

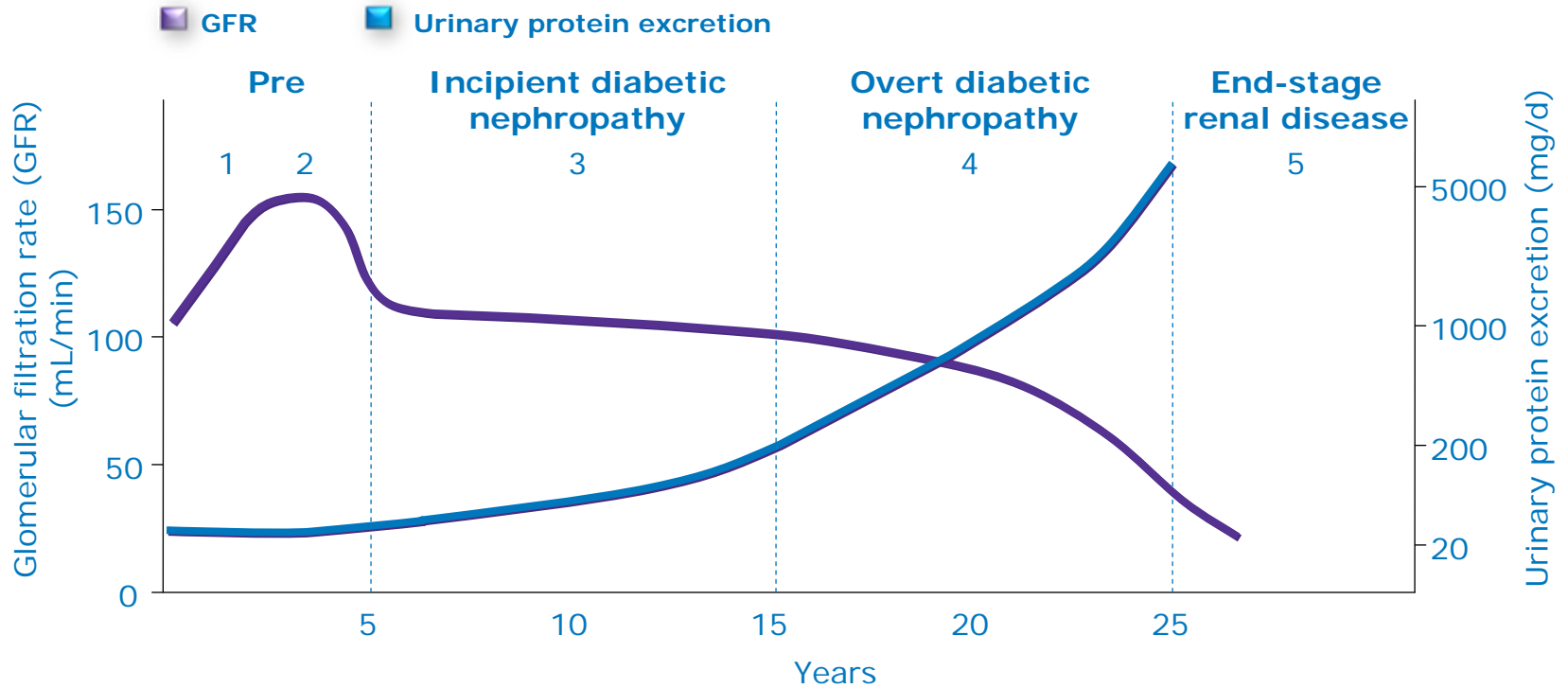
# Do we still think there is evidence for RAAS blockade?

**KDIGO Controversies Conference Diabetic Kidney Disease  
New Delhi 2012**

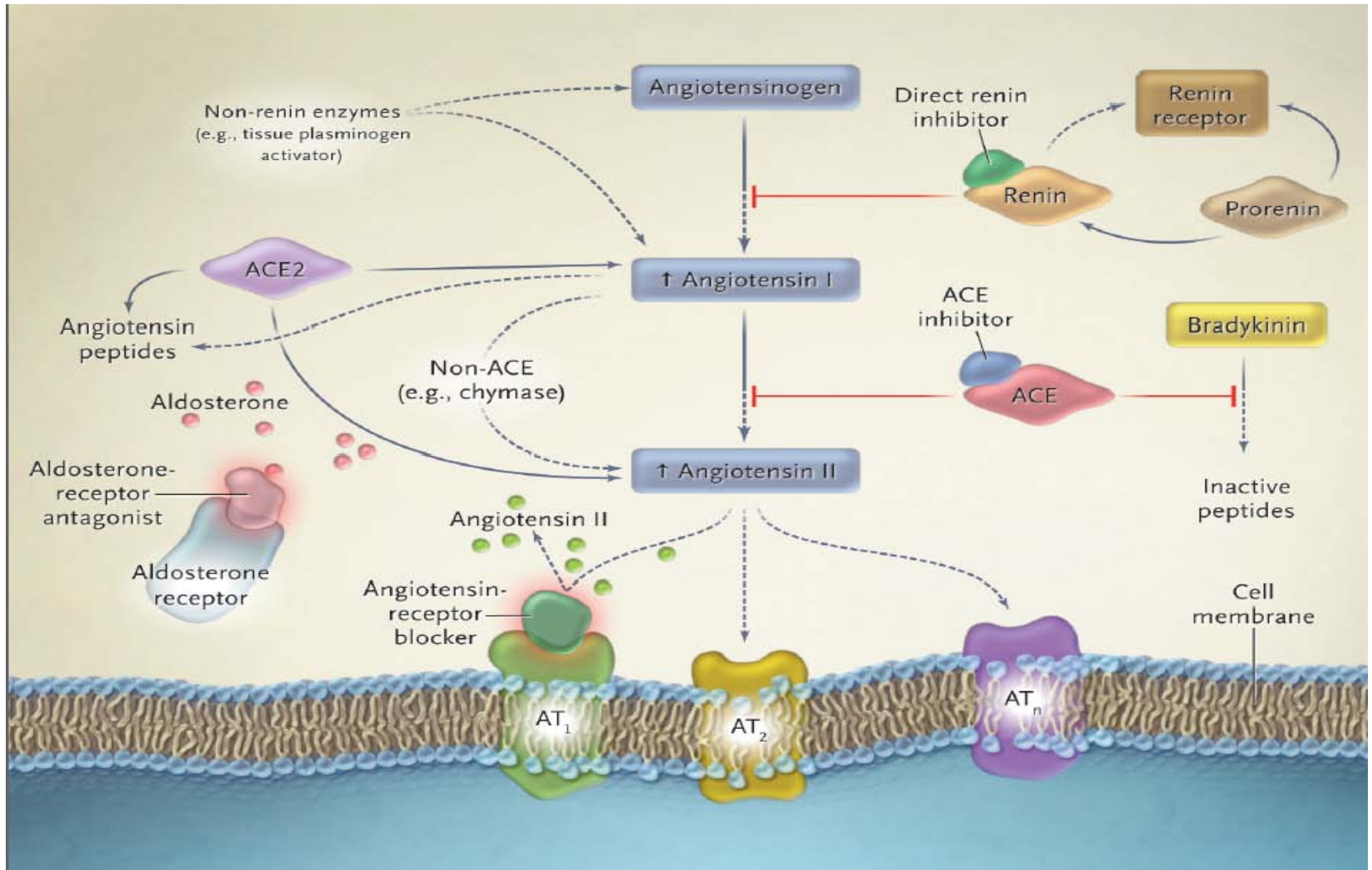
Peter Rossing MD DMSc  
Steno Diabetes Center



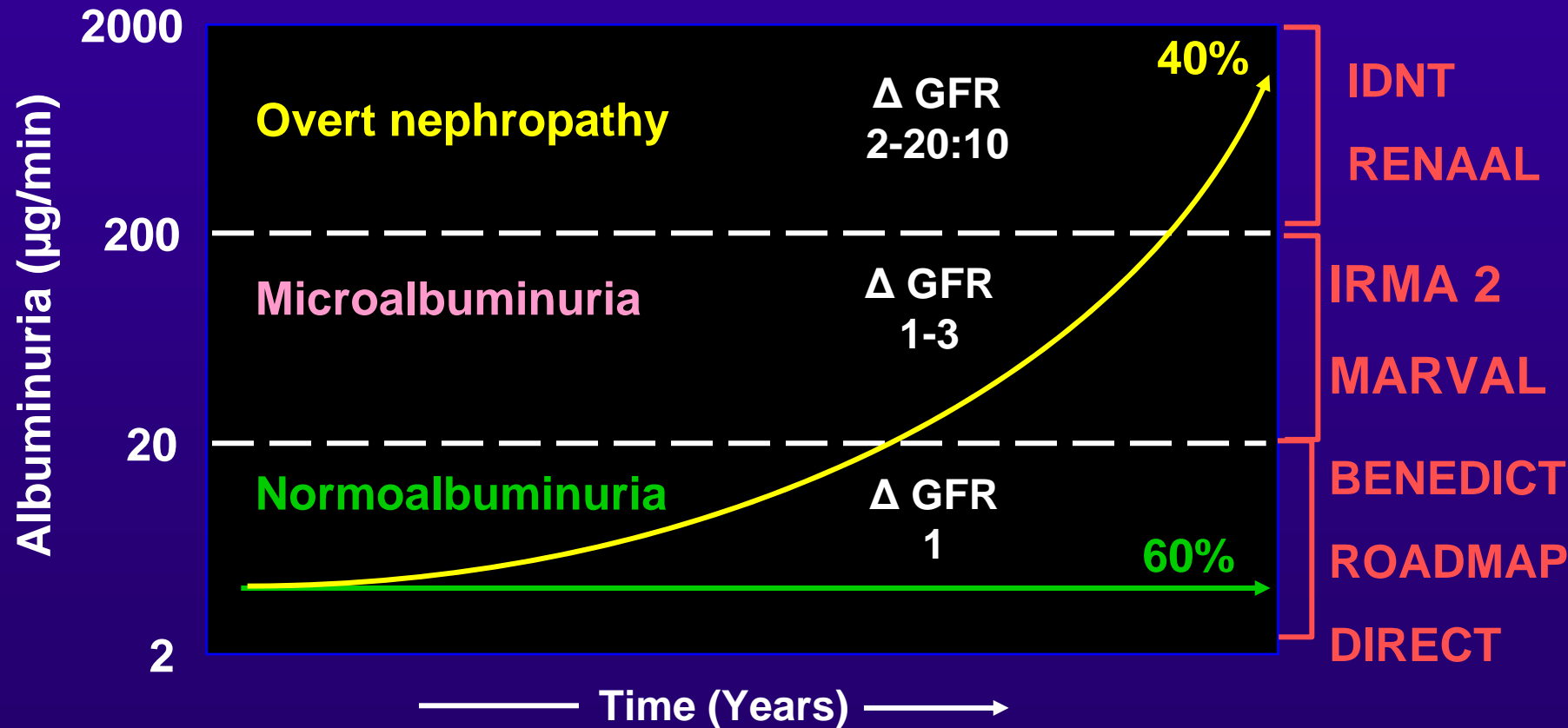
# Natural history of diabetic nephropathy

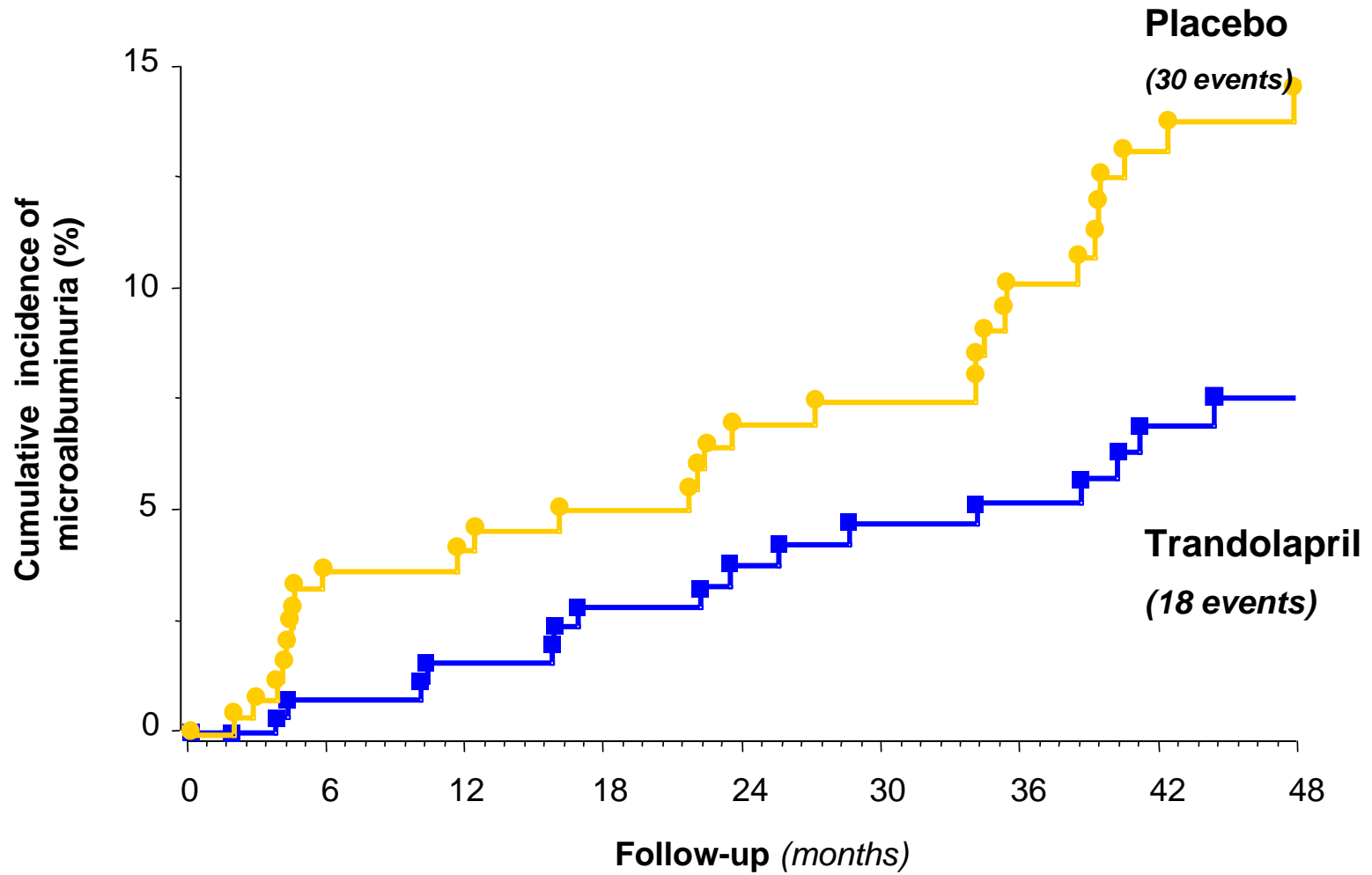


Functional	<b>GFR - (90-95%)</b>	<b>Microalbuminuria, hypertension</b>	<b>Proteinuria, nephrotic syndrome, GFR<sup>-</sup></b>
Structural	<b>Renal hypertrophy</b>	<b>Mesangial expansion, glomerular basement membrane thickening, arteriolar hyalinosis</b>	<b>Mesangial nodules (Kimmelstiel-Wilson lesions) Tubular-interstitial fibrosis</b>



# Progression of Diabetic Renal Disease in Patients with Type 2 Diabetes

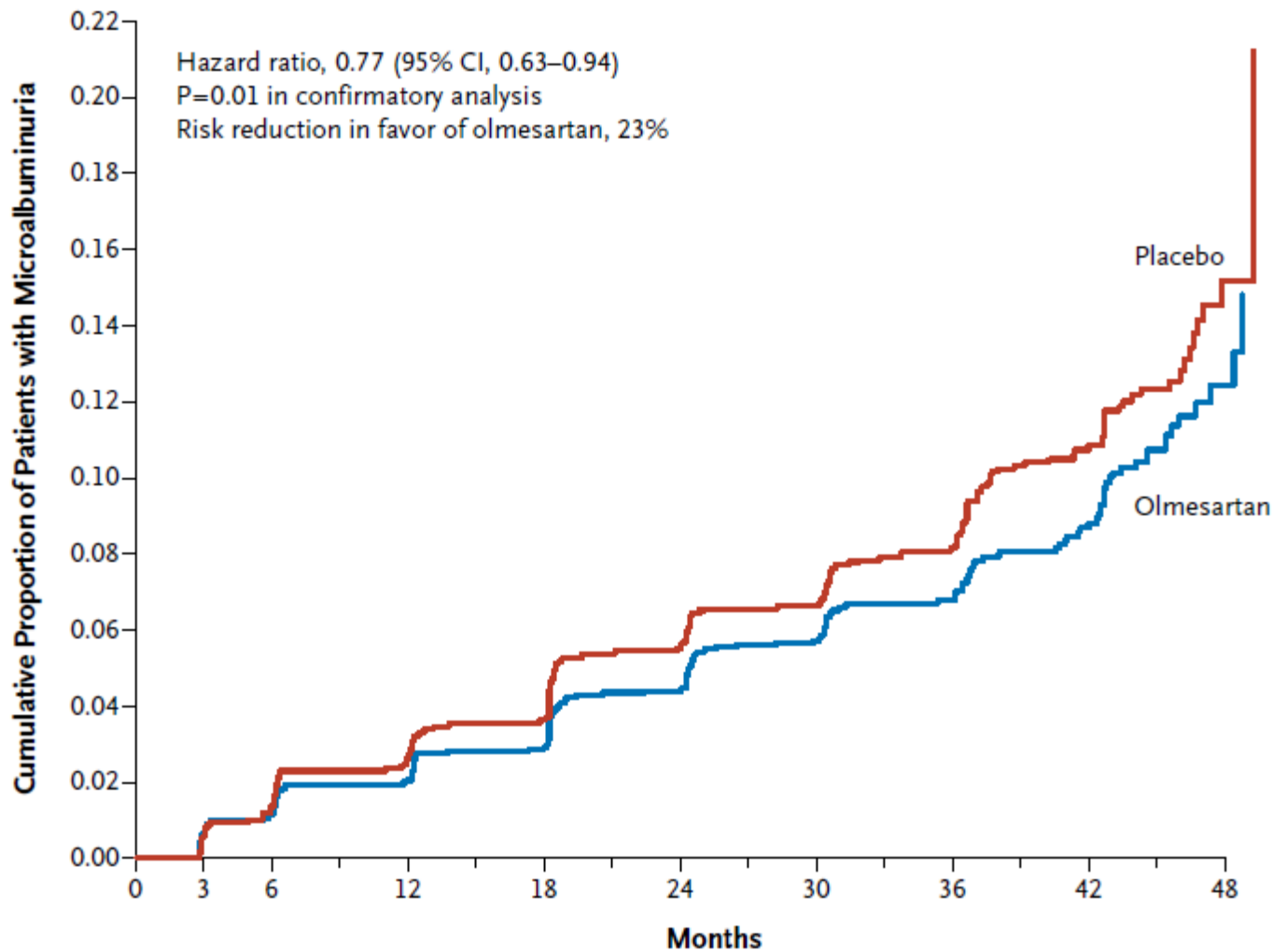




**No. at Risk**

Trandolapril	301	254	237	224	207	198	188	149	104
Placebo	300	229	214	203	187	176	164	136	89

# Occurrence of Microalbuminuria during the 48-Month Follow-up Period



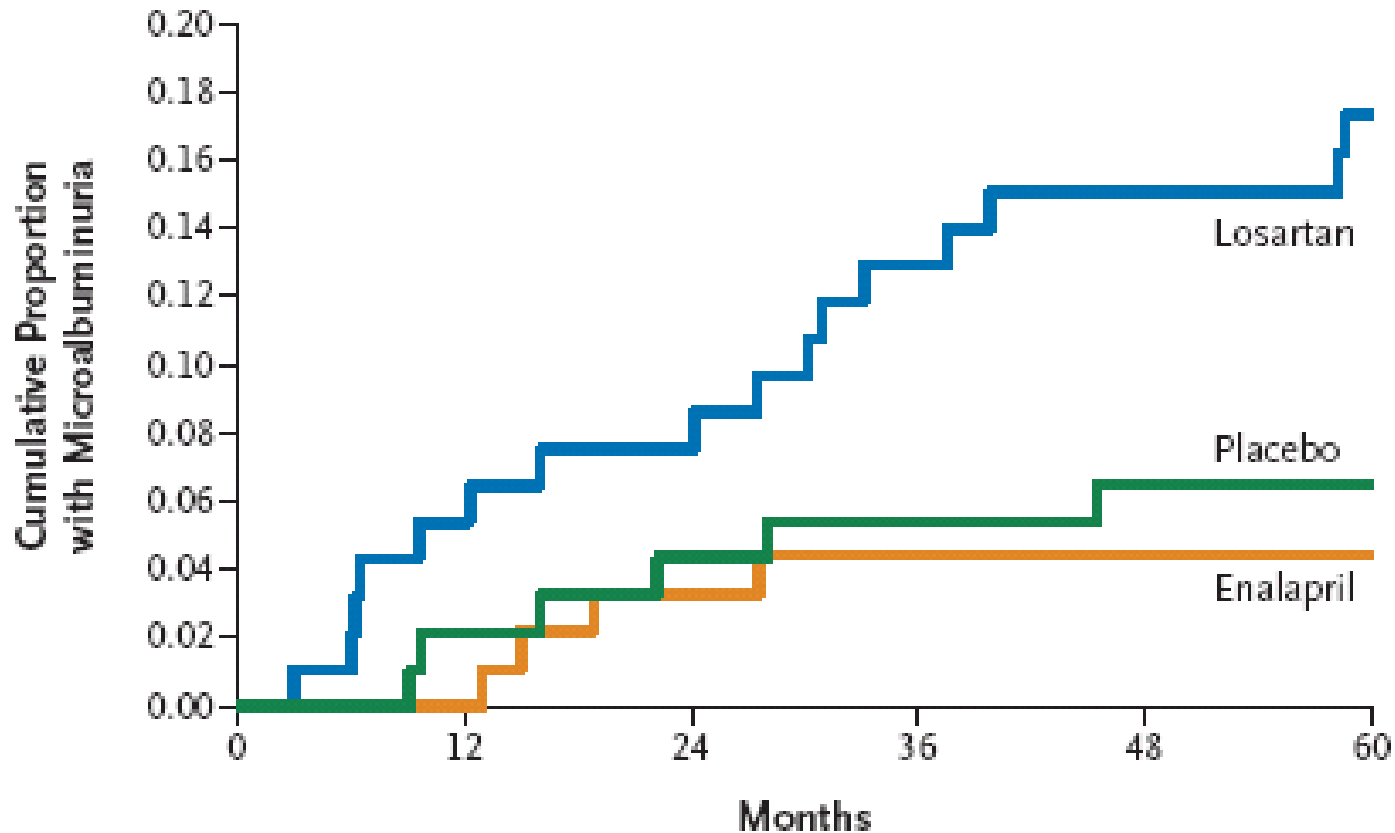
**No. at Risk**

Olmesartan	2160	2097	2025	1923	1833	1727	1629	1325	754	67
Placebo	2139	2076	2004	1887	1787	1685	1592	1308	699	49

# RAS study, normotensive normoalbuminuric Type 1 (n=285) Structural endpoint

End Point	Enalapril	Losartan	Placebo
Mesangial fractional volume			
Mean at baseline	0.201±0.044	0.189±0.041	0.187±0.045
Mean change at 5 yr	0.005±0.050	0.026±0.054	0.016±0.048
Change vs. placebo			
Mean difference	-0.011	0.010	0 (reference)
P value	0.16	0.17	
Adjusted change vs. placebo			
Mean difference	-0.006	0.008	0 (reference)
P value	0.38	0.26	

# RAS study, normotensive normoalbuminuric Type 1 (n=285)

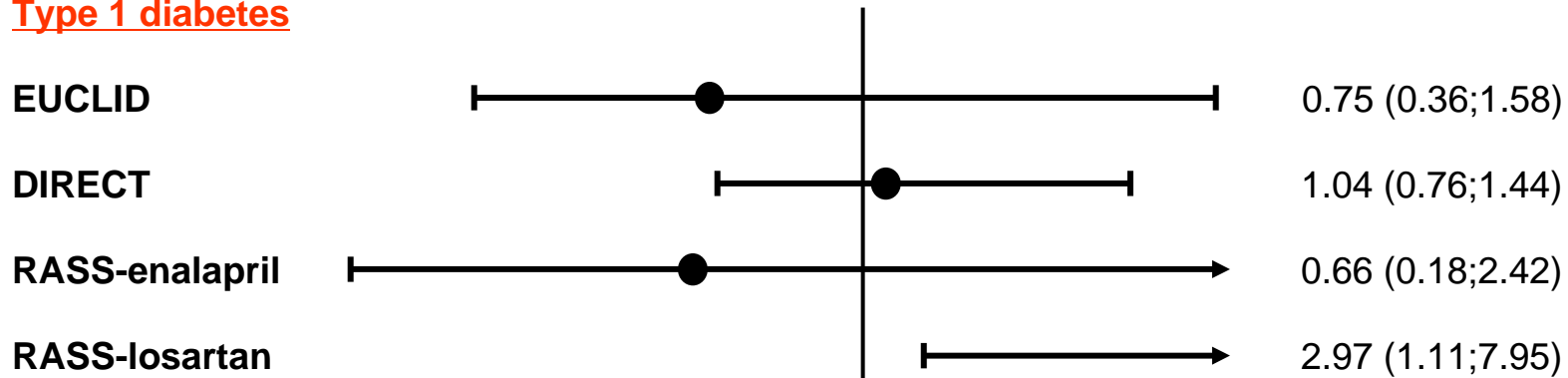


**Figure 2.** Kaplan–Meier Estimates of Time to Microalbuminuria.

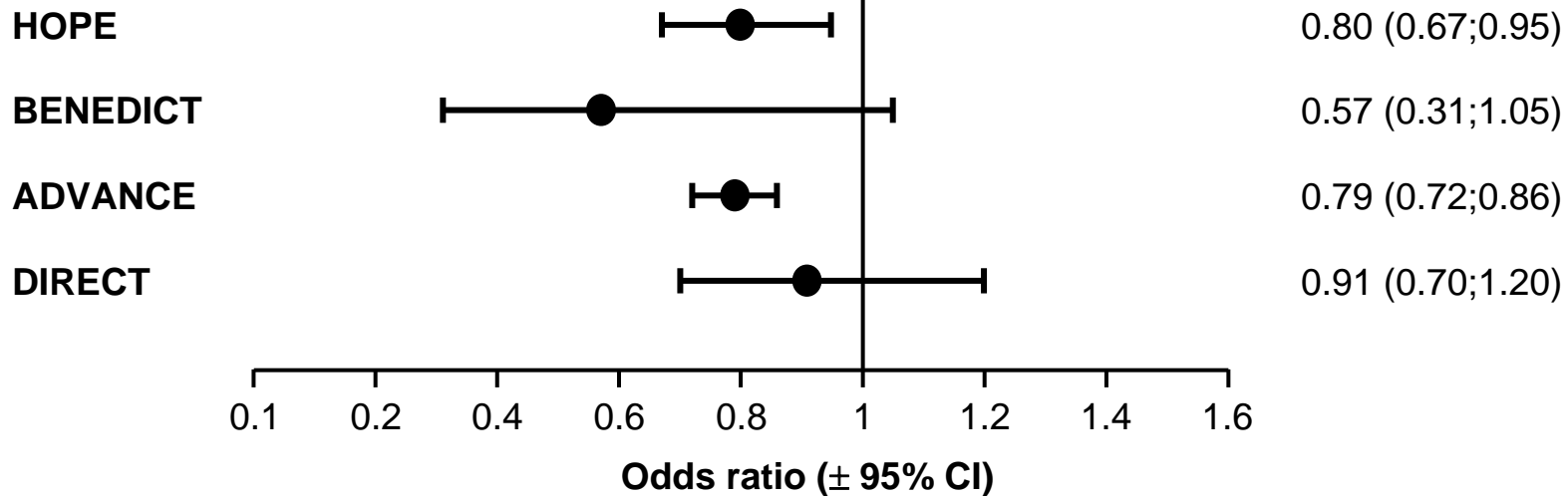


# ODDS RATIO FOR DEVELOPMENT OF MICROALBUMINURIA WITH RAS BLOCKADE

## Type 1 diabetes



## Type 2 diabetes

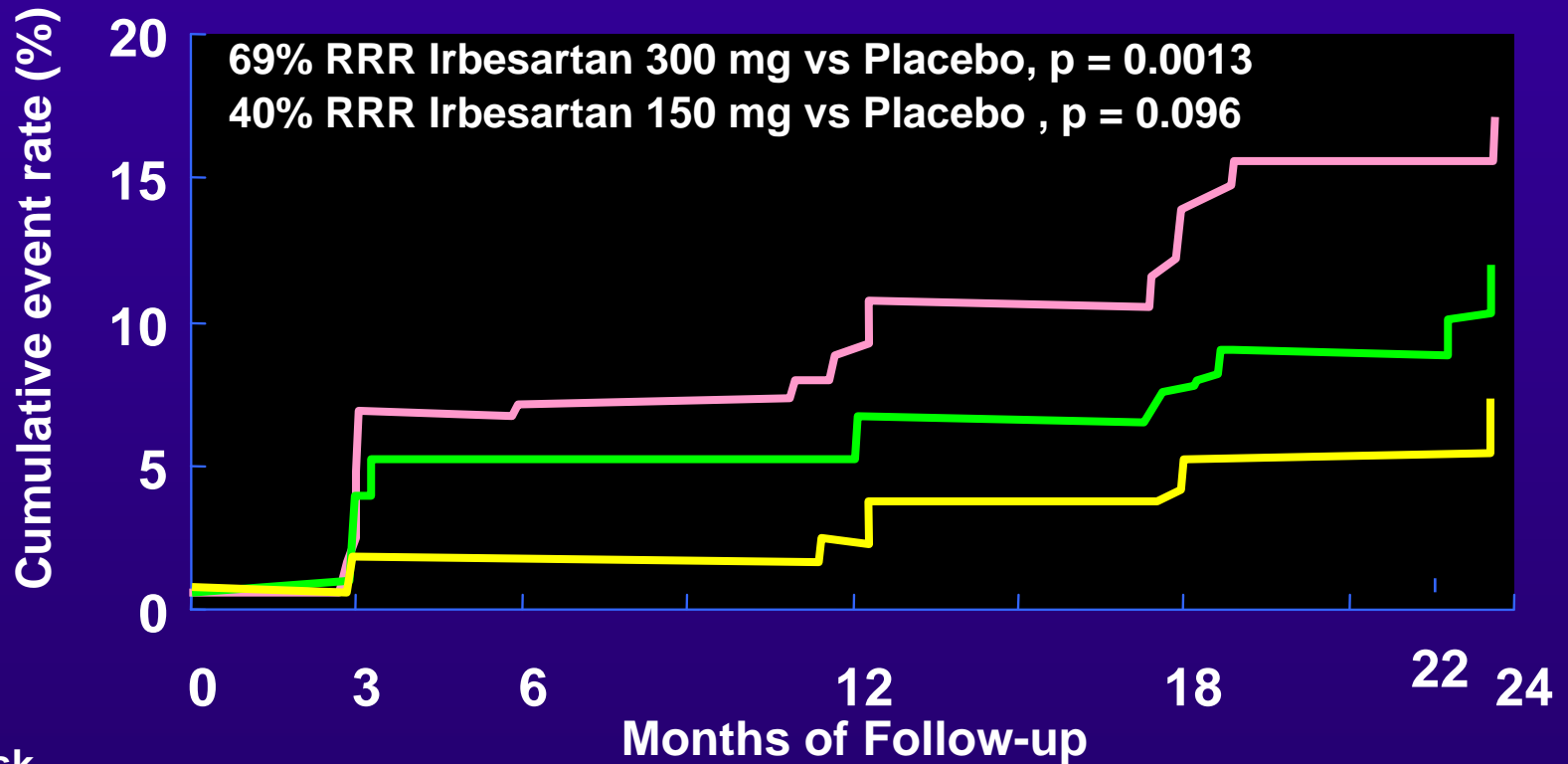


# Should all type 1 diabetic microalbuminuric patients receive ACE inhibitors? A meta regression analysis (n=698)

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- 62% reduction in progression to nephropathy
- Regression to normoalbuminuria was 3 times greater
- 50% reduction in urinary albumin excretion at 2 years
- Preservation of GFR

# IRMA 2: Primary Endpoint – Time to Development of Overt Nephropathy



No. at Risk

Placebo	172	172	142	136	122	114	31
Irbesartan 150 mg	160	160	144	139	125	120	39
Irbesartan 300 mg	162	162	152	147	139	130	40

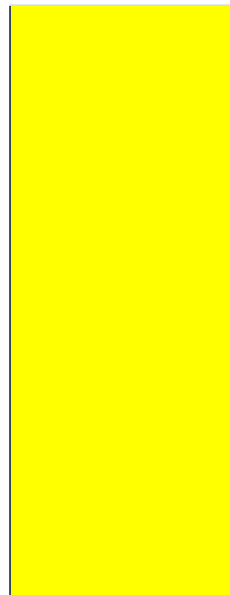
# EARLY INTERVENTION

Response to spironolactone 25 mg  
21 type 1 diabetic patients with microalbuminuria

## Albuminuria

Baseline: 90 (61-121)mg/d

Relative change (%)



**-60%**  
**(-21 to -80) %**

## 24hour Blood Pressure

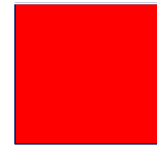
SBP

135 (3)

DBP

65 (2) mm Hg

Change (mm Hg)

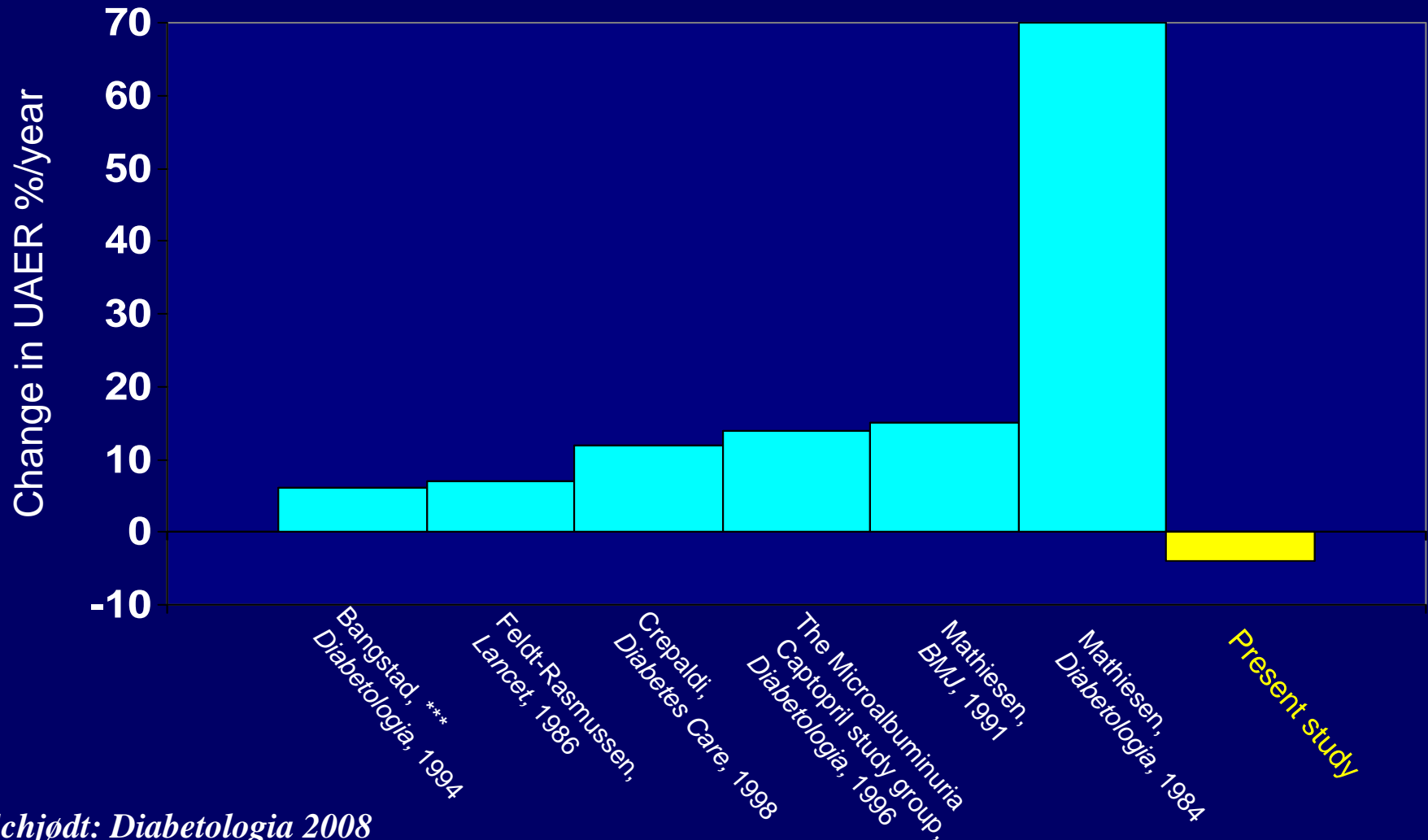


**-3**  
**(-8 to 3)**  
**mm Hg**

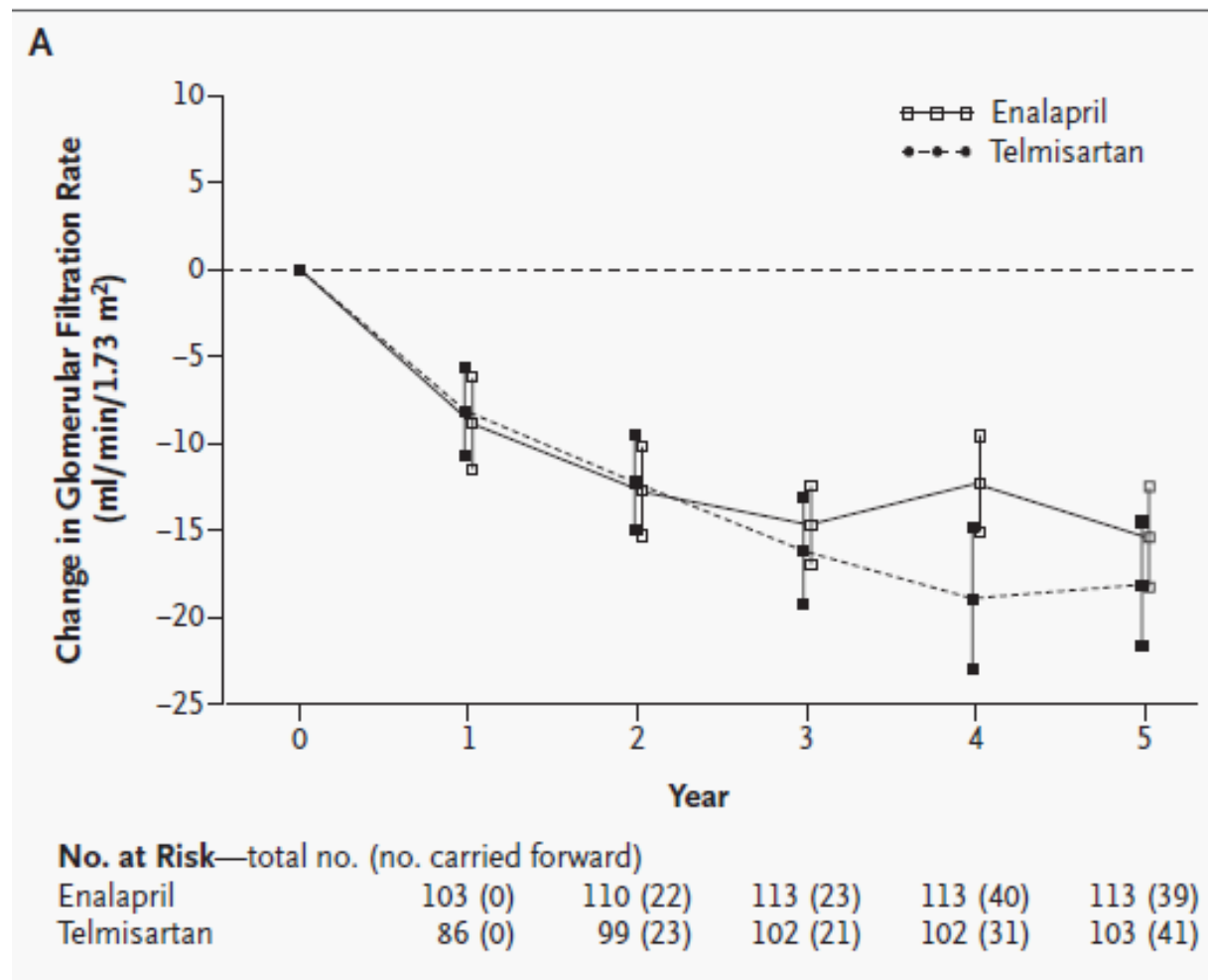
**0**  
**(-3 to 3)**  
**mm Hg**

# Progression in microalbuminuria in type 1 diabetic patients without AHT

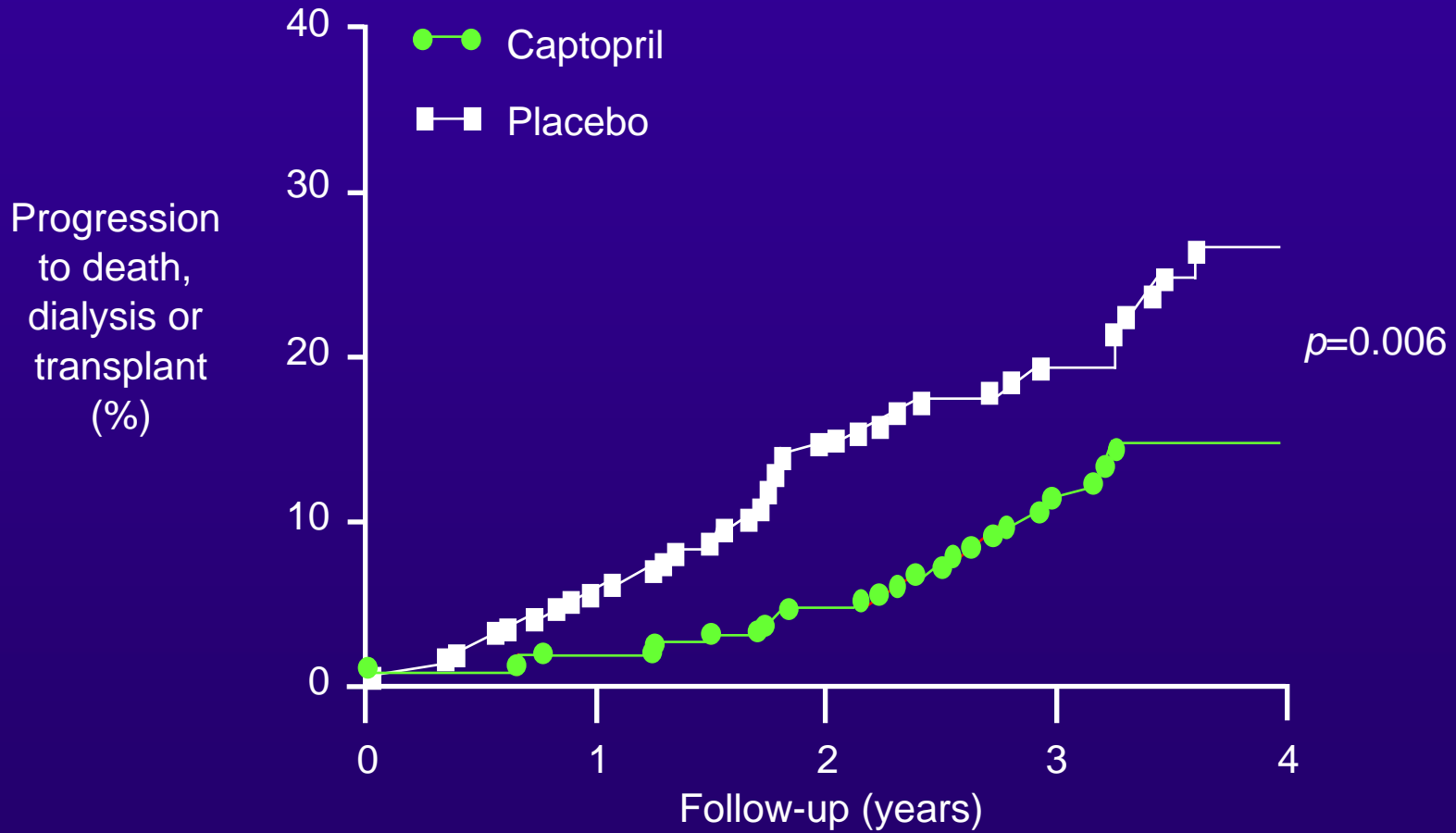
Microalbuminuria defined as UAER 20-200  $\mu\text{g}/\text{min}$  or 30-300  $\text{mg}/24\text{-h}$  except in \*\*\* (15-200  $\mu\text{g}/\text{min}$ )



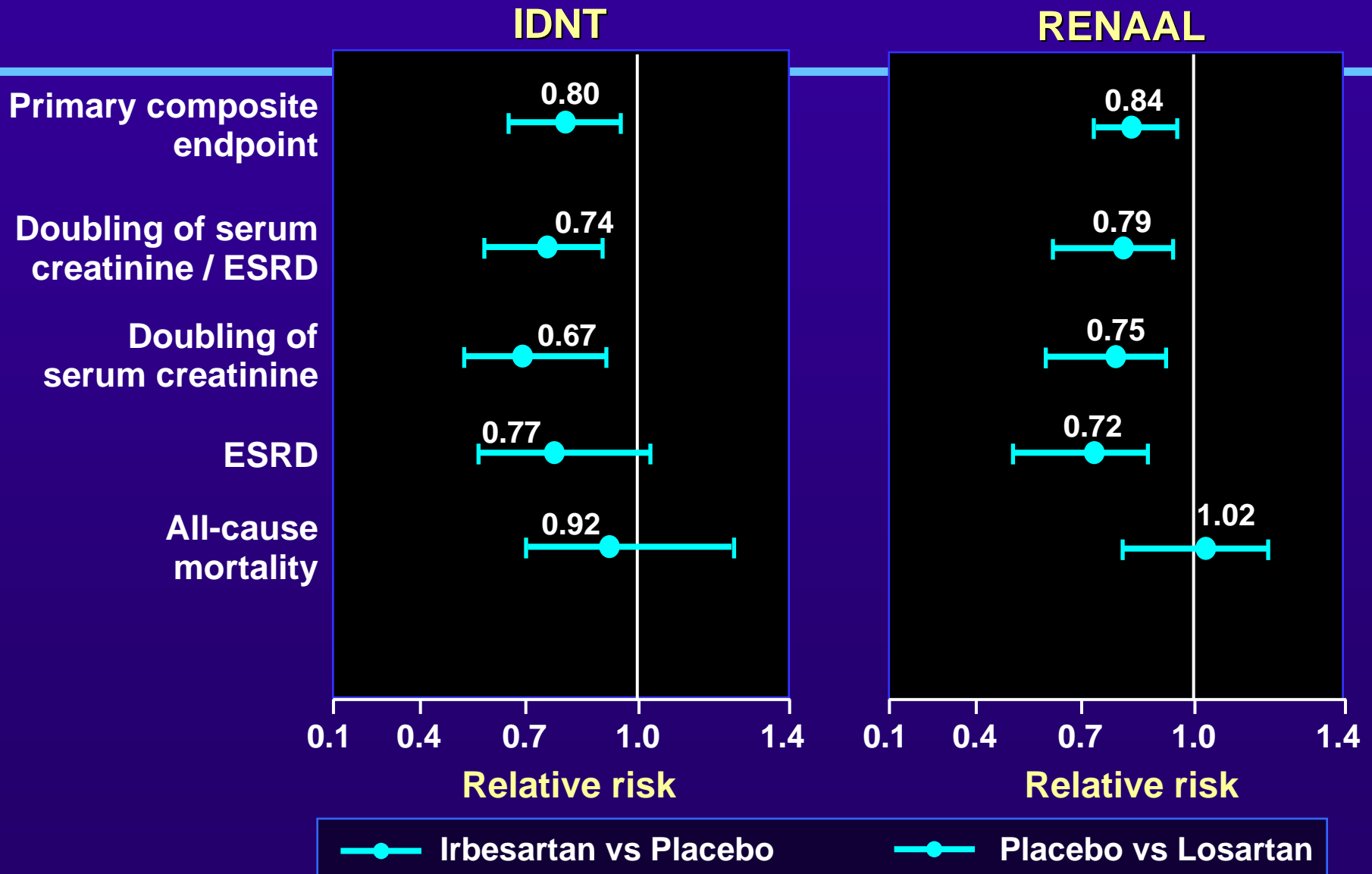
# DETAIL study: ACEi vs ARB



# Effect of ACE inhibition on diabetic nephropathy in patients with Type 1 diabetes

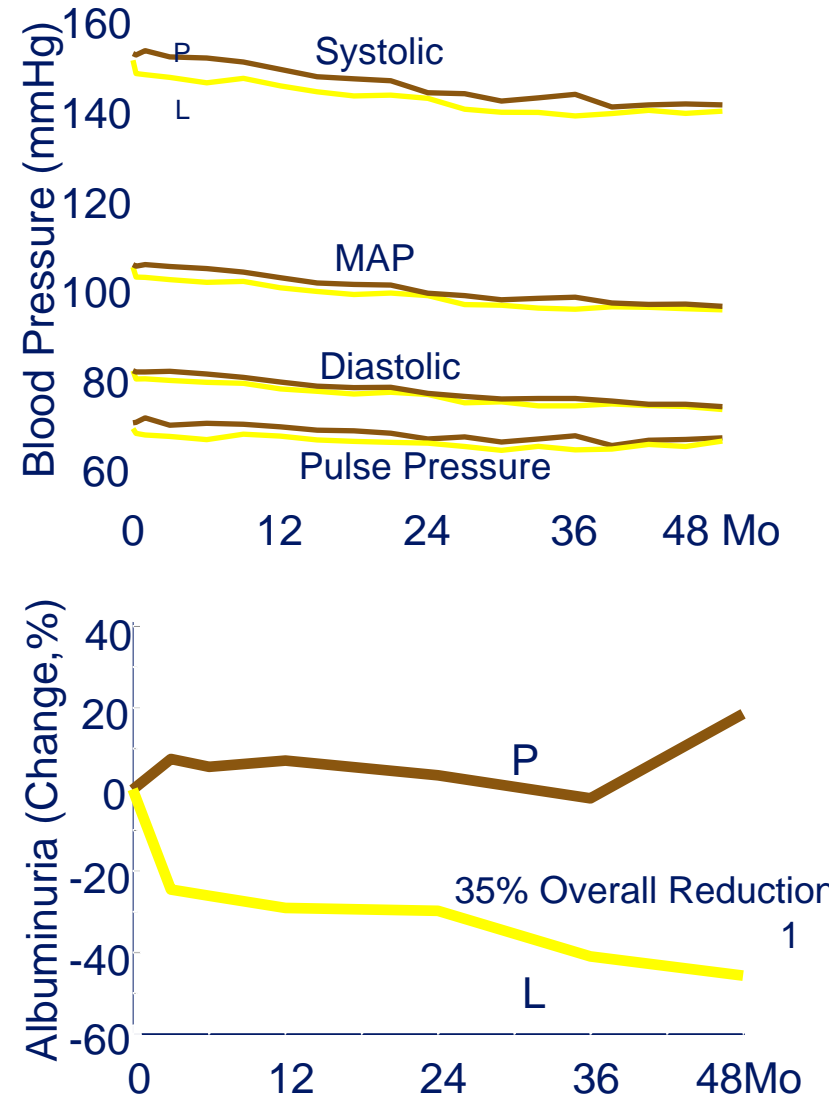
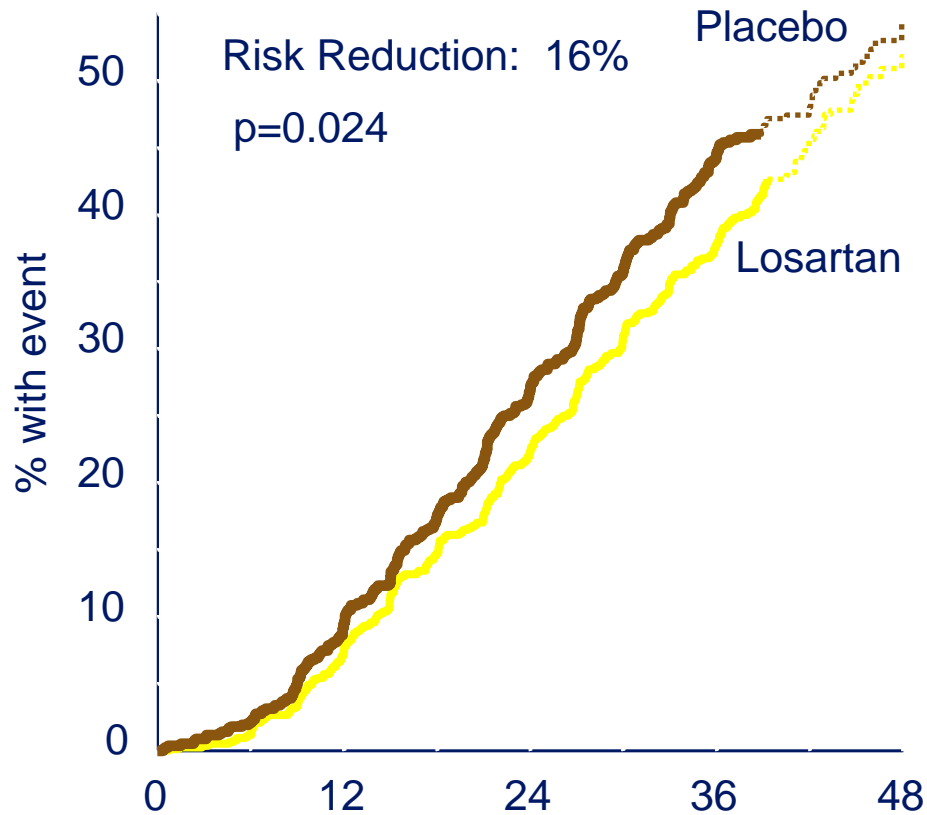


# Comparison of Clinical Studies in Overt Type 2 Diabetic Nephropathy

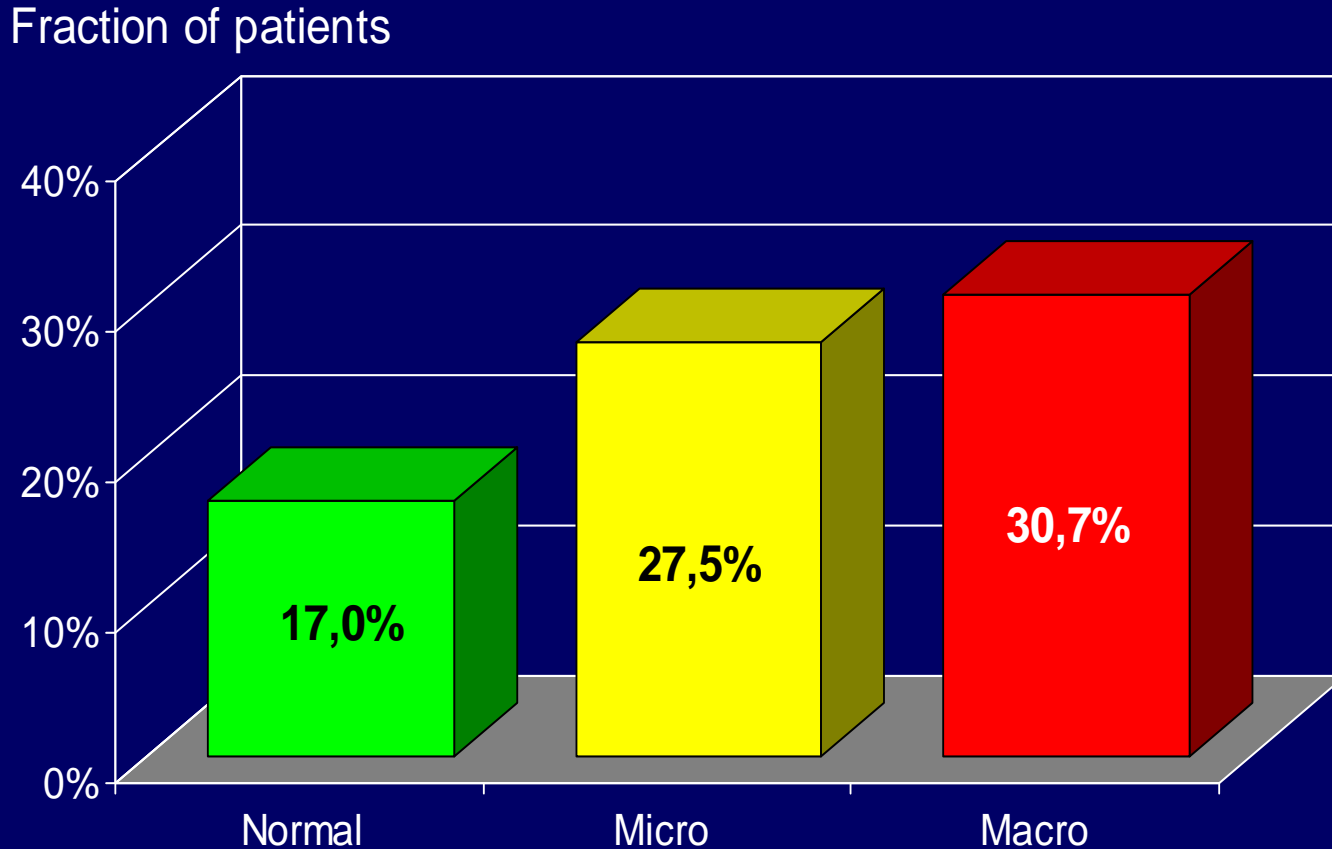




# RENAAL; Losartan more renoprotective than placebo in type 2 diabetes; similar blood pressure, different albuminuria



*What should we do in the normoalbuminuric patients?  
CKD in DEMAND eGFR<60 ml/min/1.73m<sup>2</sup>*



**NKF GFR stage 3 or worse**

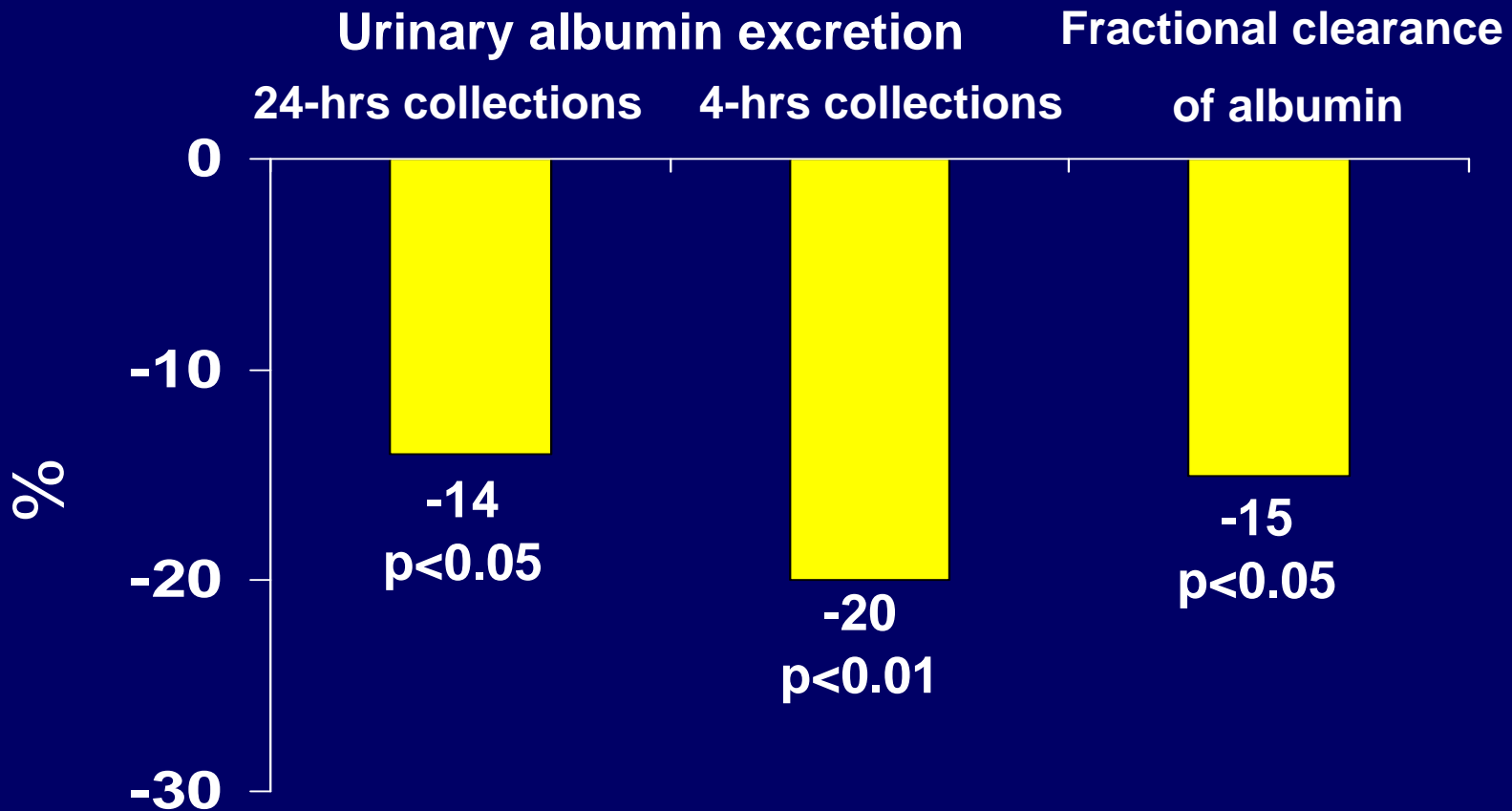
*DEMAND*

# New Renoprotective Treatment Modalities

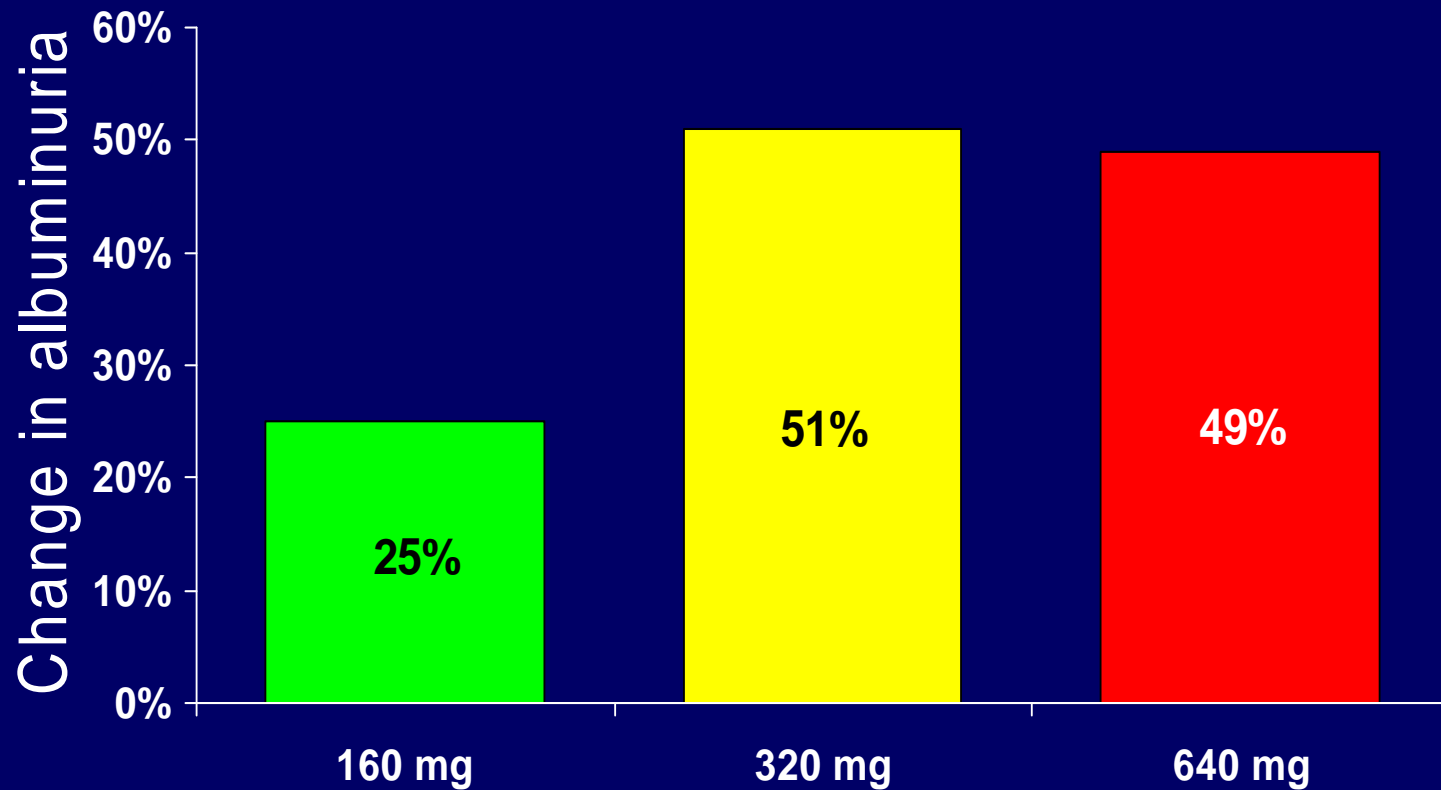
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- Dual RAS blockade
  - High dose RAS blockade
  - Aldosterone blockade
  - Renin inhibition
-

# *Additional effects of irbesartan 900 mg vs. 300 mg*



# *DROP (n=391)*



Valsartan

*Hollenberg et al J Hypertension 2007*

# CV risk factor reduction with dual RAAS blockade in diabetic nephropathy

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Δ	BP (mmHg)	8/5	P < 0.01
Δ	Albuminuria (%)	25-43	P < 0.01
Δ	LDL-cholesterol (mmol/l)	0.3	P = 0.01

## Side effects

Δ	P-potassium (mmol/l)	0.3
Δ	Hb (mmol/l)	0.3
Δ	GFR	reversible

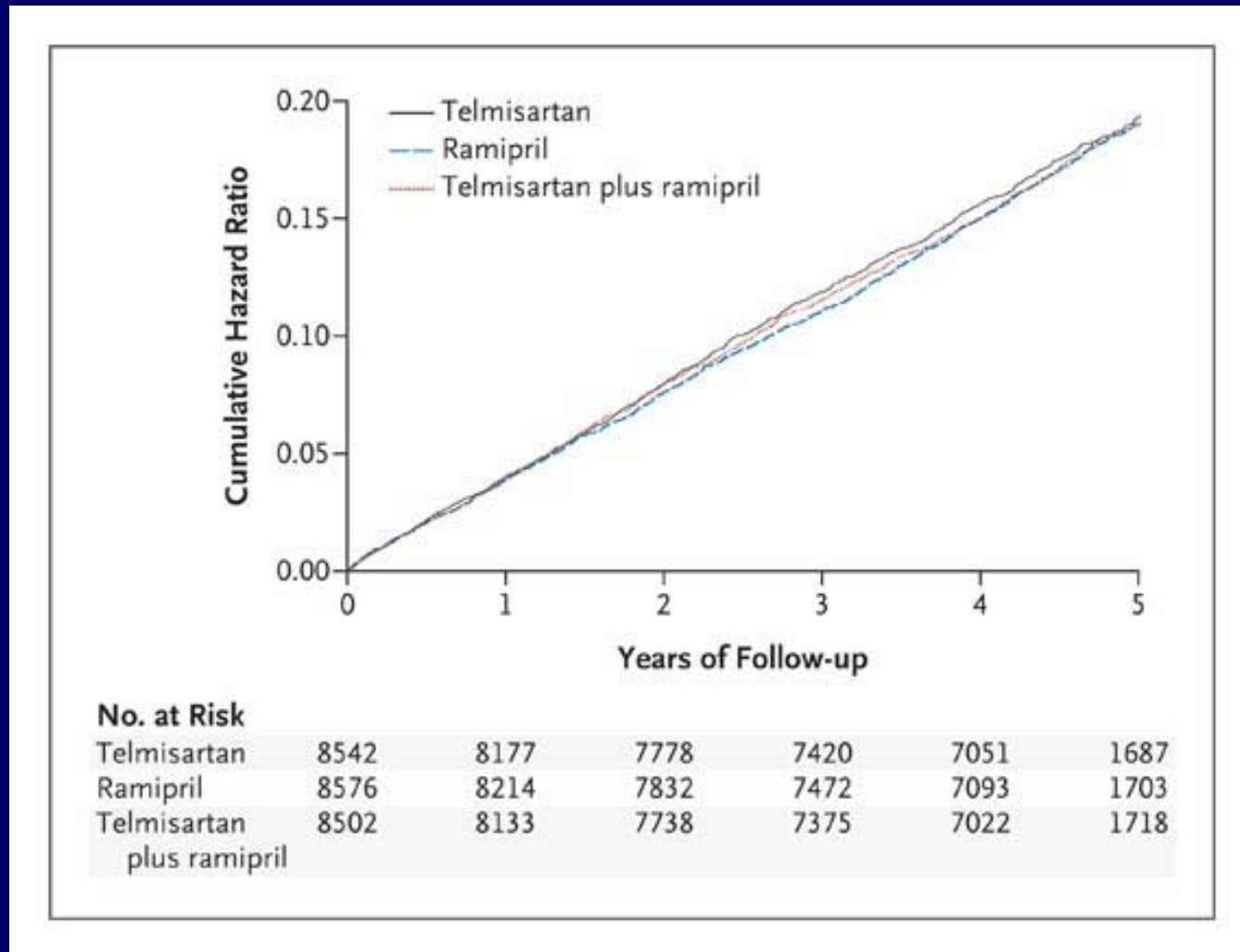
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Jacobsen et al. NDT 2002;17:1019-1024

Jacobsen et al. JASN 2003;14:992-959

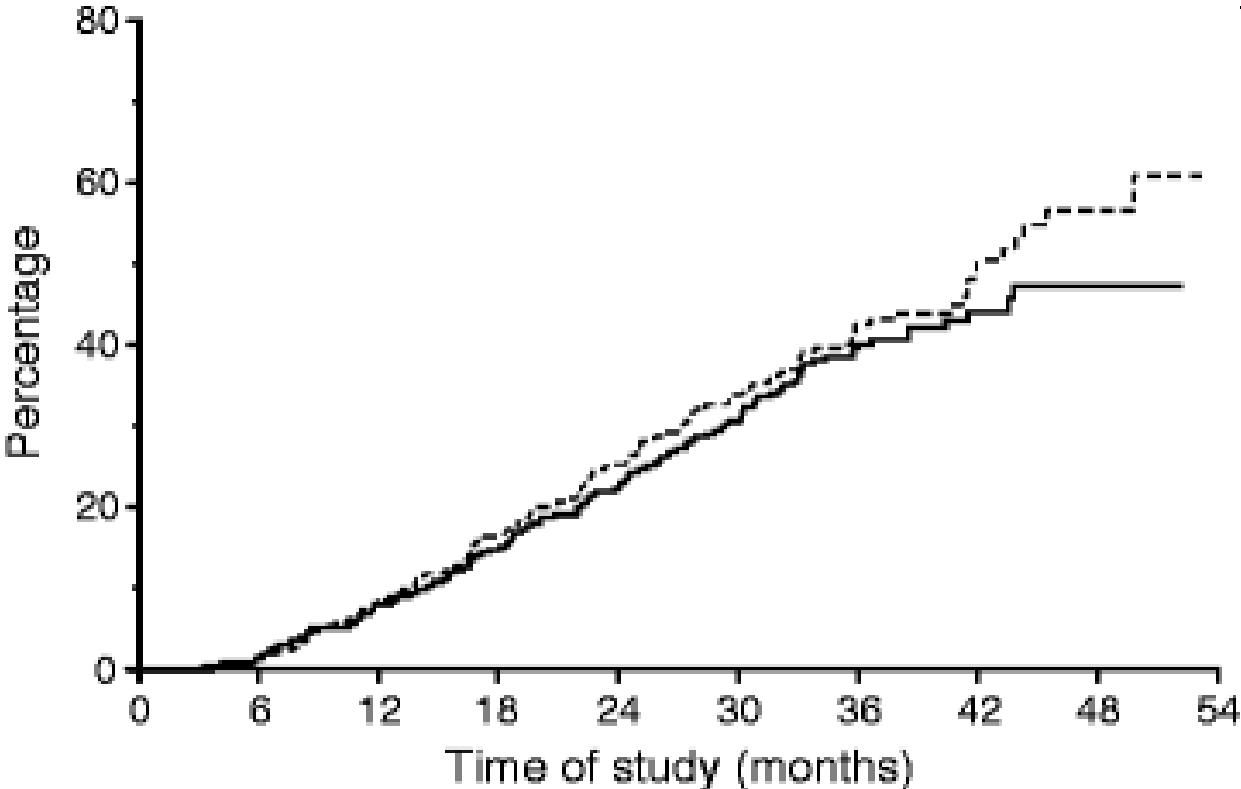
Jacobsen et al. Kidney International 2003;65:1874-1880

## Kaplan-Meier Curves for the Primary Outcome in the Three Study Groups



The ONTARGET Investigators. N Engl J Med 2008;10.1056/NEJMoa0801317

Time to primary composite renal endpoint in type 2 diabetic patients with overt proteinuria and renal insufficiency. Solid line, olmesartan; dashed line, placebo



No. at risk	0	6	12	18	24	30	36	42	48	54
Olmesartan	282	278	259	238	217	184	107	44	17	0
Placebo	284	279	259	236	211	176	102	41	17	0

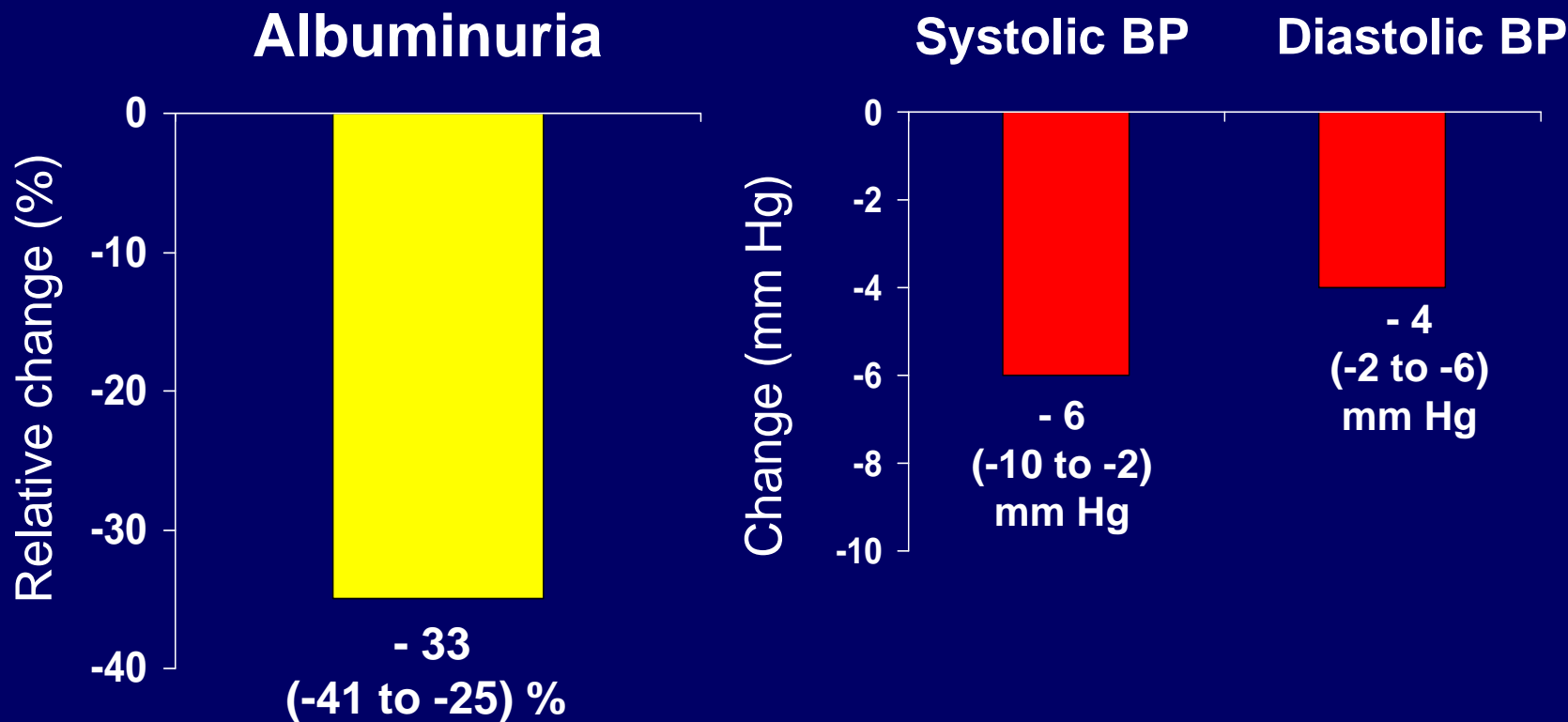


# Response to spironolactone 25 mg

20 type 2 diabetic patients with nephropathy treated with maximally recommended doses of ACE-I and/or ARB

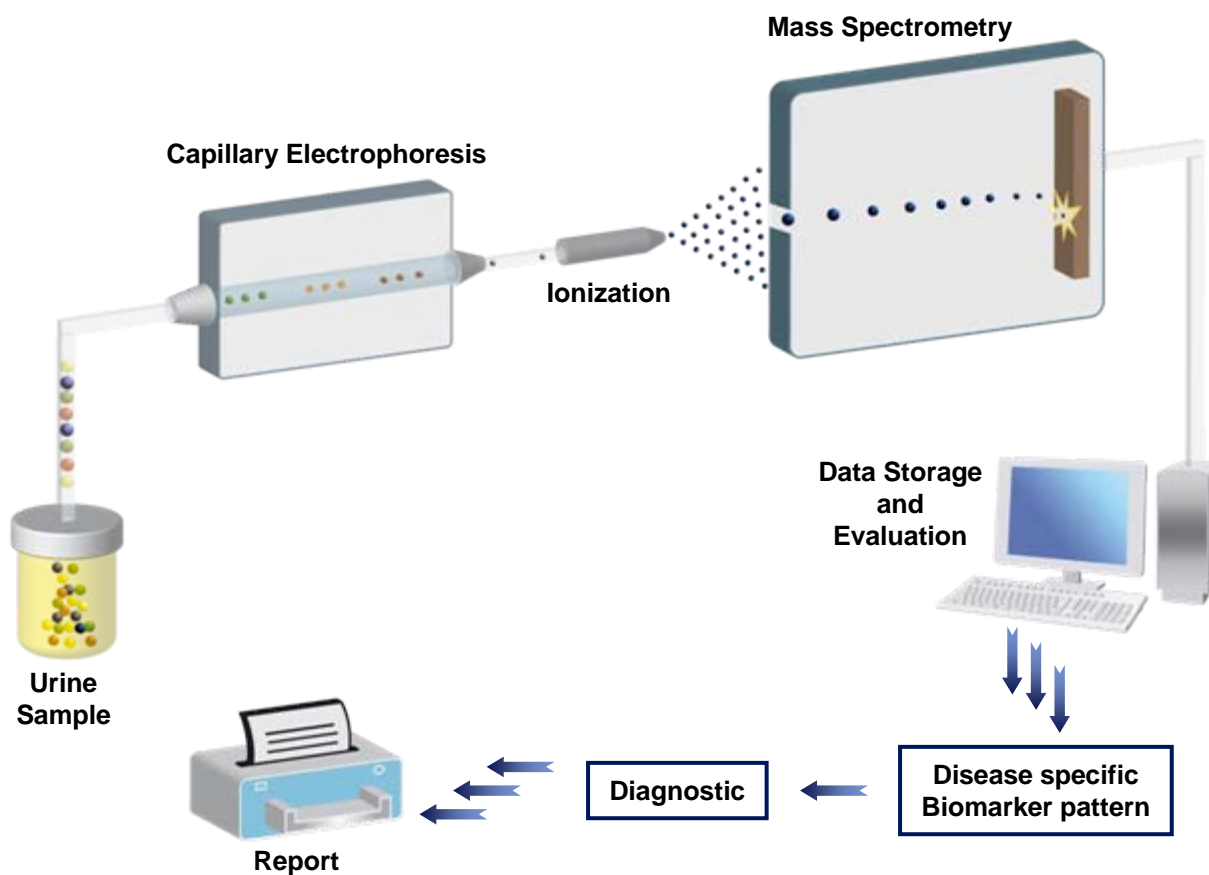
ACE-I/ARB: 1566 (655 to 7762) mg/d

24-hrs BP 138 (3) mm Hg / 71 (2) mm Hg



# Urinary Proteomics Technology platform: CE/MS Technologie

## Capillary Electrophoresis coupled to Mass Spectrometry



Separation and analysis of proteins and peptides (>1,000)

Run time ~60 min

### CE

- fast
- robust
- inexpensive
- reproducible

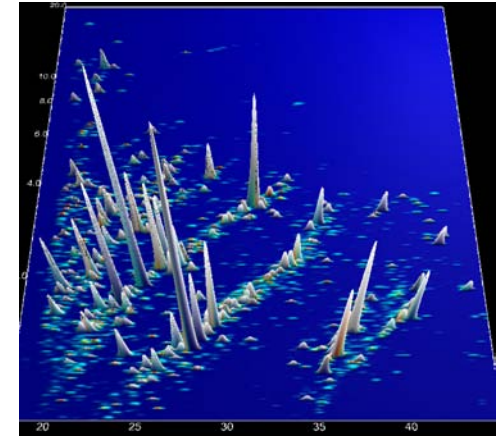
### MS

- resolution
- scan speed

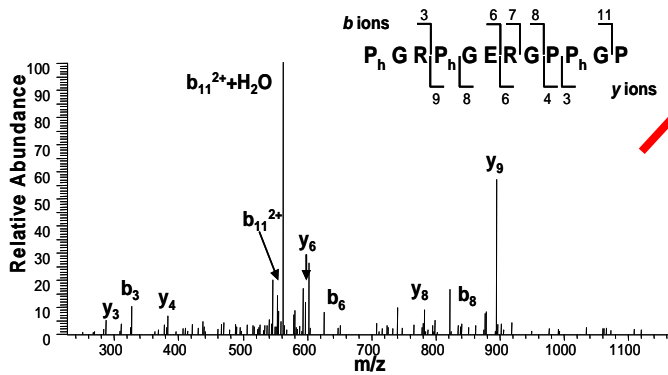
Age
Gender
Urinary albumin/creatinine
Cholesterol (mmol/l)
Creatinine (micromol/l)

Clinical data  
Patients history

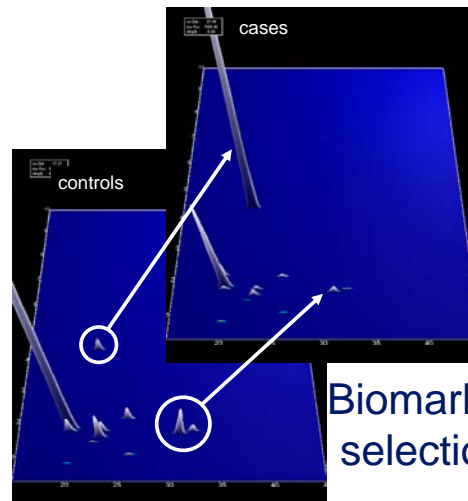
Database



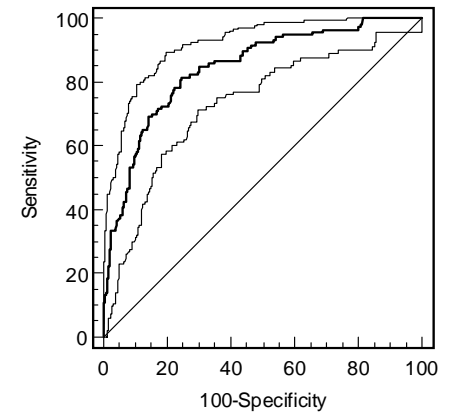
CE-MS peptidome  
profile



Sequence  
information



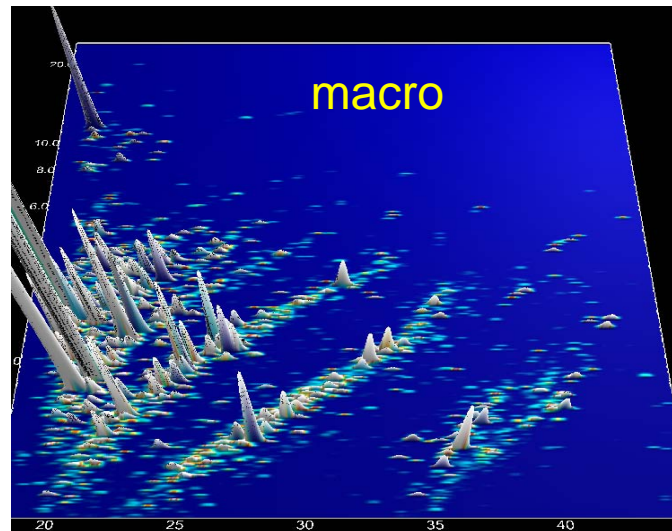
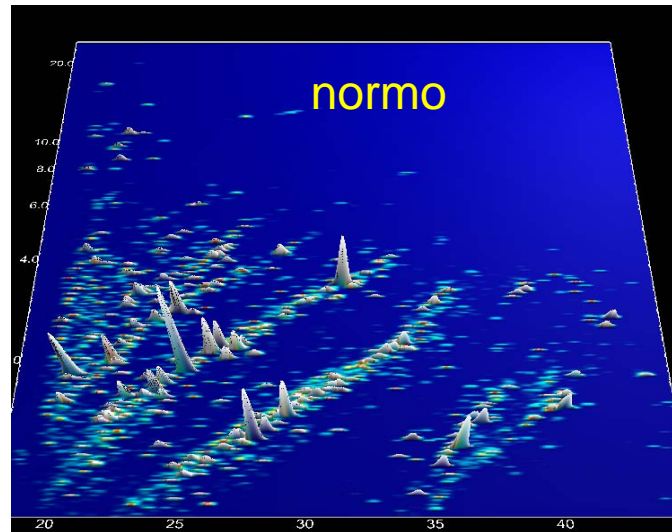
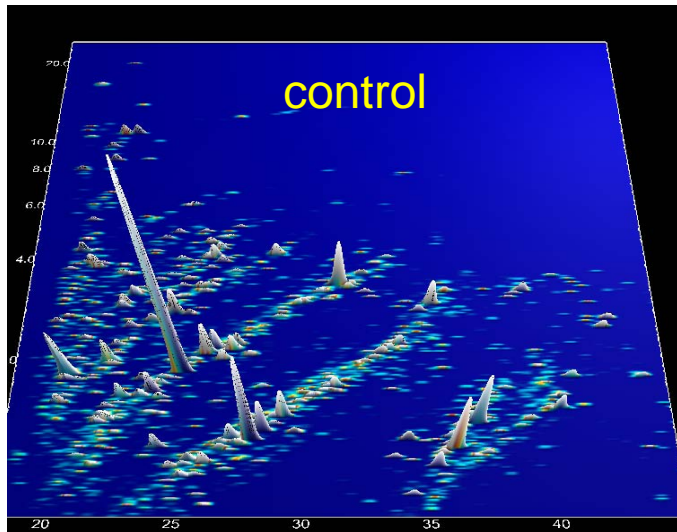
Biomarker  
selection



Statistics

# Determination of Biomarkers for Diabetes and Diabetic Nephropathy

## Type 1 diabetic patients and healthy controls



Patients with Type 2 DM and normoalb

TEST

Positive (at risk)

negative (no risk)

Intervention

Standard

Standard

Follow up

Evaluation of  
1) predictive power of test for outcome  
2) Effect of intervention in high risk patients

# ACE-inhibitor use and the long-term risk of renal failure in diabetes

S Suissa<sup>1</sup>, T Hutchinson<sup>1,2</sup>, JM Brophy<sup>1,3</sup> and A Kezouh<sup>1</sup>

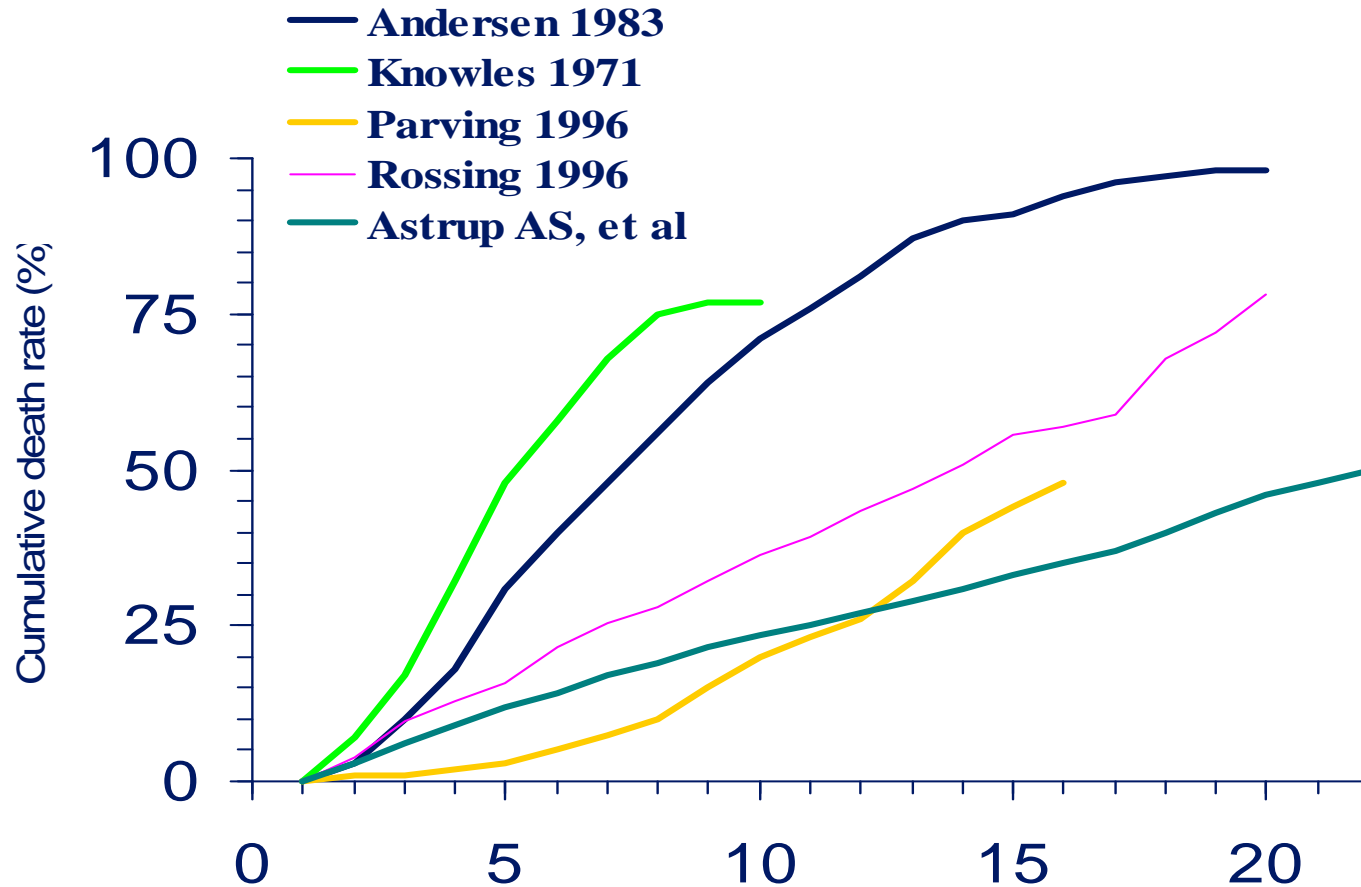
Table 3 | Crude and adjusted rate ratio of renal failure for ACE inhibitor use during the first 90 days of follow-up as a function of follow-up time

Duration of follow-up (years)	Cases		Controls		Crude rate ratio	Adjusted <sup>a</sup>	
	Number	Percent users	Number	Percent users		Rate ratio	95% CI
<3	36	16.7	1511	11.0	1.1	0.8	0.3-2.5
3-6	31	32.3	1182	9.0	5.0	4.5	1.6-12.9
>6	35	14.3	1436	3.6	3.8	3.6	1.1-11.9

ACE=angiotensin-converting enzyme; CI=confidence interval.

<sup>a</sup>Adjusted, in addition to the matching factors, for concurrent use of other antihypertensive drugs and loop-diuretics, sex, continuous age, year of cohort entry, and cardiovascular disease and congestive heart failure, both before cohort entry and during follow-up.

# Cumulative death rate in type 1 diabetes after onset of diabetic nephropathy



# RAAS Blockade in Diabetes

## Conclusions

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- Renoprotective: primary, secondary and tertiary prevention
- *but no effect in normoalbuminuric normotensive subjects*
- Postpone ESRD / death
- *Discussions about optimal blockade*
  - *high dose, dual blockade, DRI*
- Cardio-vascular protection
- *Role of aldosterone blockade?*
- *How to treat normoalbuminuric patients with low eGFR?*
- *Is ACEi and ARB the same?*