Long-term Complications of T2DM

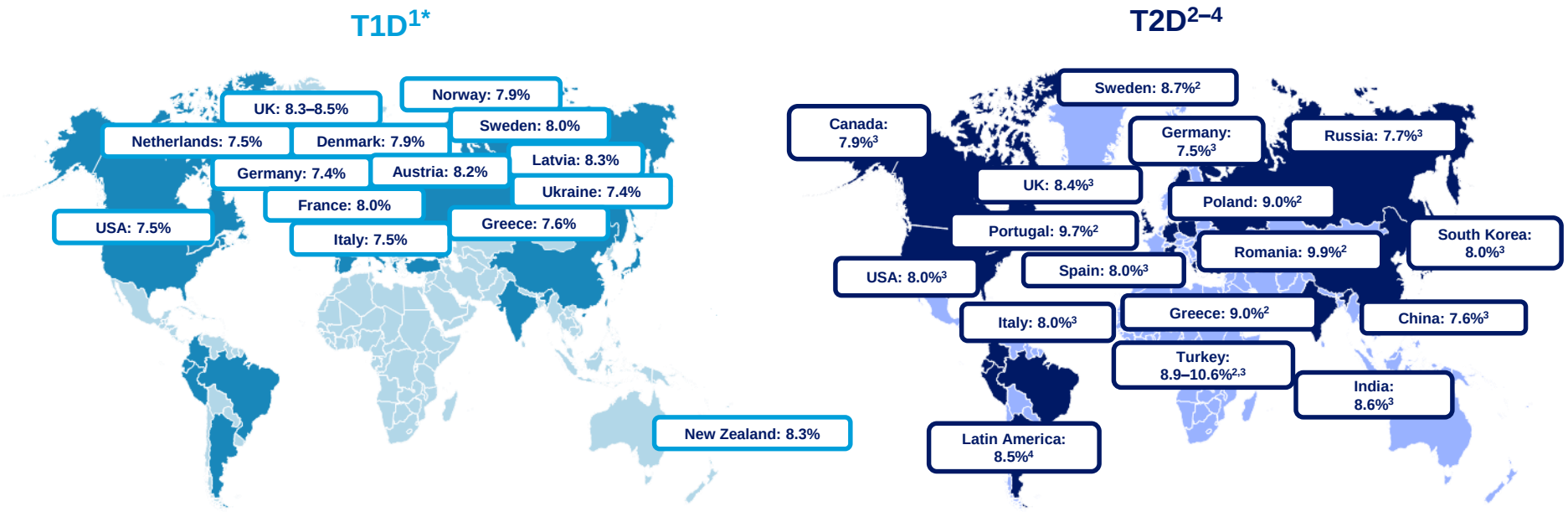
Amir Bahrami, MD

Professor of Endocrinology & Metabolism

Tabriz University of Medical Sciences

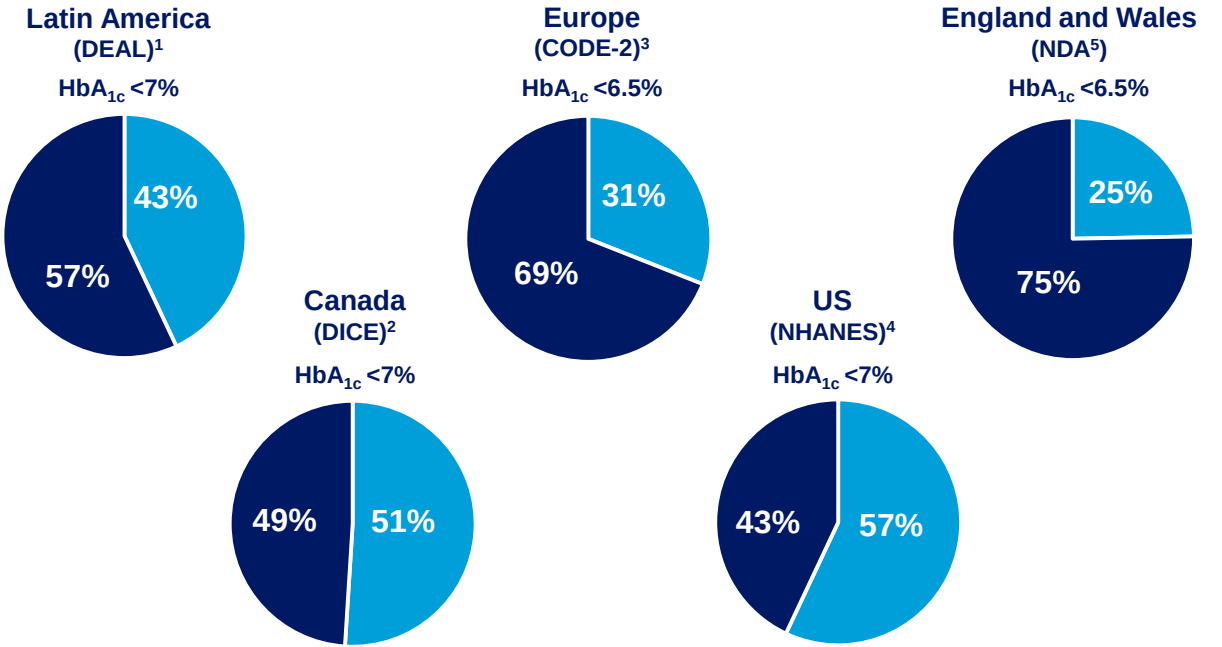
The worldwide challenge of glycaemic control

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

Diabetes is a progressive disease that requires reassessment to reach target

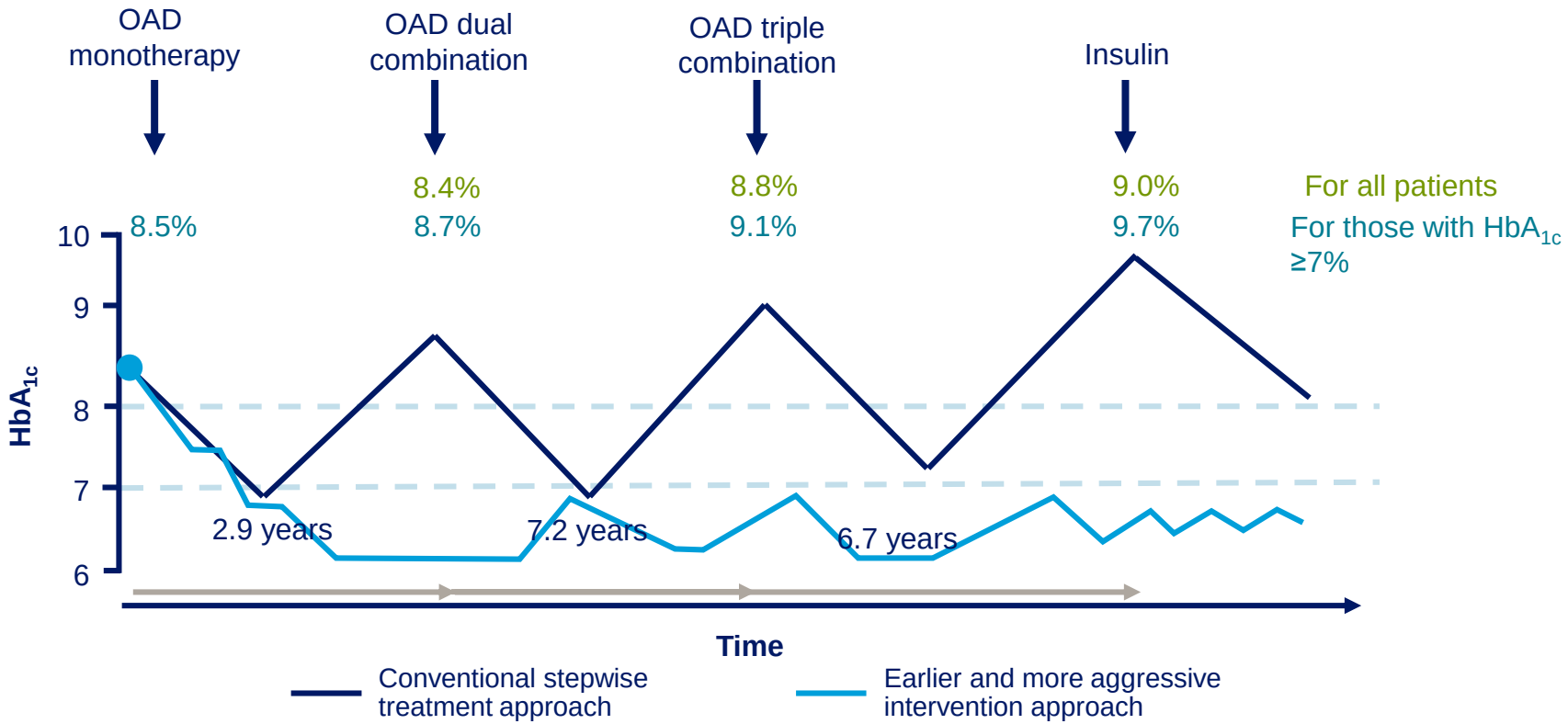


- **Diabetes progresses and requires treatment reassessment**
- **Insulin used to help achieve control**

DEAL, Diabetes En America Latina; CODE-2, The Cost of Diabetes in Europe - Type II; DICE, Diabetes in Canada Evaluation; NDA, National Diabetes Audit; NHANES, National Health and Nutrition Examination Survey

1. Lopez Stewart *et al. Rev Panam Salud Publica* 2007;22:12–20; 2. Harris *et al. Diabetes Res Clin Pract* 2005;70:90–7; 3. Liebl *et al. Diabetologia* 2002;45:S23–8;
4. Hoerger *et.al. Diabetes Care* 2008;31:81–6; 5. HSCIC *et al.* National Diabetes Audit Report, 2011-12

Earlier and appropriate intervention may improve patients' chances of reaching goal

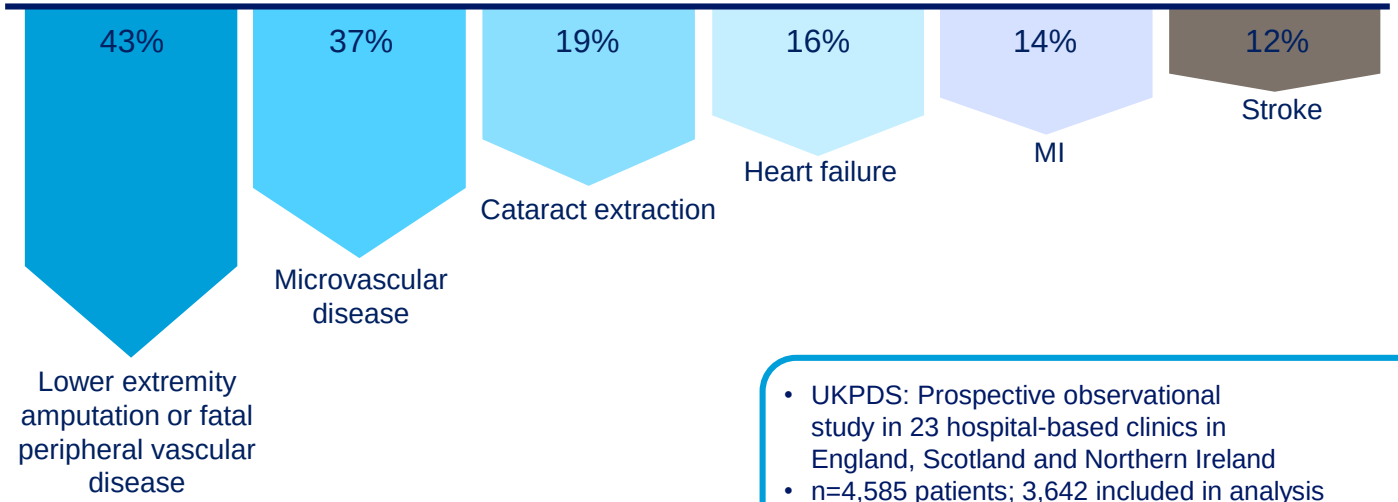


OAD, oral antidiabetic drug

Adapted from: Khunti *et al. Diab Care* 2013;36:3411–7; Del Prato *et al. Int J Clin Pract* 2005;59:1345–1355

Better HbA_{1c} control is associated with reductions in long-term health complications

Every 1% drop in HbA_{1c} can reduce long-term diabetes complications



- UKPDS: Prospective observational study in 23 hospital-based clinics in England, Scotland and Northern Ireland
- n=4,585 patients; 3,642 included in analysis of relative risk

MI, myocardial infarction; UKPDS, UK Prospective Diabetes Study
UKPDS 35: Stratton *et al. BMJ* 2000;321:405–11

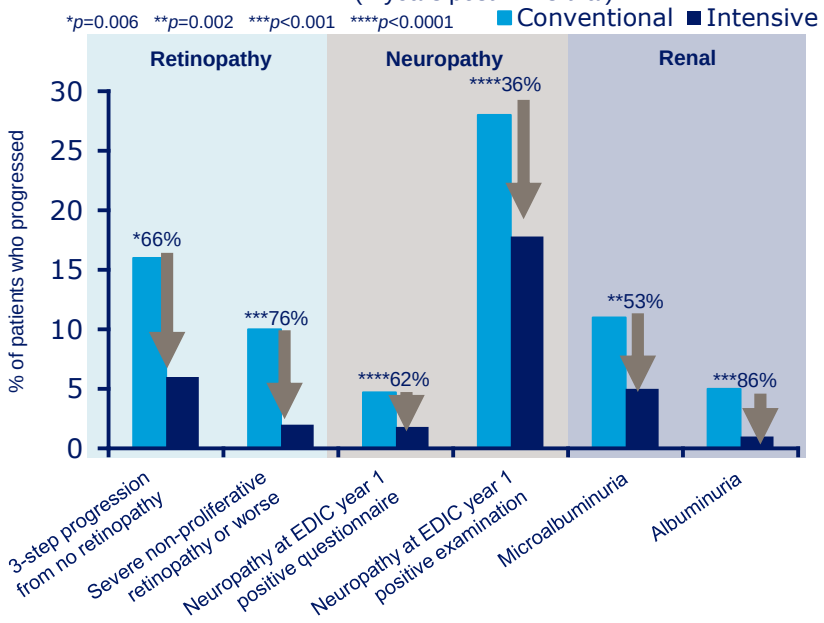
Intensive vs. conventional treatment in T1D and T2D

DCCT/EDIC and UKPDS follow-up data

T1D

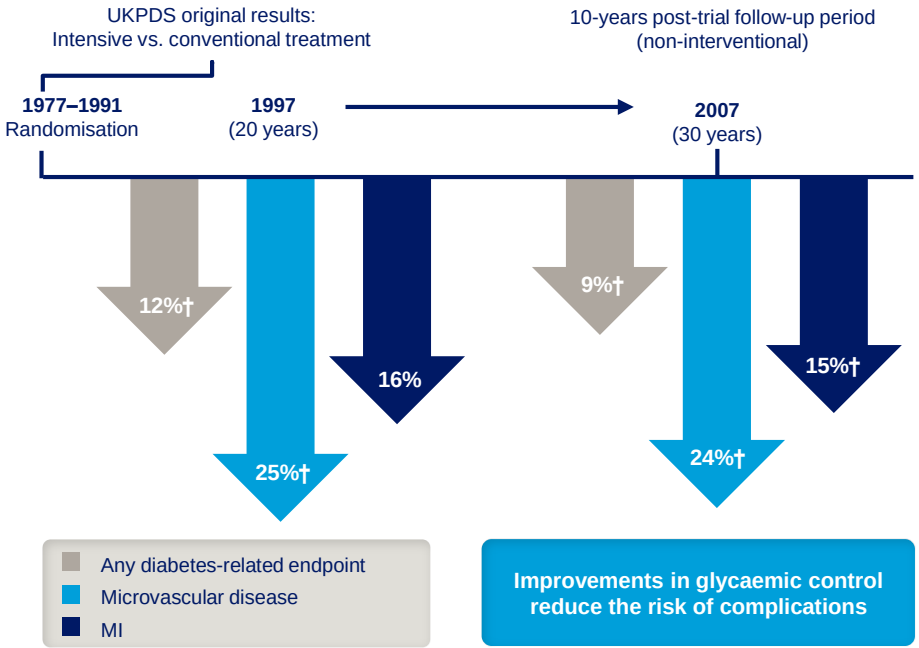
DCCT/EDIC – microvascular complications[1,2]

(4-years post-EDIC trial)



T2D

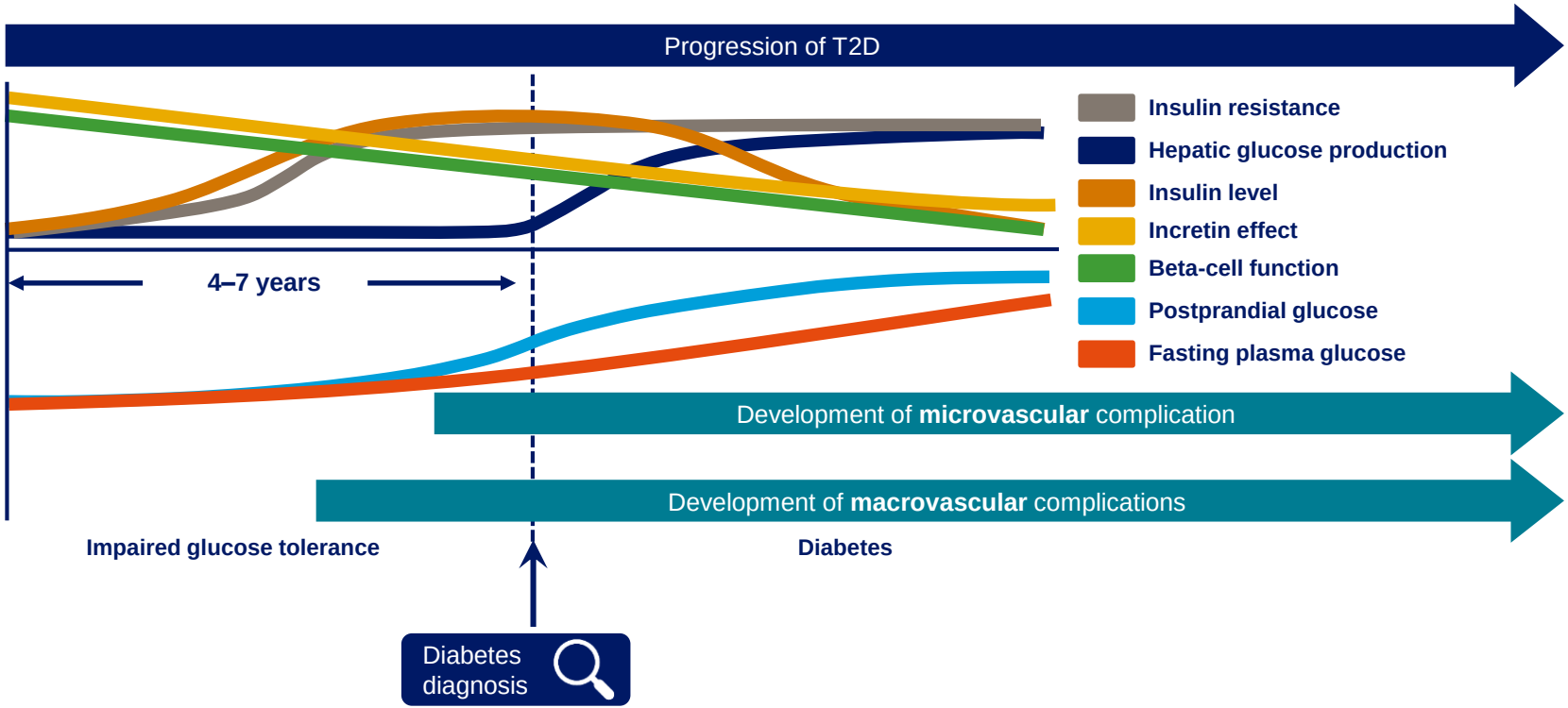
UKPDS – macrovascular complications[3,4]



†$p<0.05$; intensive vs. conventional treatment

1. DCCT/EDIC Group. *JAMA* 2002;287:2563–9; 2. Martin *et al. Diabetes Care* 2006;29:340–4; 3. UKPDS Study Group. *Lancet* 1998;352:837–53; 4. Holman *et al. N Engl J Med* 2008;359:1577–89

Progression of T2D and long-term complications

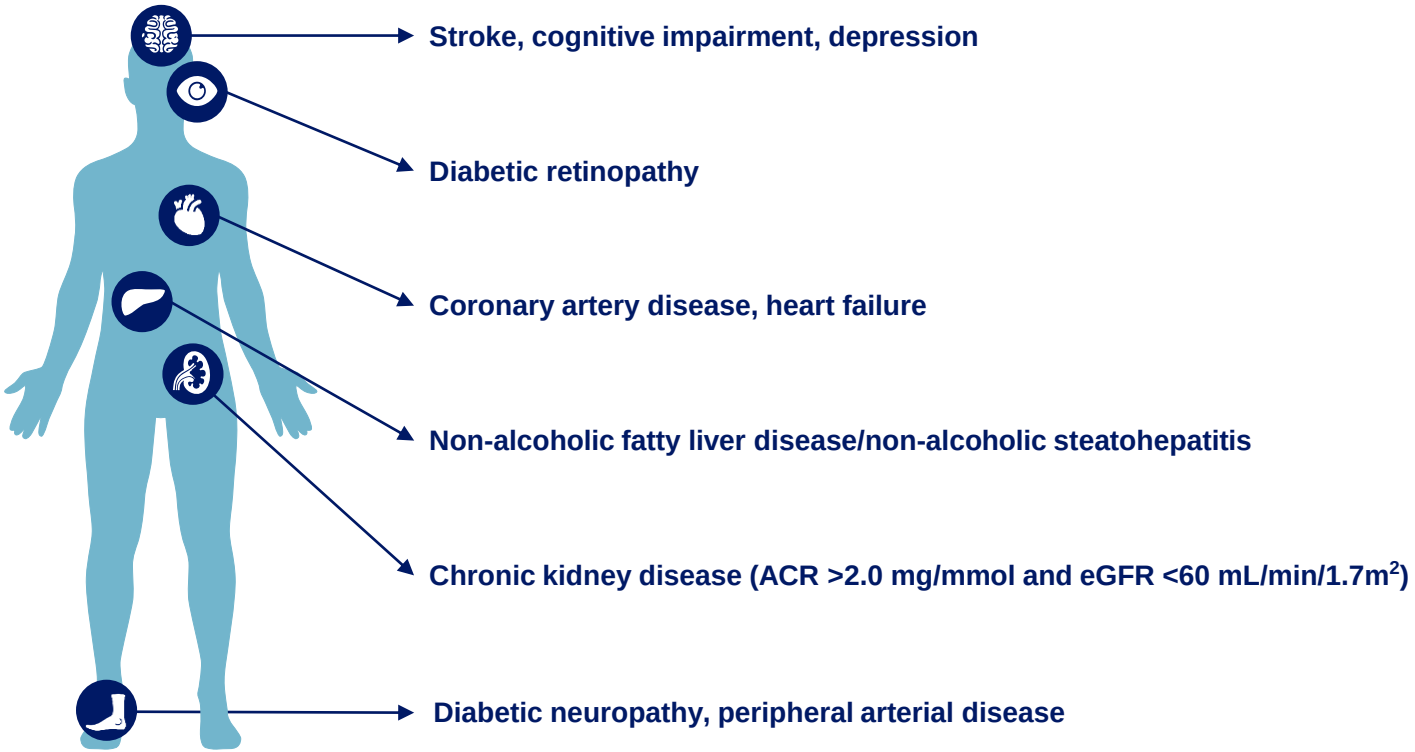


Adapted from Ryden L et al. *Eur Heart J* 2013;34:3035–3087

Understanding the pathophysiology of T2D

Adapted from DeFronzo RA. *Diabetes* 2009;58:773–795 and DeFronzo RA et al. *Nat Rev Dis Primers* 2015;1:15019

Patients and physicians are faced with a variety of diabetes-related comorbidities[1]



ACR, albumin to creatinine ratio; eGFR, estimated glomerular filtration rate

Iglay K et al. *Curr Med Res Opin* 2016;32:1243–1252

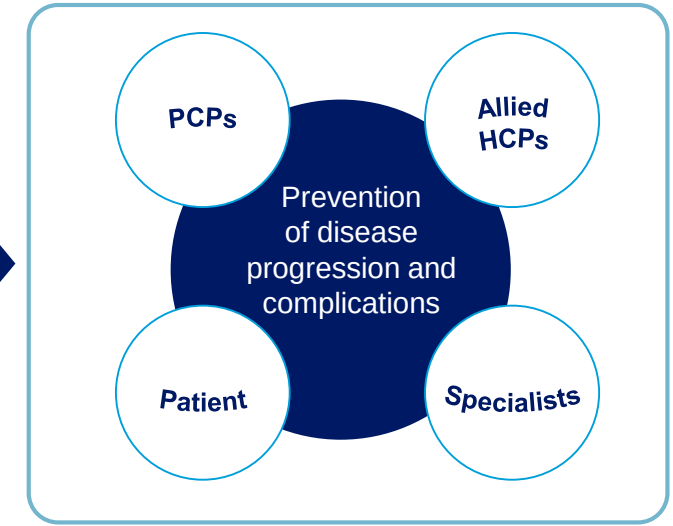
Patient-centred care provides optimal outcomes for diabetes care

- Early screening and close monitoring can prevent disease progression and complications

Timely treatment initiation and intensification

Patient empowerment

Collaborative multidisciplinary team approach and referrals



MDT, multidisciplinary team; HCP, healthcare provider; PCP; primary care physician

American Diabetes Association Standards of Medical Care in Diabetes 2020. *Diabetes Care* 2020;43(Suppl. 1); IDF Diabetes Atlas (9th edition). International Diabetes Federation. 2019. Available at: http://www.diabetesatlas.org/ (accessed January 2020); American Diabetes Association. Standards of Medical Care in Diabetes – 2019 Abridged for Primary Care Providers; Powers MA et al. *Clin Diabetes* 2016;34:70–80

A multifactorial approach can improve management of T2D and its complications

ADA recommendations

HbA_{1c}	<7.0% (<53 mmol/mol)
Physical activity	≥150 mins per week*
Blood pressure	<140/90 mmHg
Triglycerides	<150 mg/dL (1.7 mmol/L)
HDL-C	Women ≥50 mg/dL (1.3 mmol/L) Men ≥40 mg/dL (1.0 mmol/L)

Glycaemic control

Lifestyle modification

Blood pressure control
Dyslipidaemia control

*Physical activity of moderate to vigorous intensity
ACEi, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; ARB, angiotensin receptor blocker; HDL-C, high-density lipoprotein cholesterol
American Diabetes Association Standards of Medical Care in Diabetes 2020. *Diabetes Care* 2020;43(Suppl. 1)

Diabetes-related complications affect multiple aspects of patient physiology

Microvascular complications

- Retinopathy
- Chronic kidney disease
- Neuropathy

Macrovascular complications

- Coronary artery disease
- Heart failure
- Peripheral arterial disease
- Stroke

Non-classical complications

- Cognitive impairment
- Depression
- NAFLD/NASH

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

American Diabetes Association Standards of Medical Care in Diabetes 2020. *Diabetes Care* 2020;43(Suppl. 1)

Microvascular complications of T2D

Microvascular complications
Damage to **small blood vessels** caused by severe and prolonged hyperglycaemia

Diabetic retinopathy

~25%

of patients with T2D have retinopathy and the risk increases over time[1]

Chronic kidney disease

~7%

of patients with T2D already have **microalbuminuria** at the time of diagnosis[2]

Diabetic neuropathy

45%

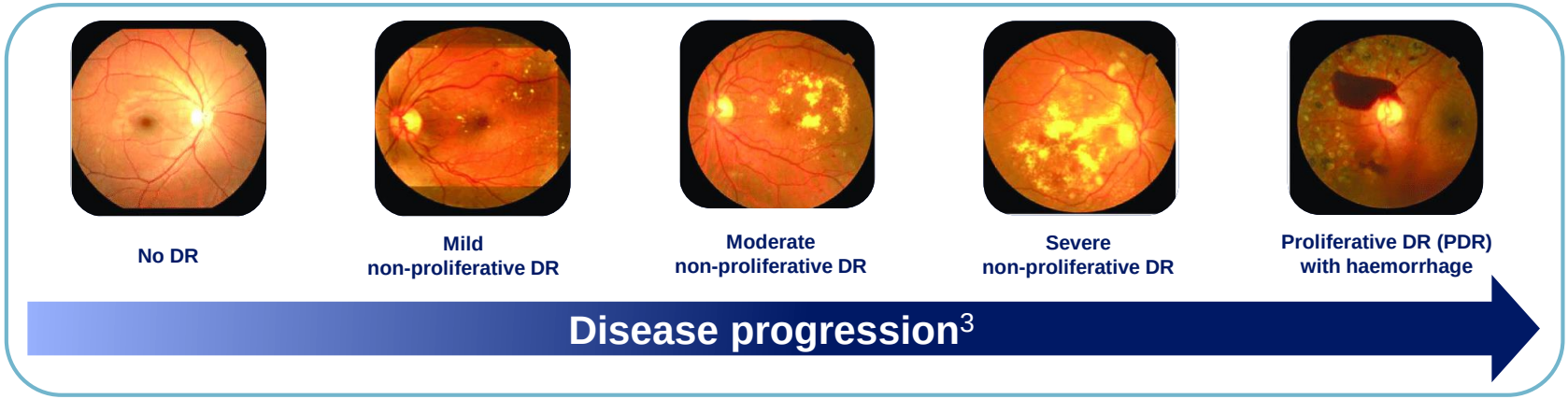
incidence of neuropathy for patients with T2D[3]

1. Yau JWY et al. *Diabetes Care* 2012;35:556–564; 2. Gross JL et al. *Diabetes Care* 2005;28:164–176; 3. Russel KW, Zilliox LA. *Continuum (Minneap Minn)* 2014;20:1226–1240

Diabetic retinopathy

Background

- Diabetic retinopathy is a **chronic, progressive disease** of the **retinal microvasculature** and is associated with **prolonged hyperglycaemia and other diabetic-related conditions** such as hypertension[1,2]



DR, diabetic retinopathy

1. The Royal College of Ophthalmologists, Diabetic Retinopathy Guidelines, 2012; 2. Wilkinson CP et al. *Ophthalmology* 2003;110:1677–1682;
3. El-Bab MF et al. *Clinical Ophthalmology* 2012;6:269–276

Diabetic retinopathy

Symptoms

- **Few visual or ophthalmic symptoms** are present until visual loss develops[1]
- Symptoms of diabetic retinopathy include:[2]

Blurred vision

Blotches or spots in vision

Normal vision

Flashes of light in the field of vision

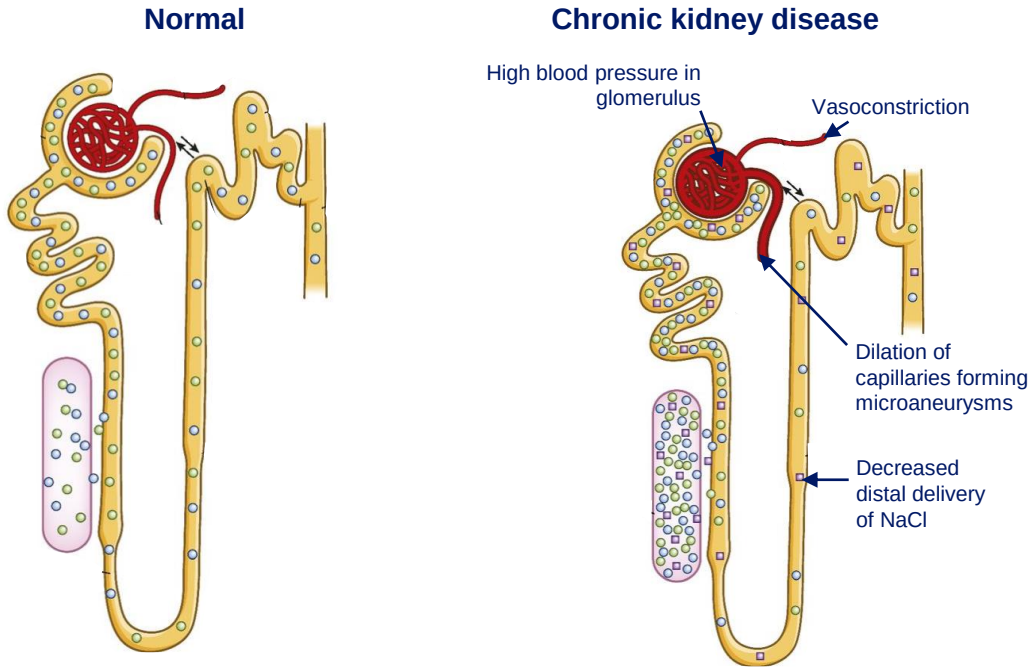
Sudden loss of vision

1. Fong DS et al. *Diabetes Care* 2004;27(Suppl. 1):S84–87; 2. Diabetes Canada Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2018;42(Suppl. 1):S210–S216

Chronic kidney disease

Background

- Chronic kidney disease: **progressive increase in albuminuria and/or creatinine**[1]
- **Pathological kidney changes** results **injury to filtration capacity**[2,3]



NaCl, sodium chloride

1. Diabetes Canada Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2018;42(Suppl. 1):S201–S209; 2. Fowler MJ. *Clinical Diabetes* 2008;26:77–82;
3. American Diabetes Association. Kidney disease (nephropathy). Available at: https://www.diabetes.org/diabetes/complications/kidney-disease-nephropathy (accessed November 2019);
4. Alicic RZ et al. *CJASN* 2017;12:2032–2045

Chronic kidney disease

Symptoms

- No symptoms of chronic kidney disease in T2D are present until the kidney function deteriorates significantly

The first symptom of kidney disease is often fluid build-up, especially in the feet and ankles

Other symptoms of chronic kidney disease include:

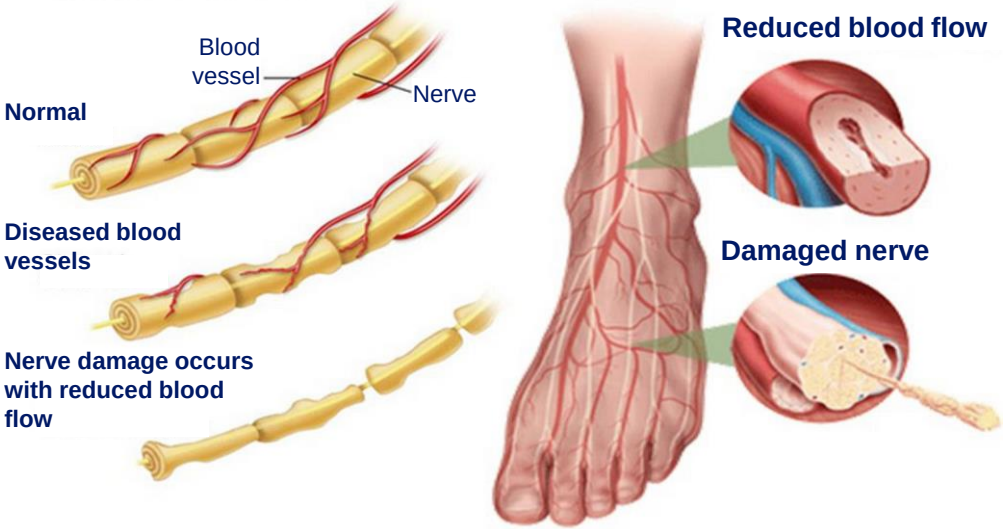
- Loss of sleep
- Lack of appetite
- Upset stomach
- Fatigue
- Difficulty concentrating

American Diabetes Association. Kidney disease (nephropathy). Available at: https://www.diabetes.org/diabetes/complications/kidney-disease-nephropathy (accessed November 2019)

Diabetic neuropathy

Background

- Diabetic neuropathy **can develop at any time during the course of diabetes** and has a **diverse range of clinical manifestations**[1–3]
- Diabetic neuropathy is characterised by **axonal thickening and eventual loss and damage of neurons**[1]



1. Beckman J-A, Creager M-A. *Circ Res* 2016;118:1771–1785; 2. Russel KW, Zilliox LA. *Continuum (Minneap Minn)* 2014;20:1226–1240;
3. American Diabetes Association Standards of Medical Care in Diabetes 2020. *Diabetes Care* 2020;43(Suppl. 1)

Diabetic neuropathy

Symptoms

Symptoms of **peripheral neuropathy**, such as:[1]

- Pain and dysaesthesia
- Numbness
- Loss of protective sensation

Diabetic peripheral neuropathy is the most common form of neuropathy in diabetes

Symptoms of **autonomic neuropathy** can include:[1]

- Hypoglycaemia unawareness
- Resting tachycardia
- Constipation/diarrhoea
- Gastroparesis
- Erectile dysfunction
- Neurogenic bladder
- Orthostatic hypotension
- Sudomotor dysfunction

1. American Diabetes Association Standards of Medical Care in Diabetes 2020. *Diabetes Care* 2020;43(Suppl. 1);
2. Russel KW, Zilliox LA. *Continuum (Minneap Minn)* 2014;20:1226–1240

Macrovascular complications of T2D

Macrovascular complications
Damage to **larger vessels** including coronary arteries and vessels in the brain and limbs

Coronary artery disease

25%
of asymptomatic diabetic patients have positive findings for coronary alterations when screened[1]

Heart failure

2x higher rate of hospitalisation from heart failure in patients with T2D versus those without[2]

Peripheral arterial disease

2- to 4-fold increase
risk of developing PAD for diabetic patients[3]

Stroke

2x
risk of stroke within 5 years of diagnosis of T2D compared with the genera population[4]

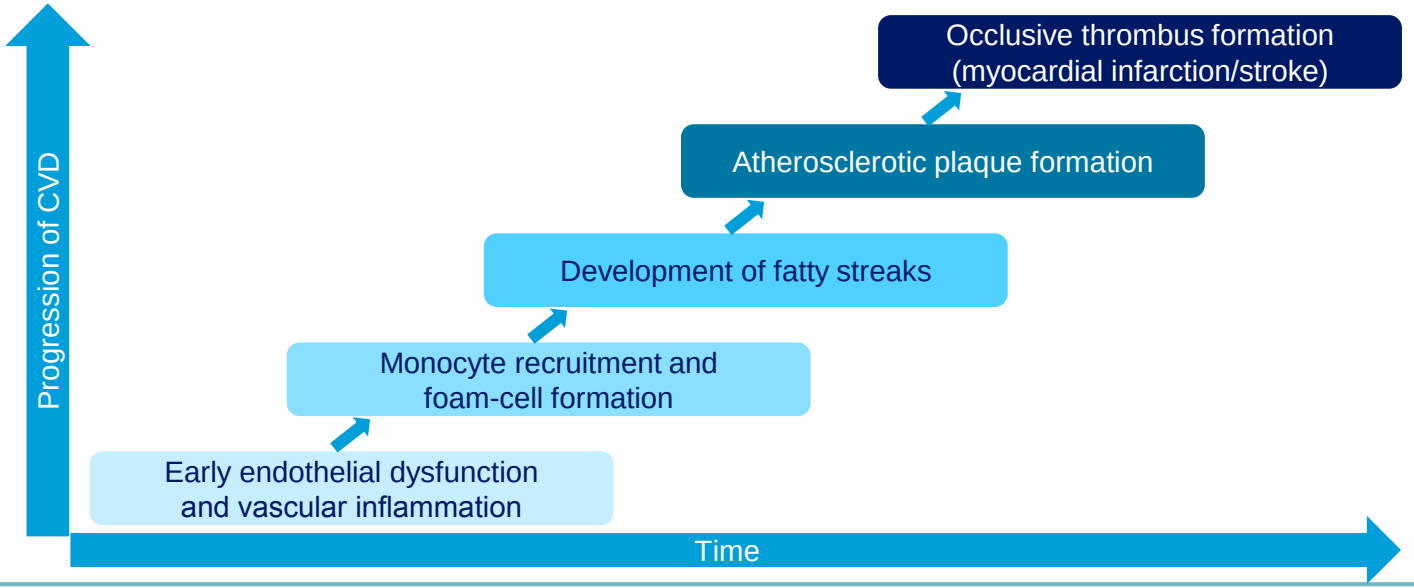
PAD, peripheral arterial disease
1. Tavares CAF et al. *Endocrinol Metab* 2016;60:143–151; 2. Diabetes Canada Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2018;42:S196–S200;
3. Beckman J-A, Creager M-A. *Circ Res* 2016;118:1771–1785; 4. Laakso M, Kuusisto J. *International Congress Series* 2007;1303:65–69

Cardiovascular disease

Background

CVD encompasses a group of disorders of the heart and blood vessels[1]

Development of CVD[2]



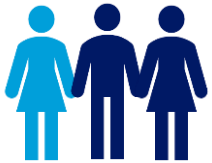
CVD, cardiovascular disease

1. International Diabetes Federation Diabetes Atlas (9th edition). IDF 2019. Available at: http://www.diabetesatlas.org/ (accessed January 2020);
2. Ryden L et al. *Eur Heart J* 2013;34:3035–3087

Cardiovascular disease

Background

CVD affects

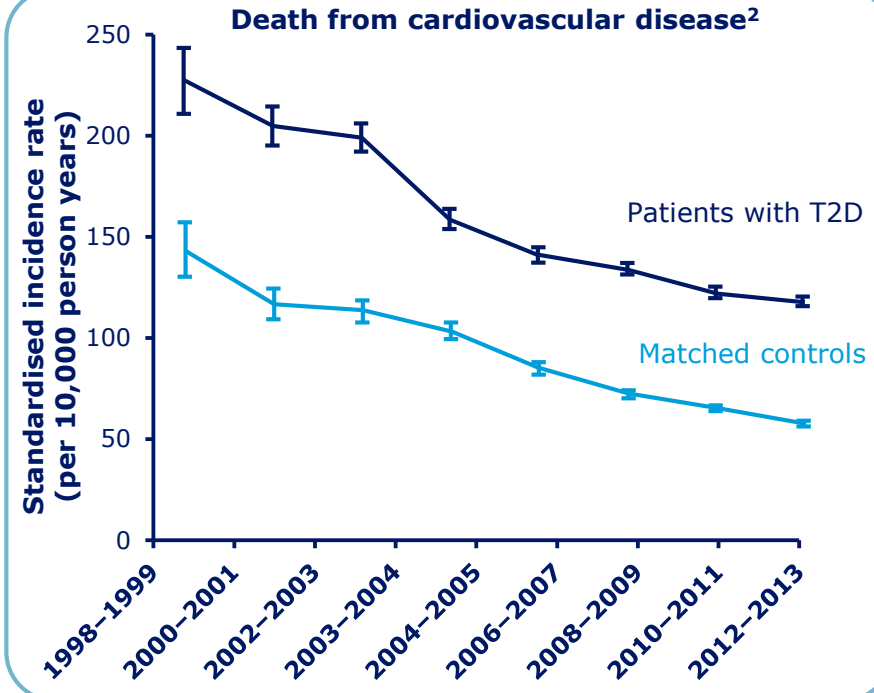


1 in 3

of all patients with T2D globally[1]

High HbA_{1c} levels increase activity of the blood coagulation system, thereby increasing the **risk of blood clots**[1]

Other CVD risk factors such as **high blood pressure** and **high cholesterol** are also common in patients with T2D[1]



CVD, cardiovascular disease

1. International Diabetes Federation Diabetes Atlas (9th edition). IDF 2019. Available at: http://www.diabetesatlas.org/ (accessed January 2020);
2. Rawshani A et al. *N Engl J Med* 2017;376:1407–1418

Cardiovascular disease

Screening

Risk factors should be systematically assessed **at least annually in all patients** with diabetes[1]

- Obesity/overweight
- Hypertension
- Dyslipidaemia
- Smoking
- Family history of CVD
- CKD
- Presence of albuminuria

A **resting ECG** should be performed **every 3–5 years** if:[2]

- Age >40 years
- Age >40 years and planning to undertake vigorous/prolonged exercised
- Duration of diabetes >15 years and age >30 years
- **>1 CVD risk factor**
- End-organ damage (microvascular, cardiovascular)

CV, cardiovascular; CKD, chronic kidney disease; CVD, cardiovascular disease; ECG, electrocardiogram

1. American Diabetes Association Standards of Medical Care in Diabetes 2020. *Diabetes Care* 2020;43(Suppl. 1);
2. Diabetes Canada Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2018;42(Suppl. 1)

Peripheral arterial disease

Background

- Peripheral arterial disease is characterised by **atherosclerotic occlusive disease of the lower extremities**, and is a marker for increased risk of myocardial infarction, stroke and death[1]
- **PAD includes:**[2]
  - Lower-extremity arterial disease
  - Limb-threatening ischaemia
  - Intermittent claudication
  - Critical limb ischaemia

~27% of patients with PAD show progression of symptoms over 5 years[1]

Limb loss occurs in **~4%** of patients[1]

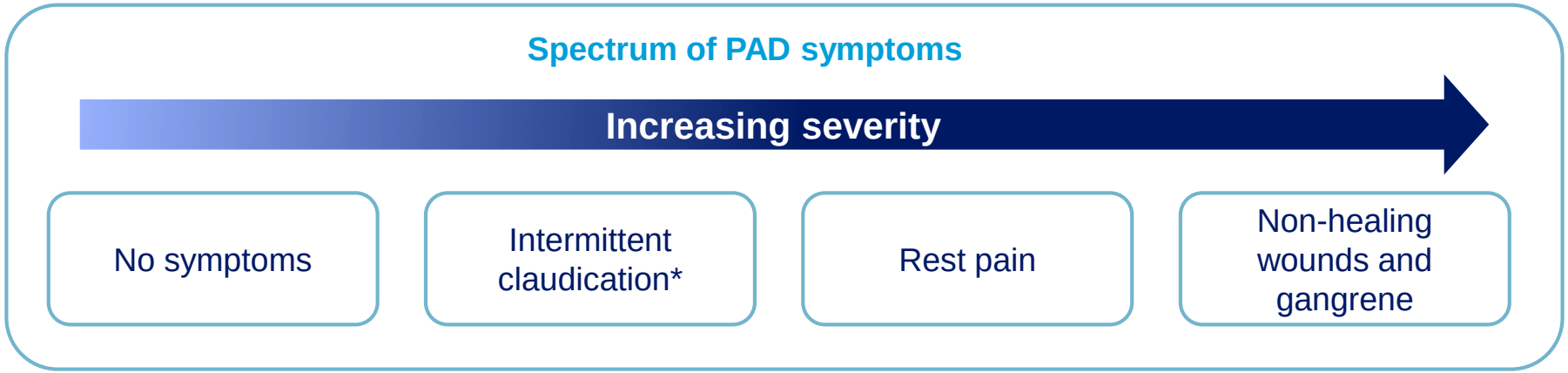
PAD, peripheral arterial disease

1. American Diabetes Association. *Diabetes Care* 2003;26:3333–3341; 2. International Diabetes Federation. Diabetes and cardiovascular disease report. Brussels, Belgium: IDF, 2016. www.idf.org/cvd (accessed November 2019)

Peripheral arterial disease

Symptoms

- Presentation of peripheral arterial disease is often more subtle in patients with diabetes than in those without



*Defined as pain, cramping or aching in the calves, thighs or buttocks that appears reproducibly with walking exercise and is relieved by rest
American Diabetes Association. *Diabetes Care* 2003;26:3333–3341

Stroke

Background

- Stroke can arise from **cerebral infarction** or **cerebral haemorrhage**[1]
- Clinical presentation of stroke in patients with T2D **differs to that in non-diabetic patients**. This includes:[2]

- T2D also **worsens stroke outcomes**, with higher rates of death and neurological deterioration seen in diabetic versus non-diabetic patients[2]

1. International Diabetes Federation. Diabetes and cardiovascular disease report. Brussels, Belgium: IDF, 2016. www.idf.org/cvd (accessed November 2019)
2. Beckman JA and Creager MA. *Circ Res* 2016;118:1771–1785

Stroke

Symptoms

- Typical warning signs of a stroke develop suddenly

Weakness or numbness on one side of the body

Sudden confusion or trouble understanding

Double vision

Aphasia

Dizziness, loss of balance, or trouble walking

Severe headache

Stroke. American Diabetes Association Diabetes.org. Available at: https://www.diabetes.org/diabetes/complications/stroke (accessed: November 2019)

Non-classical complications of T2D

Non-classical complications
cannot be categorised as microvascular or macrovascular complications

Cognitive impairment

73%

increased risk of all types of dementia in patients with T2D[1]

Depression

x2

Diabetes doubles the odds of comorbid depression[2]

NAFLD

>70%

of patients with T2D have NAFLD[4]

NAFLD, non-alcoholic fatty liver disease

1. Gudala K et al. *J Diabetes Investig* 2013;4:640–650; 2. Anderson RJ et al. *Diabetes Care* 2001;24:1069–1078; 3. Tilg H et al. *Nat Rev Gastroenterol Hepatol* 2017;14:32–34

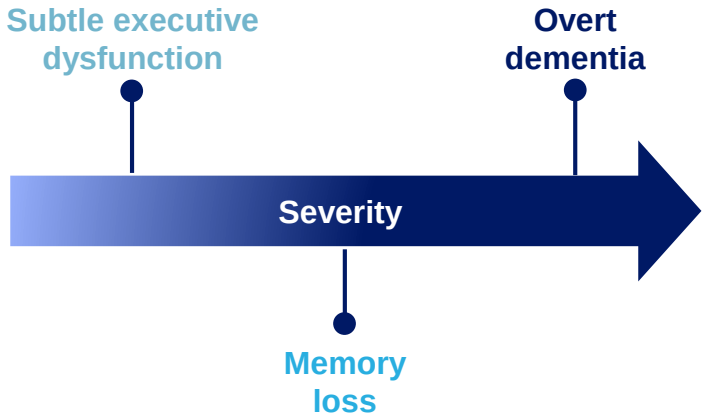
Cognitive impairment

Background

- **Diabetes is associated** with a **significantly increased risk and rate of cognitive decline, specifically in older adults**

- Cognitive impairment **impedes a clinician's ability** to help their patients reach $HbA_{1c,}$ blood pressure and lipid targets
- Cognitive impairment results in **challenges** for the patient **to complete self-care tasks** such as glucose monitoring and eating regular, balanced meals

Presentation of cognitive impairment **ranges in severity:**



American Diabetes Association Standards of Medical Care in Diabetes 2020. *Diabetes Care* 2020;43(Suppl. 1)

Depression

Background

Elevated depressive symptoms and depressive disorders affect:[1]

1 in 4
patients with T1D or T2D

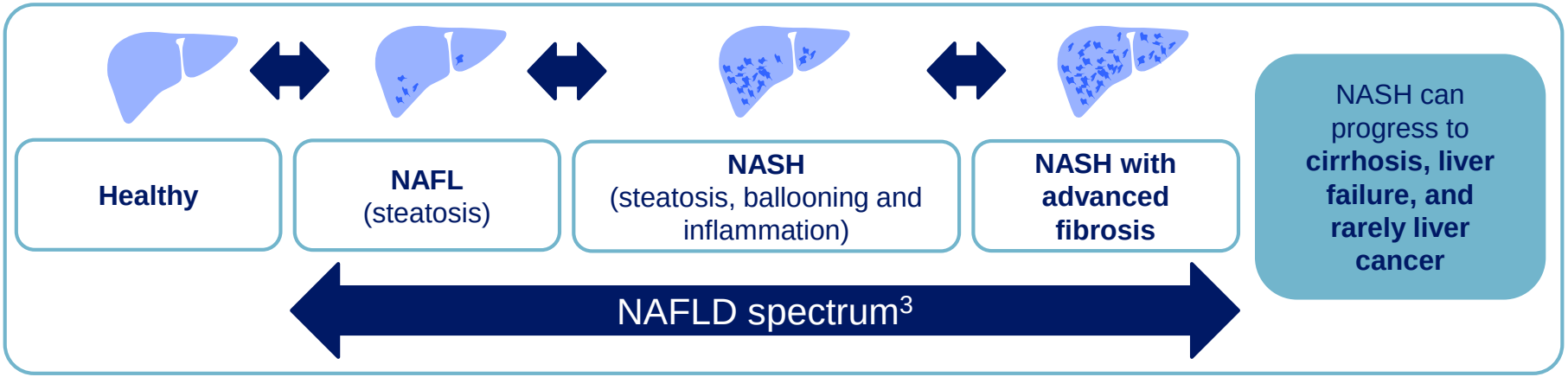
- Depressive symptoms in people with diabetes can result in **sub-optimal diabetes self-management** and **HbA_{1c}**[1,2]
- A **history of depression, current depression and use of anti-depressant medication** are also risk factors for the development of T2D[2]

1. Anderson RJ et al. *Diabetes Care* 2001;24:1069–1078;
2. American Diabetes Association Standards of Medical Care in Diabetes 2020. *Diabetes Care* 2020;43(Suppl. 1)

Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis

Background

- The concomitant presence of NAFLD and T2D **increases both the risk of developing diabetes-related complications** and the risk of **NAFLD progression**[1]
- Diabetes is associated with the development of **NAFLD** and its more severe manifestation of **NASH**[2]



NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

1. Hazlehurst JM et al. *Metabolism* 2016;65:1096–1108; 2. American Diabetes Association Standards of Medical Care in Diabetes 2020. *Diabetes Care* 2020;43(Suppl. 1);
3. Chalasani N et al. *Hepatology* 2018;67:328–357


novo nordisk®