Chronic DM complications

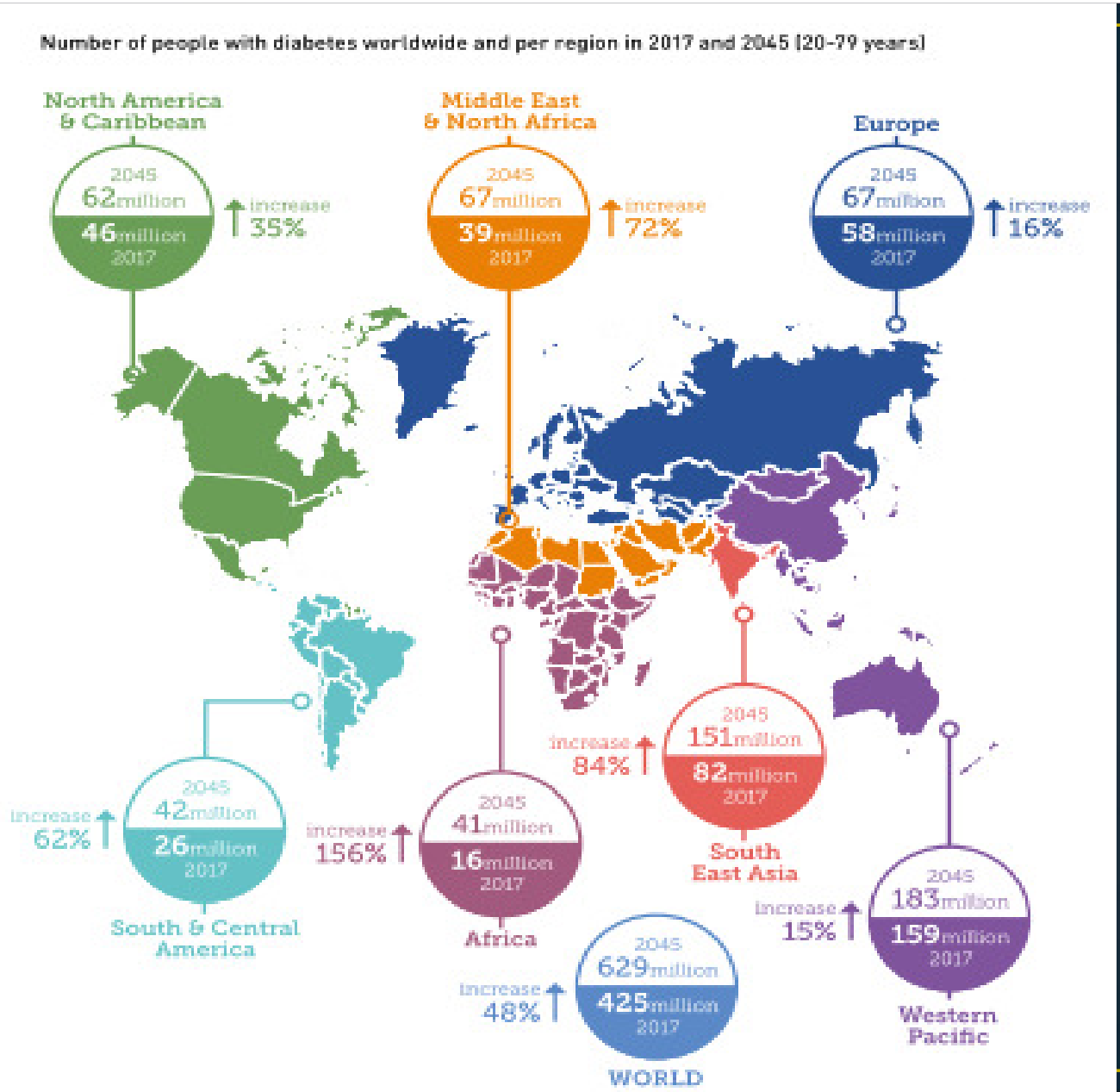
AHKDN 18 Oct 2018

C L Wong

Outline

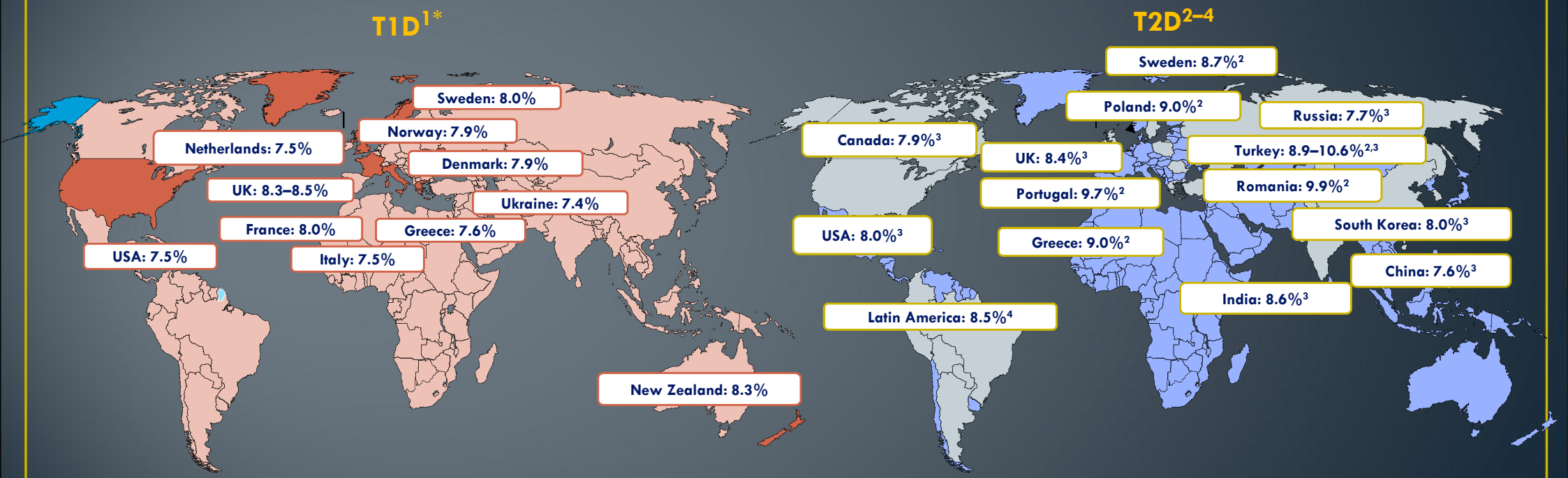
- Introduction
- Microvascular complications
- Macrovascular complications
- Miscellaneous

Burden of Diabetes



The worldwide challenge of glycaemic control

HbA_{1c} in T1D and T2D

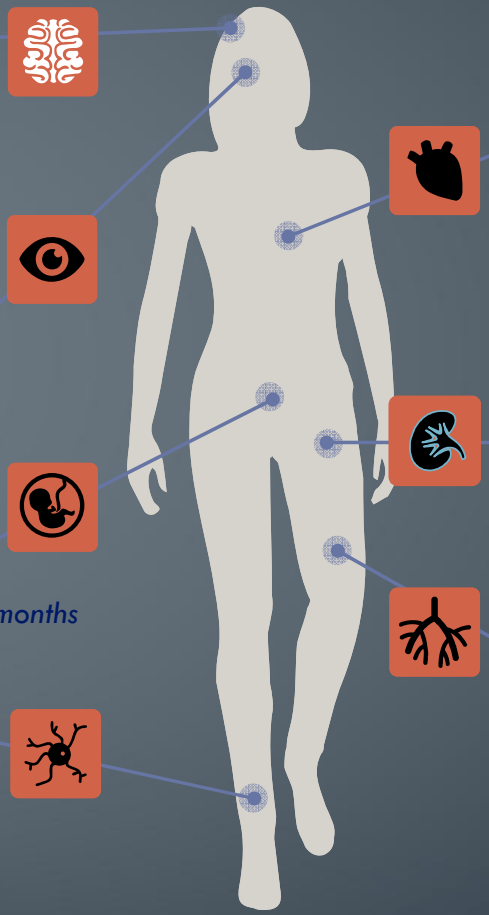


*Data are median and in adults (25+ years)

T1D, type 1 diabetes; T2D, type 2 diabetes

1. McKnight *et al. Diabet Med* 2015;32:1036–50; 2. Oguz *et al. Curr Med Res Opin* 2013;29:911–20; 3. Polinski *et al. BMC Endocr Disord* 2015;15:46; 4. Mendivil *et al. Curr Med Res Opin* 2014;30:1769–76

The consequences of hyperglycaemia



Brain

1,2 – 1.8x risk of stroke
Dementia

Eyes

Retinopathy
Macular oedema
Cataracts
Glaucoma

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

Pregnancy and birth

Babies 5x more likely to be stillborn
Babies 3x more likely to die within first months of life

Nervous system

Sensorimotor polyneuropathy
Autonomic nerve damage
Diabetic foot
Amputation

Heart

Coronary artery disease
Angina
Heart attack
Hypertension
Heart failure

75% diabetic patients die from CV events[4]

Kidneys

Nephropathy
Nephrotic syndrome
ESRF

Leading cause of end-stage renal disease[2]

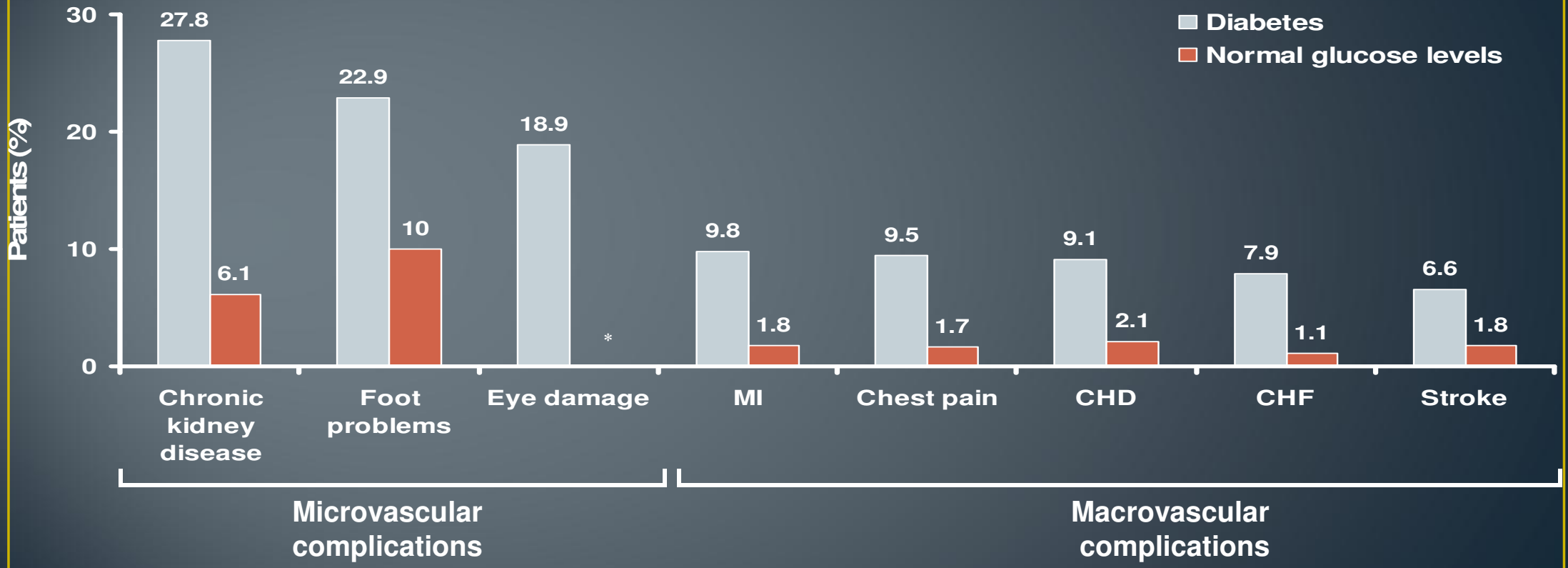
Circulation

Peripheral vascular disease

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

DCCT *N Engl J Med* 1993;329:977-86; Stratton *et al. BMJ* 2000;321:405–12

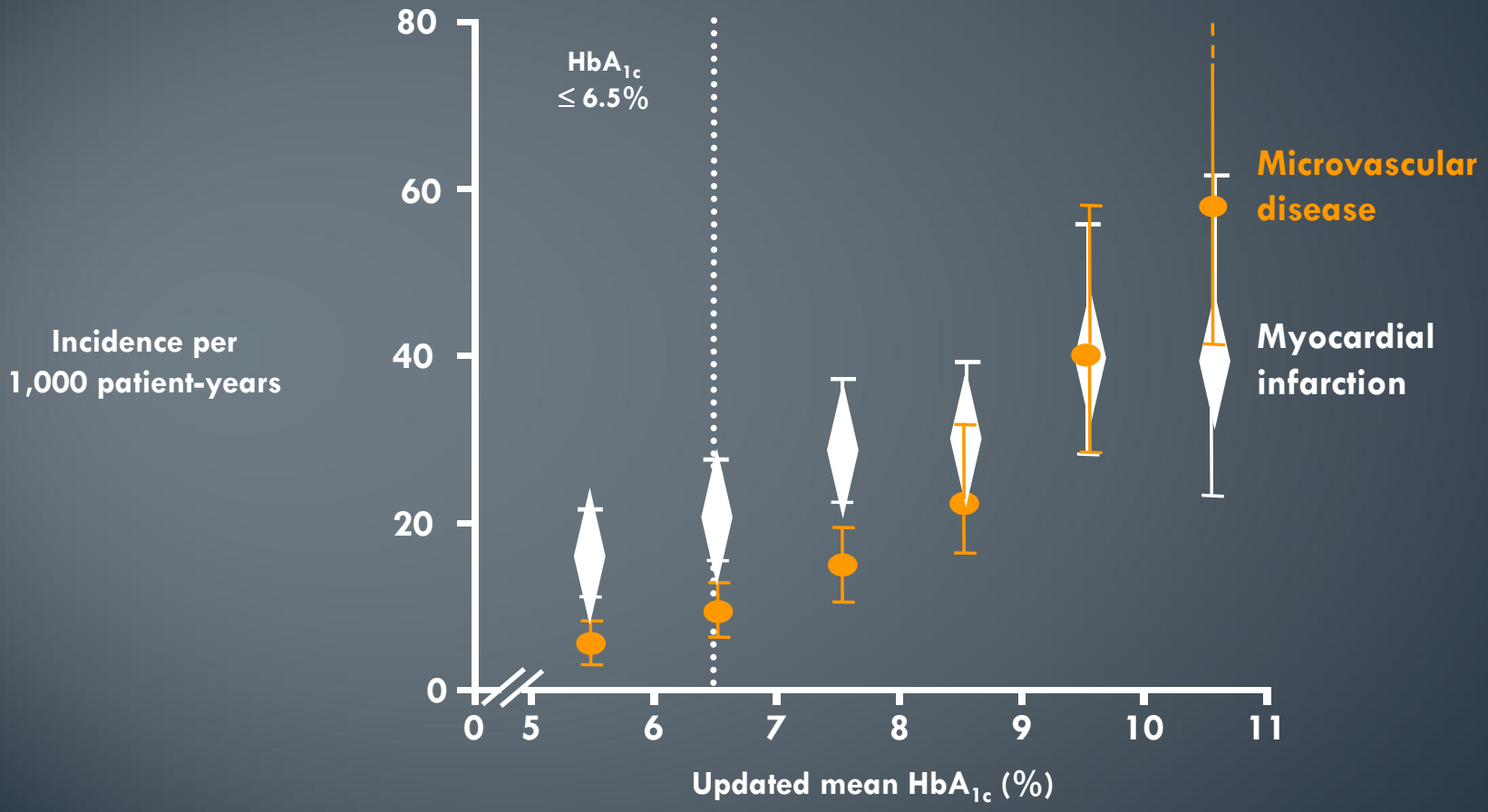
Increased prevalence of macrovascular and microvascular complications in type 2 diabetes



*Data for prevalence of eye damage for individuals with normal glucose control not available

AACE. State of Diabetes Complications in America Report, 2007. Available at: http://www.aace.com/newsroom/press/2007/images/DiabetesComplicationsReport_FINAL.pdf (accessed 23 November 2007).

UKPDS: Elevated blood glucose levels increase the risk of diabetic complications



Study population: White, Asian Indian and Afro-Caribbean UKPDS patients (n = 4,585)
Adjusted for age, sex and ethnic group
Error bars = 95% CI

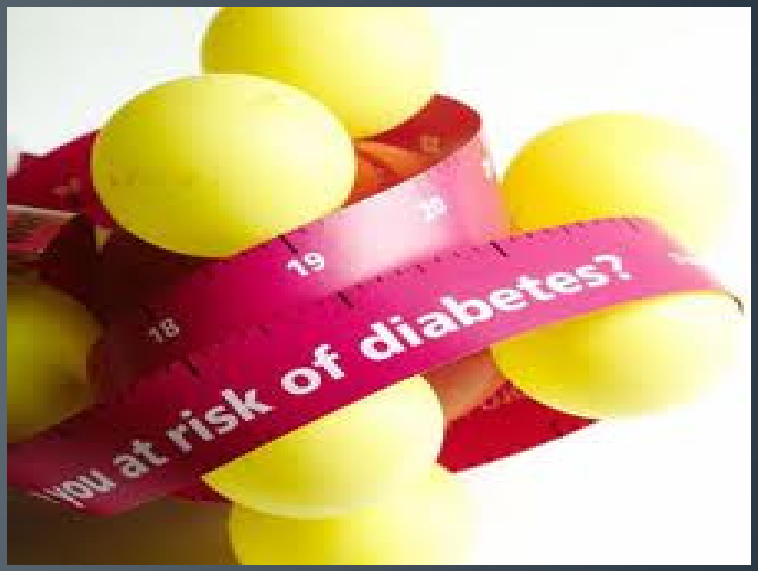
Adapted from Stratton IM, *et al. BMJ* 2000;321:405–412.

DM complication screening in CMC (2016)

- 2682 type 2 DM patients
- Nephropathy
  - Any degree of proteinuria – 46% (microalbuminuria 28%)
  - eGFR <60ml/min/1.73m^2 – 27%
- Retinopathy
  - 3.1% has sight threatening retinopathy
  - 10.2% has non sight threatening retinopathy
- Vibratory perception threshold (VPT) (reference range < 25)
  - 4.4% had impaired VPT

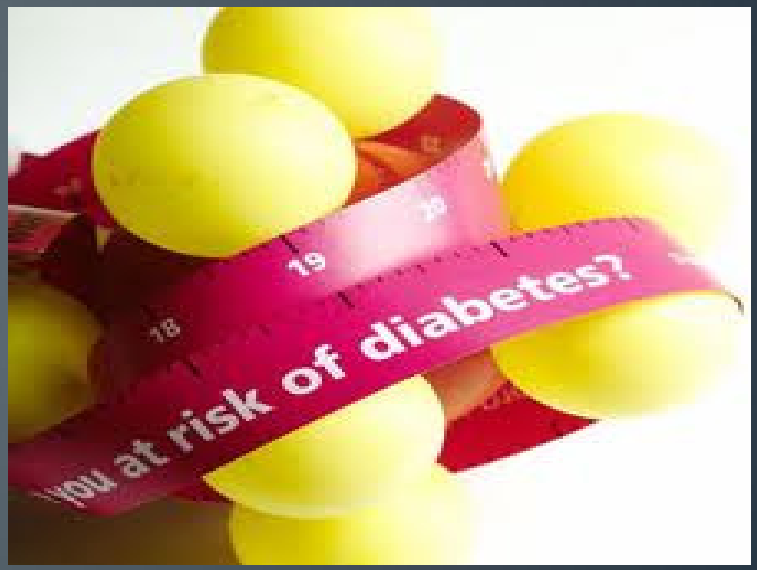
Diabetic complications - classical

- Microvascular complications
  - Retinopathy
  - Nephropathy
  - Neuropathy
- Macrovascular complications
  - Ischaemic heart disease
  - Stroke
  - Peripheral vascular disease

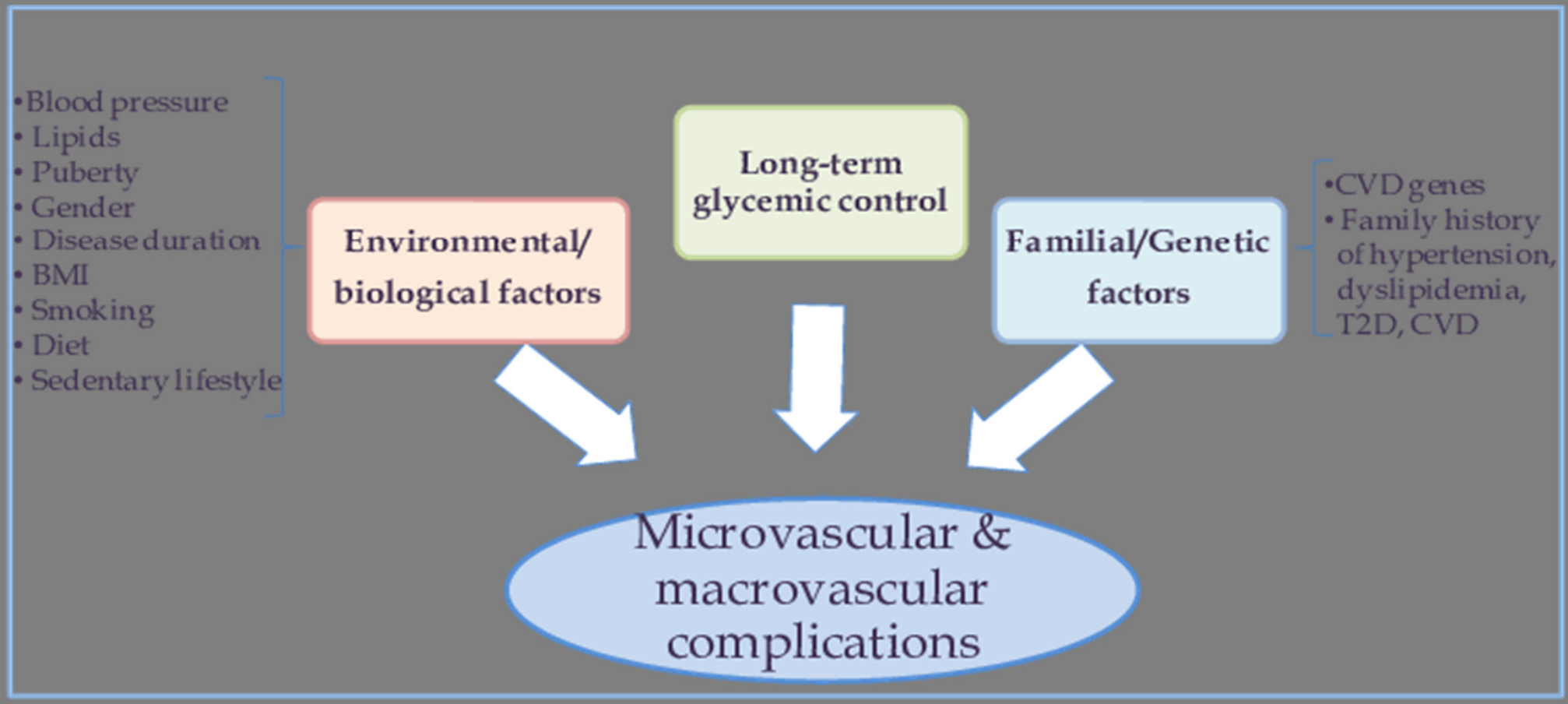


Diabetic complications - novel

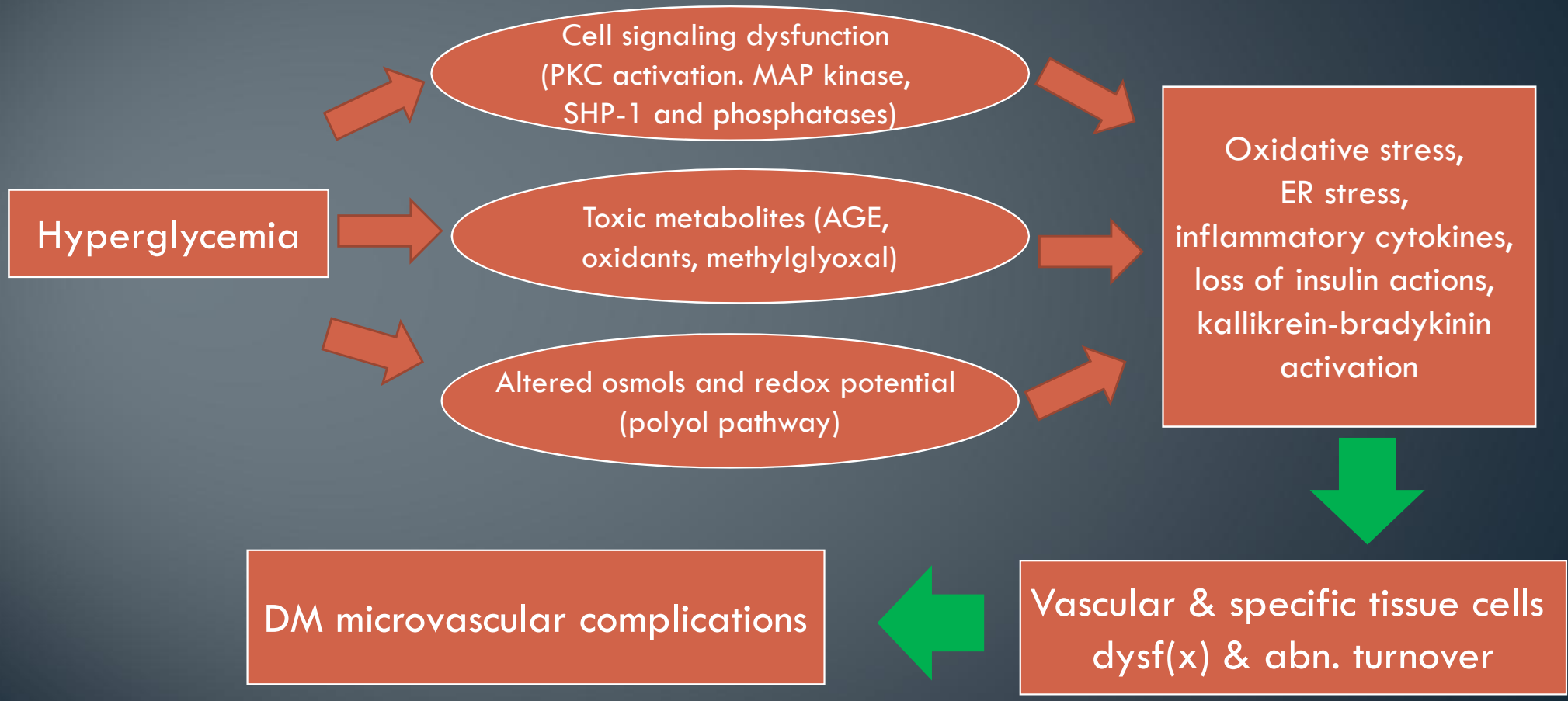
- Microvascular complications
  - Retinopathy
  - Nephropathy
  - Neuropathy
- Macrovascular complications
  - Ischaemic heart disease
  - Stroke
  - Peripheral vascular disease
- Novel
  - Heart failure
  - Dementia
  - Osteoporosis
  - Hypoglycemia

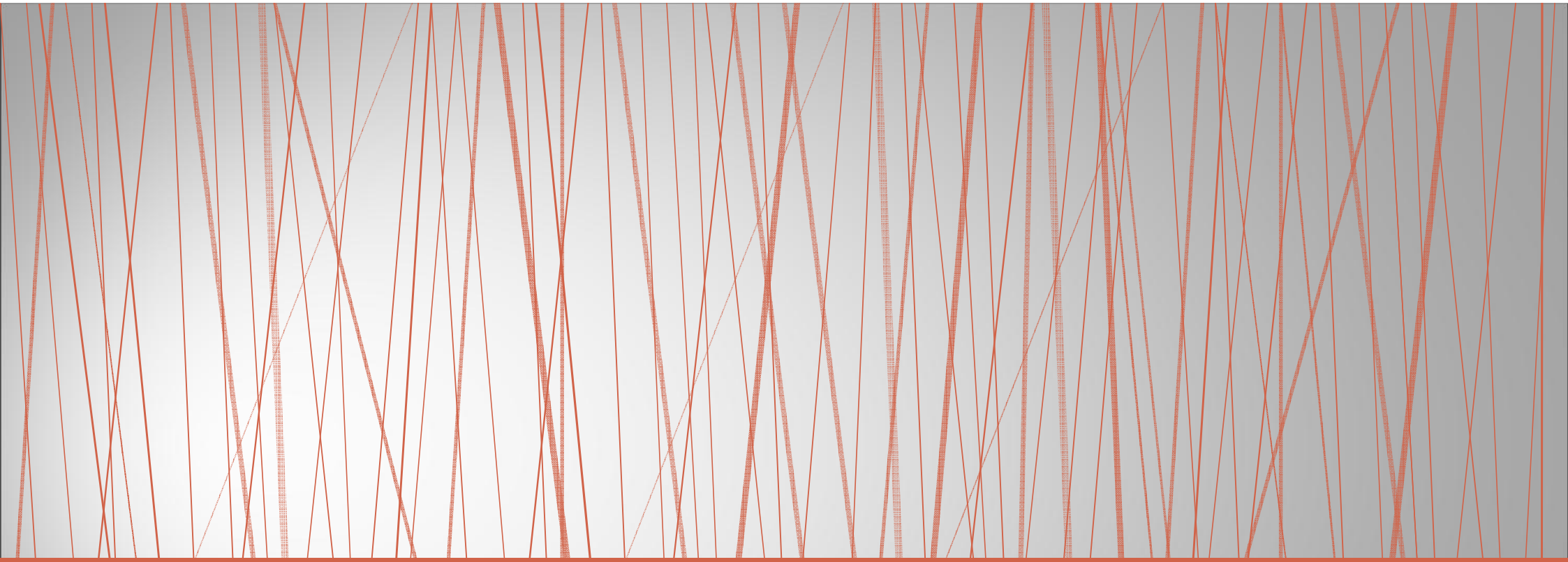


Mechanisms


•Blood pressure
• Lipids
• Puberty
• Gender
• Disease duration
• BMI
• Smoking
• Diet
• Sedentary lifestyle
Environmental/ biological factors
Long-term glycemic control
Familial/Genetic factors
•CVD genes
• Family history of hypertension, dyslipidemia, T2D, CVD
Microvascular & macrovascular complications

Hyperglycemia

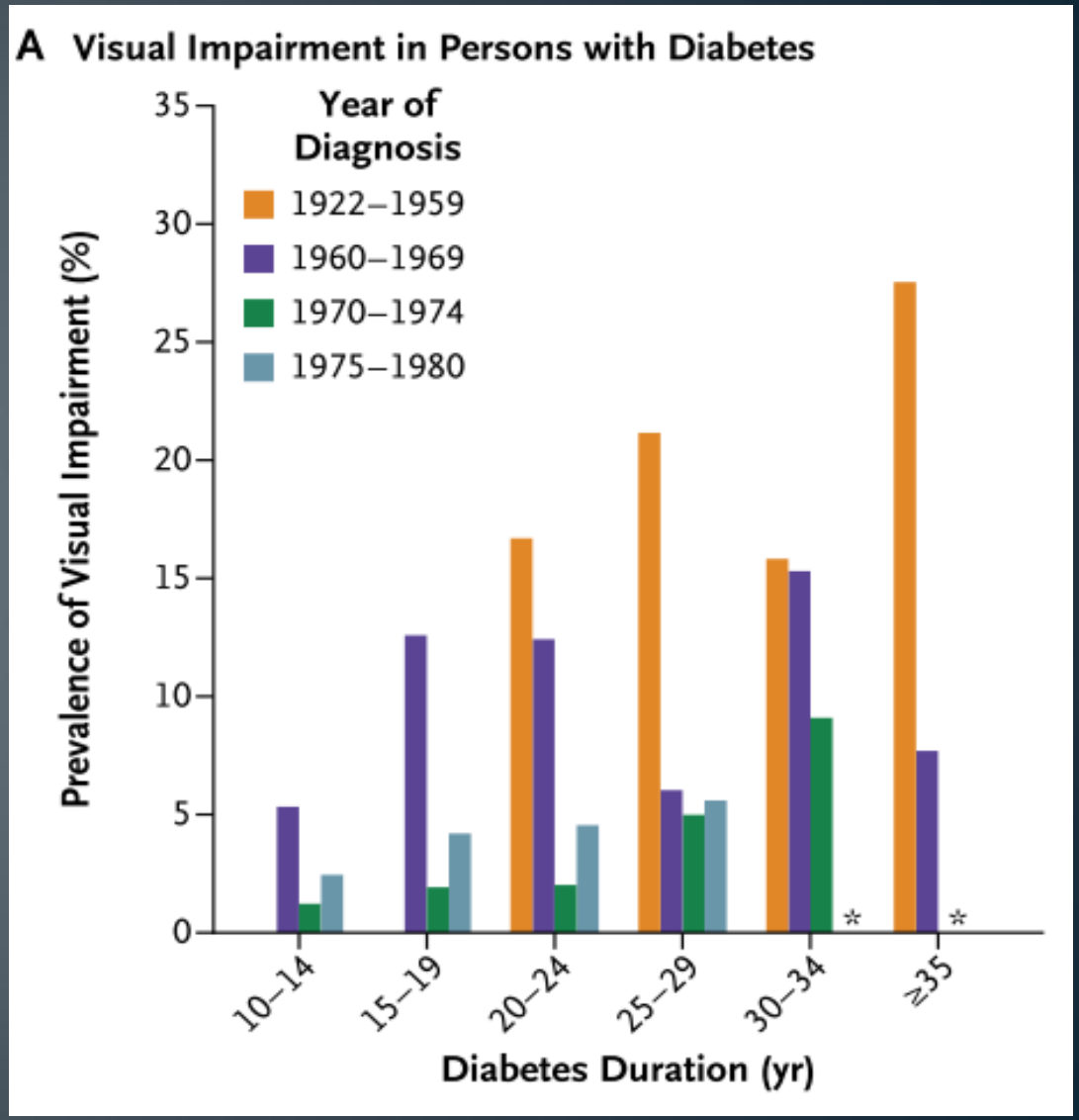




I. Diabetic retinopathy

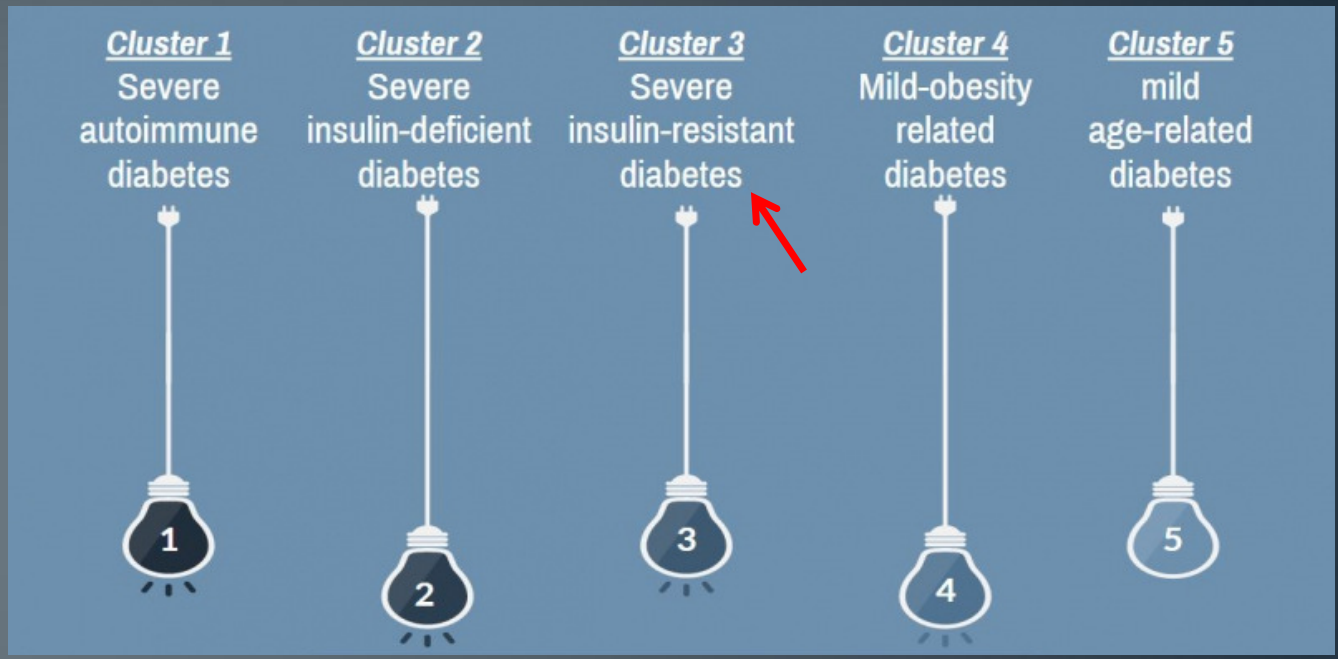
Diabetic retinopathy

- Leading cause of (preventable) blindness worldwide
- Prevalence 35-40%
- Correlate with degree of hyperglycemia and duration of diabetes
- May predate diagnosis of DM (up to 7 years)
  - 20% got DR at Dx of DM



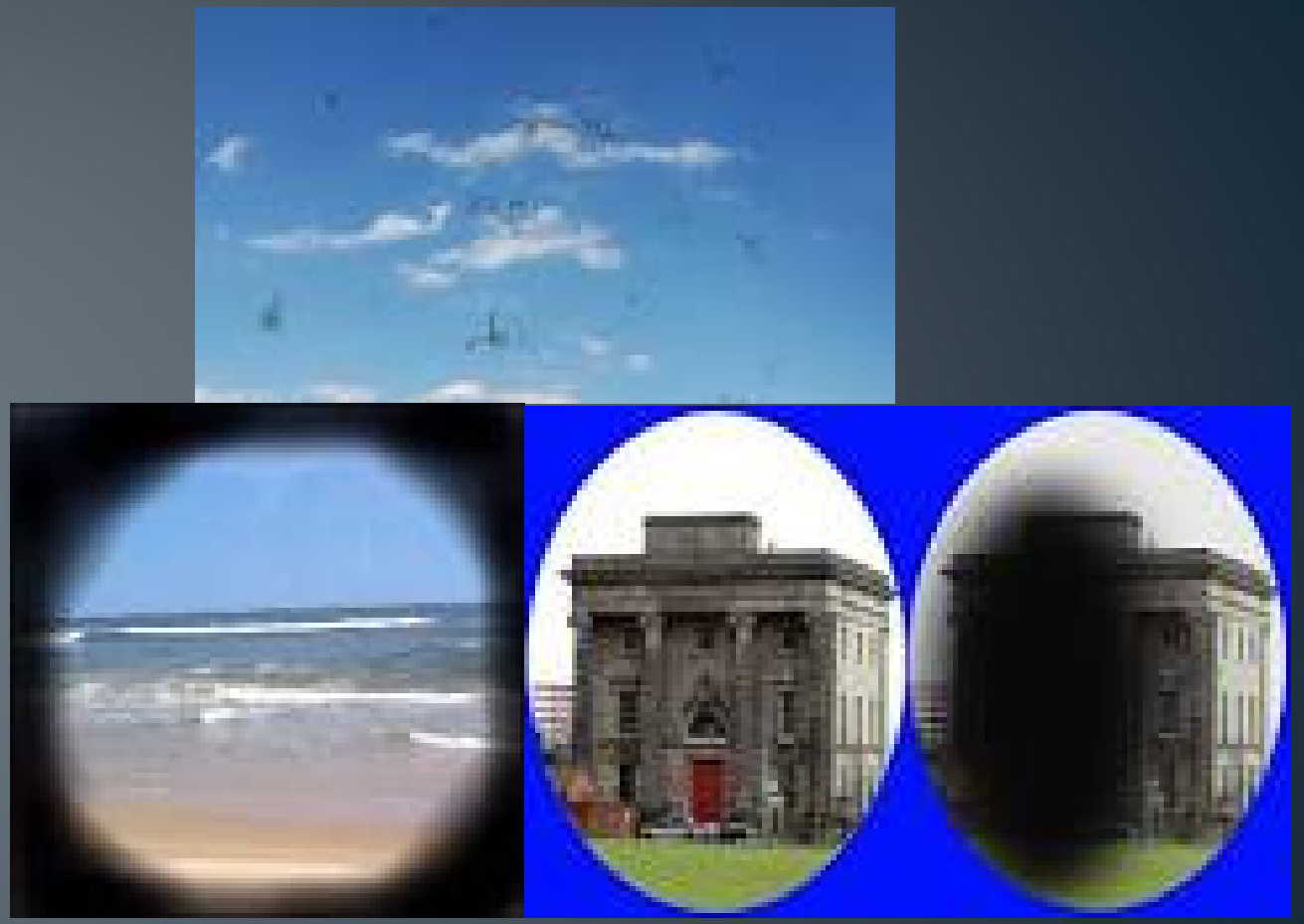
Risk factors

- Hyperglycemia
- Hypertension
- Dyslipidemia
- High BMI
- Low physical activity
- Pregnancy
- Anaemia
- Renal failure
- Smoking
- Less clear: fatty liver, OSA, adiponectin, homocysteine



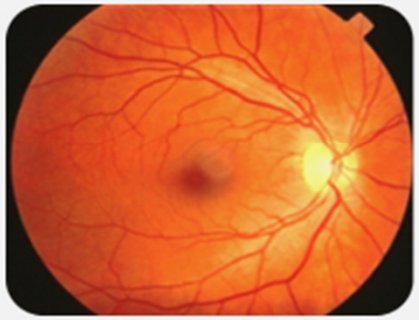
Clinical features

- Asymptomatic
- Floaters
- Impaired color vision
- Visual blurring
- Scotoma
- Vision loss



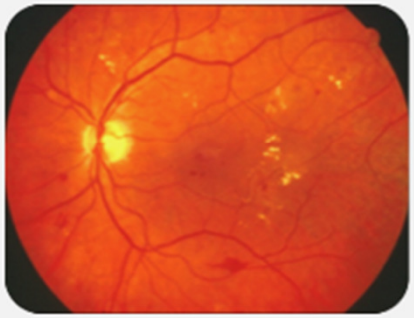
AAO & RCO (UK NHS) DR staging

Normal Fundus



UK equivalence:
R0

Moderate Nonproliferative DR (NPDR)



Mild NPDR

Microaneurysms only

Moderate NPDR

More than just microaneurysms but less than severe nonproliferativediabetic retinopathy

R1

Severe NPDR



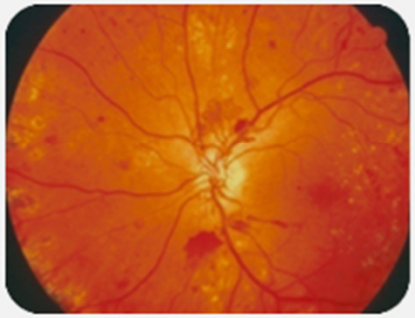
Severe Non proliferative Diabetic Retinopathy

Any of the following:

- More than 20 intraretinal hemorrhages in each of 4 quadrants
- Definite venous beading in 2+ quadrants
- Prominent IRMA in 1+ quadrant and no signs of PDR

R2

Proliferative DR (PDR)



Proliferative Diabetic Retinopathy

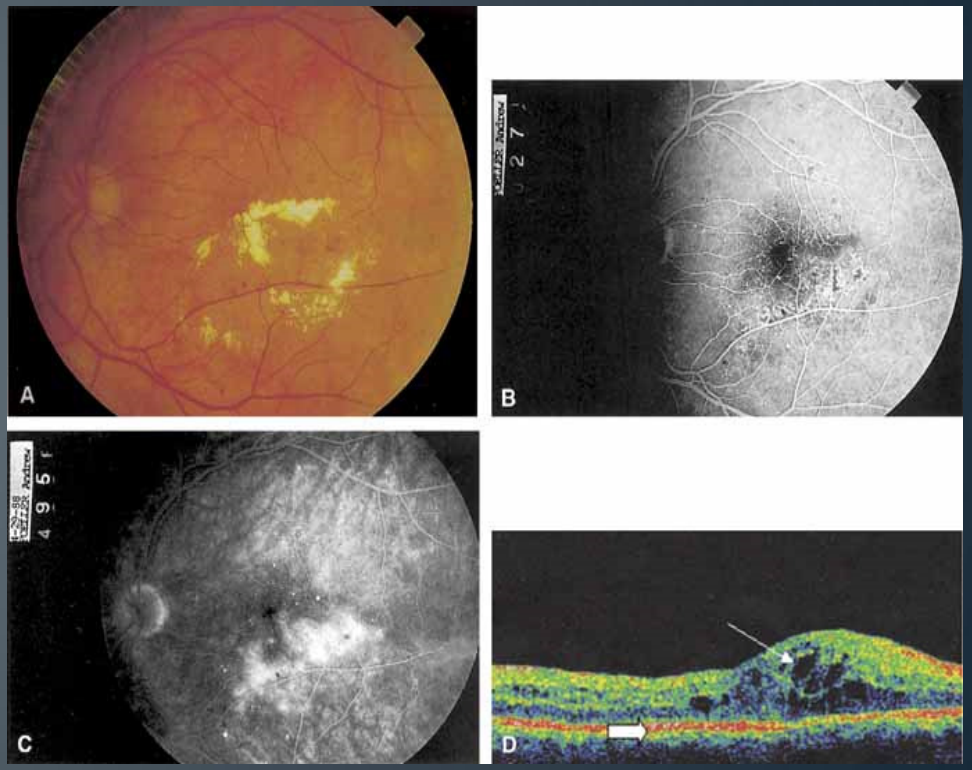
1 or more of the following:

- Neovascularization
- Vitreous/preretinal hemorrhage

R3

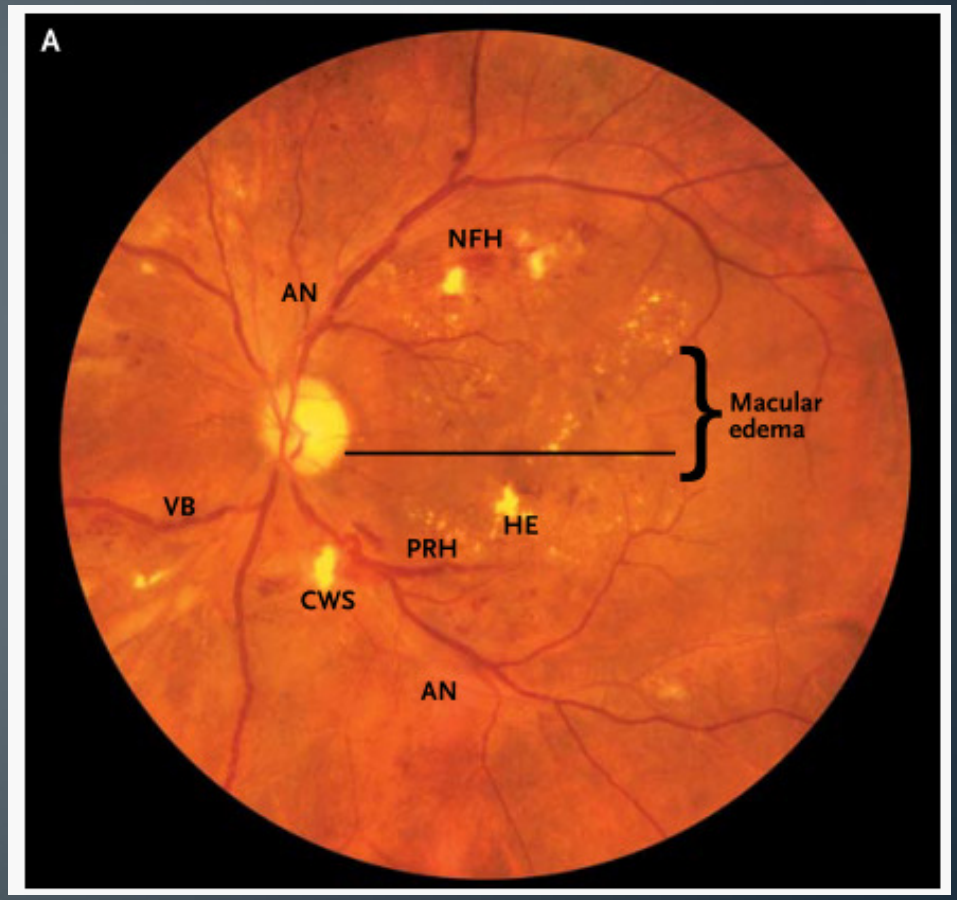
Diabetic maculopathy /macular edema

- a) exudate within 1 disc diameter (DD) of the centre of the fovea
- b) circinate or group of exudates within the macula
- c) any microaneurysm or haemorrhage within 1 DD of the centre of the fovea only if associated with a best VA of +0.3 logMAR (6/12) or worse

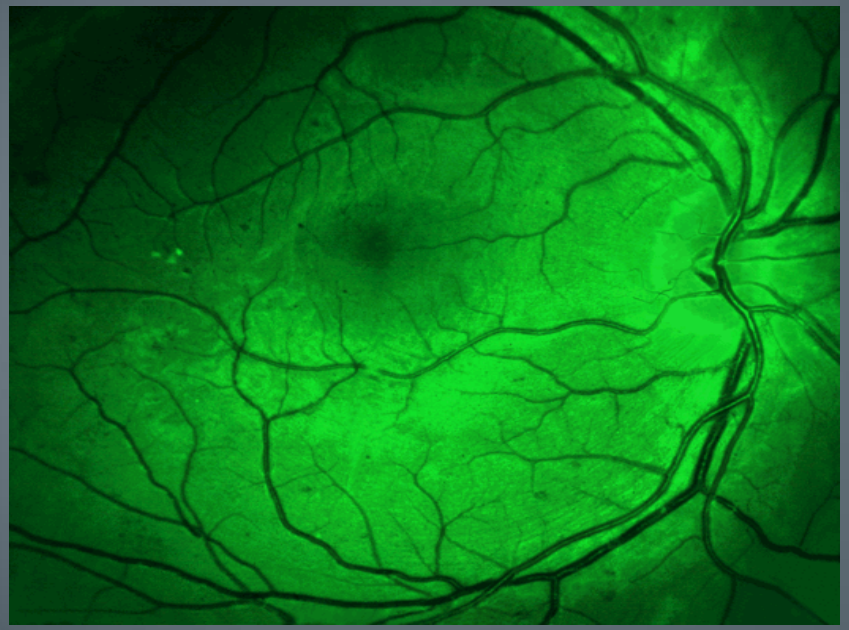


Non-proliferative retinopathy

- Micro-aneurysms
- Scattered exudates
- Hemorrhages(flame shaped, Dot and Blot)
- Cotton wool spots (<5)
- Venous dilatations



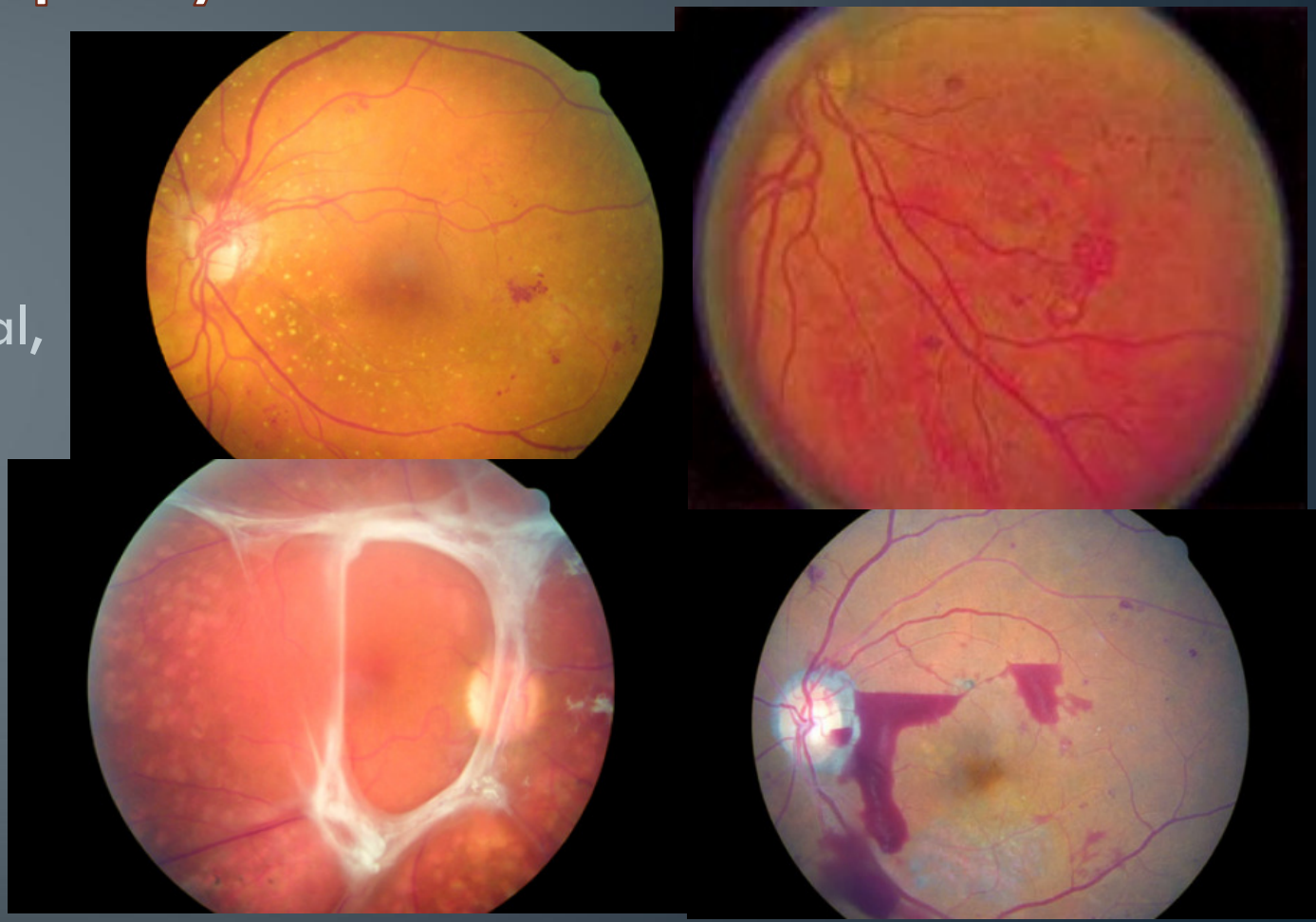
Non-proliferative retinopathy



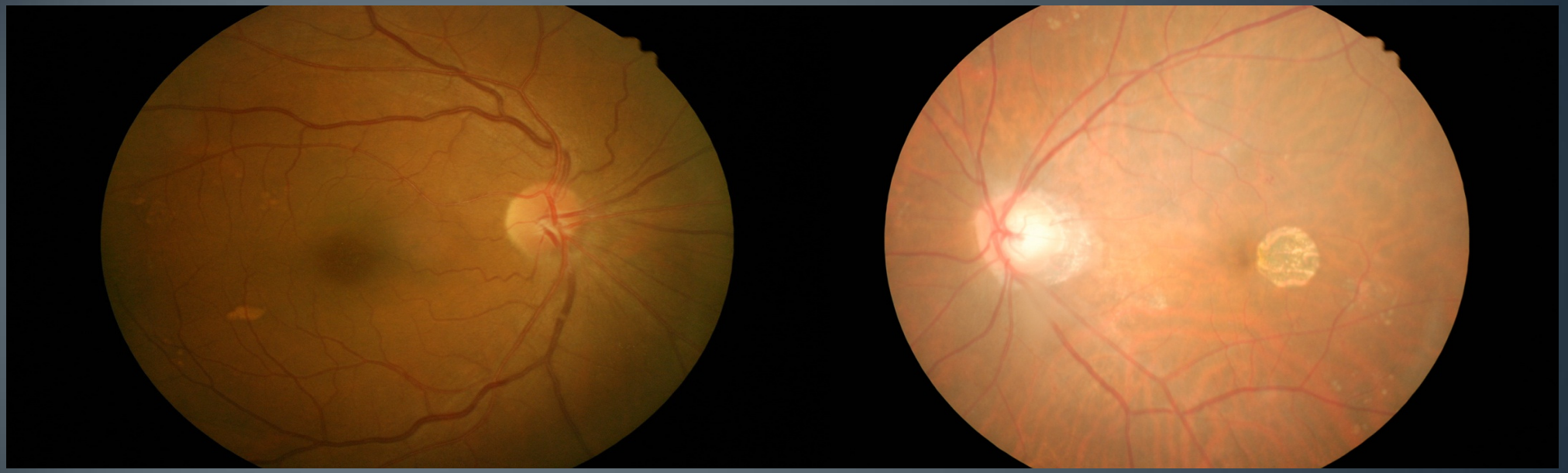


Proliferative Retinopathy

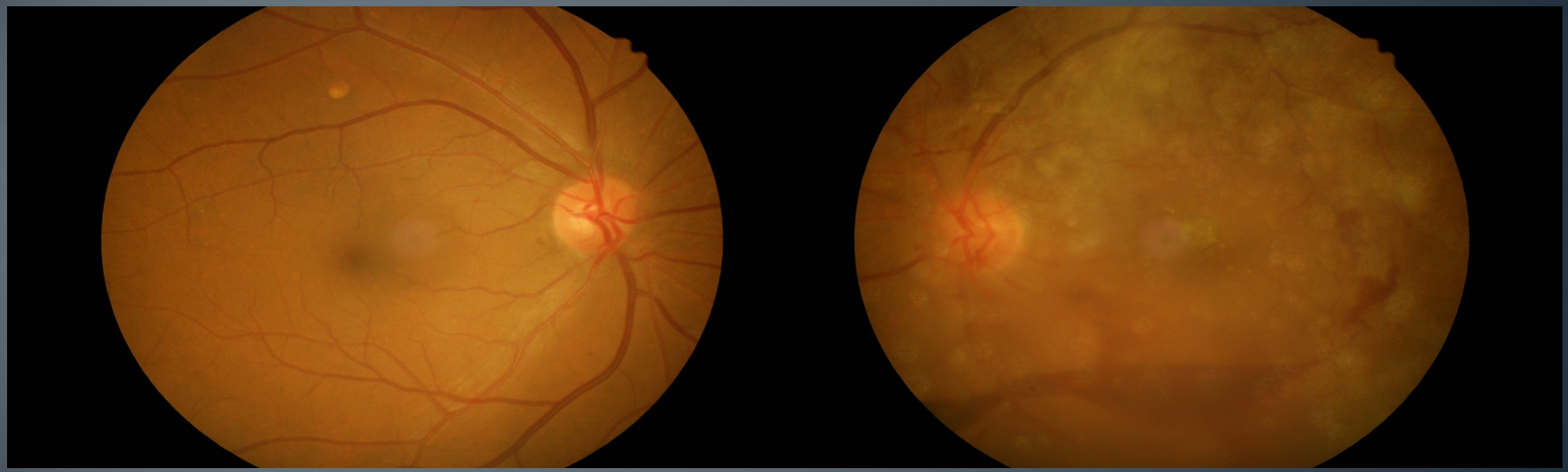
- Neovascularisation
- Fibrous proliferation
- Hemorrhages (preretinal, vitreous)



Visual acuity: Rt 0.5; Lt 0.7



Visual acuity: Rt 0.5; Lt 0.4

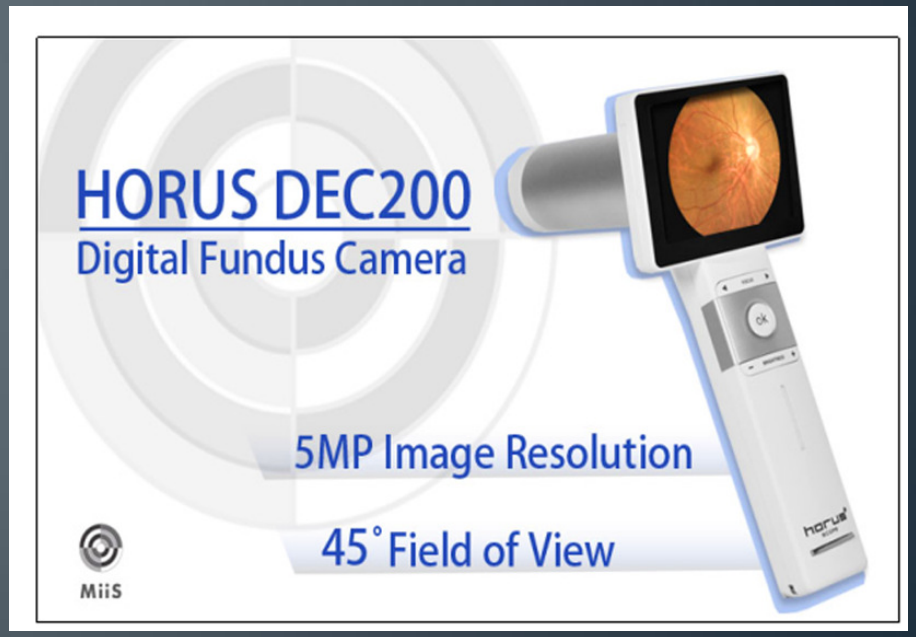


Screening and follow-up recommendations

	ADA 2018	RCO 2012	AAO 2016
1st Screening	Type 1 – 5 years after Dx Type 2 – At diagnosis		
Subsequent			
No DR	@ 1-2 years	@ 1 year	@ 1 year
Non-PDR	More frequent Severe – Refer Eye	R1 - @ 1 year R2 – Refer Eye in 3 months	Mild/moderate – @ 1 year Severe - @ 4 months
PDR	Refer Eye	Refer Eye in 2 wks	@ 4 months
Maculopathy	Refer Eye	Refer Eye in 3 months	Non-CSME - @ 4 months CSME - @ 1 month

Screening methods

- Dilated and comprehensive eye examination by ophthalmologist or optometrist (dilated slit-lamp biomicroscopy)
- Retinal photography (non-mydriatic)
- Telemedicine
  - Portable camera
  - Smartphone based
  - Intelligent Retinal Imaging System



Are we making good use of our public resources? The false-positive rate of screening by fundus photography for diabetic macular oedema

Raymond LM Wong *, CW Tsang, David SH Wong, Sarah McGhee, CH Lam, J Lian, Jacky WY Lee, Jimmy SM Lai, Victor Chong, Ian YH Wong *

RESULTS: A total of 491 patients were recruited during the study period. Of the 352 who were eligible for analysis, 44.0%, 17.0%, and 38.9% were graded as M1 due to the presence of foveal 'haemorrhages', 'exudates', or 'haemorrhages and exudates', respectively. The mean (±standard deviation) central macular thickness was 265.1±55.4 μm. Only 13.4% (95% confidence interval, 9.8%-17.0%) of eyes had a central macular thickness of ≥300 μm, and 42.9% (95% confidence interval, 37.7%-48.1%) of eyes had at least one optical coherence tomography sign of diabetic macular oedema. For patients with retinal haemorrhages only, 9.0% (95% confidence interval, 4.5%-13.5%) had a central macular thickness of ≥300 μm; 23.2% (95% confidence interval, 16.6%-29.9%) had at least one optical coherence tomography sign of diabetic macular oedema. The false-positive rate of the current screening strategy for diabetic macular oedema was 86.6%.

CONCLUSION: The high false-positive rate of the current diabetic macular oedema screening adopted by the United Kingdom and Hong Kong may lead to unnecessary psychological stress for patients and place a financial burden on the health care system. A better way of screening is urgently needed. Performing additional spectral-domain optical coherence tomography scans on selected patients fulfils this need.

Treatment

- Intensive glycemic control (DCCT, UKPDS)
  - Type 1 DM: reduce 50-70%; Type 2 DM : reduce 20-30%
- Blood pressure control (UKPDS)
- RAS inhibition
  - Enalapril & losartan : RASS , reduce risk of progression by 65%
  - Candesartan: DIRECT-1 & -2, reduce incidence by 18%
- Lipid control (PPAR-α agonist)
  - Fenofibrate : ACCORD-Eye – reduce risk of progression by 40%; FIELD – reduce risk of progression and macular edema by one-third

Treatment

	Panretinal photocoagulation	Focal / Grid laser	Anti-VEGF Therapy (bevacizumab, ranibizumab, aflibercept)
Severe NPDR	Sometimes	No	No
PDR	Recommended (esp. high risk*)	Sometimes (if ME)	Alternative** (Combined with PRP in high risk PDR***)
CSME	Sometimes	Sometimes	Usually

Other adjuncts: Intravitreal corticosterids, VEGF aptamer

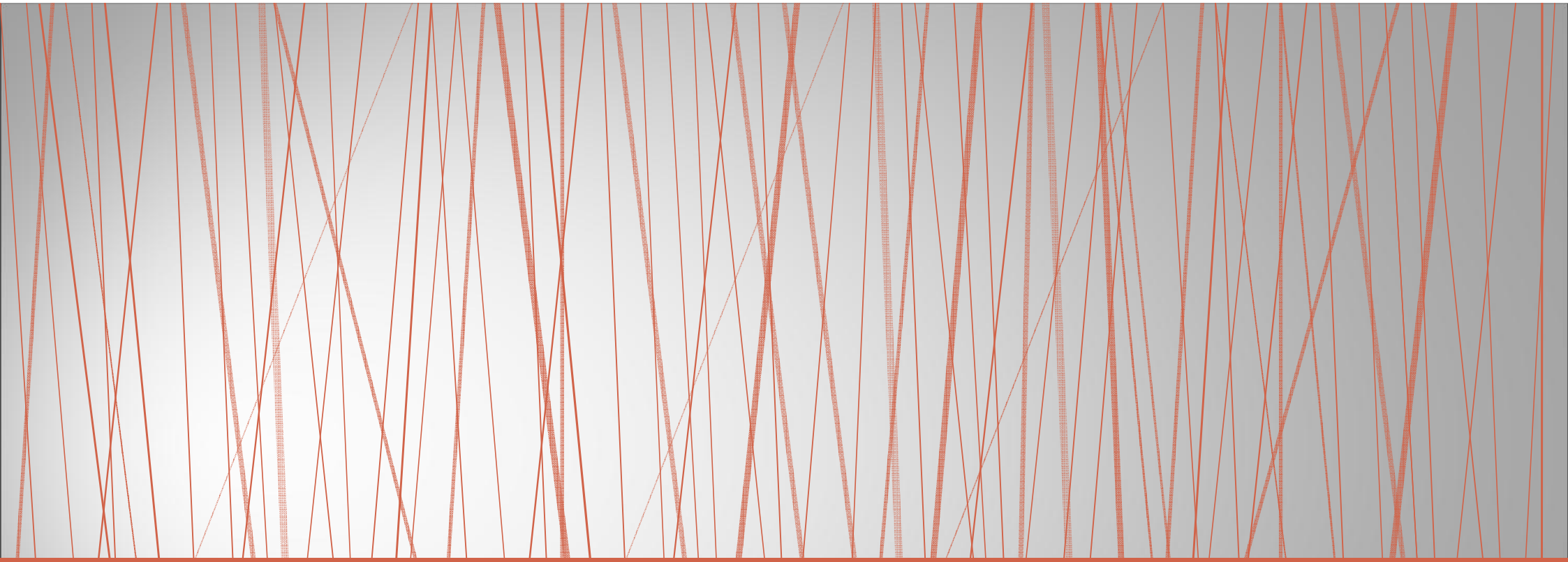
•High risk PDR: Presence of NVD greater than approximately one-third of the area of the optic disc, or any NVD associated with vitreous or subhyaloid hemorrhage, or an area of NVE greater than one-half of the area of the optic disk with concomitant vitreous or subhyaloid hemorrhage

•** Diabetic Retinopathy Clinical Research Network. JAMA 2015;314(20):2137-2146

•*** PROTEUS Study. Ophthalmology 2018, 125(5): 691 - 700

DR and pregnancy

- Risk of progression: (Diabetes in Early Pregnancy Study)
  - **No DR: 10.3%**
  - Microaneurysms only: 21.1%
  - Mild DR:18.8%,
  - Moderate to severe DR: 54.8%
- Greatest risk – 2nd trimester; Persist till 12 months postpartum
- Start screening pre-pregnancy/1st trimester
  - If No DR – repeat @ 3-12 months (US) or at 28 wks (UK)
  - If DR – repeat @ 1-3 months (US) or repeat at 16-20 wks (UK)
- GDM – no need screening
- Vaginal delivery no contraindicated
- Management – pre-conceptual councelling, prompt PRP for severe NPDR (avoid PDR)

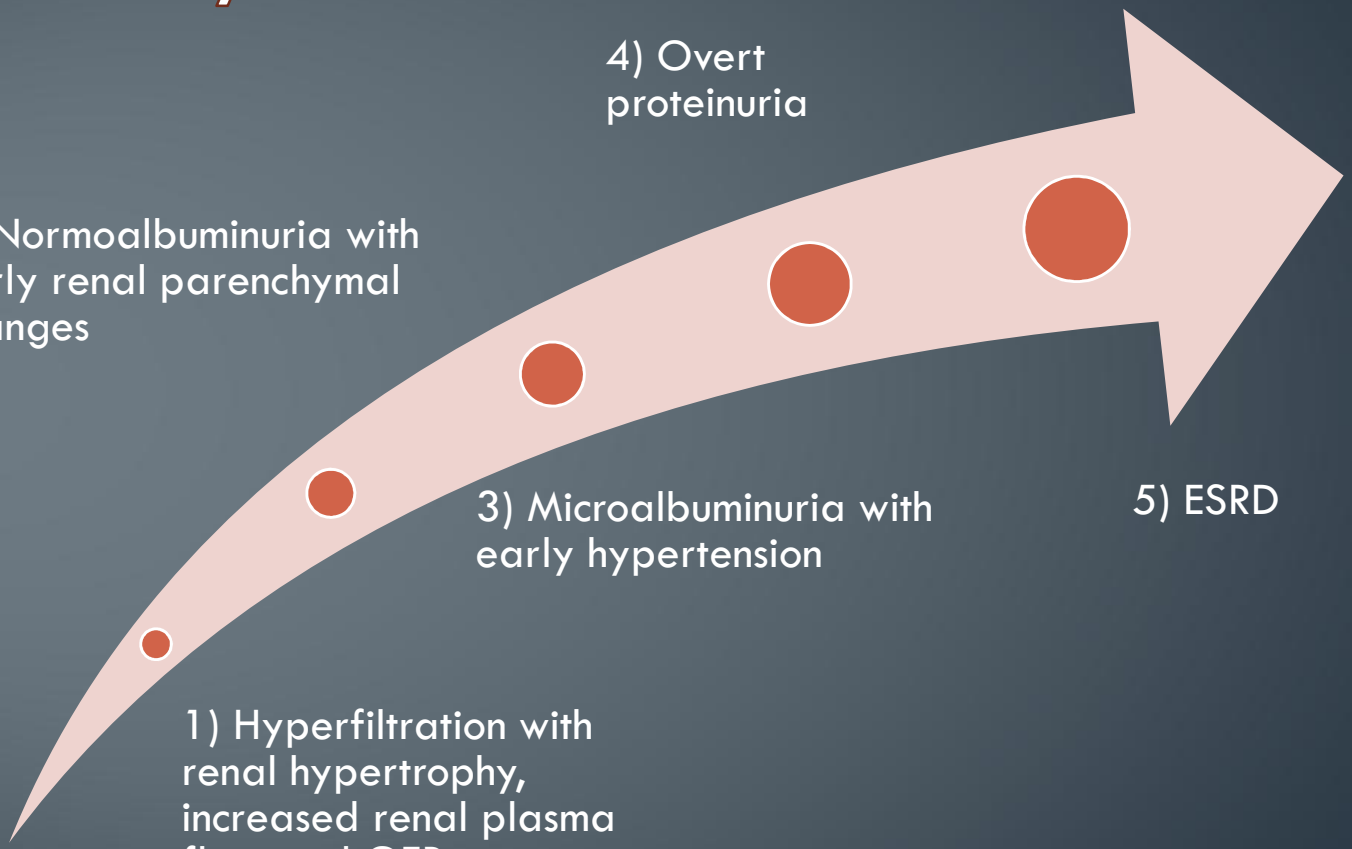


II. Diabetic Nephropathy

Diabetic nephropathy

- Leading cause of chronic renal failure worldwide
- Responsible for about 1/3 of patients undergoing dialysis
- 20-40% of DM patients with DKD
- (Micro)Albuminuria – an initial marker
- Elevated risk of cardiovascular event
- Once overt nephropathy develops, renal function progressively declines

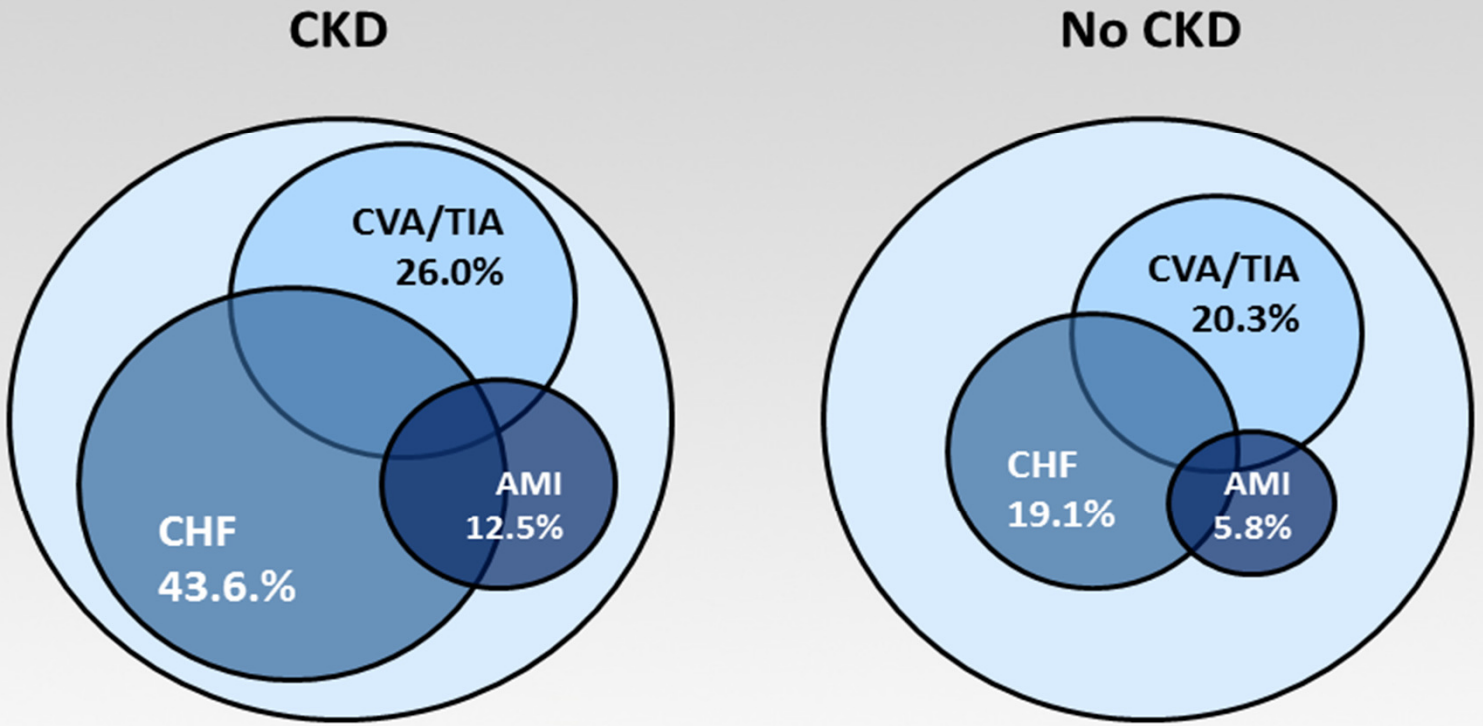
Diabetic kidney disease



Natural history

	Rate of decline in GFR (ml/min/year)	
	Type I	Type 2
Normoalbuminuria	1.2-3.6	0.96
Microalbuminuria	1.2-3.6	2.4
Overt nephropathy	9.6-12	5.4-7.2

CVD in Patients with or Without CKD, 2010*



*US Medicare enrollees age 66 and older, with fee-for-service coverage for all of 2010.

AMI = acute myocardial infarction; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; CVD = cardiovascular disease

Diagnosing DKD

- Diabetic kidney disease is usually a **clinical diagnosis** made based on the presence of **albuminuria and/or reduced** eGFR in the absence of signs or symptoms of other primary causes of kidney damage
  - uACR ≥ 30 mg/g Cr (3.5 mg/mmol Cr) and/or eGFR < 60ml/min/1.73m^2
- Consider other causes if
  - Absence of diabetic retinopathy
  - Low or rapidly decreasing GFR
  - Rapidly increasing proteinuria or nephrotic syndrome
  - Refractory hypertension
  - Presence of active urinary sediment
  - Signs or symptoms of other systemic disease
  - > 30% reduction in GFR within 2-3 months after initiation of ACEI or ARB

Table 10.1—CKD stages and corresponding focus of kidney-related care

CKD stage†			Focus of kidney-related care			
Stage	eGFR (mL/min/1.73 m^2)	Evidence of kidney damage*	Diagnose cause of kidney injury	Evaluate and treat risk factors for CKD progression**	Evaluate and treat CKD complications***	Prepare for renal replacement therapy
No clinical evidence of CKD	≥60	—				
1	≥90	+	√	√		
2	60–89	+	√	√		
3	30–59	+/−	√	√	√	
4	15–29	+/−		√	√	√
5	<15	+/−			√	√

†CKD stages 1 and 2 are defined by evidence of kidney damage (+), while CKD stages 3–5 are defined by reduced eGFR with or without evidence of kidney damage (+/−). *Kidney damage is most often manifest as albuminuria (UACR ≥30 mg/g Cr) but can also include glomerular hematuria, other abnormalities of the urinary sediment, radiographic abnormalities, and other presentations. **Risk factors for CKD progression include elevated blood pressure, glycemia, and albuminuria. ***See **Table 10.2**.

When to screen?

- At least once a year, assess urinary albumin (uACR) and eGFR in patients with type 1 diabetes with duration of 5 years and in all patients with type 2 diabetes, and in all patients with comorbid hypertension. (B)

Standard of Medical Care in Diabetes 2018. Diabetes Care 2018

Treatment of DKD

- Glycemic control – HbA1c target < 7.0%
- Blood pressure control – BP < 130/80 mmHg
- Treatment with ACEI or ARB
  - Reduce albuminuria
  - Delay the progression to nephropathy – independent of BP lowering effect
- Dyslipidemia – a statin to lower LDL < 2.6mmol/L for CKD stage 1-4
- Consider monitor uACR in patients with elevated uACR

Table 1. Summary of Key Glycemic Control Trials

Trial	Population	N	Intervention Target	Achieved Intervention	Findings in Intensive Care Group	Comments
DCCT	T1DM	1,441	Intensive therapy targeting fasting and postprandial blood glucose vs conventional therapy	HbA_{1c} 7.3% vs 9.1%	Decreased microvascular complications (including microalbuminuria, proteinuria, retinopathy, and neuropathy)	
EDIC	T1DM	1,375 patients that completed DCCT	Observational follow-up of DCCT with all getting intensive therapy	HbA_{1c} 7.8% vs 7.9%	Reduction in microalbuminuria and proteinuria	
UKPDS	Newly Diagnosed T2DM	3,867	Intensive therapy targeting a fasting blood glucose vs conventional therapy	HbA_{1c} 7% vs 7.9%	Reduction in any diabetes-related end point in aggregate	Reduction not seen in kidney-specific events (microalbuminuria, proteinuria, or doubling of Scr)
ACCORD	T2DM and CV event history or risk	10,251	HbA_{1c} < 6.0% vs 7%-7.9%	HbA_{1c} 6.4% vs 7.5%	Increased CV and total mortality	No benefit on kidney end points
ADVANCE	T2DM and CV event history or risk	11,140	HbA_{1c} < 6.5% vs routine care	HbA_{1c} 6.3% vs 7.0%	No benefit on CV outcomes; reduction in microvascular events	Albuminuria reduced by 21%
VADT	T2DM and poor BP control	1,791	Reduction in HbA_{1c} of 1.5% vs routine care	HbA_{1c} 6.9% vs 8.4%	No benefit	No benefit on kidney end points

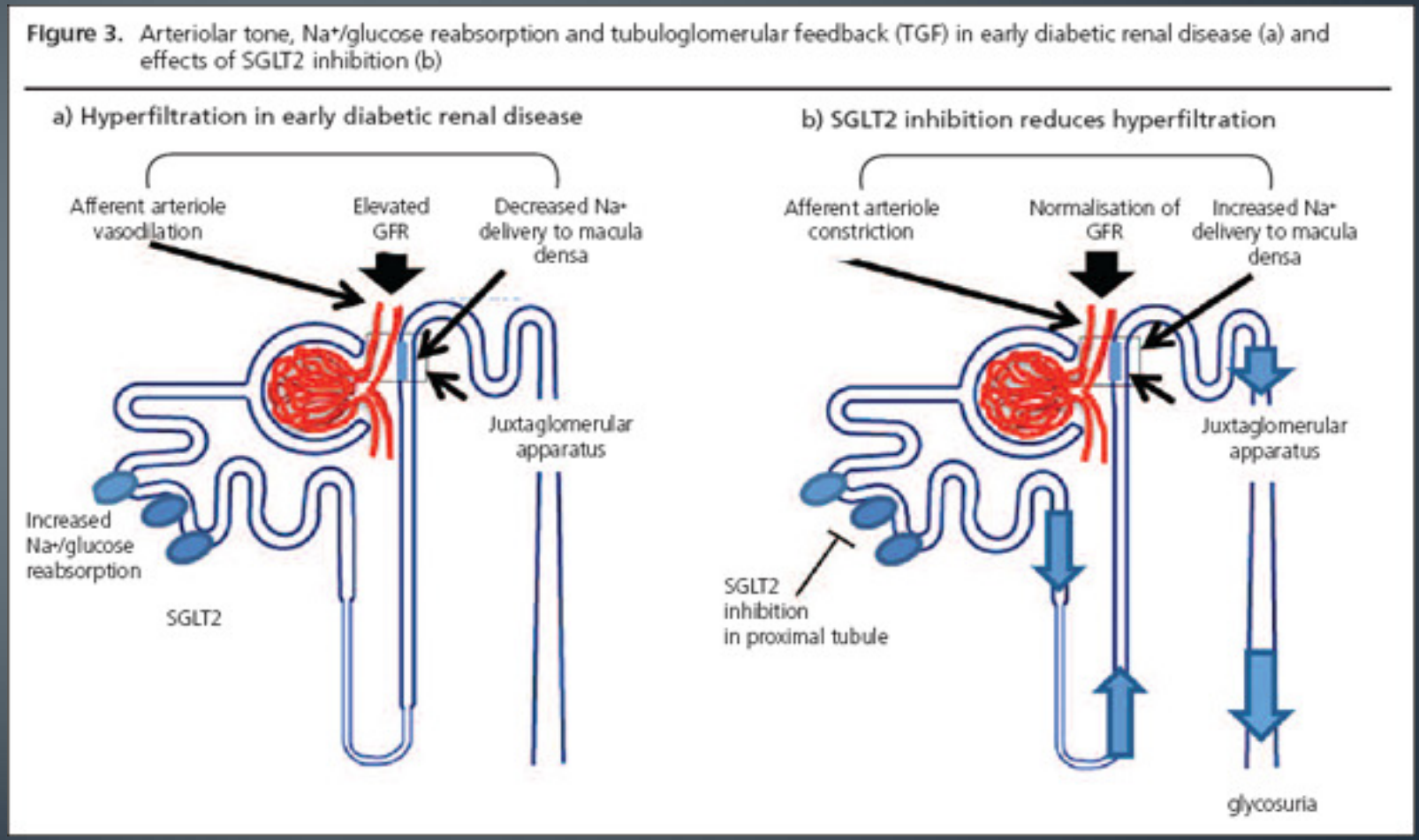
Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Cardiovascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; CV, cardiovascular; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; HbA_{1c}, hemoglobin A_{1c}; Scr, serum creatinine; T1(2)DM, type 1 (2) diabetes mellitus; UPKDS, UK Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

Table 2. Summary of Key Renin-Angiotensin System Inhibition Trials

Trial	Population	N	Intervention	Conclusions	Comments
ROADMAP	T2DM without microalbuminuria	4,449	Olmesartan vs placebo	Olmesartan delayed the onset of microalbuminuria	Olmesartan group had lower BPs and more CV deaths
IRMA-2	T2DM and microalbuminuria	590	Irbesartan 150 mg vs irbesartan 300 mg vs placebo	Irbesartan reduced the development of overt proteinuria	Subgroup analysis suggested a dose-dependent effect
Captopril Trial	T1DM with proteinuria	409	Captopril 25 mg 3×/d vs placebo	Captopril reduced the risk for doubling of SCr as a primary outcome and death, dialysis therapy, or transplantation as a secondary outcome	
IDNT	T2DM with proteinuria and reduced kidney function	1,715	Irbesartan vs amlodipine vs placebo	Irbesartan reduced the risk for doubling of SCr, ESRD, or death	
RENAAL	T2DM with proteinuria and reduced kidney function	1,513	Losartan vs placebo	Losartan reduced the risk for doubling of SCr, ESRD, or death	
ONTARGET	Patients with CV risk	25,620	Ramipril vs telmisartan vs telmisartan and ramipril	No CV benefit among the 3 arms; proteinuria reduction in combination therapy arm	Increase in "DDT" events in combination therapy arm
VA NEPRON-D	T2DM and proteinuria	1,448	Losartan and lisinopril vs losartan and placebo	Trial terminated early due to AKI events and hyperkalemia in combination therapy arm	
ALTITUDE	T2DM, proteinuria, and CV risk	8,561	ACEi or ARB and aliskiren vs ACEi or ARB and placebo	Trial terminated early due to increase in adverse events and no apparent benefit in the dual-therapy arm	

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ALTITUDE, Aliskiren Trial in T2DM Using Cardio-Renal Endpoints; ARB, angiotensin receptor blocker; BP, blood pressure; CV, cardiovascular; DDT, doubling of serum creatinine, dialysis, or transplantation; ESRD, end-stage renal disease; IDNT, Irbesartan Diabetic Nephropathy Trial; IRMA-2, Effect of Irebesrtan in the Development of Diabetic Nephropathy in Patients With T2DM; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint; RENAAL, Reduction in End-Points in Non-Insulin Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention; SCr, serum creatinine; T1(2)DM, type 1(2) diabetes mellitus; VA-NEPHRON-D, Veterans Affairs Nephropathy in Diabetes.

New therapeutic targets ?



New agents& DKD

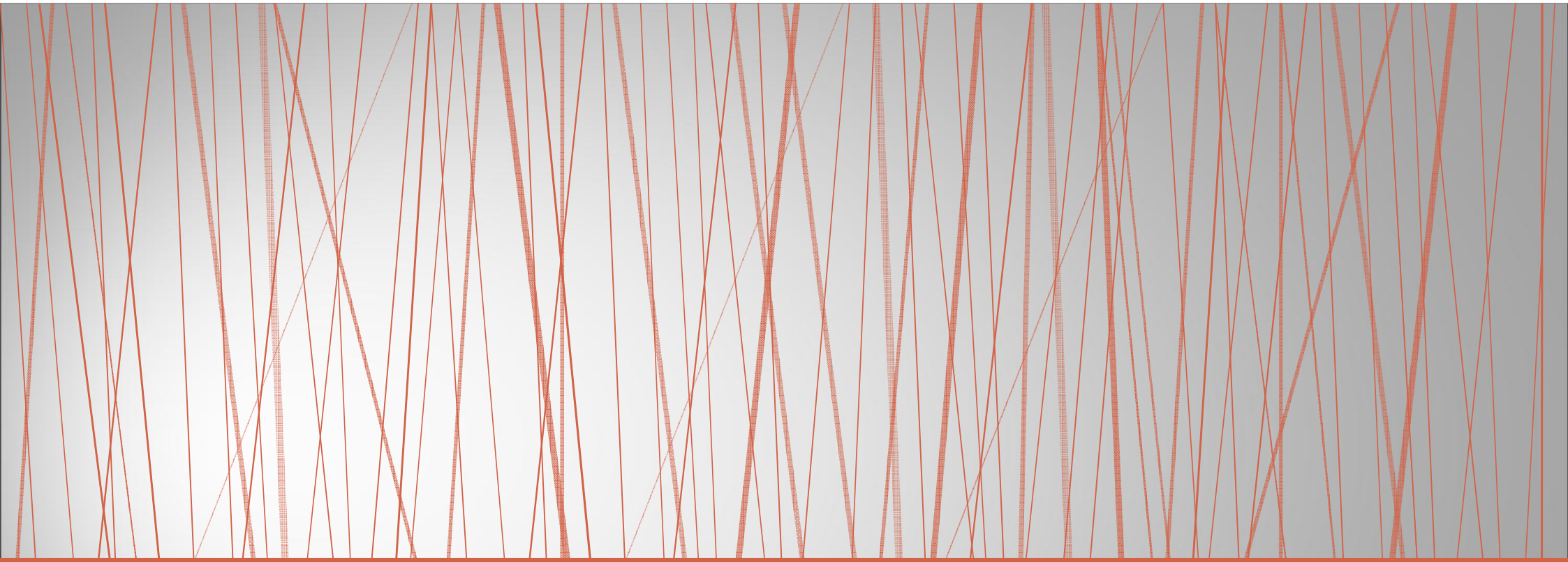
	N	Median FU	Outcomes	HR (95% CI)	P-value
EMPA-REG (2015)	7020	3.1 years	Incident or worsening nephropathy	0.61 (0.53 – 0.70)	0.003
			Renal composite outcome (2x sCr, RRT, renal death):	0.54 (0.40 – 0.75)	<0.001
CANVAS (2017)	10142	2.4 years	Progression of albuminuria	0.73 (0.67- 0.79)	- -
			Composite of 40% reduction in eGFR, RRT, renal death	0.60 (0.47-0.77)	
LEADER (2016)	9340	3.8 years	Composite renal outcomes (new onset macroalbuminuria, x2 sCr with eGFR≤45 ml/min/1.73m^2, RRT, renal death):	0.78 (0.67-0.92)	0.003
SUSTAIN (2016)	3297	2.1 years	New or worsening nephropathy	0.64 (0.46- 0.88)	0.005

Quiz

- A 52-year-old woman with T2DM diagnosed 1 year ago is referred to you for evaluation of proteinuria noted first 3 months ago. Family history is positive for diabetic nephropathy. Physical examination shows blood pressure (BP) of 140/95 mm Hg and normal fundal examination findings and is otherwise unremarkable. Laboratory studies show serum creatinine concentration of 89umol/L, and urinalysis shows protein (3 +) with unremarkable sediment.
- Question: Which of the following statements is correct?
  a) The finding of proteinuria 6 months after the diagnosis of T2DM is strongly against the diagnosis of diabetic nephropathy.
  b) Normal fundal examination findings should strongly suggest an alternative diagnosis.
  c) The most likely diagnosis is diabetic nephropathy.
  d) Increases in BP in the majority of patients with diabetic nephropathy are seen only after decline in kidney function.

Answer: (C)

- Strong family history, significant proteinuria
- Up to 25% of patients with T2DM and biopsy-proven DMN and diminished kidney function have little or no proteinuria
- Exact cause – unknown
  - ?? Long-term RAS inhibition
  - ?? Underdiagnosed unresolved acute kidney injury
- Retinopathy – seen in two-thirds of patients with DMN



III. Diabetic Neuropathy

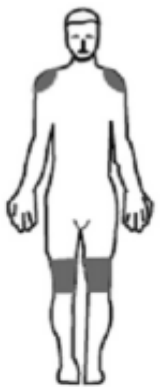
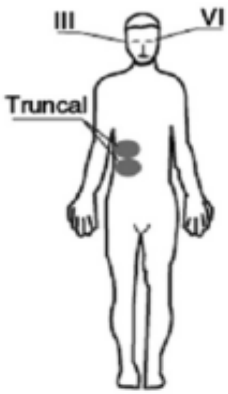
Diabetic neuropathy

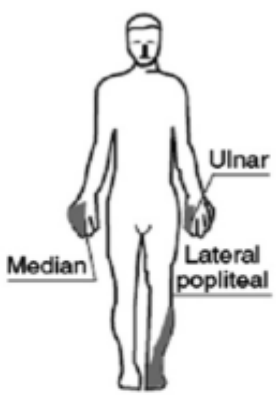
- Definition by American Diabetes Association
  - The presence of symptoms and / or sign of peripheral nerve dysfunction in people with diabetes after exclusion of other causes.
- Classification:
  - Diffuse
    - Distal symmetrical PN – Small fiber / Large fiber / Mixed
    - Acute sensory neuropathy
    - Autonomic – cardiovascular, GI, Urogenital, Sudomotor, hypoglycemia unawareness
  - Focal/ multifocal
    - Mononeuropathy / Mononeuritis multiplex
    - Entrapment
  - Radiculopathy
    - Proximal motor amyotrophy
    - Radiculoplexus neuropathy
  - Non- Diabetic neuropathies common in DM (CIDP)

Epidemiology

- Estimated 50% of patients with DM have diabetic neuropathy
- DSPN – increase risk of amputation by 1.7x; up to 36x if previous ulceration
- Autonomic neuropathy – increases mortality 25-50% within 5-10 years





Large fibre neuropathy	Small fibre neuropathy	Proximal motor neuropathy	Acute mono neuropthies	Pressure palsies
Sensory loss: 0 → +++ (touch, vibration) Pain: + → +++ Tendon reflex: N → ↓↓↓ Motor deficit 0 → +++	Sensory loss: 0 → + (thermal, allodynia) Pain: + → +++ Tendon reflex: N → ↓ Motor deficit: 0	Sensory loss: 0 → + Pain: + → +++ Tendon reflex: ↓↓ Proximal motor deficit: + → +++	Sensory loss: 0 → + Pain: + → +++ Tendon reflex: N Motor deficit + → +++	Sensory loss in nerve distribution: + → +++ Pain: + → ++ Tendon reflex: N Motor deficit + → +++

Clinical features

Table 1
Distinguishing characteristics of mononeuropathies, entrapment syndromes, and distal symmetric polyneuropathy

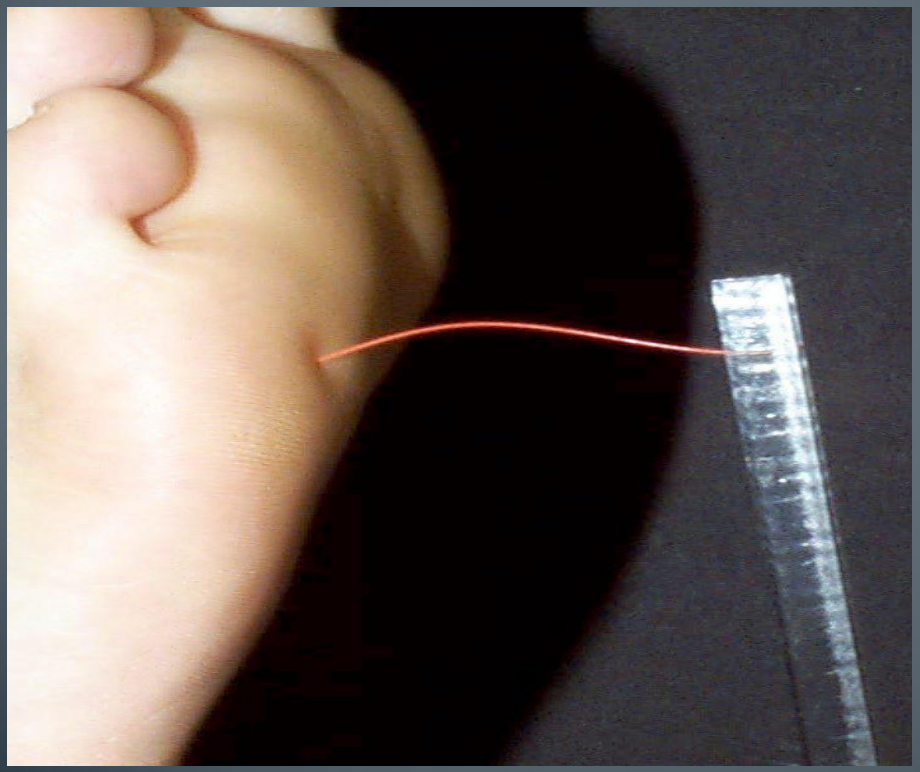
Feature	Mononeuropathy	Entrapment Syndrome	Neuropathy
Onset	Sudden	Gradual	Gradual
Pattern	Single nerve but may be multiple	Single nerve exposed to trauma	Distal symmetric poly neuropathy
Nerves involved	CN III, VI, VII, ulnar, median, peroneal	Median, ulnar, peroneal, medial, and lateral plantar	Mixed, motor, sensory, autonomic
Natural history	Resolves spontaneously	Progressive	Progressive
Distribution of sensory loss	Area supplied by the nerve	Area supplied beyond the site of entrapment	Distal and symmetric. "Glove and stocking" distribution

Assessment

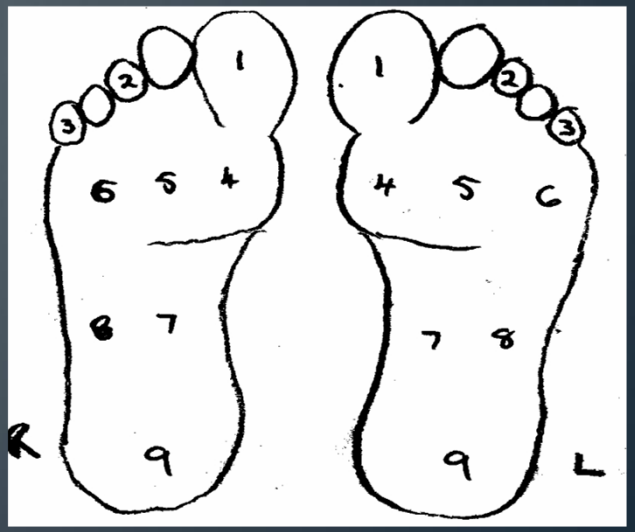
- Temperature or pinprick sensation (small fiber)
- Vibration (128-Hz tuning fork, VPT) (large fiber)
- 10-g monofilament test (large fiber; also predict ulceration and amputation)
- Deep tendon reflexes (large fiber)
- Symptoms and signs of autonomic neuropathy
- Exclude:
  - Toxins (alcohol, heavy metals)
  - Neurotoxic medications (chemotherapy)
  - Vit B12 deficiency
  - Hypothyroidism
  - Malignancies
  - Vasculitis
  - CIDP
  - Inherited neuropathies

Refer neurologist if atypical features:
Motor >> sensory
Rapid onset
Asymmetrical

10-g Monofilament test





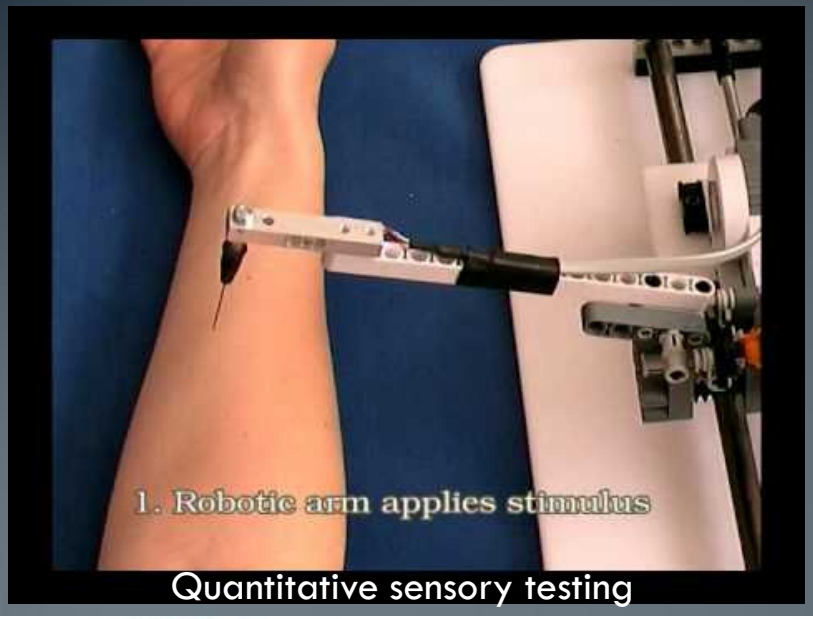


More sophisticated testing

- Nerve conduction study
- Quantitative sensory testing
- Skin biopsy and intraepidermal nerve fiber density
- Corneal confocal microscopy
- Contact heat evoked potentials
- Sudomotor function testing (sympathetic skin response, QSART)
- Autonomic function test

Small & large fibers

Small fibers

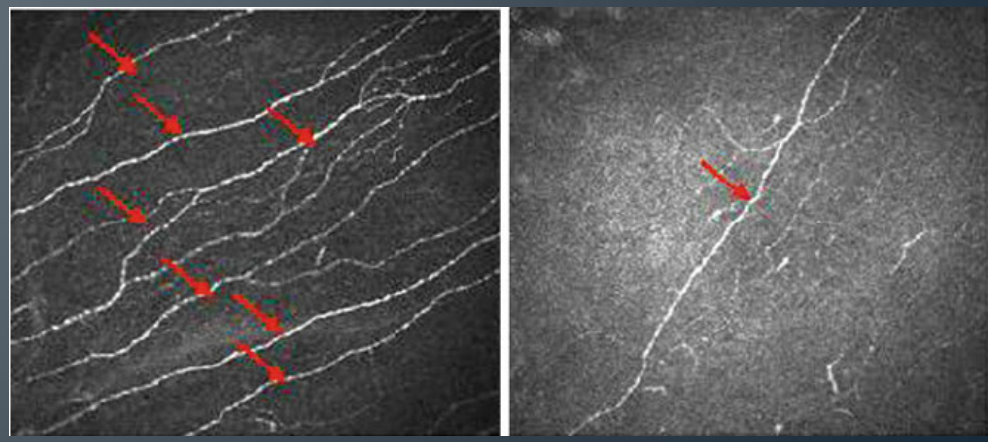


Quantitative sensory testing



QSART





Corneal confocal microscopy

Chronic sensorimotor distal symmetric polyneuropathy

- Most common forms of neuropathy in diabetes
- Symptoms:
  - Burning, tingling, electrical pain
  - Simple numbness
  - Worse at night
  - Painless foot ulcer
- Physical examination:
  - Sensory loss to light touch, vibration, temperature
  - Loss of 10-g monofilament sensation
- Abnormalities in > 1 of the test of peripheral sensation are > 87% sensitive in detecting the presence of neuropathy

Toronto Classification for distal symmetrical diabetic polyneuropathies

Diagnosis	Criteria
Possible DSPN	Presence of symptoms or signs (reduced distal sensation, absent or decreased ankle jerks) of DSPN
Probable DSPN	Presence of symptoms AND signs
Confirmed DSPN	Presnce of symptoms or signs with abnormal NCV If NCV normal – need abnormal measure of small-fiber neuropathy (SFN)
Subclinical DPSN	No symptoms of signs; just abn NCV / SFN
Small fiber neuropathy	Length-dependent S/S of SFN +/- normal sural nerve condution +/- altered IENF density
Signs (esp. multiple) are better predictors than symptoms for diagnosis of polyneuropathy	

Quantitative assessment tool

- Michigan Neuropathy Screening Instrument
- Neuropathy Symptom Score
- Neuropathy Disability Score
- Neuropathy Impairment Score

In the last two weeks:

1. **Are you experiencing unsteadiness in walking?**
2. **Do you have burning, aching pain or tenderness in your legs or feet?**
3. **Do you have a prickling or tingling sensation in your legs or feet?**
4. **Are you experiencing any numbness or loss of feeling in your legs/feet?**

Each 'yes' answer is scored as 1 point (score range = 0 to 4)

*Meijer JW, Smit AJ, Sonderen EV, Groothoff JW, Eisma WH, Links TP.Symptom scoring systems to diagnose distal polyneuropathy in diabetes: the Diabetic Neuropathy Symptom score. Diabet Med. 2002 Nov;19(11):962-5.

Complications of Sensorimotor neuropathy

- Ulceration (painless)
- Neuropathic edema
- Charcot arthropathy
- Callosities





Treatment

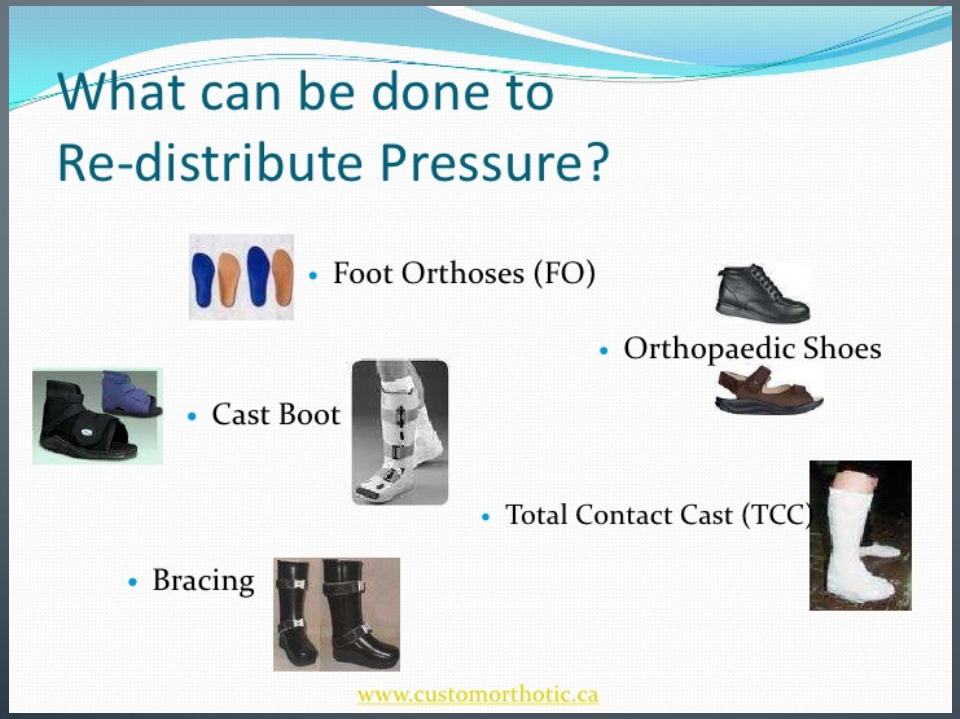
- Glycemic control
  - T1DM – reduce polyneuropathy and cardiovascular autonomic neuropathy (CAN)
  - T2DM – Lower rate of imparied VPT (UKPDS), reduce CAN (Steno-2), improve light touch and vibration (ACCORD)
- Symptoms control – Duloxetine (Class A), Gabapentin (Class A), Pregabalin, Opioid, anticonvusant, TCA
- Prevent complications – Foot care
- Oxidative stress therapeutic targets
  - Aldose reductas inhibitors
  - α-lipoic acid
  - Γ-linolenic acid
  - Benfotiamine
  - Protein kinase C inhibitors
  - Methycobalamin, methyfolate & pyridoxal phosphate

Comprehensive foot examination

- Dermatological – Skin status, sweating, infection, ulceration, calluses. Blisters
- Musculoskeletal – deformity, muscle wasting
- Neurological - 10g monofilament + 1 of the following 4 tests
  - Vibration
  - Pinprink
  - Ankle reflexs
  - VPT
- Vascular assessment – foot pulses ; ABI

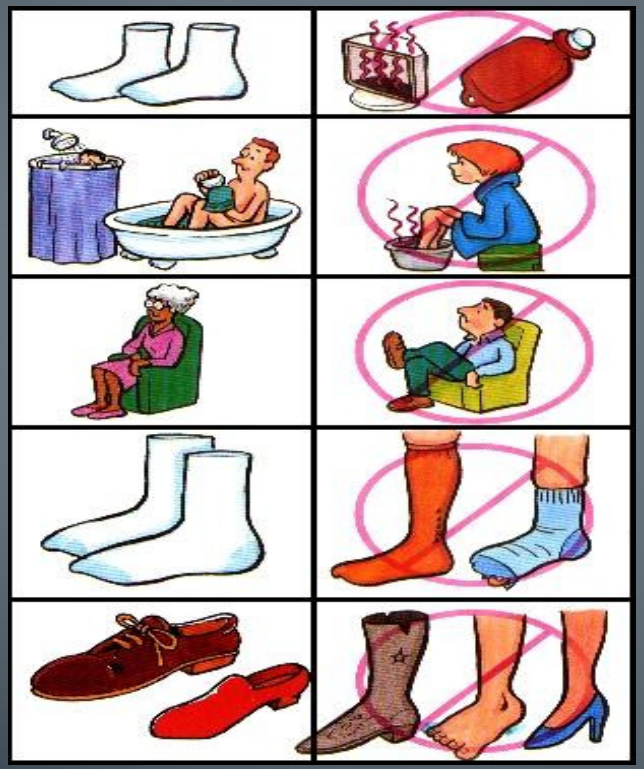

Risk category 0
Risk category 1
Risk category 2
Risk category 3
Normal Plantar Sensation
Loss of Protective Sensation (LOPS)
LOPS with either High Pressure or Poor Circulation or Structural Foot Deformities or Onychomycosis
History of Ulceration, Amputation or Neuropathic Fracture
LOW RISK
MODERATE RISK
HIGH RISK
VERY HIGH RISK

Risk category 1	Risk category 2	Risk category 3
•Custom foot orthoses •Direct mold diabetic foot inserts •Off the shelf devices with limited molding but some cushioning	•Total contact Cast •Diabetic custom foot orthoses •Diabetic Orthopaedic footwear	• Offloading with Removable Cast Walker (recommended to be rendered irremovable), Total Contact Cast or Wound shoe
6 months' review	3 months' review	1-2 months' review



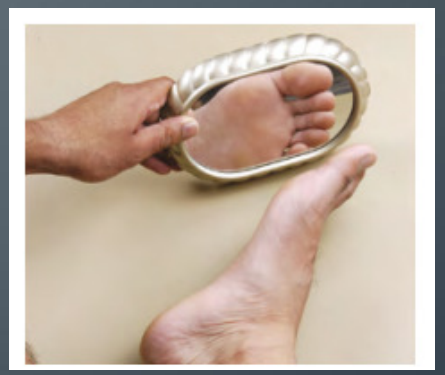
Please ask your podiatrist

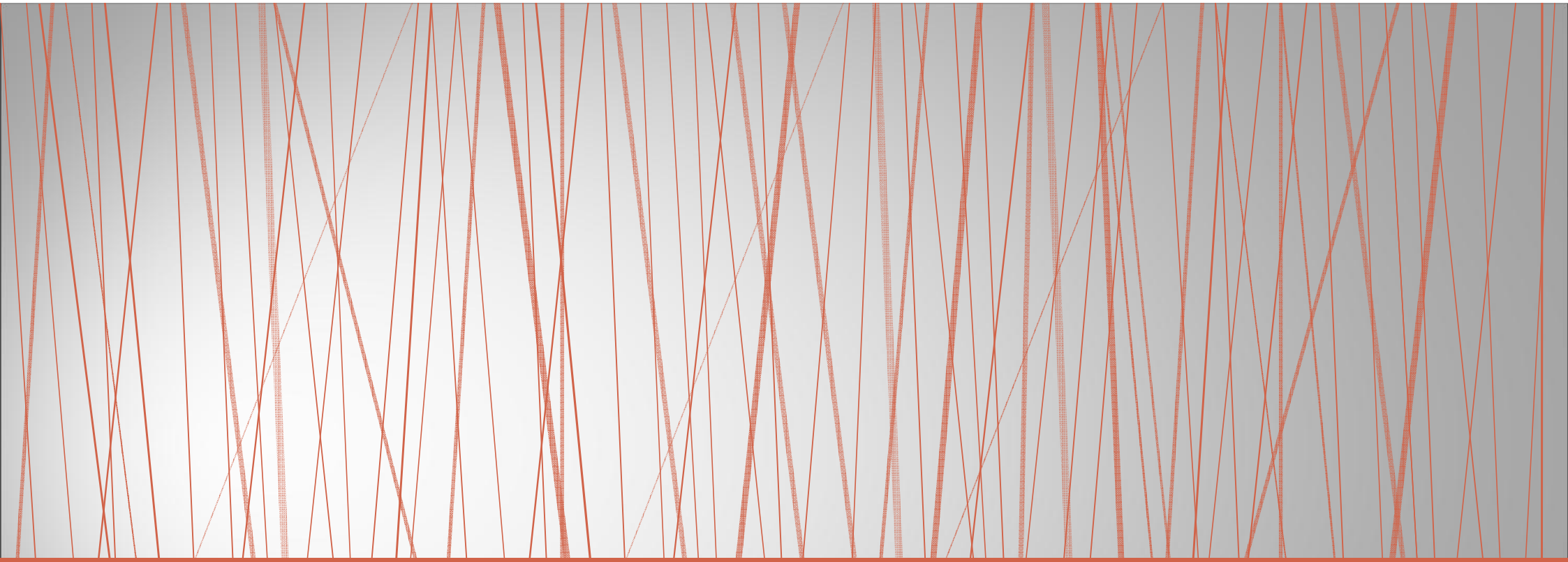
Do’s and Don'ts of foot care



Patient should

- Check feet daily
- Keep toe nails short
- Always wear shoes
- Always wear socks
- Break in new shoes gradually





IV. Macrovascular complications

Macrovascular complications (ASCVD)

- Ischemic heart disease
- Cerebrovascular disease
- Peripheral vascular disease
- Leading cause of death in T2DM

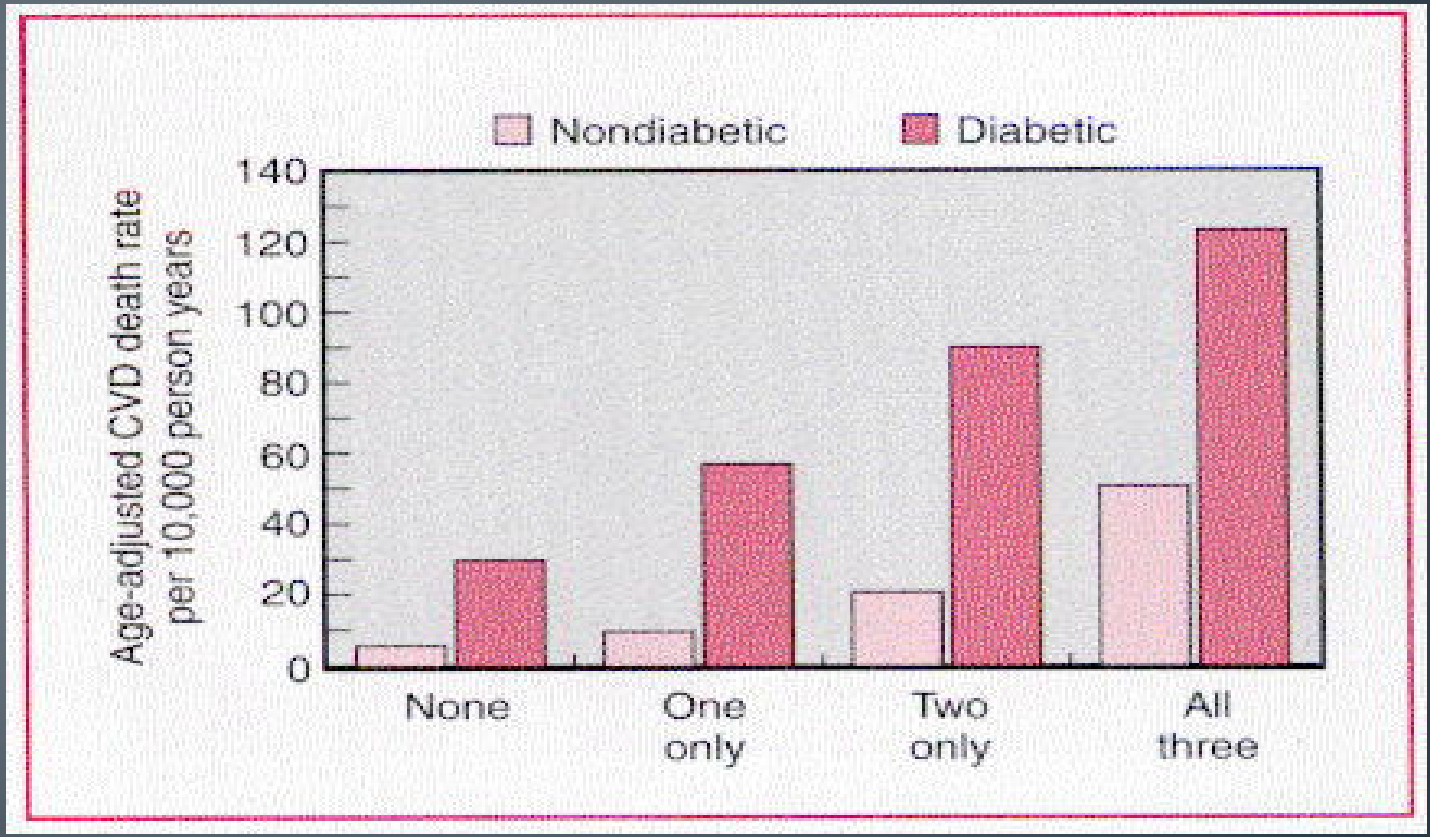
Diabetic patients have a 2 to 6 times higher risk for development of these complications than the general population

Overall life expectancy in diabetic patients is 7 to 10 years shorter than non-diabetic people

CAD Morbidity and Mortality in Type 2 DM

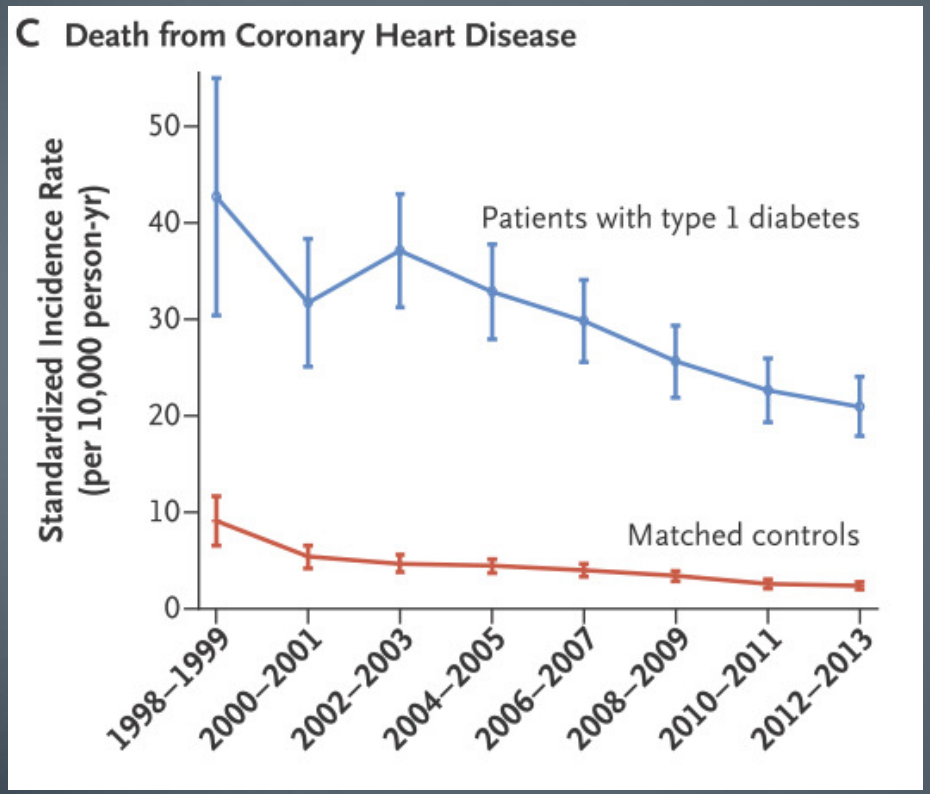
- Framingham Data:
  - 20 year follow-up
  - Age 45-74
  - 2-3 fold increase in clinically evident atherosclerotic disease in diabetics
- Multiple Risk Factor Intervention Trial (MRFIT)
  - 5000 men with type 2 DM
  - Followed for 12 years
  - Men with type 2 DM had absolute risk of CAD-related death 3 times higher than non-diabetic cohort

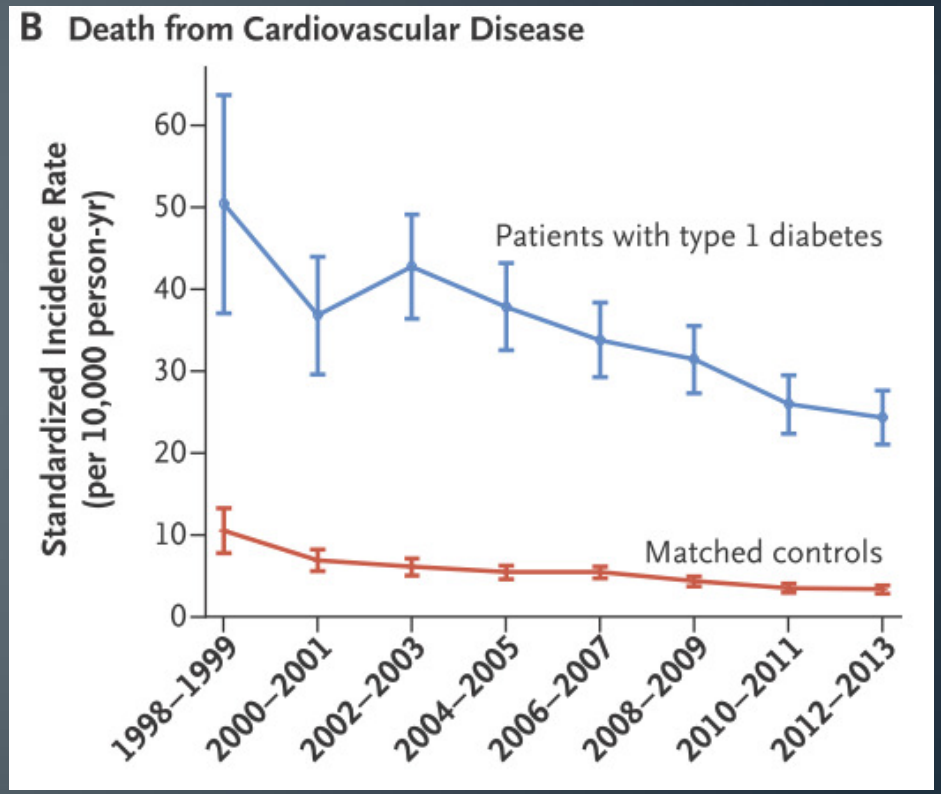
Cardiovascular Death Rates: MRFIT data



Stamler J., et al Diabetes Care: 16: 434-444

Risk of CVD in Type 1 DM





Rawshani et al NEJM 2017: 376 (15)

Association of CV risk factors and CVD events in T1DM vs T2DM

	T1DM	T2DM
Hypertension	+++	++
Cigarette smoking	++	++
Inflammation	++	++
High LDL-C	+	+++
Low HDL-C	0/+	++
Triglycerides	No data	++
Microalbuminuria	+++	+++
Insulin resistance	+	+++
Poor glycemic control	+++	+++

Managing CAD in diabetes

- Screening for CAD in asymptomatic patients- not recommended (ADA 2018)
- Consider advanced/ invasive cardiac testing if (ADA 2018)
  - 1) Typical or atypical cardiac symptoms and
  - 2) An abnormal resting ECG
- Treat risk factors aggressively
  - Hyperlipidemia: Statins
    - ASCVD – High intensity statins
    - Age ≥45 without ASCVD – Moderate intensity statins
    - Age < 45 – Calculate risk (AHA/ACC)
  - ACEI/ARB if albuminuria / CKD
  - BP control : at least < 140/90 ; if tolerable -> < 130 (not <120 [ACCORD])/ 80

Managing CAD in diabetes

- Glycaemic control – general target ~ 7%; choose agents with CV benefit
- ?? Aspirin prophylaxis
  - T1DM and T2DM ≥ 50 years old + 1 additional risk factor* + low risk of bleeding (ADA 2018)
- Evidence of CAD
  - Stable → optimal medical therapy
  - Multivessel disease → CABG

* Hypertension, dyslipidemia, smoking, albuminuria, family Hx of premature CVD

Is glycaemic control beneficial ?

UKPDS

A1c 7.0% vs. 7.9%

SU/ insulin : ↓MI by 16% (p=.52) & **15% (p=.01)** in extension study

Metformin : **↓MI by 39% (p=.01) & 33% (p=.005) in extension study**

ACCORD

A1c ≤ 6.0% vs. 7.0-7.9%

No effect on primary outcome [MACE] (p=0.16)

Increase all cause mortality in intensively treated group (p=0.04)

ADVANCE

A1c 6.5% vs. 7.3%

No effect on macrovascular disease

VADT

A1c ≤ 6.0% vs. 8-9%

No effect on macrovascular disease

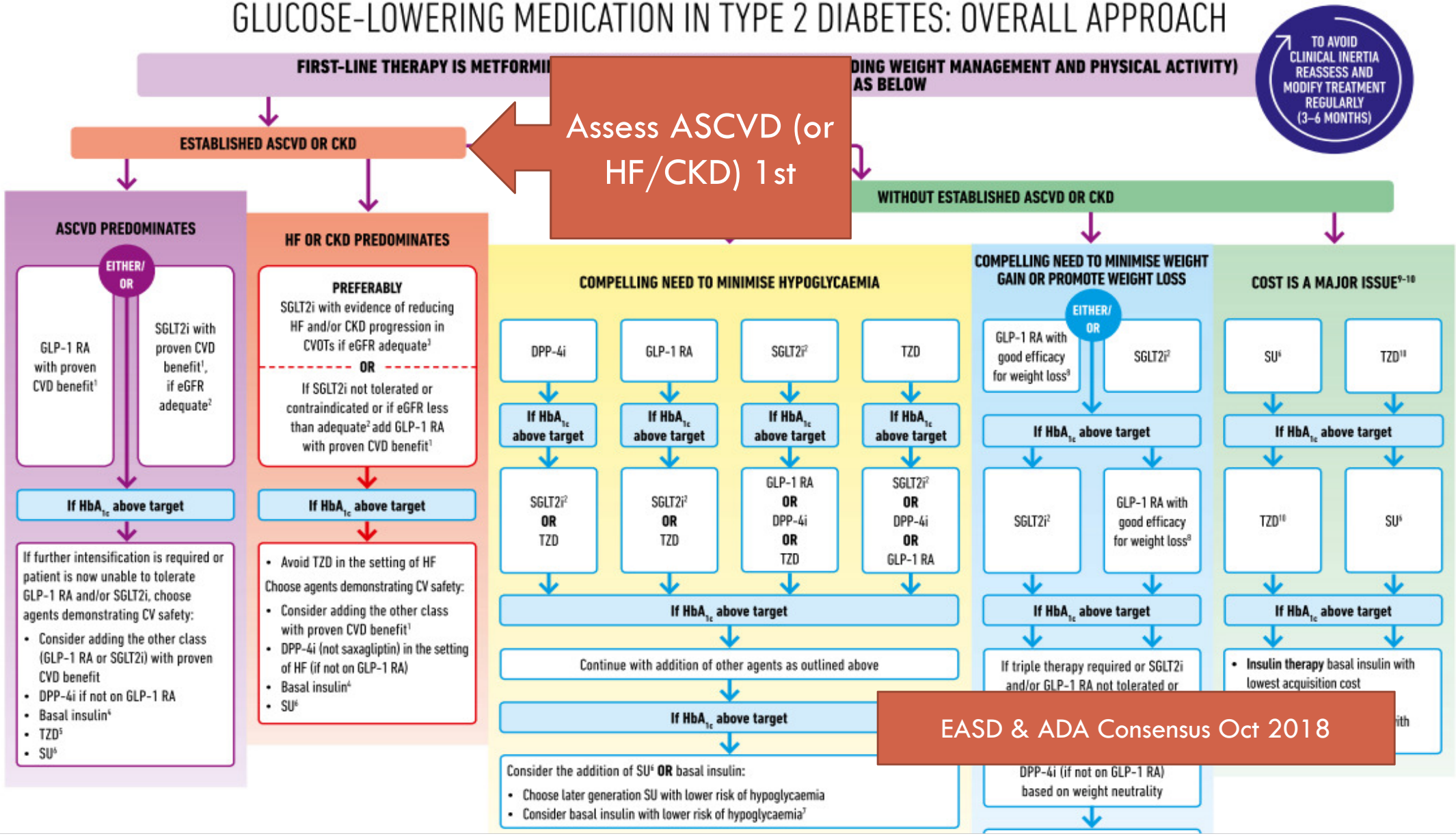
DCCT/ EDIC for type 1 DM



Figure 2—The cumulative incidence of clinical CVD outcomes during DCCT/EDIC. *A*: Any qualifying primary outcome event. *B*: MACE. Reprinted with permission from Nathan et al. (9).

Newer agents that improve CV outcomes in diabetes

	GLP-1 receptor agonists			SGLT-2 inhibitors		
Study	LEADER	SUSTAIN-6	HARMONY	EMPA-REG	CANVAS (+R)	DECLARE
Intervention (vs. placebo)	Liraglutide	Semaglutide	Albiglutide	Empagliflozine	Canagliflozin	Dapagliflozin
Main inclusion	T2DM + pre-existing CVD or CV risk at ≥60 years old		T2DM age ≥40 + CVD	Type 2 DM + CVD with BMI	T2DM + CVD or ≥2 CV risks with age ≥ 50	T2DM + CVD / multiple CV risks
Subjects (n)	9394	3297	9463	7020	4330 + 5812	17000+
Median FU (yrs)	3.8	2.1	1.6	3.1	5.7 + 2.1	Up to 5 yrs
Primary outcomes	3 point MACE					3 point MACE HF or CV death
Results	0.87 (0.78-0.97)	0.74 (0.58-0.95)	0.78 (0.68 - 0.90)	0.86 (0.74 - 0.99)	0.86 (0.75-0.97)	Pending formal announcement


GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH
FIRST-LINE THERAPY IS METFORMI
DING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
AS BELOW
TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
Assess ASCVD (or HF/CKD) 1st
ESTABLISHED ASCVD OR CKD
WITHOUT ESTABLISHED ASCVD OR CKD
ASCVD PREDOMINATES
EITHER/ OR
GLP-1 RA with proven CVD benefit[1]
SGLT2i with proven CVD benefit[1], if eGFR adequate[2]
If HbA1c above target
If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
• Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
• DPP-4i if not on GLP-1 RA
• Basal insulin[4]
• TZD[5]
• SU[6]
HF OR CKD PREDOMINATES
PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]
OR
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]
If HbA1c above target
• Avoid TZD in the setting of HF
Choose agents demonstrating CV safety:
• Consider adding the other class with proven CVD benefit[1]
• DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
• Basal insulin[4]
• SU[6]
COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA
DPP-4i
GLP-1 RA
SGLT2i[2]
TZD
If HbA1c above target
SGLT2i[2] OR TZD
SGLT2i[2] OR TZD
GLP-1 RA OR DPP-4i OR TZD
SGLT2i[2] OR DPP-4i OR GLP-1 RA
If HbA1c above target
Continue with addition of other agents as outlined above
If HbA1c above target
Consider the addition of SU[6] OR basal insulin:
• Choose later generation SU with lower risk of hypoglycaemia
• Consider basal insulin with lower risk of hypoglycaemia[7]
COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS
EITHER/ OR
GLP-1 RA with good efficacy for weight loss[8]
SGLT2i[2]
If HbA1c above target
SGLT2i[2]
GLP-1 RA with good efficacy for weight loss[8]
If HbA1c above target
If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or
DPP-4i (if not on GLP-1 RA) based on weight neutrality
COST IS A MAJOR ISSUE[9-10]
SU[6]
TZD[10]
If HbA1c above target
TZD[10]
SU[6]
If HbA1c above target
• Insulin therapy basal insulin with lowest acquisition cost
EASD & ADA Consensus Oct 2018

ASCEND trial (NEJM 2018)

- N=15480
- Subjects: DM ; no evident CV disease; age >40 years old
- Aspirin 100mg daily vs. placebo
- Primary outcome - first serious vascular event (MI, stroke/ TIA, death from any vascular cause)
- Mean FU 7.4 years; mean age 63 years old; 94% T2DM
- Event rates: Aspirin 8.5% vs. placebo 9.6% (RR 0.88 [95% CI 0.79-0.97], p0.01)
- Major bleeding: 4.1% vs. 3.2% (RR 1.29 [95% CI 1.09 – 1.52], p=0.003)

Is screening useful in asymptomatic patients ?

	DIAD (2009)	Faglia et al (2005)	DYNAMIT (2011)	FACTOR-64 (2015
N	1123	141	631	900
Design	Randomised	Randomised, open label	Randomised	Randomised
Strategy	**Stress MPS vs no screening**	**DSE +EECG**	**EECG/MPS vs no screening**	**CCTA vs. OMT**
FU	4.8 years	4.5 years	3.5 years	4 years
Baseline	Age 60, A1c 7.1%; 9 year DM, 22% on insulin	Age 60, A1c 8.5%; 11 years DM, 14% on insulin	Age 64, A1c 8.6%	Age 61.5 ; A1c 12-13 years DM 42 % insulin A1c 7.5%
Primary endpoint	MI + cardiac deaths	Fatal and non-fatal MI	Death from all causes, non-fatal MI, non-fatal stroke, or heart failure requiring hospitalization	Alll cauyse mortatliy, non-fatal MI ; hospitaliztaion for UA after 2 years of FU
Intervention	Not pre-specified	Coronary angiogram	Not pre-specified	> 50% stenosis / CAC >100 -> Stress test +/- coro > 70% stenosis -> Coro
Results	**2.7% vs 3.0% (p=0.73)**	**5.6% vs 21.4% events (p=0.018)**	Terminated early due to low recruitment	**6.2% vs 7.6% (HR 0.80, P = 0.38)**
Comment	Revascularization rate 5.5% vs 7.8%	Small sample, no consultation in non-screened		14.2% revascularlation rate in CCTA group

Optimal medical therapy (OMT) vs revascularisation in DM with stable CAD

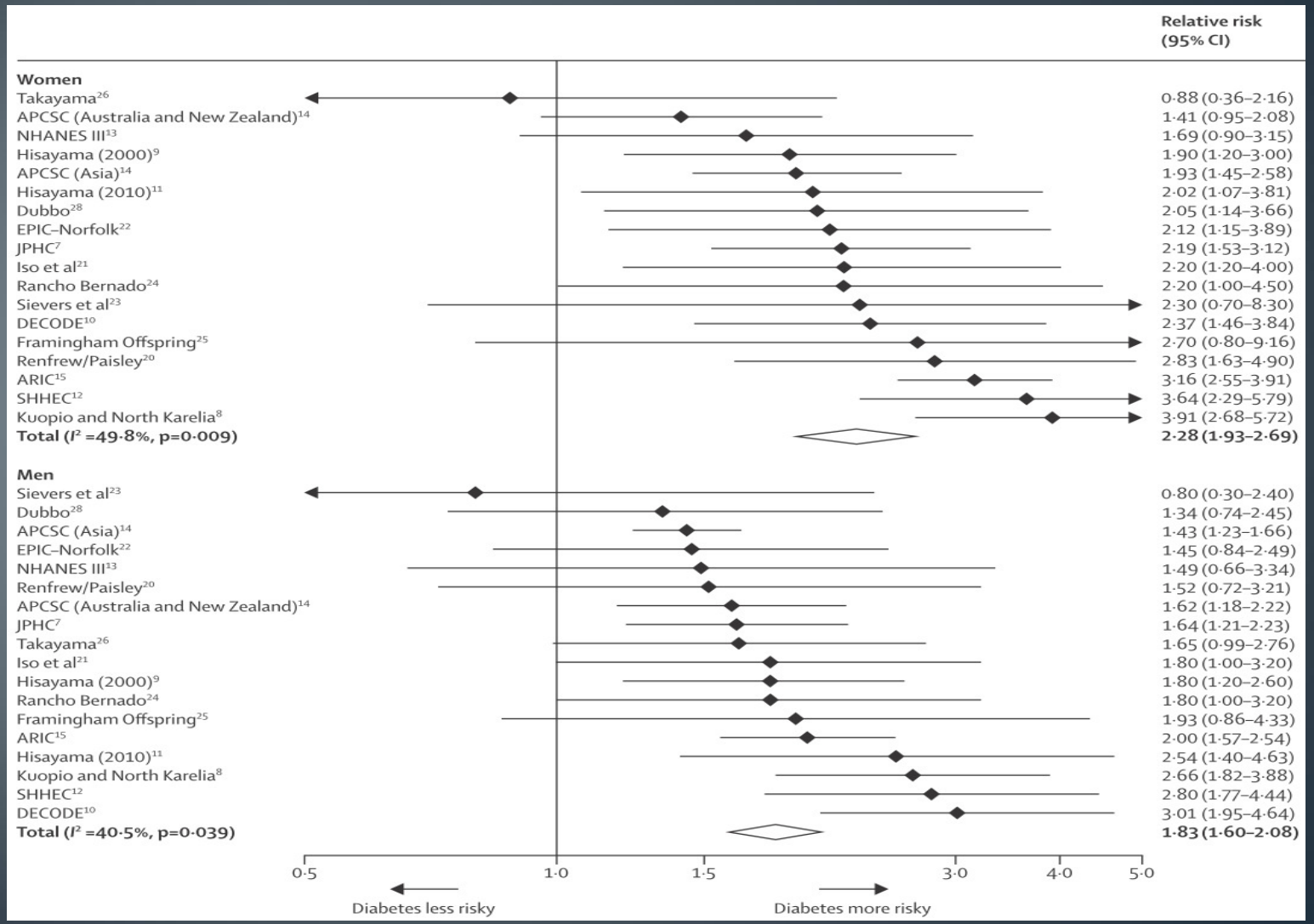
	COURAGE	BARI 2D
N	2287	2368
Design	Randomized trial	Randomized trial
Intervention	PCI + OMT vs OMT	Revascularization (CABG or PCI) + OMT vs OMT
FU	4.6 years	5.3 years
Baseline	Age 62 33.5% DM	Age 62 , DM 10.4 years 95.4% vs 13.0% received re-vascularisation
Primary outcome	Death + non fatal MI	Death from any cause
Secondary outcome	Death, MI/ unstable angina, stroke	Death, MI, stroke
Outcome -Primary -Secondary --Others	 19.0% vs 18.5% (p=0.62) 20.0% vs 19.5% (p=0.56)	 88.3% vs 87.8% (p=0.97) 77.2% vs 75.9%p=0.70) Prespecified CABG group - surgery better than OMT (non-fatal MI 7.4% vs 14.1%, [p=0.01)

CABG or PCI better (pooling COURAGE, BARI 2D & FREEDOM trials)

TABLE 2 Unadjusted, Trial-Adjusted, and Multivariable-Adjusted HRs for the Composite Endpoint and the Individual Components From Cox Regression Models (N = 5,034)

	Unadjusted HR (95% CI)	Trial-Adjusted* HR (95% CI)	p Value	Multivariable-Adjusted* HR (95% CI)	p Value
Death/MI/stroke events (n = 1,013)					
PCI + OMT vs. OMT	1.08 (0.94-1.25)	1.11 (0.95-1.31)	0.18	1.14 (0.97-1.34)	0.11
CABG + OMT vs. OMT	0.87 (0.73-1.03)	0.79 (0.64-0.97)	0.022	0.81 (0.66-1.00)	0.044
CABG + OMT vs. PCI + OMT	0.80 (0.68-0.94)	0.71 (0.59-0.85)	0.0002	0.71 (0.59-0.86)	0.0003
Death events (n = 535)					
PCI + OMT vs. OMT	1.13 (0.93-1.38)	1.12 (0.90-1.41)	0.32	1.17 (0.93-1.46)	0.19
CABG + OMT vs. OMT	1.09 (0.86-1.36)	0.85 (0.65-1.12)	0.24	0.91 (0.69-1.19)	0.48
CABG + OMT vs. PCI + OMT	0.96 (0.78-1.19)	0.76 (0.60-0.96)	0.024	0.78 (0.61-0.99)	0.042
MI events (n = 525)					
PCI + OMT vs. OMT	0.94 (0.78-1.14)	1.09 (0.88-1.35)	0.41	1.11 (0.90-1.38)	0.34
CABG + OMT vs. OMT	0.51 (0.39-0.66)	0.55 (0.41-0.74)	0.0001	0.56 (0.41-0.75)	0.0001
CABG + OMT vs. PCI + OMT	0.54 (0.42-0.70)	0.50 (0.38-0.67)	0.0001	0.50 (0.38-0.67)	0.0001
Stroke events (n = 136)					
PCI + OMT vs. OMT	1.15 (0.76-1.74)	1.08 (0.68-1.70)	0.75	1.08 (0.68-1.70)	0.75
CABG + OMT vs. OMT	1.61 (1.04-2.49)	1.66 (0.93-2.96)	0.086	1.62 (0.91-2.89)	0.10
CABG + OMT vs. PCI + OMT	1.41 (0.95-2.09)	1.54 (0.96-2.48)	0.074	1.50 (0.93-2.42)	0.094

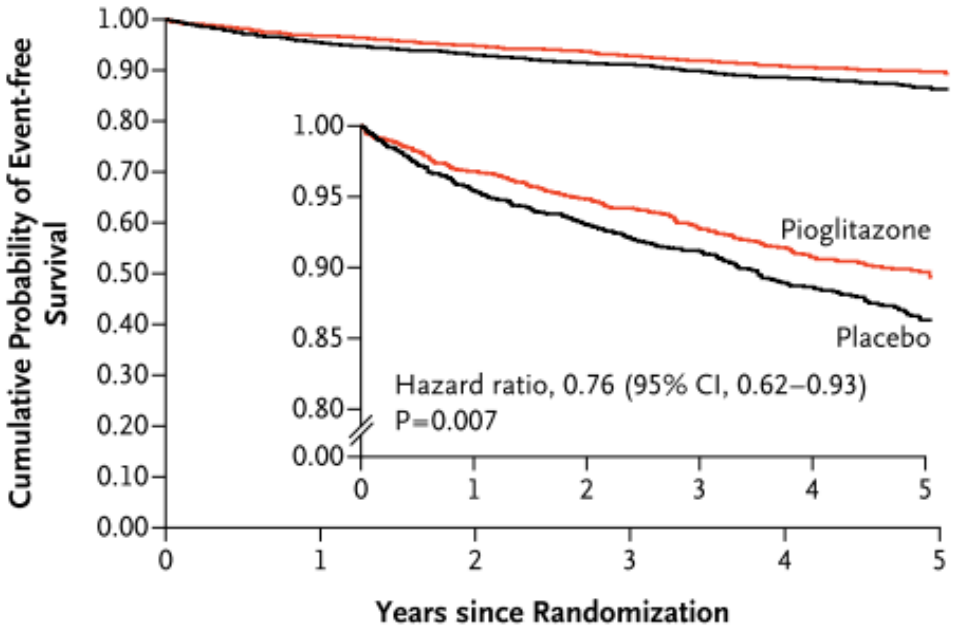
Diabetes & Stroke



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pioglitazone after Ischemic Stroke or Transient Ischemic Attack



No. at Risk

Pioglitazone	1939	1793	1701	1491	1196	481
Placebo	1937	1778	1690	1476	1182	459

Figure 1. Primary Outcome.

By 5 years, the primary outcome (fatal or nonfatal stroke or fatal or nonfatal myocardial infarction) had occurred in 175 of 1939 patients (9.0%) in the pioglitazone group and in 228 of 1937 (11.8%) in the placebo group. The inset shows the same data on an enlarged y axis. The numbers at risk were the numbers of patients who were alive without an event and still being followed at the beginning of each time point.

Peripheral vascular disease

- Screening (IDF 2017):
  - People with diabetes aged over 50
  - People with diabetes with PAD risk factors (such as cardiovascular and cerebral- vascular disease, dyslipidemia, hypertension, smoking, or duration of diabetes of more than 5 years)
  - People with diabetes with a foot ulcer or gangrene

Table 3
ABPI criteria for the diagnosis of peripheral vascular disease

ABPI	Inference
0.91–1.3	Normal
0.7–0.9	Mild obstruction
0.4–0.69	Moderate obstruction
<0.4	Severe obstruction
>1.3	Poorly compressible

Management

- Improve symptoms
- Prevent amputation
- Prevent CV morbidities

- Ways:
  - Risk factors treatment (glycemic control, HT, lipid, smoking)
  - Antiplatelet agents (aspirin , plavix)
  - Vasodilators (cilastazol, pentoxyfylline)
  - Surgery – intermittent claudication (angioplasty +/- stenting); chronic limb ischemia (endovascular / bypass)

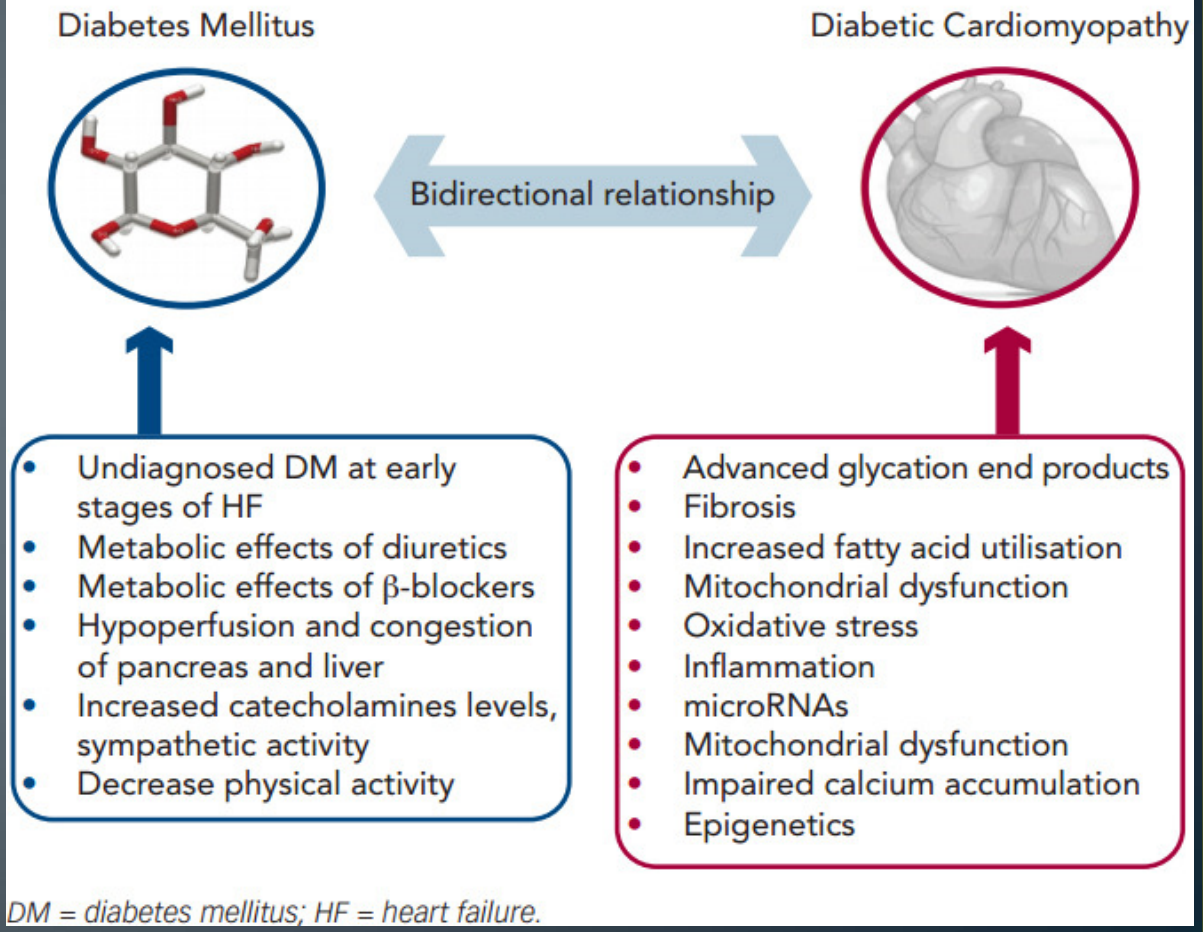


Miscellaneous

Heart failure

- 20-35% of HF patients got T2DM
- T2DM – increase 2-3x risk of HF
- Increase mortality ~1.6x if HF + DM
- Up to 75% got HFpEF (LVEF≥50%)

Figure 1: Schematic Depiction of the Bidirectional Relationship between Diabetes Mellitus and Heart Failure



DM = diabetes mellitus; HF = heart failure.

- DM should be treated as Stage A HF (i.e. at risk of HF)
- Treatment same as HF without DM
- SGLT-2 inhibitors – new agents for treatment of HF in patients with DM , and possible without DM in future
  - Postulated mechanisms:
  - 1) Restoration of tubuloglomerular feedback: volume contraction without neurohormonal activation, preserve renal function
  - 2) Improve myocardial energetics (mild ketosis)
  - 3) Reduce sympathetic tone to the heart (renal afferent)
  - 4) increase hematocrit and EPO
- ESC HF guideline – use of empagliflozin be considered (class IIa recommendation) in patients with T2DM to prevent or delay the onset of HF and prolong life

Dementia

- Increase 1.5-3x dementia; increase 40% MCI
- Type 3 insulin resistance
- Risk – hyper/hypo-glycemia, stroke, Vit B12 deficiency
- Bi-directional effects between glycemia and dementia
- Poor glycemic control/compliance/ reluctance to change can be sign of dementia
- Assessment
  - Always good history
  - Abbreviated Mental test
  - Clock Drawing test
  - MMSE/MoCA-HK
  - Functional assessment – Barthel, FAST
- Individualize treatment Rx and glycemic target (avoid hypoglycemia)

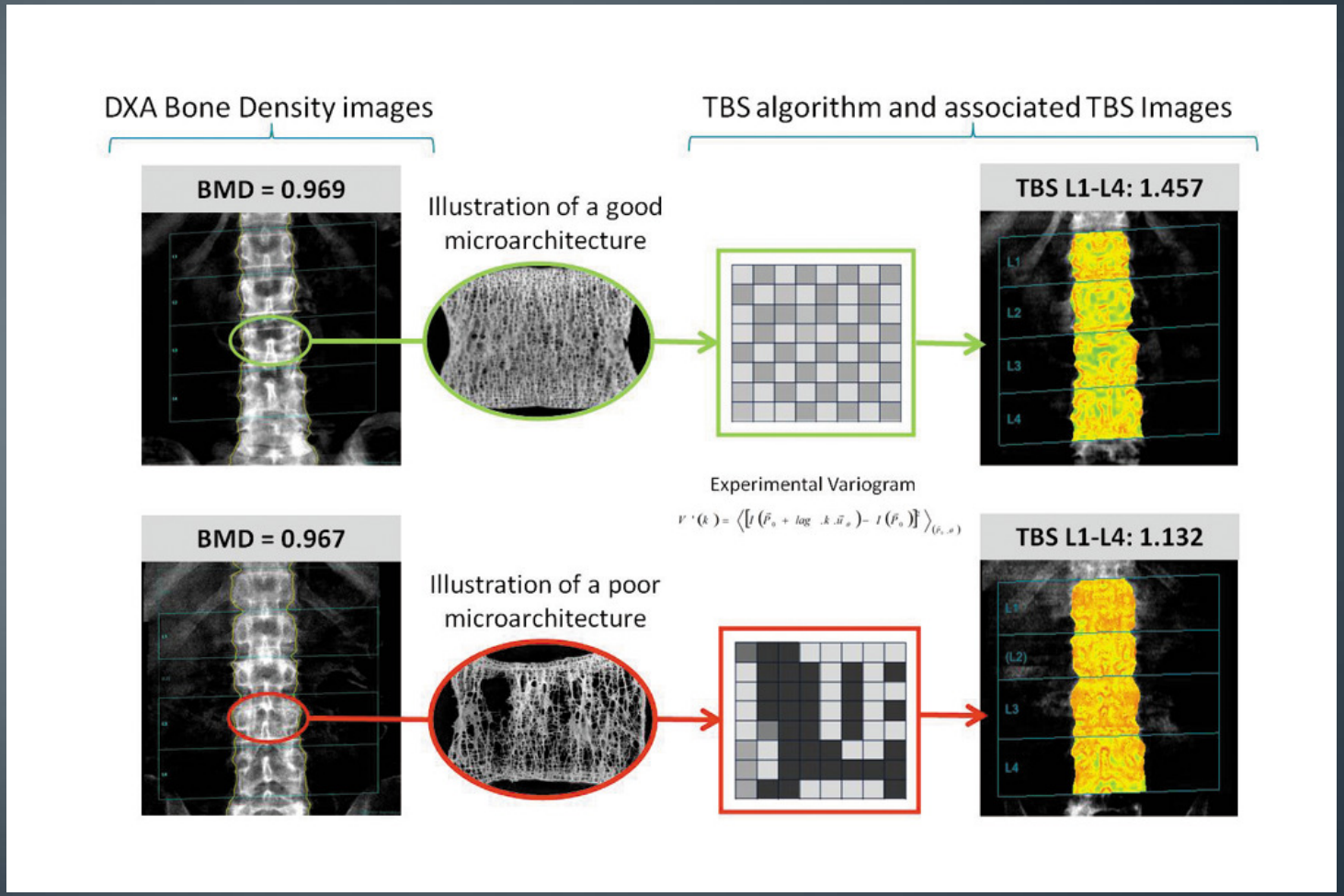
Patient Characteristics/ Health Status	A1c target	Fasting/ premeal (mmol/L)	Bedtime (mmol/L)	BP (mmHg)	Hyperlipidemia
Healthy (Few coexisting chronic illnesses, intact cognitive and functional status)	<7-7.5%	5-7.2	5-8.3	<140/80	Statin
Complex/intermediate (Multiple coexisting chronic illnesses A or or mild to moderate cognitive impairment)	<8%	5-8.3	5.6 -10	<140/80	Statin
Very complex/poor health (Long-term care or end-stage chronic illnessess or moderate to severe cognitive impairment or ADL dependencies)	<8.5-9%	5.6-10	6.1 -11	<150/90	Consider statin

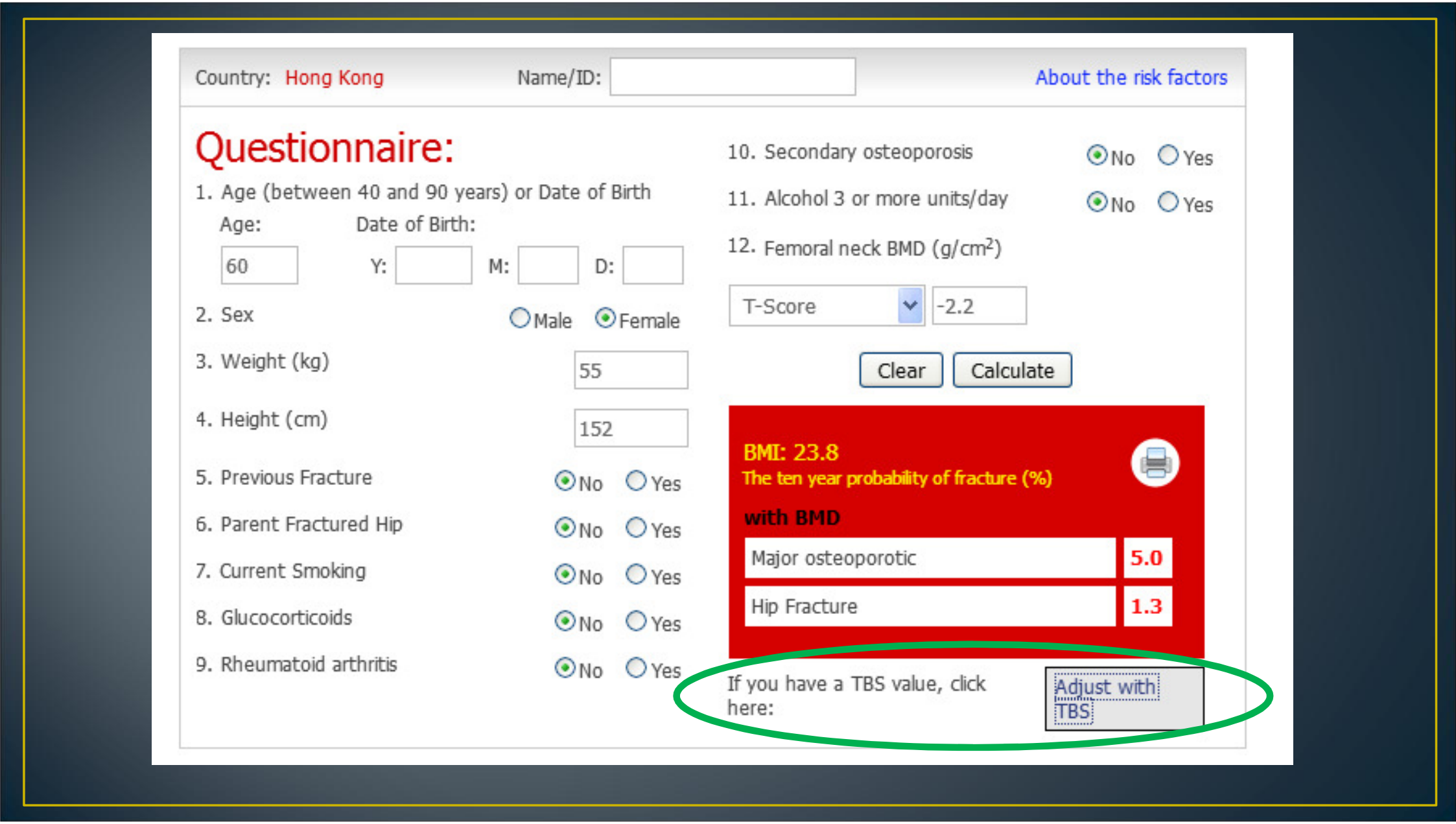
Diabetes in Older Adults: A Consensus Report JAGS 2012

Osteoporosis

- Both patients with T1DM (hip # RR 6.4) and T2DM (hip # RR 1.7) at increased risk of fractures
  - T1DM – lower BMD compared to controls; one of 6 secondary causes of osteoporsis in FRAX score
  - T2DM – increase BMD compared to controls
- Mechanisms
  - T1DM – reduced peak bone mass, insulin/IGF-1/amylin deficiency
  - T2DM – Use of TZD / SGLT2 inhibitors (canagliflozin), bariatric surgery
  - Both – hyperglycemia (oxidative stress, AGE), hypogylcemia & retinopathy (fall) , nephropathy (protein loss, 2o hyperparathyroidism)
- ADA (2018) - assess fracture history and risk factors in older patients with diabetes and recommend measurement of BMD if appropriate for the patient ' s age and sex
- Trabecular bone score – improve fracture risk assessment in T2DM

Trabecular bone score




Country: Hong Kong
Name/ID:
About the risk factors
Questionnaire:
1. Age (between 40 and 90 years) or Date of Birth
Age:
Date of Birth:
60
Y:
M:
D:
2. Sex
Male
Female
3. Weight (kg)
55
4. Height (cm)
152
5. Previous Fracture
No
Yes
6. Parent Fractured Hip
No
Yes
7. Current Smoking
No
Yes
8. Glucocorticoids
No
Yes
9. Rheumatoid arthritis
No
Yes
10. Secondary osteoporosis
No
Yes
11. Alcohol 3 or more units/day
No
Yes
12. Femoral neck BMD (g/cm2)
T-Score
-2.2
Clear
Calculate
BMI: 23.8
The ten year probability of fracture (%)
with BMD
Major osteoporotic
5.0
Hip Fracture
1.3
If you have a TBS value, click here:
Adjust with TBS

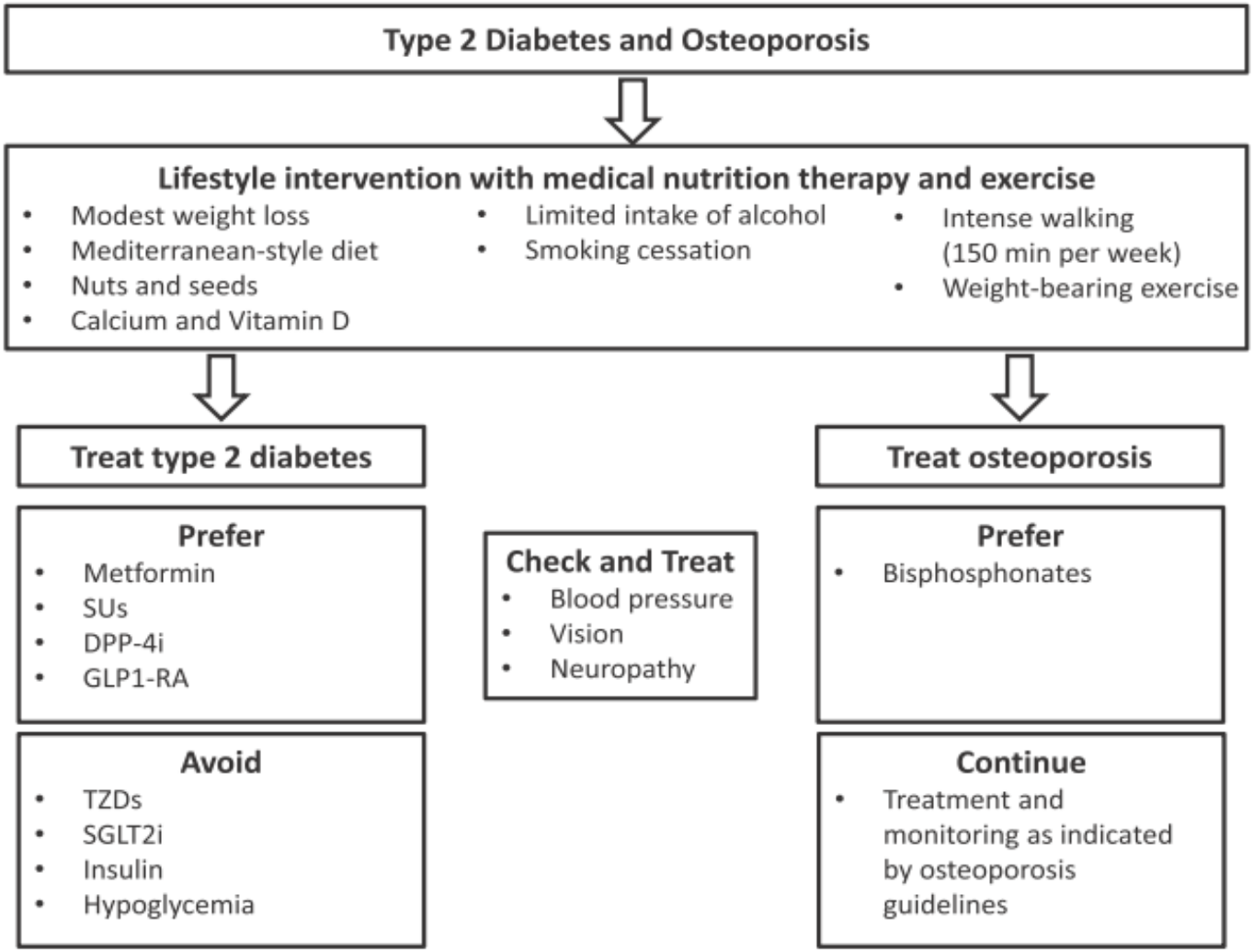


Figure 3. Algorithm for optimal management of patients with T2D and coexisting osteoporosis.

Conclusion

- DM associated with a myriad of chronic complications
- Macrovascular complications are leading cause of death in patients with DM
- Microvascular complications cause significant morbidities and impairment in QoL
- Treatment of glycemia – should take into the account of established ASCVD early
- All DM patients should be complication screening as recommended with SUBSEQUENT MANAGEMENT !

Thank you