Renal Protection in Hypertensive Patients at Cardiovascular Risk

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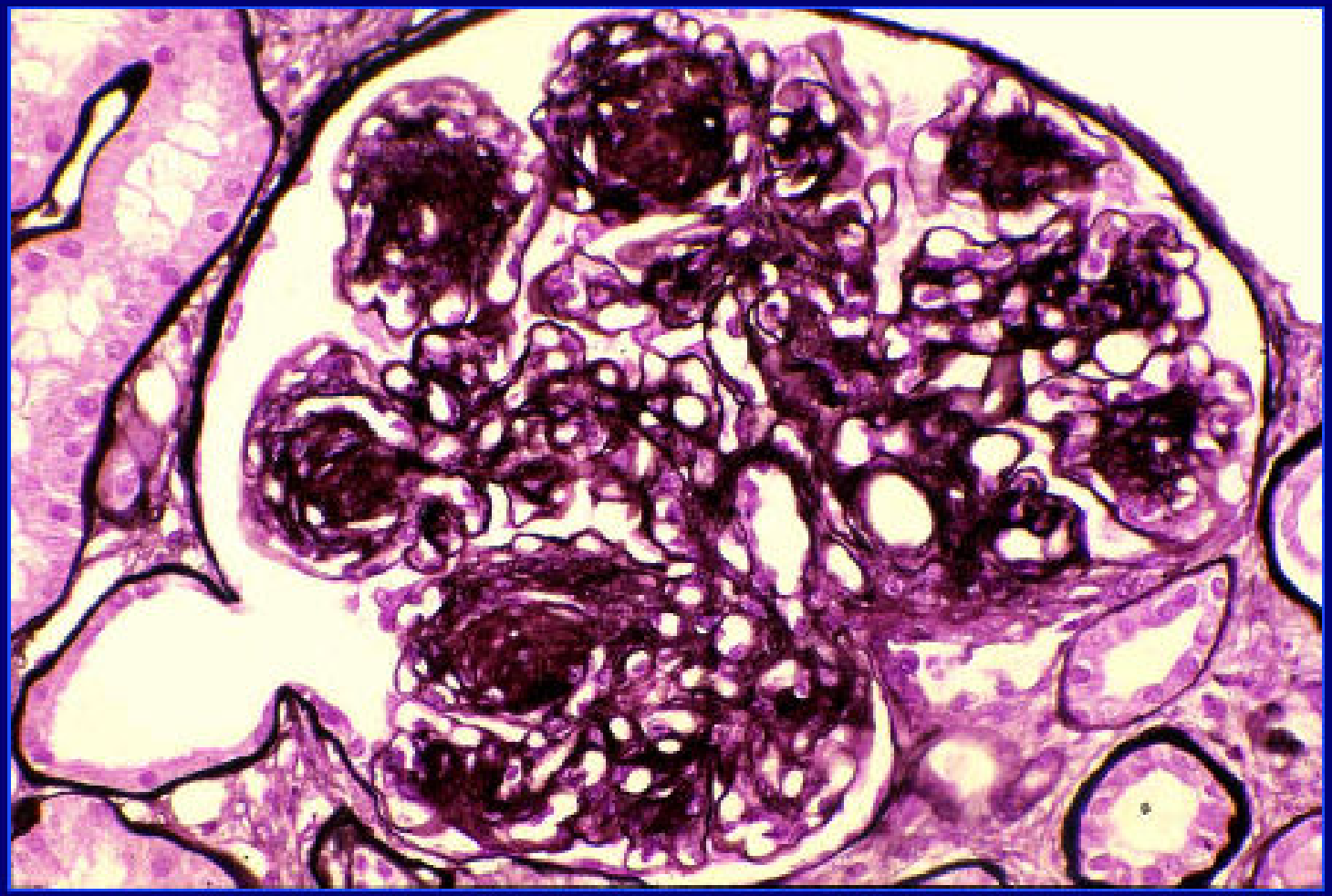
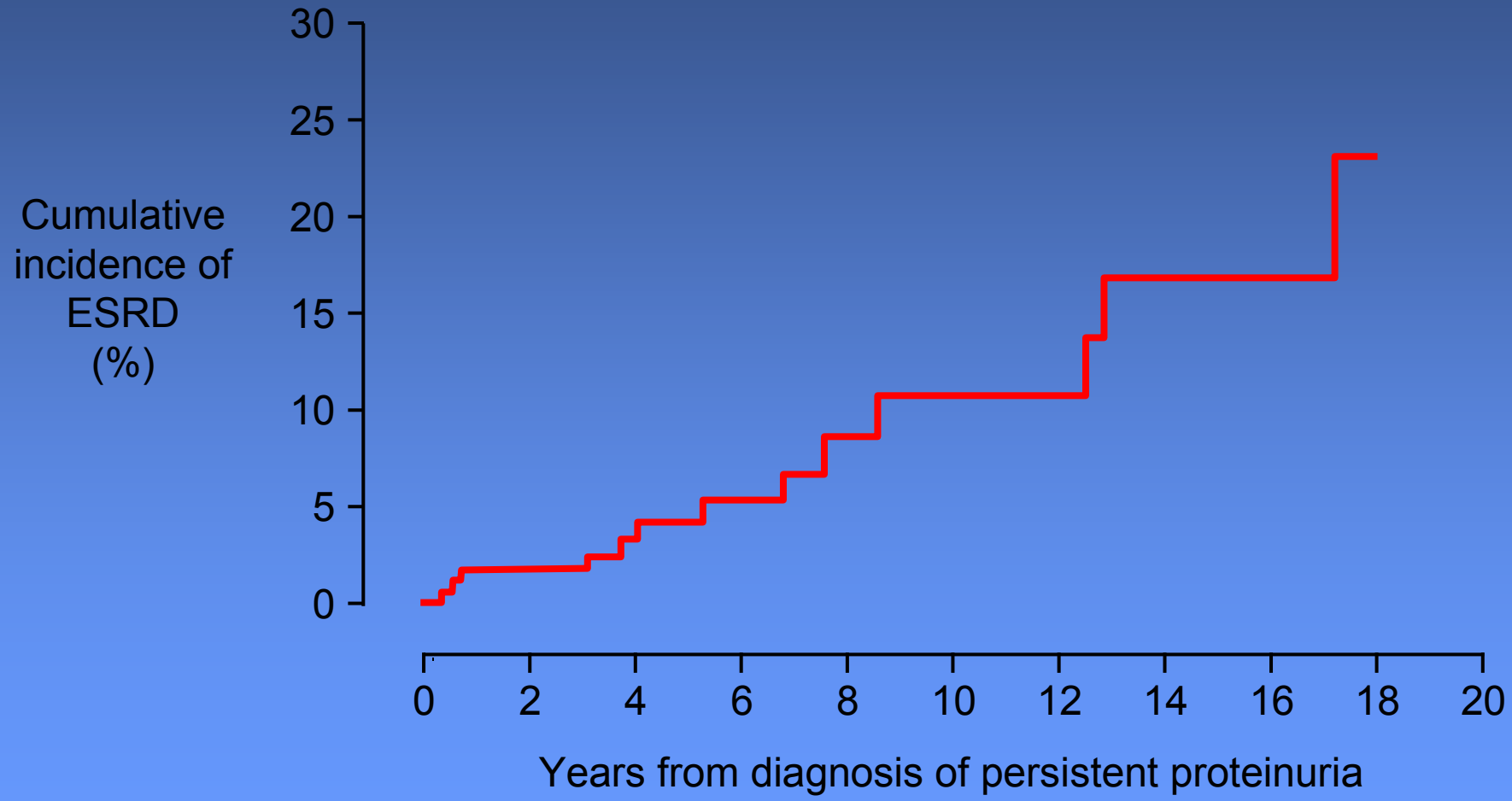
Glomerular Histopathology in Type 2 Diabetic Nephropathy

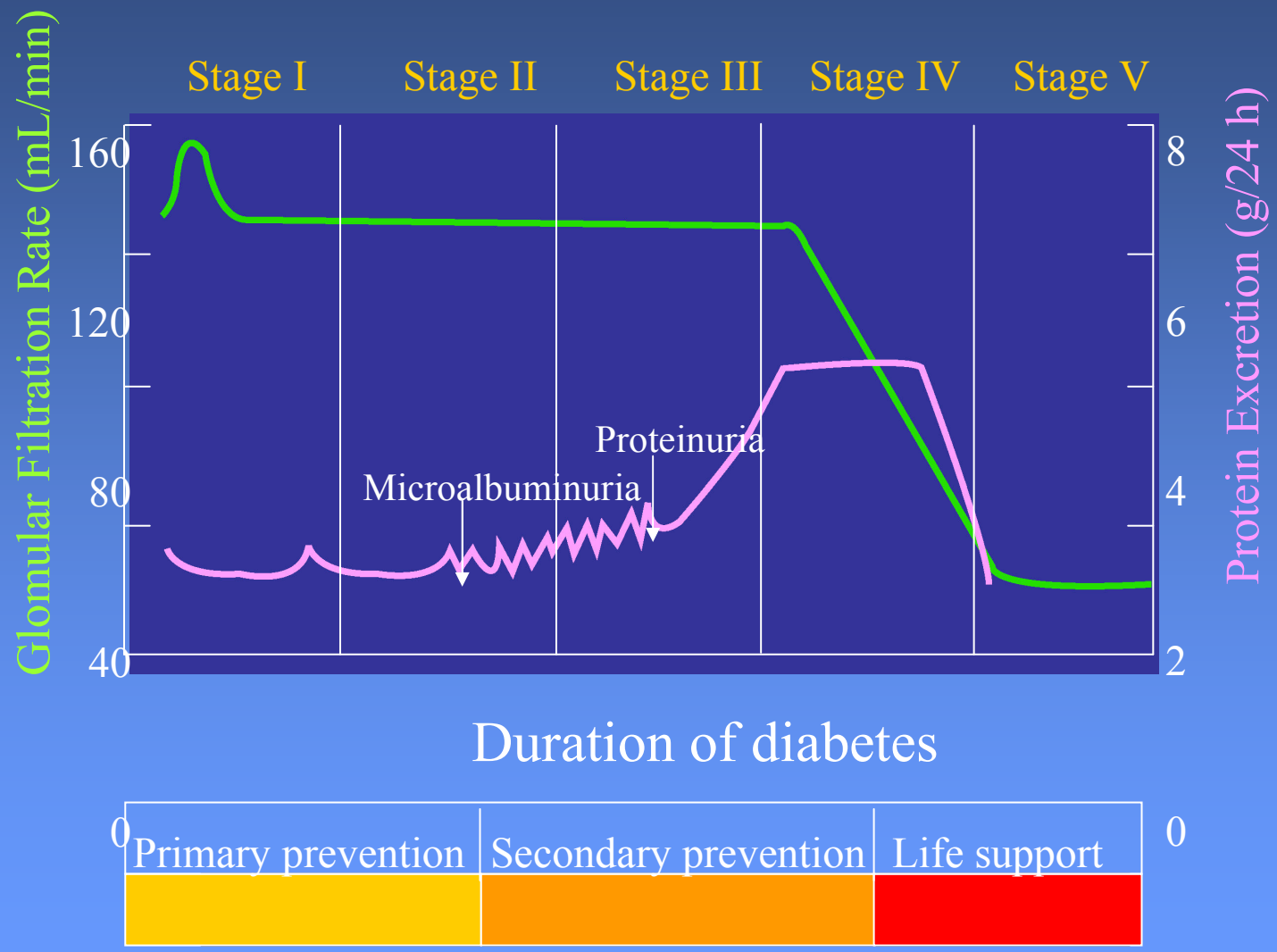


Development of ESRD in Type 2 Diabetes After Diagnosis of Proteinuria



Humphrey et al. *Ann Int Med* 1989;111:788-796.

Typical Course of Diabetic Nephropathy

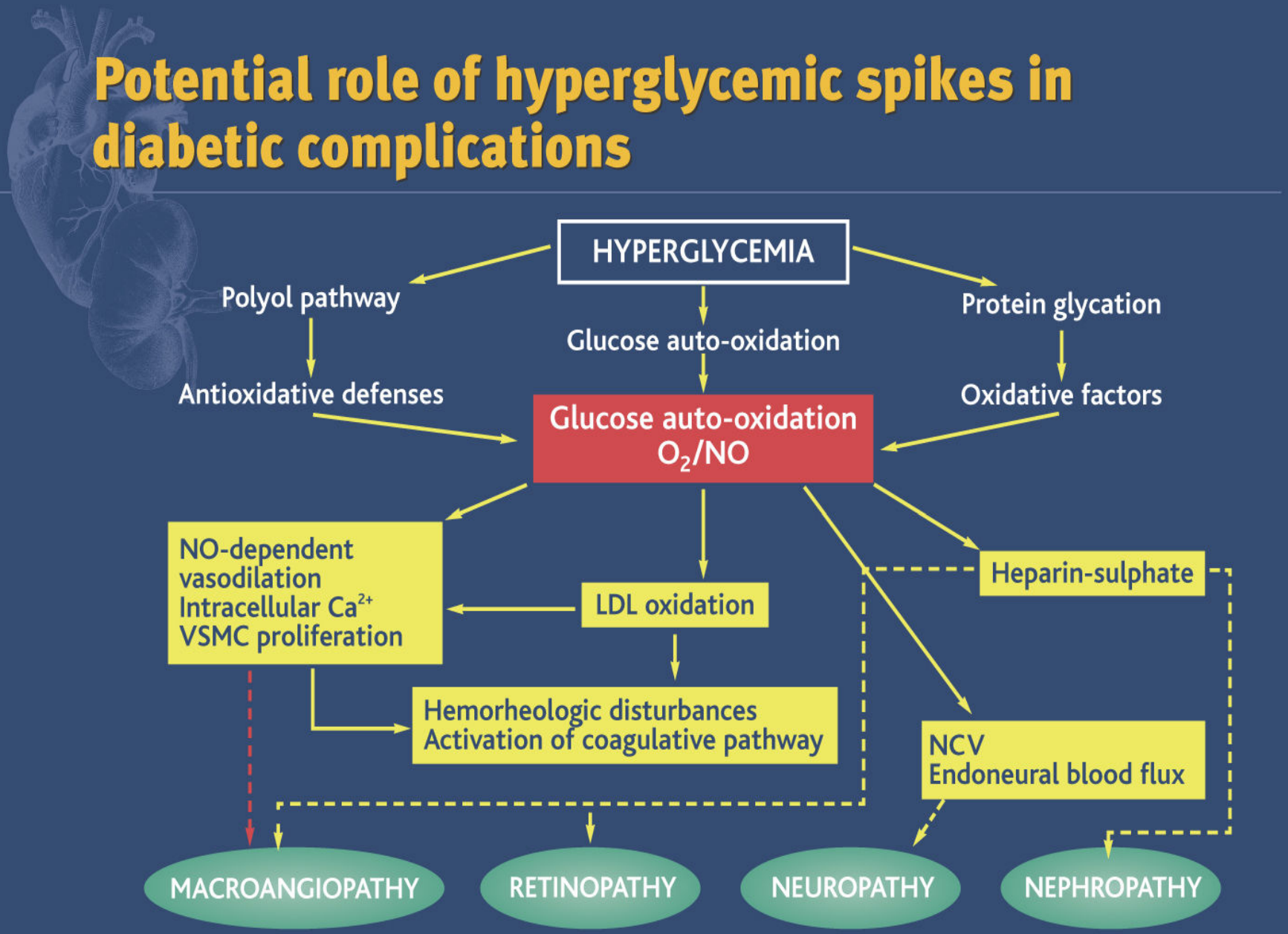


Definitions: Diabetic Nephropathy

Stages of Renal Involvement According to the Urinary Albumin Excretion			
Stage of nephropathy	**Urine dipstick for protein**	**Urine ACR (mg/mmol/L)**	**24 hour urine collection for albumin***
Normal	Negative	< 2.0 (men) < 2.8 (women)	< 30 mg/day
Microalbuminuria	Negative	2.0–20.0 (men) 2.8–28.0 (women)	30–300 mg/day
Overt nephropathy (macroalbuminuria)	Positive	> 20.0 (men) > 28.0 (women)	> 300 mg/day

*Values are for urinary albumin, not total urinary protein, which will be higher than urinary albumin levels
ACR = Albumin to creatinine ratio

Potential role of hyperglycemic spikes in diabetic complications

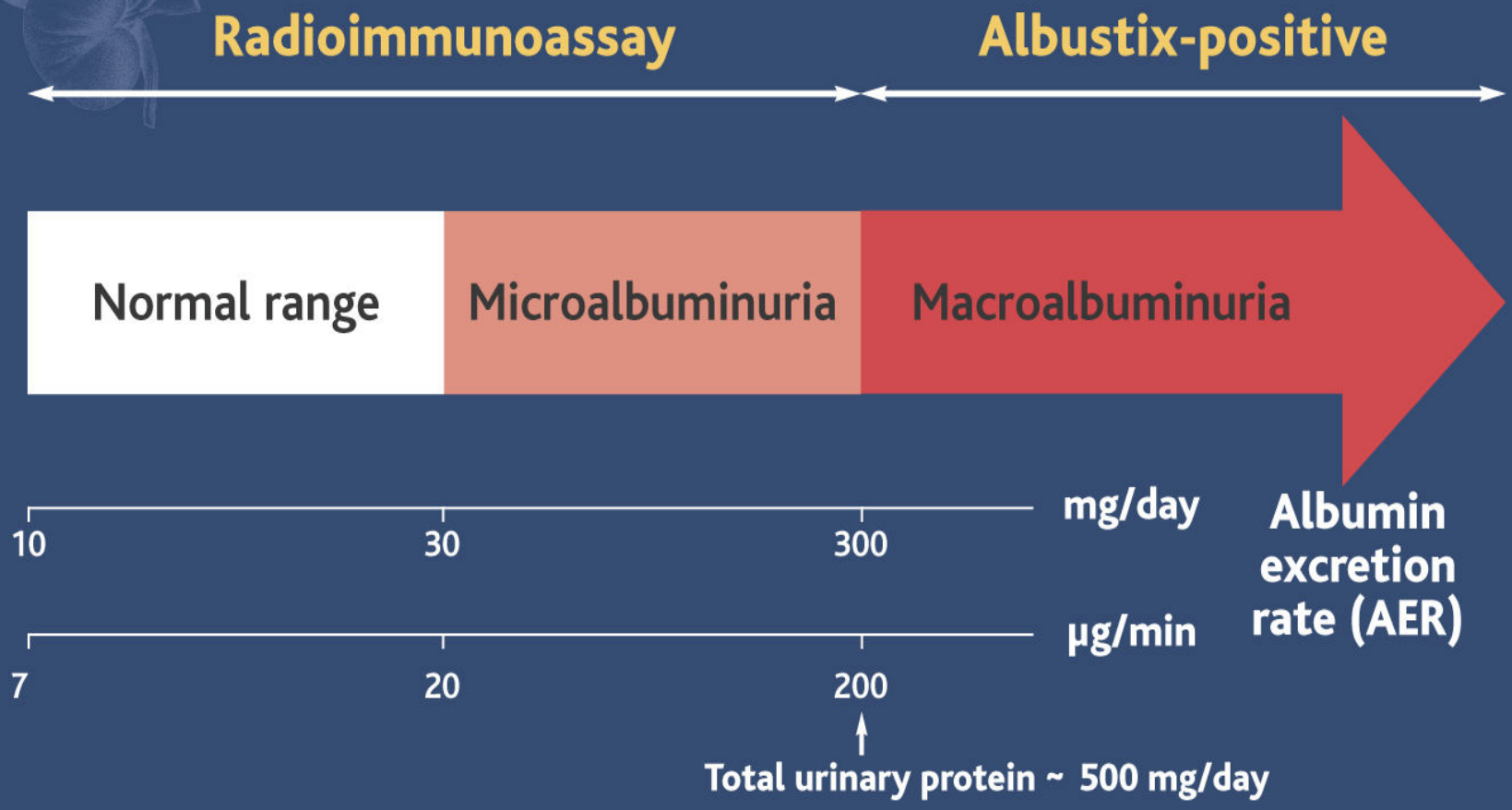


VSMC = Vascular smooth muscle cell
NCV = Nerve conduction velocity

Adapted from Giugliano et al. *Diabetes Care* 1996;19:257-267.

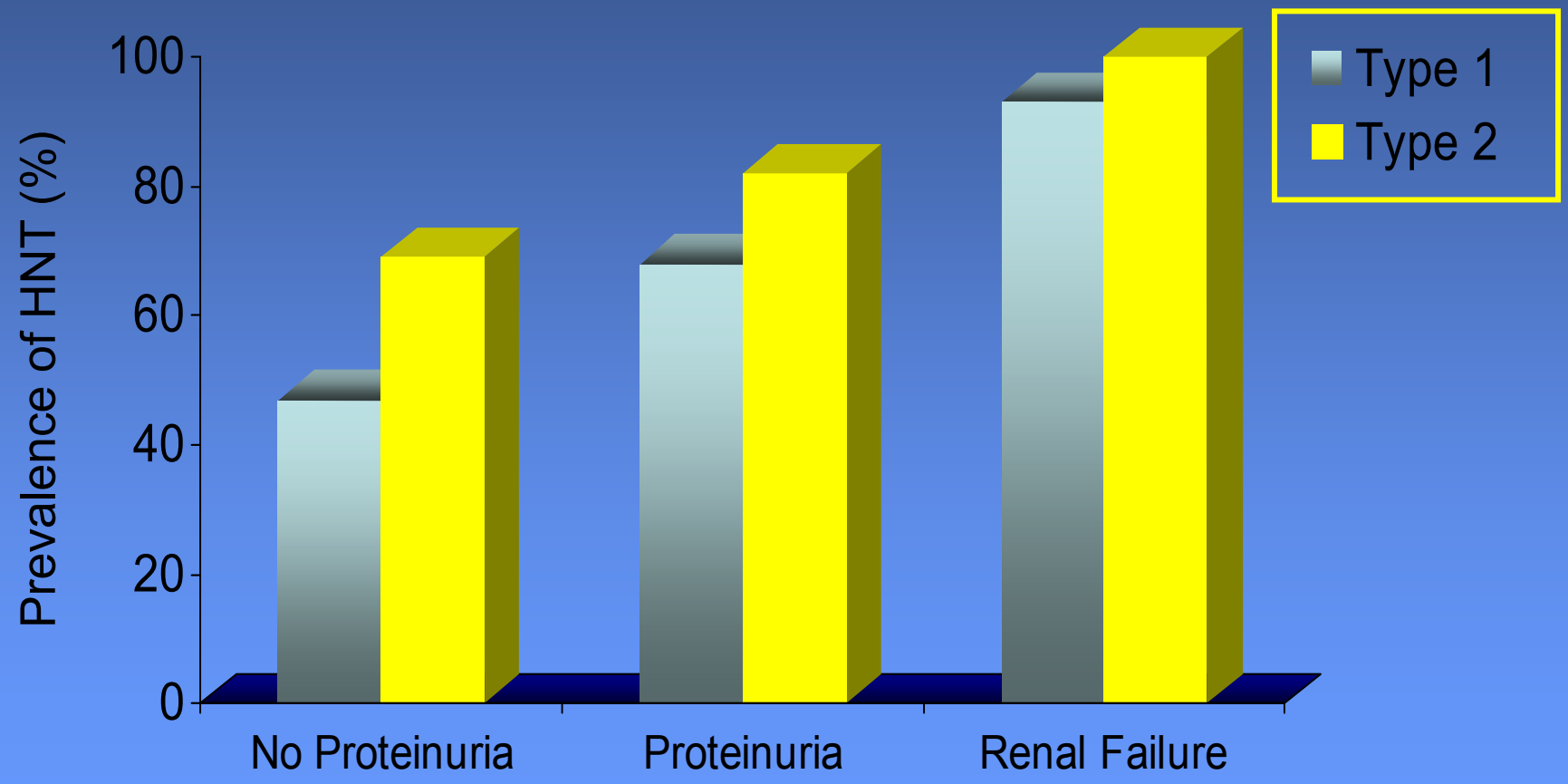
Diabetic nephropathy: Albuminuria

- Diabetic nephropathy is the #1 cause of end-stage renal failure in Canada and in the western world



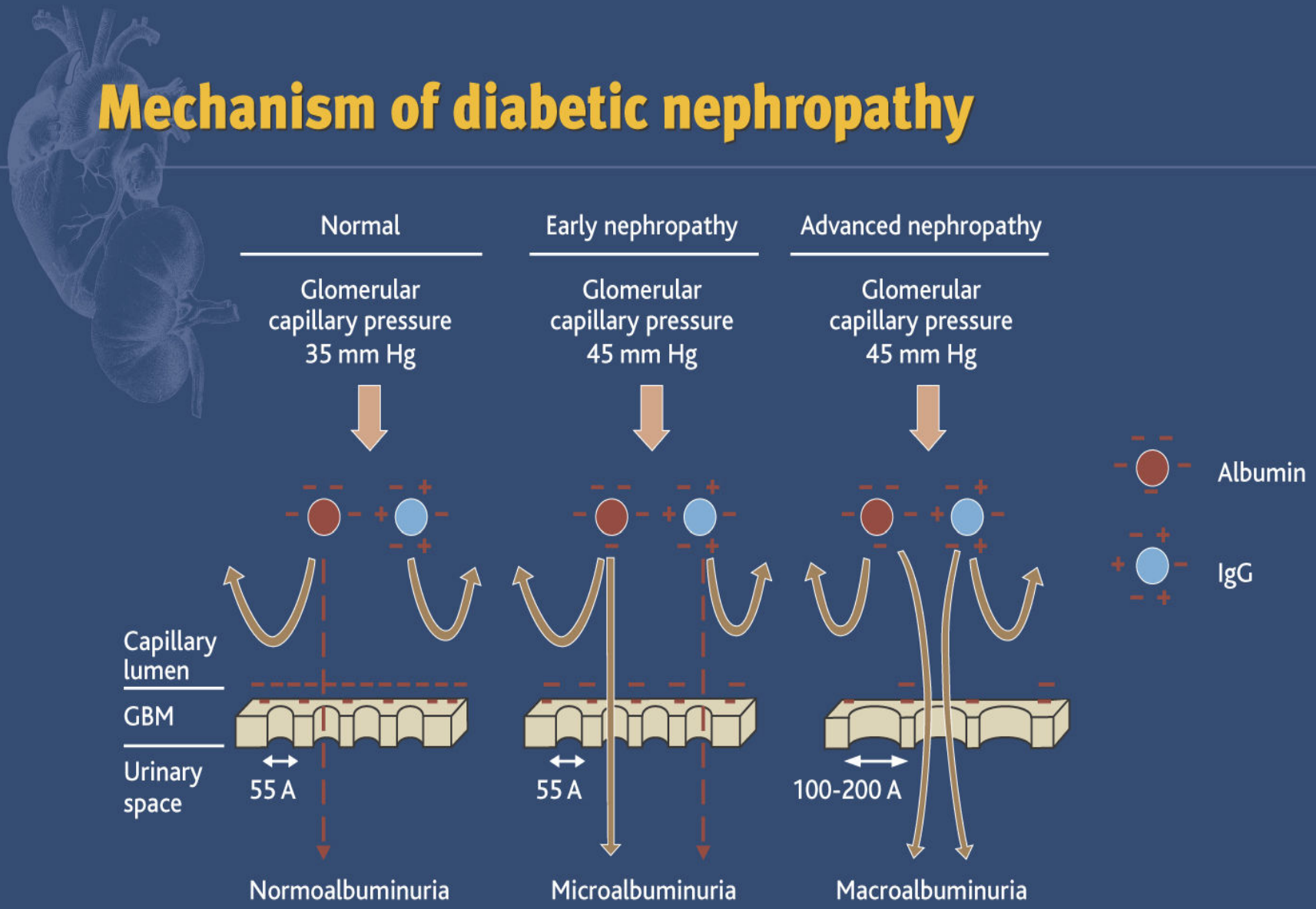
Maher JF. *Am Fam Physcian* 1992;45:1661-1668.
Meltzer S et al. *CMAJ* 1998;159 (Suppl 8):S1-S29.

Hypertension & Diabetes



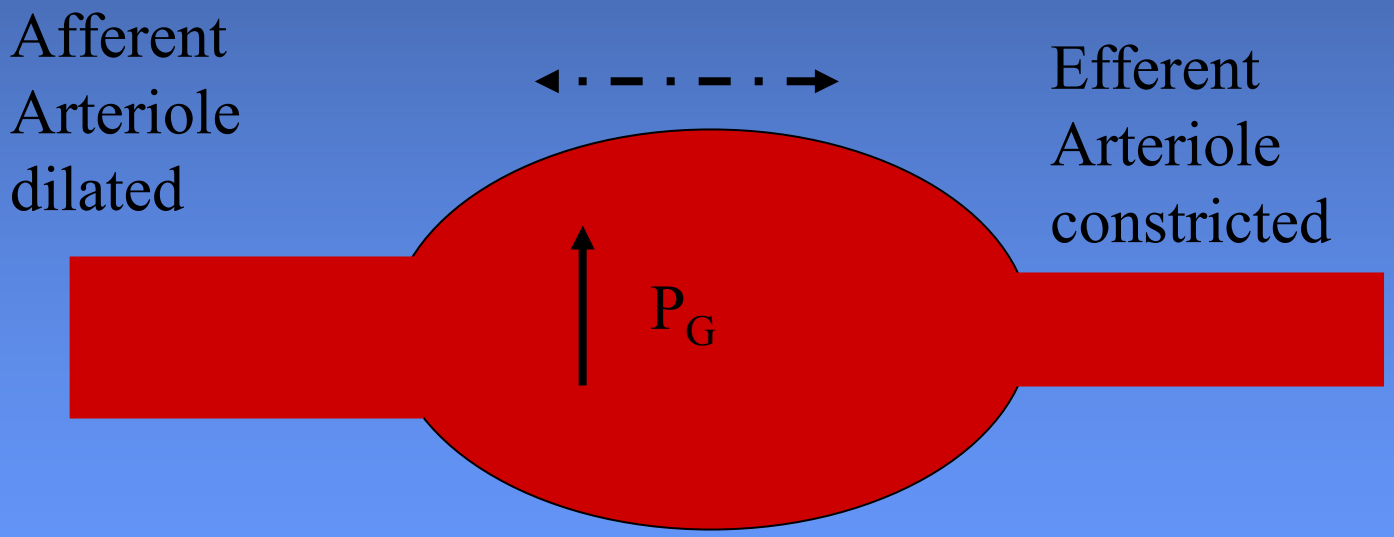
Epstein M et al., Hypertension. 1992: 19; 403-418

Mechanism of diabetic nephropathy

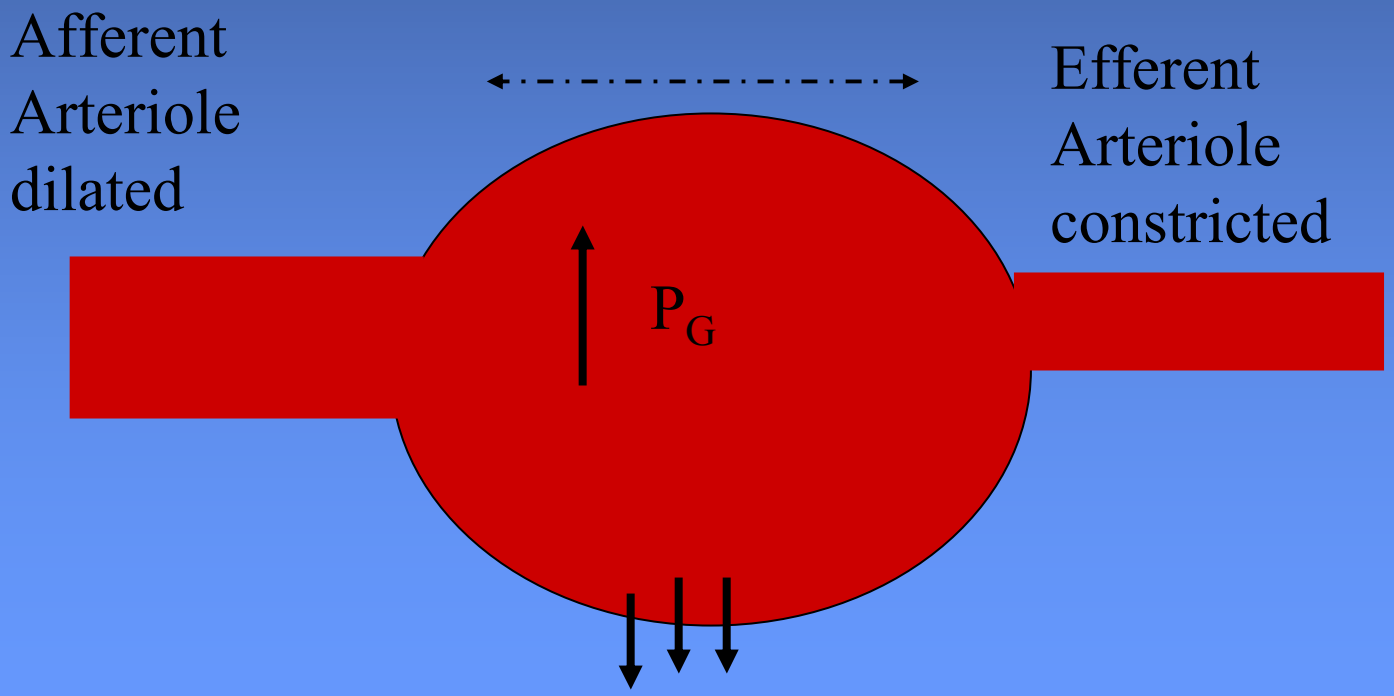


Goode NP et al. *Diabetologia* 1995;38:1455-1465.
Meltzer S et al. *CMAJ* 1998;159 (Suppl 8):S1-S29.
Selby JV et al. *JAMA* 1990;263:1954-60.

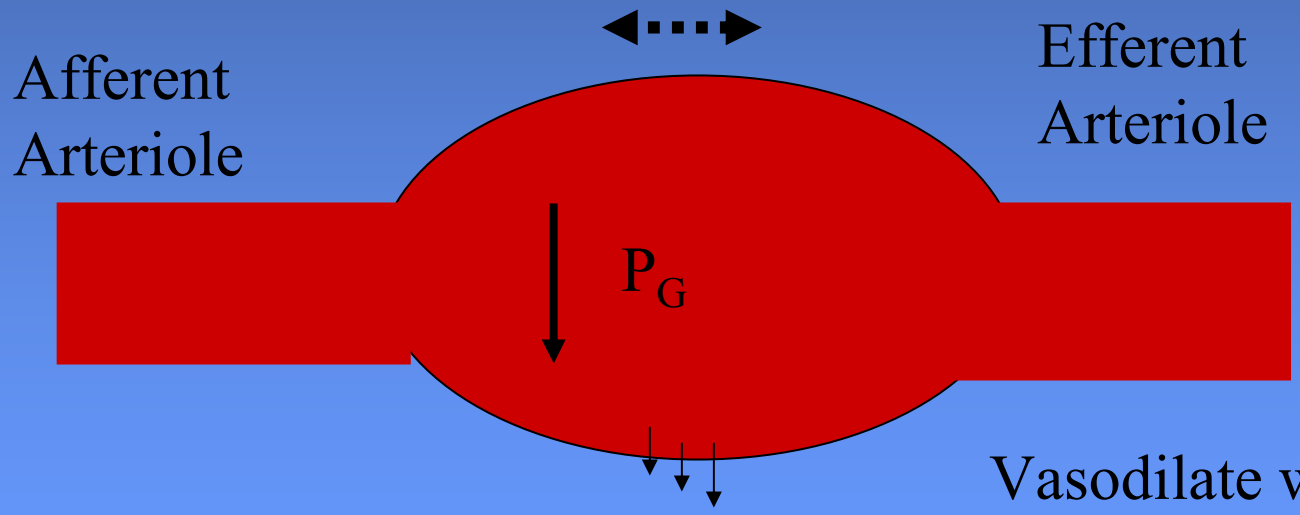
Intraglomerular Pressures



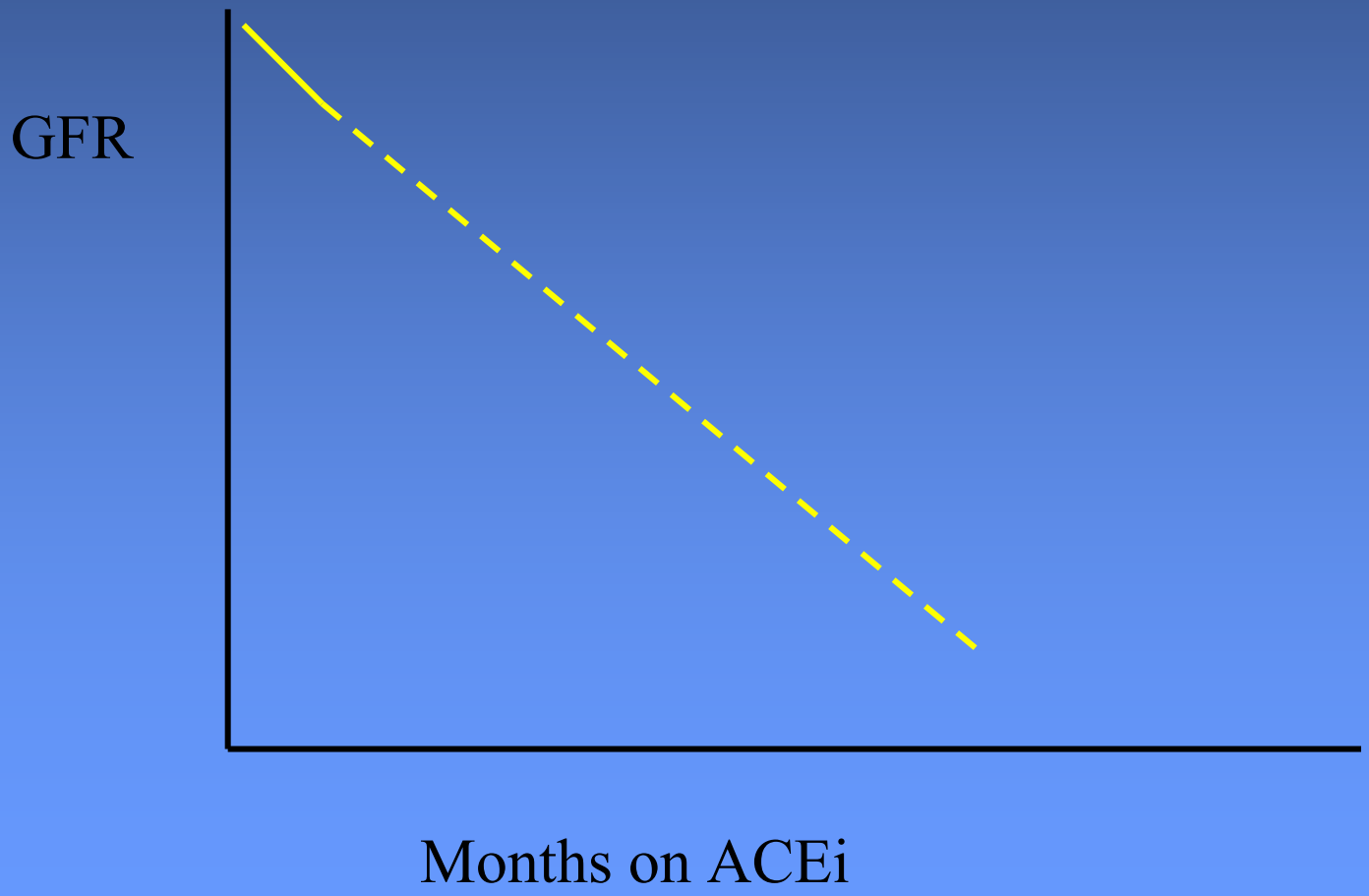
Intraglomerular Pressures



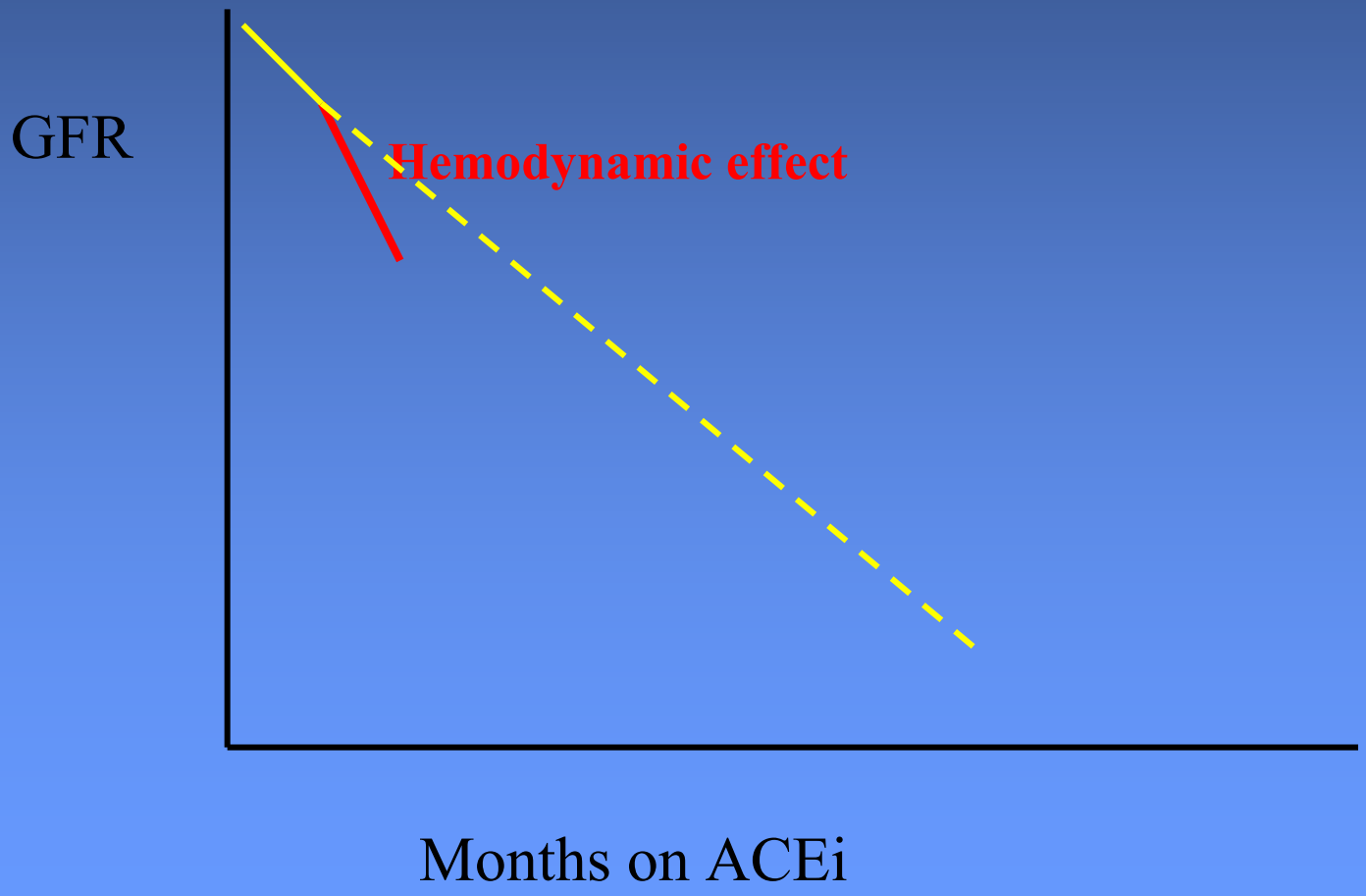
Effect of RAAS Interruption



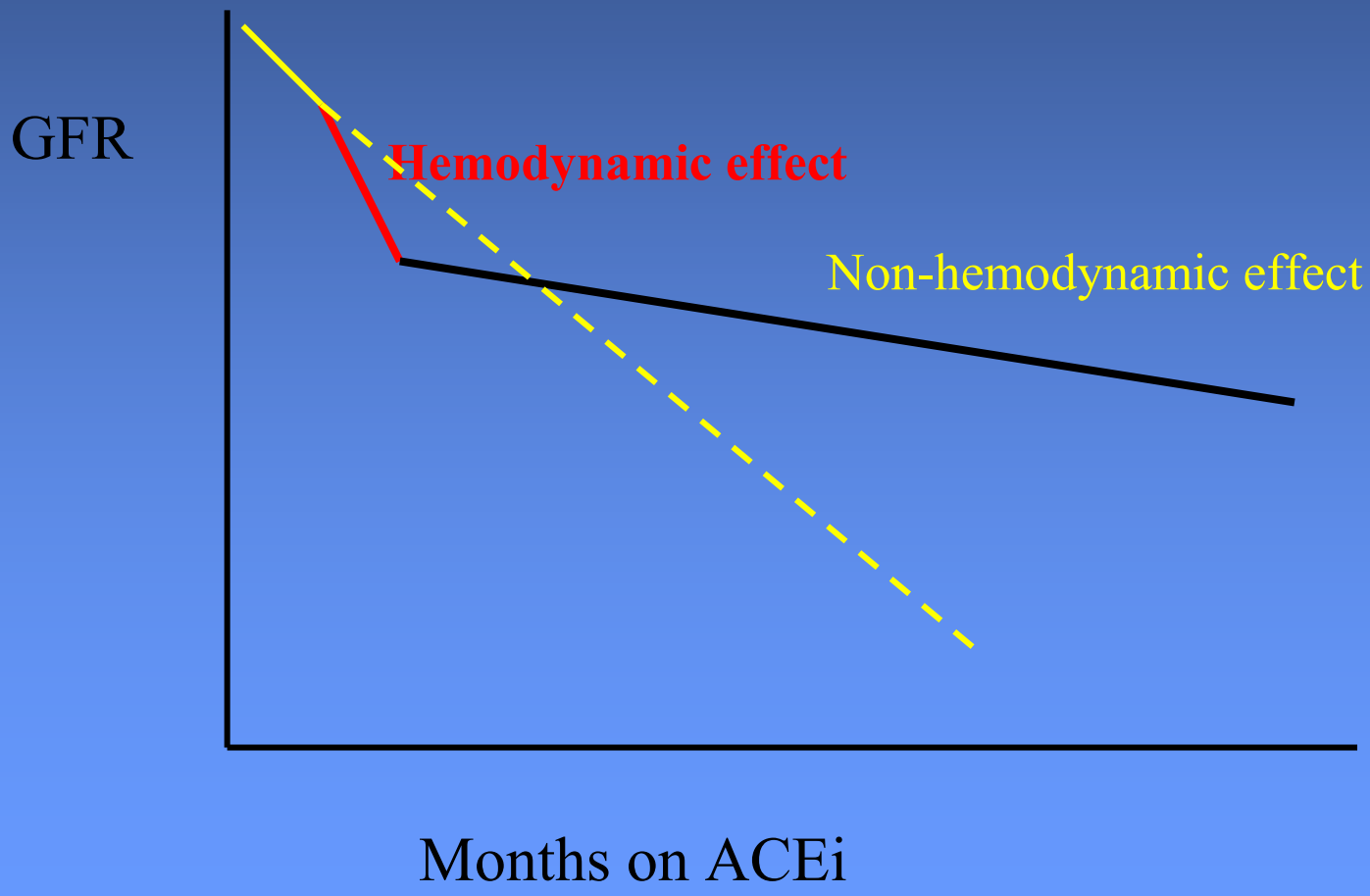
Effect of ACE-I or ARB Treatment

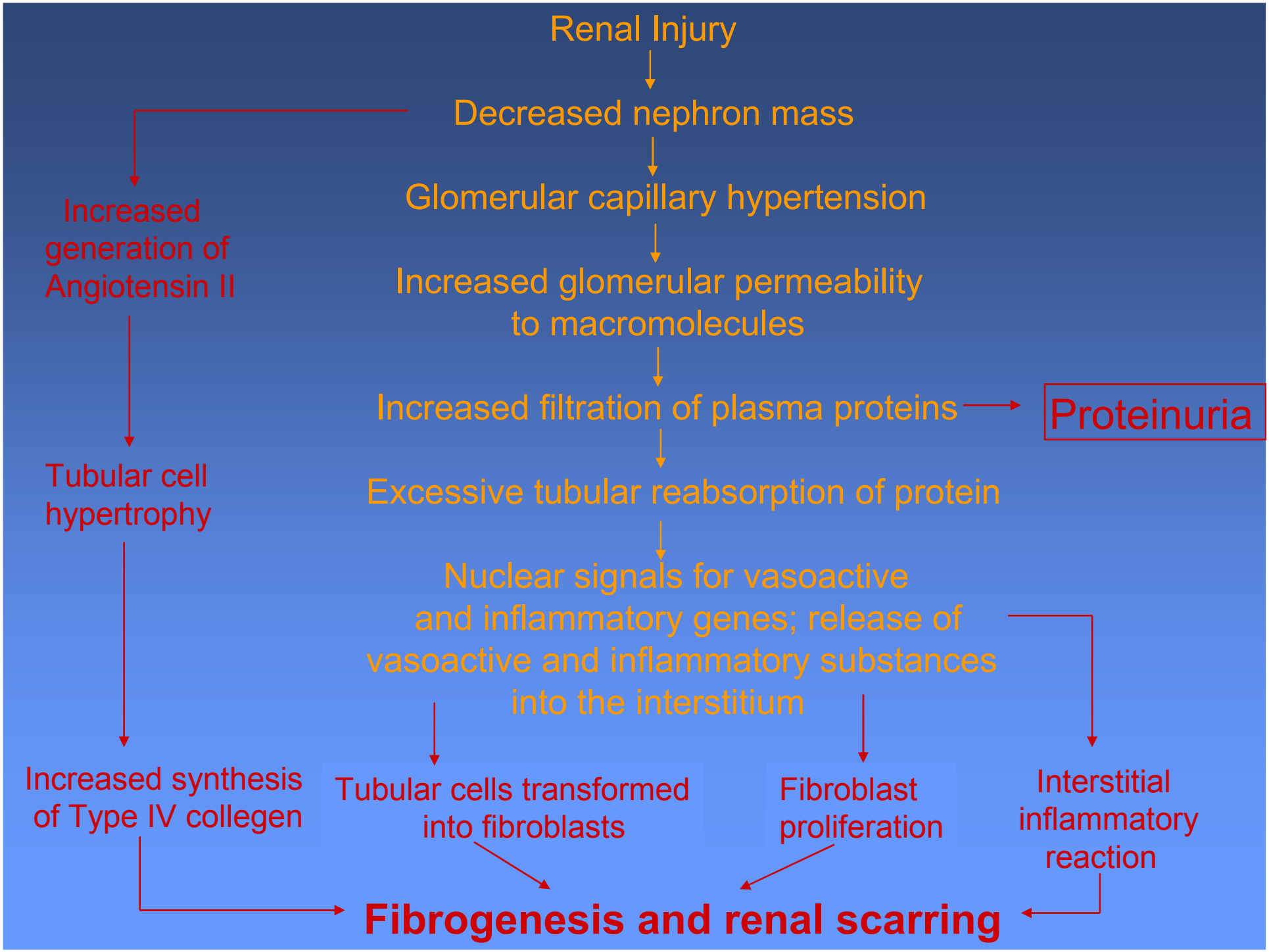


Effect of ACE-I or ARB Treatment



Effect of ACE inhibitor Treatment




Renal Injury
Decreased nephron mass
Increased generation of Angiotensin II
Glomerular capillary hypertension
Increased glomerular permeability to macromolecules
Increased filtration of plasma proteins
Proteinuria
Tubular cell hypertrophy
Excessive tubular reabsorption of protein
Nuclear signals for vasoactive and inflammatory genes; release of vasoactive and inflammatory substances into the interstitium
Increased synthesis of Type IV collegen
Tubular cells transformed into fibroblasts
Fibroblast proliferation
Interstitial inflammatory reaction
Fibrogenesis and renal scarring

What is the association between albuminuria and cv disease?

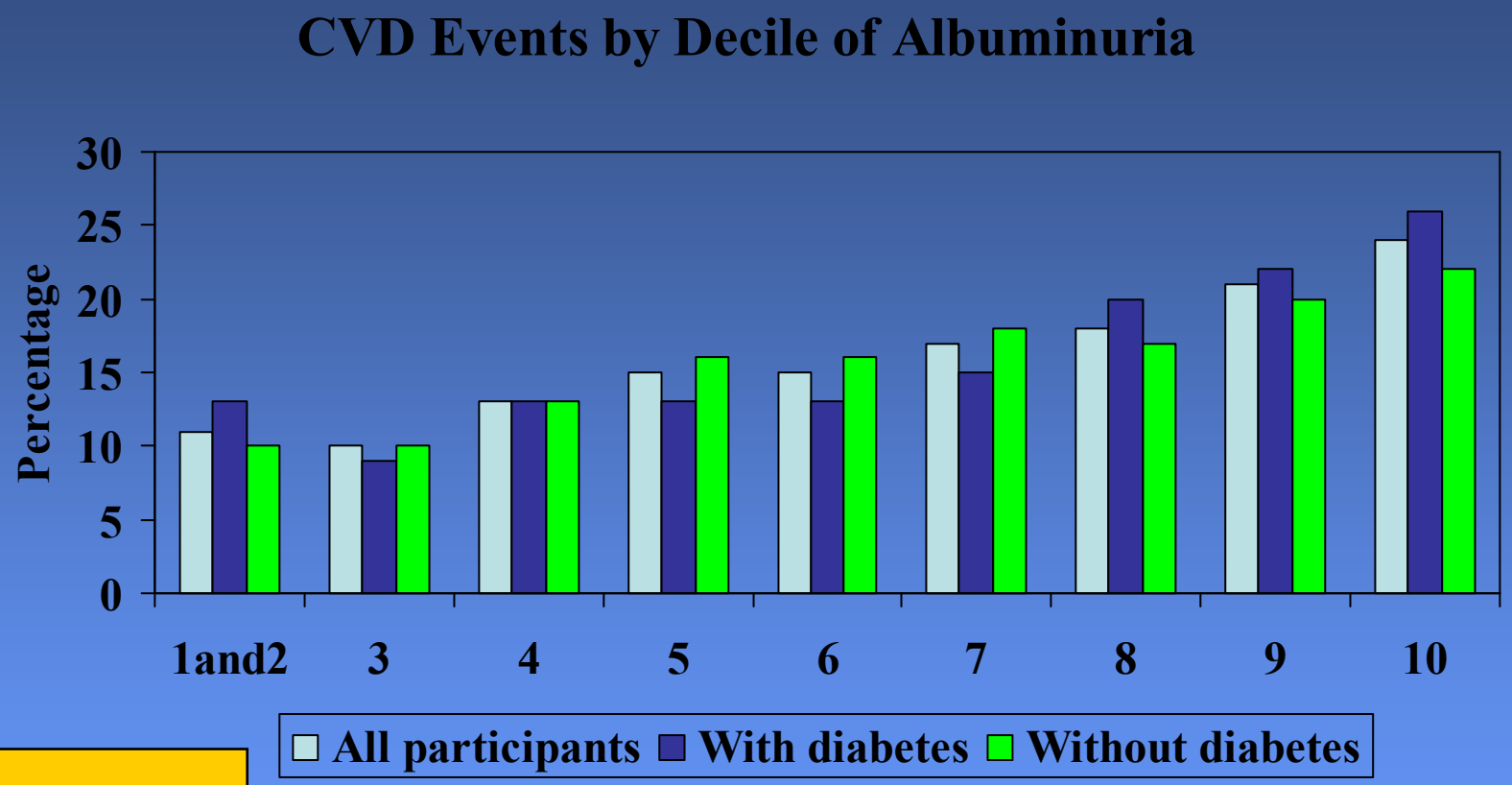
HOPE Trial - Independent Predictors of Primary Outcome

Variable	HR (95% CI)
Elevated serum creatinine	1.40 (1.16-1.69)
Microalbuminuria	**1.59 (1.37-1.84)**
Coronary artery disease	1.51 (1.22-1.85)
PVD	1.49 (1.29-1.70)
Diabetes mellitus	1.42 (1.23-1.65)
Male sex	1.20 (1.01-1.43)
Ramipril use	0.79 (0.69-0.89)
Age (1 yr increase)	1.03 (1.02-1.05)

Elevated serum creatinine = > 122 micromoles/L

Mann JFE et al. Ann Intern Med 2001;629-636

Dose Response Relation

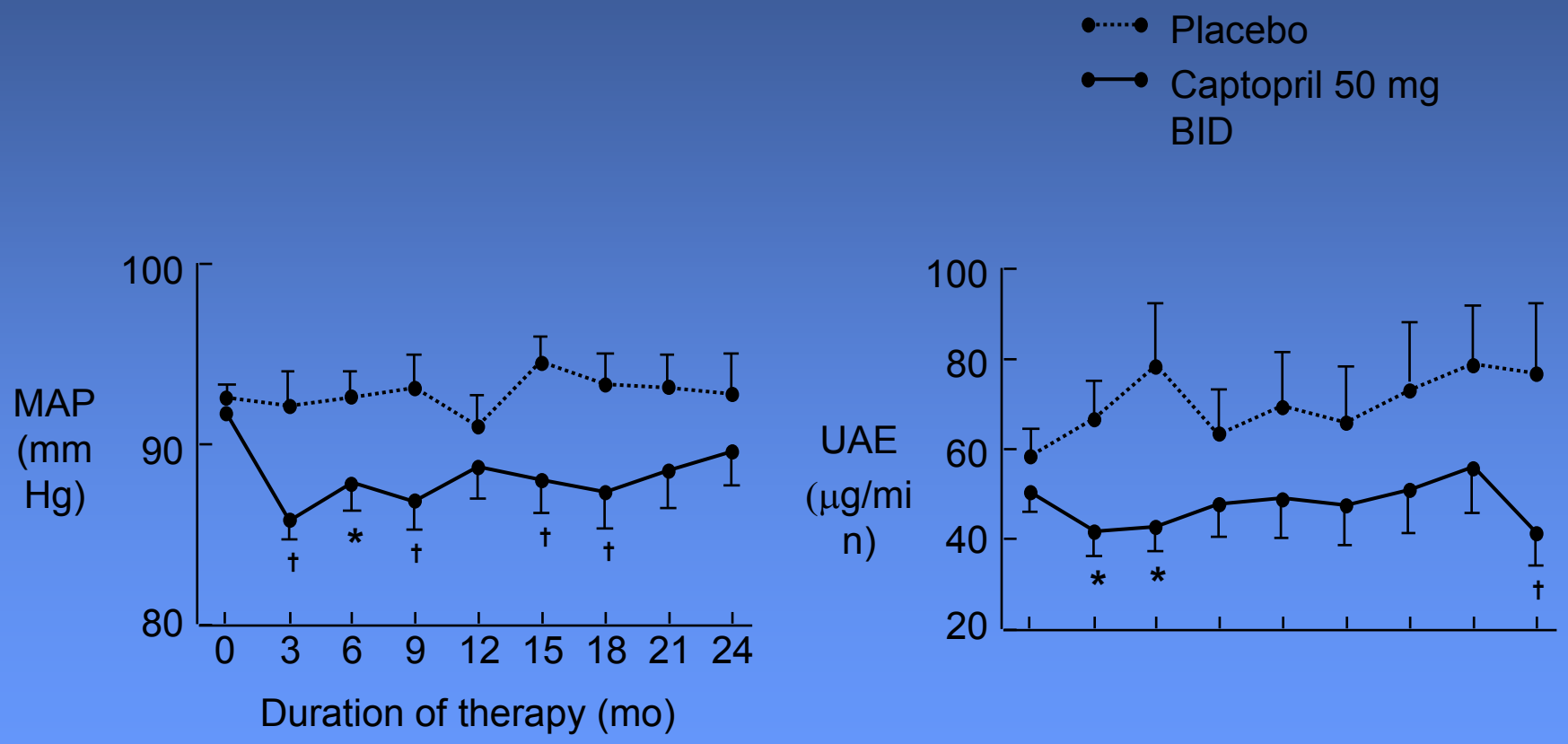


HOPE Study

- patients with dipstick proteinuria were excluded

Gerstein HC. JAMA 2001;286:421-26

Effect of ACE Inhibition in Normotensive Diabetics



*$P \leq 0.05$; †$P \leq 0.01$.

Viberti G et al. *JAMA.* 1994;271:275-279.

Effect of ACEI vs Placebo in Type I and Type II with Normotension and Microalbuminuria (2 years)

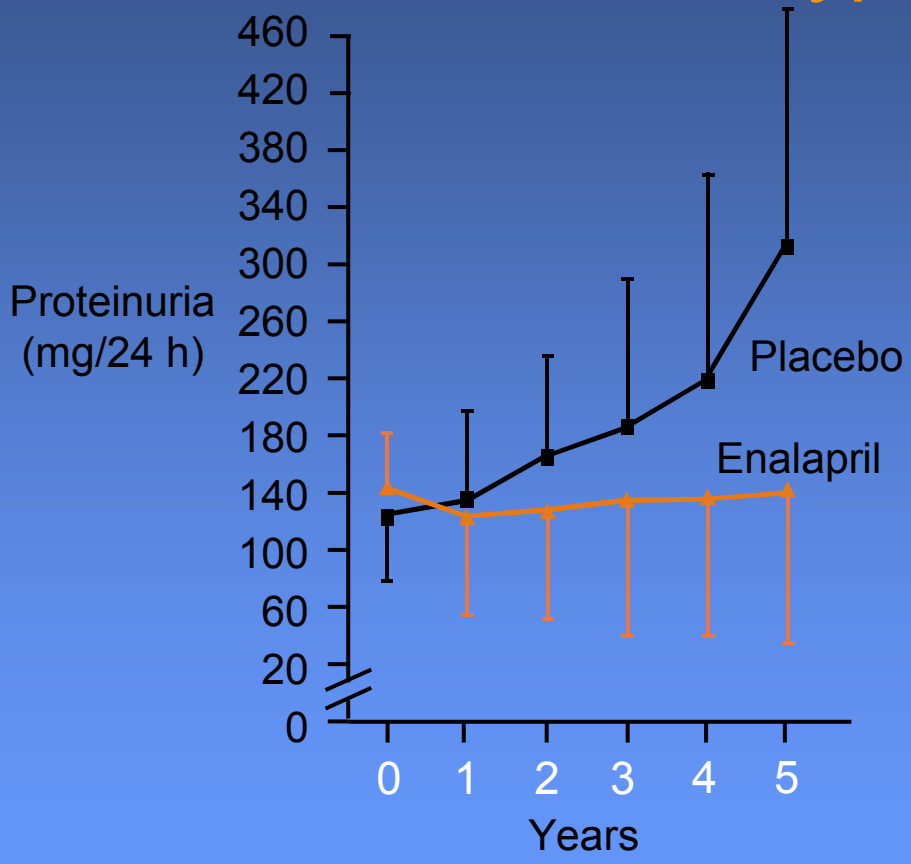
Captopril group
122/74 mmHg

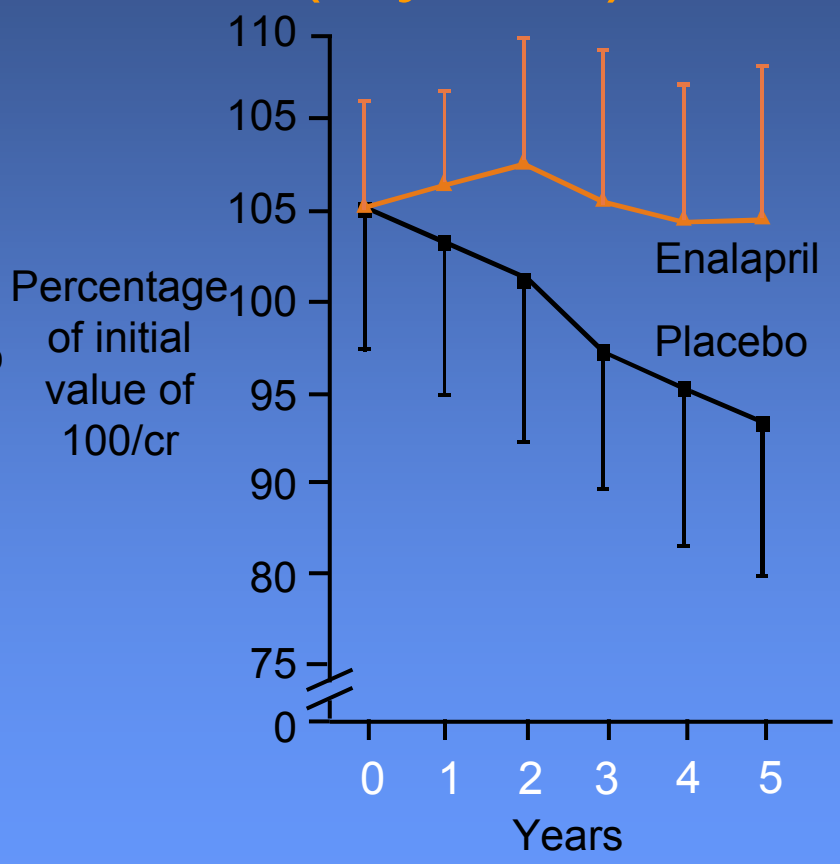
Placebo group
126/76 mmHg

4/2 mmHg difference (p<.05)

Viberti G et al. JAMA 1994;271:275-279.

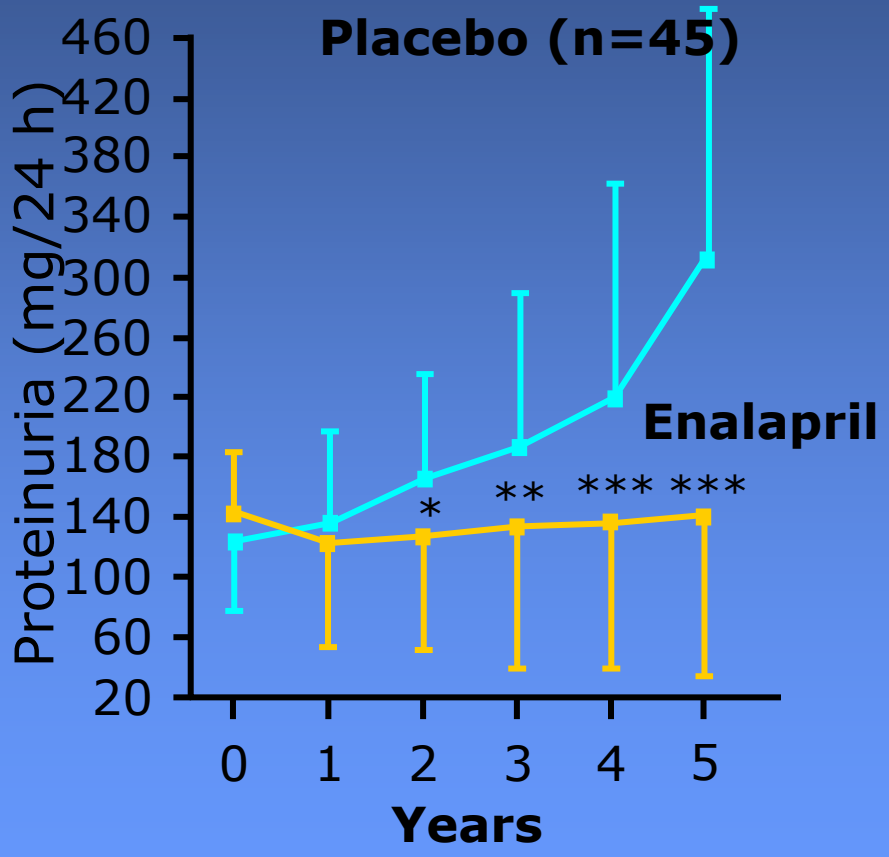
Effect of ACEI vs Placebo in Normotensive, Normoalbuminuric Patients with Type II DM (5 years)

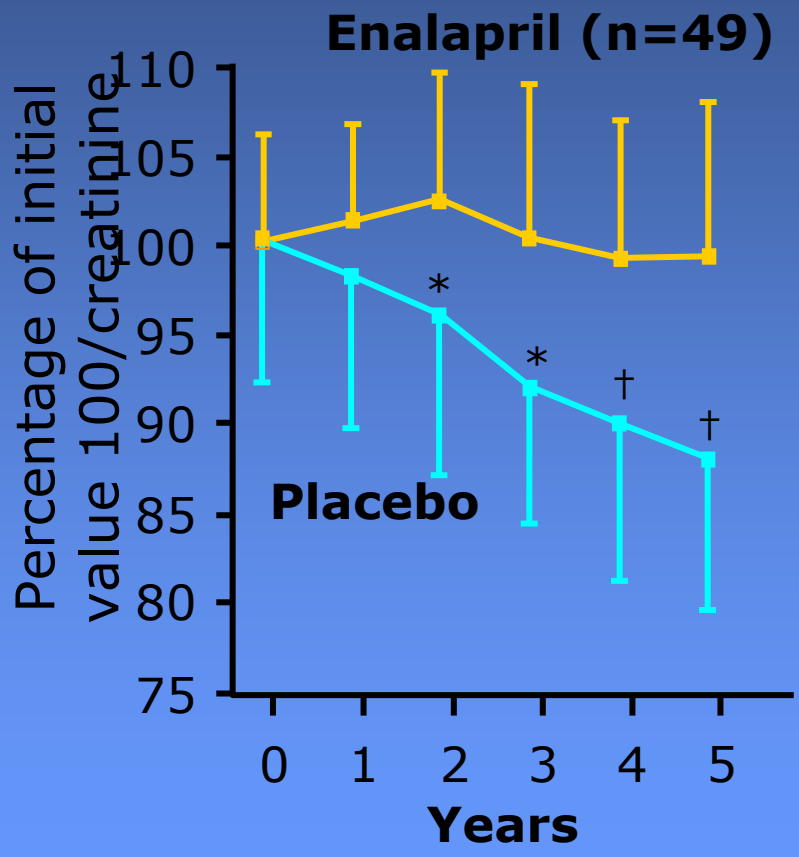




Ravid M et al. *Ann Intern Med.* 1993;118:577–581.

Long-Term Benefits of ACE Inhibition in Normotensive Type 2 Diabetics with microalbuminuria





*p < 0.05; **p < 0.01; †p < 0.02; ***p < 0.005

Ravid M, et al. Ann Intern Med. 1993;118(8):577-581.

Effect of ACEI vs Placebo in Normotensive, Normoalbuminuric Patients with Type II DM (5 years)

MAP increased from 96.1 to 102 mmHg on placebo

MAP increased from 98.2 to 100 mmHg on enalapril

Ann Int Med 1998;128:982-988

ACE Inhibitors vs Non-ACE Inhibitors in Type 2 Diabetes and Proteinuria

Investigator	Treatment	Follow-up (y)	Proteinuria		Decline in GFR (mL/min/y)	
			ACE inhibitor	Non-ACE inhibitor	ACE inhibitor	Non-ACE inhibitor
Walker et al (n=86)	ACE inhibitor vs conventional therapy	3	↓↓	↓	3.0	4.1
Lebovitz et al (n=46)	ACE inhibitor vs conventional therapy	3	↓	→	6.4	9.6
Bakris et al (n=52)	ACE inhibitor vs CCB vs beta blocker	5	↓↓	↓↓(CCB) ↓(BB)	1.0	1.4 (CCB) 3.3 (BB)
Nielsen et al (n=36)	ACE inhibitor vs beta blocker	3	↓↓	→	7.0	6.5
Estacio et al (n=83)	ACE inhibitor vs CCB	5	↓	↓	5.5	5.5
Fogari et al (n=51)	ACE inhibitor vs CCB	2	↓↓	↓	2.0	1.2

Parving H-H et al. *Curr Opin Nephrol Hypertens.* 2001;10:515-522.

Why do drugs
which block the
renin-angiotensin system
delay the progression of
renal disease?

Benefits of RAAS Blockade for Renal Protection

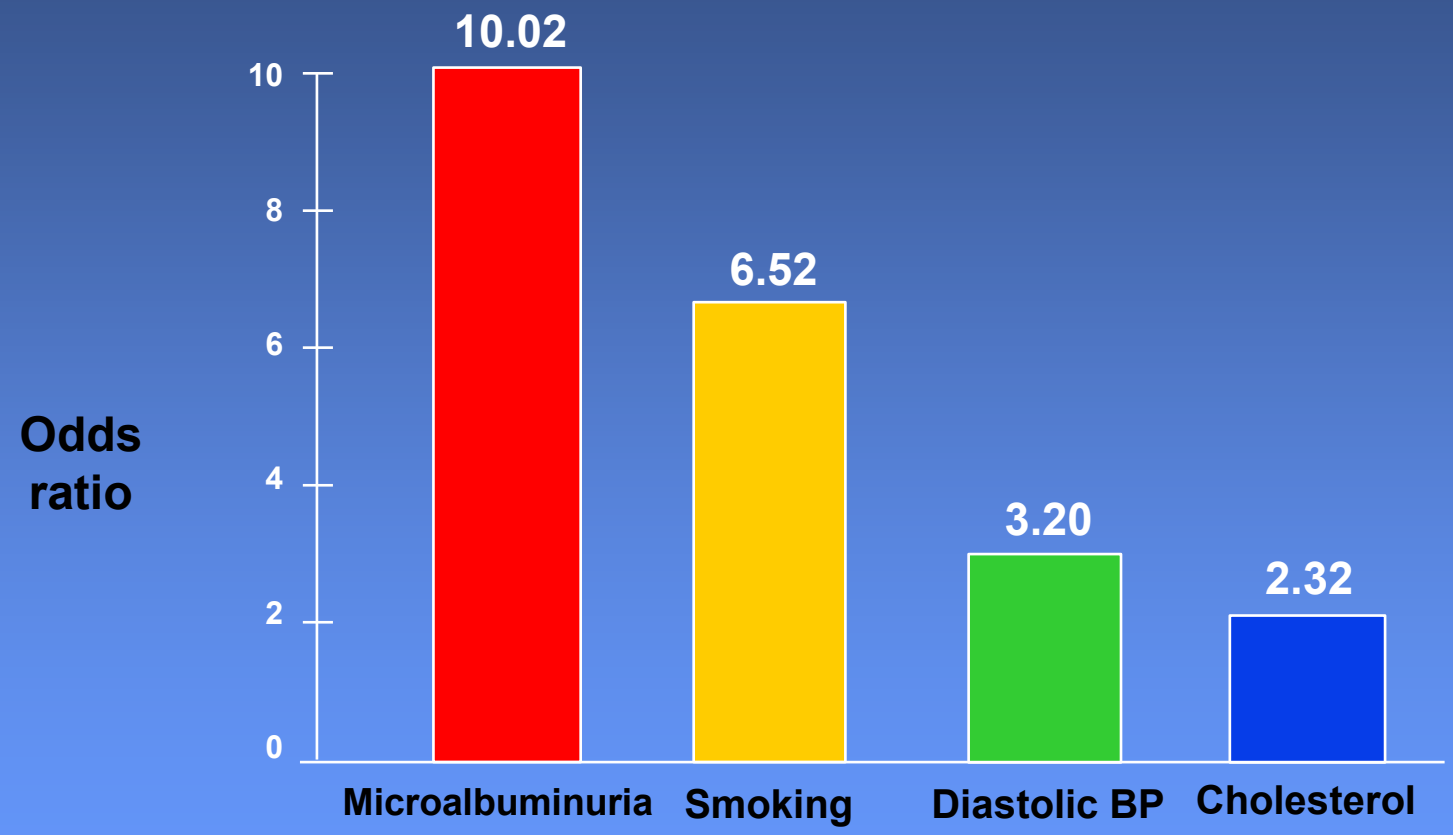
Hemodynamic Effects

Reduction in systemic BP
Reduction in glomerular capillary pressure
Reduction in proteinuria

Non-hemodynamic Effects

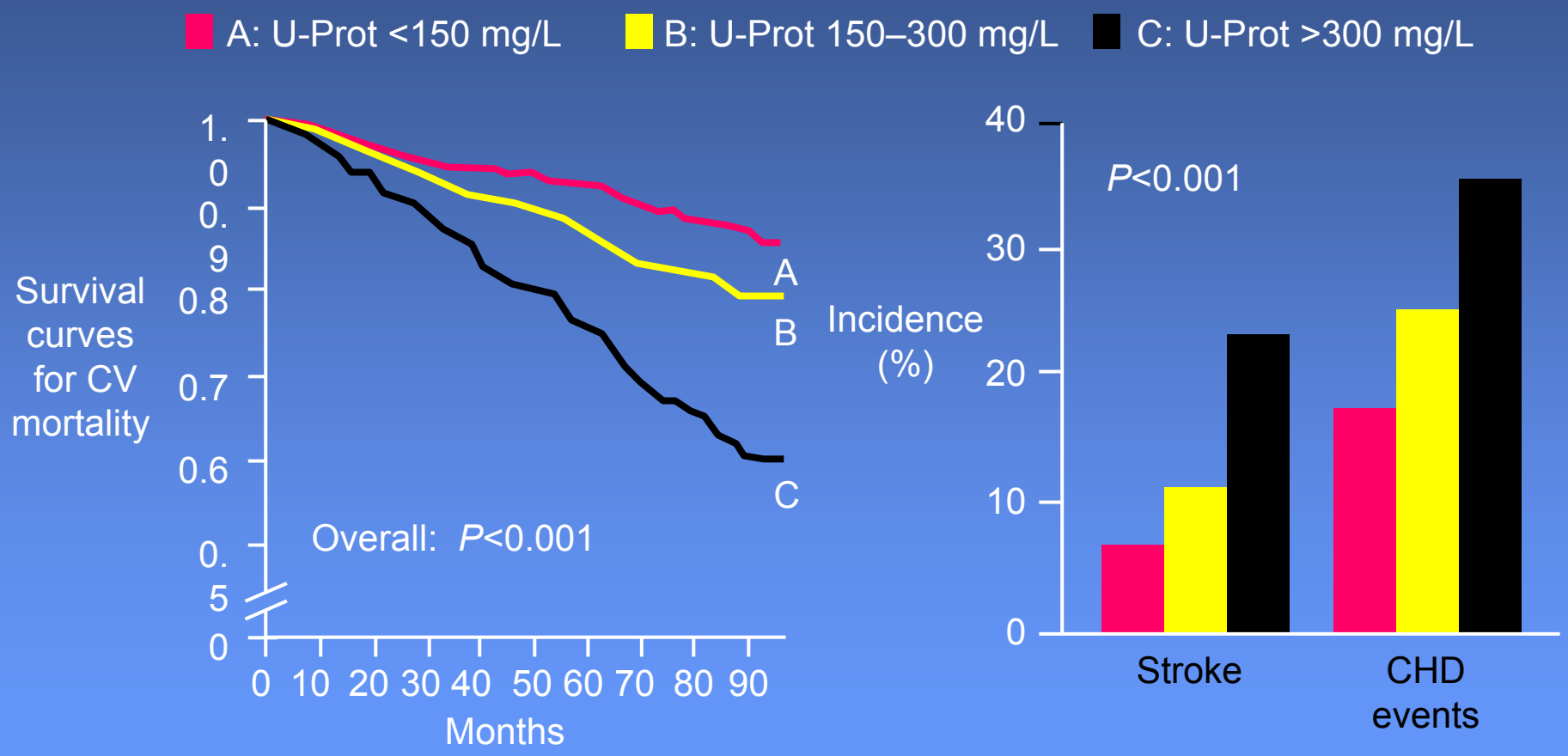
? Stimulation of extracellular matrix degradation
? Inhibition of macrophage/monocyte infiltration

Relative Importance of MAU



Eastman RC, Keen H. *Lancet* 1997;350 Suppl 1:29-32.

Proteinuria and Risk of Stroke and CHD Events in Type 2 Diabetes

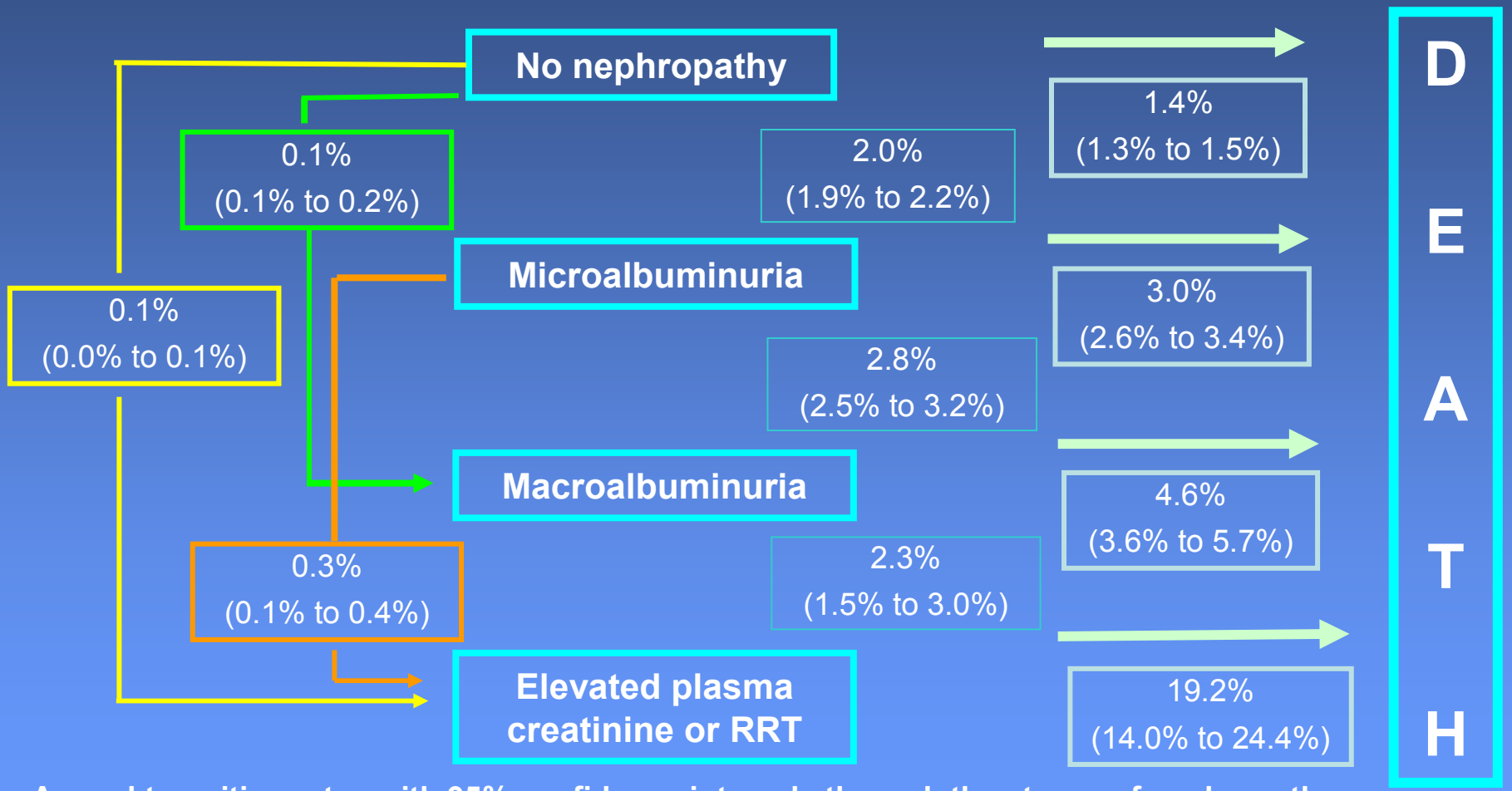


U-Prot, urinary protein concentration.

Miettinen H et al. *Stroke.* 1996;27:2033–2039.

UKPDS 64: Annual Nephropathy Transition

Rates From Stage to Stage



Annual transition rates with 95% confidence intervals through the stages of nephropathy and to death from any cause.

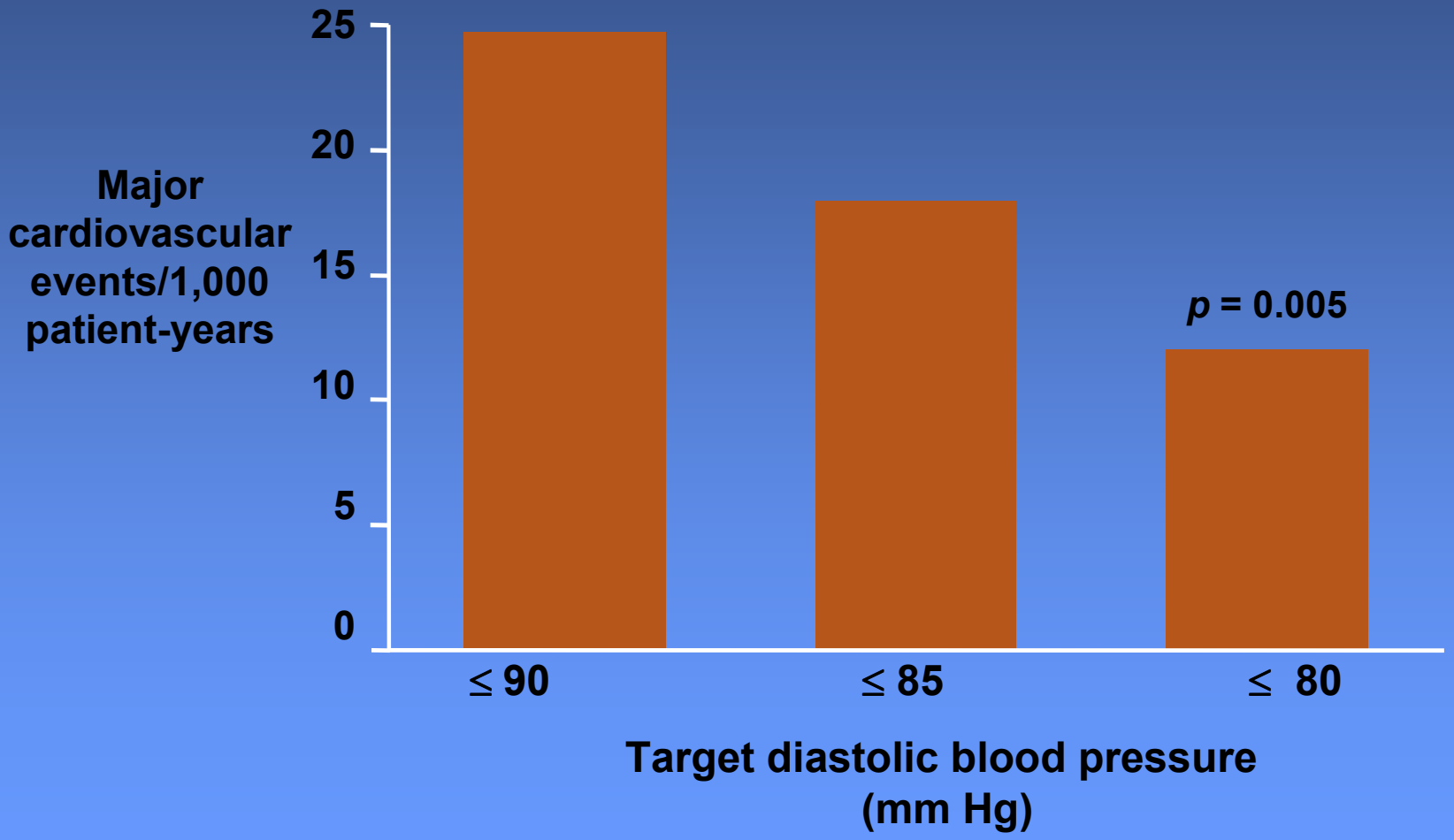
UKPDS: United Kingdom Prospective Diabetes Study

RRT: renal replacement therapy

Adler AI, et al. Kidney Int 2003;63:225-32.

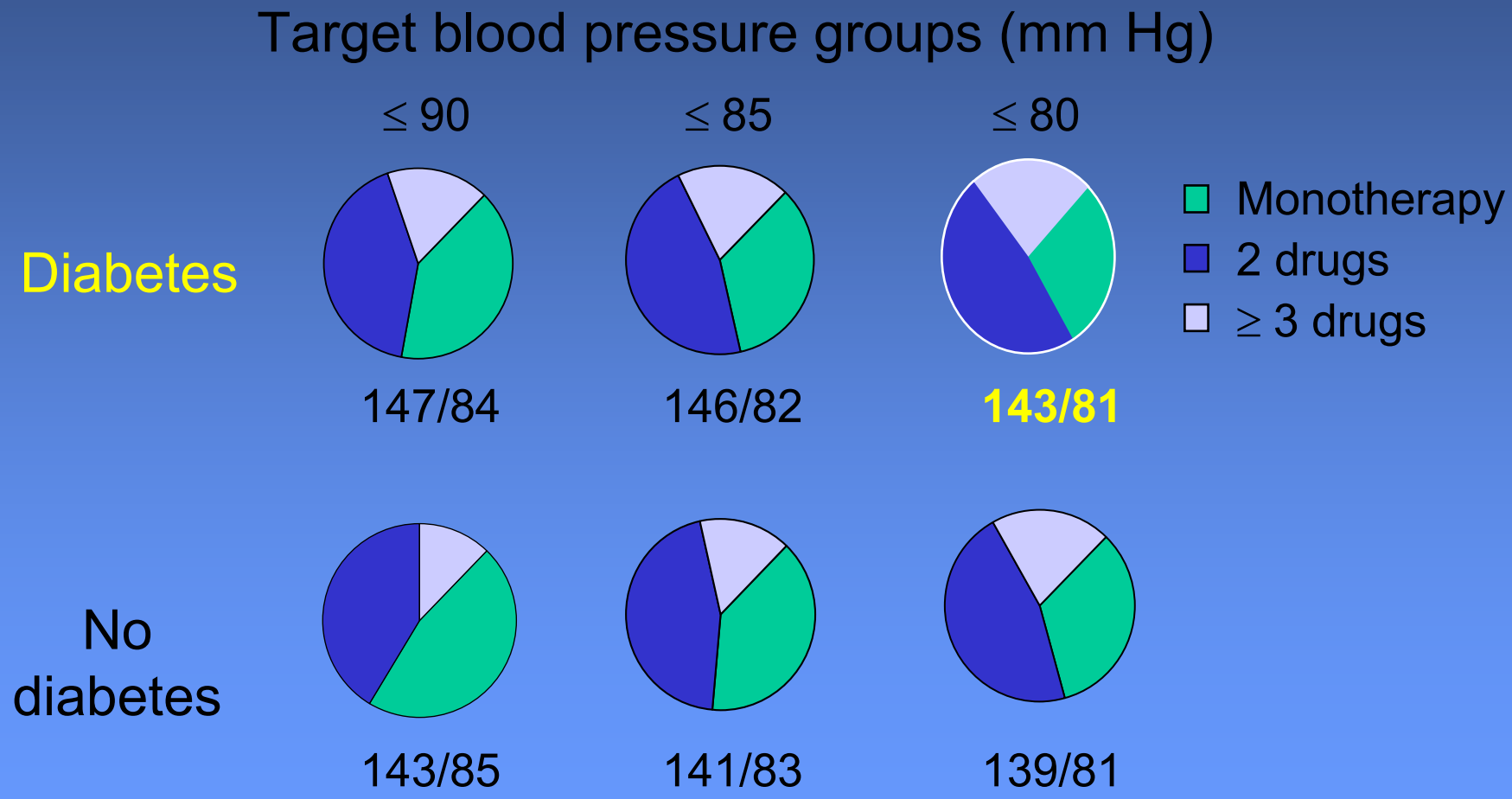
What should the target BP be for patients with diabetic nephropathy?

HOT Study: Effect of intensive treatment according to diabetes status



Hansson L et al, 1998.

Patients with diabetes, number of drugs and mean blood pressure at final visit



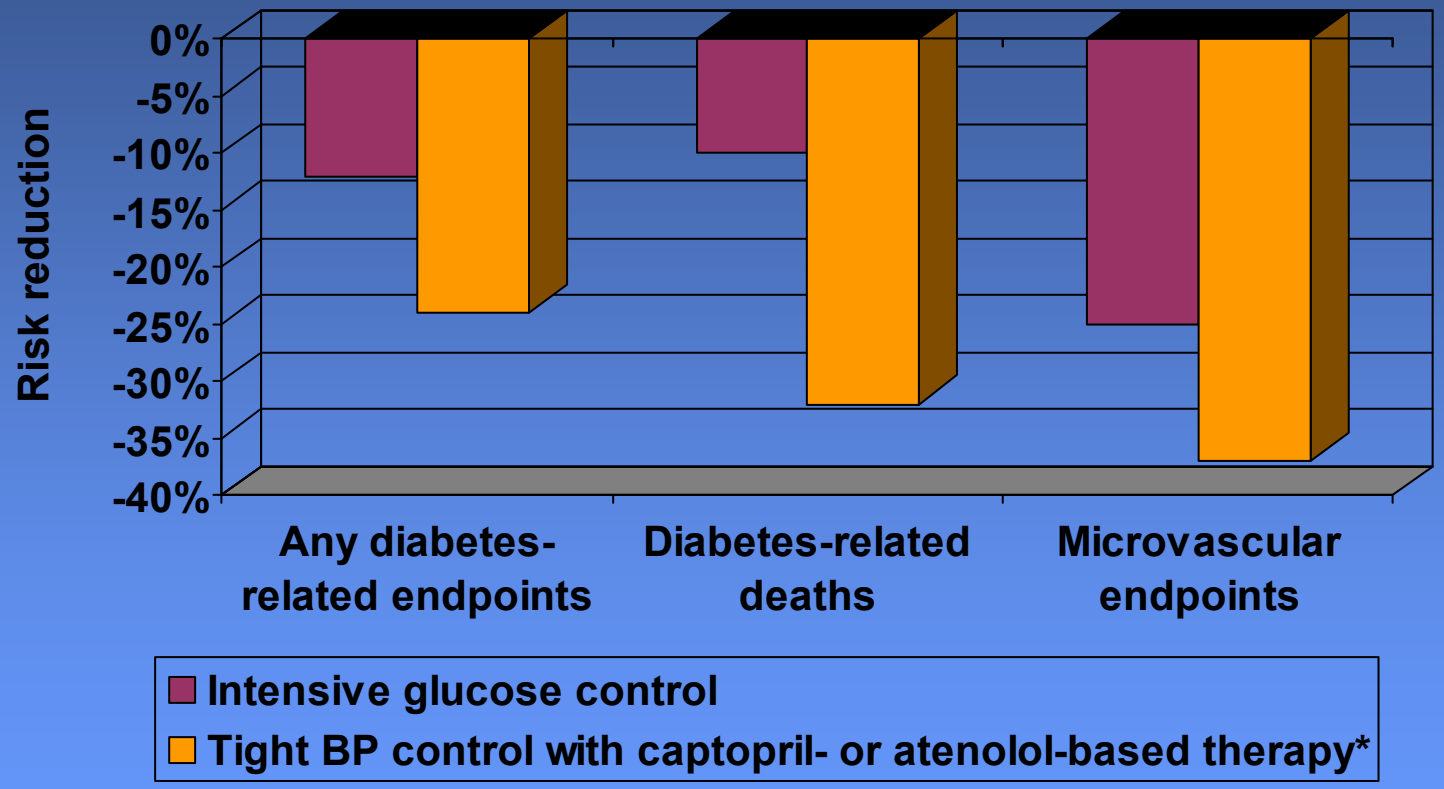
UKPDS: Results

	Risk reduction	p-value
• Intensive glucose control reduces risk of		
– Any diabetes-related endpoints	12%	0.029
– Diabetes-related deaths	10%	0.340
– Microvascular endpoints	25%	0.010
• Tight blood pressure control* with captopril- or atenolol-based therapy reduces risk of		
– Any diabetes-related endpoints	24%	0.005
– Diabetes-related deaths	32%	0.019
– **Stroke**	**44%**	**0.013**
– Microvascular endpoints	37%	0.009

* Mean blood pressure achieved: 144/82 vs. 154/87 mm Hg.

1. UK Prospective Diabetes Study Group 38, 1998.
2. UK Prospective Diabetes Study Group 33, 1998.
3. UK Prospective Diabetes Study Group 39, 1998.

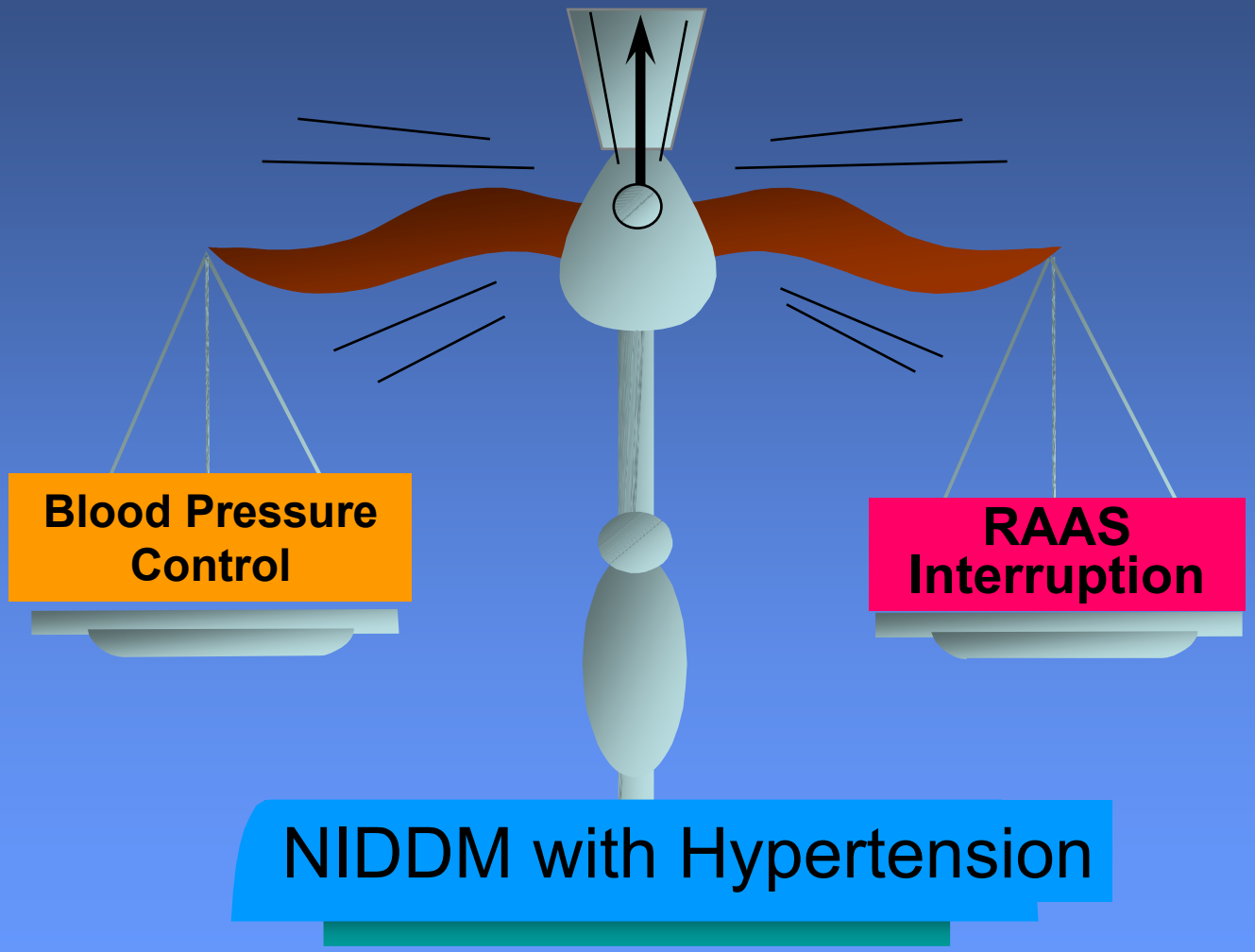
United Kingdom Prospective Diabetes Study (UKPDS): Risk Reduction



*** Mean BP achieved: 144/82 vs. 154/87 mm Hg**

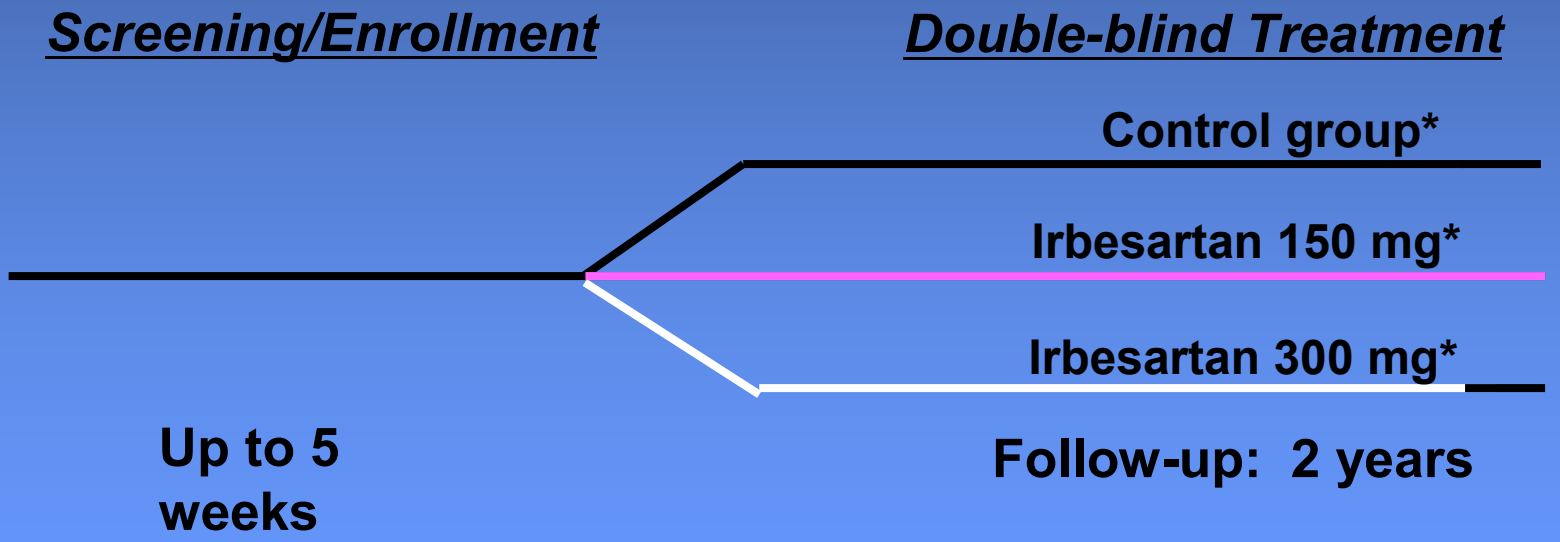
UK Prospective Diabetes Study Group. *BMJ* 1998;317(7160):703-713.
UK Prospective Diabetes Study Group. *Lancet* 1998;352(9131):837-853.

Cardiovascular-Renal Protection



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.

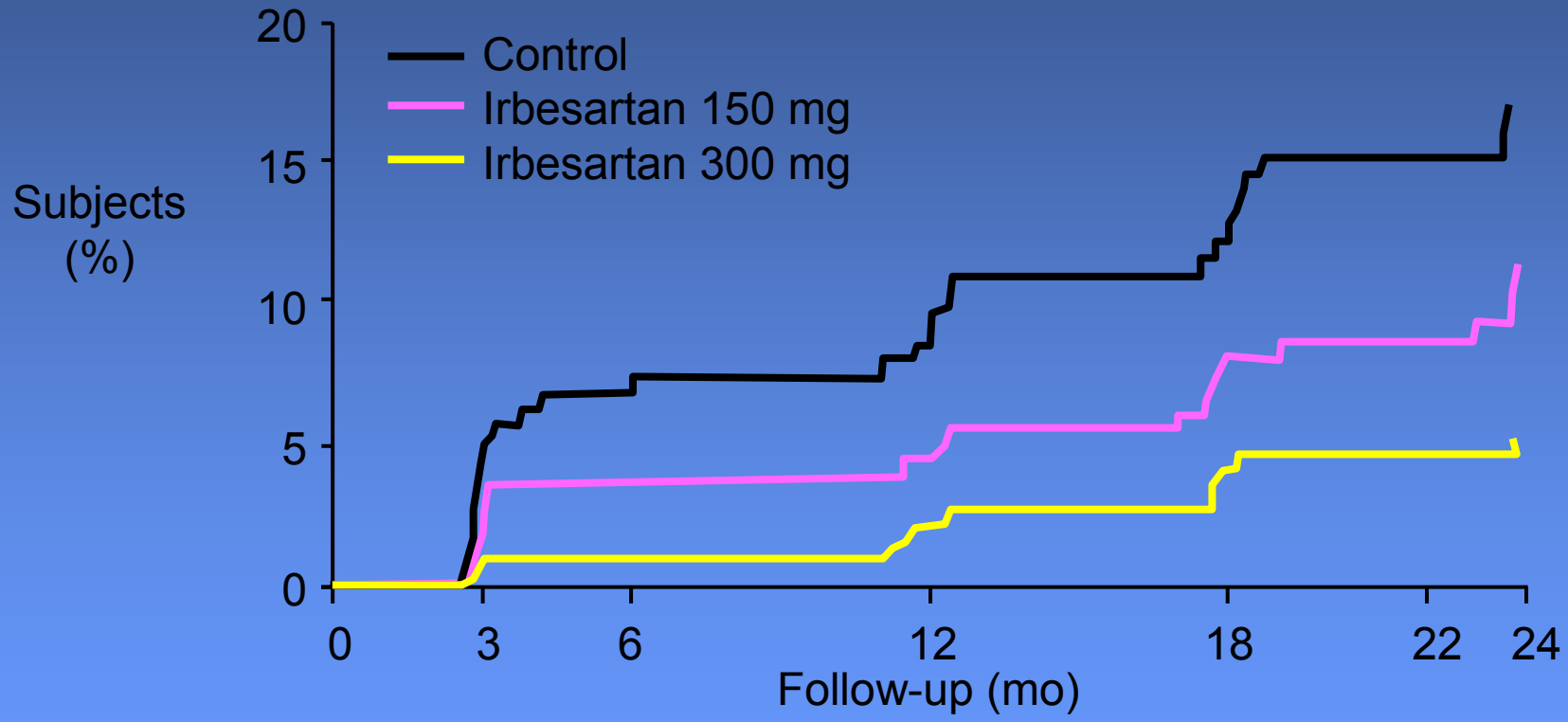
Parving H-H, et al. *N Engl J Med* 2001;345:870-878.

IRMA 2
Clinical Outcome Measures

- Primary outcome:
  - Time to occurrence of overt proteinuria (AER > 200 μg/min)
- Secondary outcomes:
  - Change in AER
  - Regression to normoalbuminuria (AER < 20 μg/min)
  - Change in creatinine clearance
  - Clotting factors and lipid profile

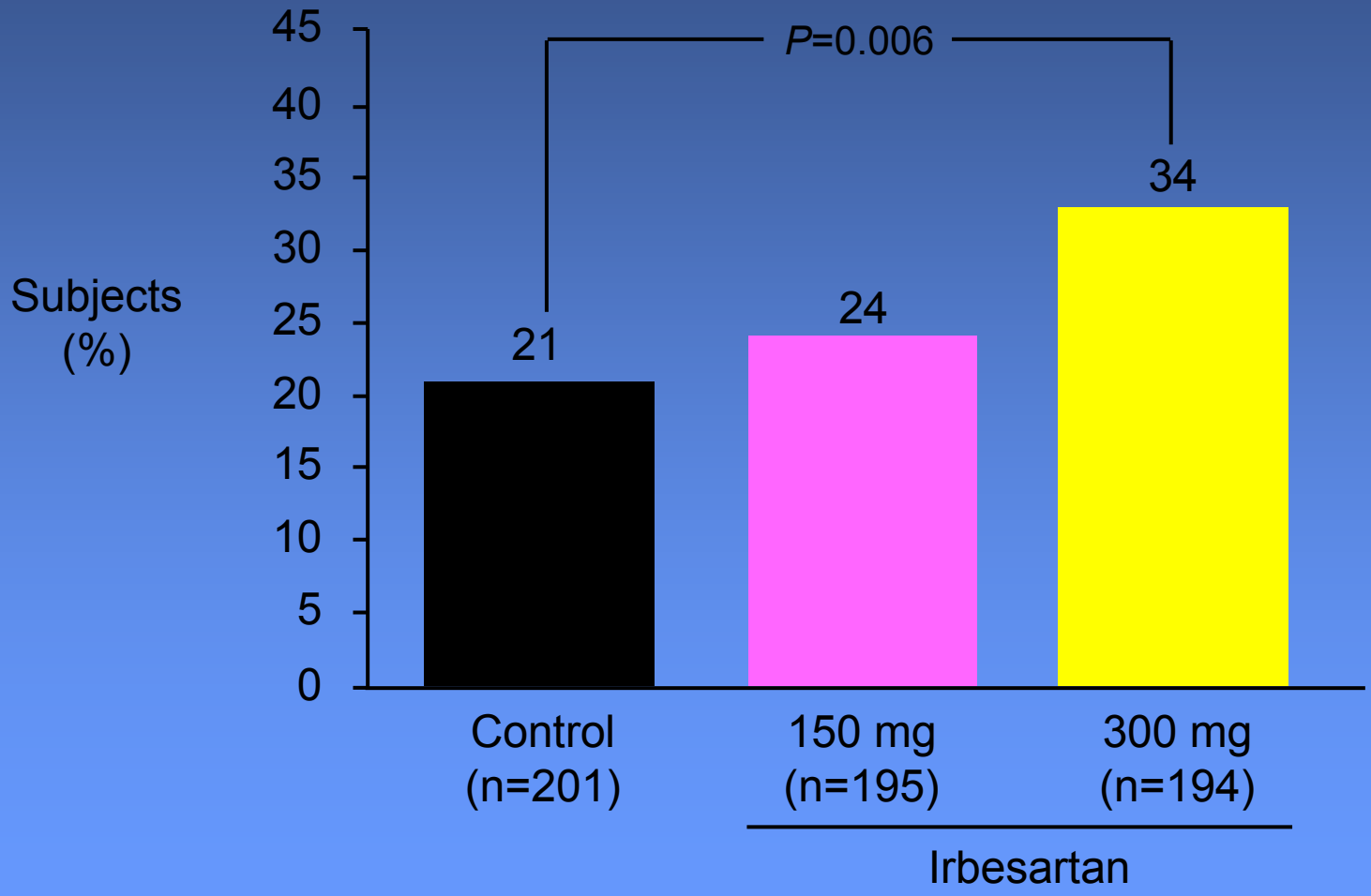
Parving H-H, et al. *N Engl J Med* 2001;345:870-878.

IRMA 2 Primary Endpoint
Time to Overt Proteinuria



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

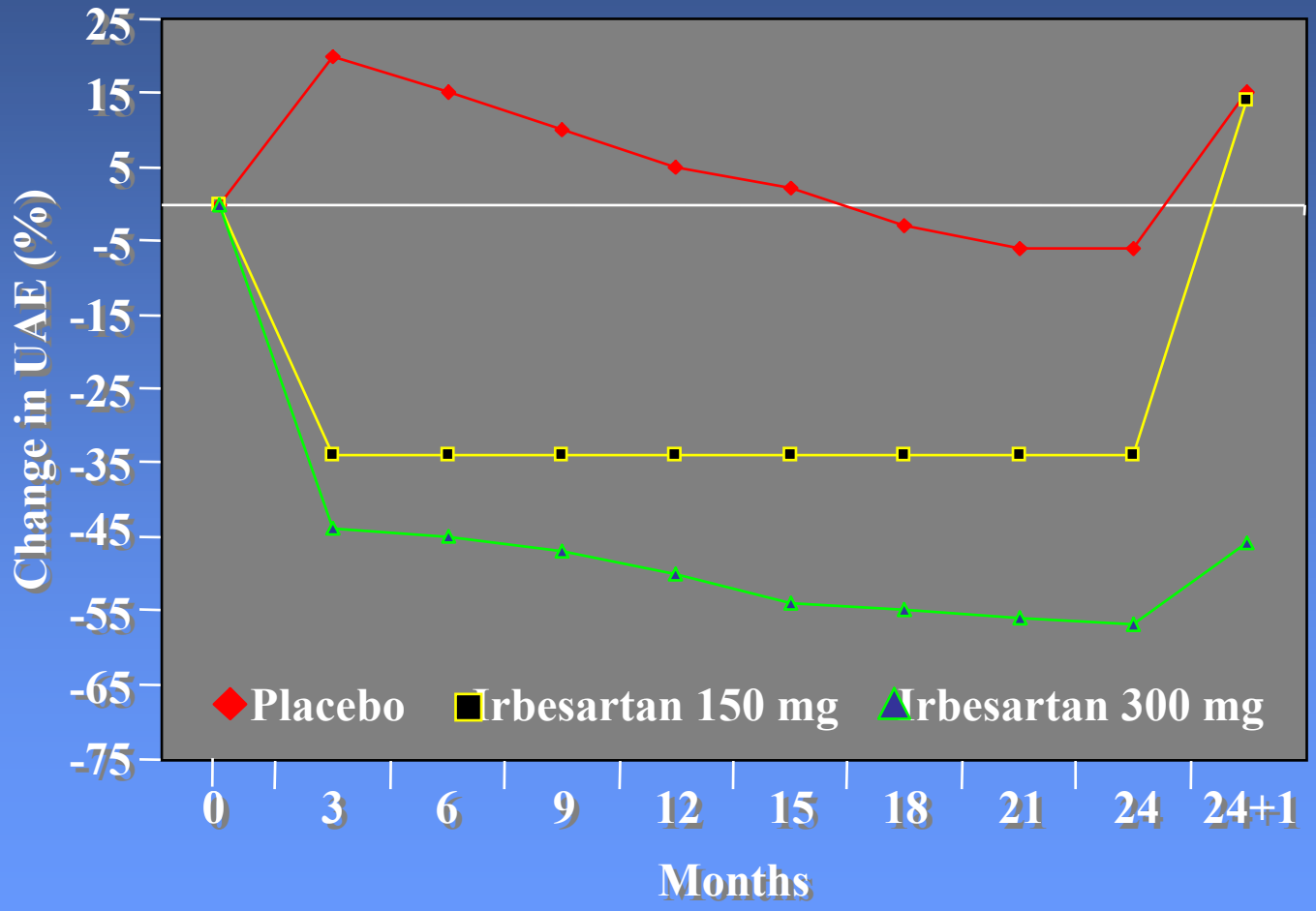
IRMA 2
Normalization of Urinary Albumin Excretion Rate



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

IRMA-2

Change in UAER



Andersen S et al. *Diabetes Care* 2003;26:3296-3302

ARB Therapy in Diabetic Microalbuminuria

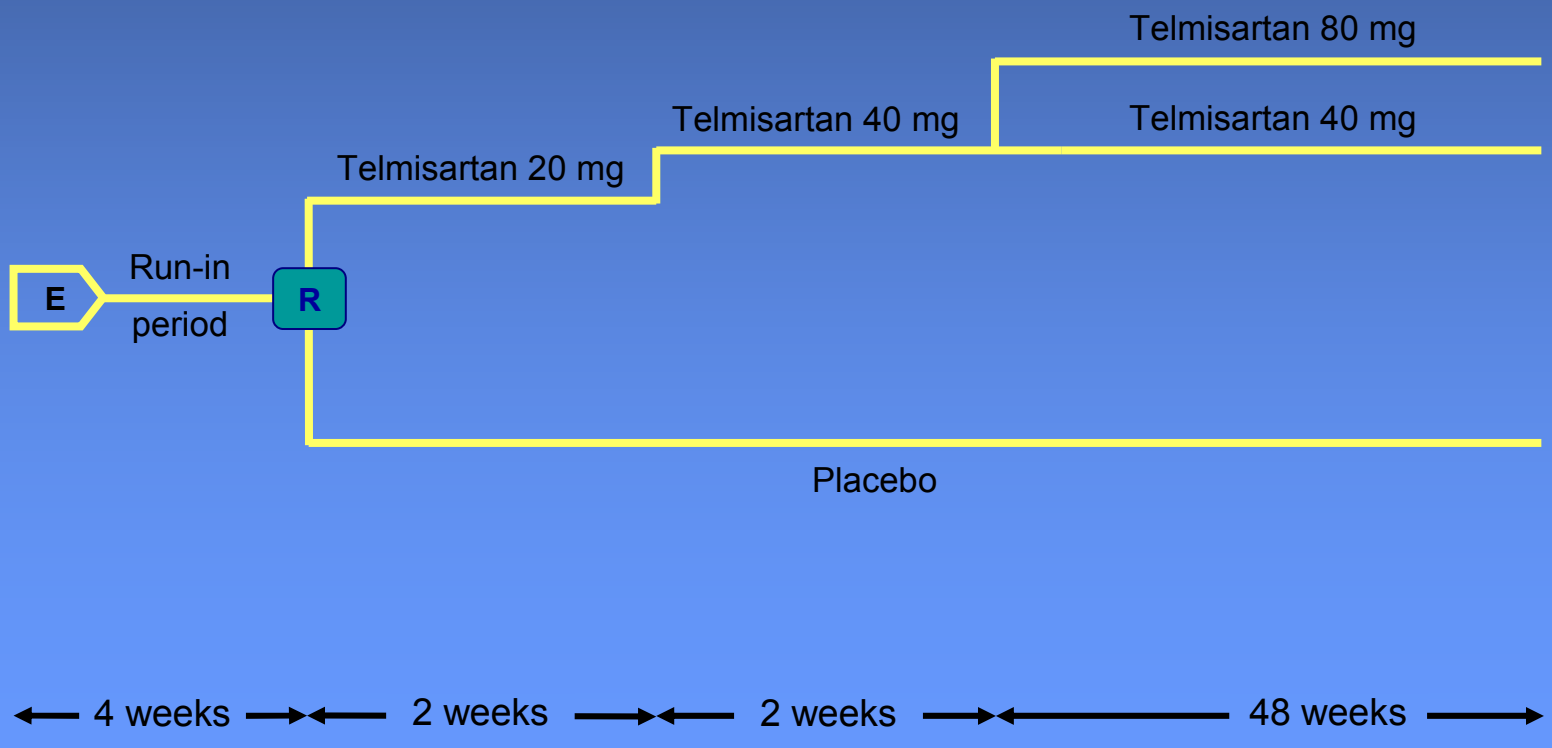
- The maximum recommended dose of Avapro is the only effective dose of Avapro
- Whether the maximum recommended dose of other ARBs provides similar benefit is not proven, only assumed

Disclaimer

Before prescribing pharmaceutical preparations containing telmisartan or any of the products mentioned in this slide resource, please consult the manufacturers' prescribing information as approved in your country. The pharmaceutical preparations containing telmisartan by Boehringer Ingelheim are

Study design

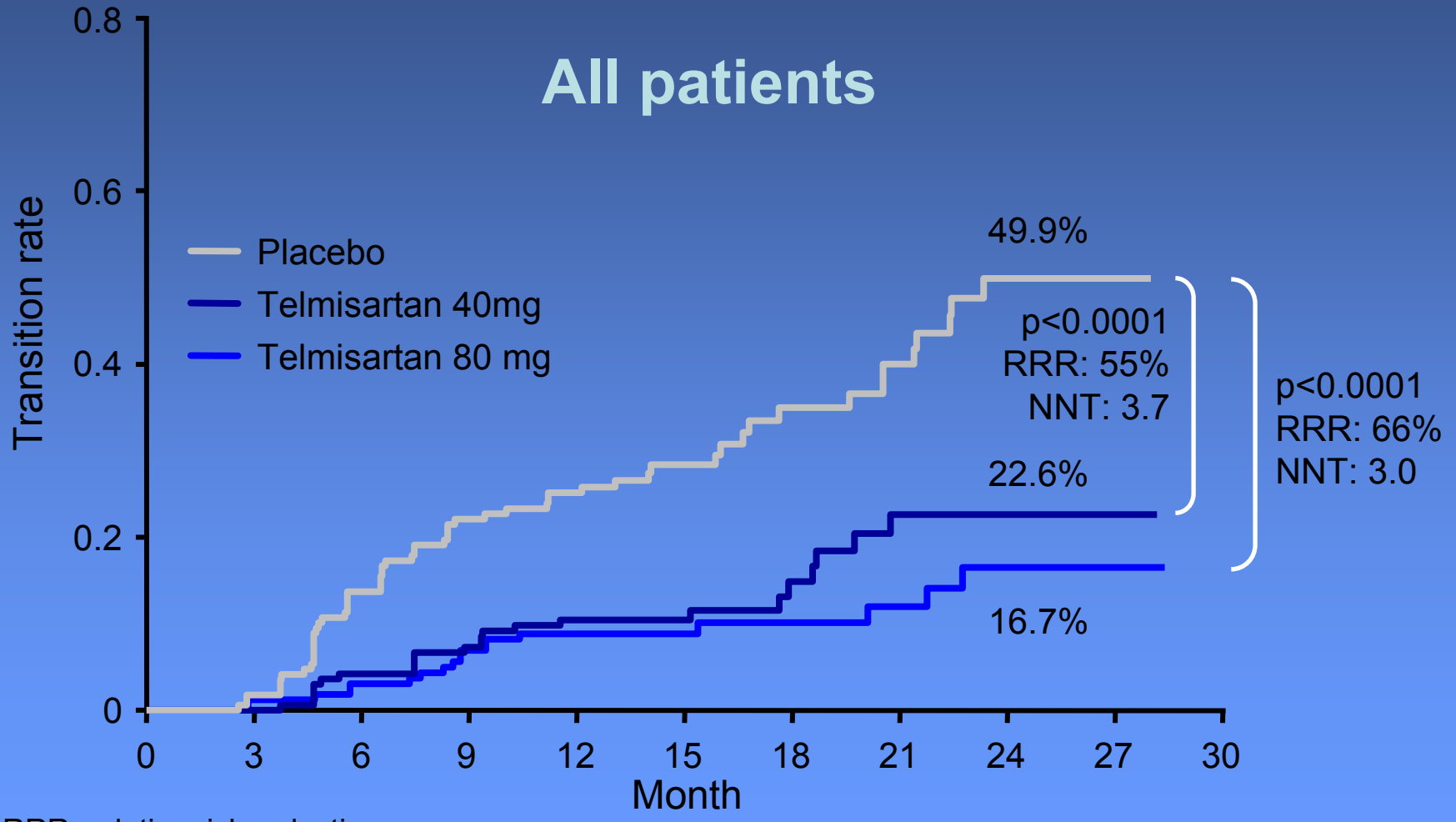
Prospective, randomized, double-blind,
forced-titration, multicentre, parallel-group, 1-year treatment



Makino, et al. *J Int Med Res* 2005;33:677–686

INNOVATION

Transition to overt nephropathy

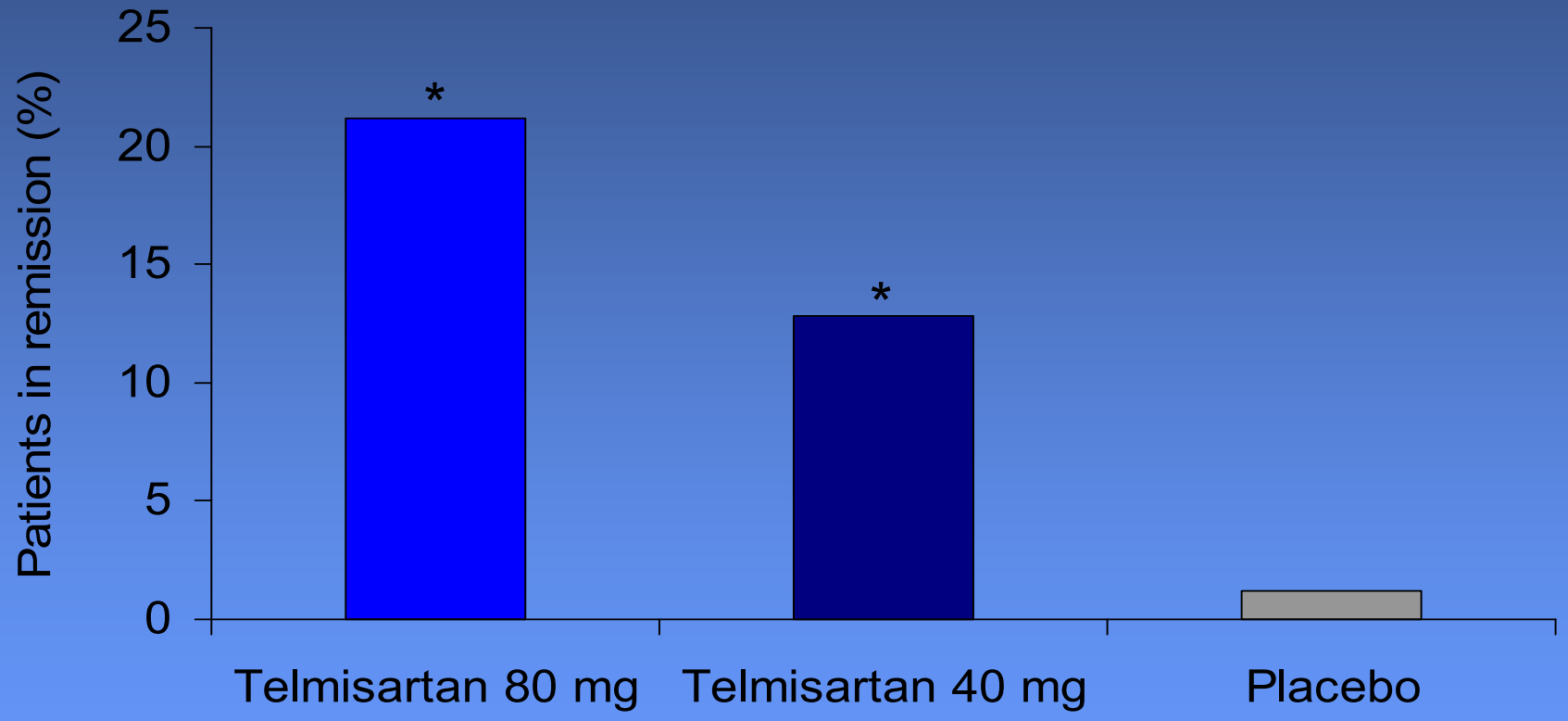


RRR: relative risk reduction
NNT: number needed to treat to prevent 1 transition

Makino et al. *Diabetes Care* 2007; in press

INNOVATION

Remission of microalbuminuria



* P<0.001 versus placebo

Makino et al. *Diabetes Care* 2007; in press

INVOVATION

BLOOD PRESSURES

GROUP	Start	End
Placebo	137/77	132/74
Micardis 40mg	137/78	128/72
Micardis 80mg	138/78	128/72

INVOVATION

Conclusions

- Both Telmisartan 40mg and 80mg were beneficial in reducing progression to overt nephropathy and in increasing regression of microalbuminuria
- Blood pressure was the same in both treatment group, but was 4/2 higher in the placebo group

RENAAL

Altering the Course of Renal Disease in Hypertensive Patients with Type 2 DM and Nephropathy with the A II Antagonist Losartan

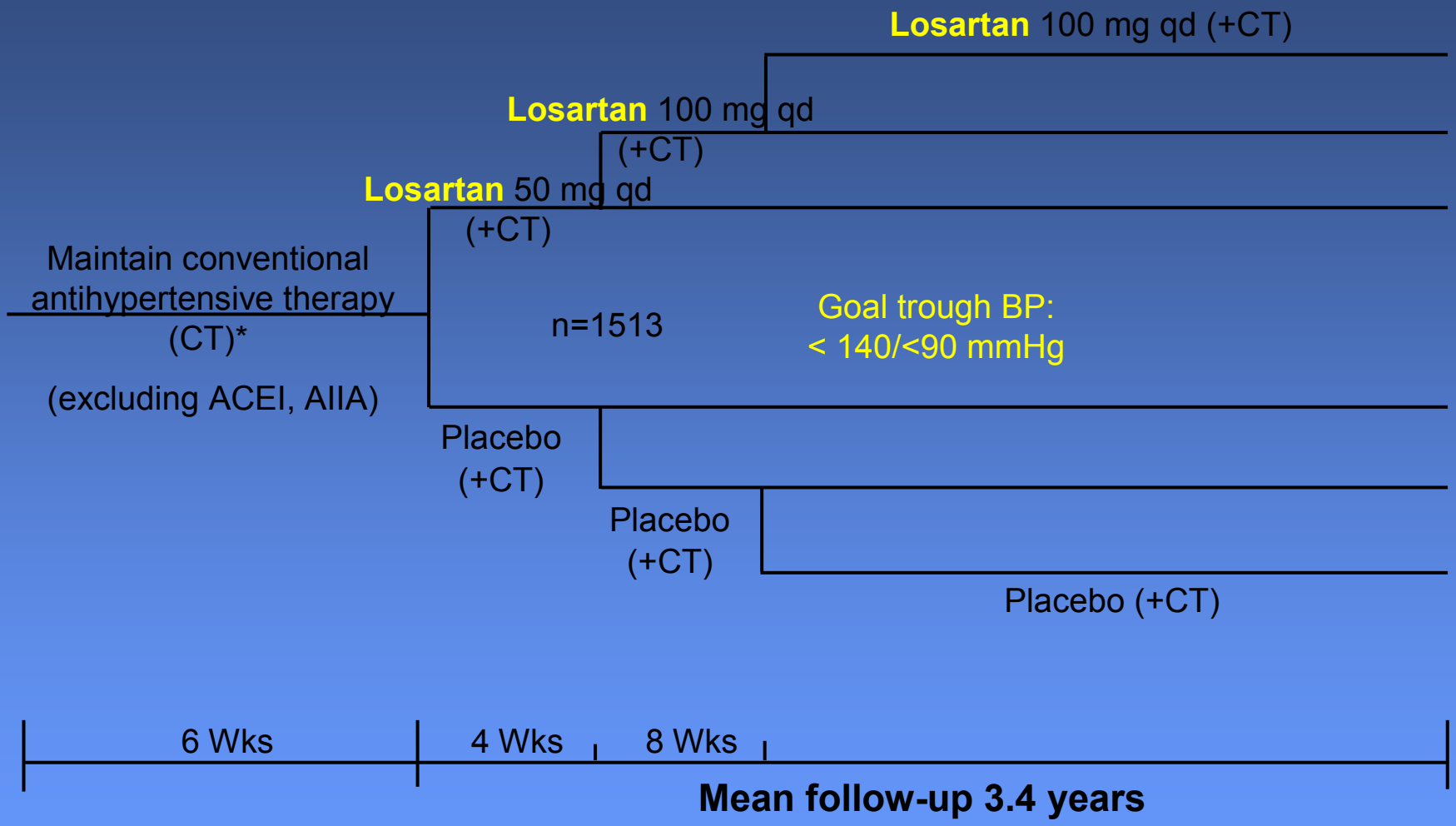
RENAAL- Primary Hypothesis

Long-term treatment with losartan versus placebo (alone or in combination with conventional antihypertensive therapy*) in Type 2 diabetic patients with nephropathy will increase the time to first event and decrease the incidence of doubling of sCr, ESRD or death.

* Excluding ACEIs and other AIIAs

Brenner BM et al *J Renin-Angio-Aldo System* 2000;1(4):328-335.

RENAAL- Study Design



*CT=conventional therapy: Open-label calcium-channel blocker, diuretic, beta blocker, alpha blocker, or centrally acting agents.

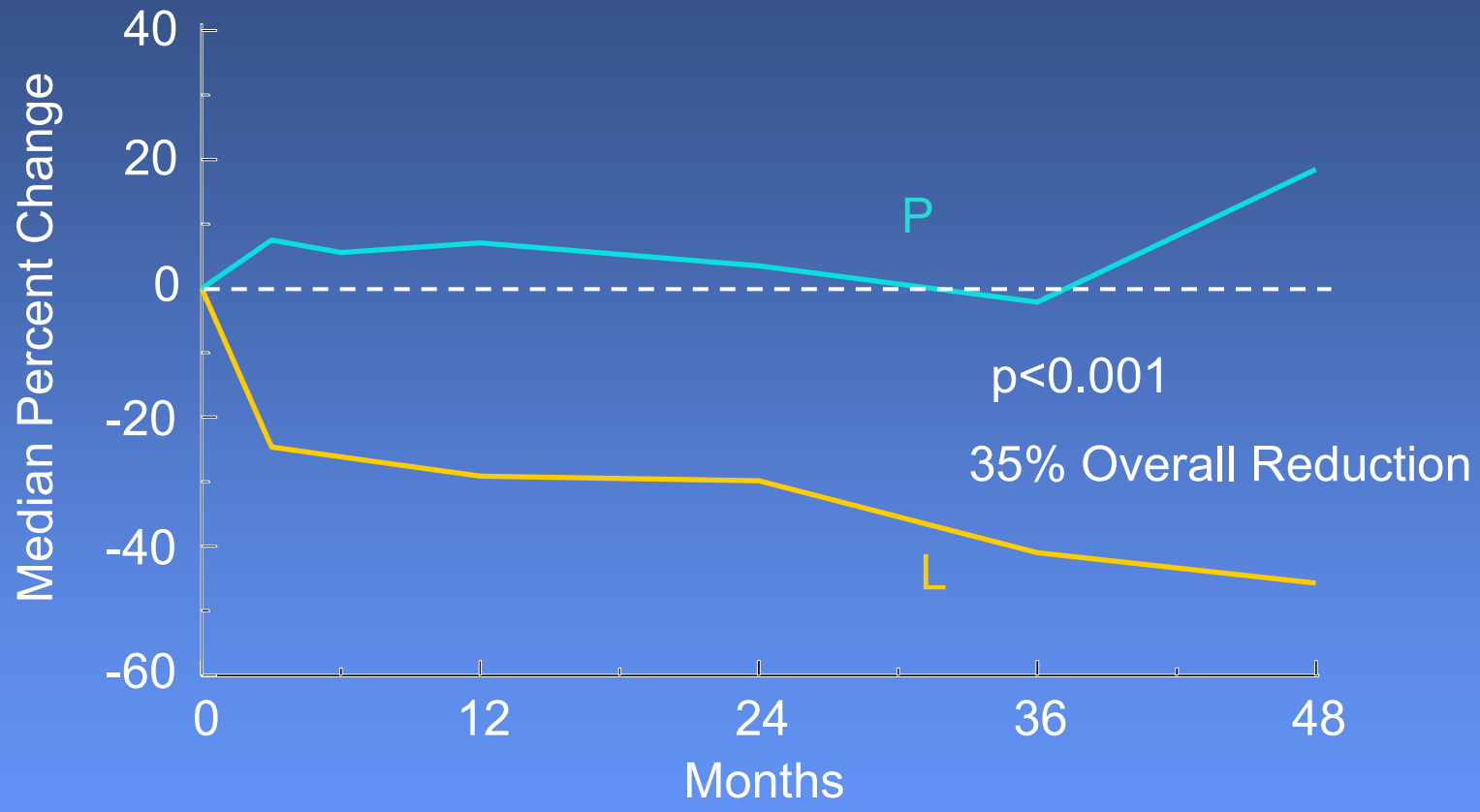
Brenner BM et al *J Renin-Angio-Aldo System* 2000;1(4):328-335.

RENAAL-Primary Composite Endpoint & Components

Composite and Components	Losartan (+CT) (n=751) n (%)	Placebo (+CT) (n=762) n (%)	P-Value	% Risk Reduction	95% CI
DsCr, ESRD, Death	327 (43.5)	359 (47.1)	0.02	**16**	(2, 28)
Doubling of sCr	162 (21.6)	198 (26.0)	0.006	**25**	(8, 39)
ESRD	147 (19.6)	194 (25.5)	0.002	**28**	(11, 42)
Death	158 (21.0)	155 (20.3)	0.88	-2	(-27, 19)
ESRD or Death	255 (34.0)	300 (39.4)	0.01	**20**	(5, 32)

Brenner BM et al *New Engl J Med* 2001;345(12):861-869.

RENAAL- Change from Baseline in Proteinuria

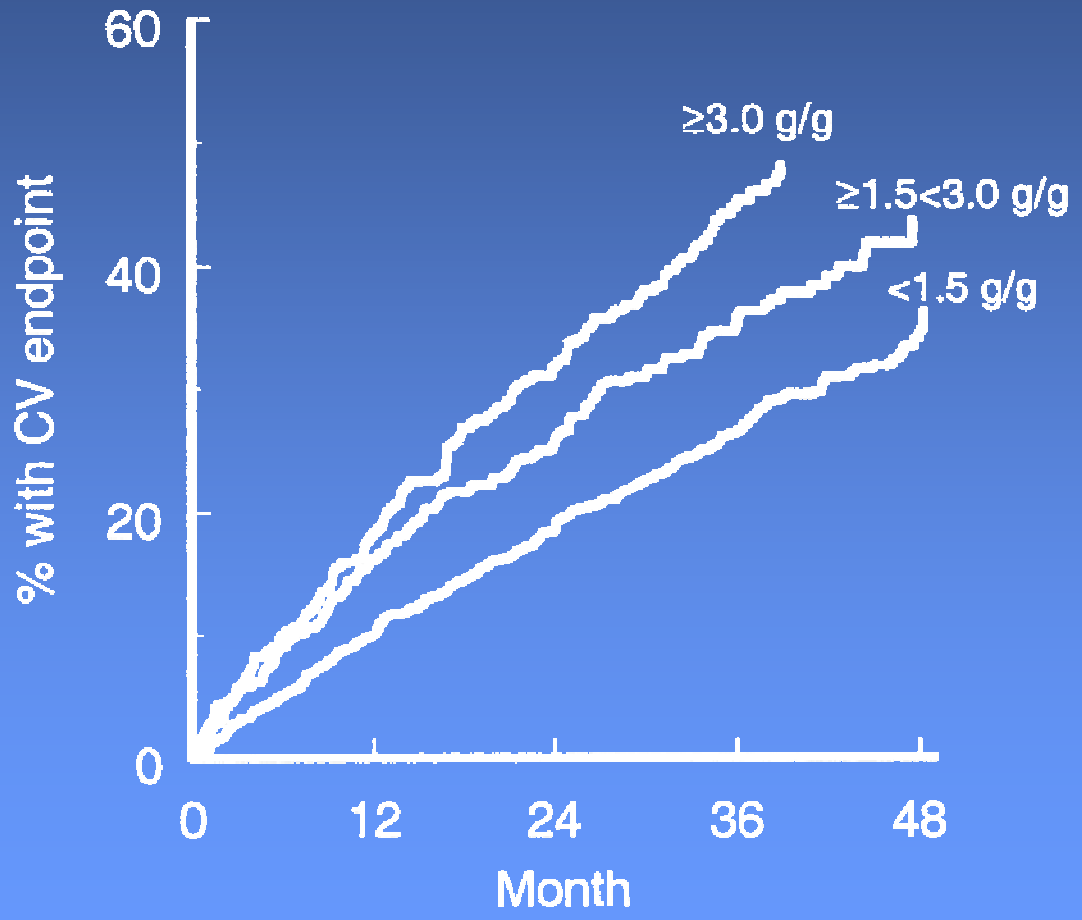


P (+CT)	762	632	529	390	130
L (+CT)	751	661	558	438	167

Proteinuria measured as the urine albumin:creatinine ratio from a first morning void.

Brenner BM et al *New Engl J Med* 2001;345(12):861-869.

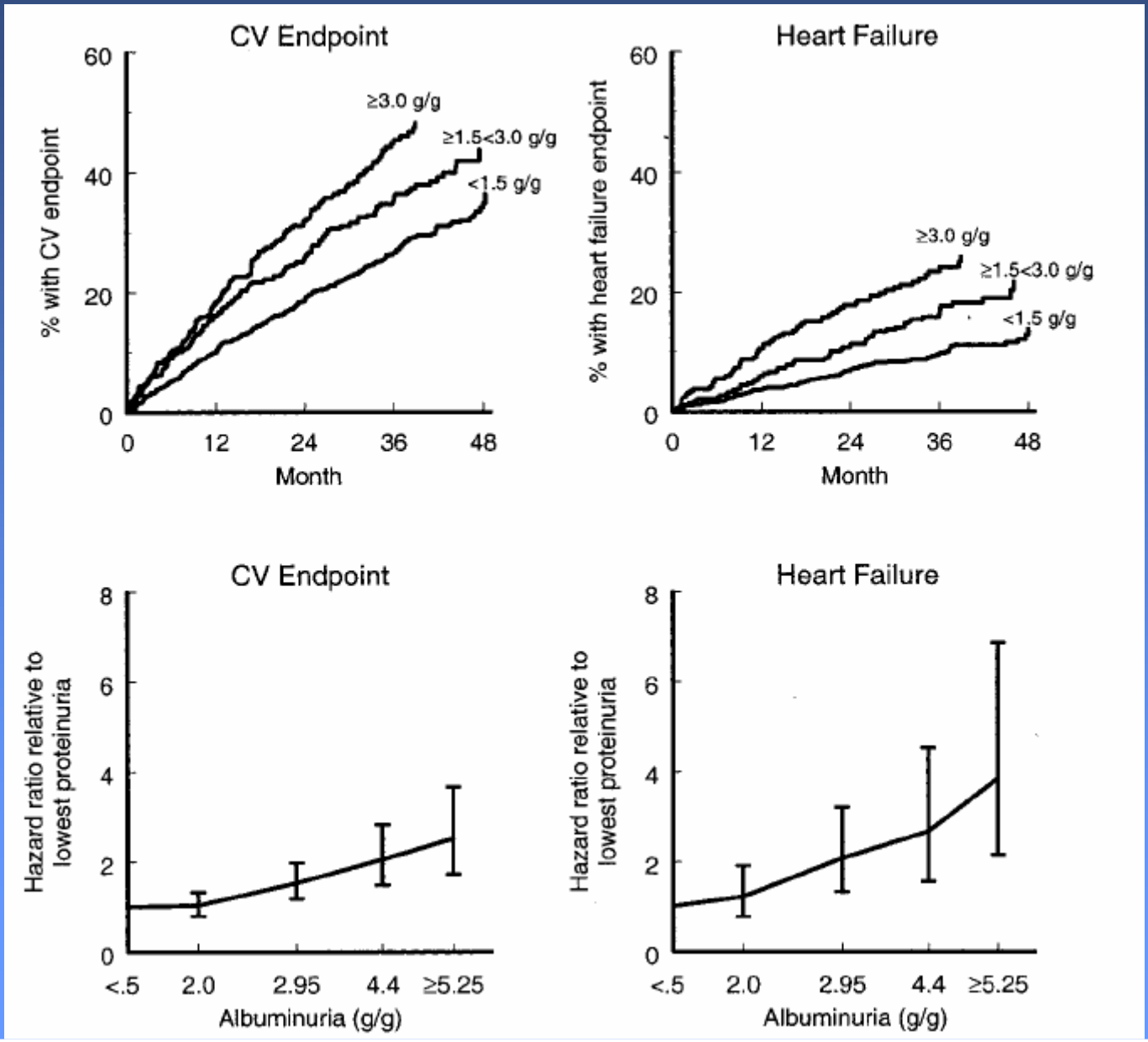
RENAAL- Occurrence of CV endpoint according to baseline proteinuria



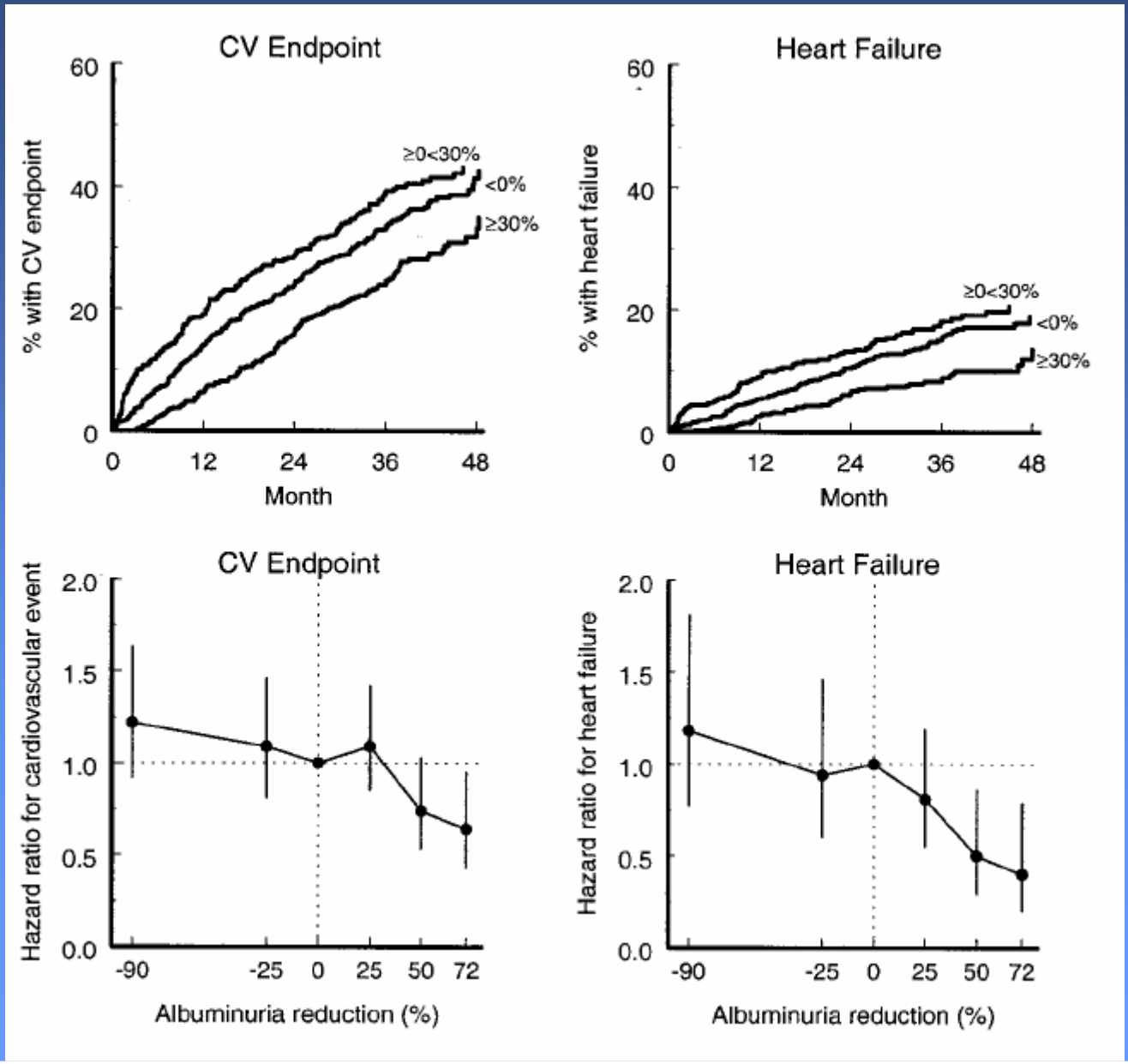
Baseline Proteinuria

de Zeeuw. *Circulation* 2004;110:921–927

RENAAL- Baseline proteinuria predicts outcome



RENAAL- Percentage reduction of proteinuria predicts outcome



AMADEO

Objectives

- To compare the long-term effect of Telmisartan 80 mg versus Losartan 100 mg in patients with type 2 diabetes and overt nephropathy on:
  - Proteinuria (primary endpoint)
  - Other renal parameters (secondary endpoint)
  - Cardiovascular protection (secondary endpoint)
  - Safety

Outcomes

Primary endpoint

- Change in proteinuria after 1 year of treatment

Secondary endpoints

- Creatinine clearance
- Surrogate renal protection endpoints

Weber. *J Hypertens* 2003;21 (Suppl 6):S37–S46.

Patient characteristics

- 860 patients

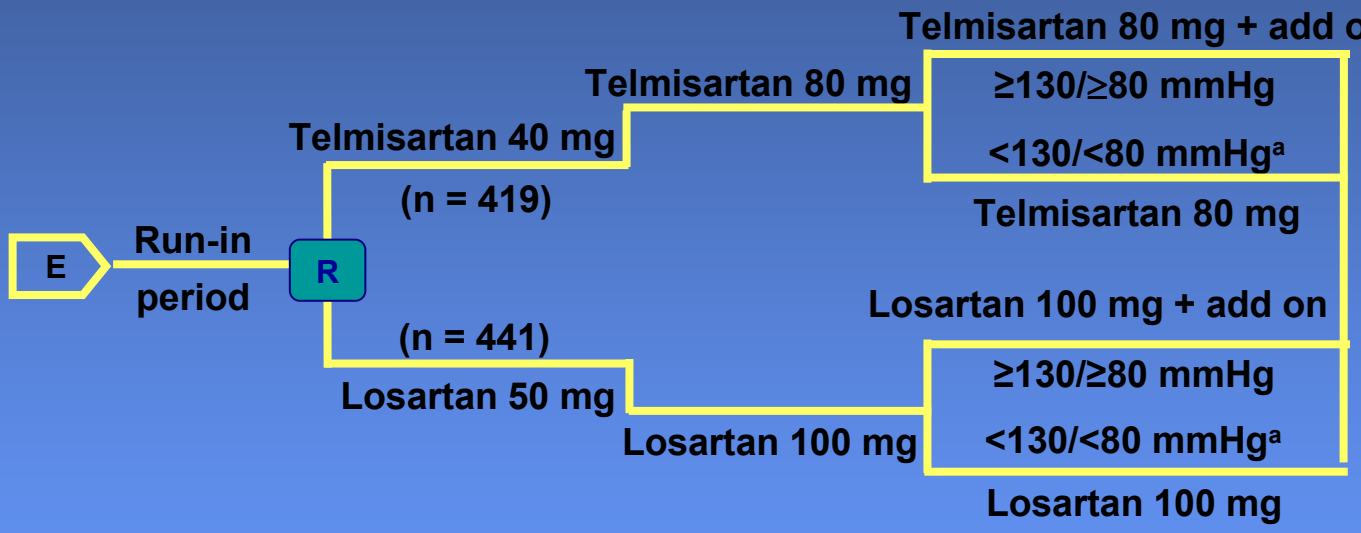
Inclusion criteria

- Type 2 diabetes
- Hypertension (seated SBP/DBP >130/>80 mmHg)
- Macroproteinuria
  (≥700 mg/g creatinine (first morning voided urine), equivalent to 900 mg/24 hours)
- Serum creatinine
  - women ≤265 µmol/L (≤3.0 mg/dL)
  - men ≤285 µmol/L (≤3.2 mg/dL)

Weber. *J Hypertens* 2003;21 (Suppl 6):S37–S46.
Rodby. *Am J Kidney Dis* 1995;26:904–909.

Study design

Prospective, randomized, double-blind, double-dummy, forced-titration, multicentre, parallel-group, 1-year treatment



4 weeks → ← 2 weeks → ← 50 weeks →

E = enrollment, R = randomization

[a] <130/<80 mmHg recommended target recommended by JNC7 for patients with diabetic nephropathy (Chobanian et al. *Hypertension* 2003;42:1206–1252).

Patient Demographics

	Telmisartan 40/80 mg (N=419)	Losartan 50/100 mg (N=441)	Total (N=860)
Male, N (%)	256 (61.1)	279 (63.3)	535 (62.2)
Age, yrs Mean (SD)	60.0 (9.2)	60.5 (9.4)	60.3 (9.3)
Race, N (%)			
➢ **Caucasian**	188 (44.9)	217 (49.2)	405 (47.1)
➢ **Asian**	172 (41.1)	180 (40.8)	352 (40.9)
➢ **Black**	59 (14.1)	43 (9.8)	102 (11.9)

Patient Baseline Characteristics

	Telmisartan 40/80 mg (N=419)	Losartan 50/100mg (N=441)	Total (N=860)
BMI, mean (SD) [kg/m^2]	30.1 (6.8)	29.9 (6.2)	30.0 (6.5)
Smokers, N (%)	63 (15.0)	71 (16.1)	134 (15.6)
Duration hypertension, mean (SD) [yrs]	9.0 (8.9)	9.7 (9.9)	9.3 (9.4)
Duration diabetic nephropathy, mean (SD) [yrs]	2.7 (5.3)	2.3 (3.5)	2.5 (4.5)
Duration type 2 diabetes, mean (SD) [yrs]	14.6 (8.4)	14.1 (8.1)	14.3 (8.3)

Baseline Characteristics of Randomized Patients

	Telmisartan (n= 419)	Losartan (n = 441)
SBP/DBP (mmHg)	144 ± 16/ 80 ± 9	143 ± 15/80 ± 10
BMI (kg/m^2)	30.1 ± 6.8	29.9 ± 6.2
Duration of diabetes (years)	16.6 ± 8.4	14.1 ± 8.1
HbA_{1C} (%)	7.93 ± 1.30[a]	7.85 ± 1.3[b]
UPC (mg/gCr)	1970.9[c]	2010.5[d]
Serum creatinine (gmean, mg/dL)	1.54[e]	1.55[f]

[a]n = 418, [b]n = 439, [c]n = 413, [d]n = 437, [e]n = 419, [f]n = 441

Patient Participation at Conclusion

	Telmisartan 40/80 mg N (%)	Losartan 50/100mg N (%)	**Total** N (%)
Enrolled			1567
Entered	419	441	860
Treated	419 (100.0)	441 (100.0)	860 (100.0)
•Completed Study	345 (82.3)	342 (77.6)	687 (79.9)
•Prematurely Discontinued	74 (17.7)	99 (22.4)	173 (20.1)

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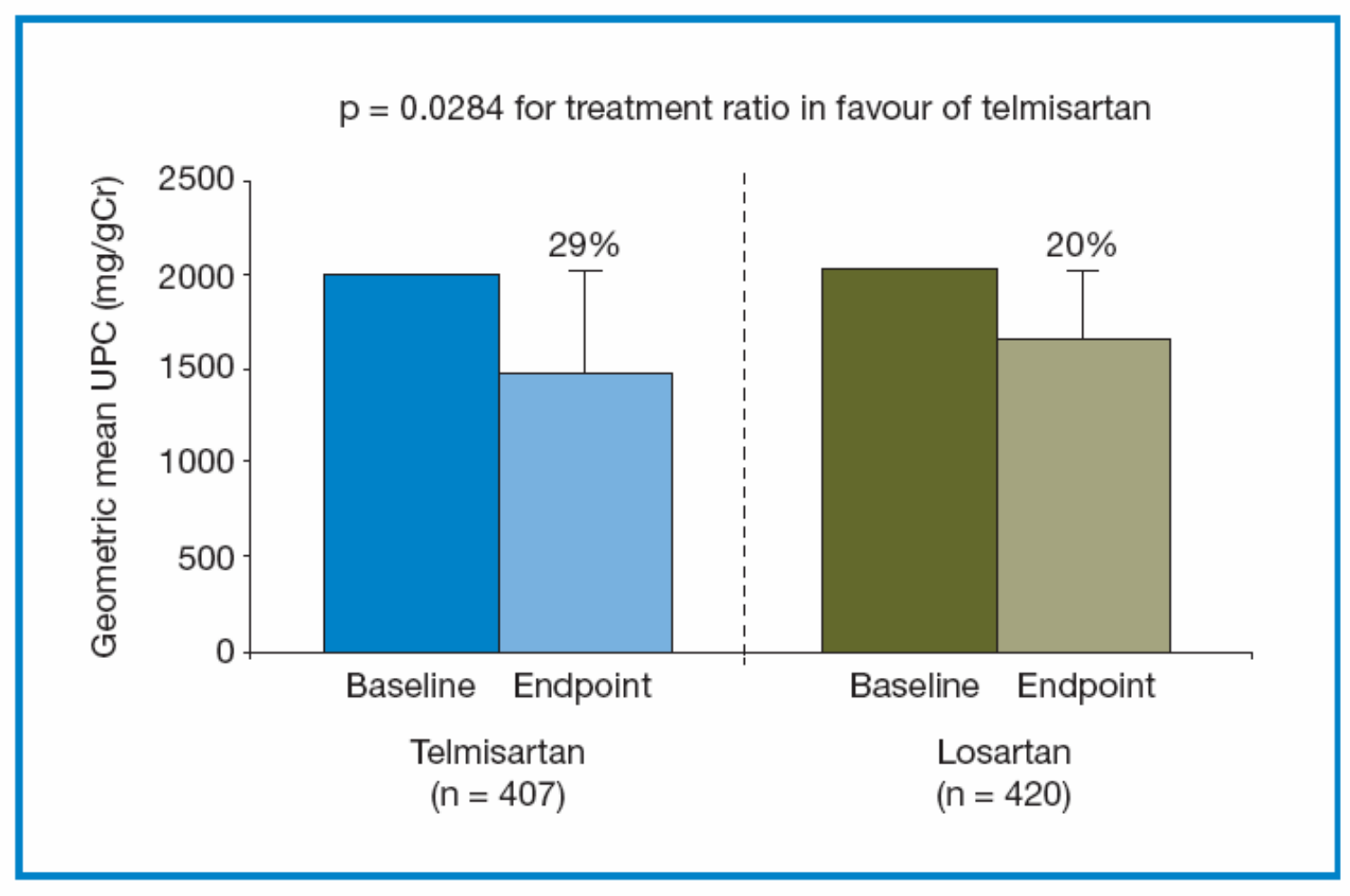
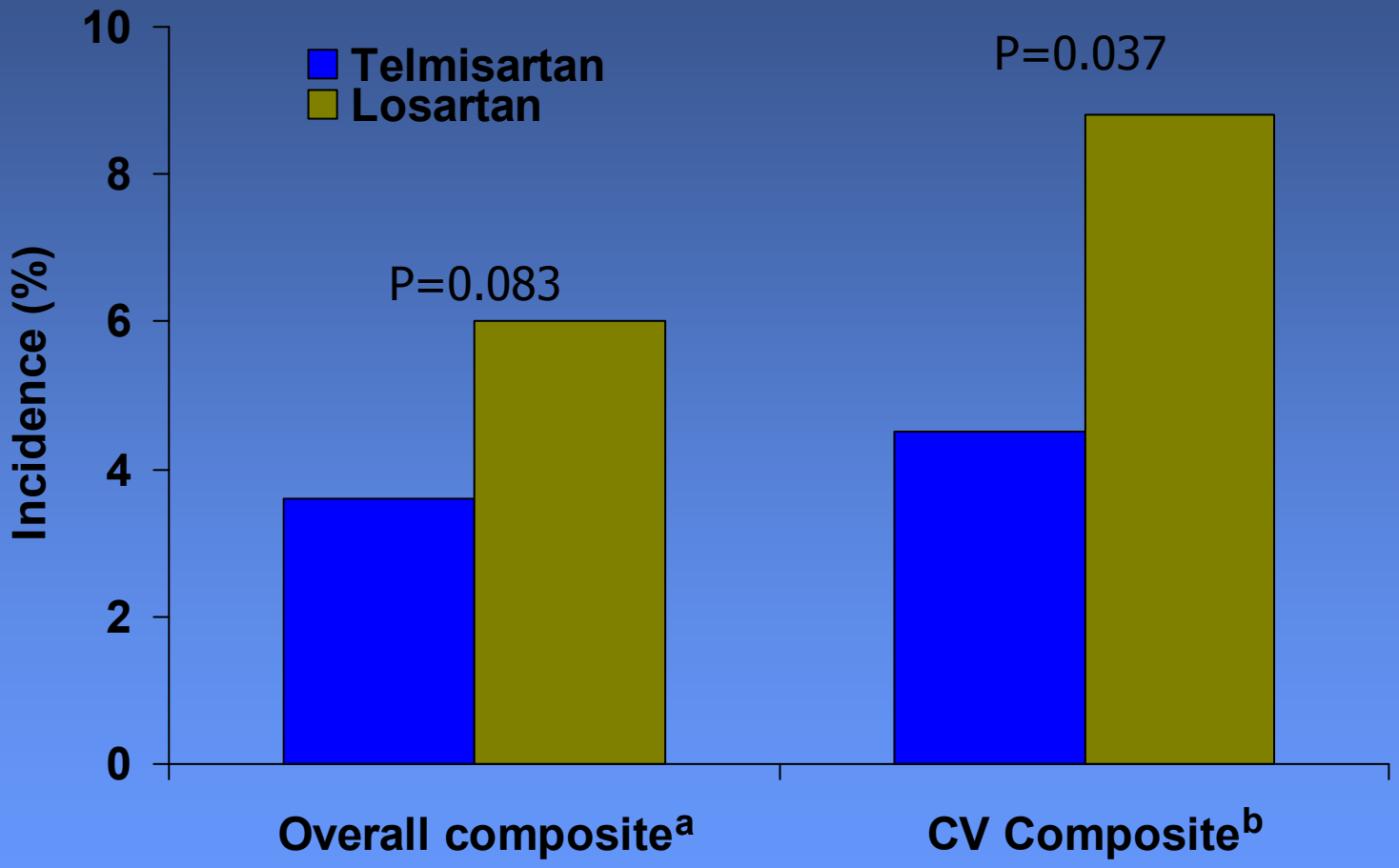
Summary of mean SBP and DBP during Active Treatment				
	Telmisartan 80 mg		Losartan 100 mg	
	Actual	Change	Actual	Change
N	414		428	
SYSTOLIC				
Baseline	144		143	
Final high dose	140	-4	141	-2
DIASTOLIC				
Baseline	80		79	
Final high dose	77	-3	77	-2

Reduction in proteinuria



Overall Renal and Cardiovascular Composite Endpoints

Overall Renal and Cardiovascular Composite Endpoints



[a] Doubling of serum creatinine, ESRD or all-cause death.

[b] Myocardial infarction, stroke, first hospitalization for heart failure or unstable angina, coronary or peripheral revascularization

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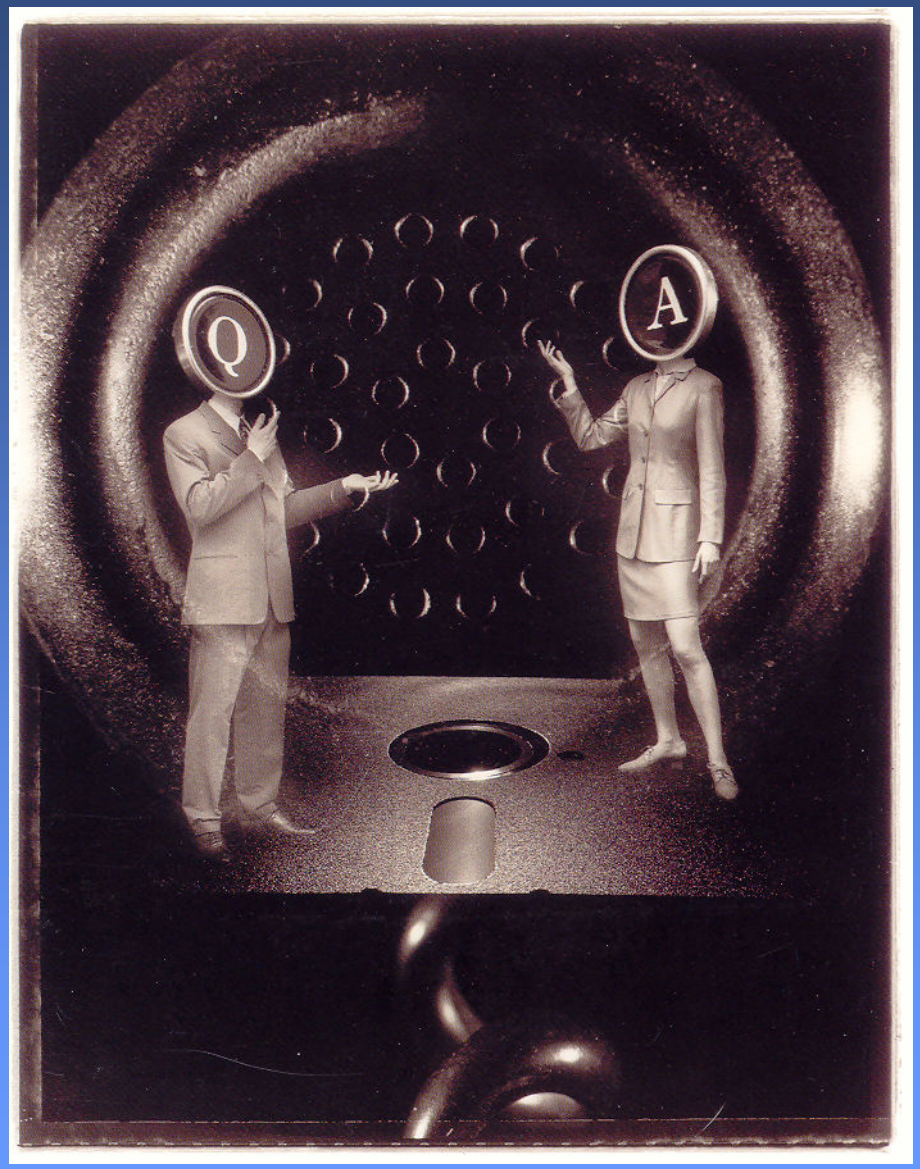
Conclusions

- The AMADEO study confirms the renoprotective profile of ARBs
- Telmisartan provides superior reduction in proteinuria compared with Losartan, despite no significant differences in blood pressure control
- Continuous use of Telmisartan may slow the progression to ESRD in patients with diabetic nephropathy and reduce the risk of cardiovascular events
- Pharmacological differences in ARBs may have implications in renal and cardiovascular protection

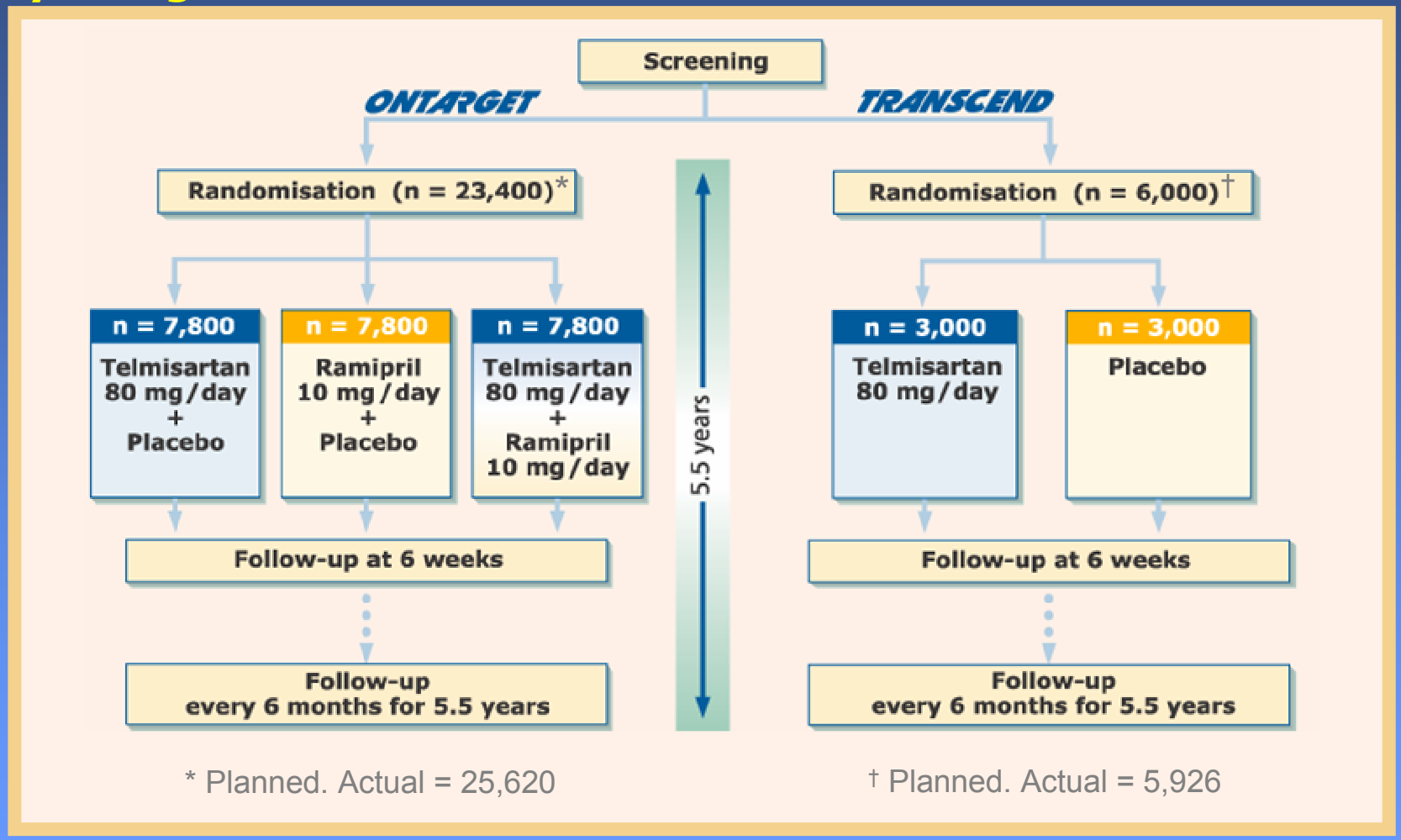
Conclusions

- The renin-angiotensin system plays an important role in diabetic kidney disease
- ARBs reduce proteinuria and the rate of deterioration of renal function
- The reduction in proteinuria predicts the reduction in ESRD and cardiovascular events in these diabetic patients
- Greater reduction in proteinuria should provide greater reduction in the risk of ESRD and cardiovascular events


Q
A

The ONTARGET Trial Programme

Study Design



The ONTARGET/TRANSCEND Investigators. Am Heart J 2004;148:52–61

The ONTARGET Trial Programme

Primary Endpoint

- Primary composite cardiovascular endpoint:
  - Cardiovascular mortality
  - Non-fatal myocardial infarction
  - Non-fatal stroke
  - Hospitalisation for congestive heart failure

The ONTARGET Trial Programme

Secondary Endpoints

- Newly diagnosed congestive heart failure
- Cardiovascular revascularisation procedure
- Newly diagnosed diabetes
- Cognitive decline/dementia
- New onset of atrial fibrillation
- Nephropathy

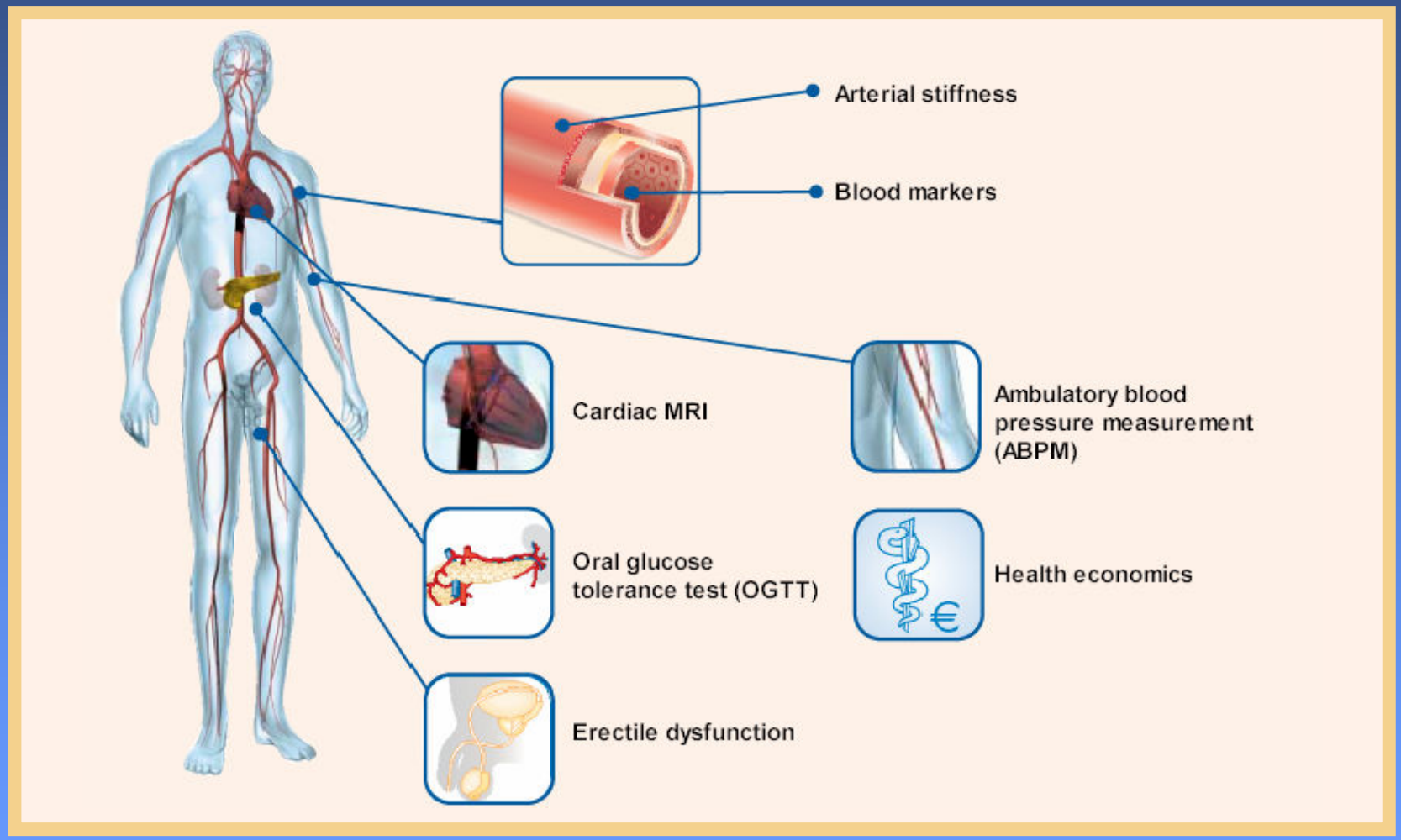
The ONTARGET Trial Programme

Other Endpoints

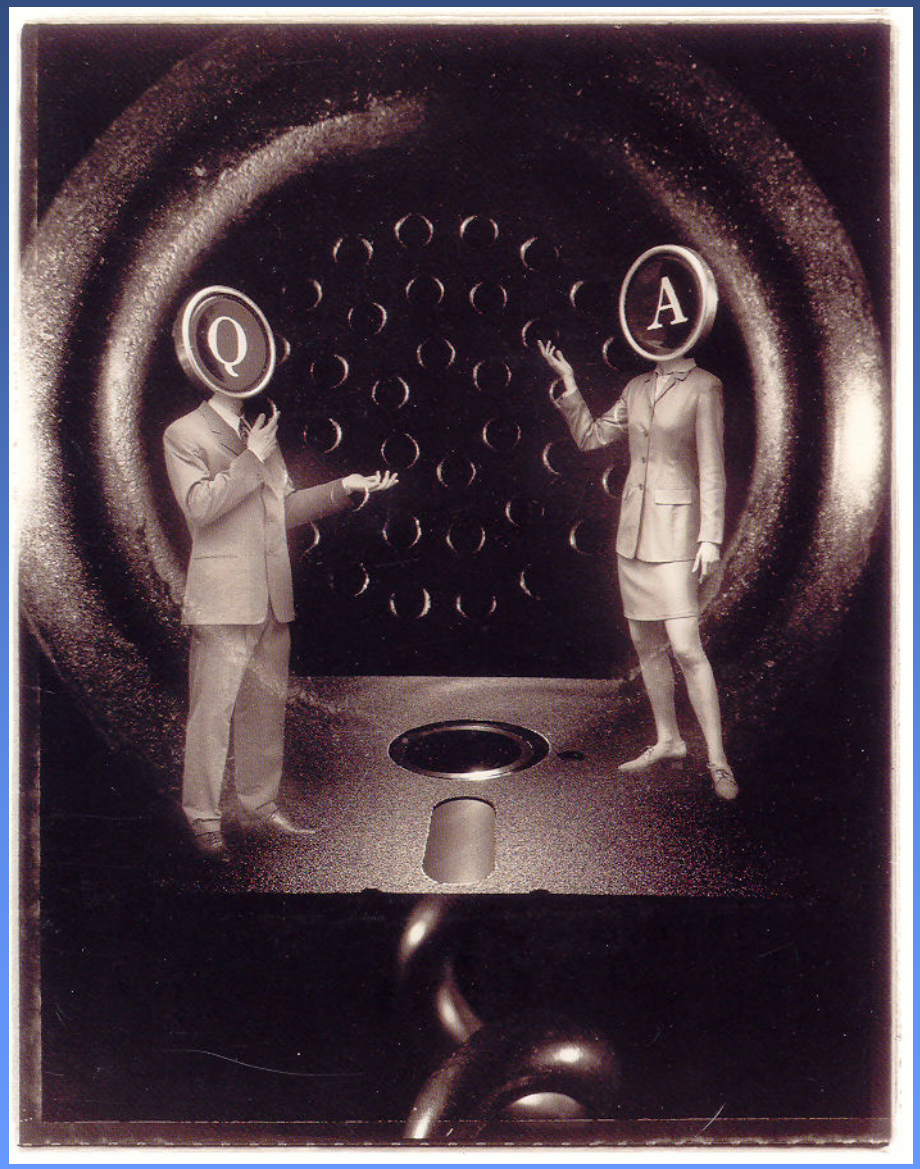
- Non-cardiovascular death, total mortality
- Unstable, new and worsening angina
- Transient ischaemic attack
- Microvascular complications of diabetes (laser therapy for diabetic retinopathy)
- Non-fatal malignancy

The ONTARGET Trial Programme

Substudies



Yusuf S., Am J Cardiol 2002;98 (suppl):18A–26A
Unger T., Am J Cardiol 2003;91 (suppl):28G–34G
Zimmerman M., Unger T., Expert Opin Pharmacother 2004;5:1201-8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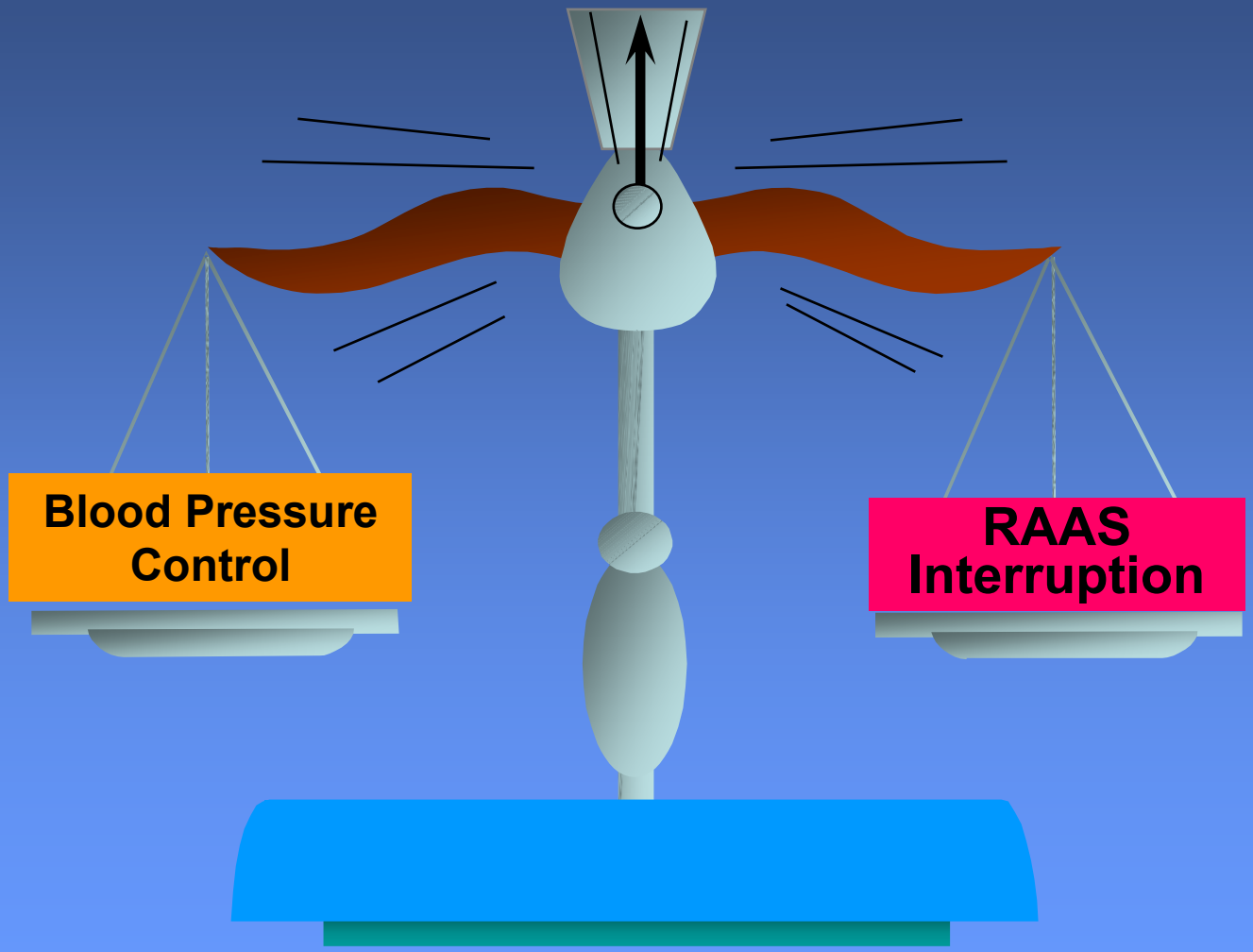
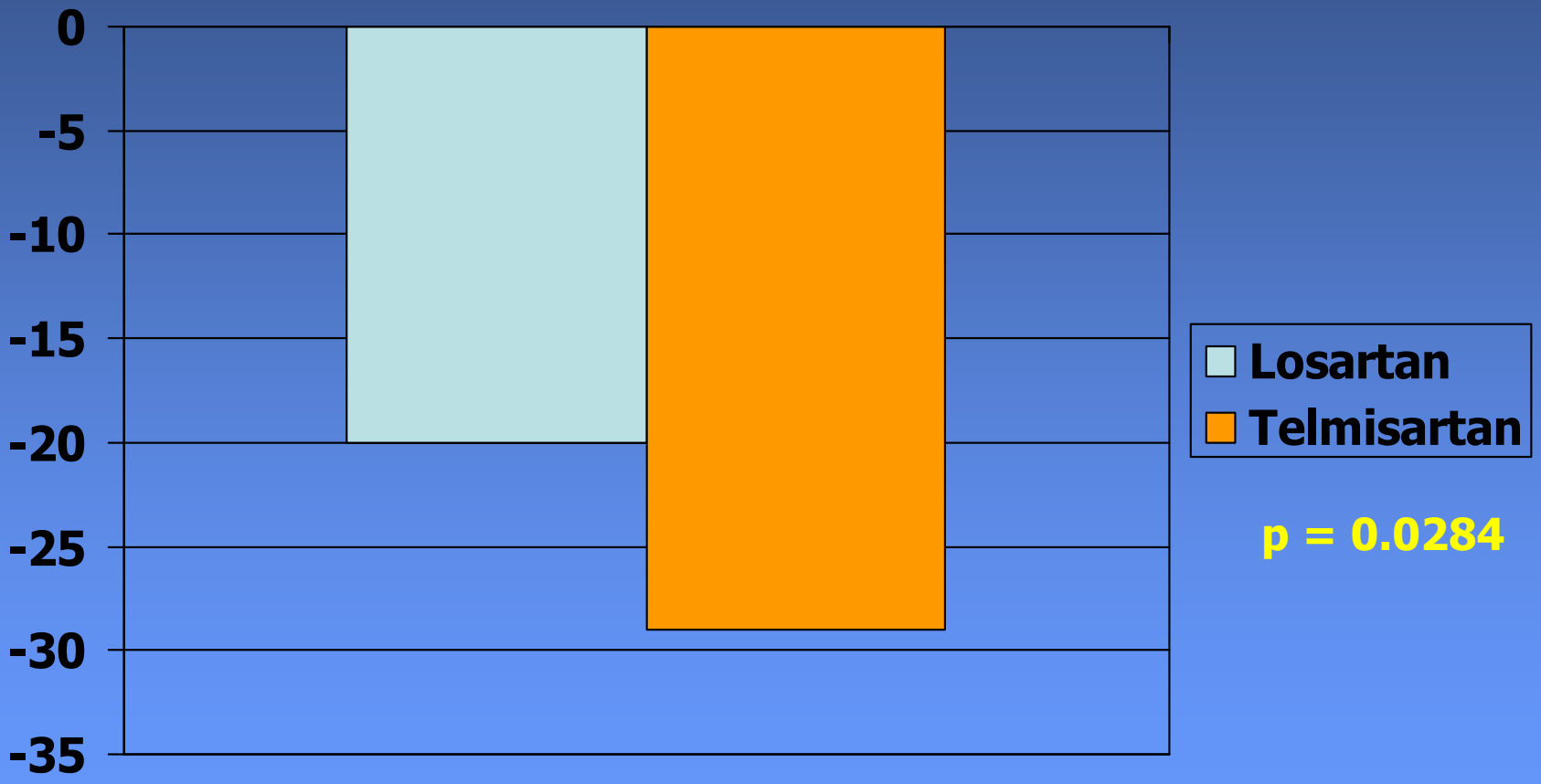
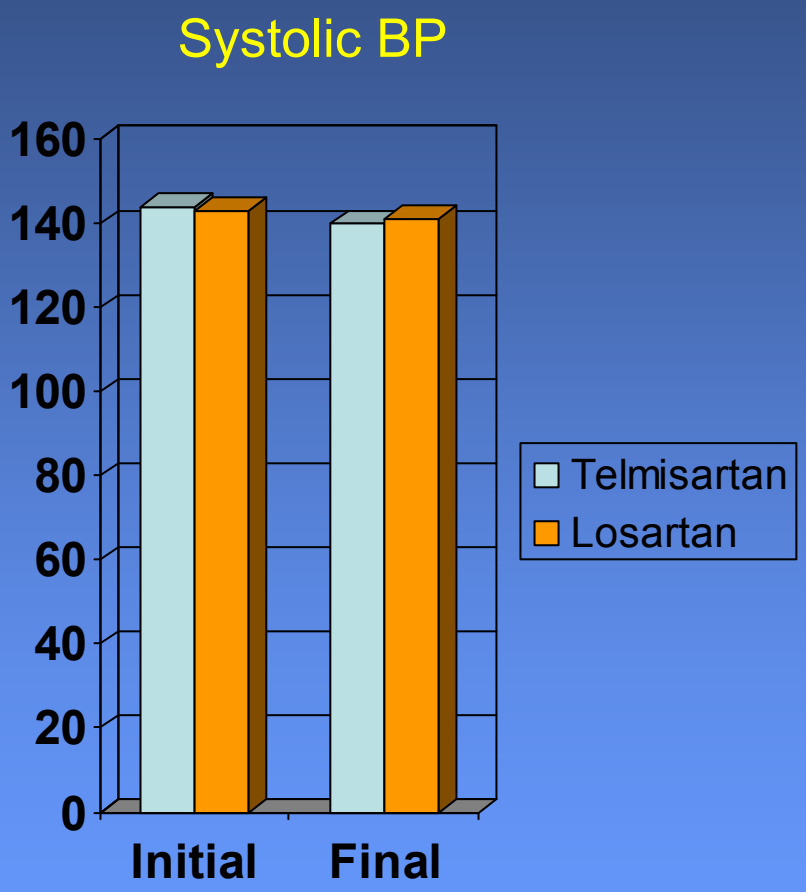
Cardiovascular-Renal Protection

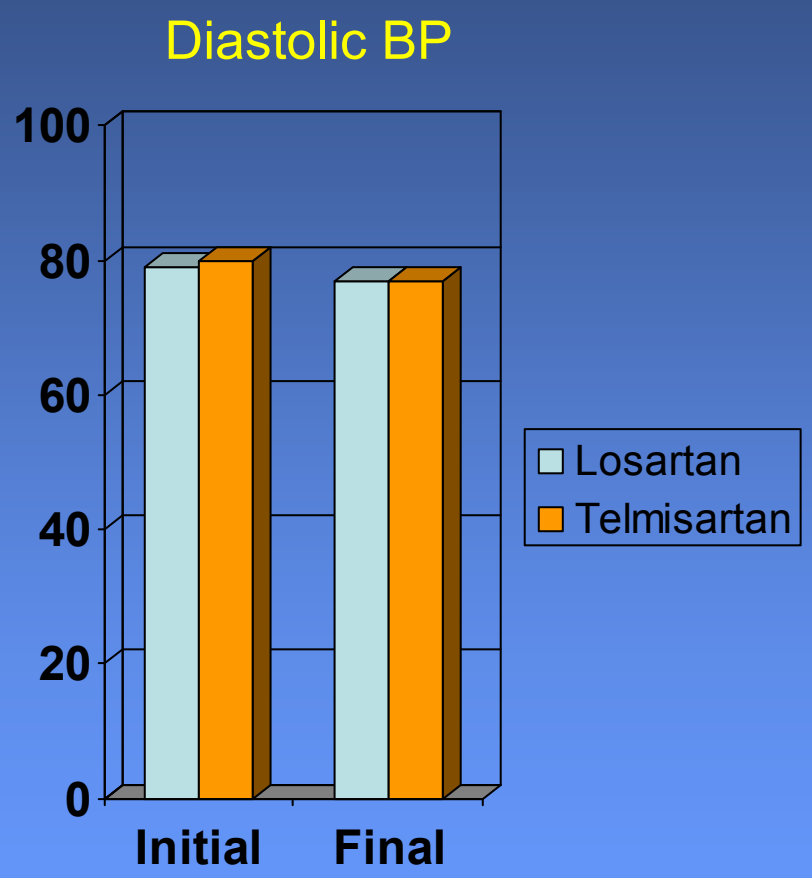


AMADEO-Percent reduction in proteinuria

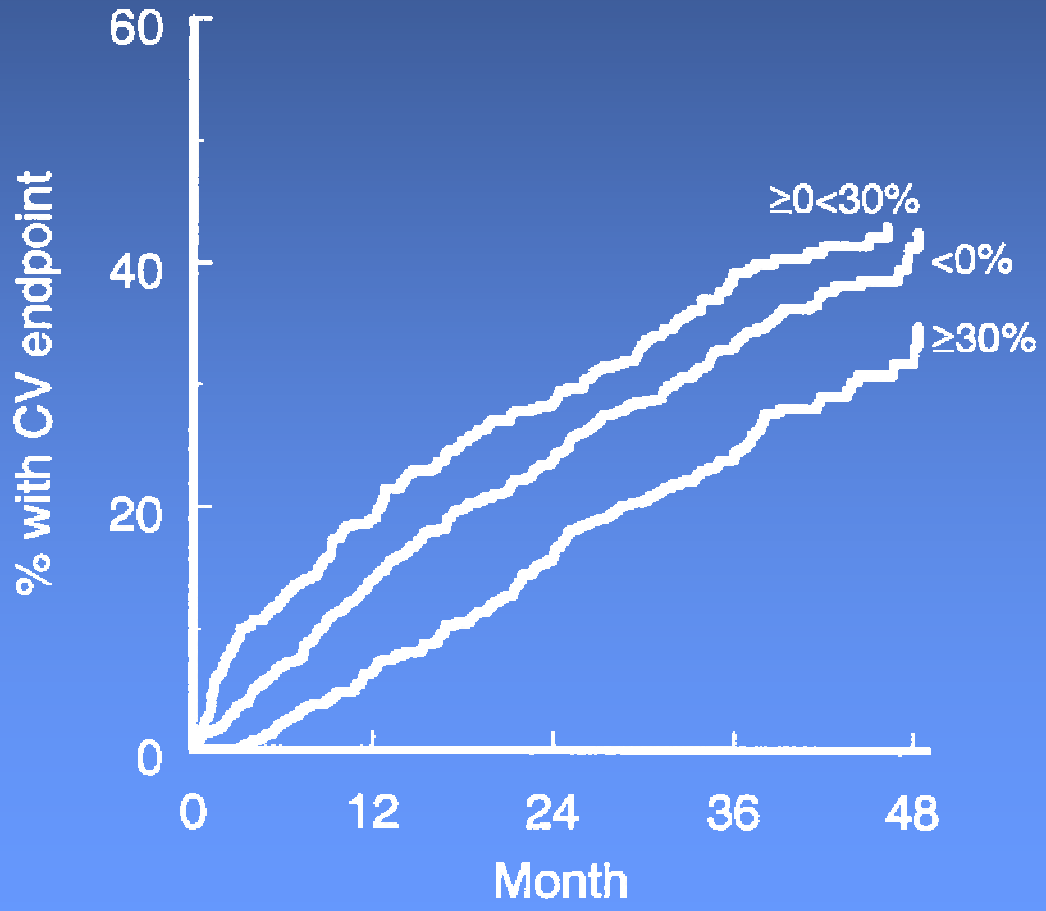


AMADEO- Systolic & Diastolic BPs





RENAAL- Occurrence of CV endpoint according to reductions after 6 months



Change from Baseline

by Month 6

de Zeeuw. *Circulation* 2004;110:921–927

RENAAL:

Predictors of Renal Outcomes

- Baseline level of proteinuria was a significant predictor of renal outcomes, ESRD
- Reduction in proteinuria at 6 months is also a significant predictor
- These are predictors regardless to which treatment the patient is randomized

Public Health Implications of RENAAL

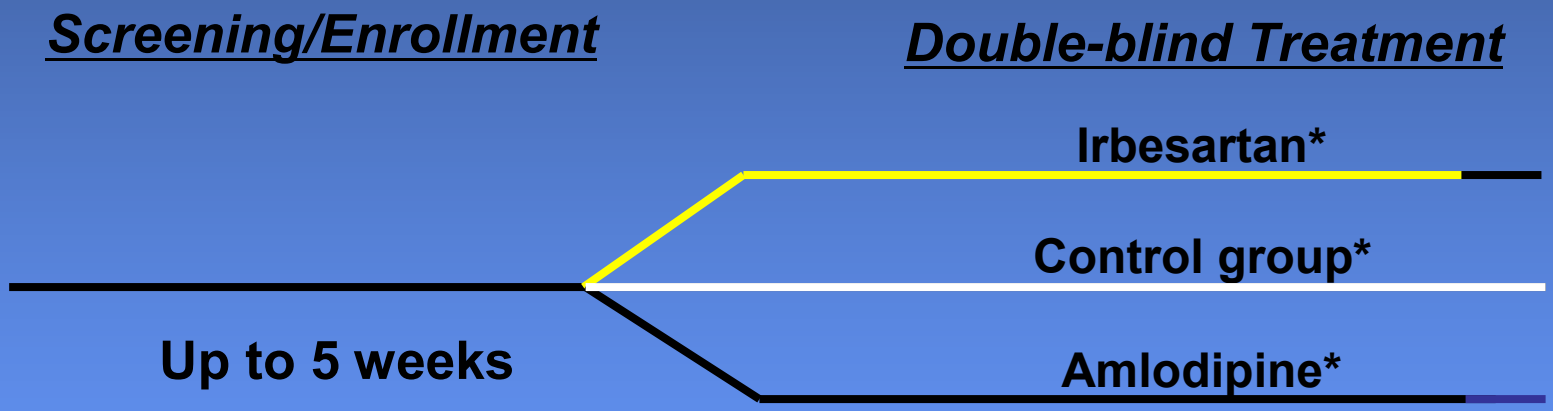
- **For diabetic patients at risk over a 3.5 year period, it is estimated:***
  - **one case of ESRD can be prevented for every 16 patients treated**
  - the reduction in days with ESRD saves $5,300 (p=0.03) per treated patient (savings increase to $7,400 at 4 years)

* Assumes annual cost of ESRD is $56,000 based on Medicare (USRDS 2000). Drug cost based on AWP.

** NHANES III diagnosed diabetic patients with proteinuria (≥ 300 mg/g) assumed to have Type 2 diabetes based on age of diagnosis ≥ 30 years

IDNT
Study Design

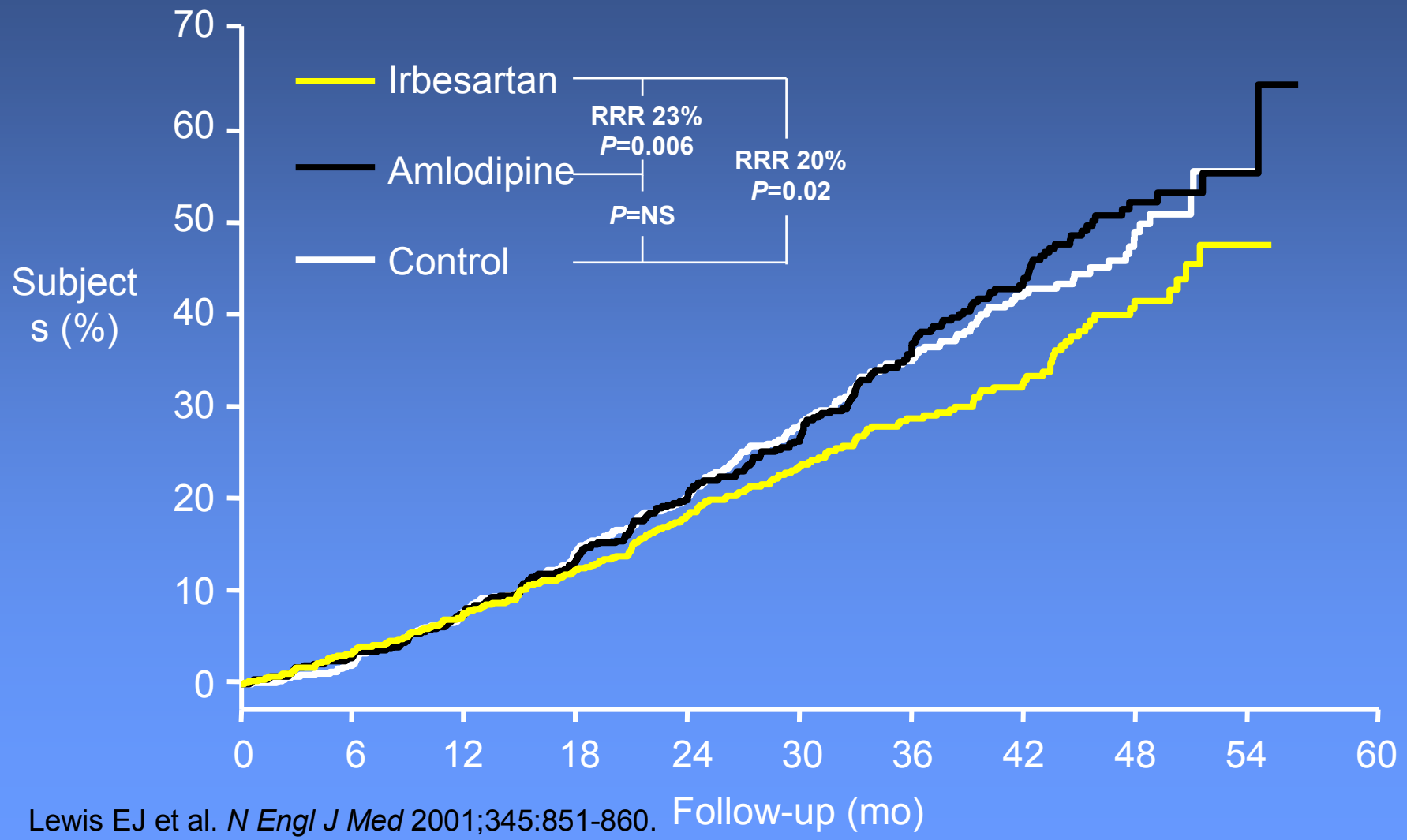
- 1,715 patients with hypertension, type 2 diabetes, and proteinuria ≥ 900 mg/day



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

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

IDNT Primary Endpoint
Time to Doubling of Serum Creatinine, ESRD, or Death



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

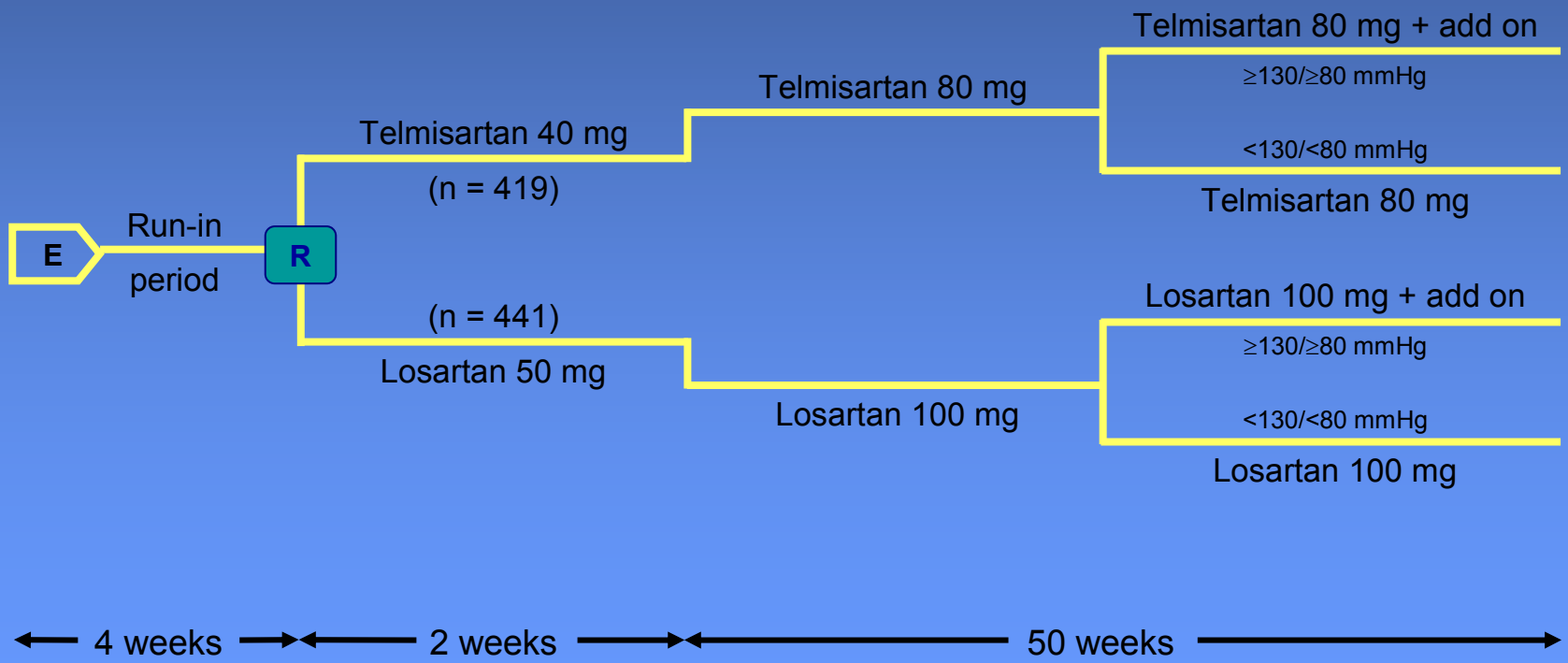
Objective

- To demonstrate that Telmisartan is effective against progression of renal disease by reducing proteinuria in hypertensive diabetic patients and possibly superior compared with Losartan

Weber. *J Hypertens* 2003;21 (Suppl 6):S37–S46.

Study design

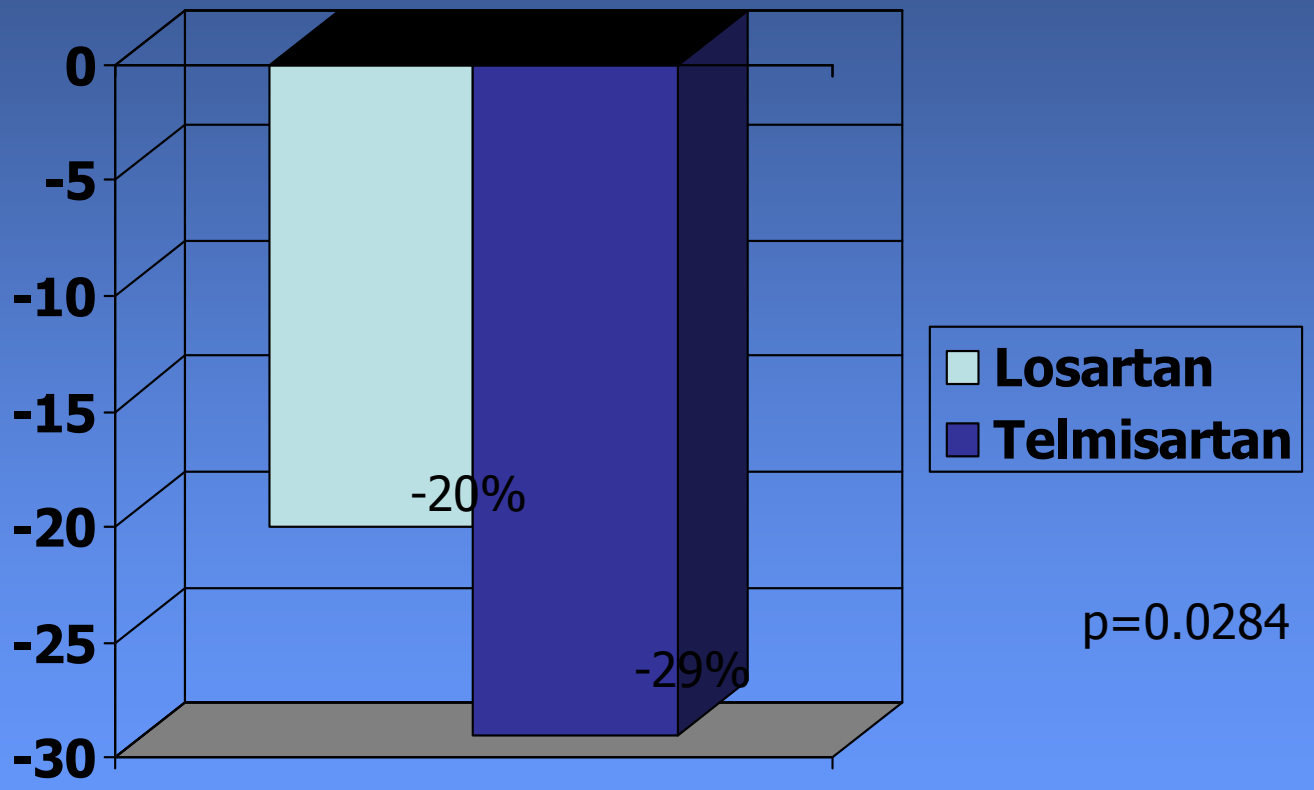
Prospective, randomized, double-blind, double-dummy, forced-titration, multicentre, parallel-group, 1-year treatment



Weber. *J Hypertens* 2003;21 (Suppl 6):S37–S46.

AMADEO

RESULTS



p=0.0284

% reduction in UPCR after 50 weeks

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RESULTS

	Losartan	Telmisartan
SBP		
DBP		