Angiotensin II antagonism and its effects on Hypertension and cardio-renal protection

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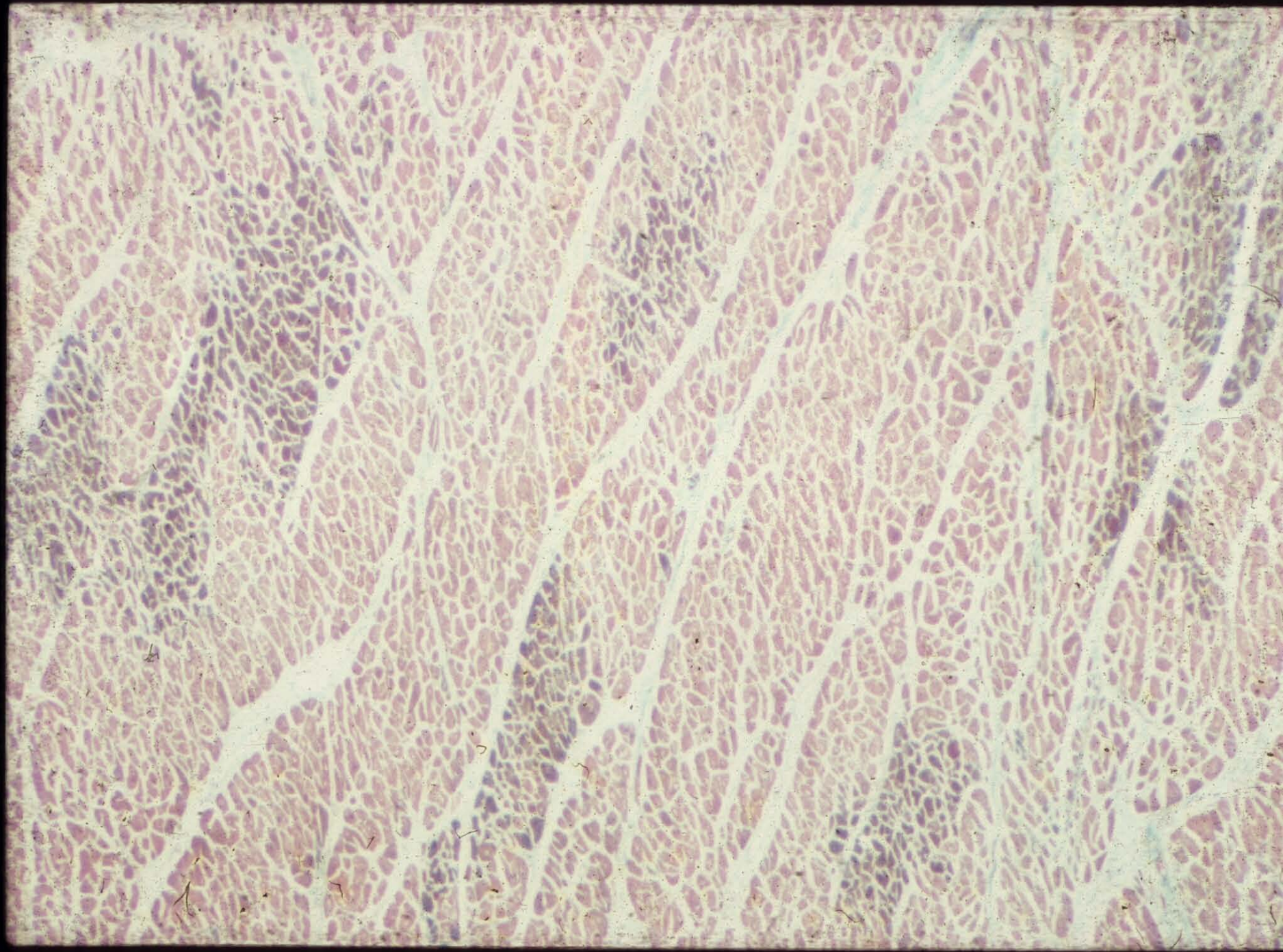
Classification of Essential Hypertension According to the Renin/Sodium Index

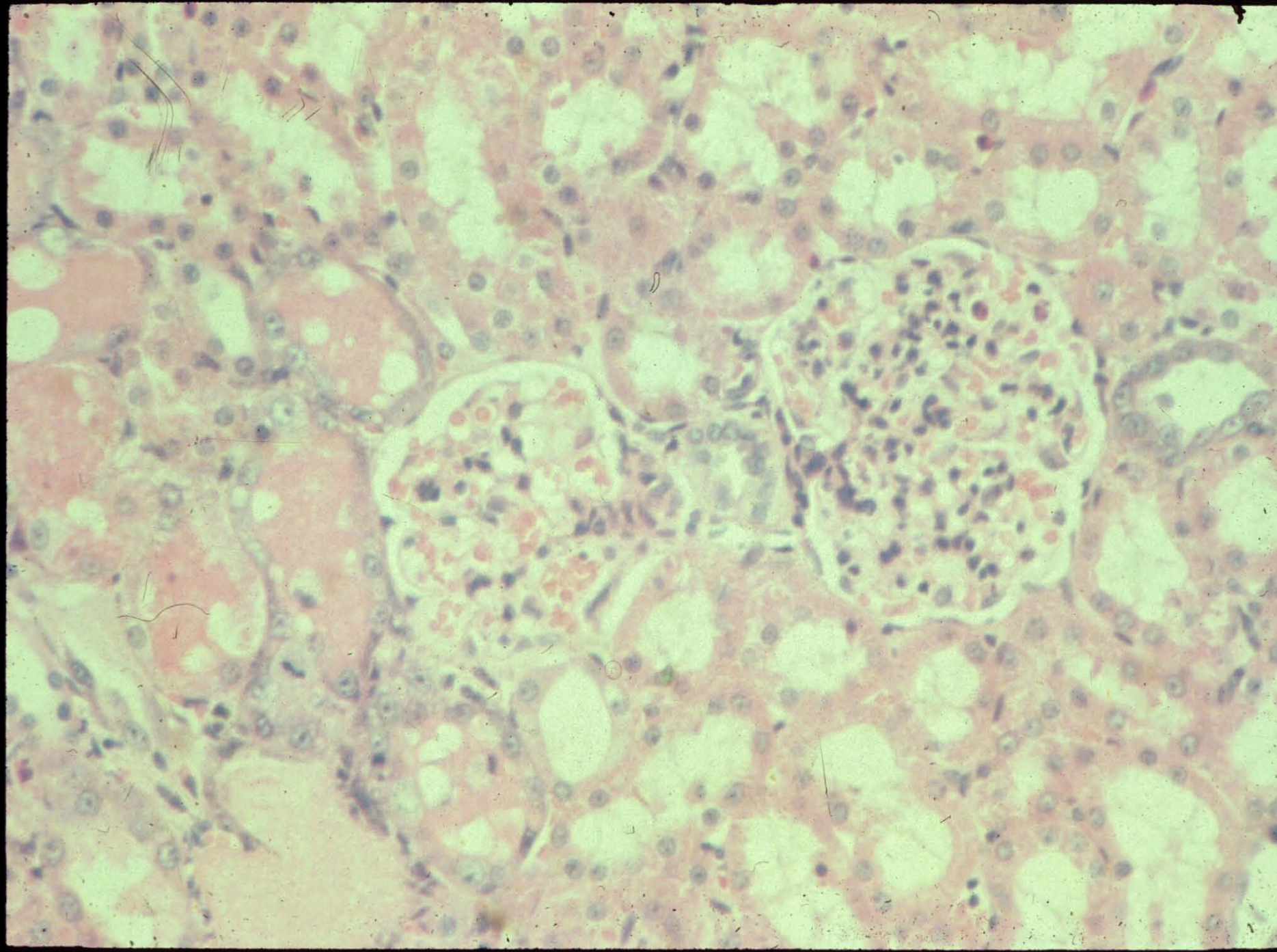
Normal plasma renin activity:	60%
Low plasma renin activity:	36–38%
High plasma renin activity:	2 – 4%

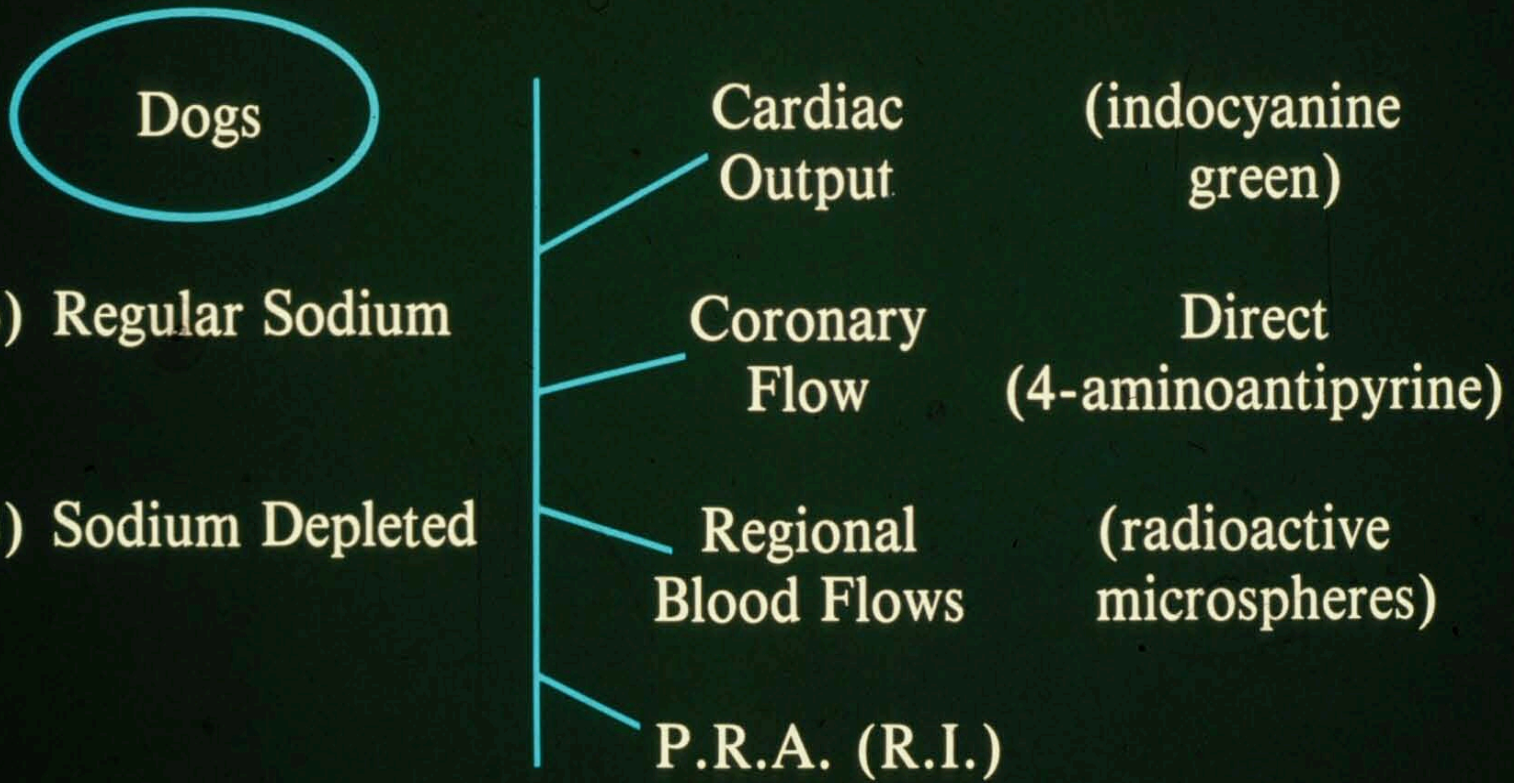
Experimental Evidence

Experimental Data

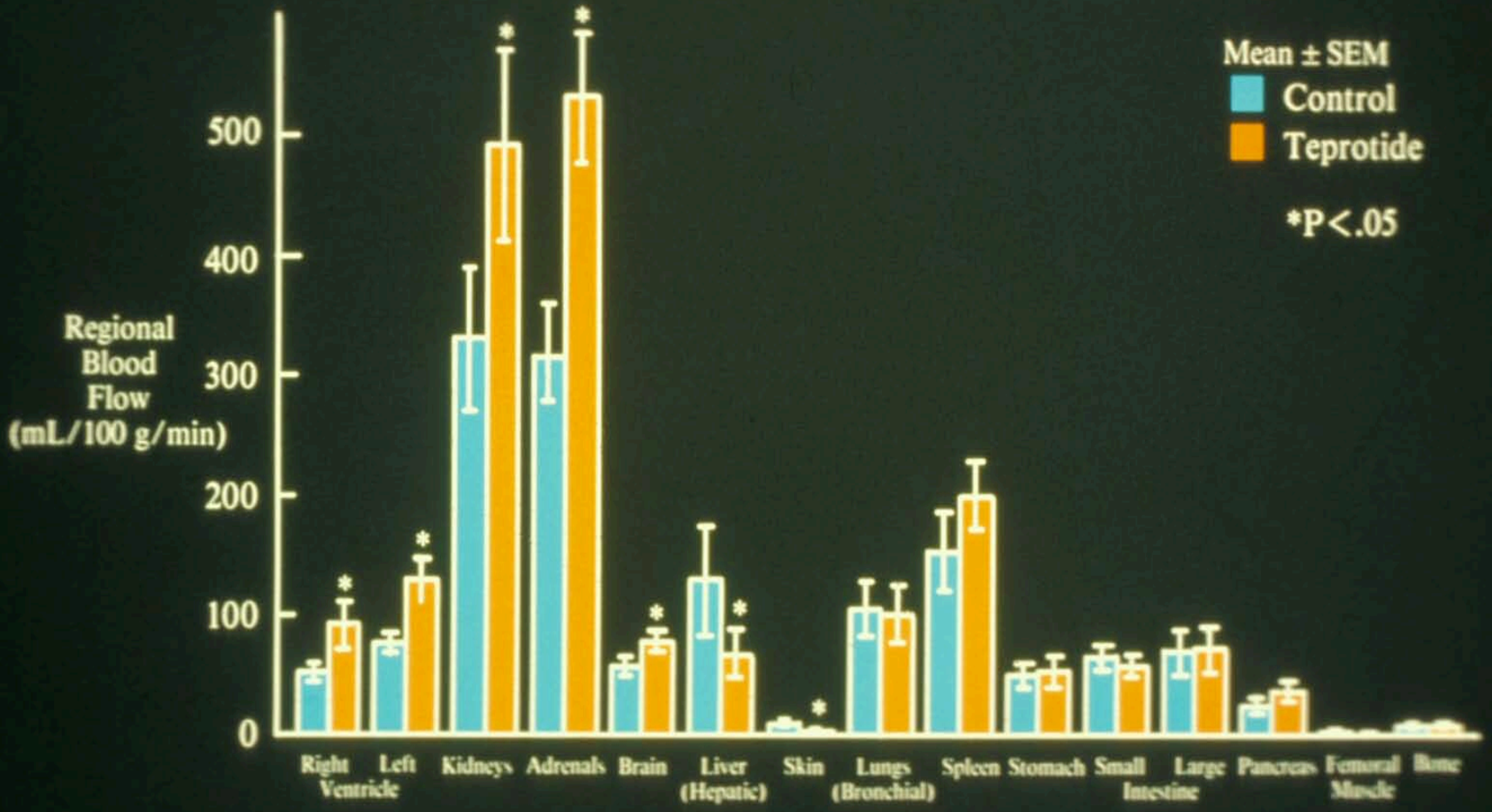
- Constant infusion of AII over a 3-day period in rabbits
- Transient BP rise, followed by maintenance of BP in normal range
- Pathology showed multiple areas of myocardial necrosis, and, less consistently, renal tubular necrosis






Dogs
(6) Regular Sodium
(8) Sodium Depleted
Cardiac Output
(indocyanine green)
Coronary Flow
Direct (4-aminoantipyrine)
Regional Blood Flows
(radioactive microspheres)
P.R.A. (R.I.)

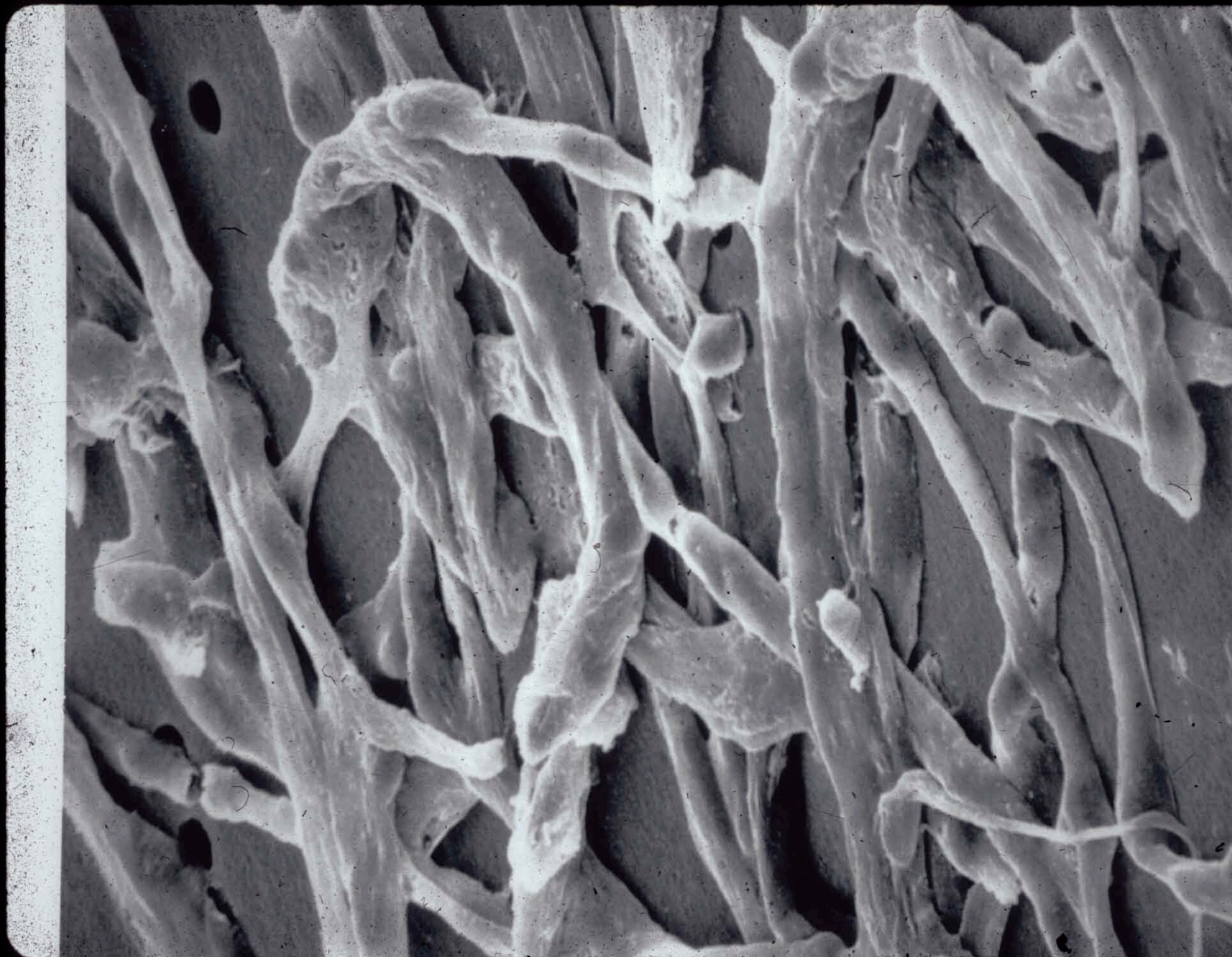
Effects of Teprotide (Low Salt Diet)



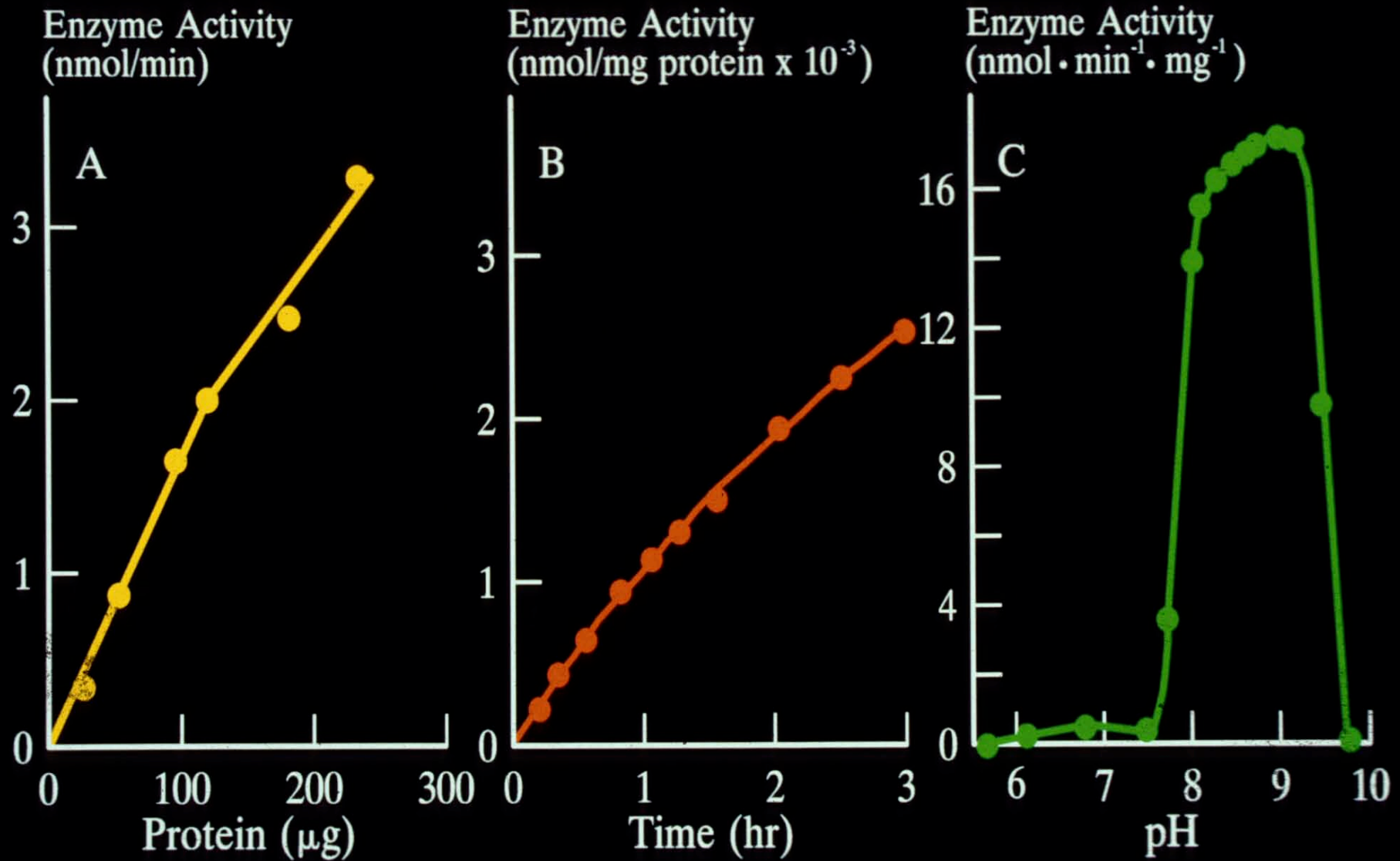
CORONARY VASCULAR EFFECTS OF TEPROTIDE IN SALT-DEPLETED DOGS

	Coronary Blood Flow ml/100g/min	Coronary Sinus Oxygen Content ml/liter	Myocardial Oxygen Extraction %	Myocardial Oxygen Consumption ml/100g/min	Diastolic Coronary Vascular Resistance dyn.s.cm^{-5},x10^{-3}
Control	69±5	44±7	75±3	8.6±0.5	96±7
Teprotide	120±13*	78±7*	50±7*	9.9±0.8*	48±10*

Mean±SE; *$p<0.05$, paired t-test



Characteristics of the Assay System for Converting Enzyme in Homogenates of Brain Microvessels



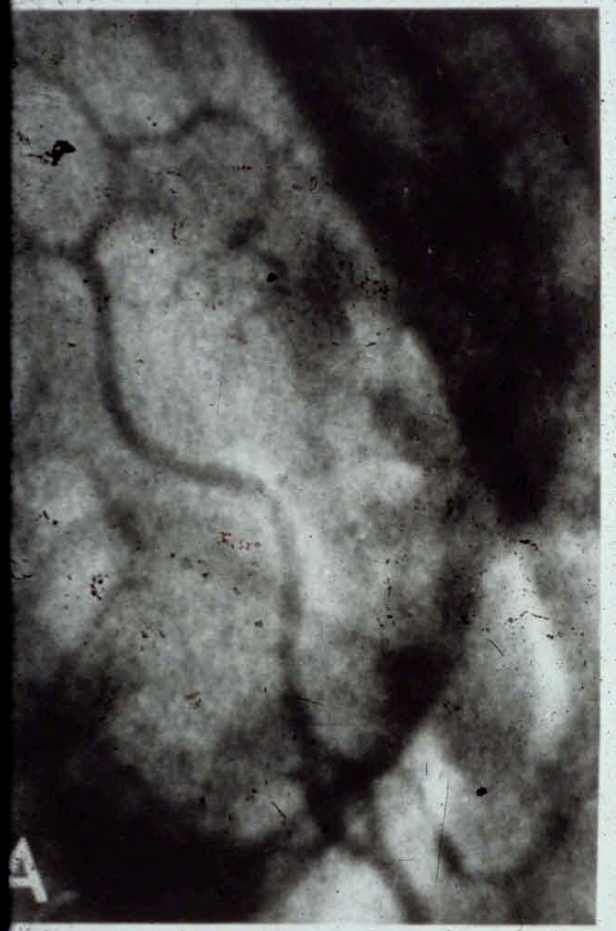
Protocol: Reversal of Delayed Experimental Cerebral Vasospasm by ACE Inhibition

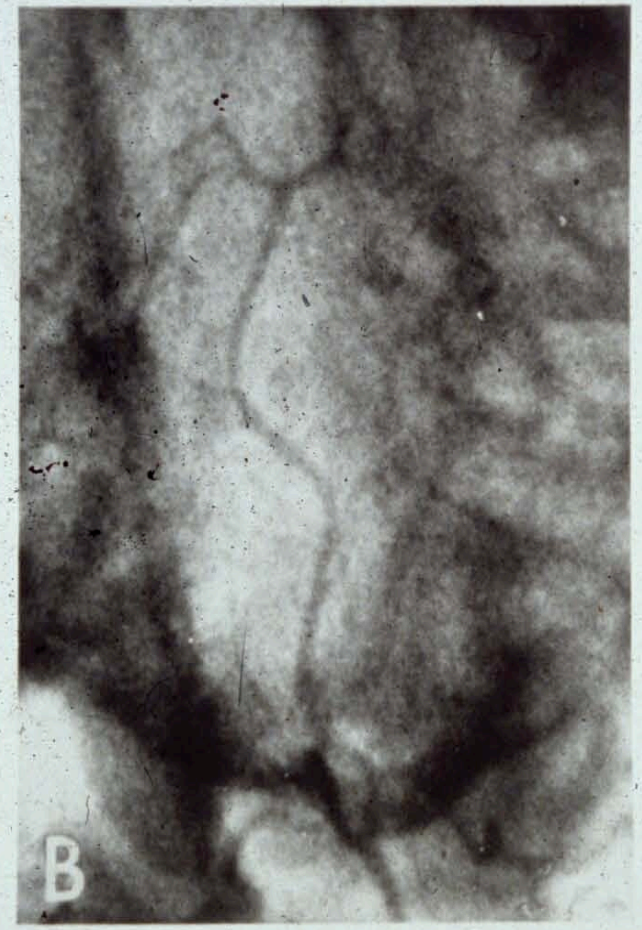
Nine Anesthetized, Intubated Dogs; 3 Control Dogs Received Saline

Day 1 Left femoral artery cannulated for blood sampling
Vertebral artery catheterized via right femoral
Baseline cineangiogram
Two mL autologous blood introduced into subarachnoid space via cisterna magna after removal of 2 mL CSF

Day 2 Another 2 mL blood in subarachnoid space

Day 4 Animal again anesthetized and catheterized
Repeat vertebrobasilar cineangiogram
Injection of 2 mg/kg ACE-I (teprotide)
Repeat cineangiogram after 30, 60, 90 min


A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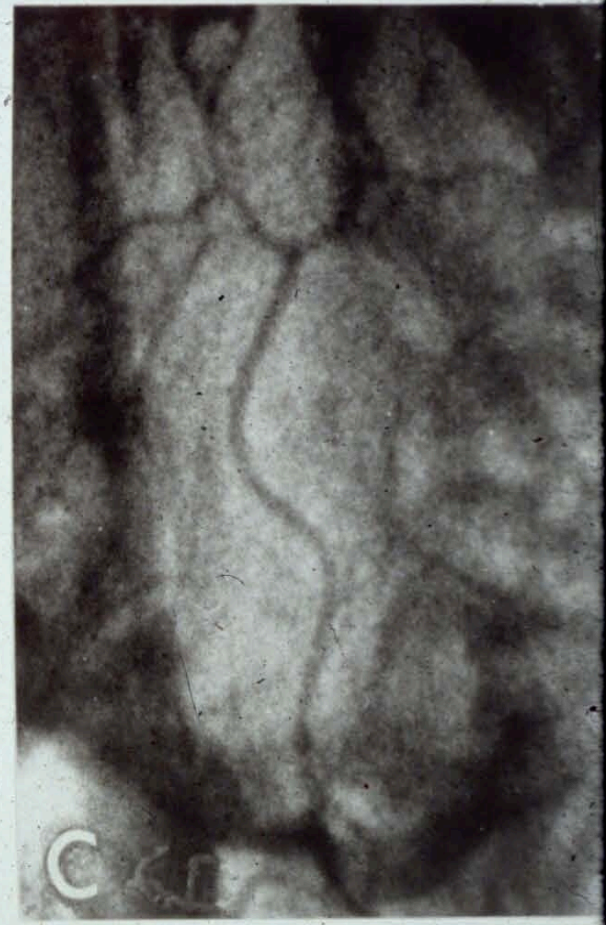
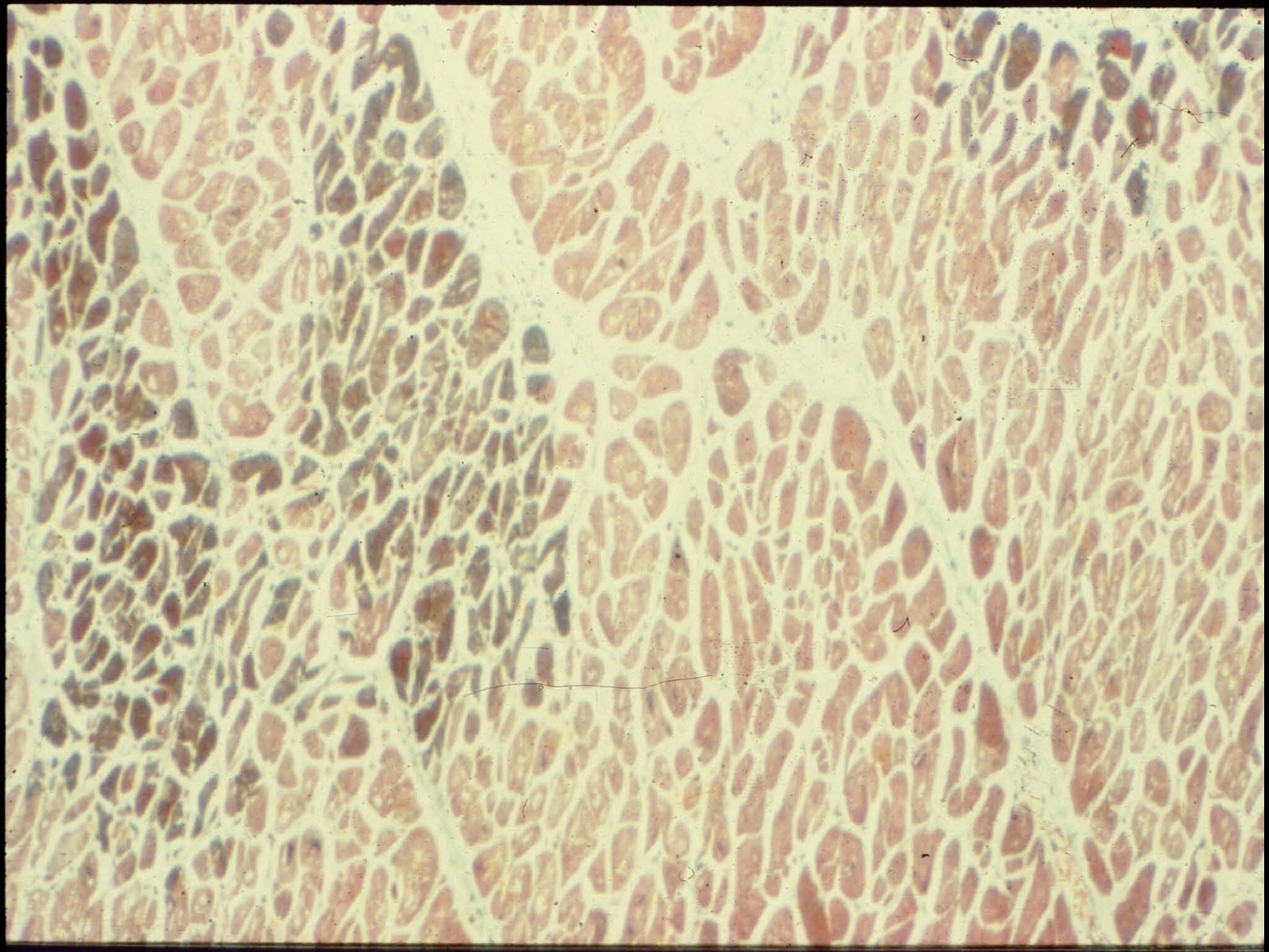

C

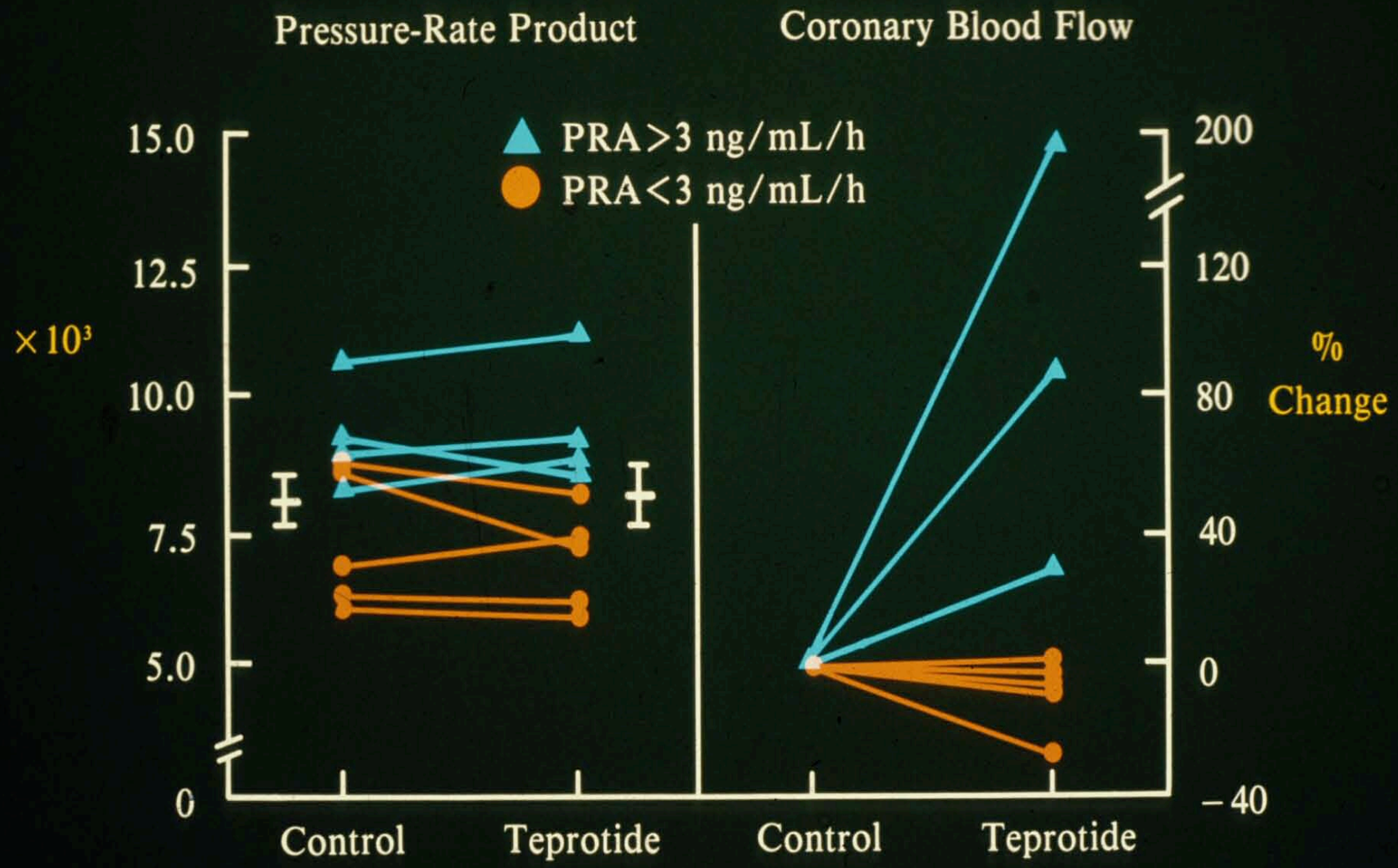
Clinical Evidence

Clinical Observations

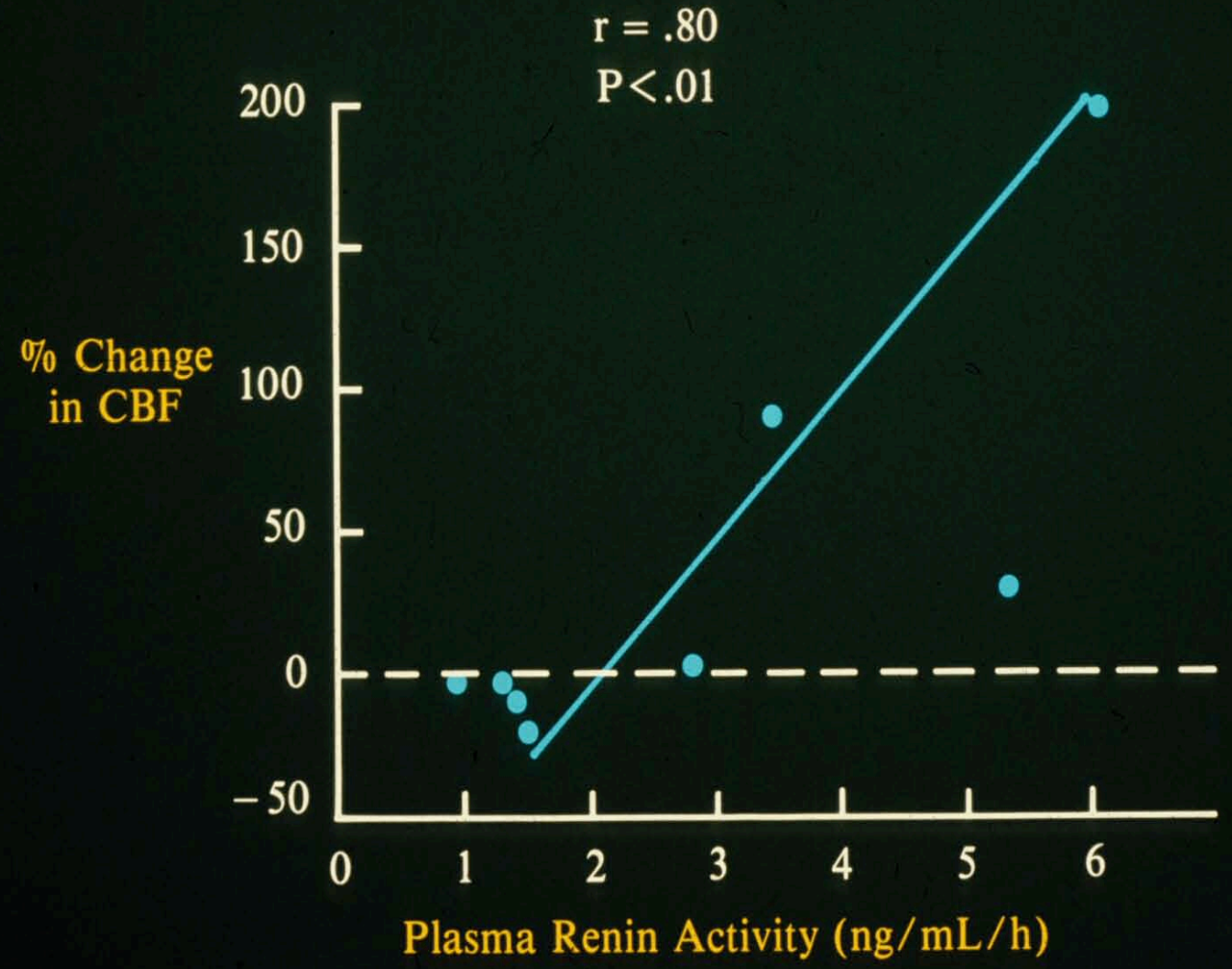
- Five patients with end-stage renal disease and excessively high AII levels sustained multiple acute coronary episodes
- Three succumbed: Post-mortem showed multiple areas of myocardial necrosis
- Two survived: After bilateral nephrectomy, no more coronary events



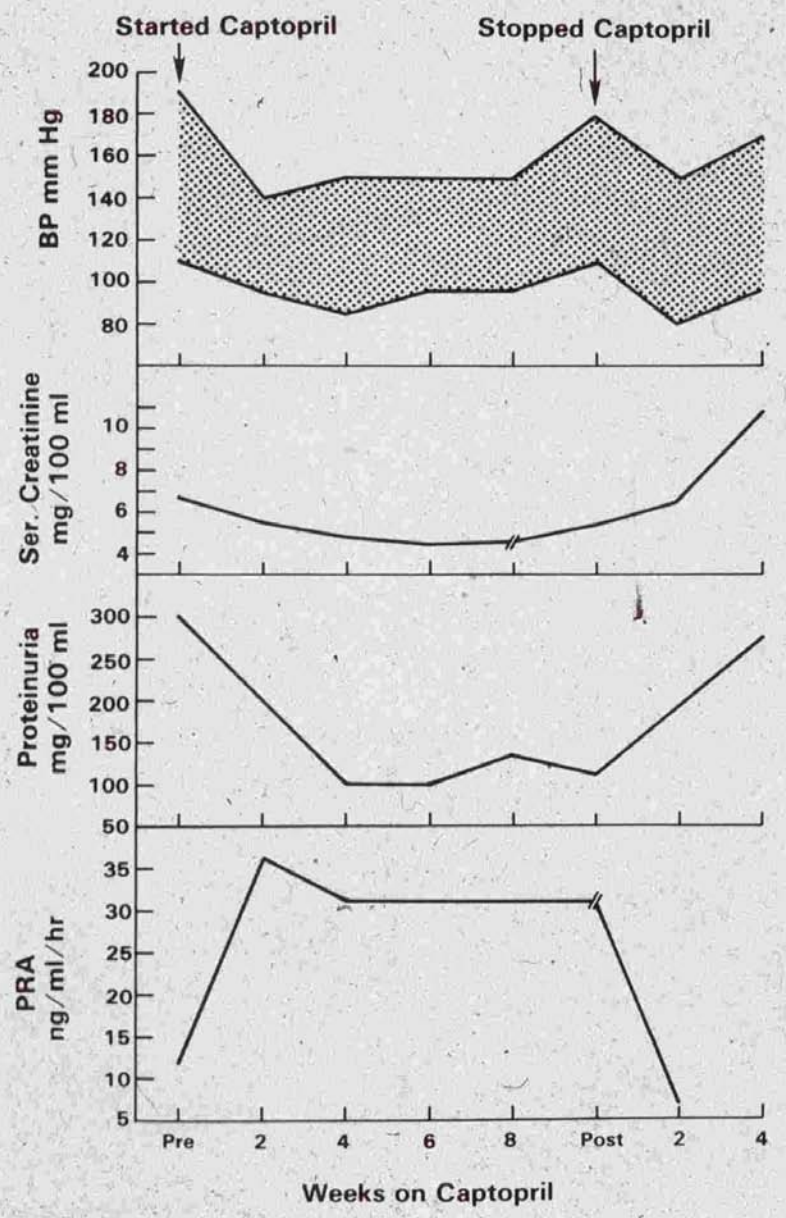
Effects of Teprotide on Coronary Circulation



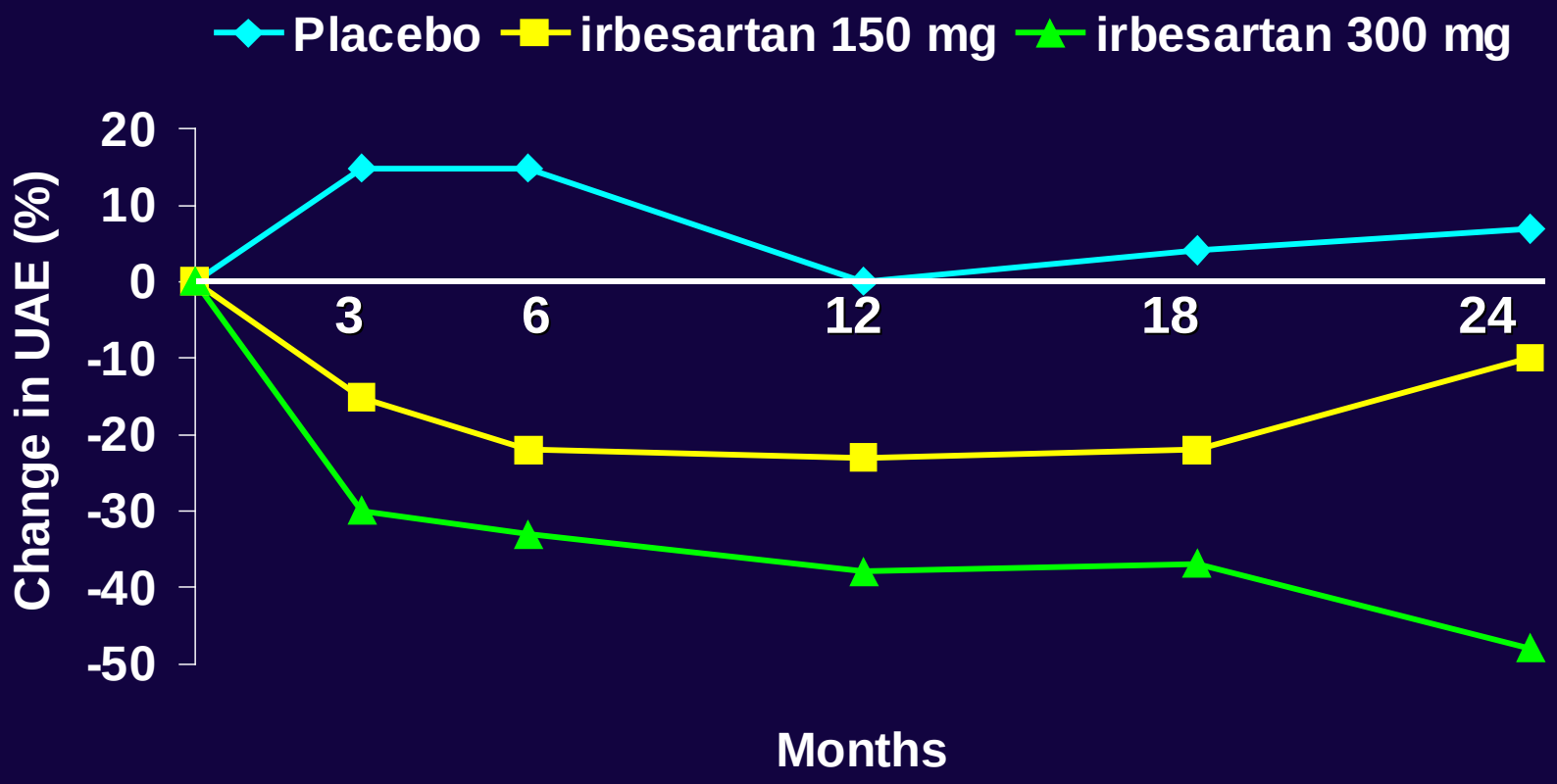
Correlation Between PRA and Percent Change in Coronary Blood Flow (CBF)



Changes in BP, serum creatinine, proteinuria and PRA during and after treatment with captopril.

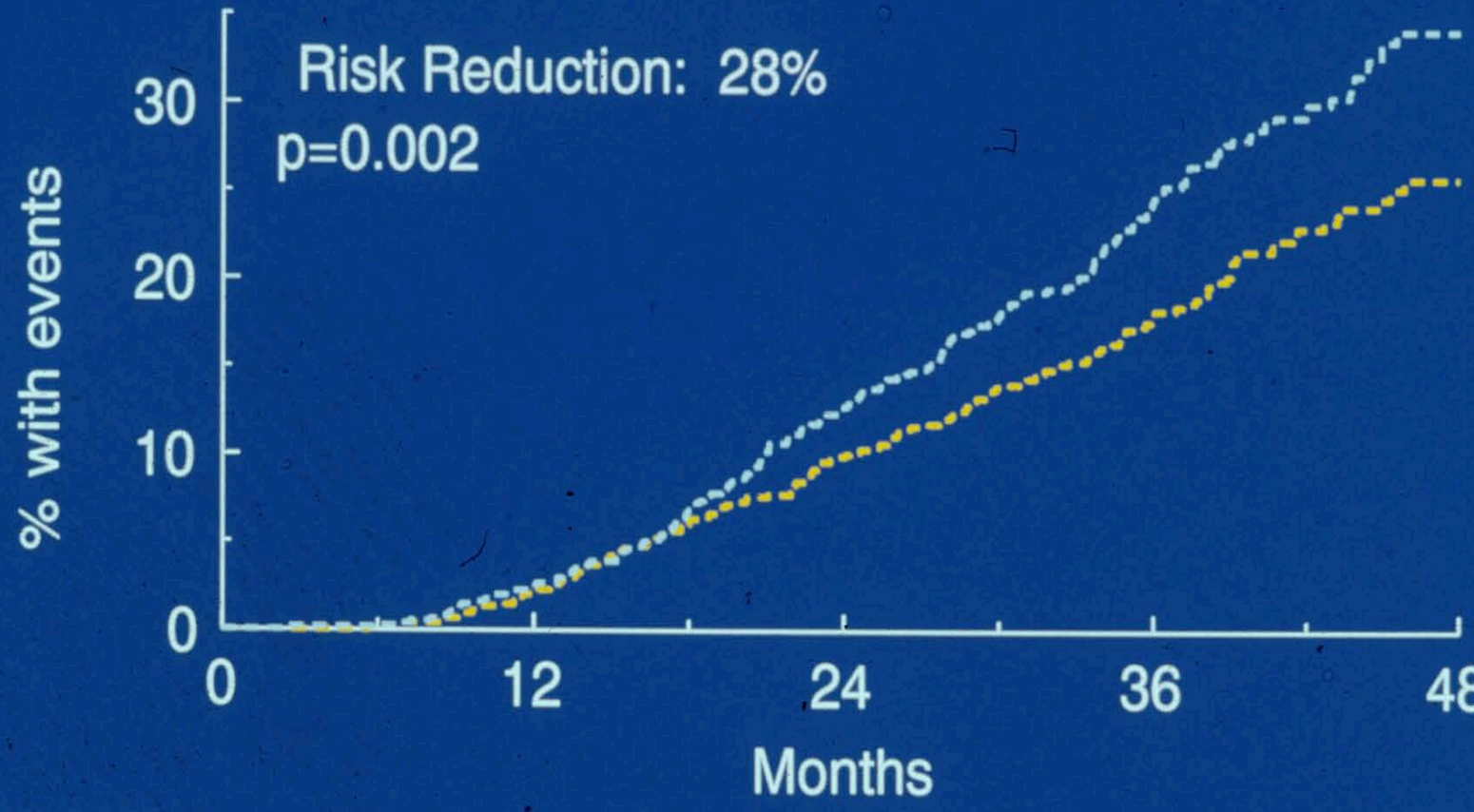


IRMA 2
Mean Change in Urinary Albumin Excretion



Parving H-H, et al. *NEJM* 345:870, 2001

RENAAL
ESRD

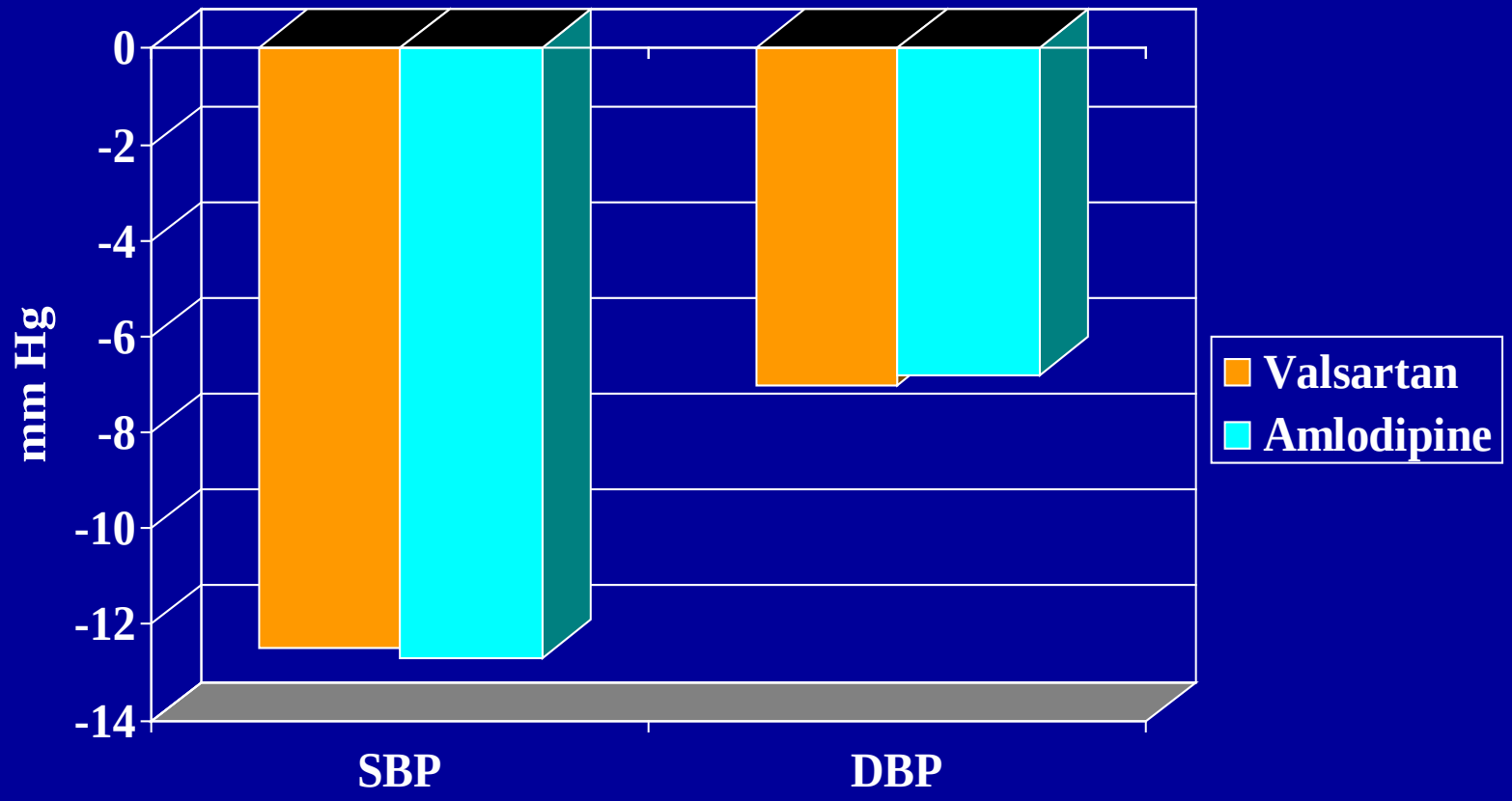


P (+ CT)	762	715	610	347	42
L (+ CT)	751	714	625	375	69

MARVAL

Microalbuminuria Reduction With Valsartan

Blood Pressure Changes in Hypertensive Cohort

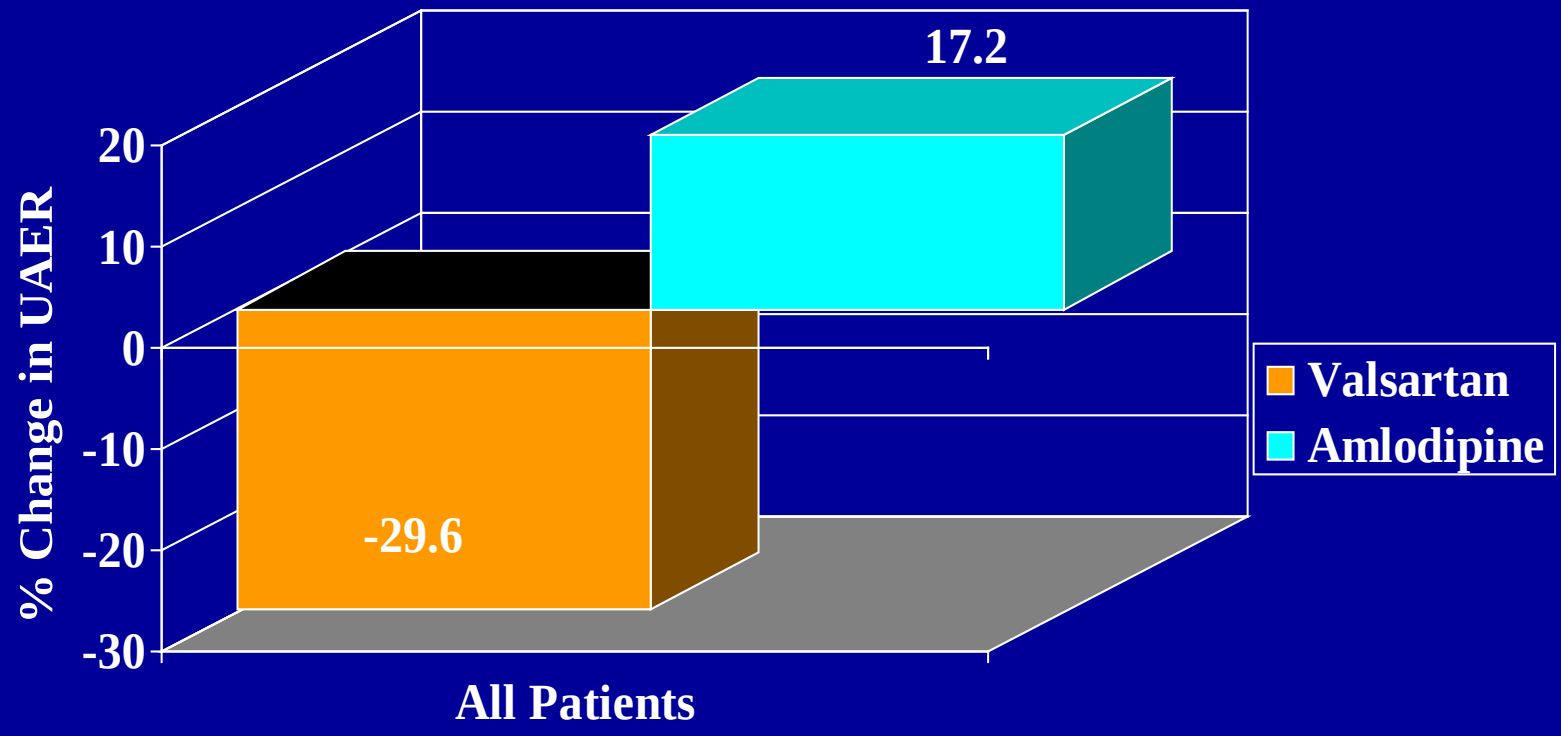


MARVAL Study Group, Presented at ASH, May 2001

MARVAL

Microalbuminuria Reduction With Valsartan

Changes in Urinary Albumin Excretion Rate From Baseline*

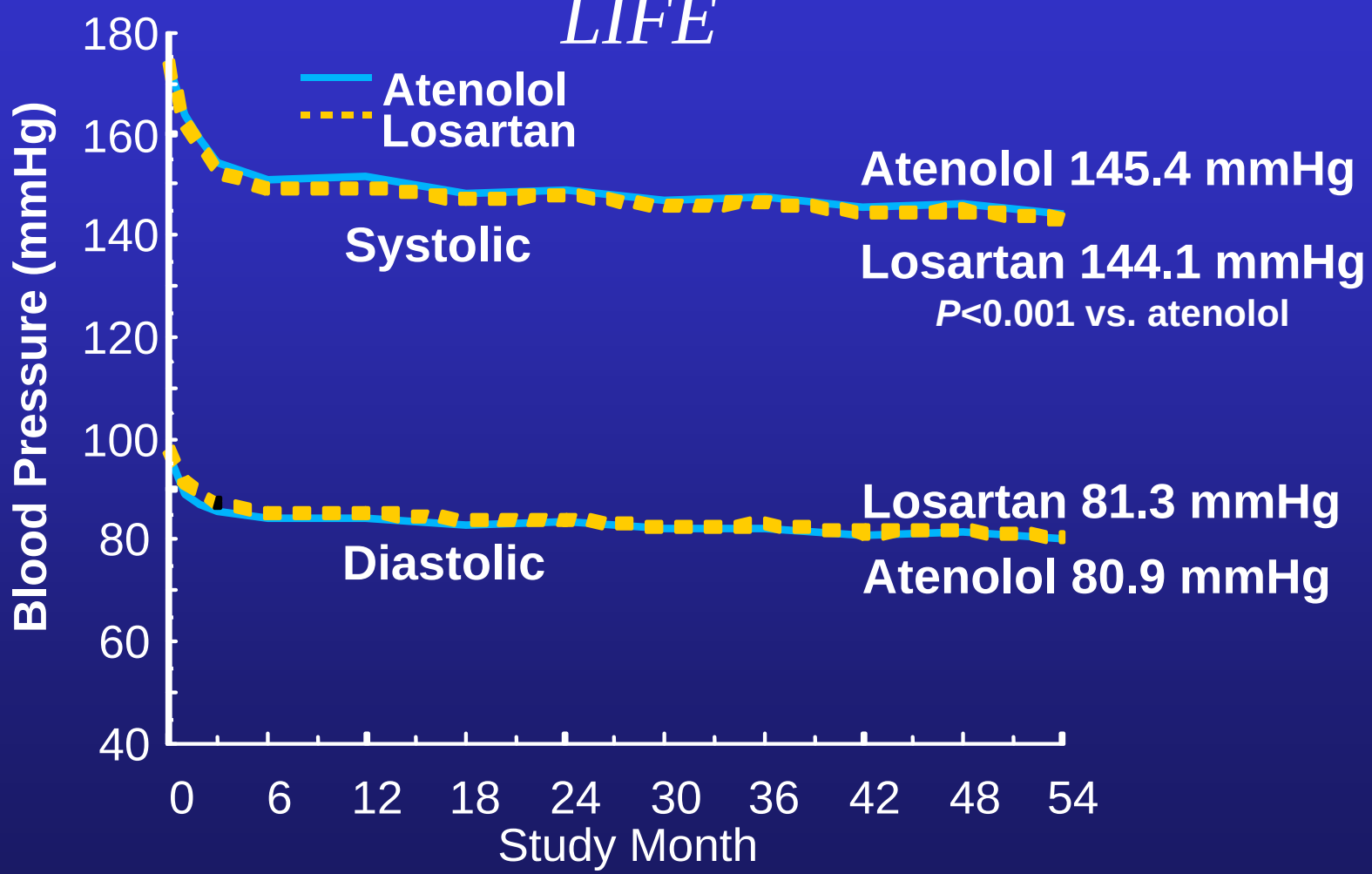


* P<0.001

MARVAL Study Group, Presented at ASH, May 2001

Blood Pressure Reduction

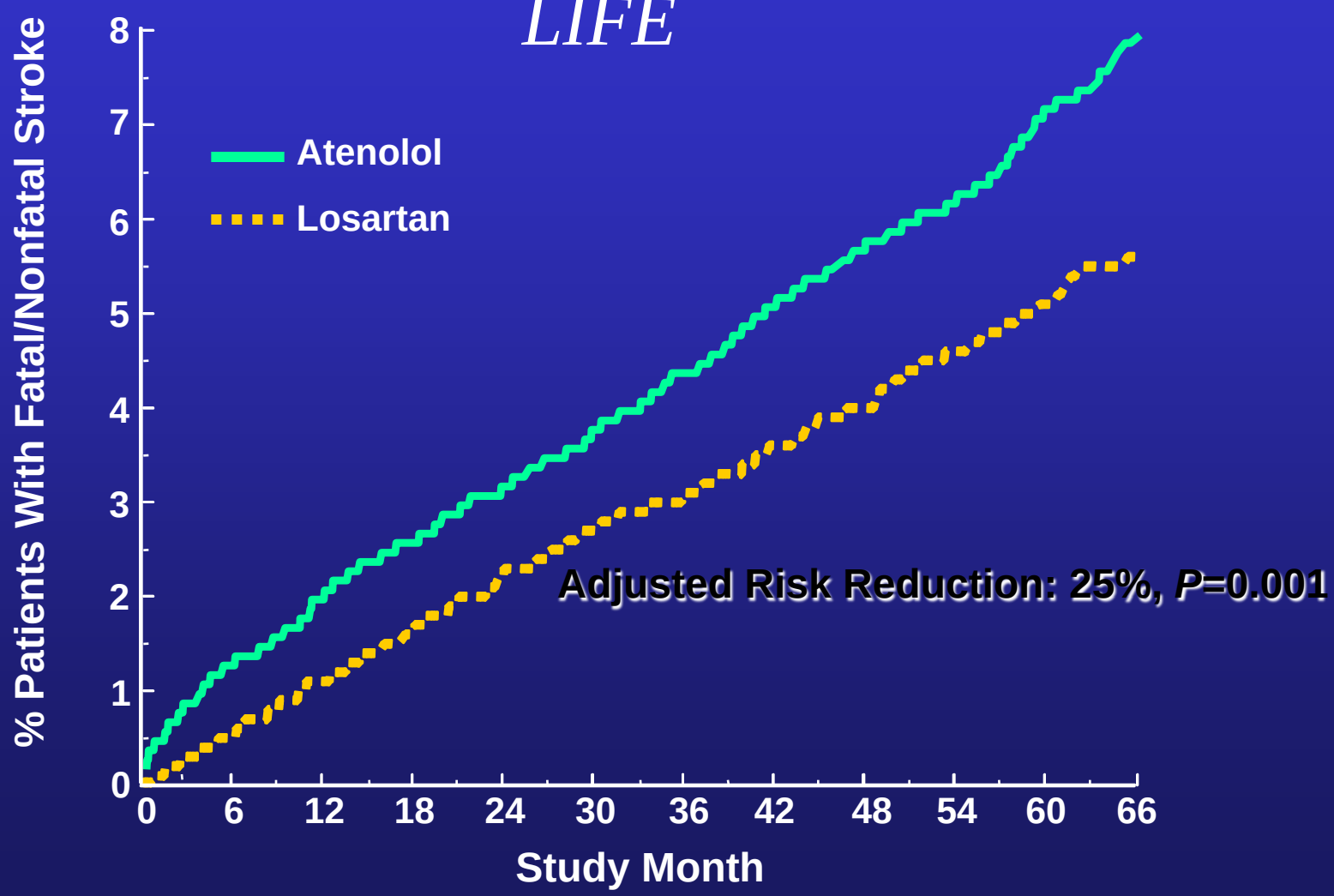
LIFE



Dahlöf et al. *Lancet.* 2002;359:995–1003.

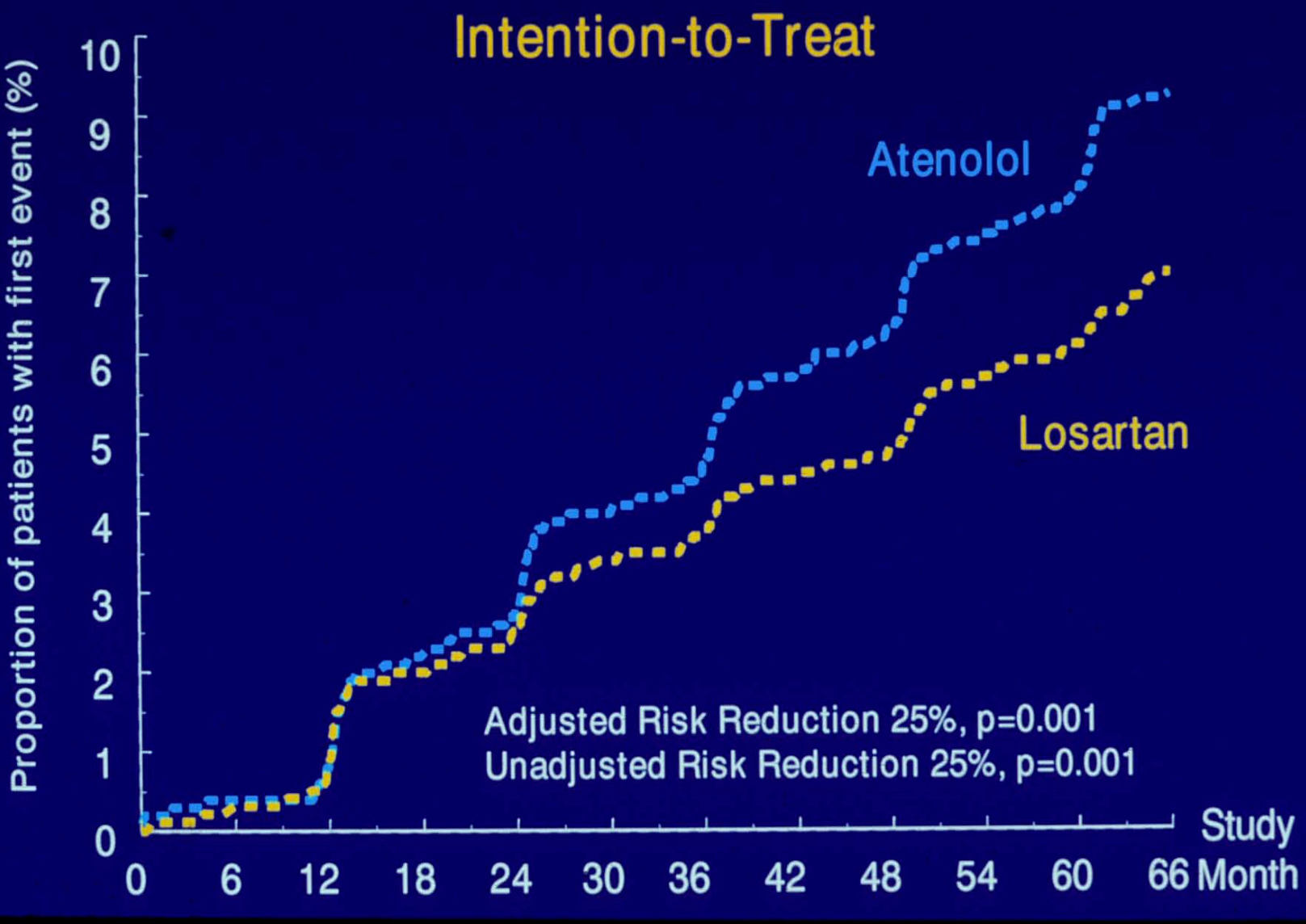
Significant Reduction in Fatal/Nonfatal Stroke with Losartan

LIFE

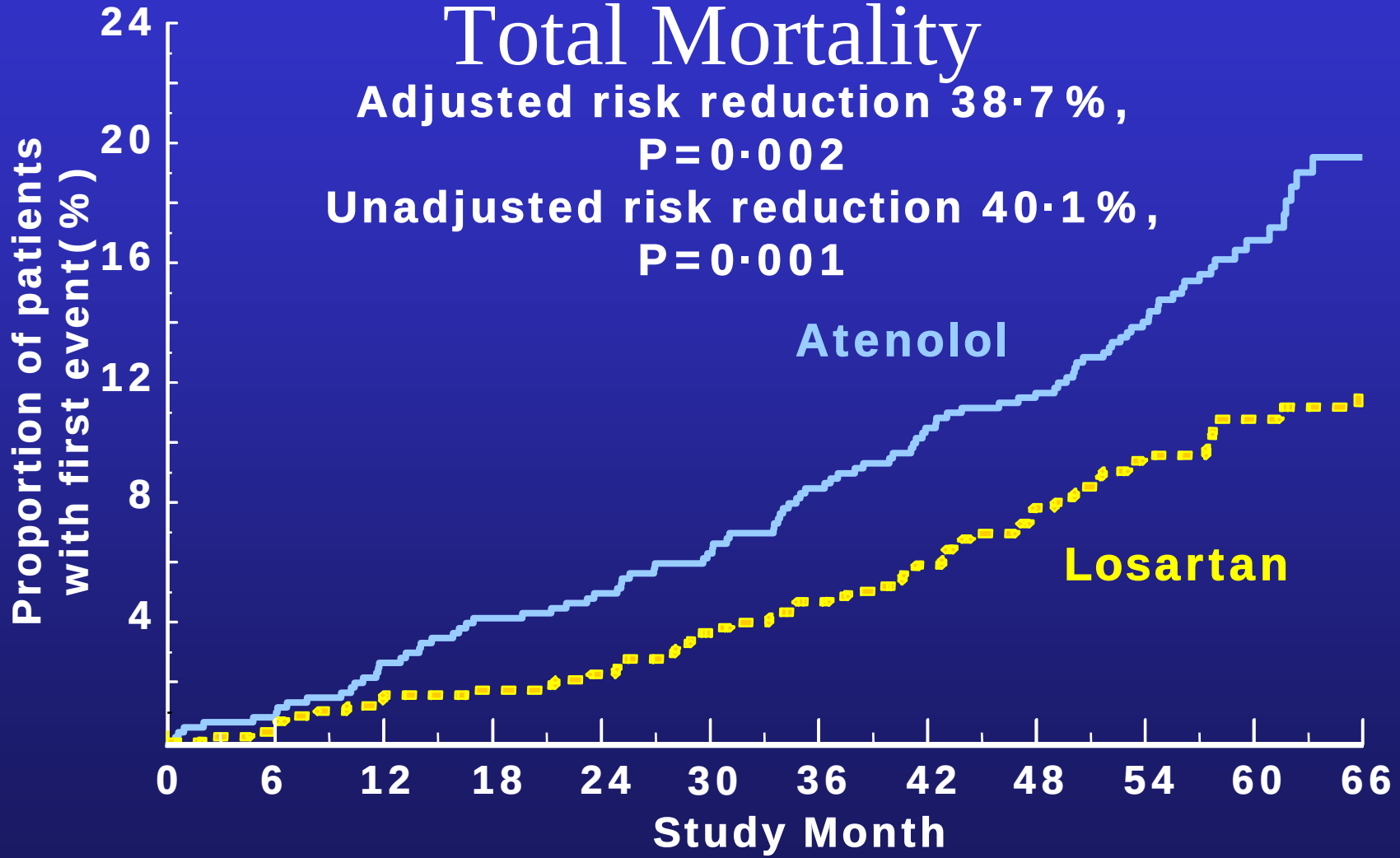


Dahlöf et al. *Lancet.* 2002;359:995–1003.

LIFE: New Onset Diabetes



LIFE Study Diabetes Subgroup Total Mortality



Lindholm LH, et al. Lancet. 2002;359:1004-1010.
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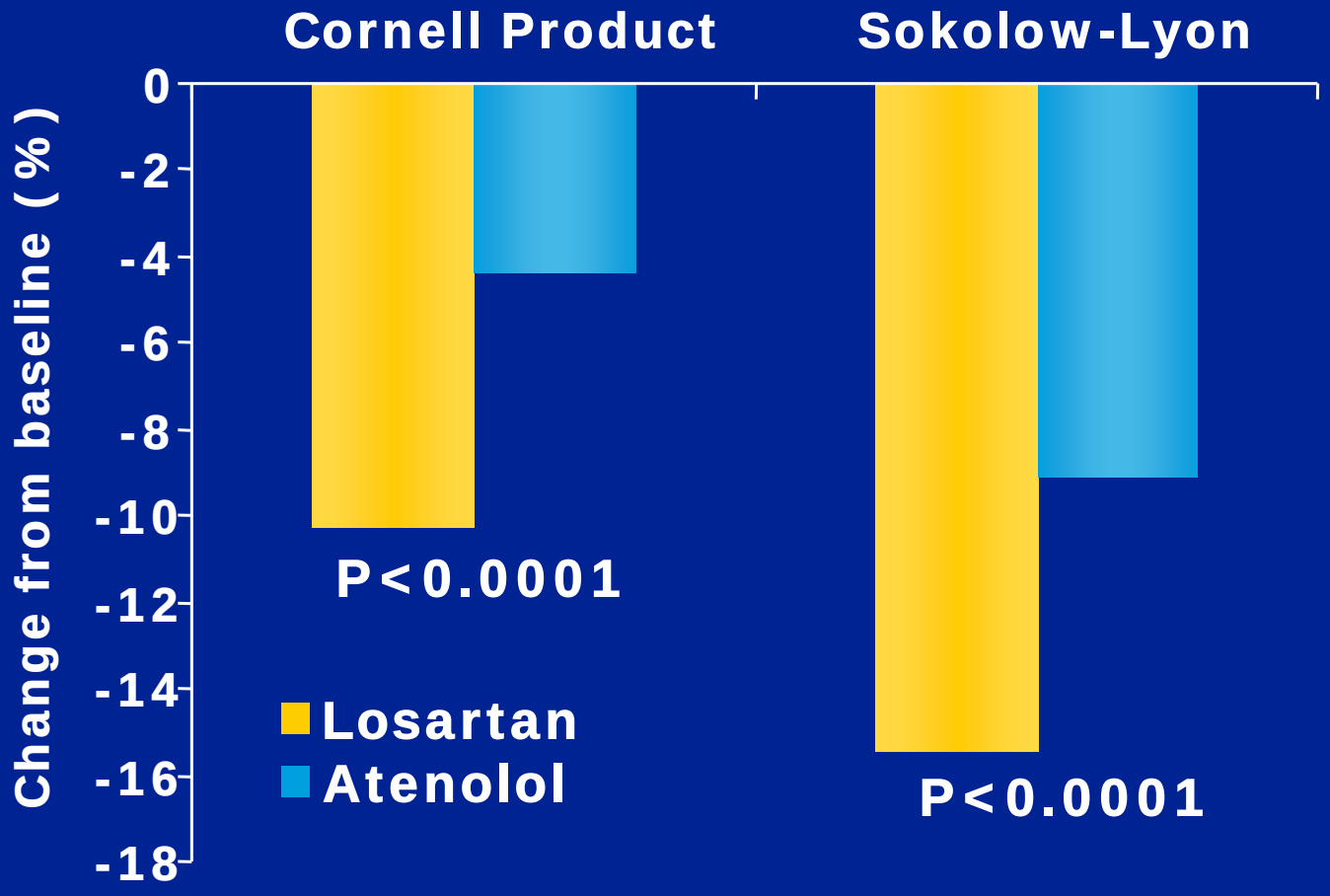
LIFE Study Change in Cornell Voltage Duration Product and Sokolow-Lyon



Dahlof B, et al. Lancet. 2002;359:995-1003.
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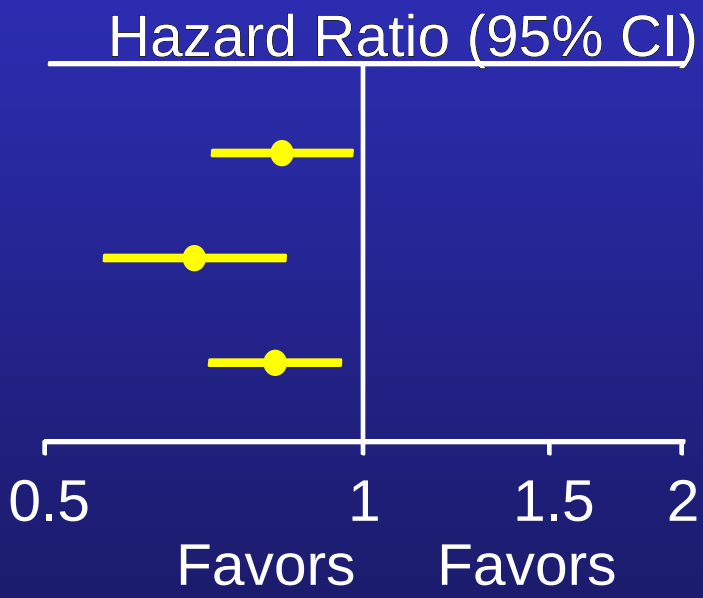
LIFE: Pre-Existing Atrial Fibrillation

	Losartan n (%)	Atenolol n (%)
Medical History	157 (3.4)	185 (4.0)
ECG	60 (1.3)	75 (1.6)
Either	166 (3.6)	196 (4.3)

LIFE: New Onset Atrial Fibrillation

Post-Hoc Analysis

Endpoints	No. of Events Los	Atl
Atrial Fibrillation by Investigator	304	360
Atrial Fibrillation by ECG	165	240
Atrial Fibrillation by Inv./ECG	346	416



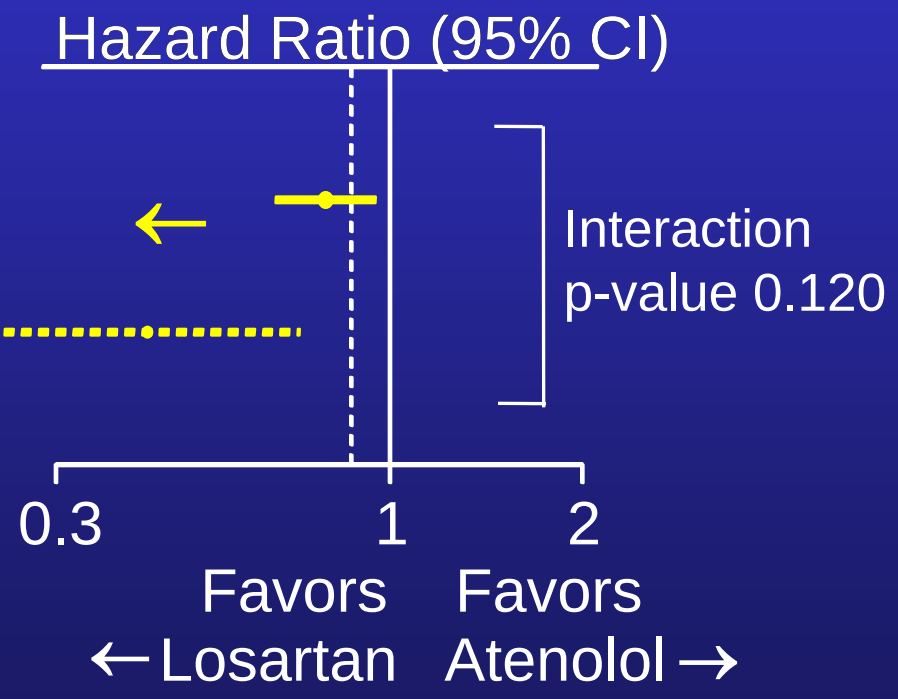
Los925 ACM Atrial Febr B Jan. 2, 2003

← Losartan Atenolol →

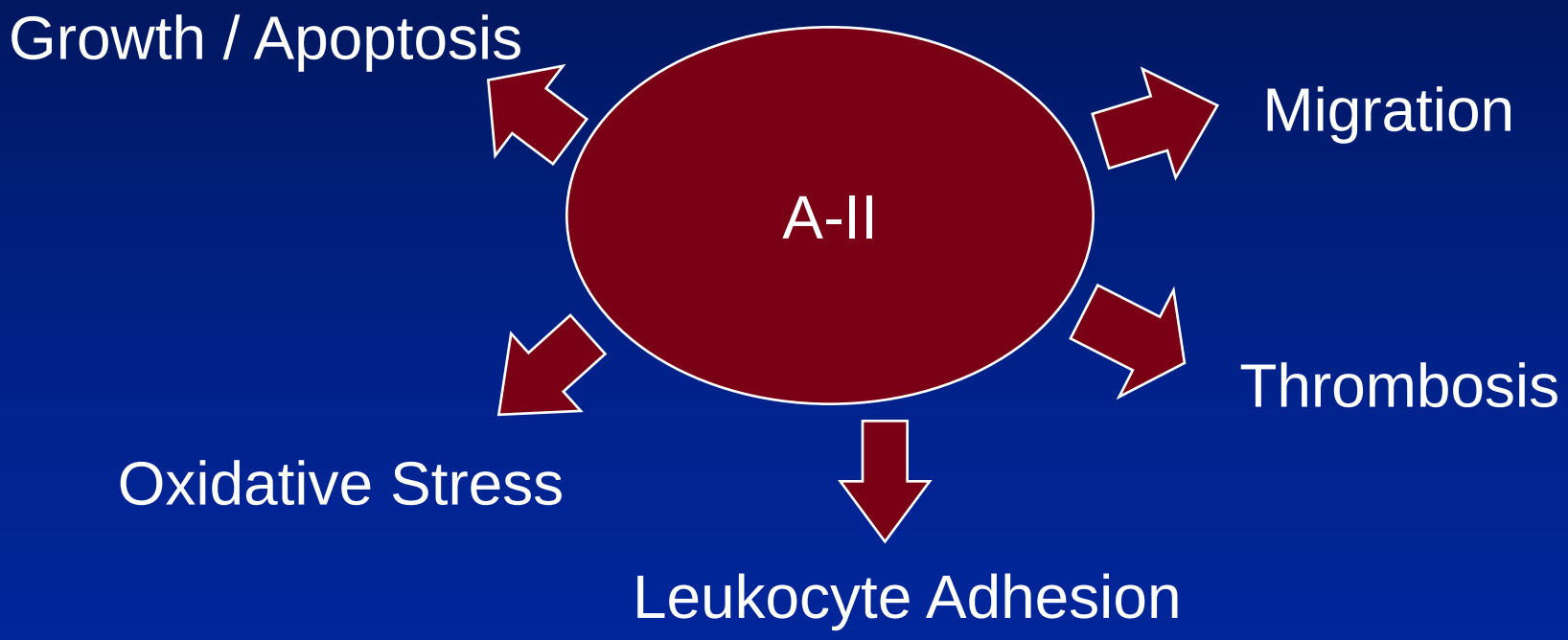
LIFE: Baseline Subgroups - Atrial Fibrillation

Stroke

Atrial Fibrillation	N	No. of Events	
		Los	Atl
No	8831	213	269
Yes	362	19	40

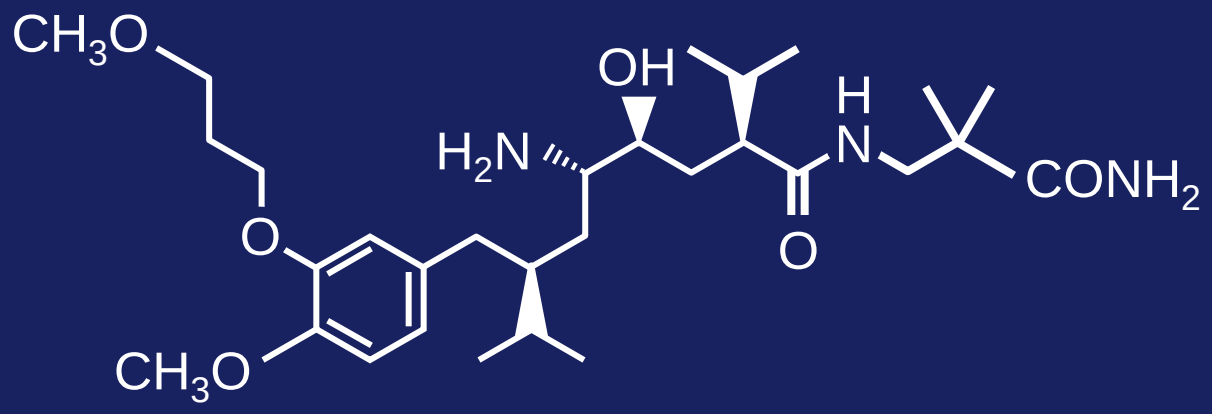


Postulated role of A-II on Structure and Function



Adapted from Gibbons, GH: Curr Opin Neph & HTN 1995, 4:189-196:
Gibbons, GH et al: NEJM. 330 : 20; 1431-1438.

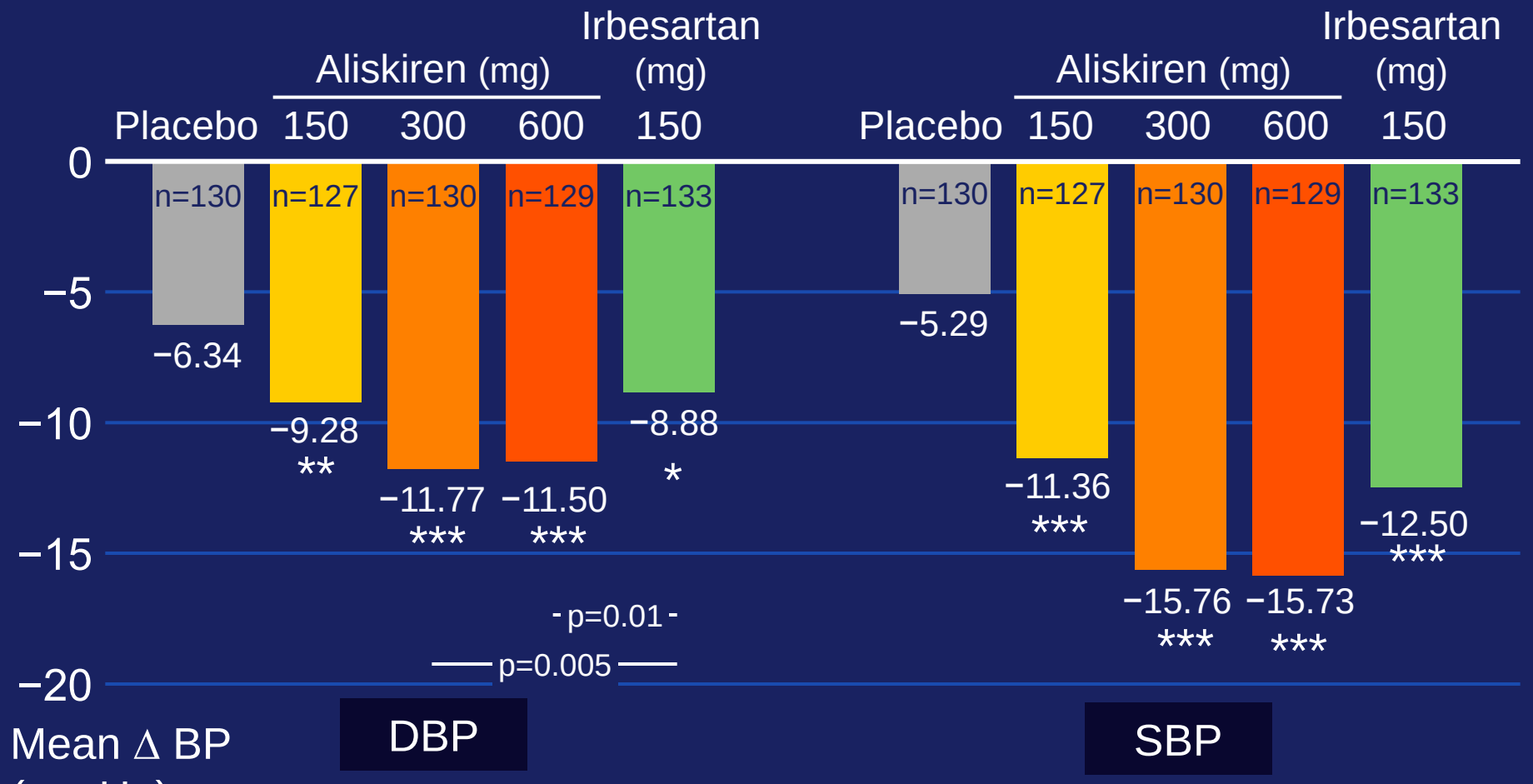
Aliskiren: the first orally available direct renin inhibitor



- Molecular weight = 609.8
- High solubility in water and biological fluids
- Non-peptide drug suitable for oral administration

Wood JM, *et al*. 2003

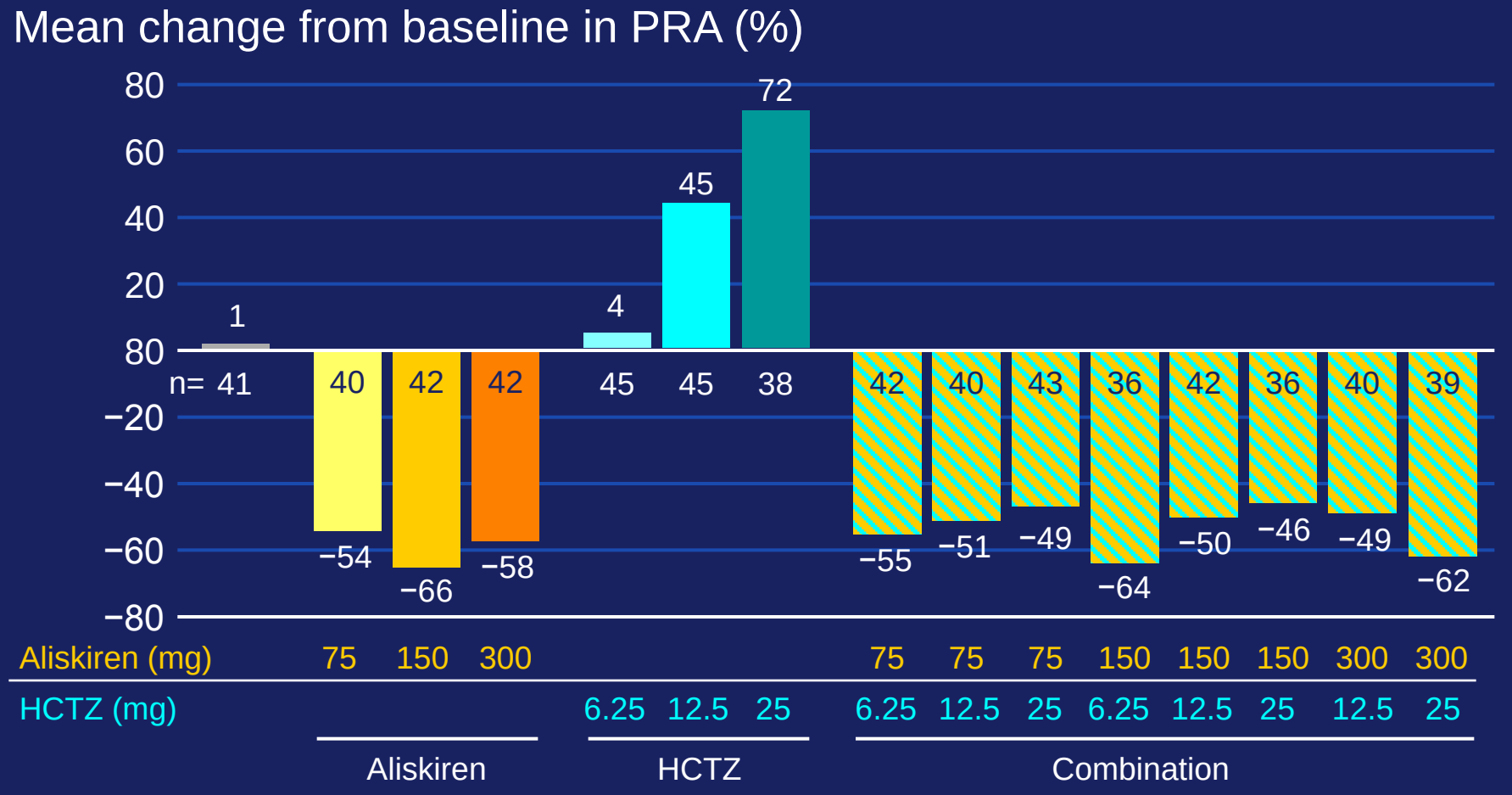
Aliskiren monotherapy provides dose-dependent reductions in DBP and SBP



*p<0.02 vs placebo; **p<0.005; ***p<0.001 vs placebo

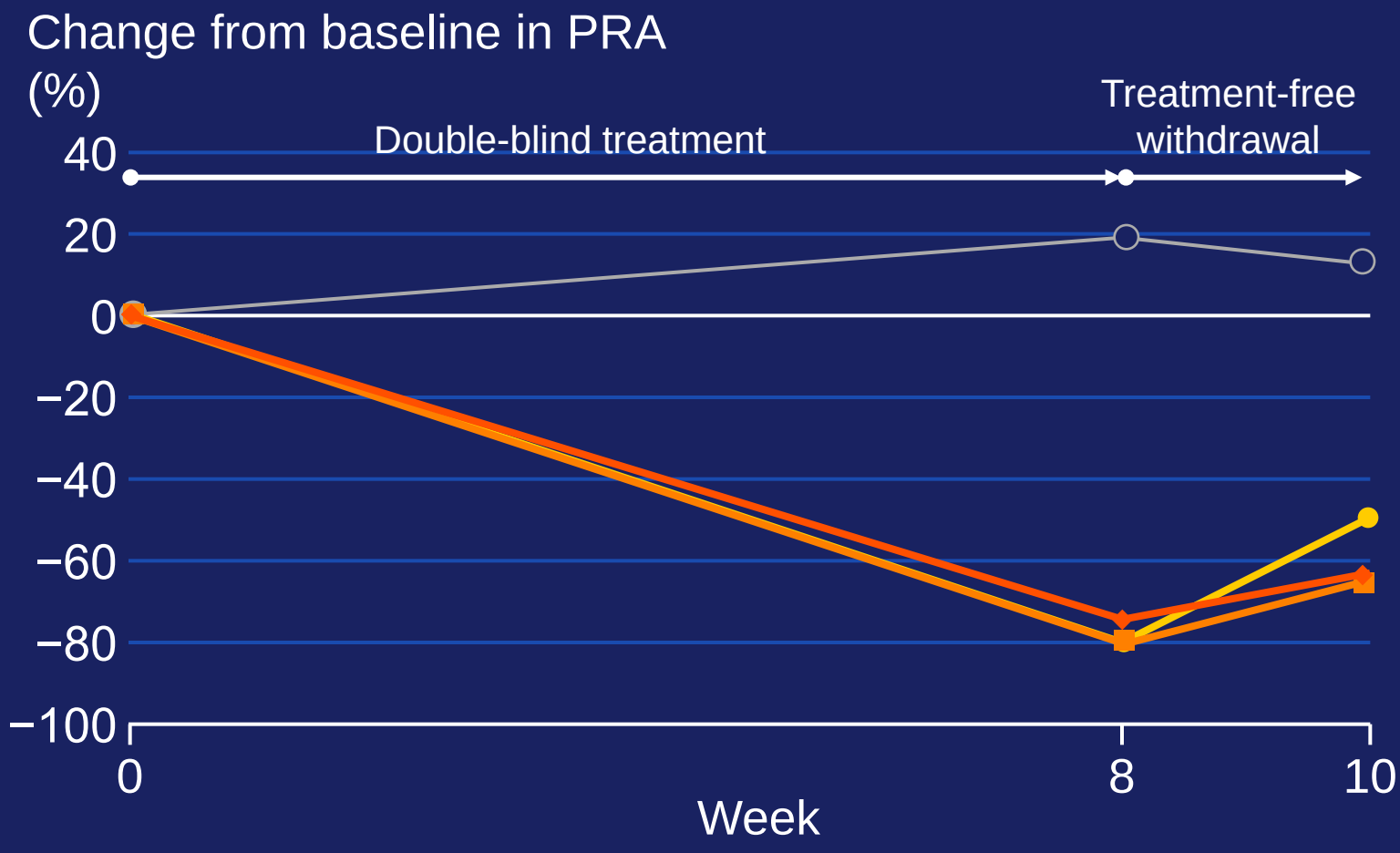
Gradman AH, *et al*. 2005 (Study 2201)

Aliskiren neutralizes the rise in PRA induced by HCTZ



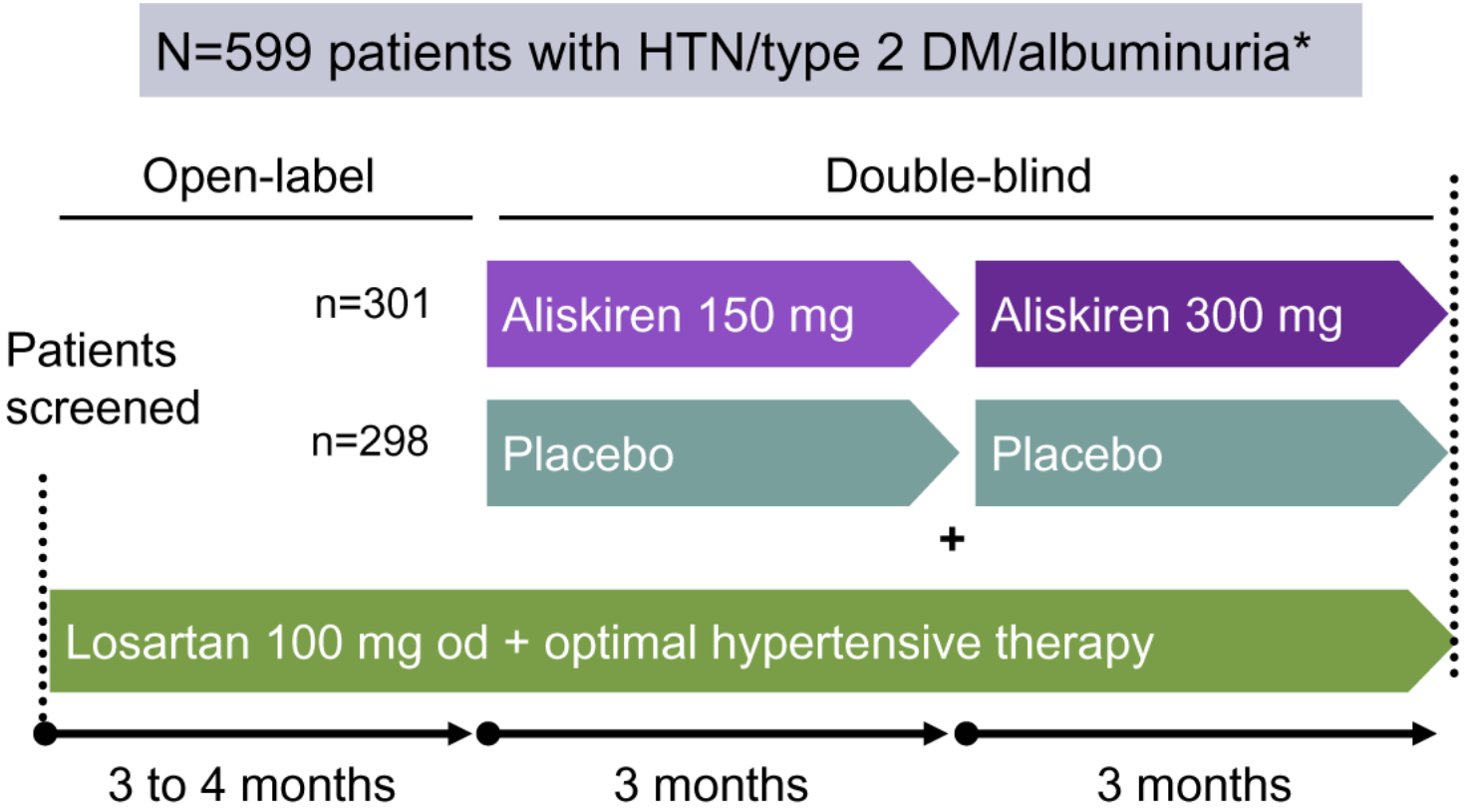
Calhoun D, *et al*. 2006 (Study 2204)

Suppression of PRA is maintained following discontinuation of aliskiren treatment



Herron J, *et al*. 2006 (Study 2308)

Study Design: Aliskiren Combined with Losartan in Type 2 Diabetes and Nephropathy



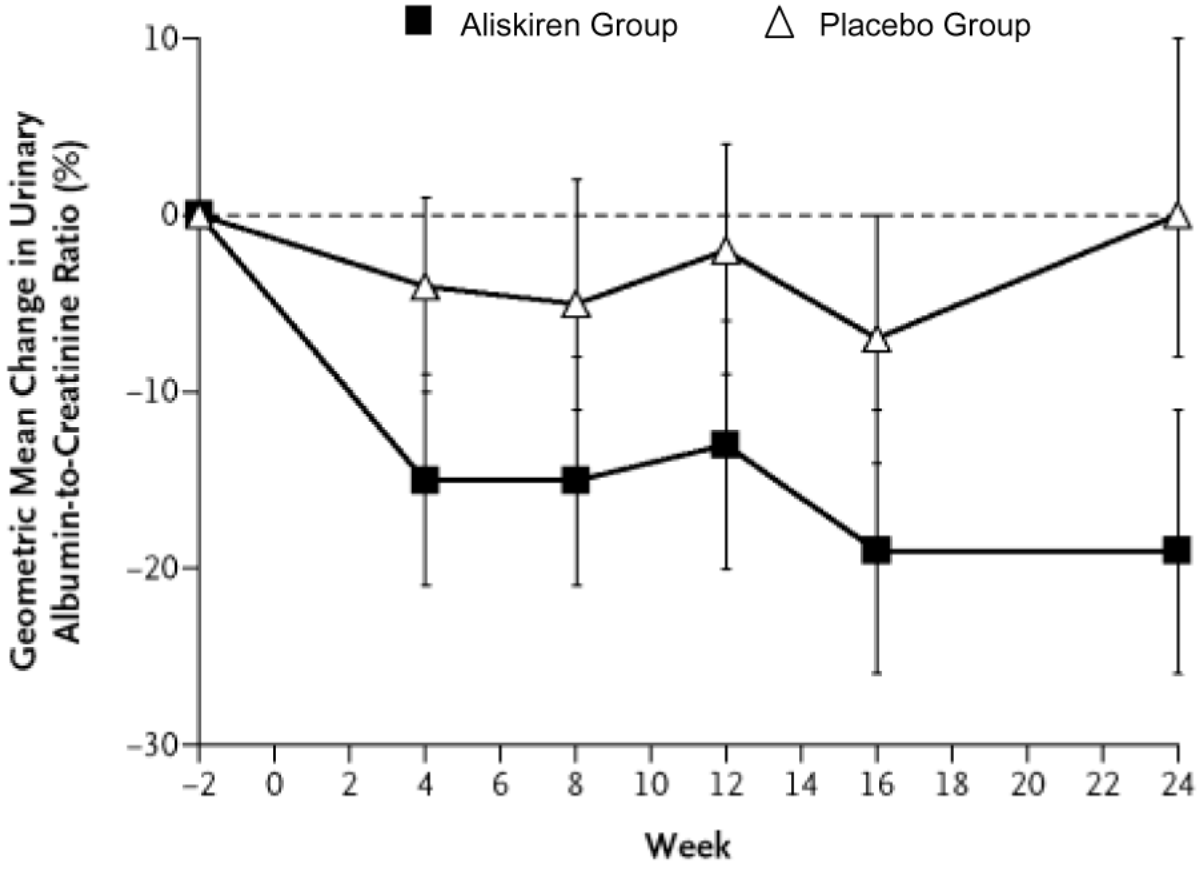
Primary endpoint: difference in proteinuria between treatment groups at 24 weeks.

*UACR >300 mg/g; or UACR >200 mg/g in patients receiving therapy targeted at blockade of the RAAS. All patients must have had a urinary albumin to creatinine ratio ≤3500 mg/g.

This information is not within approved product labeling and can only be presented in response to an unsolicited question. Discussion must be redirected back to within approved product labeling.

Parving H-H et al. *N Engl J Med.* 2008;358:2433-2446.

Primary Endpoint: Difference in UACR at 24 weeks



- At week 24, the difference in proteinuria between the groups was 20%.

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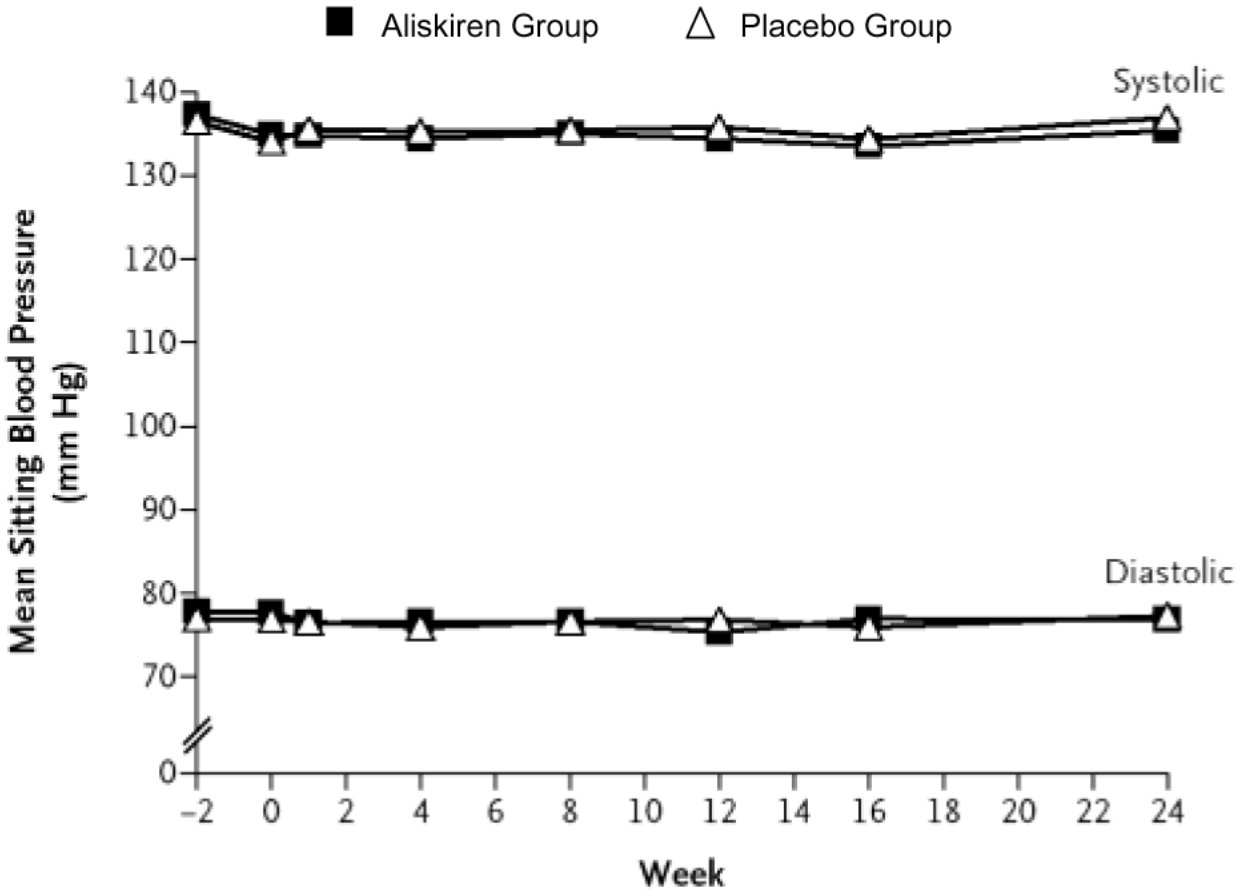
Parving H-H et al. *N Engl J Med.* 2008;358:2433-2446.

Mean Blood Pressure at Baseline and End of Study



- No difference in mean BP was seen between aliskiren and placebo.

This information is not within approved product labeling and can only be presented in response to an unsolicited question. Discussion must be redirected back to within approved product labeling.

Parving H-H et al. *N Engl J Med.* 2008;358:2433-2446.