Diabetic nephropathy

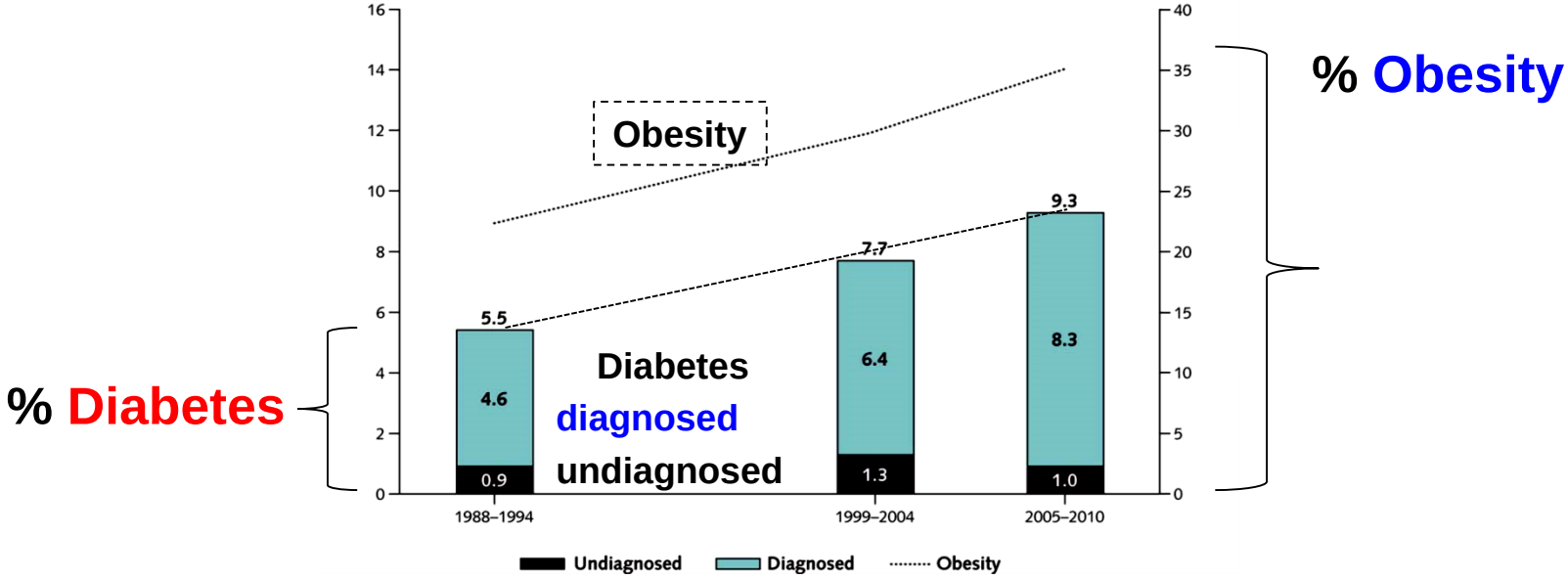
Eberhard Ritz
Heidelberg (Germany)

Diabetic nephropathy – an update

- **Epidemiology**
- *Diabetic nephropathy – all the same ?*
- *Insulin resistance*
- *Management of diabetic nephropathy – state of the art*
- *Metformin controversy*
- *Bariatric surgery*
- *Glycemia control in reduced GFR*
- *Additional interventions*

Increasing prevalence of obesity and diabetes

in the US from 1988-1994 to 1999-2010



- **prevalence of diabetes** *($HbA1_c$ >6.5%)* **5.5%** *(1994)* **to 9.3%** *(2010)*
- **undiagnosed diabetes** *($HbA1_c$ >6.5%)* **stable 11%**
- **prediabetes prevalence** *(fasting glucose100-125mg/dl)* **from 5.8% to 12.4%**
- **prevalence of $HbA1_c$ < 7.0% from 50.9%** *(1994)* **to 58.8%** *(2010)*

Selvin, JAMA (2014) 160:517

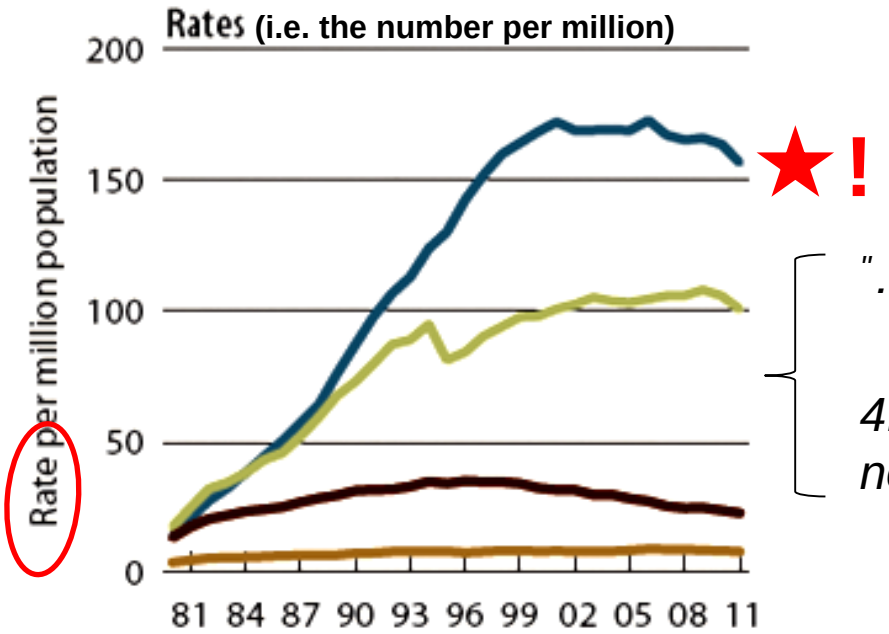
vol 2
1.7

Incident counts & adjusted rates of ESRD, by primary diagnosis

Data 2012

USRDS

United States Renal Data System

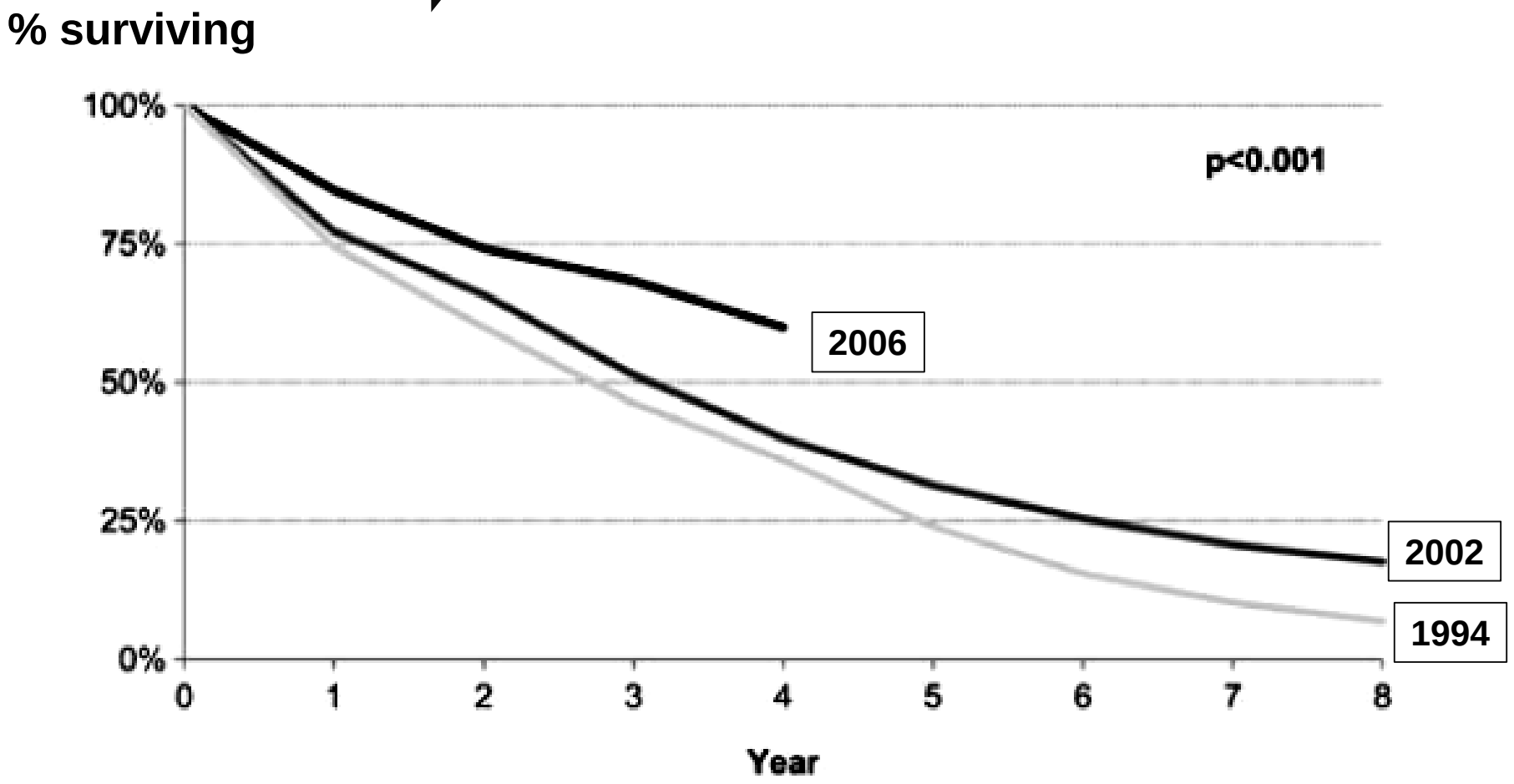


★!

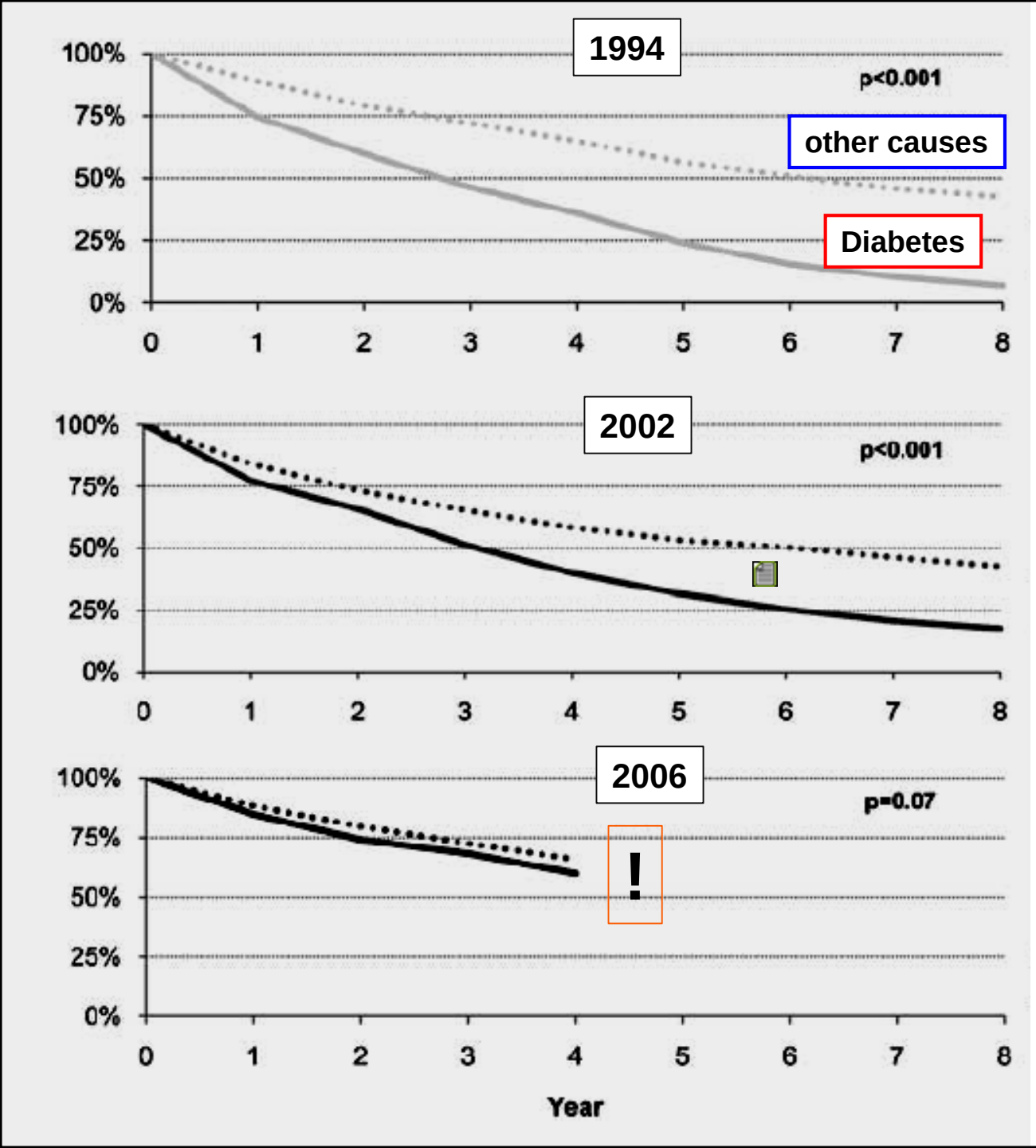
"……157 per million population in 2011; the rate of new ESRD due to diabetes is 4.2% lower than in the preceding year and has now fallen back to a level not seen since 1998"

Survival of incident diabetics on renal replacement therapy in Catalonia: 1994, 2002, 2006

⇨ progressively better



Comas, Nephrol.Dial.Transplant. (2013)28: 1191



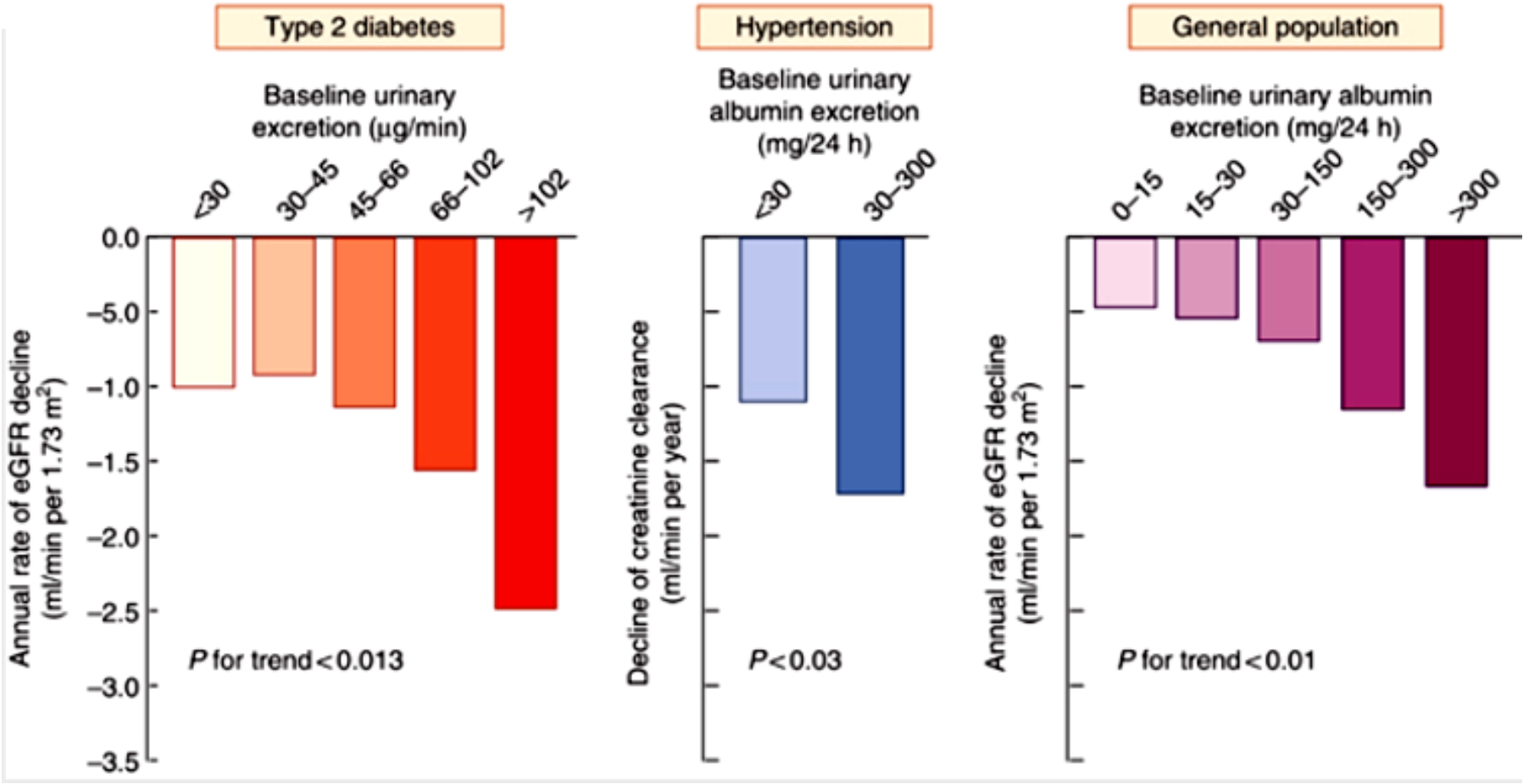
Catalonia

Incident patients with ESRD and **diabetes** vs ESRD for **other causes** taken on **renal replacement therapy** **in 1994, 2002, 2006 –**

in 2006 :
no more difference in survival !

Comas, NDT (2013) 28:1191

In type 2 diabetes albuminuria highly sensitive predictor of GFR loss



Roscioni, Kidney International (2014) 86:40

CKD in predialysis type 2 diabetes (UK)

(evolution and mortality)

Evolution of CKD in diabetes

UKPDS, 5,097 subjects, first 10 years after diagnosis :
development per year
2.0 % microalbuminuria,
2.8% macroalbuminuria,
2.3% elevated s-creatinine

Zoppini, Nutr.Metab.Cardiovasc.Dis.(2009) 19:580

Mortality in diabetic nephropathy

Annual mortality in patients :
1.4% with normoalbuminuria
4.2 % with clinical proteinuria
19.2% with renal impairment

Bilous, Diabet.Med.(2008) 25 (S2) 25

Reduced frequency of most diabetes-related complications

(US 1990-2010)

Between 1990-2010 impressively less numbers of :

- **acute MI** - 67.8%
- **mortal hyperglycemic crisis** - 64%
- **stroke** and **amputations** - 52.7% and - 51.4%

the least improvement (percent decline) was seen in:

- ***endstage renal disease*** - 28.3%

Gregg, N.Engl.J.Med.(2014) 370:1514

Type 2 diabetic patients with albuminuria/increased creatinine - renal histology not uniform

 # 1/3 nodular nephrosclerosis with mesangial thickening *(classical)*

 # 1/3 nonspecific : interstitial fibrosis, arteriolar hyalinosis and minor glomerular changes – i.e. not all renal damage classical "diabetic nephropathy“

 # 1/3 normal kidney structure (?)

Fioretto, Diabetologia (2008) 51:1347

Diabetic nephropathy – an update

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- *Insulin resistance*
- *Management of BP in diabetic nephropathy – state of the art*
- *Metformin controversy*
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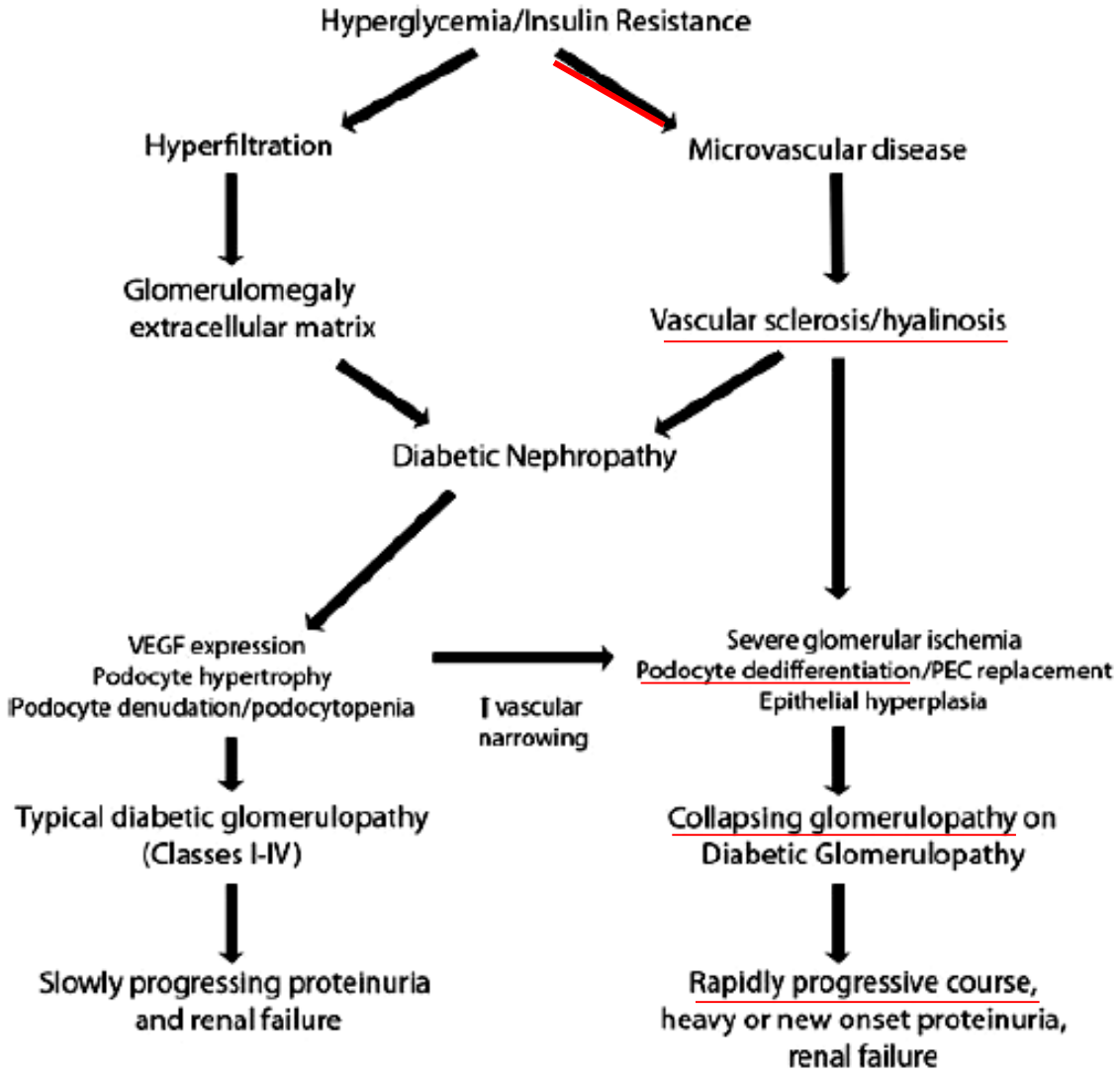
- *Additional efforts*

A newcomer

Collapsing glomerulopathy superimposed on diabetic nephropathy

(an underrecognized even more severe pattern of glomerular injury)



Salvatore, Nephrol.Dial.Transplant.(2014) 29:392

Collapsing glomerulopathy superimposed on diabetic nephropathy

(an underrecognized severe pattern of glomerular injury)

	Collapsing glomerulopathy (n=36)	Diabetic glomerulopathy (n=20)	
Age *(years)*	53.6	58.7	
Gender	12F/14M	9F/11M	
S-Creatinine*(mg/dl)*	3.75	3.68	
Proteinuria *(g/24h)*	9.4	5	*(p<0.008)*
Global glomerulosclerosis	35%	42%	
Interstital fibrosis	65%	55%	
Vascular sclerosis (0-3)	2.6	2.7	
GBM thickness *(nm)*	850	847	
foot process effacement	62%	33%	*(p<0.014)*
ESRD	78%	40%	*(p<0.0017)*

13/17 oatients ESRD within 6.9 months

HIV negative

Salvatore, Nephrol.Dial.Transplant.(2014) 29:392

Collapsing glomerulopathy superimposed on diabetic nephropathy: insights into etiology of an under-recognized, severe pattern of glomerular injury

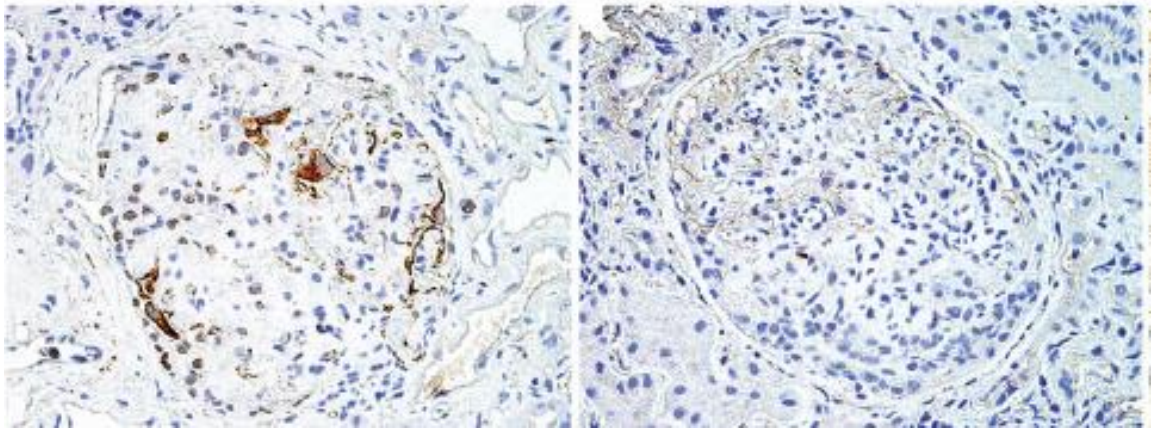
Salvatore, NDT (2014) 29:392

5% of diabetic nephropathies

loss of markers of podocyte differentiation and extensive arteriolar hyalinosis

poor prognosis

loss of podocyte differentiation markers

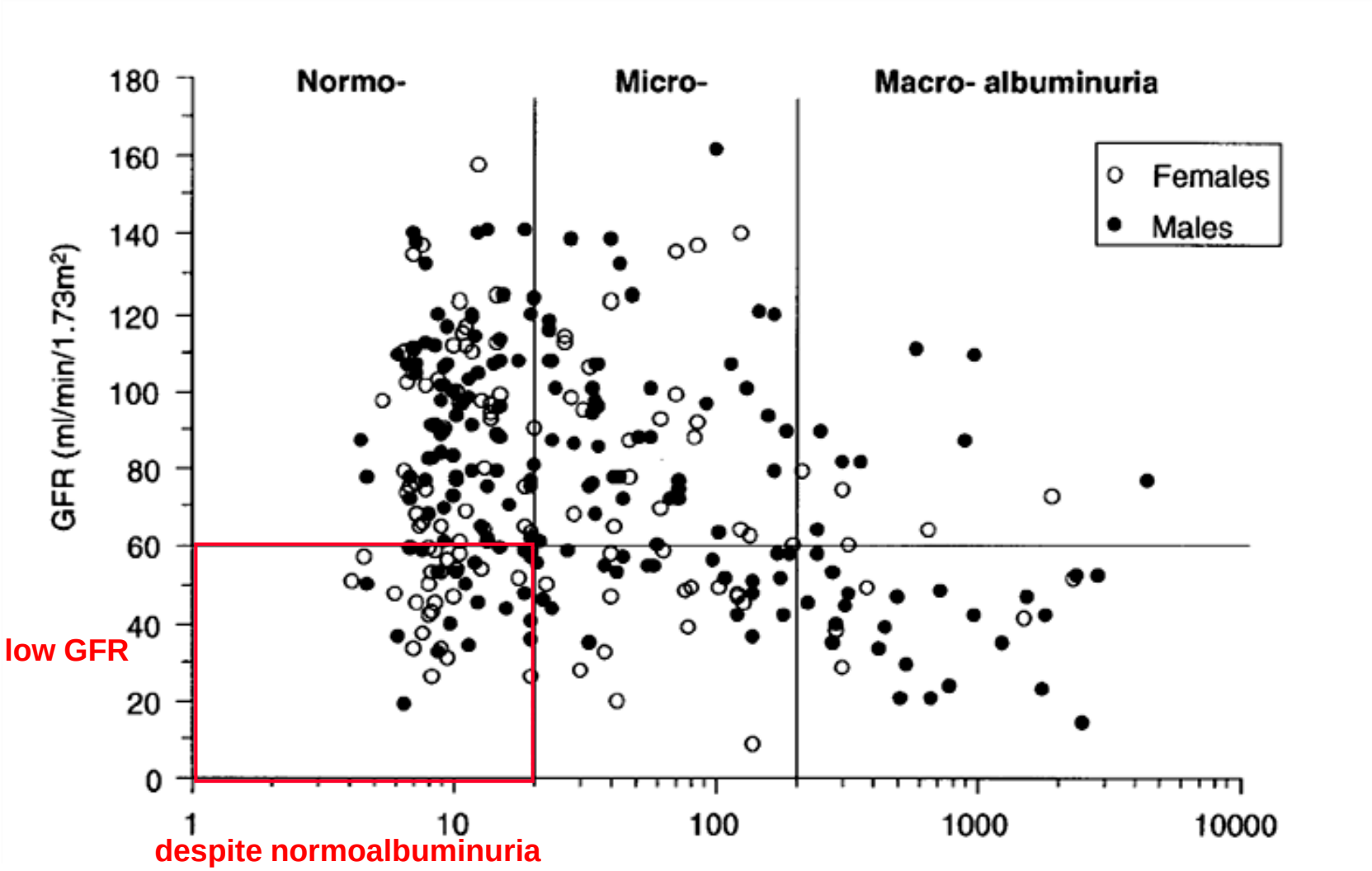


WT-1

Synaptopodin

Low GFR despite normoalbuminuria in type 2 diabetes

(ischemic nephropathy ?)



MacIsaac, Diabetes Care (2004) 27:195

Diabetes – spectrum of renal biopsy findings

New York (D'Agati 2011) :

23.5% of renal biopsies concerned patients with diabetes

 # 37% had diabetic nephropathy alone

 # 36% had nondiabetic renal disease

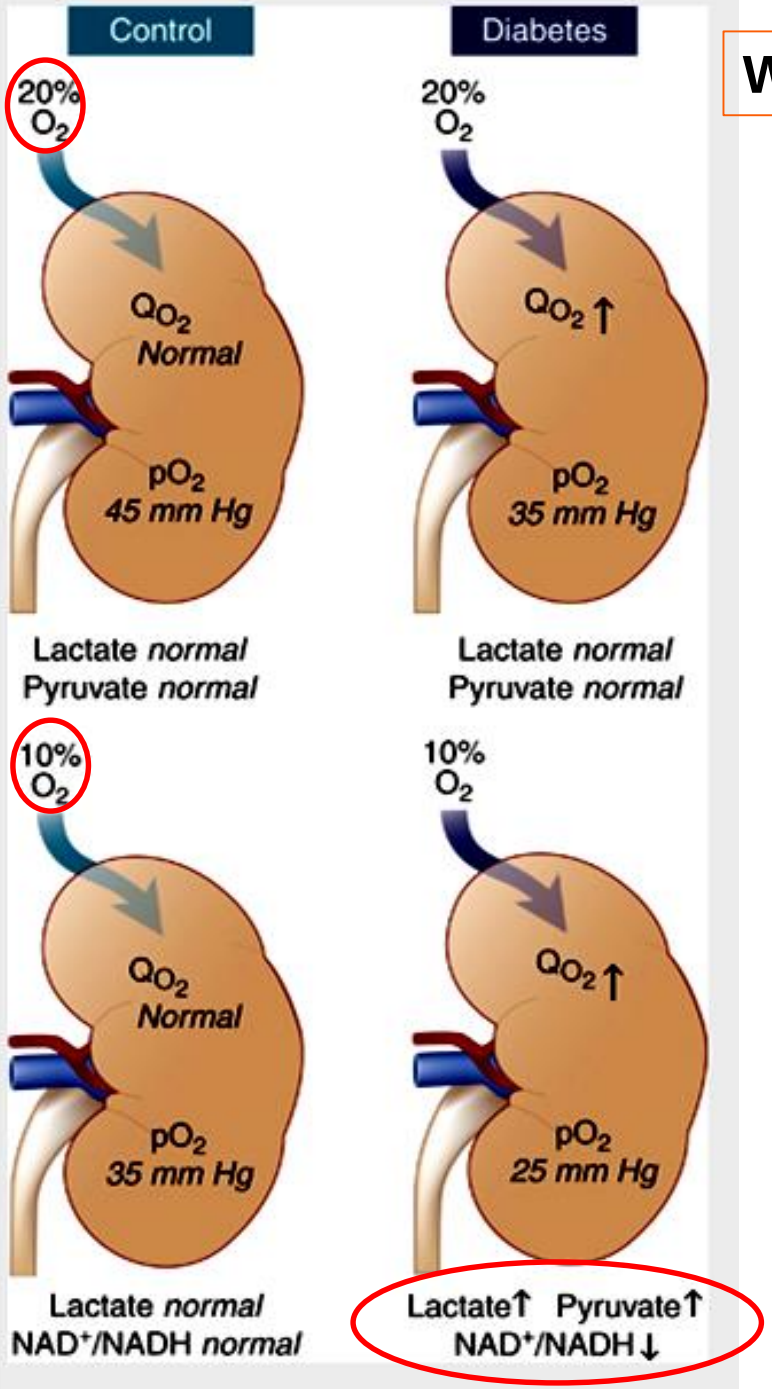
 # 27% had diabetes plus nondiabetic renal disease

nondiabetic renal disease *:*

FSGS (focal segmental glomerulo-sclerosis)	*22%*
hypertensive nephrosclerosis	*19%*
acute tubular necrosis	*17%*
IgA nephropathy	*11%*
membranous GN	*8%*
pauci-immune GN	*7%*

⇨ longer duration of diabetes – greater probability diabetic nephropathy

Sharma, Clin.J.Am.Soc.Nephrol.(2013) 8:1718



Why is the kidney so vulnerable in diabetes?

A role of cortical hypoxia in diabetes ?

Compared to renal cortex in normal animals, in diabetes :

oxygen consumption (Q_{O2}) is elevated in diabetes and as a consequence

oxygen partial pressure (pO_2) is lowered

Blantz, Kidn.Internat. (2014) 86:7

Genetic predisposition to diabetic nephropathy

one example : in blacks genetic predisposition in carriers of APOL1 gene variant

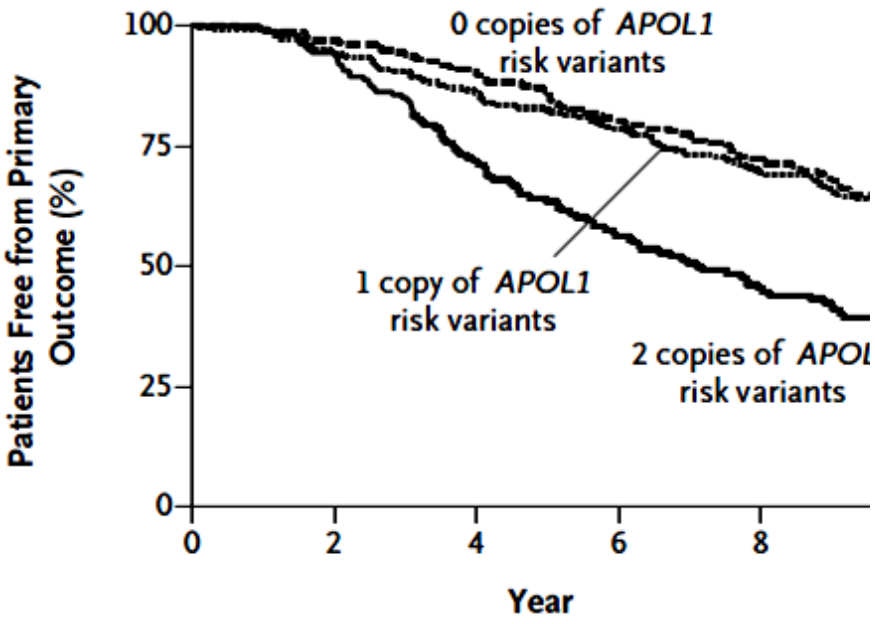
 # carriers have higher risk of diabetic nephropathy (CRIC study)

 # APOL1 expression in human podocytes

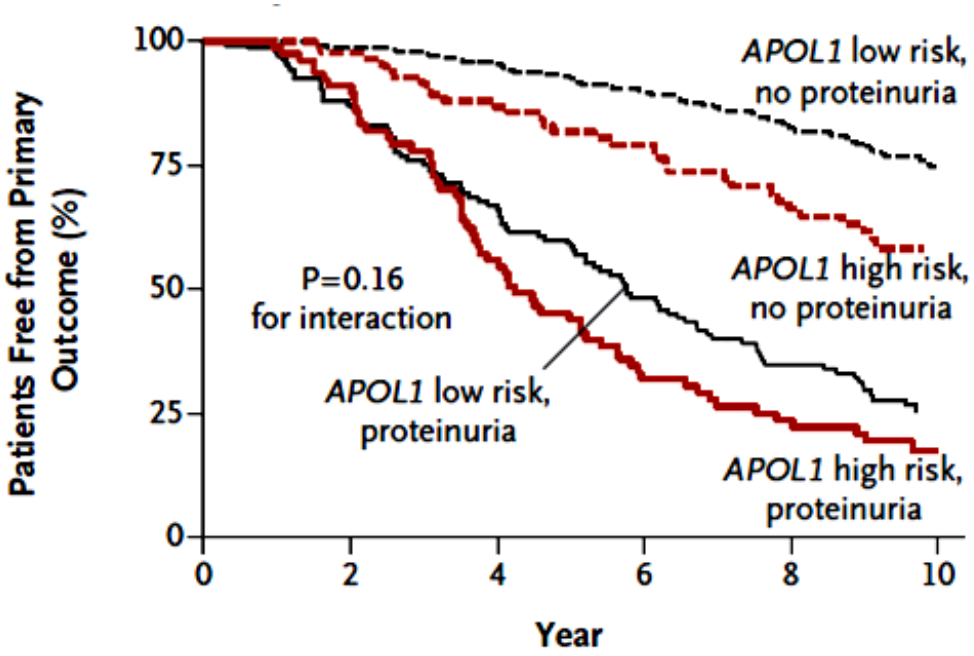
APOL1 Risk Variants in type 2 diabetes

Primary outcome

(any renal abnormalities)



Development of Proteinuria



Parsa, N.Engl.J Med.(2013) 369:2183

Hartleben J.Clin.Invest (2010) 120:1084

Kume Diabetes (2012) 61:23

Diabetic nephropathy – an update

- **Epidemiology**
- **Diabetic nephropathy – all the same ?**
- **Insulin resistance starts early on**
- *Management of BP in diabetic nephropathy – state of the art*
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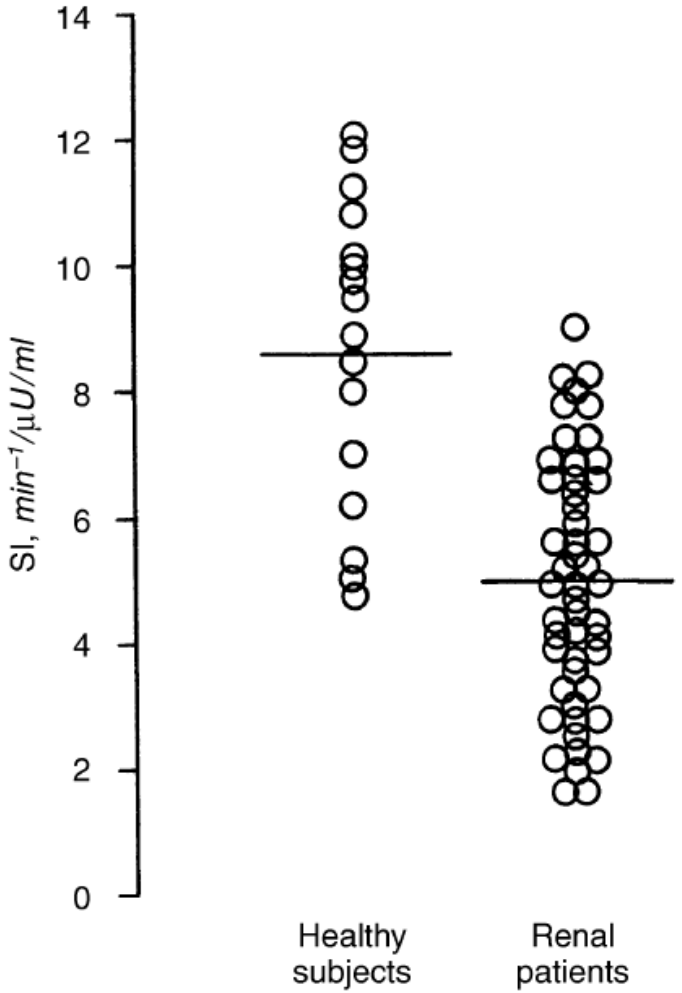
Insulin sensitivity and hyperinsulinemia – even in incipient renal disease

(euglycemic clamp technique)



Fliser, Kidn.Internat.(1998) 53:1343

The role of insulin resistance in diabetes type II

Leyking, CJASN (2014) 9: 638

Insulin resistance occurs early

Fliser, Kidn.Internat.(1998) 53:1343
Becker, J.Am.Soc.Nephrol.(2002) 13:1894

Even in nondiabetic CKD patients
insulin resistance is an independent predictor of CV mortality

Shinohara, JASN (2002) 13:1894
Xu , CJASN (2014) 9:690

Insulin-stimulated glucose transport/uptake diminished
postreceptor signalling pathways in isolated muscle fibers disturbed

Friedman Am.J.Physiol. (1991) 261:E87

Inflammation triggered overexpression of SRP *(signal regulatory protein α)*
in muscle

Thomas, Kidn.Internat.(2013) 84:308

Dietary glycemic "load" – associated with oxydative stress ! in diabetic patients on maintenance hemodialysis

58 hemodialysis patients BMI 29.5±6.8kg/m²

dietary glycemic load significantly associated with :

F_2-isoprostanes *(p=0.002)*

hsCRP *(p=0.03)*

independent of body composition and adipocytokines

Glycemic load significantly associated with markers of ***oxydative stress*** *and* ***inflammation*** *in hemodialysis patients independent of body composition and adipocytokines*

Limkunakul, NDT (2014) 29:1047

Diabetic nephropathy – an update

- **Epidemiology**
- **Diabetic nephropathy – all the same ?**
- **Insulin resistance**
- **Management of BP in diabetic nephropathy – state of the art** *(RAS and alternative antihypertensives)*
- *Metformin controversy*
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Prevention of diabetes type 2

in high risk prediabetic individuals :

a role for ACE inhibitors *(ACEi)* or

angiotensin receptor blockers *(ARB)* ?

reduced incidence has up to date been documented

in12 randomized controlled clinical trials

in individuals at high risk of diabetes

% reduction of onset of type 2 diabetes

- ACEi : reduction by **27%** vs controls
- ARB : reduction by **23%** vs controls

Abuisaa, JACC (2005) 46: 821

"The use of an ACE inhibitor or ARB should be considered
in patients with pre-diabetic conditions "

(e.g. metabolic syndrome, hypertension, impaired fasting glucose, family history of diabetes, obesity, congestive heart failure or coronary heart disease)"

RAS blockade :

does it prevent diabetes onset and CV events ?

(*Valsartan in Navigator study*)

 # minor but significant reduction of diabetes onset,
 # no change CV events

9.306 patients with impaired glucose tolerance and established CV disease
***Valsartan** up to 160 mg/day vs placebo*
*+ **lifestyle modification***

follow-up 5 years :

***diabetes onset** : 33.1% in Valsartan arm*
36.8% in placebo arm
} *small, but significant difference*
Δ 3.7%; p<0.001

***CV events** : no significant difference*

McMurray, N Engl J Med (2010) 362:1477

1 h blood glucose value *(after glucose load)* predicts risk of later hypertension after 18 years *(1968-1986)*

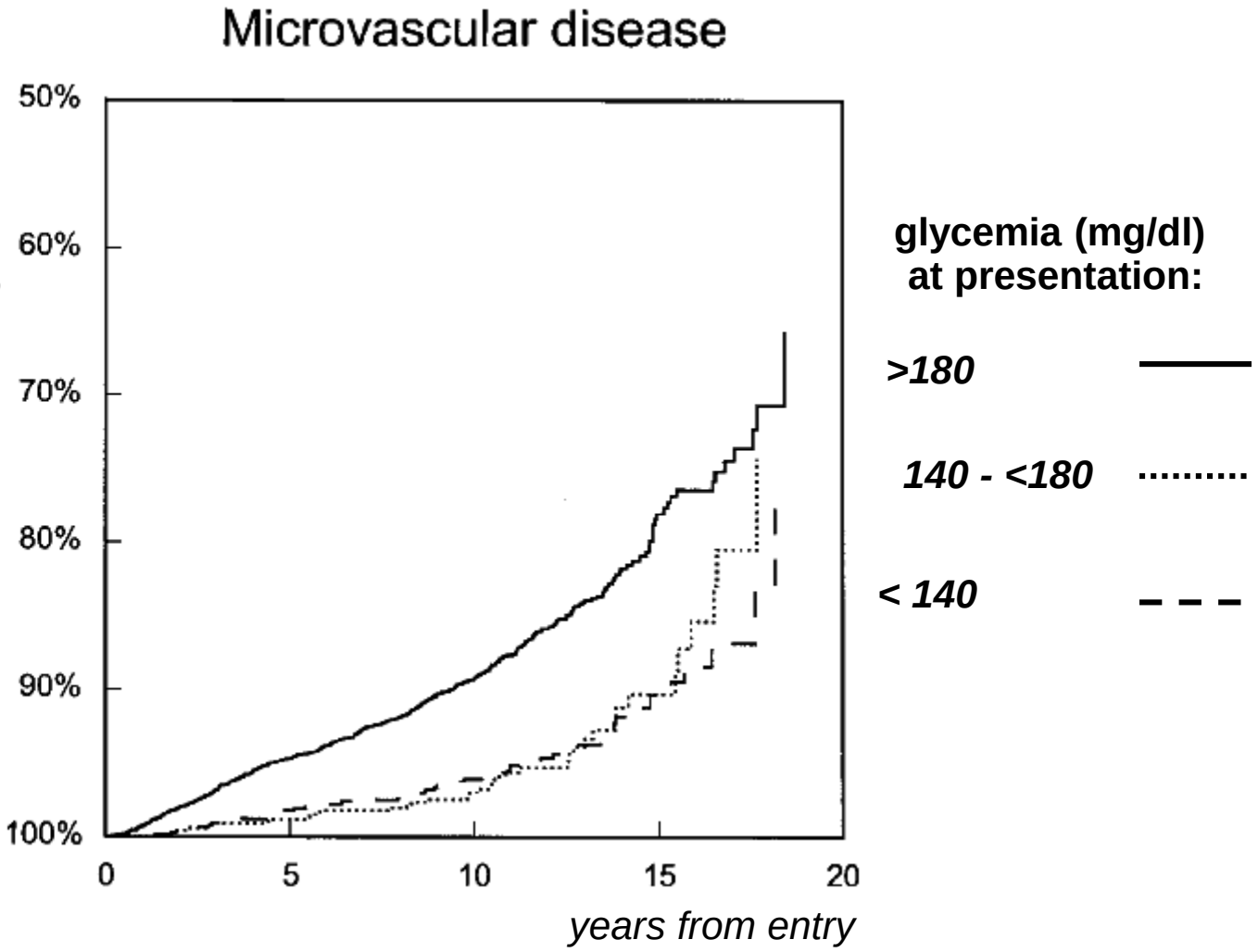
Glucose concentration after one hour in 1968 (mmol/l)	Hypertensive in 1986	Normotensive in 1986	Odds ratio† (95% confidence interval)
≤5·15 (n=198)	48 (24·2)	150 (75·8)	1·00
5·16-6·65 (n=197)	63 (32·0)	134 (68·0)	1·36 (0·84 to 2·22)
≥6·66 (n=185)	73 (39·5)	112 (60·5)	1·71 (1·05 to 2·77)

Salomaa, BMJ (1991) 302:493

The higher glycemia at presentation - the greater the risk of microvascular disease

(UK Prospective Diabetes Study # 61)

Proportion of patients remaining event-free
(microvascular disease including nephropathy)



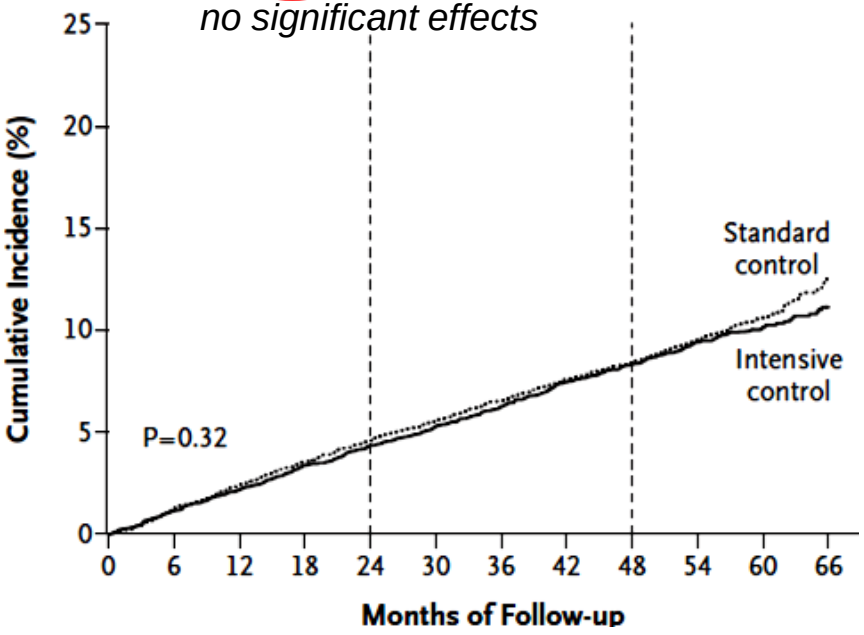
Colagiuri, Diabetes Care (2002) 25:1410

Intensive glucose lowering in type 2 diabetes : *less adverse events*

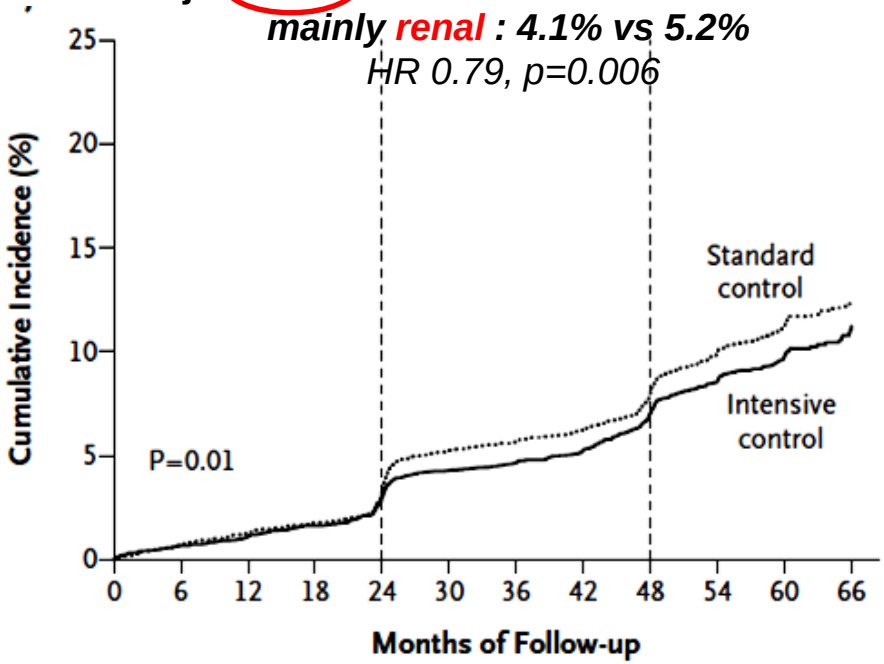
ADVANCE study

11,140 patients type 2 diabetes
standard control vs. intensive control (*Gliclazide plus other antidiabetic drugs*)
$HbA1_c$ goal: standard control 7.3% vs intensive control 6.5%
median duration 5 years

Major Macrovascular Event
no significant effects



Major Microvascular Events *9.4% vs 10.9%*
mainly renal : 4.1% vs 5.2%
HR 0.79, p=0.006



21% reduction of renal events

severe hypoglycemia 2.7% vs 1.5% *(standard control)* **HR 1.86; p<0.001**

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

Can <u>microvascular outcomes</u> in type 2 diabetes be even further reduced by very intensive *($HbA1_c$ <6%)* <u>treatment of hyperglycemia</u>

(ACCORD trial)

10 251 type 2 diabetics with $HbA1_c$ >7.5% and high CV risk

5128 assigned to **intensive** Rx ***($HbA1_c$ <6%)*** and

5123 assigned to **standard** Rx ***($HbA1_c$ 7.0-7.9%)***

*Intensive treatment ($HbA1_c$ <6%) was **stopped***

*because of **increased mortality*** **!**

Ismail-Beigi, Lancet (2010) 376:419

there is a limit for blood glucose lowering ; avoid hypoglycemia !!!

Review of 63 randomized trials on renal outcome (and mortality) by antihypertensive therapy in diabetes Which antihypertensive(s) are best ?

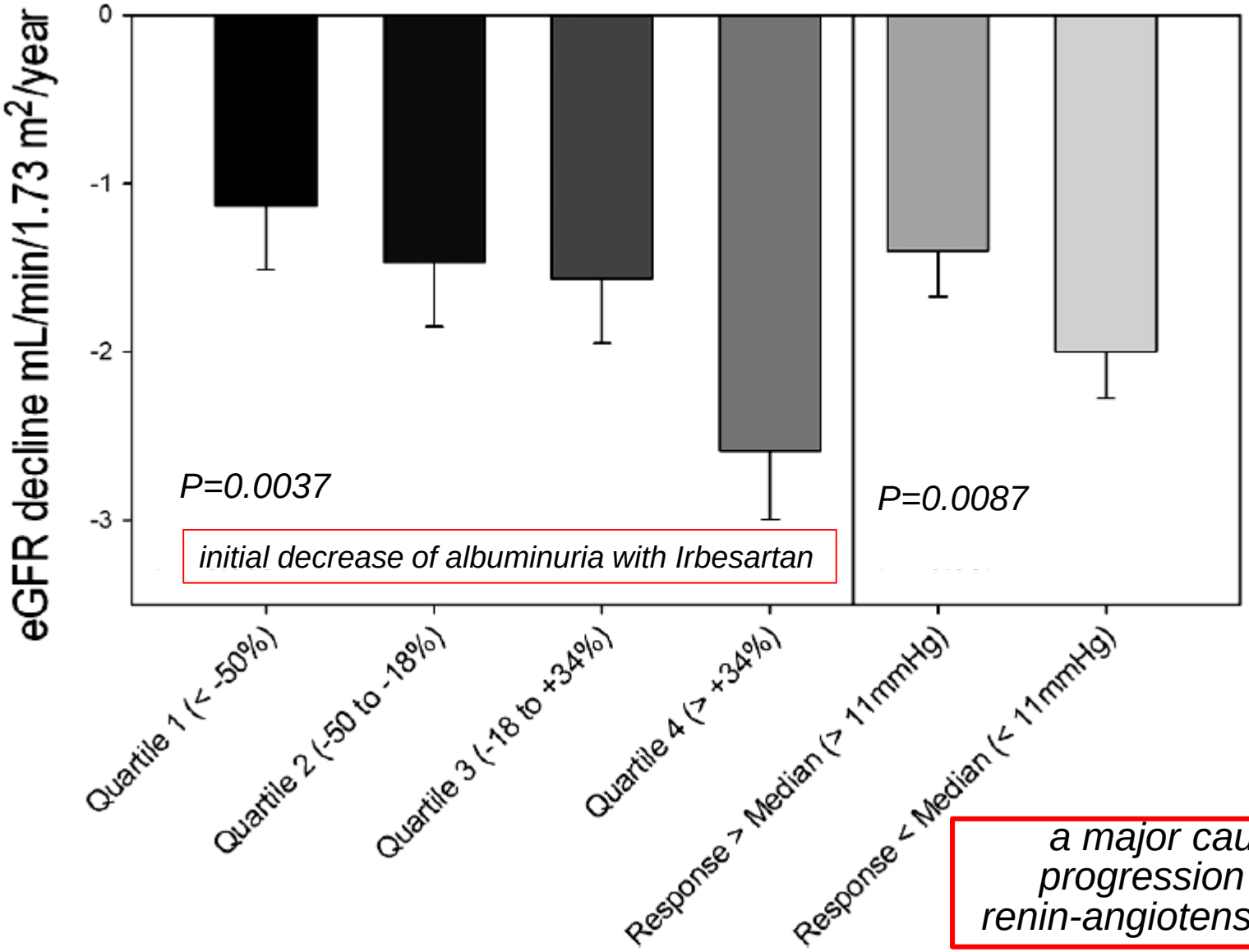
- *36917 diabetic participants, duration at least 12 months*

- *# only ACE inhibitors compared to placebo*
  reduced doubling of S-creatinine :
  odds ratio 0.56 (95%CI 0.3-0.9)

- *# only beta-blockers compared to placebo*
  achieved difference in mortality

Wu, BMJ (2013) 347:f6008

A larger initial decrease of albuminuria with RAS blockade is associated with less longterm loss of eGFR in type 2 diabetes

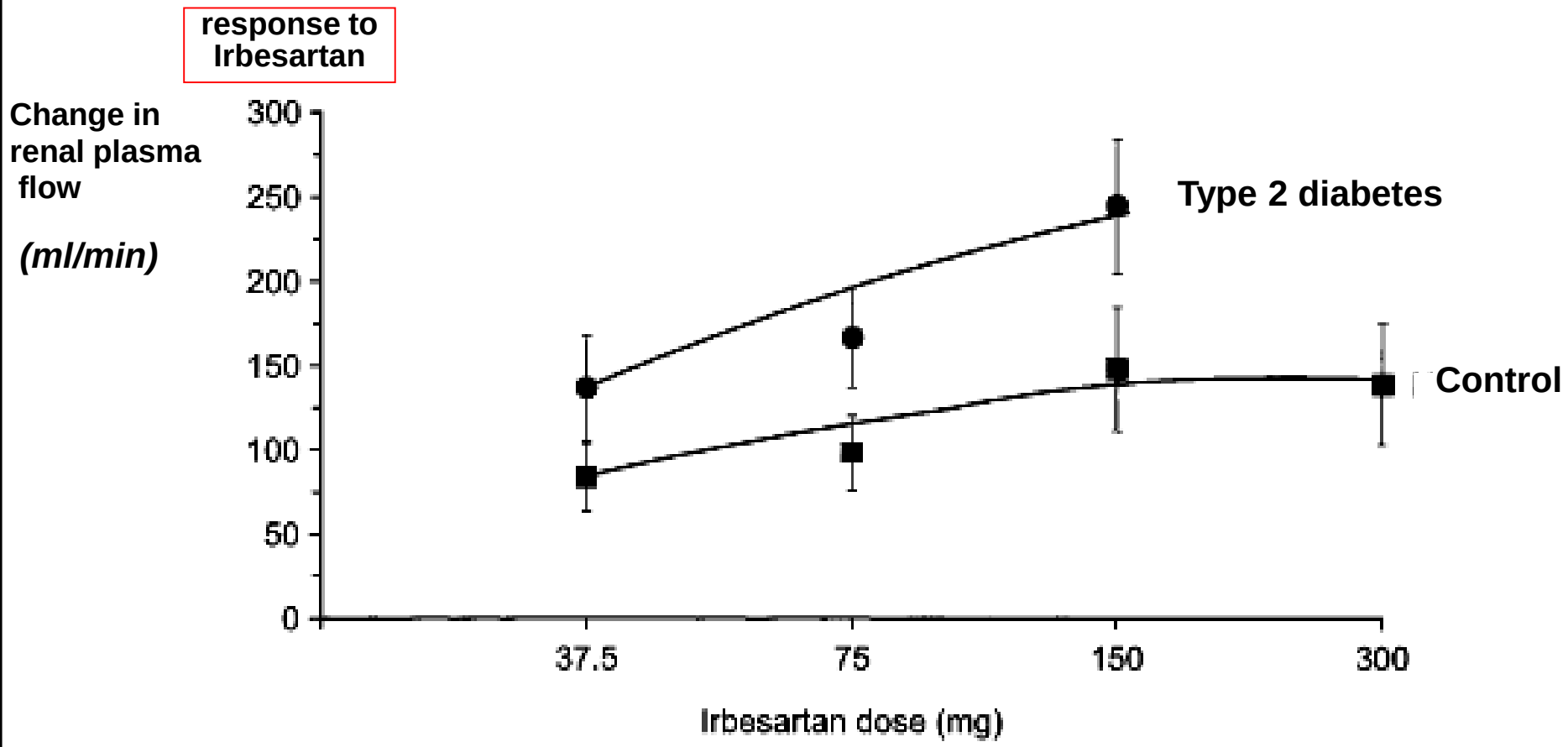


a major cause of progression is the renin-angiotensin system

Hellemons, Diabetes Care (2011) 34:2078

Diabetic nephropathy is a low renin state, *but renal plasma flow response to RAS blockade is increased compared to nondiabetic controls*

⇨ Is intrarenal ANGII production increased ?



Deborah, J.Am.Soc.Nephrol.(1999) 10:2383

Intensive blood pressure control in type 2 diabetes

(ACCORD study)

4733 type 2 diabetics assigned to
standard therapy or systolic BP < 120 mmHg
primary endpoint: nonfatal MI, nonfatal stroke, CV death

after 1 year mean systolic BP 119.3 vs 133.5 mmHg

⇩

annual death rates :
1.87% *in intensive vs.* **2.09%** *in standard Rx,*
but serious adverse events from antihypertensive treatment :
3.3% *in intensive Rx vs.* **1.3%** *standard Rx groups*

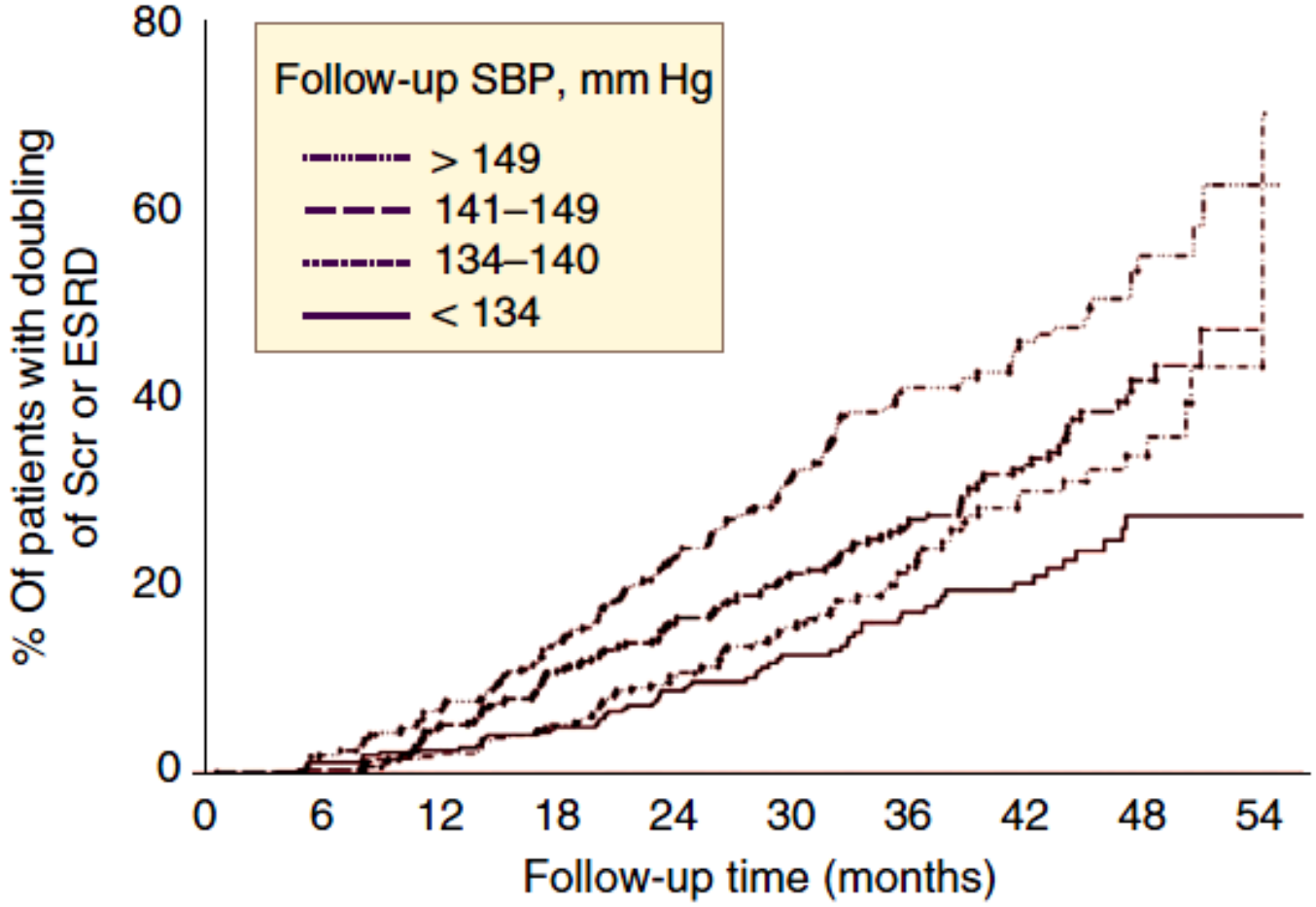
Clinic BP <140 mmHg did not reduce rate of fatal and nonfatal CV events !

Cushman, New Engl.J.Med.(2010) 362:1575

Cumulative proportions of patients reaching renal endpoint

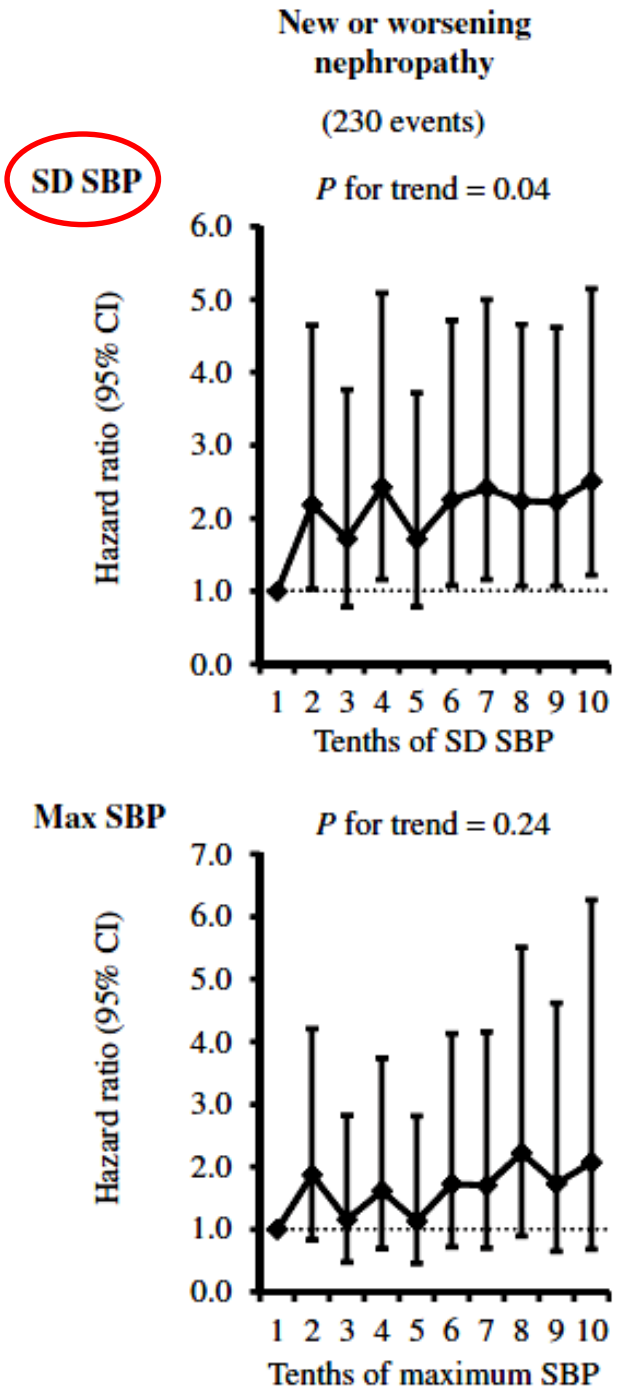
(doubling S-creatinine; endstage renal disease)

[IDNT trial]



Patients with systolic BP < 134 mmHg had the best renal survival

Sarafidis and Ruilope, Kidn.Internat.(2014) 85:536



High visit-to-visit variability
(standard deviation) **of**
systolic blood pressure
(SD SBP)

⇨ **high frequency of renal complications in type 2 diabetes**

(ADVANCE Study)

Hata, Circulation(2013) 128:1325

The higher visit-to-visit variability in systolic blood pressure - the higher **albuminuria** *(nephropathy)* and **pulse wave velocity** *(cardiovascular pathology)*

422 consecutive type 2 diabetic patients

coefficient of variation of systolic blood pressure at each visit

correlated to:

- **albuminuria** (*logUAE*) **:** *r = 0.210; p<0.0001*
- **pulse wave velocity** **:** *r = 0.409, p<0.0001*

adverse effect on kidney and vasculature

Okada, Atherosclerosis (2012) 220:155

Safety aspect : orthostatic hypotension

(Malmö Preventive Project)

Decrease of **systolic** **blood pressure > 30 mmHg** after 3 minutes standing

Mortality	**hazard ratio 1.6** *(95% CI 1.3-1.9)*	*p<0.0001*
Cardiovascular events	" **1.6** *(95% CI 1.2-2.1)*	*p=0.001*

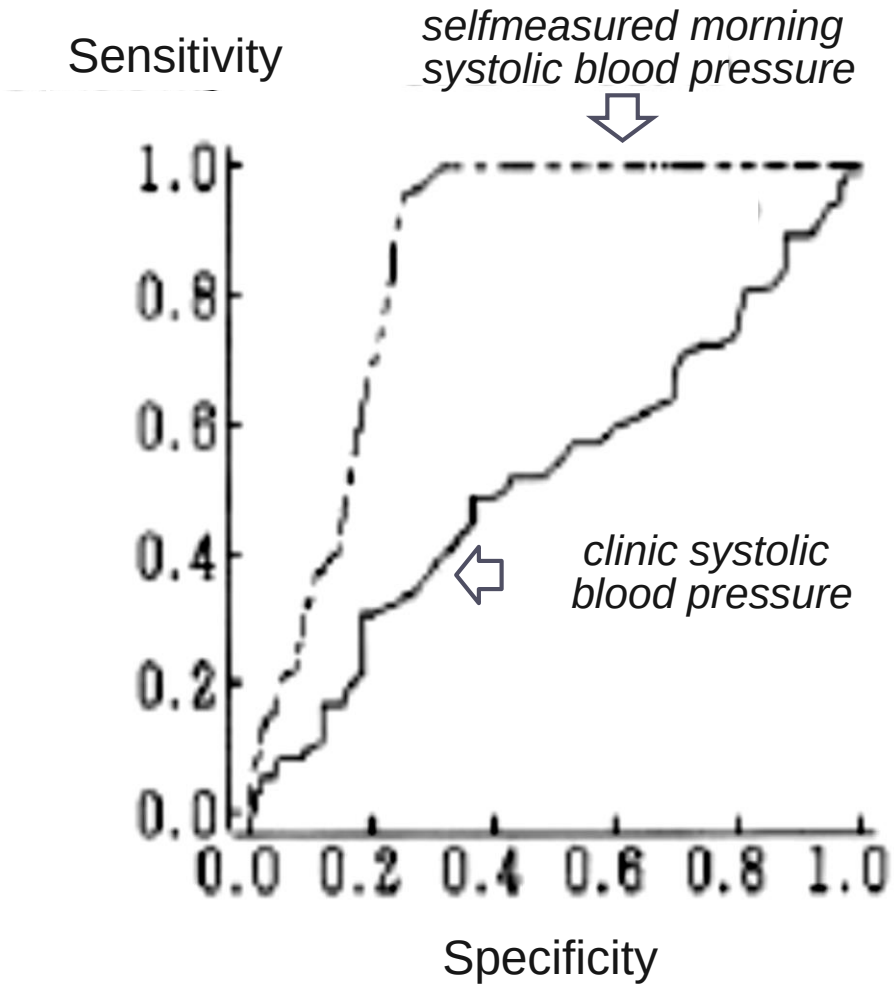
Decrease of **diastolic** **blood pressure > 15 mmHg** 3 minutes standing

Mortality	**hazard ratio 1.4** *(95% CI 1.1-1.9)*	*p=0.024*
Cardiovascular events	" **1.7** *(95% CI 1.1-2.5)*	*p=001*

Fedorowski, European Heart J. (2010) 31:85

Clinic blood pressure is inferior to self measured BP

Morning blood pressure *(self measurement)*
compared to clinic measurement
⇨ **is more sensitive to predict diabetic complications**
(nephropathy, retinopathy, coronary heart disease)



Kamoi, Diabetes Care (2002) 25:2218

In type 2 diabetic patients

nighttime (!) blood pressure is the most significant determinant predicting progression of albuminuria

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

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

The value of 24h blood pressure measuring in type 2 diabetes

(particularly to document nighttime BP decrease)

104 patients with type 2 diabetes
9.2 years follow-up

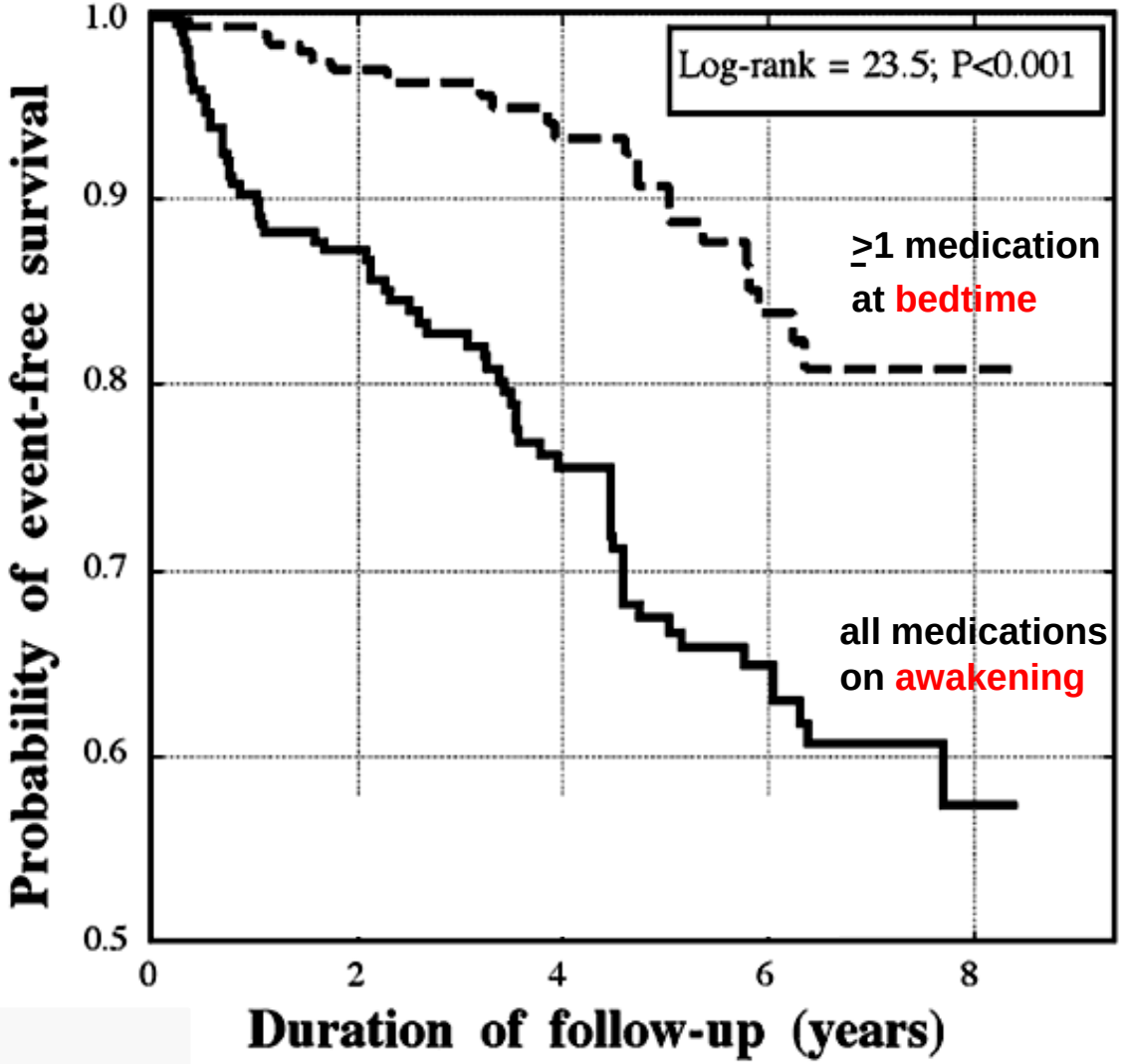
- patients with BP nighttime > daytime : mortality 88%
- patients with nighttime “dipping“ : mortality 45 %

Astrup, J.Hypertension (2007) 25:2479

Time of taking antihypertensive medication

⇨ impact on CV risk in hypertensive type 2 diabetic patients

prospective randomised open-label blinded endpoint study



MAPEC Study

448 hypertensive type 2 diabetics

5.4 year follow-up

>1 antihypertensive drug taken at bed-time :

lower adjusted cardiovascular risk : 0.33 *(CI 0.21-0.54)*

p<0.001

Hermida, Diabetes Care (2011) 34:1270

Achieving systolic blood pressure of 140 mmHg

Prospective ABPM study in patients with type 2 diabetes and CKD

118 type 2 diabetics with micro-/macro-albuminuria, observation 4 years

42% (n = 49) one or more of the following endpoints :
death, stroke, myocardial infarction, heart failure

31% (n = 36) developed uremia
17% (n = 20) required dialysis

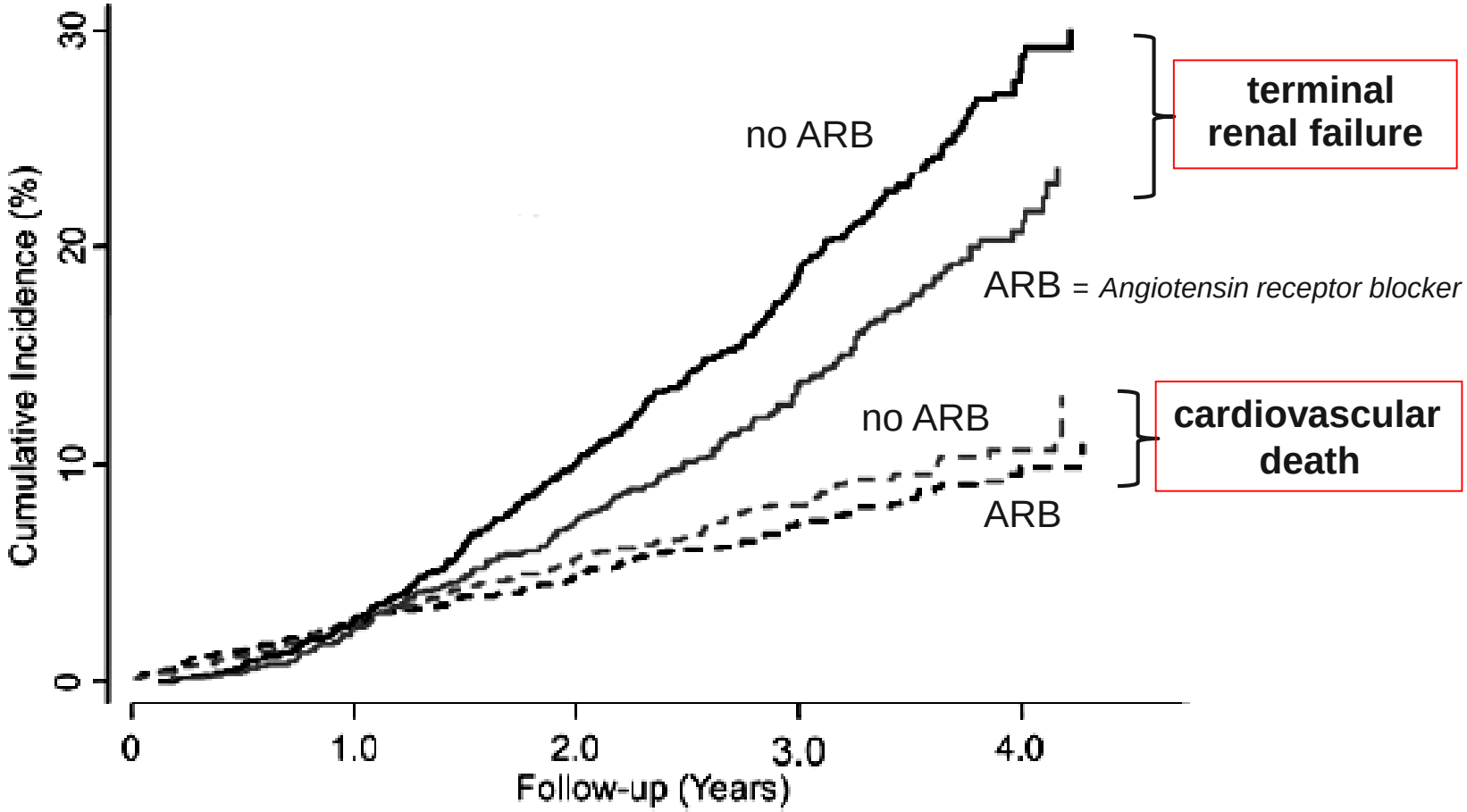
Achieving systolic BP < 140 mmHg day <u>and</u> night
⇨ lower risk of ESRD

Correlation with ABPM,
but no association with clinic blood pressure
importance of patient BP selfmeasurement !!!

Torffvit, J.Diabetes Complications (2012) 26:540

In advanced nephropathy :

RAS blockade is primarily effective in delaying preterminal renal failure less so to prevent cardiovascular death

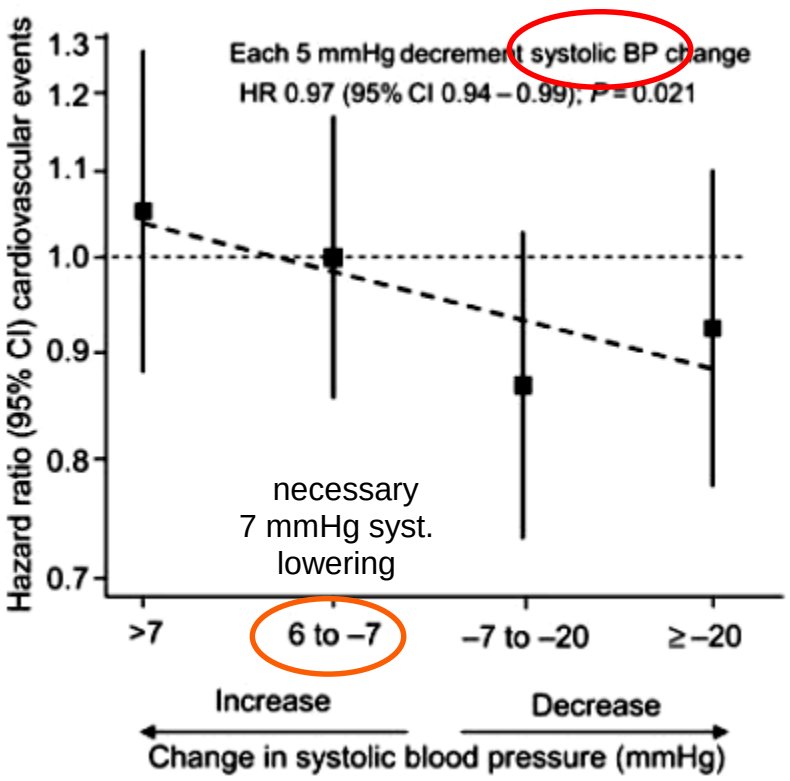


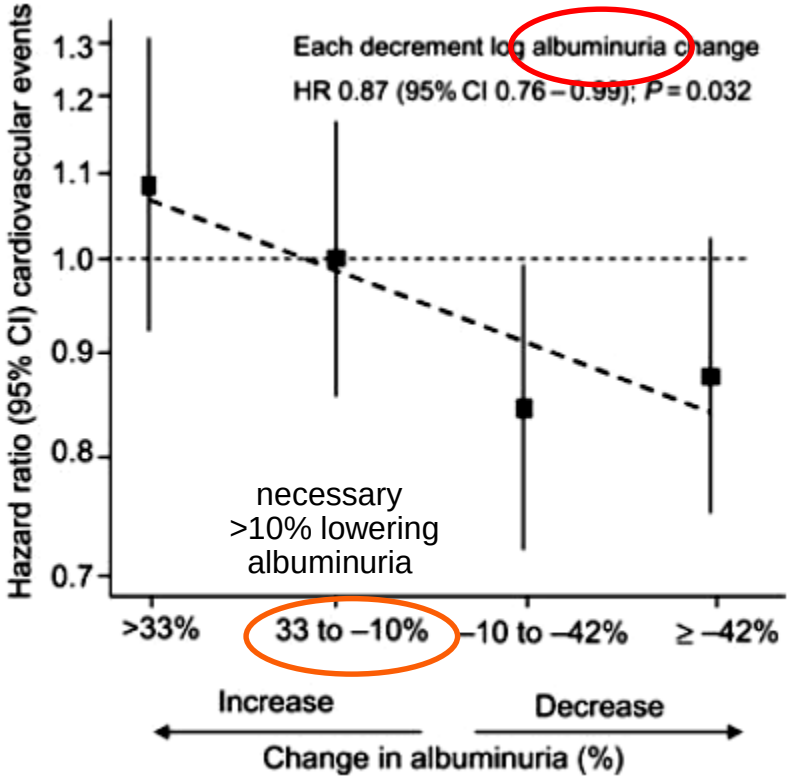
Packham, Am.J.Kidn.Dis.(2012) 59:75

Blood pressure and Albuminuria –

independent targets for lowering cardiovascular and renal events

How much lowering of BP and albuminuria is necessary?





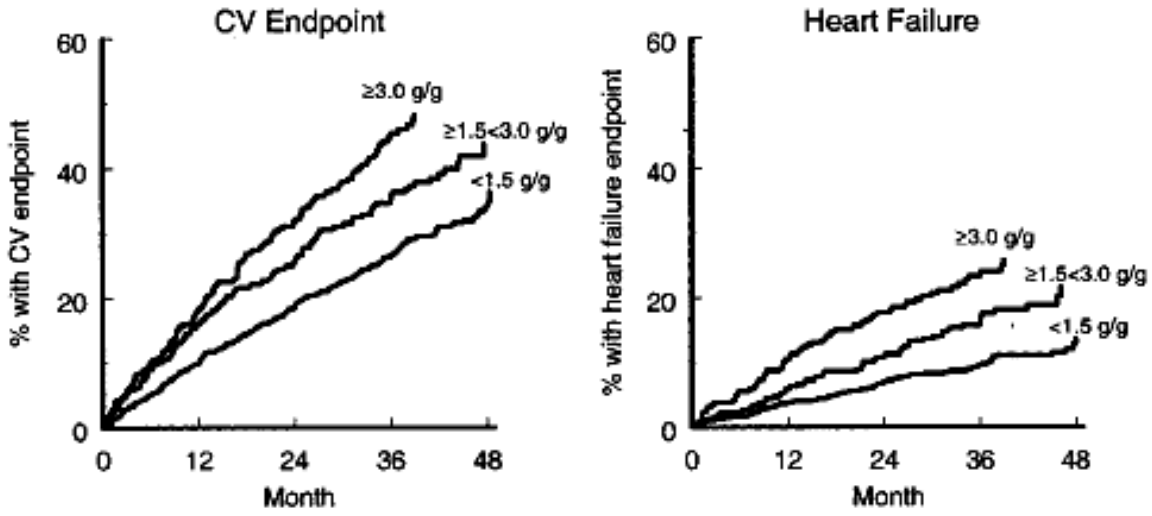
***IDNT** and **RENAAL** trials*

Holtkamp, Eur.Heart J.(2011) 32:1490

Albuminuria : indicator of the risk of cardiovascular endpoints in type 2 diabetic patients with nephropathy

RENAAL study

Evolution with time

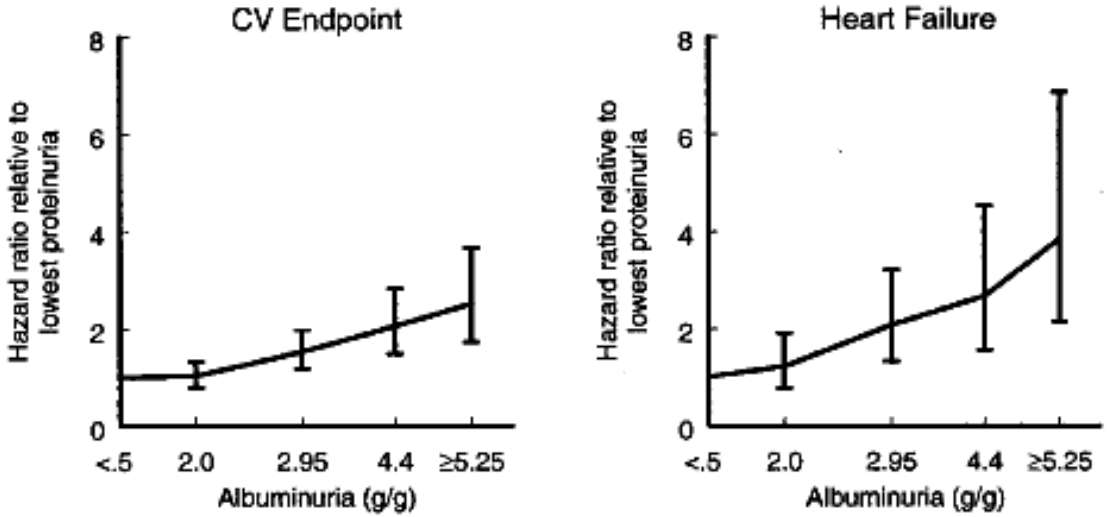


Albuminuria :

not only correlated to renal risk,

but also to CV risk incl. heart failure

Correlation with albuminuria



de Zeeuw, Circulation (2004) 110: 921

Is it beneficial to Spironolactone on top of RAS blockade in diabetic nephropathy

22 patients type 2 diabetes with nephropathy
randomized double-masked cross-over study
on top of RAS blockade in randomized order :
Spironolactone 25 mg/d and
matched placebo for 8 weeks

during addition of **Spironolactone :** reduction of
 # albuminuria
- 33%
 # 24h ambulatory BP :
- 6 mmHg systolic and
- 4mmHg diastolic BP

1/20 patients excluded because hyperkalemia !

Rossing, Diabetes Care (2005) 28:2106

Addition of Spironolactone to angiotensin receptor blockers in patients with diabetic nephropathy

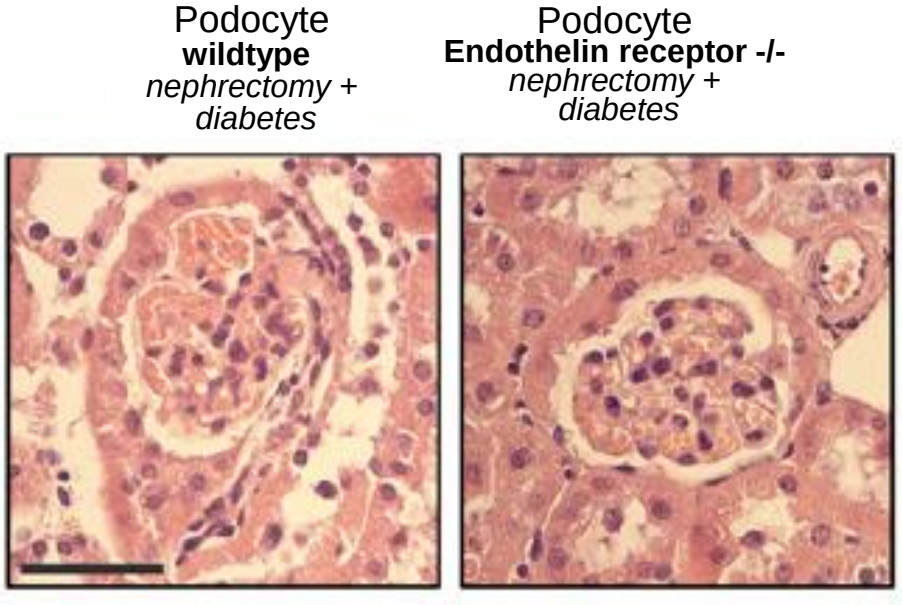
Open label, parallel group, randomized trial
136 diabetics with proteinuria on Enalapril and Losartan

62 patients: *ACEi/ARB* continued
74 patients: ACE discontinued and 25 mg Spironolactone added to ARB (SPR/ARB)

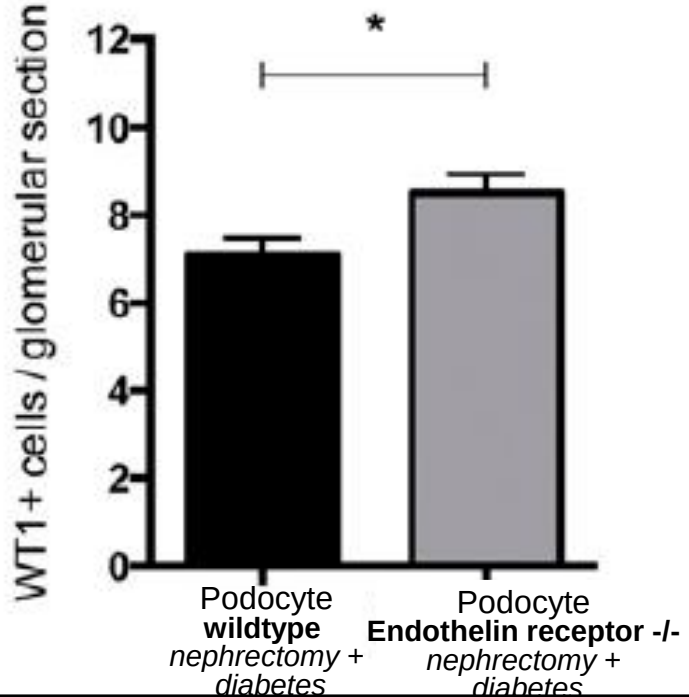
<u>after 18 months in ARB+Spironolactone</u>:
3/74 pat. on Spironolactone asymptomatic hyperkalemia

reduced systolic and diastolic BP *(p<0.001)*
significant *(p=0.017)* reduction of albuminuria
(by 46, 72, 59% after 3,12,18 months)
but no difference in eGFR loss !

Esteghamati, Nephrol.Dial.Transpl. (2013) 28:2823



Endothelin receptor knock-out - less diabetes induced glomerulosclerosis



Lenoir, JASN (2014) 25:1040

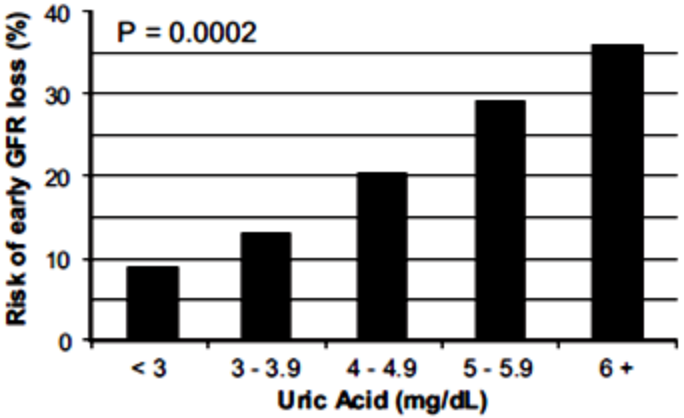
in the future also Endothelin receptor blockade ?

Ritz, JASN (2010) 21:392
Schneider, NDT (2014) S1;i69

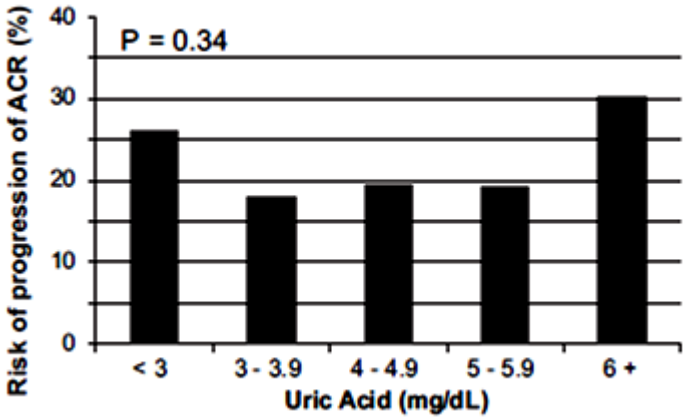
High-normal serum uric acid increases risk of early loss of renal function in type 1 diabetes

6 year follow-up

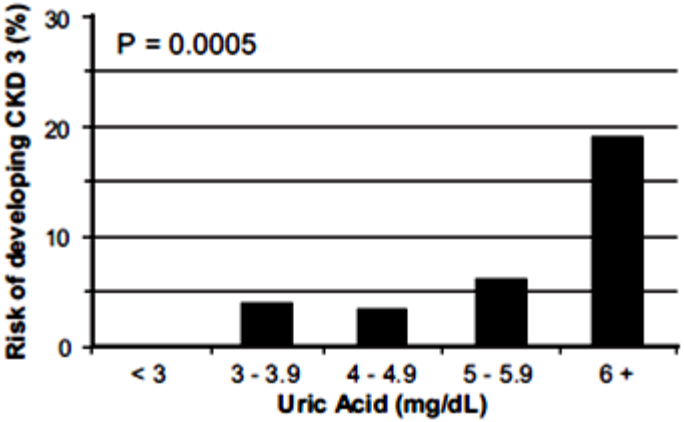
GFR loss



progression of albuminuria



onset CKD3



S-uric acid
 # novel predictor
 # treatment target

Ficociello, Diabetes Care (2010) 33:1337

Serum uric acid in type 1 diabetes predicts onset of renal decline

Baseline determinants	OR	95% CI	χ^2	*P*
Age (per 10 years)	1.53	1.18–1.97	10.7	0.0011
HbA_{1c} (per 1%)	1.60	1.31–1.95	20.9	<0.0001
Systolic BP (per 10 mmHg)	1.34	1.09–1.63	8.4	0.0038
MA vs. NA	2.28	1.28–4.08	7.7	0.0054
Uric acid (per 0.5 mg/dL)	1.86	1.33–2.62	12.8	0.0003
TNFR-1 (per 200 pg/mL)	2.93	1.90–4.52	23.6	<0.0001
Interaction (TNFR-1 and uric acid)	0.94	0.91–0.97	12.2	0.0005

Krolewski, Diabetes Care (2014) 37:226

Diabetic nephropathy – an update

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- *Additional efforts*

Metformin

suppresses gluconeogenesis

(inhibition of mitochondrial glycerophosphate dehydrogenase)

---

non-competitive inhibition of redox shuttle enzyme

mitochondrial glycerophosphate dehydrogenase

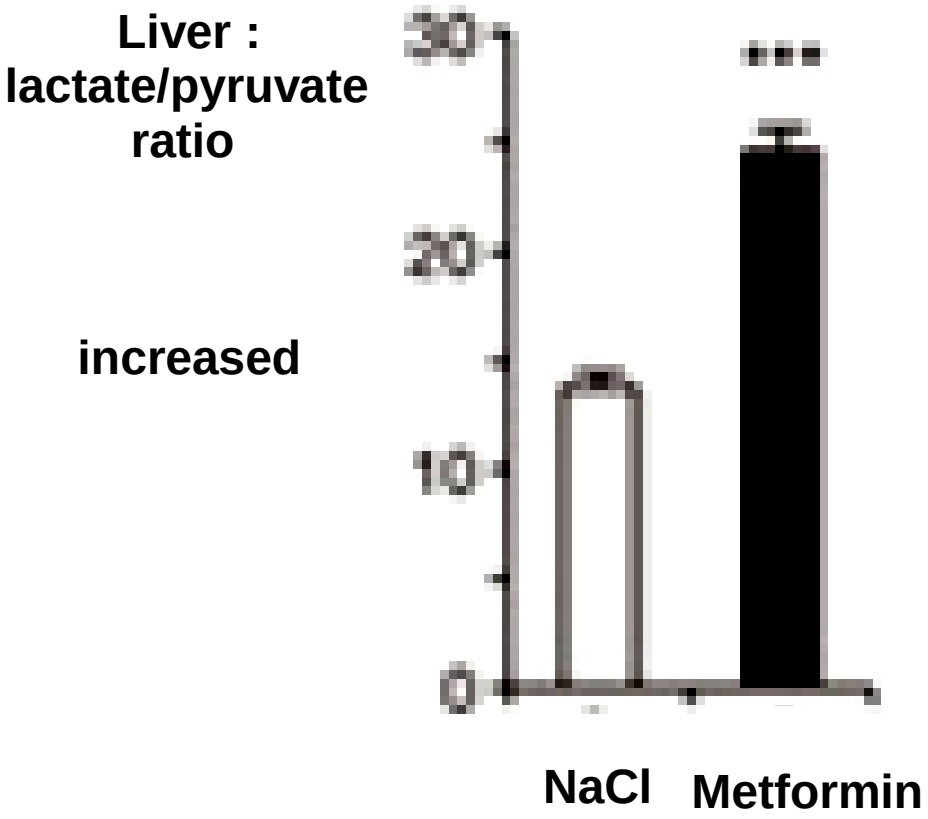
⇩

redox state ↓

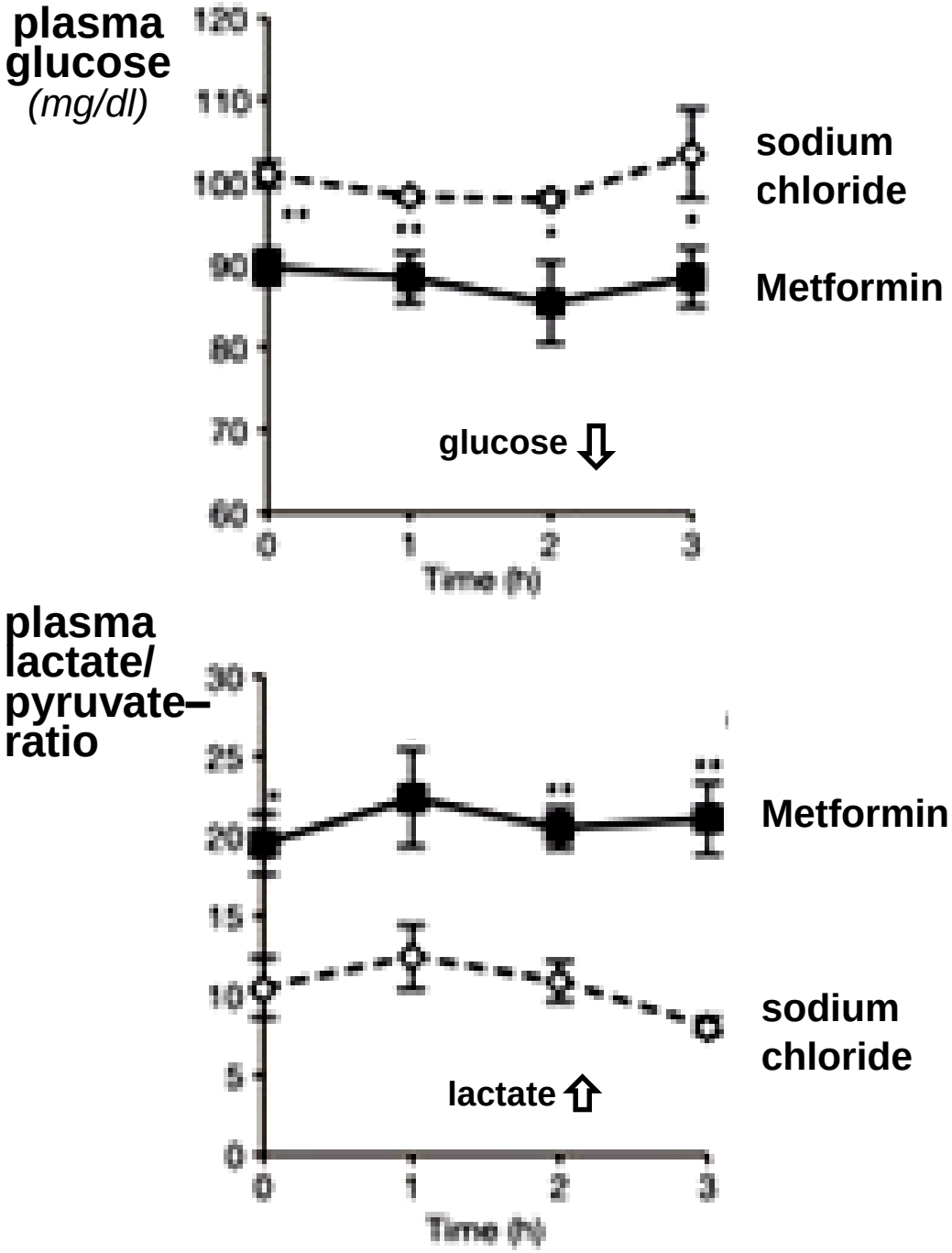
conversion lactate → glucose ↓

gluconeogenesis in liver ↓

Metformin : role of liver mitochondria



Madiraju, Nature (2014) 510:542



Metformin

raises redox ratio in liver mitochondria

[lactate]:[pyruvate]

causing

lower plasma glucose +

elevated plasma lactate/pyruvate ratio

Madiraju, Nature (2014) 510:542

Metformin

Lactic acidosis : how frequent is this complication in CKD ?

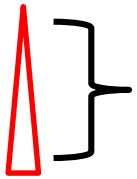
Plasma clearance of Metformin:

only **minor correlation to creatinin clearance** *(r=0.66; p<0.01)*

Tucker, Br.J.Clin.Pharmacol.(1981) 12: 235

eGFR and serum Metformin concentration at a dosis of 1500 mg/day

eGFR > 60	ml/min/1.73m^2	4.5 µmol/L
„ 30-60	ml/min/1.73m^2	7.7 µmol/L
„ < 30	ml/min/1.73m^2	8.9 µmol/L



factor 1.9

Frid, Diabetes Care (2010) 33:1291

Metformin and lactic acidosis ?

- There is still considerable discussion and question about whether metformin is a significant cause of lactic acidosis

established causes :
 # supratherapeutic doses
 # comorbidity : hepatic problems (contraindication!!)

- A recent estimation of the incidence of lactic acidosis with metformin is 3.3 cases per 100 000 patient years of treatment

  With sulfonylureas the incidence of lactic acidosis was estimated as 4.8 cases per 100 000 patient years of treatment

- Almost the all the literature referring to the toxicity of Metformin concerned patients with hepatic problems **!!**

Graham G.Clin.Pharmacokinet.(2011) 50:81

Comparison Metformin vs. other antidiabetic drugs in CKD

51 675 type 2 diabetics with different grades of impaired renal function;
follow-up 3.9 years ; Sweden

eGFR *(ml/min/1.73m²)*	**Metformin vs alternative Rx** *(n)*	**HR** *(95%interval)* Mortality/ CV events
>60	28,015 vs 31,614	0.87 *(0.81-0.94)*
59-45	4,079 vs 6.176	0.87 *(0.77-0.99)*
44-30	715 vs 2.152	1.02 *(0.84-1.24)*

no increase of incident metabolic acidosis !!!

Ekström N., BMJ open (2012) - 001076

Metformin showed lower risk of CV and all-cause mortality than insulin
*With Metformin even slightly **lower risk** compared with other oral antidiabetics*

Metformin and lactic acidosis ?

- There is still considerable discussion and question about whether metformin is a significant cause of lactic acidosis

established causes :
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 # comorbidity : hepatic problems; contraindication

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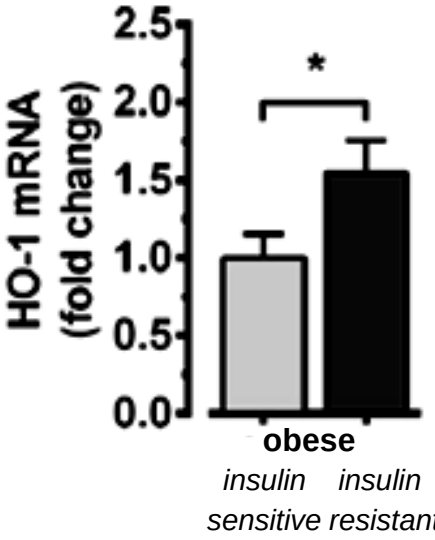
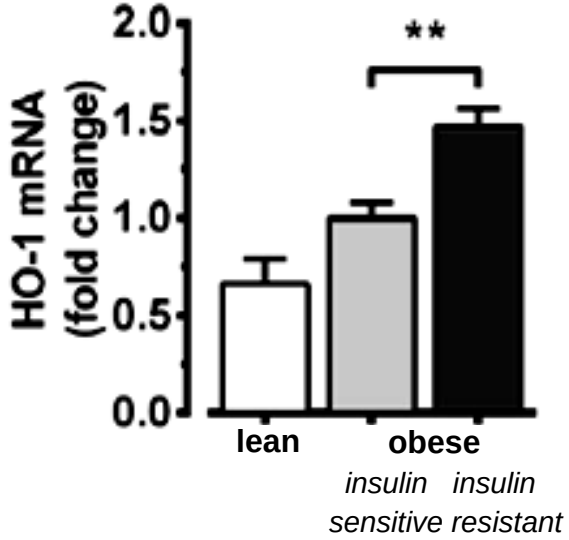
“Not all obesity is created equal“

“unhealthy“obesity“ (insulin resistant) :

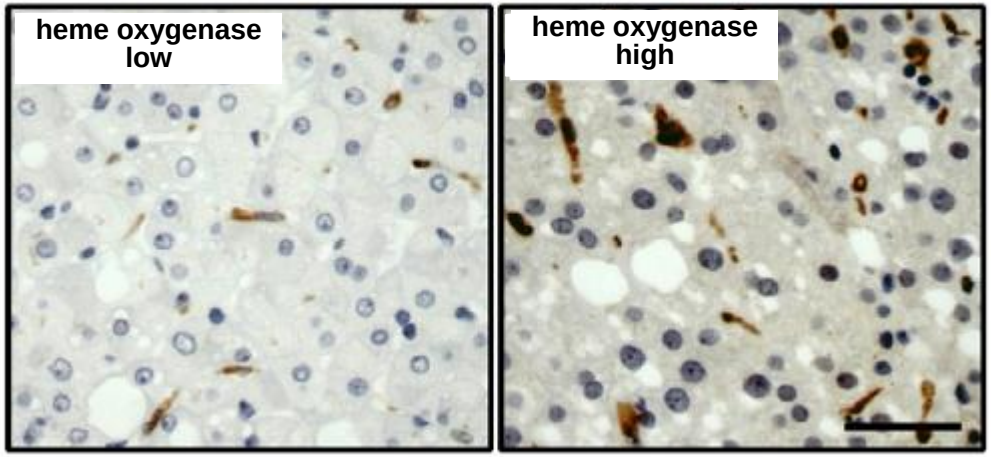
heme oxygenase (HO-1) triggers inflammatory reactions

antiinflammatory heme oxygenase (HO-1)





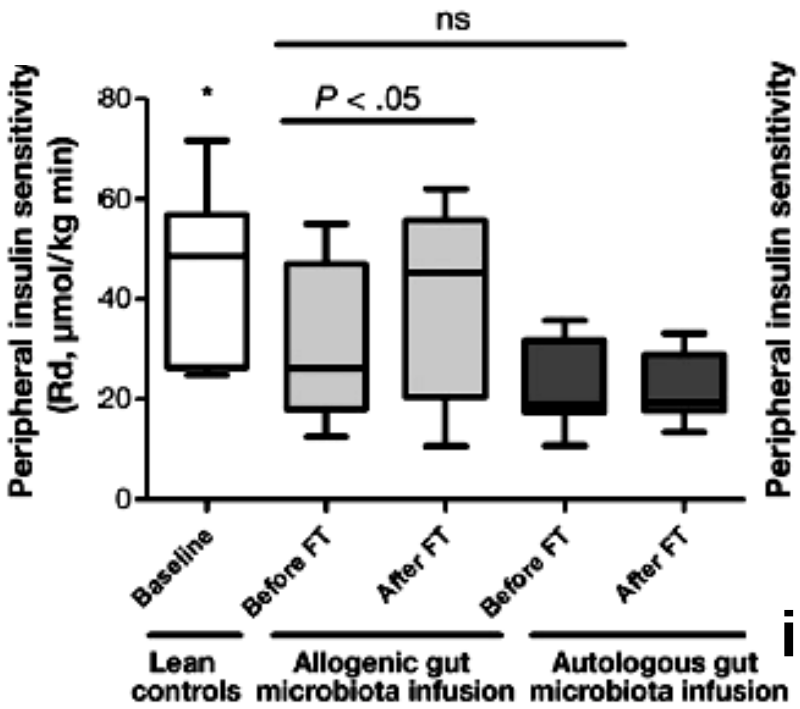
in liver and visceral fat :



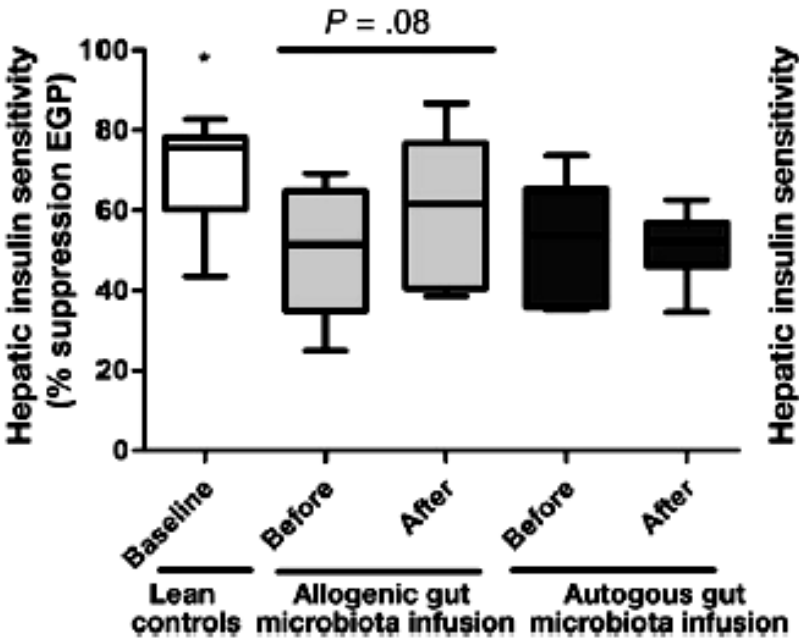
obese - *insulin sensitive (healthy)*

obese - *insulin resistant (inflammatory)*

Jais, Cell 158:25 (2014)



Transfer of intestinal microbiotica from lean donors ▢ increases insulin sensitivity in individuals with metabolic syndrome

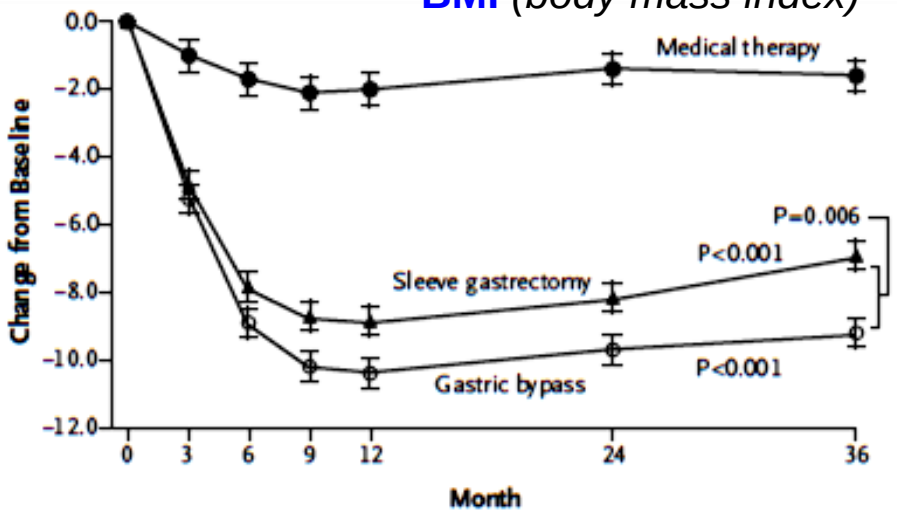


Vrieze, Gastroenterology (2012) 143:913

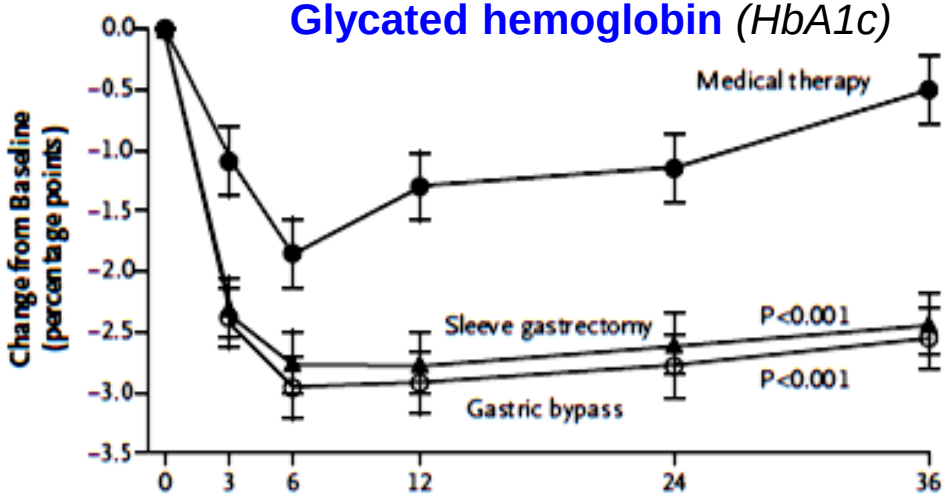
Bariatric surgery – a novel approach

Can Diabetes be surgically cured?, What is the impact on the kidney ? (3 year outcome)

BMI *(body mass index)*



Glycated hemoglobin *(HbA1c)*

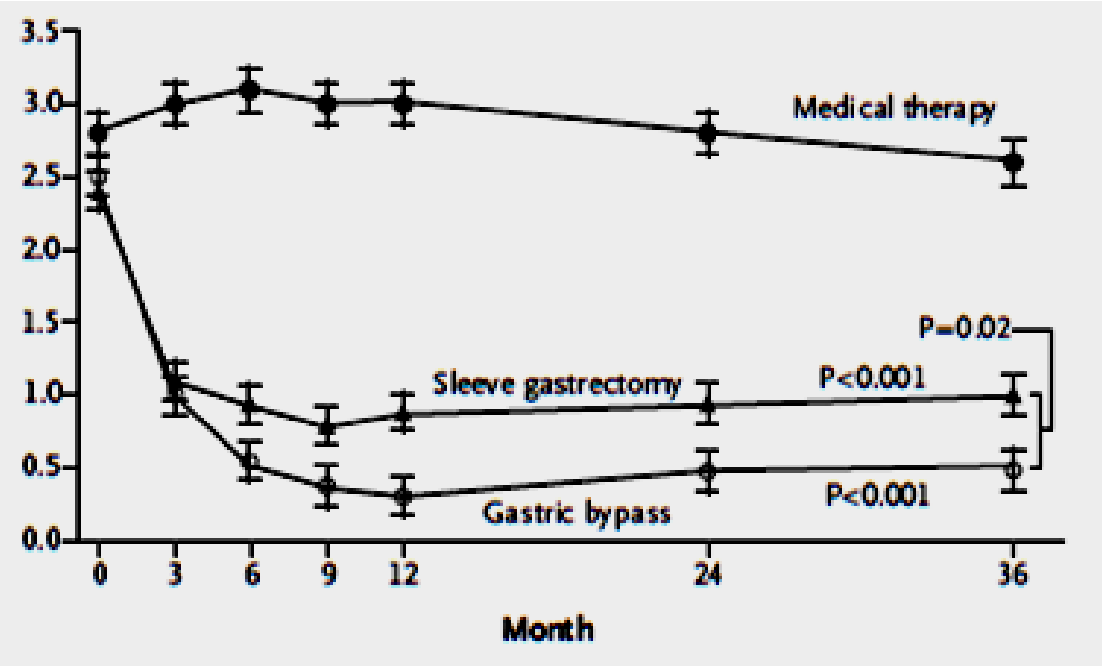


Schauer, New Engl.J.Med.(2014) 370:2002

Bariatric surgery – also impact on kidney function ?

(outcome after 3 years)

Number of diabetes medications



150 obese diabetics, 48±8 years, 68% women

baseline $HbA1_c$ 9.3±1.5%; BMI 36.0±3.5

$HbA1_c$ < 6.5 after 3rd year: 0% on medical Rx group and 48% in gastric bypass group

massive reduction or stop of lipid lowering and antihypertensive medication

no change s-creatinine

(although this had been reported in previous studies)

Schauer, New Engl.J.Med.(2014) 370:2002

Impact on bariatric surgery on albuminuria in diabetic nephropathy

217 patients, 5-9 years follow-up (mainly Roux- en -Y)
$HbA1_c$ from 7.5±1.5% to 6.5%±1.2% *(p<0.001);*
fasting blood glucose from 156±59 mg/dL to 148±40 mg/dl *(p<0.001)*

Albuminuria : regressed in 53% ; stabilized in 47%
[regression: stages of albuminuria Δ1 or more]

Brethauer, Ann.Surg.(2013) 258:628

Impact on bariatric surgery on kidney function in diabetic nephropathy

General outcome :

6 year follow-up after RYGB *(Roux-en Y gastric bypass)* :

weight loss 61.1± 24.8%
significant reduction of **HbA1c,** fasting blood glucose and diastolic **BP** *(all p=0.001)*
no major change in ACE inhibitor use

Renal function :
 # pat. with baseline nomoalbuminuria :
only 5% pat. developed de novo microalbuminuria
 # pat.with baseline albuminuria : 19 patients :
47% remained stable,53% regressed
(2 macroalbuminuric patients : 1 pat. resolved; 1 pat. microalbuminuria)
S-creatinine at follow-up: - 0.05±0.2 mg/dl(p=0.03);
eGFR not available

Brethauer, Ann.Surg.(2013) 258:628

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Treatment of glycemia in diabetics with renal failure

some general points

With decreasing GFR :

 # treatment with insulin is frequently appropriate/necessary

 # insulin requirement is decreased in relation to GFR
(cumulation both in nephropathic type 1 and 2 diabetic patients)

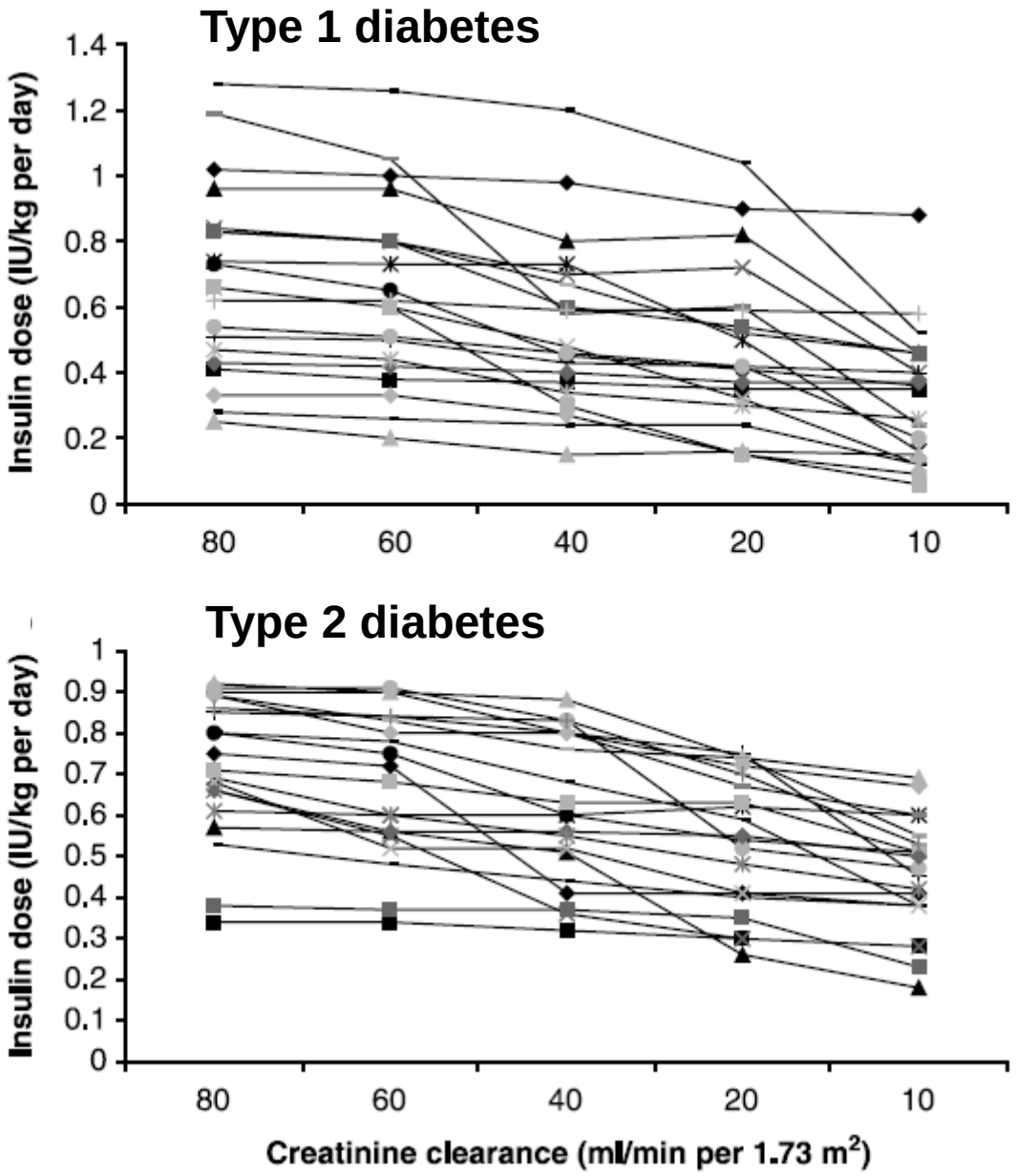
 # insulin sensitivity reduced

 # many oral antidiabetics have elimination problems,
i.e. halflife of many oral antidiabetics (and some insulins) prolonged

Biesenbach, Diabetic Medicine (2003) 20:642
Hasslacher, Therap.-Adv.Endocrinol.Medicine (2013) 4:113

Reduced insulin requirement in type 1 and 2 diabetic patients with reduced GFR

Biesenbach, Diabet.Med.(2003) 20:642



Hemodialysis in diabetic patients

(4D study)

Poor glycemic control associated with higher rates of

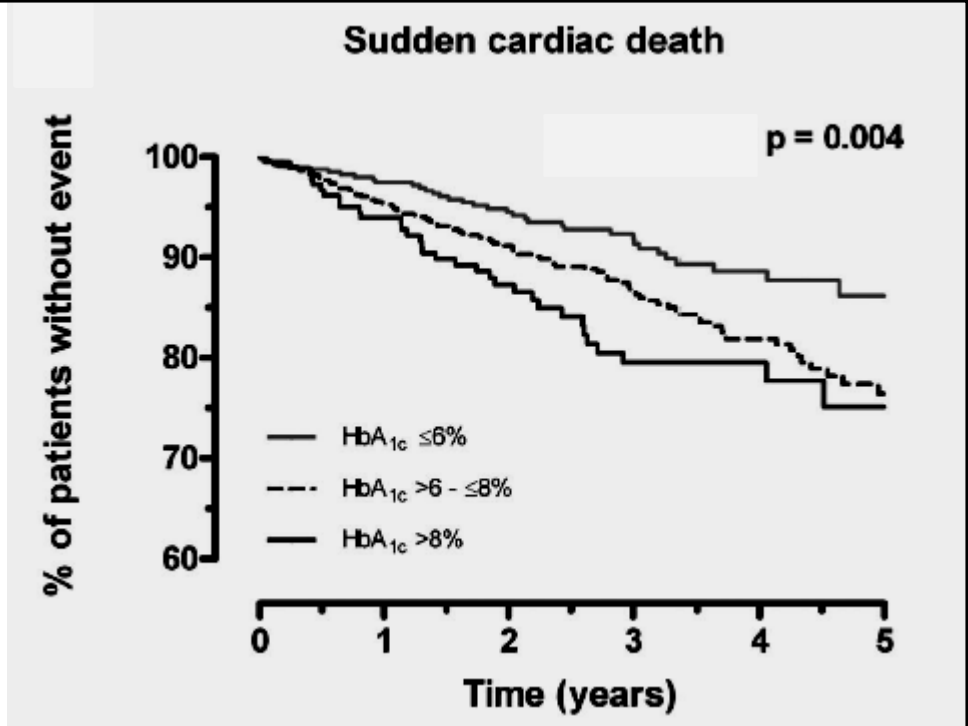
sudden death and

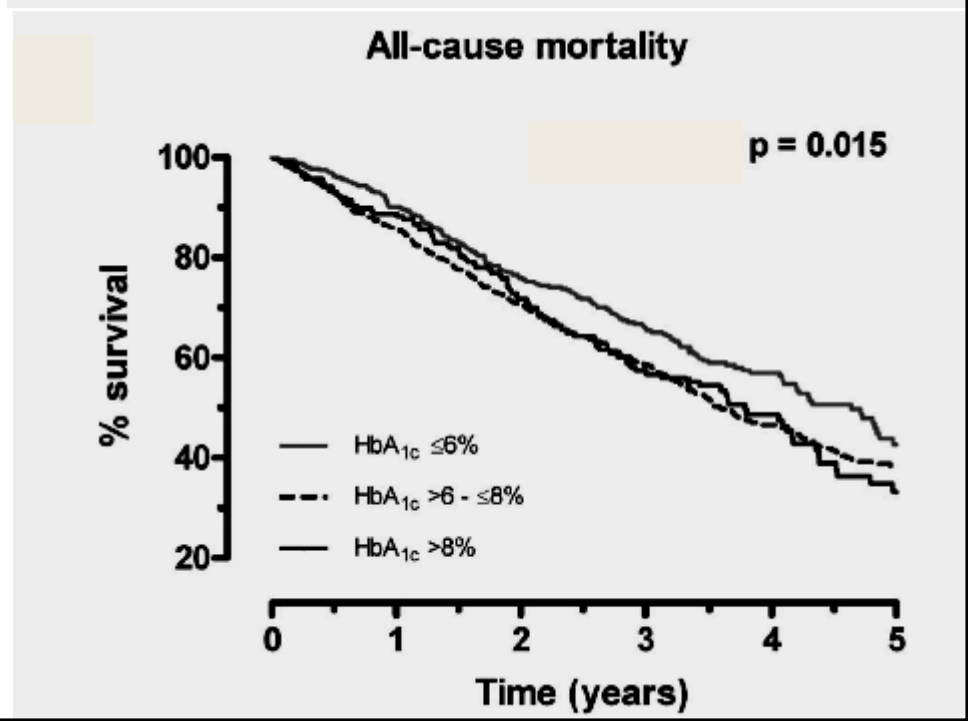
all-cause mortality

Which points concerning diabetes control are frequently altered in hemodialysis ?

-Pharmacokinetics
-Insulinresistance
-Low renal gluconeogenesis
(20-25% less gluconeogenesis)

Drechsler, Kidn.Internat.(2009)120:2421





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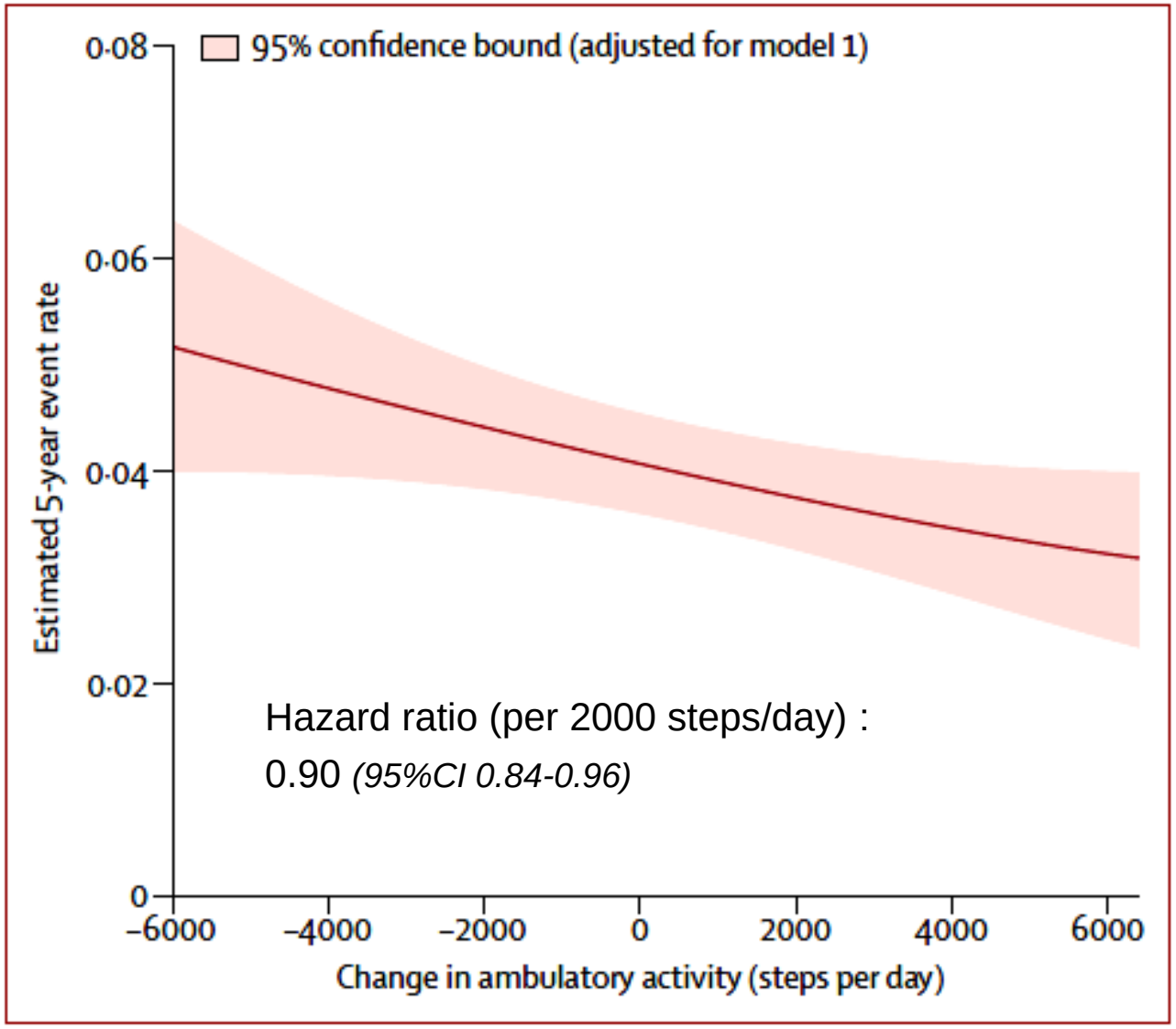
NAVIGATOR study

impact of increased physical activity

⇨ *reduced CV (renal?) risk in individuals with high risk of type 2 diabetes*



9306 individuals;
impaired
glucose tolerance
change in ambulatory activity
less CV events
⇨ independent of BMI (!)
and other confounders

Patient sport !!

Yates, Lancet (2014) 383:1059

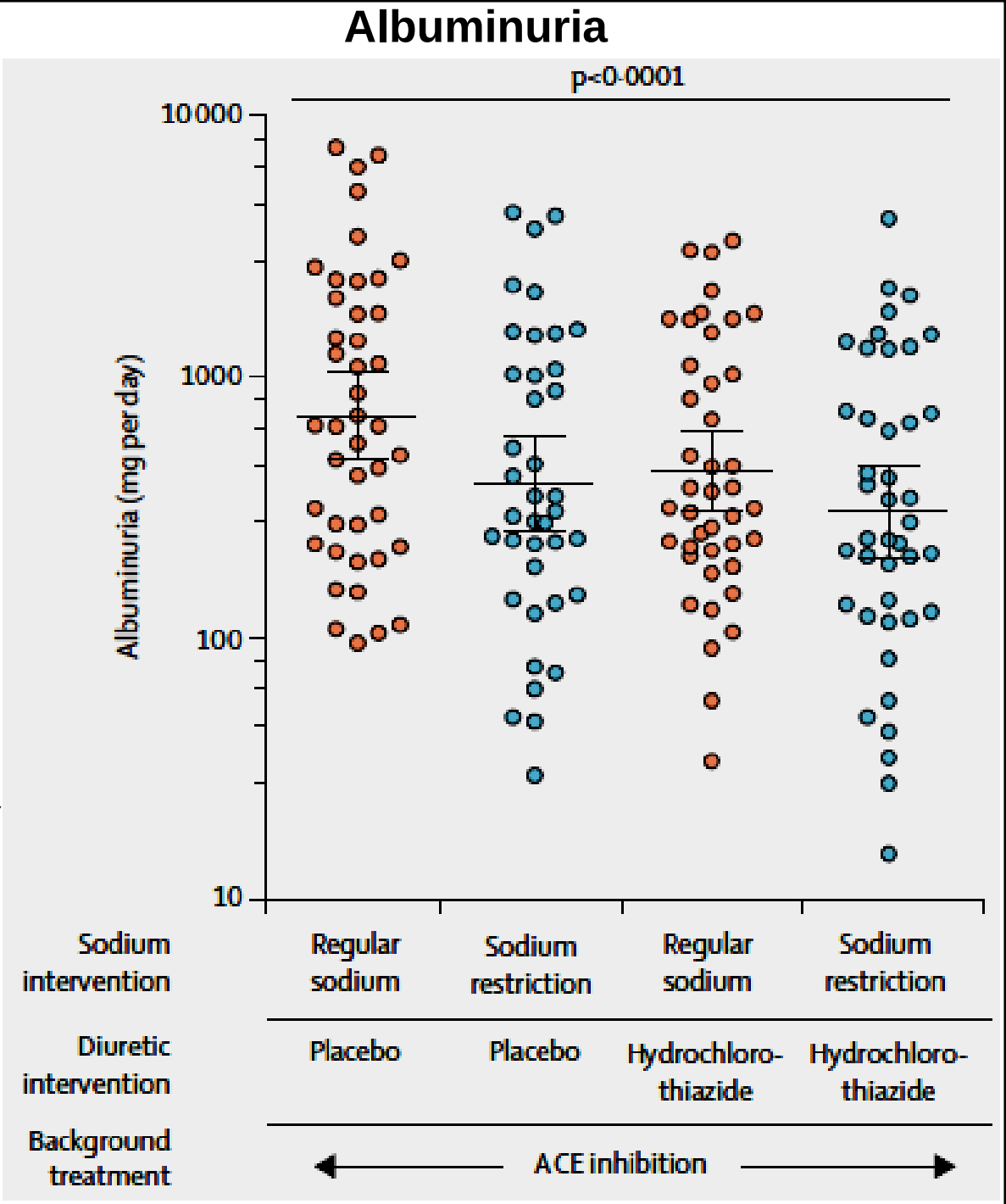
Importance of

sodium restriction

to reduce albuminuria

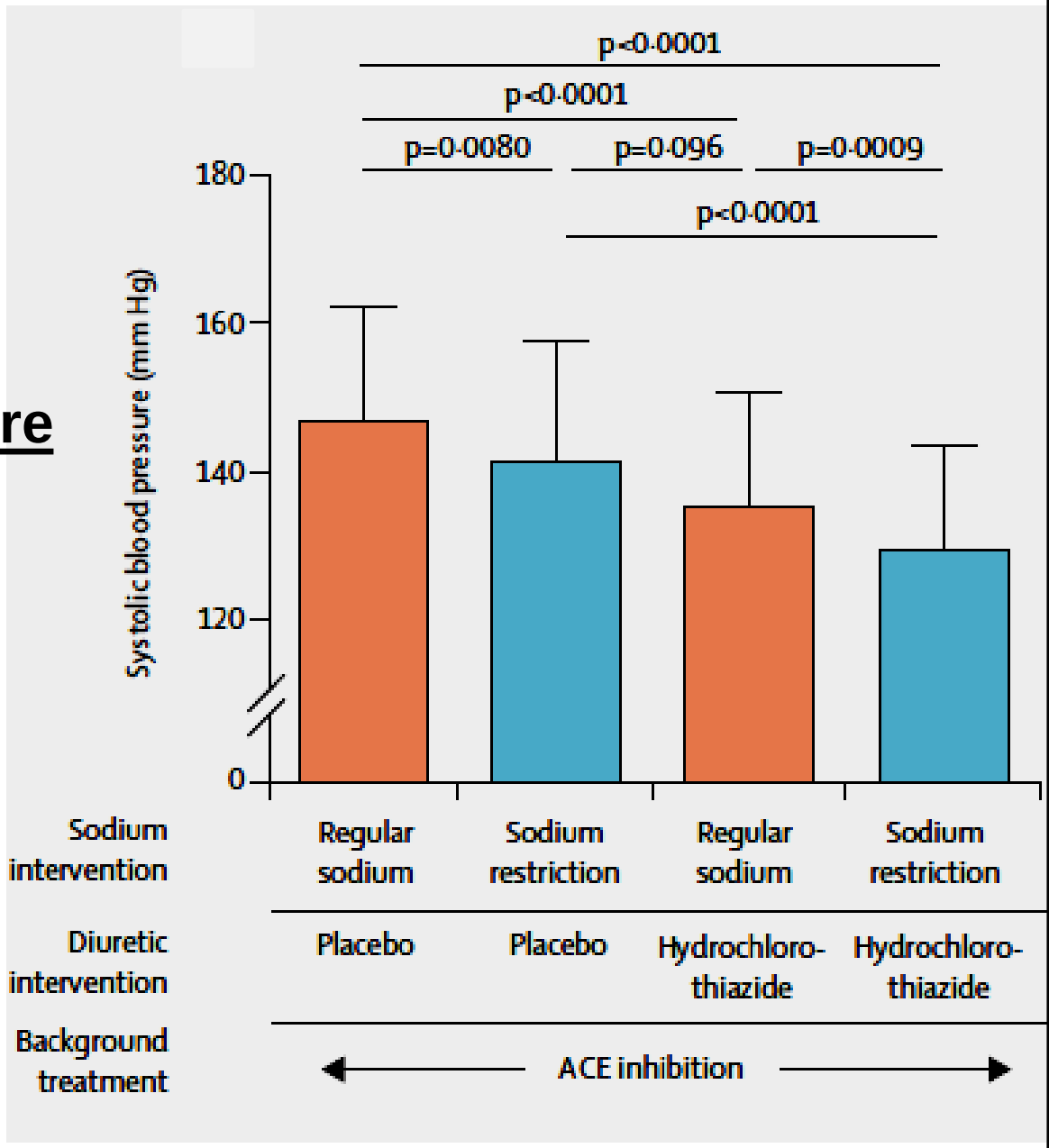
in diabetic patients

Kwakernaak,
Lancet/diabetes-endocrinology
(2014) 2:385



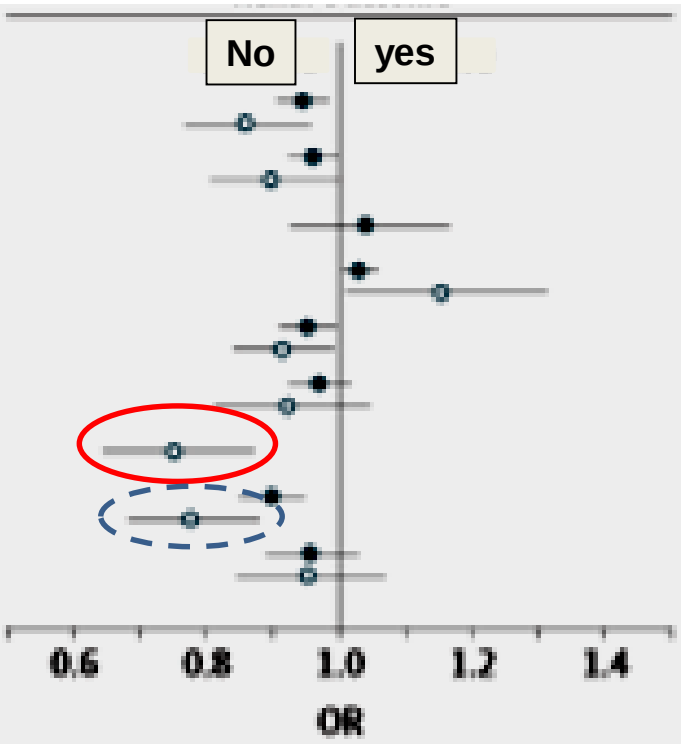
Importance of sodium restriction to <u>systolic blood pressure</u> in diabetic patients

Kwakernaak, Lancet/diabetes-endocrinology (2014) 2:385



Dietetic factors
and
odds ratio of terminal renal failure in type 2 diabetics

dietetic factors *medians of tertiles*	1	2	3
Independent variables			
Animal protein g/kg/day	0.27	0.47	0.81
Vegetable protein g/kg/day	0.04	0.10	0.20
"Deep fried/fast food"	No	Yes (46.8%)	
Carbohydrate rich food	2	9	21
Fruit and Fruitjuice	4	9	18
Vegetables	5	11	21
! Alcohol, 5 "drinks"/week	0		5
24h urine - K^+, g	1.70	2.13	2.71
24h urine - Na^+, g	3.47	4.89	6.41



second tertile ○ third tertile ●

Dunkler, JAMA Intern.Med.(2012) 173:1682

Uric acid contributes to insulin resistance/diabetes

R.Johnson Diabetes (2013) 62:3307

uric acid ⇨ ***fatty liver linked with insulin resistance***

Samuel, Lancet (2010) 375:17787

mitochondrial oxidative stress causing insulin resistance

Hoehn, Proc.Natl.Acad.Sci.USA (2009) 106:17787

Lowering of serum uric acid *reduced progression of renal disease*

Population based retrospective cohort

111,992 patients with hyperuricemia (>7mg/dl)

Factors associated with progression of renal disease were:

age, sex, hypertension, diabetes congestive heart failure, rheumatoid arthritis

- and

Patients with urate < 6 mg/dl ⇨ 37% reduction in CV/renal outcomes

Levy, J.Rheumatol.(2014) 41:955

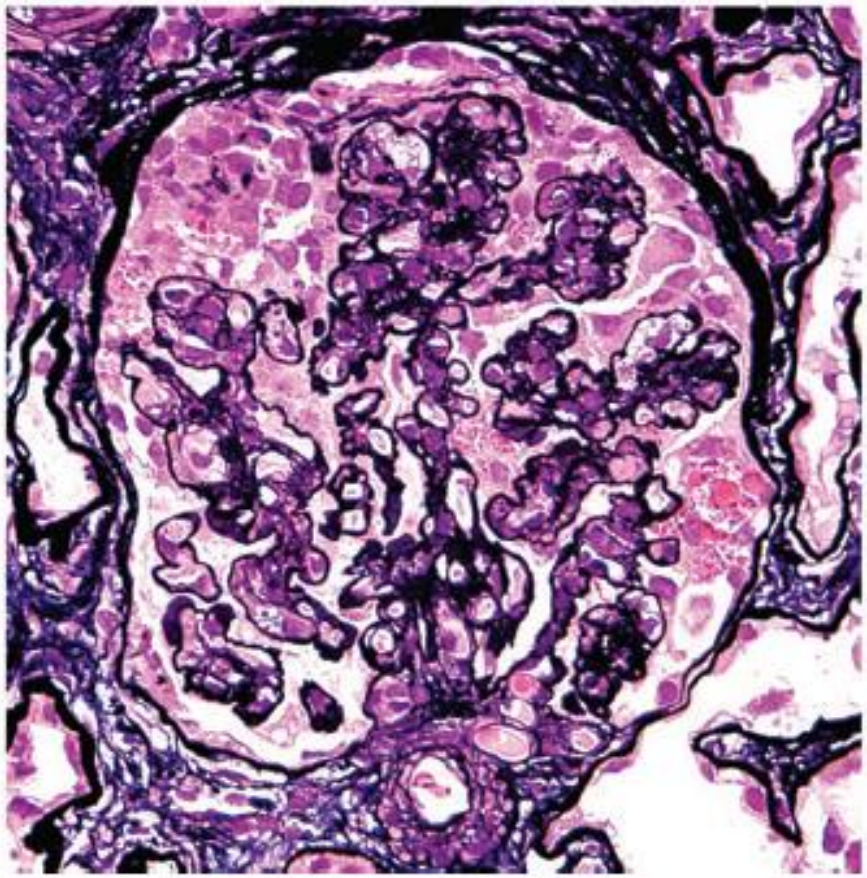
Thank you for your attention

Alte Brücke Heidelberg

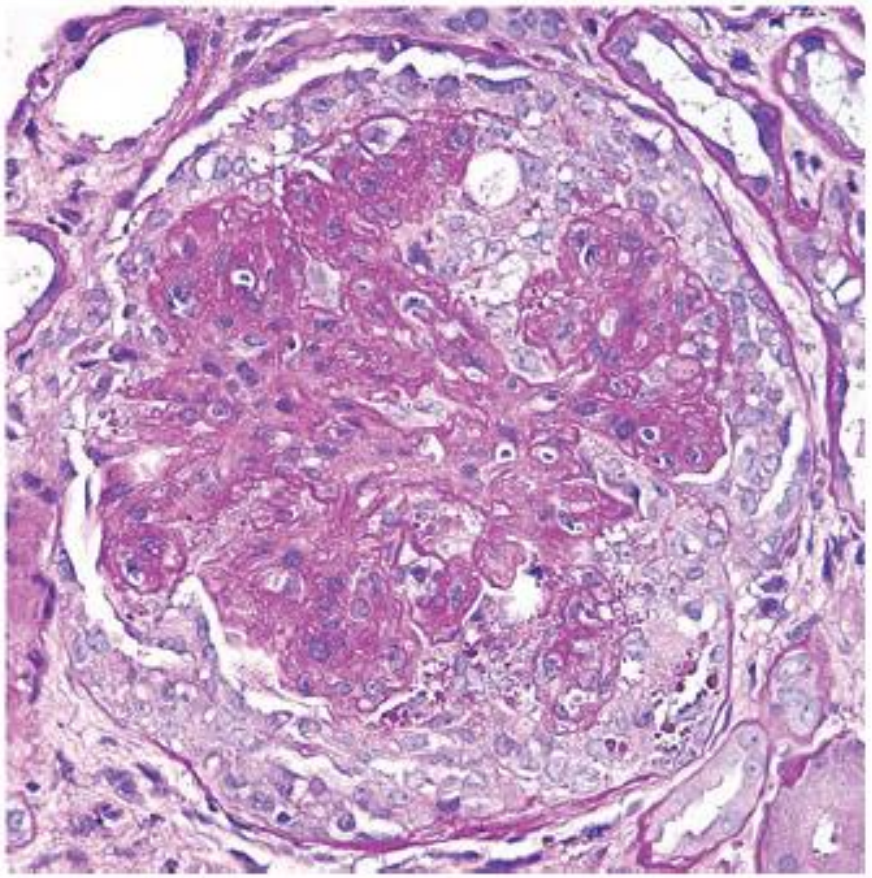
Collapsing glomerulopathy superimposed on diabetic nephropathy

(an underrecognized severe pattern of glomerular injury)

collapsing glomeruli (x40)



methenamine silver



Periodic acid-Schiff

Salvatore, Nephrol.Dial.Transplant.(2014) 29:392

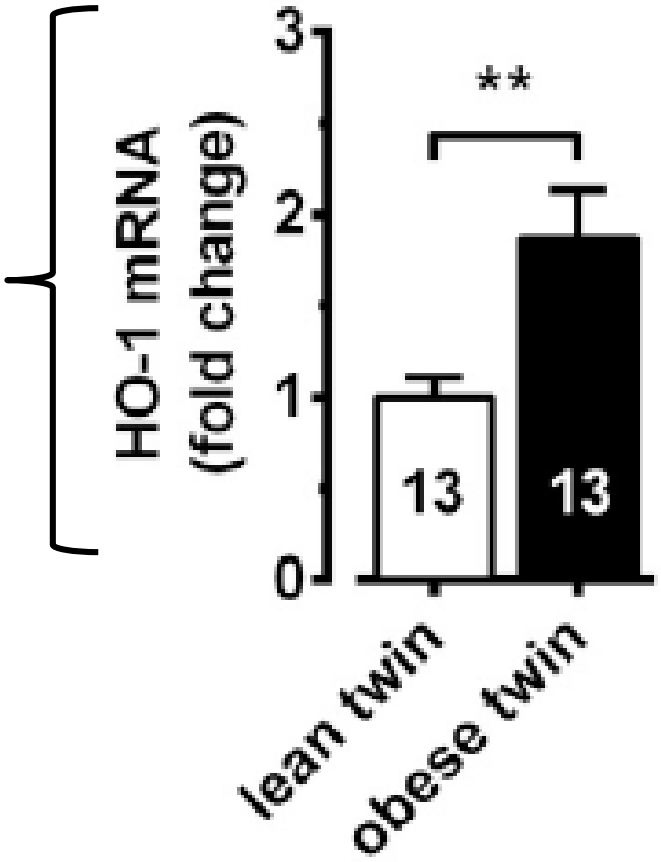
“Not all obesity is created equal“

it is a feature of subjects with “unhealthy“obesity

, i.e. elevated heme oxygenase (HO-1) triggers inflammatory reactions

comparison of <u>monozygotic</u> human twins <u>discordant for BMI</u>

proinflammatory heme oxygenase *(HO-1)*

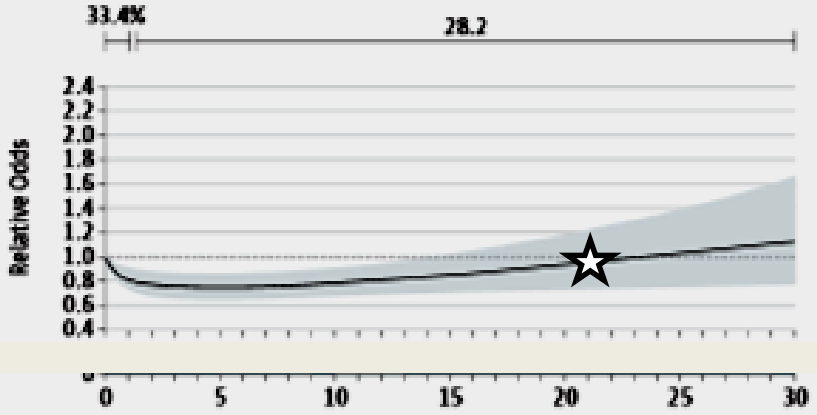


Jais, Cell 158:25 (2014)

Alcohol and type 2 diabetes
odds ratio progression of kidney disease or death
at which point does does outcome be adverse ?

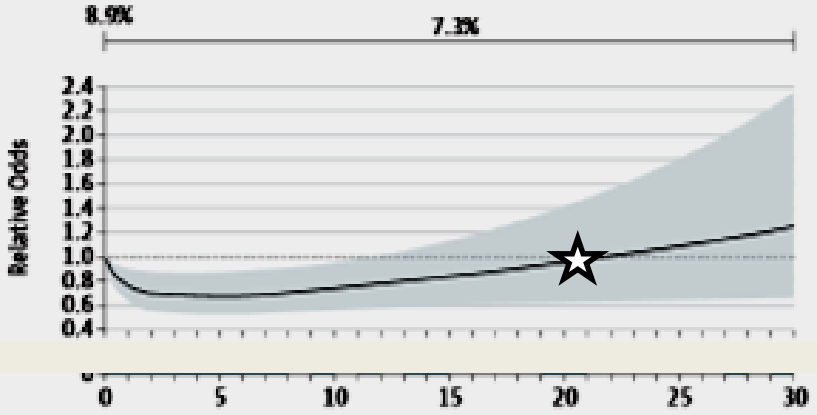
> 20 drinks – progression or death

Progressive loss of renal function



Alcoholic “drinks“ per week

Death



Alcoholic “drinks“ per week

1 drink: *1 glas wine or beer*

Dunkler, JAMA Intern Med (2013) 173: 1682

RAS blockade – does it prevent diabetes type 2 ?

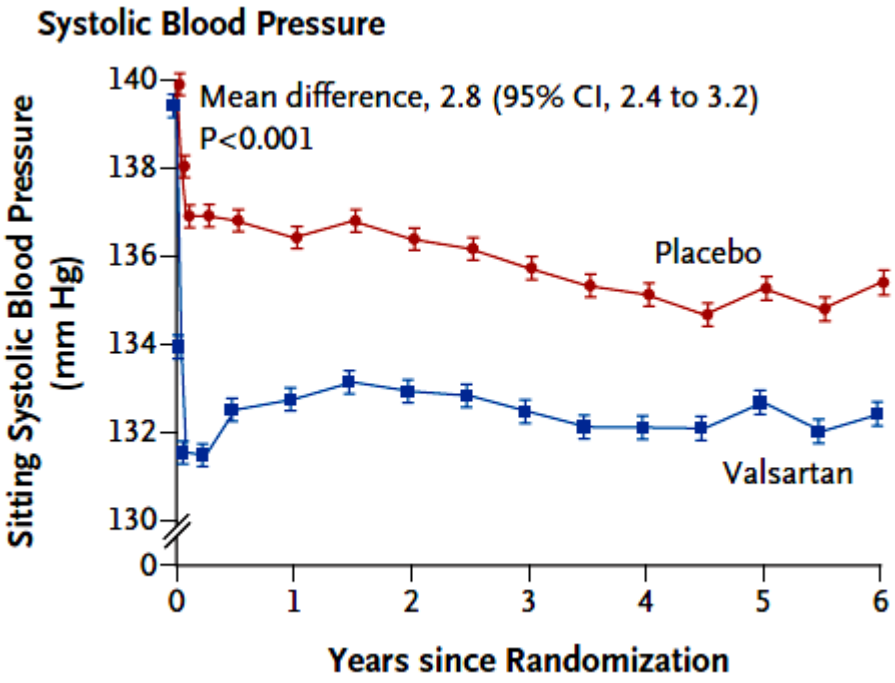
Double blind randomized trial;

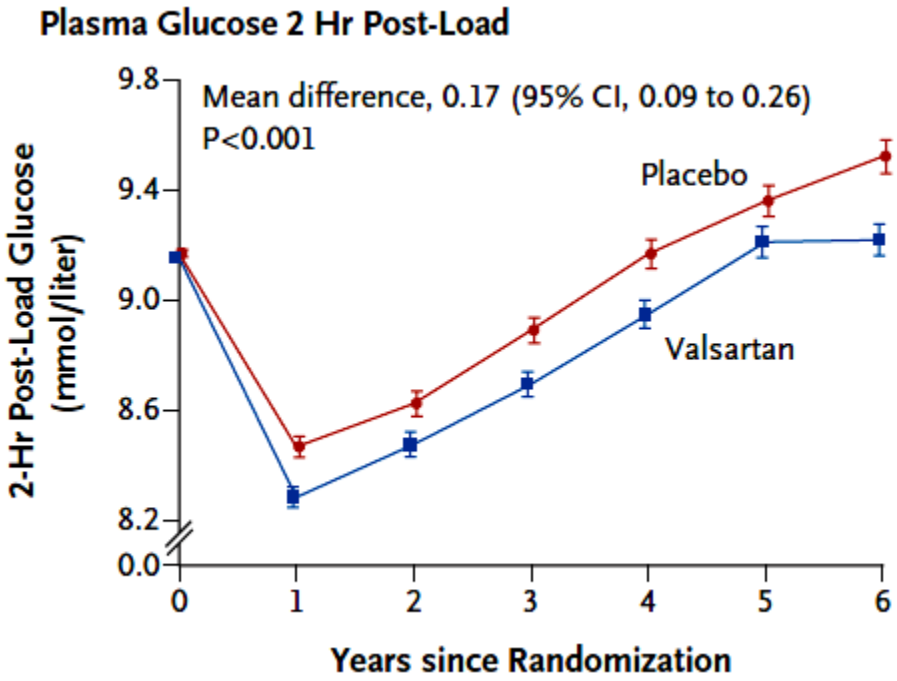
9306 patients with impaired glucose tolerance and established CV disease

Valsartan 160 mg/d or placebo

5 year follow-up :

lower plasma glucose post load (and new-onset diabetes)





Albuissa, JACC (2005) 46:621

France : change in number of treated ESRD patients

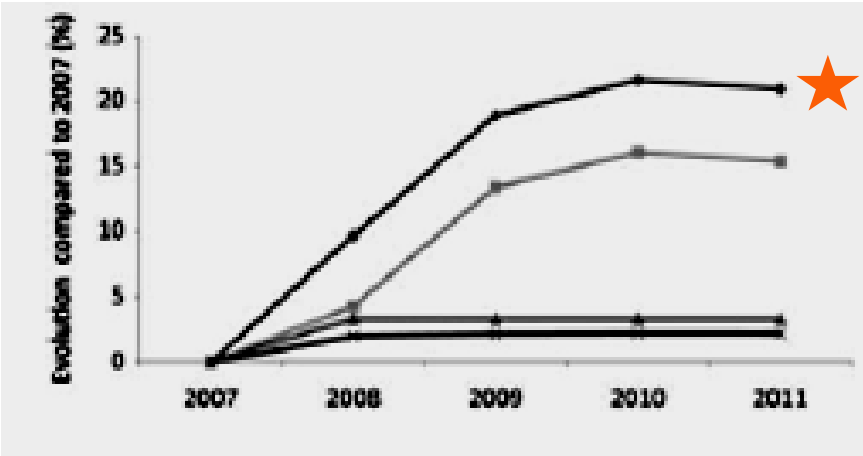
Evolution 2011 vs 2007 :

increase *(by 20.9%) in diabetic patients (by 6.7%) greater than in nondiabetic patients)*

REIN registry

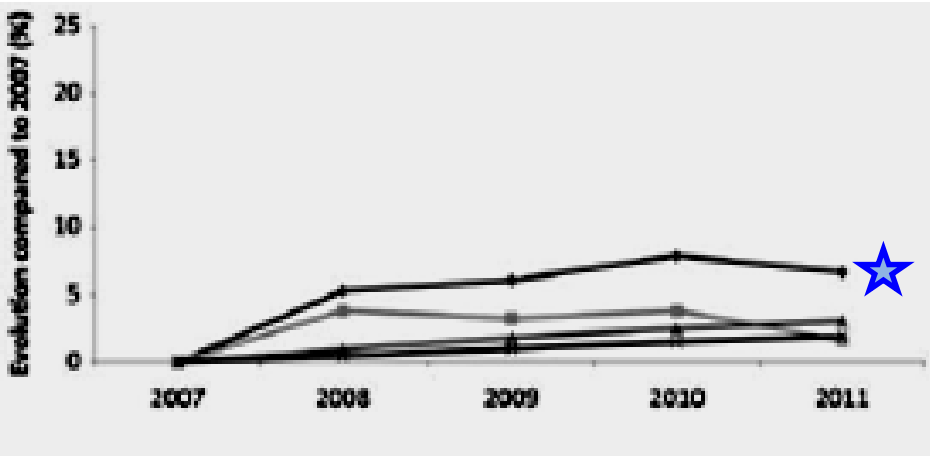
aging 3.3%
increase population size 2.2%

diabetic patients



Evolution of number of patients with diabetes type 2
Residual effect
Effect due to the age of the population
Effect due to the size of the opulation

nondiabetic patients



Evolution of number of patients without diabetes
Residual effect
Effect due to the age of the population
Effect due to the size of the opulation

higher influx?
better survival predialysis?
both?

Bashir, Int.J.Epidemiol.(2000) 29:878

Metformin

suppresses gluconeogenesis

(inhibition of mitochondrial glycerophosphate dehydrogenase)

non-competitive inhibition of redox shuttle enzyme

mitochondrial glycerophosphate dehydrogenase

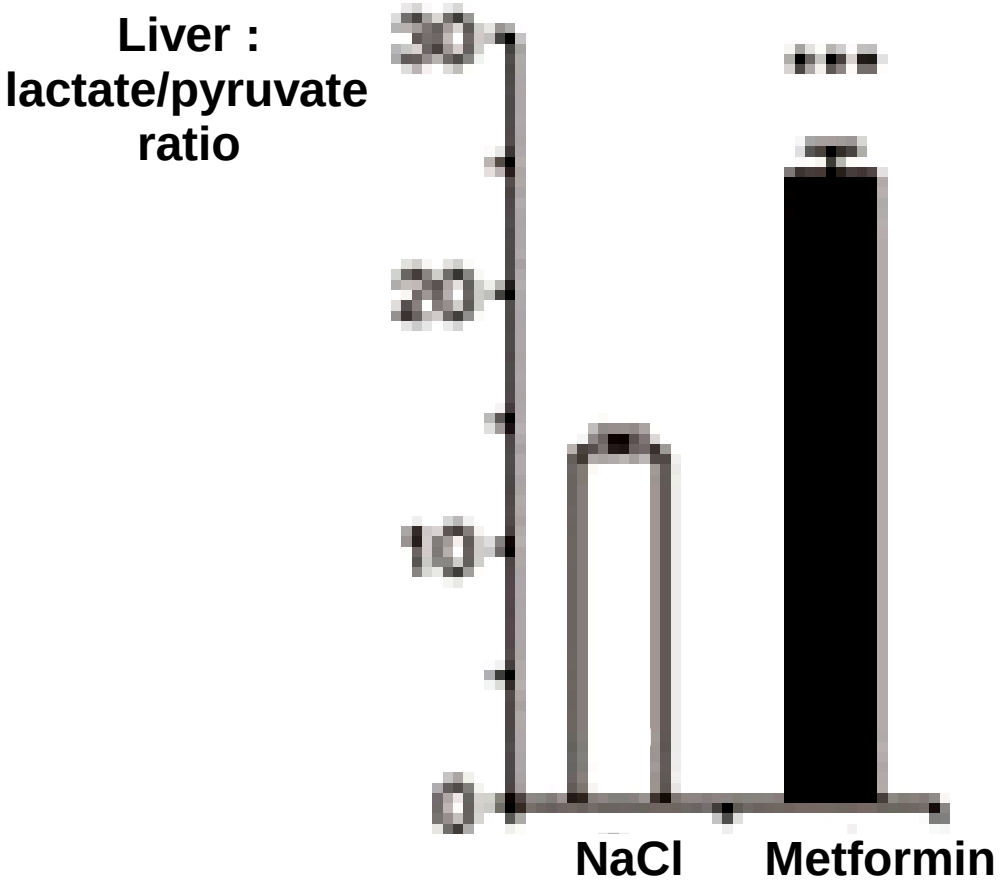
⇩

redox state ↓

conversion lactate → glucose ↓

gluconeogenesis in liver ↓

Metformin lowers redox ratio in liver mitochondria



Madiraju, Nature (2014) 510:542

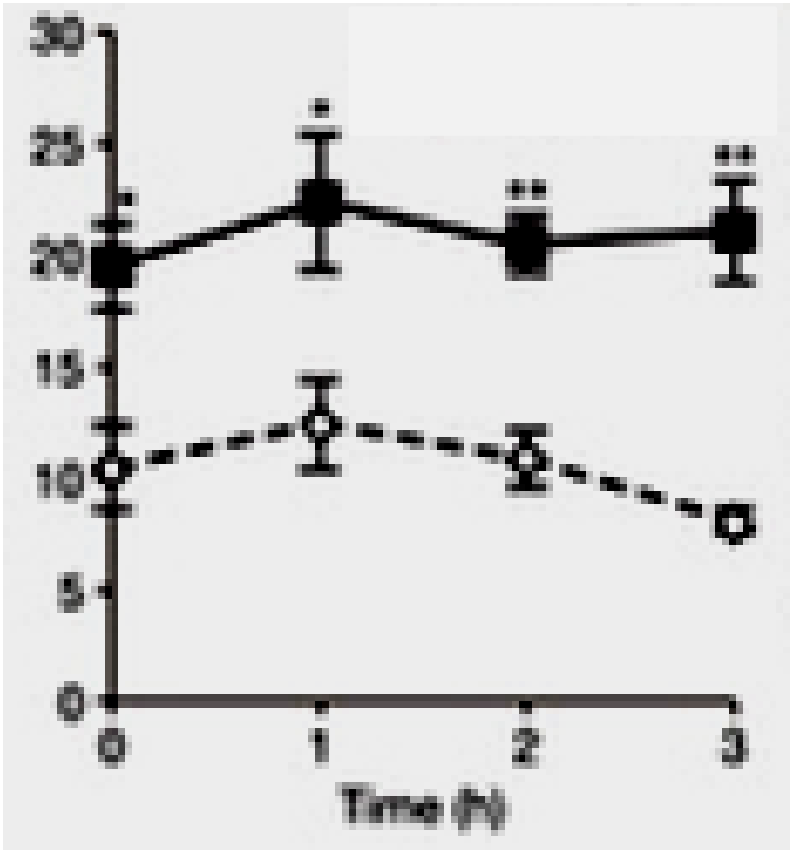
Metformin

raises liver mitochondrial redox state *[lactate]:[pyruvate] ratio*

and

increases plasma lactate/pyruvate ratio

plasma [lactate]:[pyruvate] ratio



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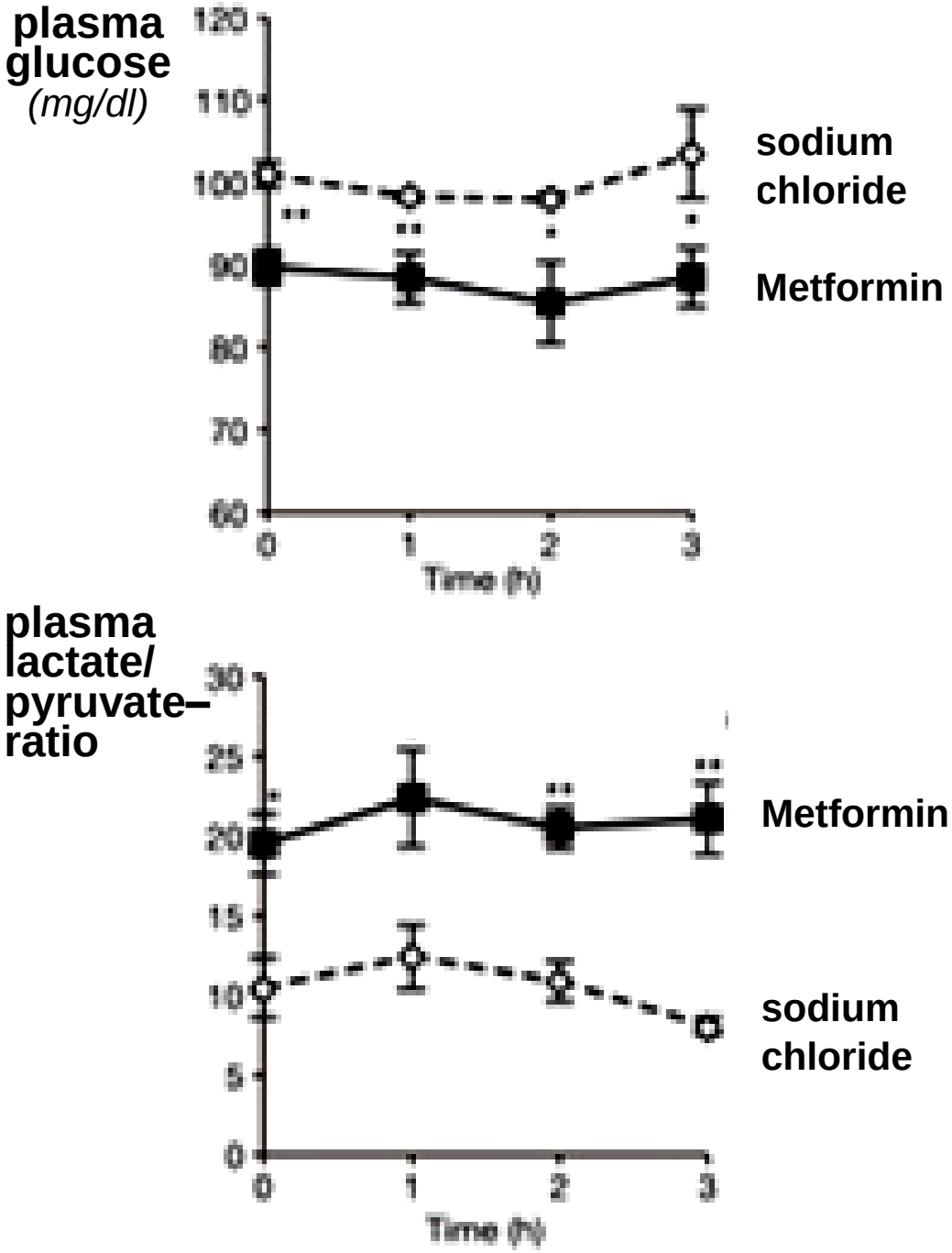


Metformin

raises redox ratio in liver mitochondria

[lactate]:[pyruvate]

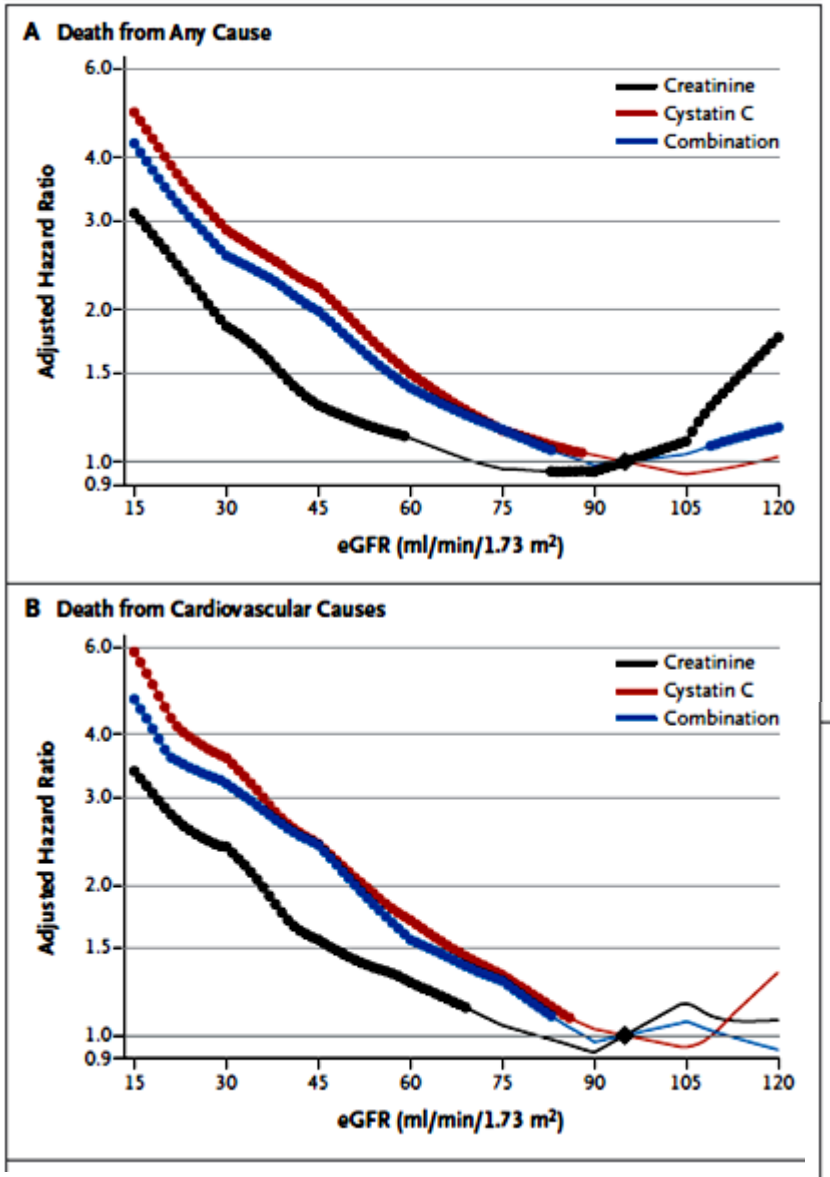
causing lower plasma glucose + elevated plasma lactate/pyruvate ratio

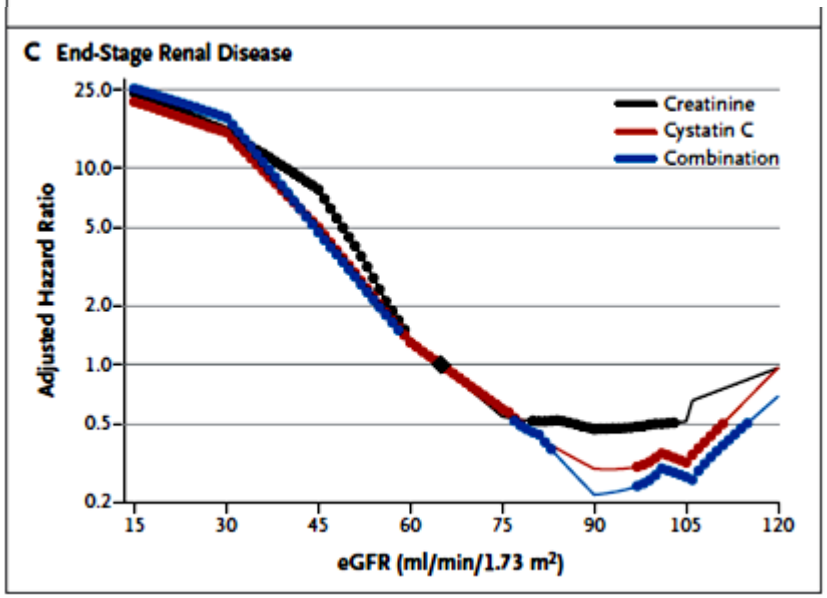
Madiraju, Nature (2014) 510:542

Cystatin-based eGFR vs creatinin-based eGFR :

prediction of ESRD and mortality

Skupien
Am.J.Kidn.Dis.(2013) 62:184





Renal decline in type 1 diabetes

(Cystatin C measured GFR)

 # begins even during normoalbuminuria

 # and is predicted by uricosemia

Renal decline (progressive eGFRcr-cys loss of at least 3.3% per year) occurred in 10% of the NA and 35% of the MA ($P < 0.001$). In both groups, the strongest determinants of renal decline were baseline serum concentrations of uric acid ($P < 0.001$) and tumor necrosis factor receptor 1 or 2 (TNFR-1 or -2, $P < 0.001$). Other significant risk factors included baseline HbA_{1c}, age/diabetes duration, and systolic blood pressure.

Krolewski, Diabetes Care (2014) 37:226

Uric acid lowering

to prevent kidney function loss in diabetes:

The PERL (preventing early renal function loss) Study

Maahs, Curr.Diab.Rep.(2013) 13:550

Renal ans retinal effects of Enalapril and Losartan in type 1 diabetes

Early blockade of the renin-angiotensin system in patients with type 1 diabetes did not slow nephropathy progression, but slowed the progression of retinopathy.

Mauer, N.Engl.J.Med.(2009) 361:40

The risk of nephropathy in diabetes (type1)

- **cumulative incidence of diabetic nephropathy 50%**
- **annual rate 2-3%**
- **25% of type 1 diabetics with nephropathy progress to ESRD**

Marshall S.M.
Diabetic nephropathy in type 1 diabetes:
has the outlook improved since the 1980ies?
Diabetologia (2012) 55:2301

Lowering of serum uric acid reduced progression fo renal disease

Population based retrospective cohort

111,992 patients with hyperuricemia (>7mg/dl)

Selection of 16,186 patients urate lowering naive age >18 years:

11,192 no urate lowering; 3902 uric acid lowering <80% of time; 1092 >80% of t

Factors associated with progression of renal disease were:

age, sex, hypertension, diabetes congestive heart failure, rheumatoid arthritis

Patients on lowering urate < 6 mg/dl ⇨ 37% reduction in outcome events

Levy, J.Rheumatol.(2014) 41:955

Uric acid contributes to insulin resistance/diabetes

R.Johnson Diabetes (2013) 62:3307

mitochondrial oxidative stress causing insulin resistance

Hoehn, Proc.Natl.Acad.Sci.USA (2009) 106:17787

uric acid ⇨ ***fatty liver linked with insulin resistance***

Samuel, Lancet (2010) 375:17787

uric acid ⇨ ***white adipose tissue:***

- uric acid taken up

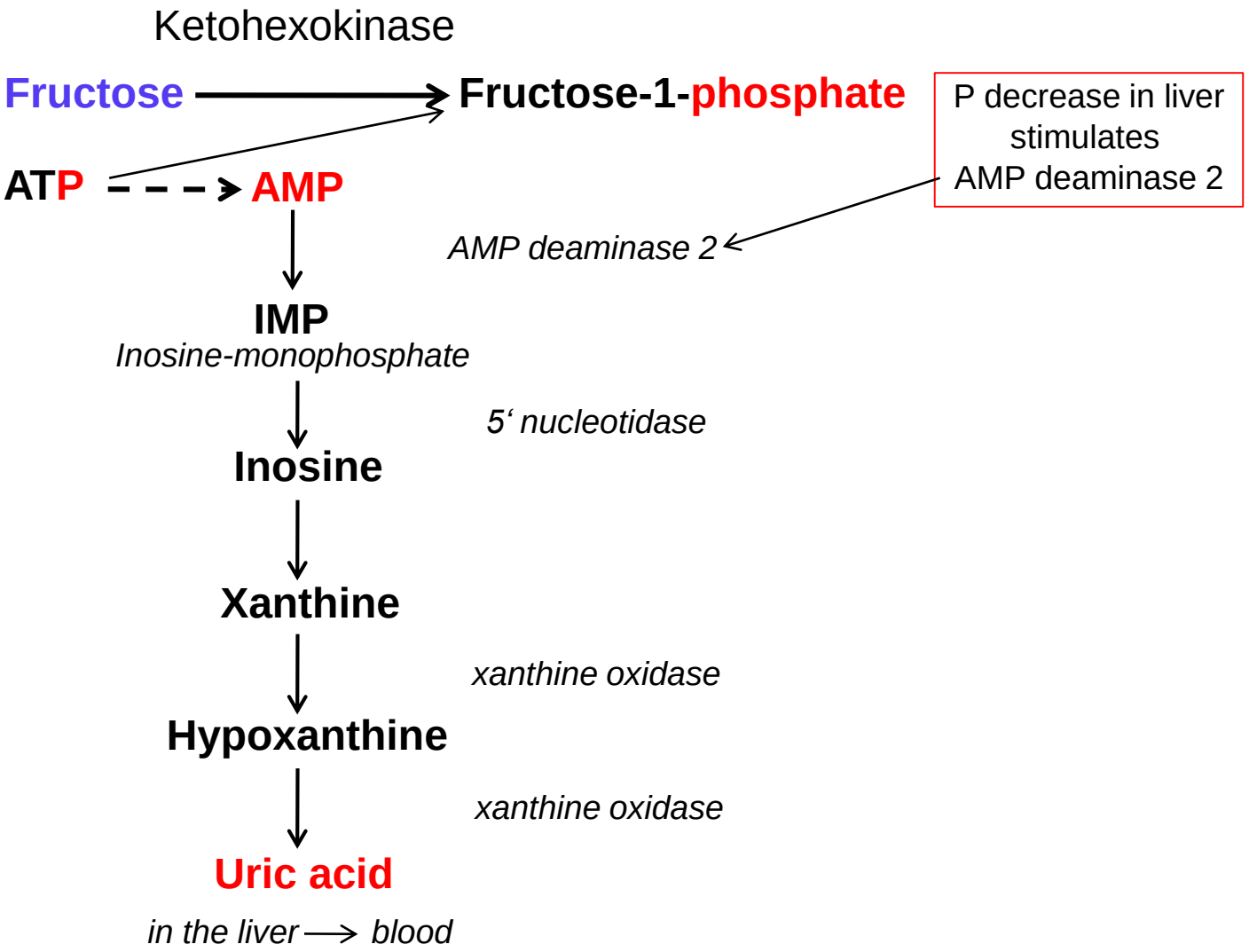
- oxydative stress

- activation of NADPH oxidase

 # oxidized lipids

 # inflammatory mediators

Fructose induced nucleotide metabolism leading to uric acid



Johnson R., Diabetes (2013) 62:3307

Etienne Lanceraux :

diabete gras 1880

Rick Johnson 2010

fructose induced hyperuricemia

contributory role

Fructose

⇩

- stimulates food intake

- lowers metabolism

⇩

- weight gain

- visceral fat accumulation

Johnson R. Diabetes (2013) 62:3307

Consumption of sugary soft drinks

⇨ **independent predictors of metabolic syndrome/diabetes**

Malik, Diabetes Care (2010) 33:2477

Overweight individuals fed 25% of diet as fructose or glucose for 10 weeks

with fructose >> glucose

- **postprandial hypertriglyceridemia**
- **increased hepatic fatta acid synthesis**
- **decreased insulin sensitivity**
- **increased visceral fat**
- **increased inflammatory mediators (MCP-1)**
- **higher uric acid levels**

Stanhope, J.Clin.Invest.(2009) 119:1322

Serum Uric Acid Predicts Development of Diabetes

Germany

Meisinger 2002

6112 adults,3-14years follow-up,type 2 diabetes

USA

Brand 1985 J.

5208 adults, 26 years follow-up, type 2 diabetes

Uric acid contributes to insulin resistance/diabetes

R.Johnson Diabetes (2013) 62:3307

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uric acid ⇨ ***white adipose tissue:***

- uric acid taken up

- oxydative stress

- activiation of NADPH oxidase

 # oxidized lipids

 # inflammatory mediators

Role of hyperuricemia in the genesis of fatty liver independent of obesity

elevated uric acid

⇩ independently predicting

development of NAFLD

(nonalcoholic fatty liver disease)

Ryu, Metabolism (2011) 60:860

Lanaspa, J.Biolö.Chem. (2012) 287:40732

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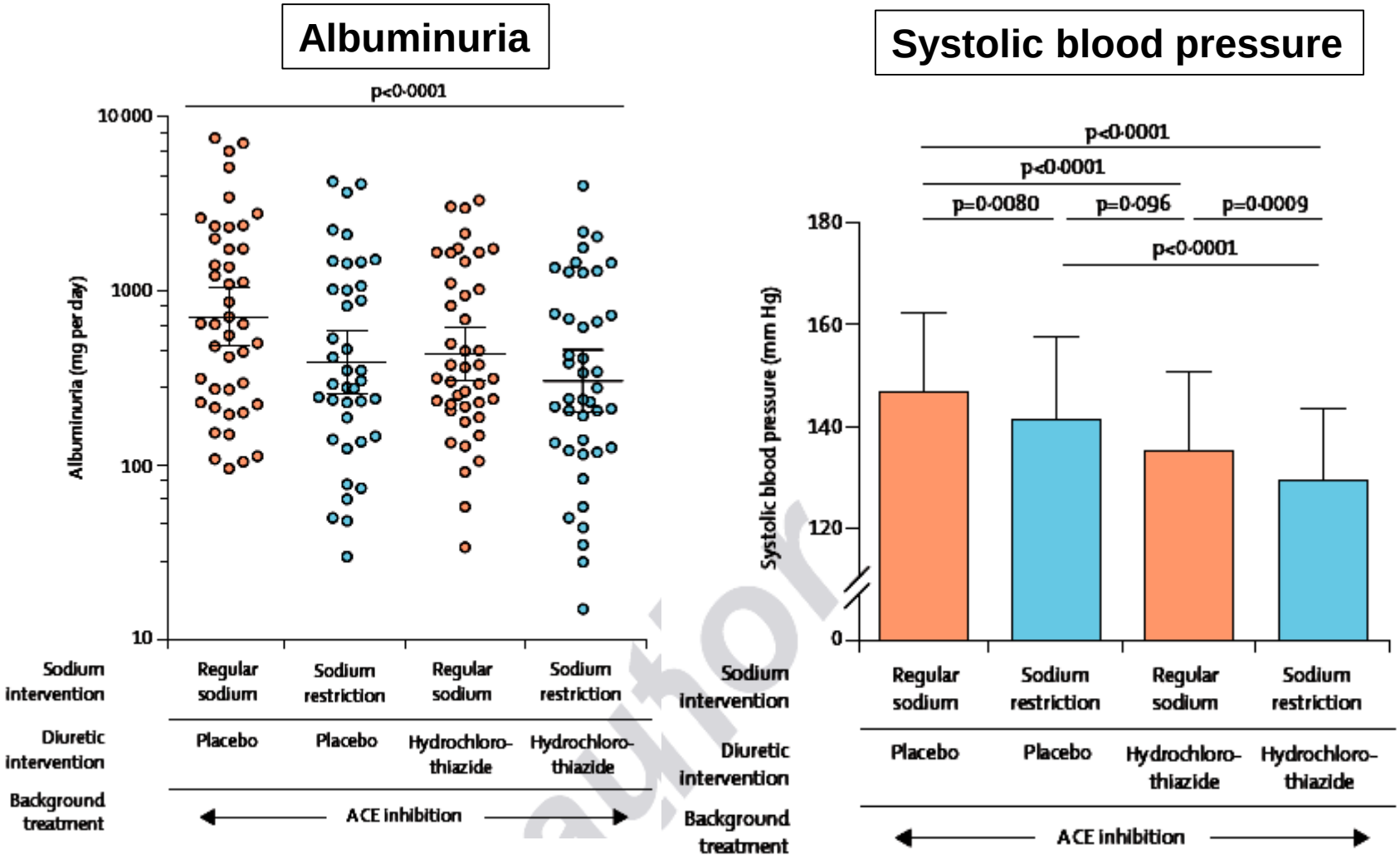
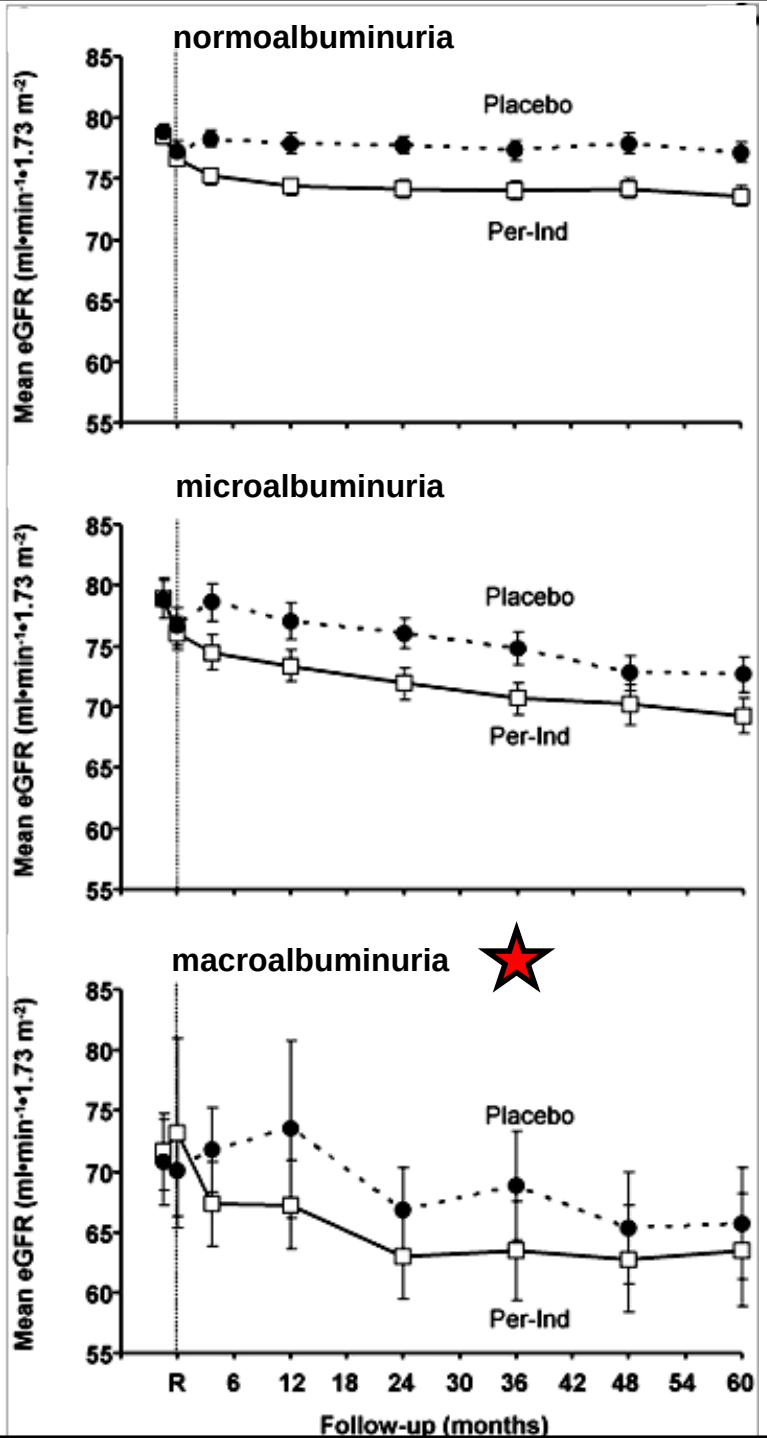
Levy, J.Rheumatol.(2014) 41:955

Effect of sodium restriction and hydrochlorothiazide on RAAS blockade efficacy in diabetic nephropathy - a randomized clinical trial



Kwakernaak, Lancet/diabetes-endocrinology (2014) 2:385



Benefit of BP lowering in type 2 diabetes at different stages of diabetic nephropathy - *demonstrable even in macroalbuminuria* ★

(ADVANCE study)

11,140 patients
follow-up 4.3 years
BP lowering (Perindopril-Indapamid)
⇨ *renal events reduced by 21%*
($p<0.0001$)

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

Type 2 diabetes : combined effects of both routine BP lowering plus intensive glucose control

ADVANCE study

11,140 participants

BP *(Perindopril-Indapamide)* and **glucose lowering** *(Gliclazide)*

patients on **combination** treatment

compared with patients on **neither** of the 2 additional interventions

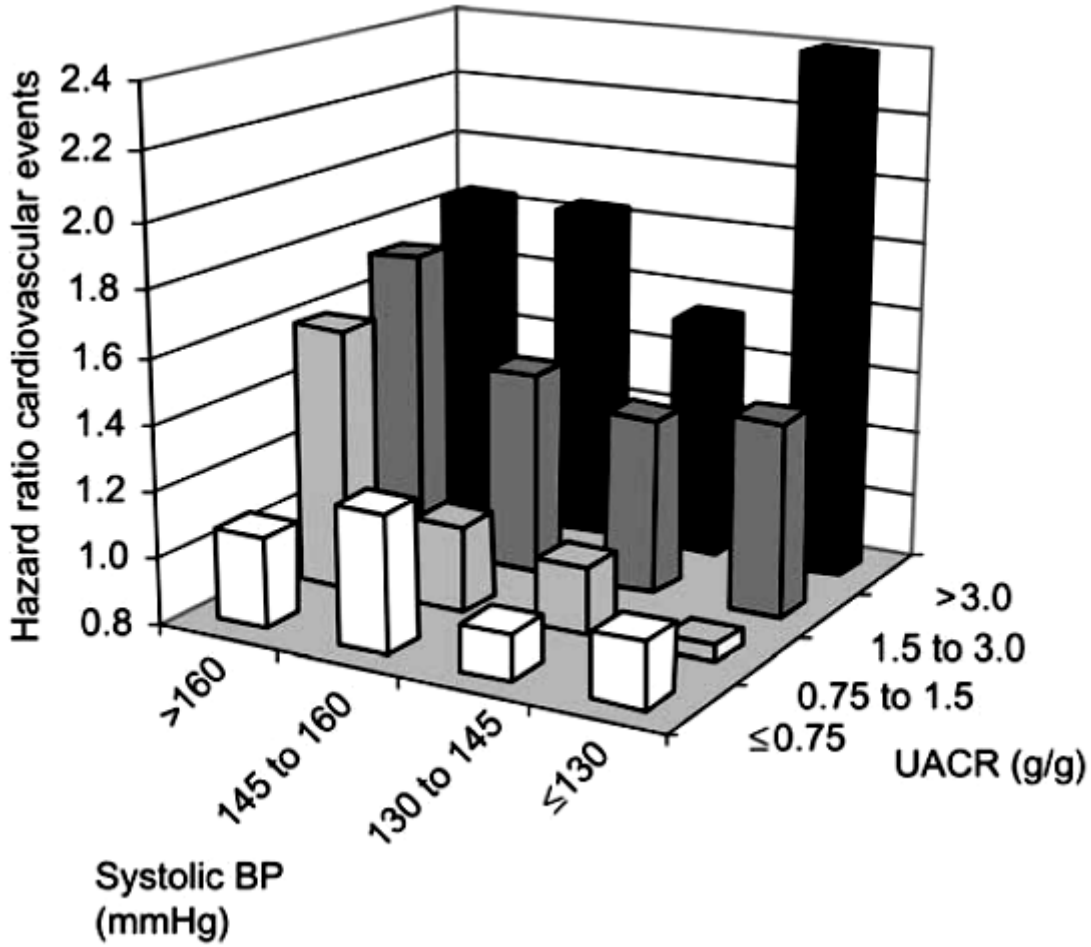
Combination of treatments : reduction of the following risks :

new or worsening of nephropathy	**- 33%** *(95% CI 12-50%; p=0.005)*
new onset of macroalbuminuria	**- 54%** *(95% CI 35-68%; p<0.0001)*
new onset of microalbuminuria	**- 26%** *(95%CI 17-34%)*
all cause death	**- 18%** *(95%CI 1-32) p=0.04)*

Zoungas, Diabetes Care (2009) 32:2068

Albuminuria and blood pressure – independent targets for cardioprotection

IDNT and RENAAL trials



Holtkamp, Eur.Heart J.(2011) 32:1490

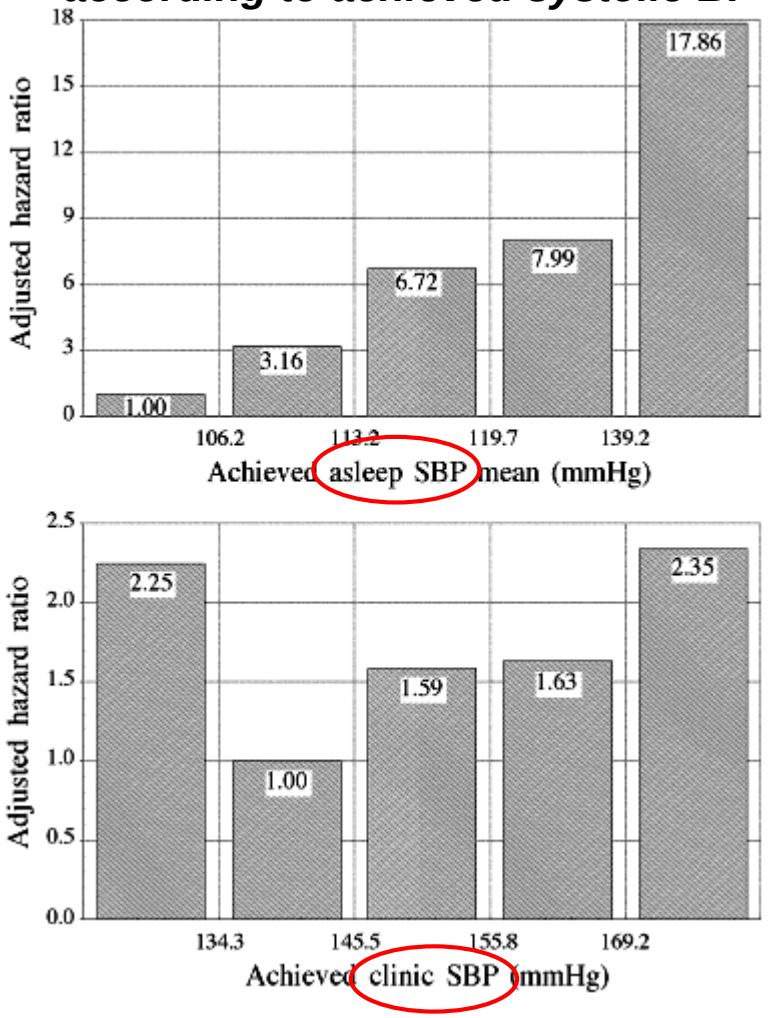
Taking antihypertensive medication at morning or morning+evening

⇨ **CV events of hypertensive type 2 diabetics**

prospective randomised open-label blinded endpoint-study

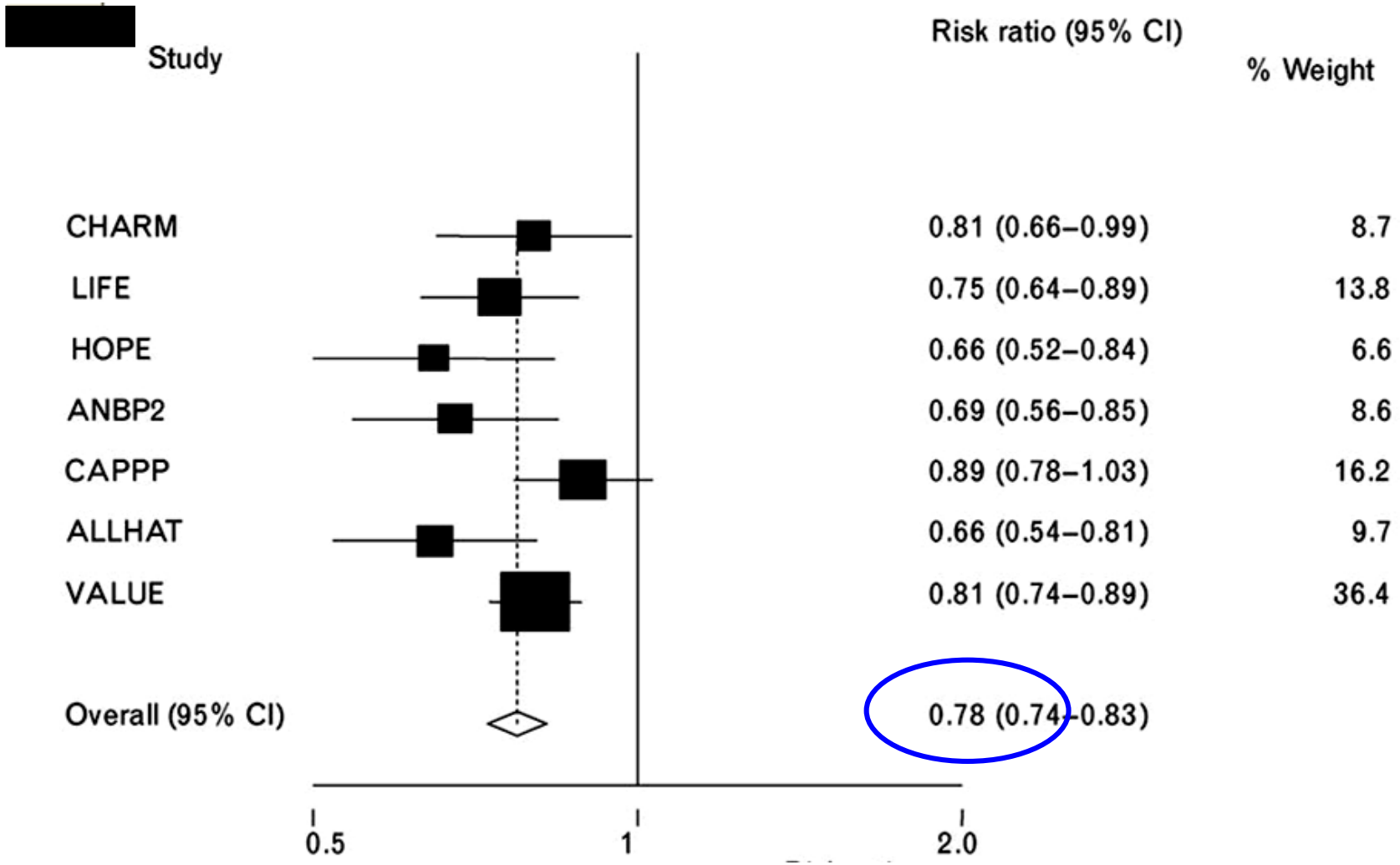
Adjusted "hazard ratio" cardiovascular events

according to achieved systolic BP



Hermida, Diabetes Care (2011) 34:1270

New onset diabetes
Metaanalysis
RAS blockade vs non-RAS blockade



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

UKPDS – annual death rate

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

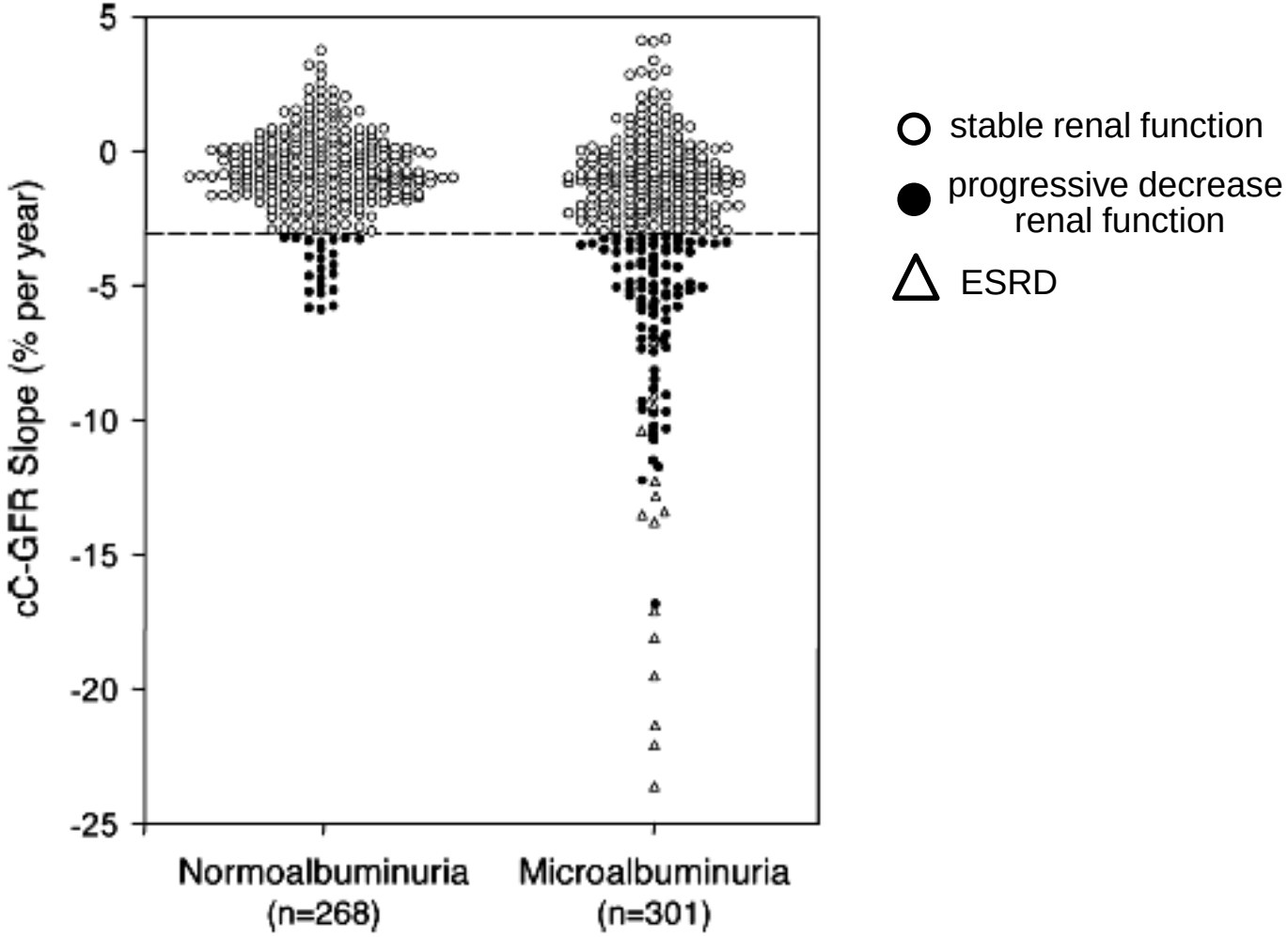
macroalbuminuria:

greater risk of CV death than of renal failure
cardiac management crucial

Adler, Kidn Intern (2003) 63: 225

Yearly percent decrease of GFR –

normoalbuminuric vs microalbuminuric diabetic patients

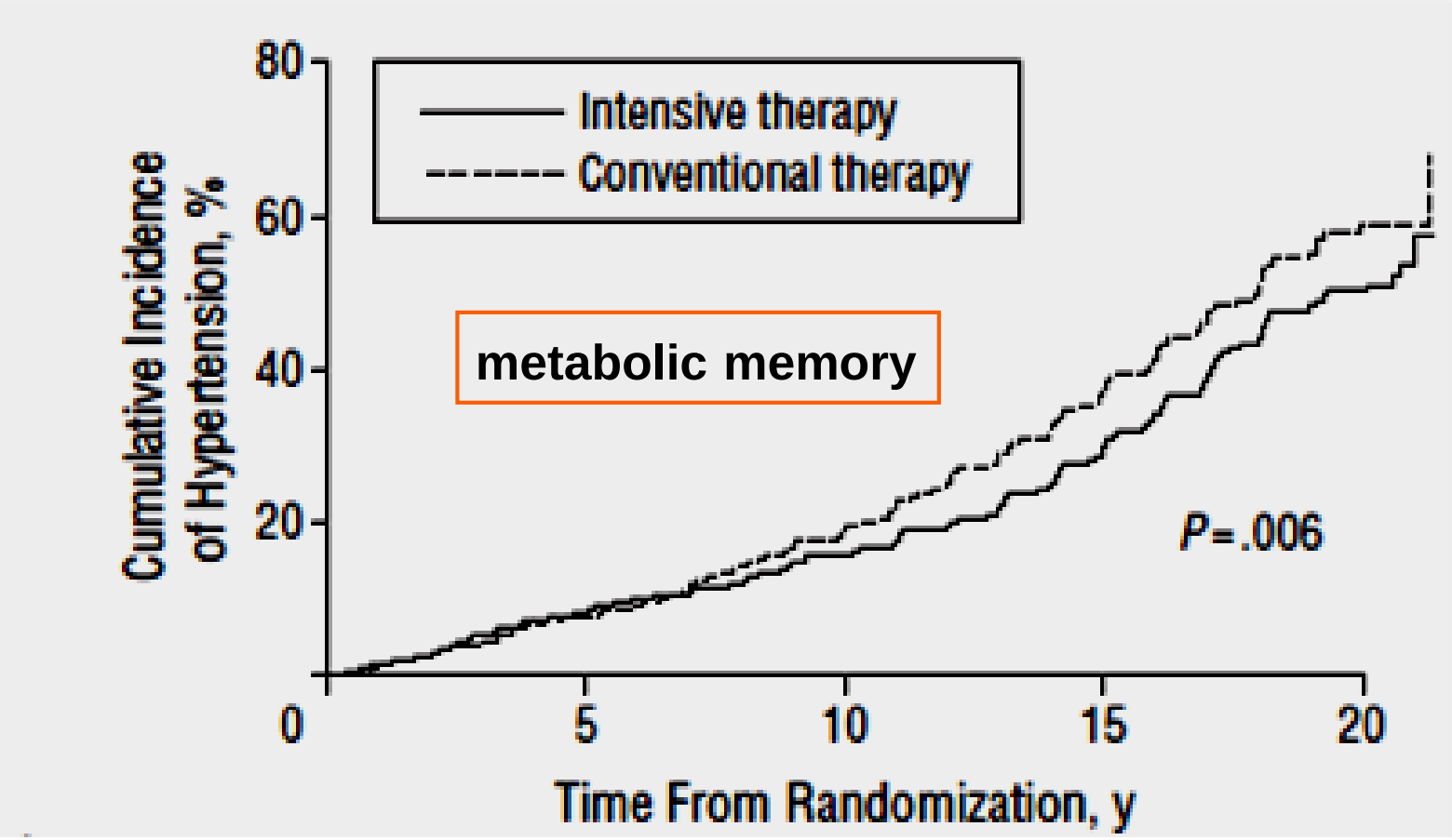


Perkins, J.Am.Soc.Nephrol. (2007) 18:1353

Cumulative incidence of hypertension by glycemic control

persisting benefit from initally intensified glycemic control

(DCCT/EDIC trial)



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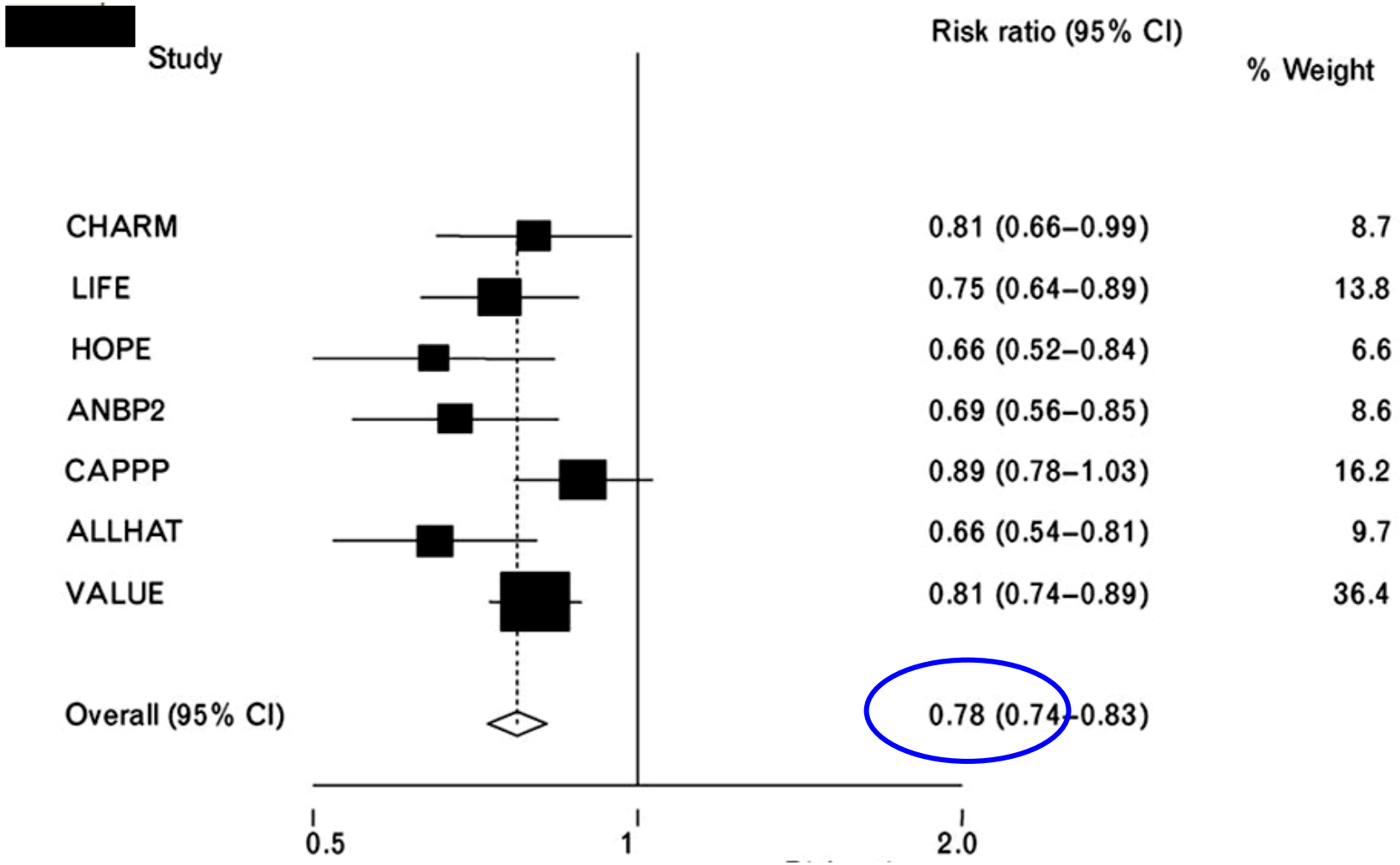

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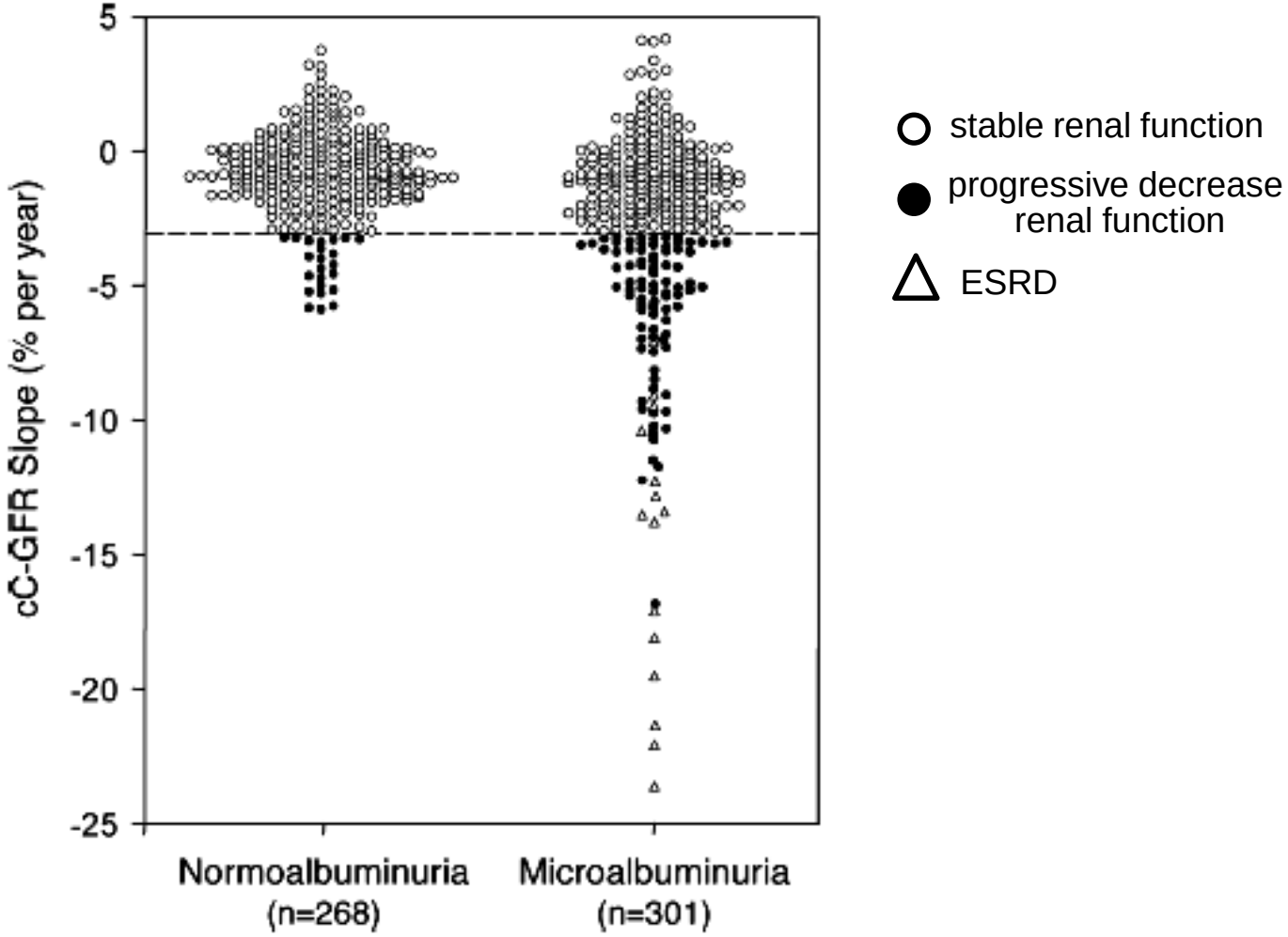

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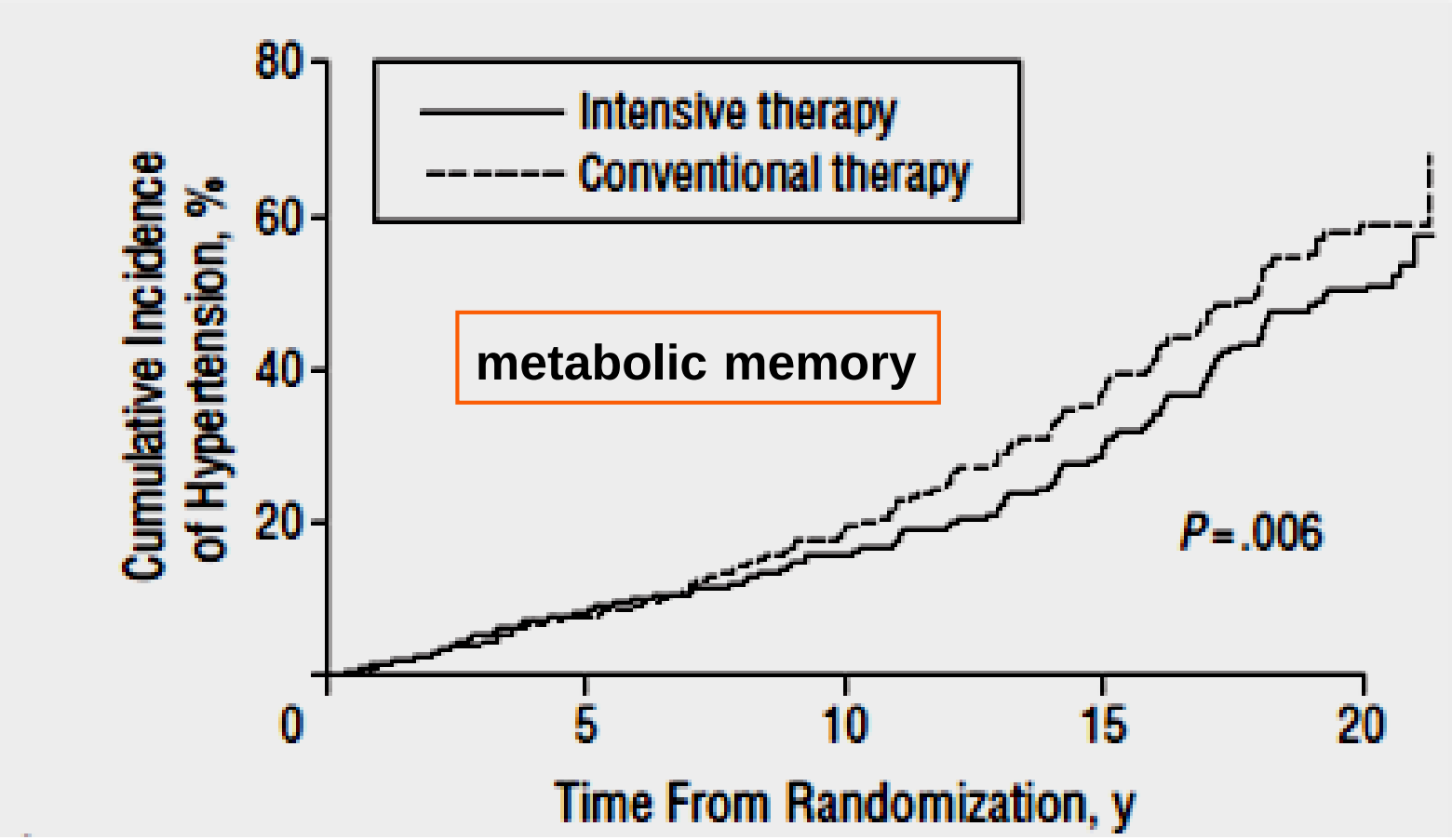

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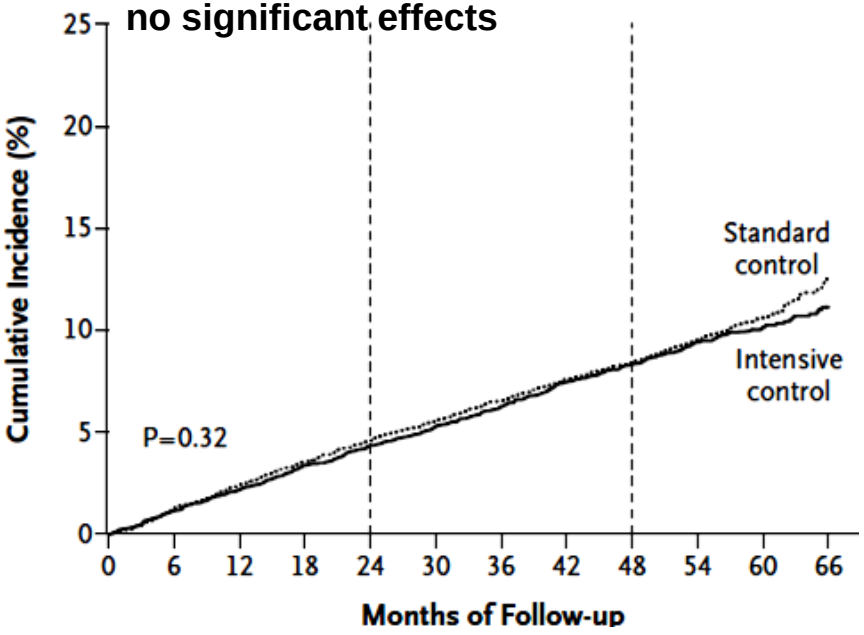
Intensive glucose lowering in type 2 diabetes : *less adverse events, but more deaths*

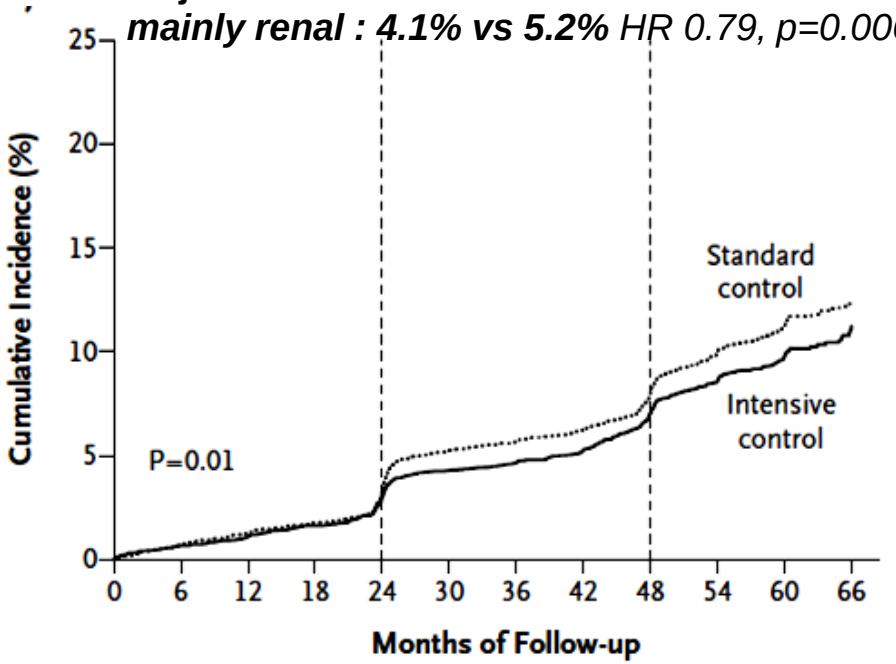
ADVANCE study

11,140 patients type 2 diabetes
standard control vs. intensive control (Gliclazide plus other antidiabetic drugs)
$HbA1_c$: standard control 7.3% vs intensive control 6.5%
median duration 5 years

Major Macrovascular Event
no significant effects



Major Microvascular Events *9.4% vs 10.9%*
mainly renal : 4.1% vs 5.2% *HR 0.79, p=0.006*



21% reduction of renal events

severe hypoglycemia 2.7% vs 1.5% (standard control) HR 1.86; p<0.001

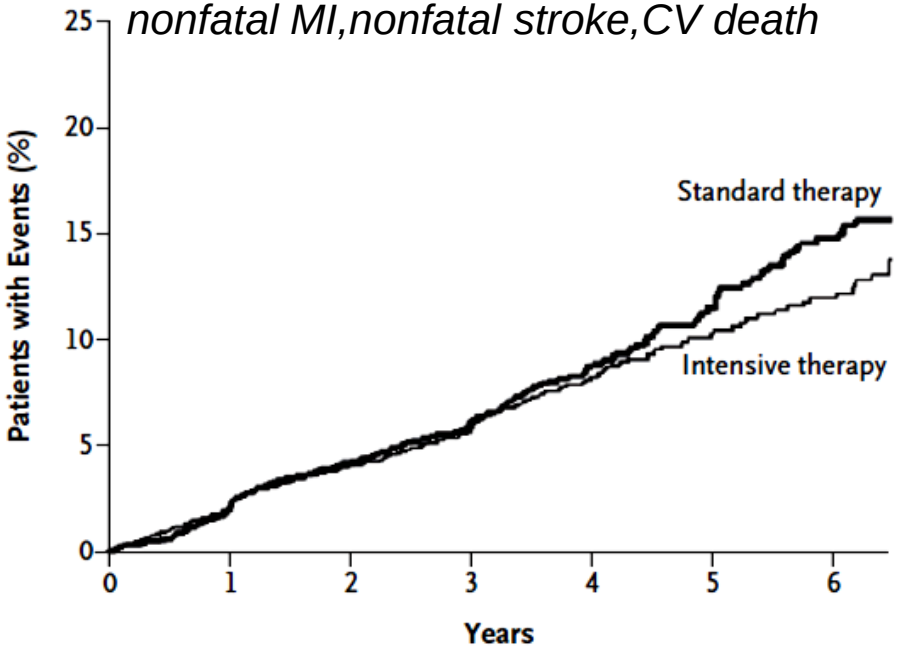
The ADVANCE Collaborative Group, New Engl.J.Med.(2008) 358:2560

Intensive glucose lowering in type 2 diabetes : *less adverse events, but more deaths*

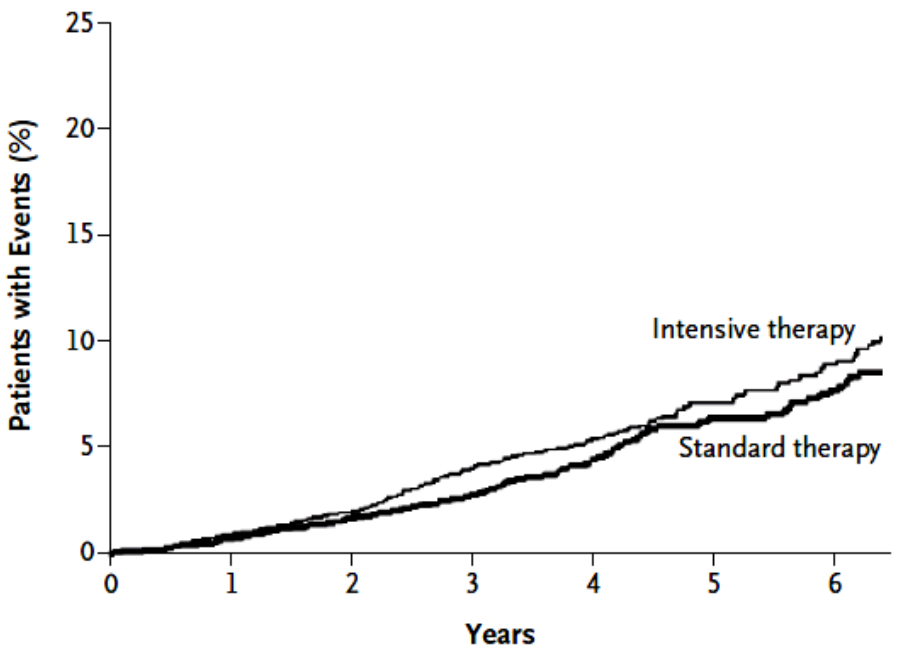
Accord trial

10,251 patients, mean age 62.2 years
baseline $HbA1_c$ 8.1% ; target $HbA1_c$<6% (intensive) vs 7.0-7.9% (standard Rx)
3.5 years

Events:
nonfatal MI,nonfatal stroke,CV death



Death:



intensive therapy group terminated 17 months before scheduled

Gerstein, New Engl J Med (2008) 358:2545

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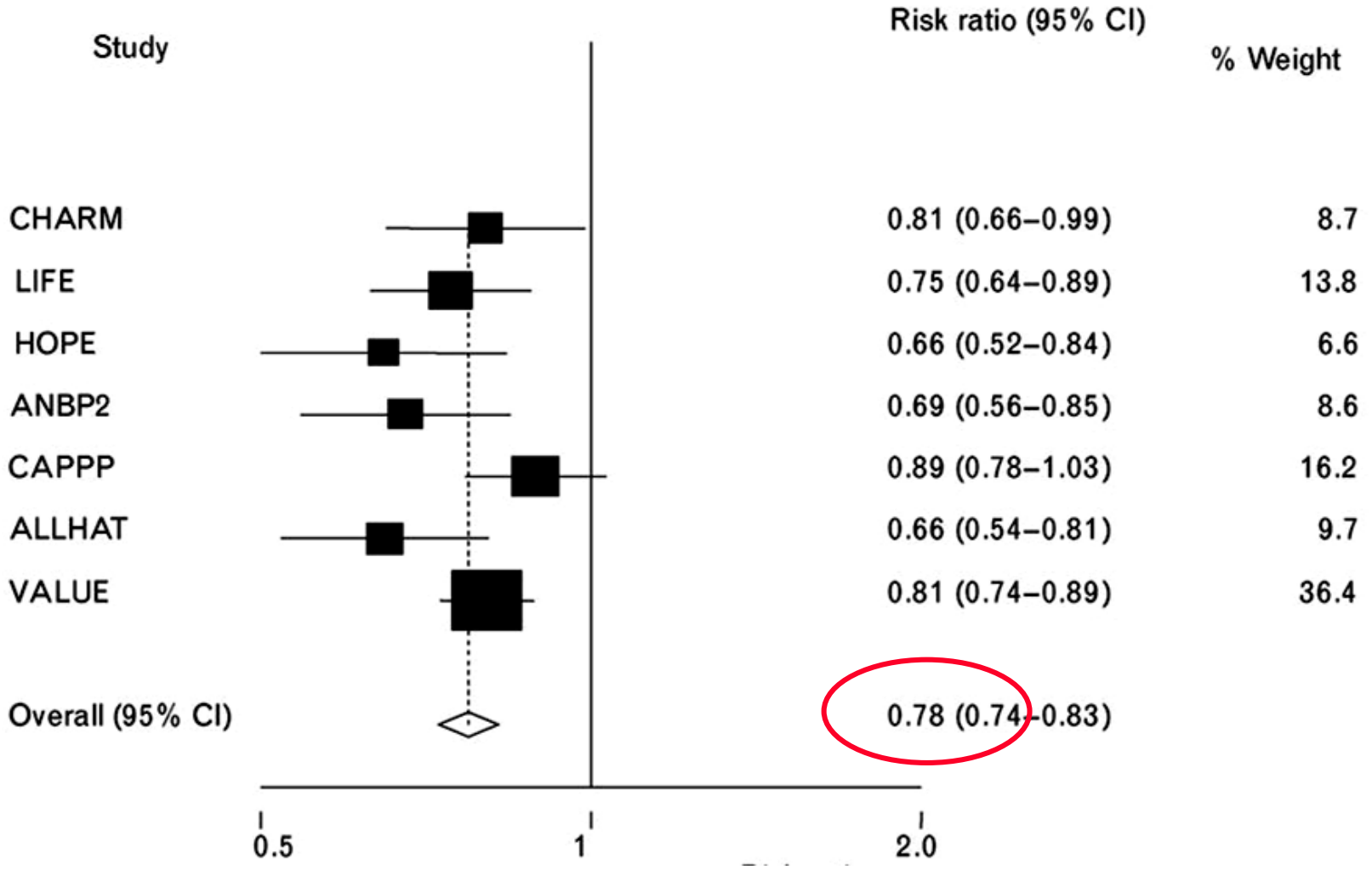

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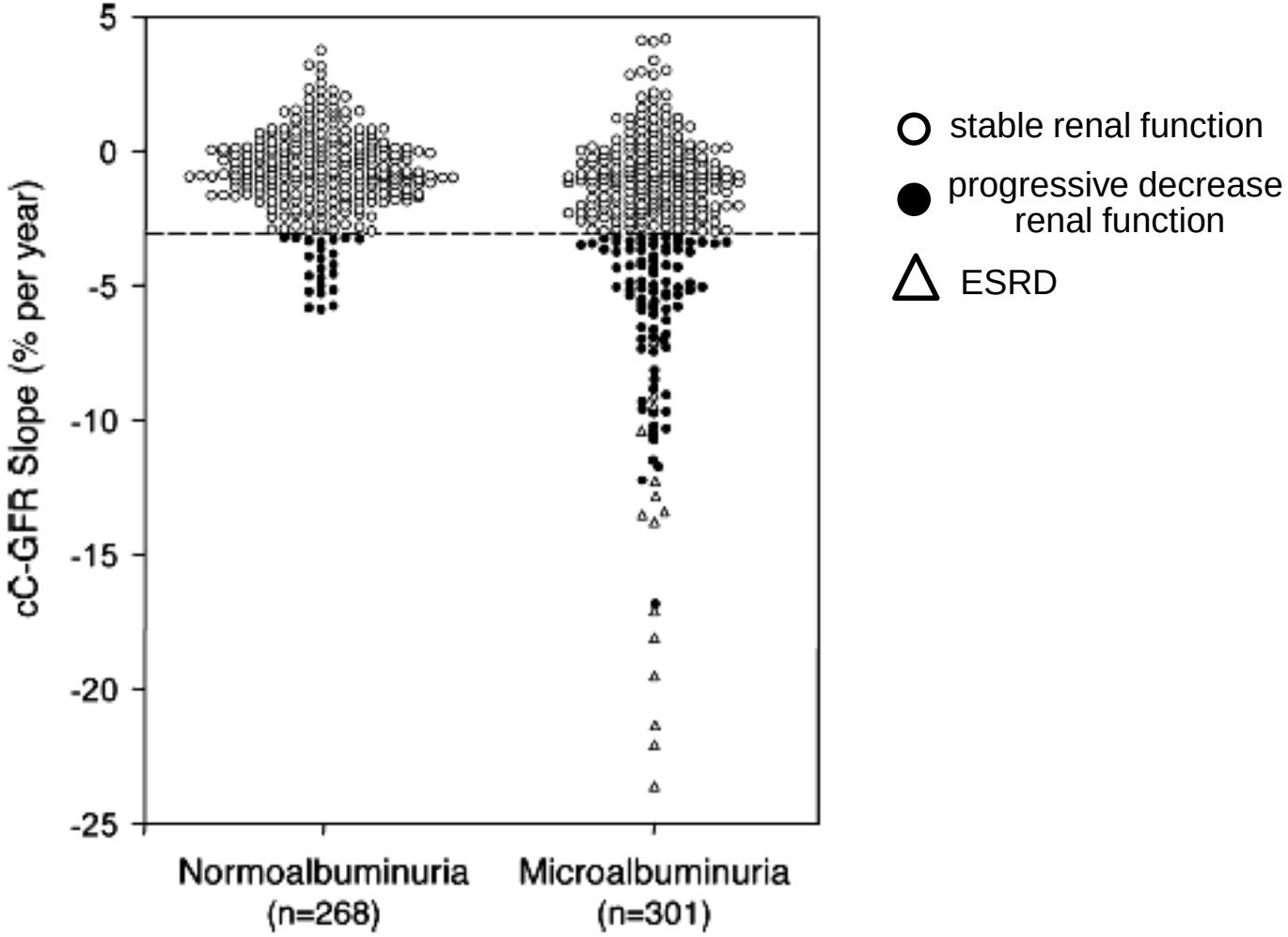

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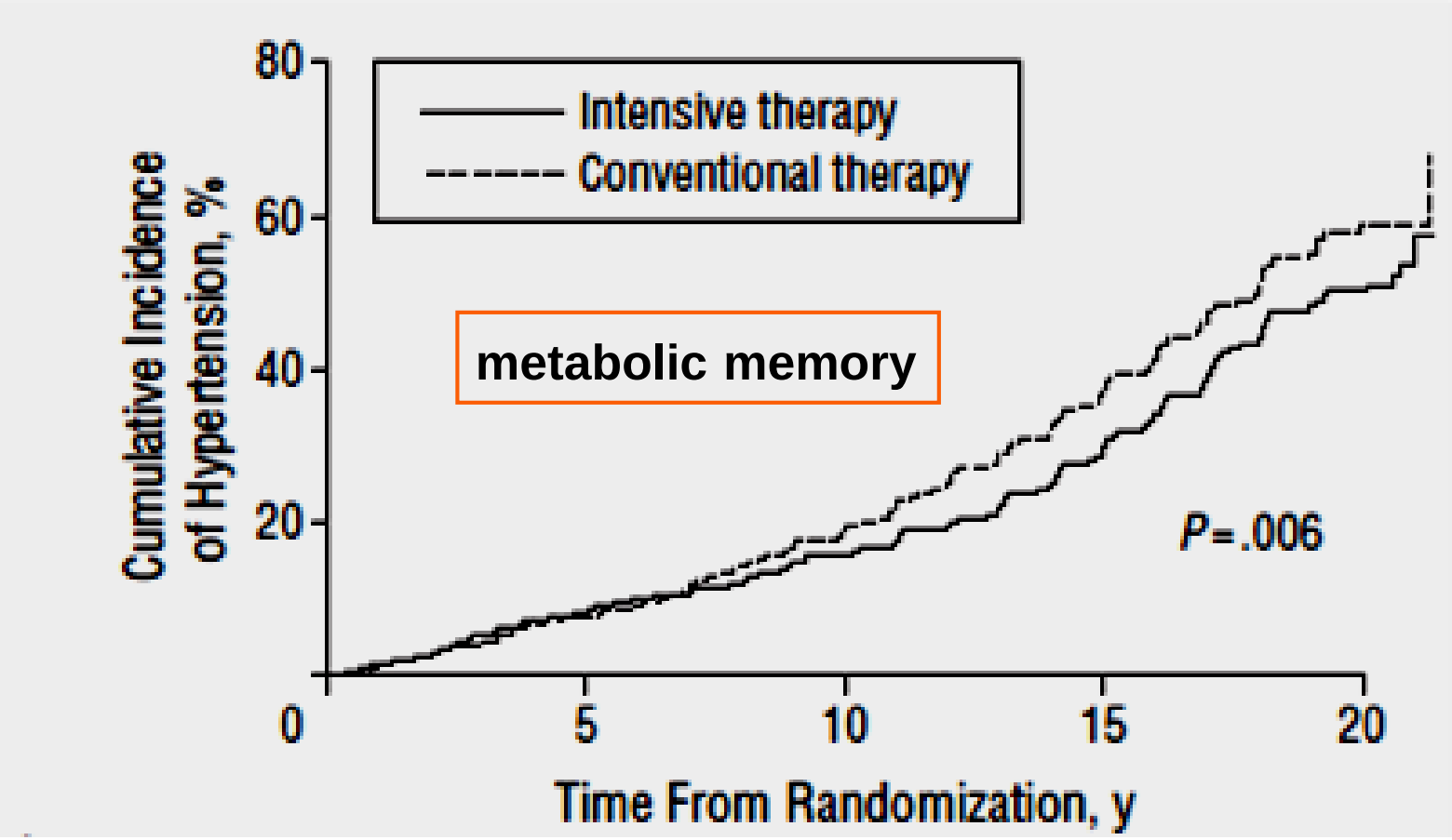

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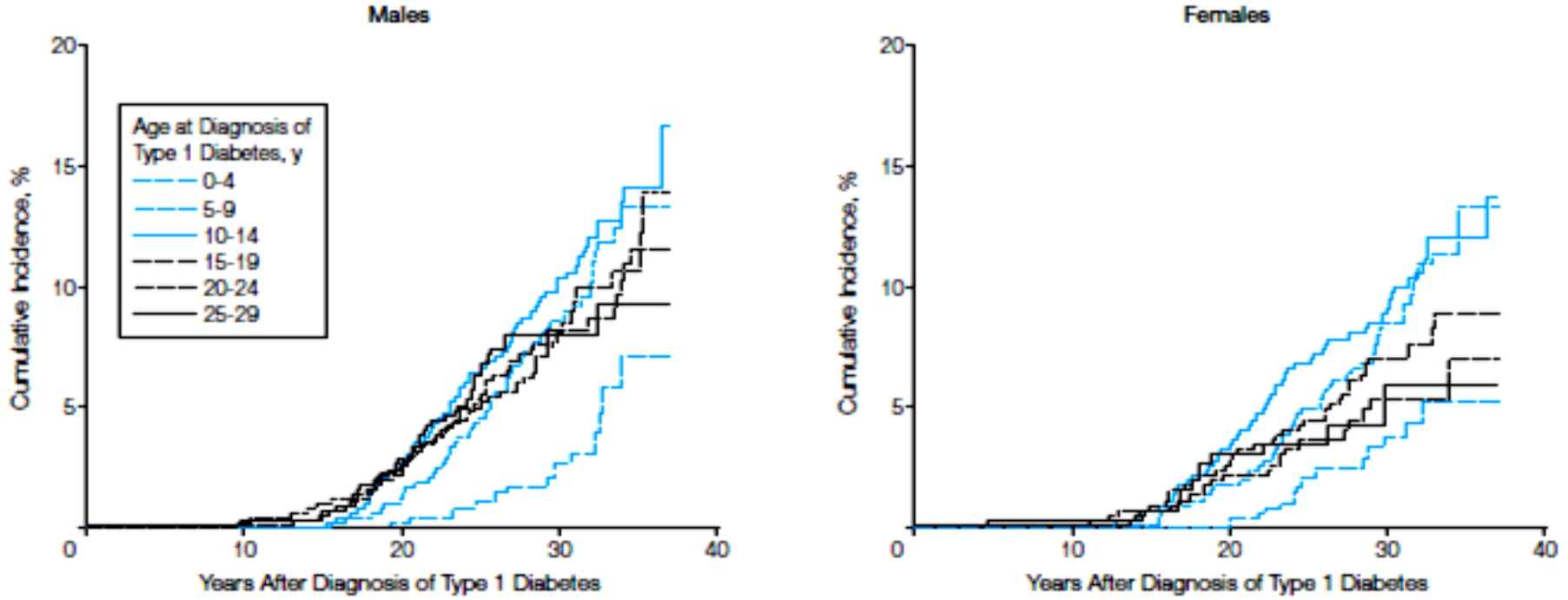
Cumulative Incidence of ESRD in Male and Female Type 1 Diabetic Patients according to Age at Diagnosis of Diabetes

(Finland Registry)



Finne, JAMA (2005) 294:1782

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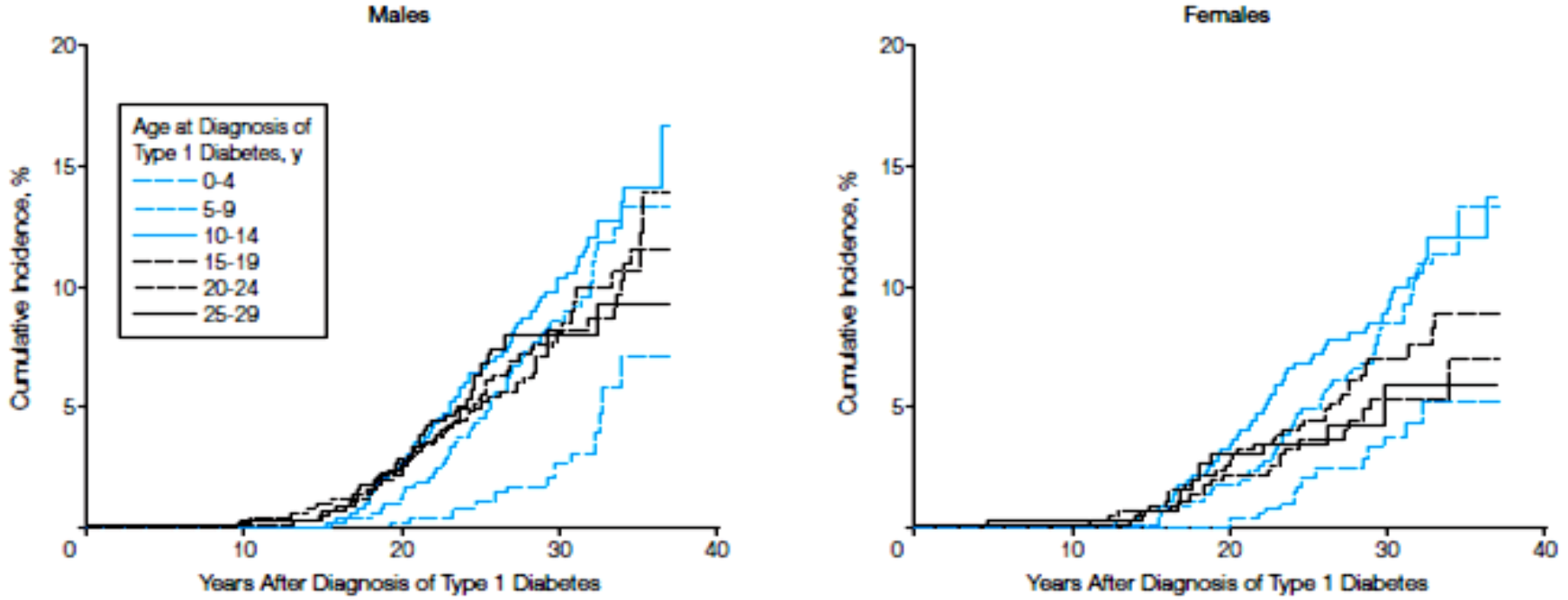

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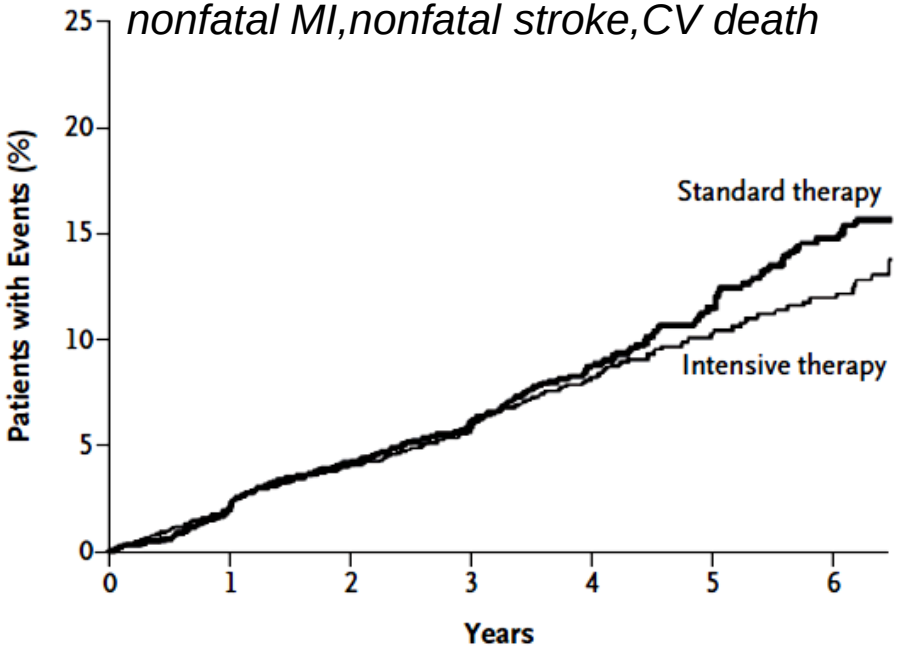

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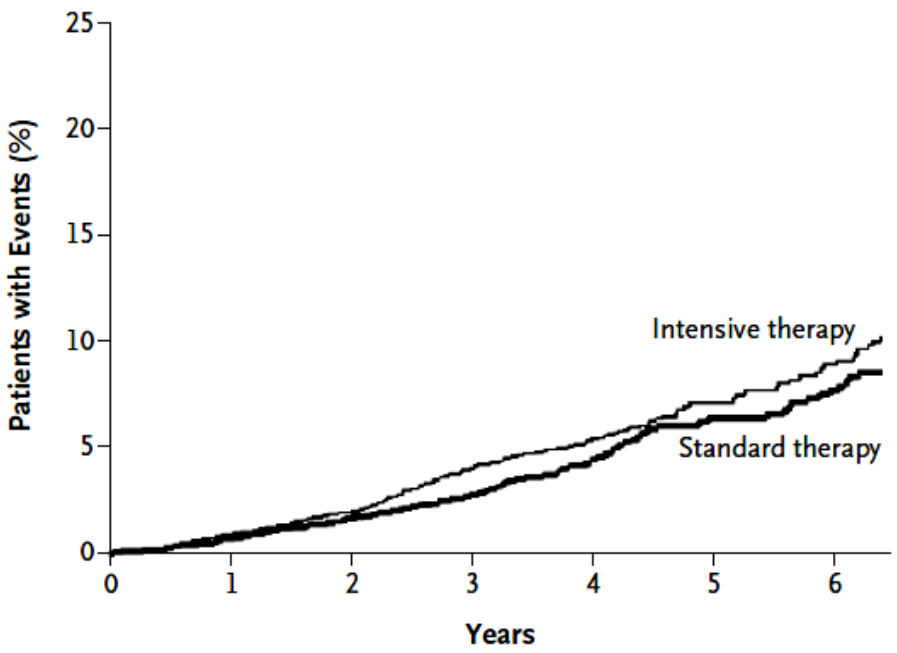
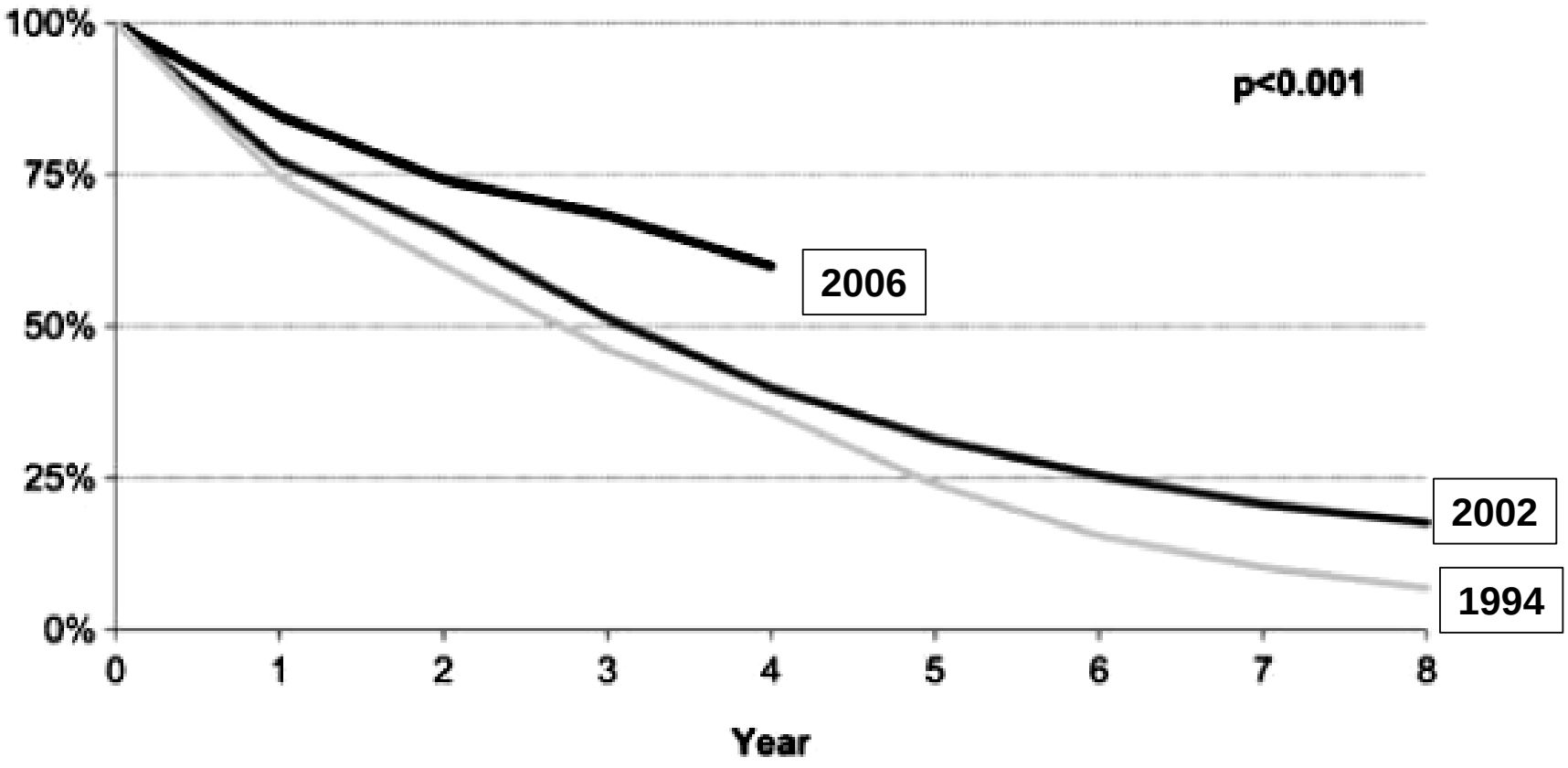


intensive therapy group terminated at 17 months

Gerstein, New Engl J Med (2008) 358:2545

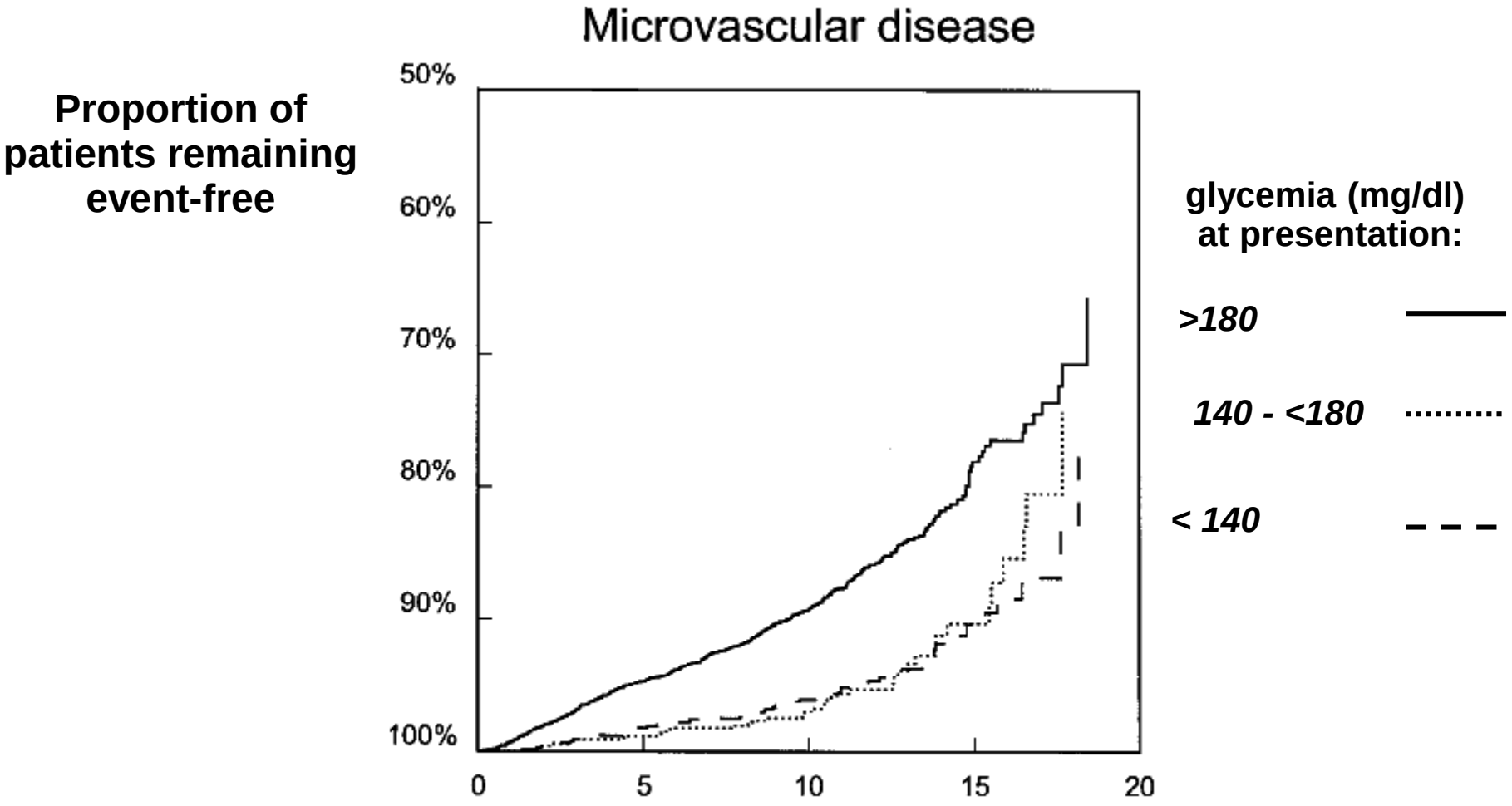
Incident patients with ESRD and diabetes in Catalonia taken on renal replacement therapy in 1994, 2002, 2006

⇨ progressive increase in survival



Comas, NDT (2013) NDT (2013) 28:1191

The lower glycemia at presentation - the less development of microvascular disease including nephropathy



Colagiuri, Diabetes Care (2002) 25:1410

Some points on treatment of diabetes in renal failure

- **with decreasing GFR :**

 # insulin more frequently necessary
 # most oral antidiabetics counterindicated

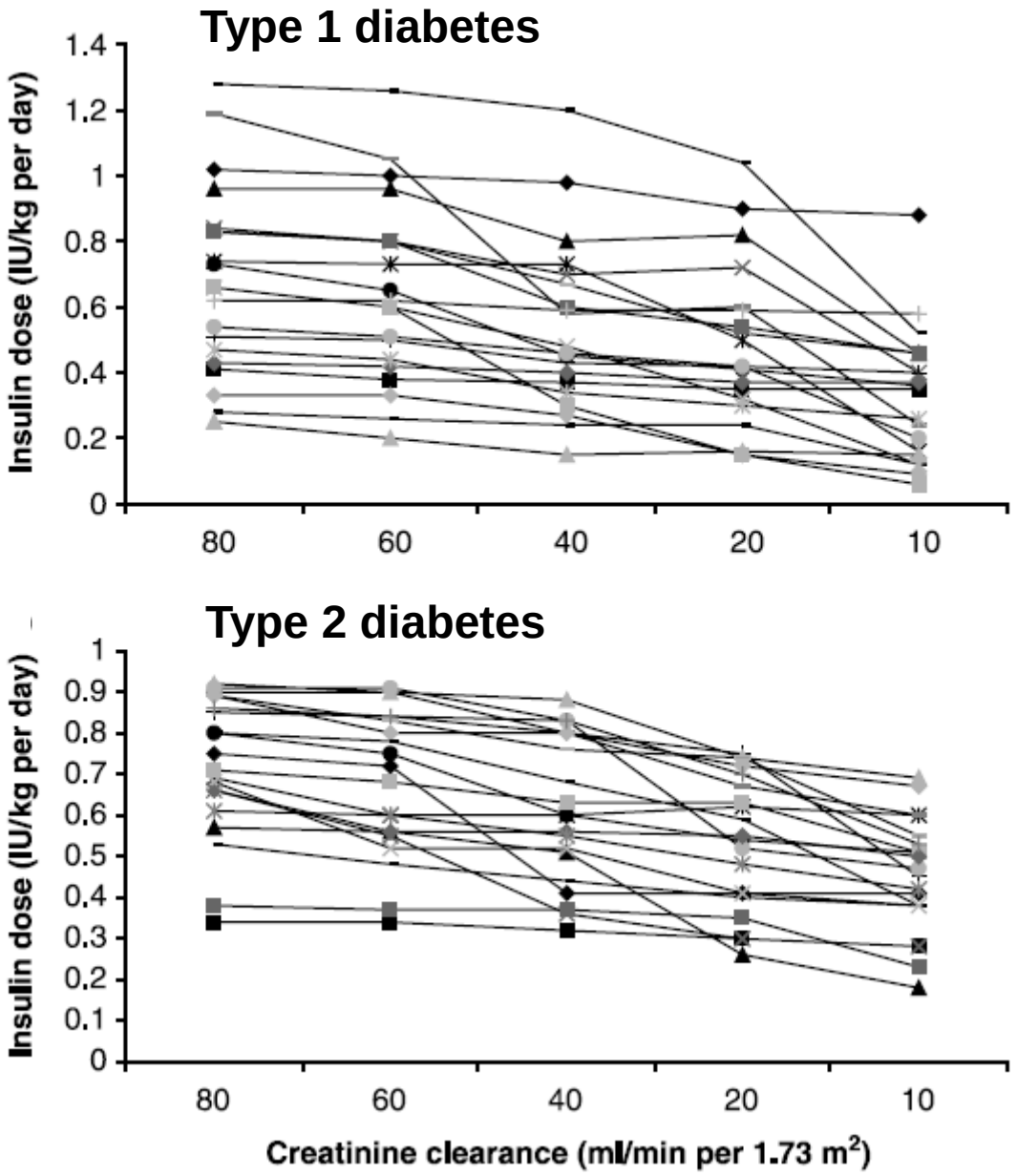
 # halflife of most oral antidiabetics and some insulins prolonged
 # insulin sensitivity reduced

decereased insulin requirement in relation to GFR in nephropathic type 1 and 2 diabetic patients

Biesenbach, Diabetic Medicine (2003) 20:642
Hasslacher, Therap.-Adv.Endocrinol.Medicine (2013) 4:113

Reduced Insulin Requirement in Type 1 and 2 Diabetic patients with reduced GFR

Biesenbach, Diabet.Med.(2003) 20:642

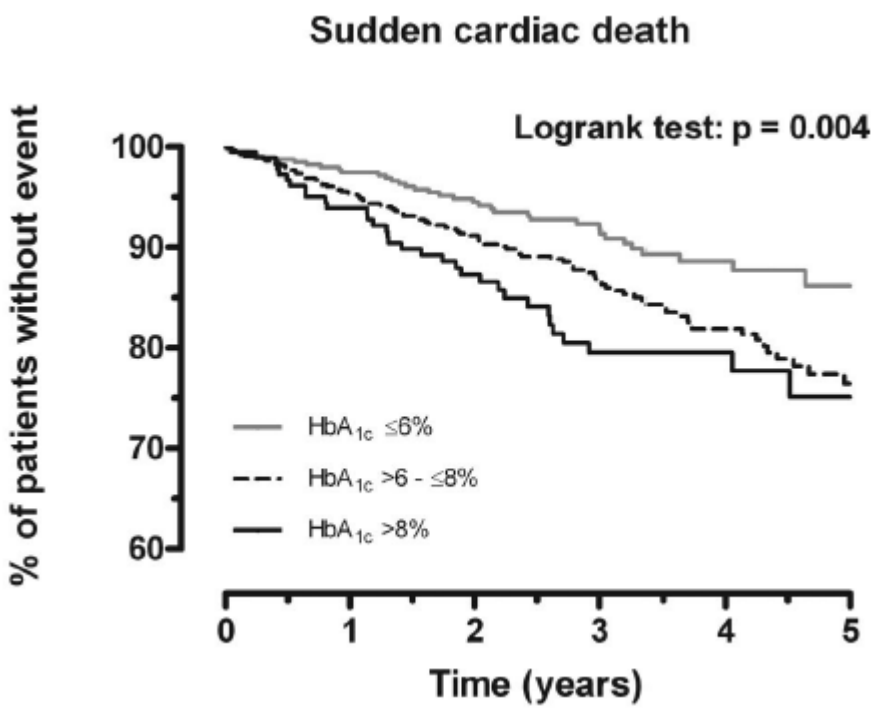


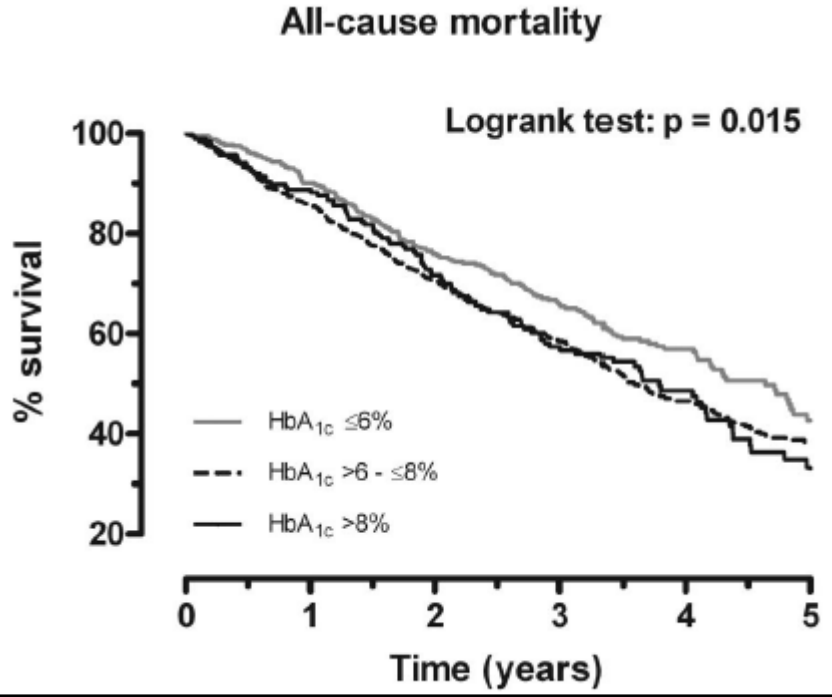
Hemodialysis in diabetic patients

Poor glycemic control : associated with higher rate of sudden death and all-cause mortality

(4D study)

- *Pharmacokinetics*
- *Insulinresistance*
- *Low renal gluconeogenesis*
  (20-25% less gluconeogenesis)



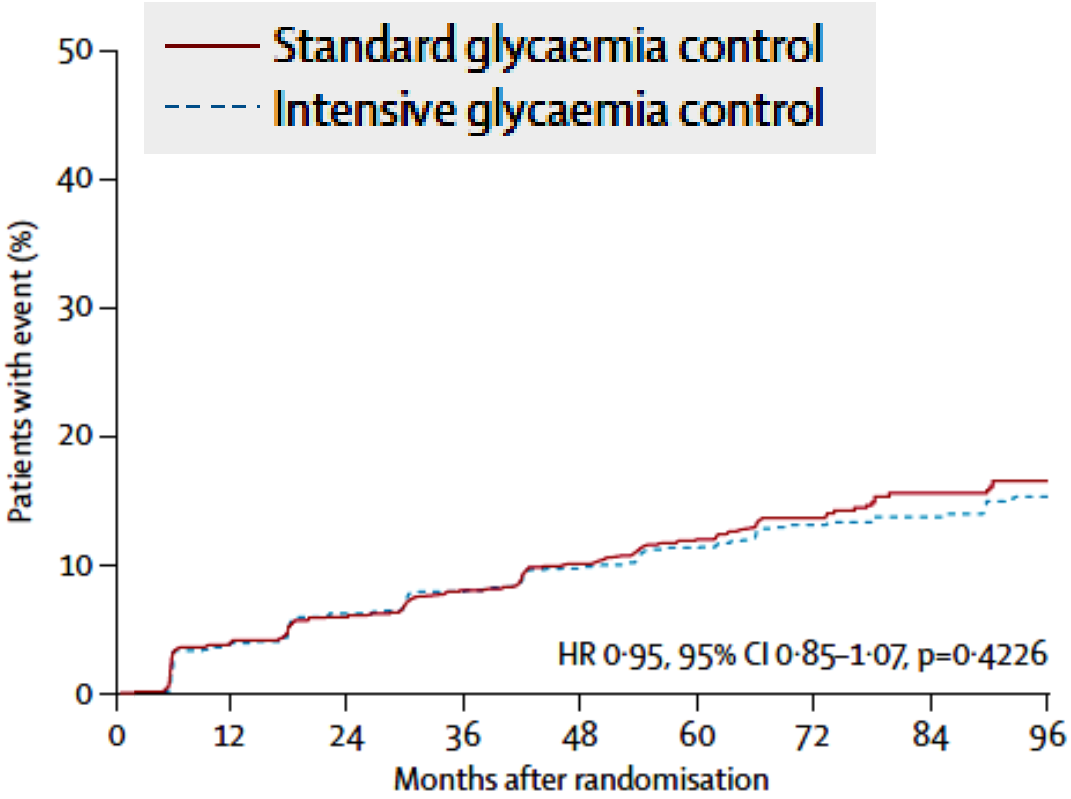


Drechsler, Kidn.Internat.(2009) 120:2421

Caution against intensive treatment of hyperglycemia - no significant impact on microvascular outcomes in type 2 diabetes

Accord trial

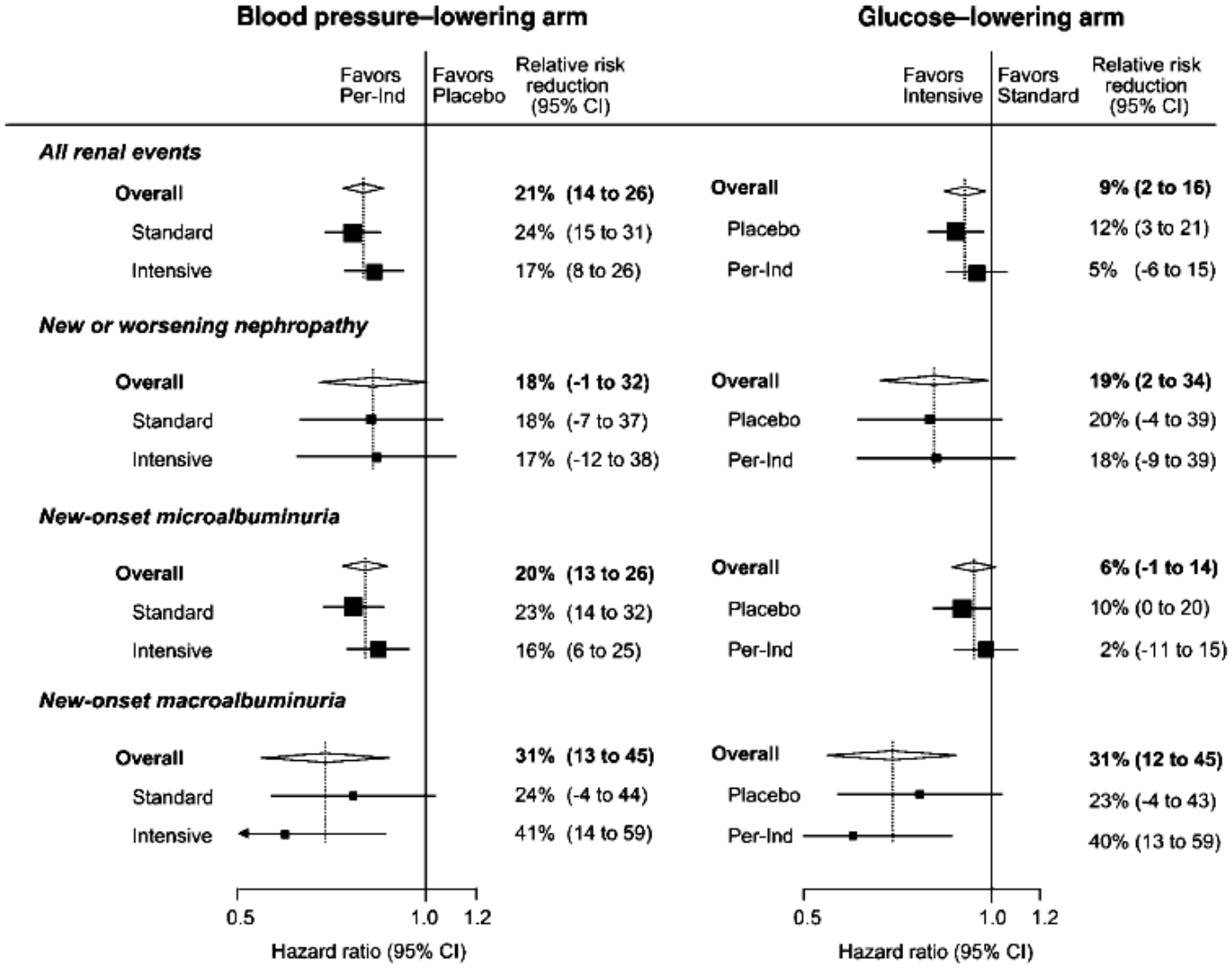
10251 patients ; intensive vs standard therapy
prespecified composite outcomes: dialysis or TX; s-creatinine > 292 µmole/L; retinal photocoagulation/vitrectomy
stopped before study end (futility)



Ismail-Beigi, Lancet (2010) 376:419

Type 2 diabetes : Combined effects of routine BP lowering and intensive glucose control

ADVANCE study



Zoungas, Diabetes Care (2009) 32:2068

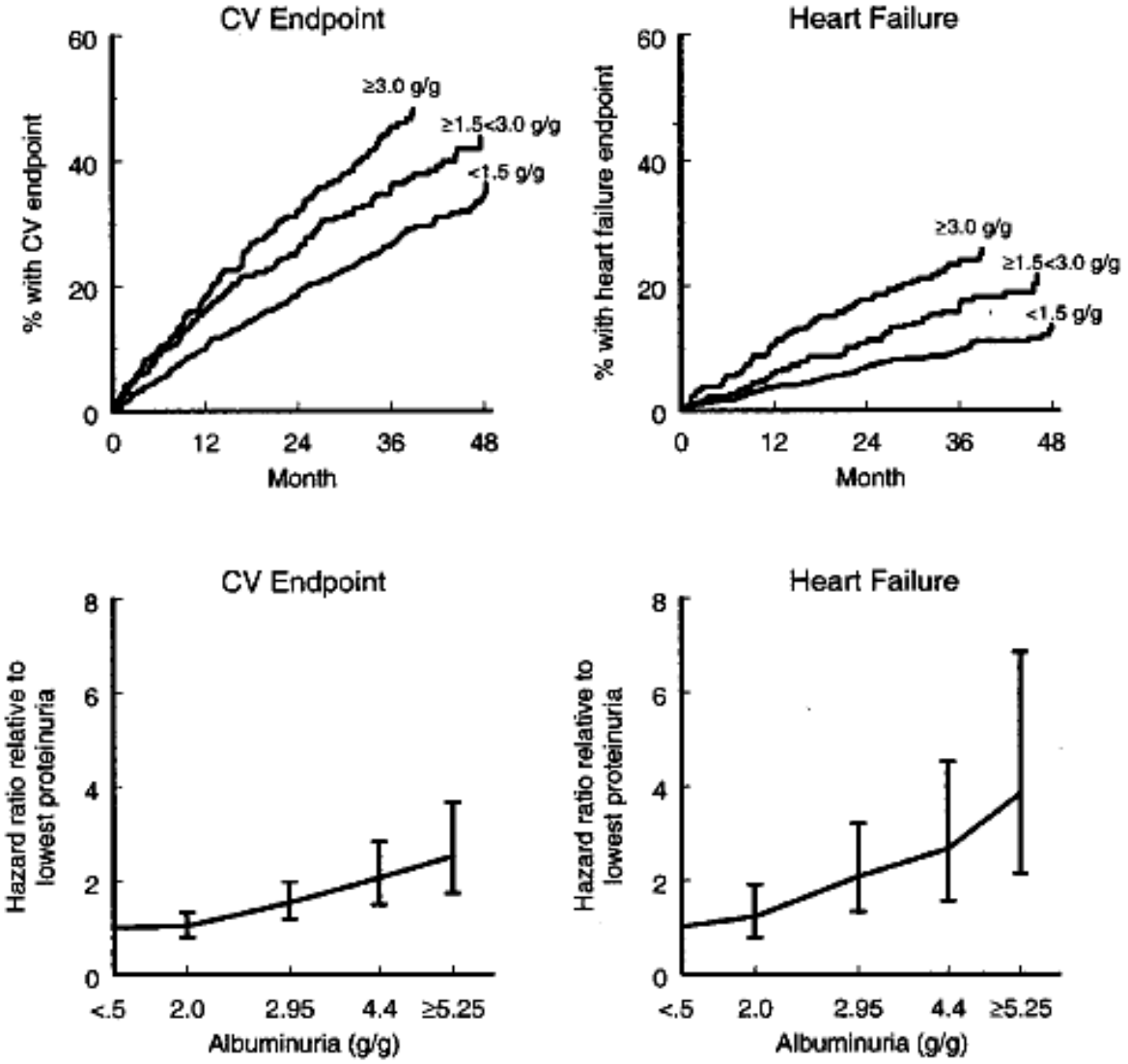
Behaviour modification and intensive pharmacological therapy
(targeting hyperglycemia, hypertension, dyslipidemia and microalbuminuria)
[Steno 2 study]

	Baseline		**End of intervention** *(7.8 years)*	
	intensified	***control***	***intensified***	***control***
Albuminuria *(mg/24h)*	**78** *32-265*	**69** *32-282*	**46** *4-5593*	**126** *3-4778*
S-creatinine *(µmol/L)*	**78** *±17*	**76** *±16*	**102** *±32*	**111** *±85*

Gaede, New Engl.J.Med.(2008) 338:580

Albuminuria and cardiovascular endpoints in type 2 diabetic patients with nephropathy

RENAAL study



de Zeeuw, Circulation (2004) 110: 921

Effects of intensive glucose lowering in type 2 diabetes

(Action to control Cardiovascular Risk in Diabetes Study Group)

10,251 patients age 62.2 years

baseline median $HbA1_c$ 8.1%

intensive R_x with < **6%** $HbA1_c$ vs. standard R_x **7-7.9**% with HbA1c > 6%

primary outcome : nonfatal MI; nonfatal stroke; CV death

⇨ 352 patients in the intensive and 371 in the standard group

nonsignificant difference (p=0.16)

death : 257 in the intensive group and 203 in standard group

significant hazard ratio 0.90 (95% HR 1,22; CI 1.91-1.46; p=0.04)

hypoglycemia or weight gain >10 kg

⇨ *more frequent in intensively treated group (p<0.001)*

Gerstein N.Engl.J.Med.(2008) 358:2545

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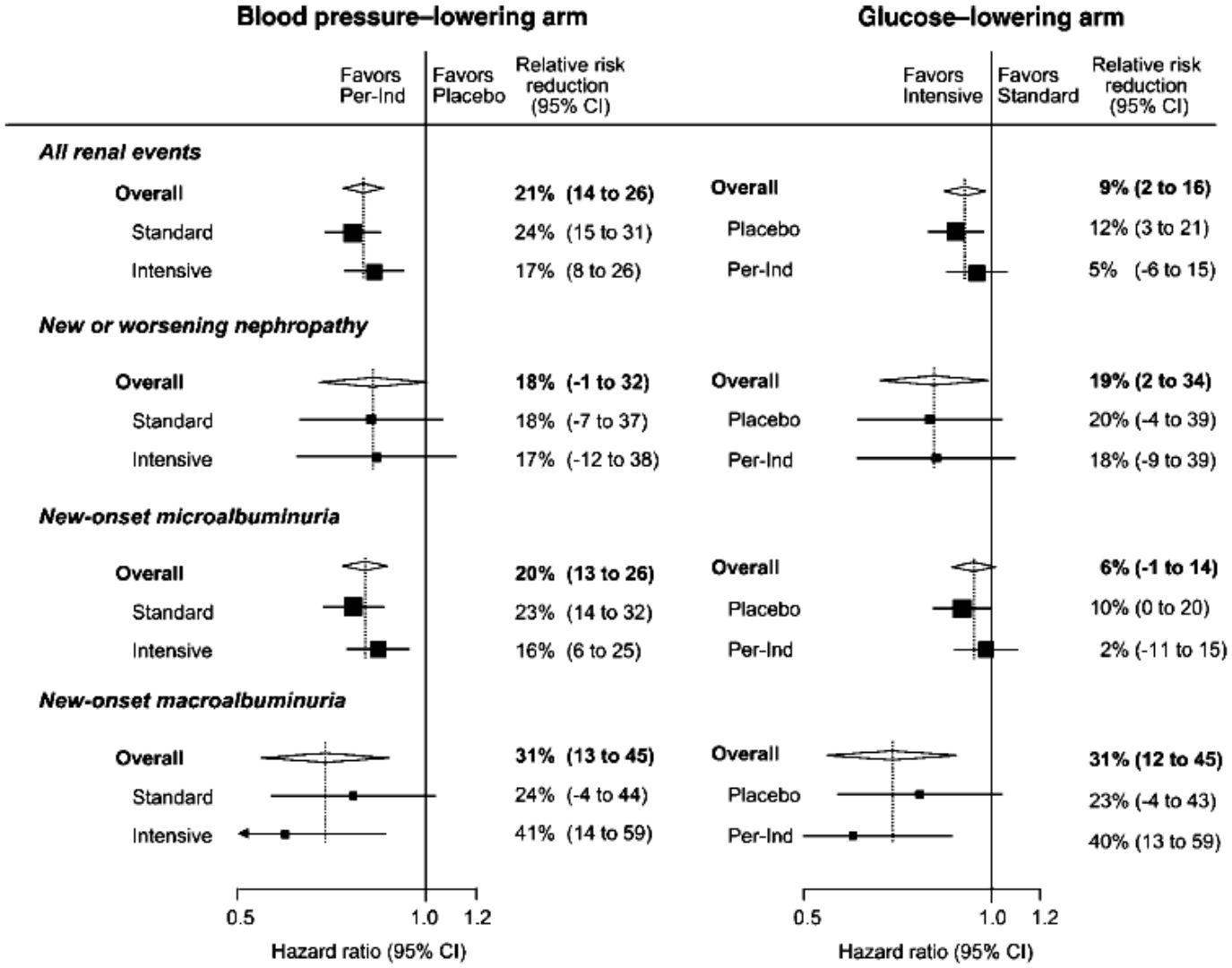

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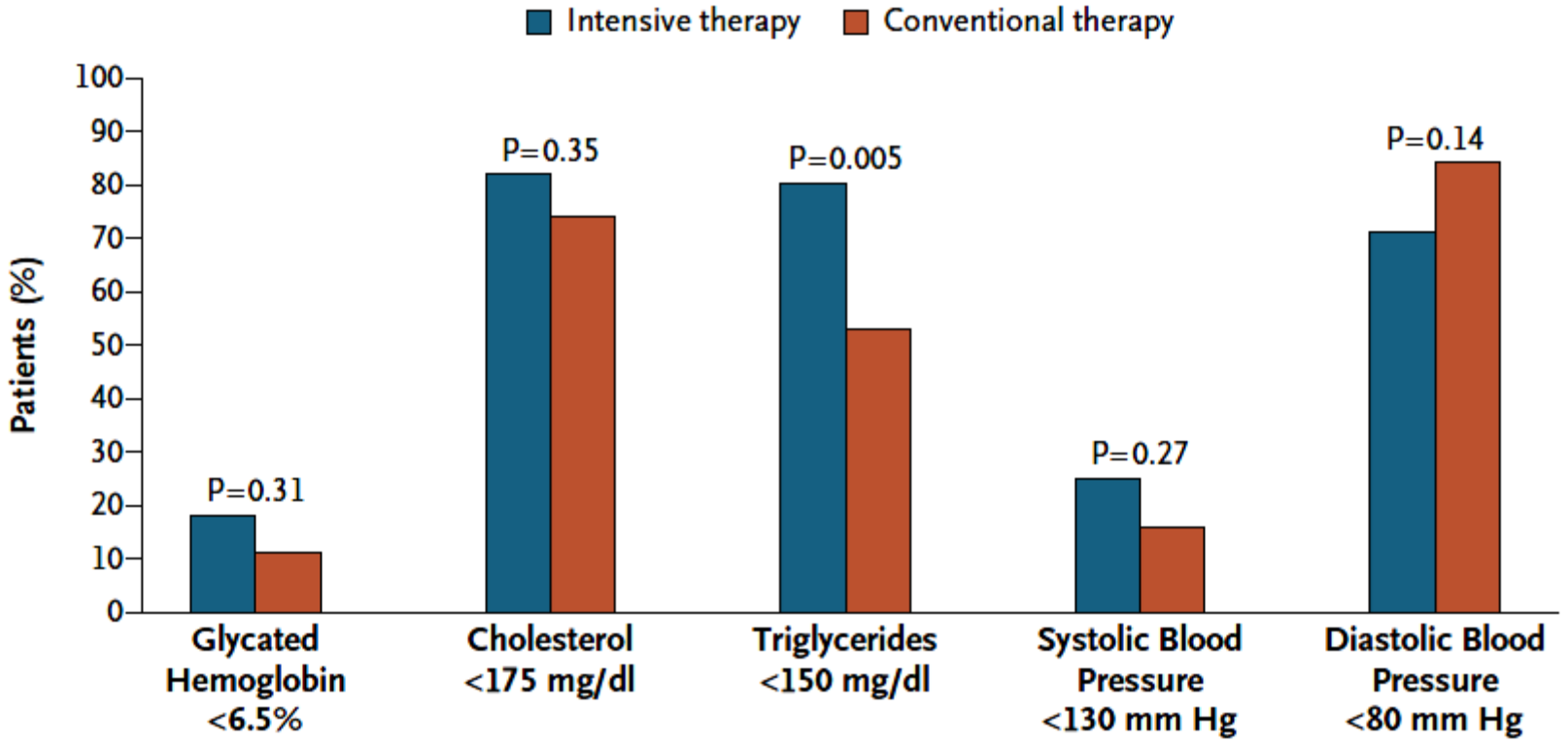


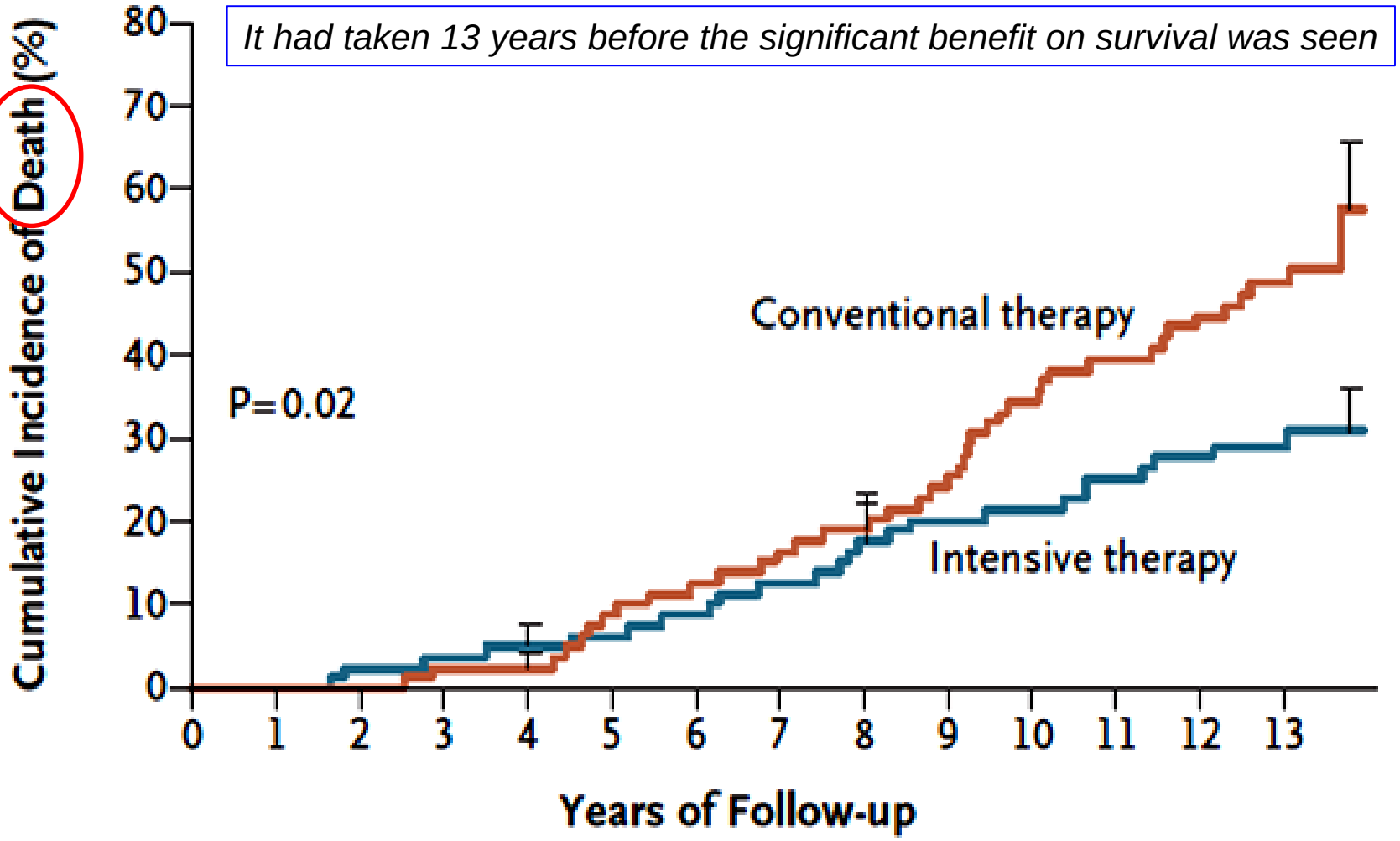
Gaede, New Engl.J.Med.(2008) 338:580

Behaviour modification and intensive pharmacological therapy

(targeting hyperglycemia, hypertension, dyslipidemia and microalbuminuria)

[Steno 2 study]

It had taken 13 years before the significant benefit on survival was seen



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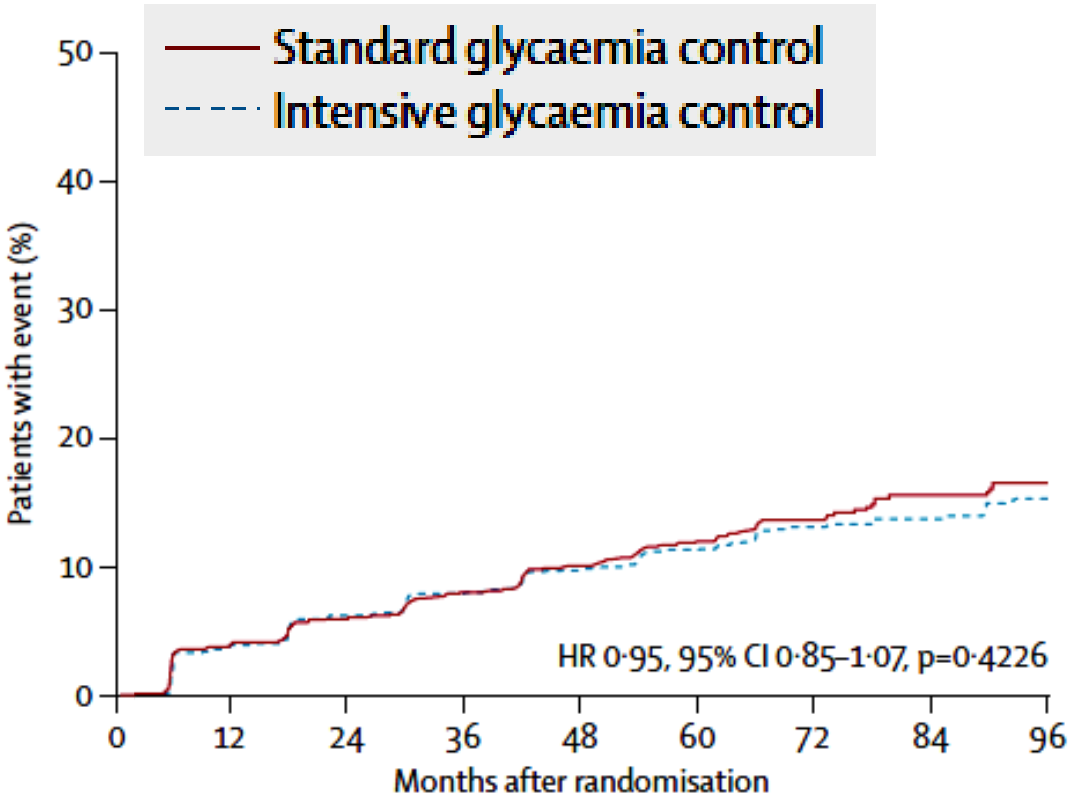

Ismail-Beigi, Lancet (2010) 376:419