Diabetes – CKD and ESRD

Eberhard Ritz
(Heidelberg)

V. Ueber die prognostische Bedeutung und die Aetiologie der Albuminurie bei Diabetes.

Von

Sanitätsrath Dr. **Richard Schmitz**-Neuenahr.

Das häufige Vorkommen von Albuminurie bei Diabetes ist schon längst bekannt. Schon 1876 erwähnt Senator in seiner trefflichen Monographie über den Diabetes dieser Complication des Diabetes und führt dabei an, dass Garrod das Vorkommen derselben auf 10 pCt., von Dusch dasselbe sogar auf 25,5 pCt. angebe.

Berliner Klinische Wochenschrift (1891) 28: 373-7.

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

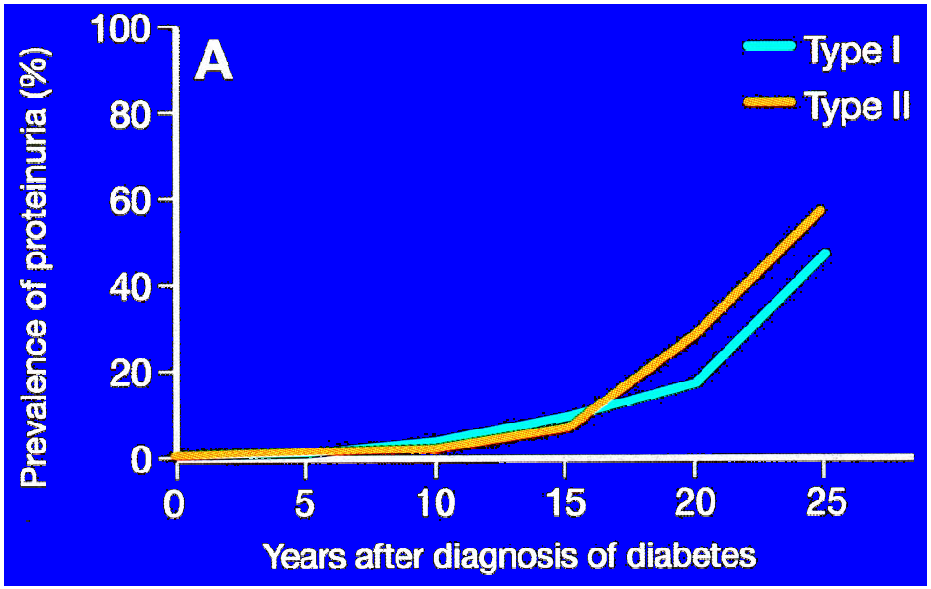
Eli Friedman

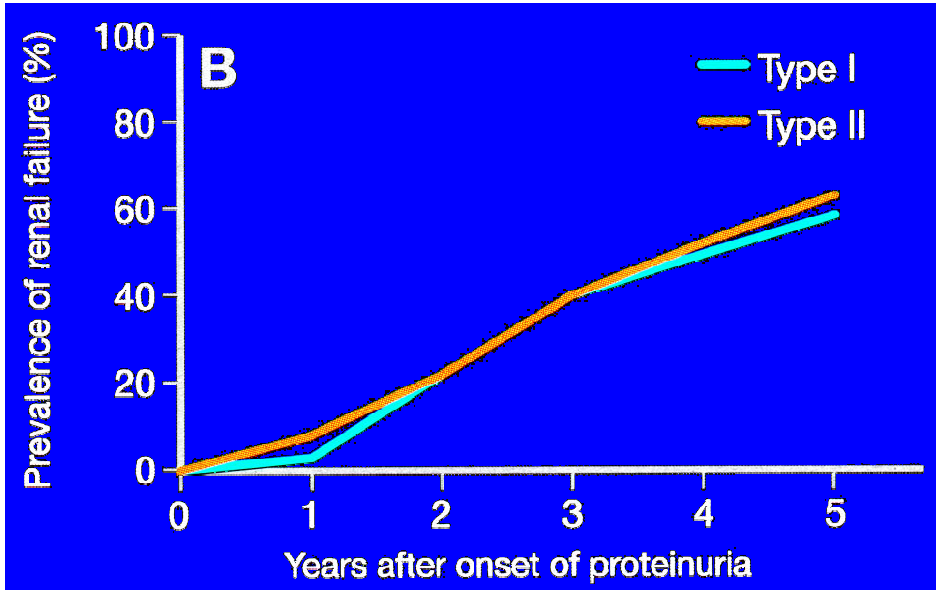
Diabetes –
CKD and ESRD

- Epidemiology

Similar renal risk

in type 1 and type 2 diabetes





Hasslacher, Nephrol Dial Transplant (1989) 4: 859

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

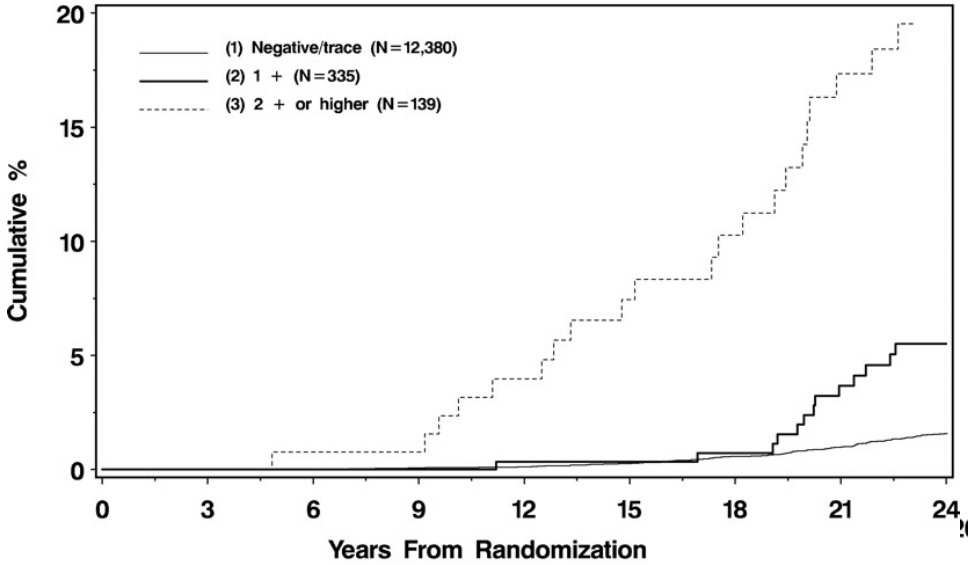
UKPDS – annual death rate

- 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

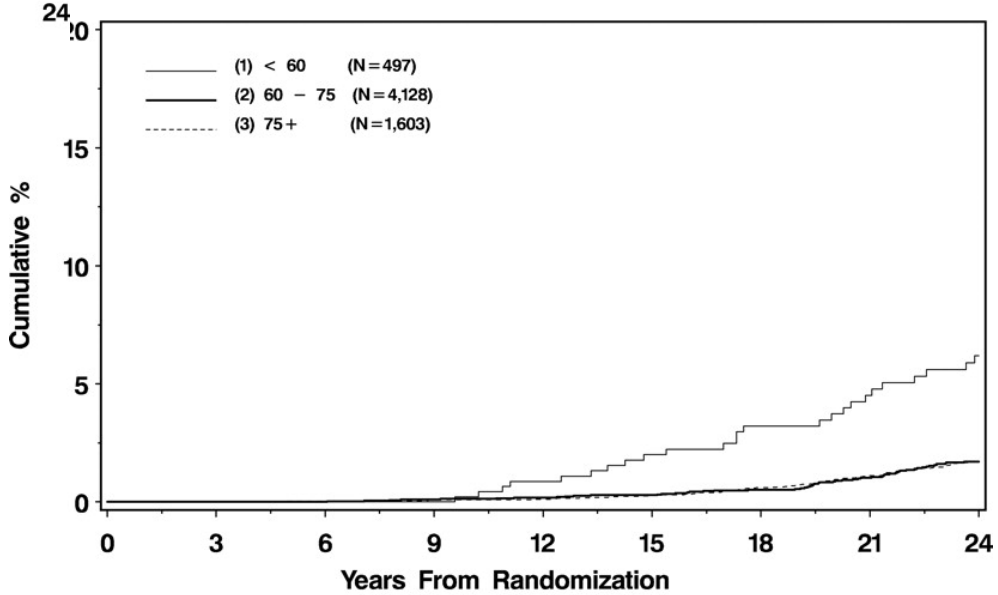
Adler, Kidn Intern (2003) 63: 225

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

Diabetes –
CKD and ESRD

- Epidemiology
- Not all diabetic nephropathy is Kimmelstiel-Wilson

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

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

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

334 ppm *(per million population per year)*

(www.USRDS.org)

- Heidelberg **49 % of incident patients**

98 ppm

6 % type 1

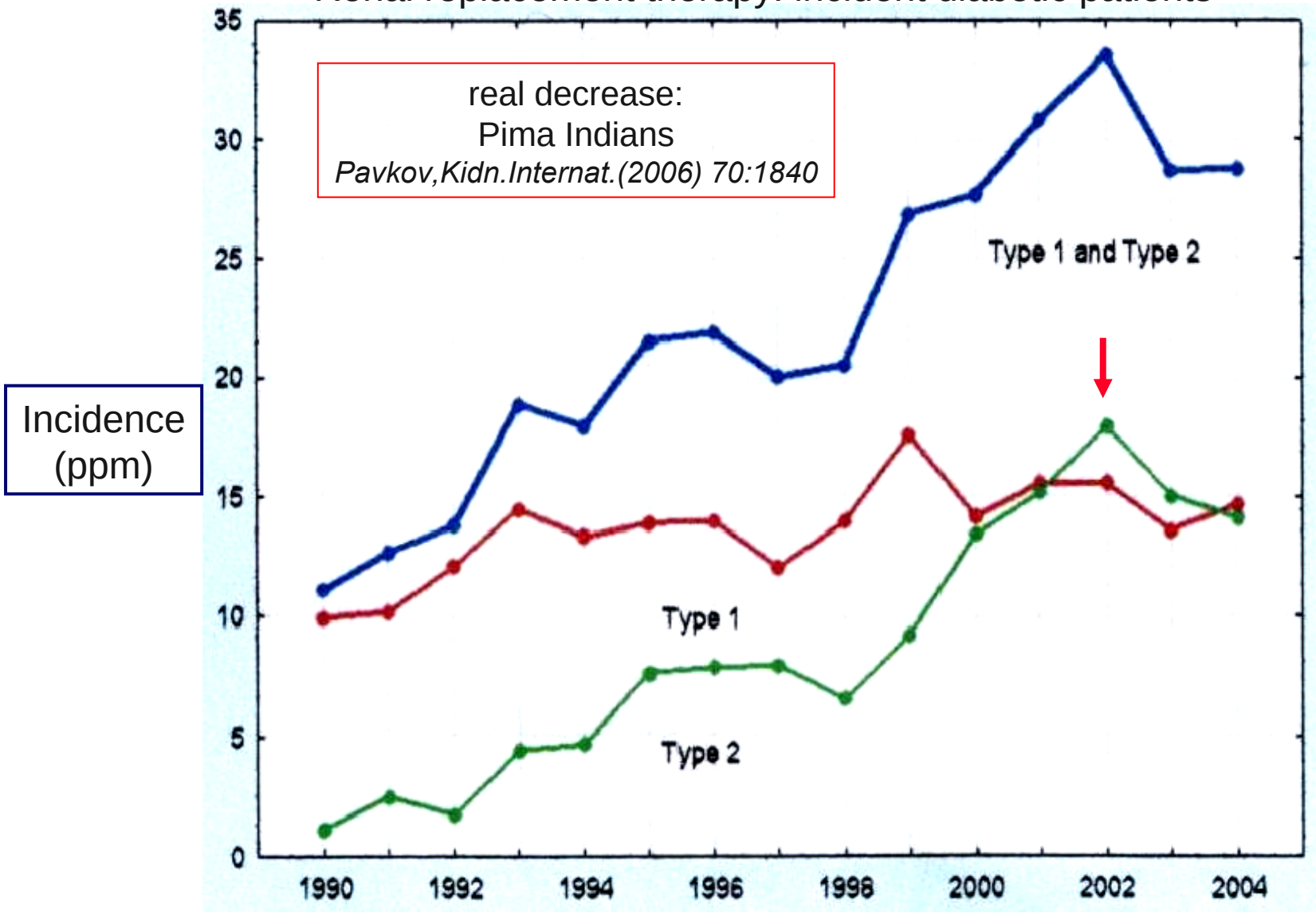
94 % type 2

Schwenger, Dtsch Med Wschr (2001) 126: 1322

New development :

Denmark registry

Renal replacement therapy: incident diabetic patients



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

original article

http://www.kidney-international.org

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Increasing incidence of proteinuria and declining incidence of end-stage renal disease in diabetic Pima Indians

ME Pavkov[1], WC Knowler[1], PH Bennett[1], HC Looker[1], J Krakoff[1] and RG Nelson[1]

[1]*Diabetes Epidemiology and Clinical Research Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Phoenix, Arizona, USA*

Kidn.Intern.(2006) 70: 1840

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

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

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

Changing clinical presentation

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

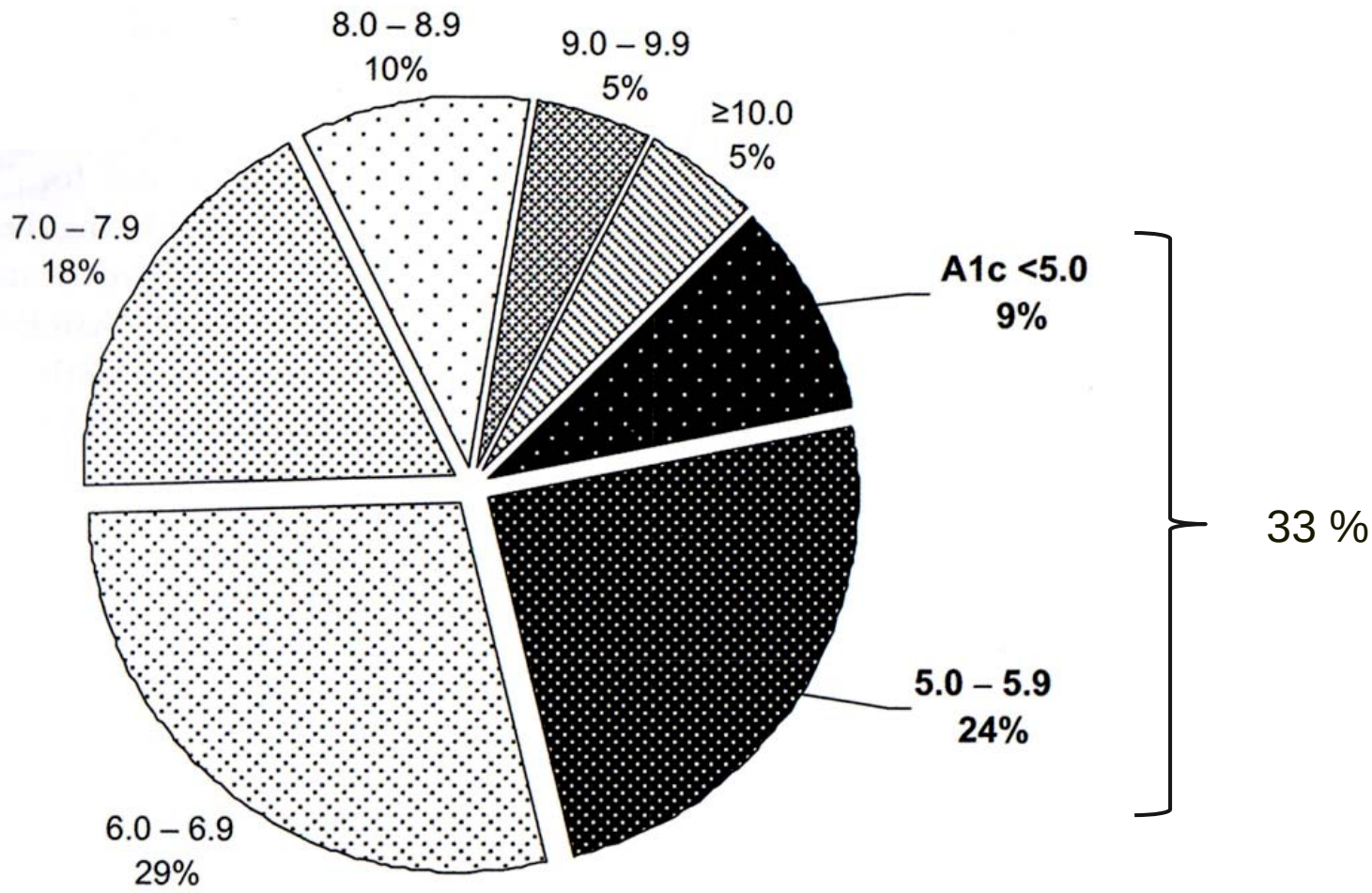
→ **irreversible acute renal failure** ***(acute on chronic)***
or progression to terminal renal failure after recovery from acute renal failure

→ **no diagnosis of diabetes by primary care physician : 11%**
(anorexia and catabolism ⇨ disappearance of hyperglycemia; distrust registry data)

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

“Burnt out” diabetes

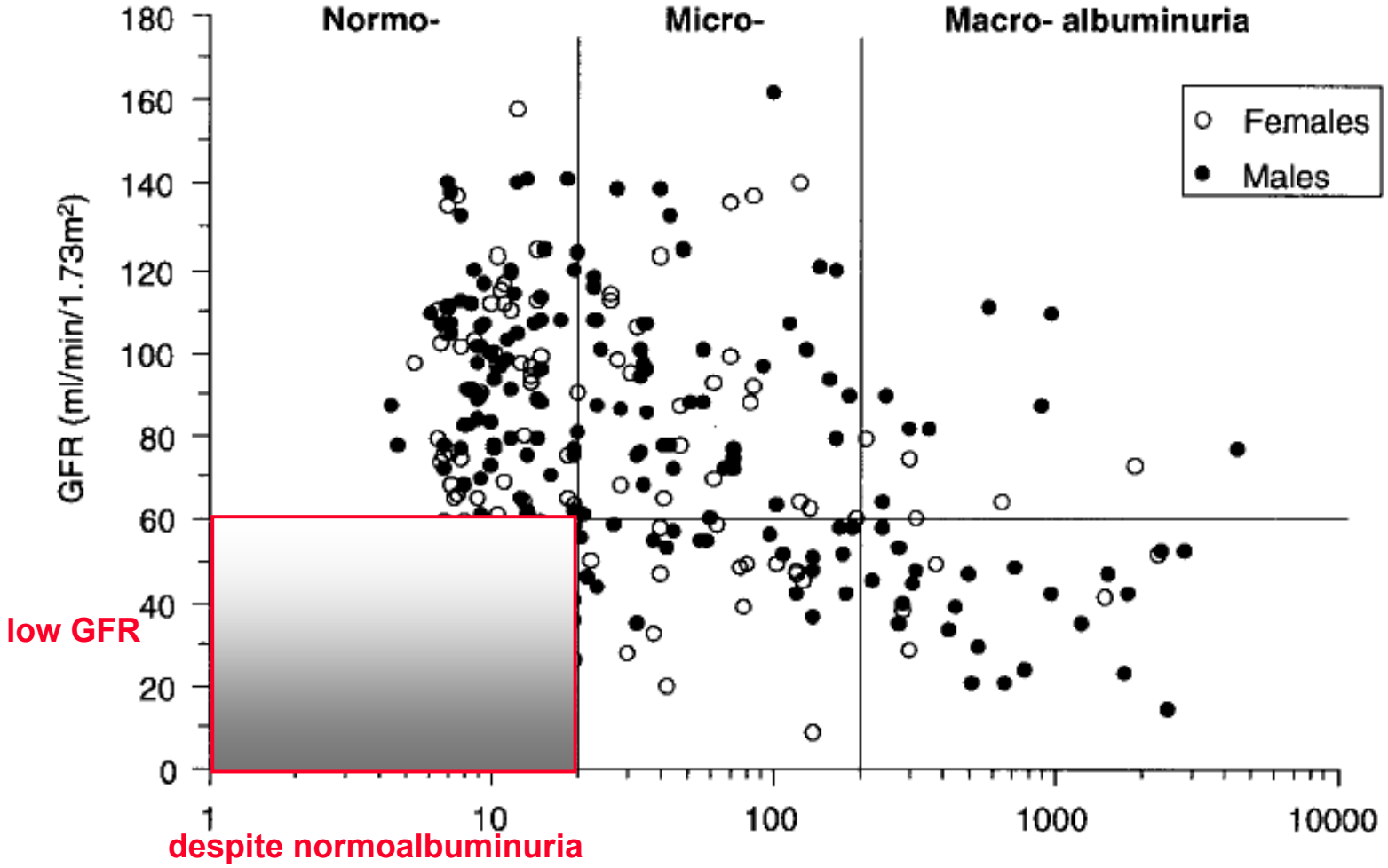
HbA1$_c$ in 23,618 diabetic patients on hemodialysis in the USA



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

Low GFR despite normoalbuminuria in type 2 diabetes

(ischemic nephropathy)



MacIsaac, Diabetes Care (2004) 27:195

CKD without albuminuria
(UKPDS)

5032 patients, initially normal S-creatinine

15 year follow-up :

de novo albuminuria	38%
de novo Ccr<60 ml/min *(Cockcroft-Gault)*	28% - 14% no preceding albuminuria

Retnakaran, Diabetes (2006) 55:1832

~ NHANES

Kramer, JAMA (2003) 289:3273

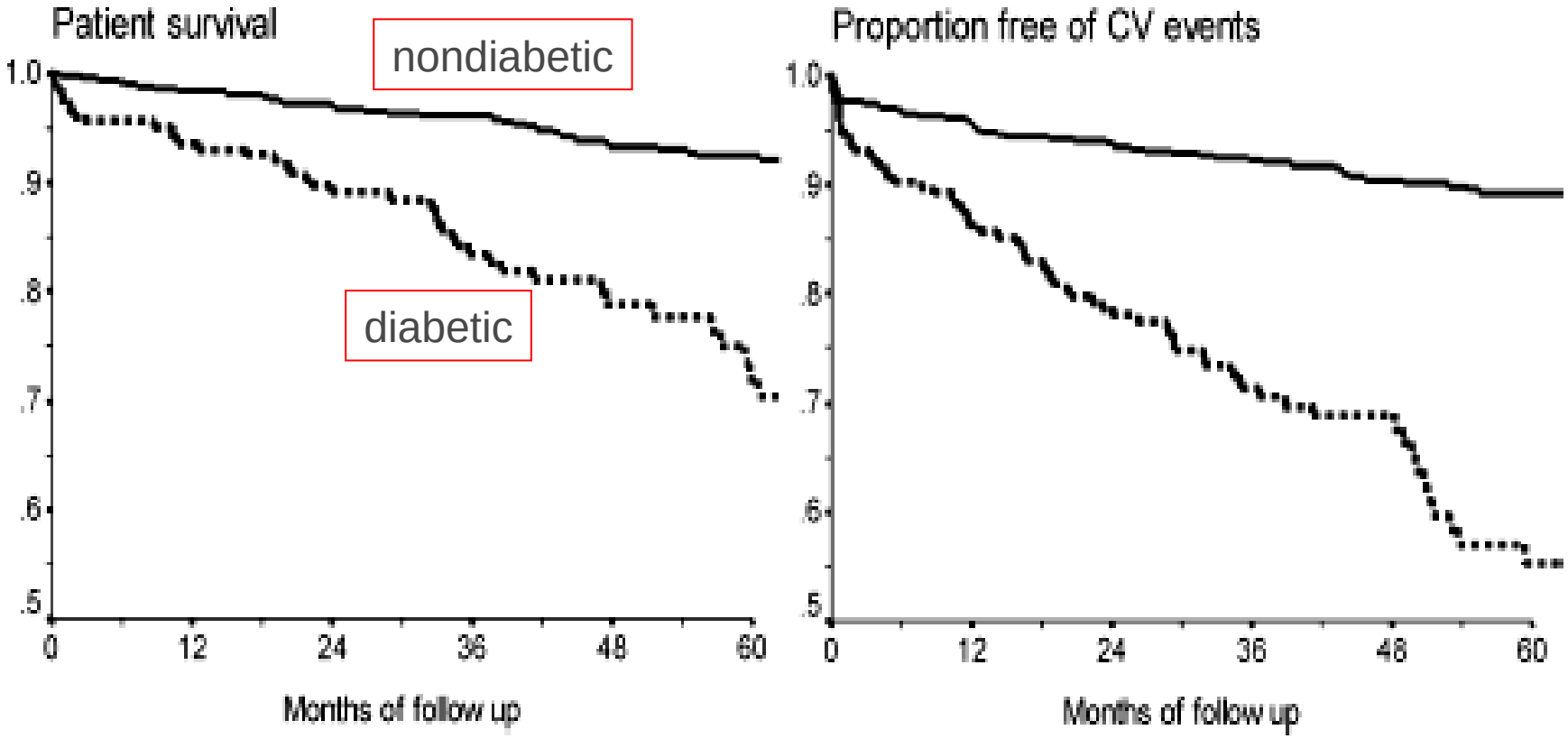
Diabetes after kidney transplantation
USA

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

Prädiktoren : Afro-Americans, Hispanics
males
hepatatis C
body mass index
Tacrolimus

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

Posttransplantation diabetes – impact on survival and cardiovascular events



Cosio, Am.J.Transplant.(2008) 8:593

Diabetes –
CKD and ESRD

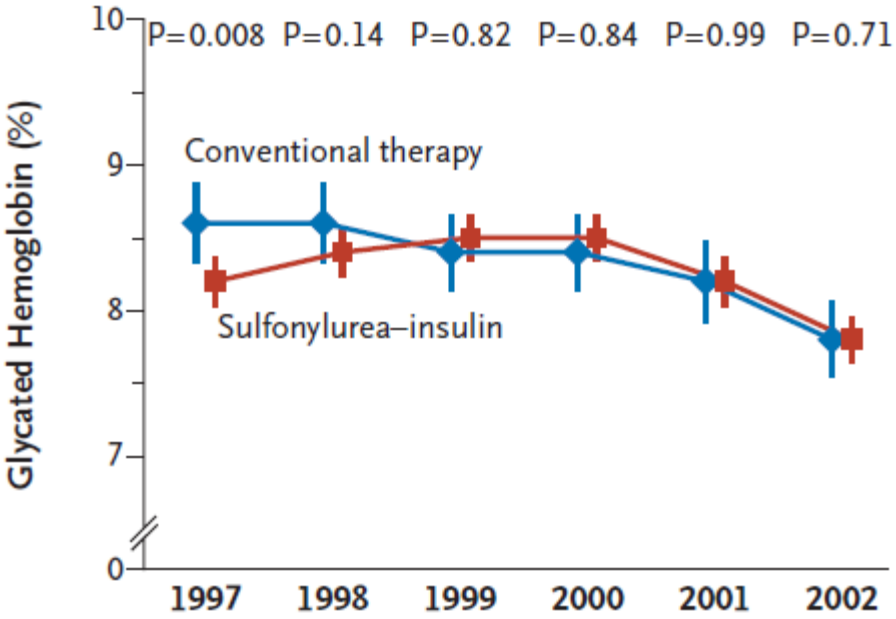
- Epidemiology
- Not all diabetic nephropathy is created equal
- The role of glycemic control

The most important targets to prevent onset and progression of diabetic nephropathy

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

Short term glucose lowering in type 2 diabetes – longterm benefit

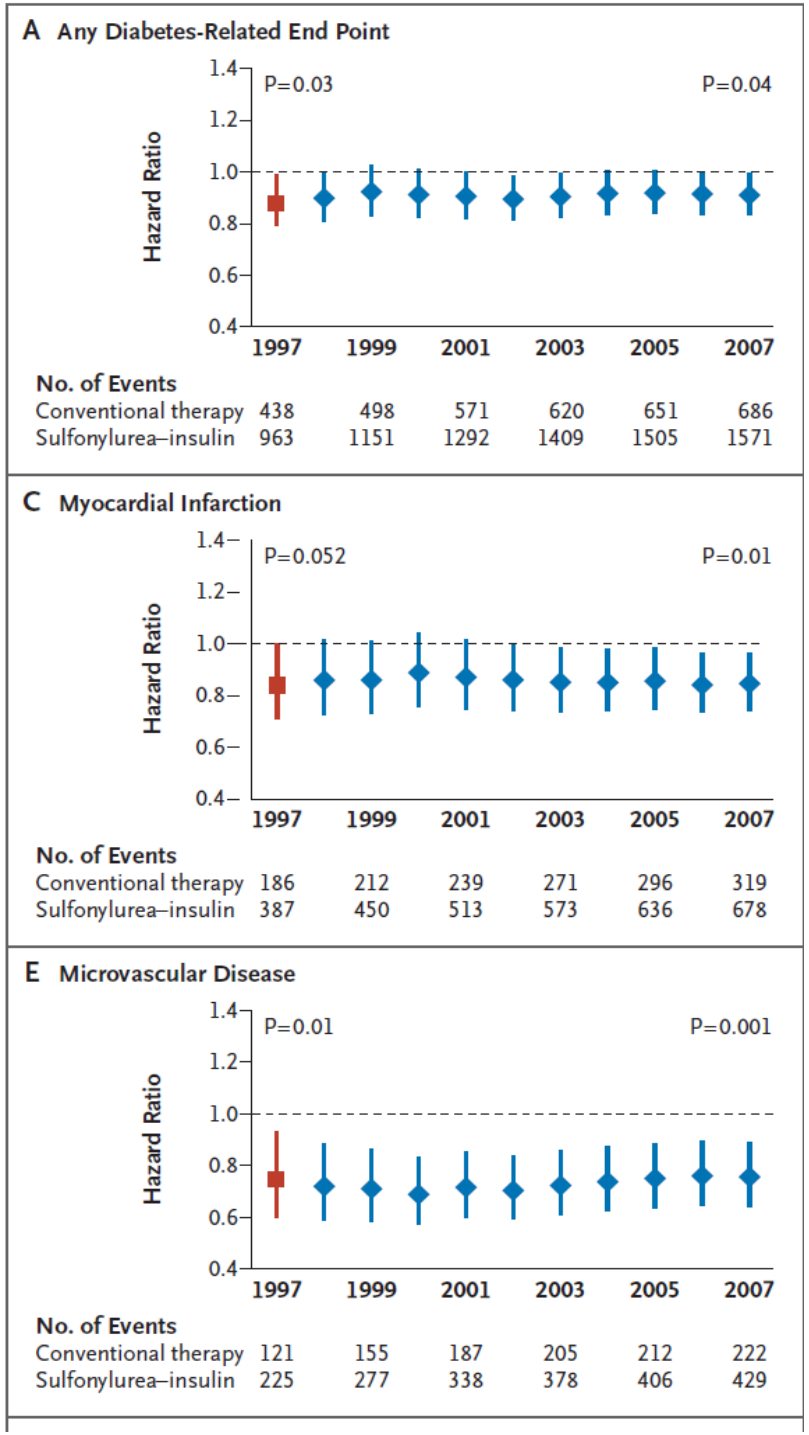
(UKPDS study)



the legacy effect

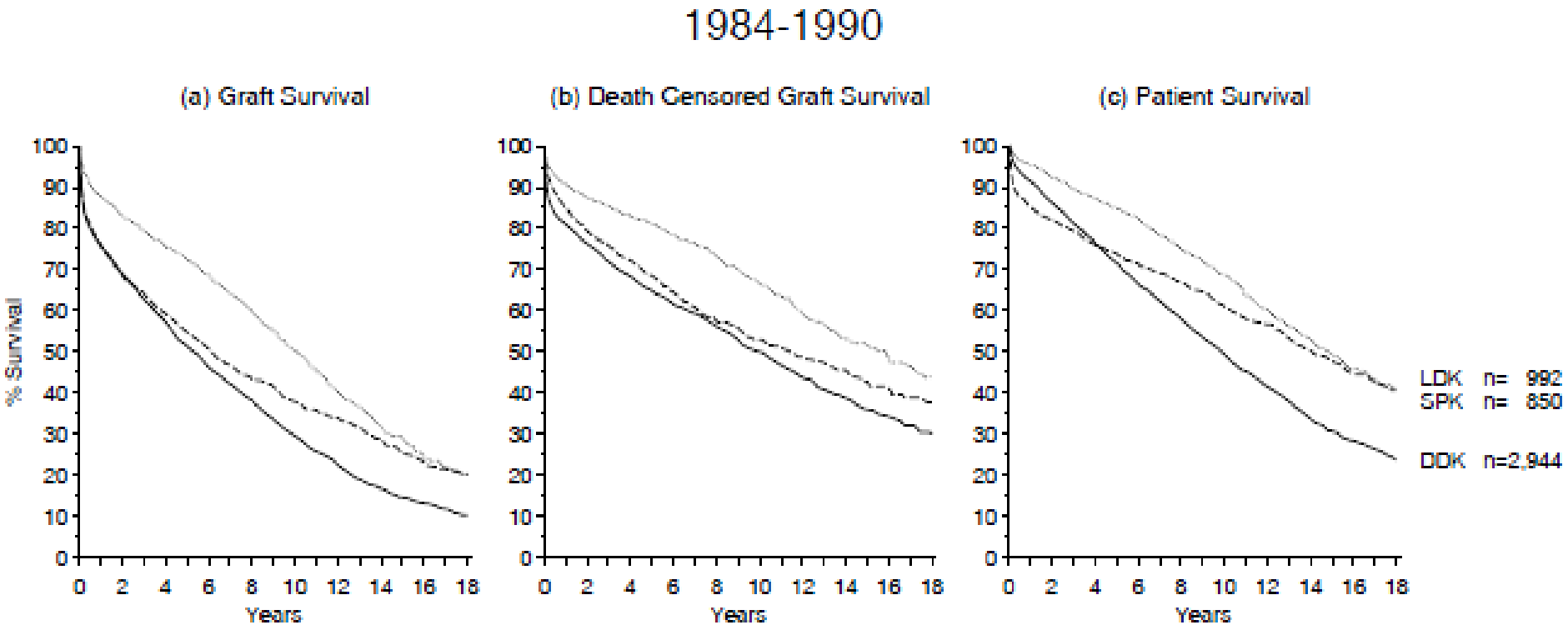
("glycemic memory")

Holman, New Engl J Med (2008)



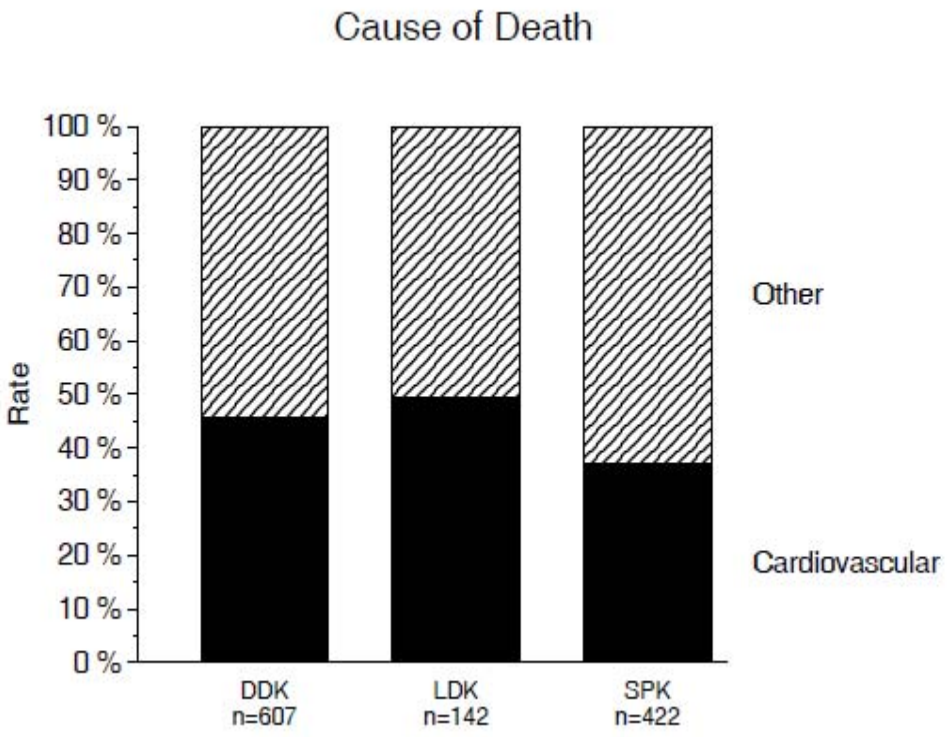
Graft and patient survival

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



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

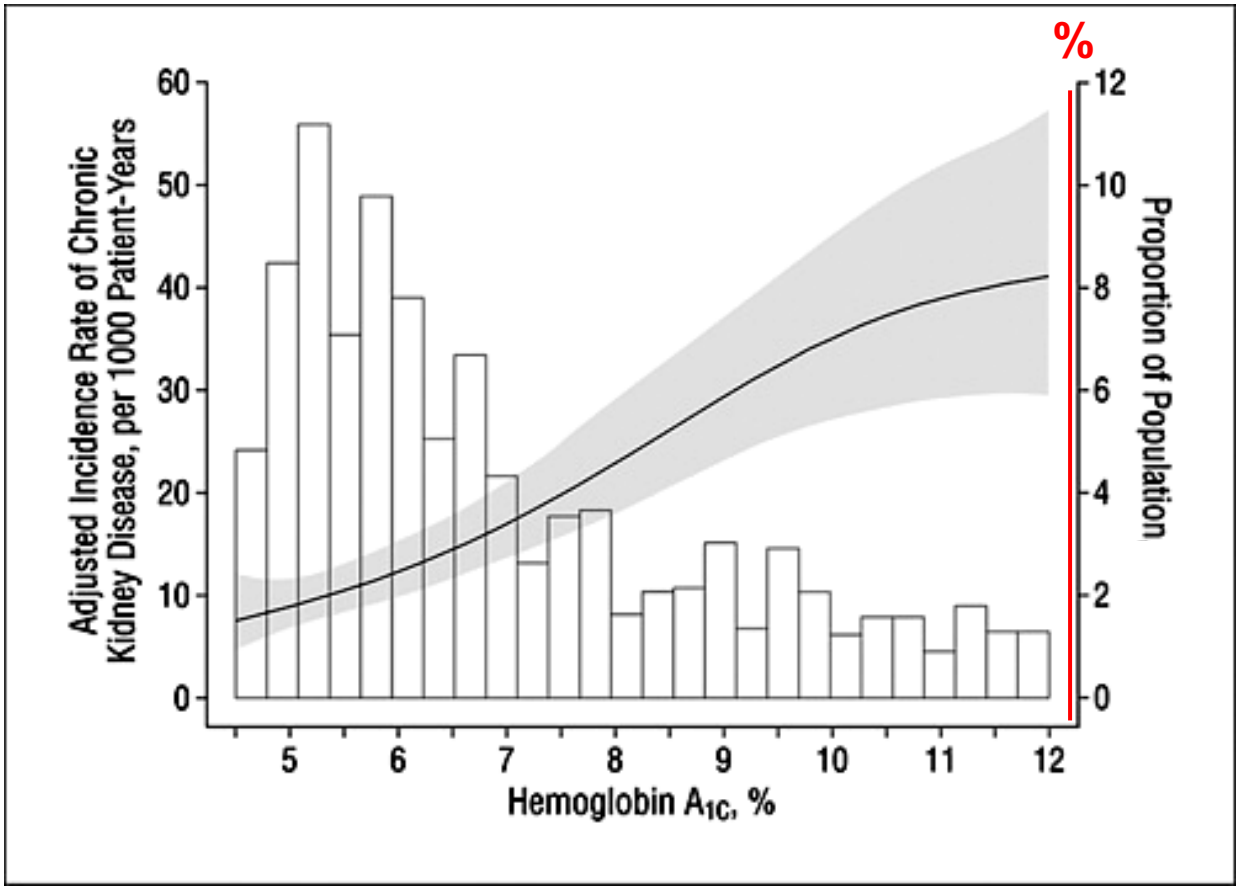
Causes of death in dead donor (DDK), life donor (LDK)and simultaneous pancreas-kidney transplantation (SPK)



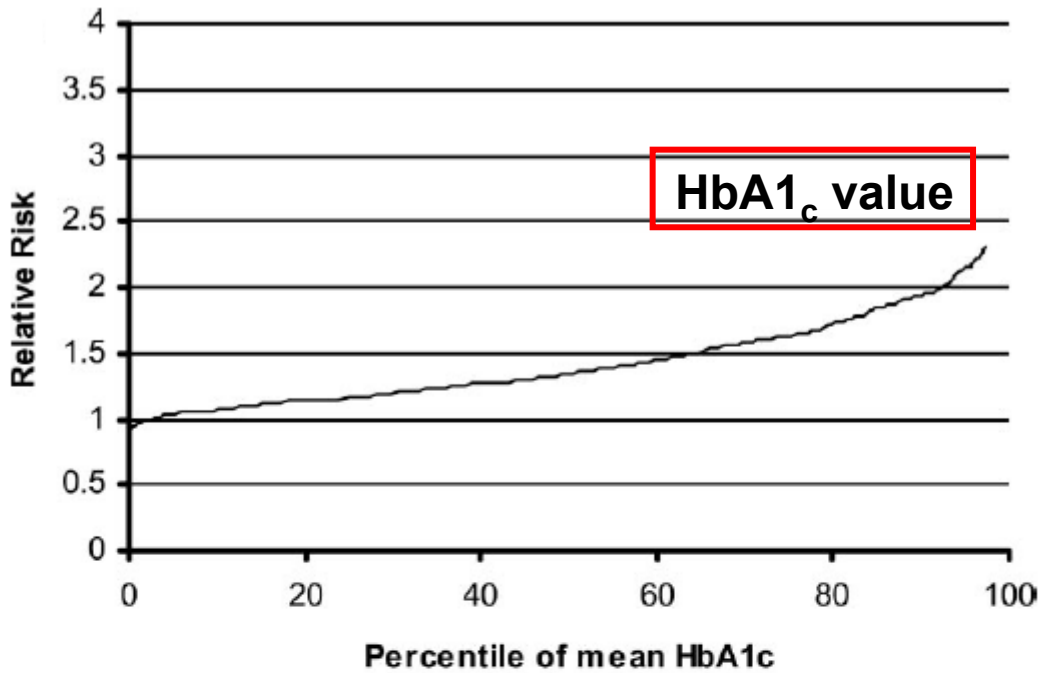
Morath, J.Am.Soc.Nephrol. (2008) 19:1557

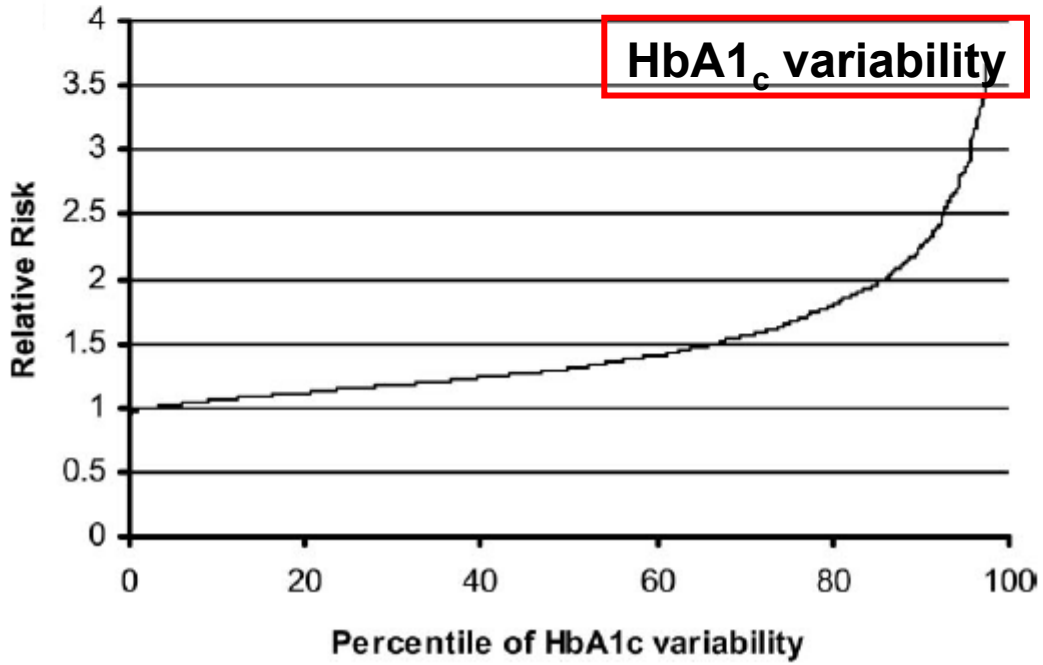
HbA1c
and incidence of diabetic nephropathy

ARIC study, 1871 adults with diabetes, 6 years follow-up



Lori, Arch.Int.Med. (2008) 168:2440





Not only HbA1$_c$ value, but also HbA1$_c$ variability predictors of nephropathy

(DCCT study)

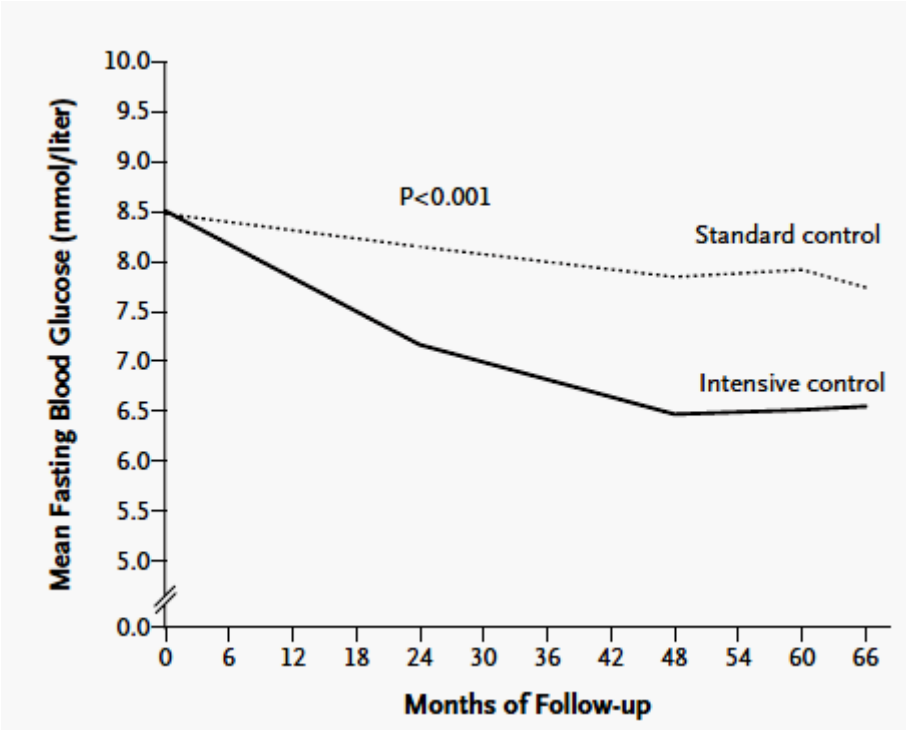
Kilpatrick, Diabetes Care (2008) 31:2198

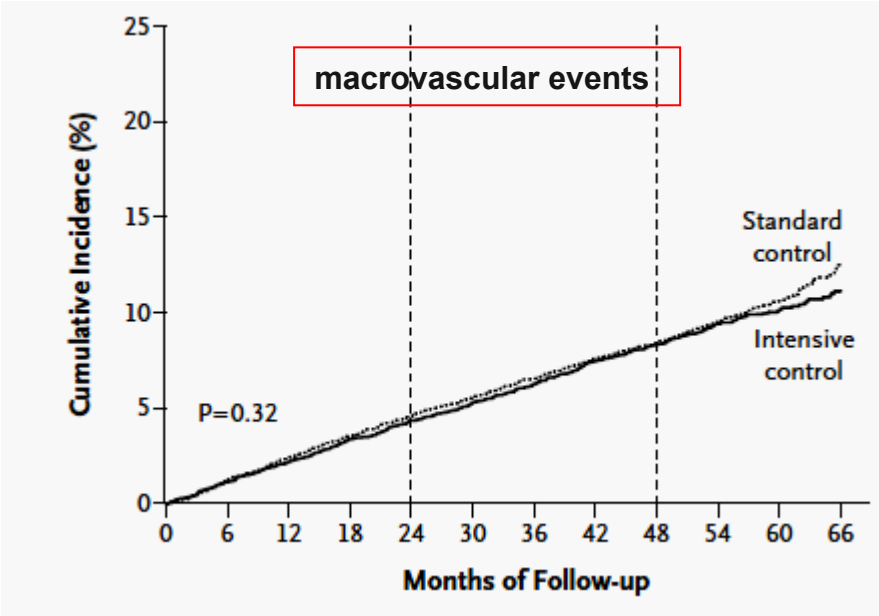
ADVANCE

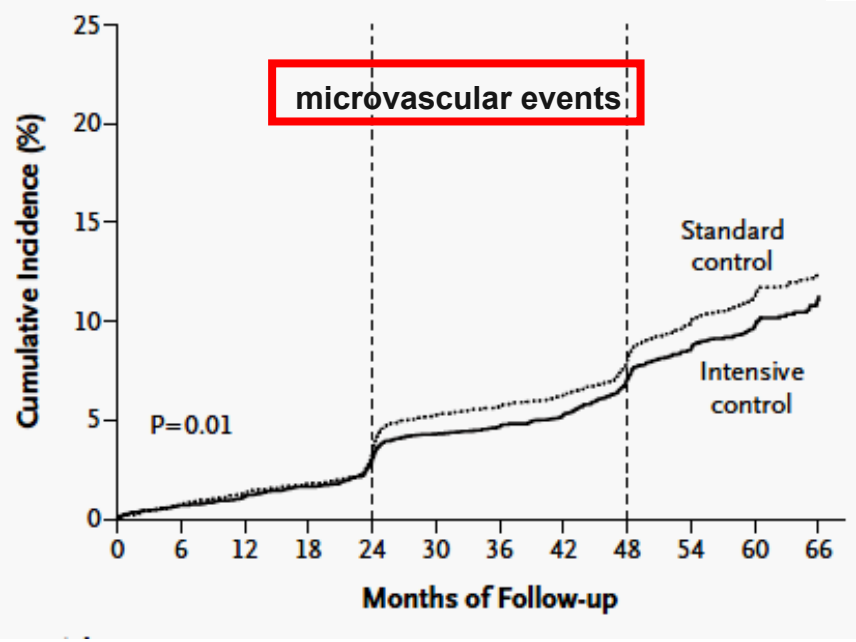
standard vs intensified blood glucose control with Gliclazide

11,140 type 2 diabetic patients

$HbA1_c$ target in intensified treatment group < 6.5%







ADVANCE, New Engl. J. Med. (2008) 358:2560

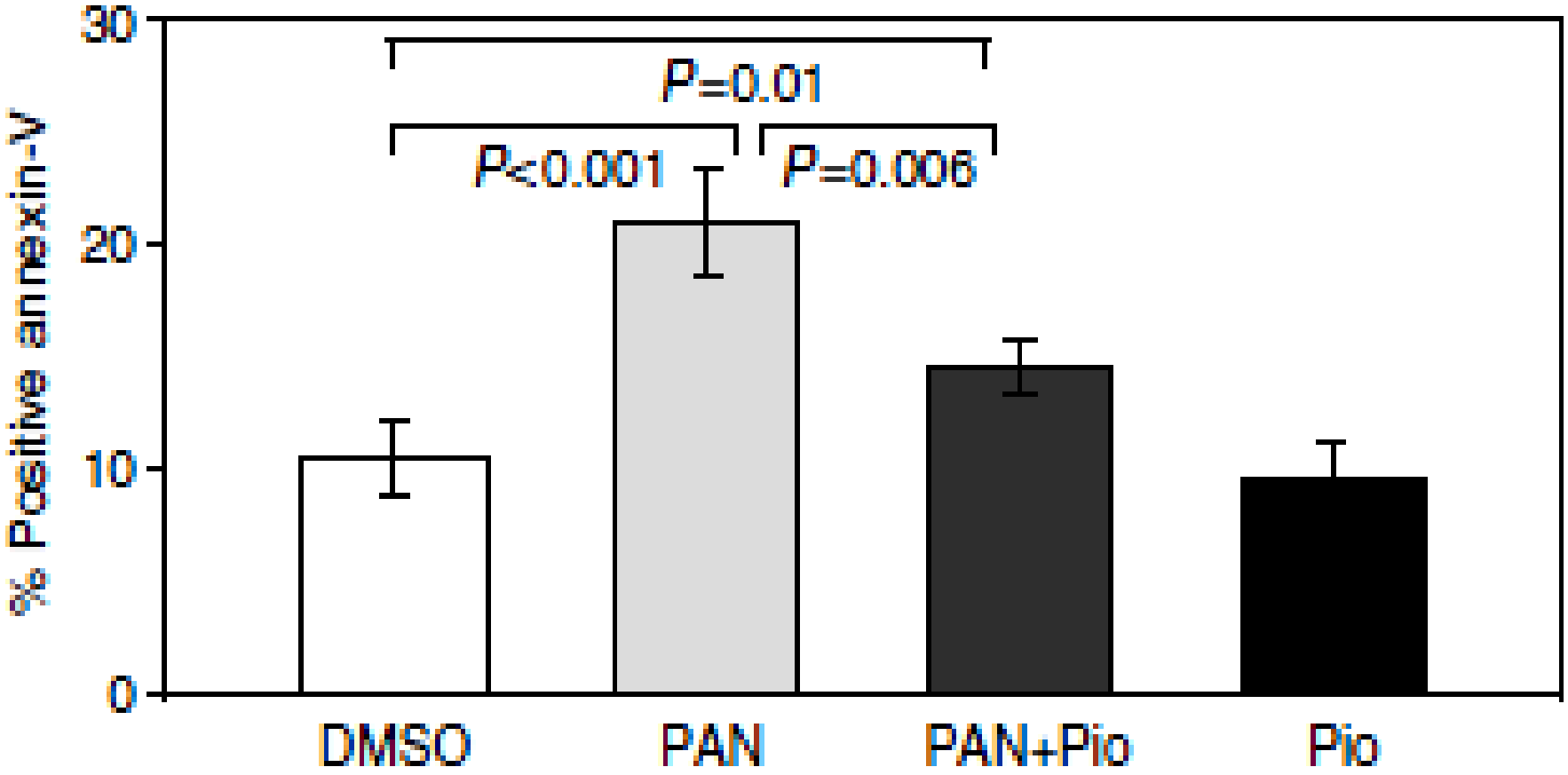
In VA diabetes trial
no significant reduction of renal events
in type 2 diabetic patients

Nephropathy	usual	intensified	
Serum creatinine			
Doubling of level	78/884 (8.8)	78/882 (8.8)	0.99
>3 mg/dl (265 μmol/liter)	16/884 (1.8)	18/882 (2.0)	0.72
Glomerular filtration rate <15 ml/min	11/884 (1.2)	7/882 (0.8)	0.35
Change in albumin level			
From normal to microalbuminuria	26/475 (5.5)	18/457 (3.9)	0.28
From normal to macroalbuminuria	4/475 (0.8)	0/457 (0)	0.12
From microalbuminuria to macroalbuminuria	18/256 (7.0)	12/271 (4.4)	0.26
From normal to microalbuminuria or macroalbuminuria	30/475 (6.3)	18/457 (3.9)	0.11
From normal to microalbuminuria to macroalbuminuria	22/731 (3.0)	12/728 (1.6)	0.12
Any increase in albuminuria	48/731 (6.6)	30/728 (4.1)	0.05

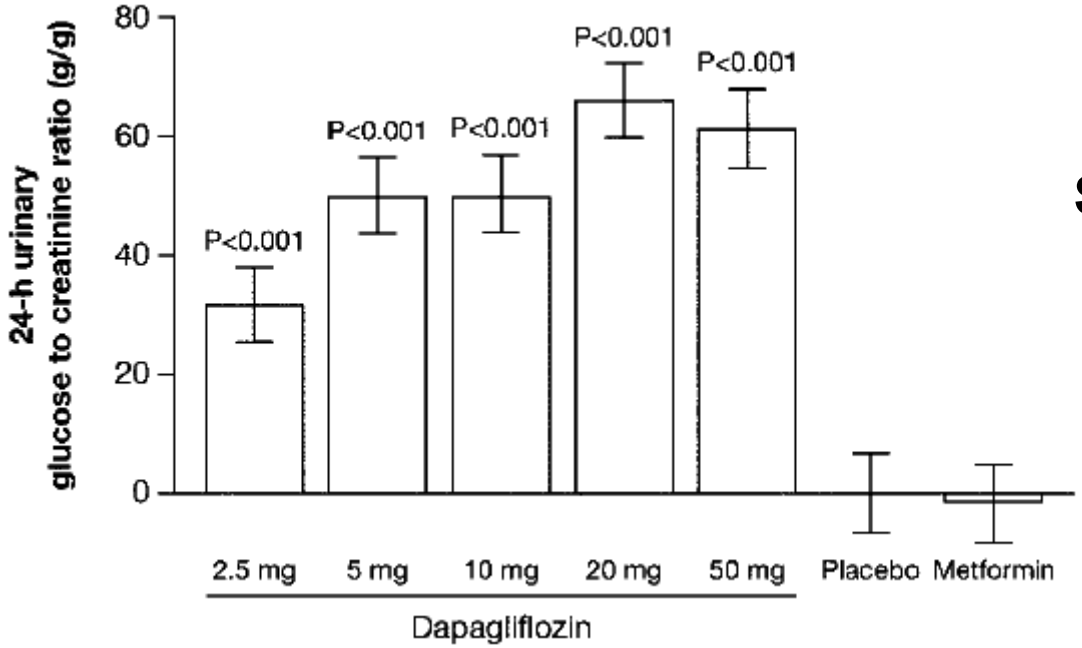
Duckworth, New Engl.J.Med. (2009) 360:129

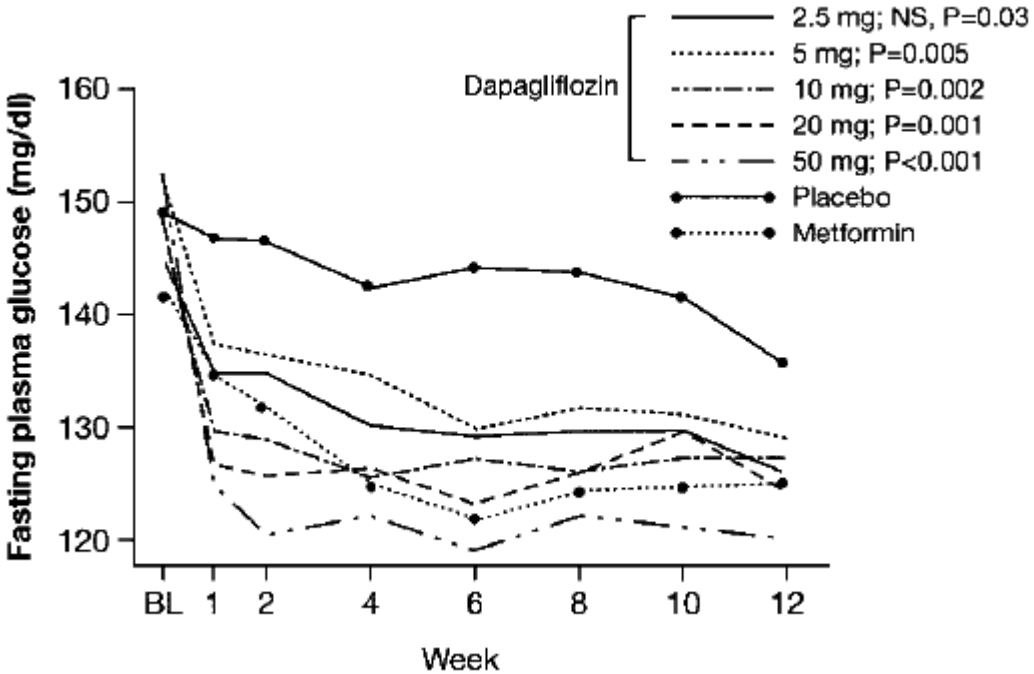
Glitazones prevent podocyte injury in the (non diabetic !) proteinuric puromycin model

(Apoptosis)



Kanjanabuch, Kidney Internat.(2007) 71:1232





Sodium-glucose-cotransport inhibition
(Dapagliflozin)

List,
Diabetes Care (2009) 32:650

- natriuresis
- moderate blood pressure decrease
- upregulation of RAS
- effectiveness of RAS blockade increased

(Ferranini E.)

Glycemic Control
in CKD

Poor glycemic control → poor survival

Glycemia → thirst

hypervolemia

hyperkalemia

Nephrol Dial Transplant (2009) 24: 338–341
doi: 10.1093/ndt/gfn616
Advance Access publication 17 November 2008

Which hypoglycaemic agents to use in type 2 diabetic subjects with CKD and how?*

Masakazu Haneda[1] and Akizuki Morikawa[2]

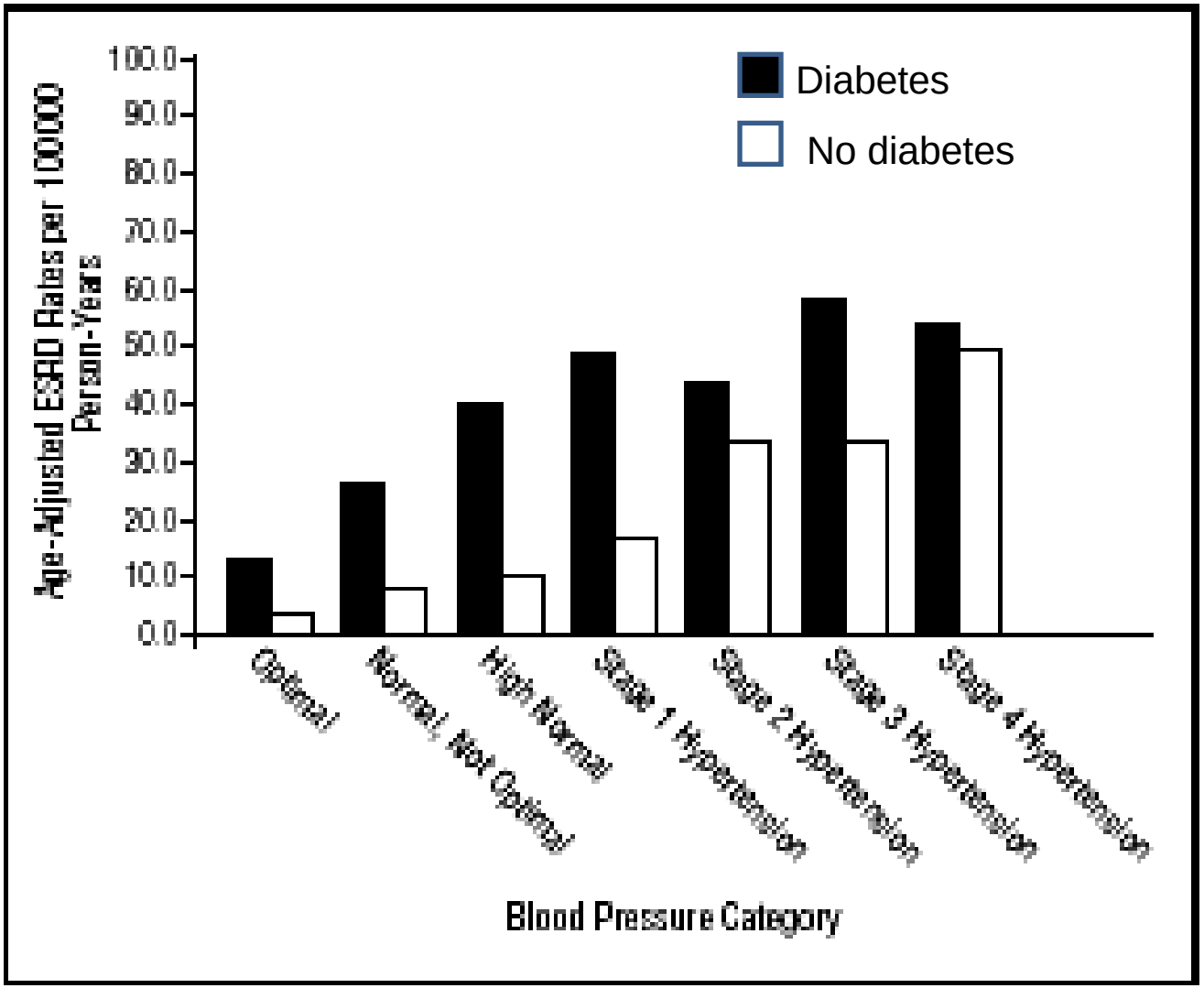
[1]Department of Medicine, Division of Metabolism and Biosystemic Science, Asahikawa Medical College and [2]Asahikawa Red Cross Hospital, Asahikawa, Hokkaido, Japan

Diabetes –
CKD and ESRD

- Epidemiology
- Not all diabetic nephropathy is created equal
- The role of glycemic control
- The role of blood pressure control and RAS blockade

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

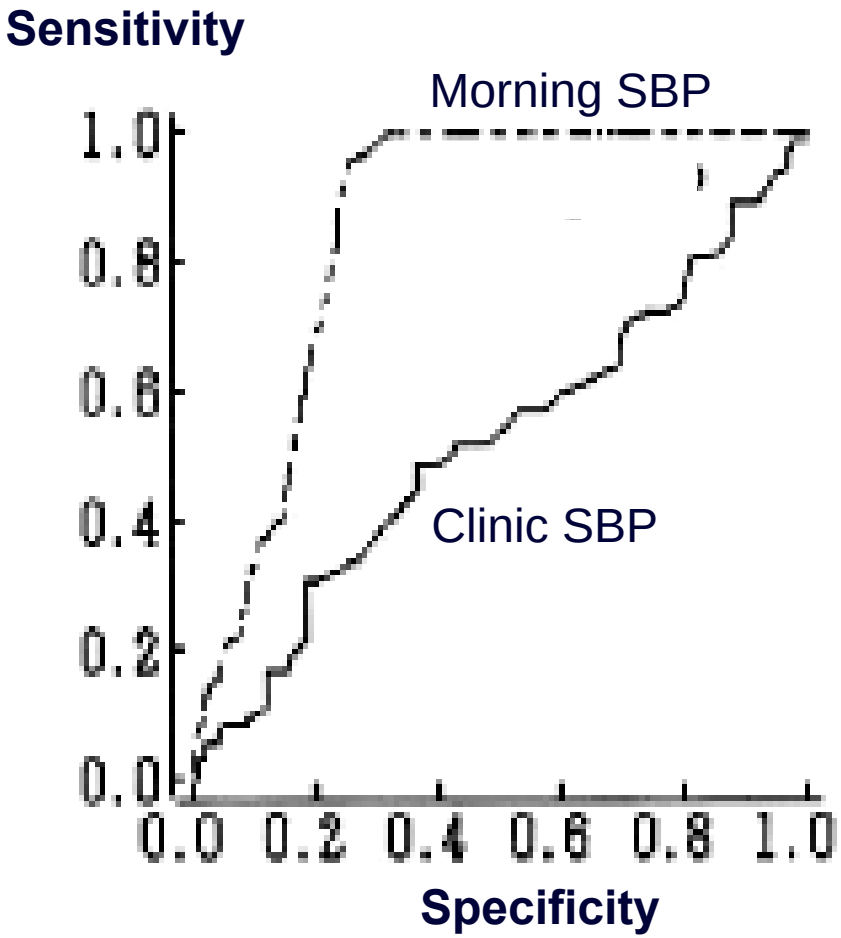
(Kaiser Permanente cohort)



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

Self-measured morning blood pressure
superior to clinic blood pressure in predicting diabetic complications

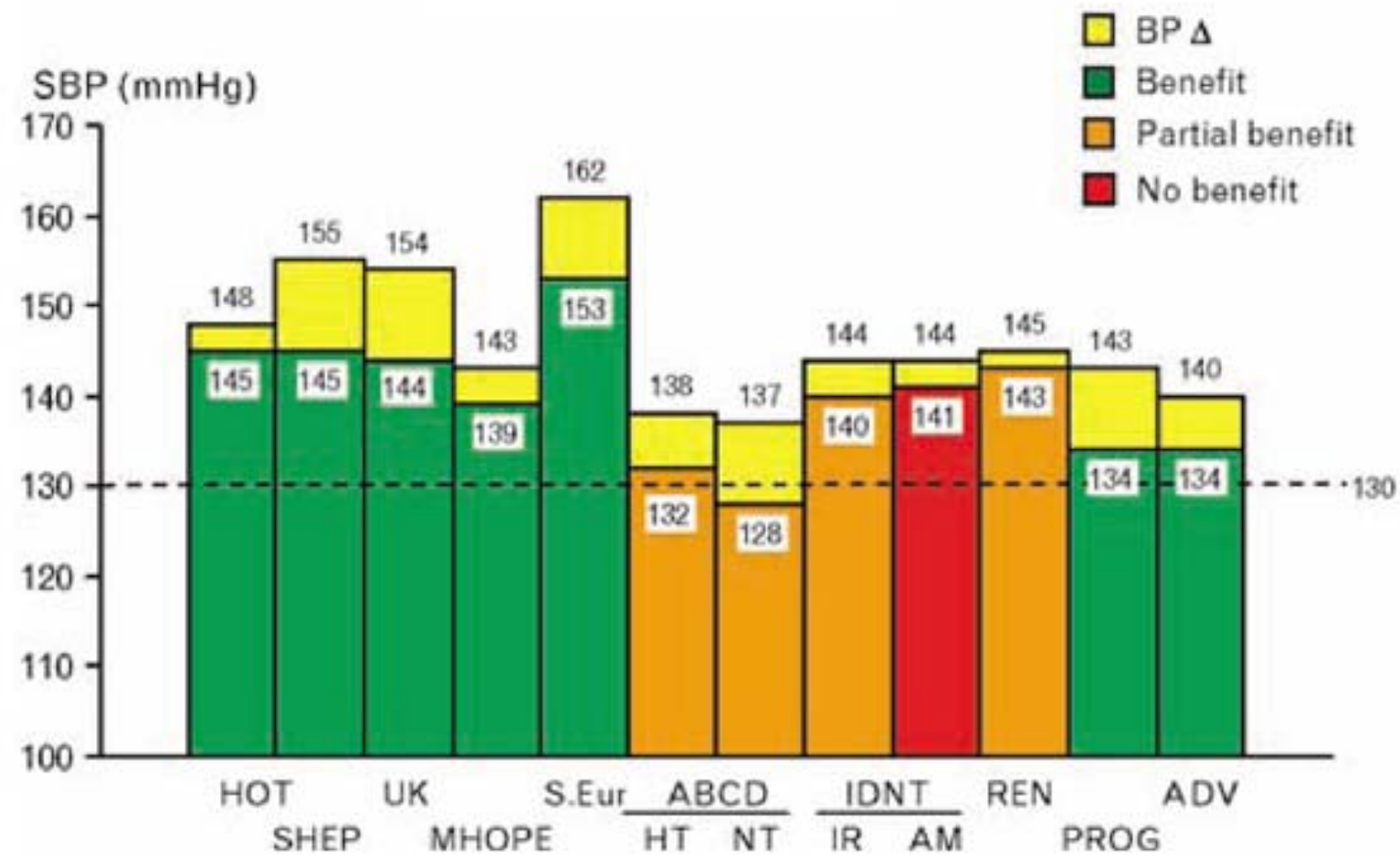
(nephropathy, retinopathy, coronary disease)



Kamoi, Diabetes Care (2002) 25:2218

Achieved systolic blood pressure of diabetic patients

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



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

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

even if BP is within the normotensive range

	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

Individualise treatment

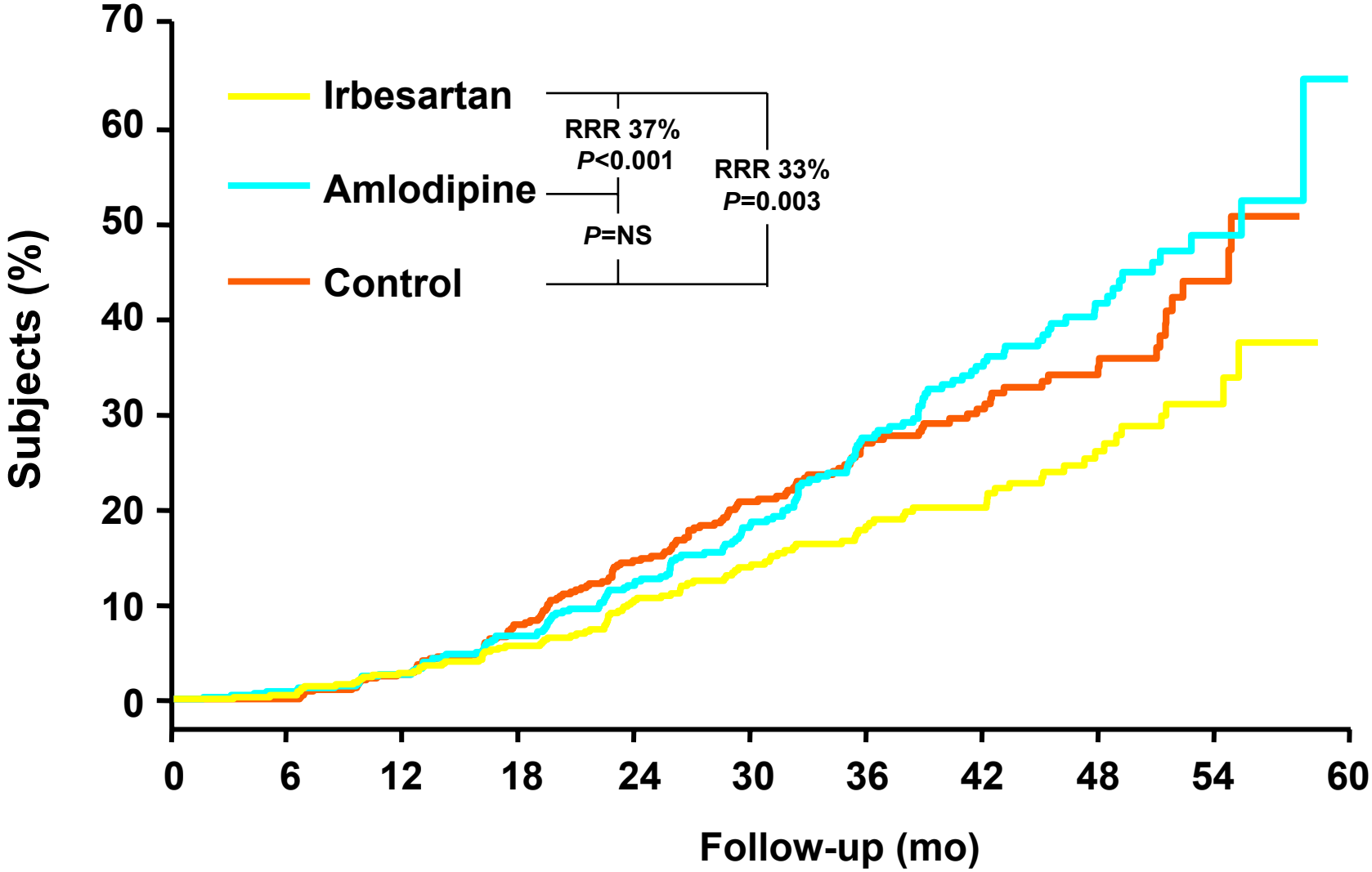
more aggressive :

- ***in young patients***
- ***in patients with short duration of diabetes***
- ***in patients with high life expectancy***
- ***in patients with small risk of hypoglycemia***

emphasis :

- ***multifactorial treatment***

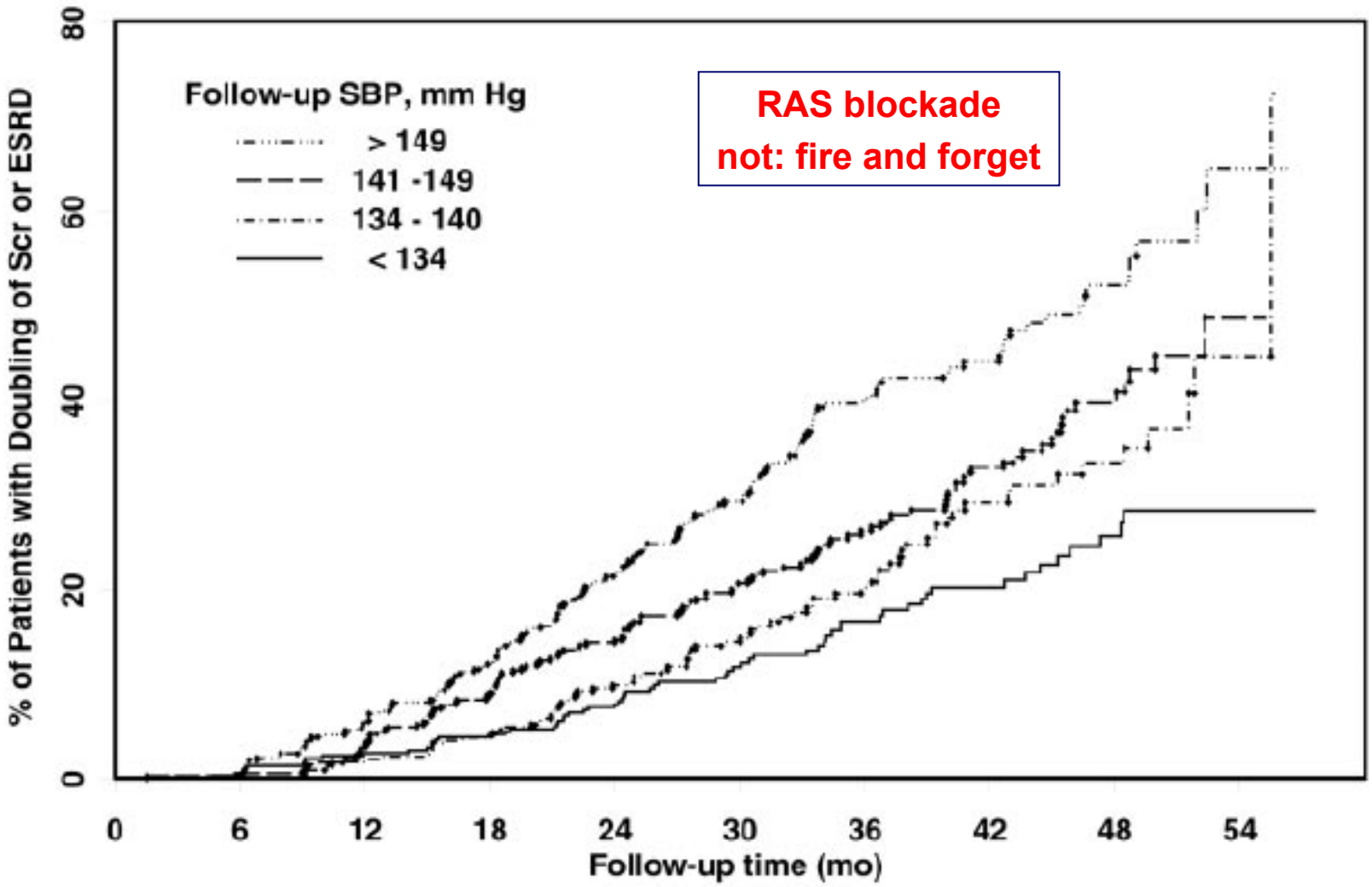
Time to Doubling of Serum Creatinine – *improved outcome with RAS blockade*



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

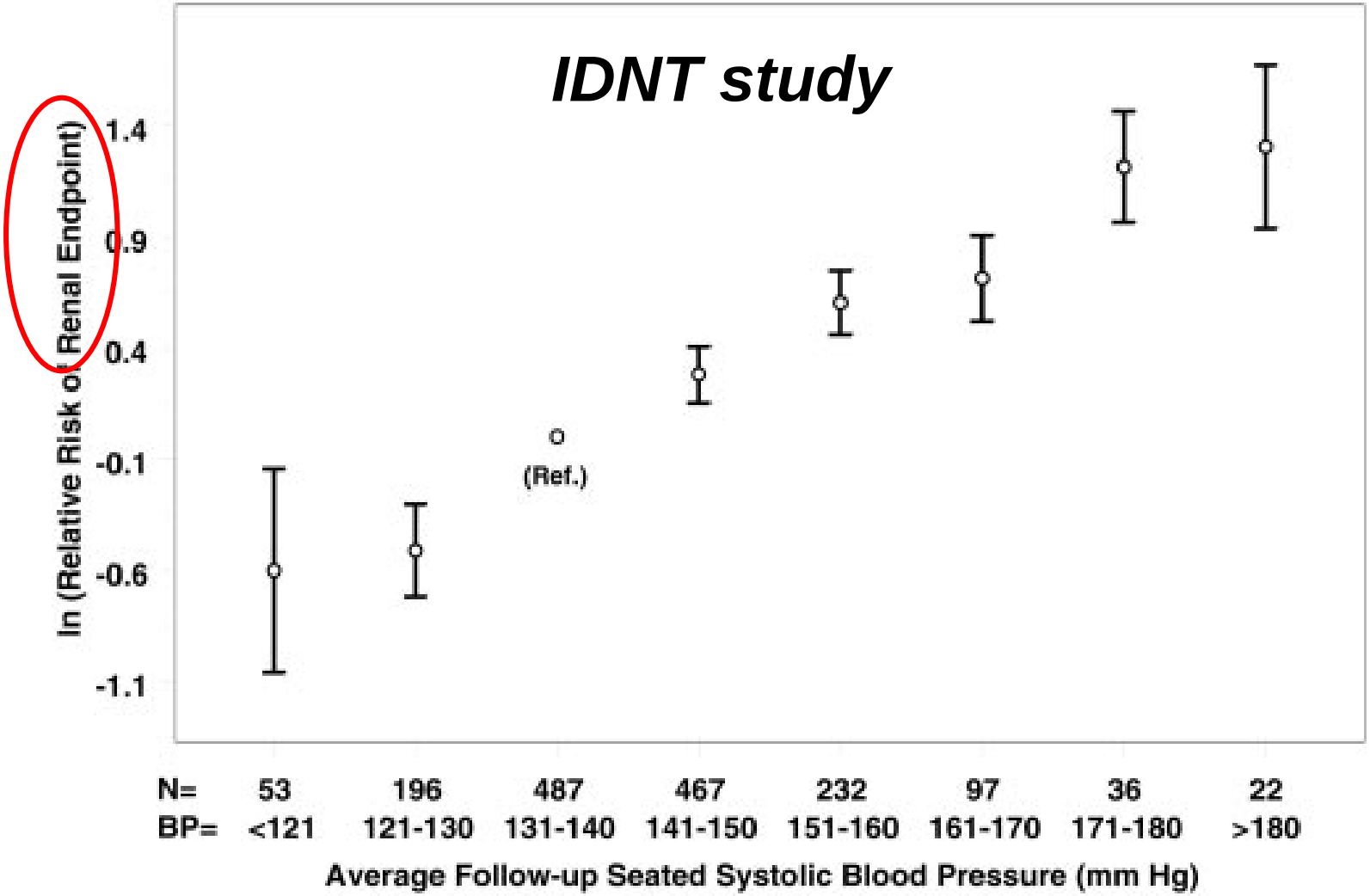
Independent and additive impact of blood pressure control and RAS blockade on progression

IDNT study



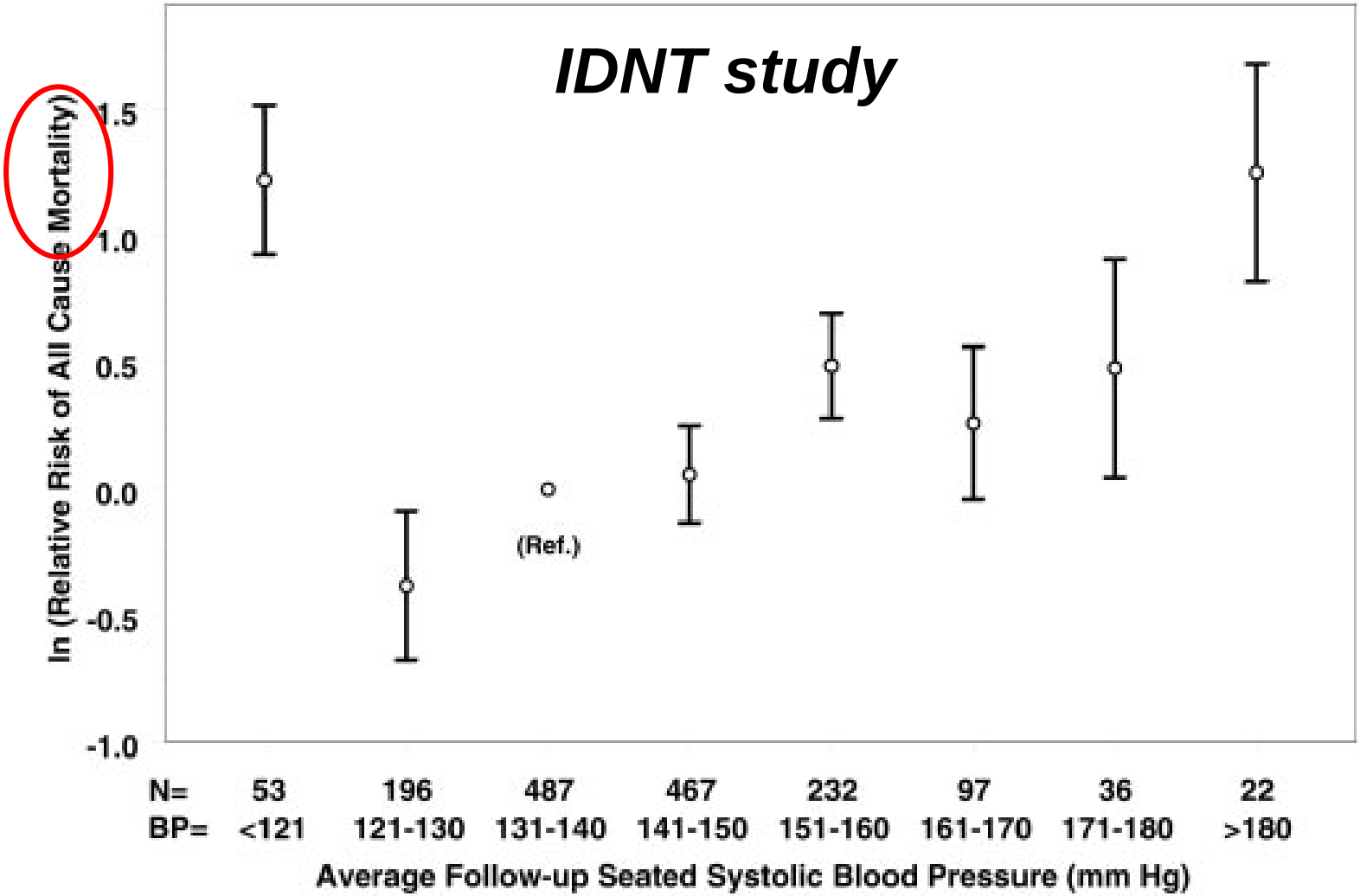
Pohl, J.Am.Soc.Nephrol.(2005) 16:3027

Intensive lowering of systolic blood pressure
renoprotection



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

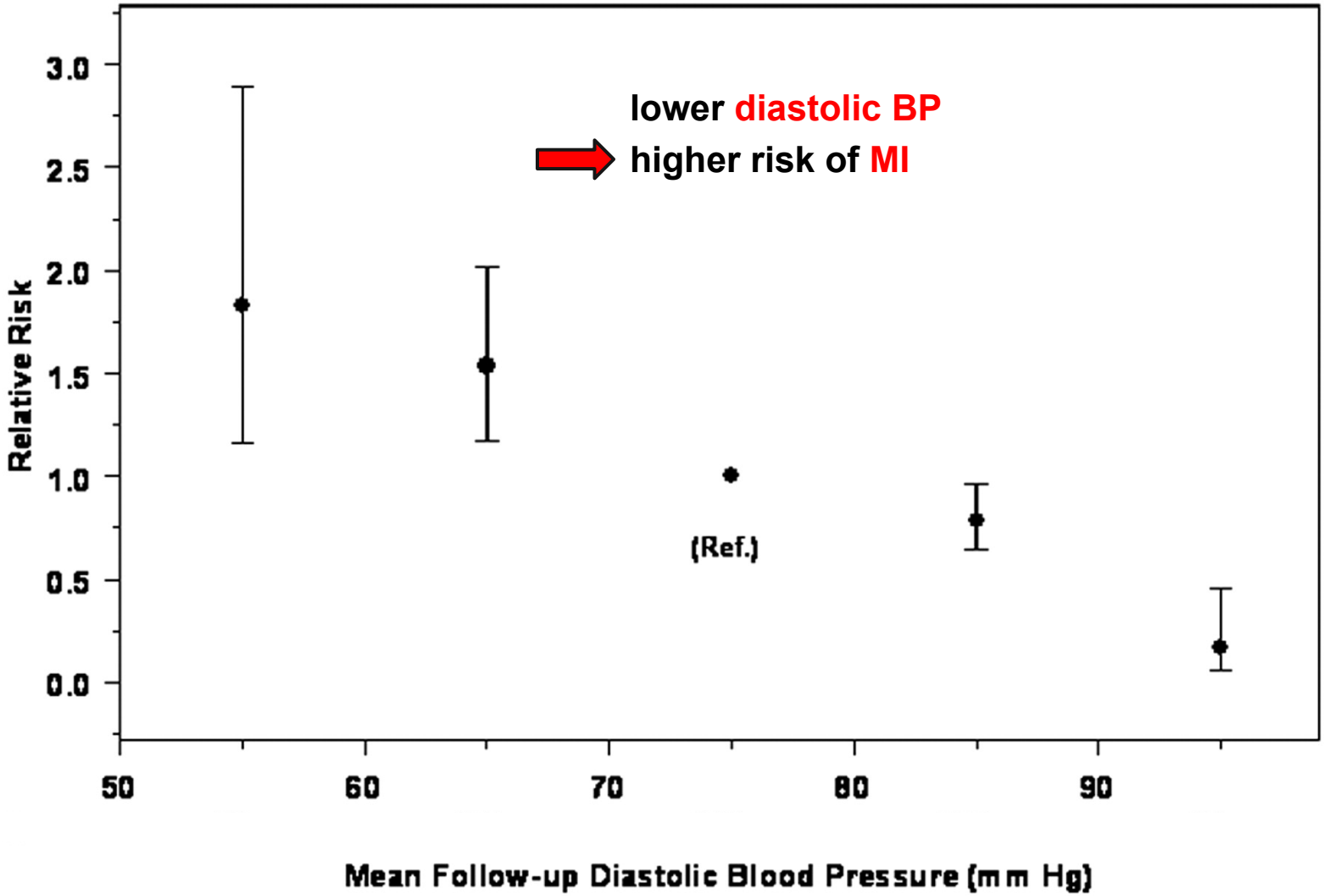
Intensive lowering of systolic blood pressure *increased mortality*



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

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

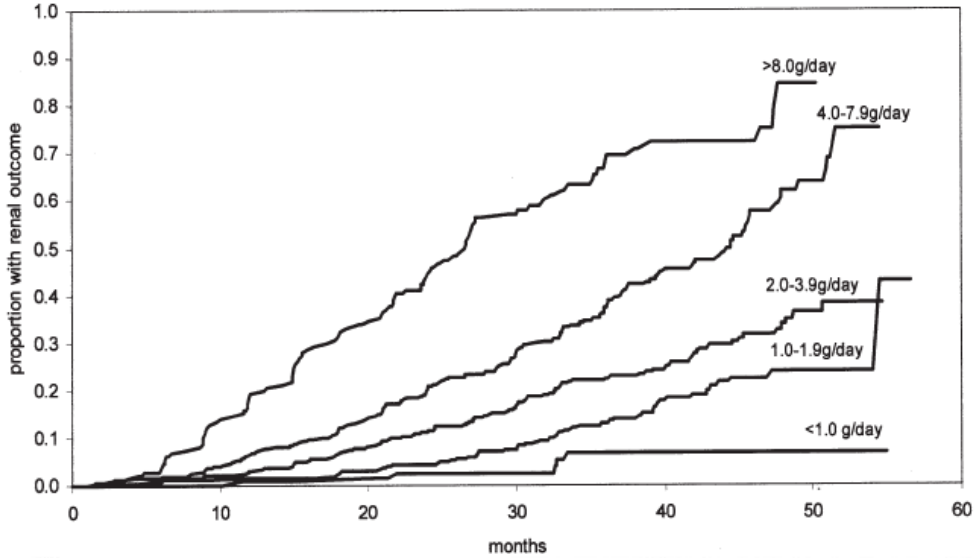
(IDNT study)



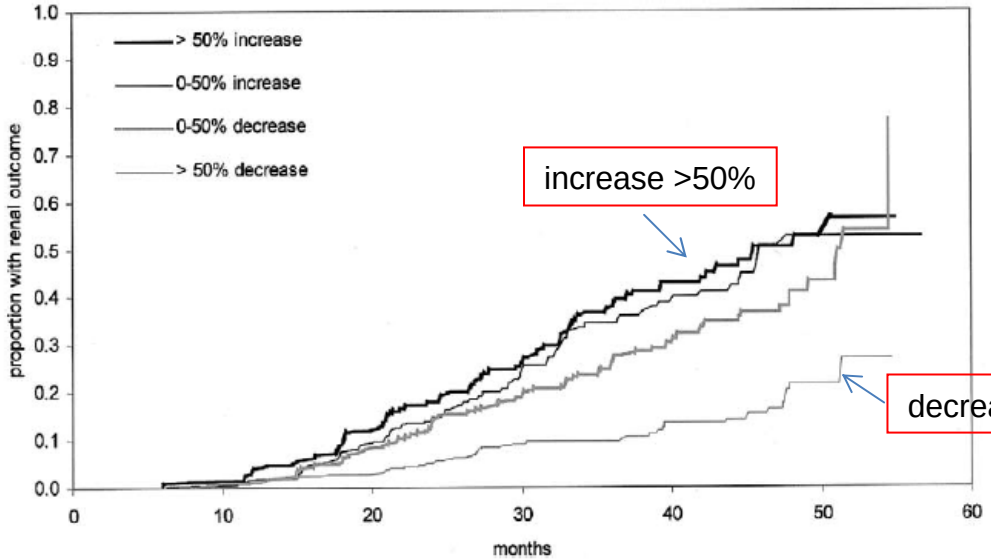
Berl., J.Am.Soc.Nephrol.(2005) 16:2170

Is proteinuria a target for intervention? What is the evidence ?

reaching a renal endpoint in IDNT



baseline value



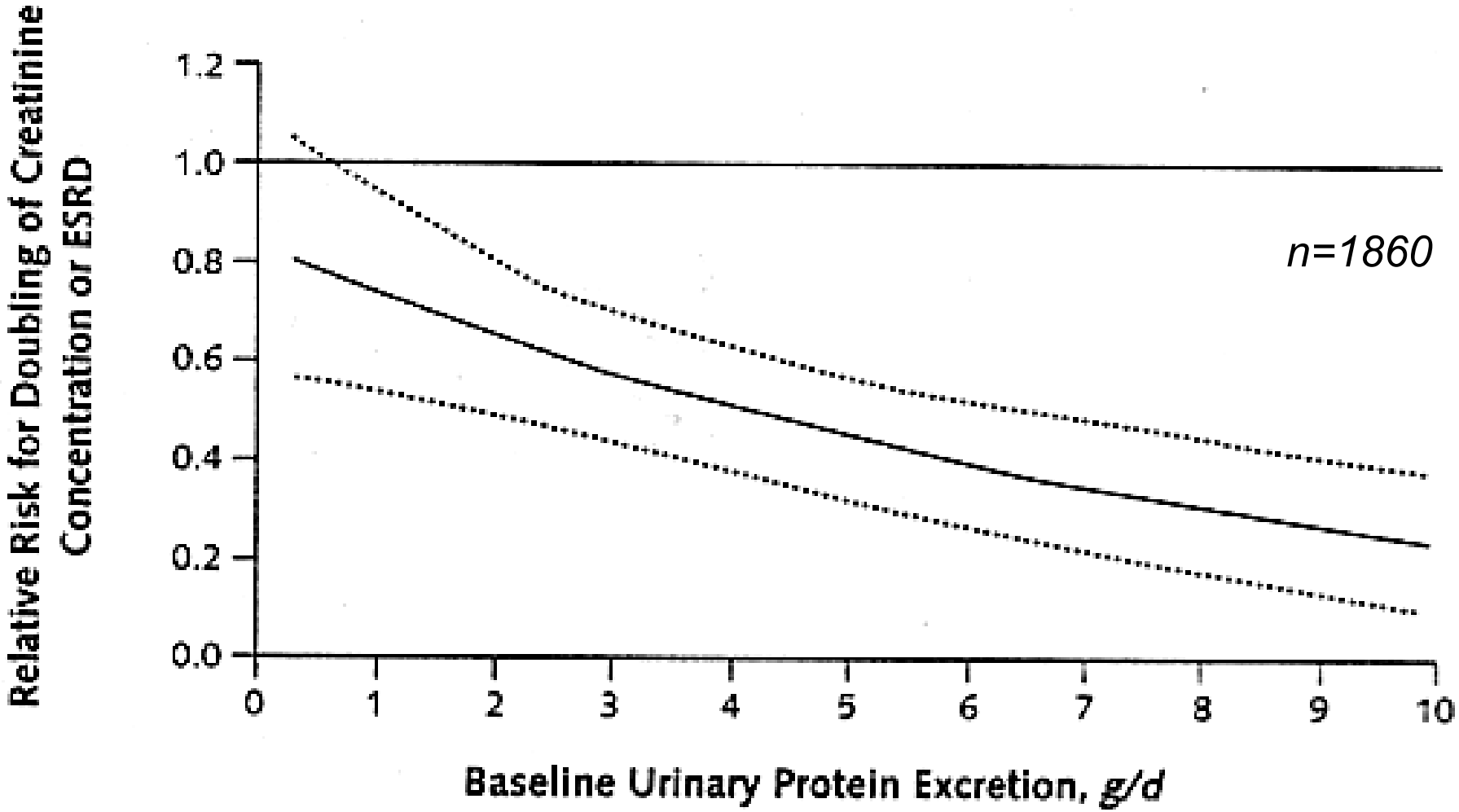
treatment effect

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

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

Escape

secondary increase of proteinuria after initial response to RAS blockade

conventional:

- dose escalation
- combination ACEi + ARB (?)
- Spironolactone / Eplerenone
- Aliskiren
- Endothelin Rezeptor Blocker
- Paricalcitol

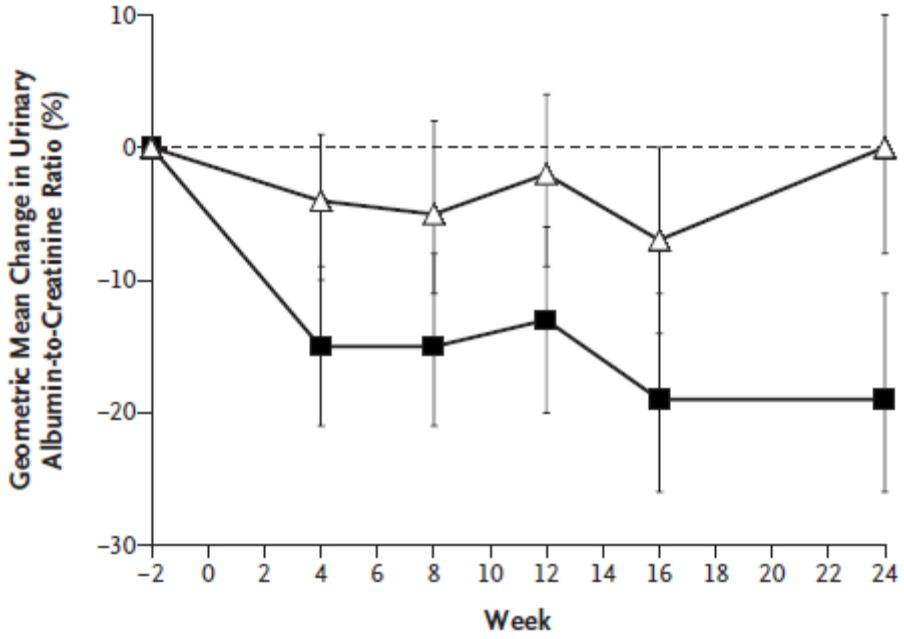
…

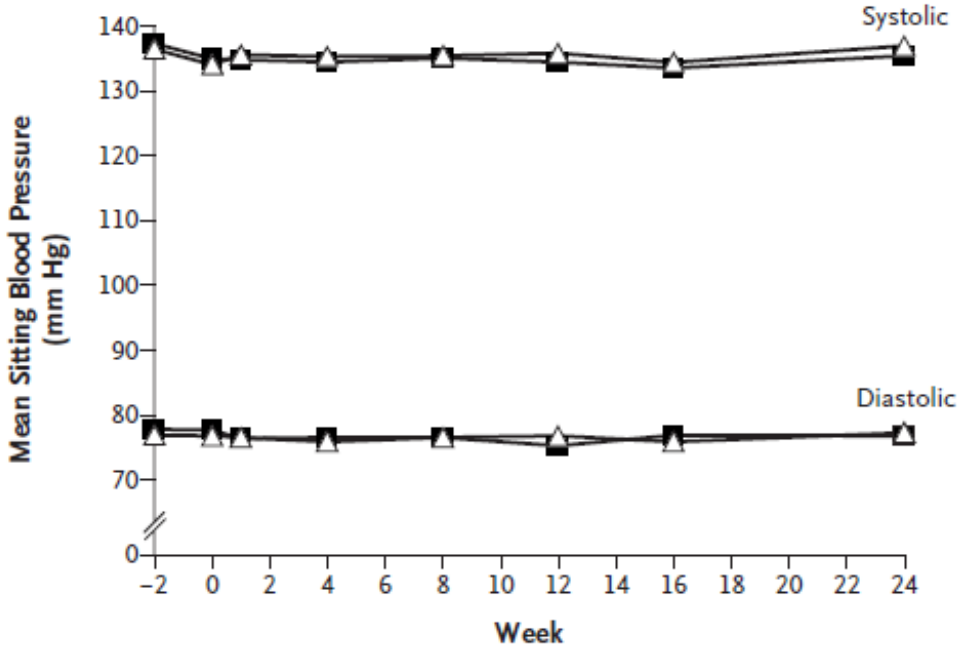
preclinical:

- renin receptor inhibitors
- AT2 receptor agonisten
- chymase-Hemmung

Reduction of proteinuria in type 2 diabetic patients by Aliskiren on top of Losartan

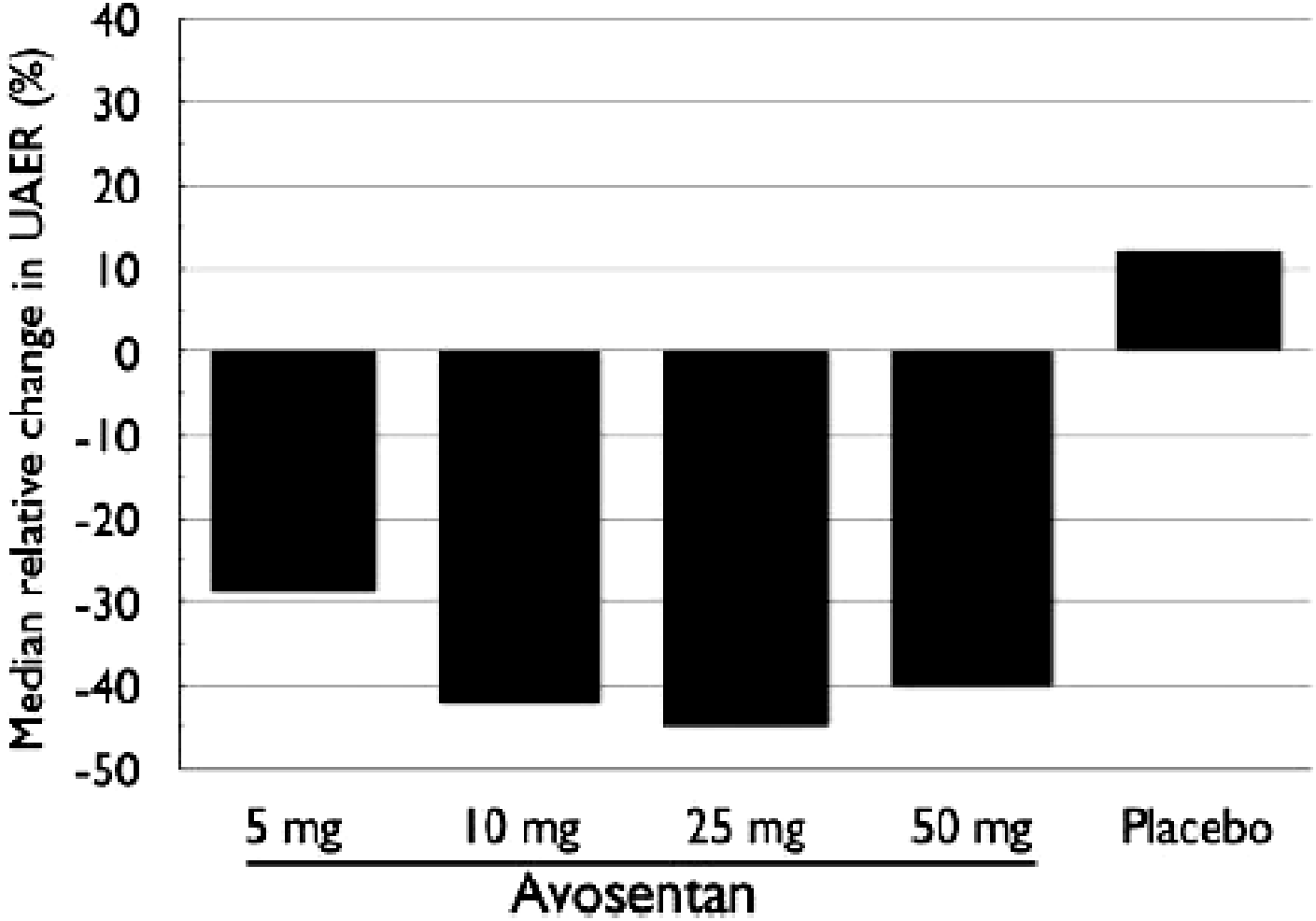
■ Aliskiren △ Placebo





Parving, New Engl J. Med.(2008) 358:2433

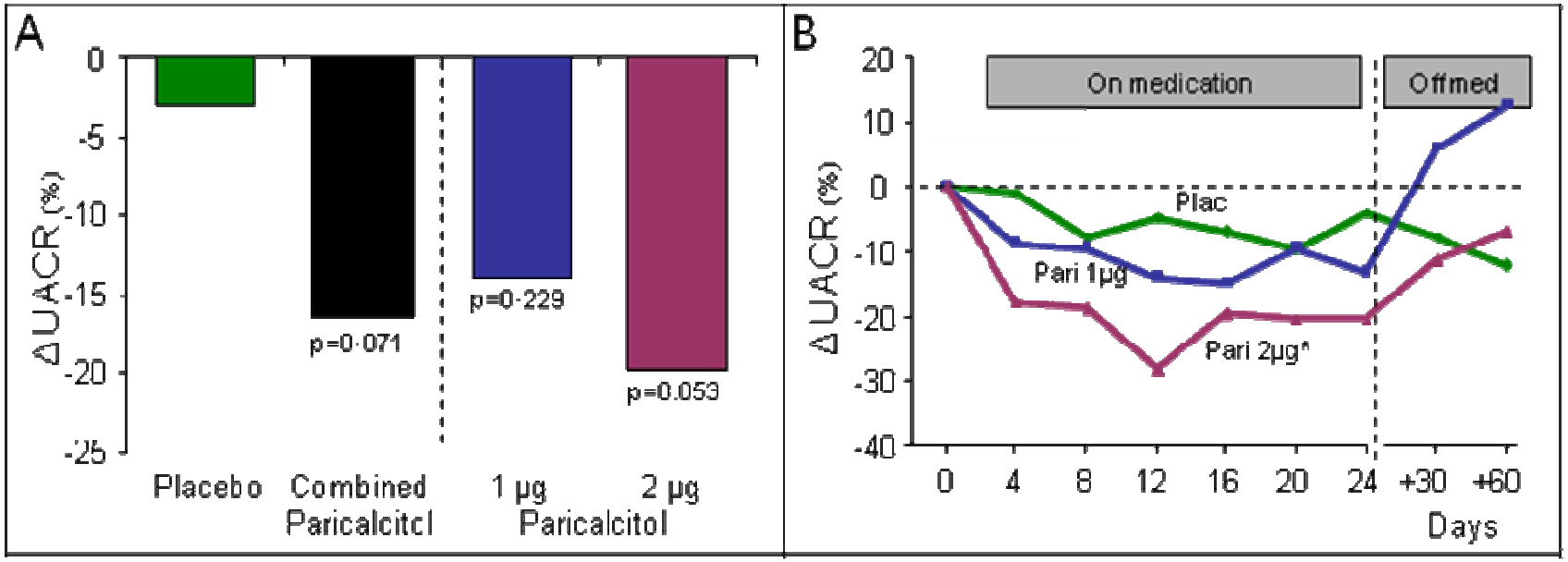
Endothelin (ET_A) receptor blocker Avosentan reduces albuminuria in early stages of type 2 diabetes with nephropathy



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

Paricalcitol 1 µg and 2 µg/day reduces albuminuria in type 2 diabetics

(VITAL study)



De Zeeuw, Lancet (in press)

Hypertension in the Diabetic Patient With Renal Failure

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

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, New Engl.J.M ed. (2003) 348, 383

Diabetes –
CKD and ESRD

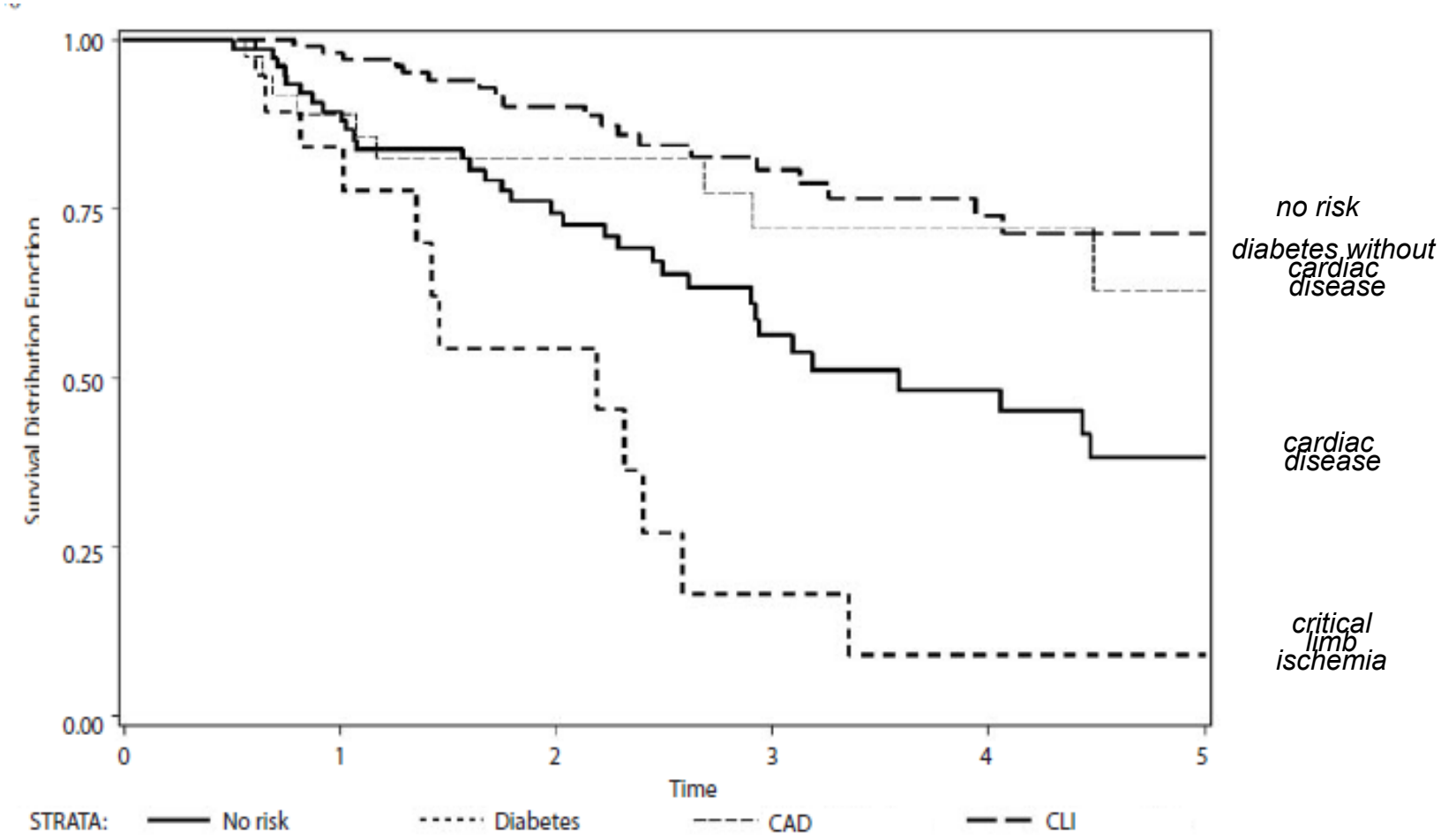
- Epidemiology
- Not all diabetic nephropathy is created equal
- The role of glycemic control
- The role of blood pressure control and RAS blockade
- The diabetic patient on hemodialysis

Survival probability of incident dialysis patients 1996-2000

	1st year	2nd year	5th year
• **all**	**89.2**	**79.8**	**55.9**
	(89.0-89.7)	*(79.5-80.1)*	*(55.5-56.3)*
• **diabetes**	**84.6**	**70.1**	**37.6**
	(84.7-85.1)	*(69.4-70.9)*	*(36.8-38.5)*

www.era-edta-reg.org/ondex.jsp

Critical limb ischemia – high mortality



Koch, Nephrol.Dial.Transplant.(2004) 19:2547

Foot Lesions in Diabetic Patients

(strongest predictor of mortality)

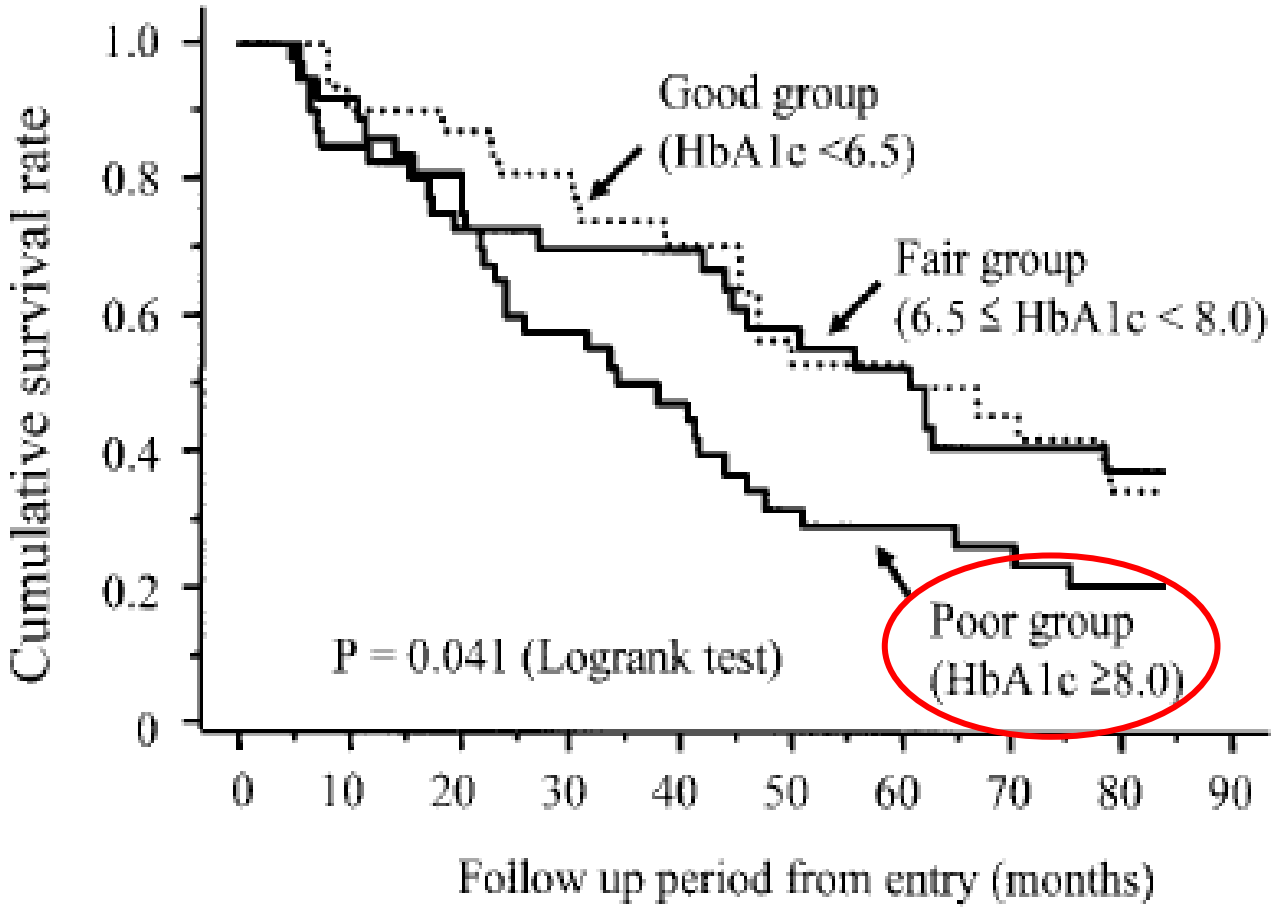
Neuropathic	Ischemic
Painless	Painful (intermittent claudication)
Foot warm, pink	Foot cold and livid
Foot pulses +	Foot pulses attenuated or absent
Sensation impaired	Sensation unimpaired
Painless metatarsal ulcer with necrosis below callus	Acral necrosis (tip of toe,heel)

Overall mortality

Parameter	RR	95 % CI	p-Wert
PTCA / bypass, MI or CHD	1.37	1.14-1.63	0.0006
heart failure	1.33	1.12-1.59	0.001
peripheral artery disease	1.75	1.48-2.08	<0.0001

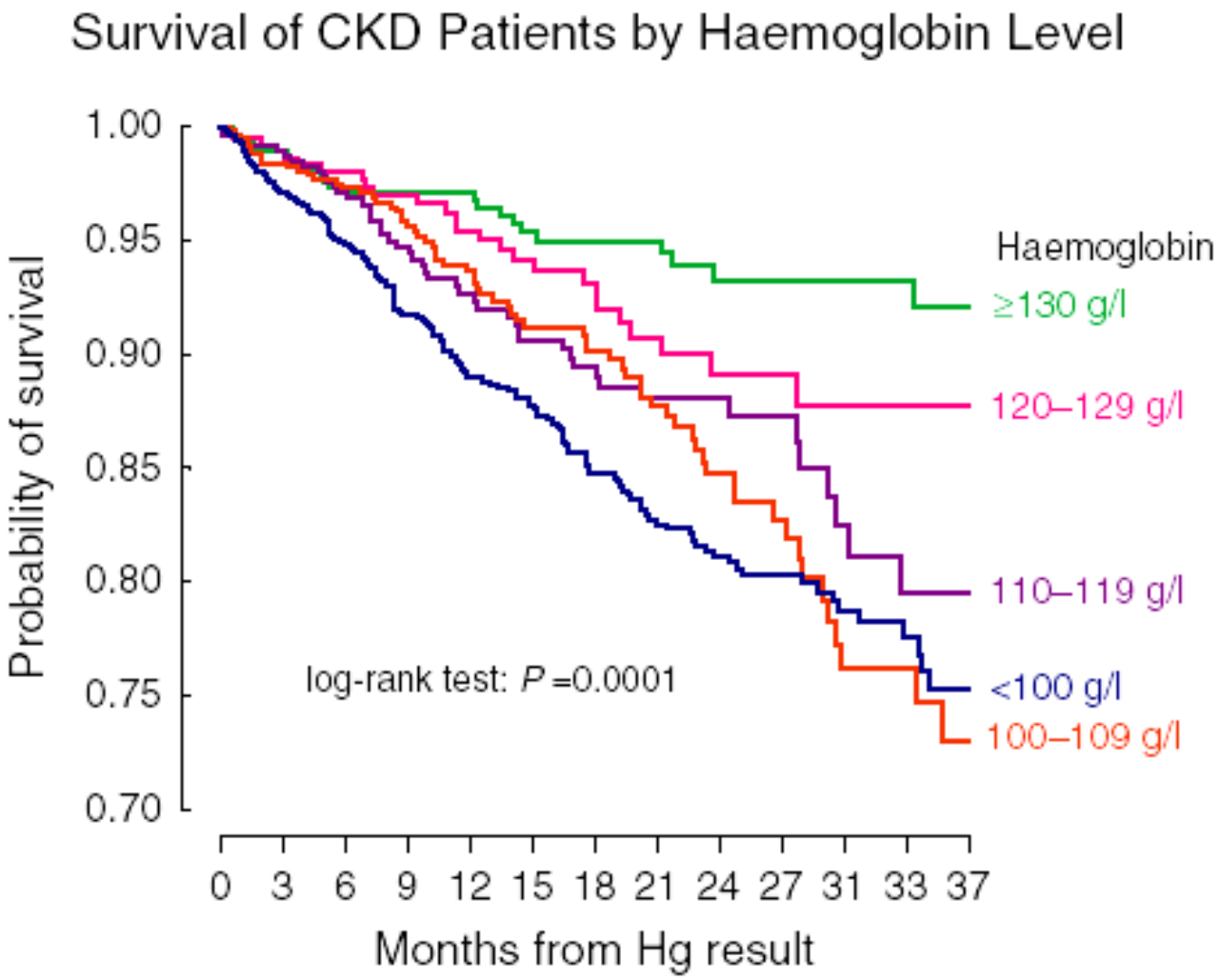
Wanner, New Engl J Med (2005) 353:238

$HbA1_c$ and survival on hemodialysis
7 year observational study



Nishizawa, Diab.Care (2006) 29:1496

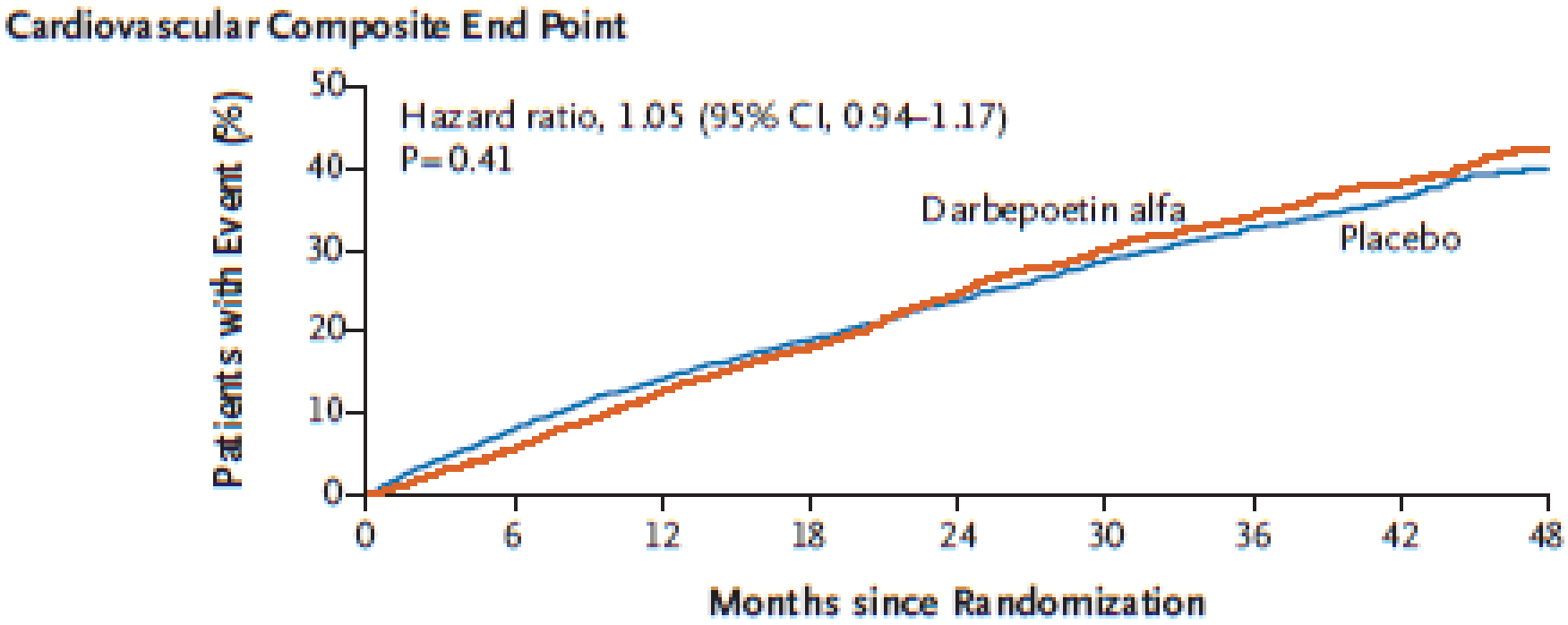
Hb at time of referral to nephrologist impacts on survival



Levin, Nephrol.Dial.Transpl.(2006) 21: 370

Treat study –

no cardiovascular benefit by Hb > 9% in predialysis type 2 diabetic patients



Pfeffer, New Engl.J.Med.(2009) 361:2019