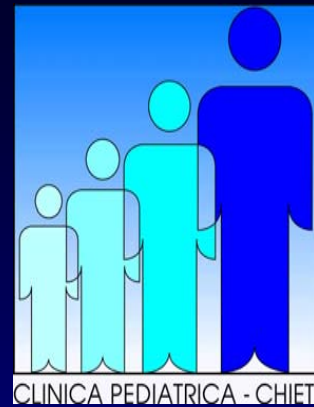




**Clinica Pediatrica
Università di Chieti**



Complicanze del diabete nel bambino e nell'adolescente

Franco Chiarelli

**XVII Congresso Nazionale SIPPS
Parma, 25 Novembre 2005**

Type 1 diabetes in childhood:

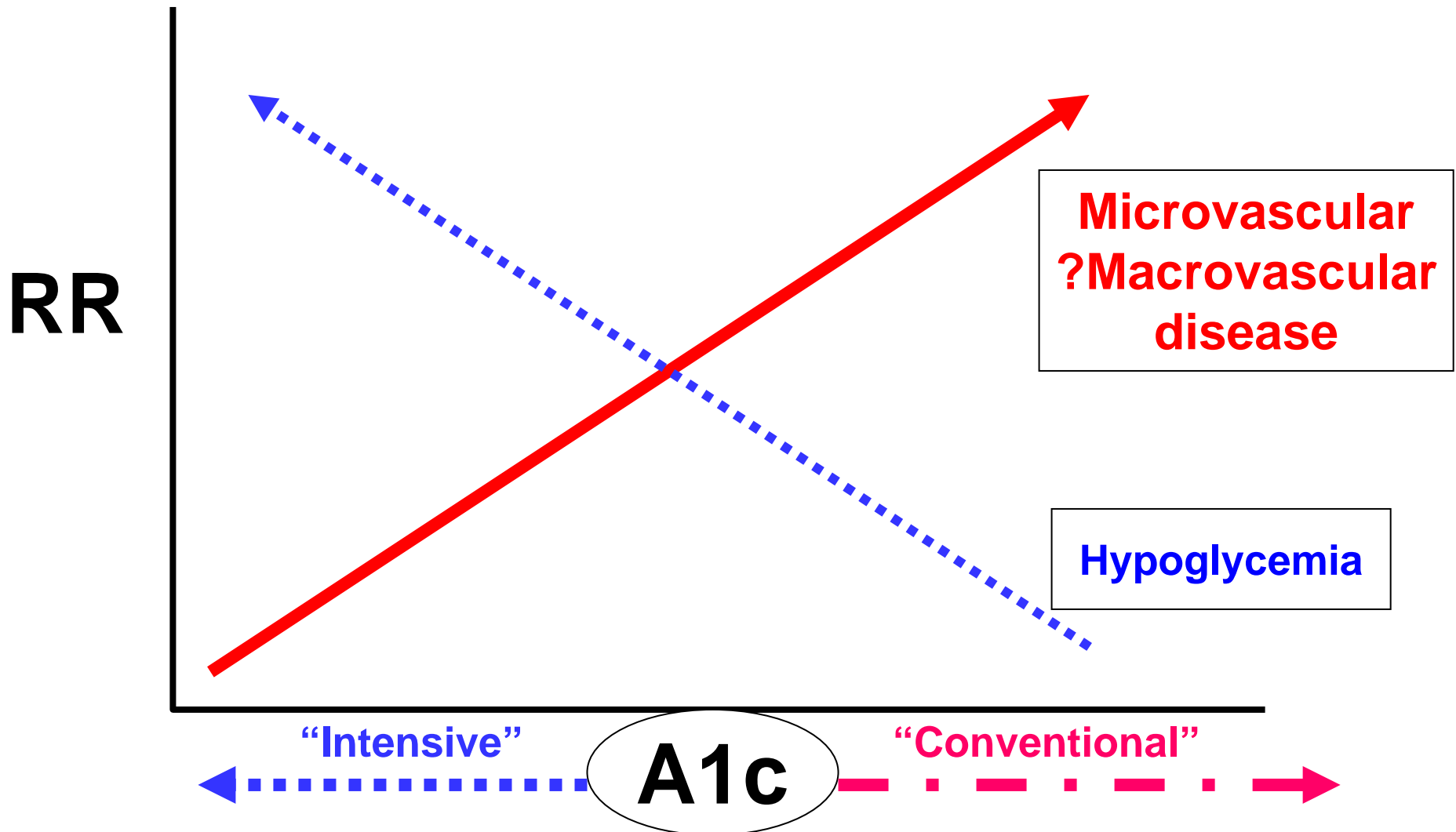
Only

- ~3% of people with diabetes in Europe and the USA are diagnosed before age 20 yr.**
- ~5-7% of total insulin usage.**

BUT

- This population appears to be at highest risk for short- and long-term complications of their disease.**

Current treatment philosophy is informed by results of the DCCT



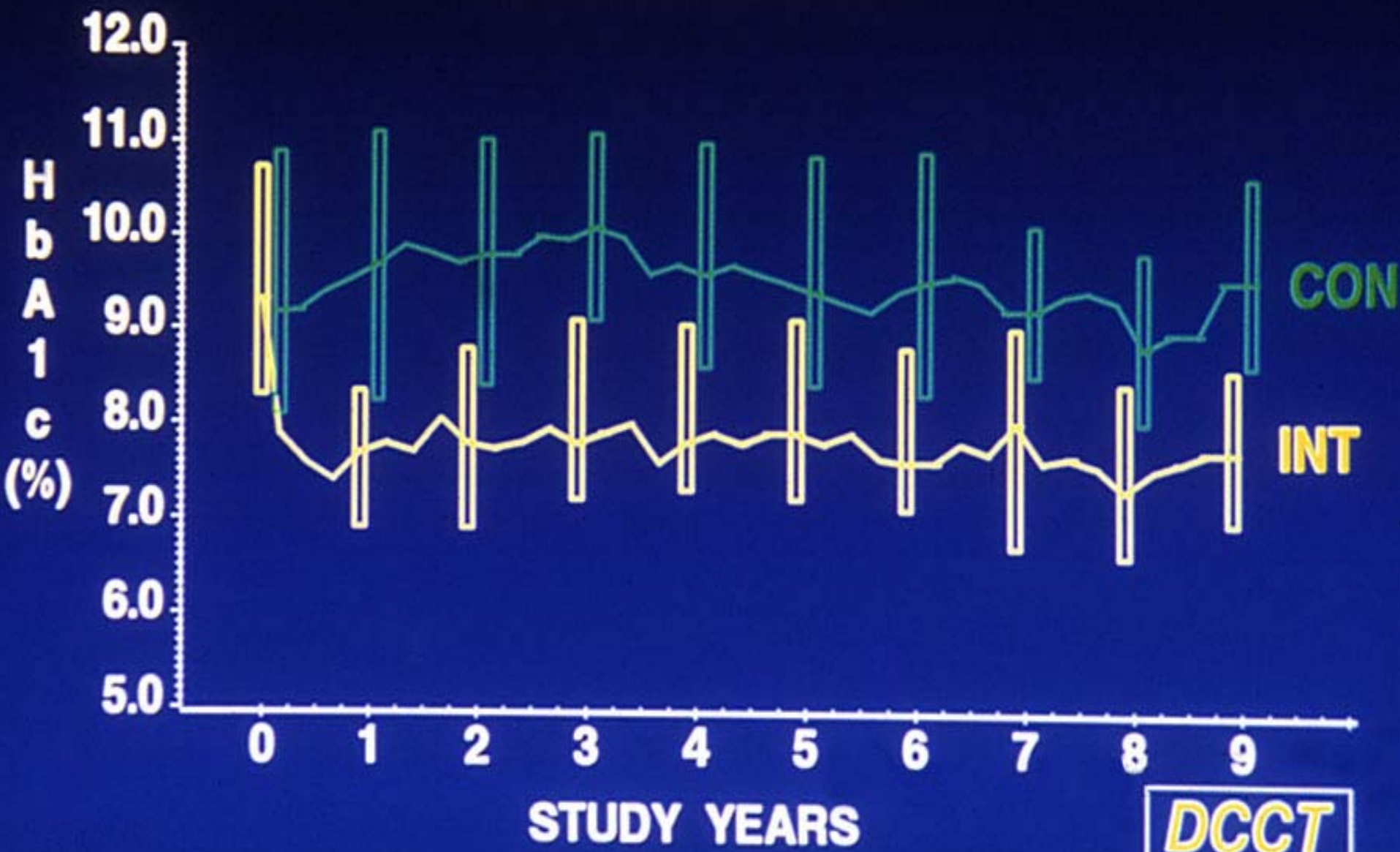
SEPARATION OF HbA1c

COMBINED COHORT



SEPARATION OF HbA1c

ADOLESCENTS



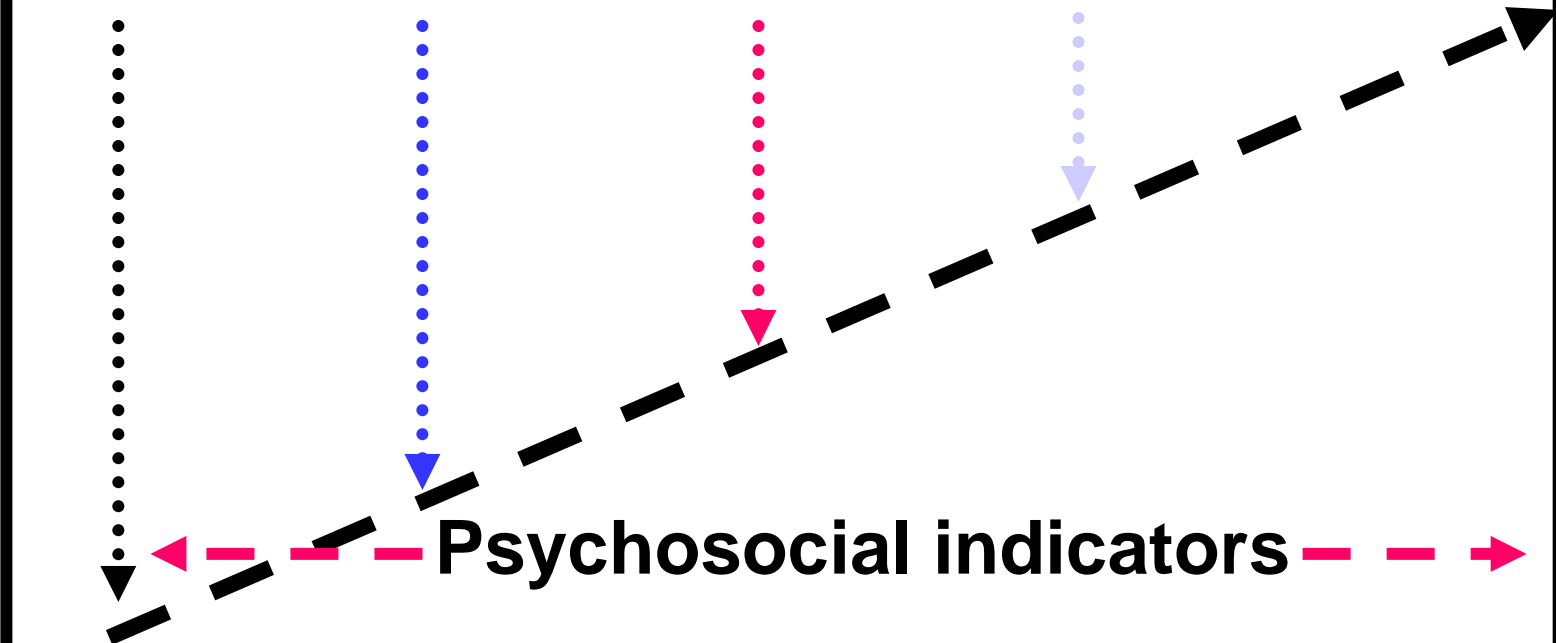
Building the burden

“Good start”

Risk factors: smoking, obesity, BP, genes

Adolescent amplification

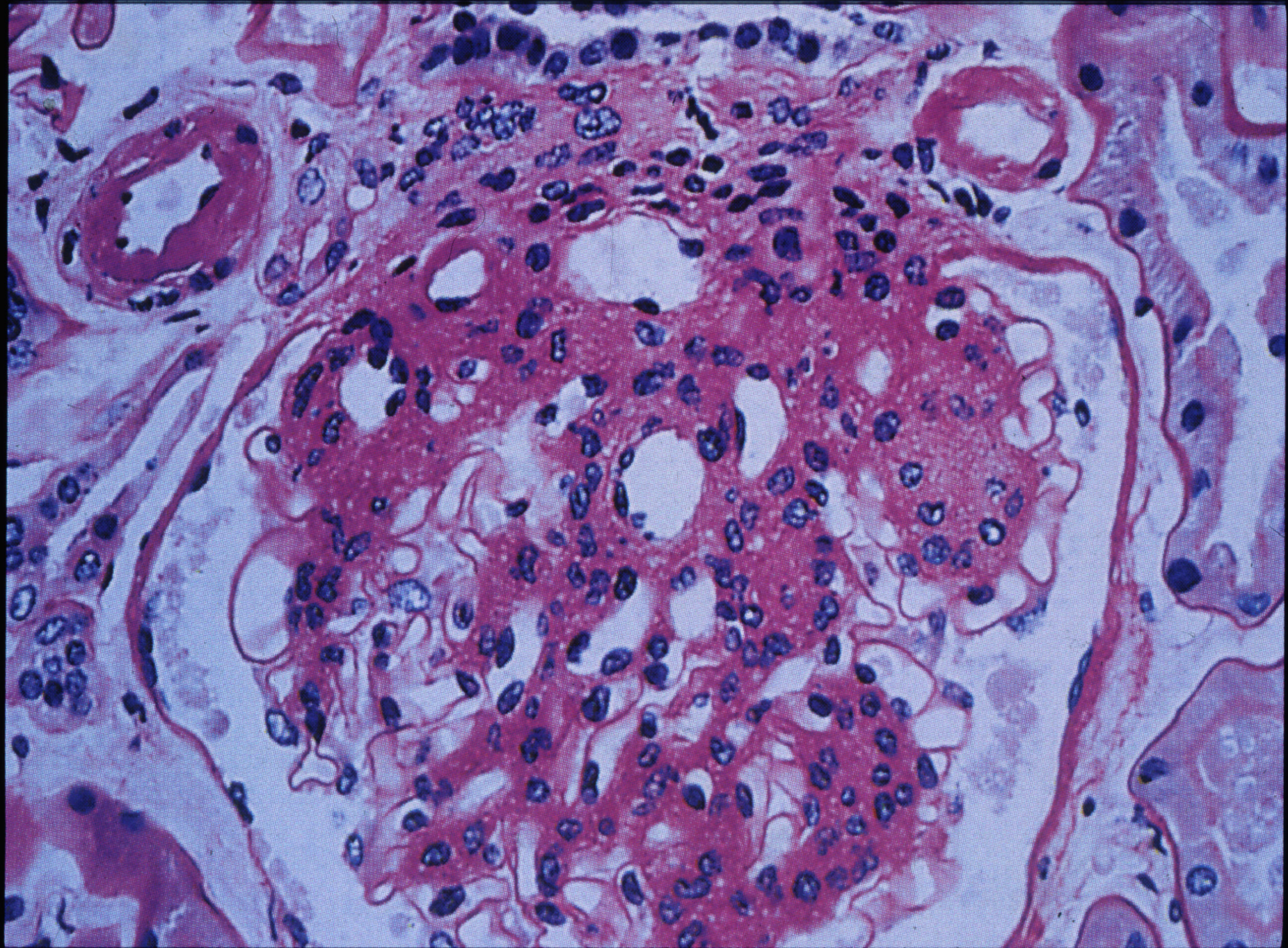
Surveillance



In childhood, A1c = best surrogate marker of success



OLIVIERI 1/1/52
00000

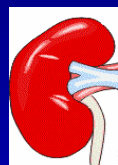


Diabetes: A Systemic Disease

Leading cause of blindness in working age adults

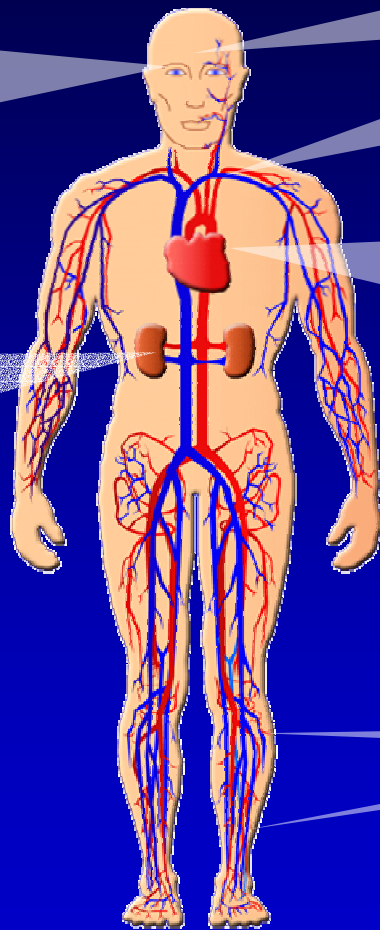


Diabetic Retinopathy



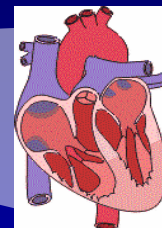
Diabetic Nephropathy

Leading cause of end-stage renal disease

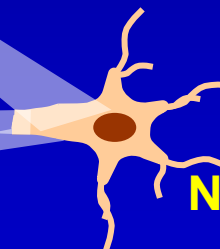


Stroke

2- to 4- fold increase in cardiovascular mortality and stroke



Cardiovascular Disease



Diabetic Neuropathy

Leading cause of non-traumatic lower extremity amputations

Risk Factors for Diabetic Angiopathy

- Disease duration
 - Poor metabolic control - high HbA1c
 - Hypertension
 - Hyperlipidemia
 - Smoking
 - Puberty
 - Genes?
-

Known Systemic Risk Factors in Diabetic Complications

Retinopathy

Hyperglycemia

Neuropathy

Hyperglycemia

Cardiovascular

Hyperglycemia

Insulin Resistance

Free Fatty Acids

Hypertension

Hyperlipidemia

Nephropathy

Hyperglycemia

Hypertension

Angiotensin Action

Role of growth factors in the pathogenesis of diabetic nephropathy

GH

bFGF

IGF-1

EGF

VEGF

PDGF

TGF-beta

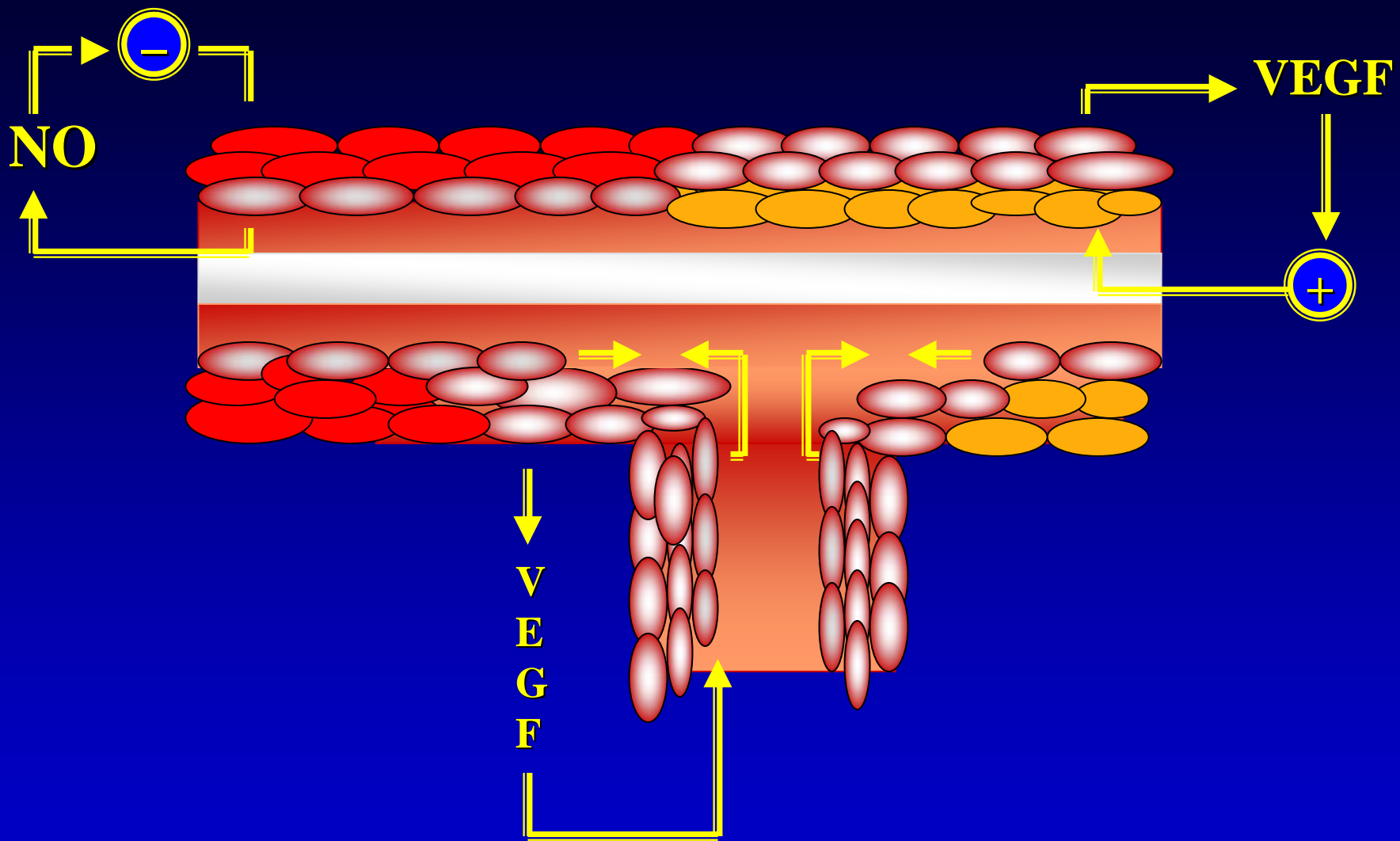
IGF-2

aFGF

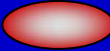
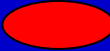
IGFBPs

VEGF

Vascular Endothelial Growth Factor

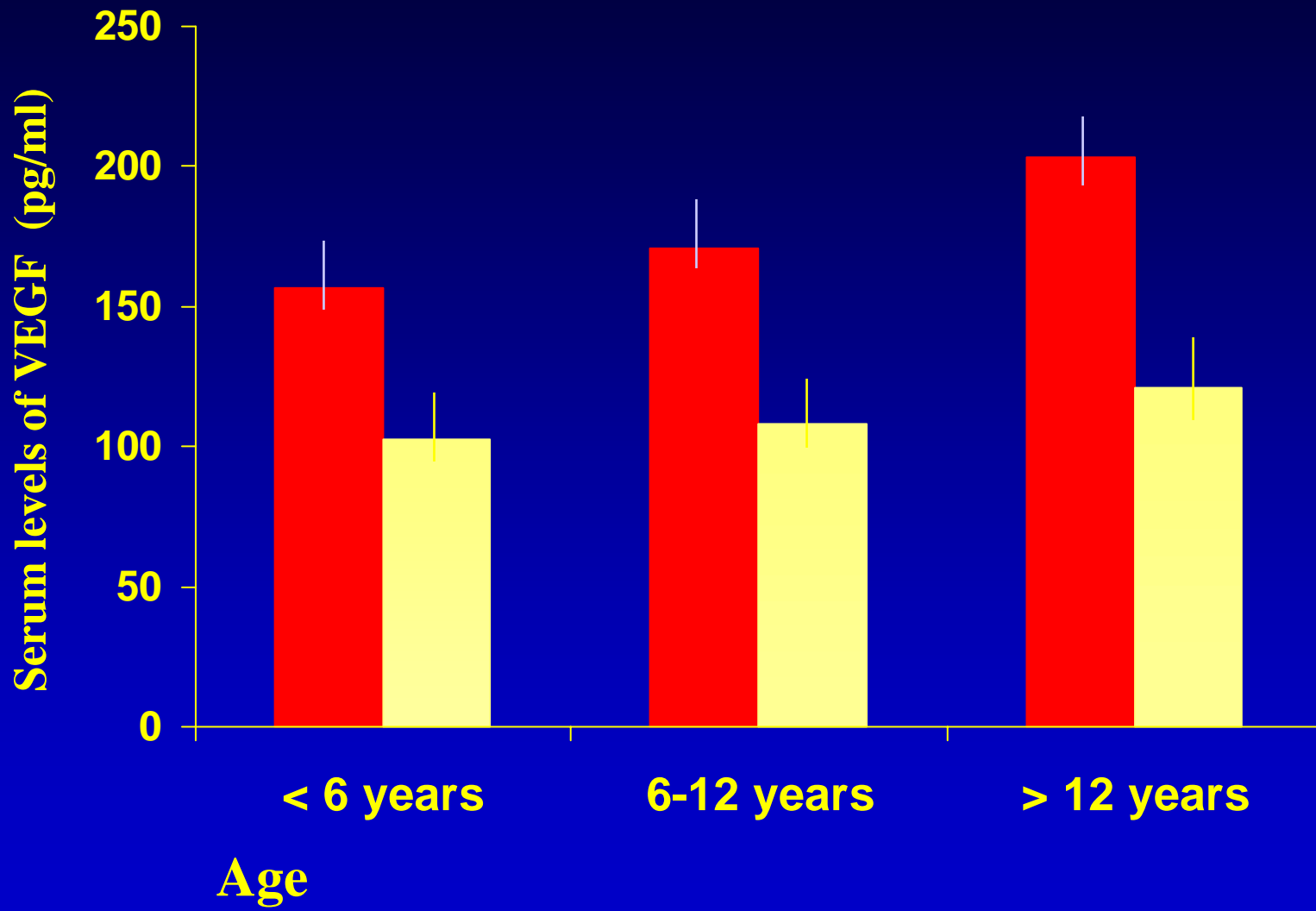


Ecs

-  Functionally intact (NO up-regulated)
-  Dysfunctional (NO down-regulated)

SMCs

-  VEGF up-regulated
-  VEGF down-regulated



VEGF concentrations and later development of microalbuminuria

Serum VEGF levels higher than 150 pg/ml are able to predict later development of persistent microalbuminuria in patients with onset of diabetes during childhood in a period of life when AER is still in normal range

SCREENING FOR DIABETIC RETINOPATHY IN CHILDREN

- **Clinical examination of the eye and ophthalmoscopy should be performed soon after diagnosis to exclude cataract formation or other disorders**
- **Fundus photography (preferably stereoscopic several fields views through dilated pupils) has been shown to be a safe, non-invasive and sensitive screening procedure**

SCREENING FOR DIABETIC RETINOPATHY IN CHILDREN

Age of retinopathy screening

- Prepubertal onset of diabetes: 5 years after onset or at age 11 years, or at puberty (whichever is earlier) and annually thereafter
- Pubertal onset of diabetes: 2 years after onset, and annually thereafter

SCREENING FOR DIABETIC NEPHROPATHY IN CHILDREN

- Screening may be performed by early morning urine albumin concentration or spot urine ACR or by timed urine collection
- Abnormal screening values should be confirmed by repeated sampling to demonstrate persistent increase of AER (microalbuminuria)

SCREENING FOR DIABETIC NEPHROPATHY IN CHILDREN

Age of nephropathy screening

- Prepubertal onset of diabetes: 5 years after onset or at age 11 years, or at puberty (whichever is earlier) and annually thereafter
- Pubertal onset of diabetes: 2 years after onset, and annually thereafter

STRATEGIES FOR PREVENTION OF DIABETIC ANGIOPATHY IN CHILDREN

- **Glycaemic control**
 - **Dietary protein and sodium intake**
 - **Blood pressure control**
 - **Others?**
-

- **Glycaemic control**

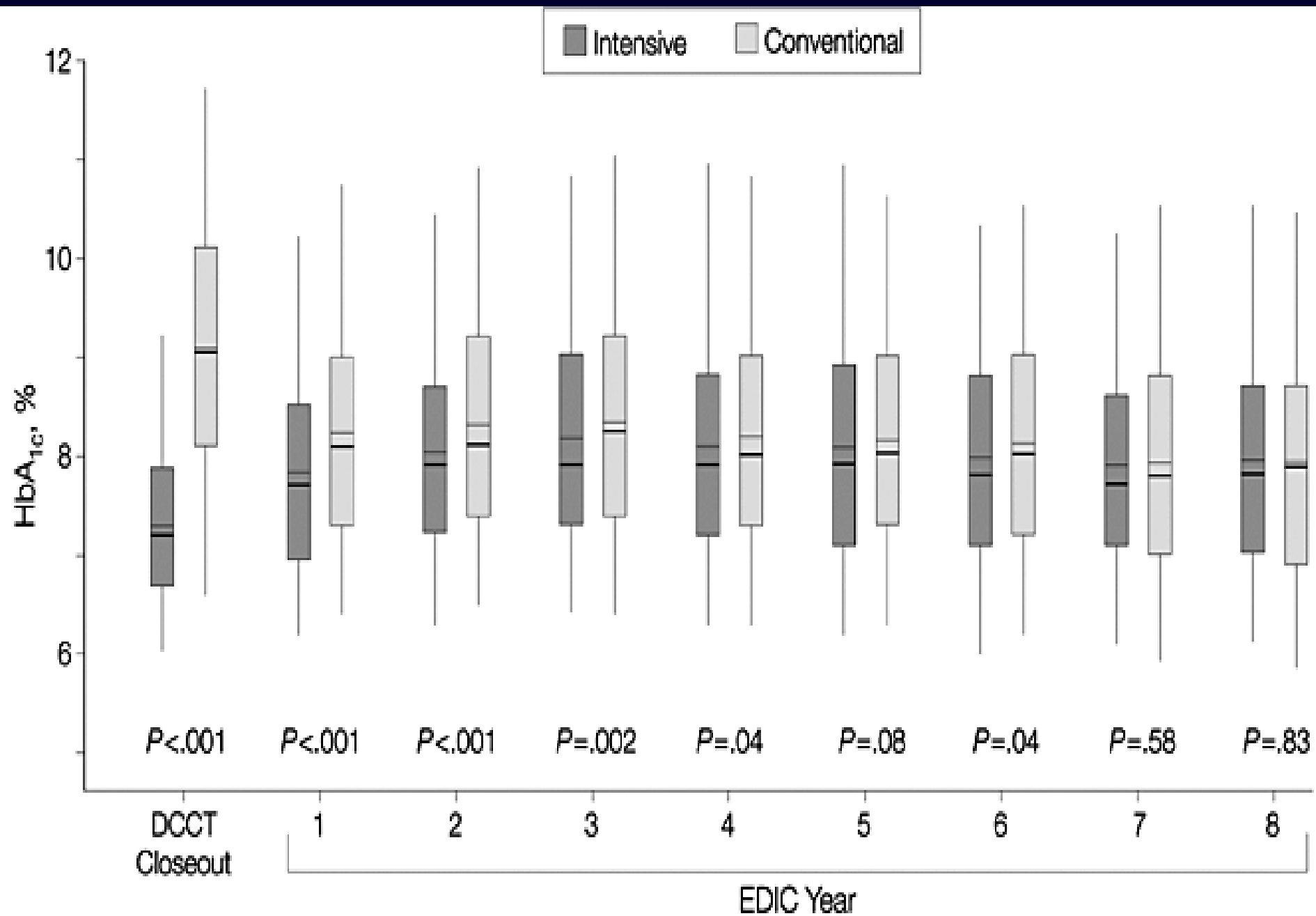
Risk Reduction per 1% Decrease in HbA1c

<i>Study</i>	<i>Eye</i>	<i>Kidney</i>	<i>Nerve</i>	<i>Heart</i>
DCCT¹	27-38%	22-28%	29-35%	40%
Ohkubo²	28%	50%	↑ NCV	25%
UKPDS³	19%	26%	18%	14%

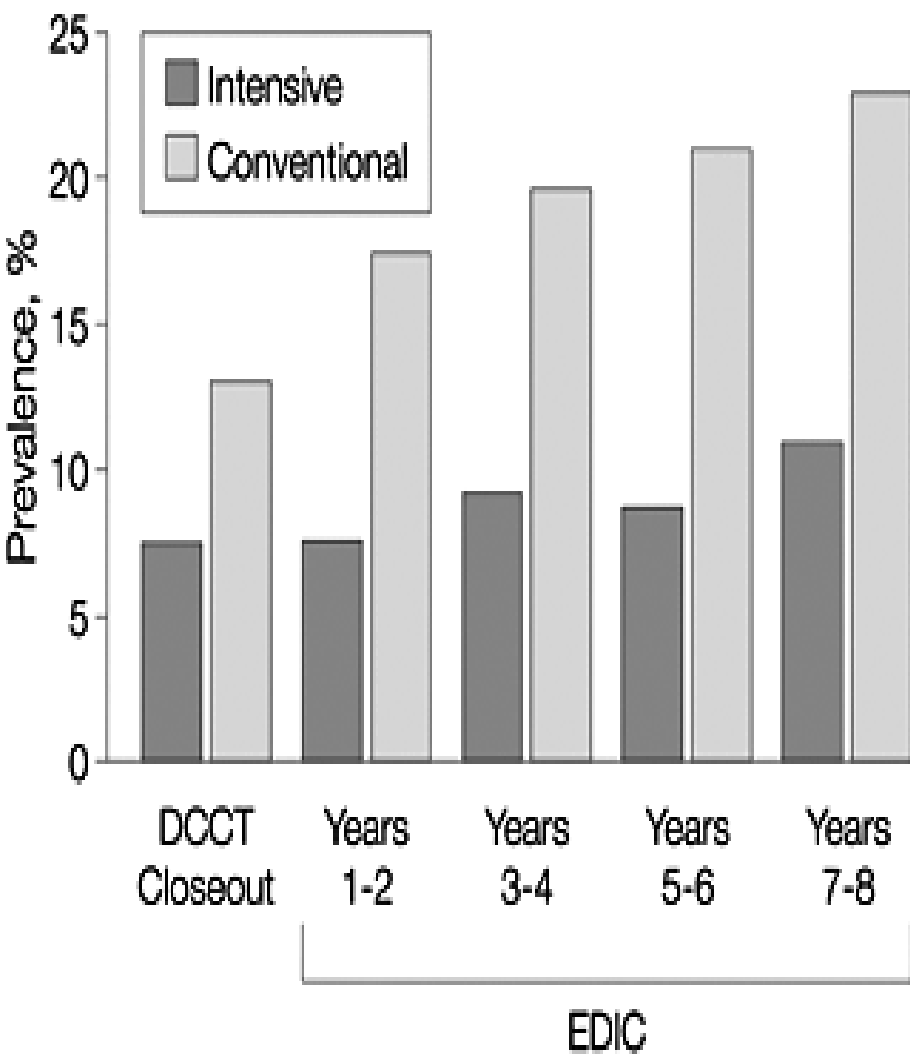
¹*N Engl J Med* 329: 977-986, 1993

²*Diabetes Res Clin Pract* 28: 103-117, 1995

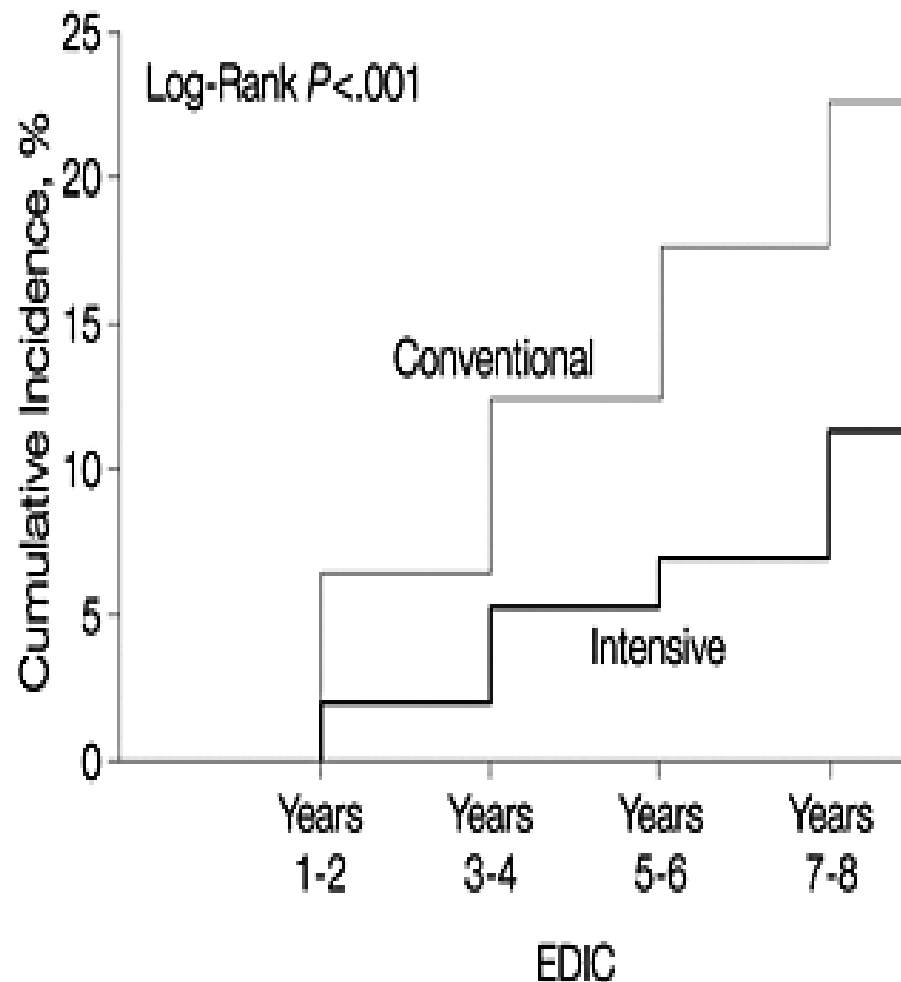
³*Lancet* 352: 837, 1998



A Annual Prevalence

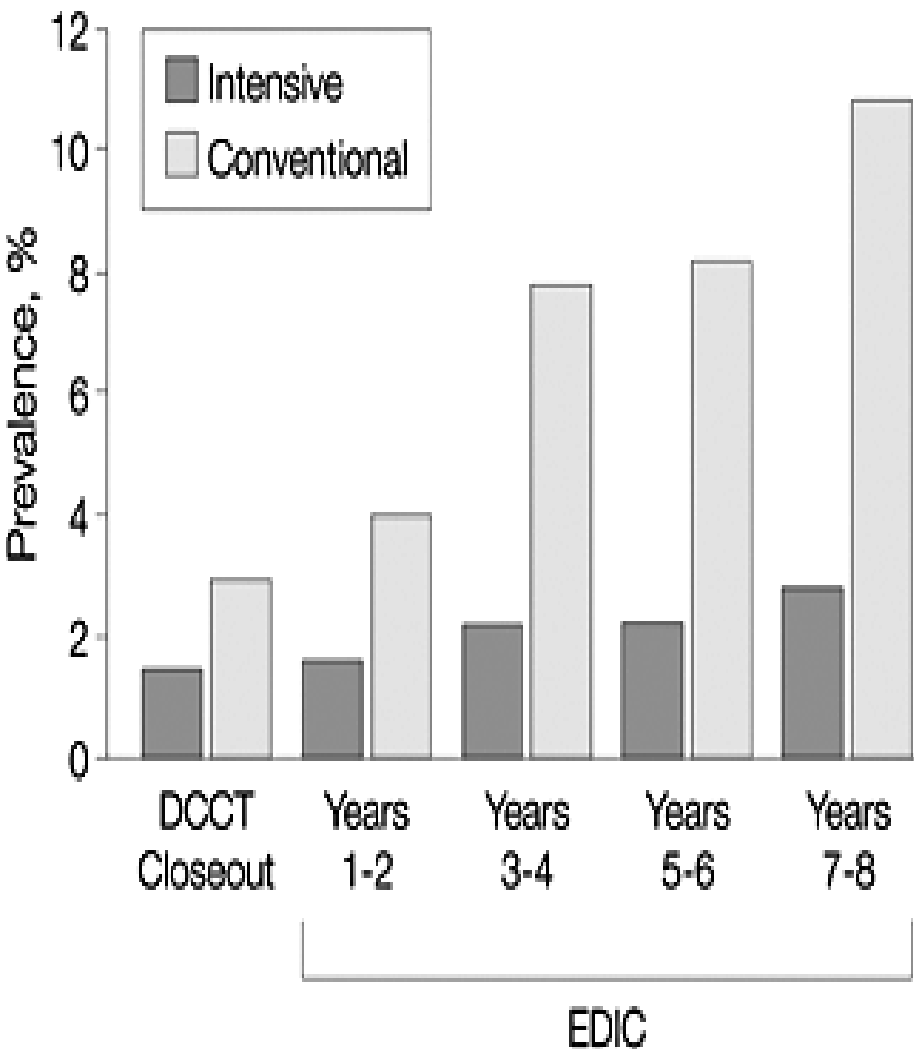


B Cumulative Incidence

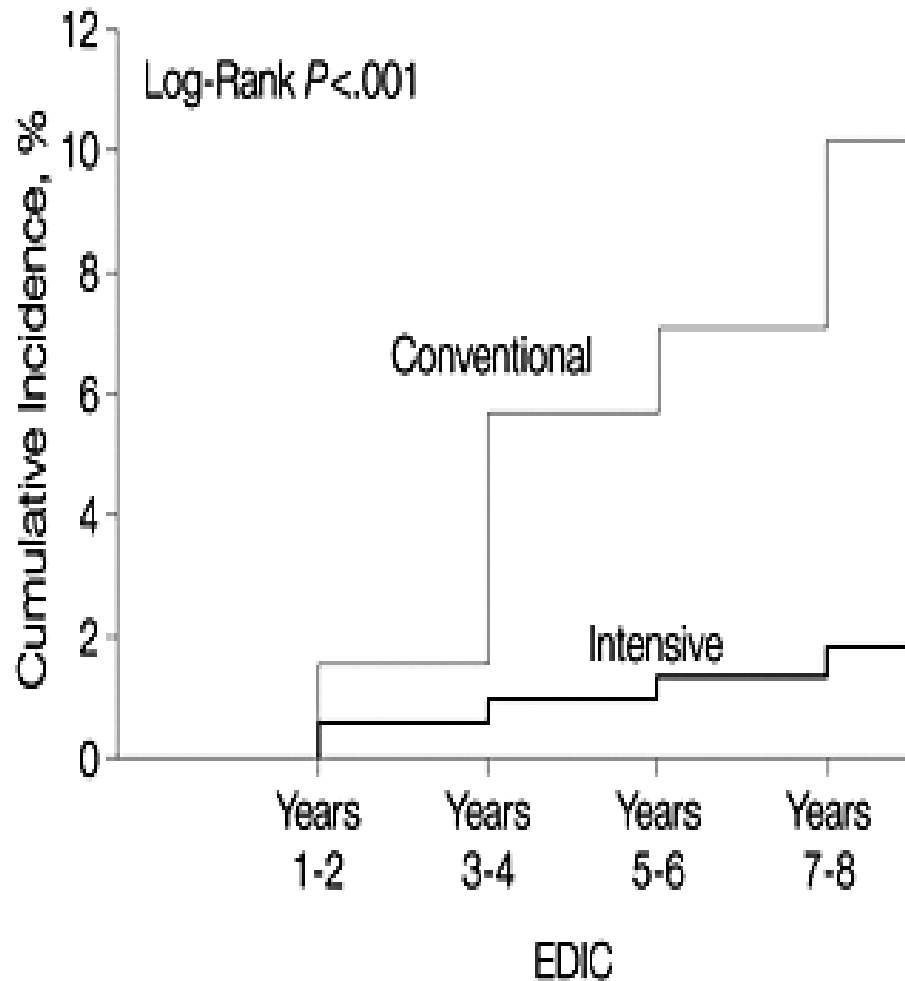


No. at Risk	Years 1-2	Years 3-4	Years 5-6	Years 7-8
Conventional	586	545	509	480
Intensive	626	609	586	576

A Annual Prevalence



B Cumulative Incidence

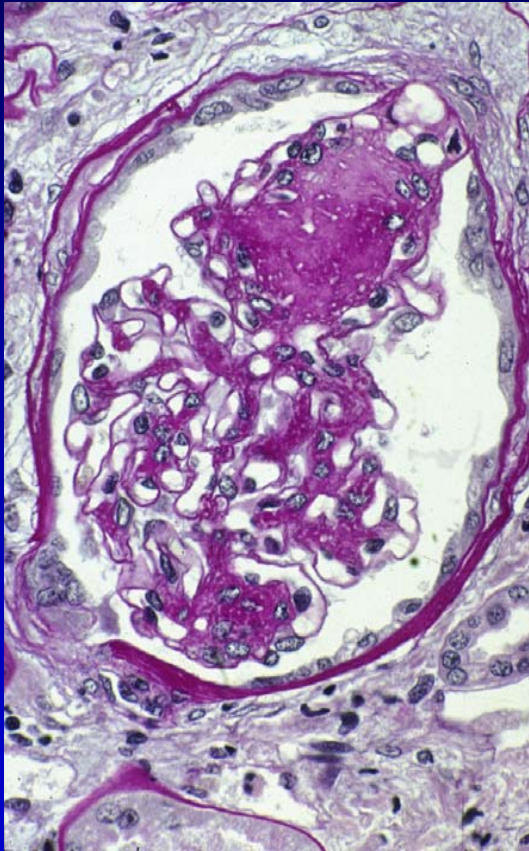


No. at Risk

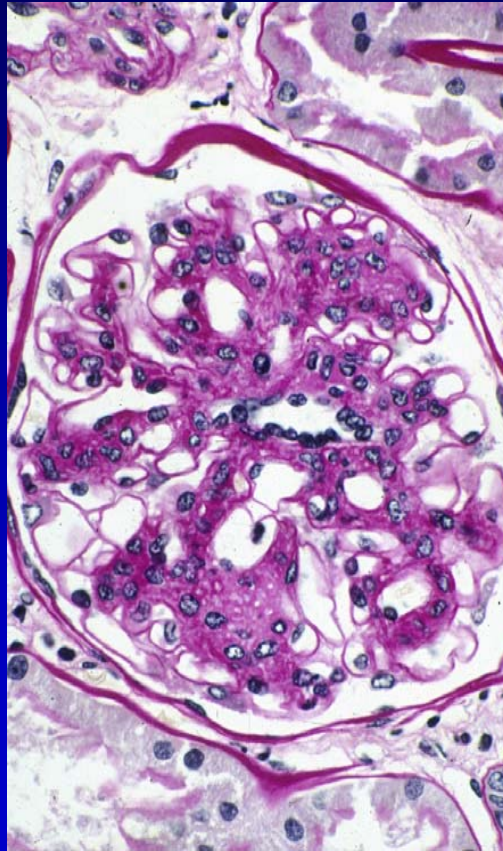
Conventional	653	643	615	607
Intensive	666	661	660	658

Reversal of lesions of diabetic nephropathy after pancreas transplantation

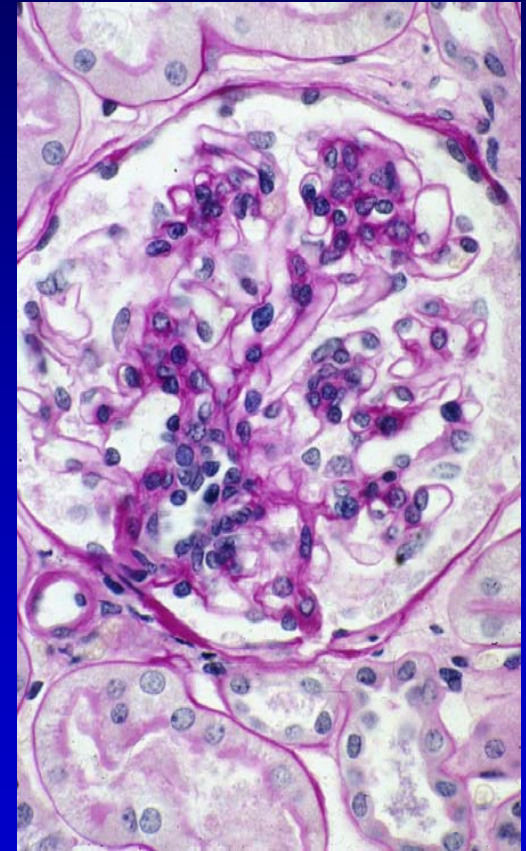
Fioretto P et al., N Engl J Med 1998



baseline



5 years



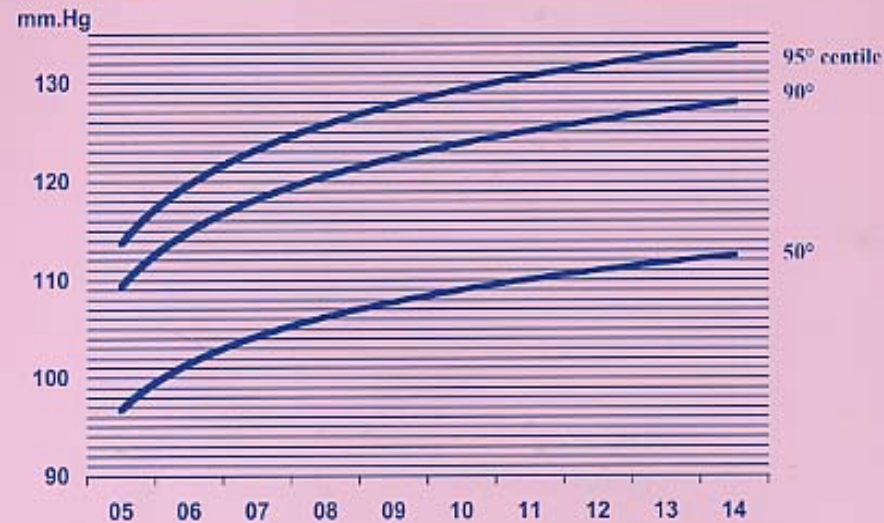
10 years

- **Dietary protein
and sodium intake**

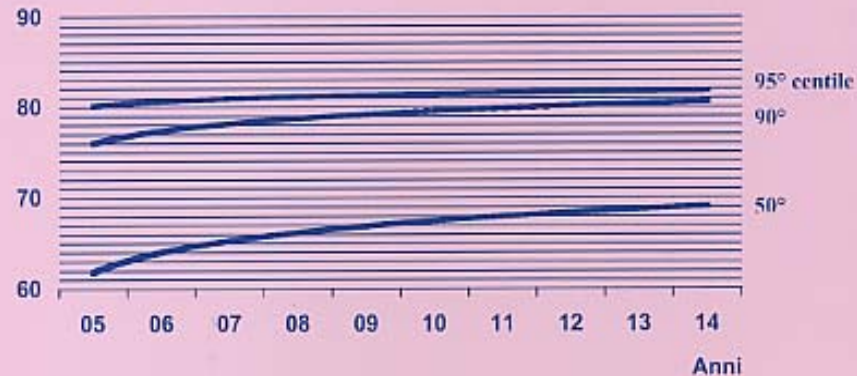
- **Blood pressure control**

FEMMINE

Sistolica



Diastolica



Bibliografia essenziale:

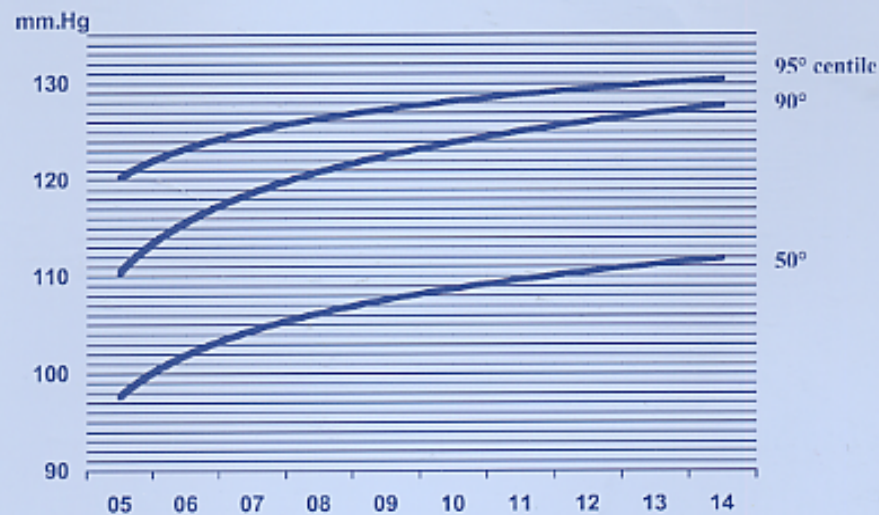
- 1) Menghetti E., Spagnolo A., Strambi M., Virdis R., e colleghi del Gruppo Ipertensione SIP. La pressione arteriosa del bambino: studio multicentrico del Gruppo di studio dell'ipertensione arteriosa della Società Italiana di Pediatria. Riv. Ital. Pediatr. 1998, 24, 1029-1034
- 2) Menghetti E., Virdis R., Strambi M., Patriarca V., Riccioni M.A. and Spagnolo A. on behalf of the 'Study Group on Hypertension' of the 'Italian Society of Pediatrics'. Blood pressure in childhood and adolescence: the Italian normal standards. J. Hypertension 1999, 17: 1-10
- 3) Romano A., La Petina F., Ricotta G., Casella T., Mostaccio L., Pontoriero L., Werth M. L'ipertensione arteriosa essenziale in età pediatrica: alterazioni strutturali del cuore sinistro. Riv. Ital. Pediatria 2002. Vol. 1 - n°4 - 2002, 30-31.

Valori normali e patologici della pressione arteriosa da 5 a 14 anni su 10.678 bambini italiani

A cura del Gruppo di Studio dell'Ipertensione della Società Italiana di Pediatria

MASCHI

Sistolica



Diastolica

Anni	95° centile (mm.Hg)	90° centile (mm.Hg)	50° centile (mm.Hg)
05	80	75	62
06	80	76	63
07	81	77	64
08	81	78	65
09	81	78	66
10	82	79	67
11	82	79	68
12	82	80	68
13	82	80	69
14	83	81	69

dal 90° al 95° centile = ipertensione borderline
oltre il 95° centile = ipertensione franca

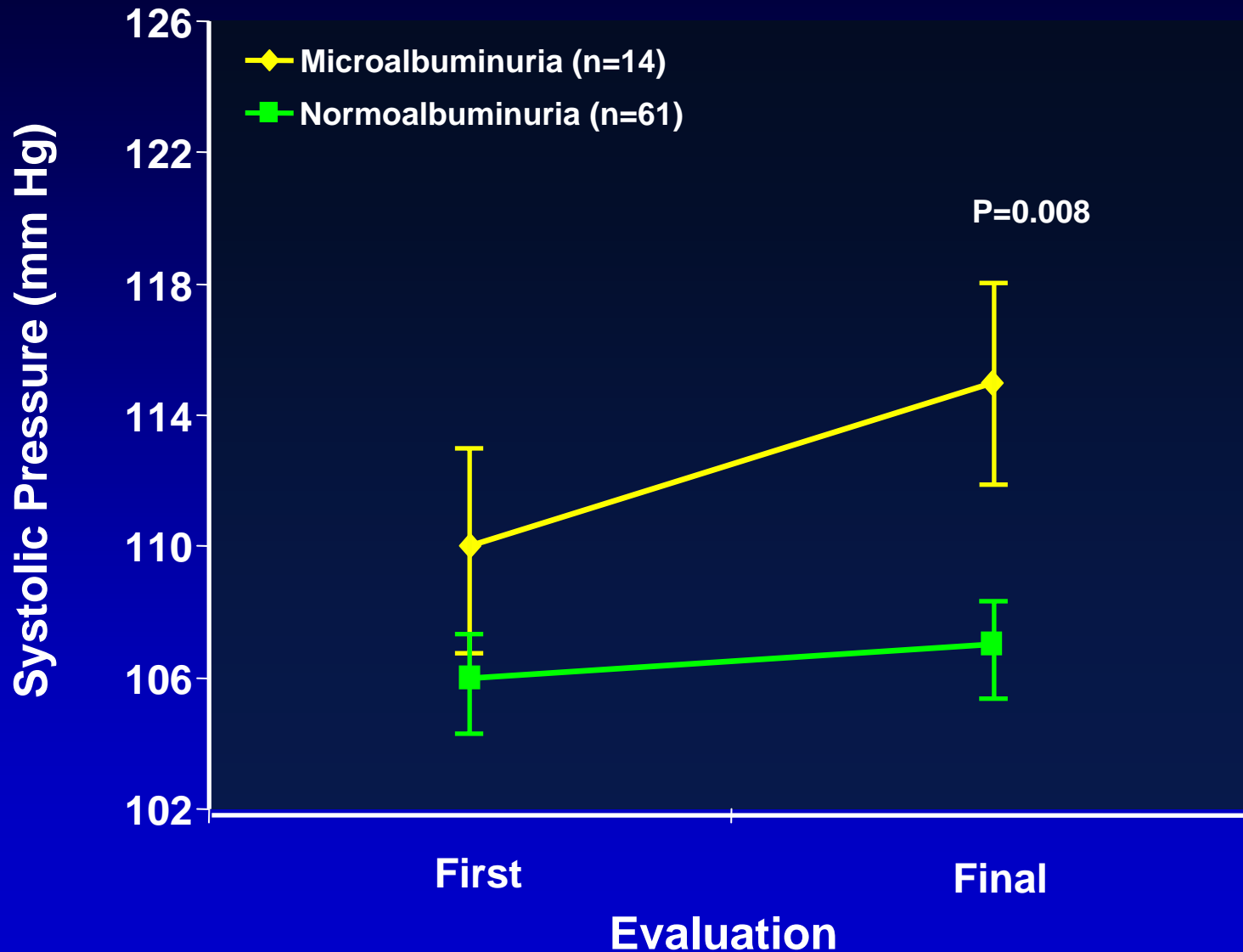
Anni

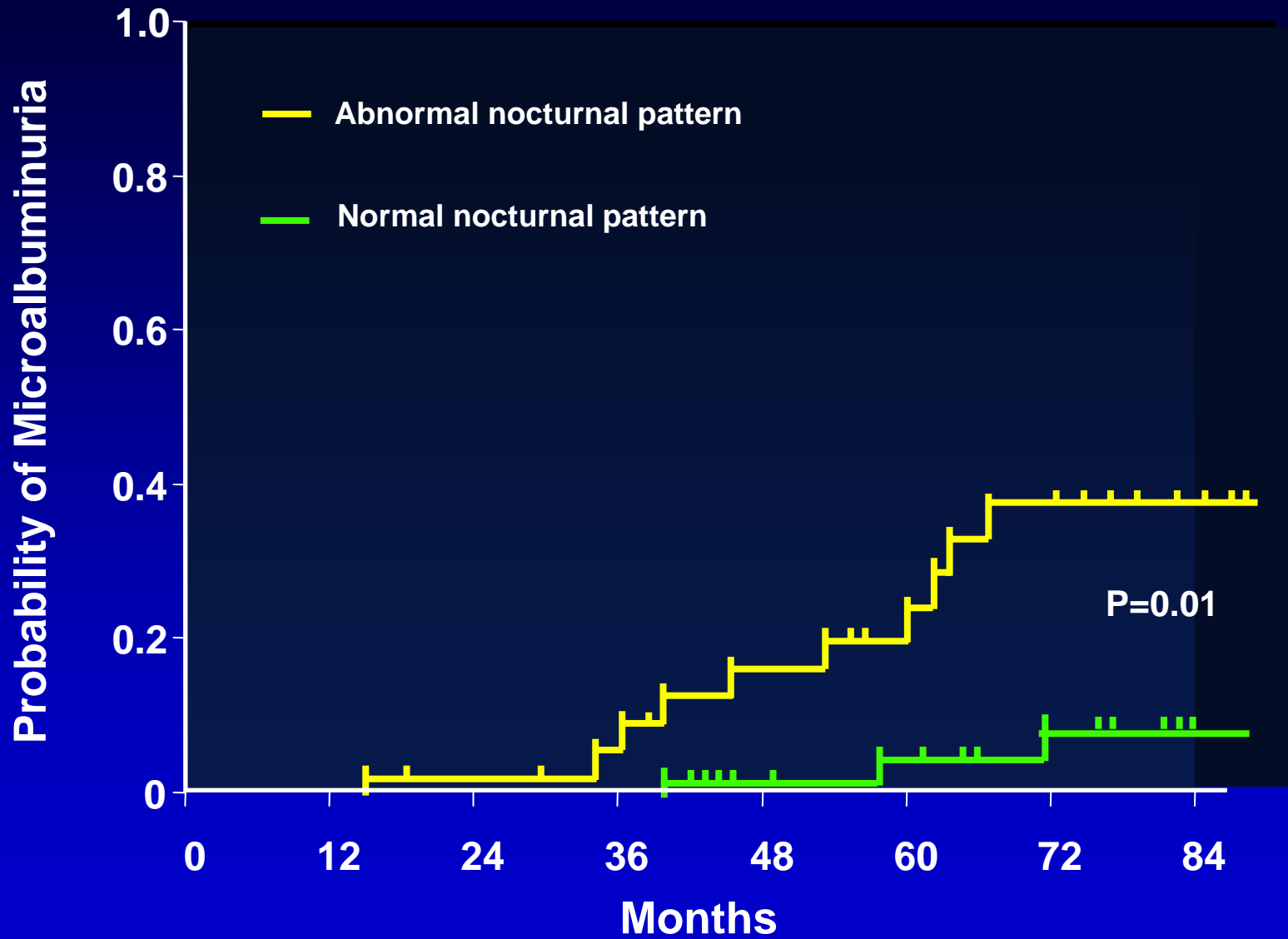
CHILD (**C**hildren with **H**ypertension in **I**taly)

www.italkid.org

child@italkid.org

Systolic blood pressure during sleep





Persistent microalbuminuria (AER 20-50 mg/min/1.73 m²)

Hypertension

Normal BP

**Treat with ACE-I
or All antagonists**

**Improve HbA1c
and reduce DPI for
6-12 months**

Stop smoking!

**No improvement
of AER**

Decreased AER

Wait and see

Target levels for different parameters to prevent CVD in children and adolescents with type 1 diabetes (Diabetologia, September 2005)

Parameter	Target level
HbA_{1c} (DCCT standard)	7.5% without severe hypoglycaemia^a
LDL cholesterol	<2.6 mmol/l
HDL cholesterol	>1.1 mmol/l
Triglycerides	<1.7 mmol/l
Blood pressure	<90th percentile by age, sex and height
BMI	<95th percentile (non-obese)
Smoking	None
Physical activity	>1 h of moderate physical activity daily
Sedentary activities	<2 h daily
Healthy diet	Caloric intake appropriate for normal growth; fat <30% of caloric intake, saturated fat <10% of caloric intake; fibre intake 25–35 g daily; increased intake of fresh fruit and vegetables

^a Different targets may be appropriate in toddlers and preschool children <6 years of age (HbA_{1c} <8.5%) and school children 6–12 years of age (HbA_{1c} <8%) (greater risk of severe hypoglycaemia)

Suggested threshold values for different parameters for intervention and the primary prevention of CVD in children and adolescents with type 1 diabetes

Threshold value

Type of intervention

• Blood pressure

- > 90th percentile for age, gender and height Lifestyle intervention
- > 90th percentile despite lifestyle intervention ACE inhibitor or AIIRA
- > 95th percentile Lifestyle intervention + ACE inhibitor or AIIRA

• LDL cholesterol

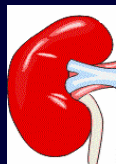
- > 2.6 mmol/l Dietary intervention
- > 4.1 mmol/l and no other CVD risk factors Statins (?)
- > 3.4 mmol/l and one or more CVD risk factor Statins (?)

Reducing the Risk of Diabetes Complications Is ... Essential

Leading cause of blindness in working age adults



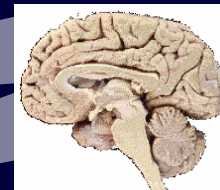
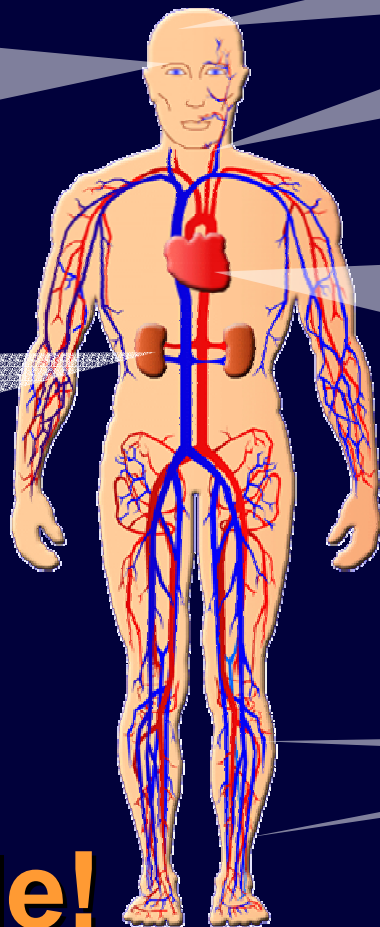
Diabetic Retinopathy



Diabetic Nephropathy

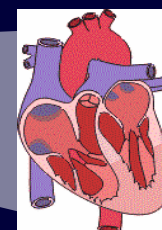
Leading cause of end-stage renal disease

... and Possible!

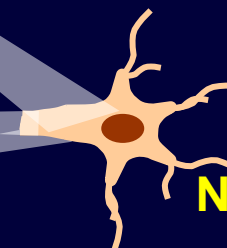


Stroke

2- to 4-fold increase in cardiovascular mortality and stroke



Cardiovascular Disease

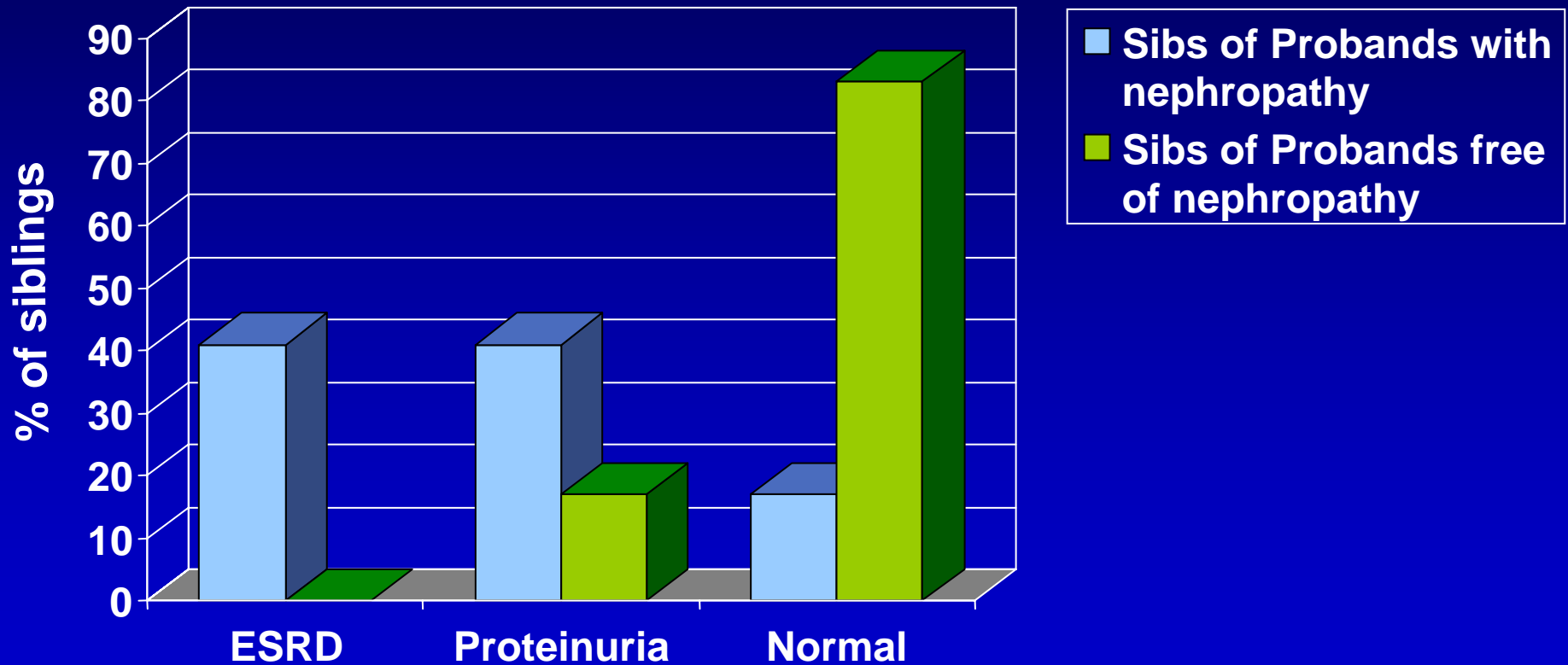


Diabetic Neuropathy

Leading cause of non-traumatic lower extremity amputations

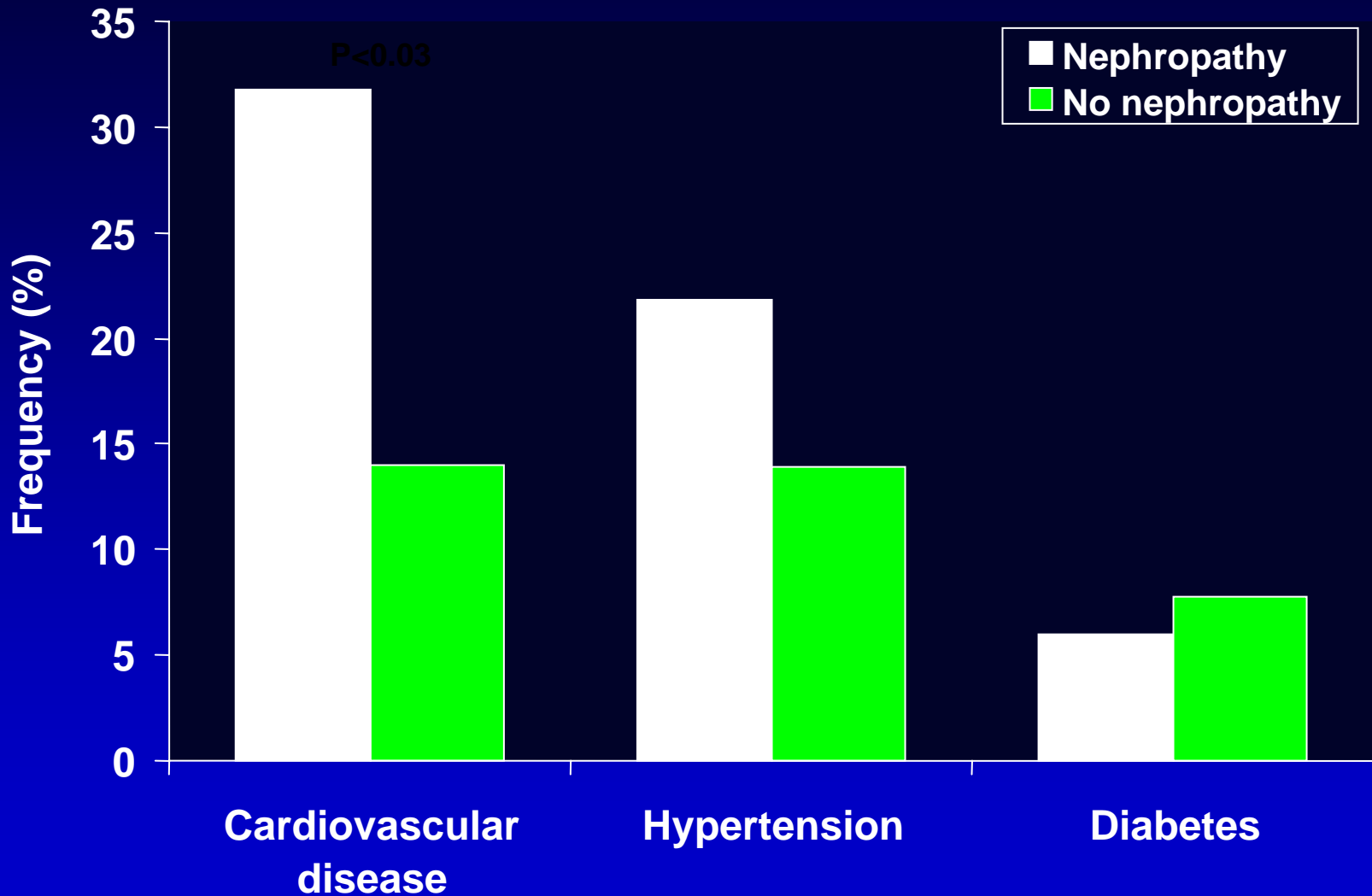
Grazie!

Familial clustering of diabetic nephropathy risk

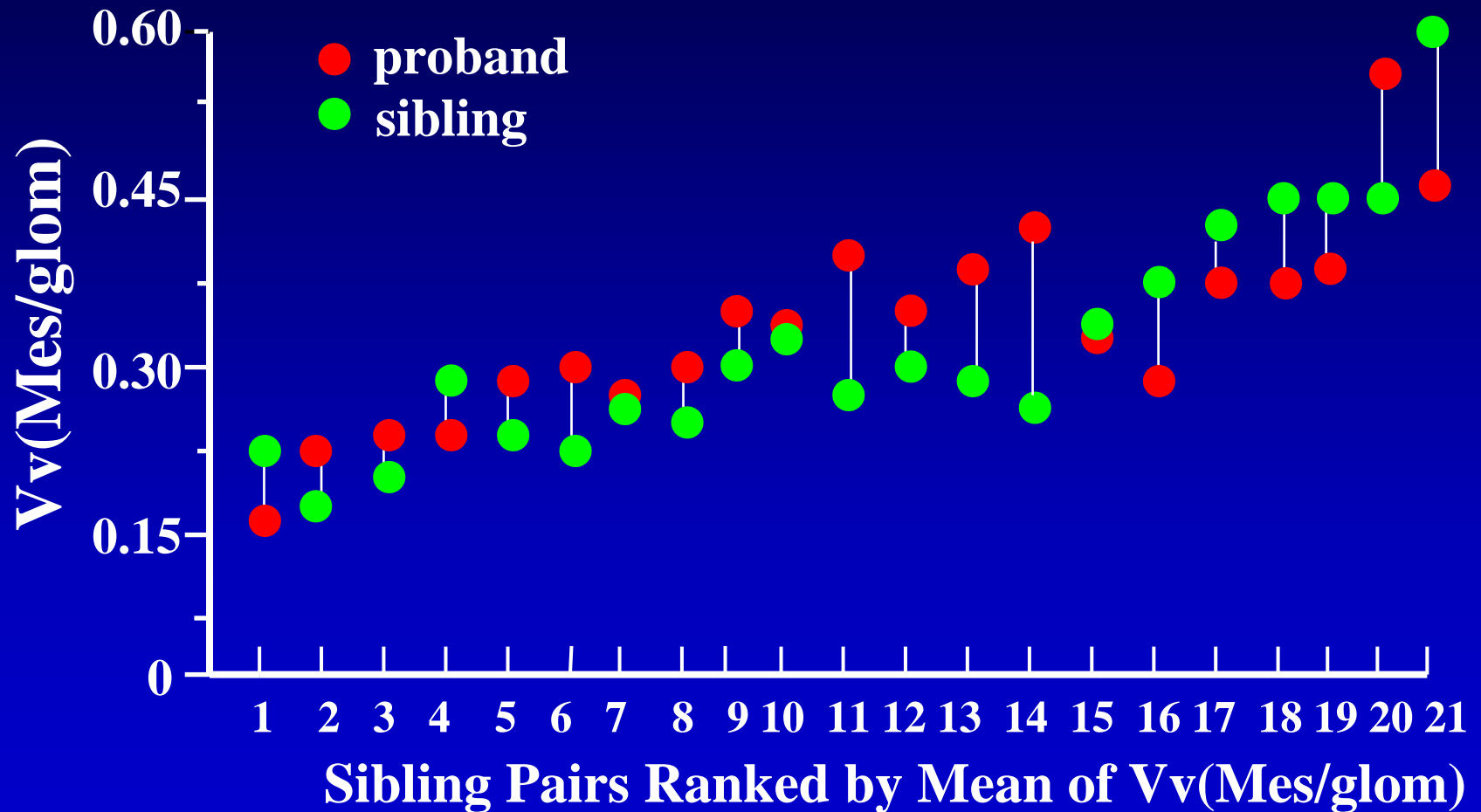


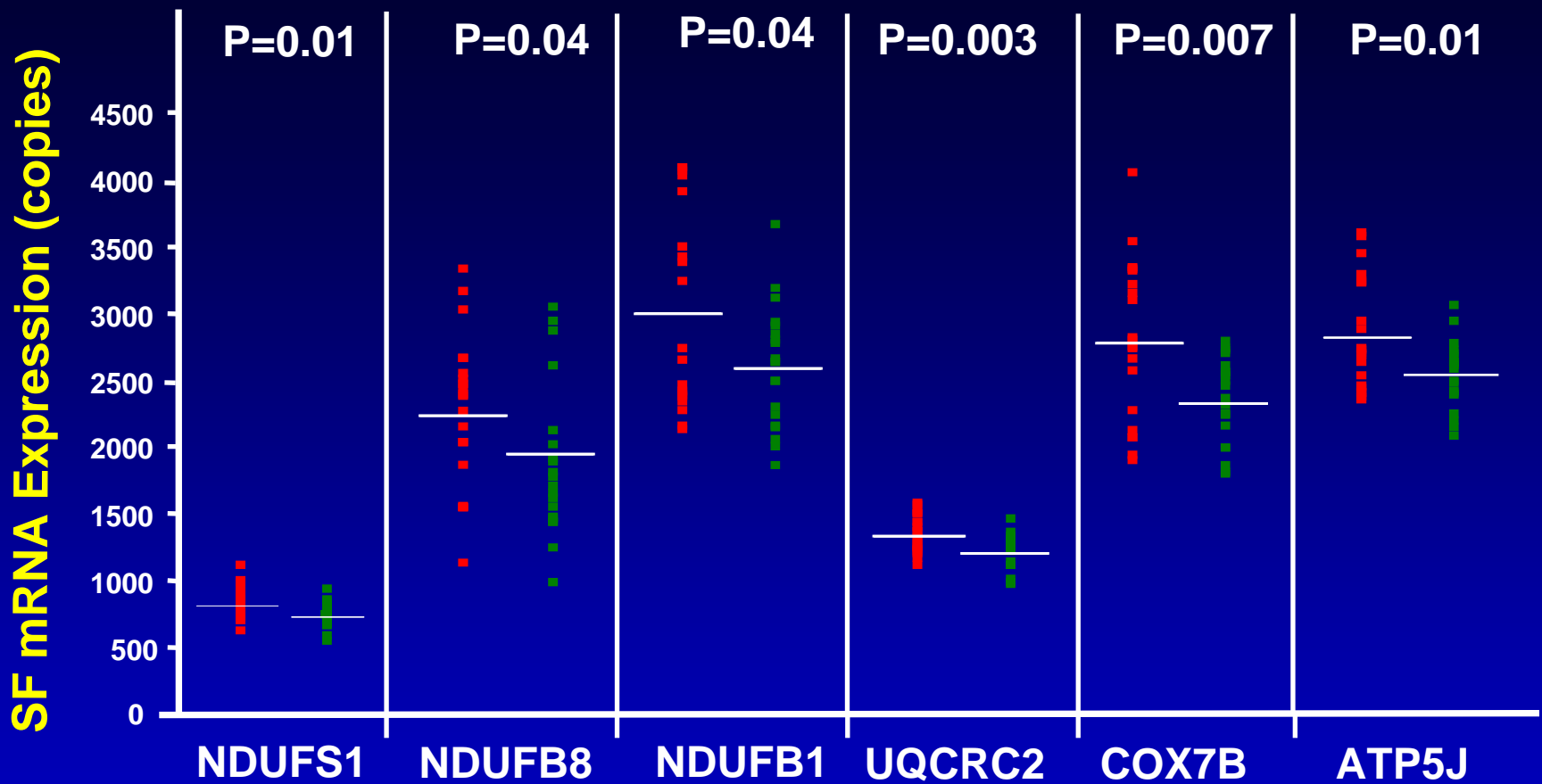
Sequist E et al., New Engl J Med, 1989

Parents of patients with type 1 diabetes



Diabetic Nephropathy Lesions in Siblings with Type 1 Diabetes





Genes encoding oxidative phosphorylation enzymes

NDUFS1=NADH dehydrogenase (ubiquinone) Fe-S protein 1; NDUFB8 = NADH dehydrogenase (ubiquinone) 1 beta subcomplex 8; NDUFB1 = NADH dehydrogenase (ubiquinone) 1 beta subcomplex 1; UQCRC2 = ubiquinol-cytochrome c reductase core protein II; COX7B = cytochrome c oxidase subunit VIIb; ATP5J = ATP synthase H⁺ transporting mitochondrial F₀ complex subunit F6