

Long-term Complications of T2DM

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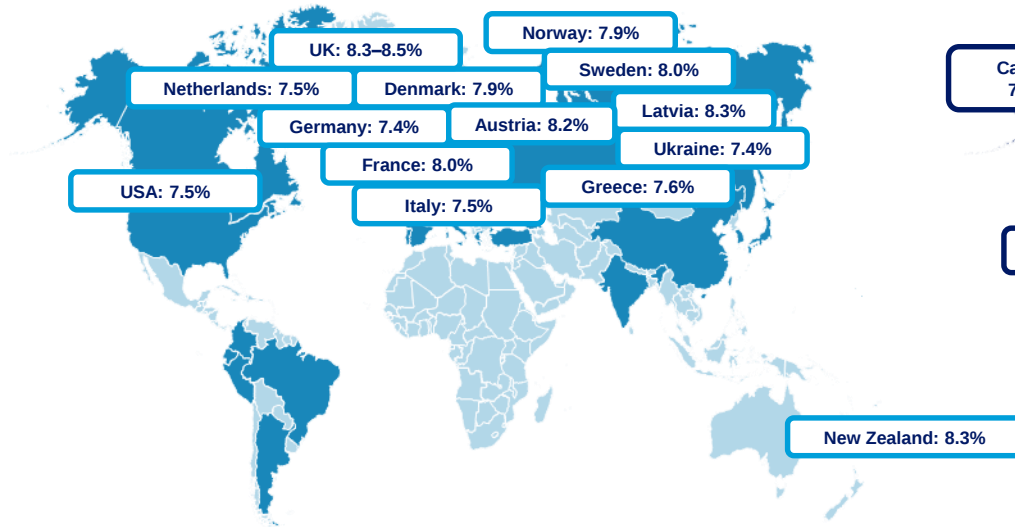
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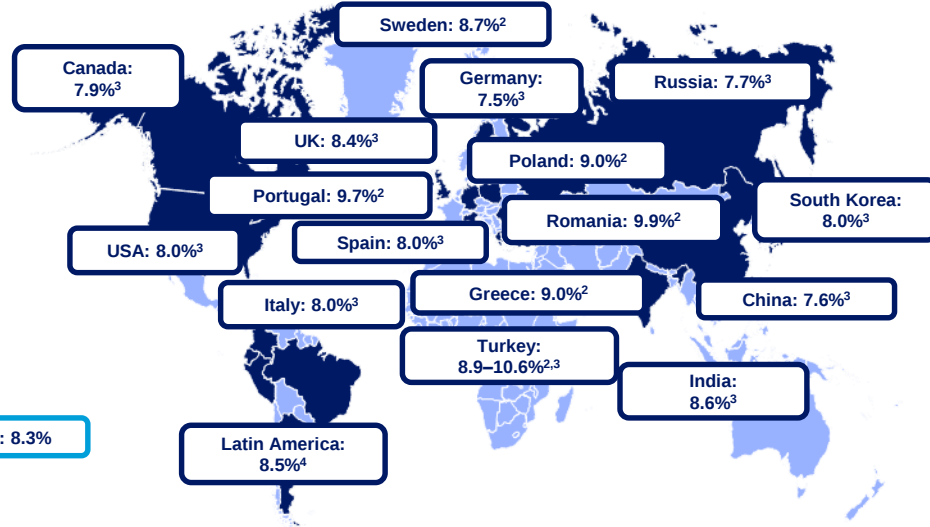
The worldwide challenge of glycaemic control

HbA_{1c} in T1D and T2D

T1D^{1*}



T2D^{2–4}

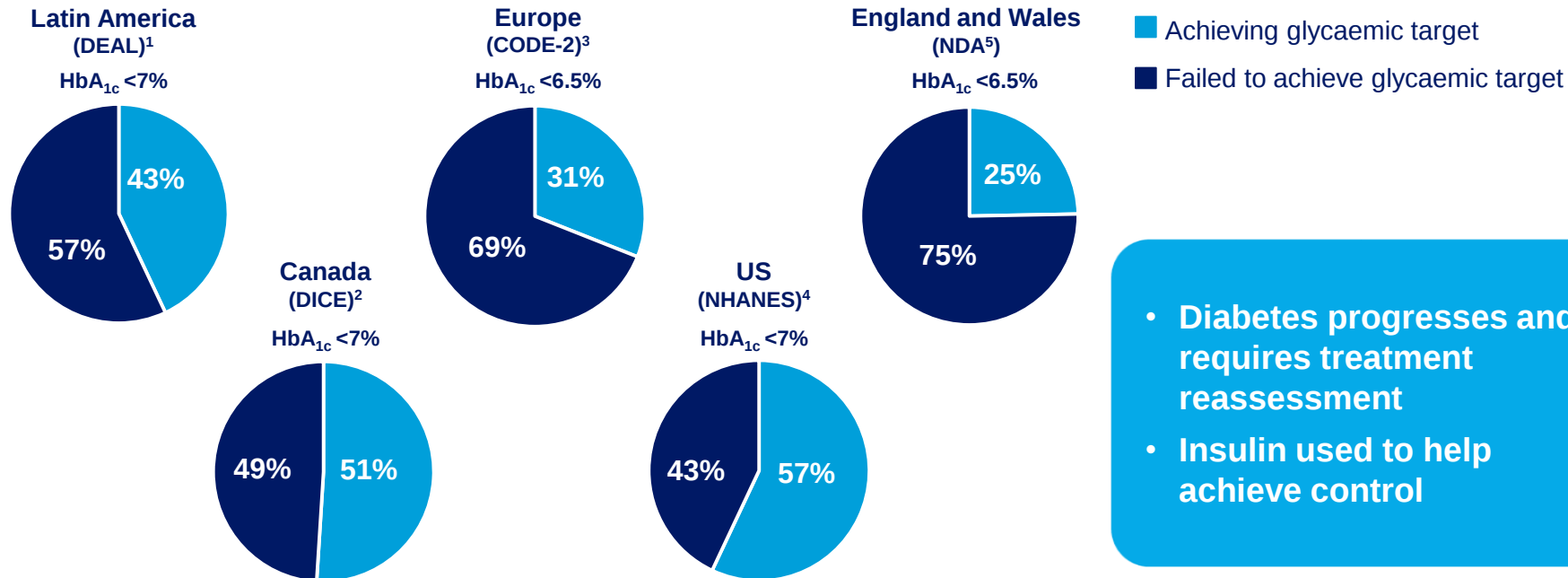


*Data are median and in adults (25+ years)

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

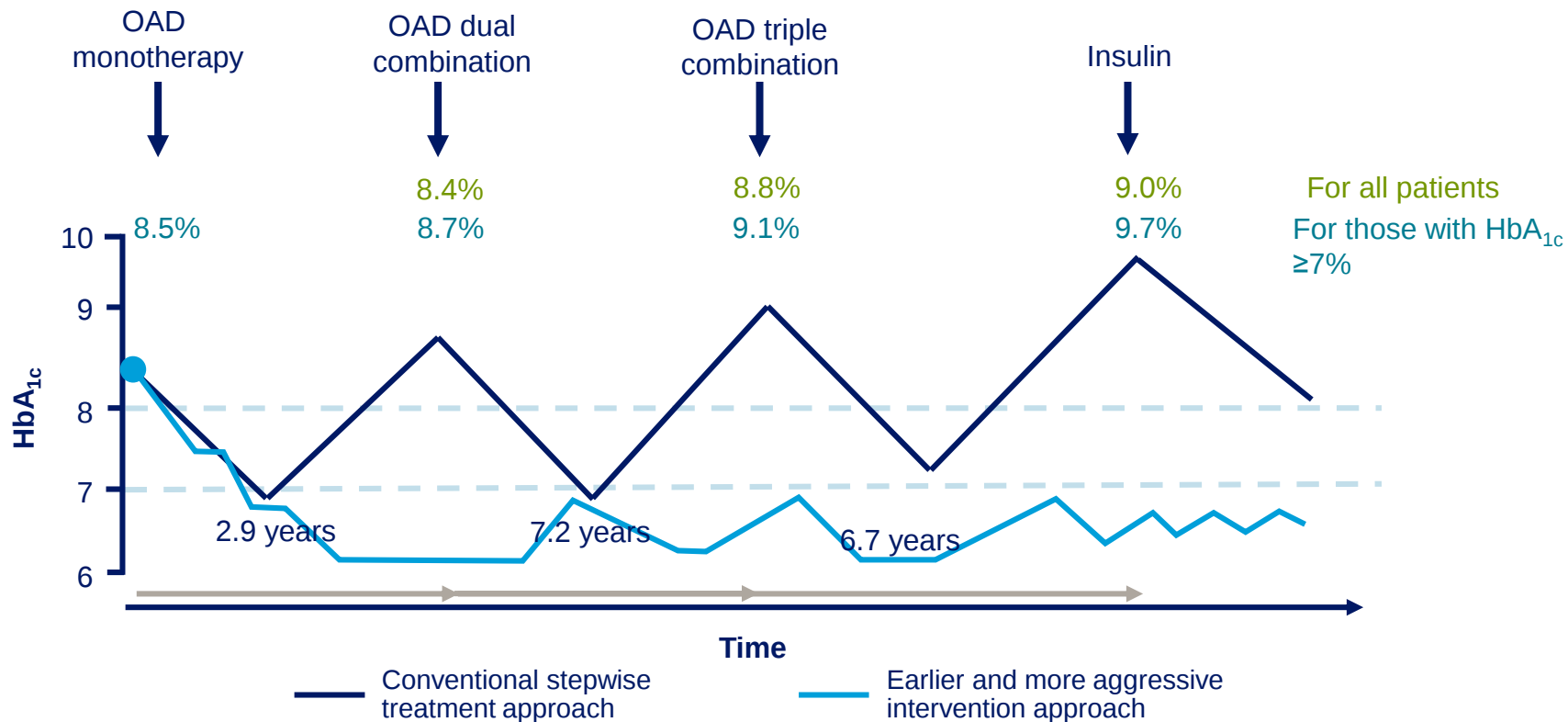


DEAL, Diabetes En America Latina; CODE-2, The Cost of Diabetes in Europe - Type II; DICE, Diabetes in Canada Evaluation; NDA, National Diabetes Audit; NHANES, National Health and Nutrition Examination Survey

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

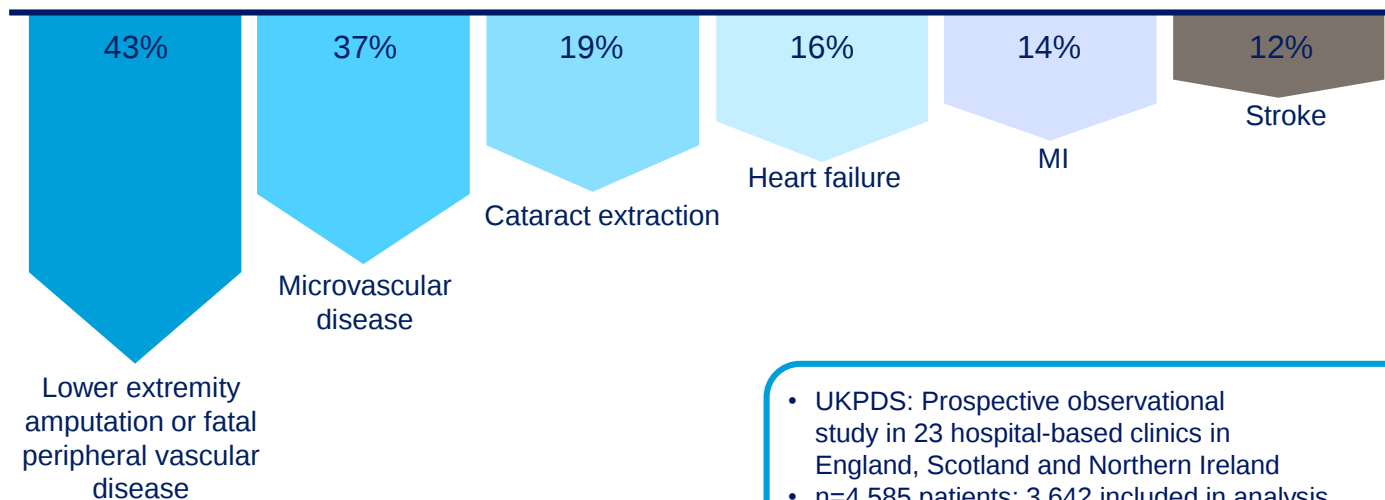


OAD, oral antidiabetic drug

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

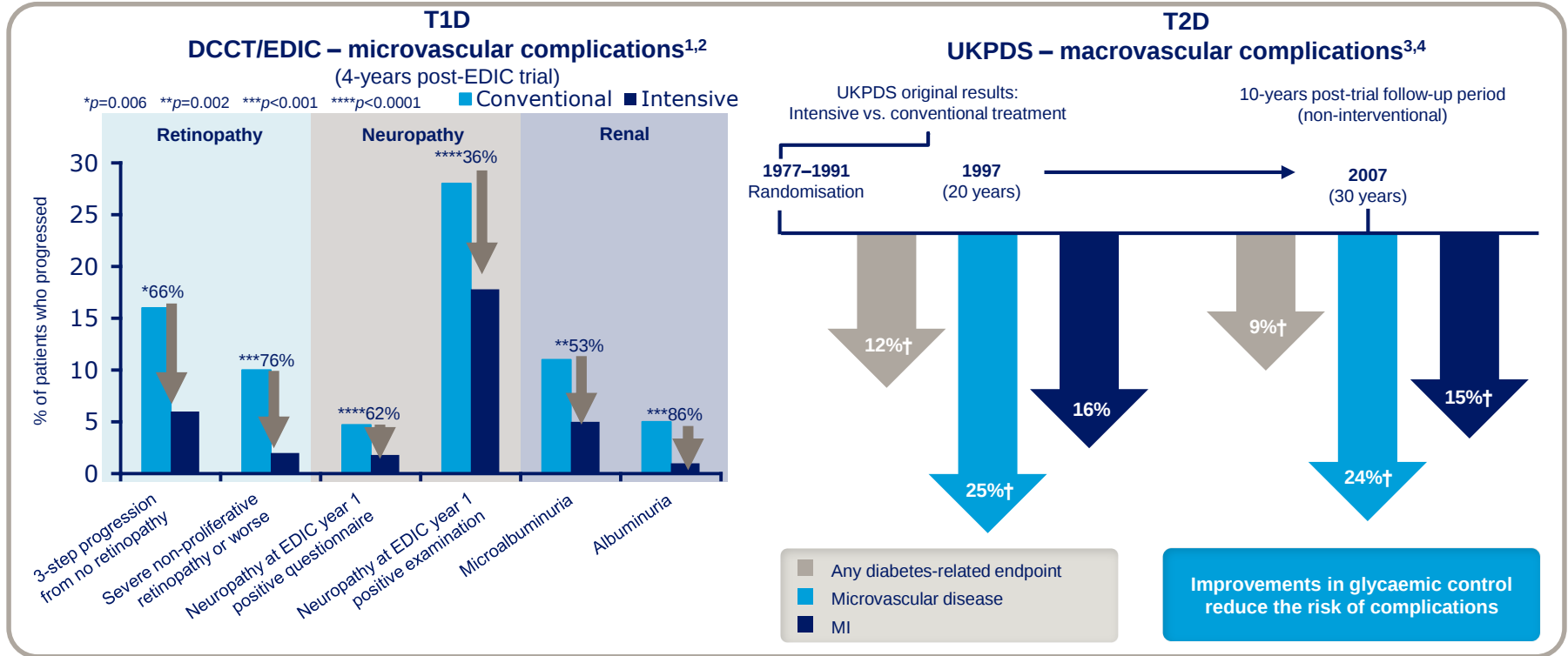
Every 1% drop in HbA_{1c} can reduce long-term diabetes complications



- 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

Intensive vs. conventional treatment in T1D and T2D

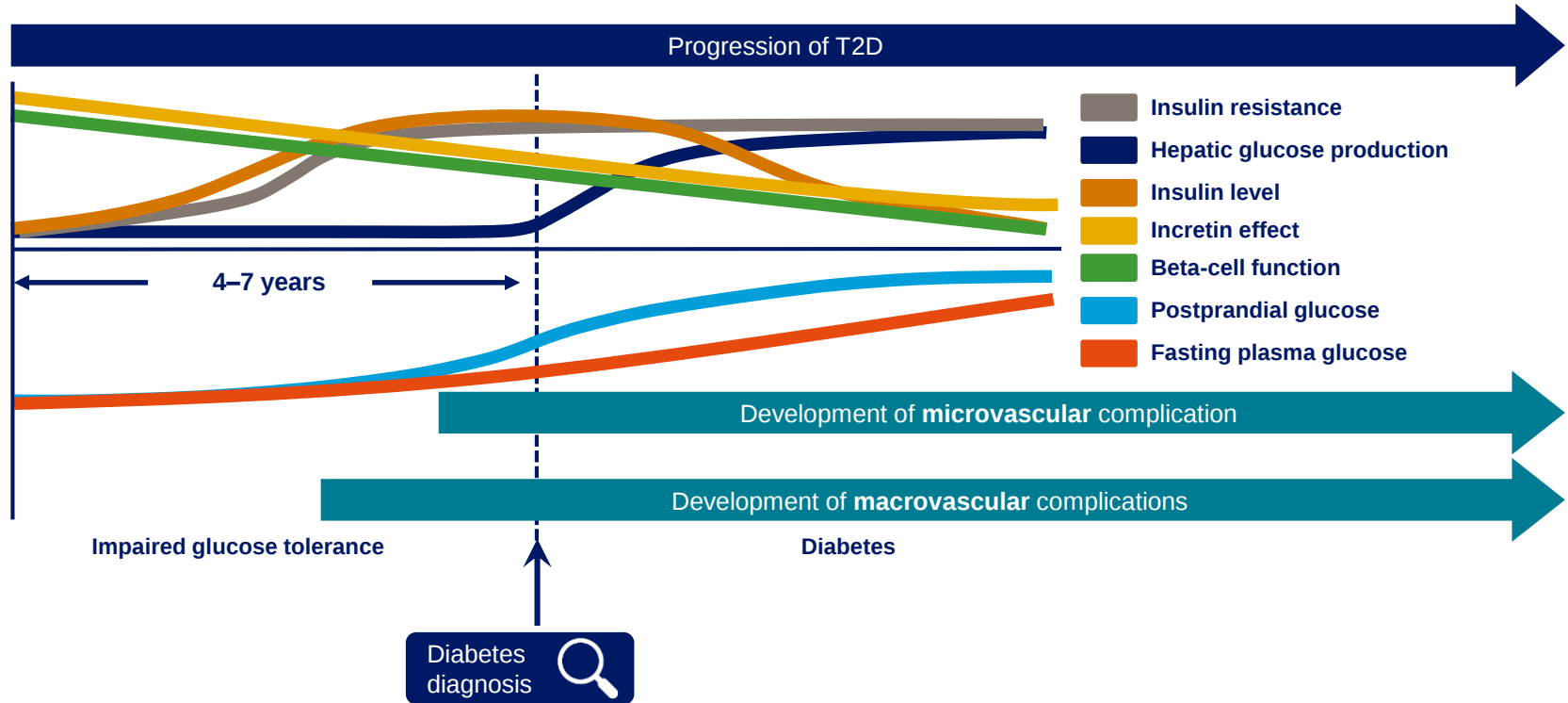
DCCT/EDIC and UKPDS follow-up data



† $p < 0.05$; 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

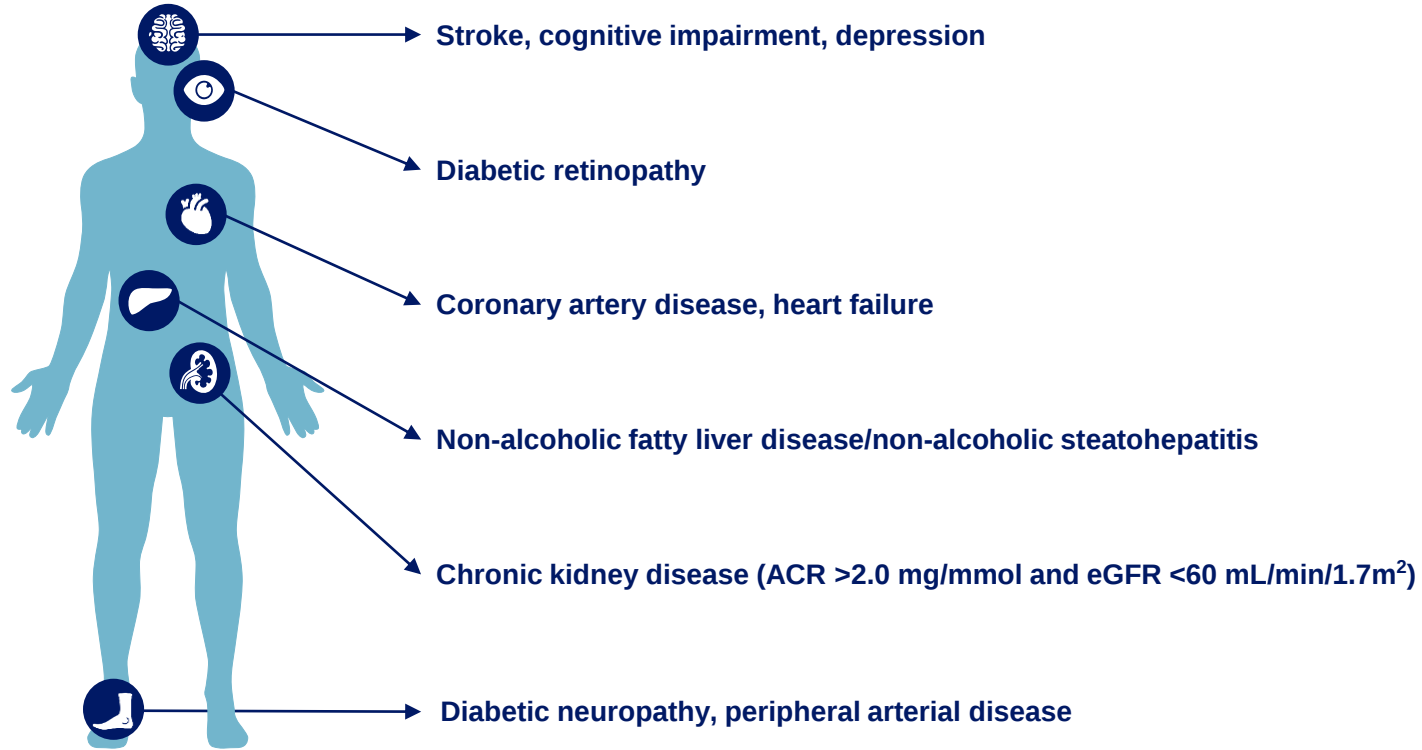
Progression of T2D and long-term complications



Understanding the pathophysiology of T2D

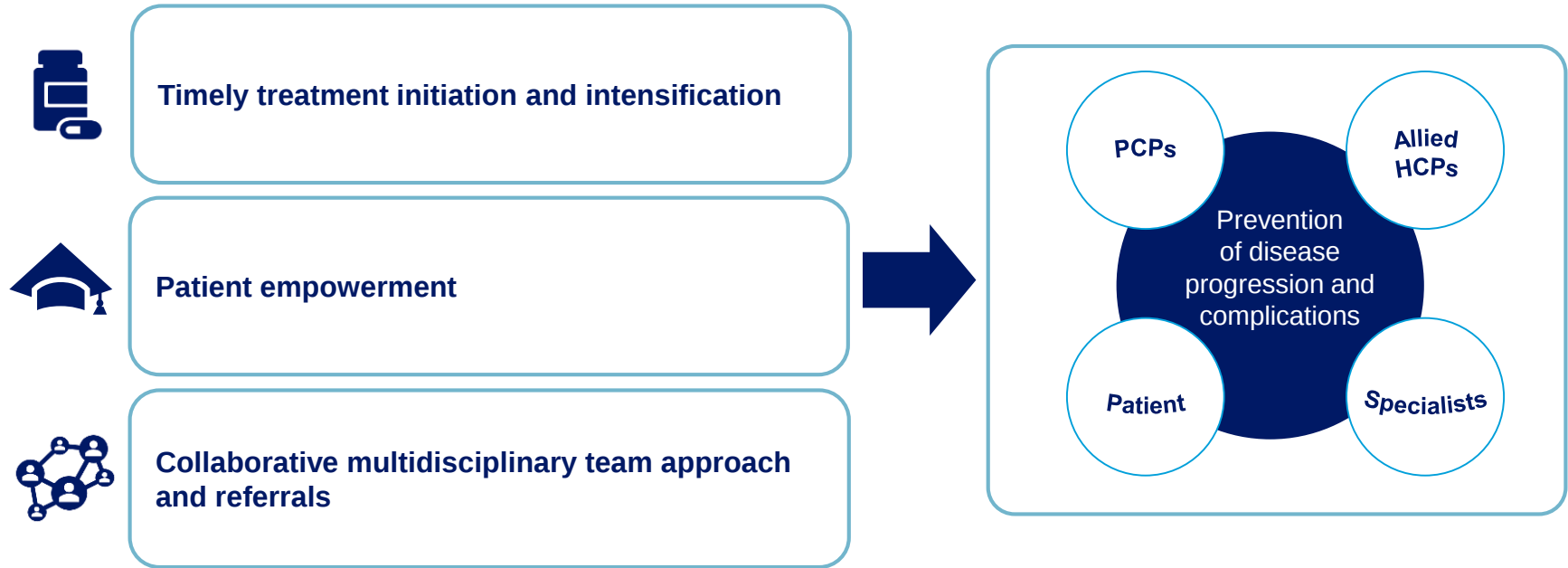


Patients and physicians are faced with a variety of diabetes-related comorbidities¹



Patient-centred care provides optimal outcomes for diabetes care

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



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

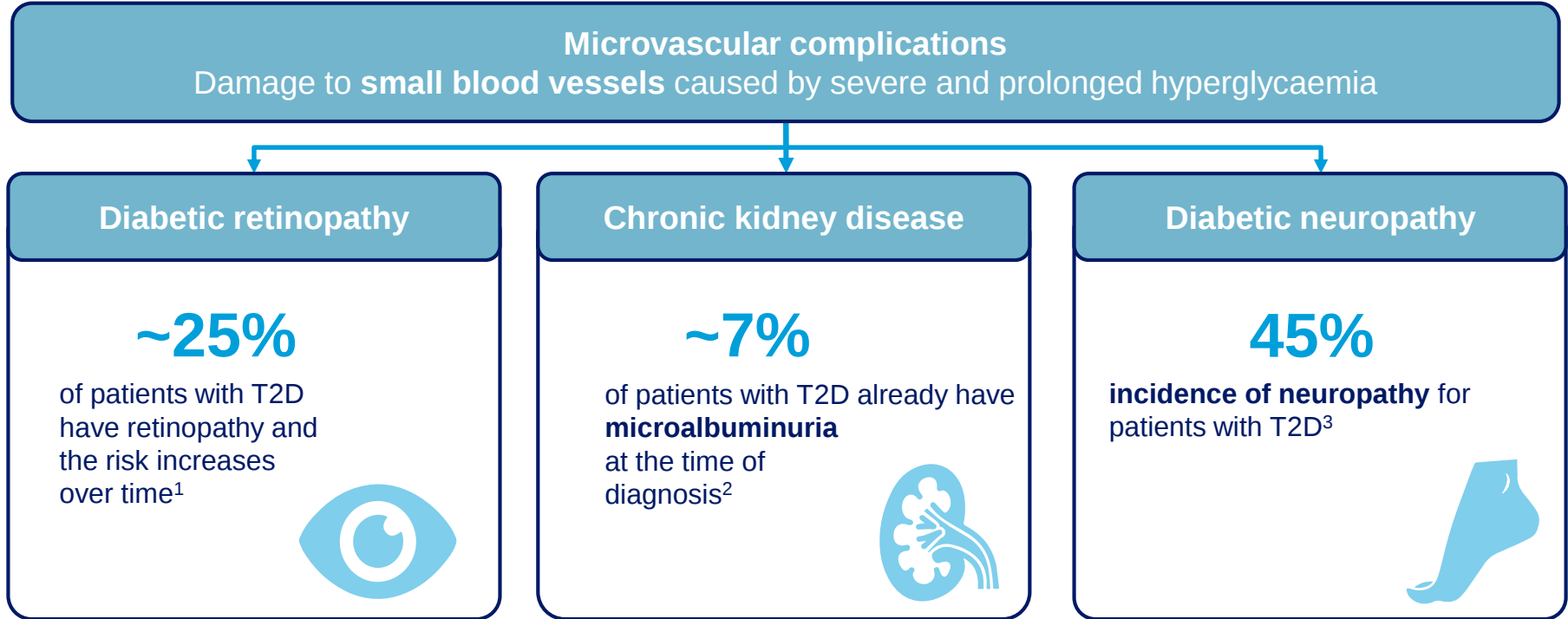
Macrovascular complications

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

Non-classical complications

- Cognitive impairment
- Depression
- NAFLD/NASH

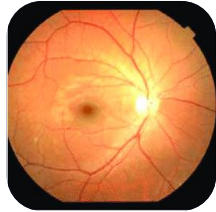
Microvascular complications of T2D



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}



No DR



Mild
non-proliferative DR



Moderate
non-proliferative DR



Severe
non-proliferative DR



Proliferative DR (PDR)
with haemorrhage

Disease progression³

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 develops¹
- Symptoms of diabetic retinopathy include:²



Blurred vision



Blotches or spots in
vision Normal vision



Flashes of light
in the field
of vision



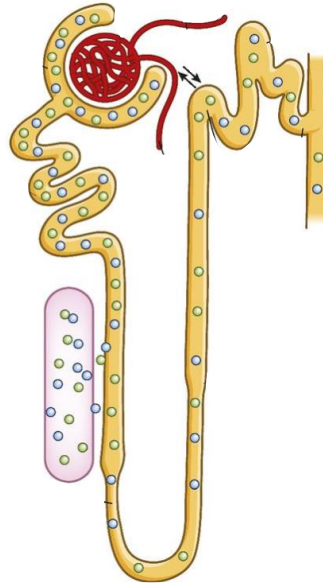
Sudden loss
of vision

Chronic kidney disease

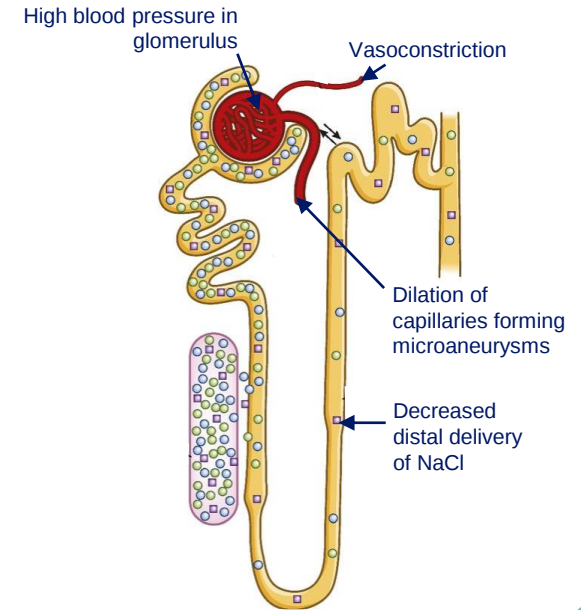
Background

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

Normal



Chronic kidney disease



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

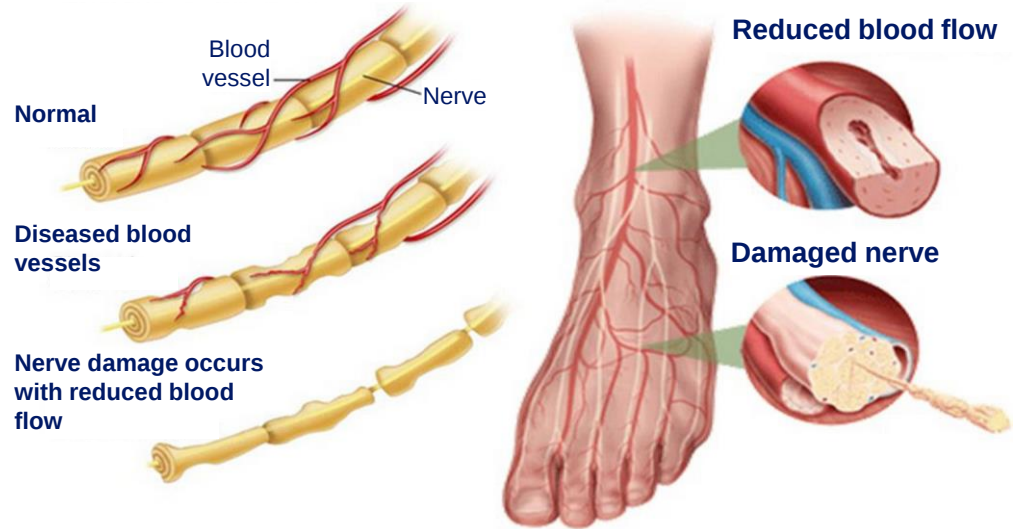
Other symptoms of chronic kidney disease include:

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

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 (Minneapolis)* 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

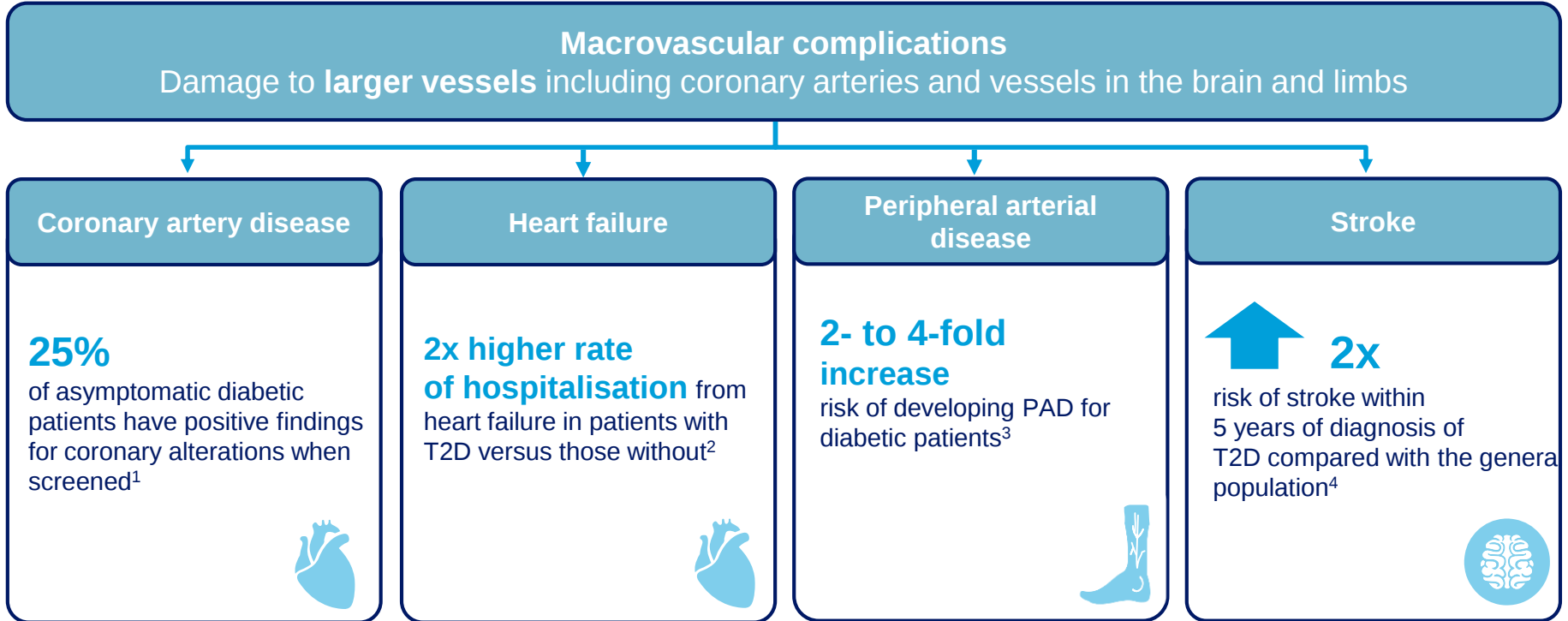
Symptoms of **autonomic neuropathy** can include:¹

- 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 (Minneapolis)* 2014;20:1226–1240

Macrovascular complications of T2D



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;

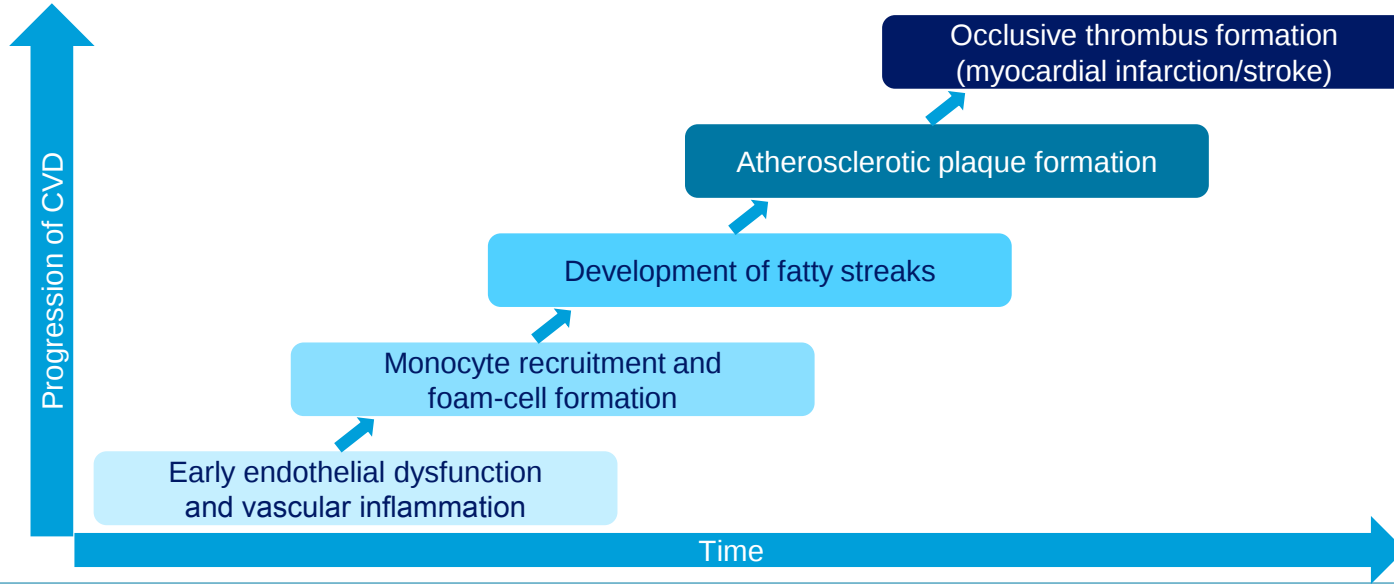
3. Beckman J-A, Creager M-A. *Circ Res* 2016;118:1771–1785; 4. Laakso M, Kuusisto J. *International Congress Series* 2007;1303:65–69

Cardiovascular disease

Background

CVD encompasses a group of disorders of the heart and blood vessels¹

Development of CVD²



CVD, cardiovascular disease

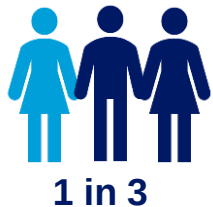
1. International Diabetes Federation Diabetes Atlas (9th edition). IDF 2019. Available at: <http://www.diabetesatlas.org/> (accessed January 2020);

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

Cardiovascular disease

Background

CVD affects



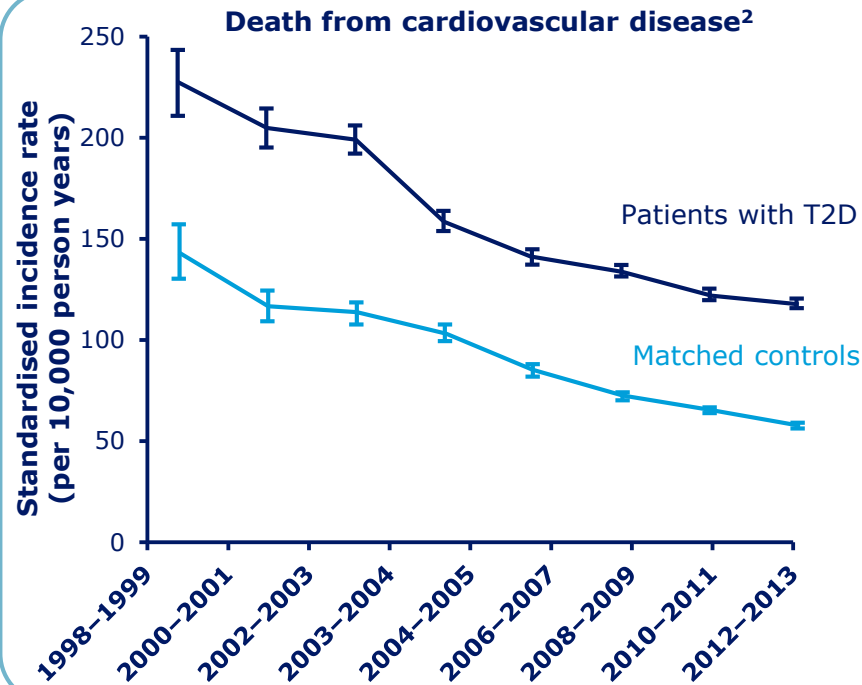
of all patients
with T2D
globally¹



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 T2D¹



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 death¹
- **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 years¹



Limb loss occurs in ~**4%** of patients¹

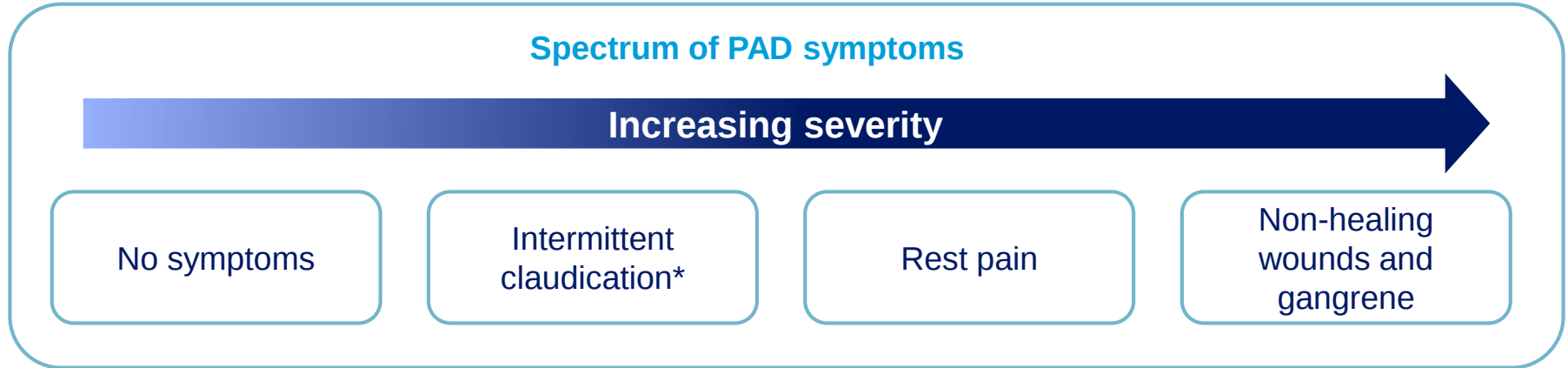
PAD, peripheral arterial disease

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 patients²

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

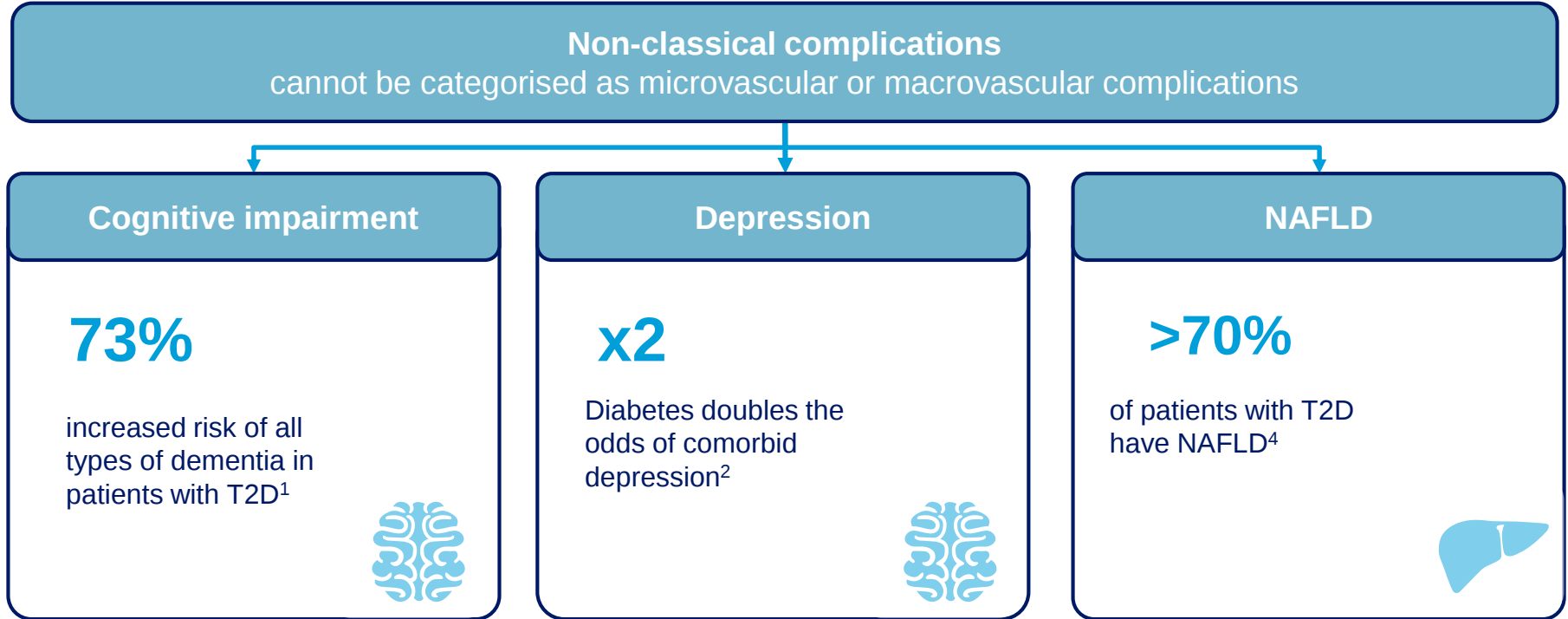


Dizziness, loss of balance, or trouble walking



Severe headache

Non-classical complications of T2D



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

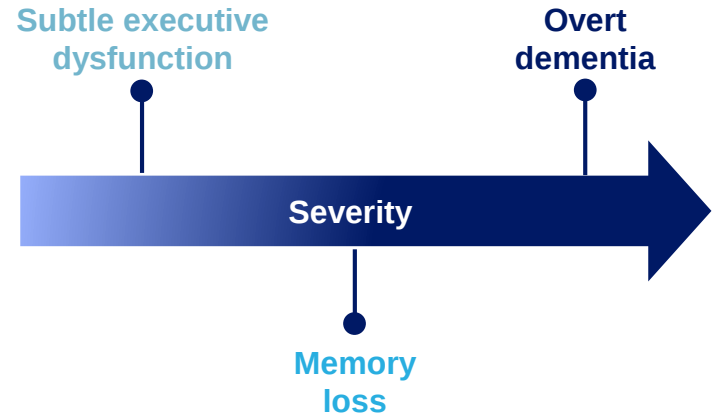
Cognitive impairment

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:**



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 T2D²

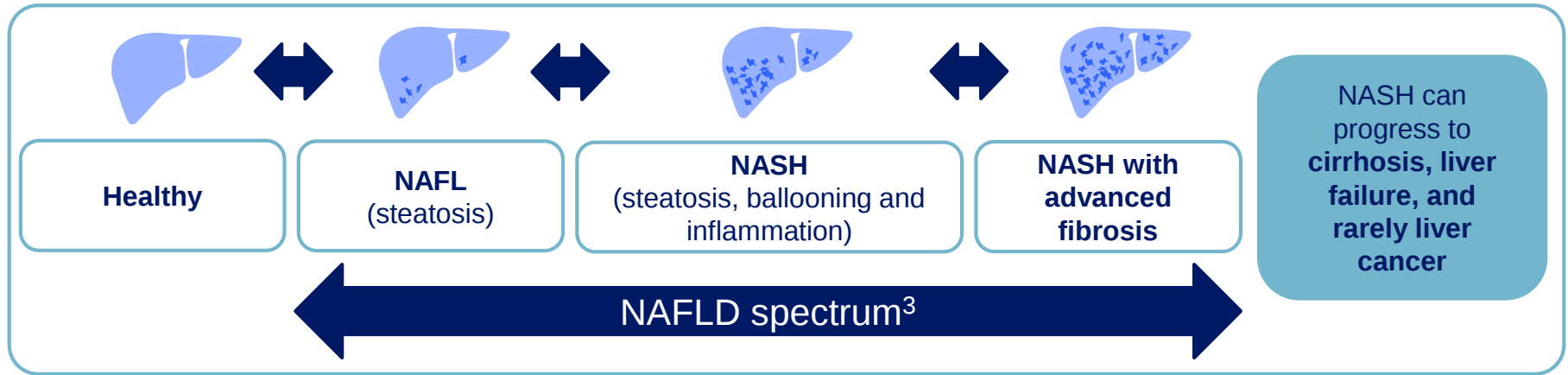
1. Anderson RJ et al. *Diabetes Care* 2001;24:1069–1078;

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

