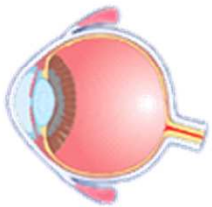
Diabetic Chronic Complications

Dr. YC Woo
Department of Medicine
Queen Mary Hospital

Outline

- The chronic complications of diabetes
  - Retinopathy
  - Neuropathy
  - Nephropathy
  - Vasculopathy
- Screening of DM Cx

Type 2 diabetes is NOT a mild disease



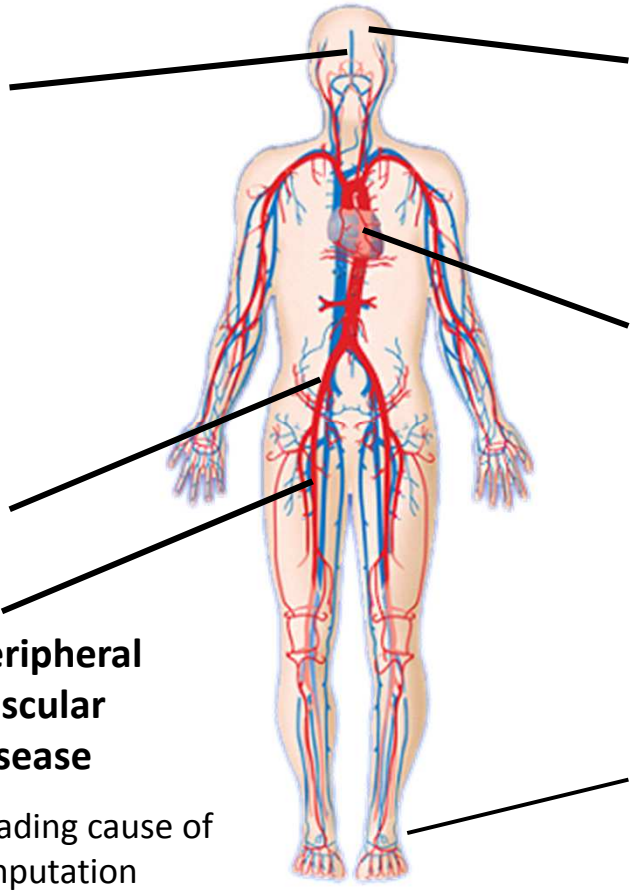
Diabetic retinopathy

Leading cause of blindness in working-age adults[1]



Diabetic nephropathy

Leading cause of end-stage renal disease[2]



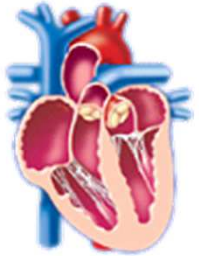
Peripheral vascular disease

Leading cause of amputation



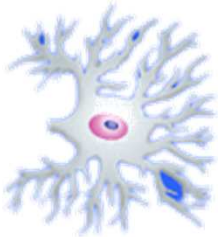
Stroke

2-fold increase in stroke[3]



Cardiovascular disease

2-4 folds increase in CHD

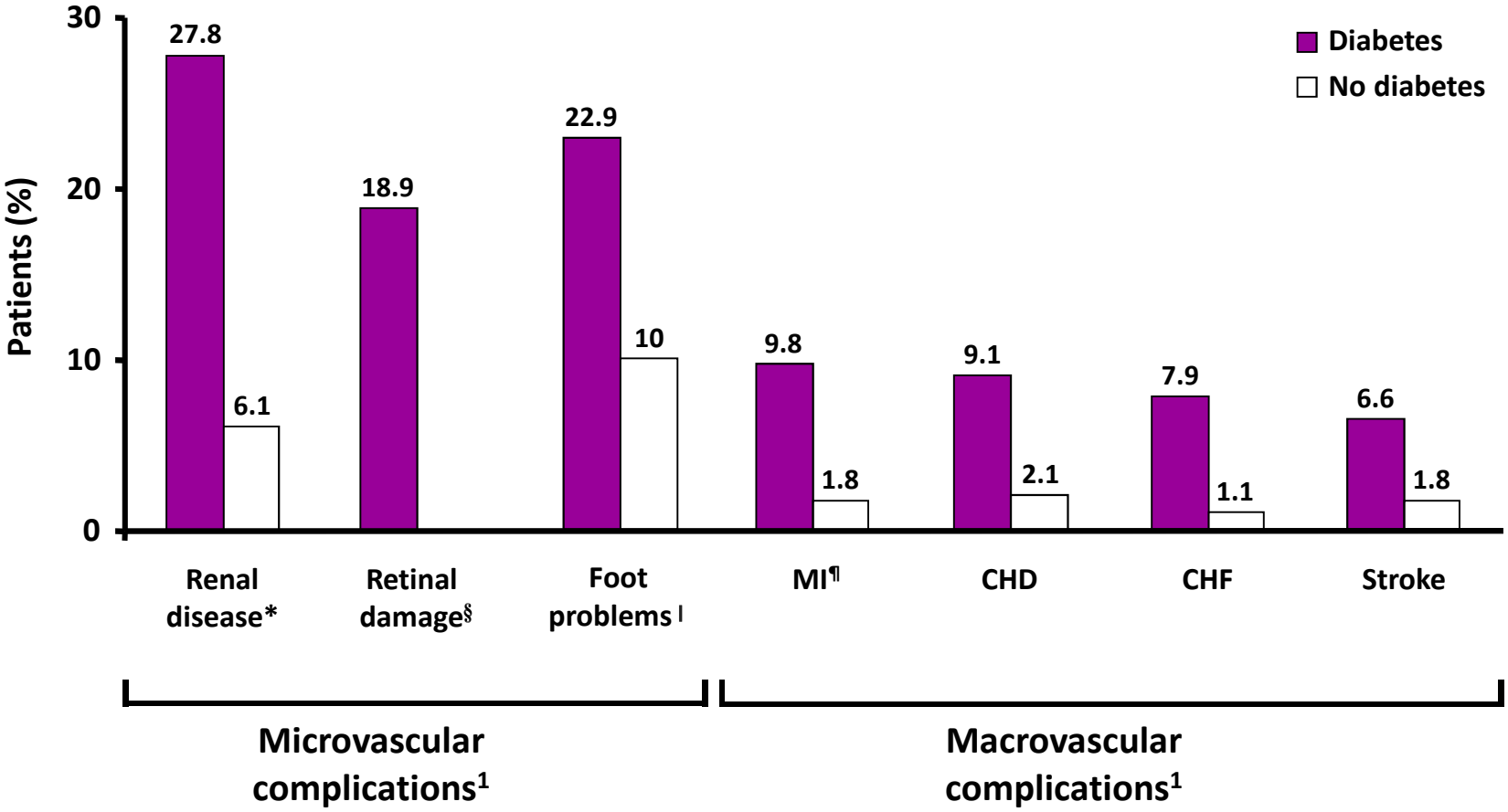


Diabetic neuropathy

Leading cause of non-traumatic lower extremity amputations[5]

[1]Fong DS, *et al. Diabetes Care* 2003;26 (Suppl. 1):S99–S102. [2]Molitch ME, *et al. Diabetes Care* 2003;26 (Suppl. 1):S94–S98.
[3]Kannel WB, *et al*. *Am Heart J* 1990;120:672–676. [4]Gray RP & Yudkin JS. In *Textbook of Diabetes* 1997.
[5]Mayfield JA, *et al. Diabetes Care* 2003;26 (Suppl. 1):S78–S79.

Increased prevalence of microvascular and macrovascular complications in diabetes



*Microalbuminuria (albumin:creatinine ratio >30 µg/mg)

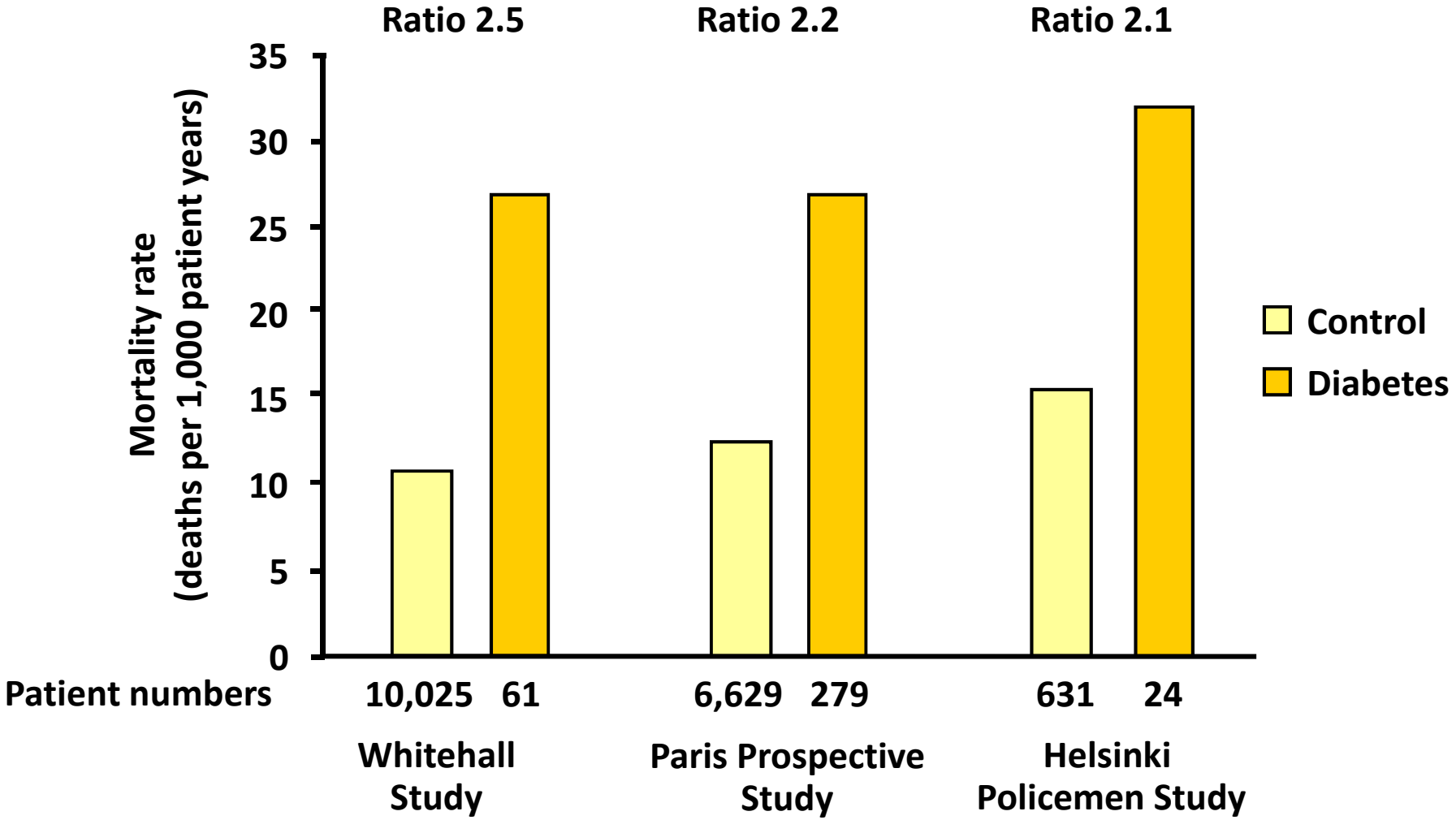
§Includes positive response to question, "Have you been told diabetes has affected your eyes/had retinopathy?" Data for individuals without diabetes not available

| Foot/toe amputations, foot lesions, numbness in feet

¶Men with diabetes 1.22 times more likely to have an acute MI than women with diabetes (95% CI 1.18–1.25)[2]

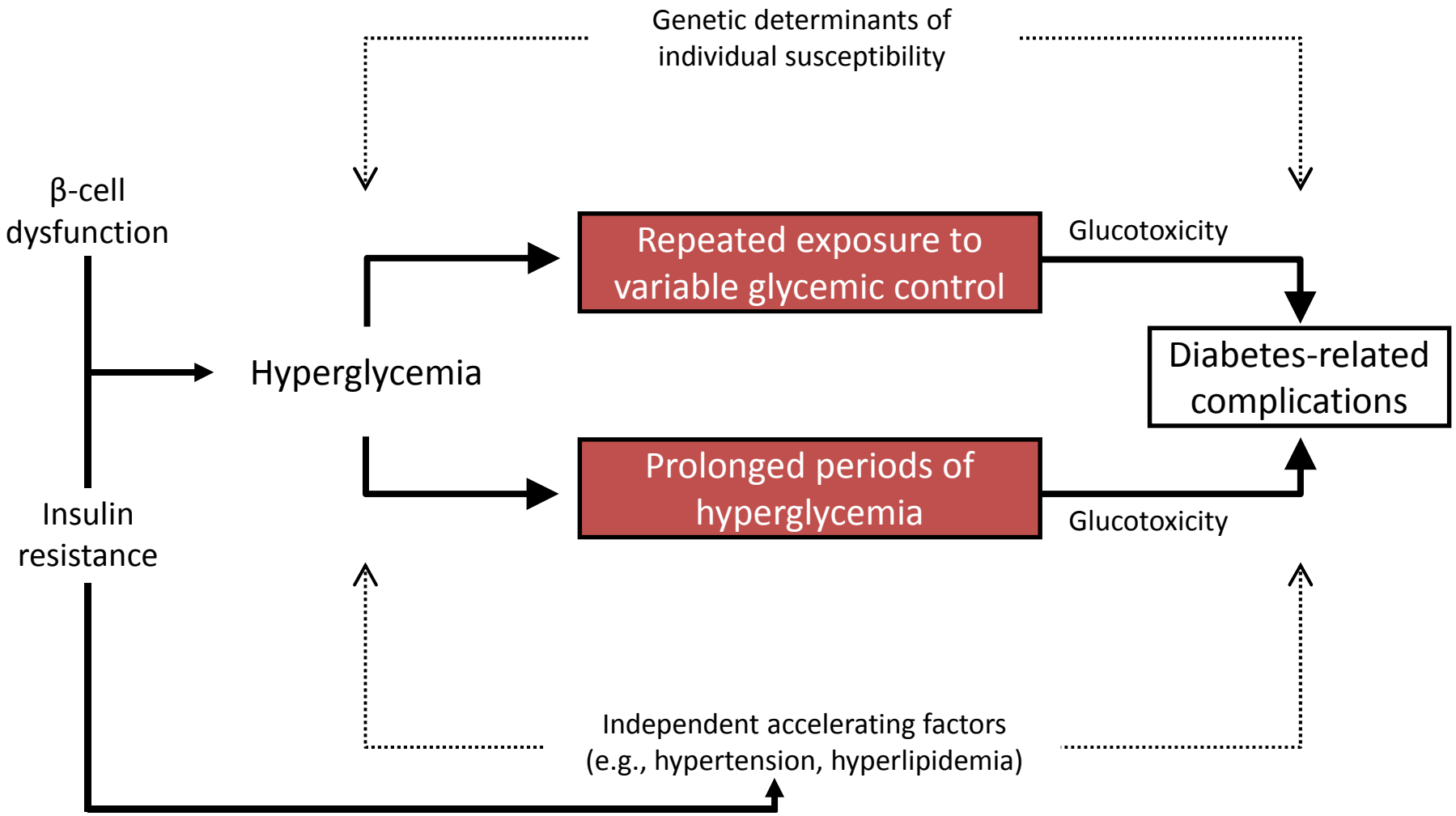
[1]Adapted from AACE. State of Diabetes Complications in America Report, 2007. Available at: http://www.aace.com/newsroom/press/2007/images/DiabetesComplicationsReport_FINAL.pdf (accessed 23.02.08). [2]Booth GL, *et al. Lancet* 2006; 368:29–36.

Mortality rate is twice as great in patients with diabetes



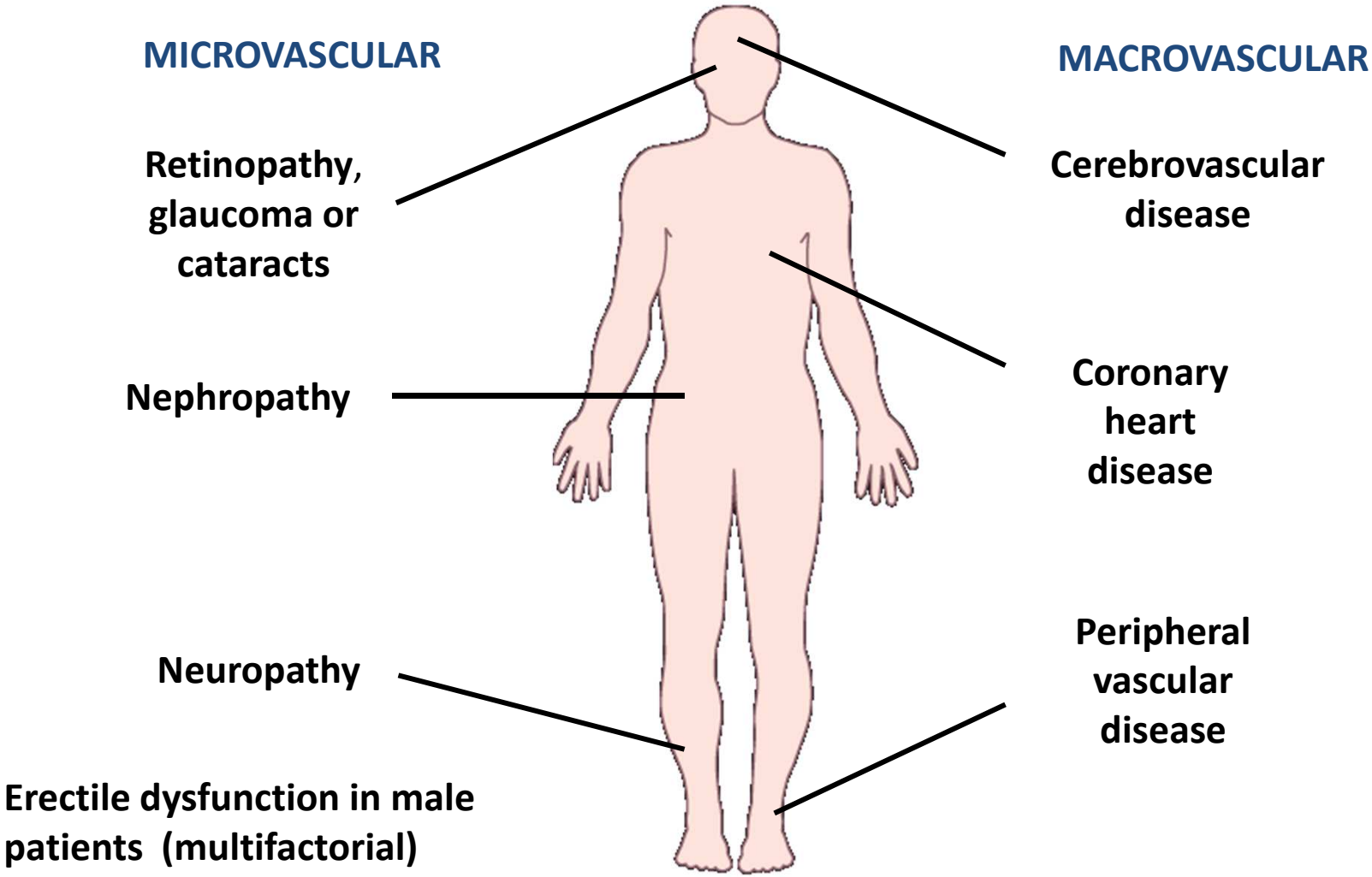
Balkau B, *et al*. *Lancet* 1997; 350:1680.

Poor glycemic control can lead to vascular damage



Adapted from Brownlee M. *Diabetes* 2005; 54:1615–1625.

50% of type 2 diabetes patients have complications at the time of diagnosis



UKPDS Group. UKPDS 33. *Lancet* 1998;352:837–53.

Eye complication

- **Retinopathy**
- **Other** – cataract, retinal artery and vein occlusion, lipaemia retinalis

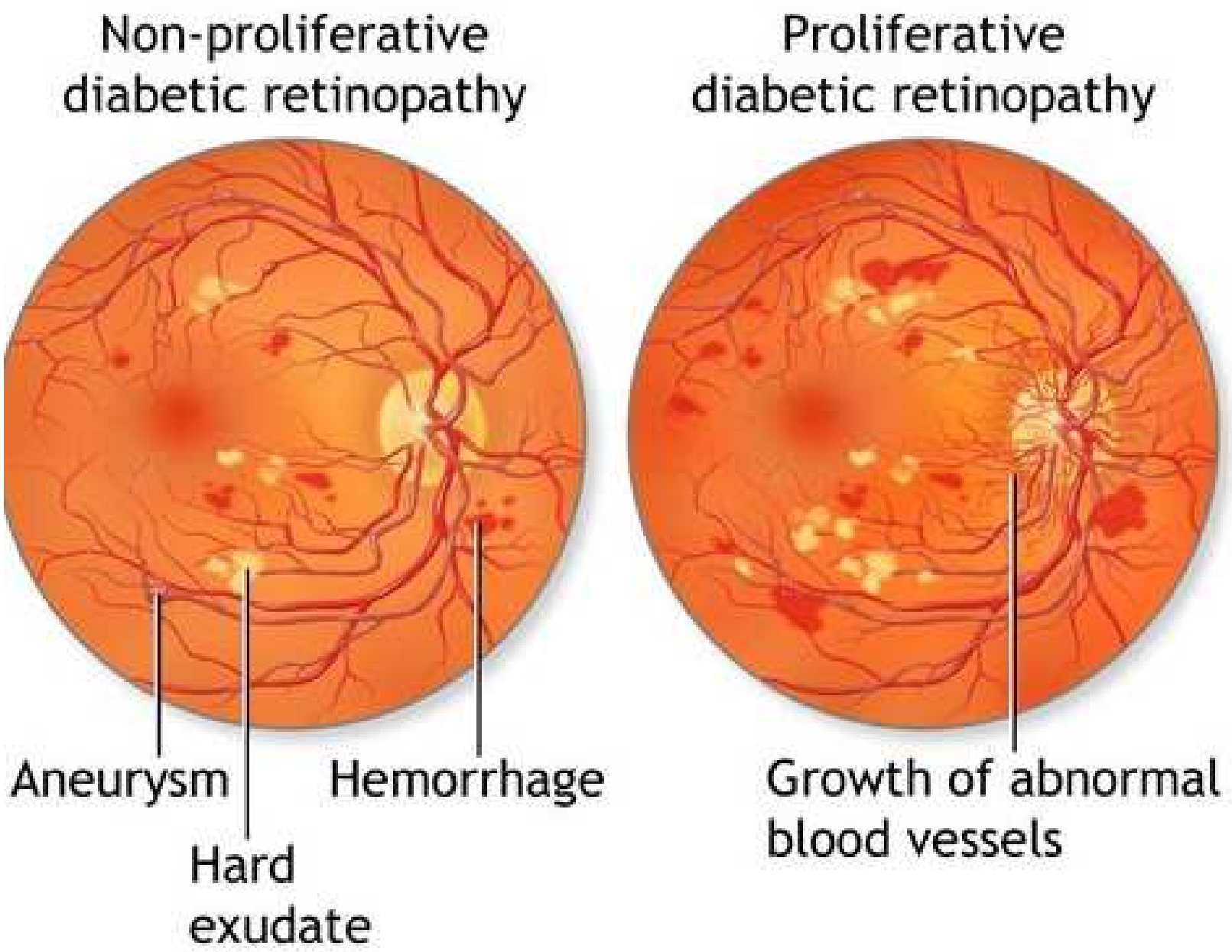
Eye complication : retinopathy

Classification	Features
Mild / Moderate non-proliferative retinopathy	Hemorrhage, edema, microaneurysms, exudates, cotton wool spots <6, IRMA in one quadrant
Severe non-proliferative retinopathy	retinal hemorrhages/microaneuryms in four quadrants, venous abnormalities, intraretinal microvascular abnomalities (IRMA) > 1 quadrants , multiple cotton wool spots ≥ 6
Proliferative retinopathy	New vessels on optic disc / elsewhere
Advanced diabetic eye disease	Vitreous hemorrhage Retinal detachment Neovascular glaucoma
Maculopathy	Lesions (exudate, microaneurysms) within 1 disc dianeter from fovea

Table 1

International clinical diabetic retinopathy disease severity scale

Proposed disease severity level	***Dilated ophthalmoscopy findings***
No apparent retinopathy	No abnormalities
Mild nonproliferative DR	Microaneurysms only
Moderate nonproliferative DR	More than just microaneurysms, but less than severe NPDR
Severe nonproliferative DR	No signs of PDR, with any of the following: • More than 20 intraretinal hemorrhages in each of four quadrants • Definite venous beading in two or more quadrants • Prominent intraretinal microvascular anomalies in one or more quadrants
PDR	One or more of the following: • Neovascularization • Vitreous or preretinal hemorrhage
NPDR = Nonproliferative DR	


Non-proliferative
diabetic retinopathy
Proliferative
diabetic retinopathy
Aneurysm
Hard
exudate
Hemorrhage
Growth of abnormal
blood vessels

Patient's reports now contain grading levels as below:

DIABETIC RETINOPATHY

- **R0 – NONE**
  No retinopathy
- **R1 – BACKGROUND**
  Microaneurysm(s) or small retinal haemorrhages
  Any exudates outside the arcades
- **R2 - PRE-PROLIFERATIVE**
  Venous beading, loop or reduplication
  Intraretinal microvascular abnormality (IMRA)
  > = 3 deep, round or blot haemorrhages
  Multiple cotton wool spots (only if in association with above features)
- **R3 – PROLIFERATIVE**
  New vessels on disc (NVD)
  New vessels elsewhere (NVE)
  Pre-retinal or vitreous haemorrhage
  Pre-retinal fibrosis +/- tractional retinal detachment

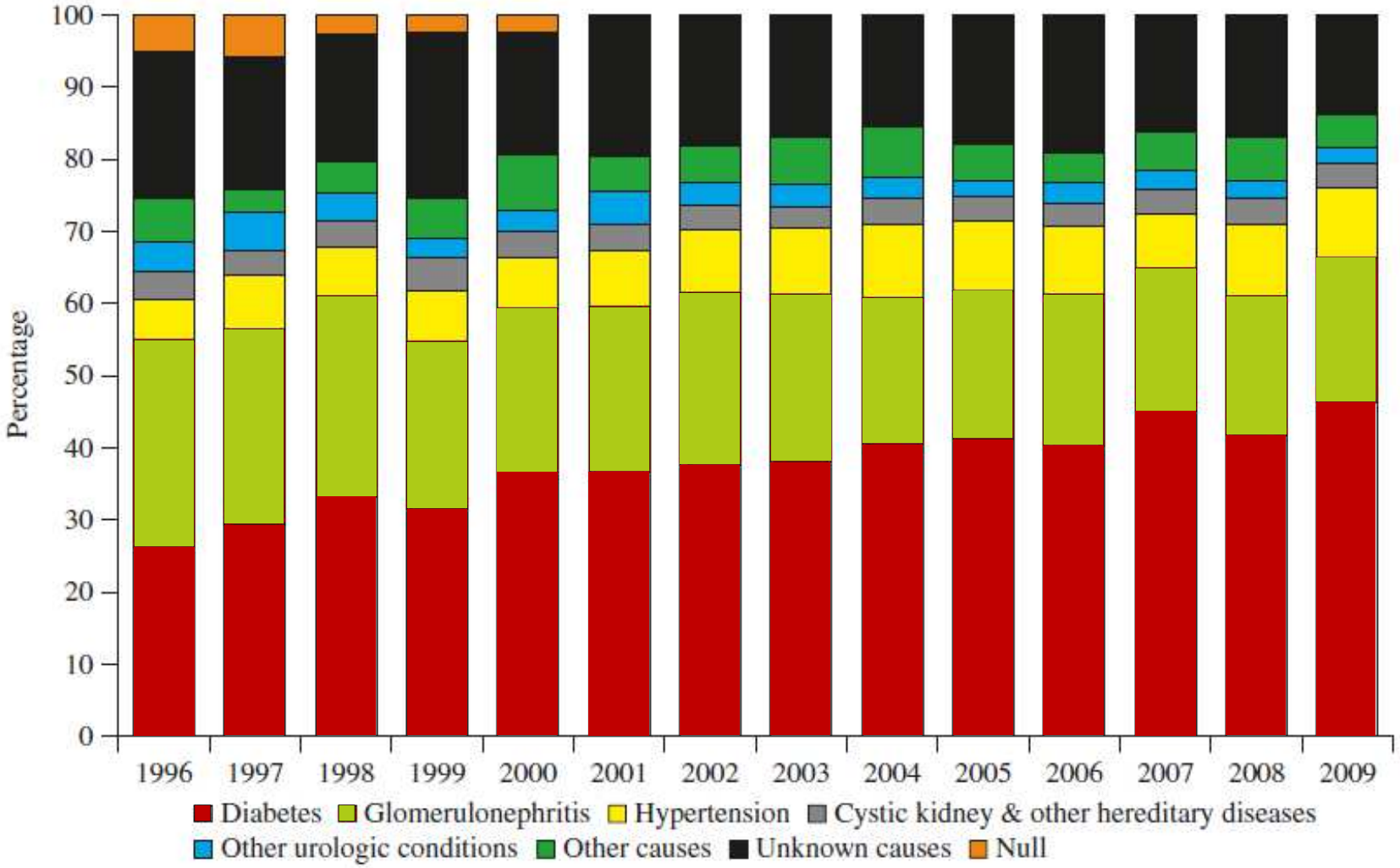
Diabetic Maculopathy

- **M0 – NO MACULOPATHY**
  No Maculopathy
- **M1 – MACULOPATHY**
  Exudates within 1 disc diameter (DD) of the centre of the fovea
  Circinate or group of exudates within the macula
  Any microaneurysm or haemorrhage within 1DD of the centre of the fovea **ONLY** if associated with a best VA of 6/12 or worse

Previous Photocoagulation

- **P0 – NONE**
  No photocoagulation
- **P – PHOTOCOAGULATION**
  Either Focal/grid to macula or Peripheral scatter

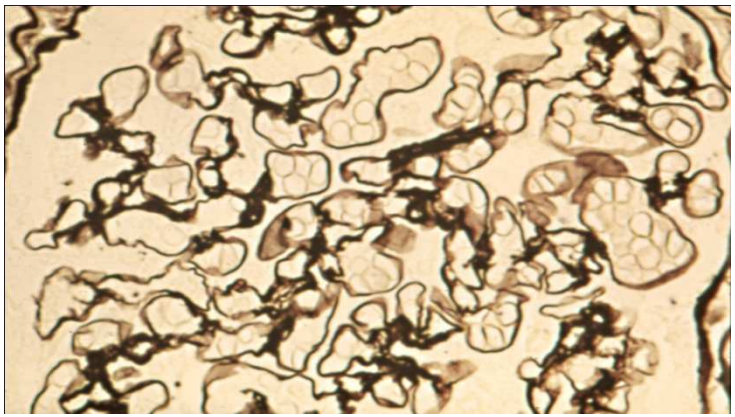
Nephropathy
Causes of ESRD in HK 1996-2009



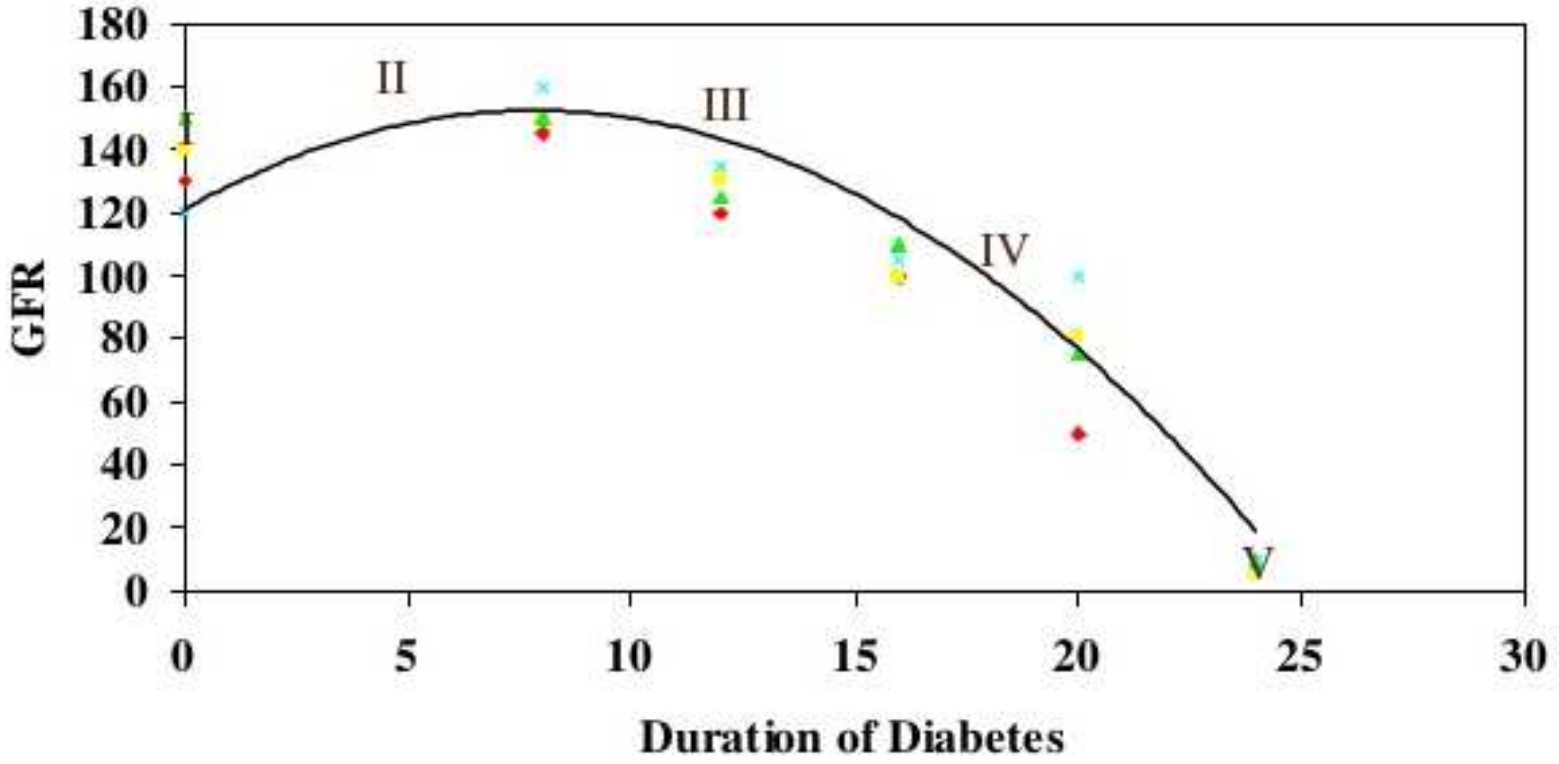
YW Ho et.al. HKJ of Nephrol 2010

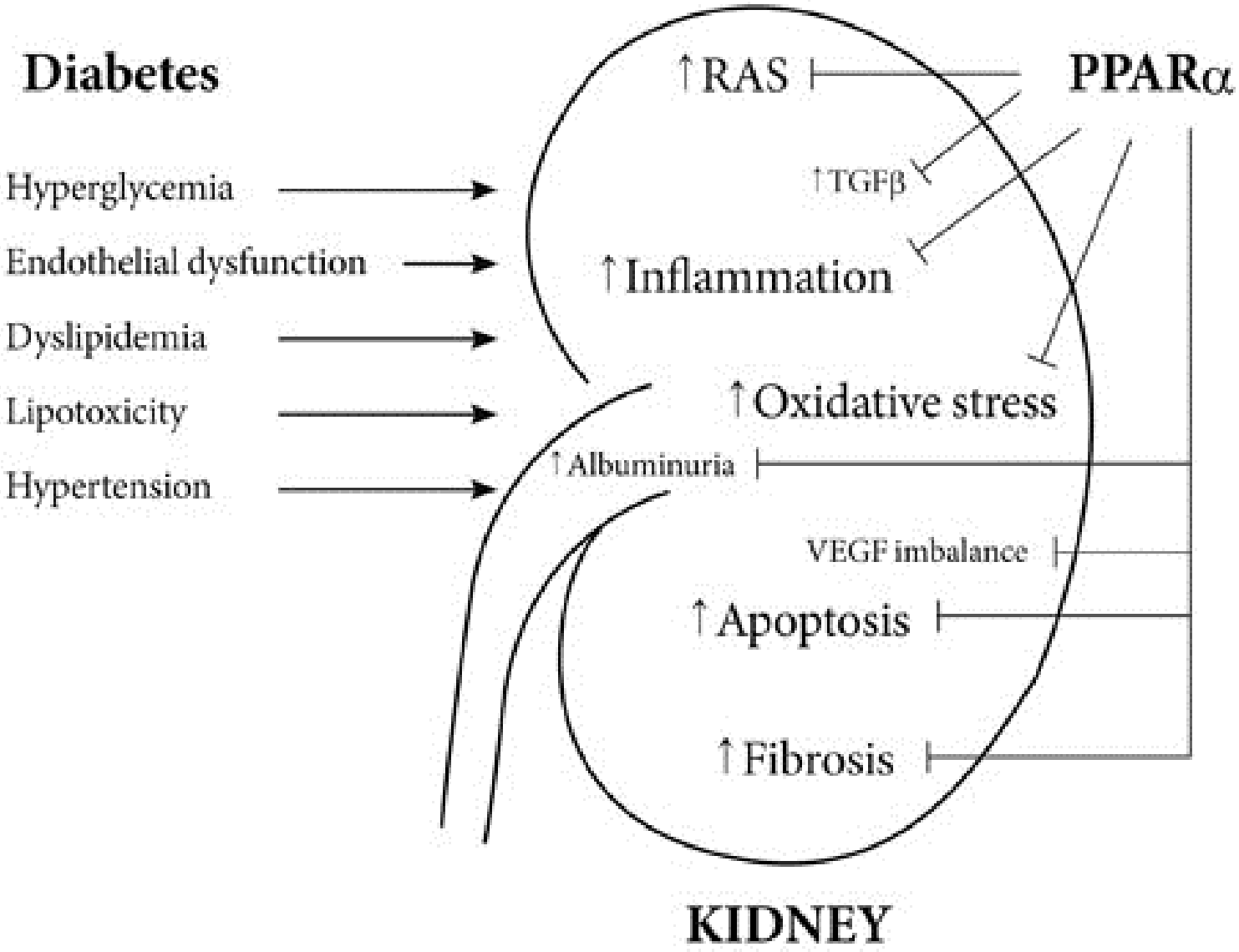
Stages of Diabetic Nephropathy in DM

- I. Acute renal hypertrophy -hyperfunction
- II. Normoalbuminuria (< 20 ug/min)
- III. Incipient diabetic nephropathy
- IV. Proteinuria, clinical overt diabetic nephropathy
- V. End-stage renal failure



Stages of DM nephropathy




Diabetes
Hyperglycemia
Endothelial dysfunction
Dyslipidemia
Lipotoxicity
Hypertension
↑RAS
PPARα
↑TGFβ
↑Inflammation
↑Oxidative stress
↑Albuminuria
VEGF imbalance
↑Apoptosis
↑Fibrosis
KIDNEY

Assessment for nephropathy

- Albumin excretion
  - Spot urine collection
    - Albumin : creatinine ratio (ACR)
    - Protein : creatinine ratio (PCR)
  - Timed urine collection
- Renal function
  - Serum creatinine
  - Golmerular filtration rate (GFR)
    - Estimated by eGFR

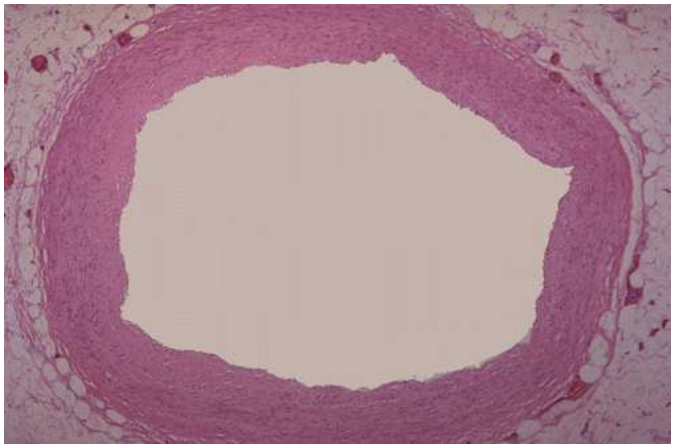
Diabetic nephropathy

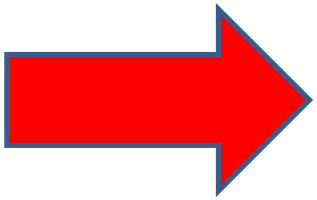
- Renal Prognosis: usually poor with eventual progression to ESRD once significant proteinuria develops; HTN, poor diabetic control, obesity →exacerbate
- Treatment:
  - ACEi, ARB* to treat BP and proteinuria
  - glycemic control
  - treat BP to < **130/80**
  - control other cardiovascular risk factors

Diabetic neuropathy

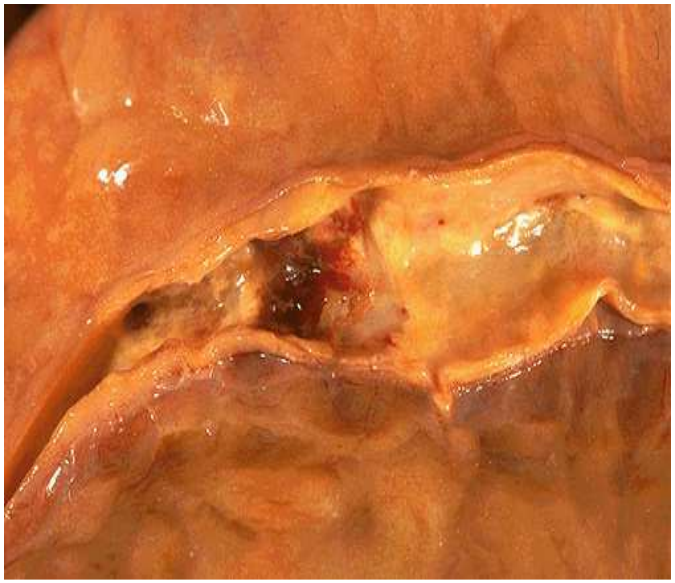
I. Focal neuropathies
   A. Mononeuropathies
      1. Sudden onset
      2. Asymmetrical
      3. Probably ischemic etiology
      4. Self-limited
      5. Examples
         Mononeuropathies
         Femoral neuropathies
         Radiculopathies
         Plexopathies
         Cranial neuropathies
   B. Entrapment neuropathies
      1. Gradual onset
      2. Usually asymmetrical but can be bilateral
      3. Compression etiology
      4. Waxing and waning progressive course without spontaneous recovery
      5. Examples
         Carpal tunnel syndrome
         Ulnar entrapment
         Lateral cutaneous femoral nerve entrapment
         Tarsal tunnel syndrome
II. Diffuse neuropathies
   A. Insidious onset
   B. Symmetrical
   C. Abnormalities due to both structural and metabolic components
   D. Progressive
   E. Examples
      Distal symmetrical polyneuropathy
      Autonomic neuropathies

Atherosclerosis









Cardiovascular disease (CVD)

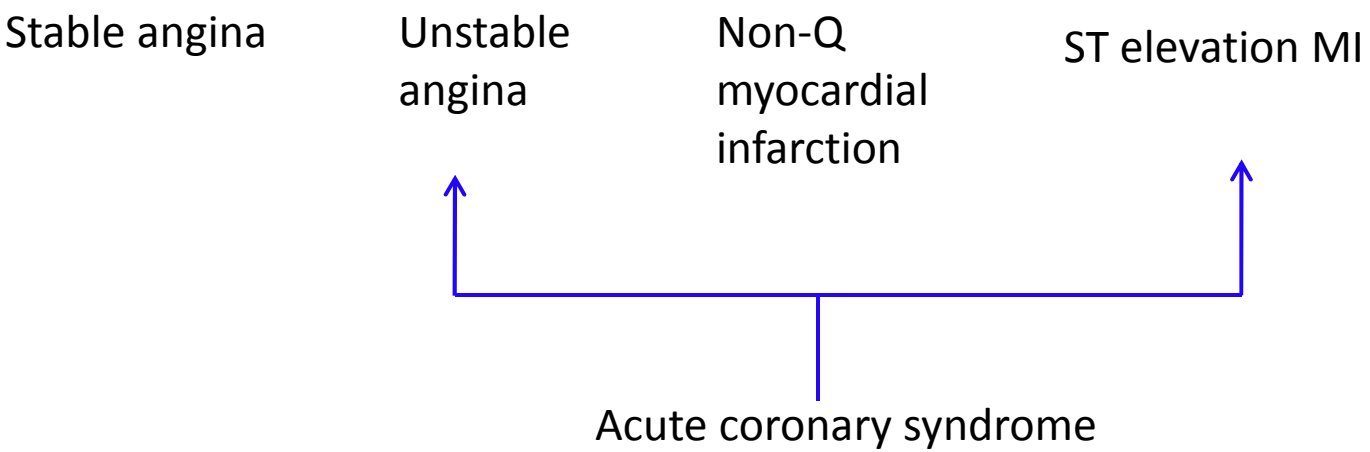
- Coronary artery disease (CAD)
  - Diseases of the blood supply
- Congestive heart failure (CHF)
  - Pump failure
- Arrhythmia
  - Rate problem
  - Eg. Atrial fibrillation, Ventricular tachycardia, heart block

Coronary artery disease

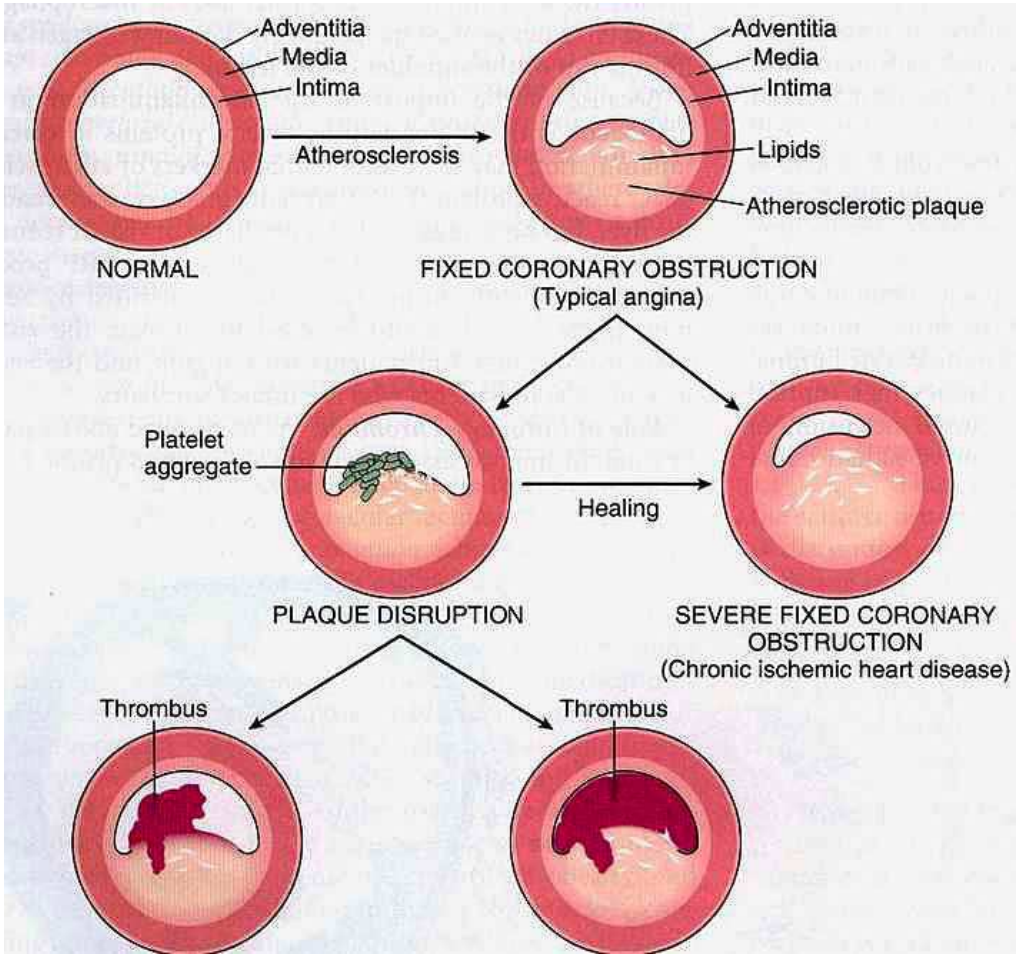
- Different terms:
  - Coronary heart disease (CHD)
  - Coronary artery disease (CAD)
  - Ischemic heart disease (IHD)
  - Acute coronary syndrome (ACS)

Ischemic heart disease

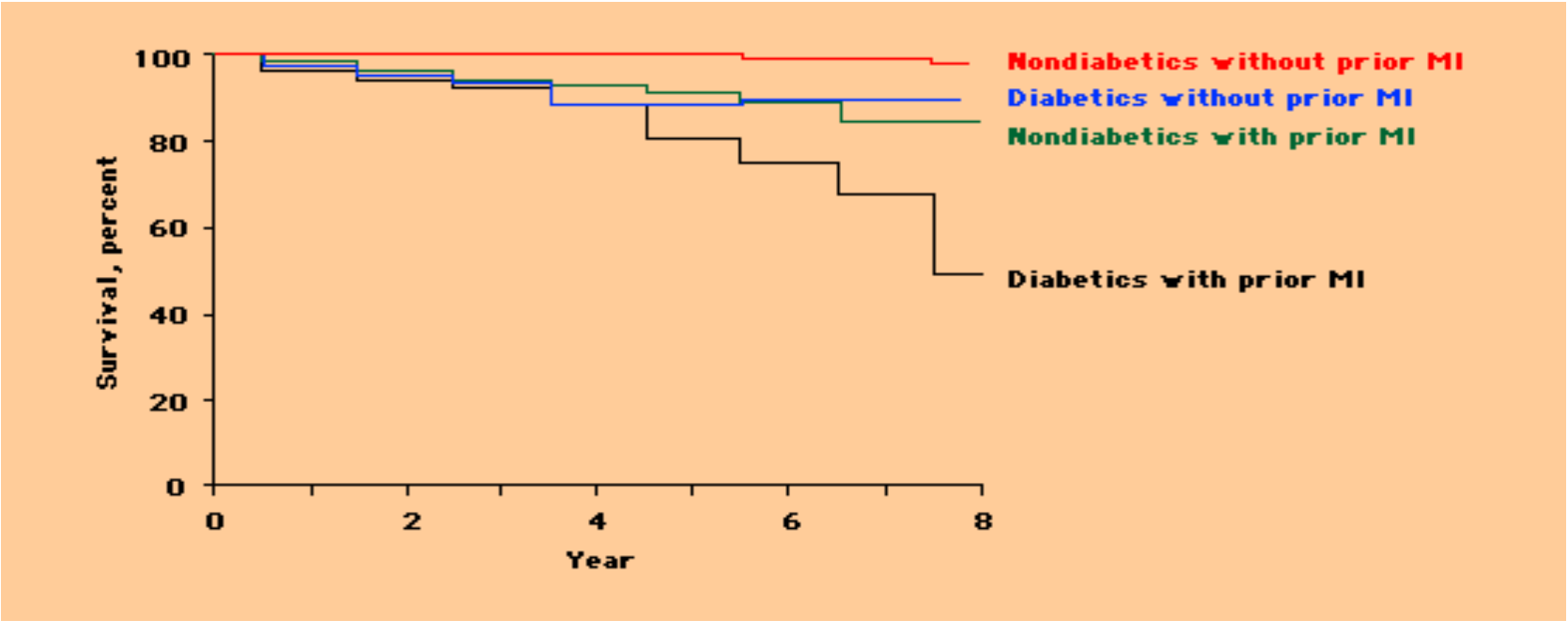
Spectrum :



Ischemic heart disease



DM as CAD equivalent



Diabetes increases coronary mortality with and without a prior MI In a seven year follow up of 1059 subjects with type 2 diabetes and 1378 nondiabetics, diabetics with or without a prior myocardial infarction (MI) had a greater mortality from coronary disease compared to nondiabetics (42 versus 16 percent for those with a prior MI and 15 versus 2 percent for those without a prior MI. The rate of coronary death and fatal and nonfatal MI in diabetics without a prior MI was the same as in nondiabetics with a prior MI, providing part of the rationale for considering type 2 diabetes a coronary equivalent. (Data from Haffner, SM, Lehto, S, Ronnemaa, T, et al, N Engl J Med 1998; 339:229.)

Stroke
Cerebrovascular accident (CVA)

- Transient ischemic attack (TIA)
  - Complete resolution within 24 hours
- CVA
  - Ischemic
  - Hemorrhagic

Stroke

- Symptoms
  - Depending on site of lesion
  - Usually unliateral (opposite to site of lesion, Except if brainstem is involved)
  - Sensation : numbness, loss of sensation
  - Motor : facial asymmetry, swallowing, speech, limb weakness, walking instability etc

Diabetic foot

Develop foot wounds 9-12%[1]



9 -20% of ulcers end in amputation[2]





Diabetes :
Commonest cause of non-traumatic amputation
15-40 X higher chance[3]
One lower limb lost to diabetes every 30 sec

10.6% perioperative mortality
-10.2% for mitral valve replacement[6]
5 year mortality > 50%[7]

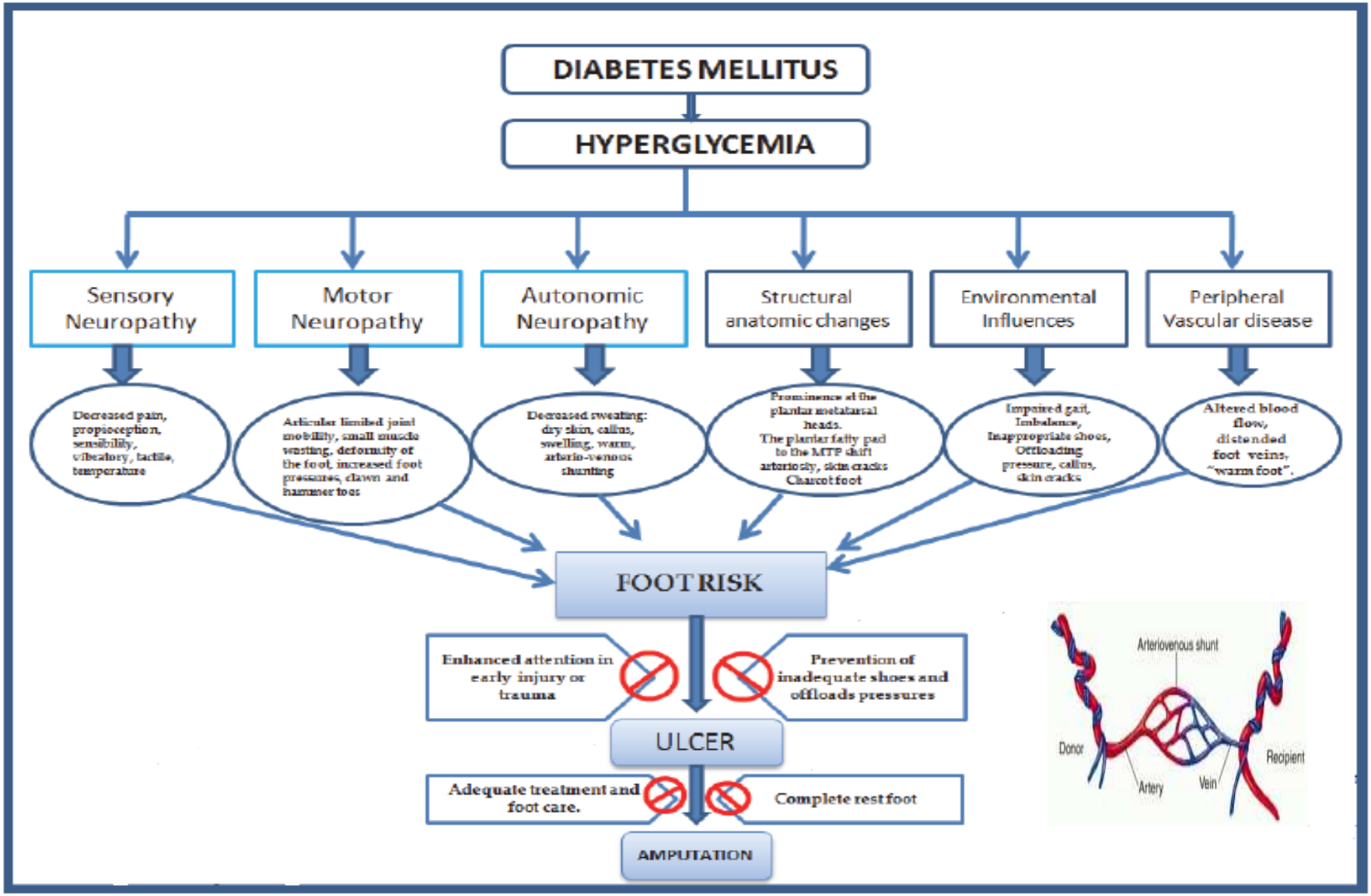


59% longer LOS compared with those without ulcer [5]



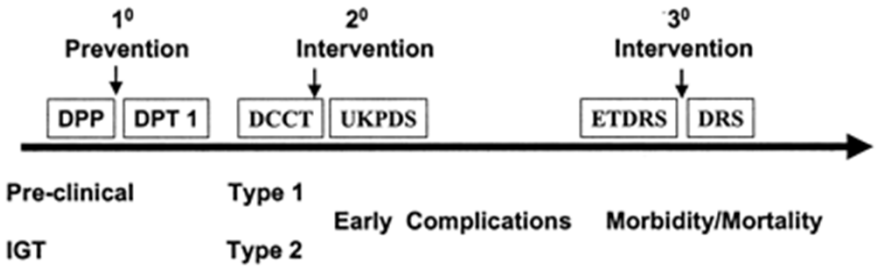
[1]Lavery et al. Diabetes Care 2004 [2] Lavery e al. Diabetes Care 2001 [3] ADA 2000
[4] Bakker K et al. Diabetes Voice 2005 [5] Reiber et al. NIH publication 1995
[6] Wong MW. Am J Surg 2006 [7] Armstrong et al. Int Wound J 2004

Pathogenesis



Modified from Aguilar et al. Global Perspectives on Diabetic Foot Ulceration. InTech Press 2011

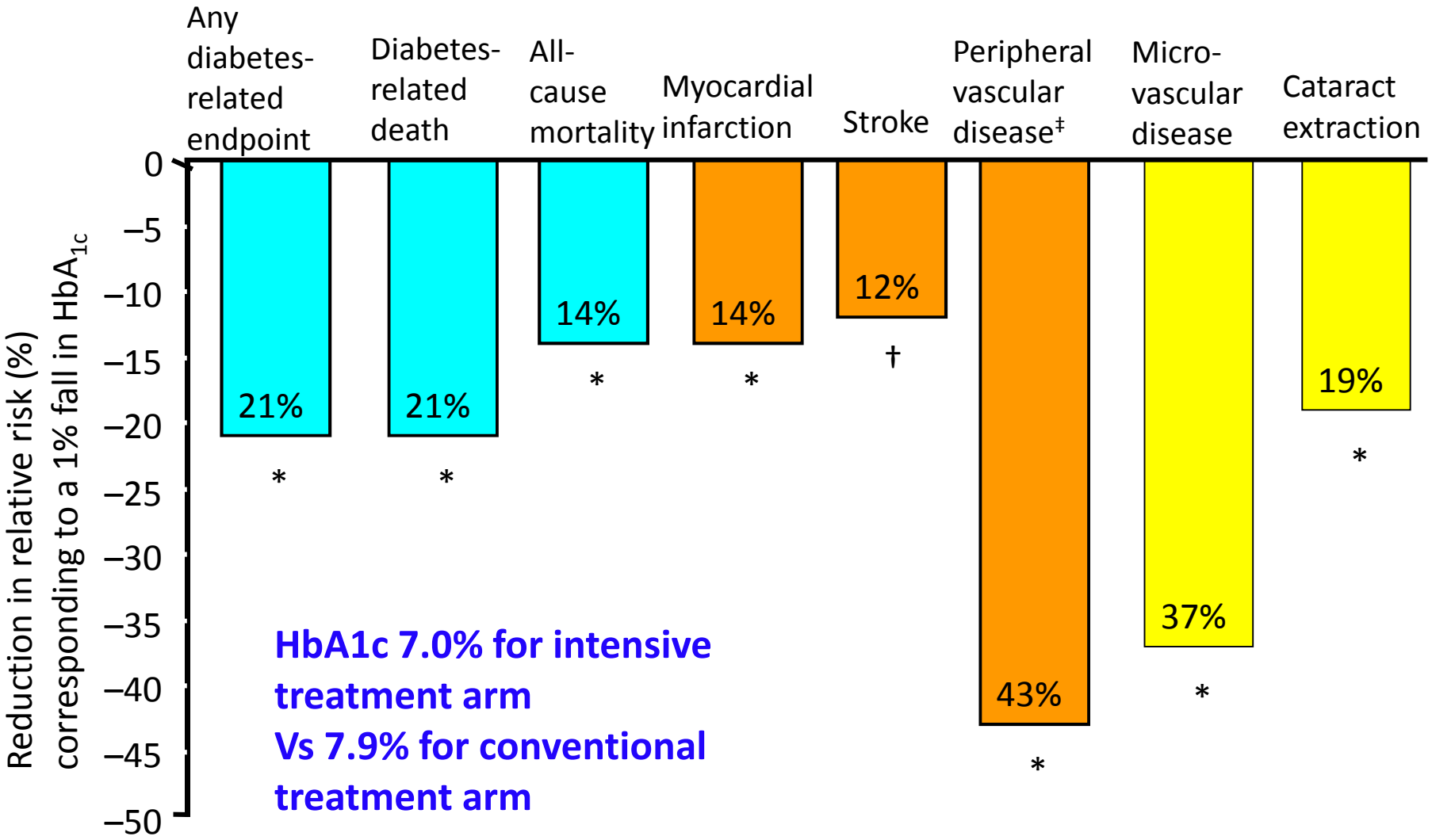
Screening
Basic concepts



Why screening is needed?

- Complications are common and prevalence increased with duration of diabetes
- Cause significant morbidities and mortality
- Early complications are asymptomatic
- Treatments (general and specific) are available to reverse early complications or prevent/slow down deterioration
- Opportunity to improve patients' metabolic control if they realize they already have complications

UKPDS: over 10 years every 1% fall in HbA_{1c} is associated with a reduced relative risk of complications



*p<0.0001 *vs* baseline; †p=0.035

‡Lower extremity amputation or fatal peripheral vascular disease

Adapted from Stratton IM, *et al. BMJ* 2000;321:405–412.

Impact of intensive glycaemic management on diabetes complications: summary of major clinical trials

	Microvascular	Cardiovascular disease	Mortality
DCCT/EDIC[1,2] (T1DM)	↓ ↓	↔ ↓	↔ ↔
UKPDS[3,4] (T2DM)	↓ ↓	↔ ↓	↔ ↓
ACCORD[5] (T2DM)	↓ Albuminuria Neuropathy	↔	↑
ADVANCE[6] (T2DM)	↓ Nephropathy	↔	↔
VADT[7] (T2DM)	↓ Albuminuria	↔	↔

Initial trial

Extended follow-up

T1DM: type 1 diabetes mellitus
T2DM: type 2 diabetes mellitus

[1]DCCT. *N Engl J Med* 1993;329:977–986. [2]DCCT/EDIC study. *N Engl J Med* 2005;353:2643–2653. [3]UKPDS Group. *Lancet* 1998;352:837–853. [4]Holman R, *et al. N Engl J Med* 2008;359:1577–1589. [5]ACCORD Study Group. *N Engl J Med* 2008;358:2545–2559. [6]ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560–2572. [7]Duckworth W, *et al. N Engl J Med* 2009;360:129–139.

UKPDS enrolled newly diagnosed patients

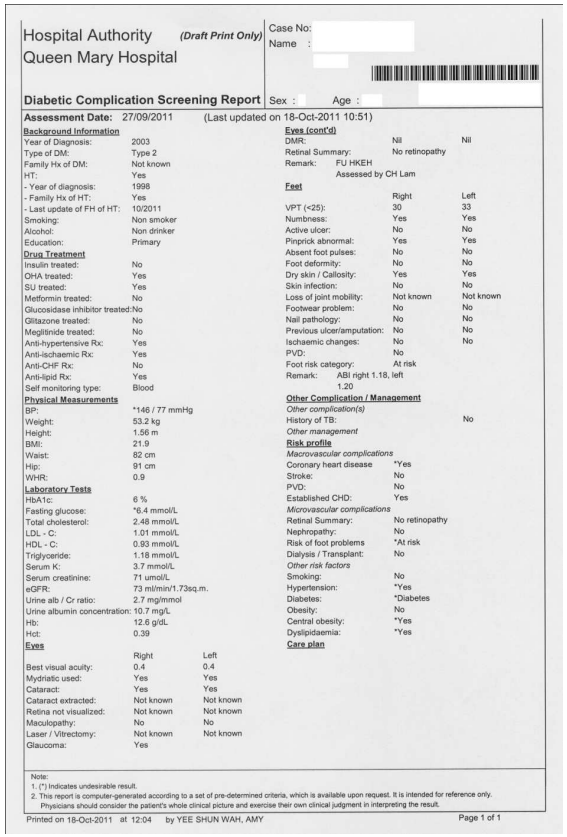
Importance of early intensive treatment

	UKPDS[1] (n=3867)	ADVANCE[2] (n=11,140)	ACCORD[3] (n=10,251)	VADT[4] (n=1791)
	Disease progression			
	Early *vs* late glycaemic intervention:			
Duration of diabetes (years)	0*	8	10	11.5
Mean baseline HbA_{1c} (%)	7.1	7.5	8.3	9.4
Mean baseline FPG (mmol/L)	8.0	8.5	9.7	11.4
Mean age (years)	53	66	62	60

*Newly diagnosed patients
FPG: fasting plasma glucose

[1]UKPDS Group. *Lancet* 1998;352:837–853. [2]ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560–2572. [3]ACCORD Study Group. *N Engl J Med* 2008;358:2545–2559.
[4]Meyers C, *et al. Am J Cardiol* 2006;98:63–65.

Annual diabetes complications screening



Hospital Authority *(Draft Print Only)*
Queen Mary Hospital

Case No:
Name :

Diabetic Complication Screening Report Sex : Age :

Assessment Date: 27/09/2011 (Last updated on 18-Oct-2011 10:51)

Background Information

Year of Diagnosis:	2003
Type of DM:	Type 2
Family Hx of DM:	Not known
HT:	Yes
- Year of diagnosis:	1998
- Family Hx of HT:	Yes
- Last update of FH of HT:	10/2011
Smoking:	Non smoker
Alcohol:	Non drinker
Education:	Primary

Drug Treatment

Insulin treated:	No
OHA treated:	Yes
SU treated:	Yes
Metformin treated:	No
Glucosidase inhibitor treated:	No
Glitazone treated:	No
Meglitinide treated:	No
Anti-hypertensive Rx:	Yes
Anti-ischaemic Rx:	Yes
Anti-CHF Rx:	No
Anti-lipid Rx:	Yes
Self monitoring type:	Blood

Physical Measurements

BP:	*146 / 77 mmHg
Weight:	53.2 kg
Height:	1.56 m
BMI:	21.9
Waist:	82 cm
Hip:	91 cm
WHR:	0.9

Laboratory Tests

HbA1c:	6 %
Fasting glucose:	*6.4 mmol/L
Total cholesterol:	2.48 mmol/L
LDL - C:	1.01 mmol/L
HDL - C:	0.93 mmol/L
Triglyceride:	1.18 mmol/L
Serum K:	3.7 mmol/L
Serum creatinine:	71 umol/L
eGFR:	73 ml/min/1.73sq.m.
Urine alb / Cr ratio:	2.7 mg/mmol
Urine albumin concentration:	10.7 mg/L
Hb:	12.6 g/dL
Hct:	0.39

Eyes

	Right	Left
Best visual acuity:	0.4	0.4
Mydriatic used:	Yes	Yes
Cataract:	Yes	Yes
Cataract extracted:	Not known	Not known
Retina not visualized:	Not known	Not known
Maculopathy:	No	No
Laser / Vitrectomy:	Not known	Not known
Glaucoma:	Yes	

Eyes (cont'd)

DMR:	Nil	Nil
Retinal Summary:	No retinopathy	
Remark:	FU HKEH Assessed by CH Lam	

Feet

	Right	Left
VPT (<25):	30	33
Numbness:	Yes	Yes
Active ulcer:	No	No
Pinprick abnormal:	Yes	Yes
Absent foot pulses:	No	No
Foot deformity:	No	No
Dry skin / Callosity:	Yes	Yes
Skin infection:	No	No
Loss of joint mobility:	Not known	Not known
Footwear problem:	No	No
Nail pathology:	No	No
Previous ulcer/amputation:	No	No
Ischaemic changes:	No	No
PVD:	No	
Foot risk category:	At risk	
Remark:	ABI right 1.18, left 1.20	

Other Complication / Management

Other complication(s)	
History of TB:	No
Other management	

Risk profile

Macrovascular complications	
Coronary heart disease	*Yes
Stroke:	No
PVD:	No
Established CHD:	Yes
Microvascular complications	
Retinal Summary:	No retinopathy
Nephropathy:	No
Risk of foot problems	*At risk
Dialysis / Transplant:	No
Other risk factors	
Smoking:	No
Hypertension:	*Yes
Diabetes:	*Diabetes
Obesity:	No
Central obesity:	*Yes
Dyslipidaemia:	*Yes

Care plan

Note:
1. (*) Indicates undesirable result.
2. This report is computer-generated according to a set of pre-determined criteria, which is available upon request. It is intended for reference only. Physicians should consider the patient's whole clinical picture and exercise their own clinical judgment in interpreting the result.

Printed on 18-Oct-2011 at 12:04 by YEE SHUN WAH, AMY Page 1 of 1

- Type 1 DM with onset of DM $\geq$ 5 yrs
- All Type 2 DM patients , from onset of disease
- Yearly afterwards
  - Maybe longer in uncomplicated patients with good metabolic control

Screening (1)
Eye



- Visual Acuity
- Fundus Photo

Screening (2)
Nephropathy : Urine Albumin excretion :
2 samples out of 3 abnormal

- Cut-off values for different types of urine test

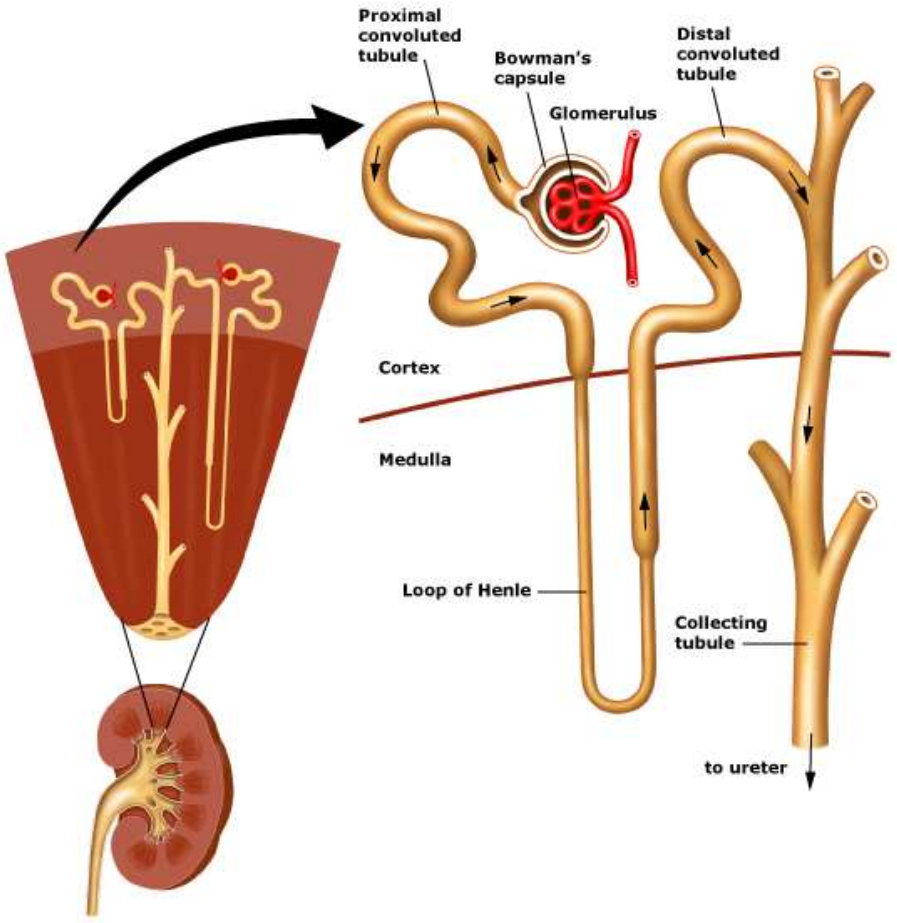
Test	Units	Normal	Micro-albuminuria	Macro-albuminuria
24-hour albumin	mg/d	<30	30-299	≥300
4-hr AER	mcg/min	<20	20-200	>200
Albumin:Creatinine ratio	mg/mmol cr mg/g cr	<3.5 <30	3.5to 35 30-299	>35 ≥300
24 hour urine protein	g/day	____	____	>0.5

Screening (2)
Nephropathy

Stage	Description	GFR (ml/min per 1.73 m^2 body surface area)
1	Kidney damage* with normal or increased GFR	≥90
2	Kidney damage* with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	Kidney failure	<15 or dialysis

Stages of chronic kidney disease by GFR

What is eGFR?



Glomerular filtration rate
Measure number of funtioning nephrons
Normal 120-130ml/min/m2
24 hour urine collection for CrCl

eGFR: estimation
MDRD : sex, age, race, sCr
Cockcroft-Gault
CKD-EPI

Screening (3)
CVA and CAD

- CVA :
  - From history
- CAD :
  - From medical history
  - Symptoms : angina, symptoms of CHF
  - Resting ECG : limited value unless gross abnormalities present
  - Stress test : treadmill / Thallium / MRI or CT angiogram
    - Not recommended as routine screening in asymptomatic patients

Screening (4)
Feet at risk for ulcer and amputation



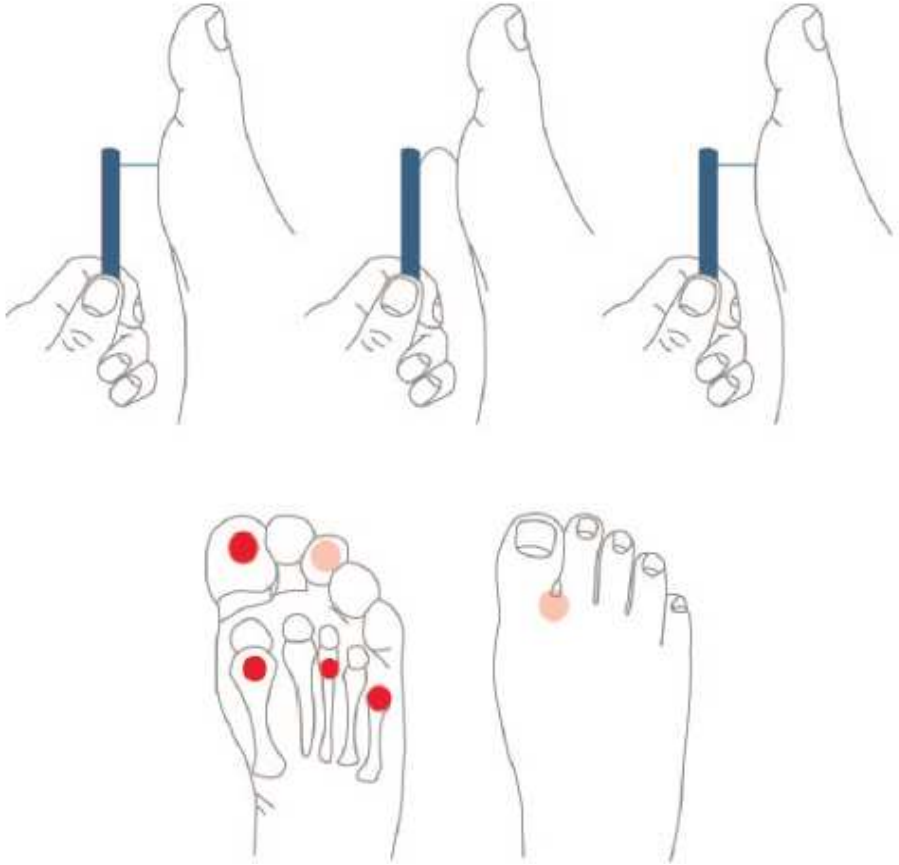
- **Local**
  - Neuropathy and PAD
  - Deformity, loss of joint mobility
  - Dermatological
    - Callus, areas of redness or abrasion
    - Dry skin
    - Tinea Pedis
    - Fungal nails
    - Beware of interdigital lesions
  - Previous Ulcer and amputation
    - **50% contralateral LEA in 2.5 year**

Screening (4)
Feet at risk for ulcer and amputation
Loss of Protective Sensation

- 10-g monofilament sensation
- Vibration sense
  - 128-Hz tuning fork
  - Vibration perception threshold (VPT)
- Pinprick sensation
- Ankle reflexes
- Thermal threshold

- Simple tests
- Require no expensive equipment
- Evidence from prospective clinical cohorts to predict foot ulcer development

Loss of Protective Sensation
10-g monofilament sensation
Semmes-Weinstein monofilament



Boulton et al. Diabetes Care 2008

- Different cohorts consistently showed abnormal sensation to monofilament independently predicted foot ulcer development with Odd Ratio 2-10
  - Boyko et al. Diabetes Care 1999
  - Litzelman et al. Diabetes Care 1997
  - VeVes et al. Diabetologia 1992

Loss of Protective Sensation
Vibration perception threshold (VPT)

- A VPT > 25 V is regarded as abnormal and has been shown to strongly predict foot ulceration
  - Young et al. Diabetes Care 1994
  - Armstrong et al. Arch Intern Med 1998

Loss of Protective Sensation

- 10-g monofilament sensation
- Vibration sense
  - 128-Hz tuning fork
  - Vibration perception threshold (VPT)
- Pinprick sensation
- Ankle reflexes
- Thermal threshold

- **Any one test abnormal => LOPS**
- **Need 2 normal tests for screening**
  - **Recommend monofilament + 1 other**

Screening (4)
Feet at risk for ulcer and amputation

- **Assess for Peripheral Arterial disease (PAD)**
  - Cold foot
  - No hair / Tissue Loss
  - Dependant rubor
  - Absent pulses
    - Posterior tibial and dorsalis pedis
    - Check with Doppler
  - Ankle-Brachial Index
    - Khan et al. JAMA 2006

Ankle-Brachial Index (ABI)

- ABI =
  - **ankle systolic pressure / higher of two brachial systolic pressures**
  - **Normal : >0.9 to 1.3**
  - <0.8 is associated with claudication
  - <0.4 is associated with ischemic rest pain and tissue necrosis
- In the presence of incompressible calf or ankle arteries (ABI>1.3)
  - measurements of digital arterial systolic pressure (toe pressure)
  - or transcutaneous oxygen tension

Screening (5)
Assessment of concomitant metabolic risk factors

- Obesity
  - Weight
  - BMI
  - Waist circumference
  - Waist – Hip Ratio
- Blood Pressure
- Lipid profile

ABC + 2A + 2S

- HbA1c 7%
- Blood Pressure
- Cholesterol

+ Aspirin

+ ACEI or ARB

+ Stop Smoking