Understanding diabetes pathophysiology and the mechanisms of diabetic complications

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Disclosures

- My attendance at this symposium is sponsored by Sanofi
- MC has received honoraria for educational symposia conducted on behalf of Boehringer Ingelheim, Lilly, AstraZeneca, Abbott, Servier, Novartis, Sanofi, Bayer and Merck Sharpe and Dohme
- MC has received support to attend and participate in advisory boards for Boehringer Ingelheim, Lilly, MundiPharma and AstraZeneca
- MC had received research funding from Boehringer Ingelheim and Novo Nordisk

Objectives

1. Discuss the current epidemiology of diabetes and its complications
2. Explore the latest understanding about the pathogenesis of diabetes and cardiorenal complications
3. Highlight the evidence supporting a **personalised approach** to treating diabetes **based on patient needs**

Epidemiological considerations of diabetes and its complications

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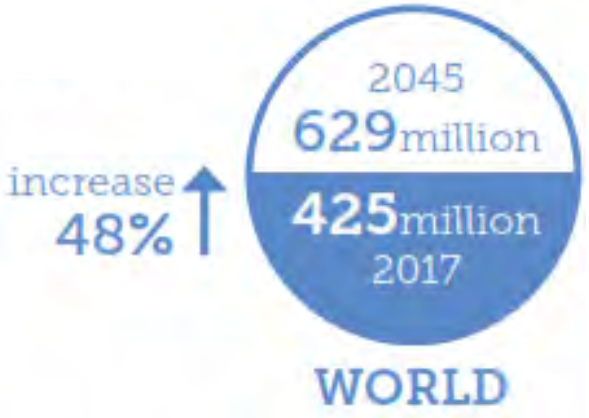
Diabetes is an increasing global epidemic

~4.0 million people died from diabetes and its complications in 2017

Total health expenditure on diabetes is estimated at 654 billion Euros*

Diabetes complications can be prevented by good glycaemic control



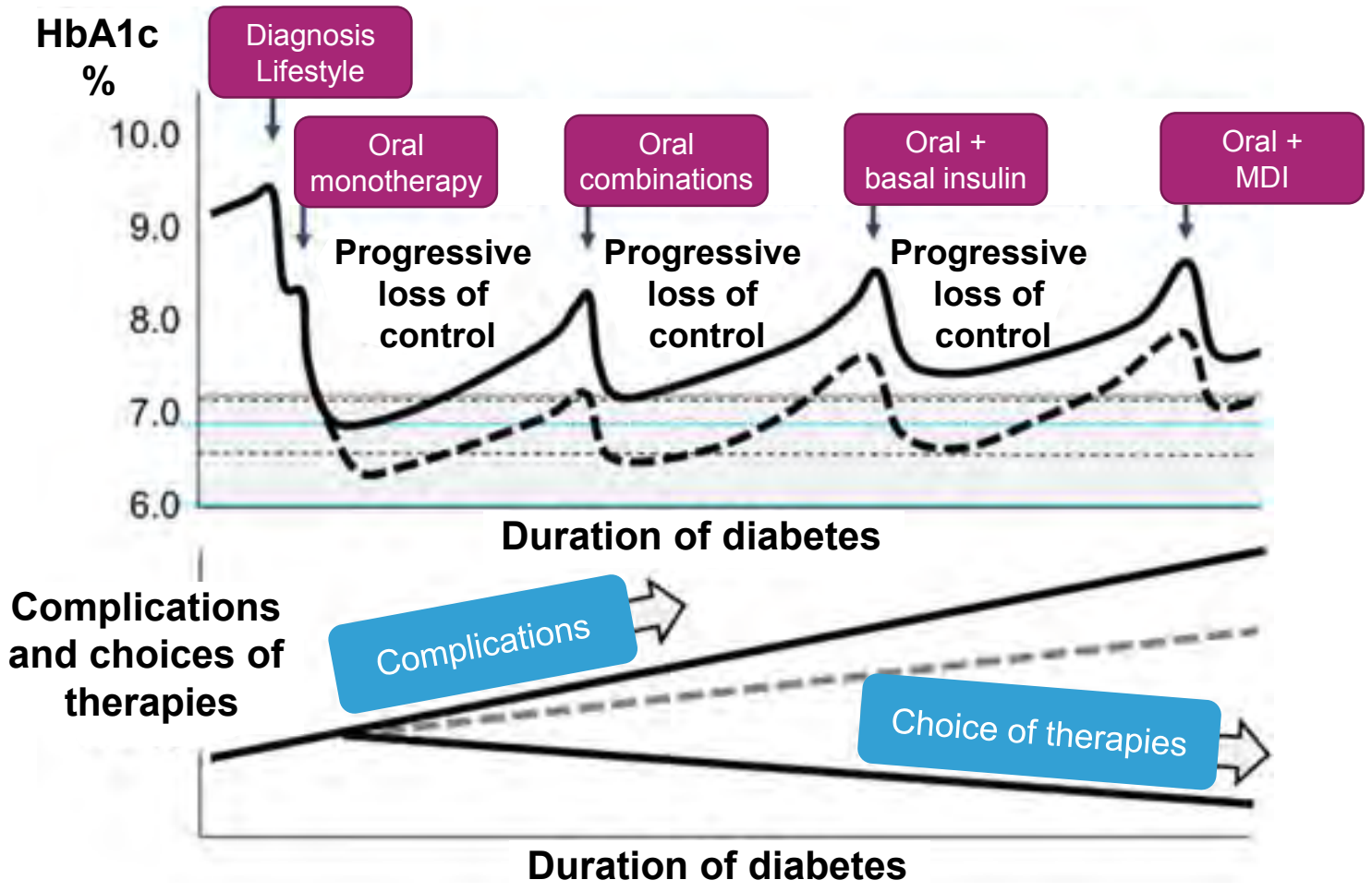
Data from 20–79-year-olds
*2017 IDF Atlas estimates 727 billion USD. Conversion of 1 USD = 0.9 Euro applied to estimate

2017 8th Edition. International Diabetes Federation Atlas

Progressive nature of diabetes leads to increased risk of complications, including CKD and CVD

- As the duration of diabetes increases, more therapies are needed, whilst the choice of therapies declines due to increased complications; for instance **cardiovascular disease** or **chronic kidney disease**

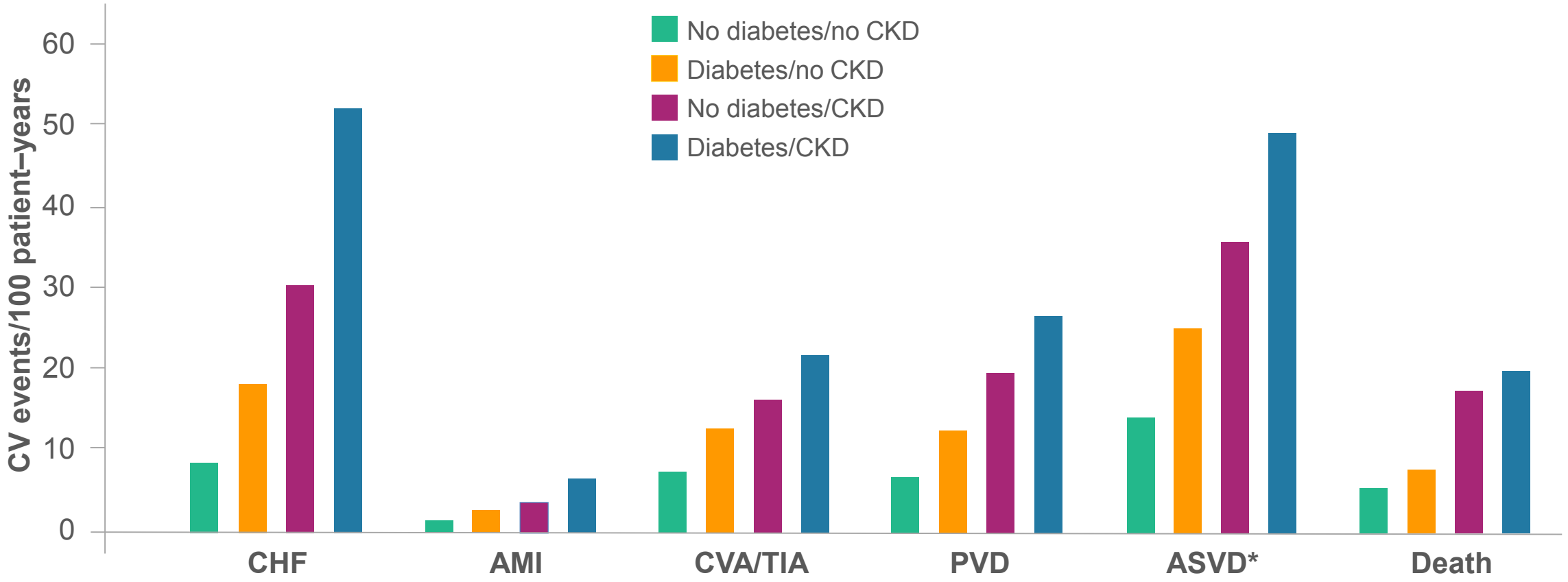
Schematic representation of typical and desirable glycaemic control in T2D



CKD, chronic kidney disease; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; MDI, multiple daily insulin injections; T2D, type 2 diabetes mellitus

Bailey CJ, Day C. Br Med Bull 2018;126:123–37

CVD risk is greatest when diabetes and CKD co-exist

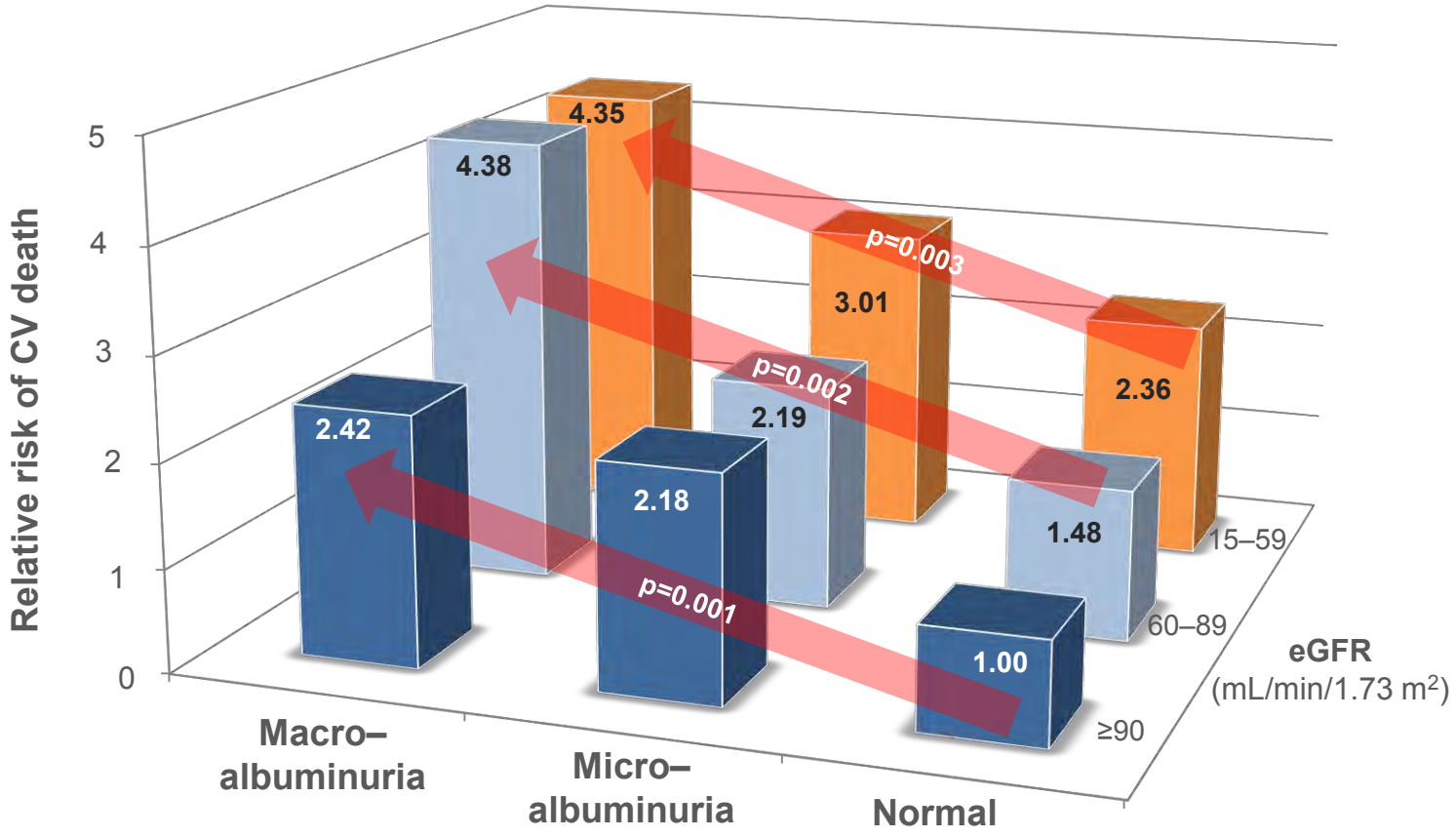


*ASVD was defined as the first occurrence of AMI, CVD/TIA, or PVD.
AMI, acute myocardial infarction; ASVD, atherosclerotic vascular disease; CHF, congestive heart failure;
CV, cardiovascular; CVA, cerebrovascular accident; PVD, peripheral vascular disease; TIA, transient ischaemic attack

Foley RN, et al. J Am Soc Nephrol 2005;16:489–95

CV mortality increases as renal function declines

NHANES III 1988–2000

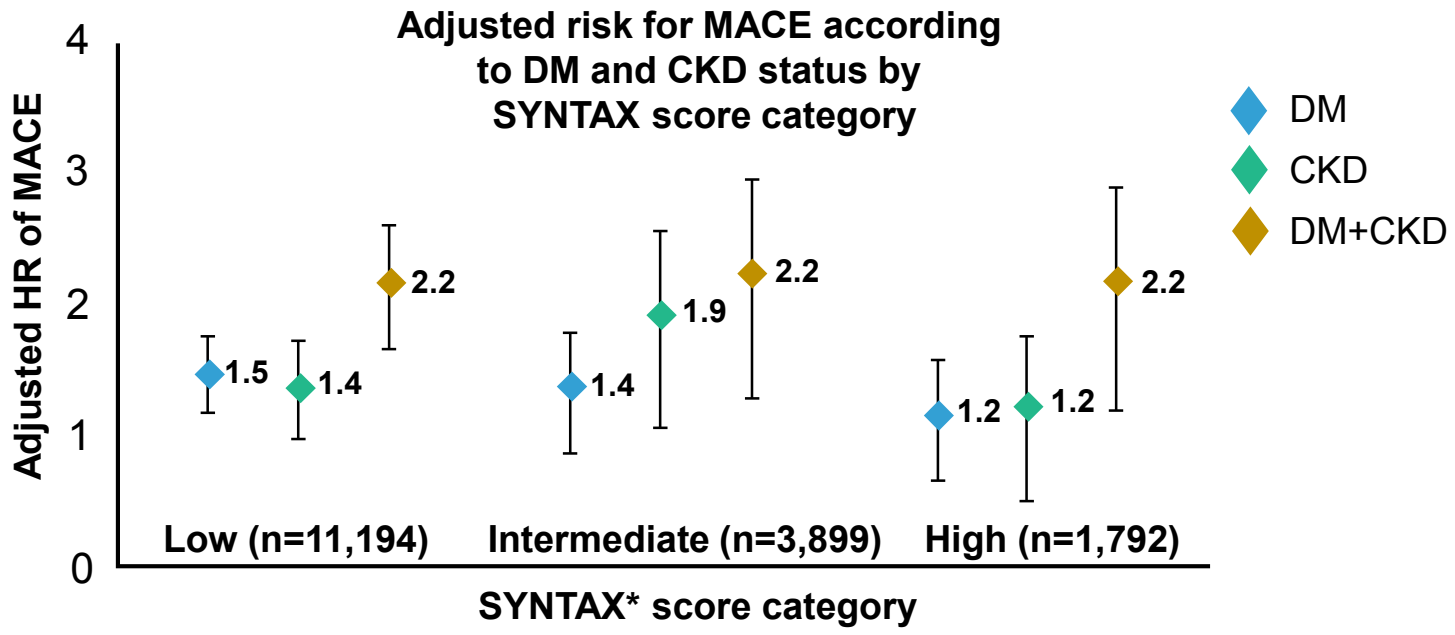


Adjusted for multiple demographic, disease and treatment factors
eGFR, estimated glomerular filtration rate; NHANES, National Health and Nutrition Examination Survey

Astor BC, et al. Am J Epidemiol 2008;167:1226–34

Risk of MACE according to DM and CKD status

- Study of 16,885 consecutive coronary artery disease patients undergoing PCI[1]
- Highest MACE risk was for patients with DM **and** CKD



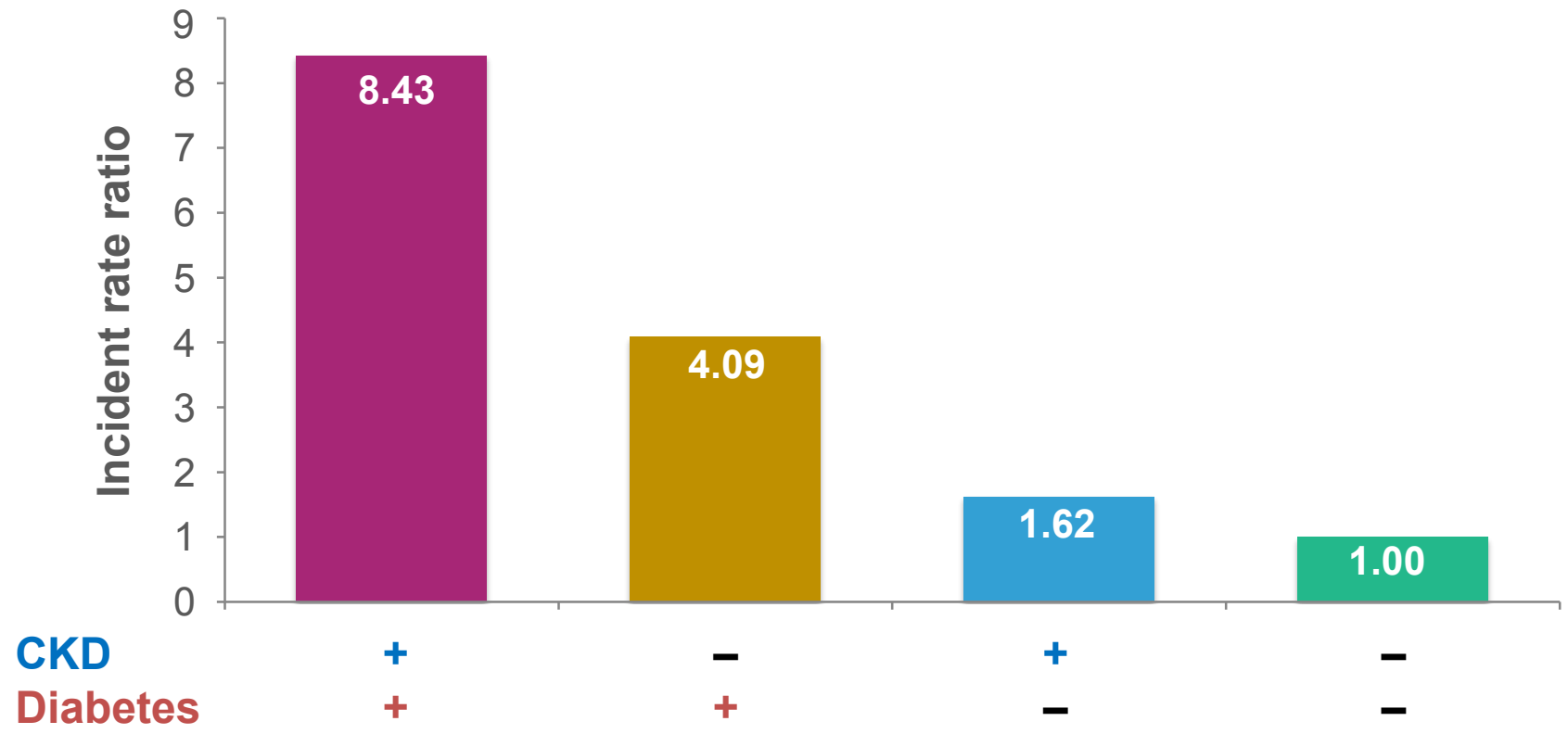
*A score for severity of coronary artery disease based on the number and severity of coronary artery lesions (higher score = higher CV risk).
DM, diabetes mellitus; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention

1. Vogel B, et al. J Am Coll Cardiol 2017;70(Suppl B):B93

CKD increases hypoglycaemia risk in DM

- CKD increases hypoglycaemia risk in patients with diabetes[1]
- Hypoglycaemia occurs more frequently in elderly subjects (aged >70 years) with CKD 3–5[1]

Risk for severe hypoglycaemia (<3 mmol/L) in elderly adults classified by CKD and diabetes status[2*†]

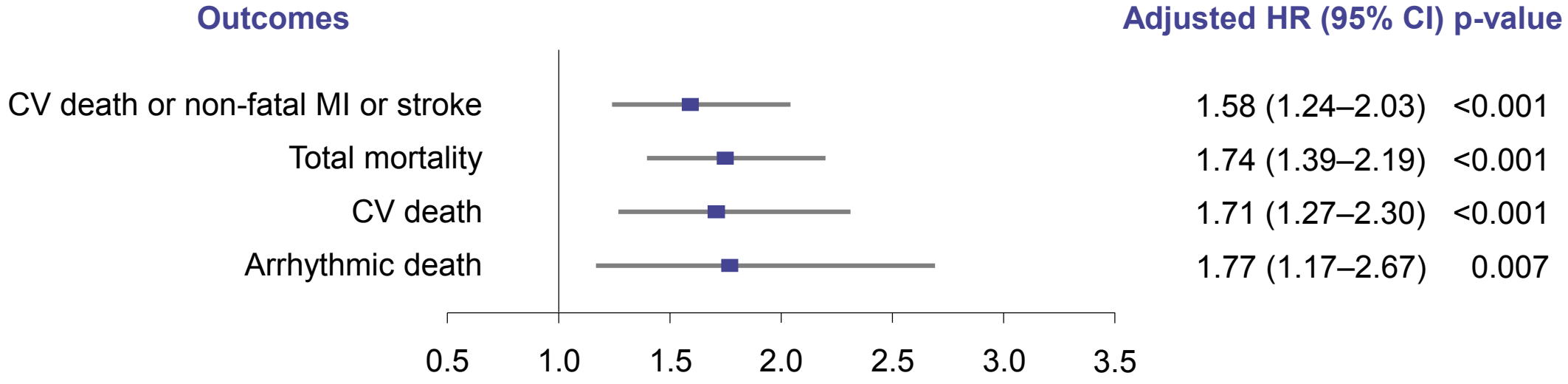


*Reference group was adults without CKD or diabetes (for whom the incident ratio =1)
†Groups adjusted for race, gender, age, cancer, diabetes and CVD (all rate ratios p<0.0001)

1. Haneda M, Morikawa A. Nephrol Dial Transplant 2009;24:338–41
2. Moen M, et al. Clin J Am Soc Nephrol 2009;4:1121–27

The ORIGIN trial showed that severe hypoglycaemia was associated with an increased risk of major CV outcomes

Secondary analysis of ORIGIN trial investigating associations of severe hypoglycaemia with CV outcomes and mortality[1]



In ORIGIN, **28% of participants reported non-severe hypoglycaemia and 3.8% reported severe hypoglycaemia.**[2] Severe events were associated with a greater risk for major CV events, mortality, CV death and arrhythmic death[1]

ORIGIN included patients with impaired glucose tolerance, impaired fasting glucose or early T2D at high CV risk (n=12,537). Patients were randomised to glargine 100 units/mL (target fasting plasma glucose ≤95 mg/dL [5.3 mmol/L]) vs standard care for 6.2 years. Glargine 100 units/mL was associated with a neutral effect on CV outcomes vs standard care.
CI, confidence interval; HR, hazard ratio; MI, myocardial infarction

1. ORIGIN Investigators. Eur Heart J 2013;34:3137–44
2. ORIGIN Investigators. Diabetes Care 2015;38:22–8

Understanding the pathogenesis of diabetes and cardiorenal complications

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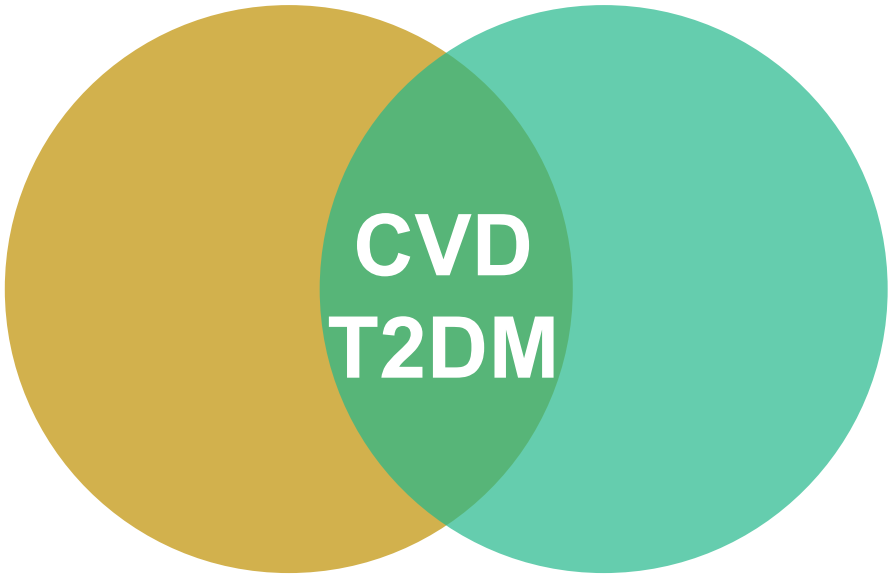
Overlapping pathophysiology of CV disease and T2D

The ‘common soil’ hypothesis

- Obesity
- Insulin resistance
- Dyslipidaemia



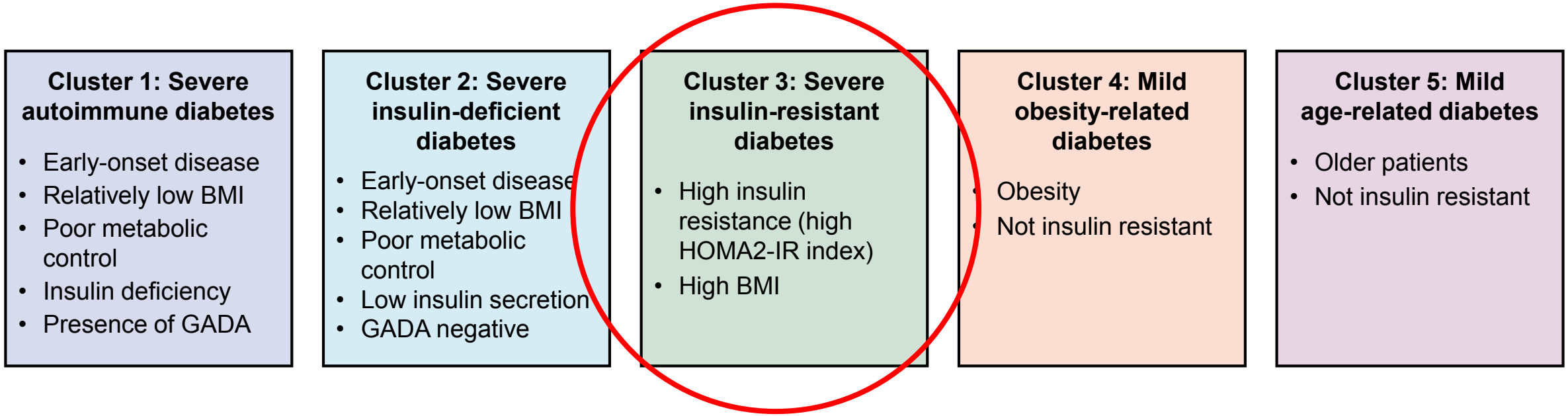
- Hypercoagulability
- Hypertension
- Inflammation
- Oxidative stress

**Both conditions ‘spring from a common soil’,
i.e. share common genetic and environmental factors**

De Rosa S, et al. Front Endocrinol 2018;9:2

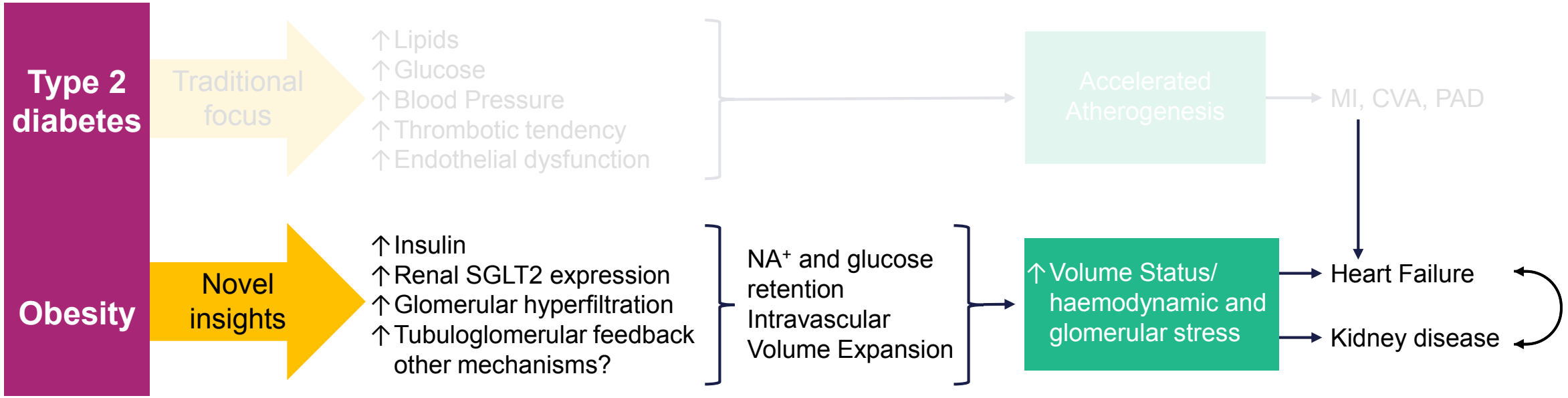
Diabetes heterogeneous phenotypes

- Diabetes can be classified more diversely:



Ahlqvist E, et al. Lancet Diabetes Endocrinol 2018;6:361–9

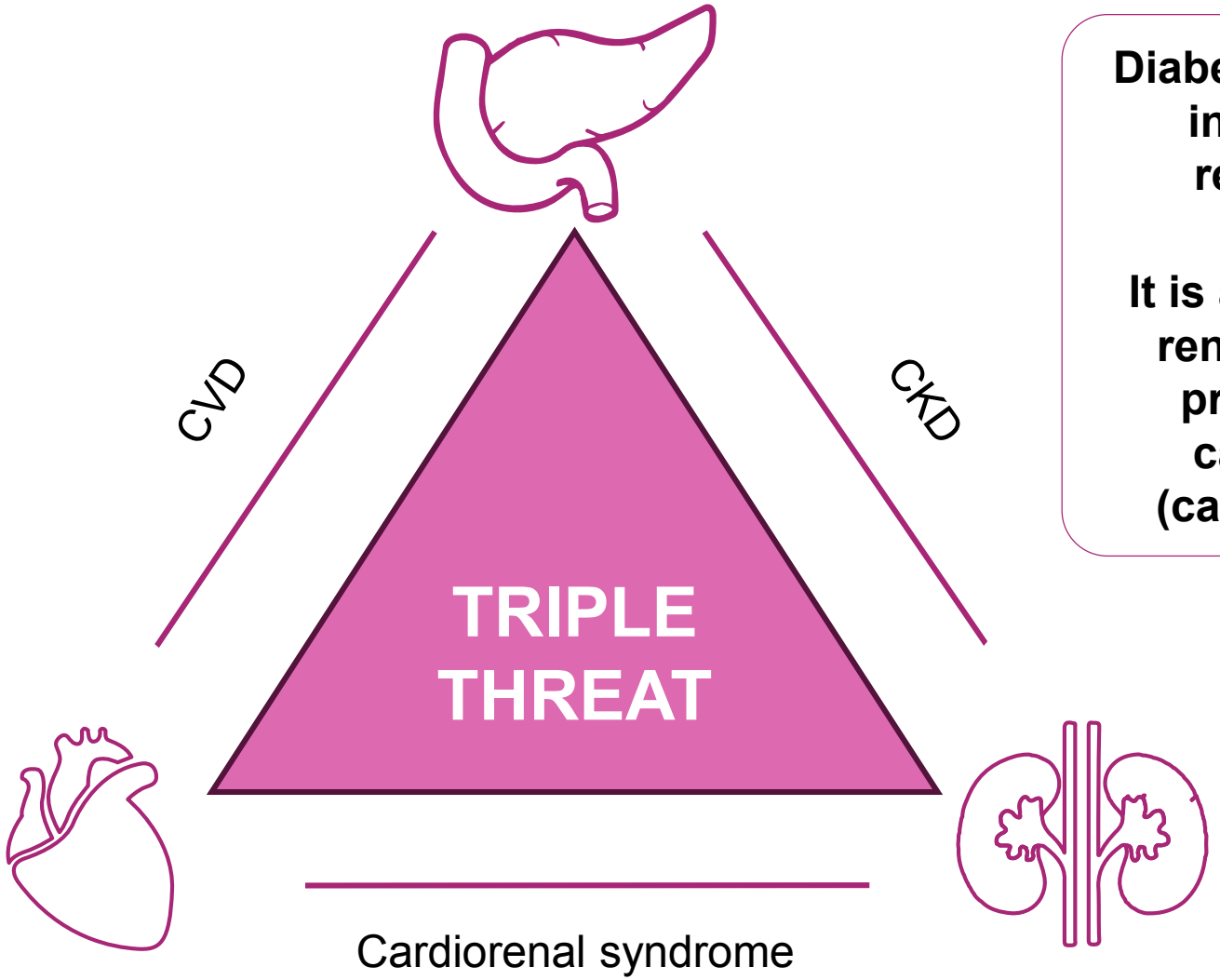
Our understanding of this ‘triple threat’ and the interplay between morbidities is evolving



PAD, peripheral artery disease

Sattar N, McGuire DK. Circulation 2018;138:7–9

Linking diabetes and cardiorenal complications



Diabetes is associated with independent CV and renal complications

It is also linked to primary renal failure, which can progressively lead to cardiac dysfunction (cardiorenal syndrome)

Banerjee S. Hellenic J Cardiol 2017;58:342–7

A multifactorial approach to treating the triple threat

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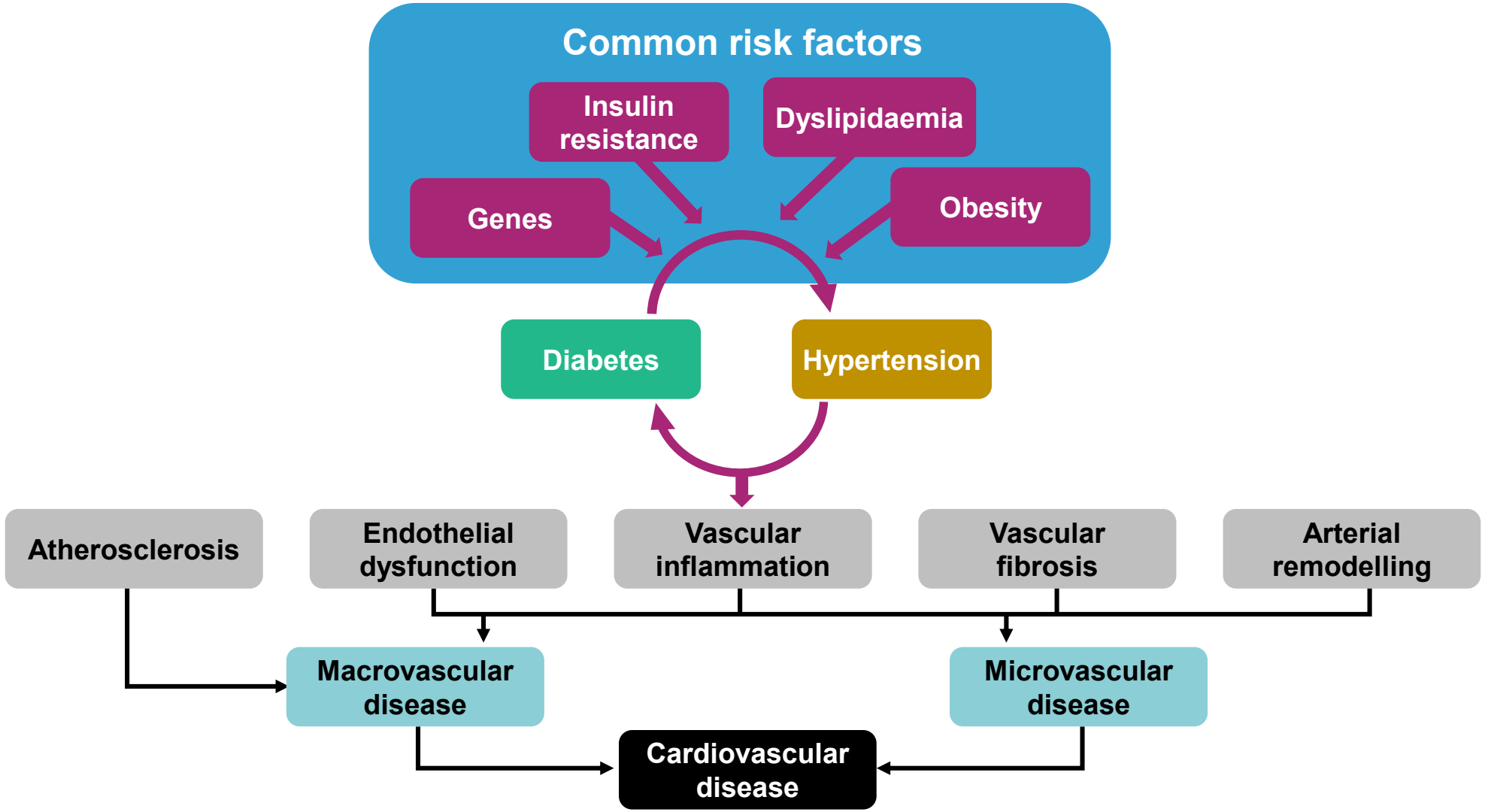
Diabetes management – are we treating cause or effect?

- When treating diabetes we often focus on treating the marker of disease – **hyperglycaemia**
- We may fail to acknowledge the **complexity** and **heterogeneity** of this disease
- We may miss opportunities for **disease modification** and for attenuation of the risk of both **microvascular** and **macrovascular complications**

Holistic approach to treating diabetes and CVD: Management of all risk factors

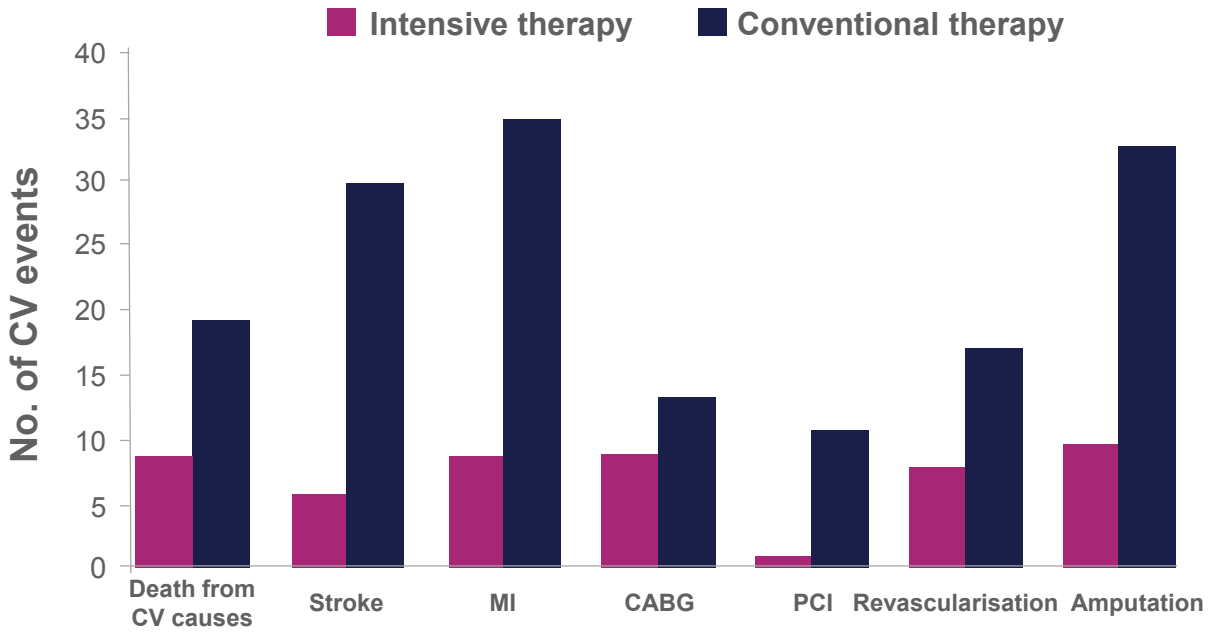


Petrie JR, et al. Can J Cardiol 2018;34:575–84

Intensive multifactorial intervention in patients with T2D and microalbuminuria reduces CV risk

- Steno–2 trial in patients with **T2D and albuminuria**
- Intensified multifactorial intervention* had sustained beneficial effects
- After a mean of 13.3 years† there was an absolute risk reduction for death from any cause of 20%

Number of CVD events among patients on intensive vs conventional therapy

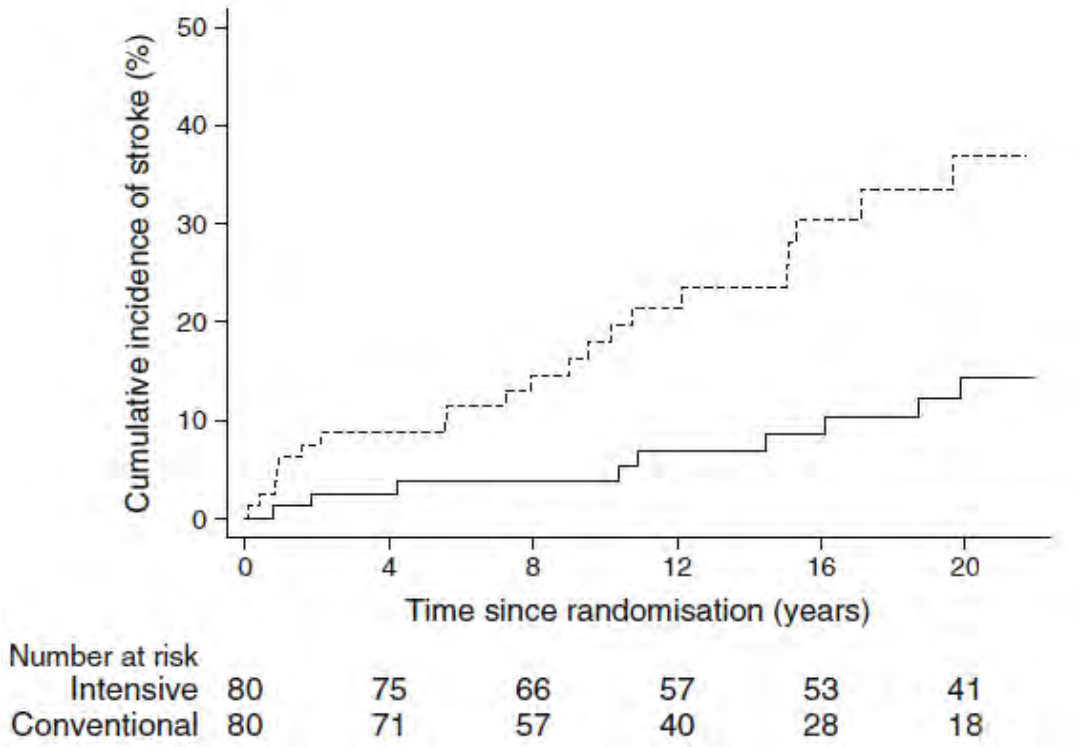


*Tight glucose regulation+renin-angiotensin system blockers, aspirin, and lipid-lowering agents
†7.8 years of multifactorial intervention and an additional 5.5 years of follow–up
CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention

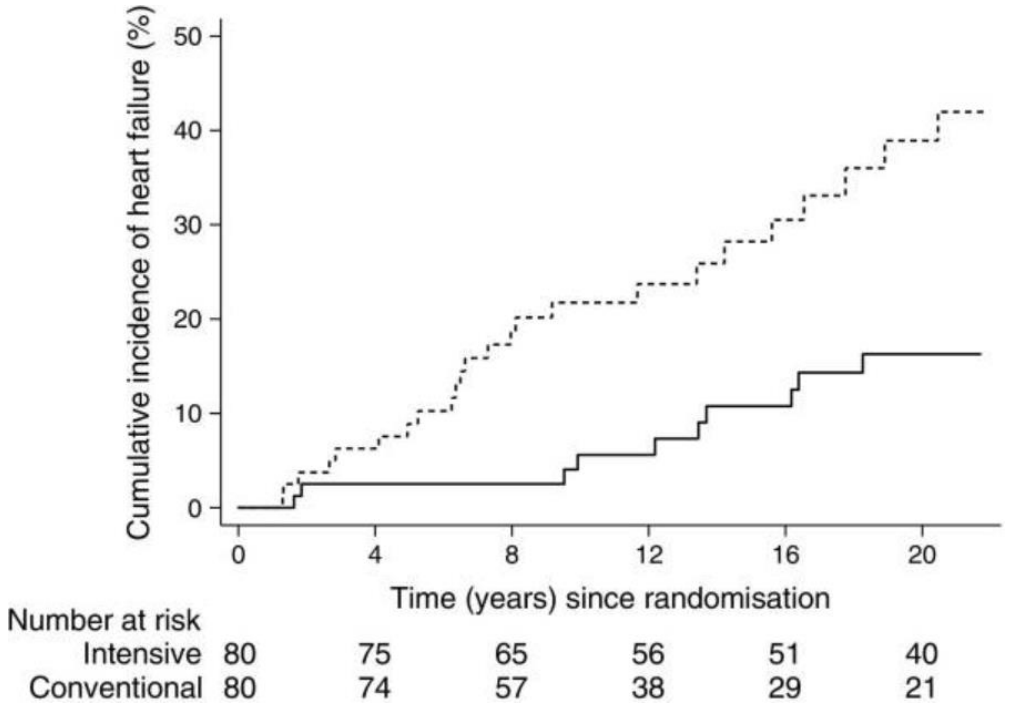
Gæde P, et al. N Engl J Med 2008;358:580–91
Gæde P, et al. Diabetologia 2016;59:2298–307

STENO-2 after 20 years: Multifactorial intensive intervention improved survival and reduced the risk of stroke and heart failure

At 21.2 years follow-up, patients in the intensive-therapy group survived for a median of 7.9 years longer than standard therapy[1]



Hazard for stroke reduced by 69% in the intensive therapy group (p=0.004)[2]



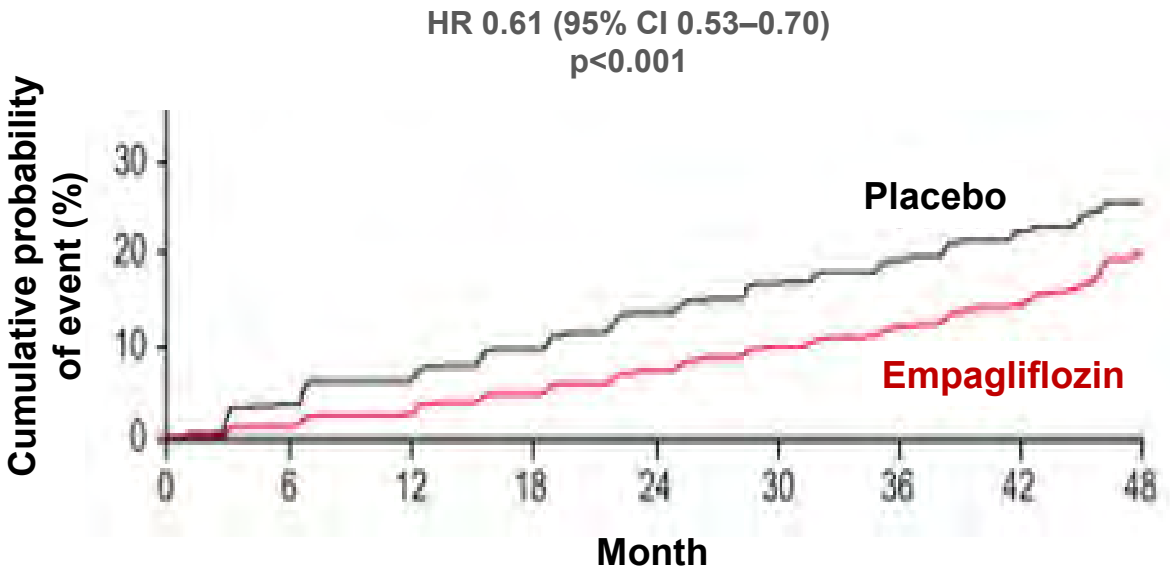
Hazard for heart failure reduced by 69% in the intensive therapy group (p=0.001)[3]

1. Gæde P, et al. Diabetologia 2016;59:2298–307; 2. Gæde P, et al. Diabetologia 2019;62:1575–80; 3. Oellgaard J, et al. Diabetologia 2018;61:1724–33

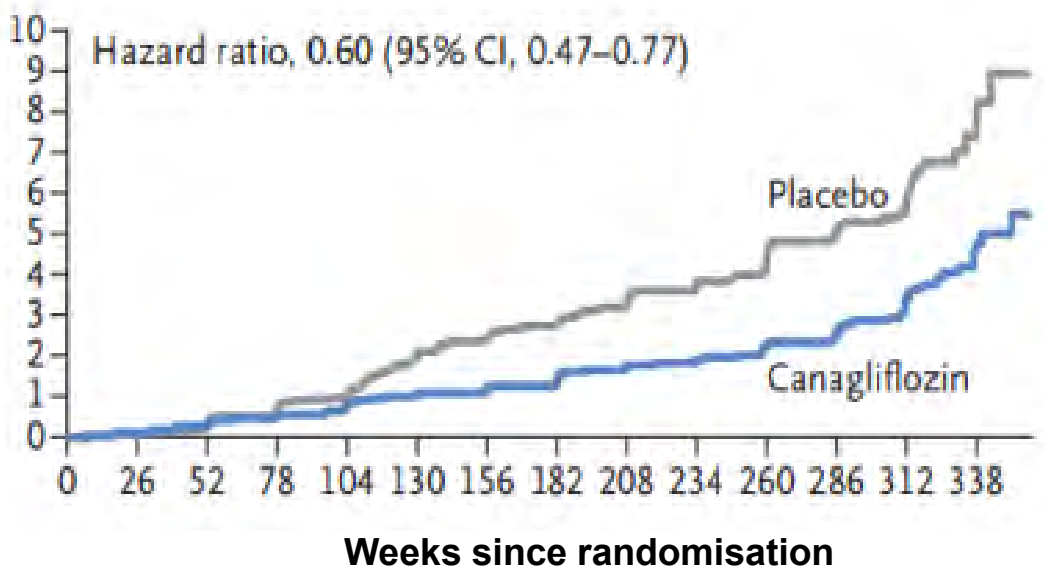
SGLT2i improves renal outcomes in patients with T2D

- Significant reductions in incident progression in albuminuria and 40%+ reduction in eGFR decline with empagliflozin[1] and canagliflozin[2] in CV outcomes trials

New/worsening nephropathy (EMPA–REG OUTCOME)[1]



40% ↓eGFR, ESRD or renal death (CANVAS Program)[2]

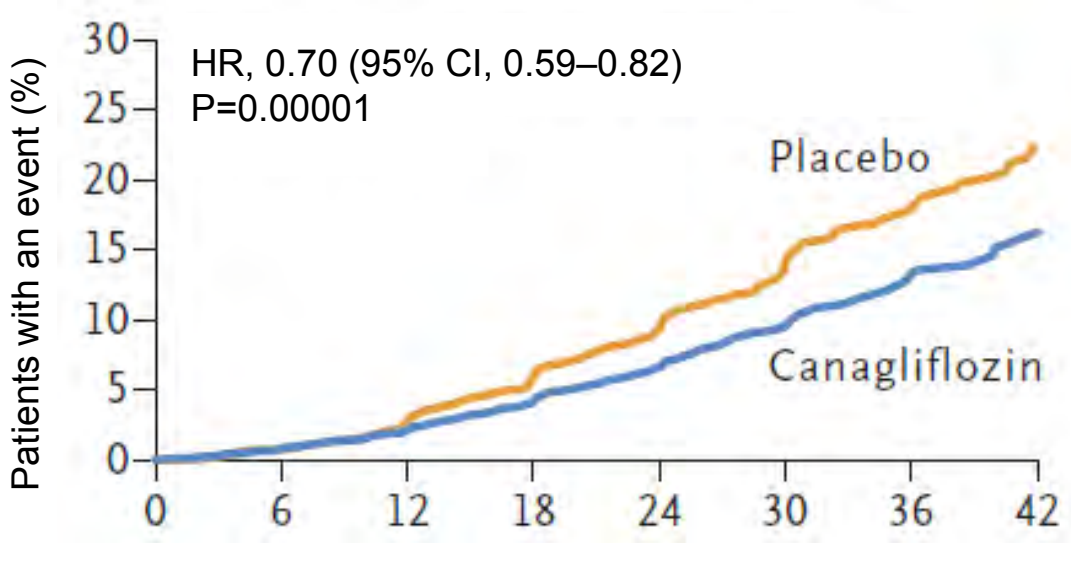


ESRD, end-stage renal disease

1. Wanner SE, et al. N Engl J Med 375;2016:323–34; 2. Neal B, et al. N Engl J Med 2017;377:644–57

CREDENCE: SGLT2i improves renal outcomes in patients with T2D and kidney disease

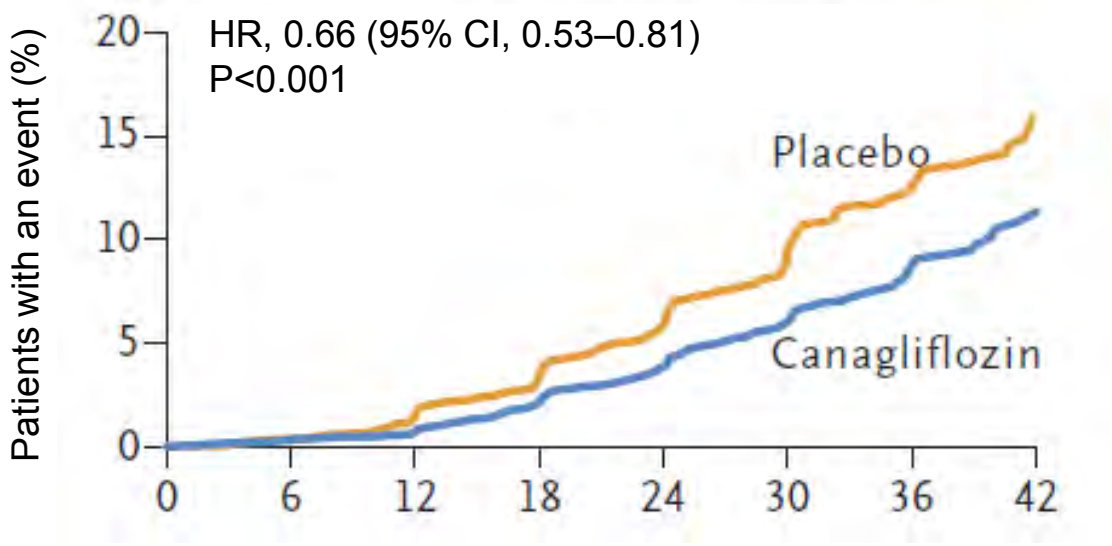
Primary composite outcome



No. at risk

Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

Renal-specific composite outcome



No. at risk

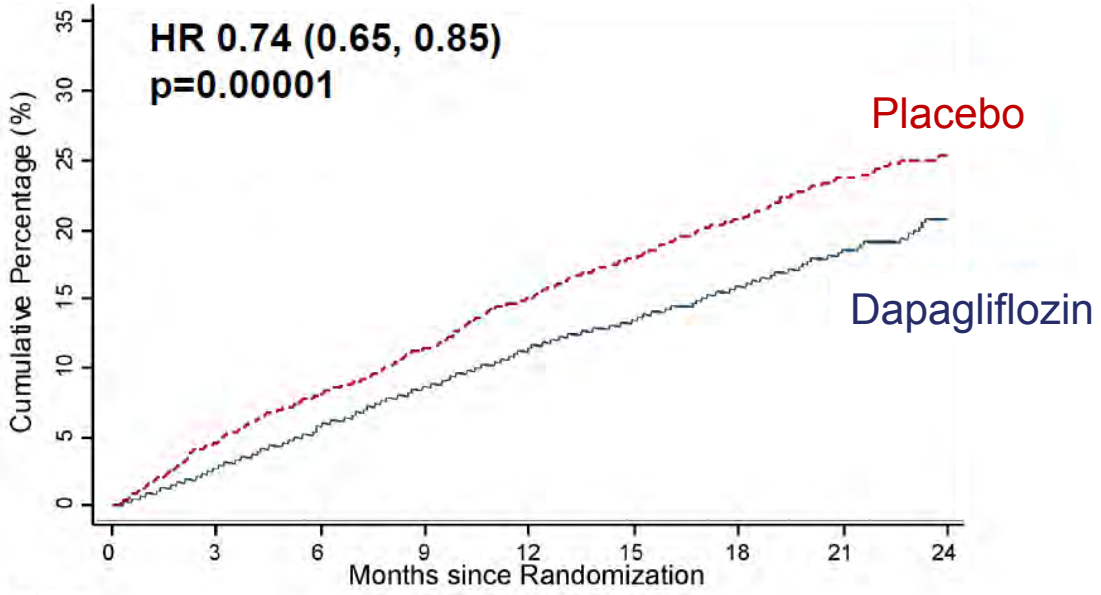
Placebo	2199	2178	2131	2046	1724	1129	621	170
Canagliflozin	2202	2181	2144	2080	1786	1211	646	196

Perkovic V, et al. N Engl J Med 2019;308:2295–306

DAPA-HF: Reduced risk of HF events in patients with and without diabetes

Primary composite outcome

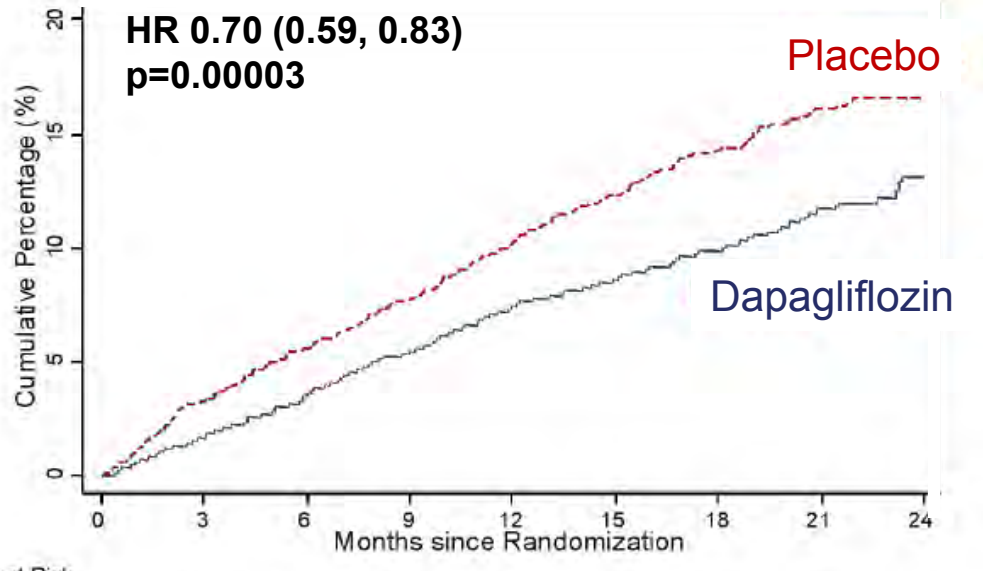
CV death/HF hospitalisation/urgent HF visit



Number at Risk

Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

Worsening HF event



Number at Risk

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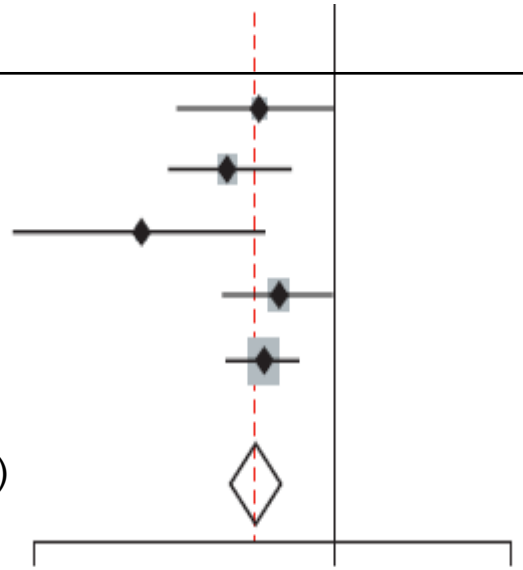
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

McMurray JJV, et al. ESC 2019

GLP-1 RA improves renal outcomes in patients with T2D

Composite kidney outcome including macroalbuminuria

	GLP-1 RA n/N (%)	Placebo n/N (%)	HR (95% CI)	NNT (95% CI)	P value
ELIXA	172/2639 (6%)	203/2647 (6%)	0.84(0.68, 1.02)		0.083
LEADER	268/4668 (6%)	337/4672 (7%)	0.78 (0.67, 0.92)		0.003
SUSTAIN-6	62/1648 (4%)	100/6222 (6%)	0.64 (0.46, 0.88)		0.006
EXSCEL	366/6256 (6%)	407/6222 (7%)	0.85 (0.77, 0.93)		0.065
REWIND	848/ 4949 (17%)	970/4952 (20%)			0.0004
Overall (I^2=0.0%,p=0.413)	1716/20160 (9%)	2017/20142 (10%)	0.83 (0.78, 0.89)	62 (48, 96)	<0.0001



Kristensen SL, et al. Lancet Diabetes Endocrinol 2019 [Epub ahead of print] doi: 10.1016/S2213-8587(19)30249-9

Managing our vulnerable patients

SGLT2i and GLP-1 RA can improve renal outcomes.
But how should we modify diabetes treatment in vulnerable patients with CKD?

- In patients with eGFR ≤60 mL/min/1.73 m^2 recommendations for use of many antihyperglycaemic agents advise caution, dose reduction or use of an alternative

- CKD is also an independent risk factor for hypoglycaemia and adds to the risk of hypoglycaemia in people with T2D

There is a need to understand the antihyperglycaemic efficacy and safety of these agents in these high risk patients

Personalisation of care:
The latest clinical guidelines

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The latest guidelines emphasise a personalised approach to treating diabetes and diabetic comorbidities[1]

ASSESS KEY PATIENT CHARACTERISTICS

- Current lifestyle
- Comorbidities i.e. ASCVD[1], CKD[2], HF[3]
- Clinical characteristics i.e. age, HbA1c, weight
- Issues such as motivation and depression
- Cultural and socio-economic context

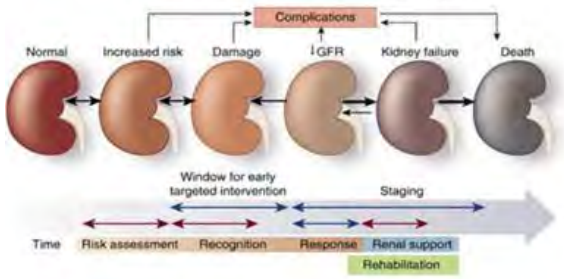
Hypoglycaemia risk should be recognised by clinicians when agreeing glycaemic goals with patients and choosing appropriate glucose-lowering therapies[1,2]

1. Davies MJ, et al. Diabetes Care 2018;41:2669–701
2. International Hypoglycaemia Study Group. Lancet Diabetes Endocrinol 2019:385–96

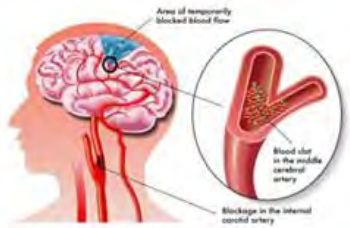
Evolving outcomes with evolving understanding: From MACE to MARCE

Major adverse renal and cardiac events (MARCE)

Acute kidney injury



Stroke



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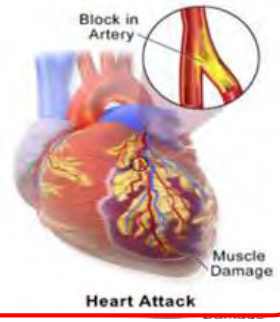
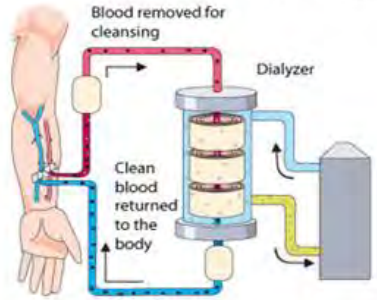
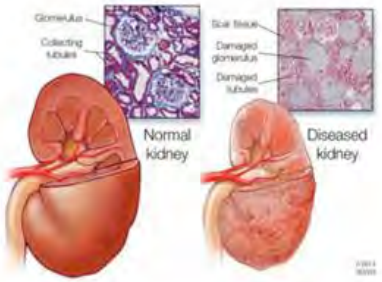


Hospitalization

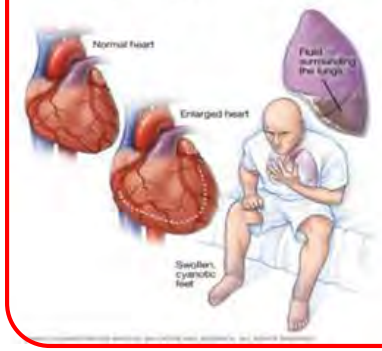
Renal replacement therapy (dialysis)



Progression of CKD



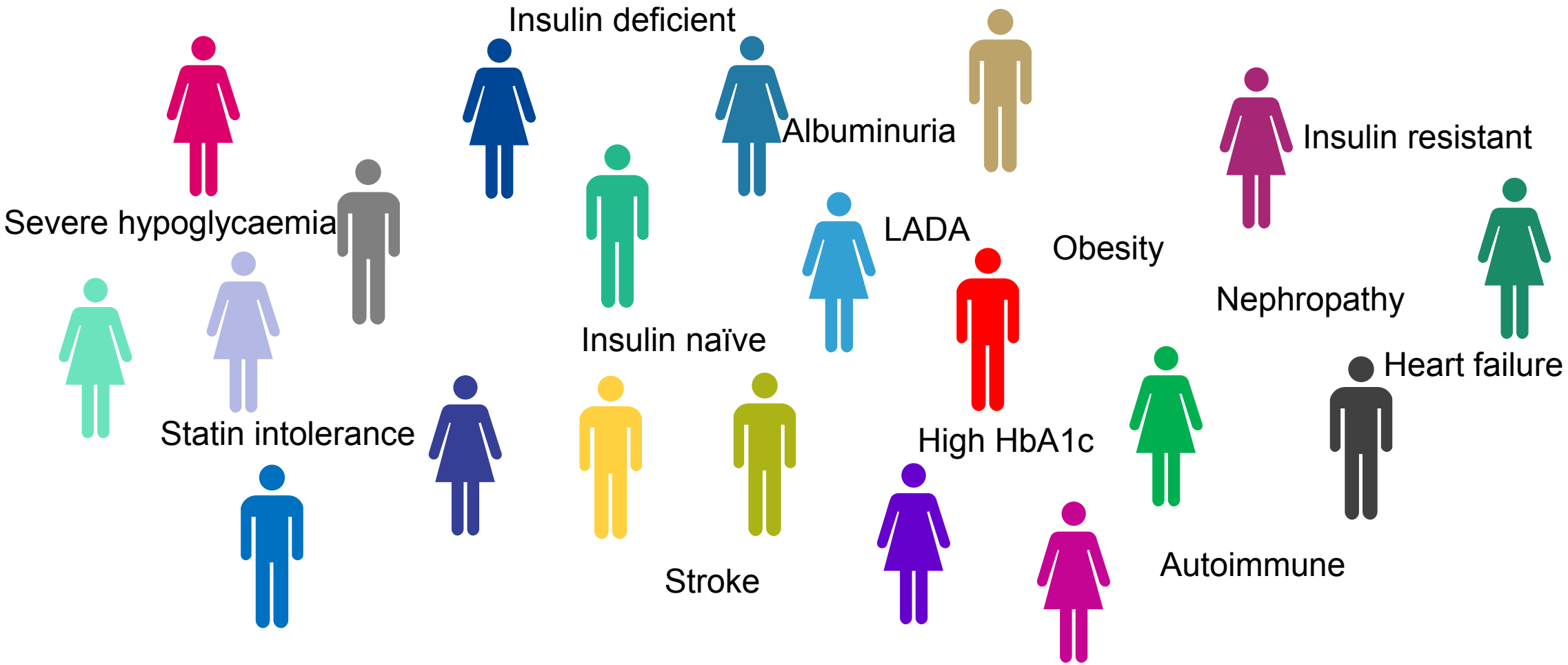
HF



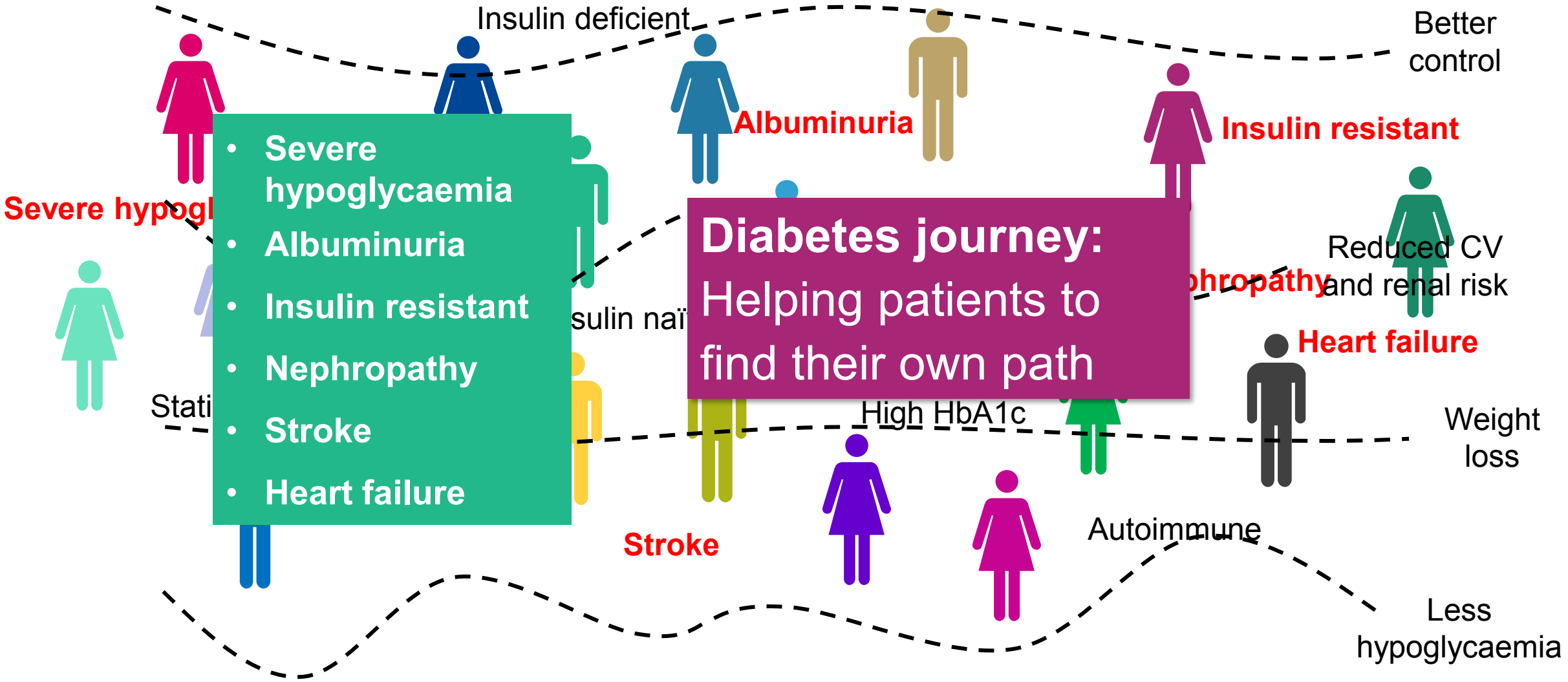
Death

Rangaswami J, et al. Circulation 2019;139:e840–78

What does this mean for the patient?



What does this mean for the patient?



55th EASD Annual Meeting

Diabetes journey: Innovative solutions for individual needs

Monday
16th September 2019

Fira Barcelona Gran Via
Barcelona, Spain

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