New Treatment Options for Diabetic Nephropathy patients

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Diabetes and nephropathy

- Diabetic nephropathy is the most common cause of end-stage renal disease[1]
- About 40% of patients with Type 1 diabetes develop diabetic nephropathy[2]
- Similarly, 30–40% of patients with Type 2 diabetes develop diabetic nephropathy[1]
- In type 2 diabetes, the incidence of nephropathy ranges from 25% in people of European origin to 50% in people of Afro-Caribbean or Asian origin[2]

1. Rossing K, *et al*. *Diabetes Care* 2003; **26**(1): 150–155.
2. Thomas S, Viberti G. *Medicine* 2006; **34**(3): 83–86.

Diabetic nephropathy

Stages of diabetic nephropathy:

1. Hypertrophy and hyperfiltration
2. Renal lesions without clinical signs
3. Microalbuminuria (>20 mg/min or 30 mg/24 h)
4. Macroalbuminuria (>200 mg/min or 300 mg/24 h)
5. End-stage renal disease

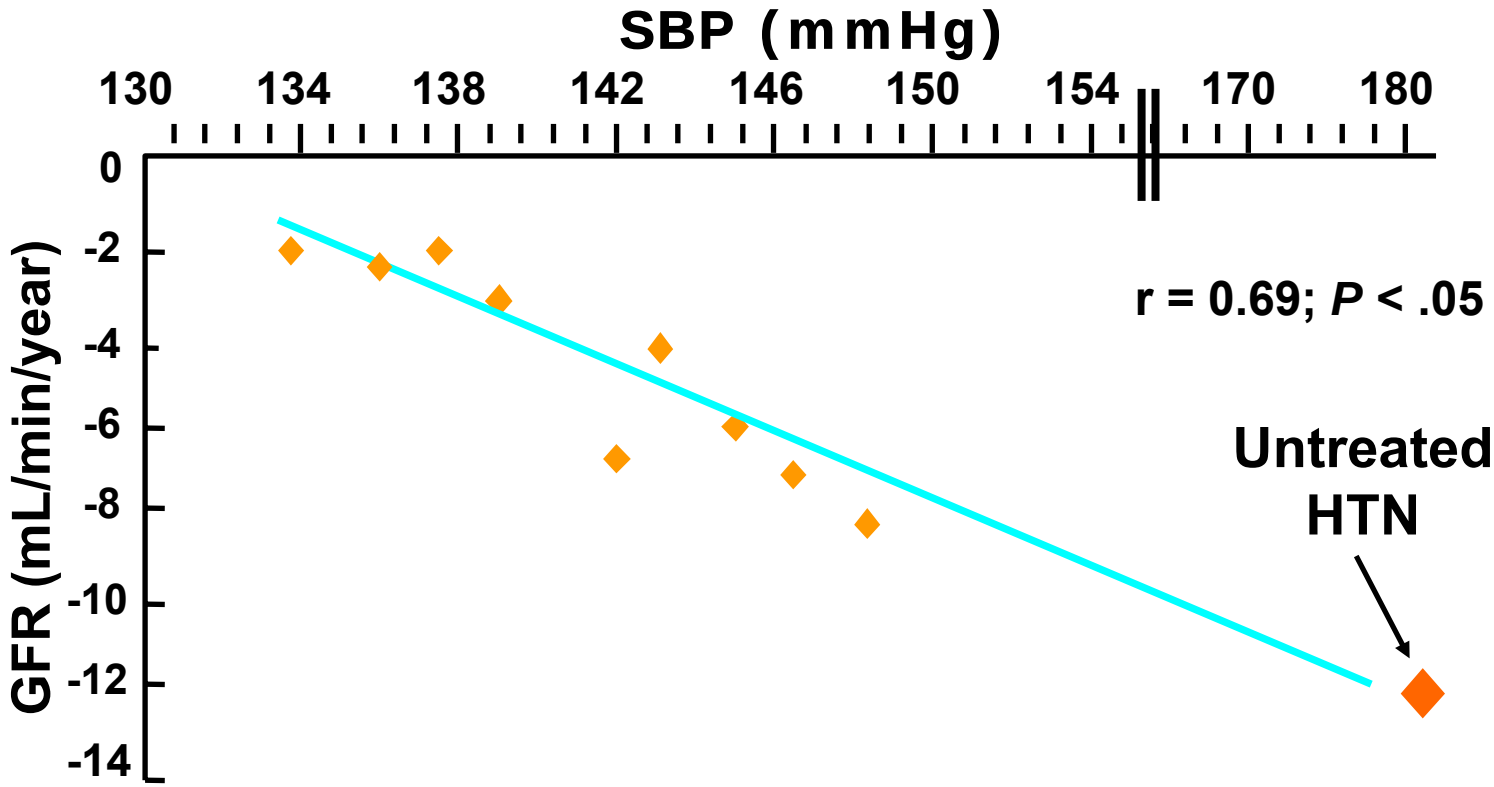
Tagle R, *et al. Cleveland Clin J Med* 2003; 70: 255–261.

Prevention of diabetic nephropathy: A multifocal approach

Blood pressure	< 120/80 mmHg
Proteinuria	< 0.3 g/24 h
LDL	< 100 mg/dl
LDL + VLDL	< 130 mg/dl
HbA1c	< 7.5 % (diabetics)

Ruggenenti et al., *Lancet,* 2001

Meta Analysis: Lower Systolic BP Results in Slower Rates of Decline in GFR in Diabetics and Non-Diabetics



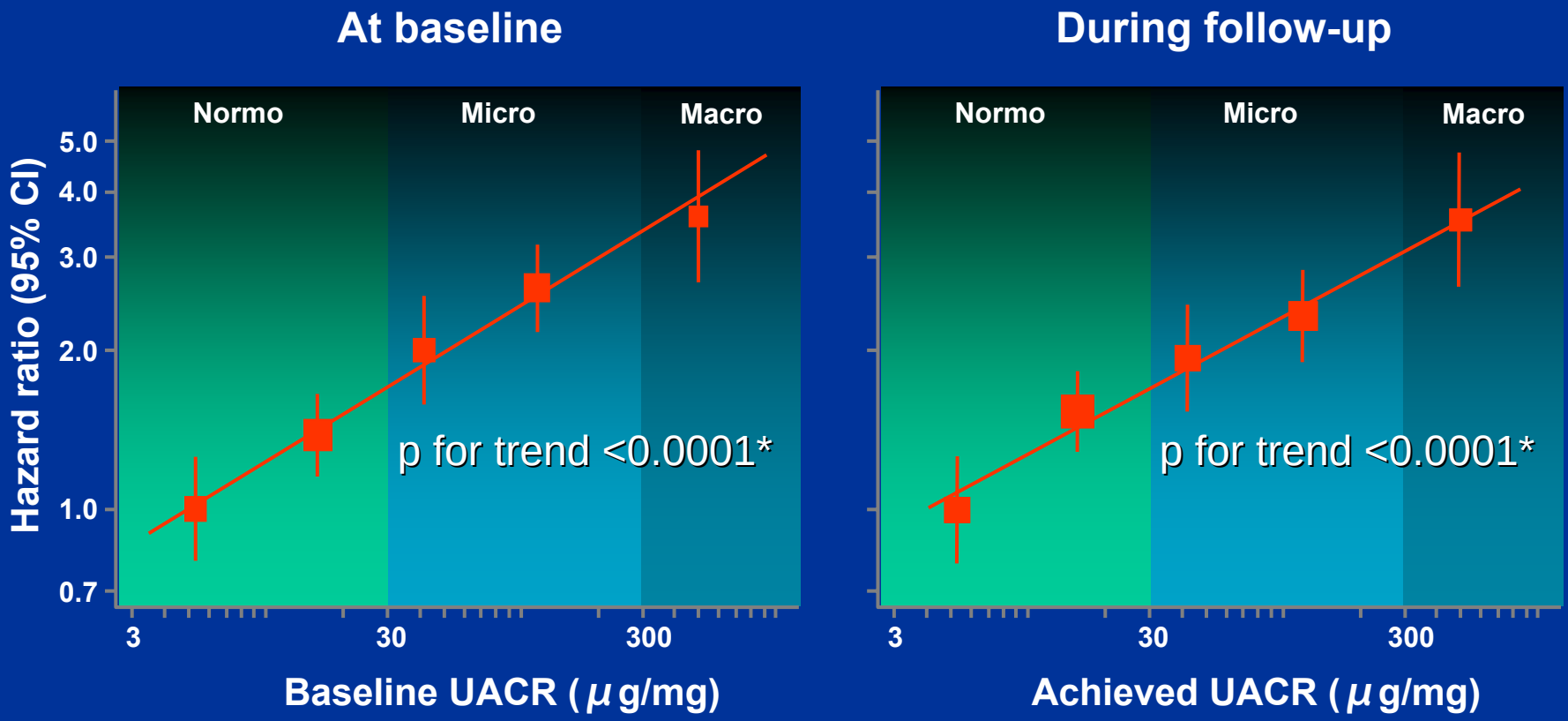
Bakris GL, et al. Am J Kidney Dis. 2000;36(3):646-661.

Recommended blood pressure targets

JNC-7[1]	ESH/ESC[2]	WHO-ISH[3]	BHS IV/NICE[4]
<140/90 mm Hg	<140/90 mm Hg or lower if tolerated	<140/90 mm Hg	<140/90 mm Hg
<130/80 mm Hg in patients with diabetes or renal disease	<130/80 mm Hg in patients with diabetes	<130/ <80 mm Hg in patients with diabetes, existing CVD and renal insufficiency	<130/90 mm Hg in patients with diabetes

1. Chobanian AV, *et al. JAMA* 2003; **289**(19): 2560–2572.
2. ESH/ESC Guidelines Committee. *J Hypertens* 2003; **21**: 1011–1053.
3. WHO. *J Hypertens* 2003; **21**(11): 1983–1992.
4. BHS/NICE, 2006: 1–94.

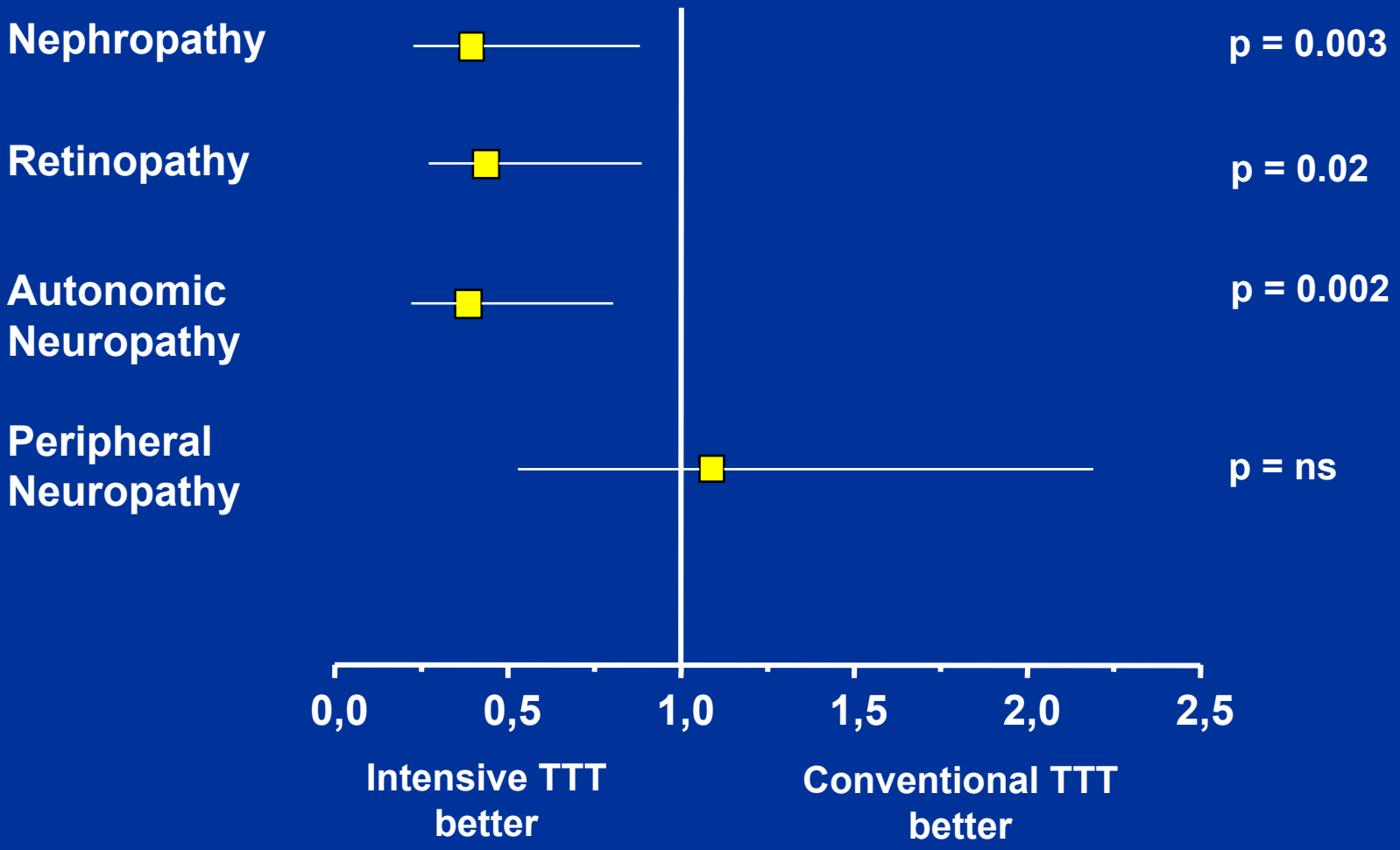
Risk of CV death by albuminuria at baseline and achieved during follow-up in ADVANCE



11’140 patients with type 2 diabetes

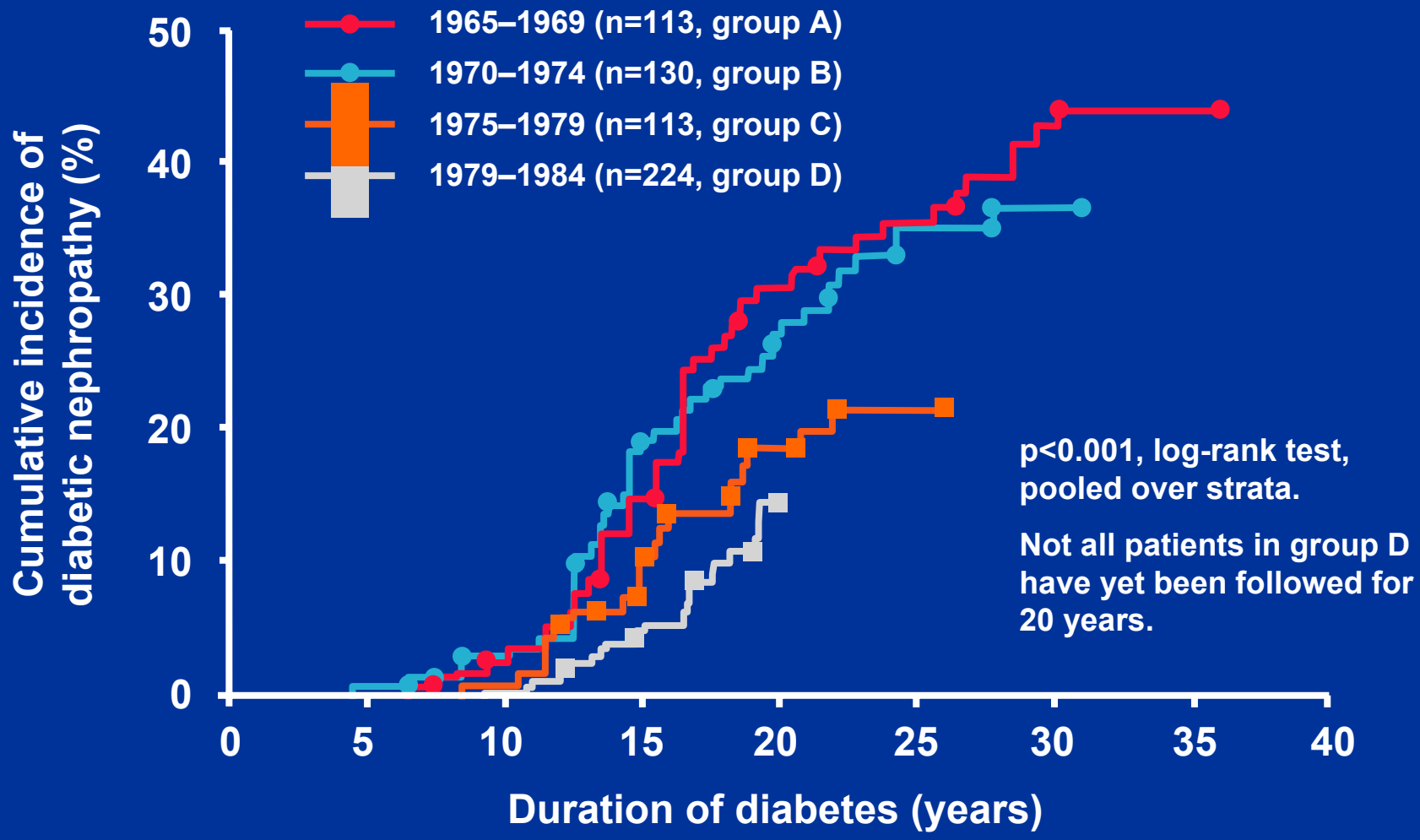
**Adjusted for age, sex, HbA_{1c}, serum lipids, BMI, smoking, alcohol use, and study drug*

Effect of an intensive vs conventional management of risk factors in type 2 diabetes

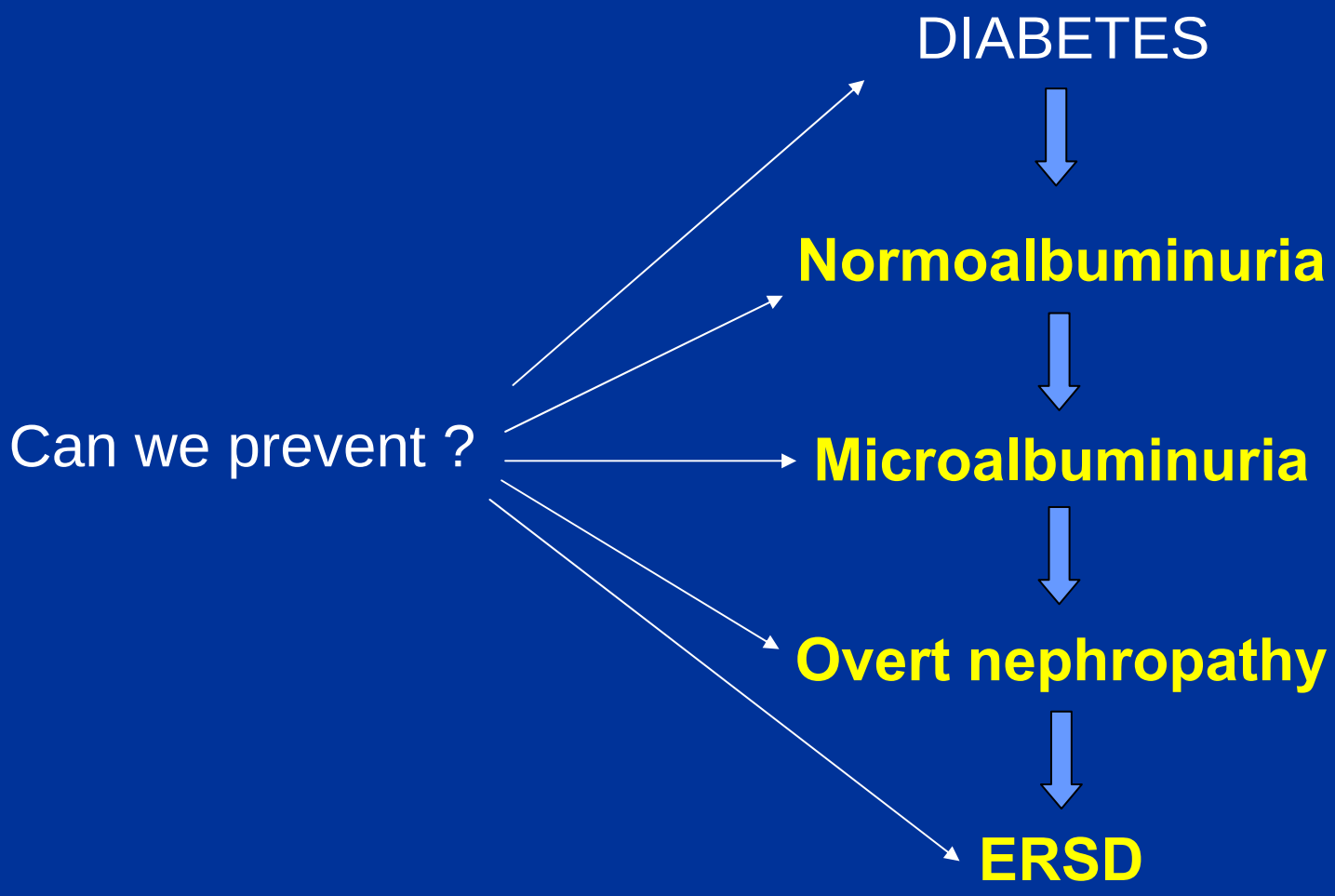


Goede P et al, NEJM, 2003

Incidence of diabetic nephropathy according to onset of type 1 diabetes



Hovind P, *et al*. *Diabetes Care* 2003; 26: 1258–1264.


DIABETES
Normoalbuminuria
Microalbuminuria
Overt nephropathy
ERSD
Can we prevent ?

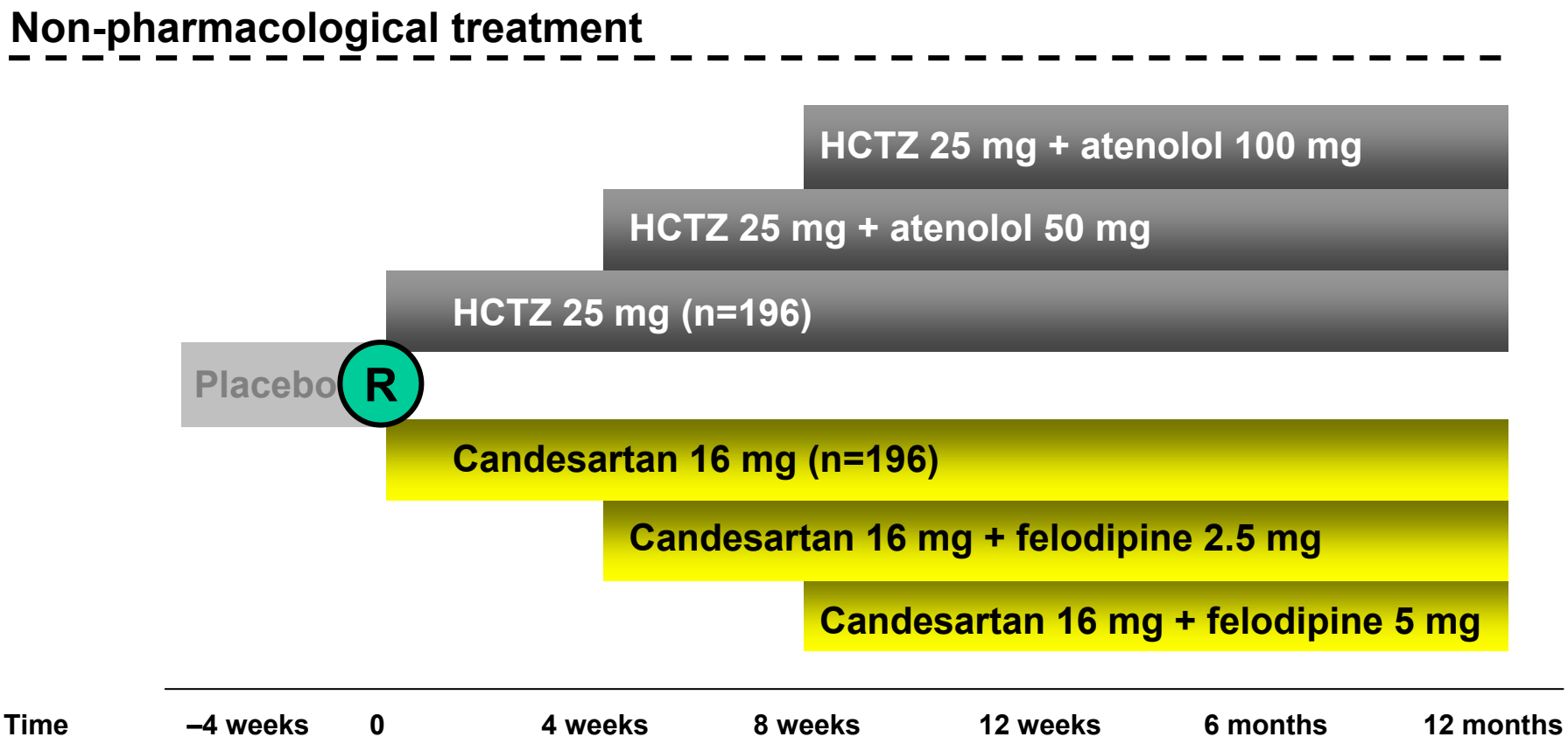
Can we prevent the diabetes ?

Evidence of role of ARBs for the prevention of new-onset diabetes

Study	Treatment	Duration (years)	New-onset diabetes (%)	p-value
LIFE[1]	Losartan vs. atenolol	4.8	6.0 vs. 8.0	<0.001
ALPINE[2]	Candesartan vs. HCTZ	1.0	0.5 vs. 4.1	<0.05
VALUE[3]	Valsartan vs. amlodipine	4.5	13.1 vs. 16.4	<0.001
CHARM[4]	Candesartan vs. placebo	3.2	6.0 vs. 7.5	0.02
SCOPE[5]	Candesartan vs. placebo	3.7	4.9 vs. 6.0	0.09

1. Ong HT. *Lancet* 2003; **362**: 1416.
2. Lindholm LH, *et al*. *J Hypertens* 2003; **21**: 1563–1574.
3. Julius S, *et al*. *Lancet* 2004; **363**: 2022–2031.
4. Yusuf S, *et al*. *Circulation* 2005; **112**: 48–53.
5. Lithell H, *et al*. *J Hypertens* 2003; **21**: 875–886.

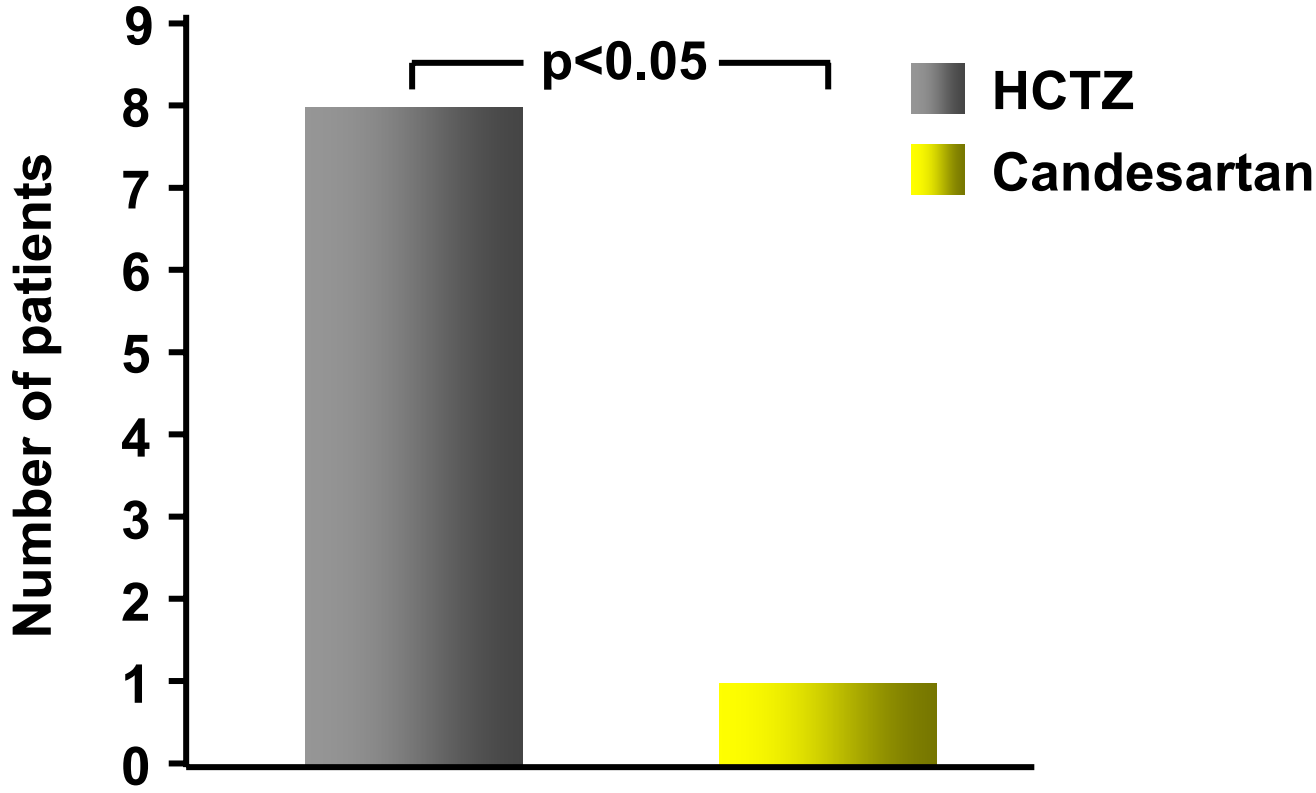
ALPINE: study design



No other antihypertensive drugs allowed
Goal blood pressure: <135/<85 mm Hg; 65+ years of age <140/<90 mm Hg

Lindholm LH, *et al. J Hypertens* 2003; **21**(8): 1563–1574.

ALPINE: new-onset diabetes

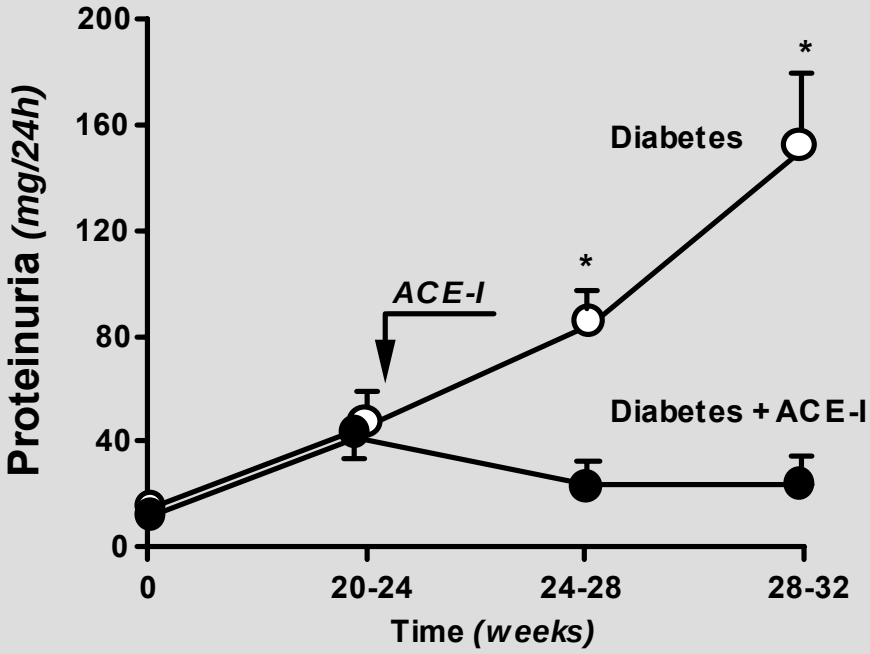


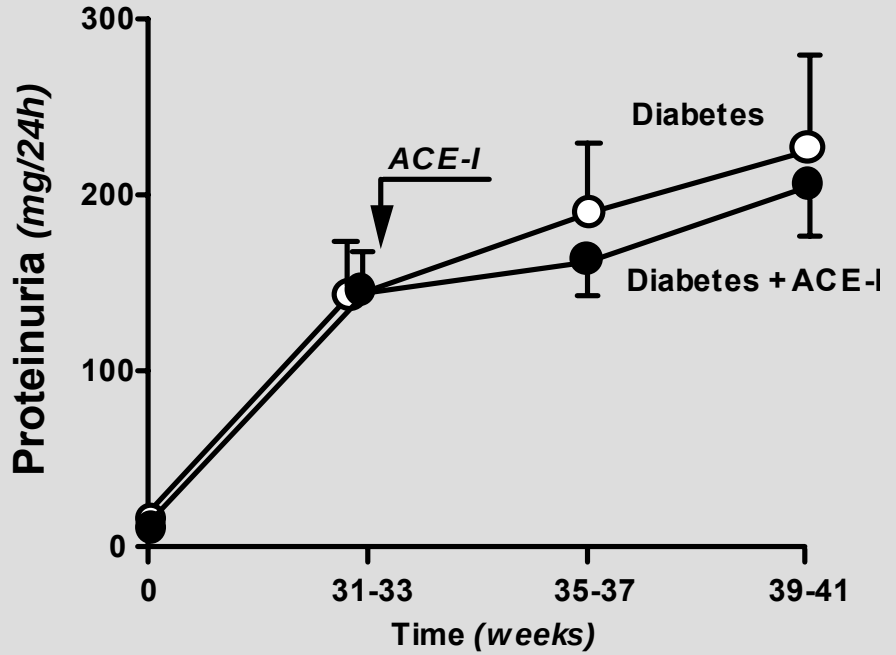
During follow-up, 1 patient in the candesartan group and 8 patients in the HCTZ group developed diabetes

Lindholm LH, *et al. J Hypertens* 2003; **21**(8): 1563–1574.

Can we prevent the development of microalbuminuria ?

ACE-I HAS A DIFFERENT EFFECT ON GLOMERULAR INJURY ACCORDING TO THE DIFFERENT PHASE OF THE DISEASE AT WHICH THE TREATMENT IS STARTED



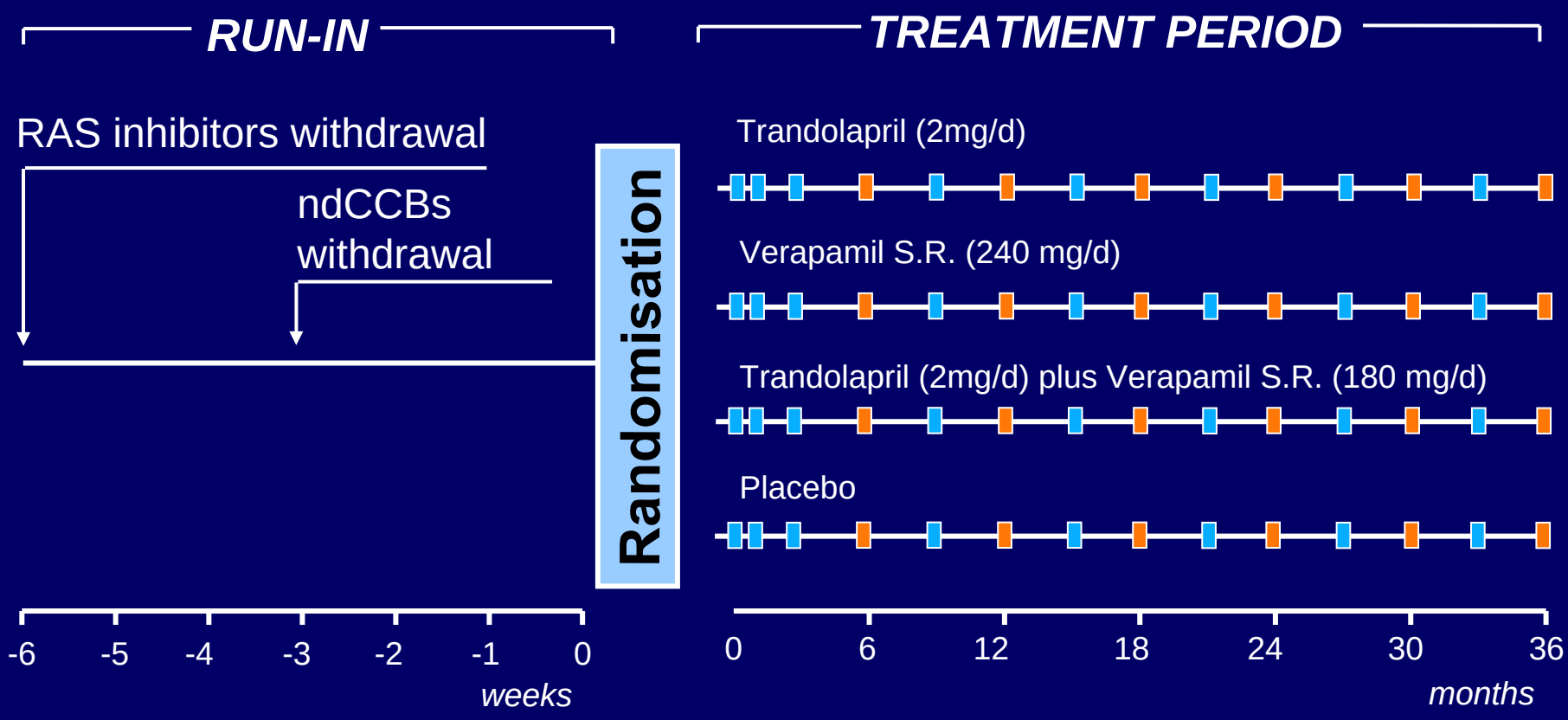


Perico et al., *J Am Soc Nephrol,* 1994

The **BE**rgamo **NE**phrologic **DI**abetic **C**omplications **T**rial **(BENEDICT)** was primarily aimed to assess whether microalbuminuria can be prevented in people with type 2 diabetes and normal urinary albumin excretion

Ruggenenti et al, NEJM, 2004

Study design



Ruggenenti et al, NEJM, 2004

Efficacy variables

- *Primary*

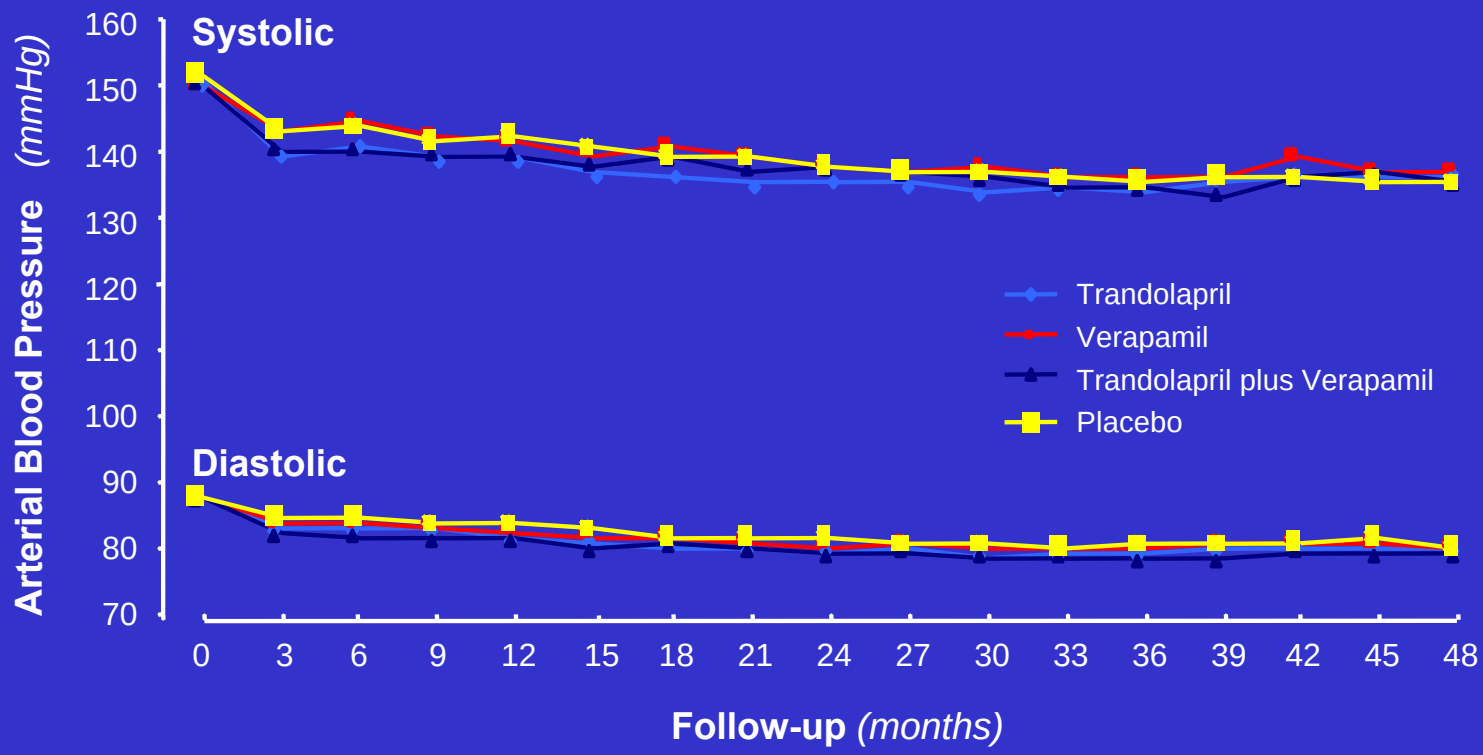
  - **Incidence of persistent microalbuminuria**
    (UAE > 20 µg/min) in 2 of 3 consecutive overnight collections confirmed 2 months apart

- *Secondary*

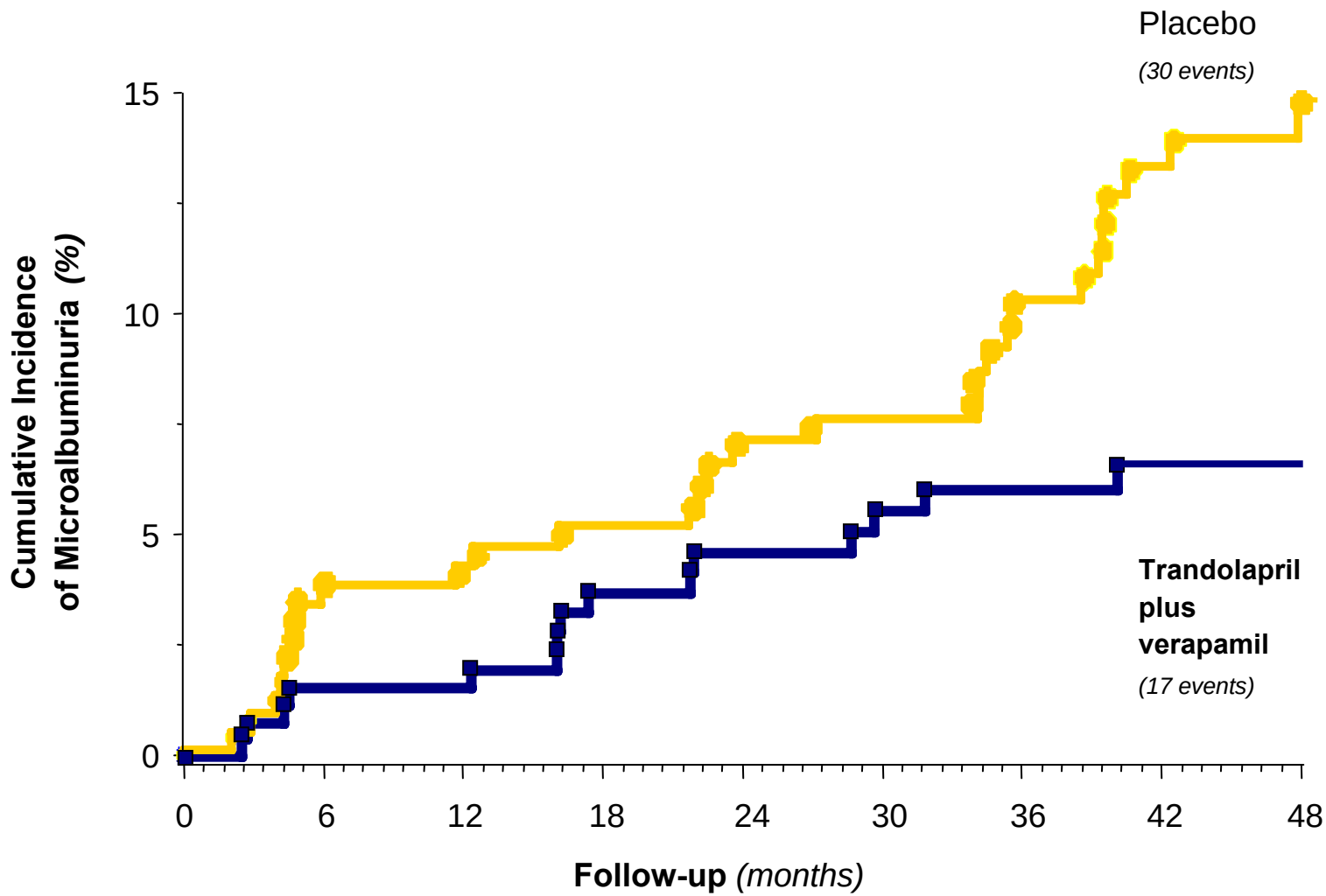
  - Rate of GFR decline *(in a subgroup)*
  - Rate of progression of retinopathy (in a subgroup)
  - Cumulative incidence of major cardiovascular events
  - Overall and cardiovascular mortality rate

Ruggenenti et al, NEJM, 2004

Blood pressure according to treatment group



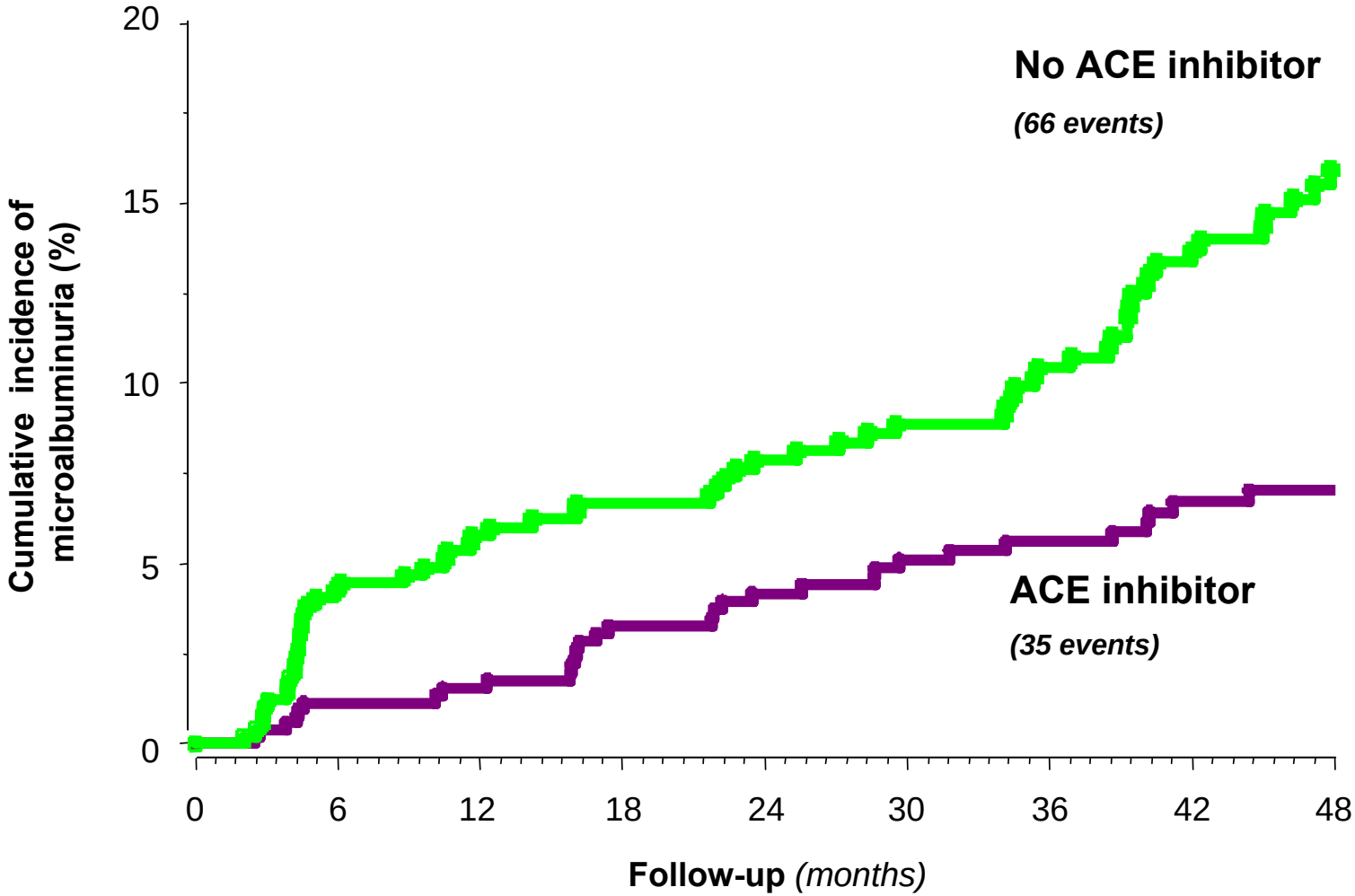
Ruggenenti et al, NEJM, 2004



No. at Risk

Trandolapril plus Verapamil	300	249	232	217	210	201	192	162	115
Placebo	300	229	214	203	187	176	164	136	89

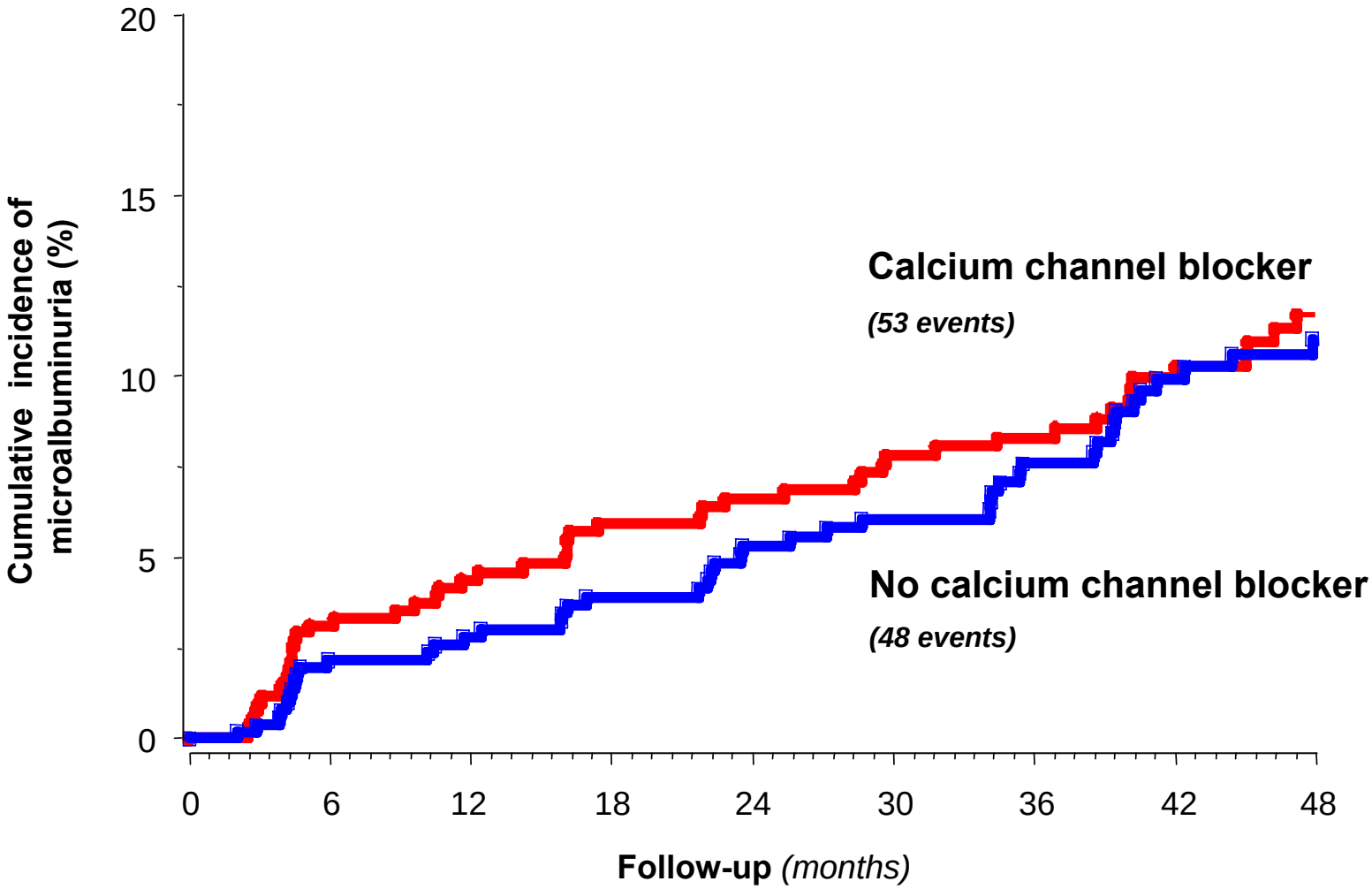
Ruggenenti et al, NEJM, 2004



No. at Risk

ACE inhibitor	601	503	469	441	417	399	380	311	220
No ACE inhibitor	603	463	424	405	376	357	338	270	188

Ruggenenti et al, NEJM, 2004



No. at Risk

Calcium channel blocker	603	483	442	419	399	382	366	296	214
No calcium channel blocker	601	483	451	427	394	374	352	285	194

Ruggenenti et al, NEJM, 2004

Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial

*ADVANCE Collaborative Group**

Summary

Background Blood pressure is an important determinant of the risks of macrovascular and microvascular complications of type 2 diabetes, and guidelines recommend intensive lowering of blood pressure for diabetic patients with hypertension. We assessed the effects of the routine administration of an angiotensin converting enzyme (ACE) inhibitor-diuretic combination on serious vascular events in patients with diabetes, irrespective of initial blood pressure levels or the use of other blood pressure lowering drugs.

Methods The trial was done by 215 collaborating centres in 20 countries. After a 6-week active run-in period, 11140 patients with type 2 diabetes were randomised to treatment with a fixed combination of perindopril and indapamide or matching placebo, in addition to current therapy. The primary endpoints were composites of major macrovascular and microvascular events, defined as death from cardiovascular disease, non-fatal stroke or non-fatal myocardial infarction, and new or worsening renal or diabetic eye disease, and analysis was by intention-to-treat. The macrovascular and microvascular composites were analysed jointly and separately. This trial is registered with ClinicalTrials.gov, number NCT00145925.

Lancet 2007; 370: 829–40

Published Online September 2, 2007 DOI:10.1016/S0140-6736(07)61303-8

See Comment page 804

*Collaborators listed at end of paper

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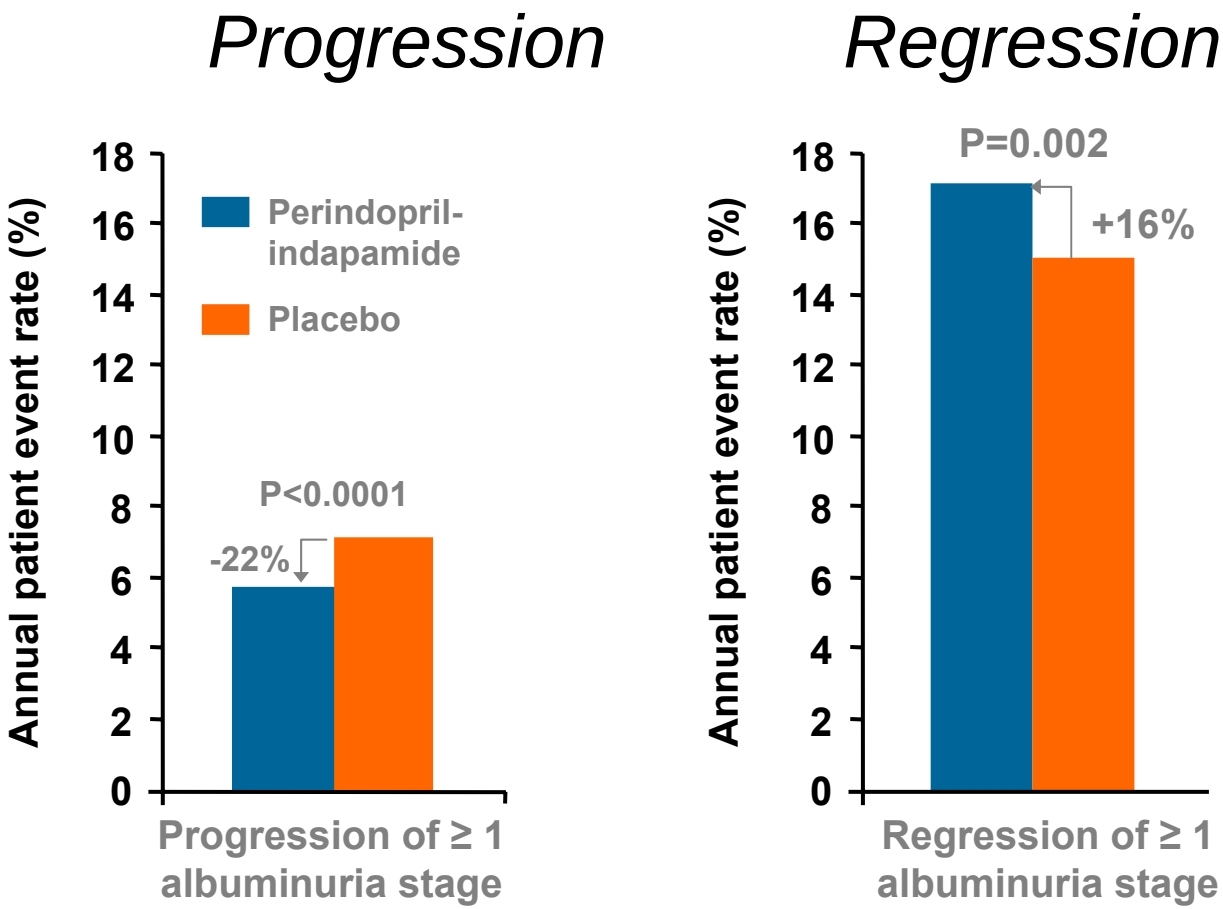
Renal outcomes

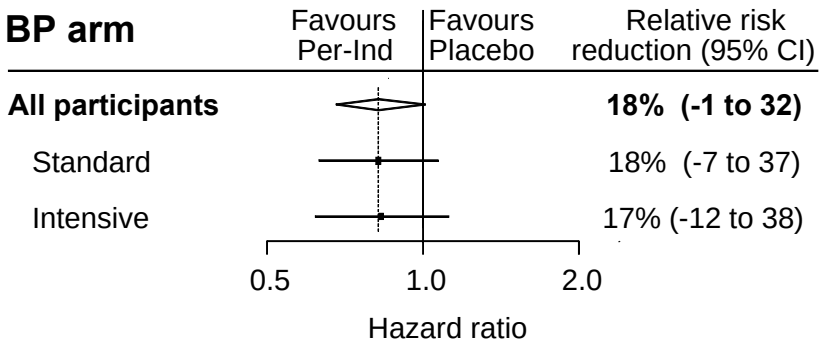
- Major composite renal outcome
  - New-onset microalbuminuria (UACR 30-300 µg/mg)
  - New-onset nephropathy (UACR >300 µg/mg)
  - Doubling of serum creatinine >200 µmol/L (2.3 mg/dL)
  - Requirement for renal replacement therapy or renal death

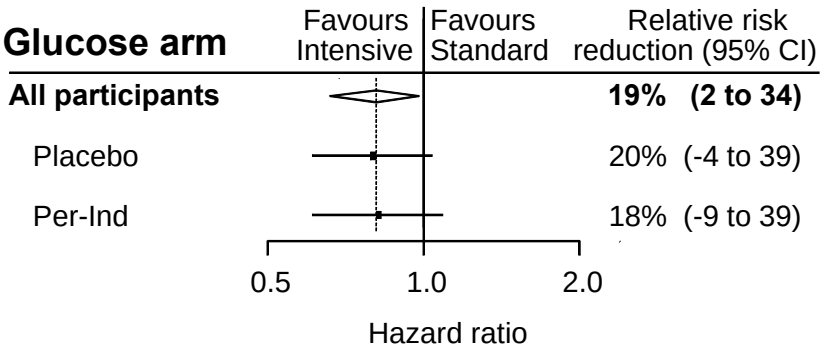
Changes in albuminuria in ADVANCE



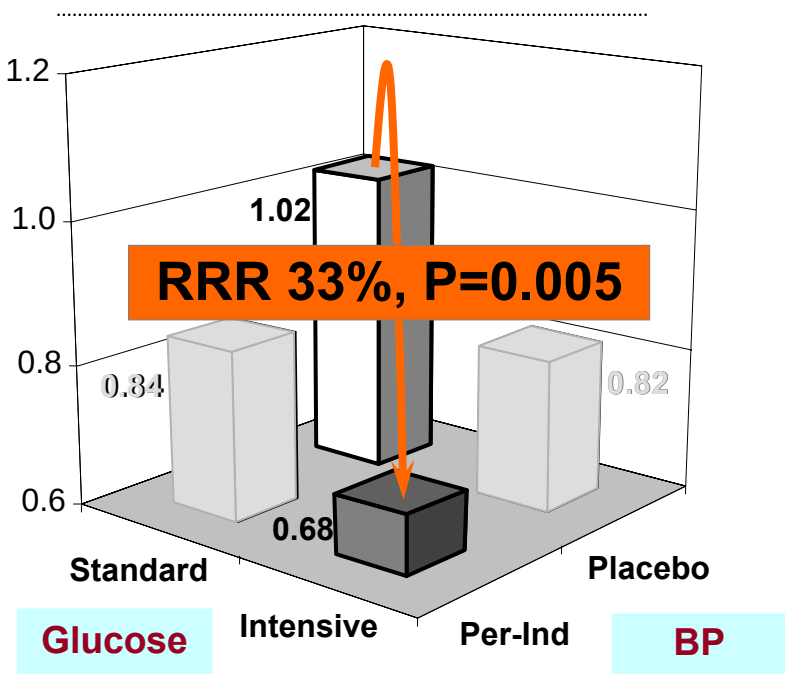
New or worsening nephropathy

Hazard ratios



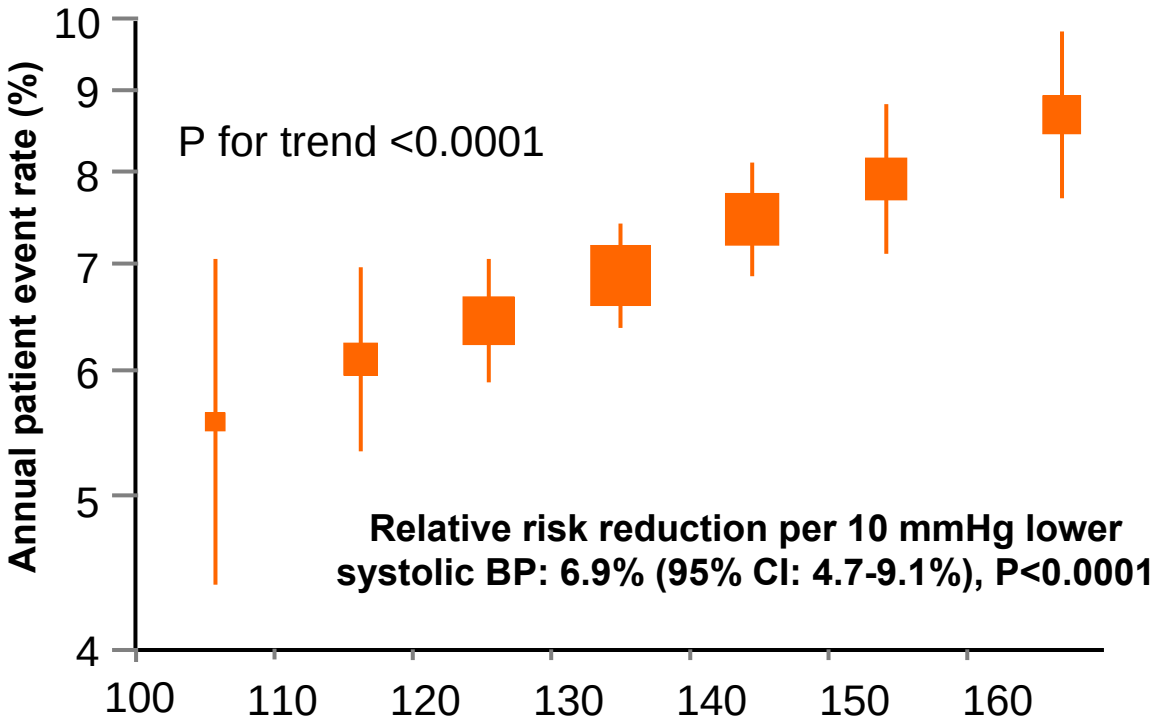


Annual event rate %



P for interaction=0.93

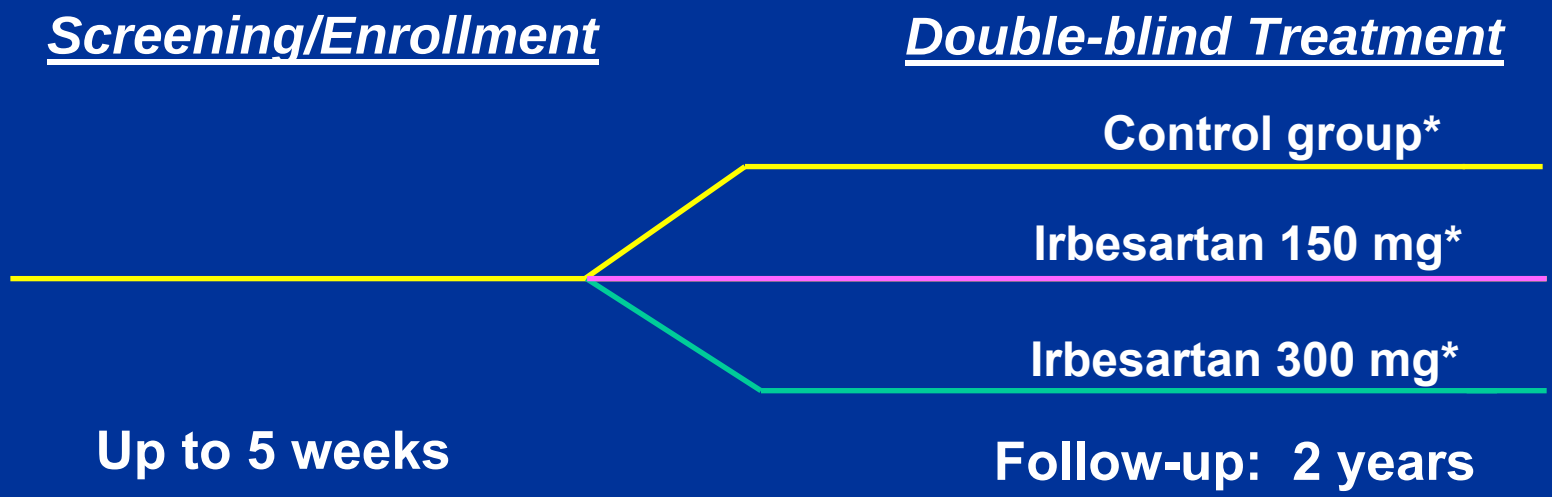
Major renal outcomes by systolic blood pressure achieved during follow-up*



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

IRMA 2: Study Design

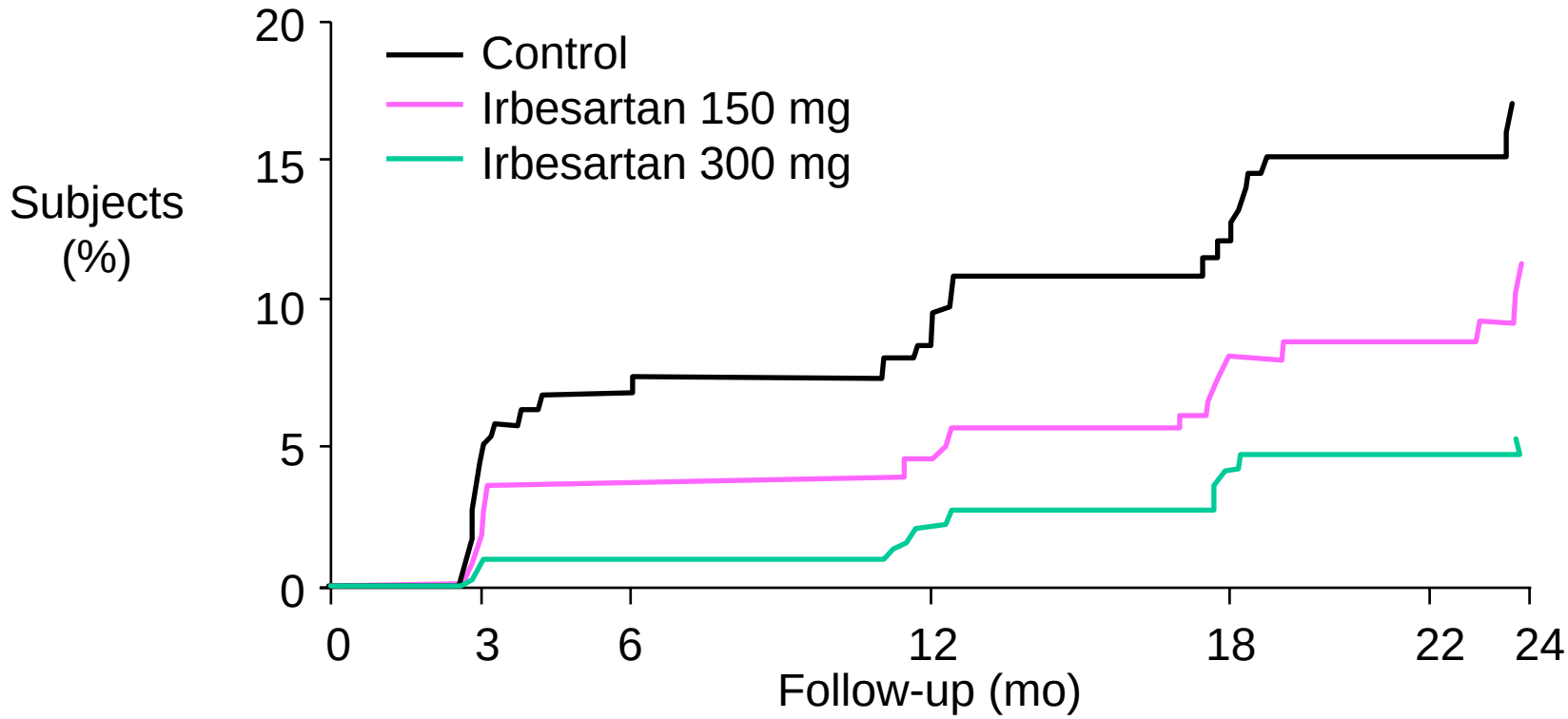
- **590 patients with hypertension, type 2 diabetes, microalbuminuria (albumin excretion rate 20–200 µg/min), and normal renal function**



* Adjunctive antihypertensive therapies (excluding ACE inhibitors, angiotensin II receptor antagonists, and dihydropyridine calcium channel blockers) could be added to all groups to help achieve equal blood pressure levels.

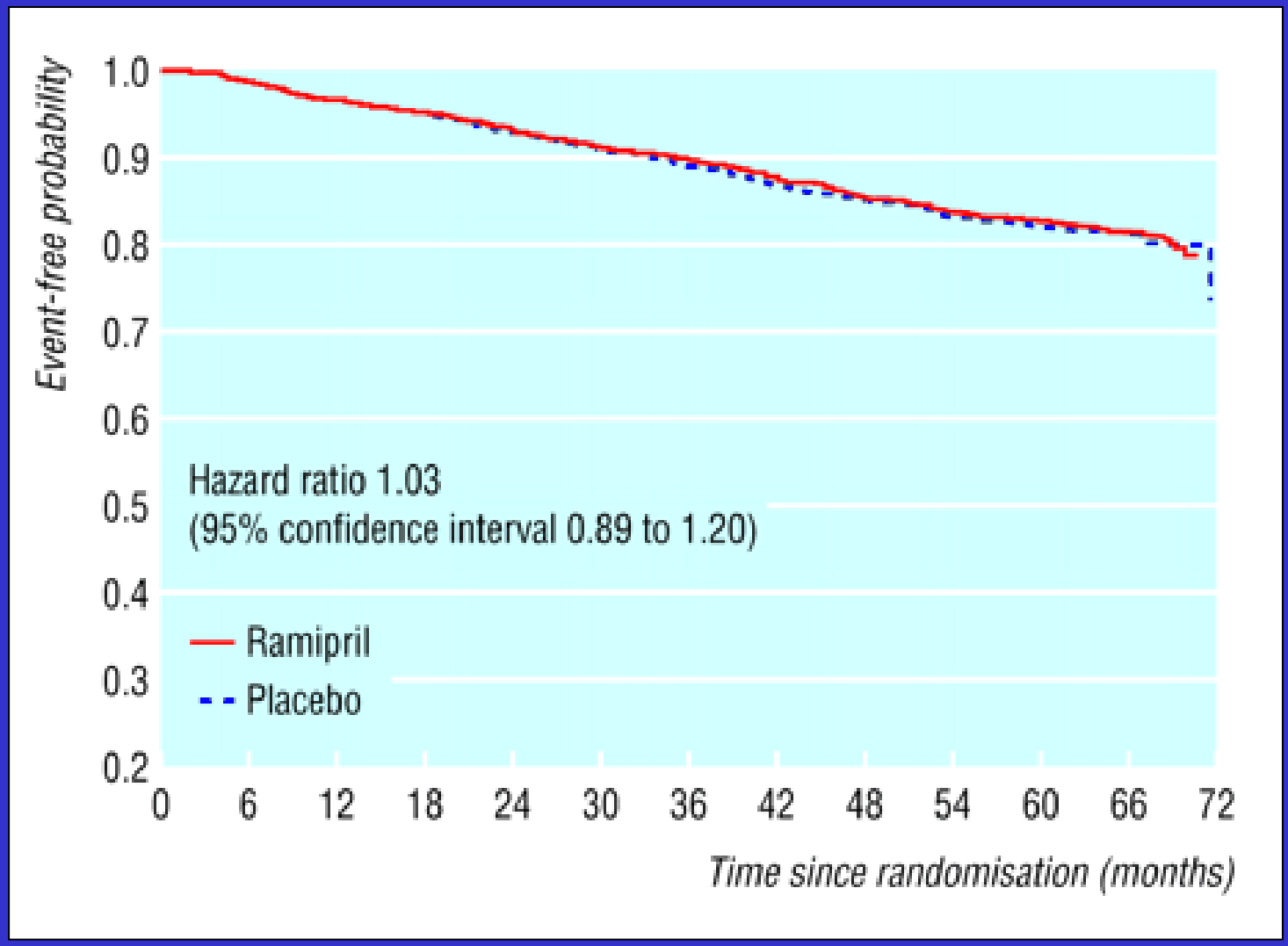
Parving H-H, et al. *N Engl J Med* 2001;345:870-878.

IRMA 2 Primary Endpoint
Time to Overt Proteinuria



Parving H-H, et al. *N Engl J Med* 2001;345:870-878.

The DIABHYCAR study: a low dose of ramipril (1.25mg) is not protective in diabetes



BMJ 2004; 328:495

The DROP study: Objectives

Purpose:

- To assess the ability of high-dose valsartan to reduce proteinuria in subjects with diabetic nephropathy

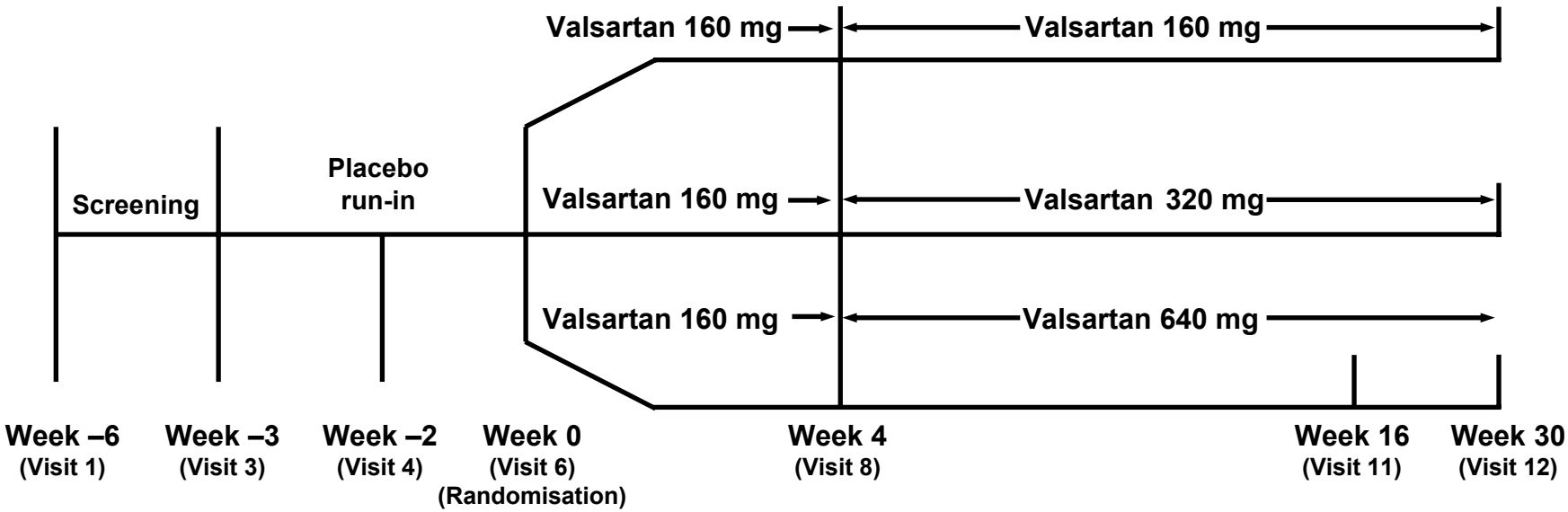
Primary Objective:

- To compare responses to valsartan at 160, 320, and 640 mg/day in patients with hypertension, type 2 diabetes mellitus, and albuminuria (30–1,000 mg/d)

Hollenberg NK et al, J Hypertens, 2007, 25:1921-1926

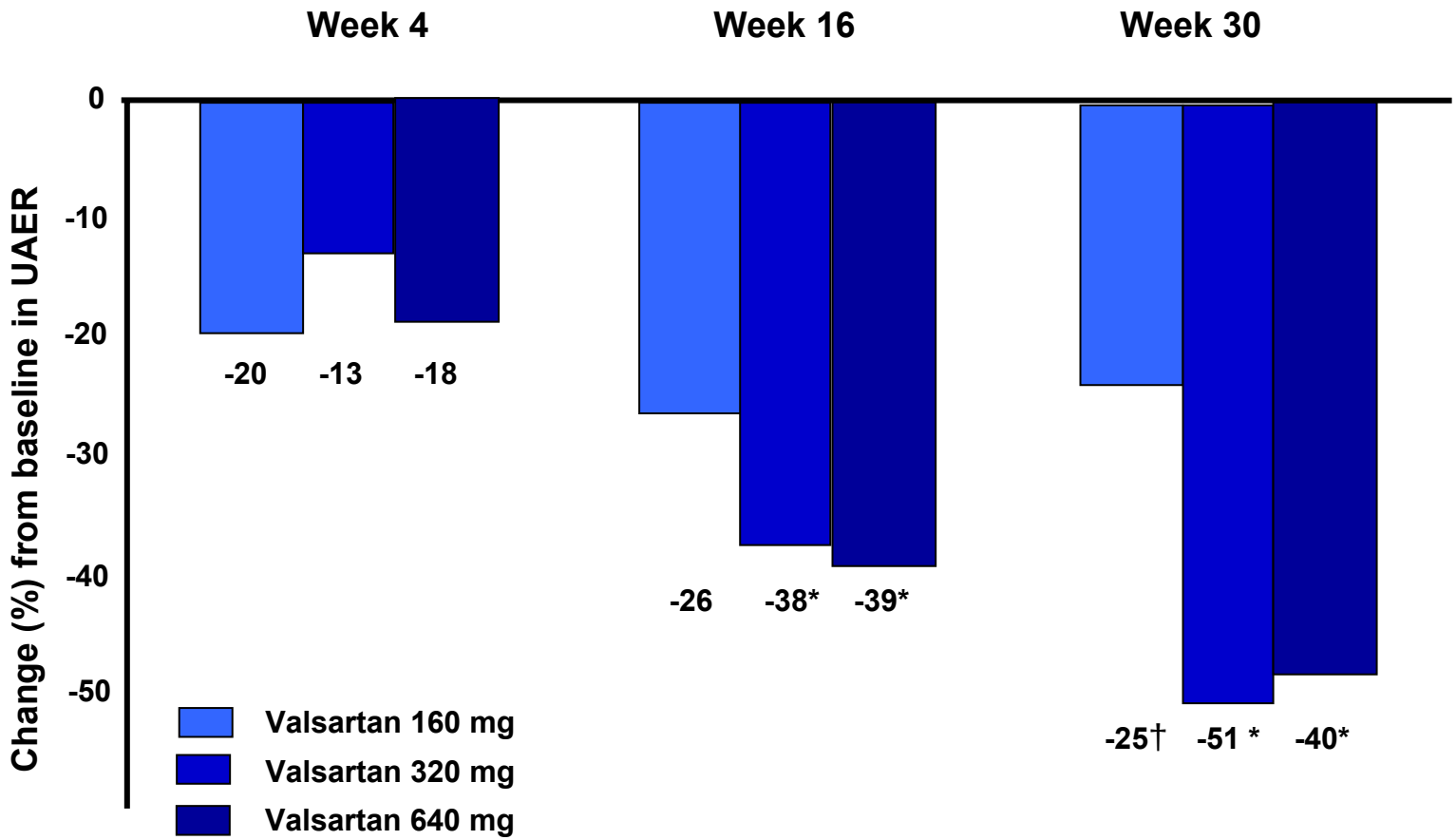
Study Design

- Design: multicentre, double-blind, randomized, parallel group study
- Patient population: subjects with hypertension, proteinuria and T2DM



Hollenberg NK et al, J Hypertens, 2007, 25:1921-1926

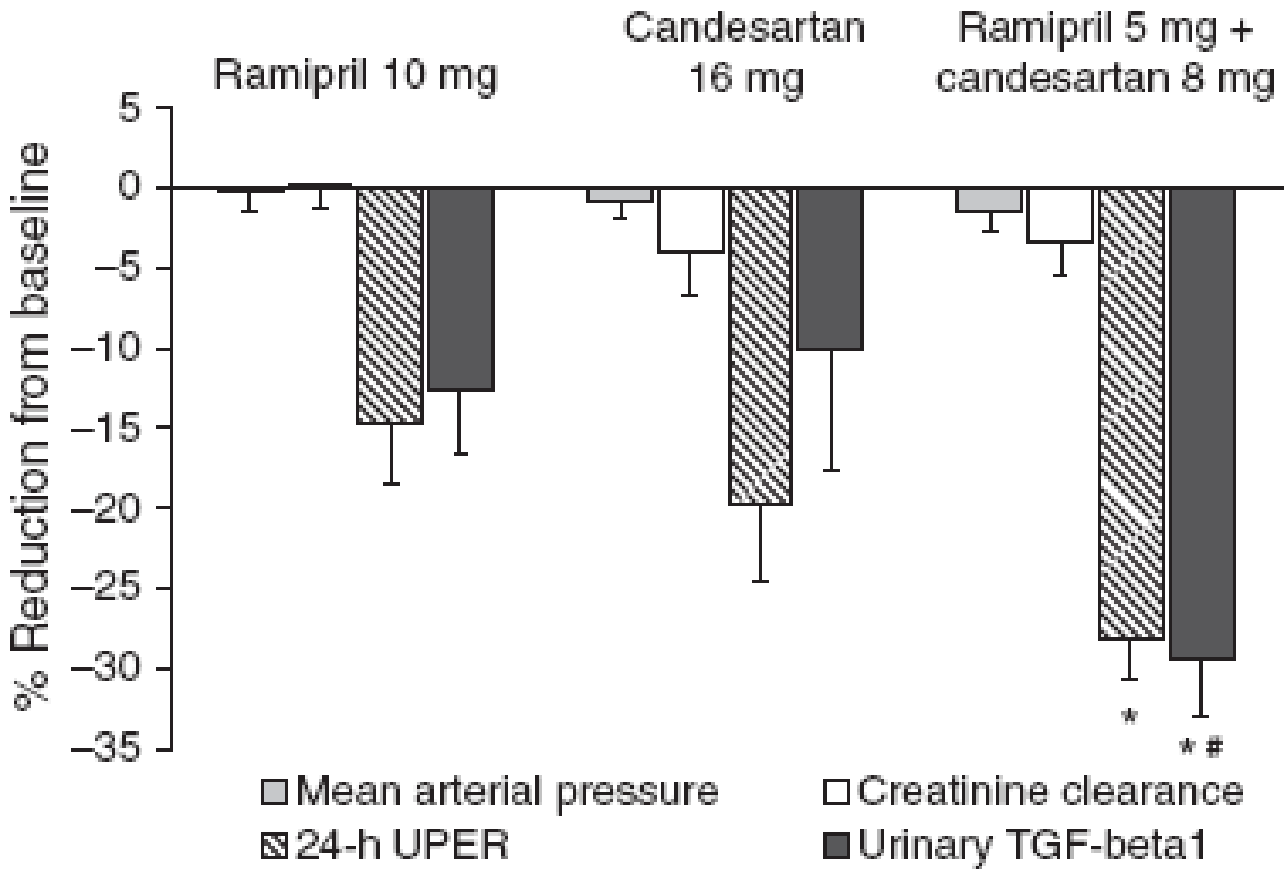
Time Course for Change from Baseline in Urinary Albumin Excretion Rate



*p<0.001 (320 mg and 640mg vs baseline); †p=0.03 (160 mg vs baseline).

Hollenberg NK et al, J Hypertens, 2007, 25:1921-1926

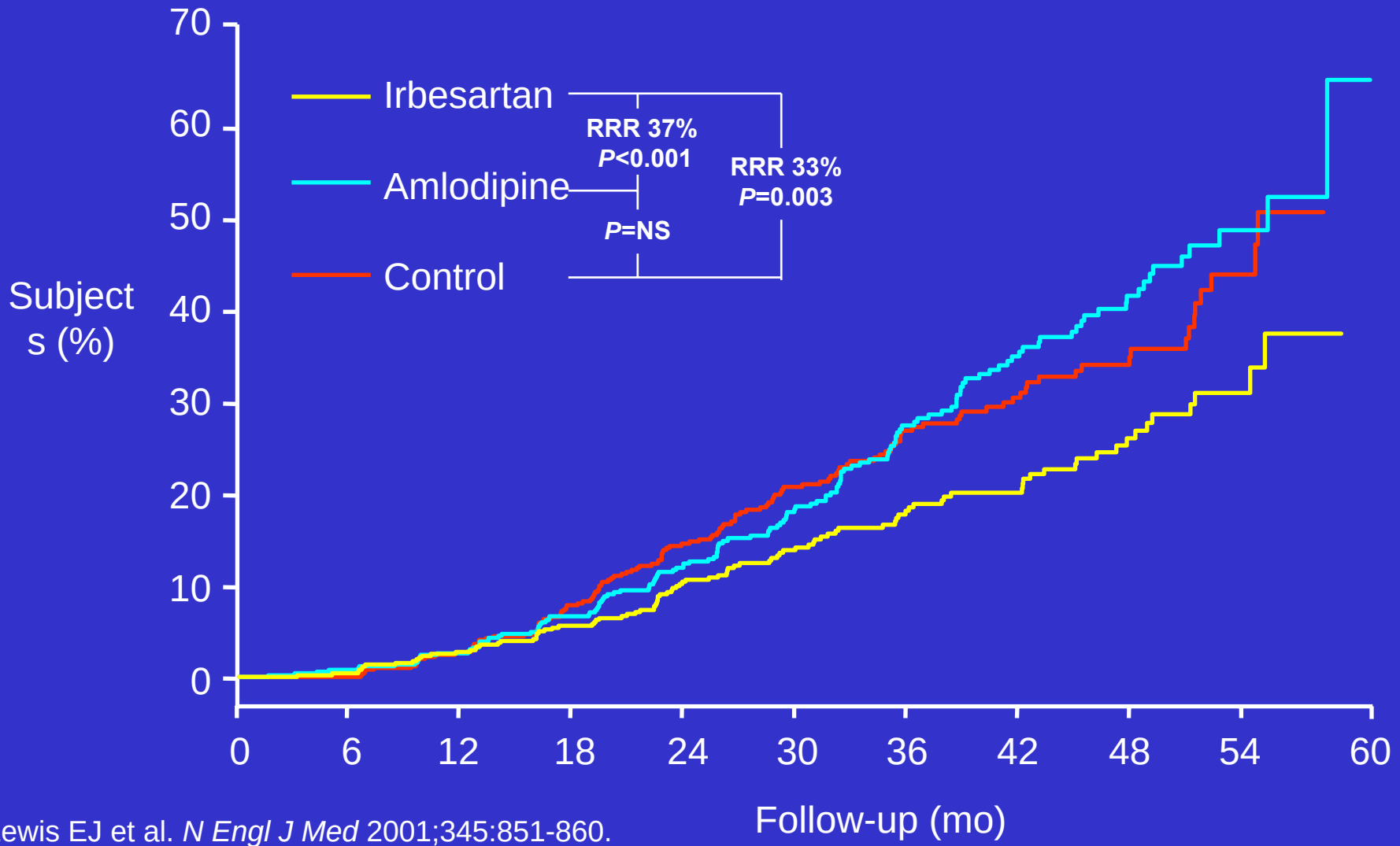
Effect of candesartan and ramipril alone or in combination on urinary protein and TGFbeta1 excretions



Song JH et al, NDT, 2006

IDNT

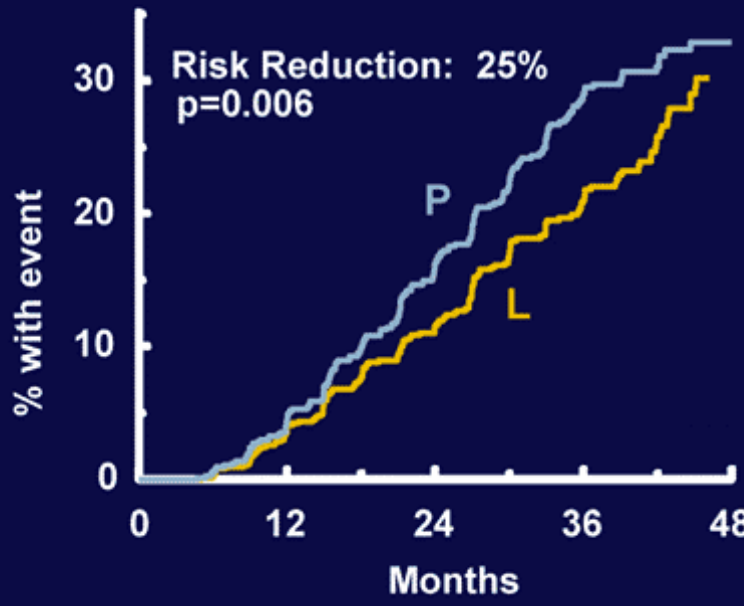
Time to Doubling of Serum Creatinine



Lewis EJ et al. *N Engl J Med* 2001;345:851-860.

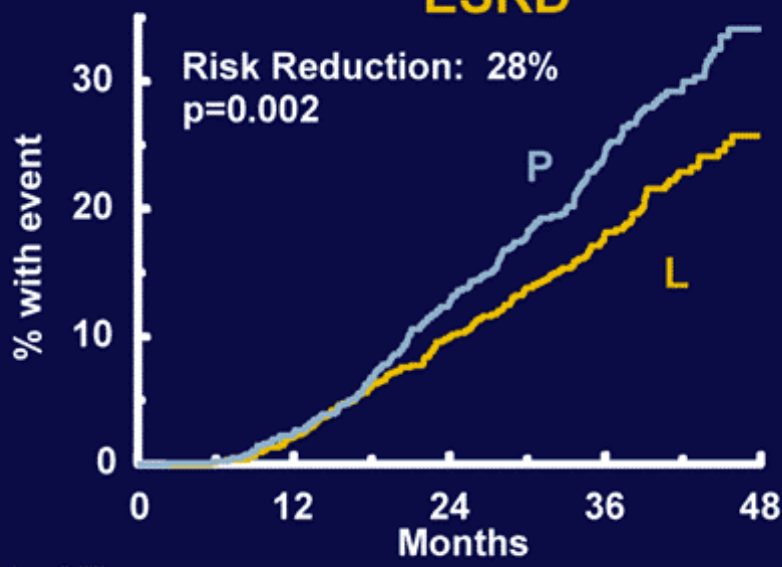
RENAAL Primary Components

Doubling of Serum Creatinine



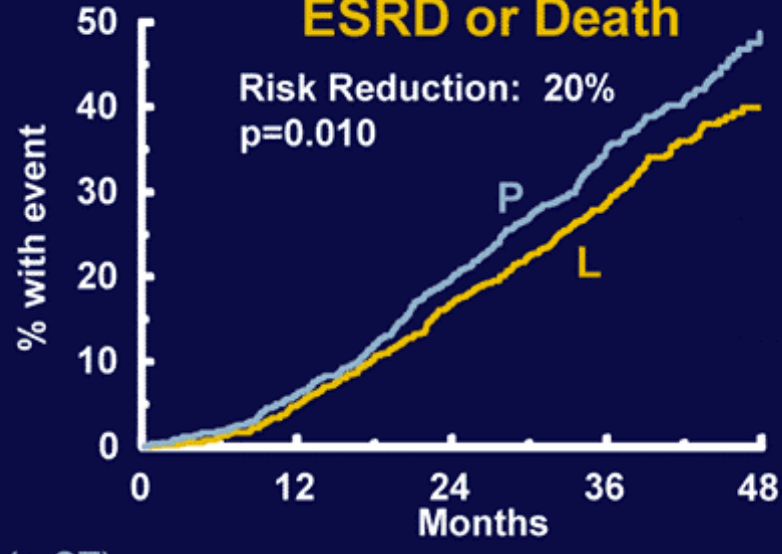
P (+ CT)	762	689	554	295	36
L (+ CT)	751	692	583	329	52

ESRD



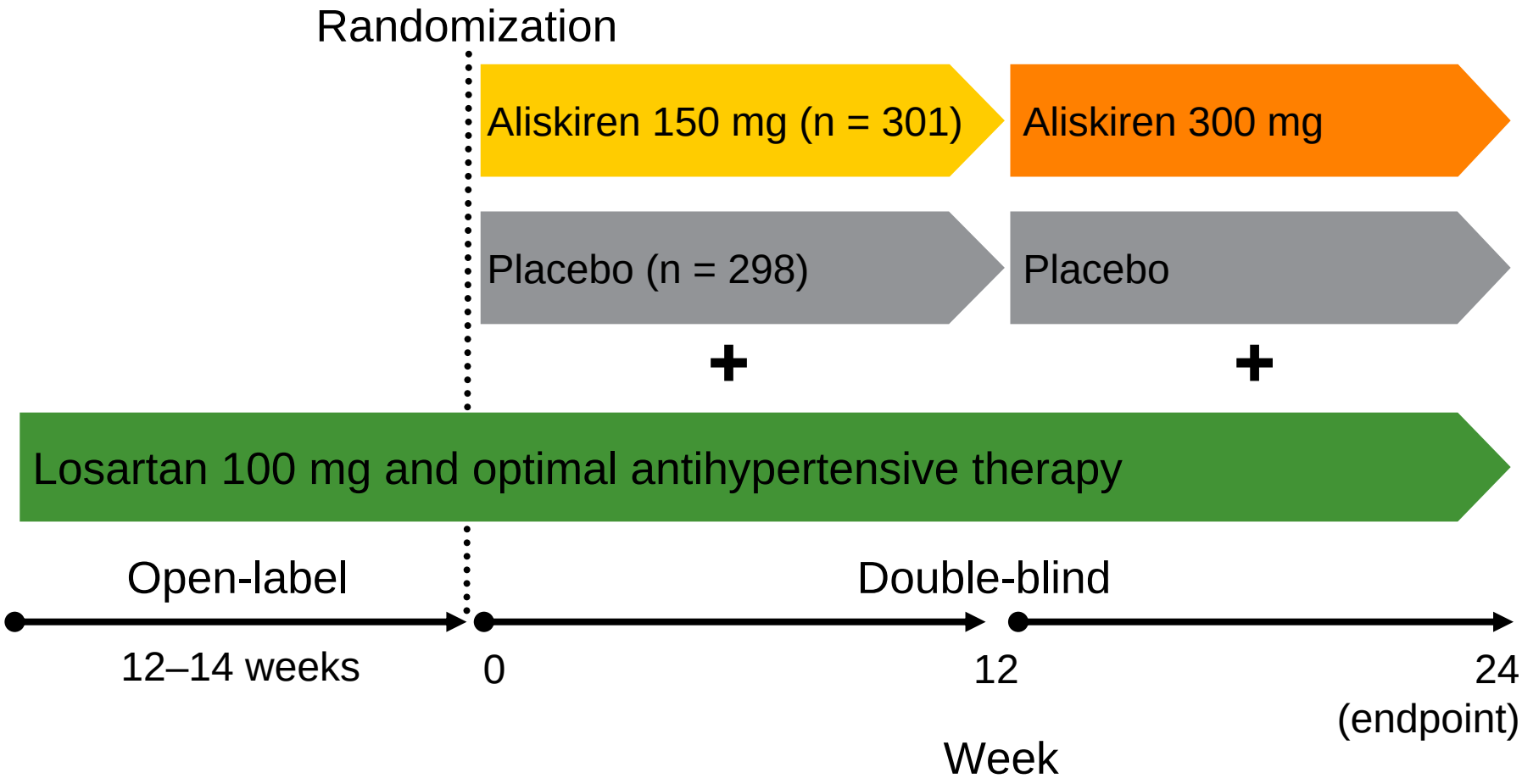
P (+ CT)	762	715	610	347	42
L (+ CT)	751	714	625	375	69

ESRD or Death



P (+ CT)	762	715	610	347	42
L (+ CT)	751	714	625	375	69

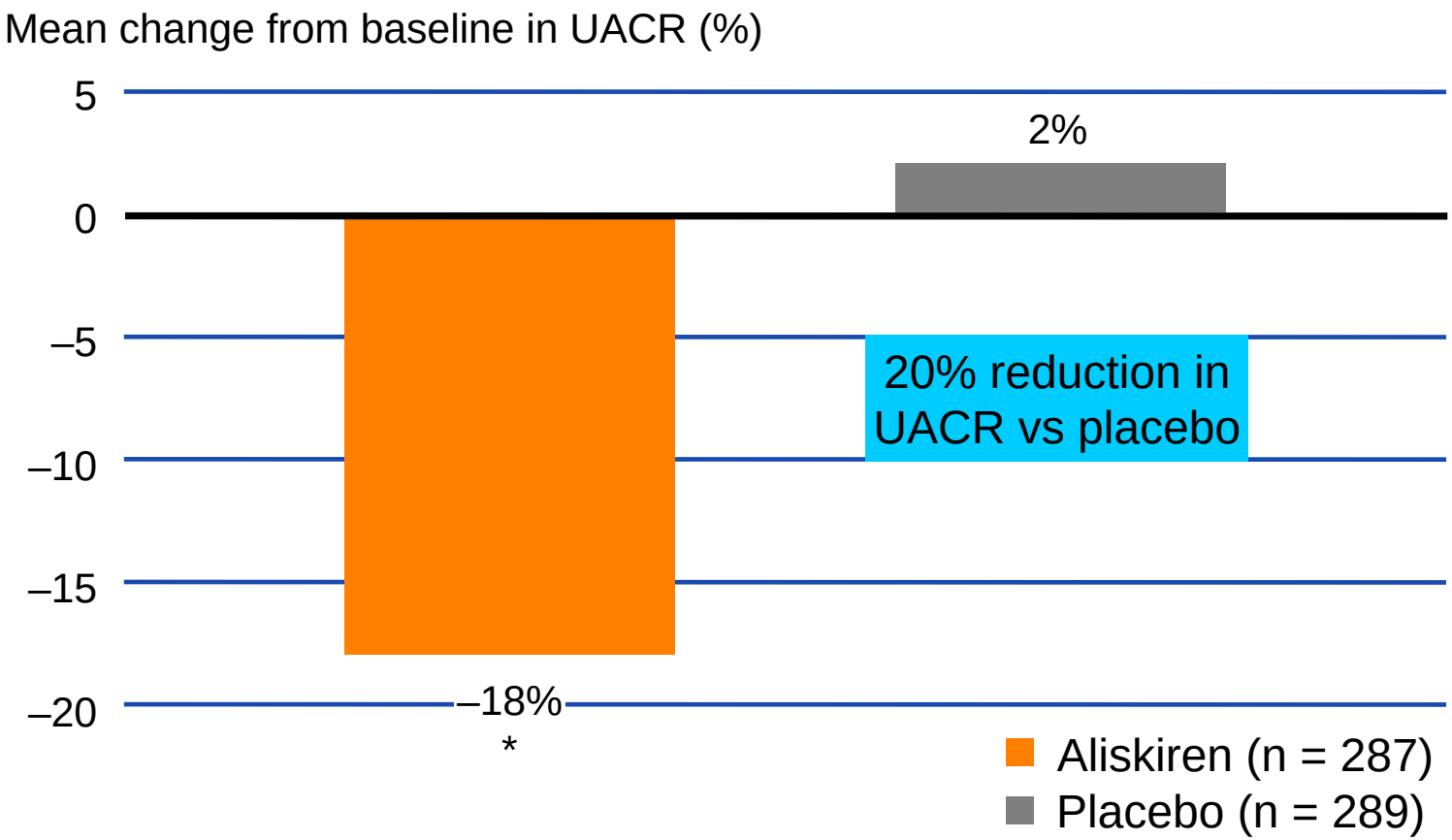
A double-blind, randomized, placebo-controlled study in hypertensive patients with type 2 diabetes and nephropathy



Forced titration at week 12
All doses were administered once daily

ASN, 2007, oral presentation

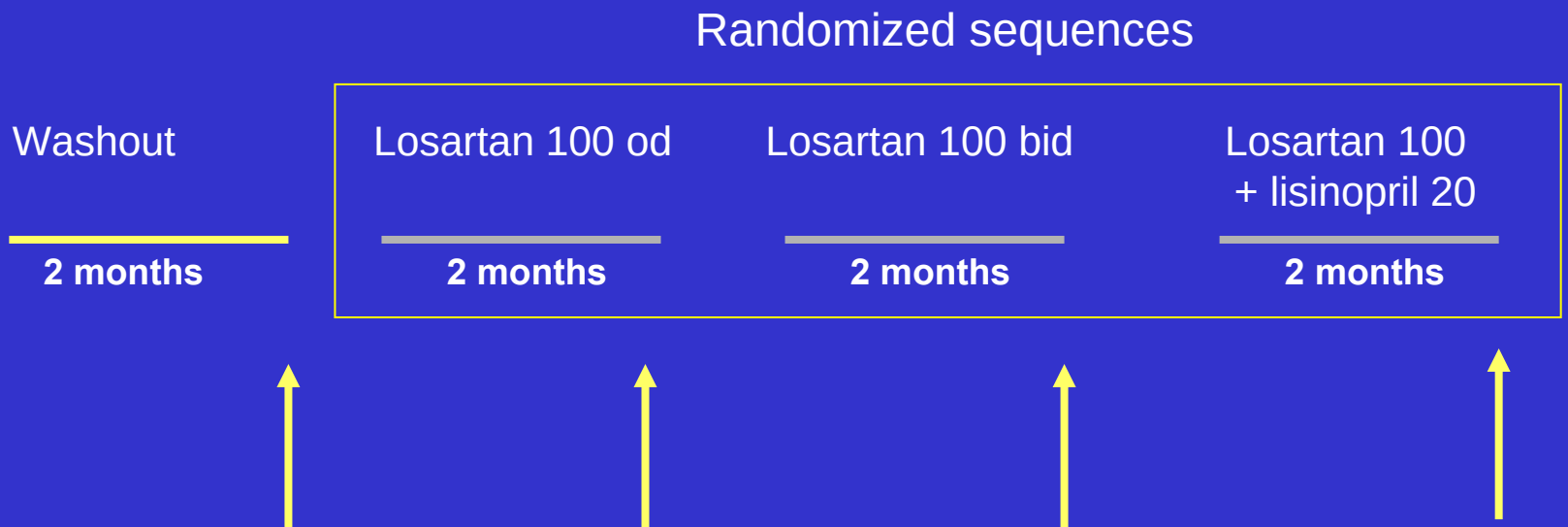
Aliskiren significantly reduced UACR from baseline to week 24 endpoint compared with placebo



*p = 0.0009
Data are shown as percentage change in geometric mean
Baseline was week −2 value
UACR, urinary albumin:creatinine ratio

Study design of the PROTECT study

Monocentric study, triple cross-over in non-diabetic patients with proteinuric nephropathies.

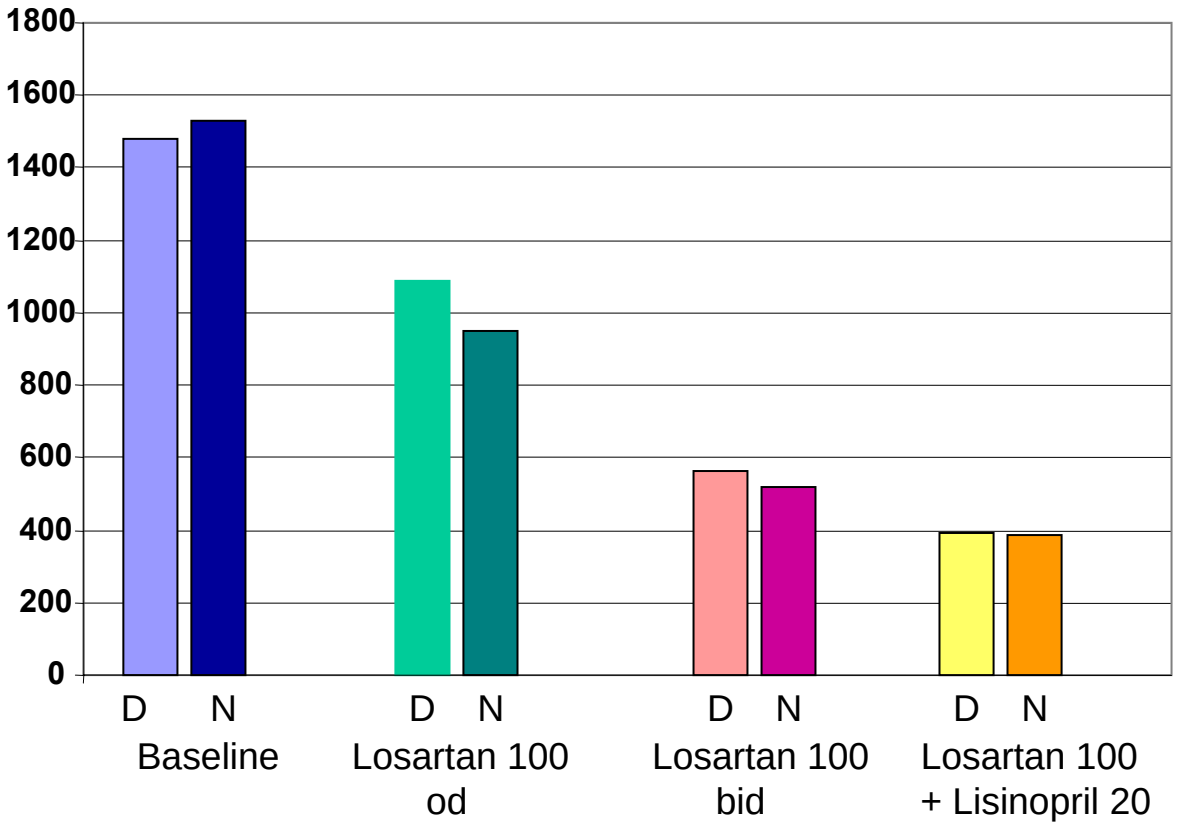


Proteinuria (D/N)
Renal hemodynamics (inulin, PAH clearances)
ABPM

Meier et al, abstract ASN 2008

Effect of a high dose of losartan on proteinuria in patients with diabetic and non-diabetic nephropathies

Proteinuria (ug/min)



Median (n=20)

Meier et al, abstract ASN 2008

EFFECTIVENESS OF RAS INHIBITION IN TYPE 2 DIABETES

Preventive Intervention	*Model structure*
BENEDICT, ADVANCE	**Normoalbuminuria** →
IRMA-2, ADVANCE	**Microalbuminuria** →
RENAAL, IDNT	**Overt nephropathy** →
	ERSD →

Aldosterone Blockade in Diabetic Kidney Disease

TABLE 1. CLINICAL CHARACTERISTICS AND FINDINGS BEFORE AND AFTER TREATMENT WITH SPIRONOLACTONE IN EIGHT PATIENTS.

SEX	AGE	URINARY PROTEIN		CREATININE CLEARANCE		SYSTOLIC PRESSURE		DIASTOLIC PRESSURE		DIAGNOSIS
		BEFORE TREATMENT	AFTER TREATMENT	BEFORE TREATMENT	AFTER TREATMENT	BEFORE TREATMENT	AFTER TREATMENT	BEFORE TREATMENT	AFTER TREATMENT	
	yr	g/day		ml/sec		mm/Hg				
Male	62	2.87	0.94	1.30	0.66	120	120	80	70	Type 2 diabetes
Male	60	8.90	3.30	0.58	0.59	120	110	80	70	Type 2 diabetes
Female	43	2.83	2.94	2.50	2.02	120	110	90	70	Systemic lupus erythematosus
Male	71	3.00	1.80	0.62	0.45	200	170	100	90	Type 2 diabetes
Male	55	2.21	0.86	2.40	3.90	170	130	90	80	Type 2 diabetes
Male	74	6.17	2.02	1.24	1.30	120	130	90	80	Focal sclerosis with segmental hyalinosis
Male	61	1.17	0.36	1.71	1.51	140	160	90	70	Type 2 diabetes
Female	31	3.30	1.75	0.48	0.53	120	115	90	80	Vasculitis
Mean ±SD*		3.81±2.50	1.75±1.02	1.35±0.80	1.37±1.17	138.8±30.4	130.6±22.7	88.8±6.4	76.3±7.4	

*$P<0.02$ for the comparison between pretreatment and post-treatment urinary protein, by the paired t-test. There were no other significant differences between pretreatment and post-treatment values.

54% reduction in proteinuria after 4 weeks add-on treatment with spironolactone.

No significant differences in BP or creatinine clearance

Chrysostomou et al: N Engl J Med 345:925-926, 2001

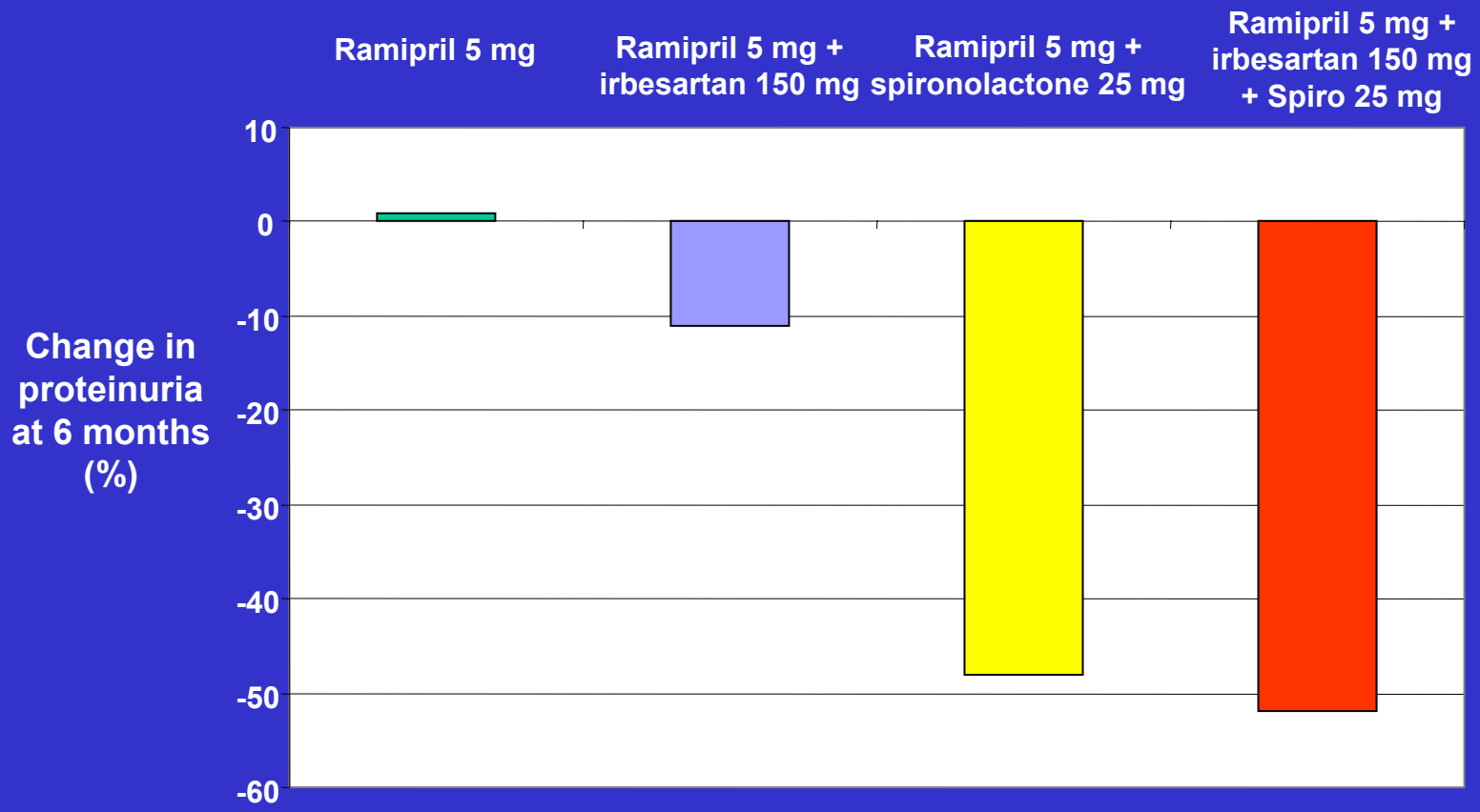
Metanalysis of studies using mineralocorticoid receptor blockade in diabetic and non-diabetic nephropathies

Paralle-group RCTs	N	Drug	Dose	Duration	Effect on prot.
Bianchi et al, 2006	165	Spironolactone	25	12 m	-54 vs 6%
Chrysostomou et al, 2006	41	Spironolactone	25	3 m	-45 vs -9
Epstein et al, 2006	268	Eplerenone	50/100	12 w	-45 vs -7
Van den Meiracker, 2006	59	Spironolactone	25/50	12 m	-44 vs -4
Cross-over RCTs					
Rachmaniet al, 2004	23	Spironolactone	50	24w	-38
Rossing et al, 2005	20	Spironolactone	25	8w	-33
Schjoedt et al, 2005	20	Spironolactone	25	8w	-30
Schjoedt et al, 2006	20	Spironolactone	25	8w	-32
Non-RCTs					
Bianchi et al, 2005	42	Spironolactone	25	8w	-50
Chrysostomou et al, 2001	8	Spironolactone	25	4w	-54
Furumatsu et al, 2003	12	Spironolactone	25	8w	-32 vs –19
Nitta et al, 2004	9	Spironolactone	25	6m	-15
Nowicki et alm 2003	5	Spironolactone	12.5	4w	-38
Sato et al, 2005	32	Spironolactone	25	12w	-38
Shiigai et al, 2003	26	Spironolactone	25	10m	-20

Hyperkalemic events were significant in only 1 of 8 randomized controlled trials.

Significant decreases in BP and GFR in approximately 40% and 25% of included studies, respectively.

Effect of aldactone on proteinuria in patients receiving a blocker of the renin-angiotensin system



N=10 patients per group,
Double-blind, placebo-controlled

Chrysostomou et al, Clin JASN, 2006; 1:256-262

Aldosterone Blockade in Diabetic Kidney Disease

Be careful of hyperkalemia

Conclusions

Diabetic nephropathy can be effectively prevented by blockade of the renin angiotensin system prescribed at the right dose

Prevention of DN also needs:

- a perfect control of BP
- a maximal decrease in proteinuria
- the control of glycemia
- the control of dyslipidemia