy, Clin.Biochem (2000) 33:47
Isaia, Diabetes Care (2001) 24: 1496

Vitamin D intervention studies

- **no effect of short term small studies in healthy individuals and in type 2 diabetics with sufficient vitamin D levels**

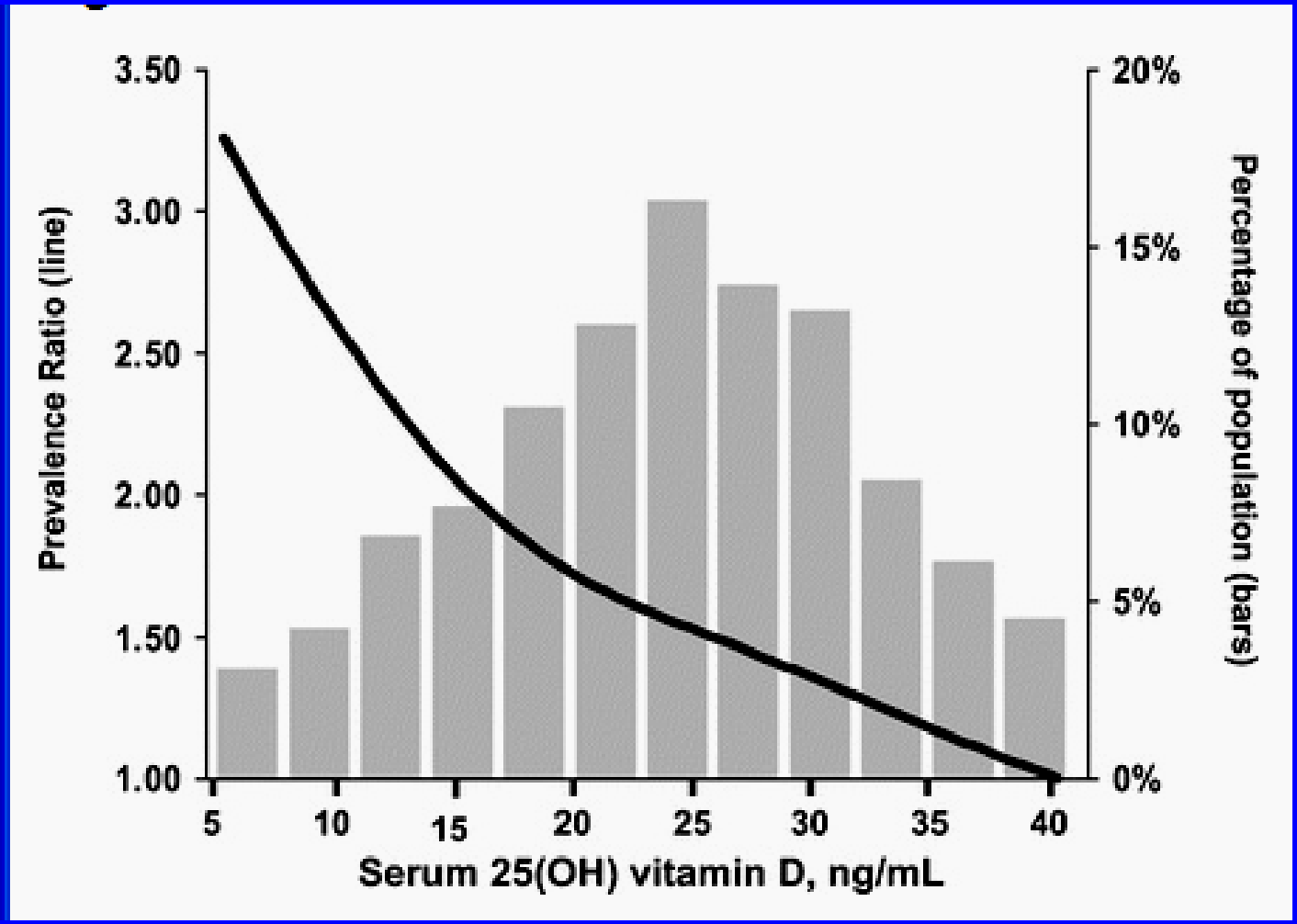
  Fliser, Eur.J.Clin.Invest (1997) 27:629
  Ljunghall, Acta Med.Scand.(1987) 222:361

- **potential benefit of vitamin D in delaying progression from glucose intolerance to type 2 diabetes :**

  700 IU vitamin D + 500 mg Ca-citrate →
  # individuals with normal glucose tolerance
  ►no effect on glycemia or insulin sensitivity
  # individuals with impaired fasting glucose at baseline
  ►slower rise in fasting glucose and insulin resistance at 3 years compared to placebo
  effect size comparable to metformin !

  Pittas, Diabetes Care (2007) 30:980

Low 25(OH)D concentrations – higher risk of peripheral arterial disease



Melamed, Arterioscler.Thromb.Vasc.Bio.(2008) 28:1179