Neurological Complications of Diabetes

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Disclosures

- Insulet Corporation- advisory board member

Neurological disease associated with diabetes

Stroke

- 1.5-2x higher risk increasing with longer DM duration
- Hyperglycemia at time of stroke associated with worse outcomes
- Worse post-stroke outcomes and increased risk future stroke

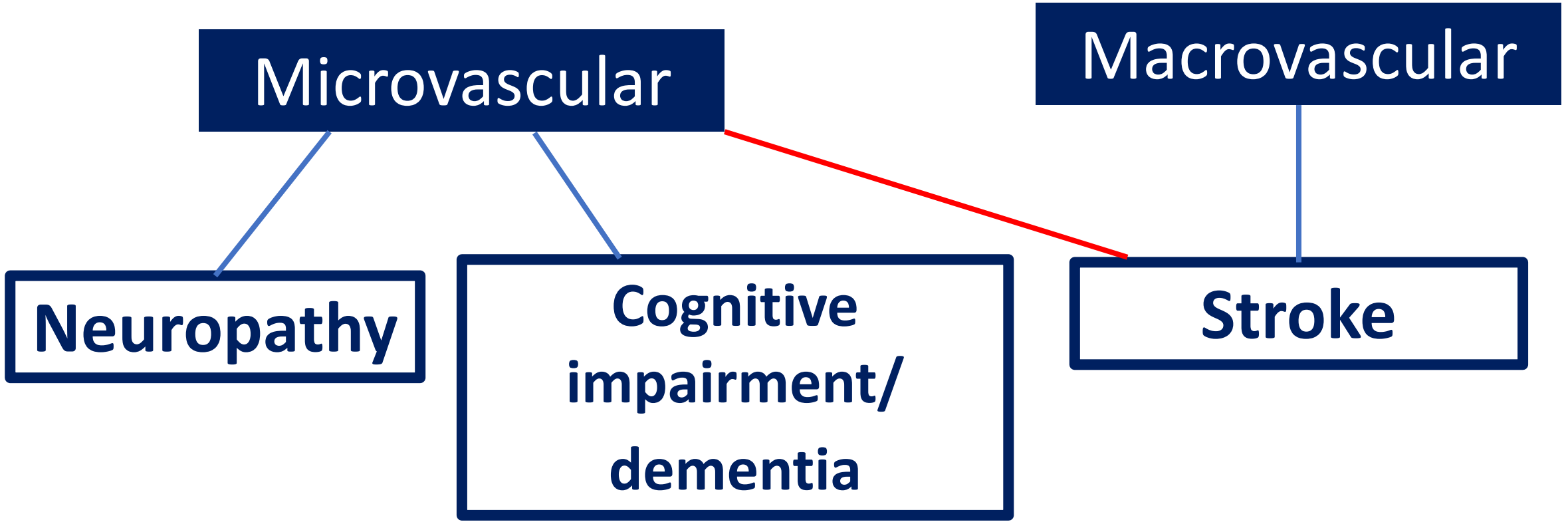
Neuropathy

- Often present at time of diagnosis of T2DM
- Risk lower with good glycemic control

Dementia

- Increased risk with longer DM duration
- Impairs patient's ability to adequately manage DM
- Increasing concerning particularly in aging DM population

Neurological complications of diabetes



Lancet Diabetes Endocrinol 2020; 8: 325–36

Glycemic control and vascular complications T2DM

- Association between reduction in glycemic control and microvascular events in T2DM established in UKPDS
- Less clear association between glycemic control and macrovascular complications
  - VADT- no significant change
  - ADVANCE- reduced risk of major macrovascular events
  - ACCORD- no benefit and increased mortality
- Subsequent meta-analysis showed reduced risk MI but no difference in stroke, HF, mortality
- Hypoglycemia known to increase risk of CV events and mortality

UKPDS Group. UKPDS 33. Lancet 1998; 352:837-53.
UKPDS Group. UKPDS 34. Lancet 1998;352:854-65
Diabetes Care 2018; 41:104-111

Reduction of Diabetes Complications

Glycemic control

BP Management

Lipid Management

Agents with cardiovascular and renal benefit

Cardiovascular Outcome Trials

- Primarily designed to rule-out risk (FDA required)
  - Some powered for superiority if non inferiority demonstrated
- Heterogeneity between trials
- 3 vs 4 point Major Adverse Cardiac Event (MACE)
  - 3 point: CV death, Nonfatal MI, nonfatal stroke
  - 4 point: + Hospitalization for unstable angina
- Secondary or Primary/secondary outcome trial
  - Majority of participants had CVD or multiple high risk features
  - Longer duration of DM
- Not designed to show A1c control of study drug

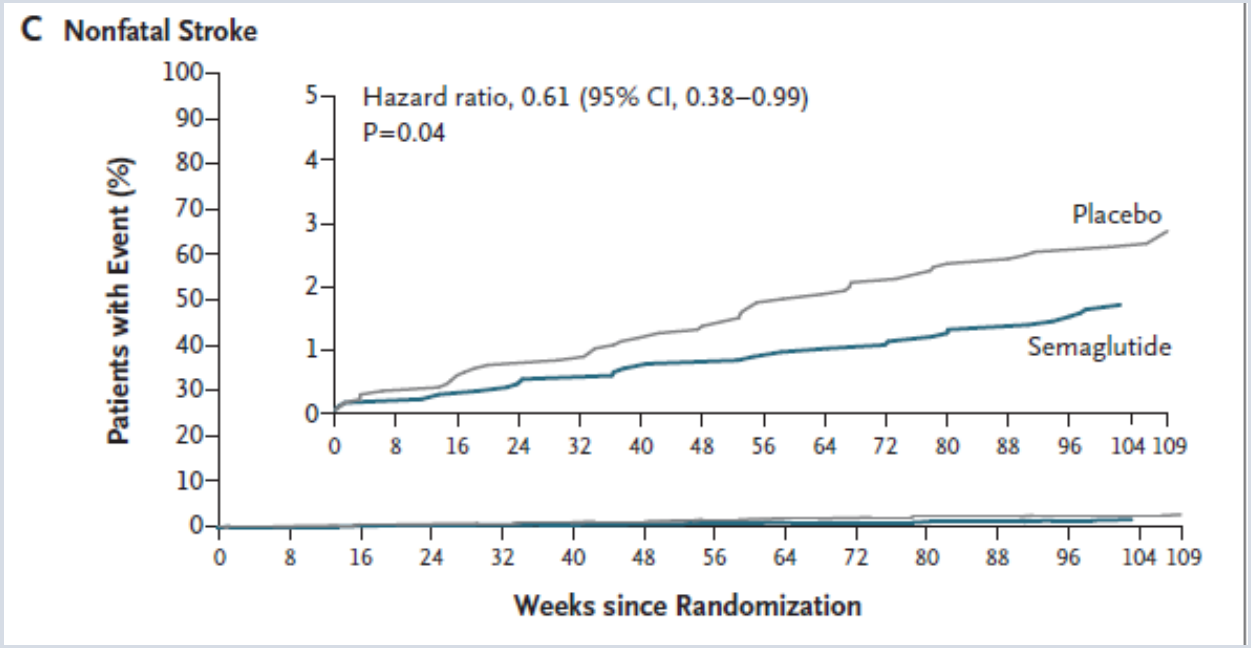
Cefalu et al. *Diabetes Care* 2018;41:14-31

Results of GLP1 RA CVOT in high risk patients

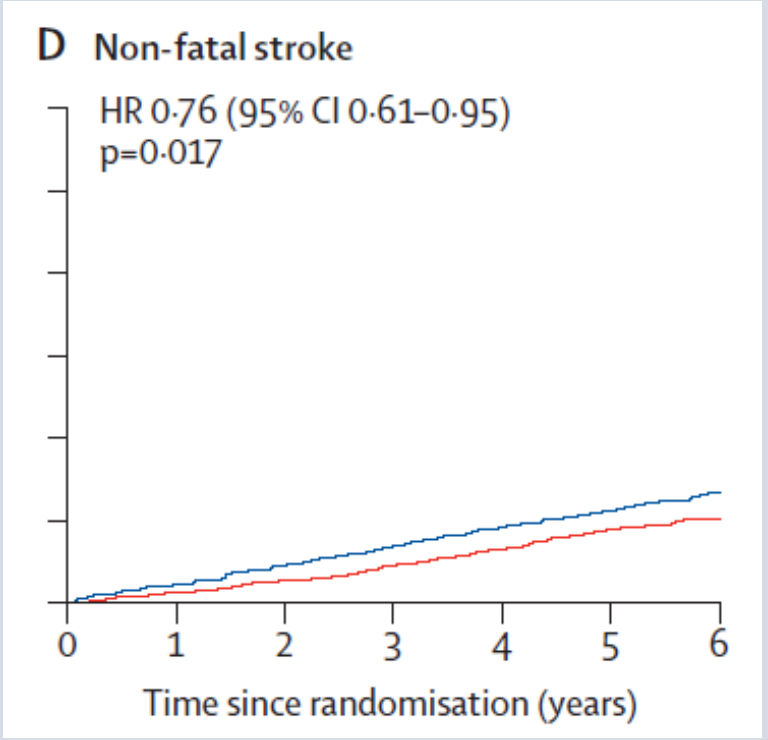
LEADER Liraglutide (Victoza)	SUSTAIN-6 Semaglutide SQ (Ozempic)	PIONEER-6 Semaglutide PO (Rybelsus)	REWIND Dulaglutide (Trulicity)
9,340 with CVD or high CV risk	3,297 with CVD or high CV risk	3,183 with CVD or renal disease or high CV risk	9,901 with prior CVD (32%) or high CV risk
3-point MACE HR 0.87 (0.78–0.97)	3-point MACE HR 0.74 (0.58–0.95)	3-point MACE HR 0.79 (0.57-1.11)	3-point MACE HR 0.88 (0.79–0.99)
↓CV mortality	**Positive; driven by ↓stroke**	Neutral	**Positive; driven by ↓stroke**

Nonfatal Stroke Incidence

Semaglutide (Ozempic)



Dulaglutide (Trulicity)



N Engl J Med 375;19

Lancet 2019; 394: 121–30

What about SGLT2i?

SGLT2 inhibitors		
EMPA-REG Empagliflozin	CANVAS and CANVAS-R Canagliflozin	DECLARE-TIMI 58 Dapagliflozin
7,020 with preexisting CVD	10,142 with CVD or high CV risk	17,160 patients; 10,186 without CVD
3-point MACE HR 0.86 (0.74–0.99)	3-point MACE HR 0.86 (0.75–0.97)	3-point MACE HR 0.93 (0.84–1.03)
Stroke 1.18 (0.89-1.56)	Stroke 0.87 (0.69-1.90)	1.01 (0.84-1.21)

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†
Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions

+Indicators of high risk
While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+HF
Current or prior symptoms of HF with documented HFrEF or HFpEF

+CKD
eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

Agents should be added regardless of background therapy, current A1c or goal A1c

GLP-1 RA[#] with proven CVD benefit

EITHER/OR

SGLT2i[§] with proven CVD benefit

population

≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If HbA_{1c} above target

- For patients on a GLP-1 RA consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

If HbA_{1c} above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:
Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate:
DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition

Intensive evidence-based structured

glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

Intermediate:
GLP-1RA (not listed above), SGLT2i

Neutral:
DPP-4i, Metformin

If HbA_{1c} above target

Identify barriers to goals:
- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

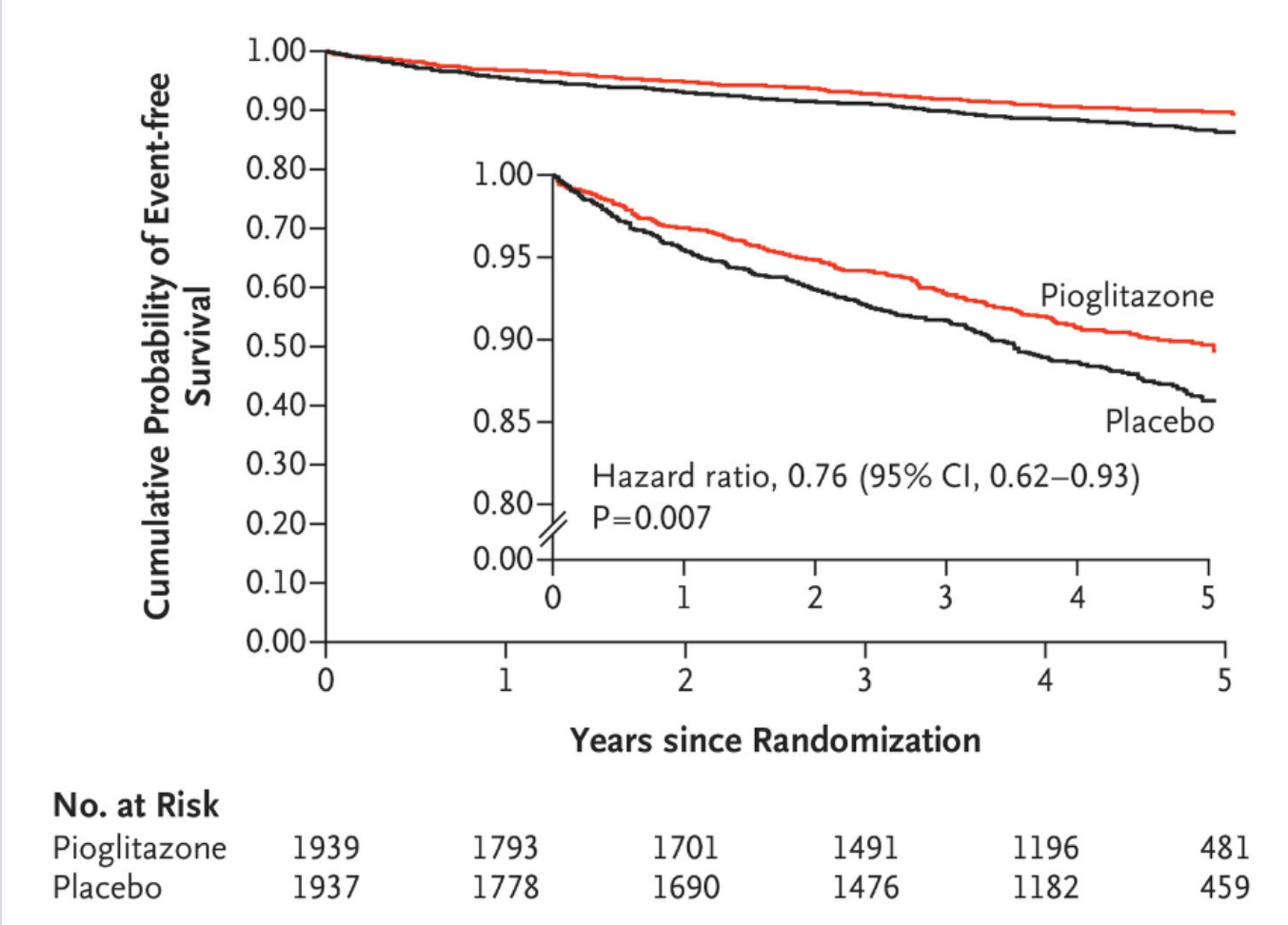
* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

Pioglitazone after Ischemic Stroke or TIA:IRIS

- 3876 patients with recent ischemic stroke or TIA randomized to either pioglitazone (target dose, 45 mg daily) or placebo
- No DM but insulin resistance based on HOMA-IR of more than 3.0

- After 4.8 years the treatment group had lower risk of stroke or MI as well as lower progression to DM

- Treatment group had more weight gain, edema, fracture



N Engl J Med 2016;374:1321-1331

Diabetes and cognitive impairment

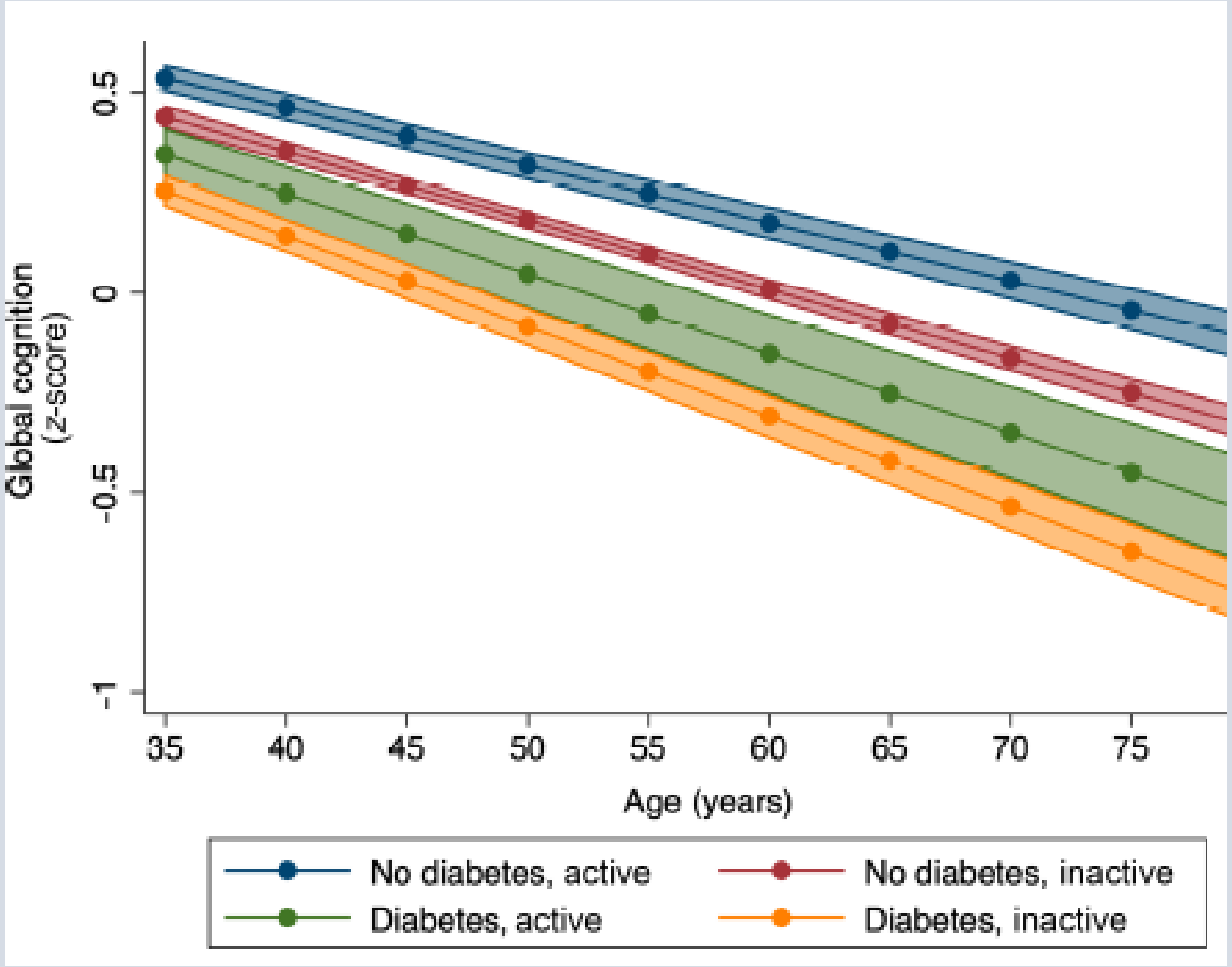
- Studies show increased incidence of cognitive impairment and dementia in those with both prediabetes and diabetes
- Longer duration of DM increases risk
- Etiology is not fully understood but likely multifactorial
  - Brain metabolic dysfunction
  - Insulin resistance
  - Microvascular dysfunction
  - Direction effects of hyperglycemia
  - Episodes of hypoglycemia
- Limited data to support strategies to prevent decline
  - ?GLP1 RA, actos, metformin

Ageing Research Reviews 55 (2019) 10094

JAMA. 2021;325(16):1640-1649

Physical activity and cognitive decline in DM

- 15,105 participants (age 35–74 years) in Brazil
- 6 standardized tests for memory and verbal fluency on 8 years
- 150+ min/week of moderate to vigorous defined as active
- Increased risk of impairment in inactive group with DM with some protection from activity in active group with DM



Diabetes Care 2024;47:427–434

Thank you!