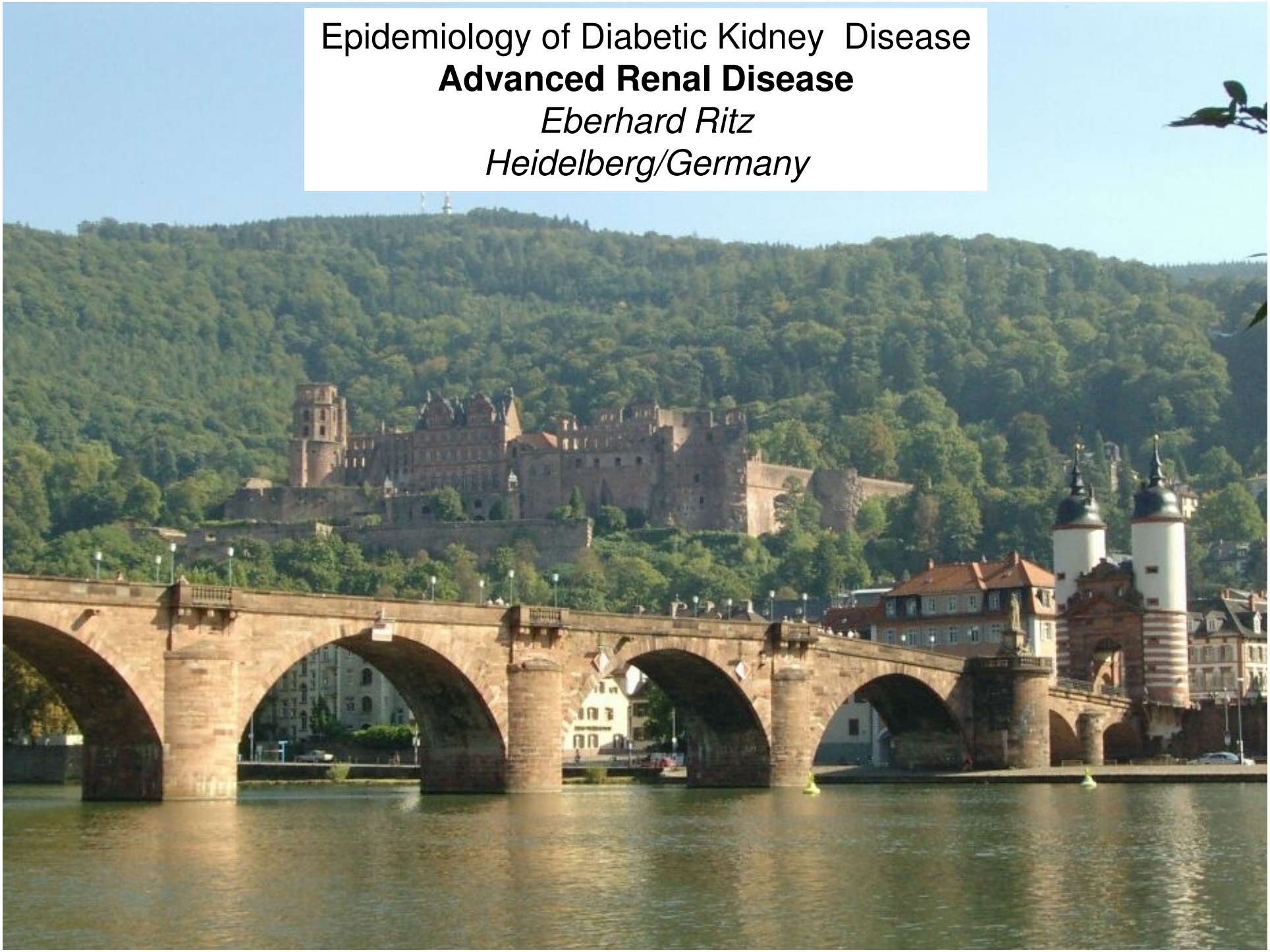
Epidemiology of Diabetic Kidney Disease

Advanced Renal Disease

Eberhard Ritz
Heidelberg/Germany



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

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

Heidelberg **49 % of incident patients**

98 ppm

6 % type 1

94 % type 2 **OGTT !**

Schwenger, Dtsch Med Wschr (2001) 126: 1322

Undiagnosed Glucose Metabolism Disorders in Dialysis Patients:
Oral Glucose Tolerance Test in German Dialysis Centers

Krämer B.K.,Mannheim

ASN-Philadelphia November 2011

Result :

38,4% known type 2 diabetes
9,4% unknown type 2 diabetes !
47,8% diabetes

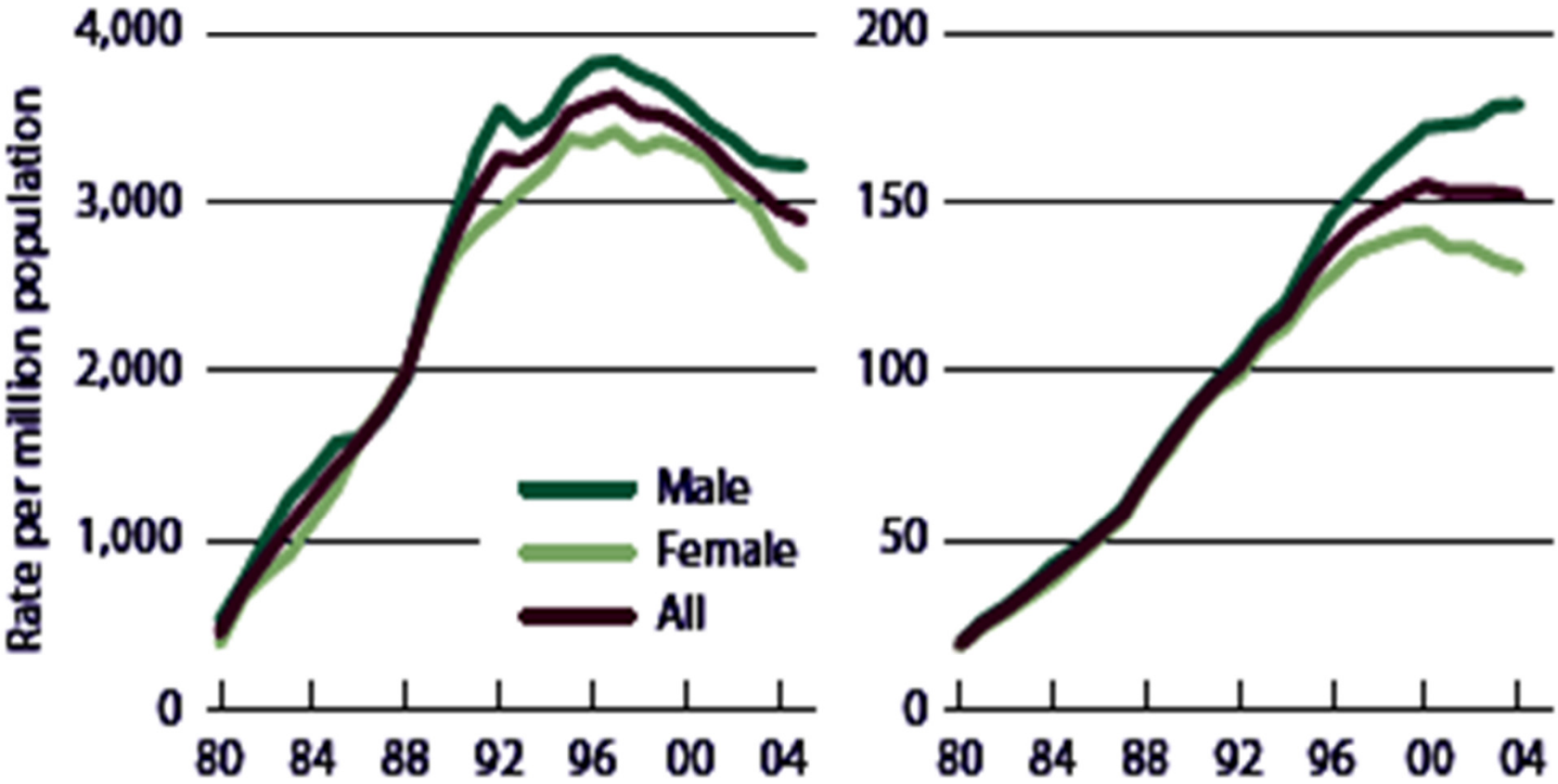
12,3% IFG (impaired fasting glucose)
18,9% IGT (impaired glucose tolerance)

higher risk of diabetes particularly post-transplantation

Adjusted incident rates of ESRD with primary diagnosis diabetes - stabilization

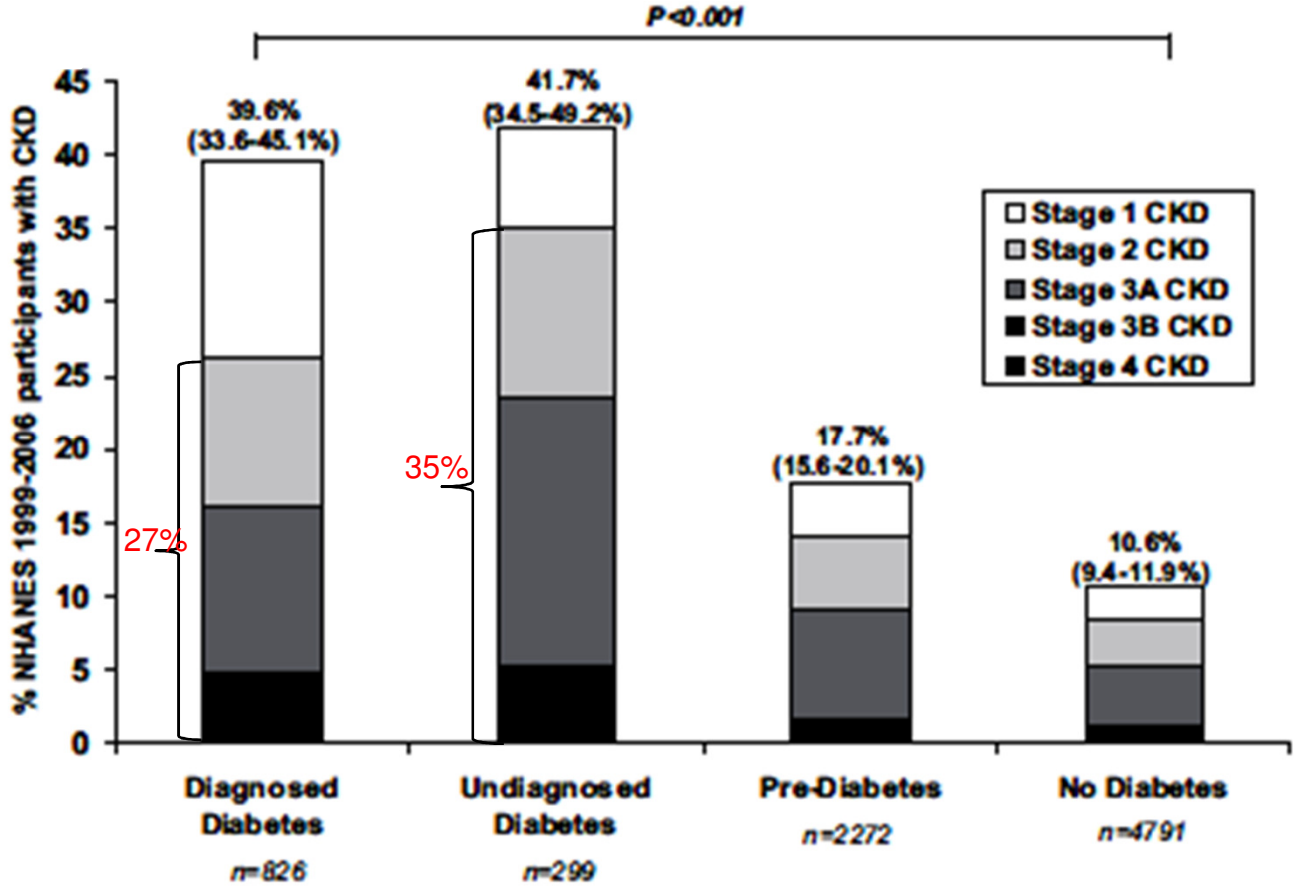
per million diabetics (lead time bias?)

per million general population



USRDS 2007

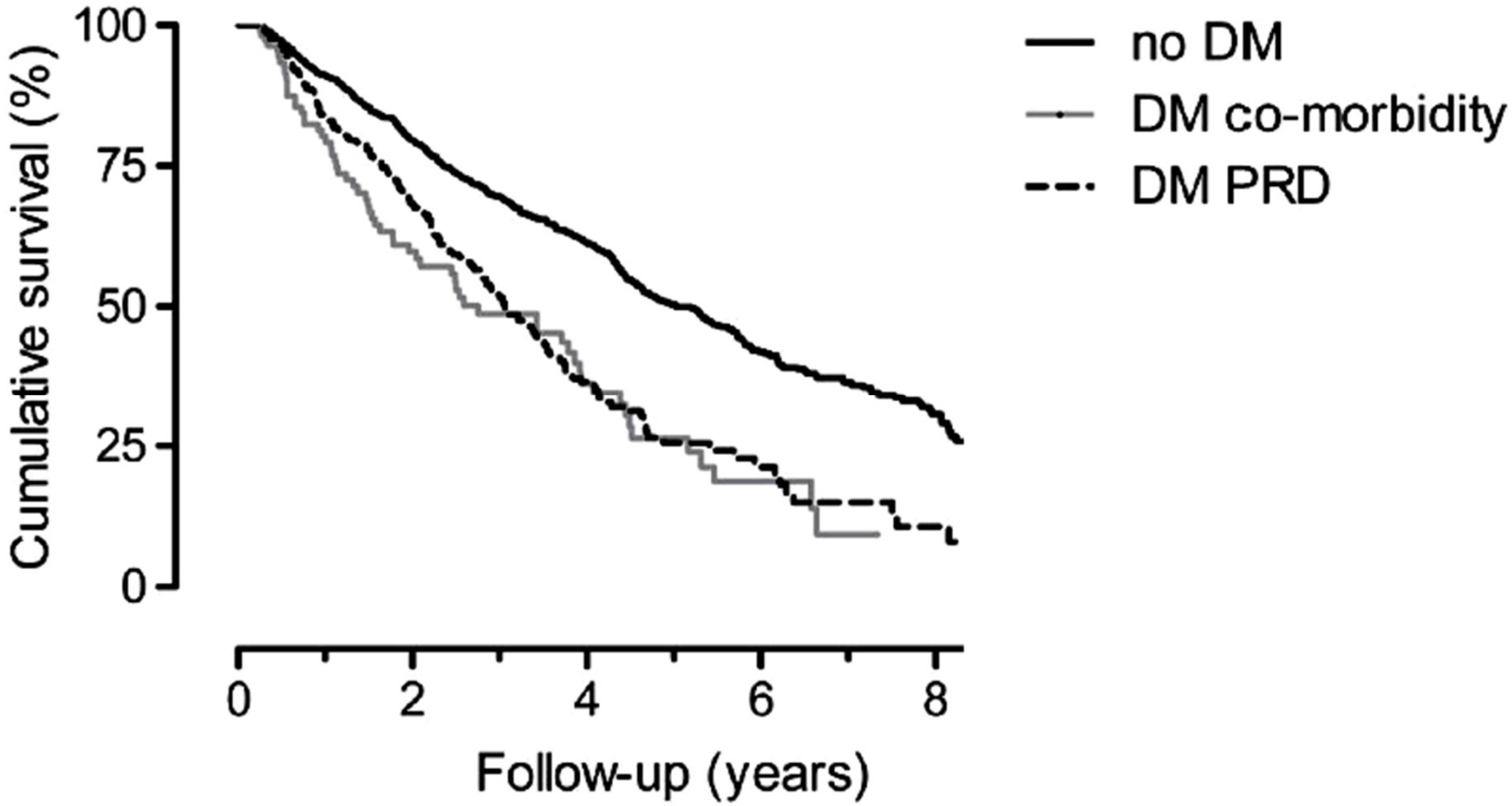
Prevalence of CKD in US Adults with undiagnosed Diabetes or Prediabetes
(NHANES cohort)



39.6% with diagnosed and 41.7% with undiagnosed diabetes had CKD

Plantinga, CJASN (2010) 5: 673

No difference of survival on hemodialysis between
- patients with diabetes as primary renal disease and
- patients with diabetes as a comorbid condition

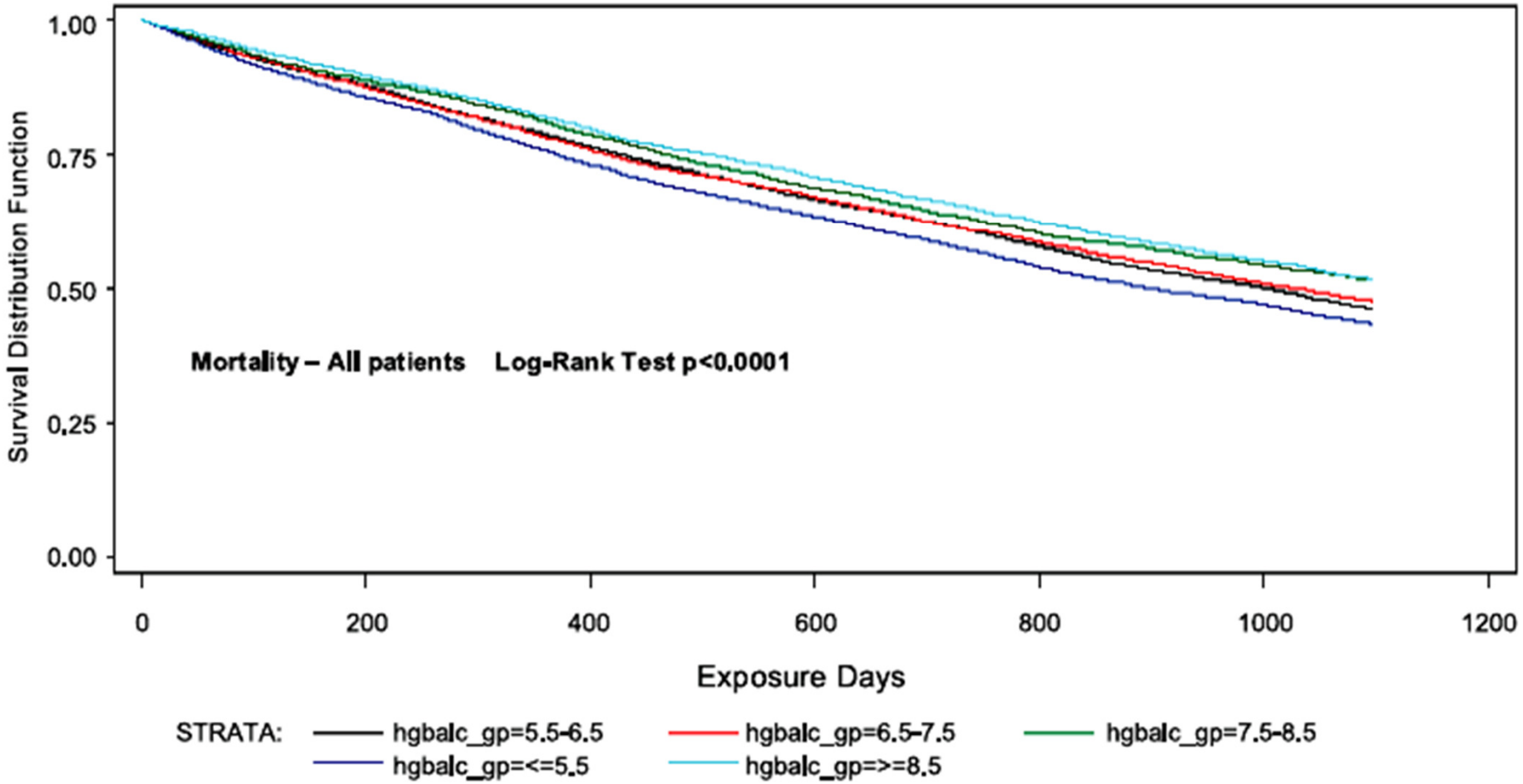


Schroijen, BMC Nephrol.(2011) 12: 69

$HbA1_c$ on Hemodialyis

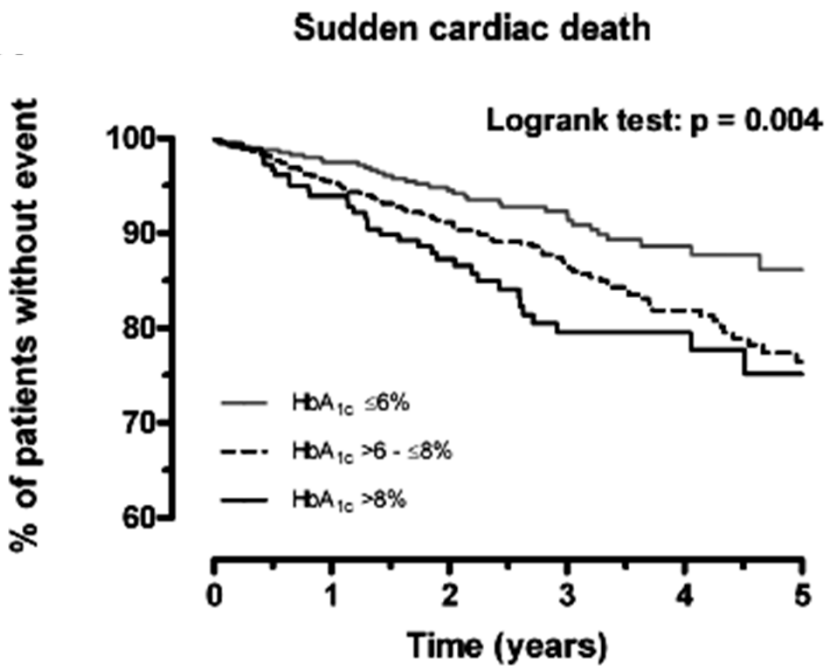
(Does one size fit all?)

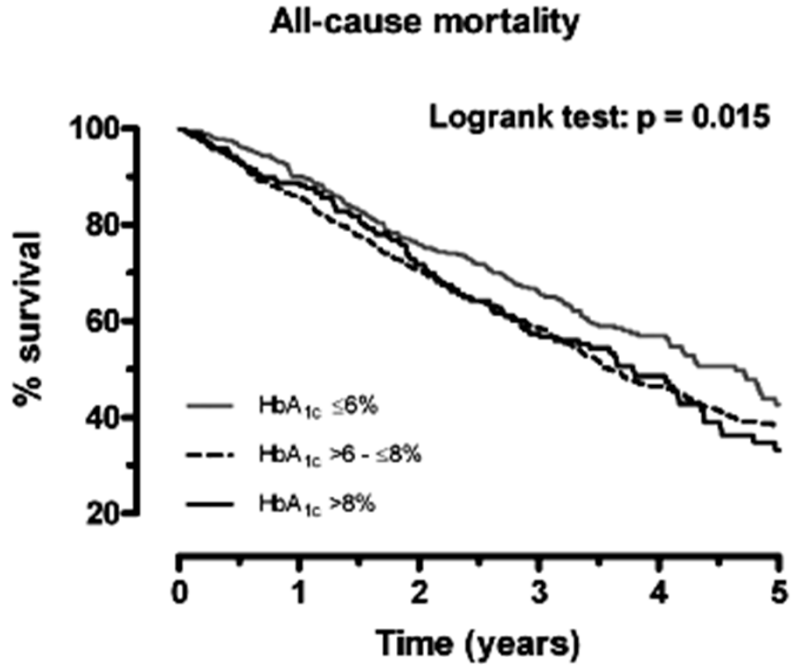
Ix,CJASN(2010) 5:1539



Williams, CJASN (2010) 5:1595

~ Kalantar-Zadeh Diabetes Care (2007) 30:1049





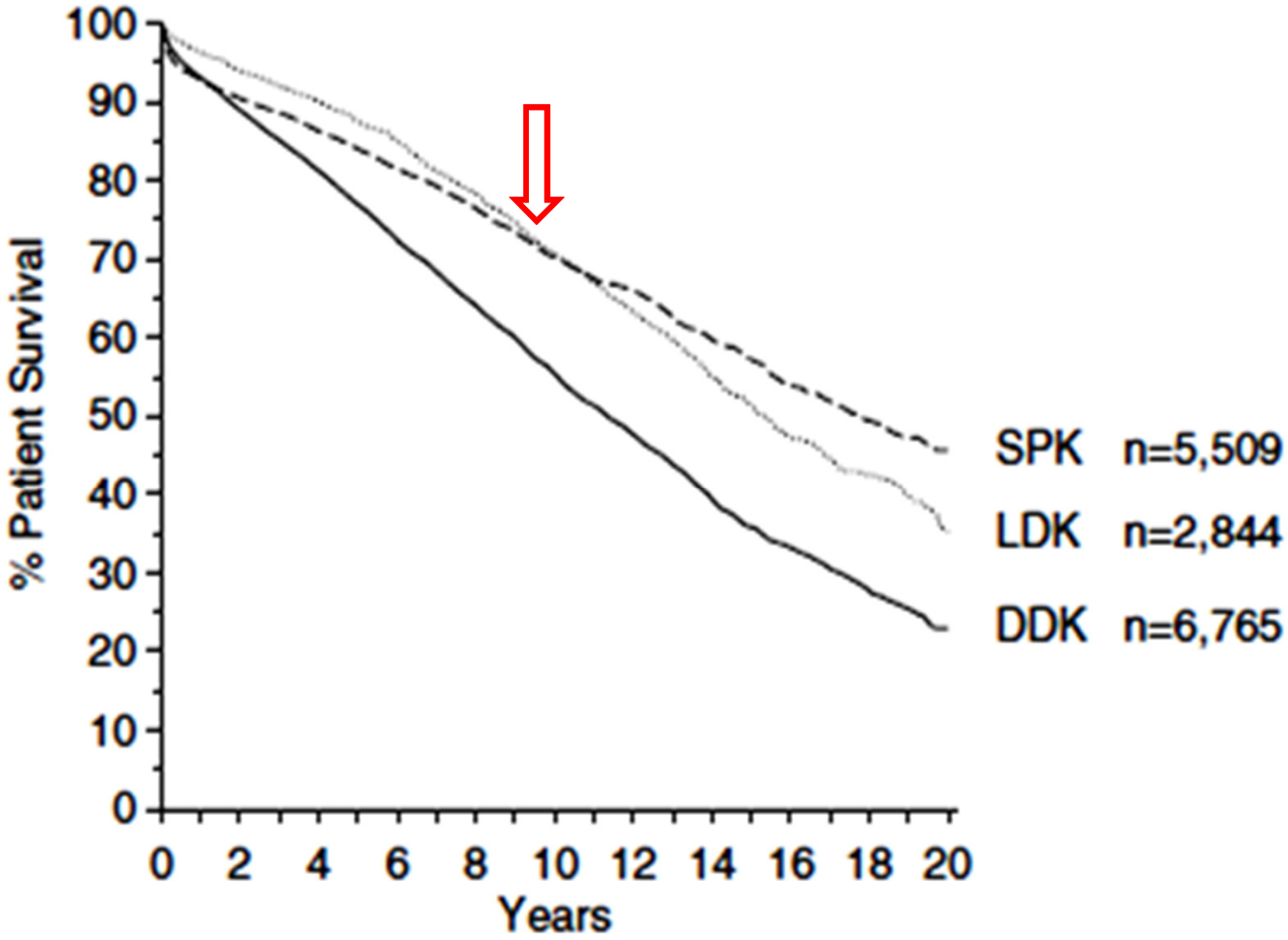
Glycemic control and cardiovascular outcomes in type 2 diabetic patients on HD

(4D study)

Drechsler Circulation (2009) 120:2421

Example of glycemic memory

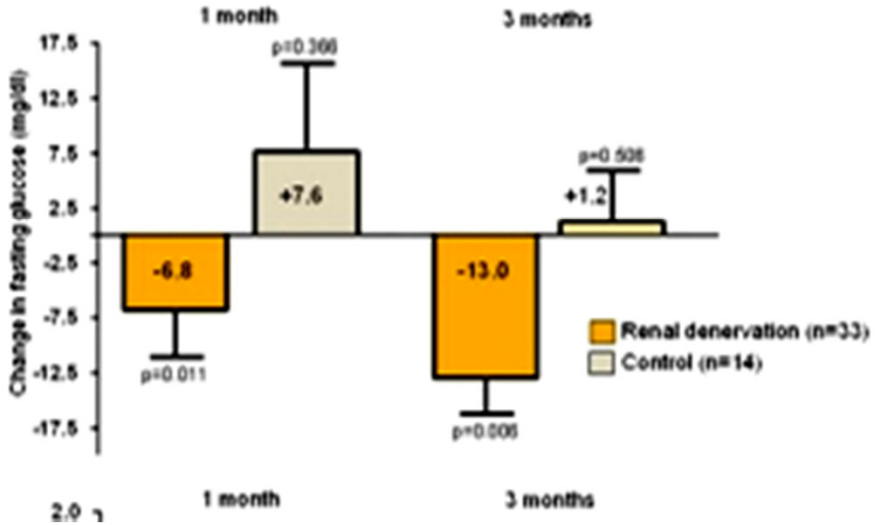
Longterm survival of type 1 diabetic patients
after simultaneous pancreas-kidney-transplantation (SPK), versus life donor kidney- (LDK) or cadaver kidney transplantation (DDK)



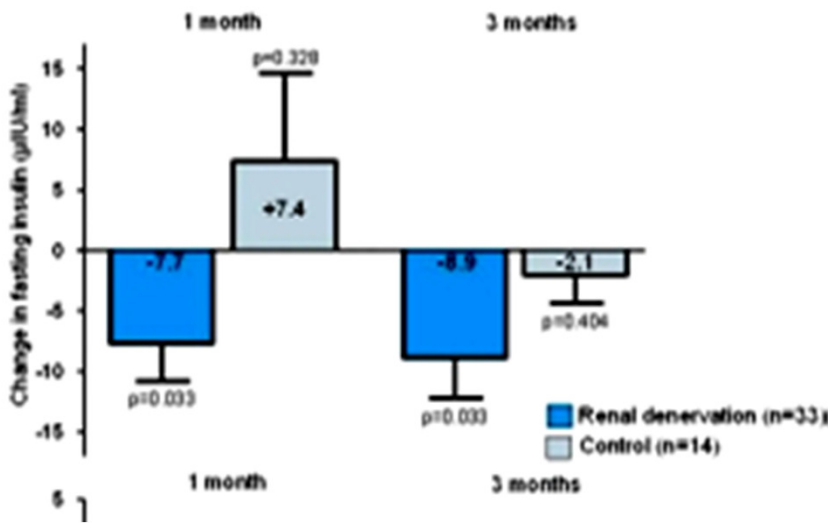
Morath, Clin.J.Am.Soc.Nephrol. (2010) 5:549

Effect of renal denervation :
change of fasting glucose,fasting insulin and insulin resistance

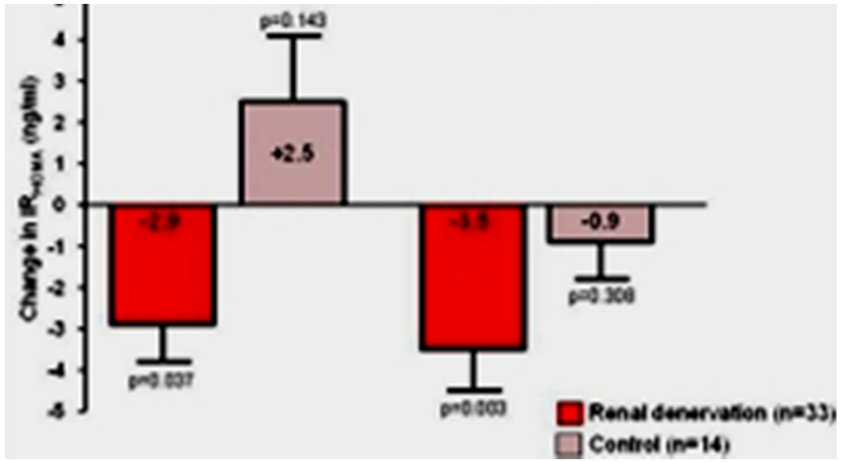
Δ fasting glucose



Δ fasting insulin



Δ insulin resistance



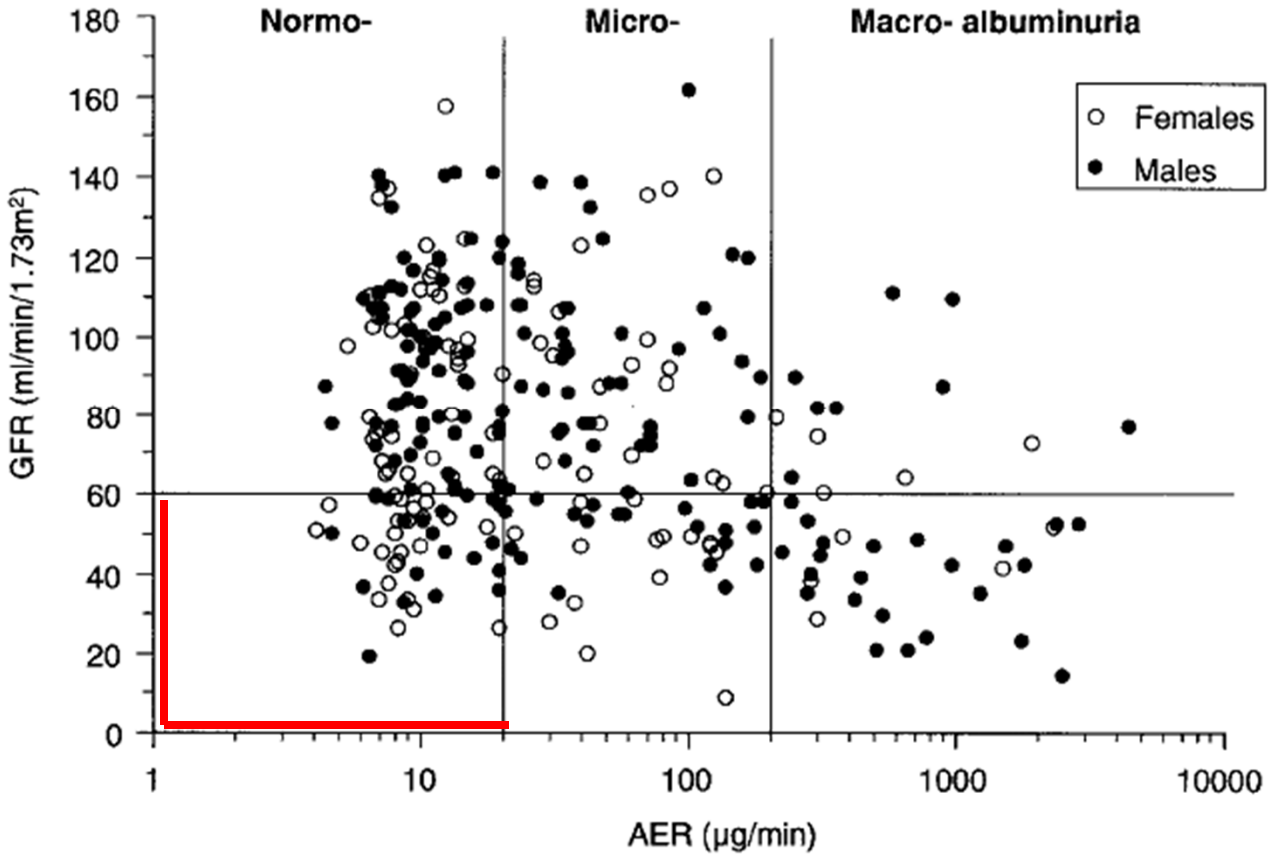
Schlaich, Front.Physiol.(2012) 3: e-pub Feb.2

Is all kidney disease in diabetes created equal ?

- classical Kimmelstiel-Wilson
- **ischemic nephropathy**
- acute kidney injury and accelerated progression after AKI
- primary kidney disease + diabetes

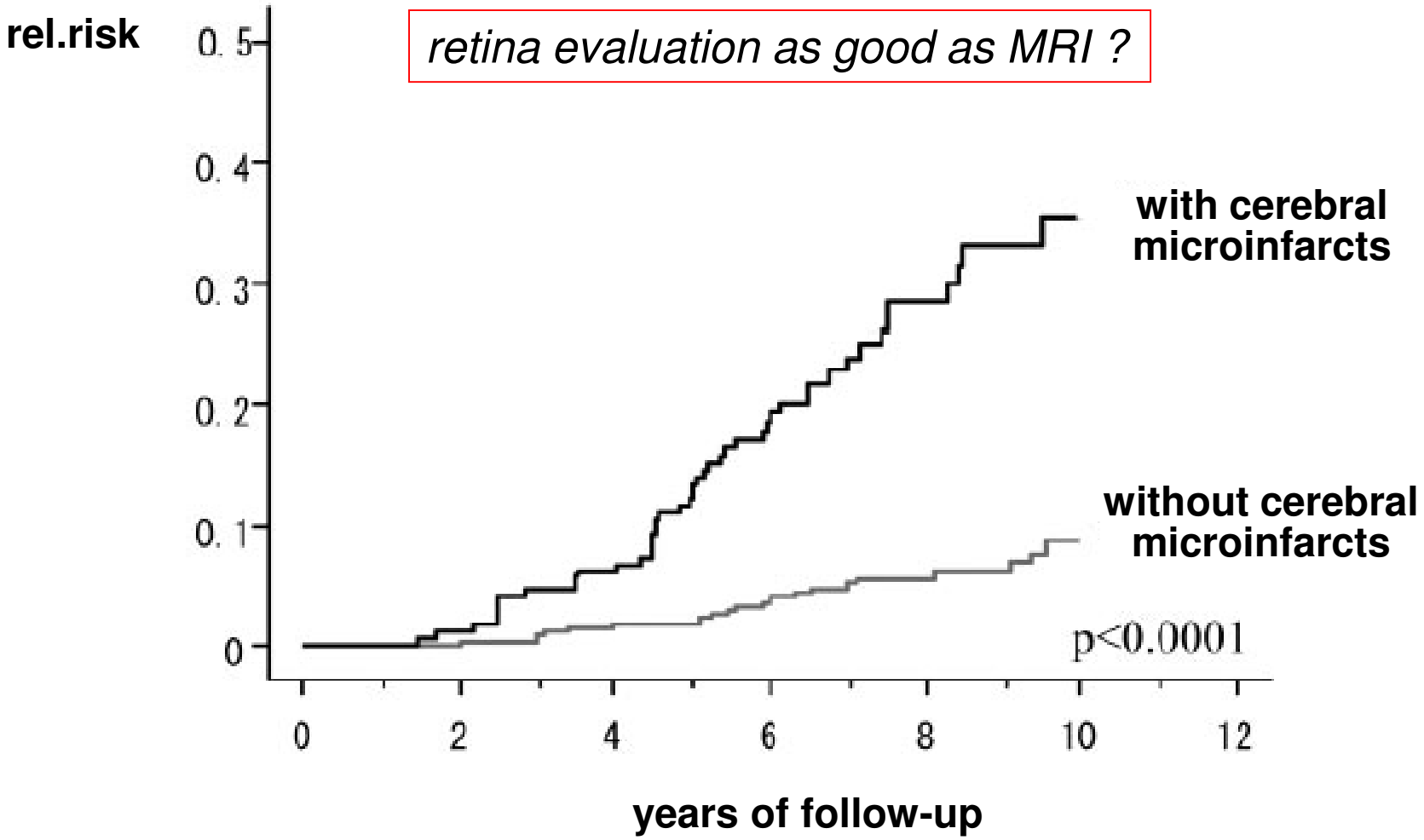
[Chinese herb disease *(as a confounder in Asian populations)*]

Type 2 Diabetes with renal failure and 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

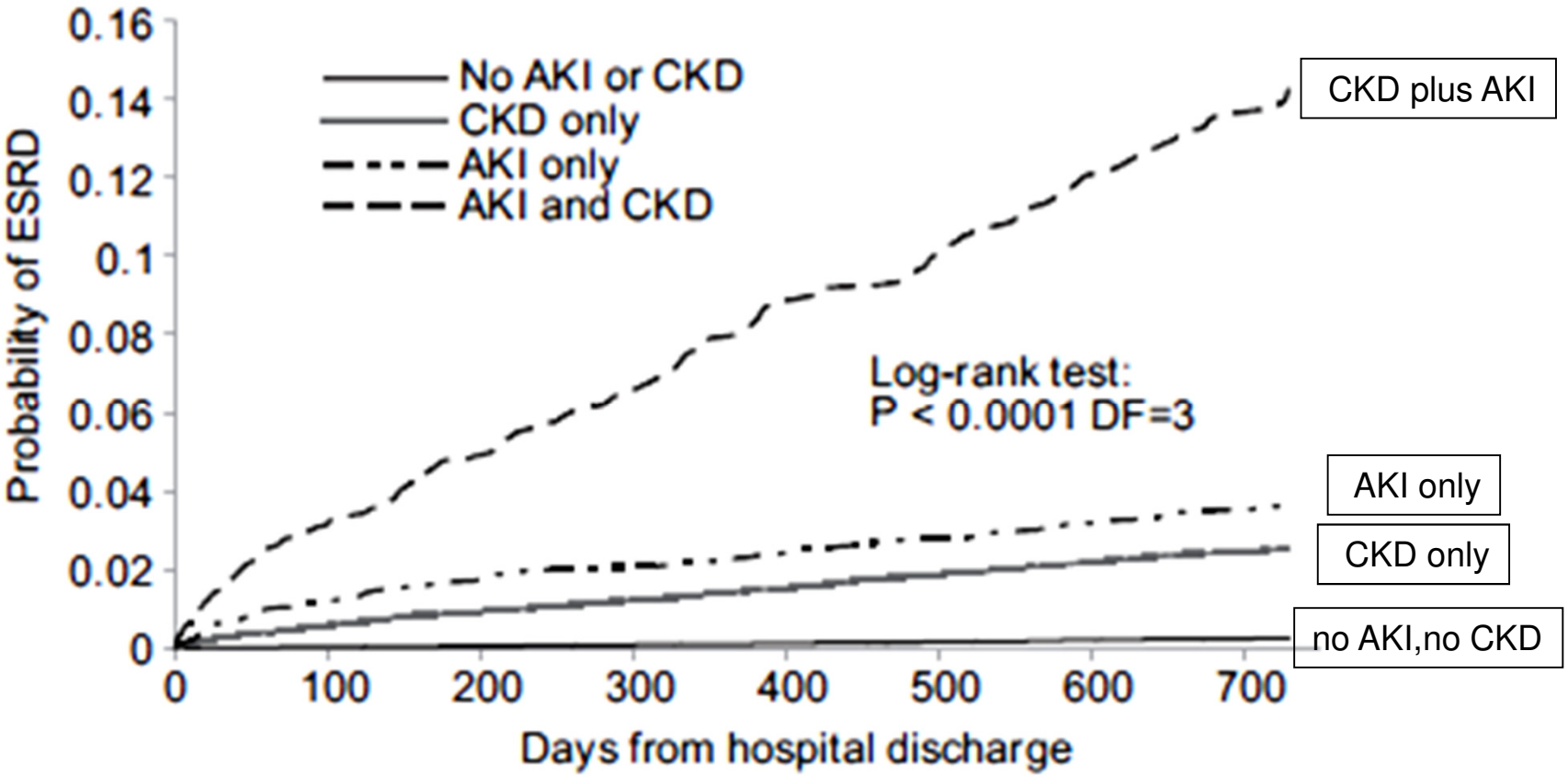
Is all kidney disease in diabetes created equal ?

- classical Kimmelstiel-Wilson
- ischemic nephropathy
- **acute kidney injury and accelerated progression after AKI**
- primary kidney disease + diabetes

[Chinese herb disease *(as a confounder in Asian populations)*]

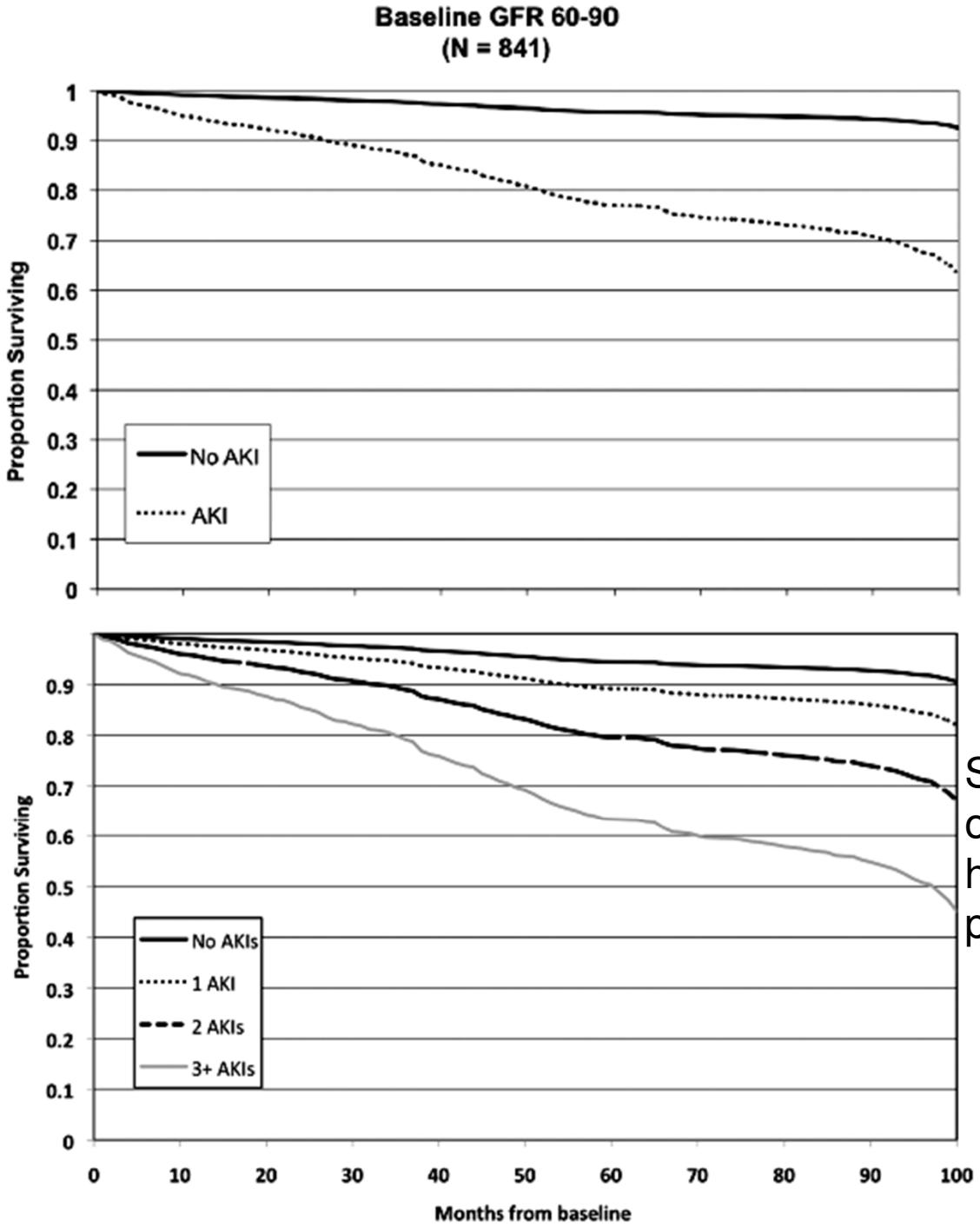
Acute kidney injury (AKI) in the elderly

- increased risk of ESRD and
- accelerated progression of preexisting CKD



with diabetes at baseline 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/1.73m^2)

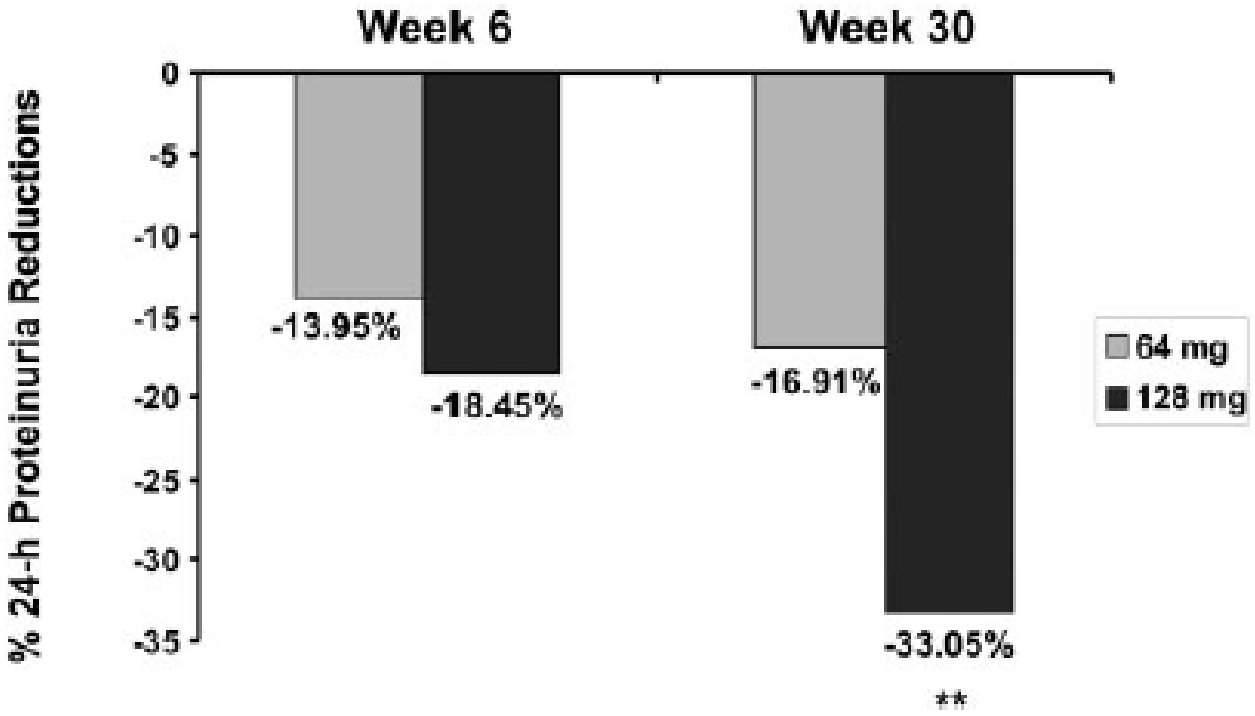
S-Crea	1.44±*0.42* vs 1.05±*0.26 mg/dl*
obesity	17% vs 37.9% !!
hypertension	41.7% vs 67.5%
proteinuria	76% vs 59.8%

Thakar,
CJASN (2011) 6:2567

Beyond doses licensed for BP lowering

Percentage reduction of albuminuria by raising Candesartan dose from 16 to 64 and 128 mg/day

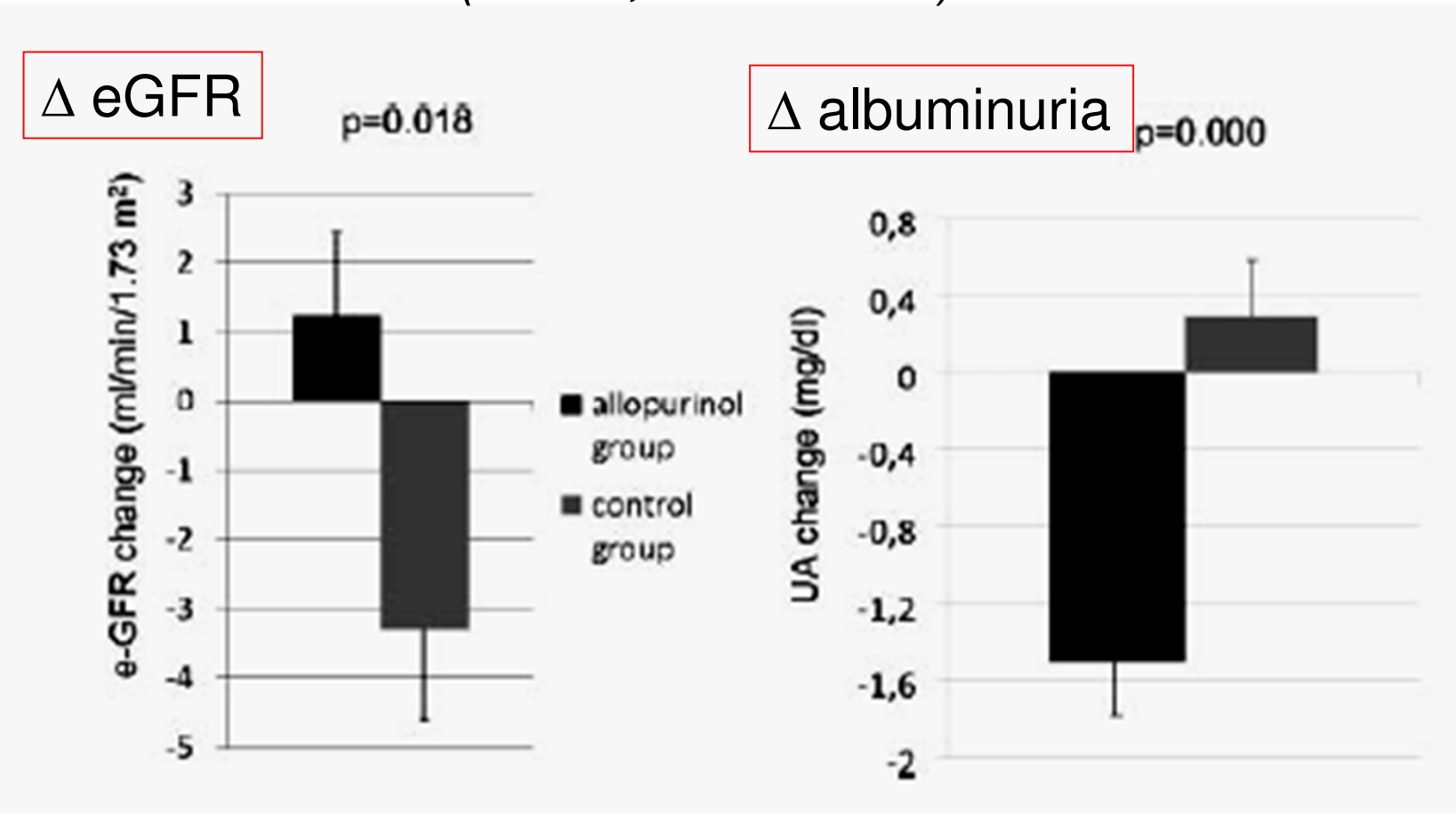
269 patients with proteinuria < 1g/day on 16 mg/day Candesartan



Burgess, J.Am.Soc.Nephrol. (2009) 20:893

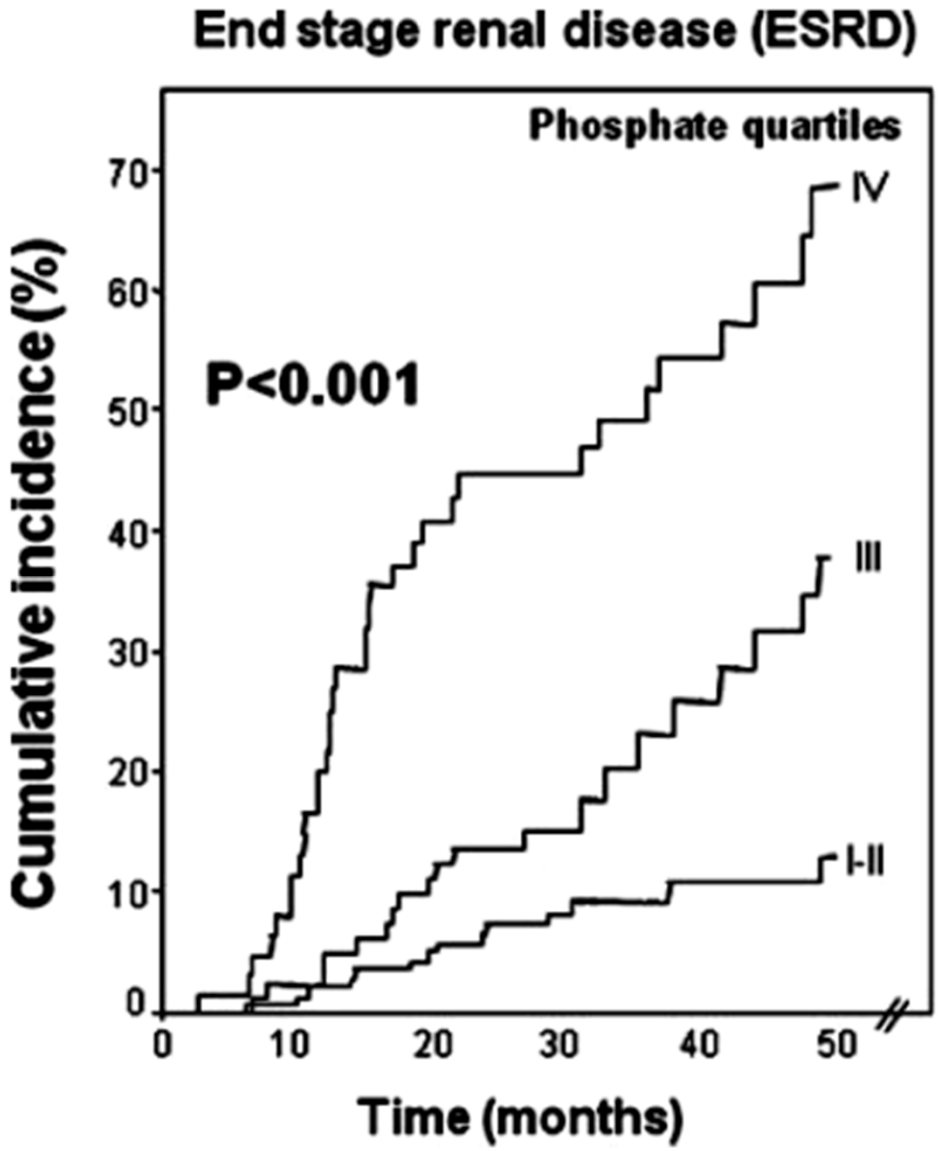
Unexpected confounders

Allopurinol *(100mg/day)*
reduces progression of chronic kidney disease
(eGFR,albuminuria)



Goicoechea, CJASN (2010) 5:1388

Unexpected confounders



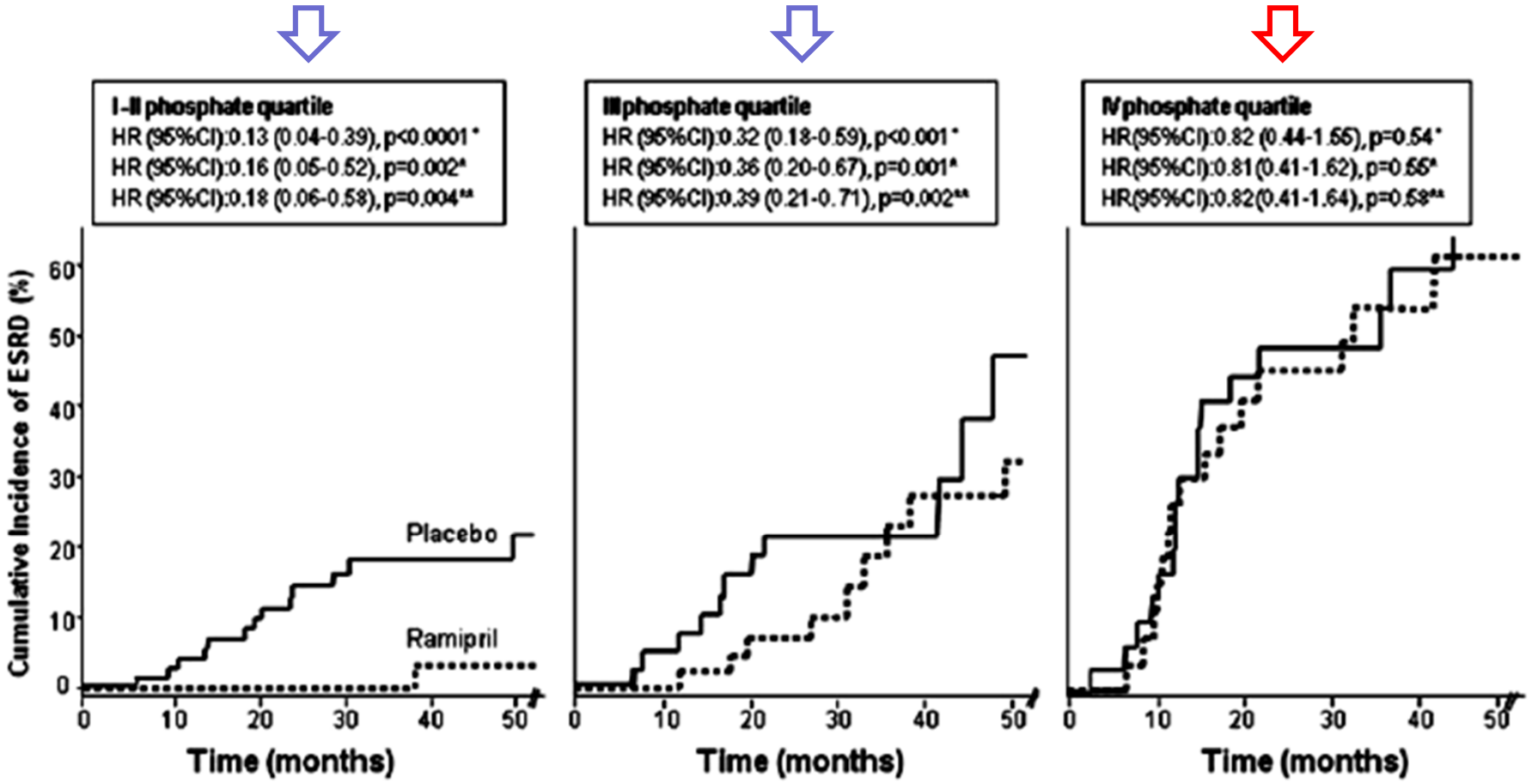
S-phosphate predicts deterioration of chronic kidney disease

(REIN study)

rel.risk ESRD per 1 mg/dl :
1.84 *(1.27-2.67p<0.001*

Zoccali,
J.Am.Soc.Nephrol.(2011) 22:1923

Efficacy of Ramipril to reduce incidence of ESRD ⇩ abolished in highest S-Pi quartile ⇩



Zoccali, J.Am.Soc.Nephrol.(2011) 22:1923

RAS blockade

efficacy on GFR loss dependent on

stage of diabetic nephropathy at start of treatment

start of Tx

advanced stage — **IDNT and RENAAL**

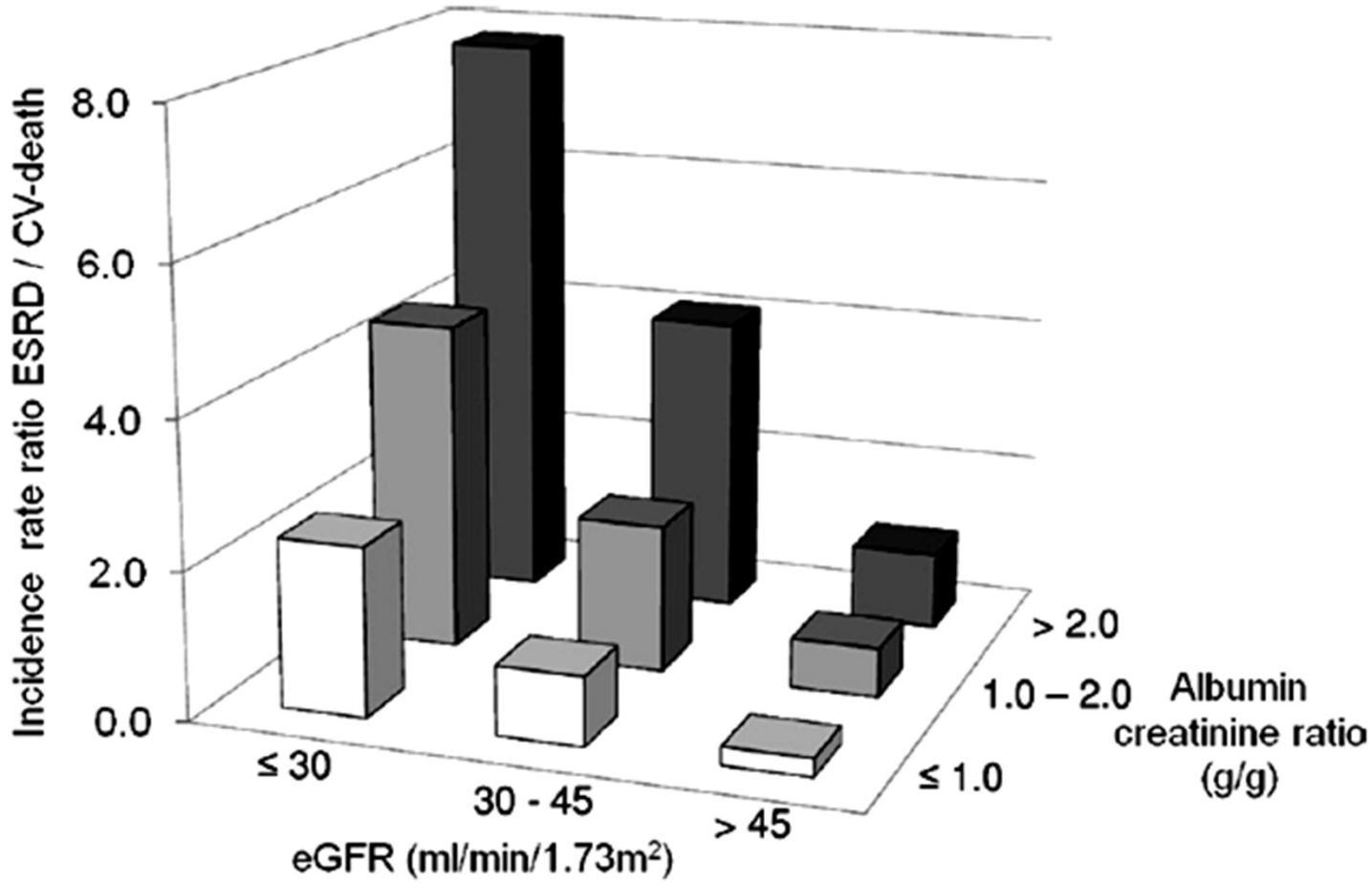
Lewis, New Engl. J. Med.(2001) 345: 851

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

early — **DETAIL**

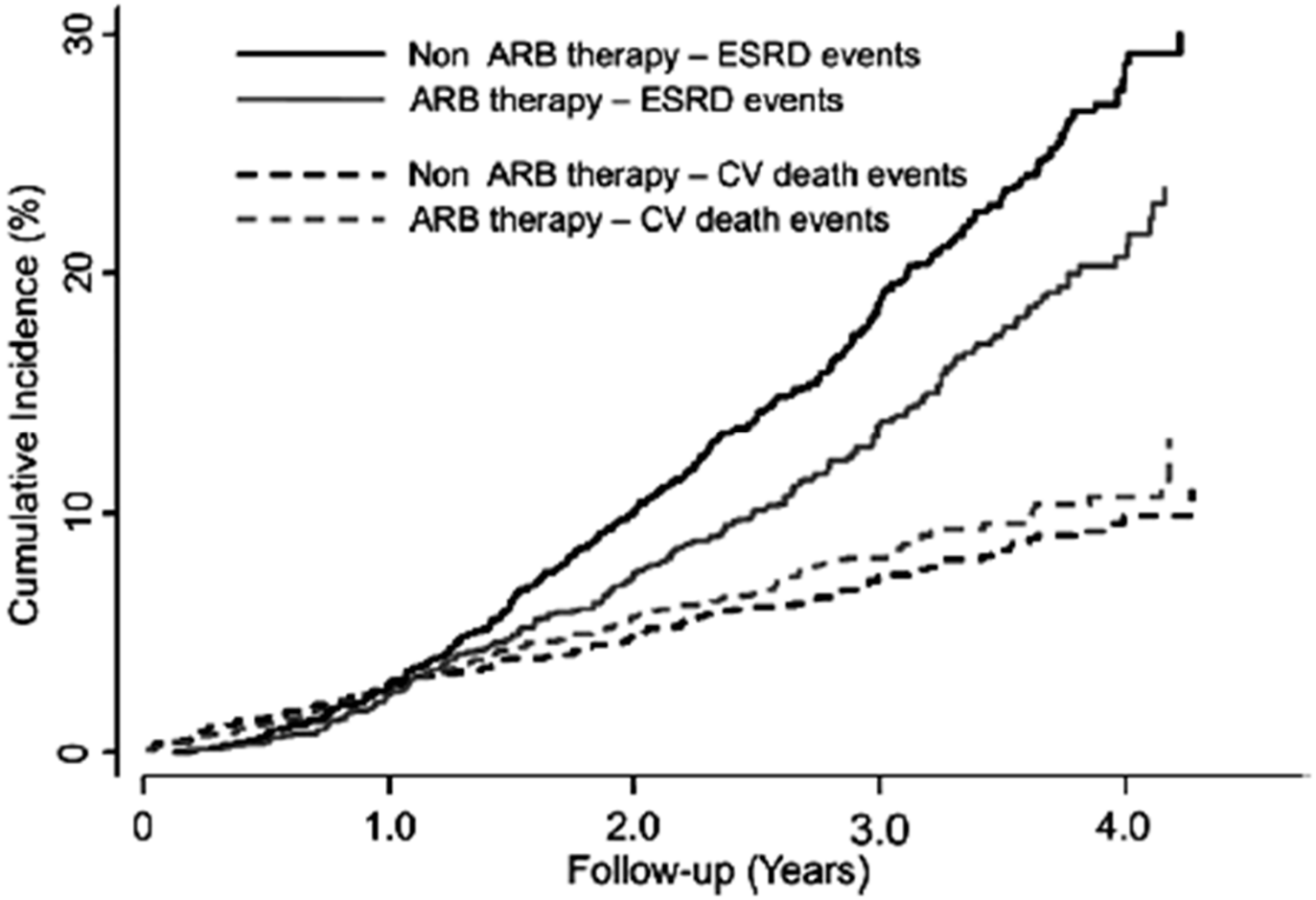
Barnett, New Engl.J.Med.(2004) 351:1952

Incidence rate ratio
ESRD versus CV death by eGFR and albuminuria



Packham, AJKD (2012) 59:75

Incidence risk ratio: the impact of RAS blockade on ESRD vs. cardiovascular events



Packham, AJKD (2012) 59:75

Stopping renin-angiotensin system inhibitors in chronic kidney disease : predictors of response

Goncalves A.Khawaja A.,Ahmed A.,El Kossi M., El Nahas

Nephron Clin.Pract.(2011) 119:c348

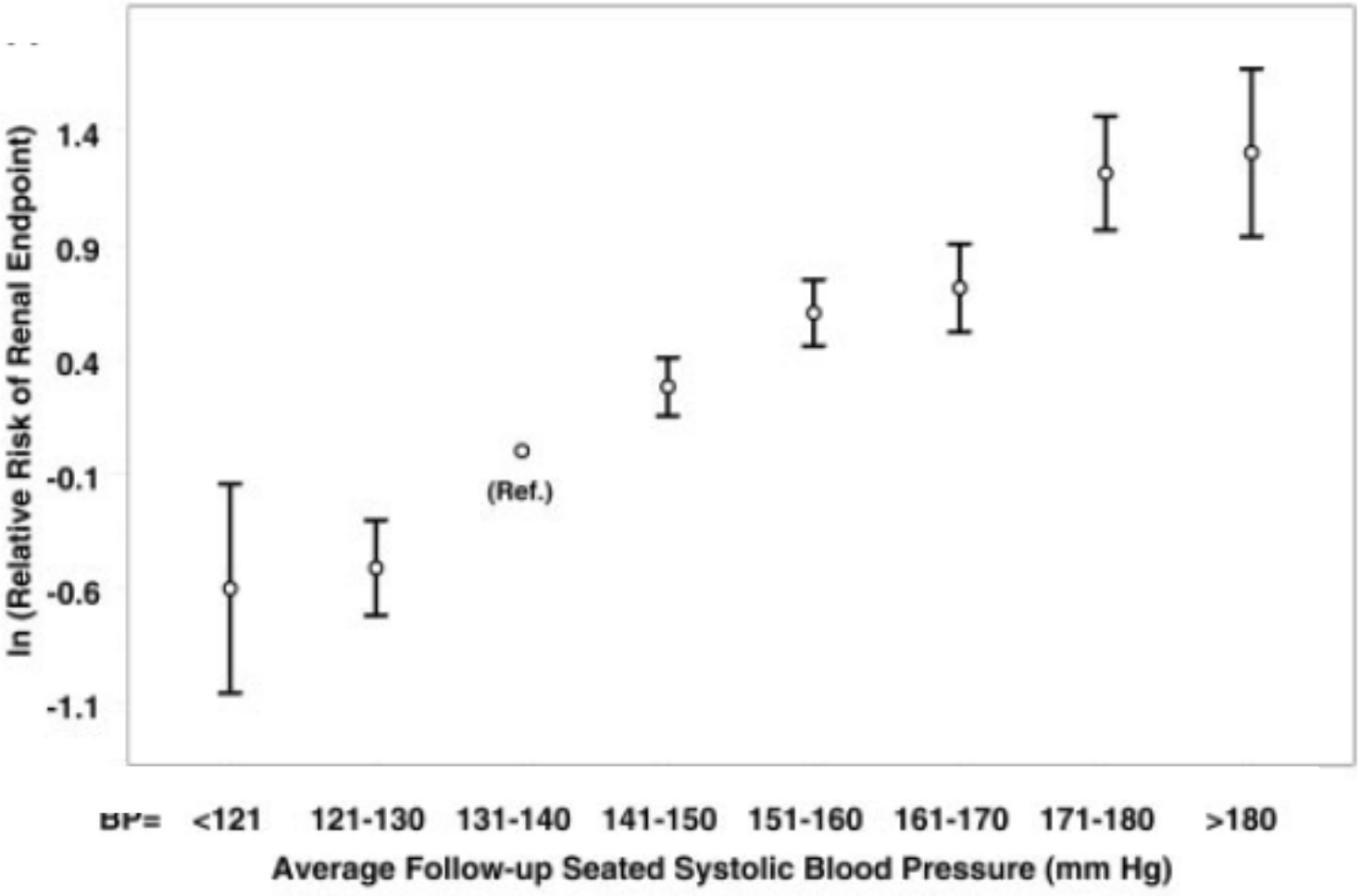
43 patients CKD stage 4, treated with RAS inhibitors
(ACE-inhibitors, angiotensin receptor blockers)
RAS inhibition stopped and patients followed for 24 months

patients with GFR increase > 5 ml/min/1.73m^2 ⇨ higher probability
not to require renal replacement therapy withih the following 24 months *(p=0.03)*

Blood pressure increase correlated with eGFR increase
(do kidneys in the preterminal stage actually benefit from an active RAS ?)

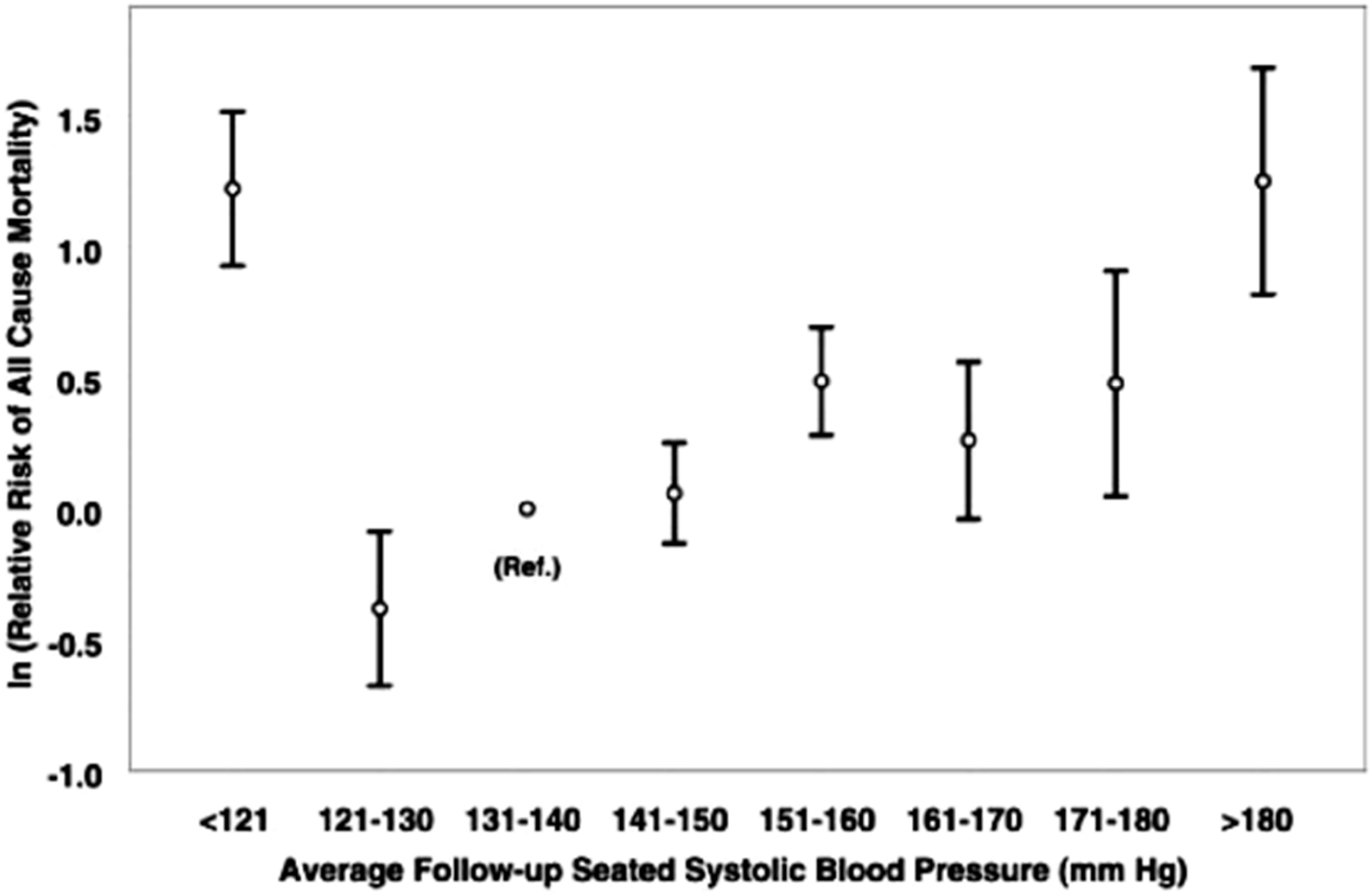
Target blood pressure

Achieved Systolic Pressure and Renoprotection



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

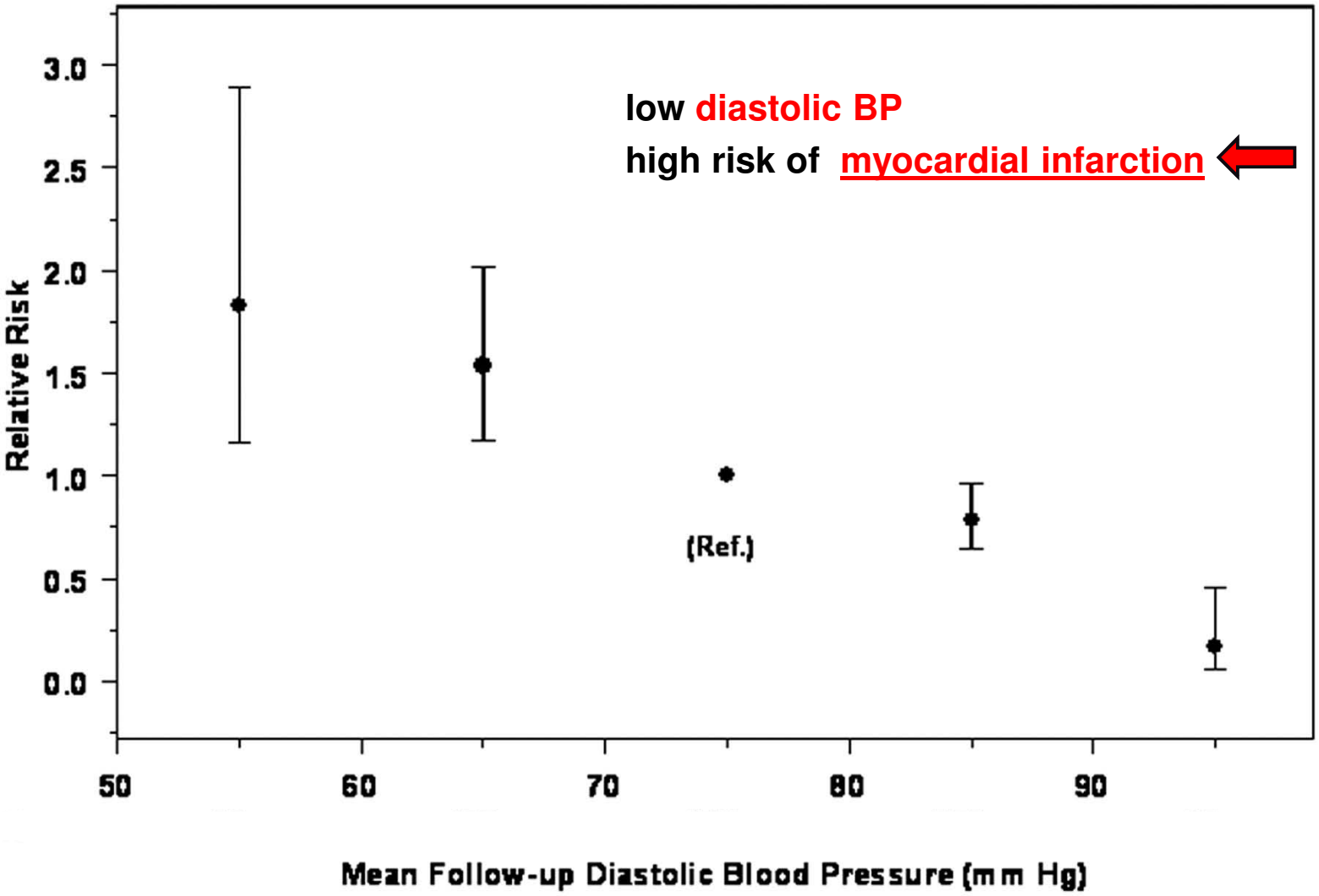
Achieved Systolic Pressure and all cause mortality



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

Diastolic blood pressure and MI
type 2 diabetic patients with nephropathy

(IDNT study)



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

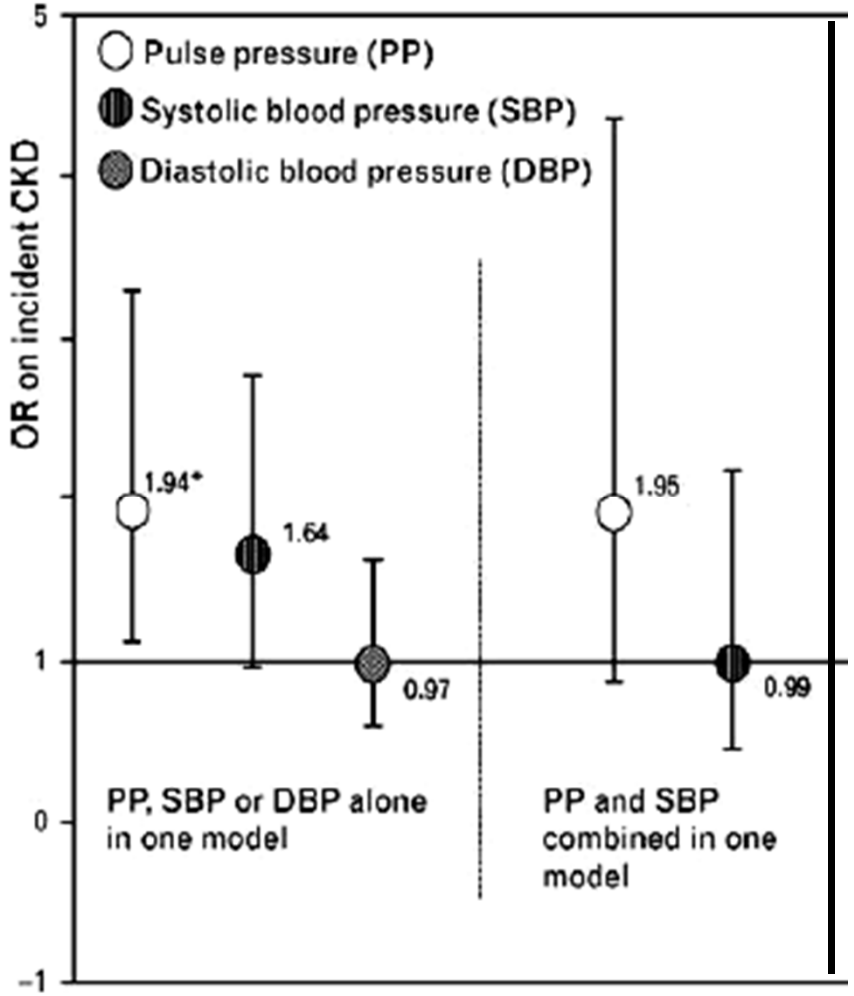
Type 2 diabetes
association between pulse pressure (PP) and CKD
(vascular stiffening)

	nondiabetics	type 2 diabetes
Δ decline eGFR	0.32 ml/min *(p<0.006)*	*1.10 ml/min (p=0.011)*
odds ratio for CKD	1.29 *(95%CI1.09-1.53)*	*1.94 (95%CI1.14-3.29)*

*"In individuals with type 2 diabetes higher systolic pressure was only significantly associated with **eGFR decline** if the **diastolic BP was < 70 mmHg**"*

van den Hurk, J.Hypertension (2011) 29: 953

Type 2 diabetes
association between pulse pressure (PP) and CKD
(vascular stiffening)



van den Hurk, J.Hypertension (2011) 29:953

Which BP most relevant for progression ?

Nocturnal blood pressure the most important determinant of increase in albuminuria in type 2 diabetics

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[d]
Dipping (n=295)	17.6	
Flat (n=475)	22.9	
Rising (n=187)	27.3	

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

Pulse pressure vs systolic pressure

Progression* of nephropathy in type 2 diabetes

(% patients above or below the median)

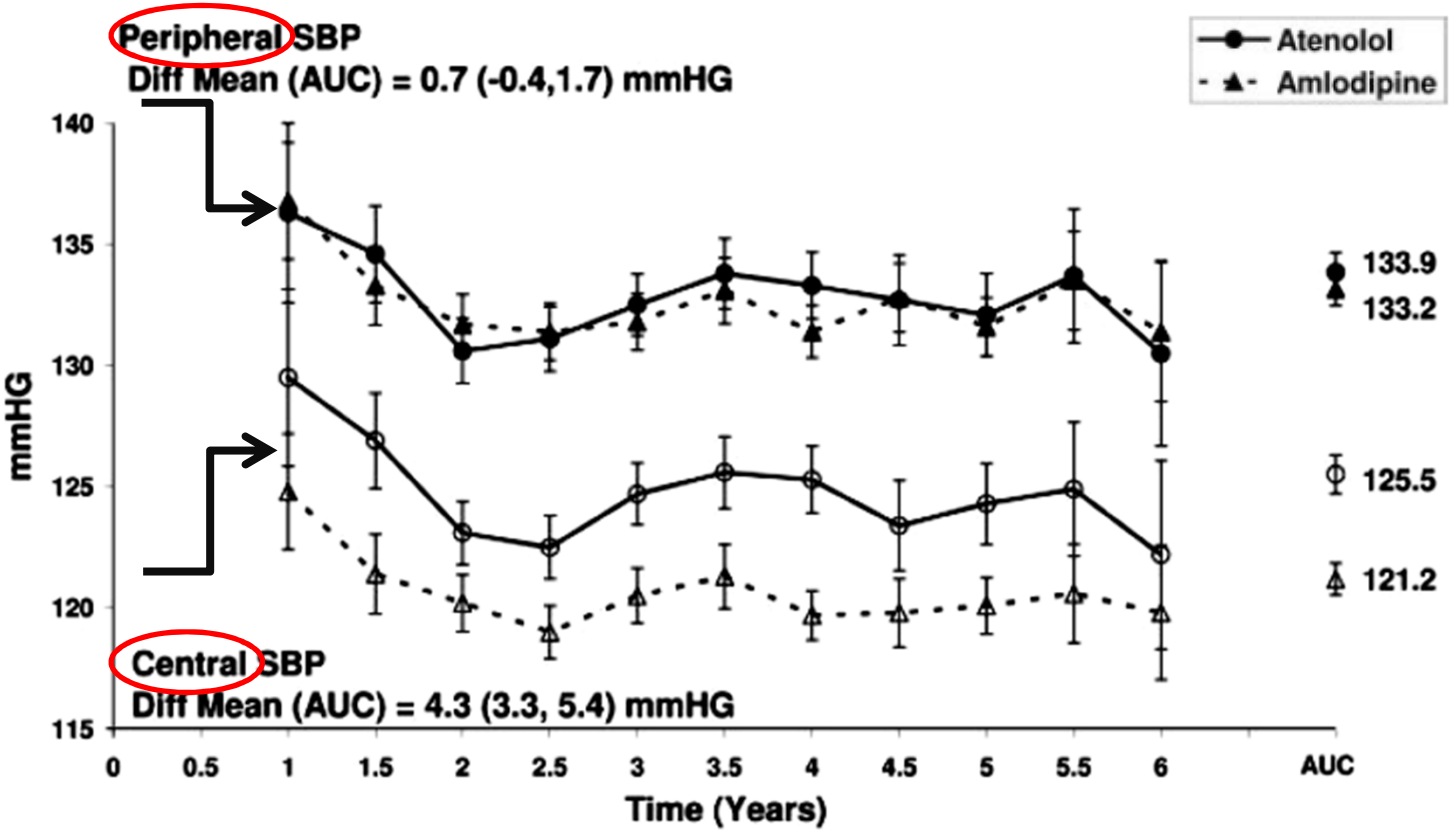
** progression to macroalbuminuria or elevated S-creatinine*

Variable	Progression of nephropathy (%)	*p* value
Smoking		0.01
No	24.7	
Yes	47.2	
24 h systolic blood pressure		0.02
<138.3 mmHg	19.6	
≥138.3 mmHg	41.1	
24 h PP		<0.001
<57.5 mmHg	16.1	
≥57.5 mmHg	46.4	
Diastolic night:day blood pressure ratio		<0.01
<85.0%	17.9	
≥85.0%	44.6	

Knudsen, Diabetologia (2009) 52:698

Brachial vs central (aortic) pressure in the 2 treatment arms of the CAFE study –

with β blocker compared to CCB treatment ⇨ central BP different



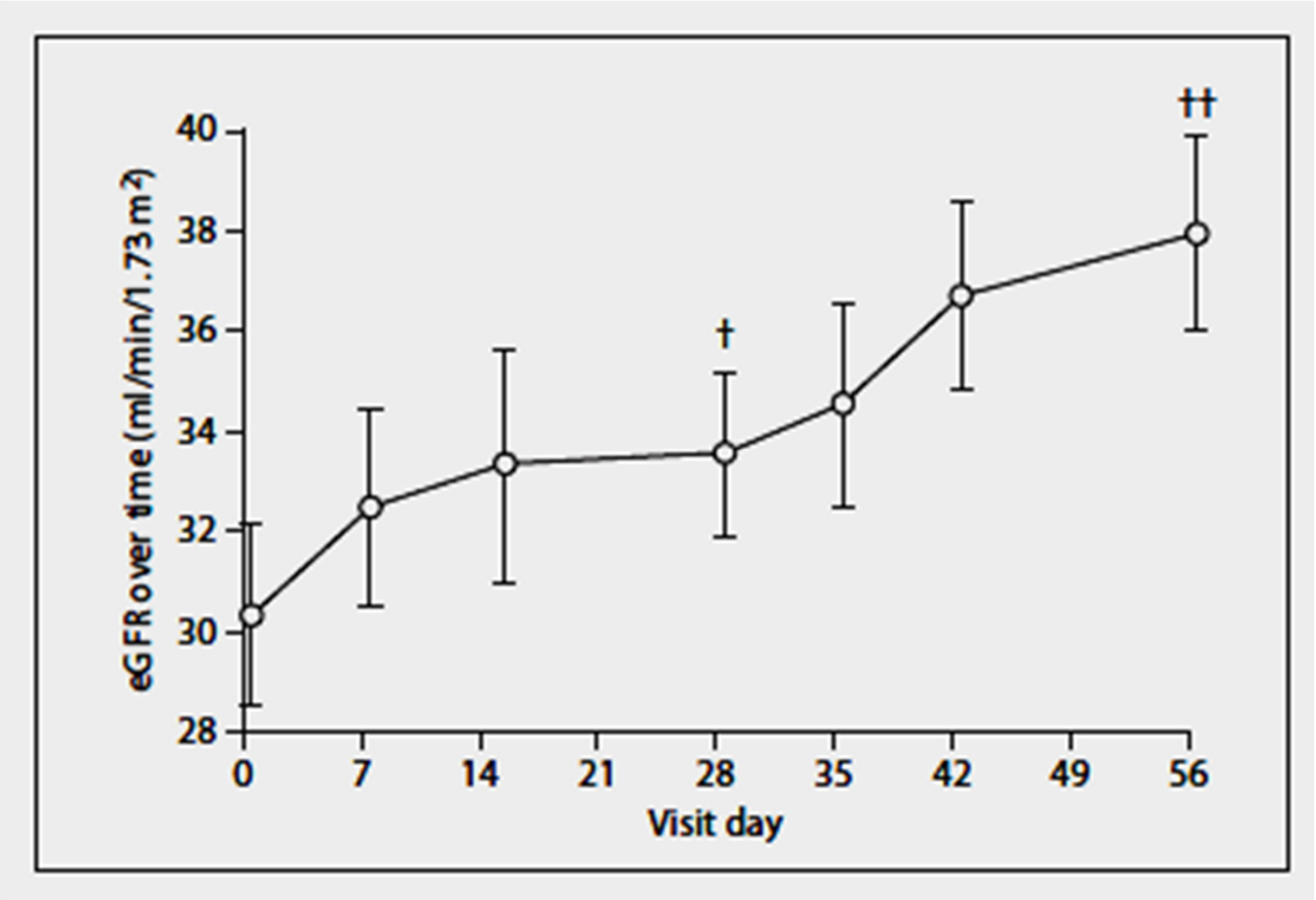
difference *between brachial and central pressures* ***accentuated*** *in* ***diabetic*** *compared to nondiabetic patients (F=37.3; p<0.0001)*

Williams, Circulation (2006)113:1213

Subacute increase in eGFR in patients with type 2 diabetes and nephropathy upon treatment with Bardoxolone *(triterpenoid)*

an exploratory multicenter study

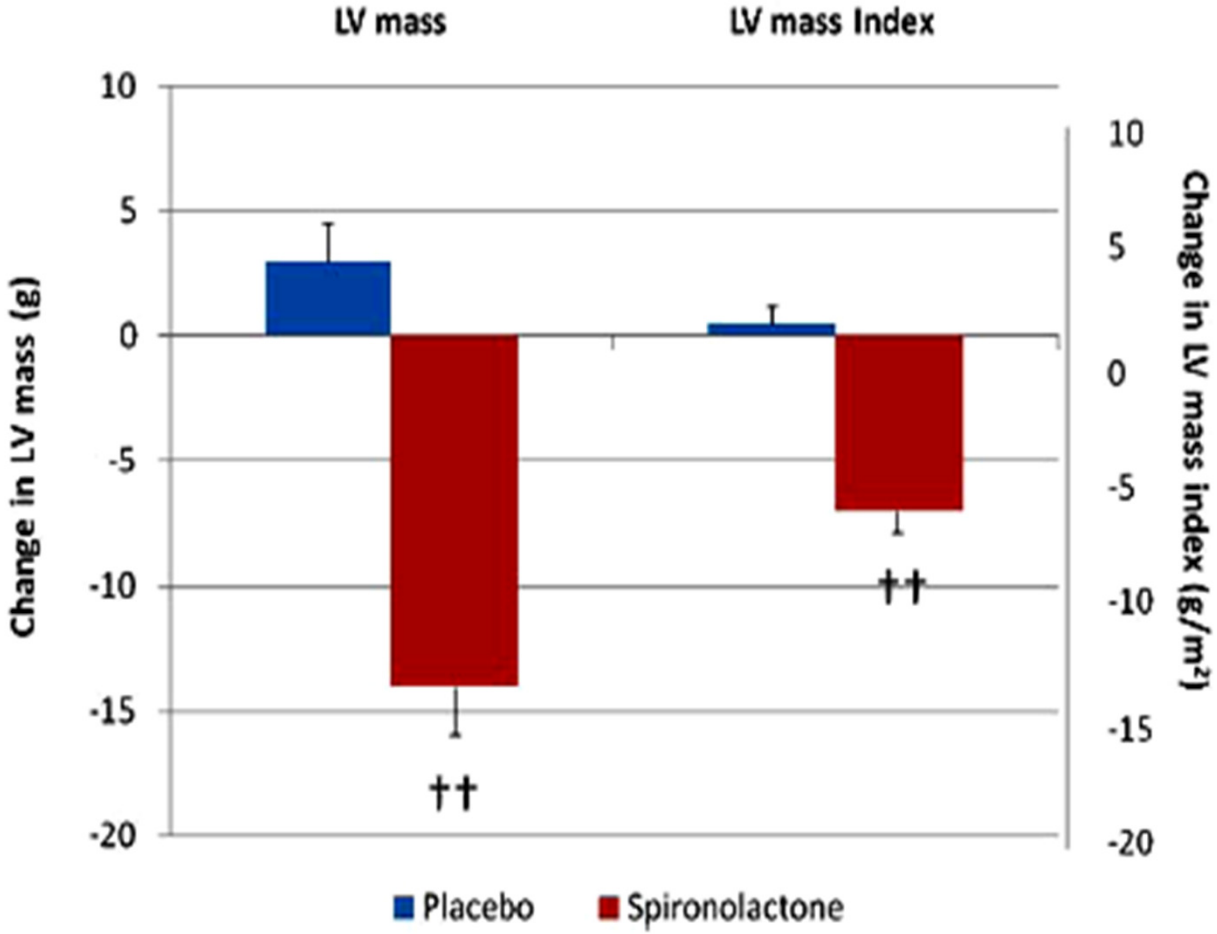
antiinflammatory, interacting with Nrf2/Keap



Pergola, Am.J.Nephrol.(2011) 33:469

Reduction of LV mass by Spironolactone in CKD 2-3

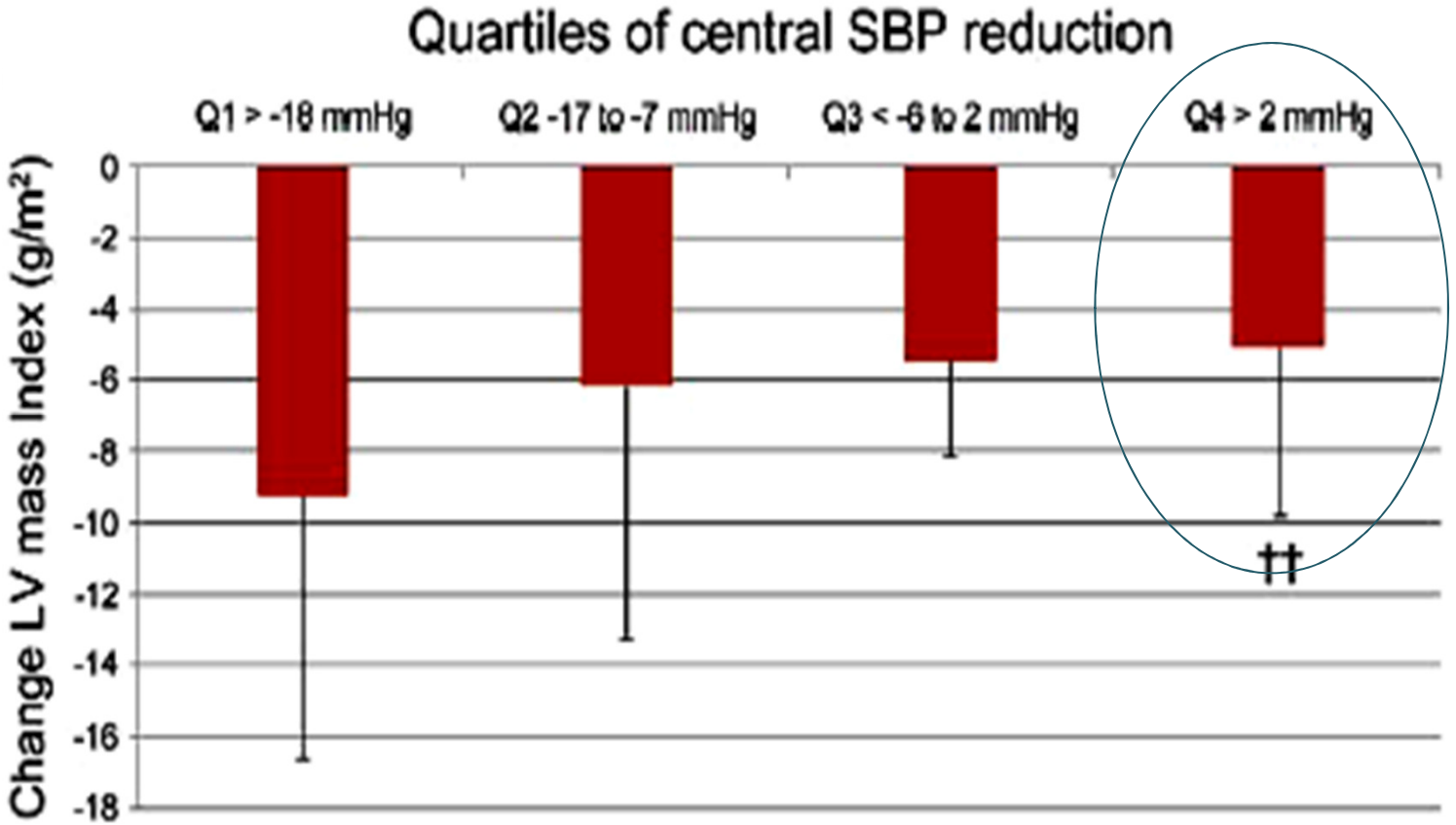
112 pat. CKD 2,3 and daytime *ABPM* < 130/85 mmHg on *RAS blockade*
Spironolactone 25 mg/day or placebo



Edwards, J.Am.Coll.Cardiol.(2009) 54: 505

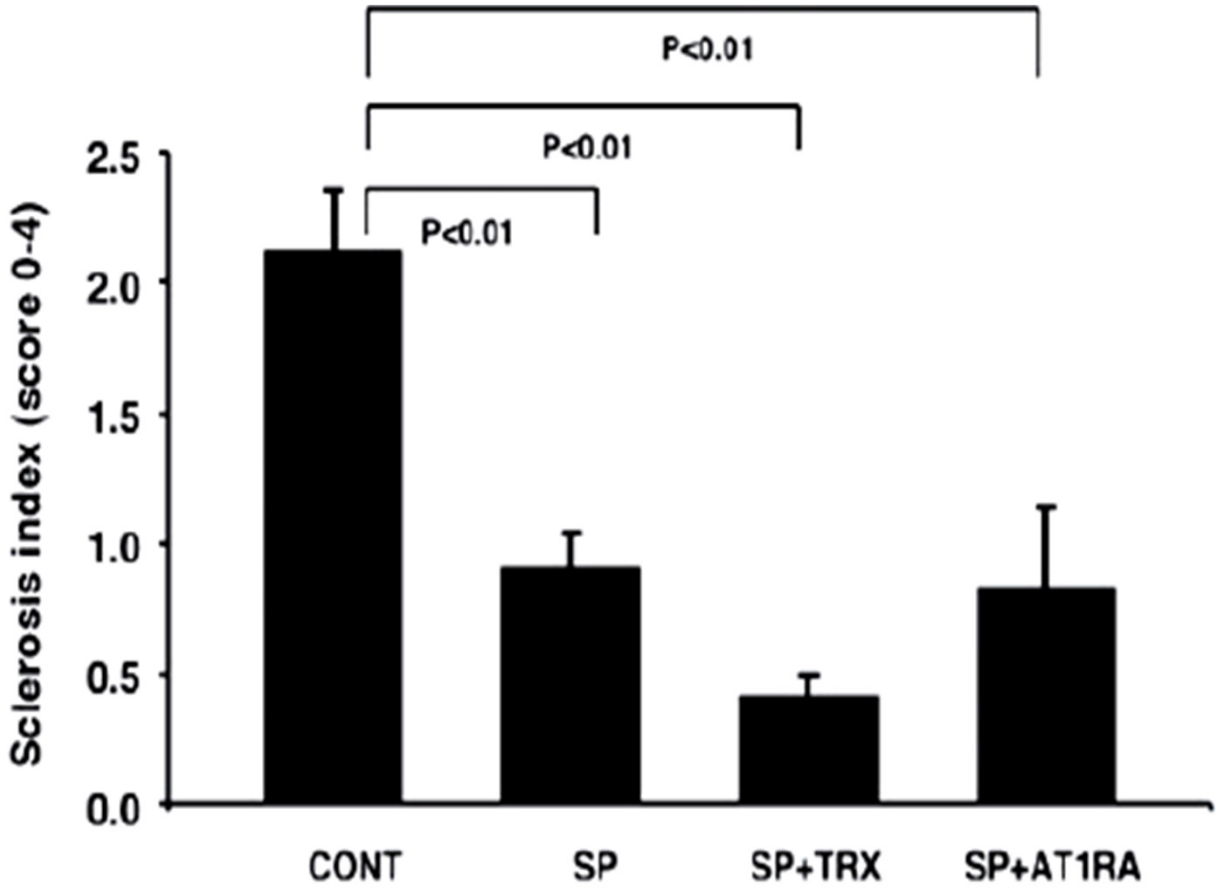
Reduction of LV mass by Spironolactone in CKD 2 / 3 – **independent of blood pressure change with Spironolactone**

112 pat. CKD 2,3 and daytime ABPM < 130/85 mmHg on RAS blockade
Spironolactone 25 mg/day or placebo



Edwards, J.Am.Coll.Cardiol.(2009) 54: 505

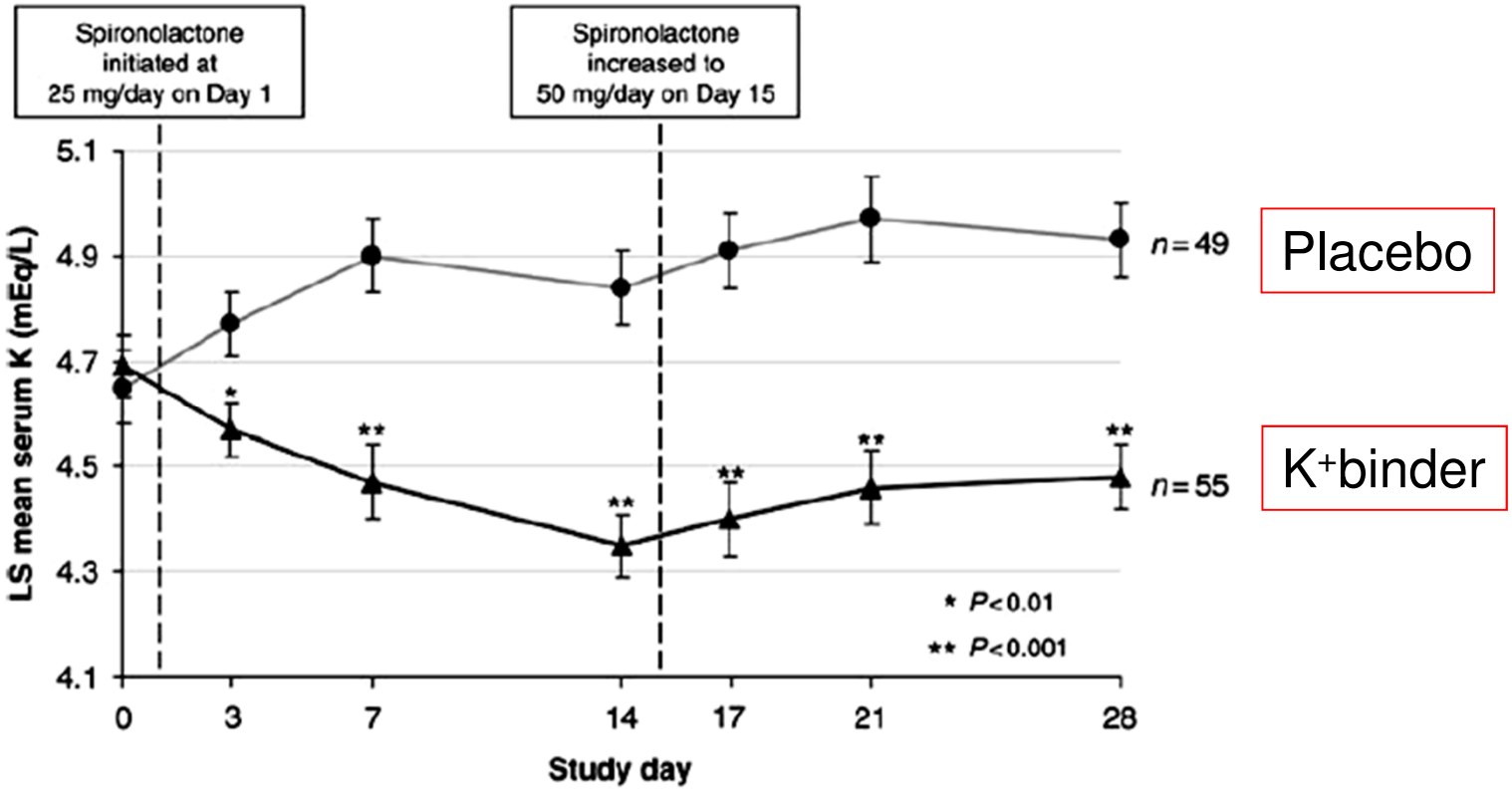
Spironolactone causes even regression of established glomerulosclerosis after subtotal nephrectomy



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

Polymeric K^+ binder RLY5016 in chronic heart failure

(PEARL-HF trial)



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

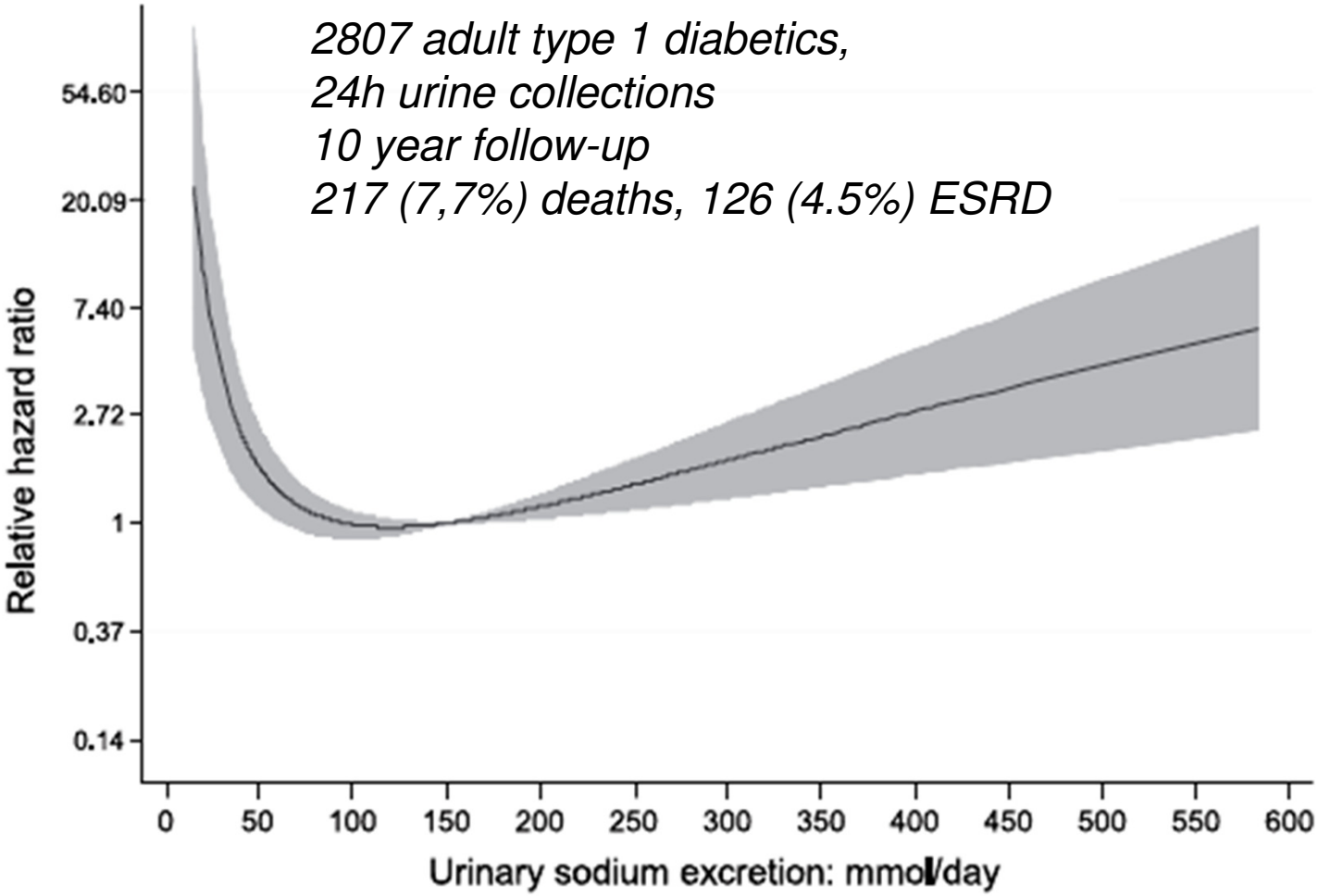
<60 1/15 on RLY5016 vs 5/13 on placebo

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

Sodium intake and all-cause mortality in type 1 diabetic patients

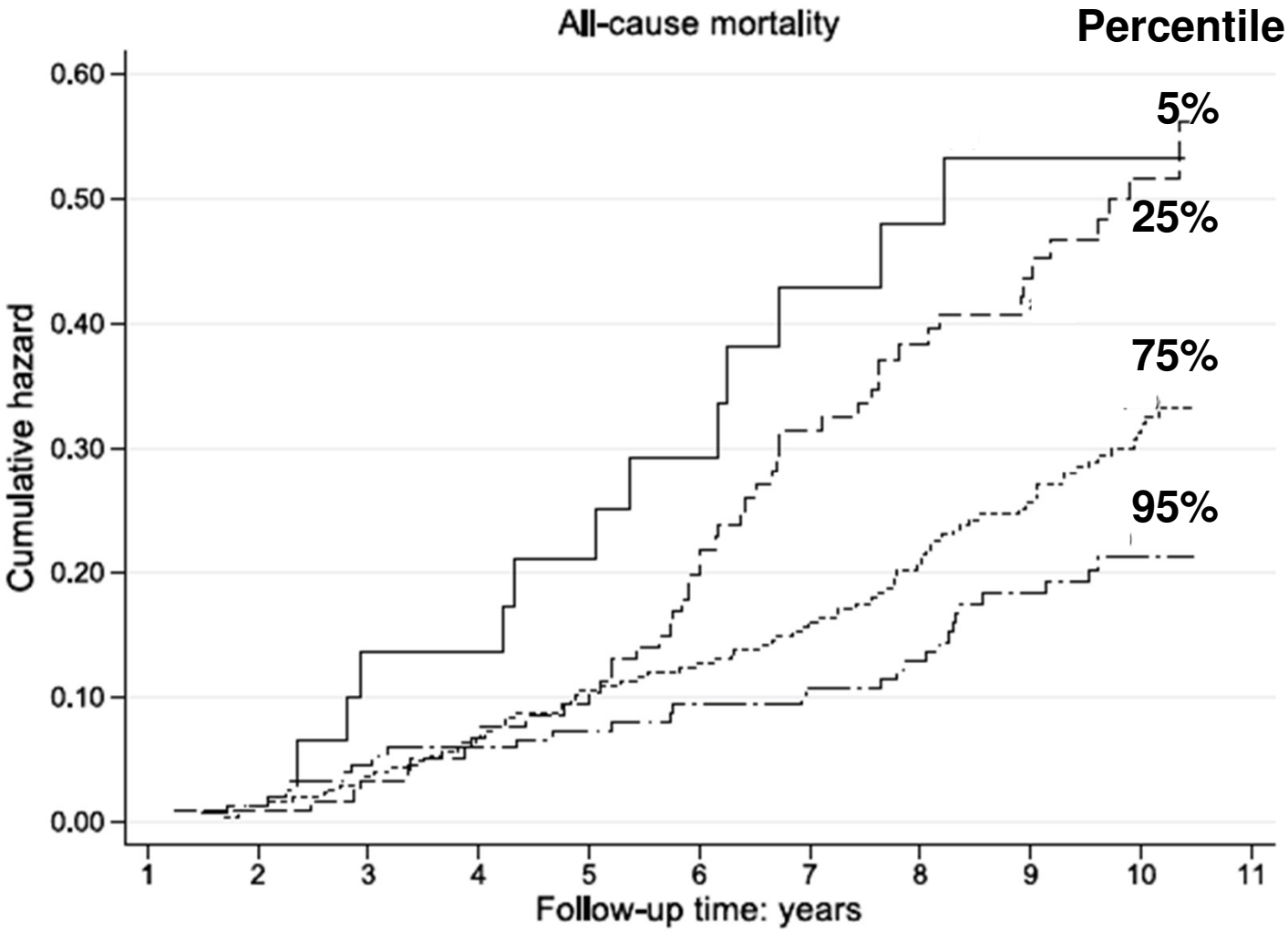
(FinnDiane study)

what is the impact on nephropathy ?



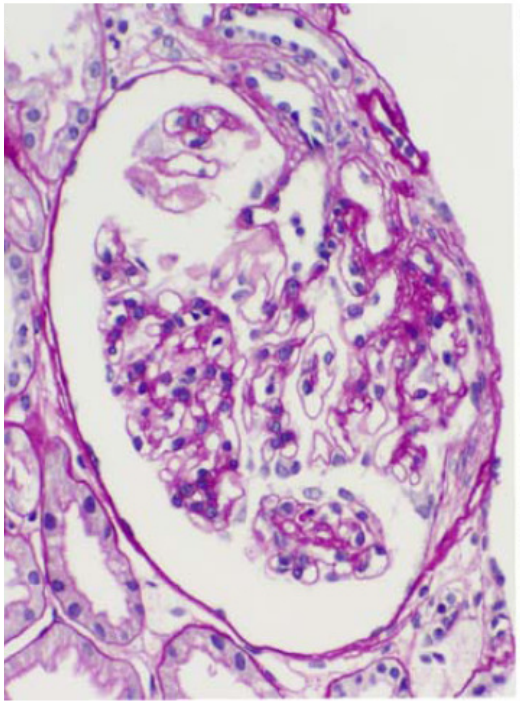
Thomas, Diabetes Care (2011) 34:861

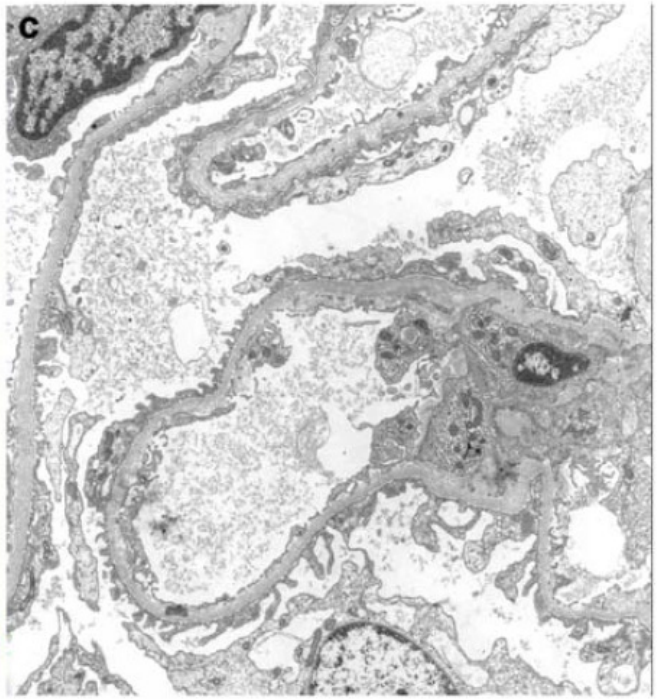
Dietary salt intake and mortality in type 2 diabetes



Ekinci, Diabetes Care (2011) 34: 703

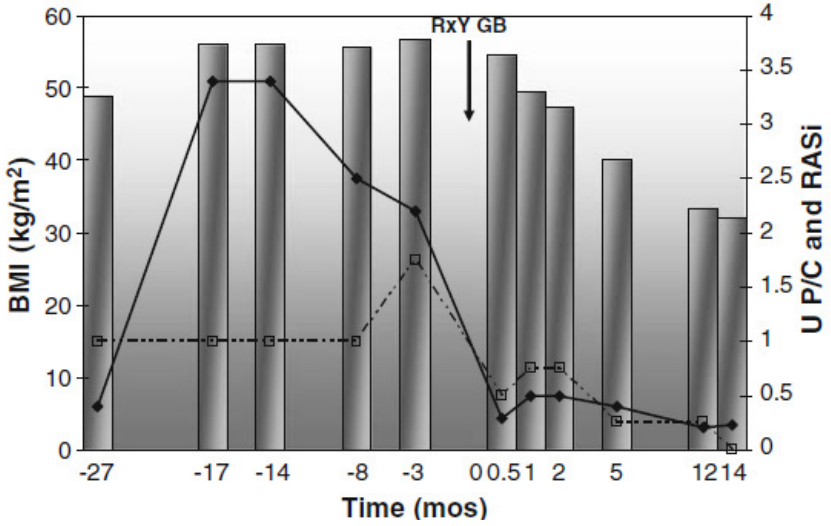
Obesity-related focal and segmental glomerulosclerosis:
normalization of proteinuria in an adolescent after ***bariatric surgery***





17 year girl
BMI 56.8 kg/m^2
1y post-op normoalbuminuric
off RAS blockade

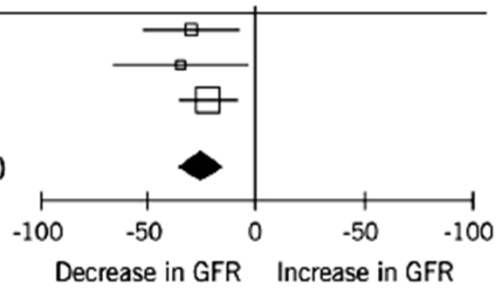
Fowler, Ped.Nephrol.(2009) 24:851



Effect of surgical interventions on glomerular hyperfiltration

(also on hyperfiltration in diabetic nephropthy?)

Study or Subgroup	After surgery Mean	SD	Total	Before surgery Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Brochner-Mortensen 1980	123	27	8	153	16	8	24.1%	-30.00 (-51.75, -8.25)
Chagnac 2003	110	39.59	8	145	19.79	8	12.1%	-35.00 (-65.67, -4.33)
Navarro-Diaz 2006	117.9	33.99	61	140	40.96	61	63.8%	-22.10 (-35.46, -8.74)
Total (95% CI)			**77**			**77**	**1.00%**	**-25.56 (-36.23, -14.89)**



Navaneethan, CJASN (2009) 4:1565

Diabetic nephropathy and bariatric surgery

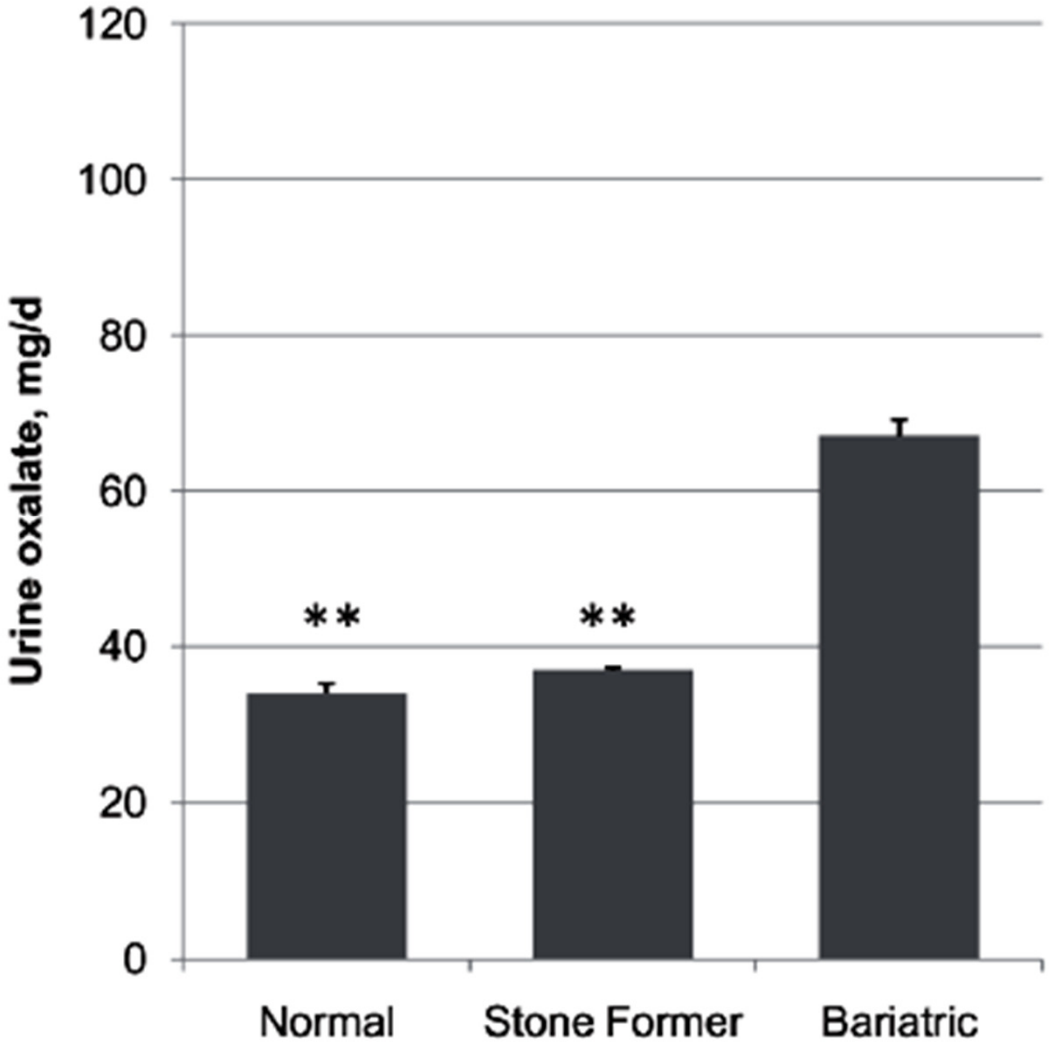
Moutzouris D.A. et al.
Oxalate nephropathy in a diabetic patients after gastric bypass
Clin.Nephrol.(2011) Suppl 1:16-9

Cohen P.G.
Bariatric surgery for diabetic nephropathy
Nephrol.Dial.Transplant.(2011) 26:1755

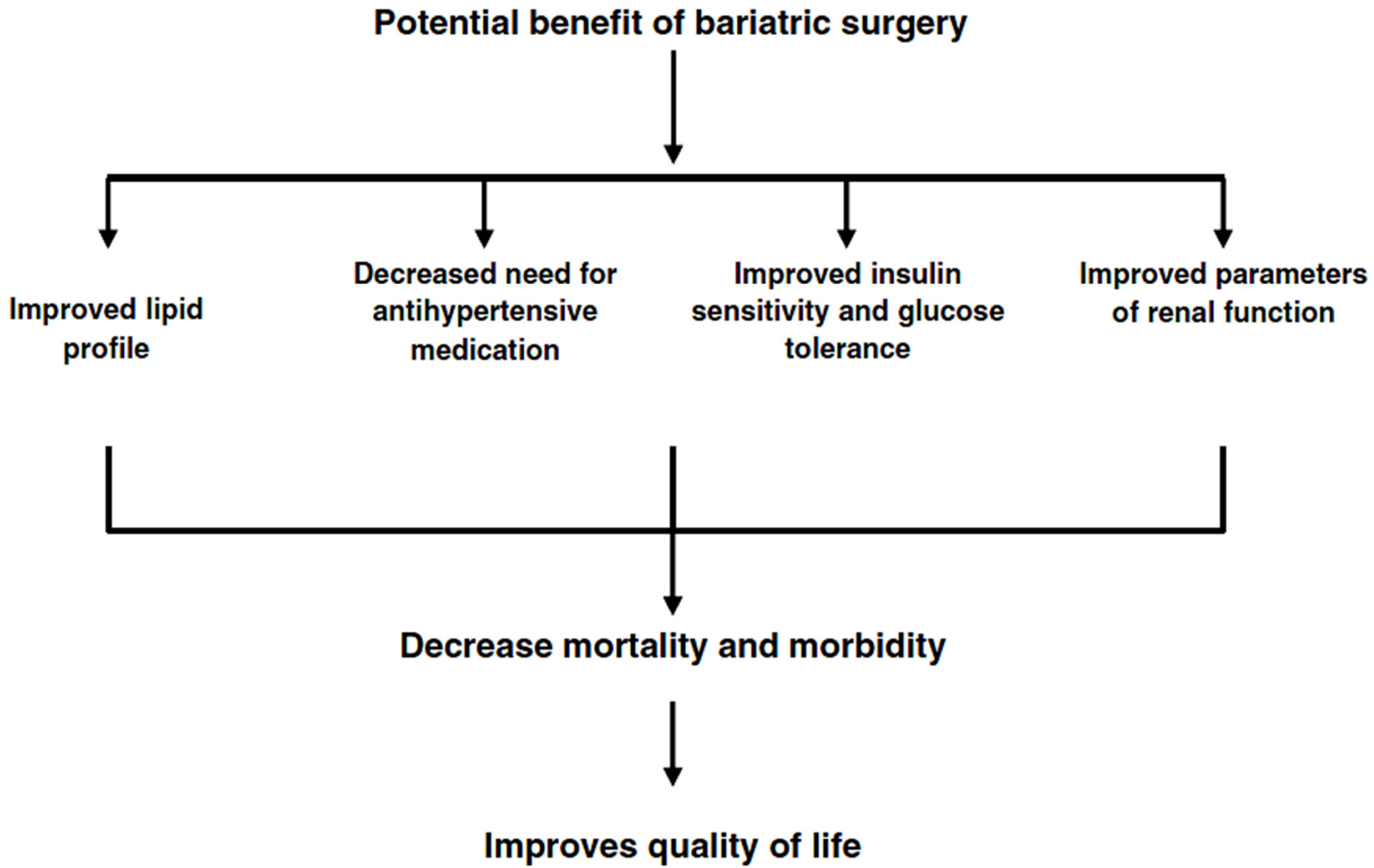
Mumme D.E. et al
Effect of laparascopic Roux-en-Y **gastric bypass surgery on hemoglobinA1c** levels in diabetic patients: a matched-cohort analysis
Surg.Obes.Relat.Dis. (2009) 5:237

Bonatti H. et al
Laparascopic gastric banding in a **kidney-pancreas transplant recipient** with new onset type II diabetes mellitus associated with obesity
Clin.Transplant.(2008) 22:829

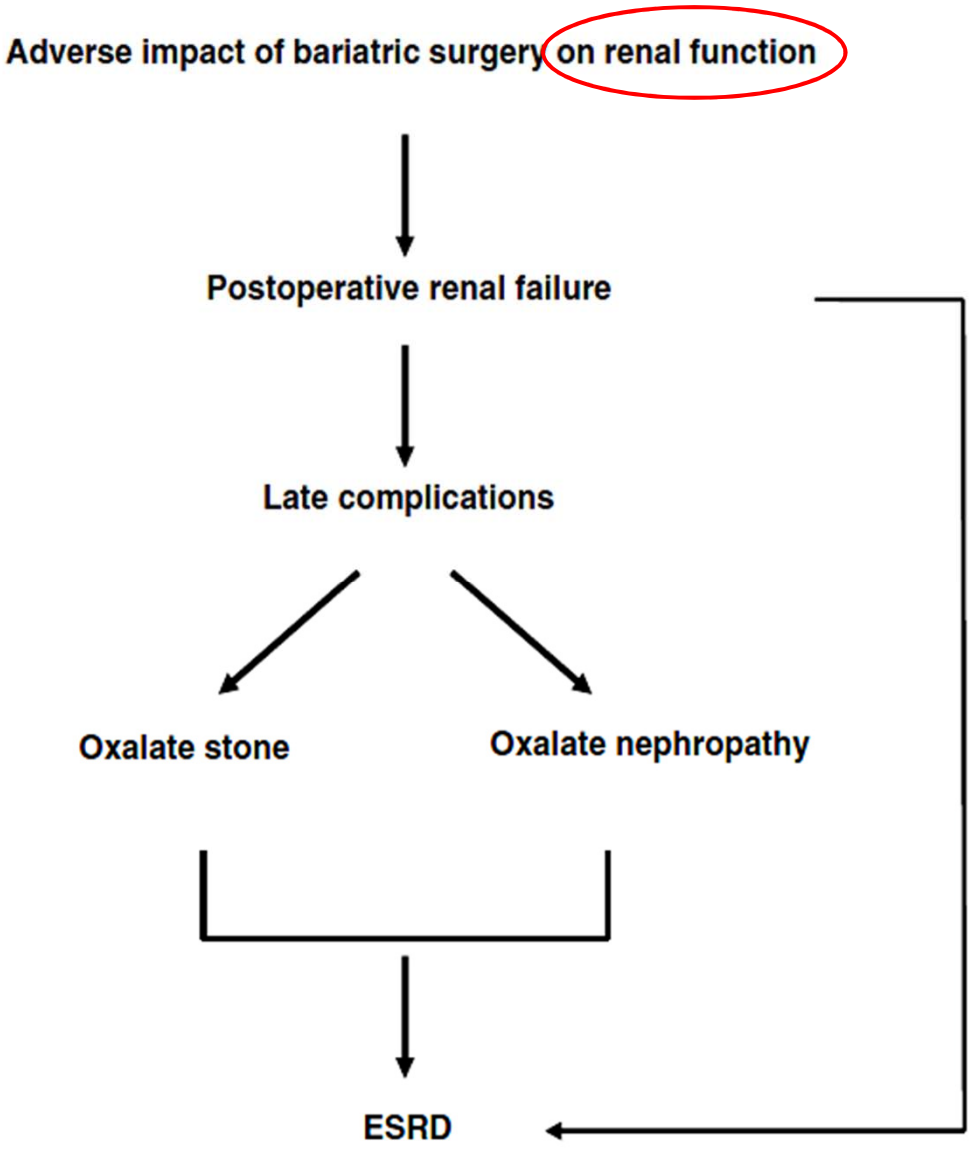
Hyperoxaluria after bariatric surgery



Patel, J.Urol.(2009) 181: 161



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



Acute renal failure after gastric bypass

1800 patients
*42 **(2.3%)** ARF*
n=6 dialysis, of which:
n=2 dialysis dependent

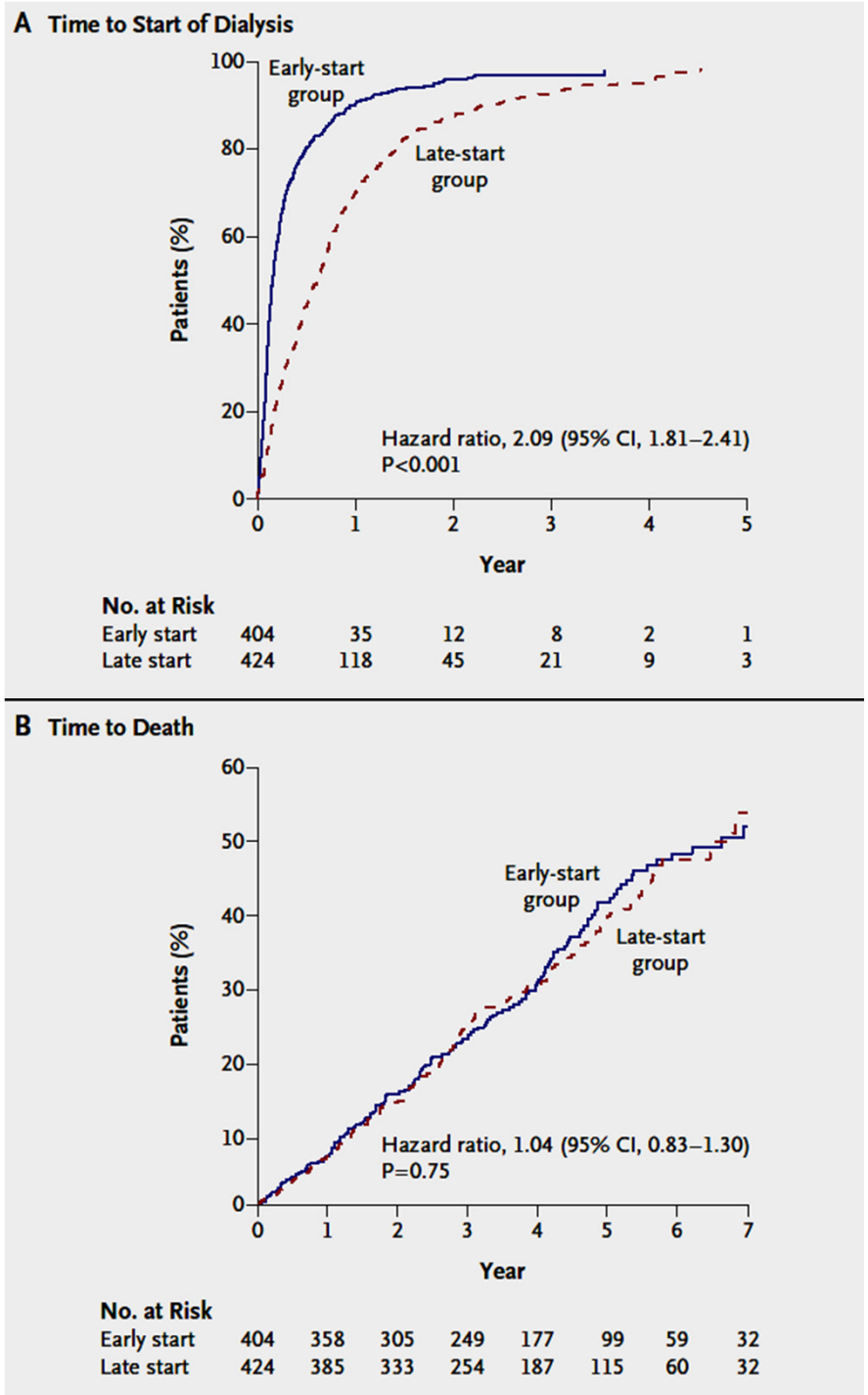
Sharma, Surg.Obes.Relat.Dis.(2006) 2:389

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

Thank you for your attention



IDEAL study

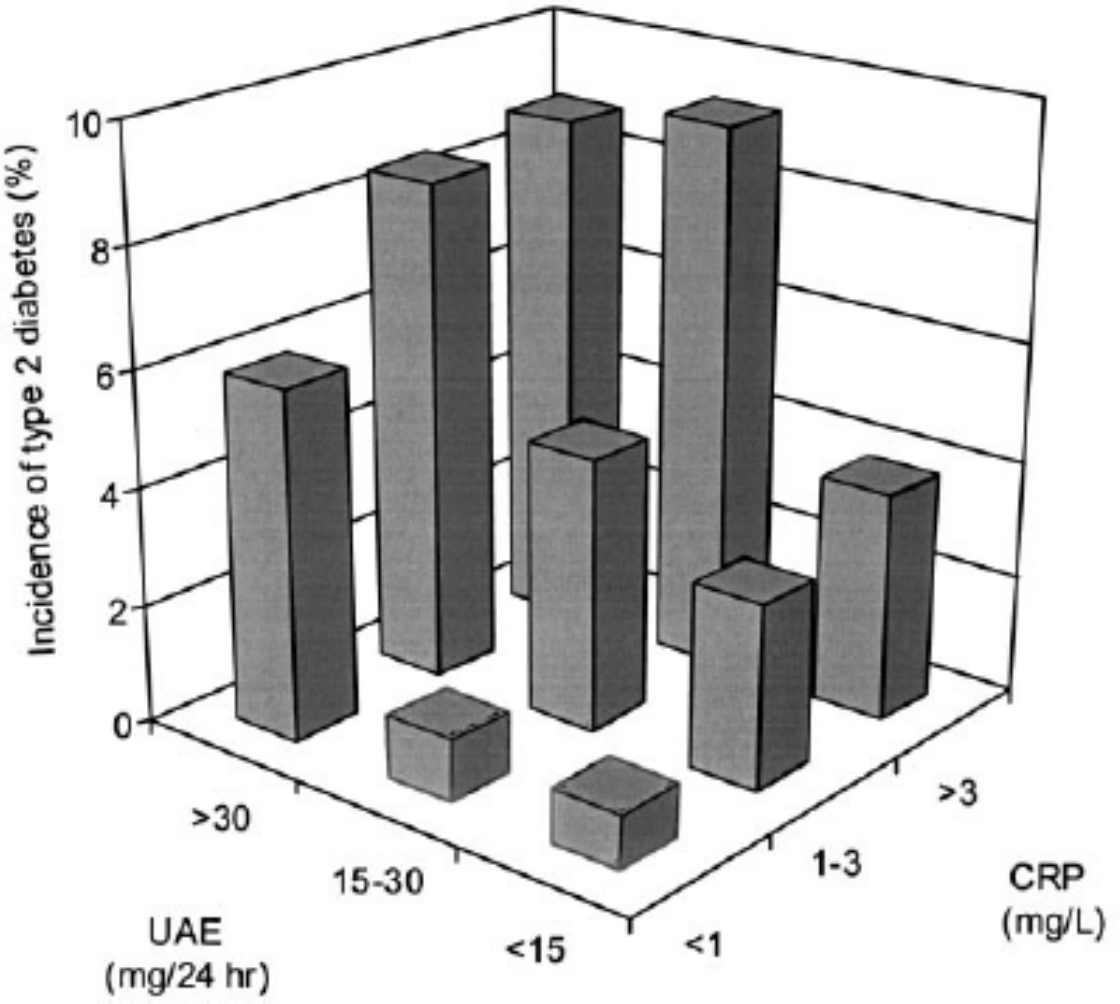
(Initiating Dialysis Early And Late)

828 adults, (incl.355 diabetics
mean age 60.4 years,
Cockroft-Gault GFR 10-15 ml/min/1.73m^2
early start 10-14 ml/min/1.73m^2
late start 5.0-7.0 ml/min/1.73m^2

early start **1.8 months**
late start **7.4 months**

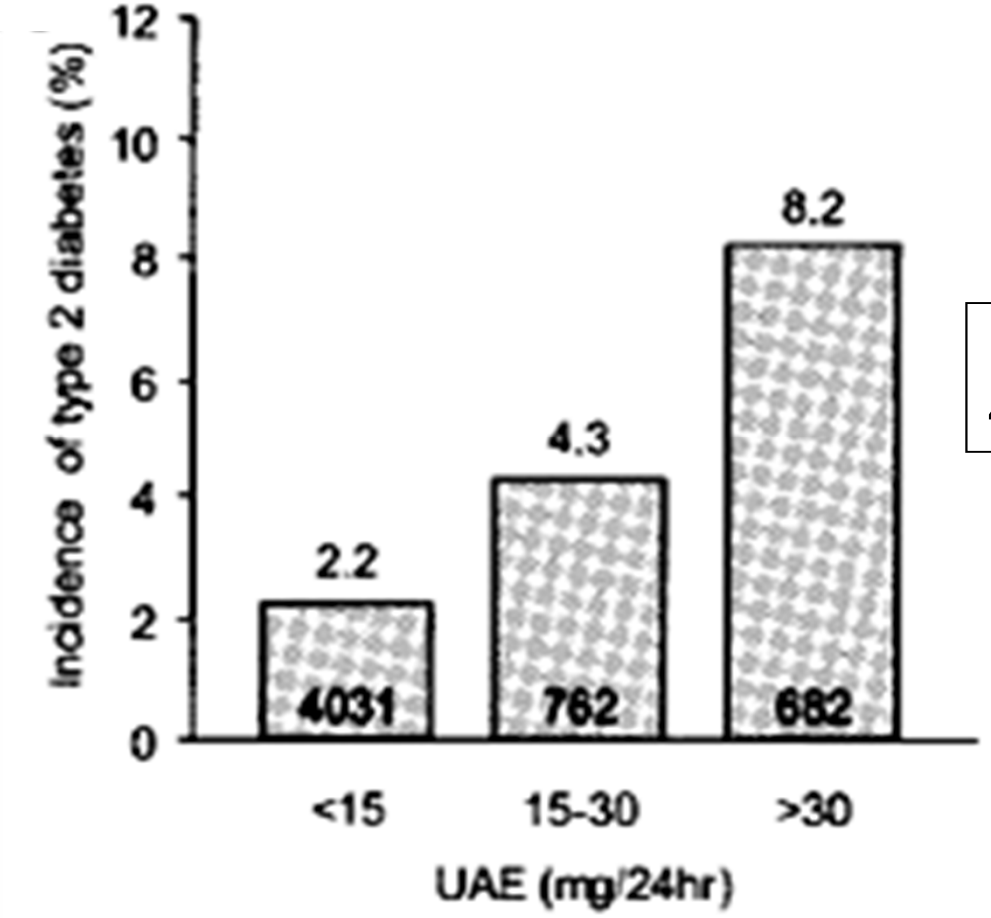
Cooper, New Engl.J.Med.(2010) 363:609

Incidence of type 2 diabetes after 4.2 years according to albuminuria (UAE) and CRP



Brantsma, Diabetes Care (2005) 28:2525

Urinary albumin excretion (UAE) predicts onset of type 2 diabetes



5654 subjects
4 year observation

Brantsma, Diabetes Care (2005) 28:2525

Bariatric surgery and renal function

813 patients; follow-up >24 months

n= 757		
baseline:		S-crea < 1.3 mg/dl
6 months:	8	S-crea >1.6 mg/dl
2 years:	757	S-crea < 1.3 mg/dl

n= 56		
baseline		S-crea > 1.3 mg/dl
2 years		S-crea < 1.3 mg/dl n= 43
		1.3-1.6 mg/dl n= 7
		> 1.6 mg/dl n= 6

Schuster, Surg.Obes.Relat.Dis.(2011) 7:459

“early start worse“ ???
higher mortality ?

Korevaar, “When to initiate dialysis:effect of proposed US guidelines on survival, Lancet (2001) 358: 1046

Traynor, “Early initiation of dialysis fails to prolong survival in patients with end-stage renal failure, JASN(2002) 13:2125

Stel, Residual renal function at the start of dialysis and clinical outcomes NDT(2009) 24:3175

Hwang, Impact of the clinical conditions at dialysis initiation on mortality in incidence hemodialysis: a national cohort study in Taiwan NDT (2010)25:2616

When to start chronic dialysis: tunnel vision induced by numbers?

Wim van Biesen and Raymond Vanholder
Nephrol.Dial.Transplant.(2010) 25:2405

linear inverse association between start eGFR and mortality
with not a single indication of a J shape

lead time bias: “only the fittest are strong enough to survive until eGFR has decreased low enough !“

would this indicate : delay dialysis until the patient is anuric ???

several registries report historical trend towards starting dialysis at higher eGFR over the last decade associated with a decline in mortality

Was ist meine Schlussfolgerung?

eGFR allein ist nicht das richtige Mass um den Dialysebeginn festzulegen
- niederes Kreatinin: gute GFR oder geringe Muskelmasse !
- klinische Parameter (Ernährungszustand, Elektrolytstatus, Volumenstatus…) mindestens genau so wichtig
- eGFR erfasst nicht wichtige urämische Toxine deren klinische Wichtigkeit belegt ist :
  # SDMA, p-Cresyl Sulfat, Indoxyl-Sulfat
  (Seneszenz, oxydativer stress, klotho) …
  # Inflammationsgrad,
  # Endotoxin intestinalen Ursprungs etc ….

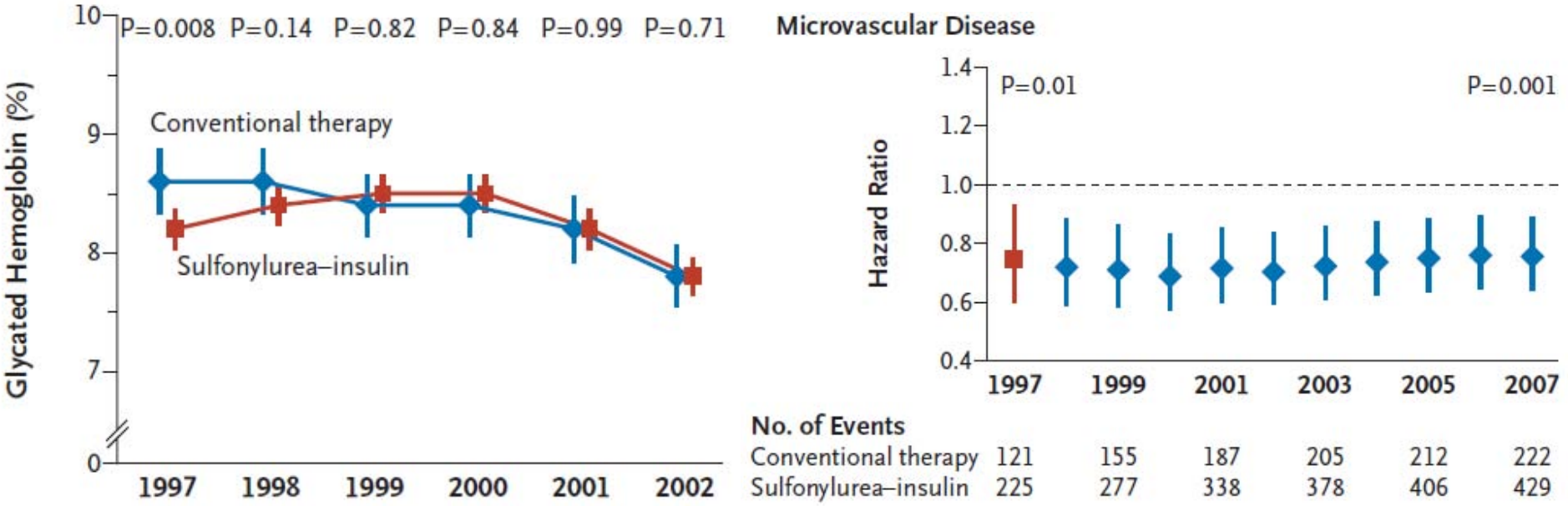
Pirart J.

Diabetes mellitus and its degenerative complications: a prospective study of 4400 patients observed between 1947 and 1973

Diabete Metab. (1977) 3:245

epigenetics: covalent modification of histones and DNA respectively
Goh, Curr.Diab.Rev.(2010) 6:255

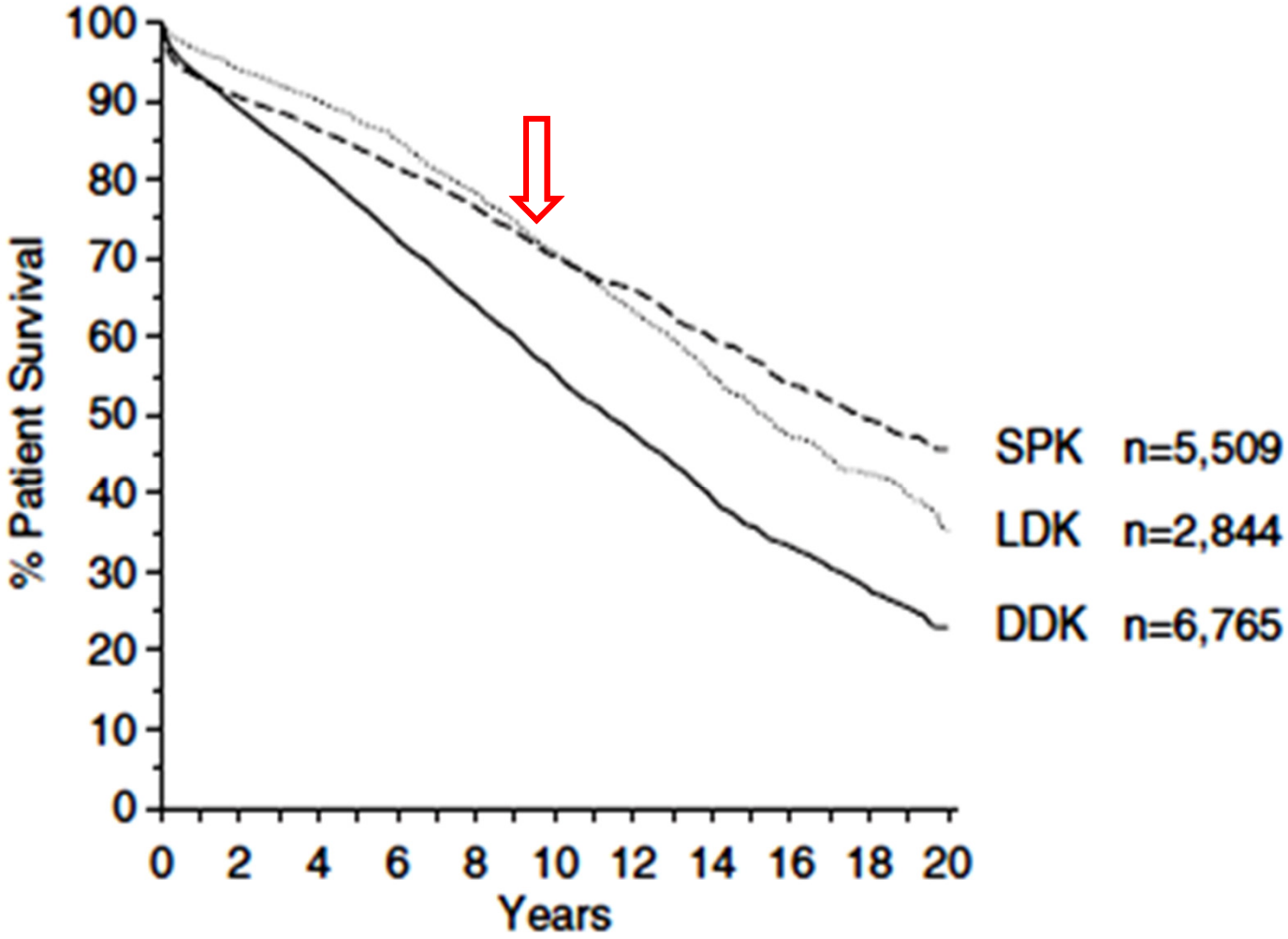
Glycemic memory (legacy effect)
UKPDS



Holman, New Engl.J.Med.(2008) 359:1577

Another example of glycemic memory

Longterm survival of type 1 diabetic patients
after simultaneous pancreas-kidney-transplantation (SPK),
versus life donor kidney- (LDK) or cadaver kidney transplantation (DDK)



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

First major breakthrough :

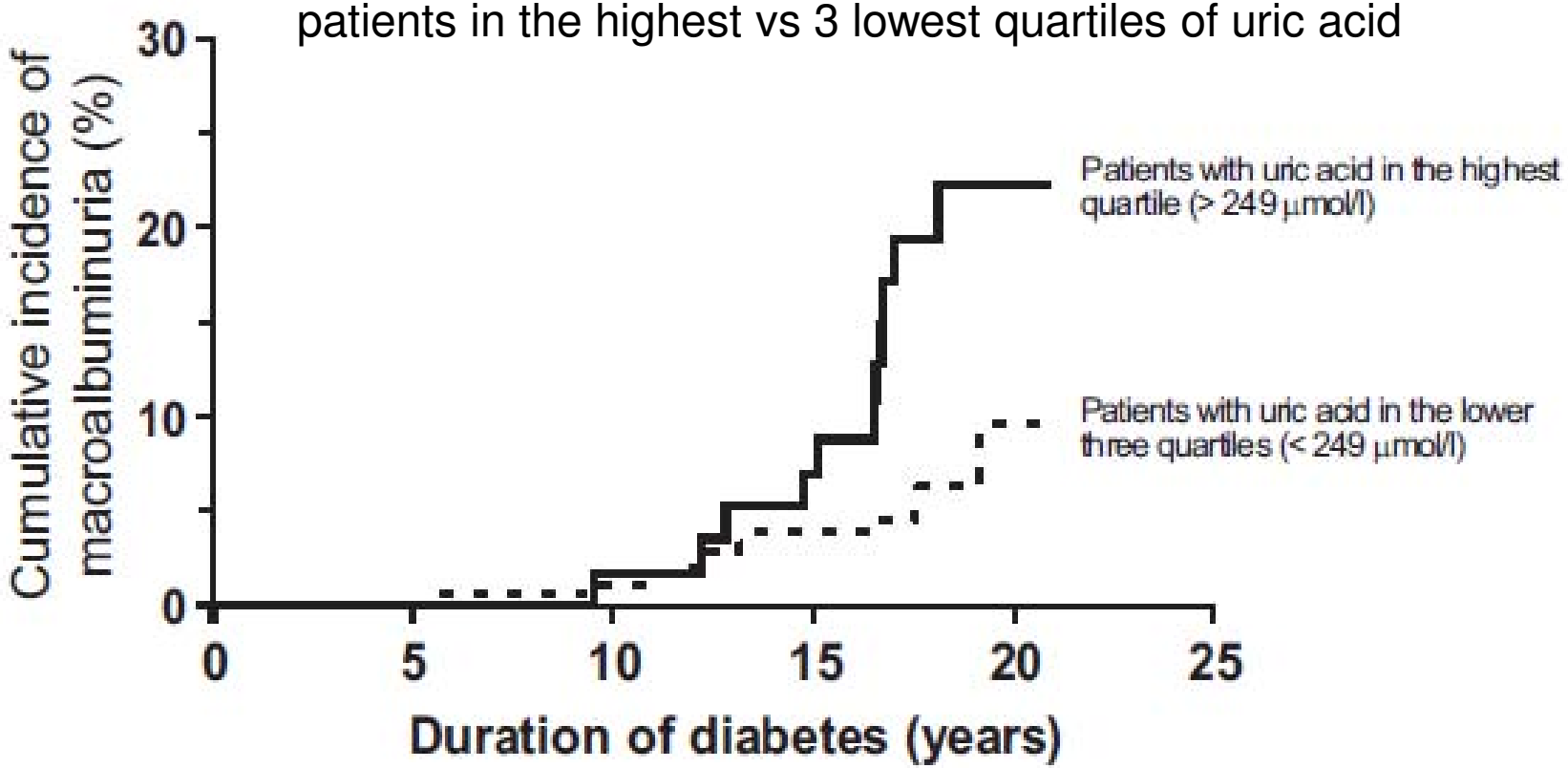
RAS blockade

efficacy on GFR loss dependent on stage at start of treatment

start of Tx	
advanced stage	**IDNT and RENAAL** *Lewis, New Engl. J. Med.(2001) 345: 851* *Brenner, New Engl.J.Med.(2001) 345:861*
early	**DETAIL** *Barnett, New Engl.J.Med.(2004) 351:1952*

Plasma uric acid concentration – a novel predictor of macroalbuminuria ?

263 type 1 diabetic patients
onset 1979-1984
patients in the highest vs 3 lowest quartiles of uric acid



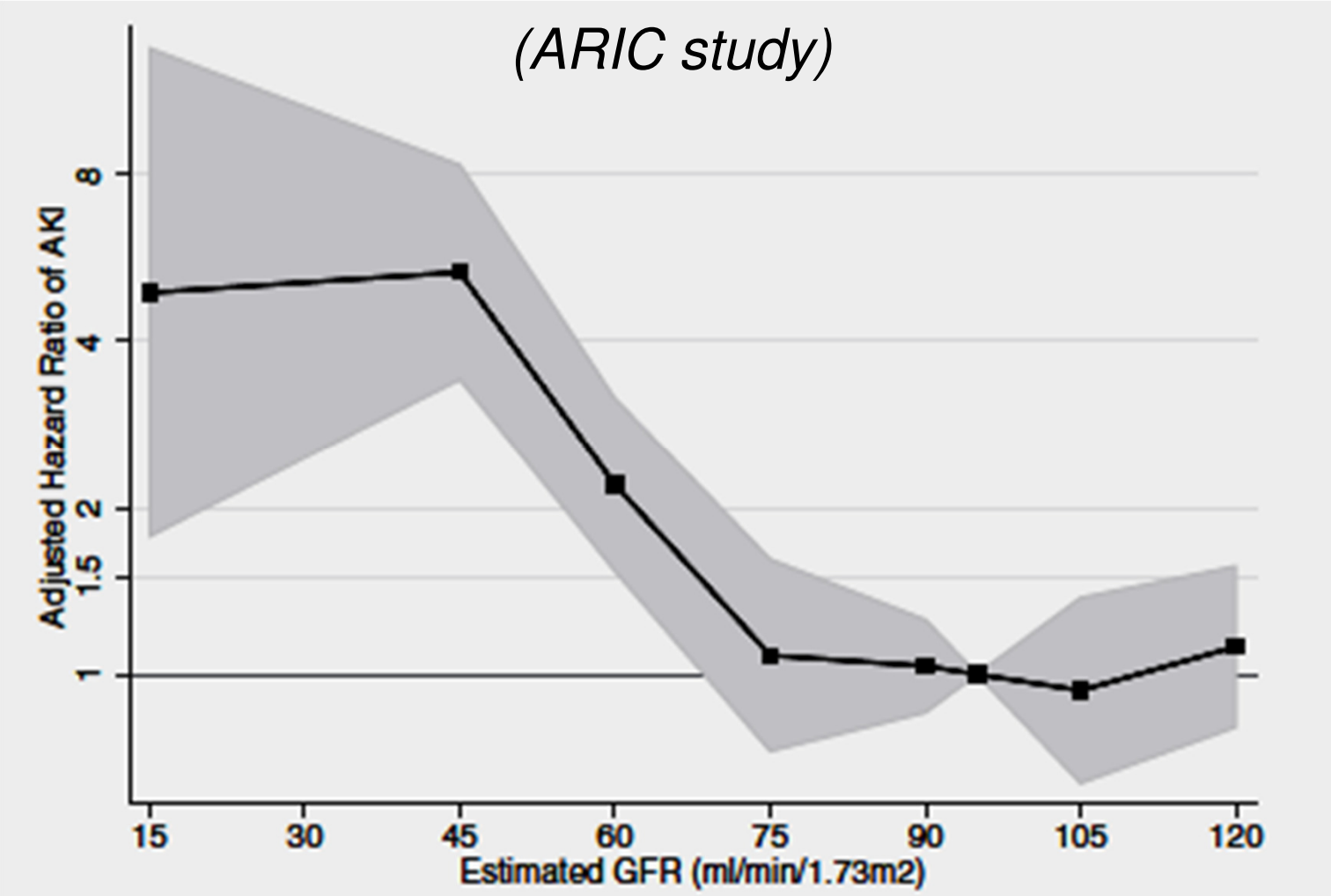
Hovind, Diabetes (2009) 58:1668

In the past : ESRD in type 1

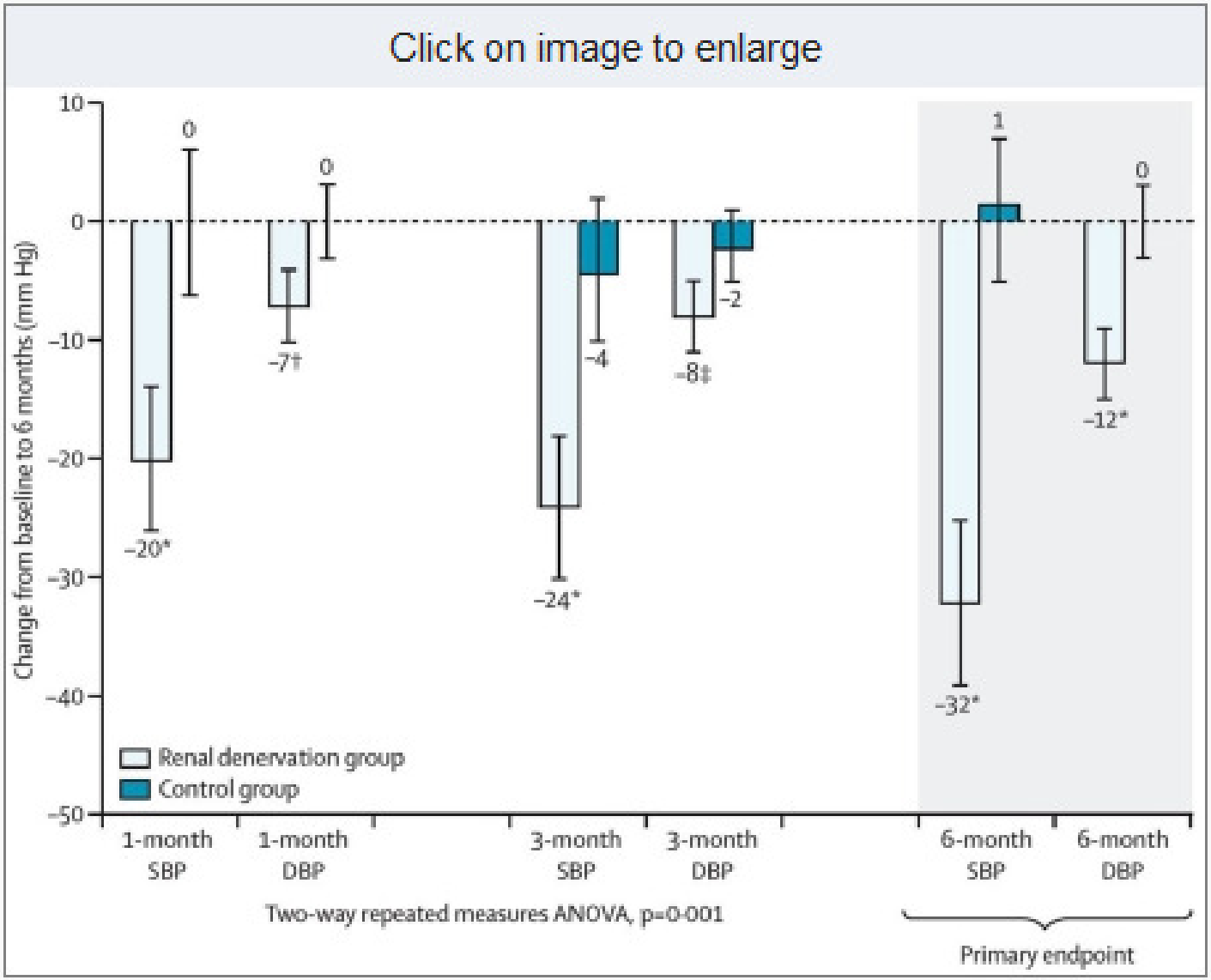
Currently : ESRD in type 2

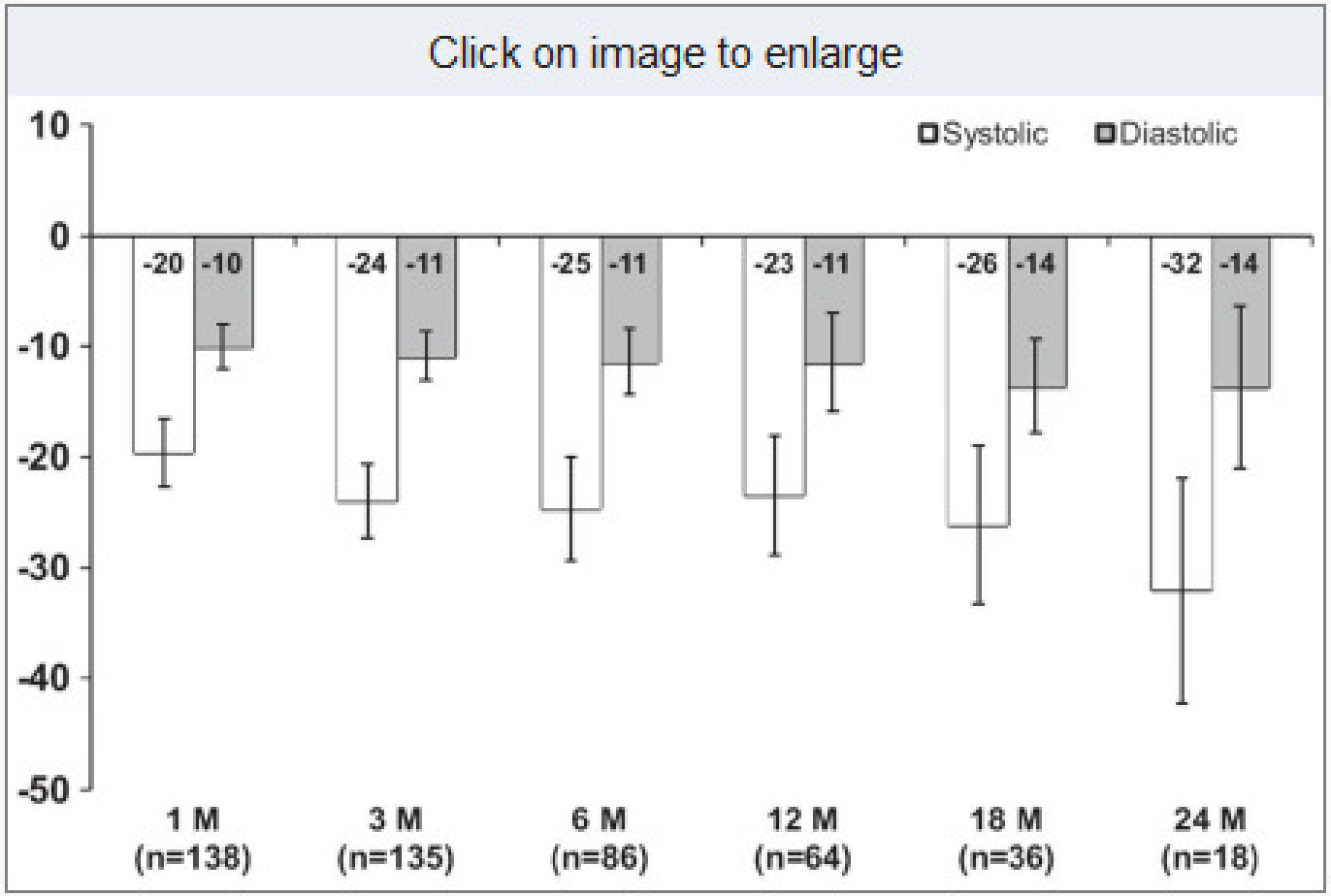
- older age
- less intense management / compliance
- higher renal risk ?
- superimposition of primary hypertension
- preexisting renal sequelae of obesity

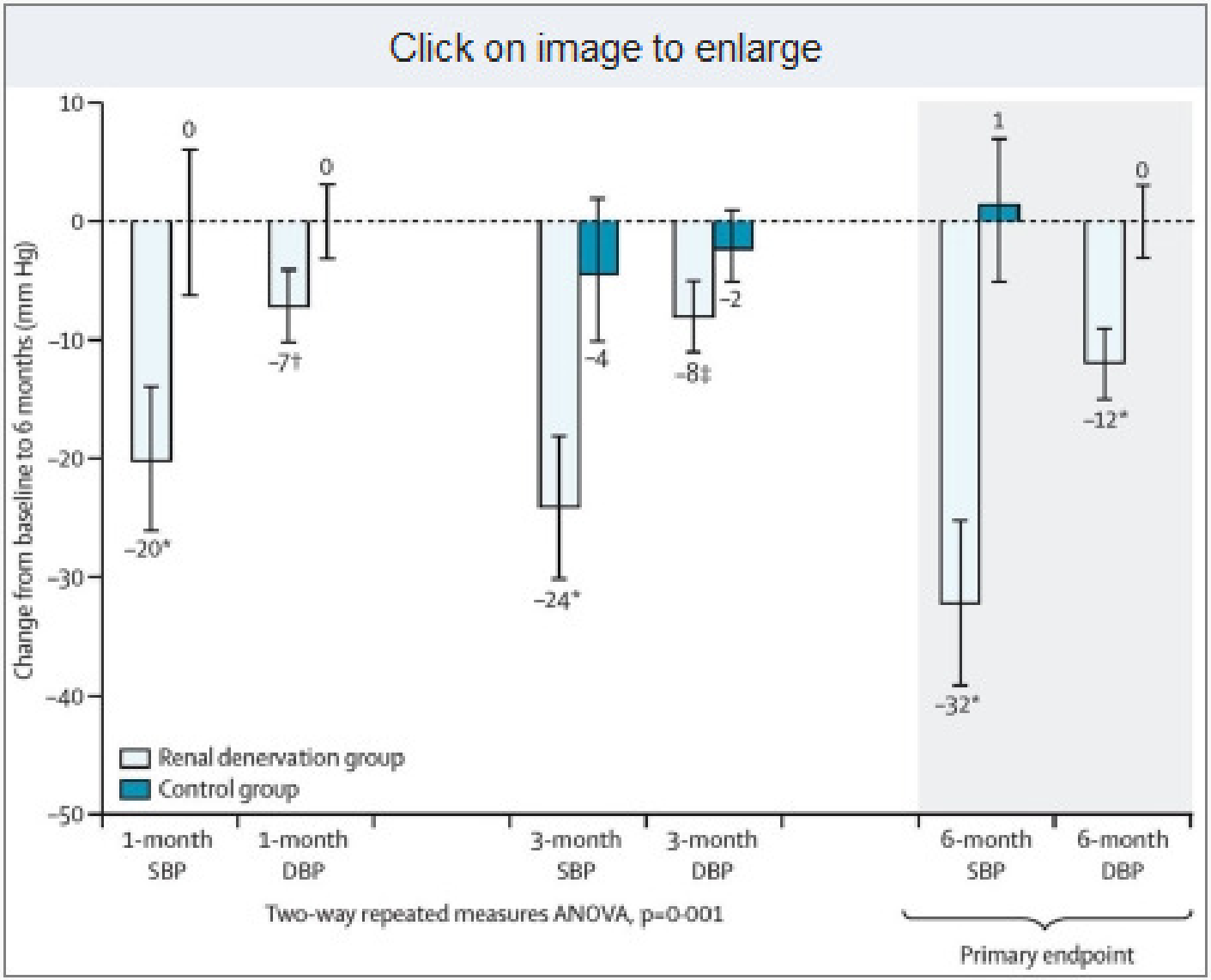
Low eGFR increases the risk of acute kidney injury



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


Click on image to enlarge
Change from baseline to 6 months (mm Hg)
10
0
−10
−20
−30
−40
−50
0
0
1
0
−20*
−7†
−24*
−4
−8‡
−2
−32*
−12*
Renal denervation group
Control group
1-month SBP
1-month DBP
3-month SBP
3-month DBP
6-month SBP
6-month DBP
Two-way repeated measures ANOVA, p=0·001
Primary endpoint


Click on image to enlarge
Systolic
Diastolic
10
0
-10
-20
-30
-40
-50
-20
-10
-24
-11
-25
-11
-23
-11
-26
-14
-32
-14
1 M
(n=138)
3 M
(n=135)
6 M
(n=86)
12 M
(n=64)
18 M
(n=36)
24 M
(n=18)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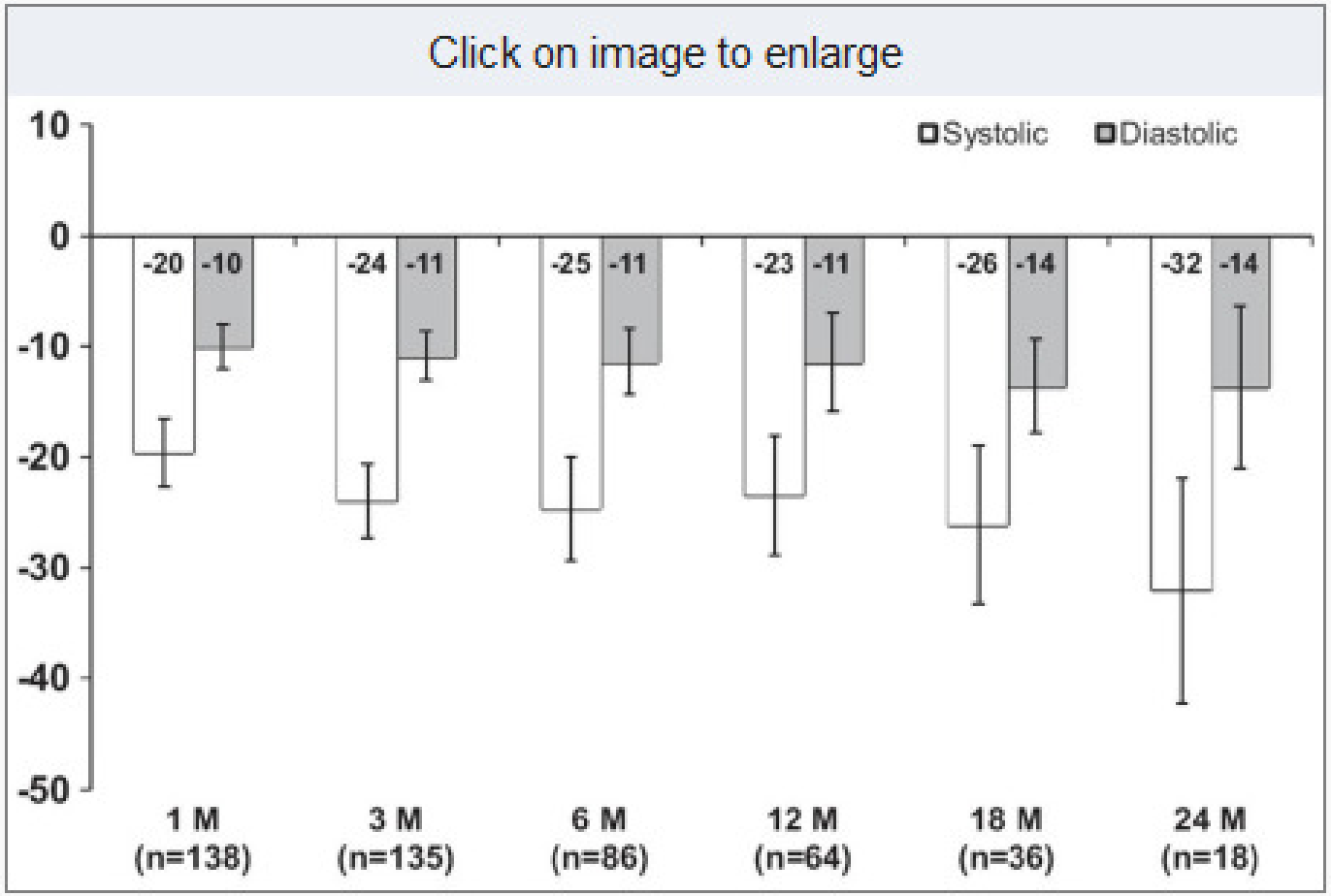
Click on image to enlarge
Systolic
Diastolic
10
0
-10
-20
-30
-40
-50
-20
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-24
-11
-25
-11
-23
-11
-26
-14
-32
-14
1 M
(n=138)
3 M
(n=135)
6 M
(n=86)
12 M
(n=64)
18 M
(n=36)
24 M
(n=18)

Obesity and the kidney

- ***Hemodynamic***
  - *elevated RPF, GFR, FF, albuminuria*
- ***Structural***
  - *increased kidney weight, glomerular size, mesangial expansion, podocyte injury*
- ***Pathology***
  - *glomerulomegaly, glomerulosclerosis, obesity relaetd glomerulopathy*
- ***Chronic kidney disease***
  - *increased risk of onset CKD, progression of CKD, proteinuria*
- ***Endstage kidney disease***
  - *increased incidence and prevalence, survival advantage on dialyis, increased graft loss in kidney transplant recipients*
- ***Further renal complications***
  - *increased renal cell carcinoma, nephrolithiasis*

Eknoyan, Revista Nefrologia (2011) 31: 397

Relative Incidence of **Endstage Kidney Disease** vs. **Cardiovascular Mortality** in Proteinuric Type 2 Diabetes

(DIAMETRIC database)

In the IDNT and RENAAL trials
mean follow-up 2.8 years

19.5% developed ESRD

⇨ 2.5 *times the incidence of CV death*
1.5 *times the incidence of all cause mortality*

Packham, Am.J.Kidn.Dis.(2012) 59:75