Disease Background

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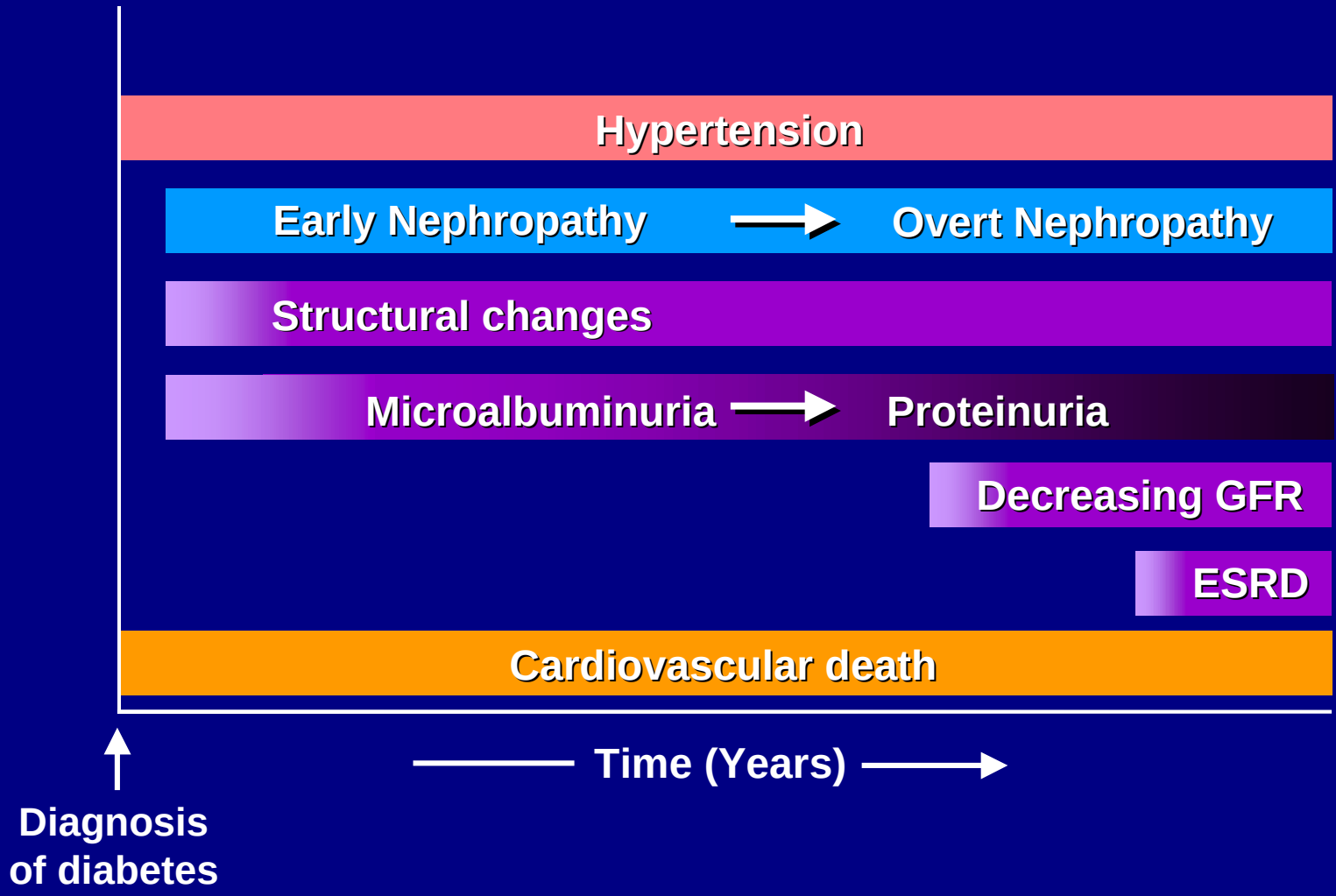
Magnitude of the Problem

- An estimated 135 million people have diabetes worldwide and it is expected that the prevalence will increase to 300 million by the year 2025[1]
- Diabetes is the primary cause of ESRD and accounts for approximately 45% of new cases in the US[2]
- Type 2 diabetes accounts for approximately 90% of all cases of diabetes
- The annual costs associated with ESRD in 2010 has been projected to be $28 billion in the United States alone[2]

[1]The World Health Organization. *The World Health Report* 1997.

[2]U.S Renal Data System, USRDS 2001 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. National Institutes of Health, Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2001

Natural History of Type 2 Diabetic Nephropathy



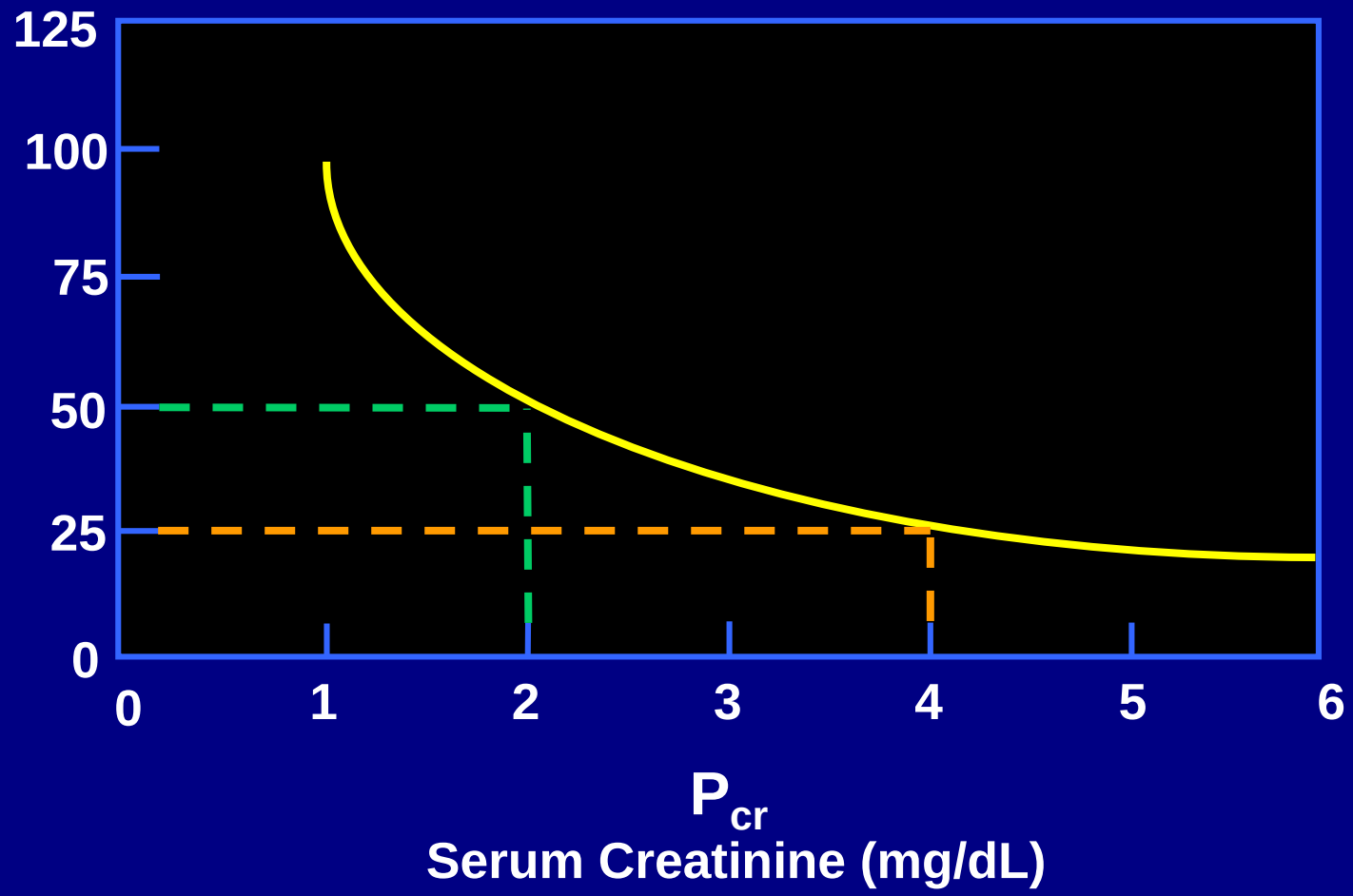
Renal Failure

A decrease in the ability of the kidney to carry out its primary function of filtering impurities from the blood. This is measured by the glomerular filtration rate (e.g., creatinine clearance) or evidence of retention of filterable molecules (e.g., creatinine, urea).

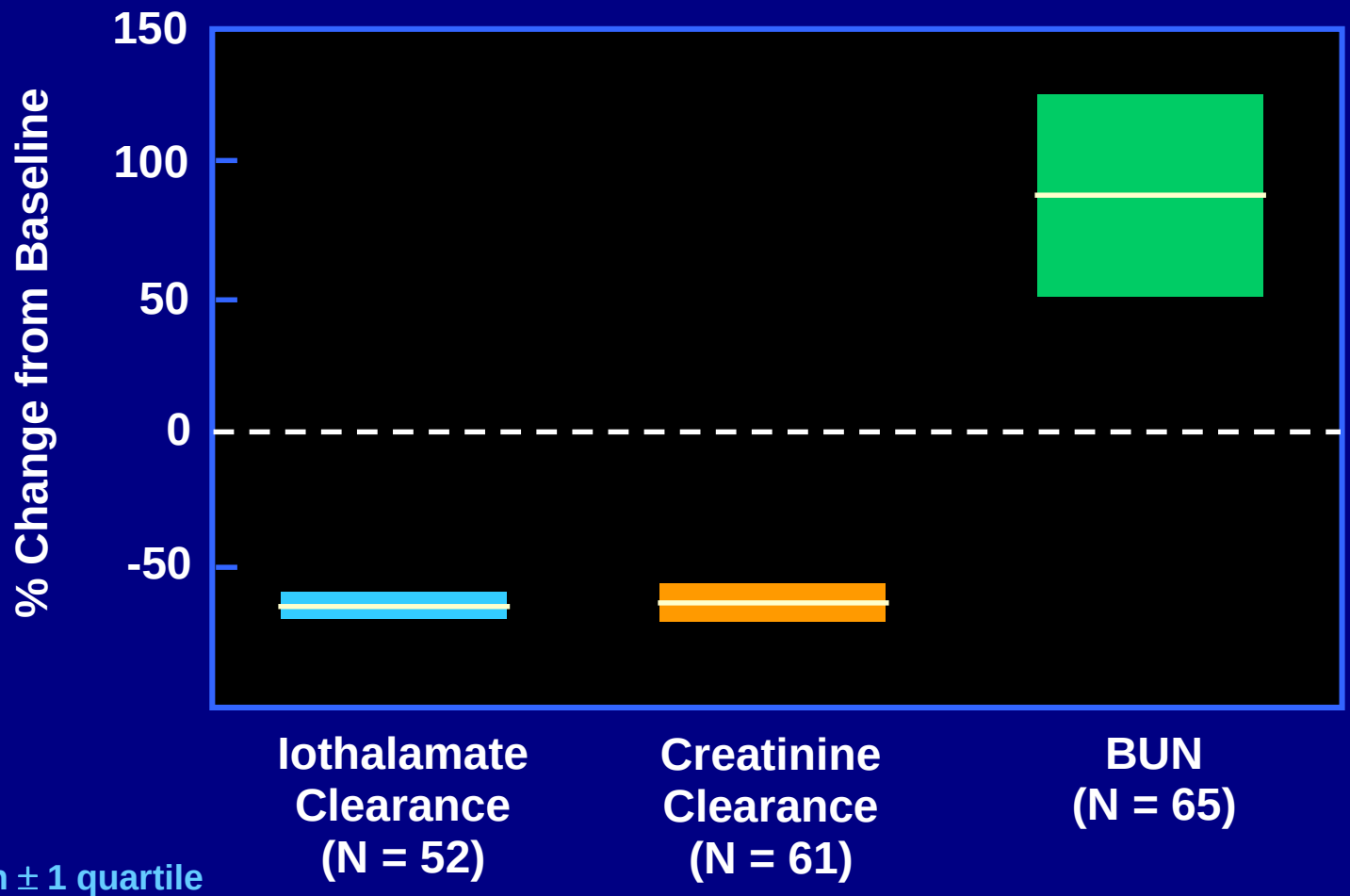
Relationship Between Serum Creatinine and Glomerular Filtration Rate (GFR)

Creatinine Clearance

$$\frac{U_{cr}\ V}{P_{cr}}$$



Change in Renal Function at the Time of Creatinine Doubling in Patients with Type 1 Diabetic Nephropathy



Reference: Protocol 12,928-257

End Stage Renal Disease

- The clinical requirement for renal replacement therapy (i.e., dialysis or transplantation)
- Medicare definition of ESRD for patients with diabetic nephropathy:

Serum creatinine:	$\geq$ 6 mg/dL
Creatinine clearance:	$\leq$ 15 ml/min

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Creatinine Clearance

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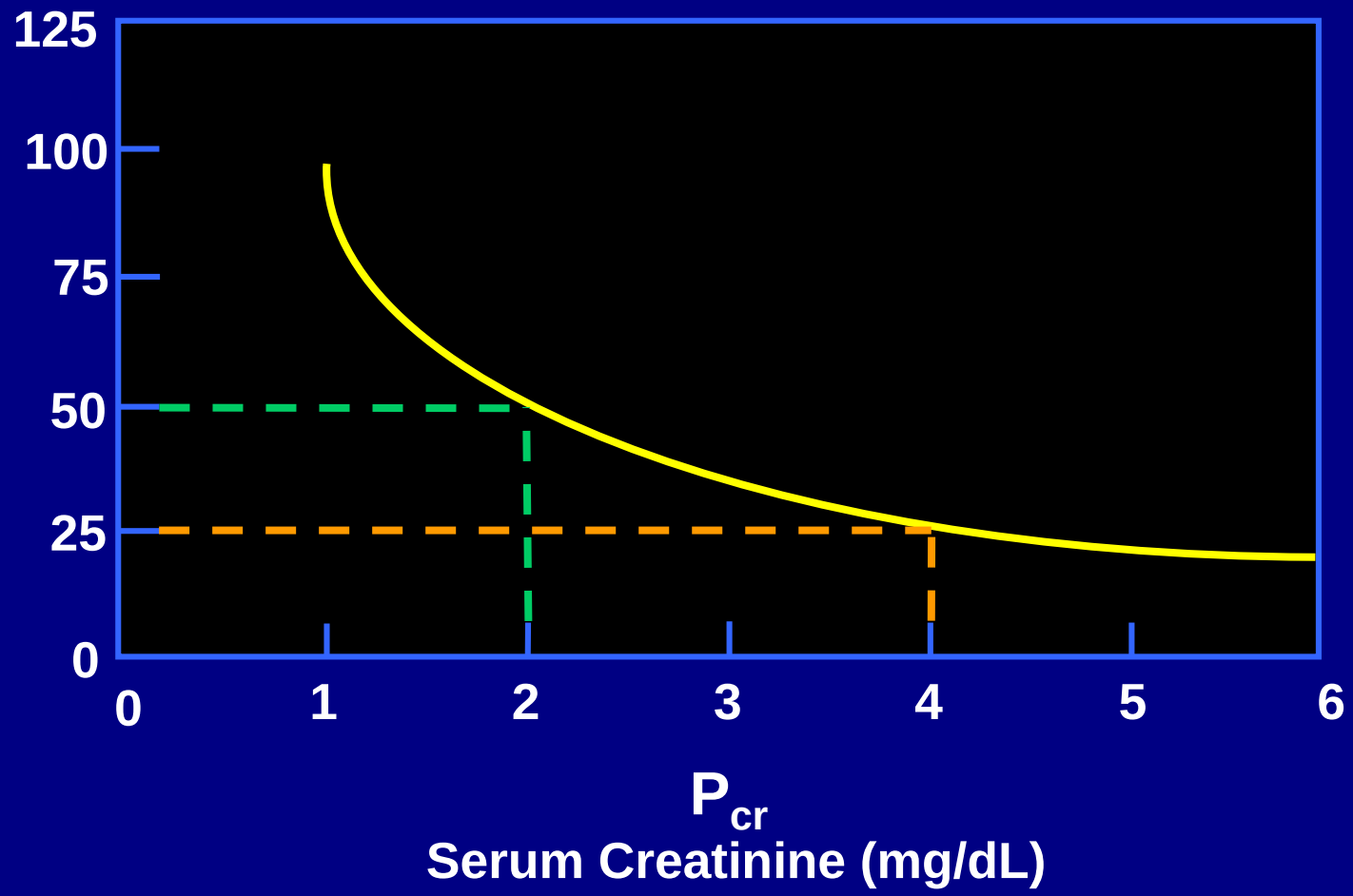
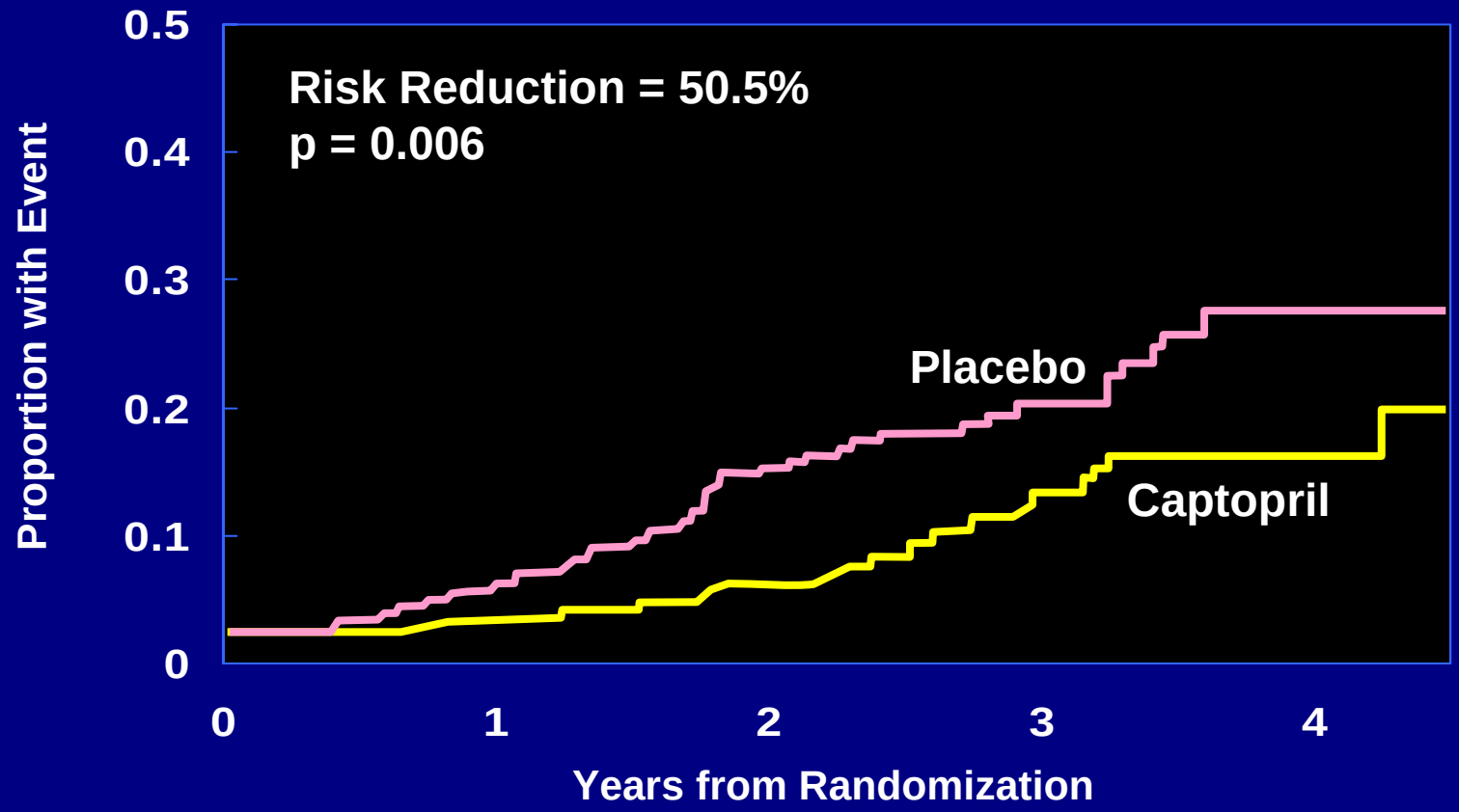


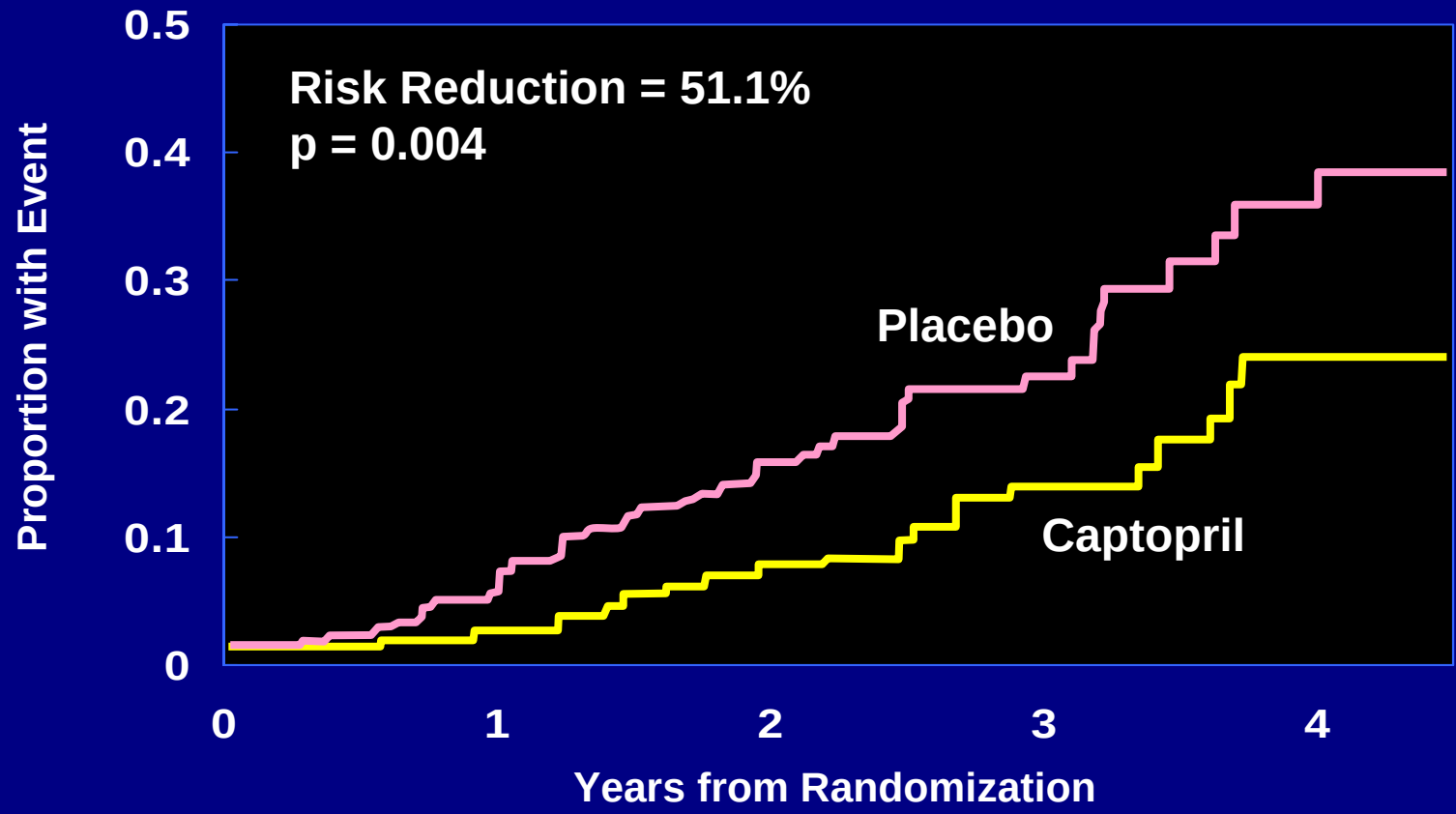
Effect of Captopril on End-Stage Renal Disease or Death in Type 1 Diabetic Nephropathy



No. at Risk					
Placebo	202	192	172	101	28
Captopril	207	204	195	103	37

Reference: Protocol 12,928-257

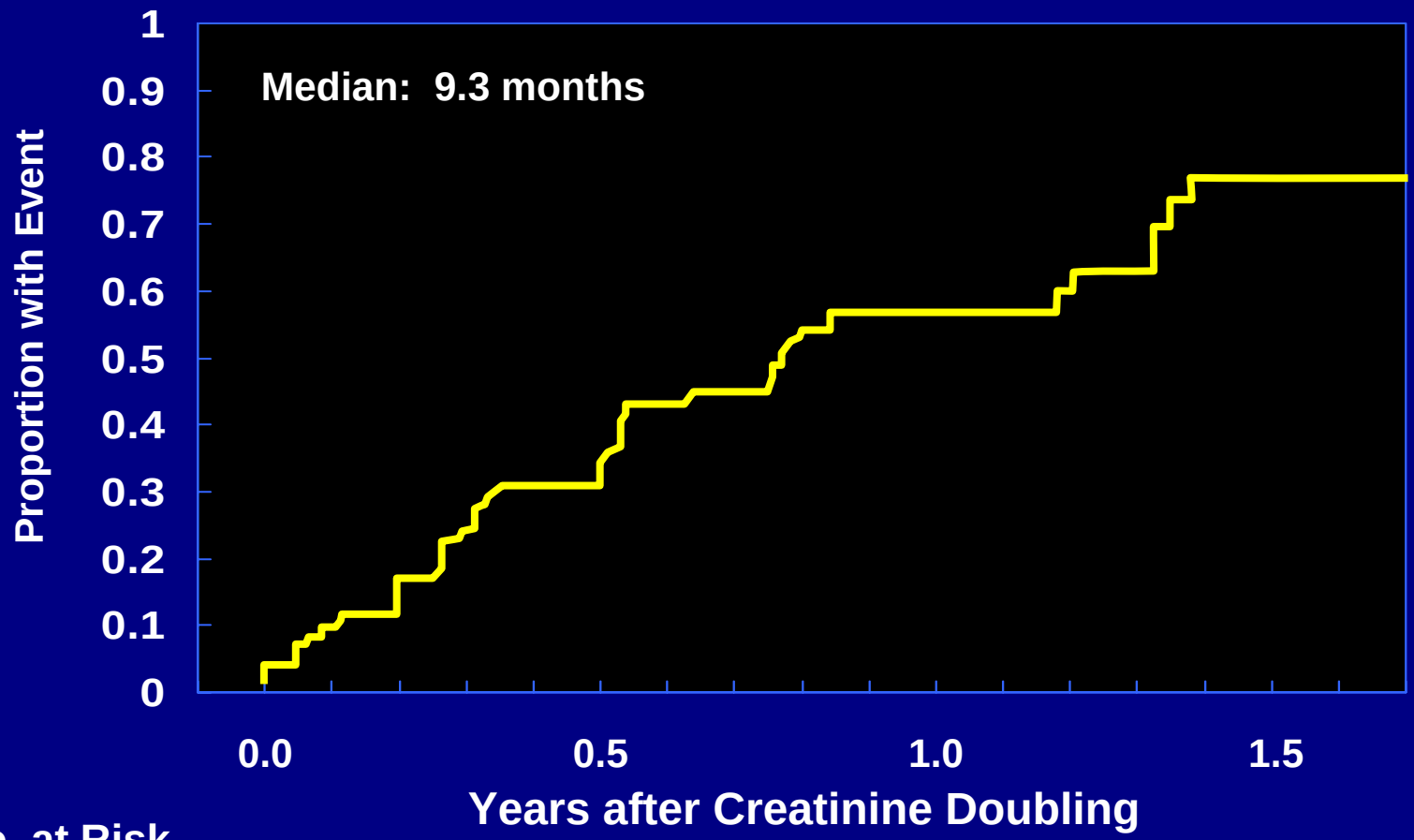
Effect of Captopril on Doubling of Serum Creatinine, in Type 1 Diabetic Nephropathy



No. at Risk					
Placebo	202	169	135	69	18
Captopril	207	190	167	80	24

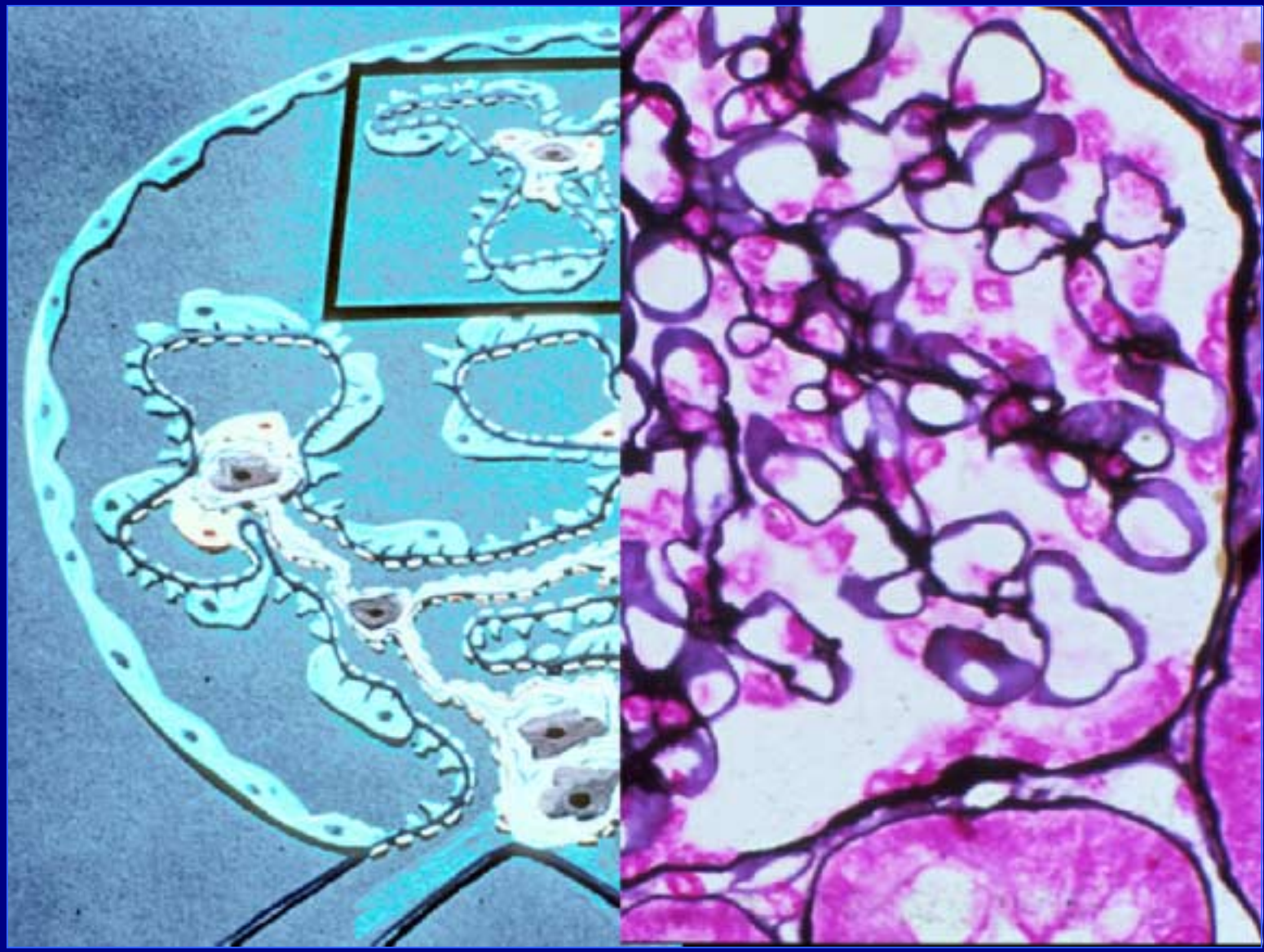
Reference: Protocol 12,928-257

Time to the Development of ESRD after Doubling Serum Creatinine in Type 1 Diabetic Nephropathy

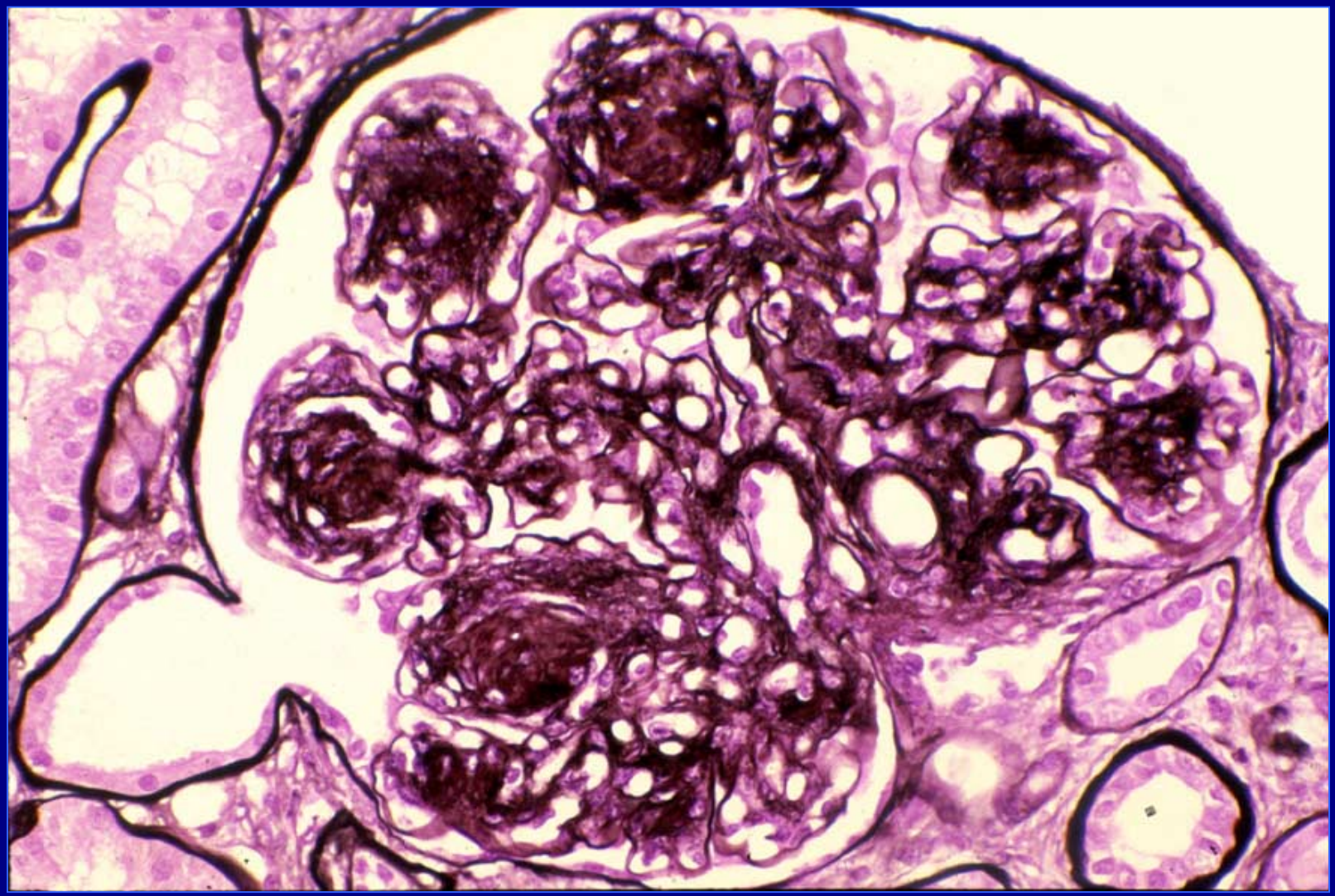


Reference: Protocol 12,928-257

Glomerular Structure and Histology



Glomerular Histopathology in Type 2 Diabetic Nephropathy



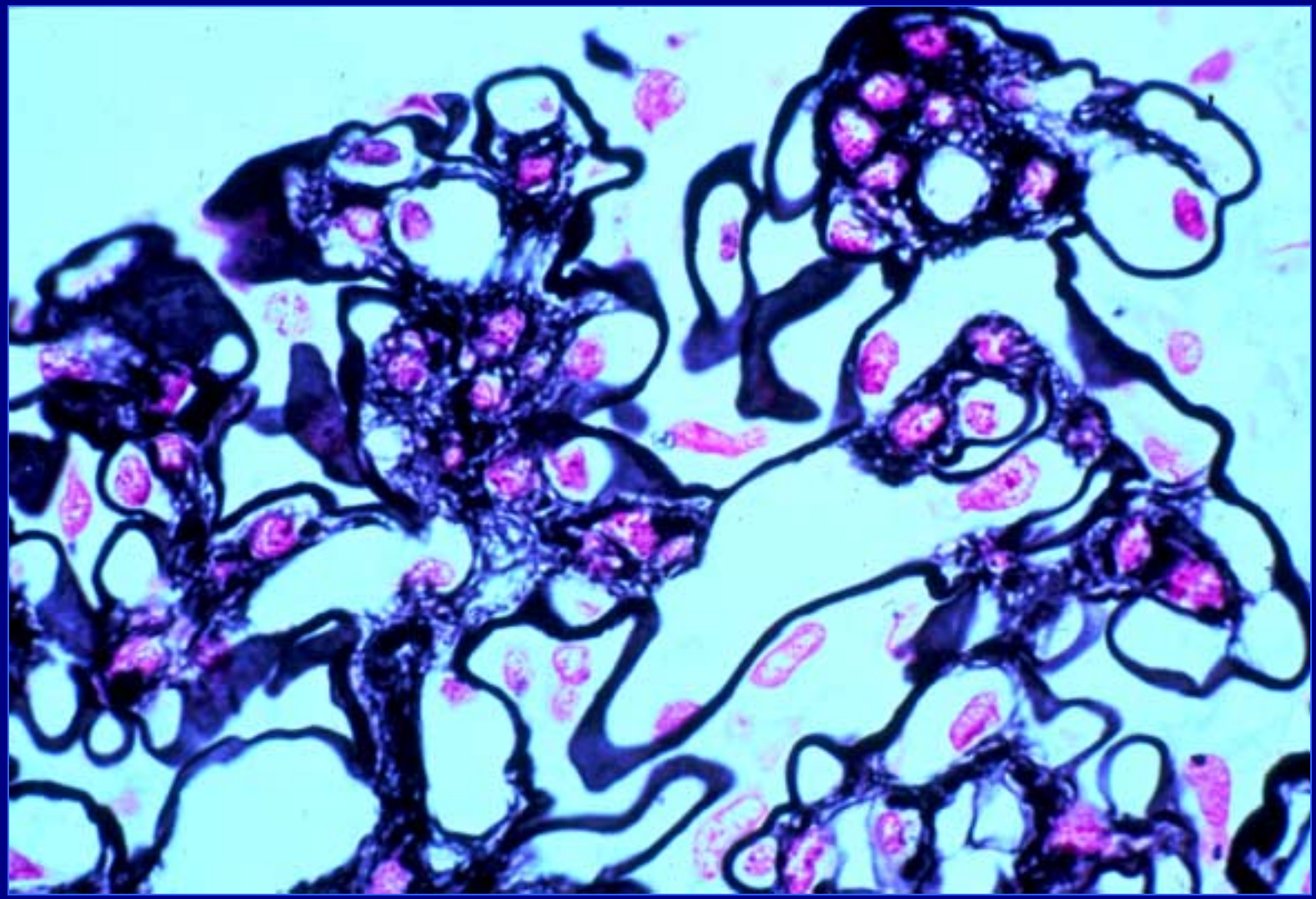
Manifestations of Early Diabetic Nephropathy

- **Structural:**
  - **Thickening of the glomerular basement membrane**
  - **Expansion of the glomerular mesangium**
  - **Increased glomerular type IV collagen signal**
- **Alteration of glomerular capillary wall selective permeability function**
  - **Increased albumin filtration *minus* renal tubular albumin absorption *equals* microalbuminuria**

Microalbuminuria

Urinary excretion of abnormal quantities albumin (20 - 200 μg/min) which is undetected by standard clinical test for proteinuria

Mesangial Changes Associated with Microalbuminuria

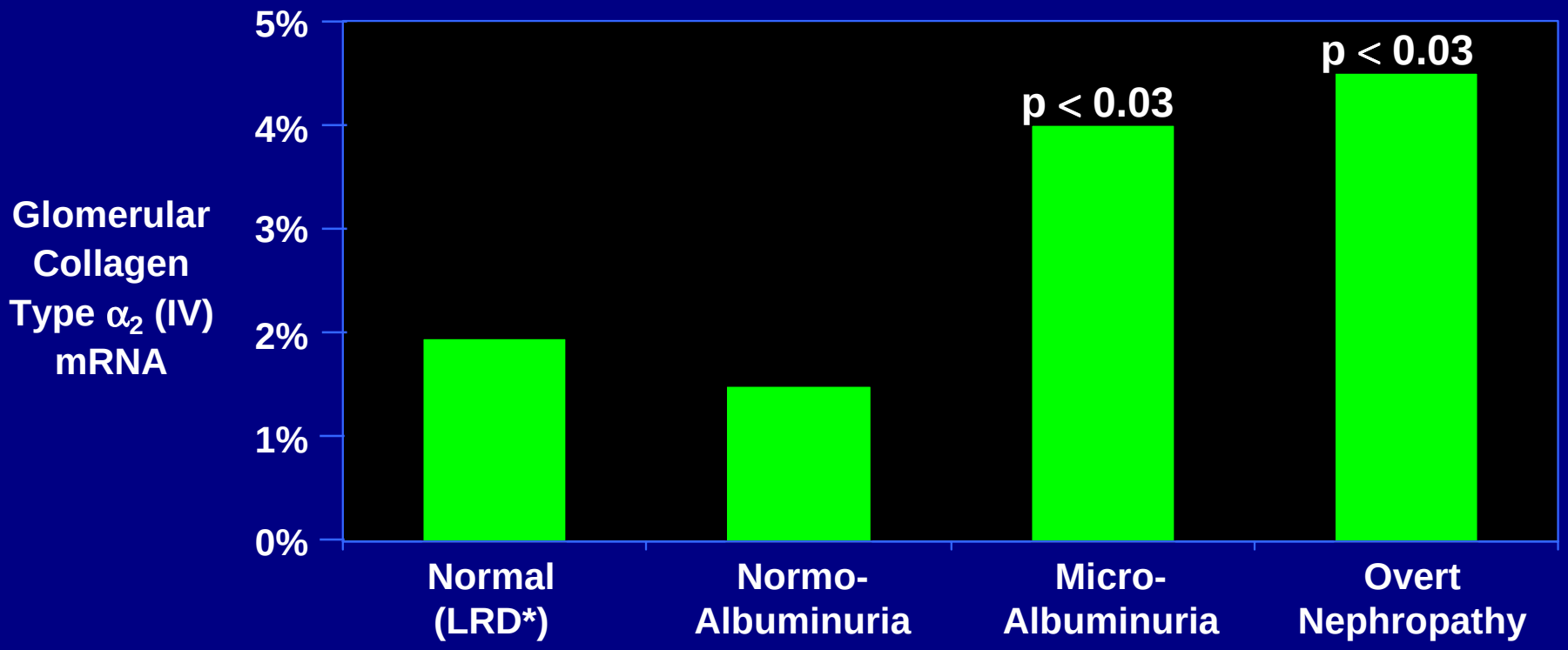


Structural Changes in Insulin-Dependent Diabetic Patients with Nephropathy

	Basement Membrane Thickness (nm)	Mesangial Expansion (Mesangial Area / Glomerulus)
Control[1,2] N = 8	343	0.18
Microalbuminuria[3] N = 10	580	0.22
Proteinuria[2] N = 14	643	0.37

[1]Living-renal donors
[2]Osterby *et. al.,* Diabetes 1990; 39: 1057
[3]Osterby *et. al.,* Kidney Int. 1992; 41: 703

Connective Tissue Metabolism in Diabetic Nephropathy



SCr (mg/dL)	0.8 ± 0.05	0.9 ± 0.06	0.9 ± 0.07	1.7 ± 0.3
Ccr (ml/min)	121 ± 8	100 ± 5	102 ± 8	71 ± 17
AER (mg/d)		9.6 ± 2.2	56 ± 18	4270 ± 1490

*Living renal donors

Adler *et. al.*, Kidney Int. 2001; 60:2330-2336

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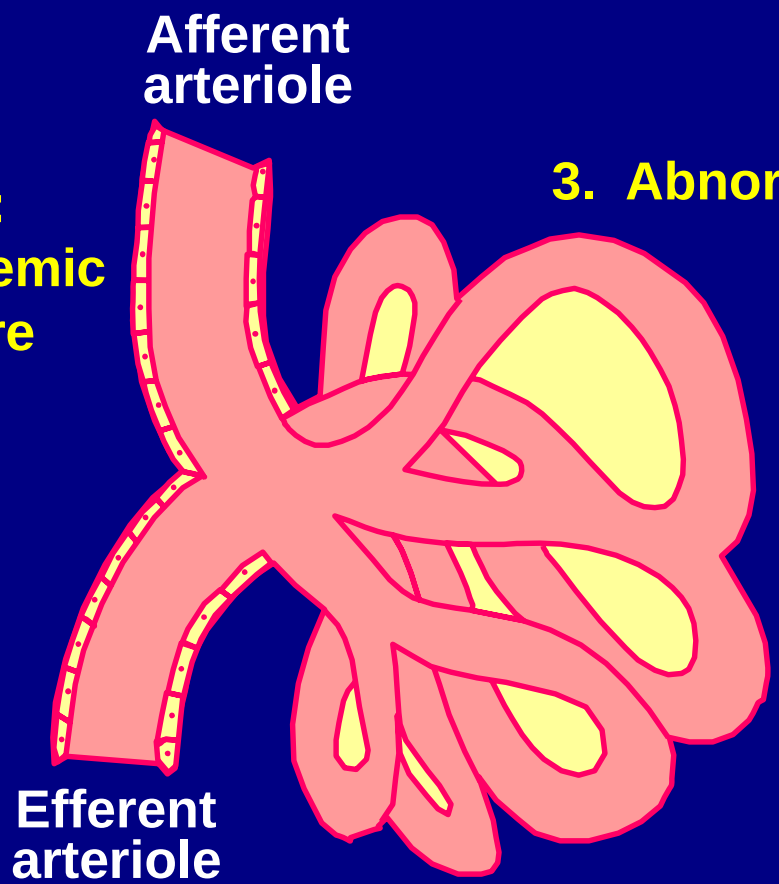
Rationale for the Clinical Development Program

Inhibition of the renin-angiotensin system has a renoprotective effect in patients with nephropathy caused by type 1 diabetes, but there has previously been no prospective clinical trial data with similar definitive renal outcomes in patients with type 2 diabetes

Therapeutic Interruption of Diabetic Nephropathy

1. Deficient autoregulation: control of systemic arterial pressure



3. Abnormal matrix metabolism: decrease angiotensin II modulation

2. Increased efferent resistance: decrease intrarenal angiotensin II effect

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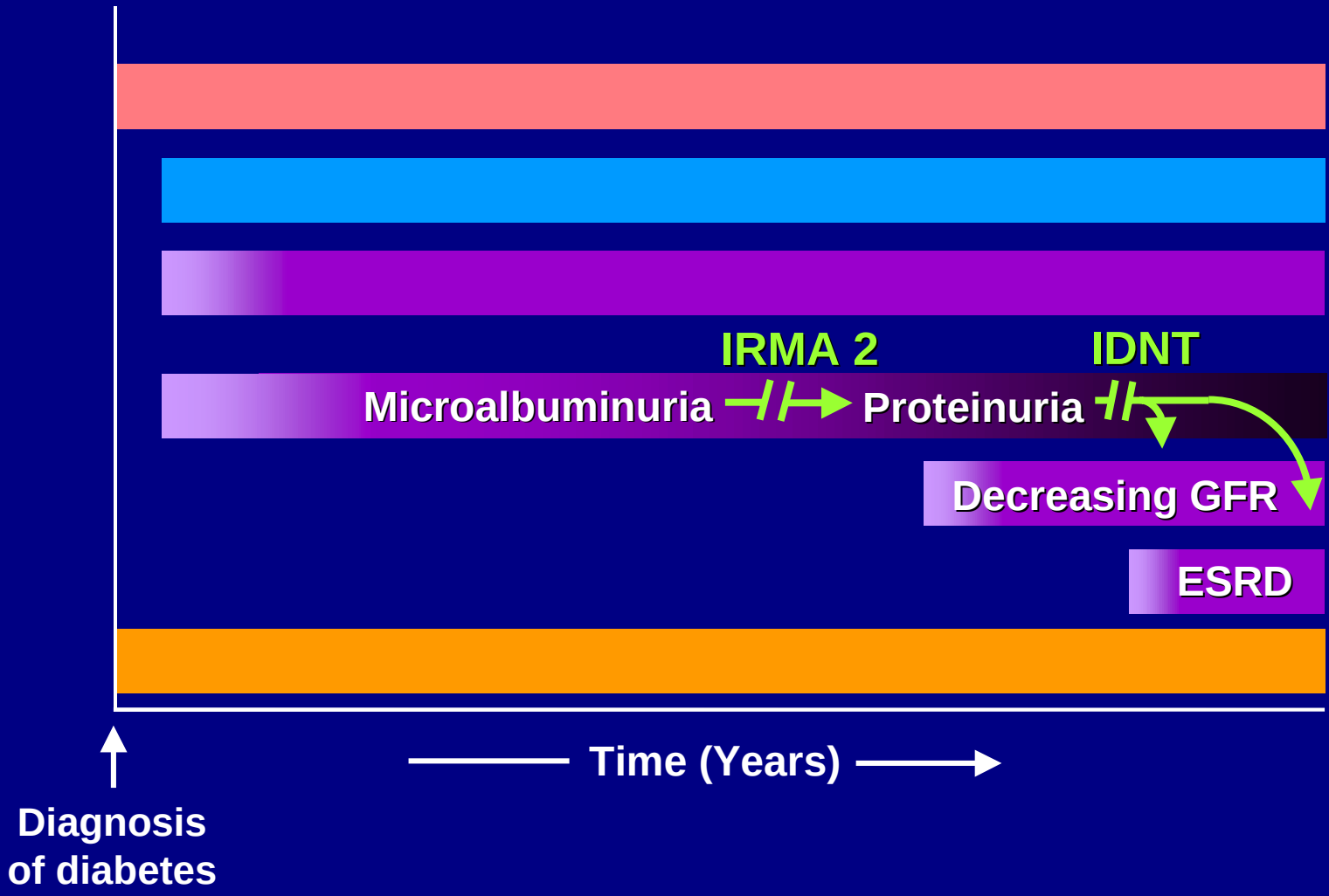

Glomerular Histopathology in Type 2 Diabetic Nephropathy