ALBUMINURIA as a TARGET for TREATMENT

Michel MARRE,
Hôpital Bichat-Claude Bernard, APHP,
and INSERM U695, Université Denis Diderot Paris7
Paris, France

Michel Marre : conflicts of interest

Pharmas	*boards*	*lectures*	*scient. supports*
Abbott	no	yes	no
Lilly	no	yes	no
MSD	yes	yes	yes
Novartis	no	no	yes
Novo-N	yes	yes	yes
Sanofi	yes	yes	yes
Servier	yes	yes	yes

ALBUMINURIA? A target for what?

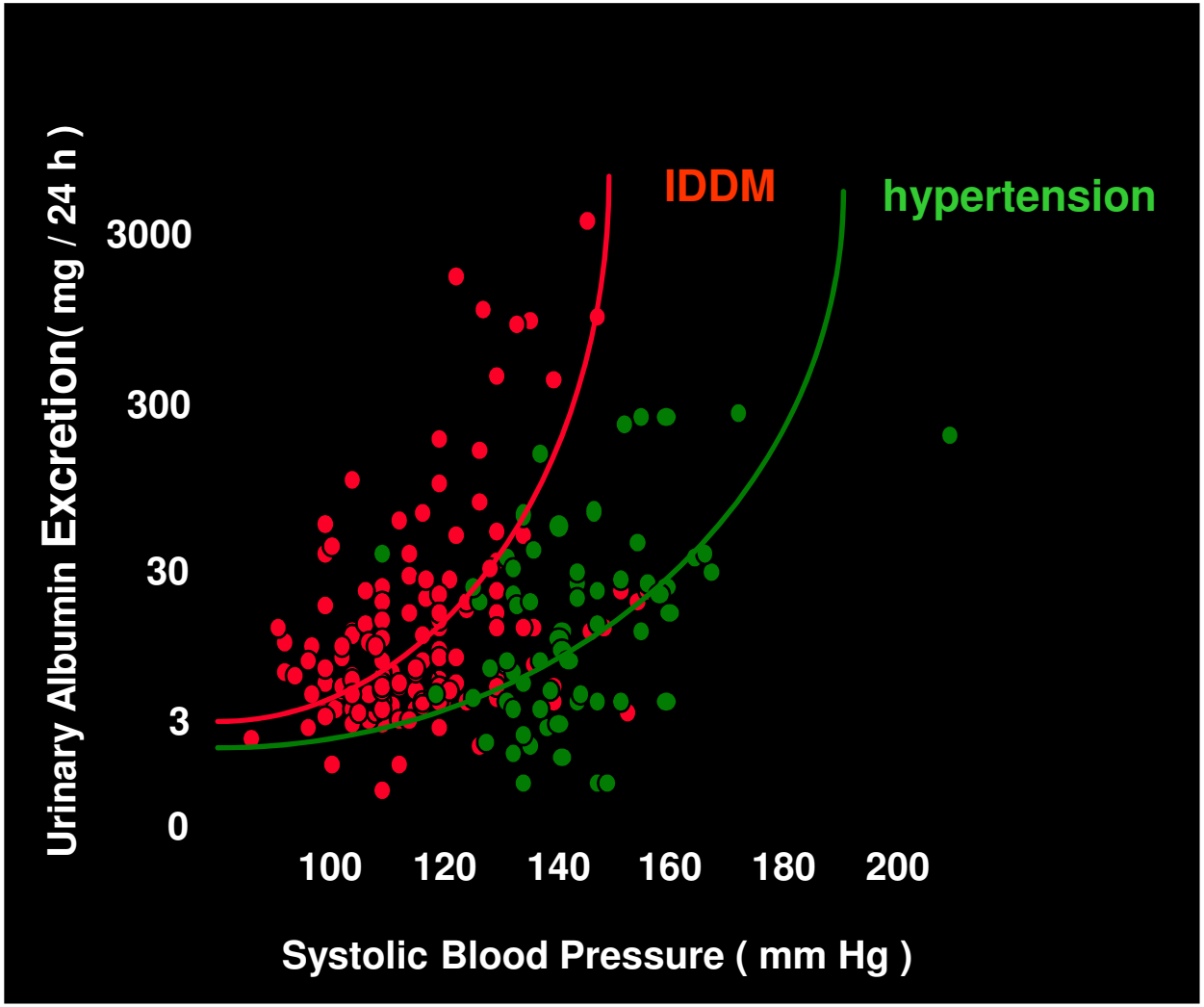
- To allocate a patient to a treatment strategy
- To predict treatment efficacy

Bijective relationship between High Blood Pressure and High Urinary Albumin

- **KIDNEY CULPRIT :**
- A glomerular disease, signaled by high urinary albumin, provokes high blood pressure

- ***Type 1 Diabetes***

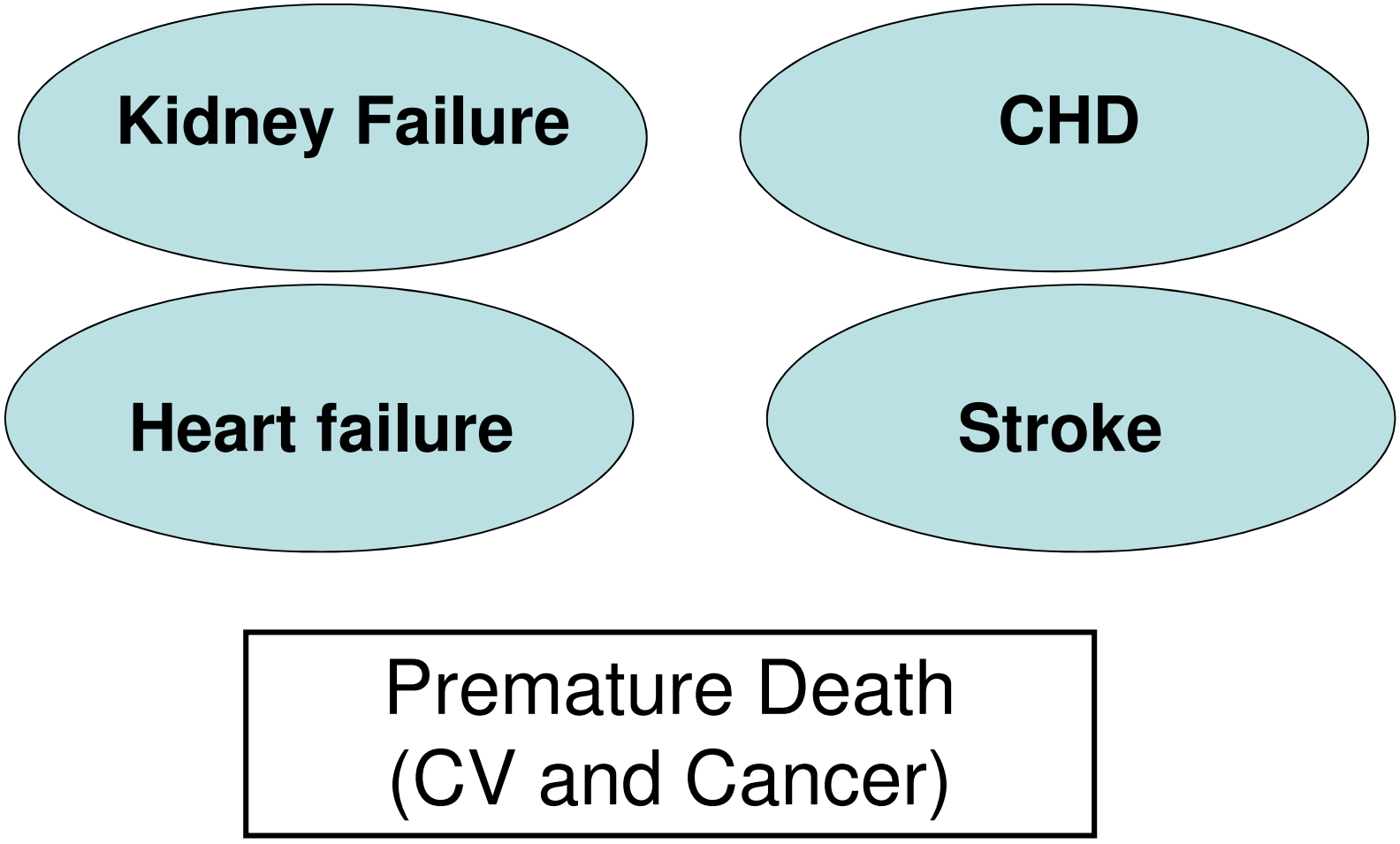
- **KIDNEY VICTIM :**
- Essential hypertension affects target organs :
- ->Heart : LVH
- ->Kidney: UAE
- Often associated with ***Type 2 diabetes***


IDDM
hypertension
Urinary Albumin Excretion(mg / 24 h)
3000
300
30
3
0
100
120
140
160
180
200
Systolic Blood Pressure (mm Hg)

Albuminuria as a marker of a generalized exsudation phenomenon

- **Parving HH:** *Microvascular permeability to plasma proteins in hypertension and diabetes mellitus in man -on the pathogenesis of hypertensive and diabetic microangiopathy. Dan Med Bull, 1975, 22(6): 217-33*
- **T Deckert et al:** *Albuminuria reflects widespread vascular damage. The Steno hypothesis. Diabetologia, 1989, 32(4): 219-26.*

Prognostic Value of Micro/Macroalbuminuria



ALBUMINURIA to allocate a patient to a Treatment Strategy:

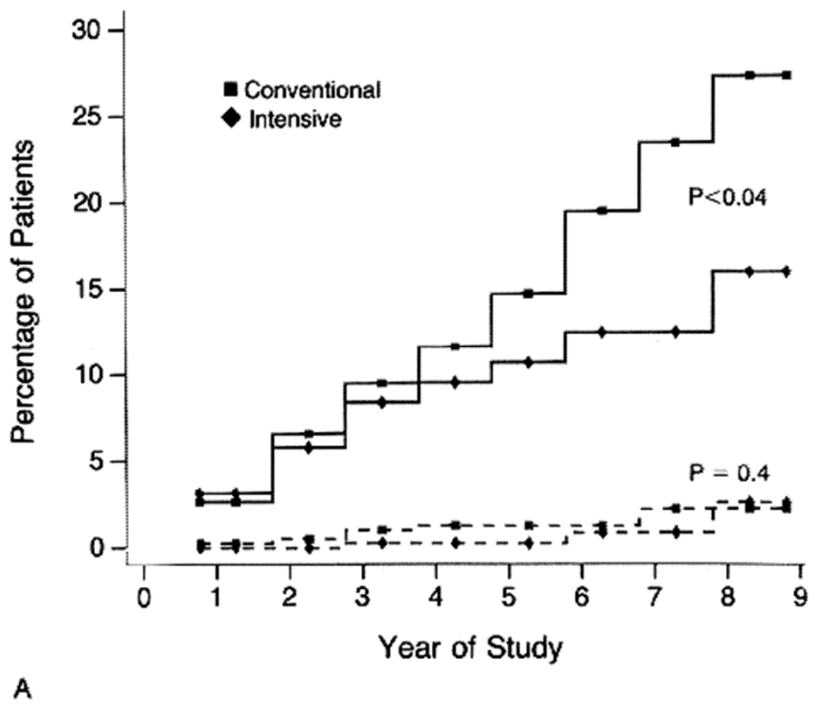
- ***Primary*** vs ***secondary*** **preventions**
- **Tools:** intensified blood glucose/pressure treatments
- **Diabetes:** type 1/ type 2

- =>2X2X2= ***8 options***

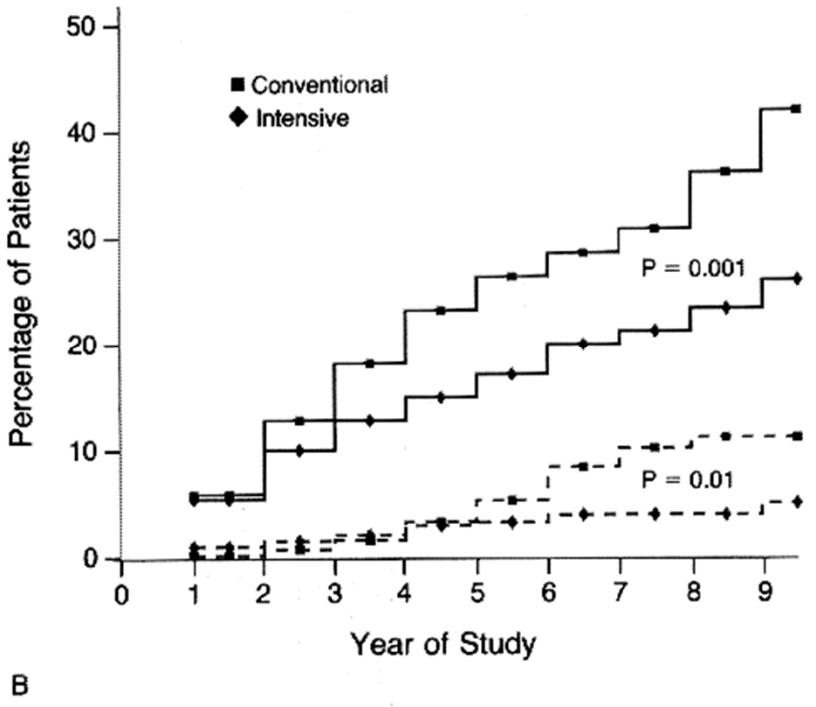
Primary Prevention: to prevent Micro/Macro and their predicted outcomes

- Intensified ***blood glucose*** strategy:
- **-type 1 diabetes:**
- Preventing **µ/Malbuminuria**: YES (DCCT)
- Preventing **Kidney Failure**: YES (DCCT/EDIC)
- **CV outcomes**: YES (DCCT/EDIC)
- Preventing **Death** (wait for DCCT/EDIC study end)

DCCT primary prevention



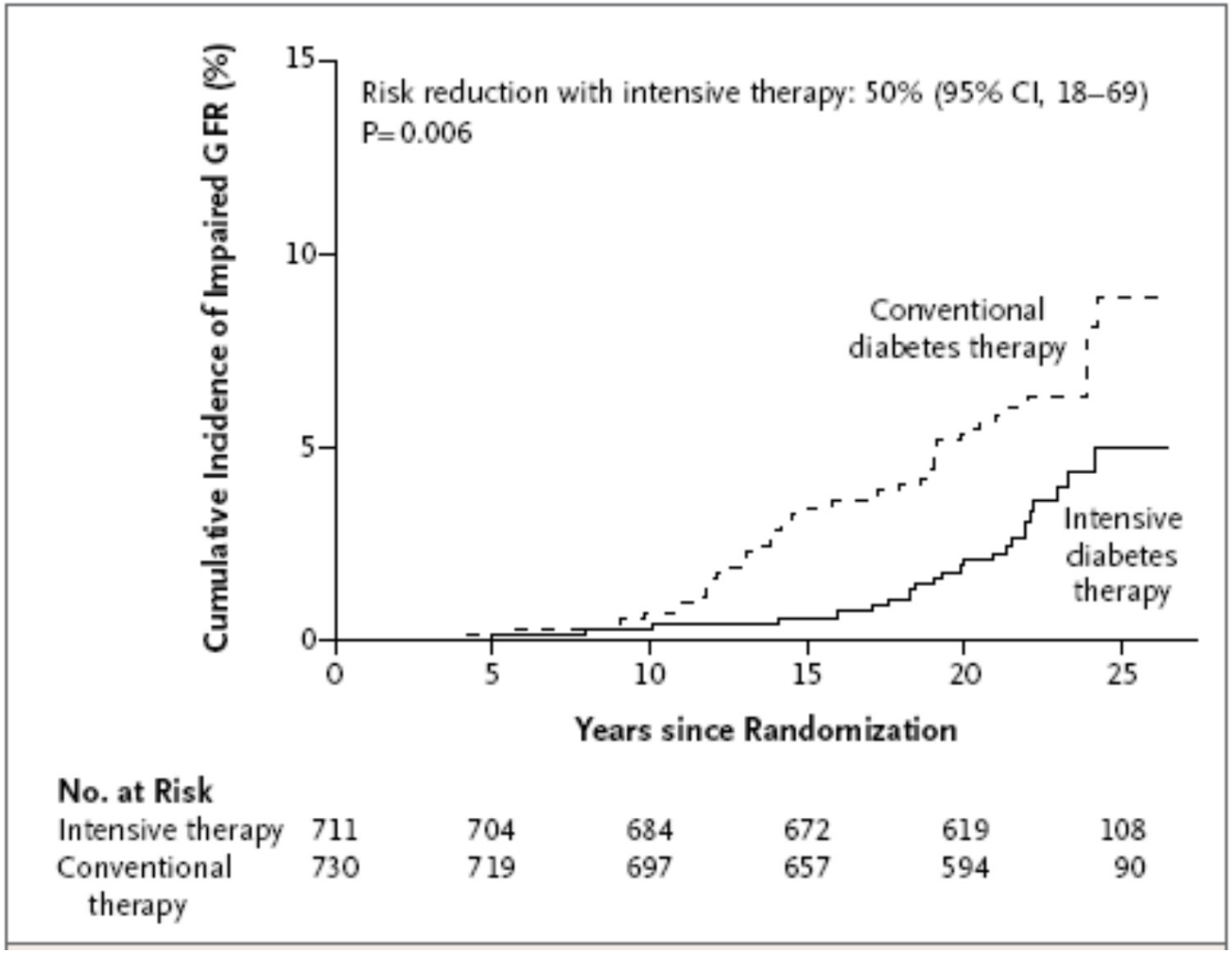
A



B

Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes

DCCT / EDIC Research Group. N Engl J Med 2011, 365, 2366-76

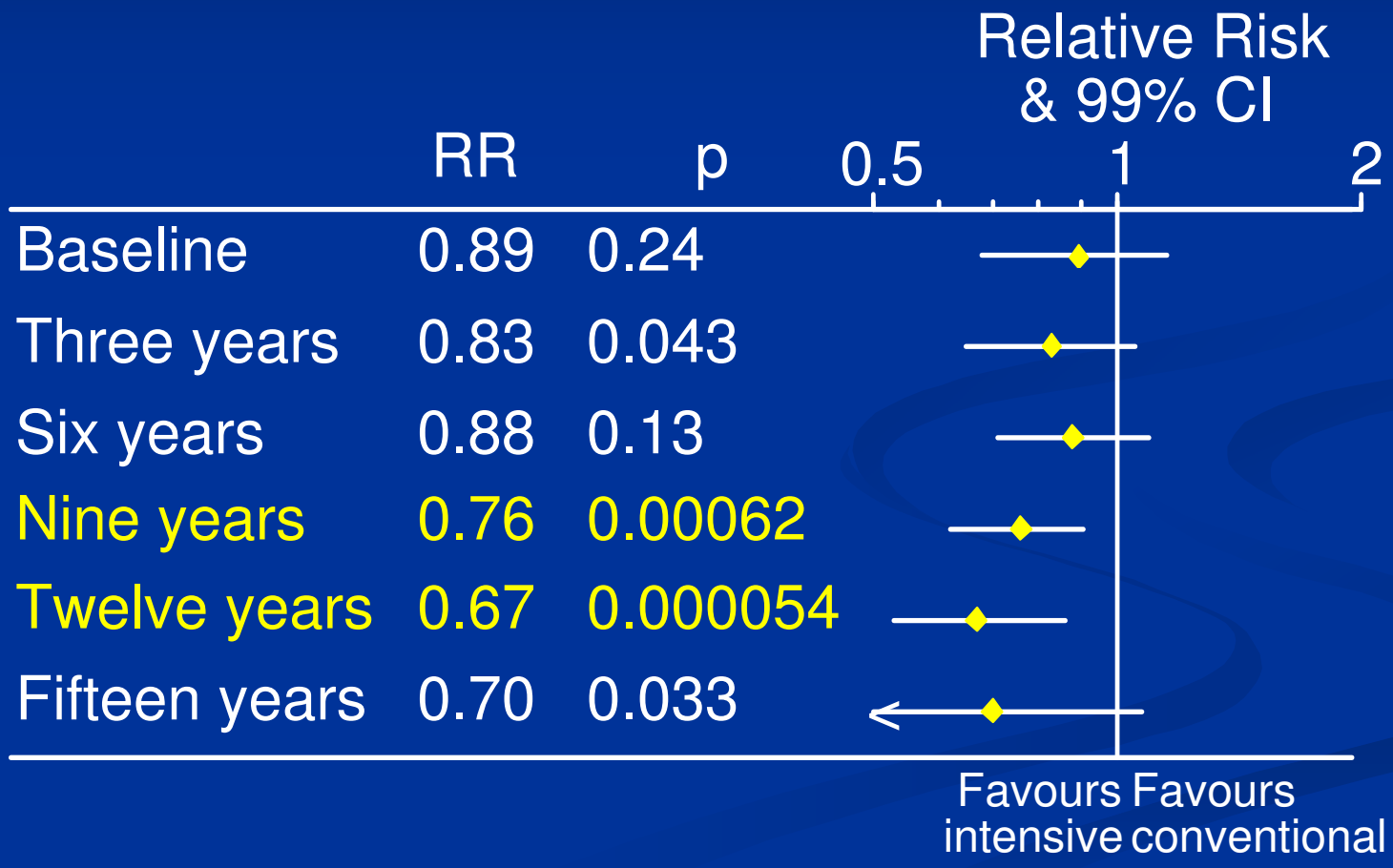


Primary Prevention: to prevent Micro/Macro and their predicted outcomes

- Intensified ***blood glucose*** strategy:
- **-type 2 diabetes:**
- Preventing **µ/M**: YES (UKPDS)
- Preventing **Kidney Failure**: YES (ADVANCE)
- **CV outcomes**: YES (UKPDS follow-up)
- **DEATH:** YES (UKPDS follow-up)

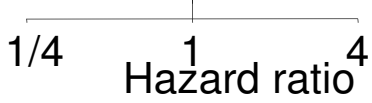
UKPDS : Microalbuminuria onset

Urine albumin >50 mg/L



Summary of major outcomes

	Number of events	Hazard ratio	95% CI	P-value
ESKD	27	0.35	(0.15 - 0.83)	0.0167
Renal death	37	0.85	(0.45 - 1.63)	0.6250
ESKD or renal death	59	0.64	(0.38 - 1.08)	0.0930
Doubling to > 200	129	1.15	(0.82 - 1.63)	0.4207
Sustained doubling > 200	84	0.83	(0.54 - 1.27)	0.3859
All sustained doubling	220	0.80	(0.61 - 1.04)	0.0965



Doubling of creatinine: 45 reversed
84 sustained

Primary Prevention: to prevent Micro/Macro and their predicted outcomes

- Intensified ***blood pressure*** strategy:
- **-type 1 diabetes:**
- Preventing **µ/M**: NO (RAS Study)
- Preventing **Kidney Failure**: not shown
- **CV outcomes**: not shown
- **DEATH**: not shown

Primary Prevention: to prevent Micro/Macro and their predicted outcomes

- Intensified ***blood pressure*** strategy:
- **-type 2 diabetes:**
- Preventing **µ/M**: YES (UKPDS)
- Preventing **Kidney Failure**: ?
- **CV outcomes**: YES (HOPE)
- **DEATH:** YES

Secondary Prevention: to prevent the outcomes predicted by Micro/Macro

- Intensified ***blood glucose*** strategy:
- **-type 1 diabetes:**
- Preventing **Kidney Failure:** not clear (DCCT/EDIC)
- **CV outcomes:** YES (DCCT/EDIC)
- **DEATH:** wait…

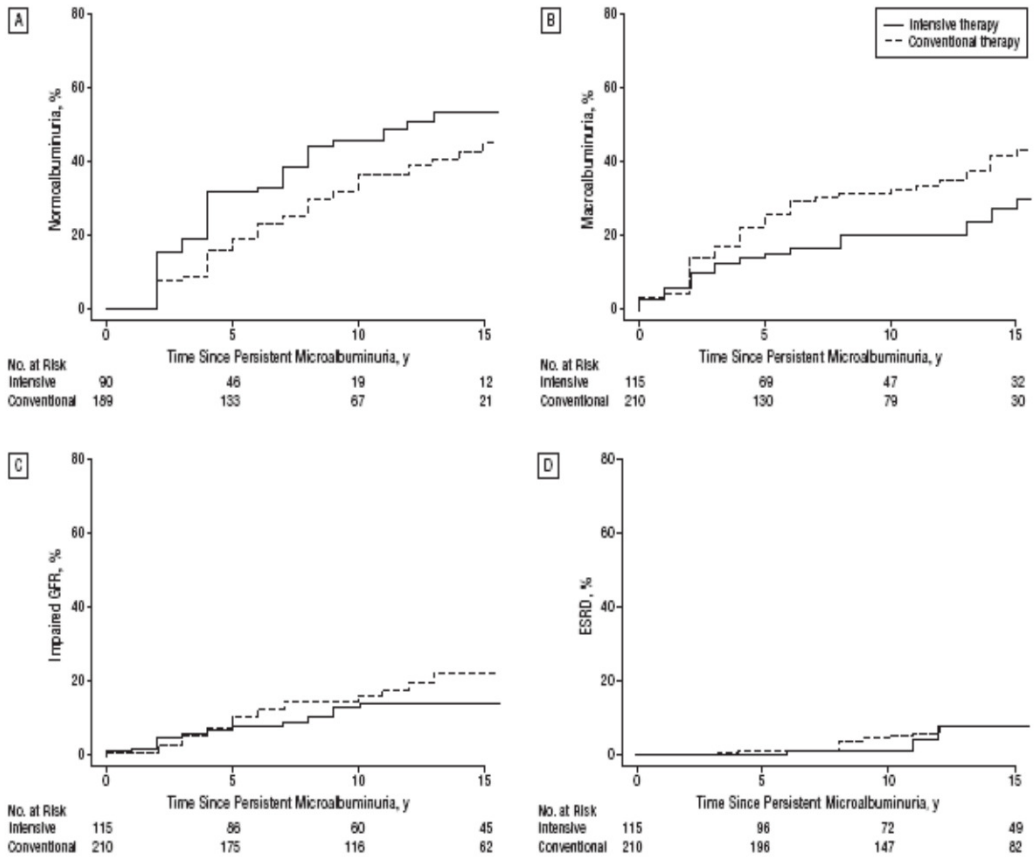


Figure 4. Cumulative incidence of long-term renal outcomes after the development of persistent microalbuminuria (time 0) among 325 participants in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study by Diabetes Control and Complications Trial treatment assignment. A, Regression to normoalbuminuria. B, Progression to macroalbuminuria. C, Impaired glomerular filtration rate (GFR). D, End-stage renal disease (ESRD).

Secondary Prevention: to prevent the outcomes predicted by Micro/Macro

- Intensified ***blood glucose*** strategy:
- **-type 2 diabetes:**

- Preventing **Kidney Failure:** YES (ADVANCE)
- **CV outcomes:** NO (ADVANCE)
- **DEATH:** YES (UKPDS follow-up)

Secondary Prevention: to prevent the outcomes predicted by Micro/Macro

- Intensified ***blood pressure*** strategy:
- **-type 1 diabetes:**
- Preventing **Kidney Failure**: YES (Lewis et al, NEJM, 1993)
- **CV outcomes**: not shown (DCCT/EDIC)
- **DEATH:** no

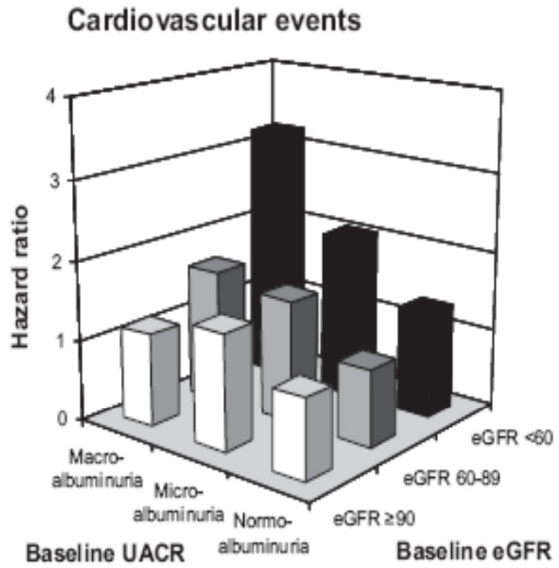
Secondary Prevention: to prevent the outcomes predicted by Micro/Macro

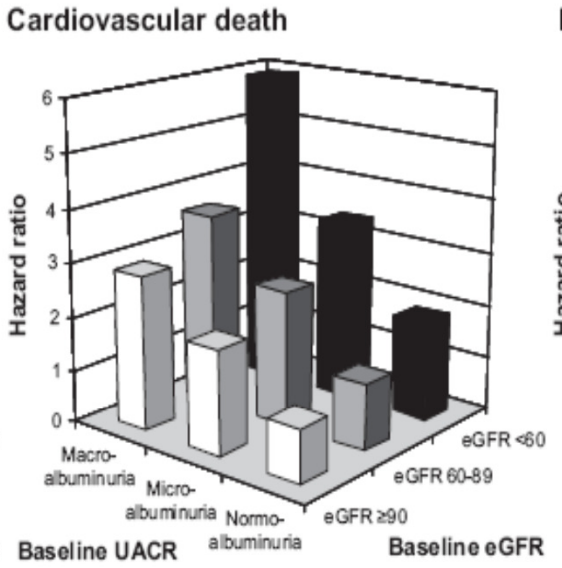
- Intensified ***blood pressure*** strategy:
- **-type 2 diabetes:**
- Preventing **Kidney Failure**: YES (Lewis et al, Brenner et al, 2001, ADVANCE)
- **CV outcomes**: YES (UKPDS, ADVANCE)
- **DEATH**: YES (UKPDS, ADVANCE)

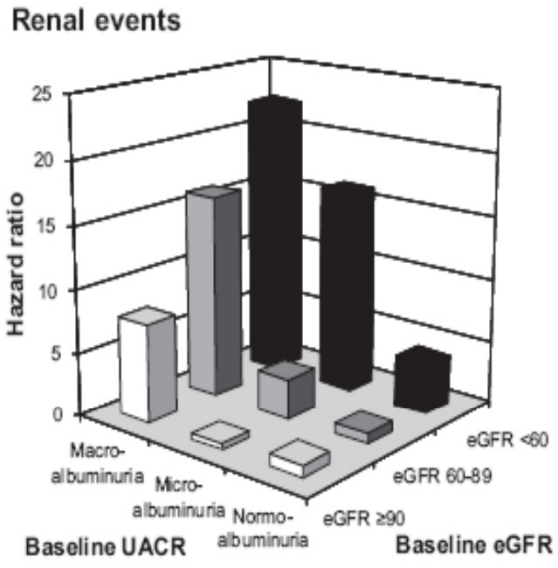
Toshiharu Ninomiya et al.

Albuminuria and Kidney Function Independently Predict Cardiovascular and Renal Outcomes in Diabetes

JASN 20: 1813-1821, 2009







	Baseline eGFR (ml/min/1.73 m²)		
	GFR ≥90	GFR 60-89	GFR <60
Baseline UACR			
Normoalbuminuria	1.00 (Reference)	0.98 (0.78-1.22)	1.33 (1.02-1.75)
Microalbuminuria	1.48 (1.09-2.01)	1.54 (1.20-1.98)	2.04 (1.54-2.69)
Macroalbuminuria	1.18 (0.52-2.69)	1.67 (1.09-2.57)	3.23 (2.20-4.73)

	Baseline eGFR (ml/min/1.73 m²)		
	GFR ≥90	GFR 60-89	GFR <60
Baseline UACR			
Normoalbuminuria	1.00 (Reference)	1.22 (0.81-1.84)	1.85 (1.17-2.92)
Microalbuminuria	1.96 (1.16-3.32)	2.52 (1.65-3.84)	3.37 (2.15-5.30)
Macroalbuminuria	2.87 (1.01-8.18)	3.61 (2.02-6.43)	5.93 (3.45-10.20)

	Baseline eGFR (ml/min/1.73 m²)		
	GFR ≥90	GFR 60-89	GFR <60
Baseline UACR			
Normoalbuminuria	1.00 (Reference)	0.89 (0.31-2.58)	3.95 (1.38-11.34)
Microalbuminuria	0.45 (0.05-3.83)	3.17 (1.15-8.74)	16.19 (6.16-42.54)
Macroalbuminuria	7.82 (1.51-40.53)	16.13 (5.49-47.42)	22.20 (7.62-64.72)

ALBUMINURIA as a target for treatment efficacy

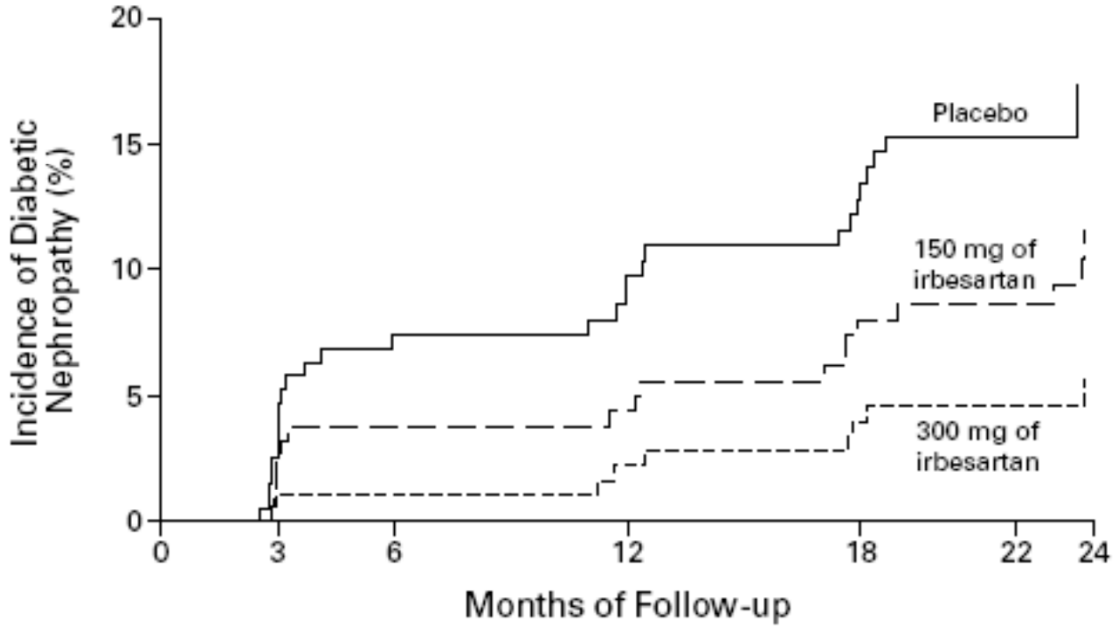
- ***Does alteration in a surrogate marker alter the final outcome?***
  -the matter of the dose
- *-the matter of the outcome*

ALBUMINURIA as a target for treatment efficacy -the matter of the dose

- In type 1 diabetes patients with persistent microalbuminuria, very small doses (1.25 mg/d) of ramipril reduced µalb as did usual (5 mg/d) doses (Marre et al, J Cardiovas Pharmacol, 1990, ATLANTIS study, Diabetes Care, 1992)

ALBUMINURIA as a target for treatment efficacy -the matter of the dose

- In type 2 diabetes patients with persistent microalbuminuria and hypertension, high doses (300 mg/d) of irbesartan reduced Malb better than lower (150 mg/d) doses (Parving et al, NEJM, 2001)



No. AT RISK

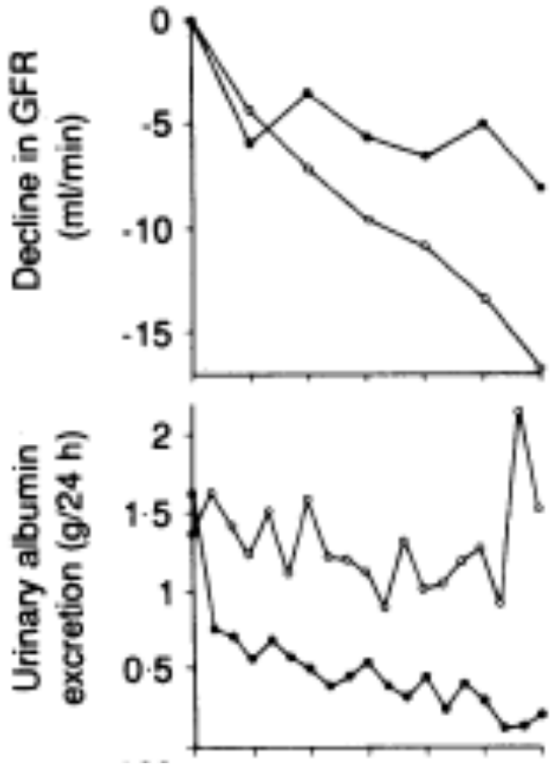
Placebo	201	201	164	154	139	129	36
150 mg of irbesartan	195	195	167	161	148	142	45
300 mg of irbesartan	194	194	180	172	159	150	49

In patients with proteinuria, does reducing albuminuria with high doses make risk?

- The matter of renal autoregulation:
- Kept safe in type 1 diabetic patients with µalb (Mathiesen E et al, Diabetologia, 1990)

- In those with proteinuria, short term vs long term (Björk et al, BMJ, 1992)…

Renal protective effect of enalapril in diabetic nephropathy
Björk S et al, BMJ, 1992

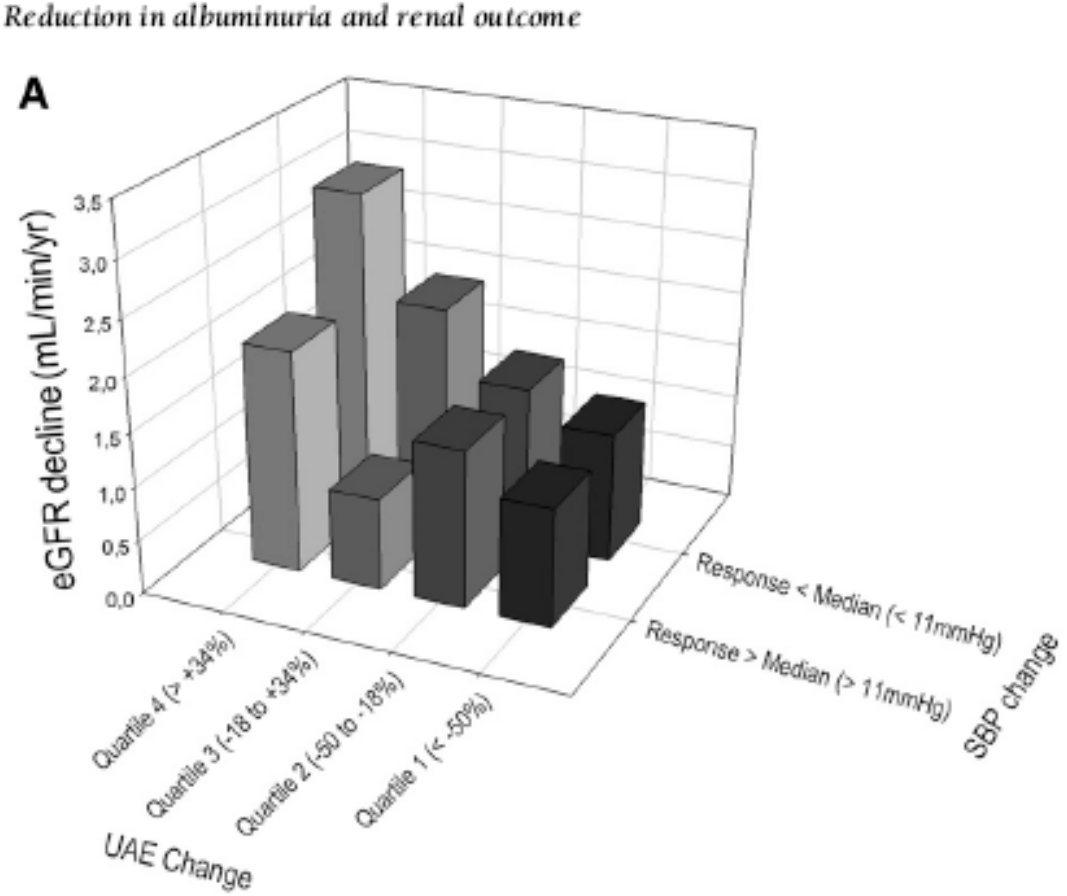


Advice to clinicians:

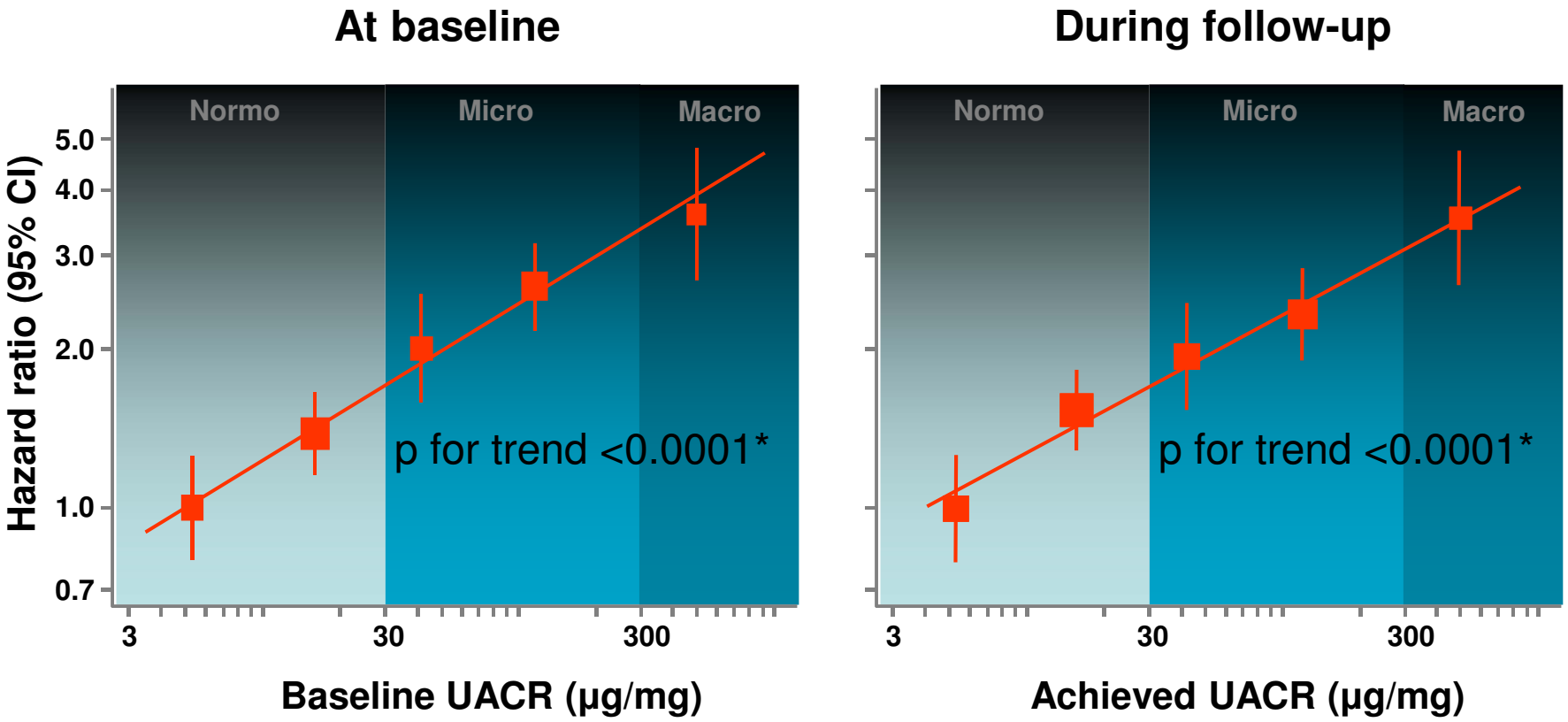
- In patients with proteinuria and reduced GFR, look at serum **potassium**, rather than creatinine, on the short term, when doses of renin blockers are increased.

Rapid response to treatment predicts final renal outcome

Initial angiotensin receptor blockade-induced decrease in albuminuria is associated with long-term renal outcome in type 2 diabetic patients with microalbuminuria
Hellemons ME et al. Diabetes Care 2011, 34, 2078-83



Risk of CV death by albuminuria at baseline and achieved during follow-up in ADVANCE

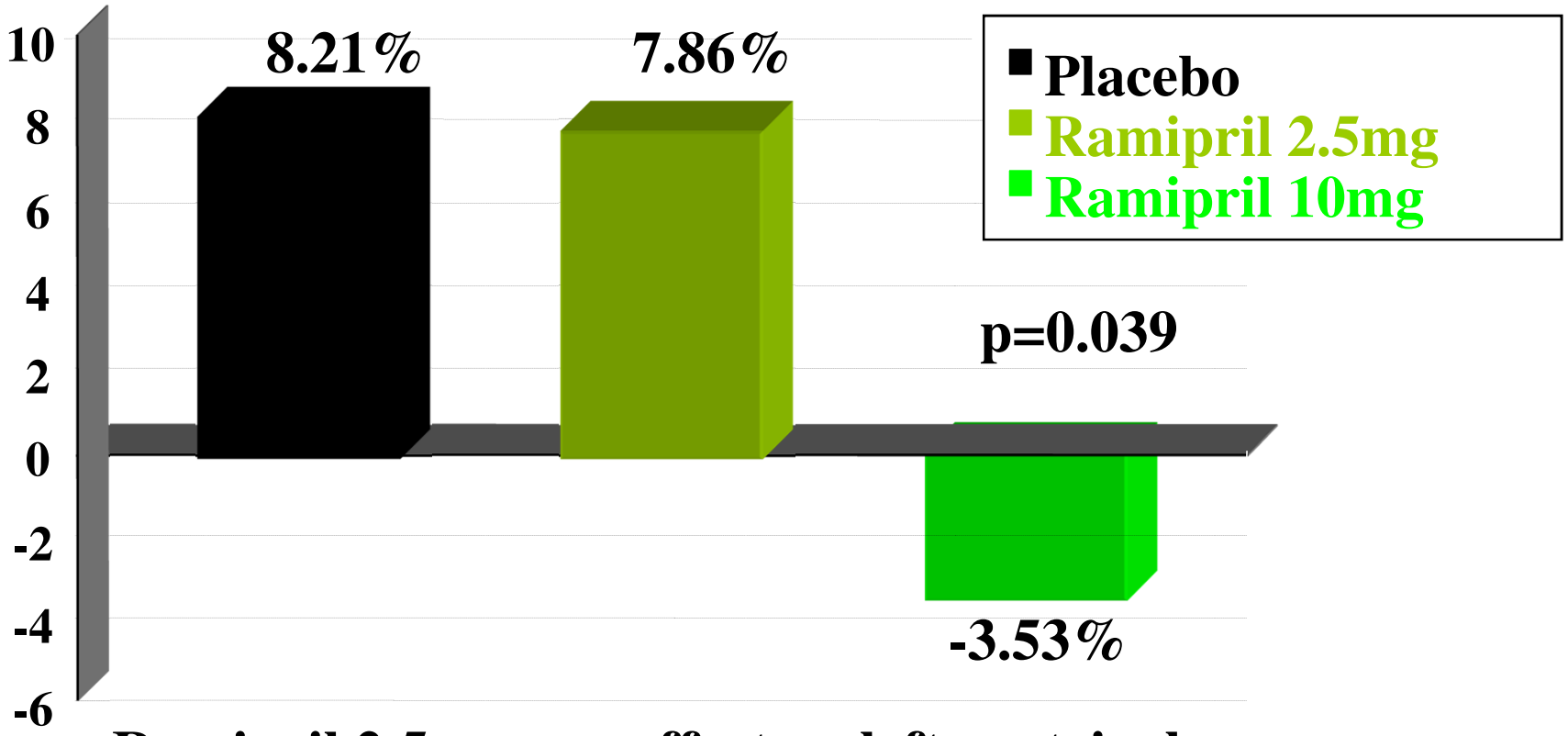


**Adjusted for age, sex, HbA_{1c}, serum lipids, BMI, smoking, alcohol use, and study drug*

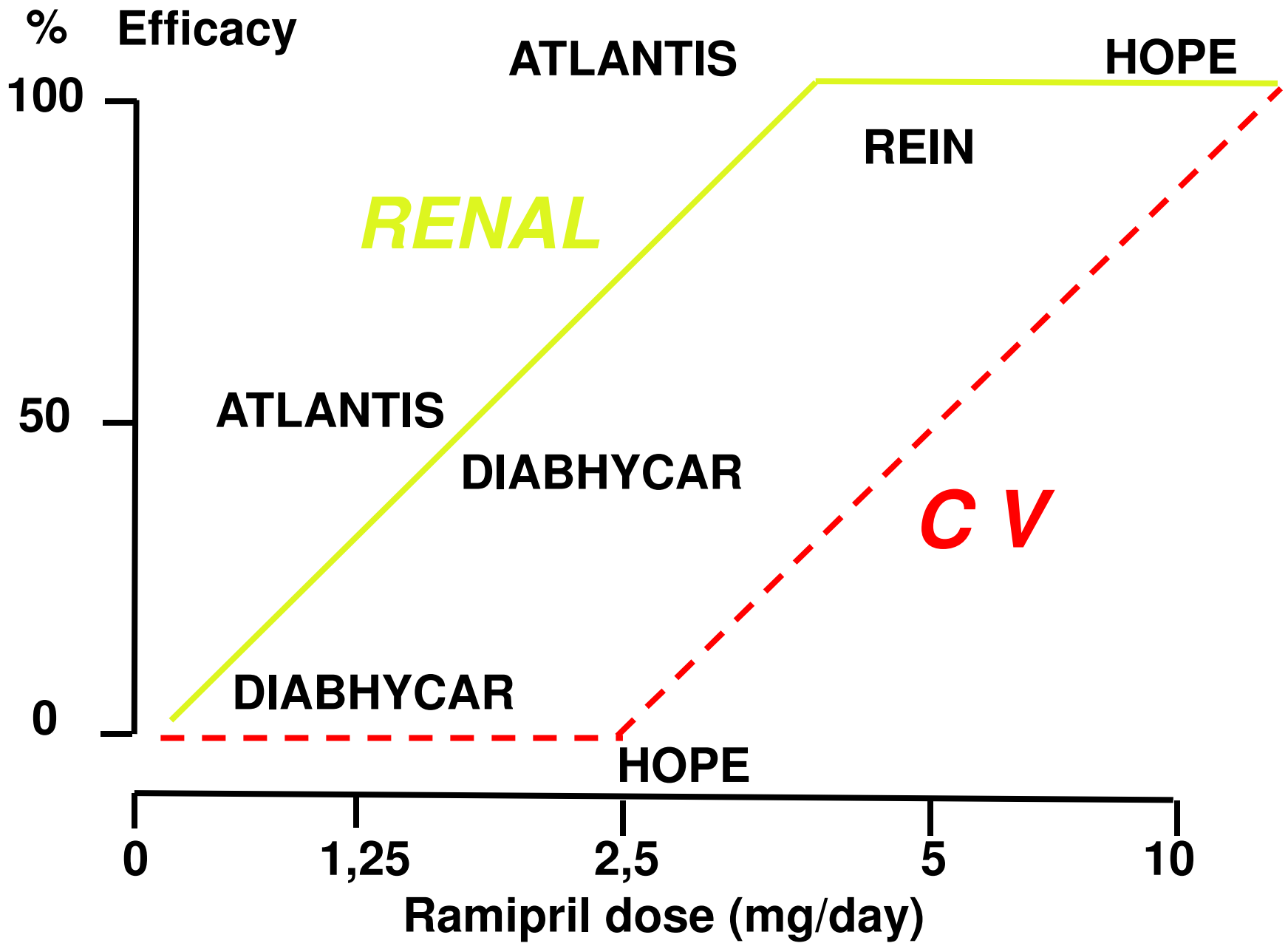
ALBUMINURIA as a target for treatment efficacy: the matter of the outcome

- **Renal outcomes vs CV outcomes:**
- In the DIABHYCAR study, µ/M was reduced by small (1.25 mg/d) doses ramipril, but CV outcomes were not (Marre M et al, BMJ, 2004)
- In the micro-HOPE study, µ/M was reduced similarly by high (10 mg/d) doses ramipril, and CV outcomes were too (Gerstein H et al, Lancet, 2001)

Left ventricular mass regression (SECURE)
732 randomised patients. Follow-up : 1.5-2.2 years



Ramipril 2.5mg : no effect on left ventricular mass ; no effect on atherosclerosis progression


% Efficacy
100
50
0
ATLANTIS
HOPE
REIN
RENAL
ATLANTIS
DIABHYCAR
C V
DIABHYCAR
HOPE
0
1,25
2,5
5
10
Ramipril dose (mg/day)

Albuminuria as a target for treatment in patients with diabetes:

- Primary prevention of µ/M albuminuria is a valuable target for strict blood glucose and pressure controls and their final (renal and CV) outcomes
- Secondary interventions (strict blood glucose and pressure controls) on µ/M albuminuria are valuable for their final (renal and CV) outcomes
- Changes in µ/M albuminuria as responses to treatment are useful tools
- The lower the blood glucose and pressure (and the highest the renin blockers doses), the best it is for the final renal (and CV) outcomes