Epidemiology of complications of diabetes

A) Microvascular

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Complications of Diabetes

Acute complications:

- Diabetic ketoacidosis
- Hyperosmolar coma
- Infections e.g. mucormycosis, TB, septicaemia

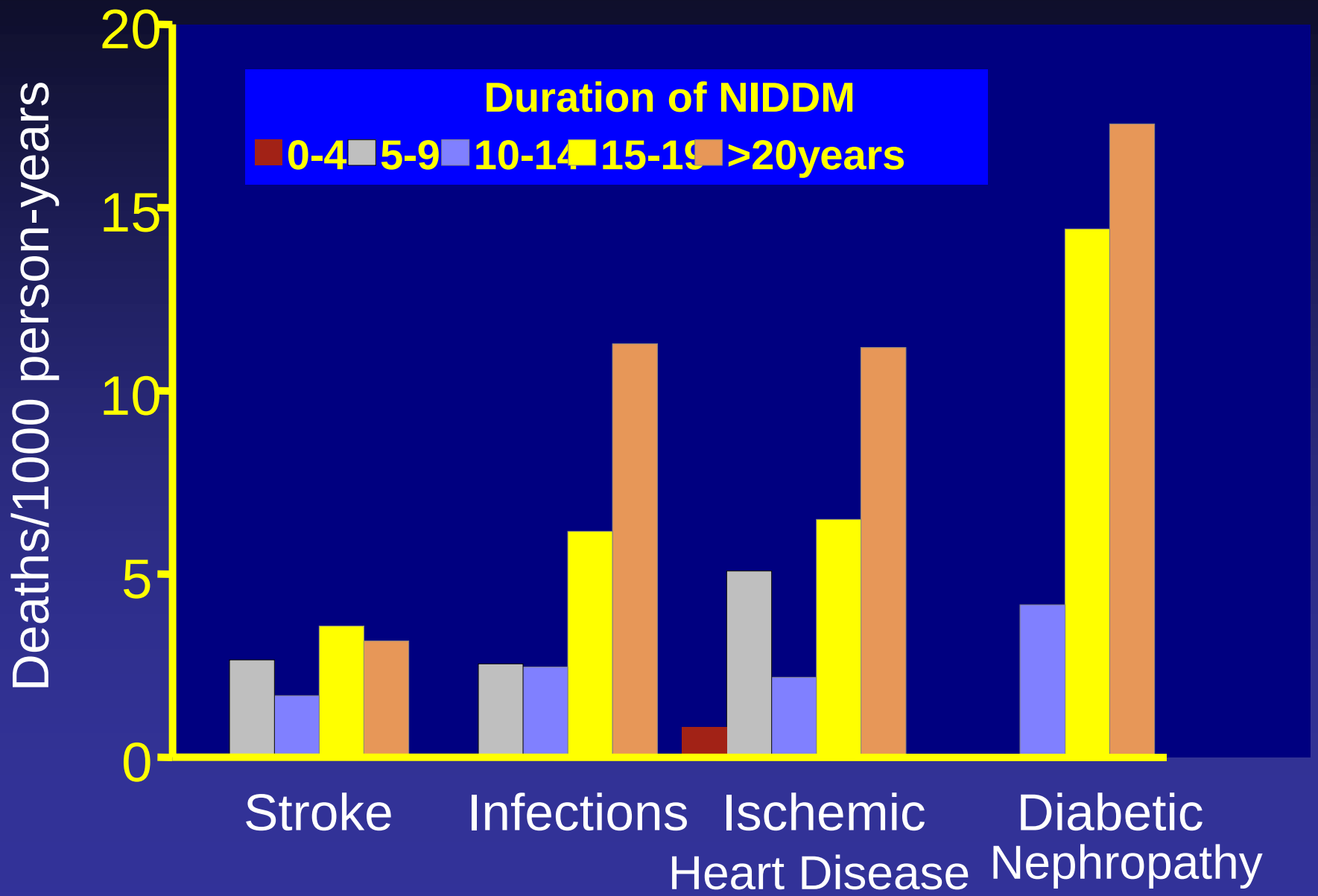
Chronic complications:

- Microvascular
  - Retinopathy
  - Nephropathy
  - Neuropathy
- Macrovascular
  - Cardiovascular
    - Angina
    - Myocardial Infarction
    - Heart failure
  - Cerebrovascular
    - TIA
    - Stroke
  - Peripheral vascular
    - Intermittent claudication
    - Arterial occlusion

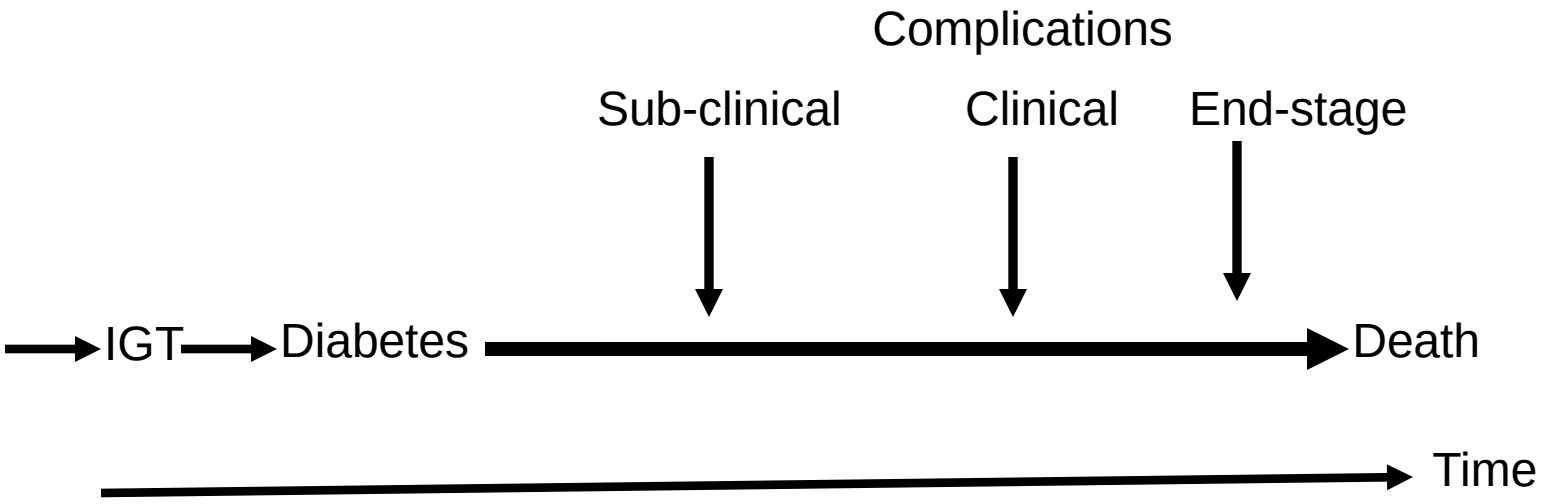
Others:

Periodontal disease, Cognitive decline, Physical disability, cataract, glaucoma

Underlying Cause-specific Death Rates by Duration of Diabetes



Natural history of diabetes



Microvascular complications

Complications	Sub-clinical	Clinical Stage 1	Clinical Stage 2	End Stage
Retinopathy	Occasional microaneurysms	Background or nonproliferative retinopathy	Preproliferative or proliferative retinopathy Macular oedema	Vitreous haemorrhage Retinal detachment Blindness
Nephropathy	Microalbuminuria	Clinical proteinuria	Nephrotic syndrome Renal insufficiency	Uraemia Renal dialysis Renal transplant Death
Peripheral Neuropathy	Abnormal 10g monofilament test Abnormal VPT	Loss of deep tendon reflexes Sensory or motor neuropathy	Focal peripheral neuropathy Amyotrophy	Motor paralysis Paraplegia Charcot joint
Autonomic Neuropathy	Abnormal sweat tests	Cardiac conduction defects (long Q-T interval; loss of R-R variation)	Erectile dysfunction Impotence Postural hypotension	Gastroparesis Nocturnal diarrhoea Sudden death
Diabetic Foot	Abnormal 10g monofilament test Abnormal VPT Loss of peripheral pulses, Reduced blood flow Medial arterial calcification	Sensory neuropathy Callosity Deformity Dry skin, skin fissures Skin atrophy	Diabetic ulcer Cellulitis Osteomyelitis	Tissue necrosis Gangrene Amputation Charcot joint

Retinopathy

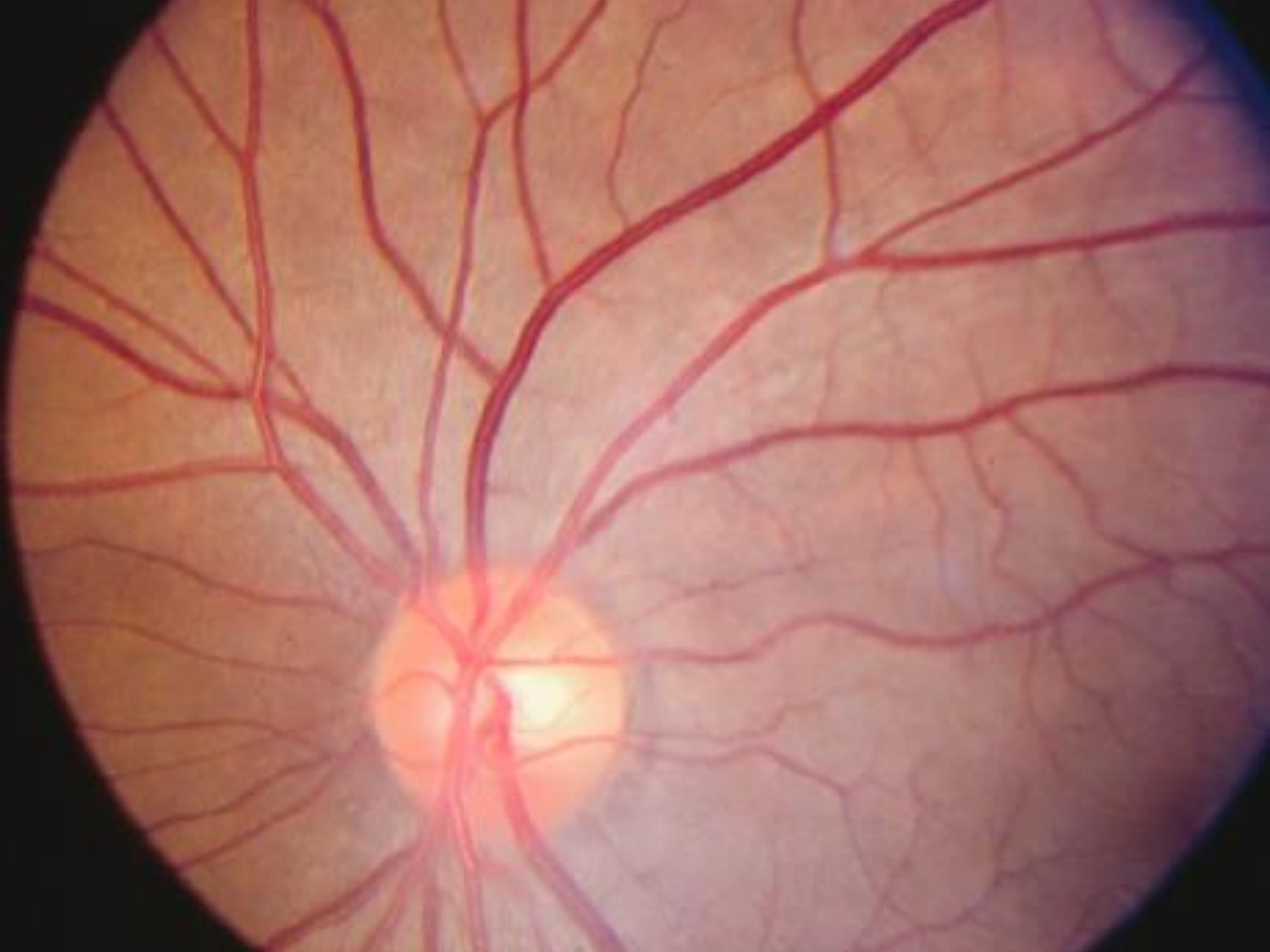
Lesions seen in Diabetic Retinopathy

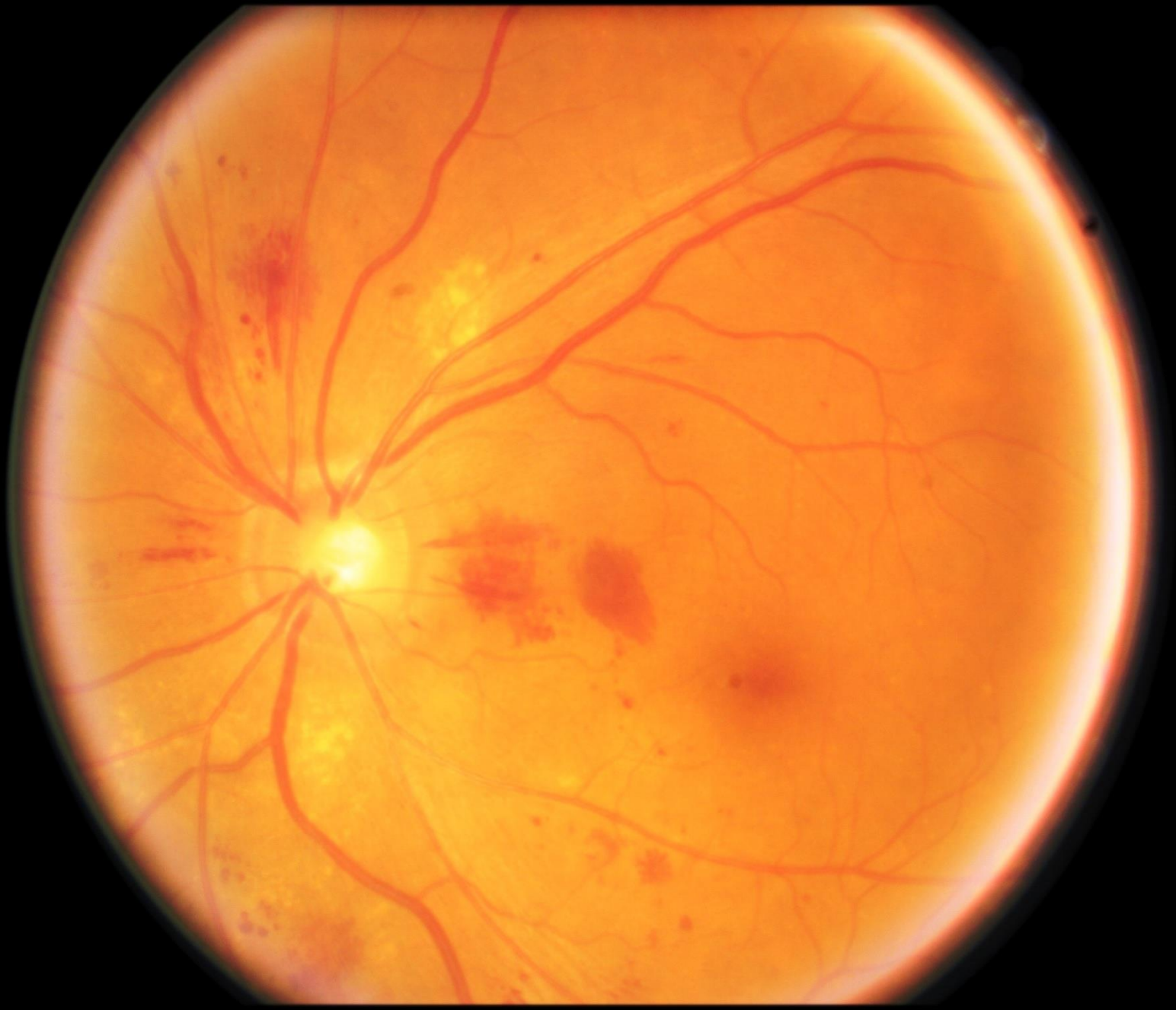
Lesions	Description
Microaneurysms	•small red dots 15-60 μm in diameter
Retinal haemorrhages	•larger red 'dots and blots', regular or irregular in outline, intraretinal, sub-hyaloid, retino-vitreal or vitreal
Hard exudates	•yellow-white opaque retinal deposits
Soft exudates (cotton wool spots)	•pale lesions with blurred borders
Intraretinal microvascular abnormalities (IRMA)	•localised retinal capillary dilatation and tortuosity
New vessels	•single or multiple new vessels growing either into the plane of the retina or into the vitreous body
Rubeosis iridis	•new vessels growing in the iris
Venous beading	•segmented dilation of retinal veins
Proliferative retinopathy	•new vessels appearing on surface of retina or optic nerve
Preproliferative retinopathy	•severe non-proliferative retinopathy with multiple soft exudates
Maculopathy	•hard exudates and/or haemorrhage in the macular region
Macular oedema	•thickening of retina in the macular region
Vitreous haemorrhage	•bleeding from new vessels into the vitreous body
Retinal fibrosis	•Fibrotic stands growing either in the plane of the retina or into the vitreous body.
Retinal detachment	•Detachment of the retina from the sclera due to retraction of fibrotic strands

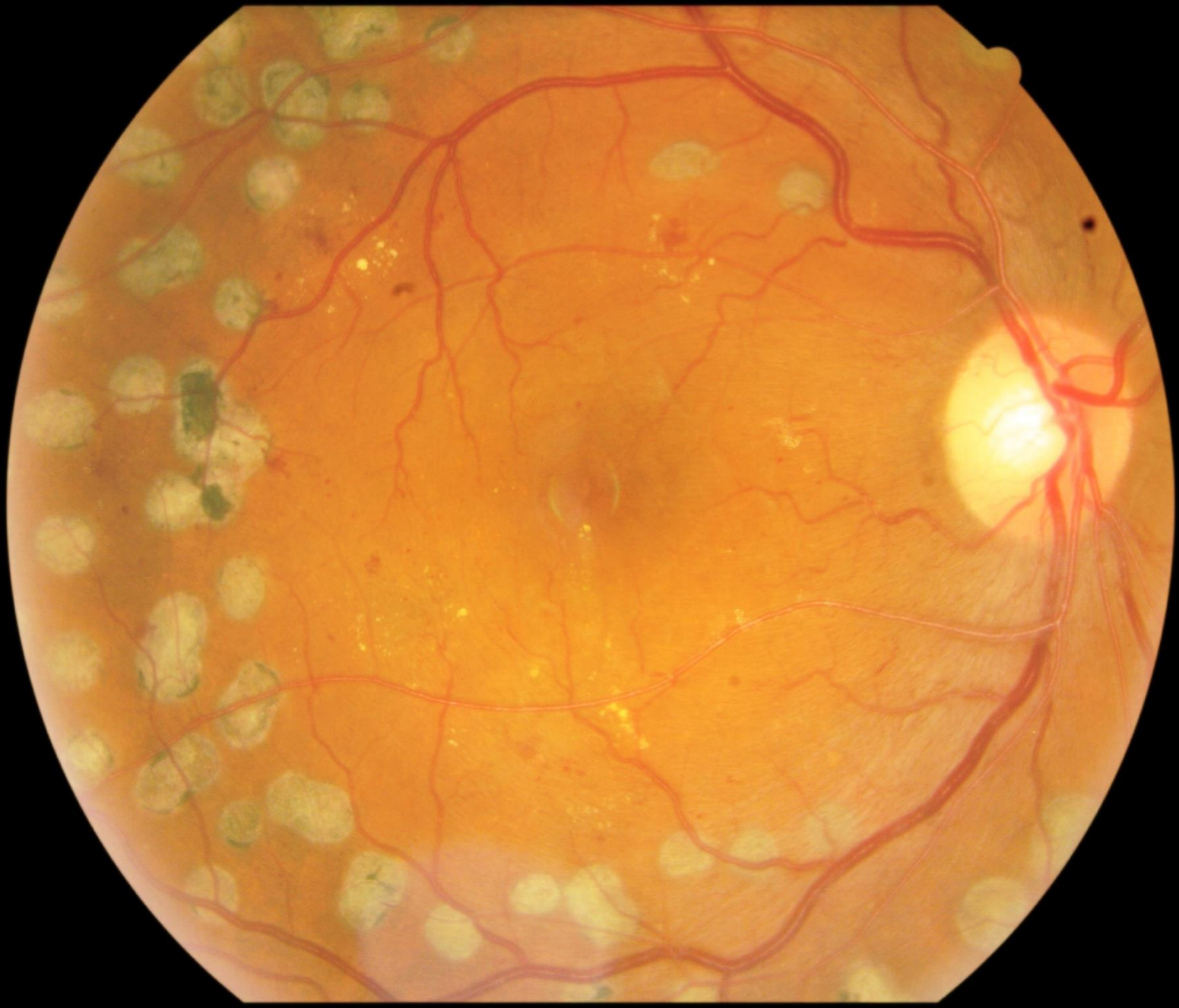
Clinical Stages of Retinopathy

Stage	Description*
Normal	**No visible lesions of diabetic retinopathy** **ETDRS level 10 in both eyes**
Subclinical (minimal)	**Microaneurysms only.** **Level 20 in one or both eyes.**
Clinical stage 1 (mild/moderate)	**Background or non-proliferative retinopathy.** **Levels 35–47 in one or both eyes.**
Clinical stage 2 (severe)	**Preproliferative or proliferative retinopathy** **Macular oedema.**
End stage	**Levels 53,65,71 or 75 in one or both eyes** **Vitreous/preretinal haemorrhage, retinal detachment, blindness.** **Level 85 in one or both eyes.**

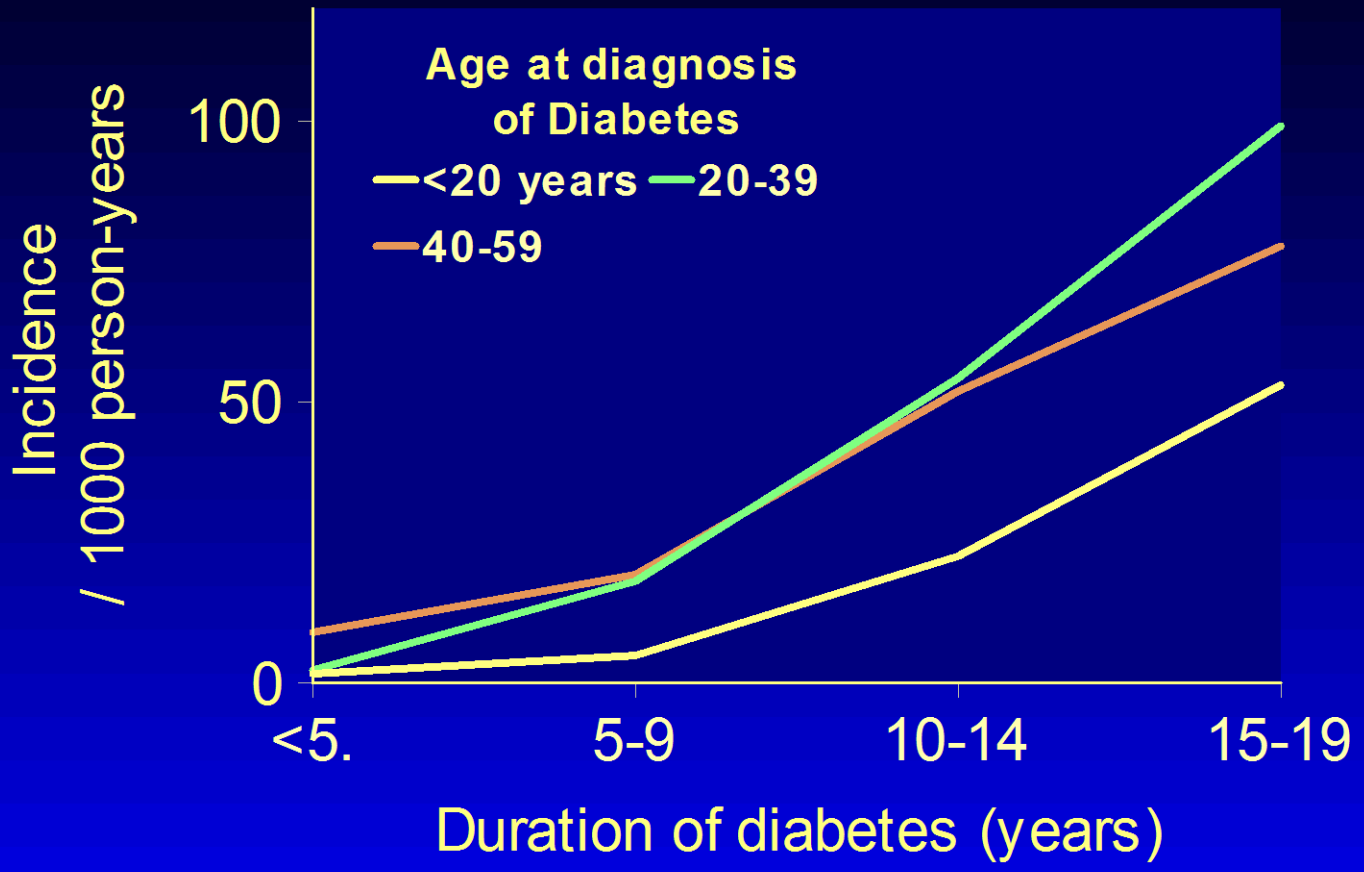
*Level of retinopathy based on the ETDRS scale. See Annex 1 for further detail.



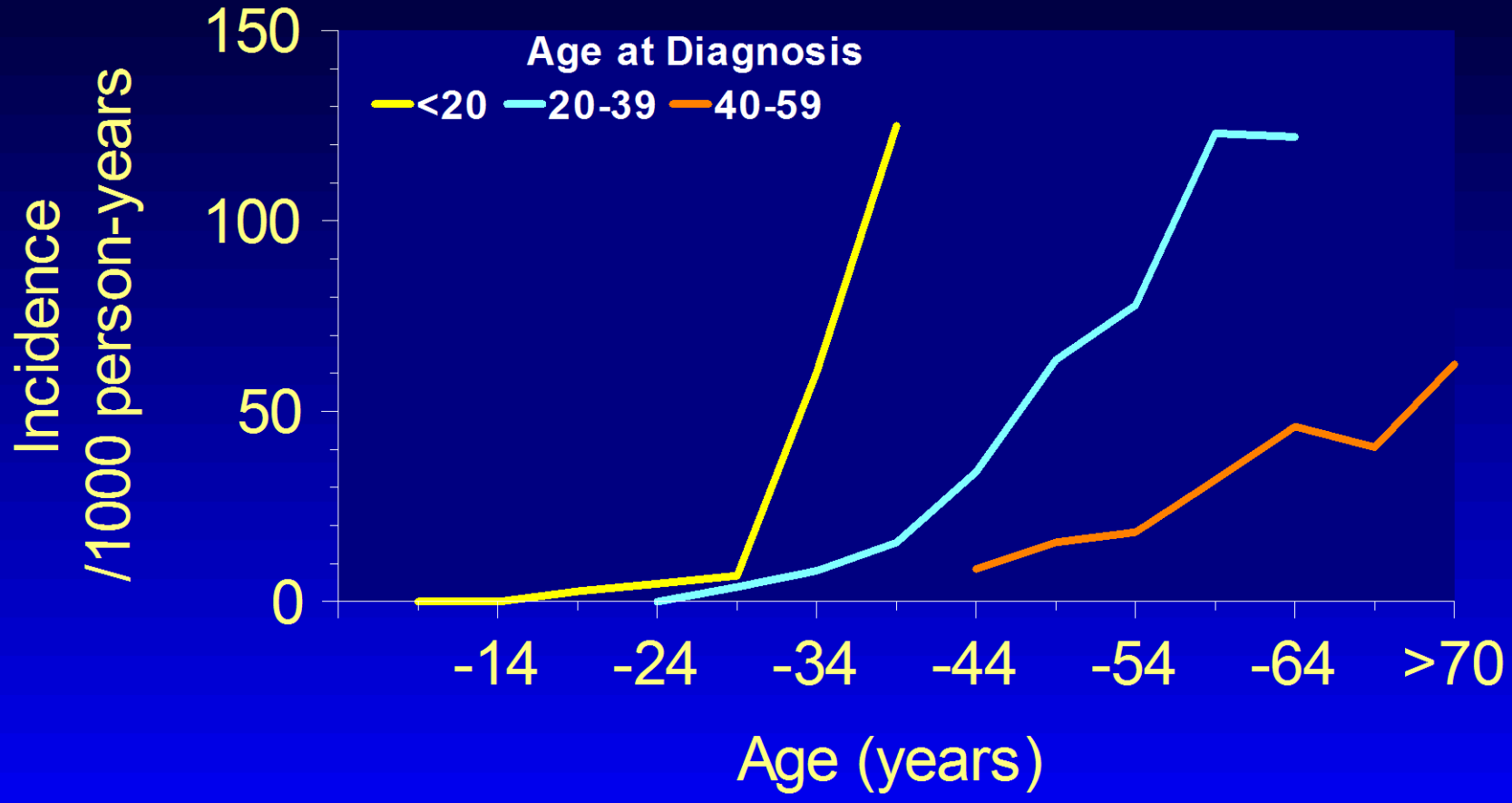




Incidence of Retinopathy in Pima Indians by Age at diagnosis and duration of diabetes

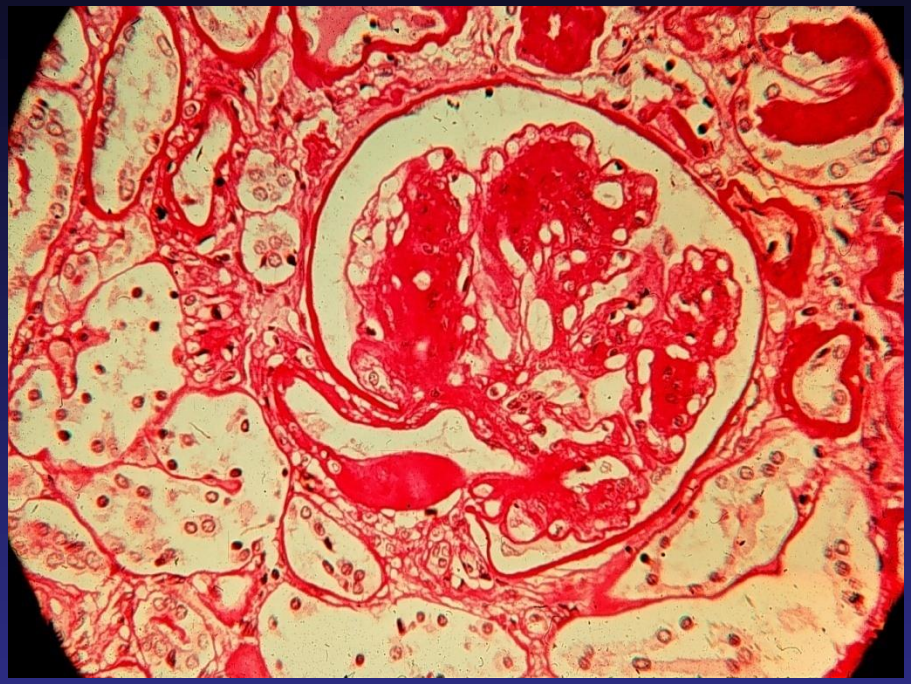


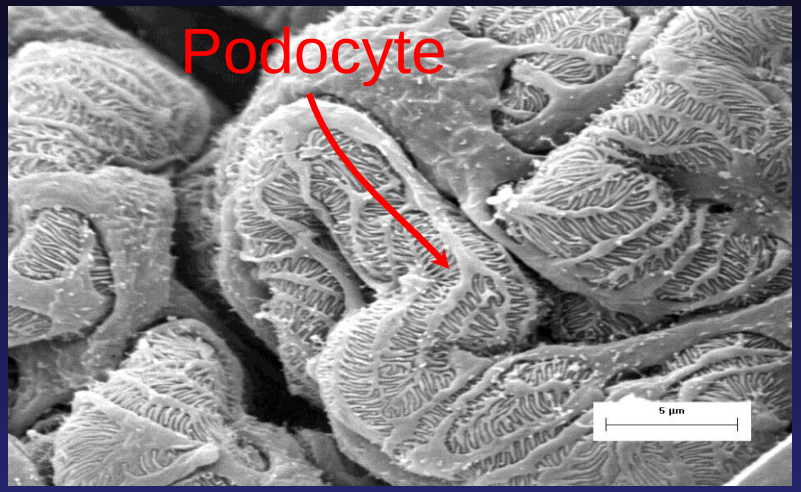
Incidence of Retinopathy by Age at Diagnosis and Attained Age

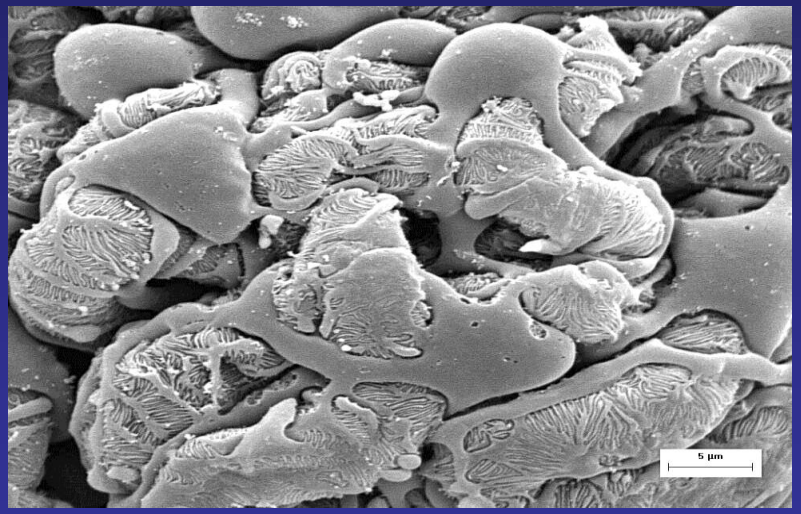


Nephropathy

Diabetic Kidney Disease







Left: diabetic glomerulopathy in a Pima Indian.

Right upper: podocytes on a glomerular capillary in a healthy subject.

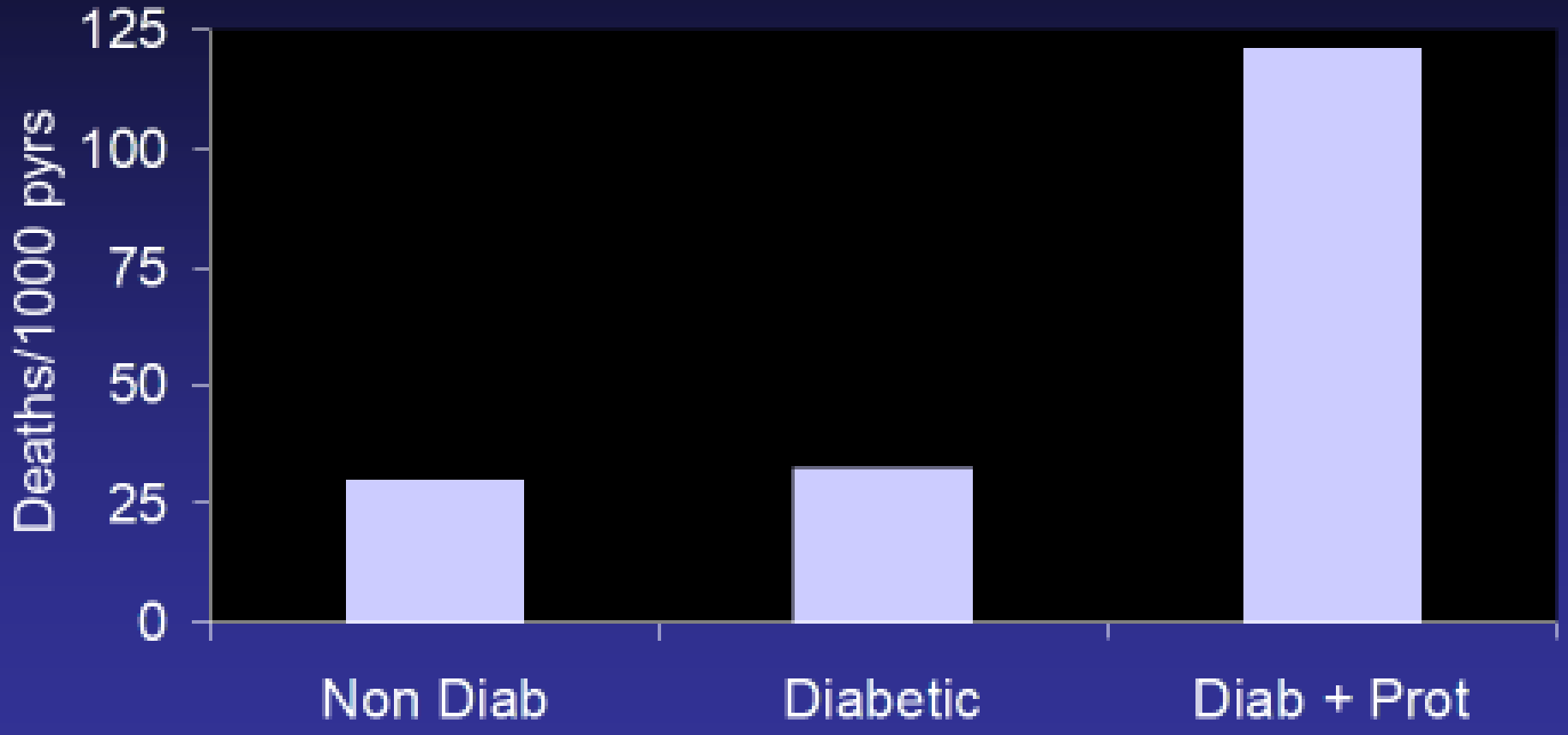
Right lower: podocyte effacement on a glomerular capillary in a diabetic subject.

Table 5.3 Clinical Stages of Nephropathy*

Subclinical (minimal)	Increased urinary albumin excretion (30-300 mg/day)
Clinical stage 1 (mild/moderate)	Clinical proteinuria (serum creatinine in normal range; eGFR >60ml/min/1.73 m^2)
Clinical stage 2 (severe)	Renal insufficiency or nephrotic syndrome
End stage	Raised serum creatinine or Albuminuria >3g /24h) Serum creatinine > 400 µmol/L (4.5mg/dl) or on renal replacement therapy

*Non-diabetic renal disease should be suspected if diabetic retinopathy is absent.

Death Rates in Pima Indians ≥45 Years Old



Diabetes 37:1499-1504, 1988

Definitions in Diabetic Nephropathy

Clinical Stage	Urinary albumin excretion	Albumin:Creatinine ratio	Urinary albumin concentratn.	Serum creatinine
Normal	<30 mg/24h (<20 µg/min)	<30 mg/g (<2.5mg/mmol in men; <3.5mg/mmol in women)	<20 mg/L	<1.4 mg/dl or <110 µmol/L in women; <1.5 mg/dl or <125 µmol/L in men
Microalbuminuria	30-300 mg/24h (20-200 µg/min)	30-300 mg/g (2.5-30mg/mmol in men; 3.5-30mg/mmol in women)	20-200 mg/L	ditto
Macroalbuminuria (clinical proteinuria)	>300 mg/24h (>200 µg/min	>300 mg/g (>30 mg/mmol)	>200 mg/L	ditto
Renal insufficiency				>1.5mg/dl (> 135 µmol/L) in men; >1.4mg/dl (> 125 µmol/L) in women
ESRD				Renal failure requiring renal replacement therapy or serum creatinine > 400 µmol/L (4.5mg/dl)

Stages in Development of Diabetic Renal Disease

Development of :

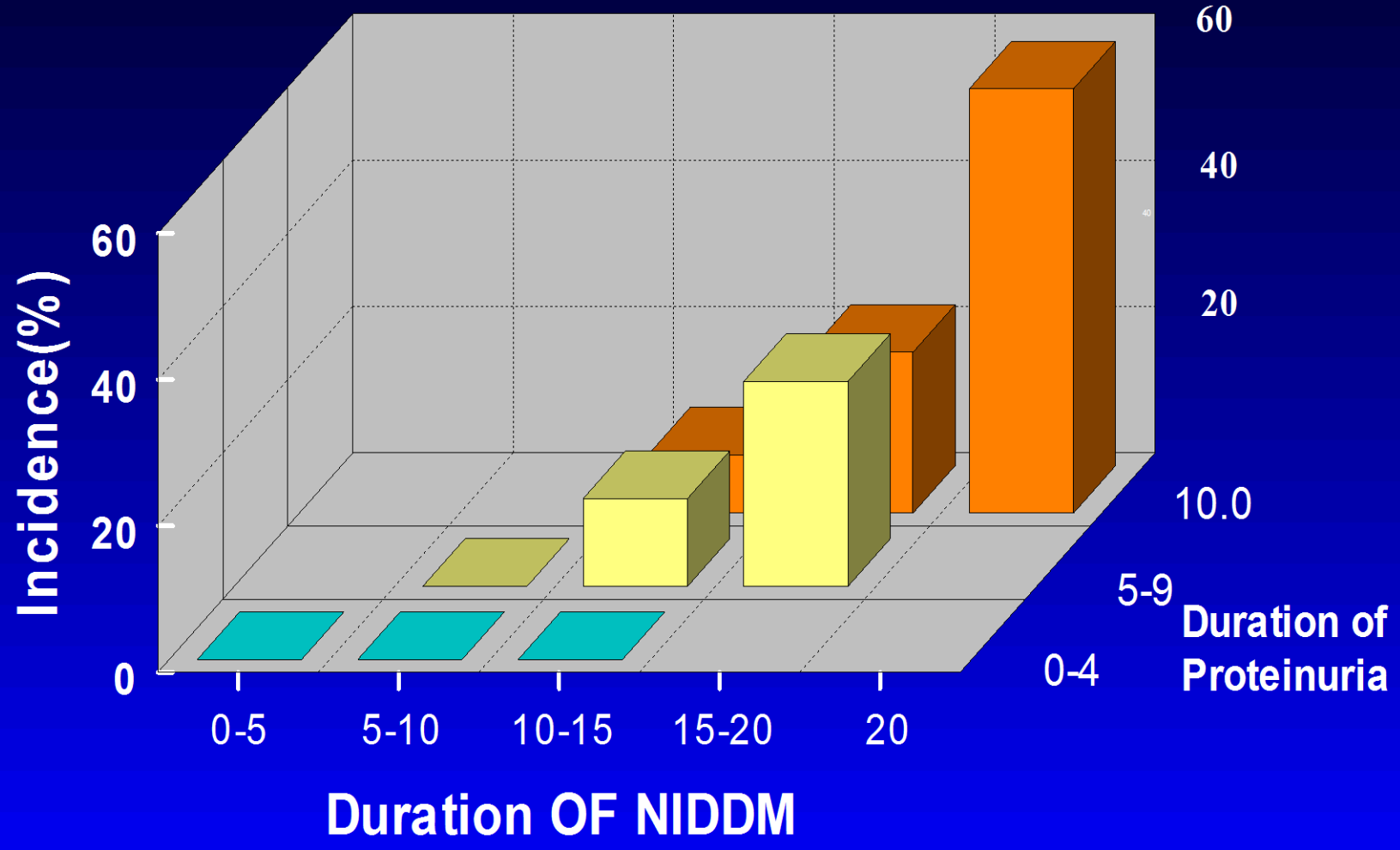
1. Diabetes
2. Microalbuminuria
3. Clinical Proteinuria
4. End-stage Renal Disease

GFR ↑

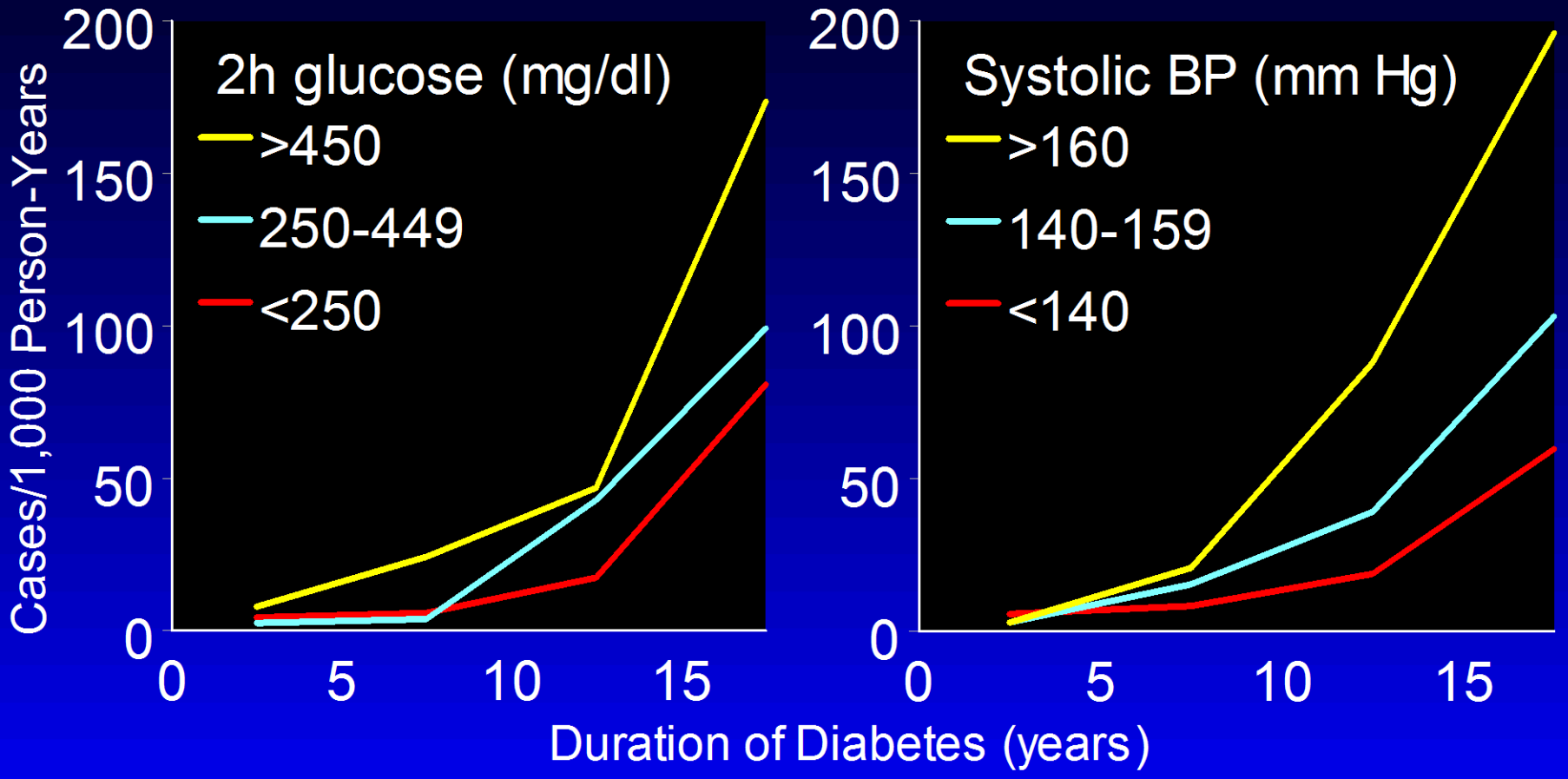
GFR ↓

Cumulative Incidence of ESRD

by Duration of Diabetes and Duration of Proteinuria

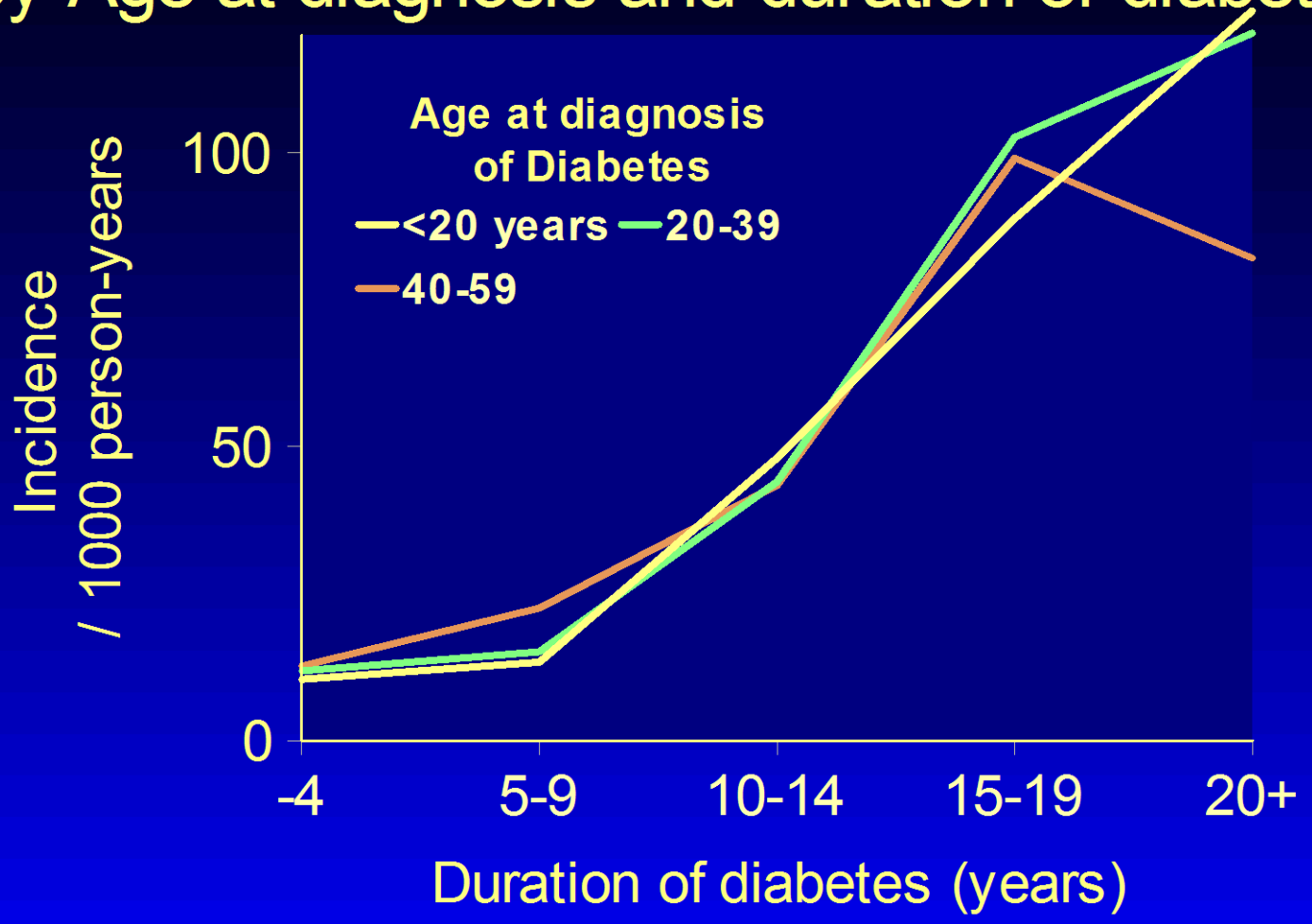


Incidence of Proteinuria by Duration of Diabetes



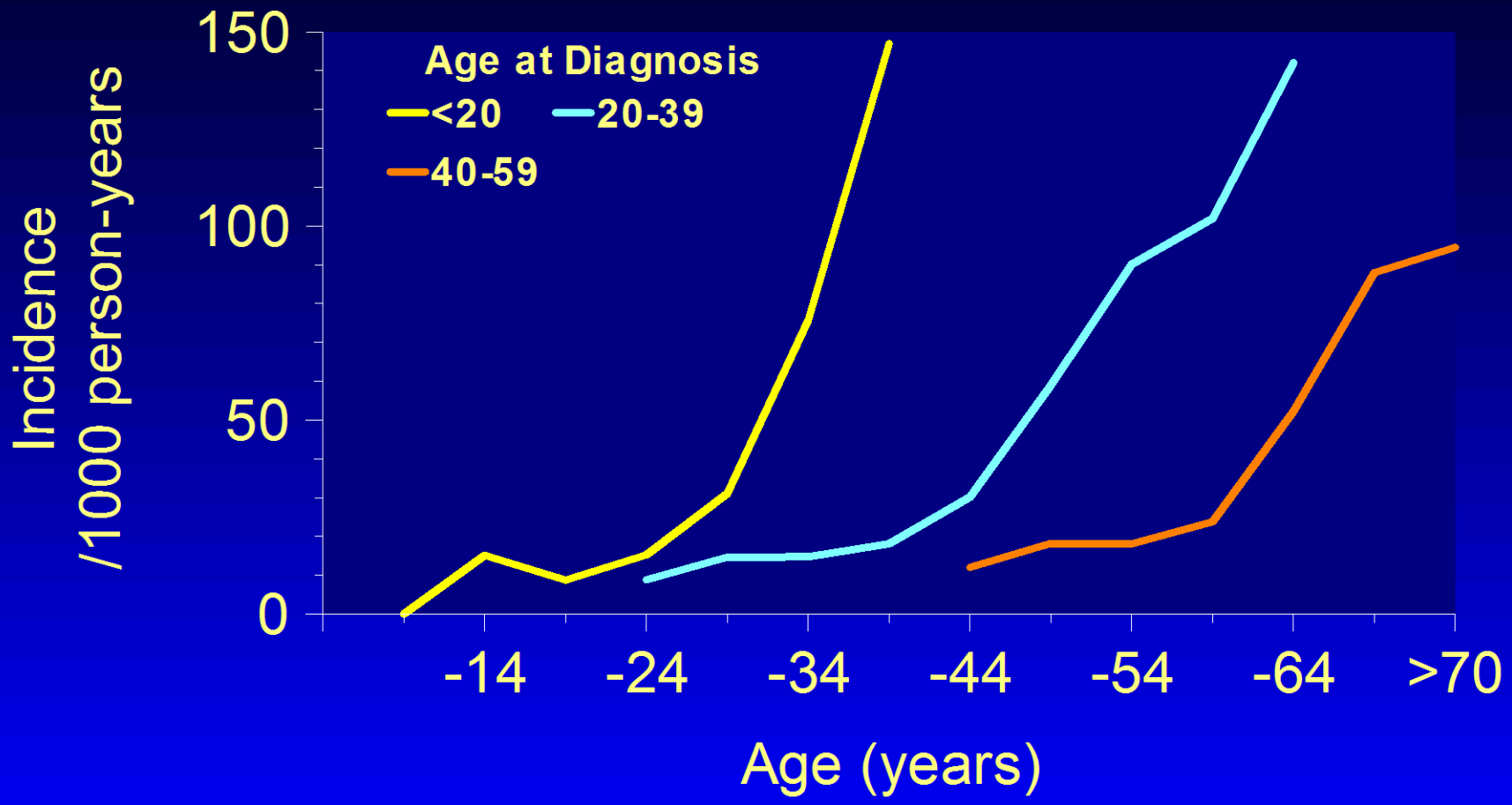
Kidney Int 35:681-687, 1989

Incidence of Nephropathy* in Pima Indians by Age at diagnosis and duration of diabetes

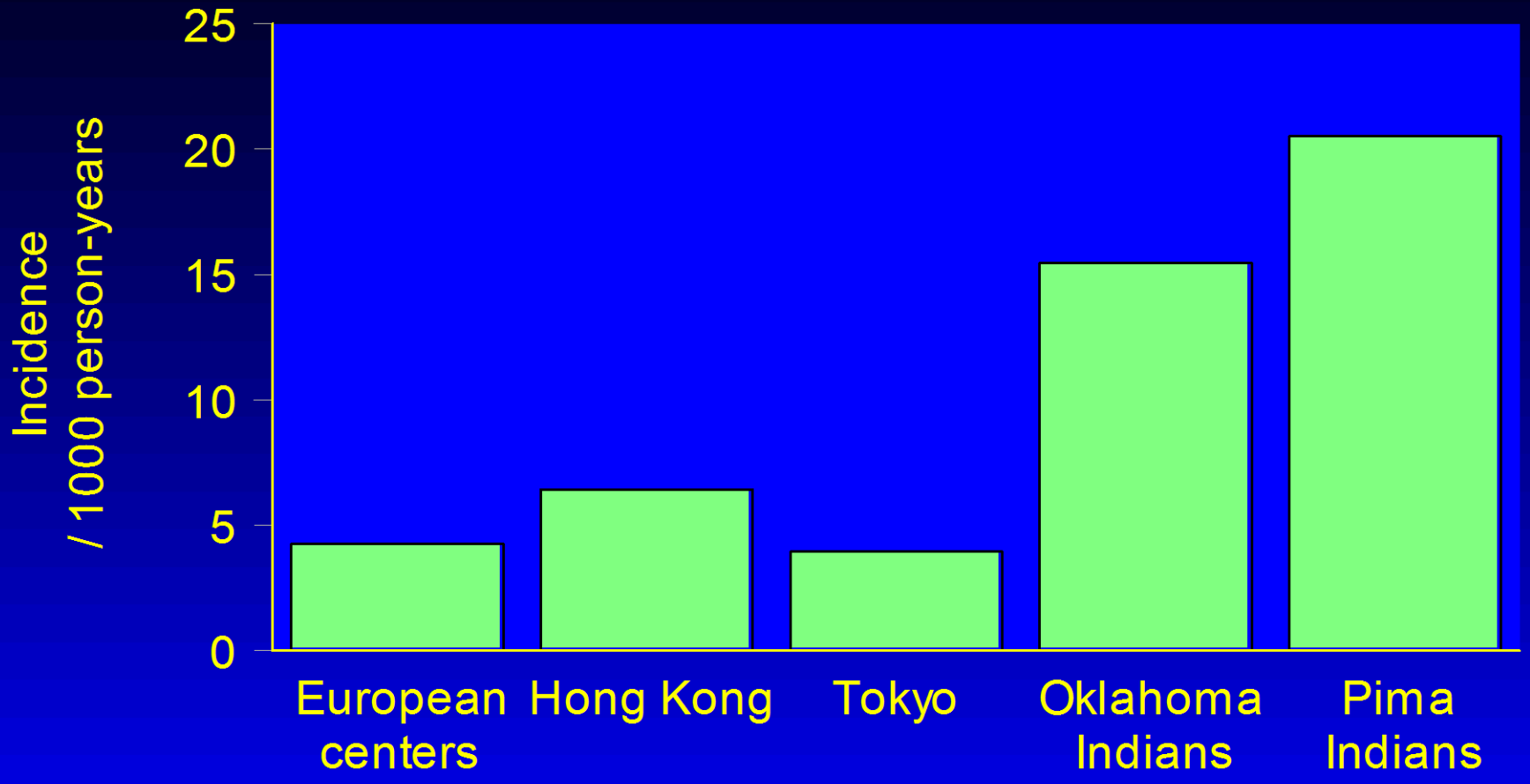


*Urinary protein/creatinine ratio >0.5

Incidence of Nephropathy by Age at Diagnosis and Attained Age



Incidence of renal failure* in Type 2 diabetes
WHO multinational follow-up study



* Renal dialysis or transplant, death from renal failure, or S. creatinine >2.0mg/dl

Lee ET et al. Diabetologia 2000 (in press)

Neuropathy

Table 6.1 Definitions of Diabetic neuropathy and its subtypes

	Definition
Diabetic Neuropathy	**Damage and dysfunction of sensory, motor or autonomic nerves attributable to diabetes**
Sub-types	
Diabetic sensorimotor neuropathy	**Distal, symmetric abnormalities of sensation and progression to motor loss in small muscles of feet and hands**
Diabetic mononeuropathy	**Loss of motor function, sometimes with abnormal sensation or pain, limited to a single nerve distribution**
Diabetic amyotrophy	**Severe, often asymmetrical muscle wasting and weakness of the buttocks and thighs**
Autonomic neuropathy	**Neuropathy involving fibres of the sympathetic and parasympathetic nervous system, affecting the function of many organs**

Table 6.3

Clinical Stages of Diabetic Neuropathy

Subclinical (minimal)	**Electrophysiology – decreased nerve conduction velocity and/or amplitude of evoked muscle or nerve action potential.**
Clinical stage 1 (mild/moderate)	**Reduced vibration, tactile and thermal sensation on quantitative tests. Diminished tendon reflexes*, reduced pain, vibration or touch (cotton /monofilament) sensation. coldness of feet on clinical exam. Decreased beat-to-beat variation in heart rate on standing or deep breathing. Diminished pupillary response to light.. Neuropathic pain/dysaesthesia.**
Clinical stage 2 (severe)	**Absent reflexes, vibration, touch or pain sensation. Postural hypotension. Weakness of small muscles of hands/feet Postural hypotension. History of erectile and ejaculatory dysfunction.**
End stage (Late)	**'Wet' gangrene, Charcot joint, Amputation. Bladder atonia, gastroparesis/diarrhoea.**

* Present only with reinforcement

Table 6.2 Neuropathy: Levels of Ascertainment

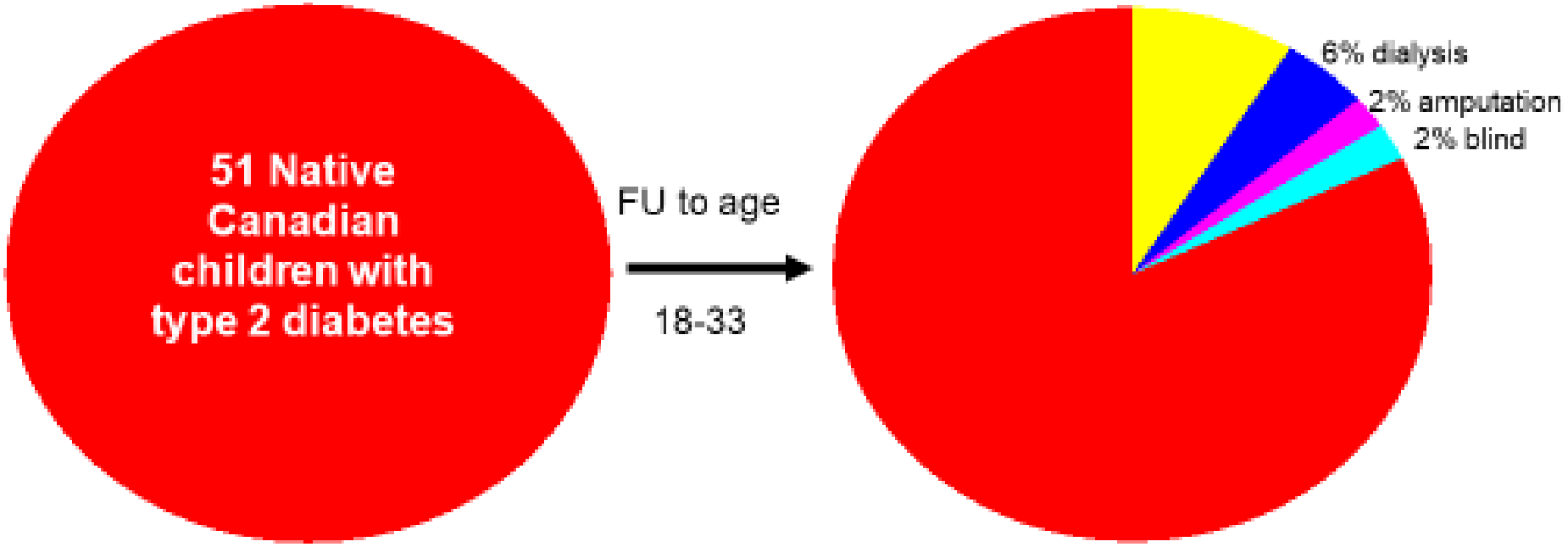
Ascertainment Level	Test
Level 1 (Basic)	**•History : pain, paraesthesiae, numbness, motor weakness, foot lesions, palsies. Autonomic symptoms relating to postural hypotension, nocturnal diarrhea, gastroparesis etc.** **•Examination : skin, muscle wasting, deformity, pulses, temperature, mobility** **•Clinical tests : pin prick, light touch (monofilament or cotton), vibration (tuning fork)** **•Beat to beat variability** **•Postural hypotension** **•Deep tendon reflexes**
Level 2 (Supplementary)	**•Vibration threshold (biosthesiometry)** **•Standard motor nerve conduction velocity tests** **•Beat to beat heart rate variability (ECG)**
Level 3 (Advanced)	**•Full autonomic nerve function tests** **•Evoked nerve potential** **•Pedobarometry** **•Biopsy**

Table 7.2

Diabetic foot: Levels of Ascertainment

Ascertainment Level	Test
Level 1 (Basic)	•History : pain, paraesthesiae, numbness, motor weakness, in foot or leg. Injury. •Examination : nails, skin, callus, fissuring, redness, blisters, ulceration, infection, muscle wasting, deformity, temperature and mobility of feet •Clinical tests : pin prick, light touch (cotton) pressure(monofilament), vibration (tuning fork) •Ankle/brachial blood pressure •Dorsalis pedis and posterior tibial pulses by palpation. •Deep tendon reflexes
Level 2 (Supplementary)	•Vibration threshold (biosthesiometry) •Pulses by Doppler ultrasound. •P-A foot x-ray
Level 3 (Advanced)	•Arteriography •Pedobarometry •Electrophysiology and nerve conduction

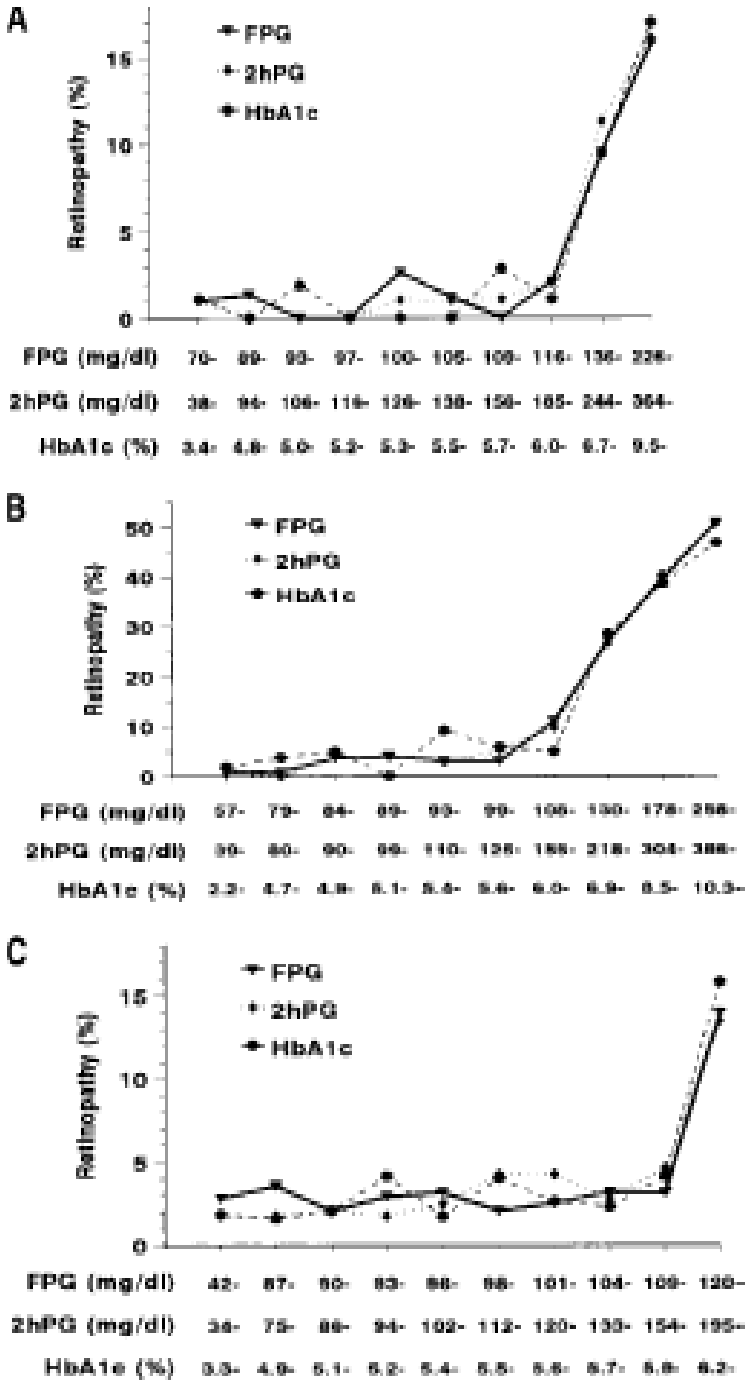
Development of complications in childhood type 2 diabetes



Dean *Diabetes*, 2002

Prevalence of Retinopathy by deciles of FPG, 2hPG and HbA1c in:

A) Pima Indians
B) Egyptians
C) 40-74 year old NHANES participants



International Expert Committee Report on the Role of the A1c Assay in the Diagnosis of Diabetes. Diabetes Care 32:1327-1334, 2009

Risk factors for Diabetic Nephropathy

- Family history of nephropathy
- Ethnicity
- Low birth weight
- Age of onset of diabetes
- Duration of diabetes
- Blood pressure
- Hyperglycemia

Risk Factors for Microalbuminuria or Worse in the UKPDS

485 events of 2588 total in model

Risk factor	Reference	Relative Risk	95% CI	p
Systolic blood pressure	10 mmHg ↑	1.17	1.11 – 1.23	<0.0001
Waist to hip ratio	0.1 ↑	1.13	1.02 – 1.26	0.018
White blood cell	1000 ↑	1.08	1.04 – 1.13	0.0001
HbA1c	1% ↑	1.07	1.01 – 1.13	0.015
Retinopathy	no retinopathy	1.31	1.10 – 1.58	0.003
South Asian ethnicity	white	1.54	1.11 – 2.14	0.01
Afro-Caribbean	white	1.40	0.99 – 1.99	0.06
Triglyceride	doubling	1.34	1.11 – 1.62	0.002

Age and sex adjusted. Male sex was associated with a RR 1.3 (1.02-1.62)

Intervention Trials

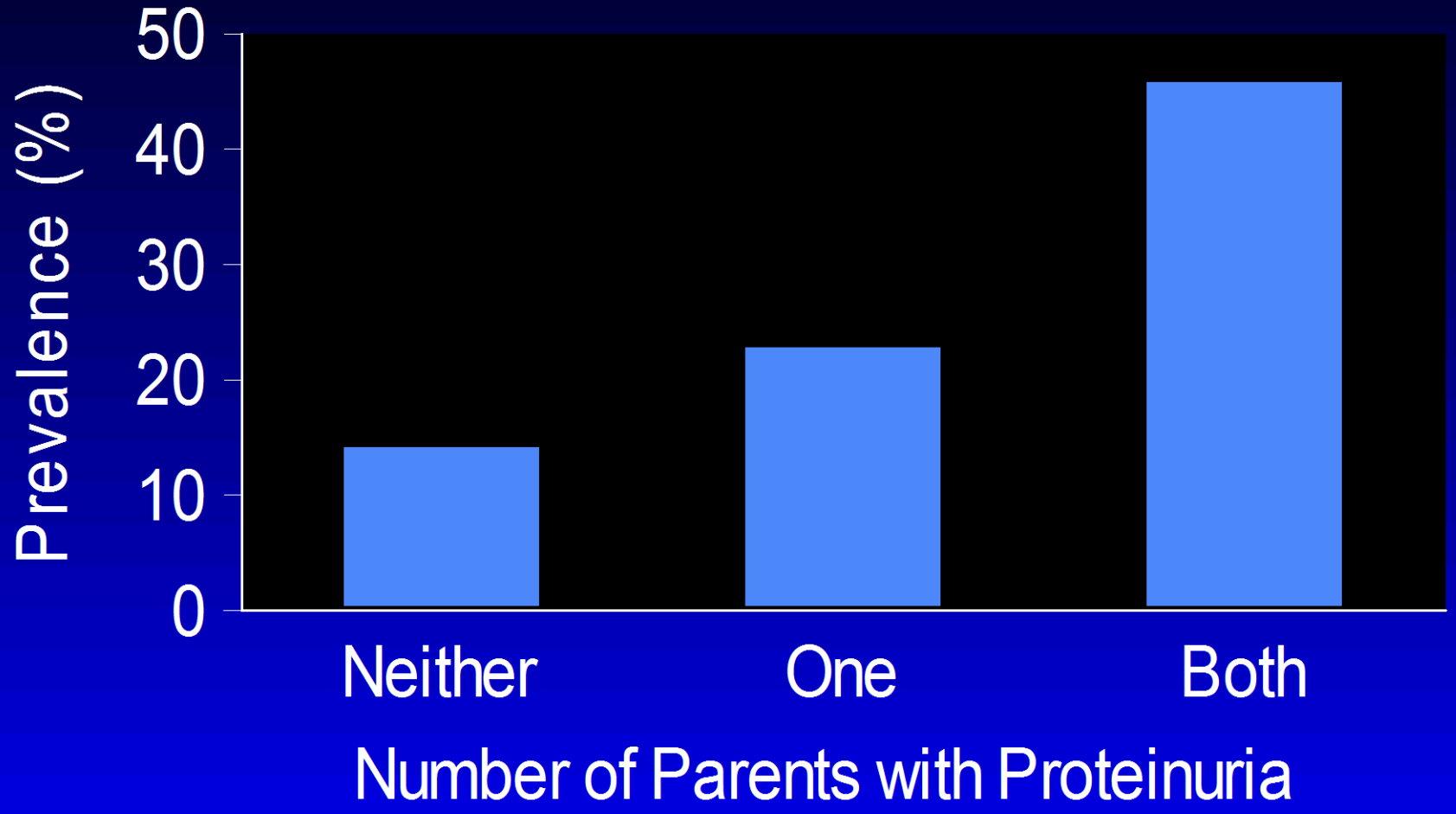
- UKPDS (new onset type 2 diabetes)
  - Glycemia
  - Blood pressure
- MICRO-HOPE (diabetes + CVD or 1 or more CVD risk factors)
  - Ramapril 10mg/d
- IRBESARTAN study 1 (type 2 diabetes + BP >135/85 + albumin excretion 20-200ug/min; s. creatinine <1.5 in men, <1.1mg/dl in women)
  - Irbesatan 150mg or 300mg/d
- IRBESARTAN study 2 (type 2 diabetes + A/C >300mg/g + s. creatinine 1.3-3.0 mg/dl)
  - Irbesatan to 300 mg/d, or amlodipine to 10mg/d
- RENALL (type 2 diabetes+ A/C >300mg/g; s. creatinine 1.3-3 mg/dl)
  - Losartan 100mg/d

Blood Pressure Control Study (UKPDS)

In 1148 Type 2 diabetic patients, a tight blood pressure control which achieved blood pressure of 144 / 82 mmHg gave reduced risk for :

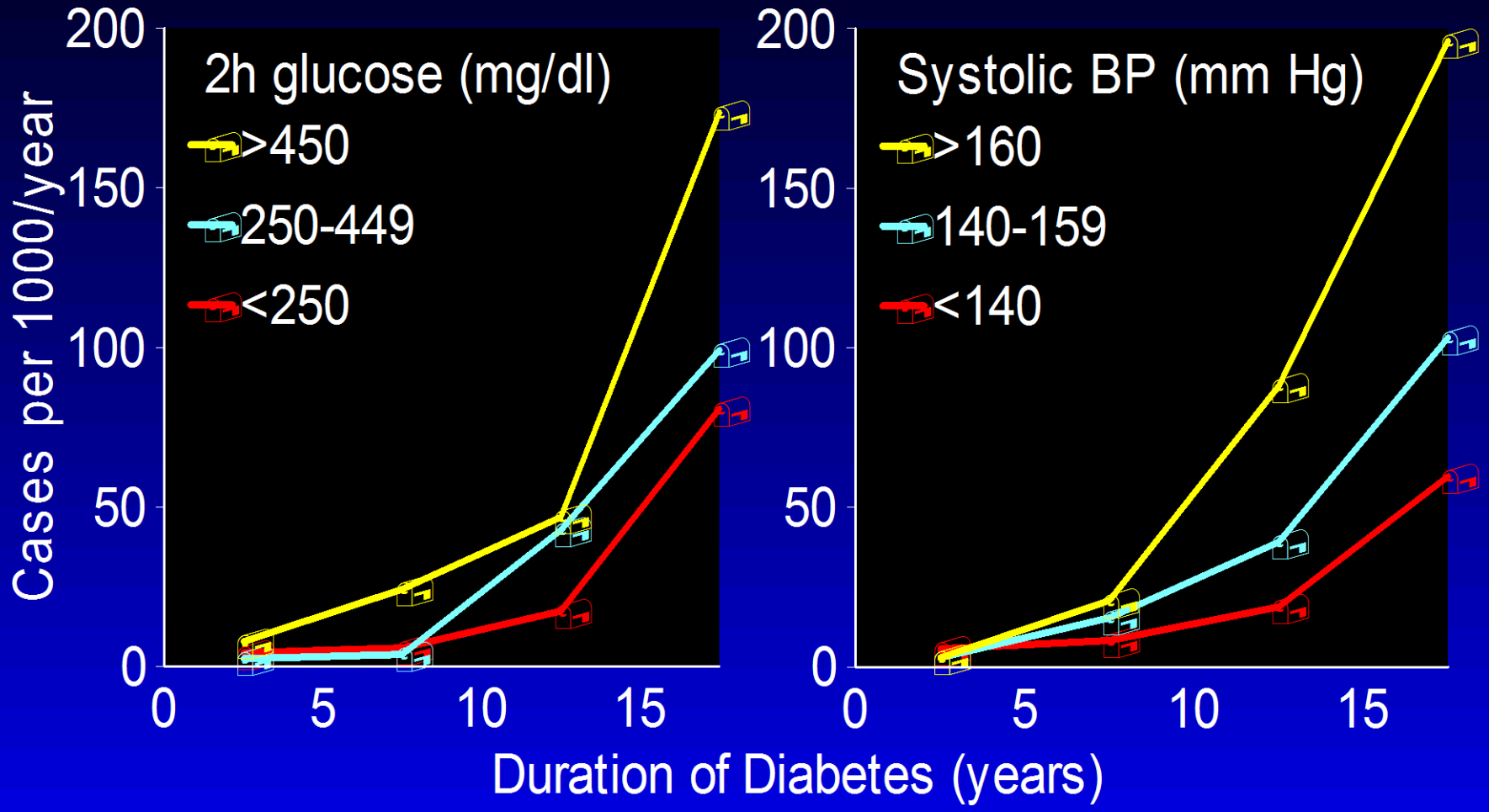
any diabetes-related endpoint	24%	p=0.0046
diabetes-related deaths	32%	p=0.019
stroke	44%	p=0.013
microvascular disease	37%	p=0.0092
heart failure	56%	p=0.0043
retinopathy progression	34%	p=0.0038
deterioration of vision	47%	p=0.0036

Prevalence of Proteinuria in the Diabetic Offspring of Diabetic Parents



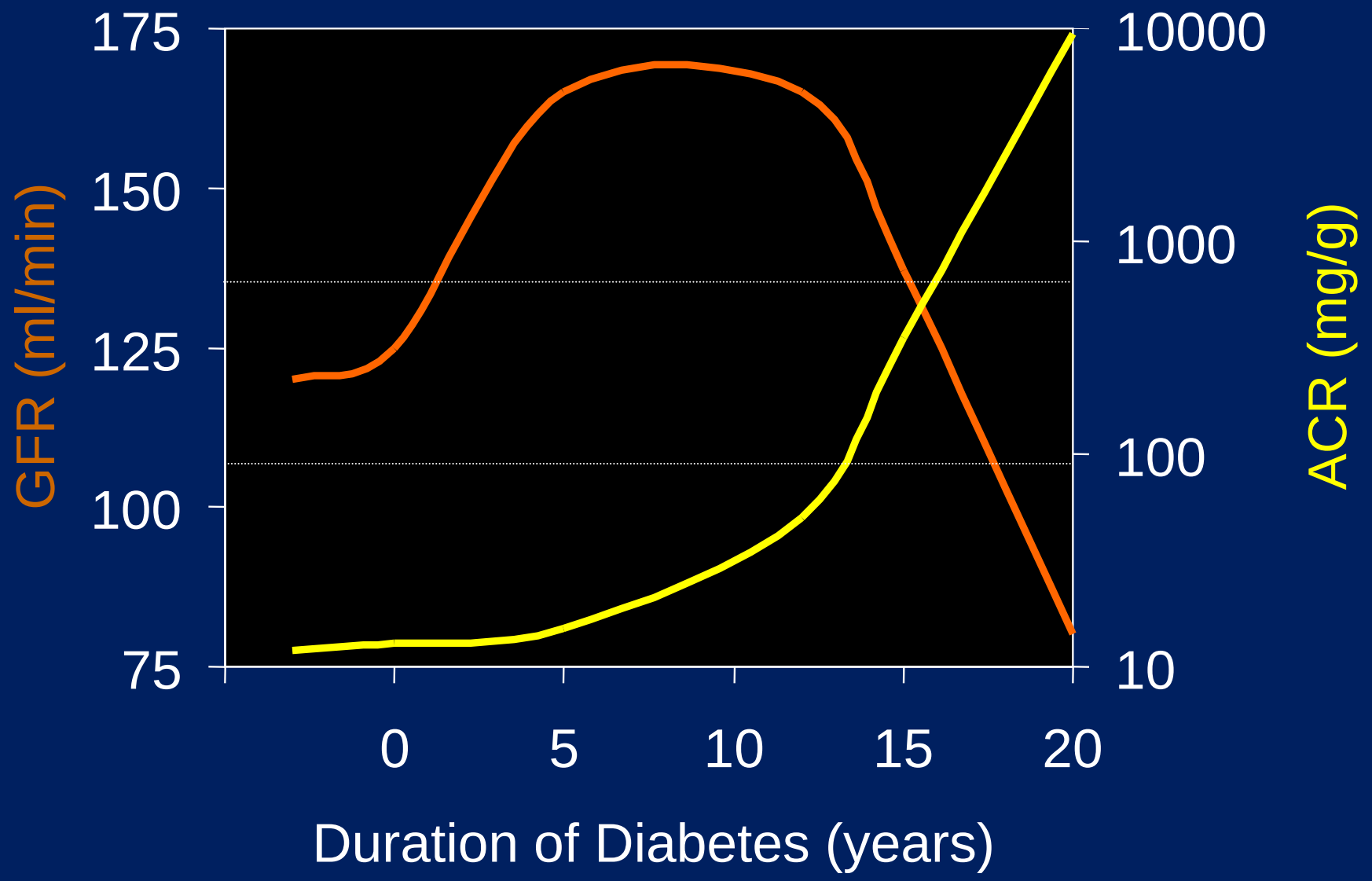
*Pettitt et al. Diabetologia*33:438-443, 1990

Incidence Rate of Proteinuria



*Kidney Int*35:681-687, 1989

Change in Glomerular Filtration Rate (GFR)



N Engl J Med 335:1636-1642, 1996

Prognostic significance of ‘microalbuminuria”

Predicts:

Clinical proteinuria and renal failure in Type 1 DM (Viberti G-C et al. 1982

Cardiovascular disease and mortalityin Type 2 DM (Mogensen C-E et al. 1984

Effect of Chronic Kidney Disease on CVD risk in patients with diabetes

- Risks of all-cause mortality and CVD events increase considerably with:
  - increasing albuminuria
  - falling e-GFR

Relative risk of cardiovascular disease according to albumin excretion and e-GFR

	ACR <10	ACR 10–29	ACR 30–299	ACR ≥300
eGFR >105	0.9	1.3	2.3	2.1
eGFR 90–105	Ref	1.5	1.7	3.7
eGFR 75–90	1.0	1.3	1.6	3.7
eGFR 60–75	1.1	1.4	2.0	4.1
eGFR 45–60	1.5	2.2	2.8	4.3
eGFR 30–45	2.2	2.7	3.4	5.2
eGFR 15–30	14	7.9	4.8	8.1

Kidney International 2011;80(1):17-28

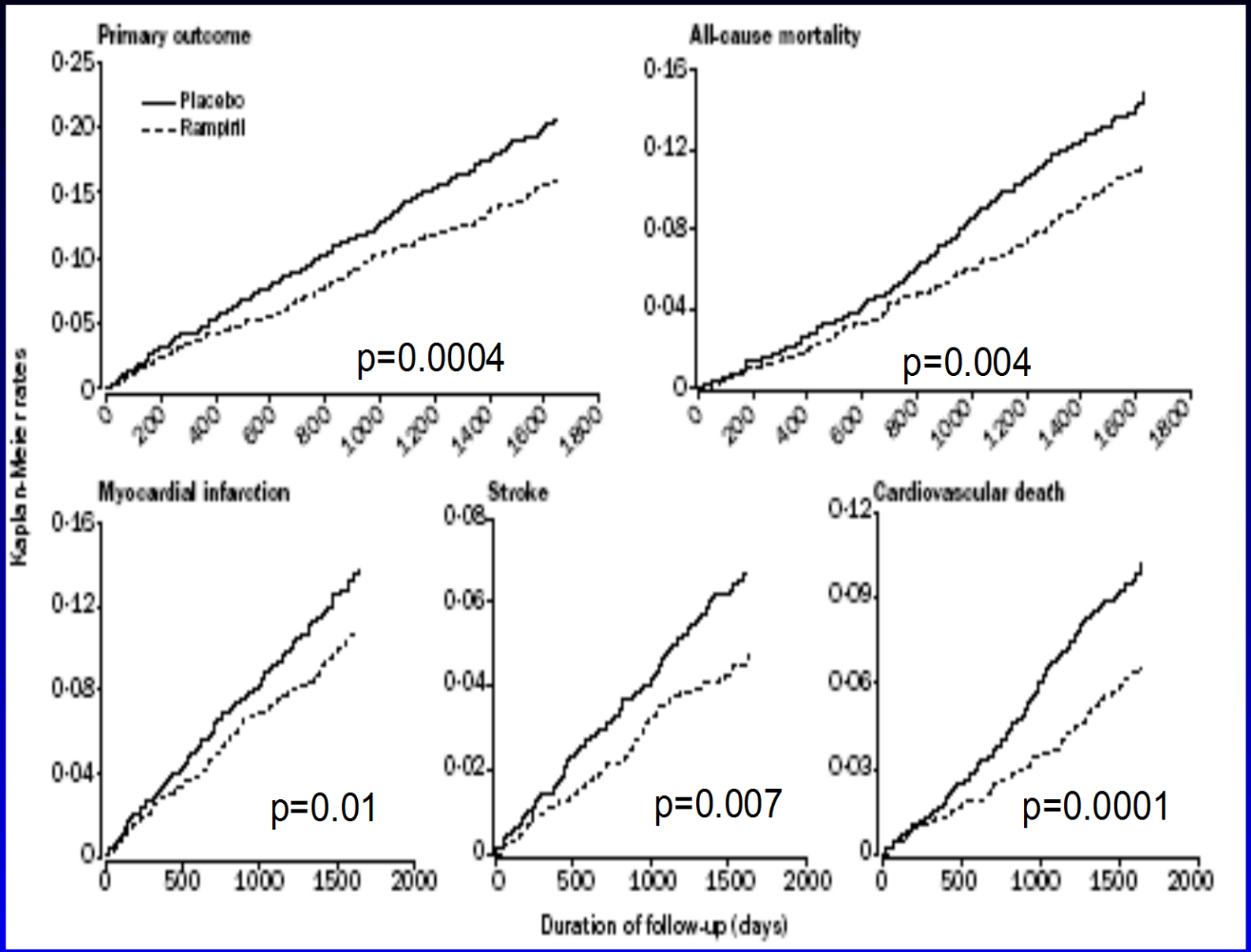
Interventions in Diabetic Nephropathy

- Glycemic control
- Blood Pressure
- Angiotensin-renin blockade

Effect of treatment for Micro- and Macro-albuminuria on CVD

- ACEs
- ARBs

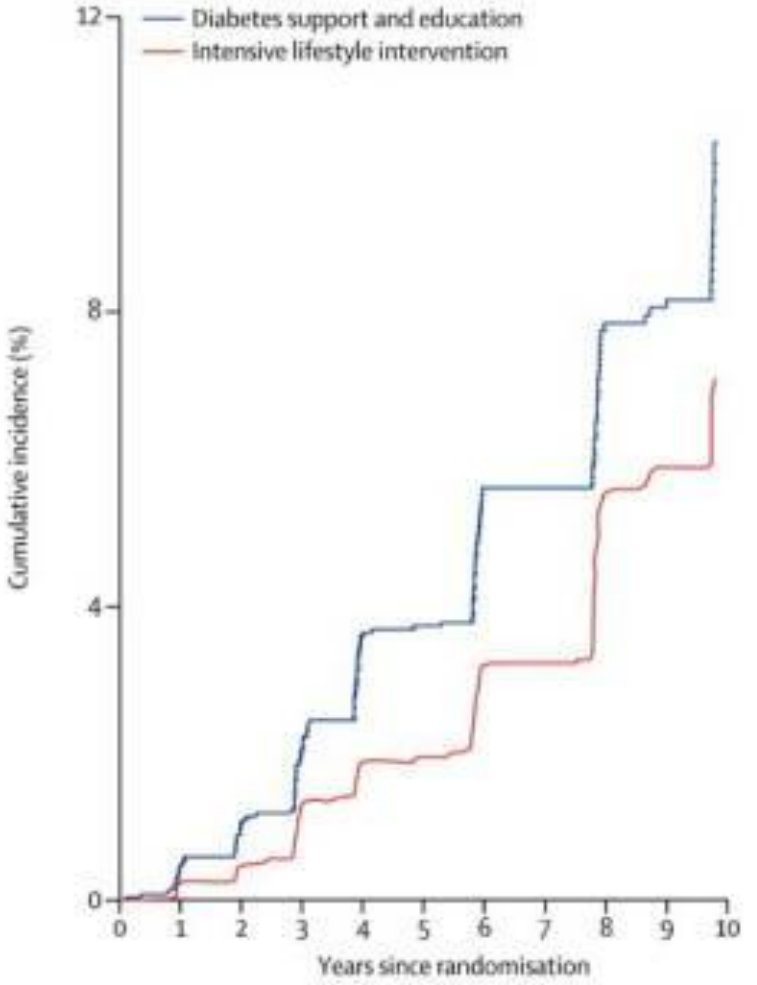
MICRO-HOPE: Outcome in 3577 patients with diabetes



HOPE investigators. Lancet 355: 253–259, 2000

Look Ahead Study:
Cumulative incidence of very-high-risk CKD

The hazard ratio (ILI vs. DSE) is 0.69, 95% CI = 0.55 to 0.87, p=0.002.



Lancet Diabetes Endocrinol. 2014; 2(10): 801–809

Complications of Diabetes Mellitus and their Clinical Stages

Complications		Sub-clinical	Clinical Stage 1	Clinical Stage 2	End Stage
Micro-vascular	**Retinopathy**	Occasional microaneurysms	Background or nonproliferative retinopathy	Preproliferative or proliferative retinopathy Macular oedema	Vitreous haemorrhage Blindness
	Nephropathy	Microalbuminuria	Clinical proteinuria	Nephrotic syndrome Renal insufficiency	Uraemia Renal dialysis Renal transplant Death
	Peripheral Neuropathy	Abnormal 10g monofilament test Abnormal VPT	Loss of deep tendon reflexes Sensory or motor neuropathy	Focal peripheral neuropathy Amyotrophy	Motor paralysis Paraplegia Charcot joint
	Autonomic Neuropathy	Abnormal sweat tests	Cardiac conduction defects (long Q-T interval; loss of R-R variation)	Erectile dysfunction Impotence Postural hypotension	Gastroparesis Nocturnal diarrhoea Sudden death
Macro-vascular	**Coronary Artery Disease**	Asymptomatic ECG changes Left ventricular hypertrophy Abnormal exercise stress test	Stable angina Abnormal ECG Mild congestive heart failure	Unstable angina Myocardial Infarction, Congestive heart failure	Intractable congestive heart failure Cardiac transplant Death
	Cerebrovascular Disease	Carotid intimal /medial thickening Reduced cerebral blood flow	Transient ischaemic attacks Carotid bruits	Cerebral thrombosis Focal neurological signs Cognitive impairement	Hemiplegia with functional incapacity Dementia Death
	Peripheral Vascular Disease	ABI<0.9 or >1.3 Loss of peripheral pulses, Reduced blood flow Intimal /medial arterial calcification	Intermittent claudication Skin changes Hair loss	Rest pain in legs Ischaemic ulcer	Gangrene Amputation
Other	**Diabetic Foot**	Abnormal 10g monofilament test Abnormal VPT Loss of peripheral pulses, Reduced blood flow Medial arterial calcification	Sensory neuropathy Callosity Deformity Dry skin, skin fissures Skin atrophy	Diabetic ulcer Cellulitis Osteomyelitis	Tissue necrosis Gangrene Amputation Charcot joint
	Infections		Specific local / systemic infections	Septicaemia, Interstitial fascitis Osteomyelitis	Death
	Pregnancy		Gestational diabetes	Large for gestational age foetus or infant	Still birth Congenital malformation

ABI = Ankle/Brachial blood pressure ratio (Ankle–brachial Index); VPT= Vibration perception threshold