



EVENTO TERRITORIALE **SID/AMD LAZIO**

Protezione cardio-renale nel Diabete di Tipo 2:

L'integrazione tra **Medici di Medicina generale**
e **Specialisti nella cura del Diabete**

Update su
SGLT2-i e GLP1 RA

Lelio Morviducci

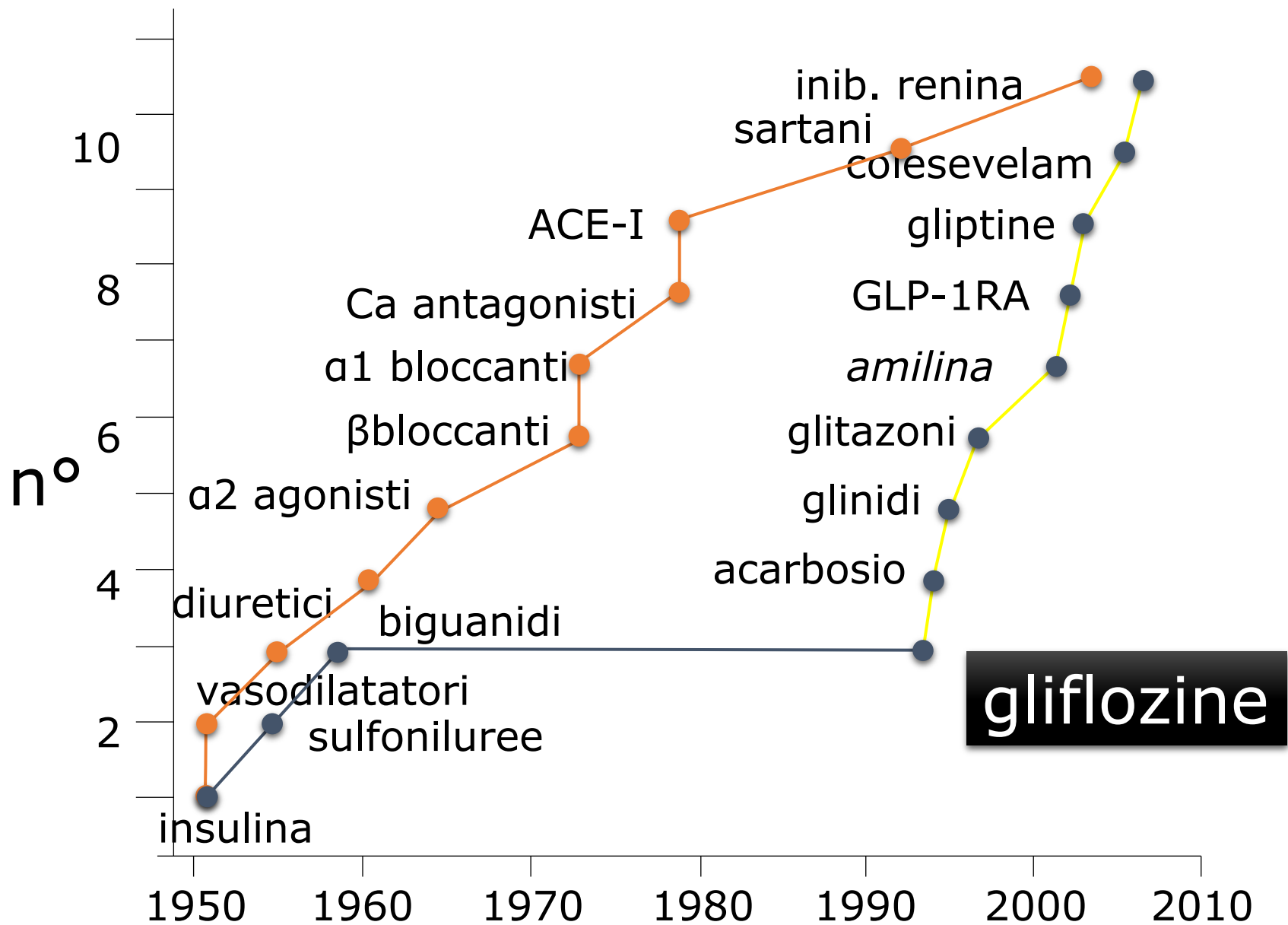
Direttore UOC Diabetologia e Dietologia
ASL Roma 1

Il dr. Lelio Morviducci dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Novo Nordisk
Lifescan
Roche Diagnostics
MSD
Boehringer
Eli-Lilly
Sanofi
Astra Zeneca

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Classi di farmaci disponibili



DPP4-i CV Outcomes Trials

CLASS	MOLECULE	TRIAL	CV SAFETY	CV BENEFIT ⁺¹⁵
DPP-4i	Saxagliptin	SAVOR-TIMI-53 ¹	Yes	No
	Alogliptin	EXAMINE ²	Yes	No
	Sitagliptin	TECOS ³	Yes	No
	Linagliptin	CARMELINA ^{*4}	Yes	No

GLP1-RA CV Outcomes Trials

	 REWIND Dulaglutide CV Outcomes Trial	 ELIXA	 EXSCEL Exenatide Study of Cardiovascular Event Lowering	 SUSTAIN™ SEMAGLUTIDE UNABATED SUSTAINABILITY IN TREATMENT OF TYPE 2 DIABETES	 LEADER® Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results	PIONEER
Drug	Dulaglutide	Lixisenatide	Exenatide ER	Semaglutide	Liraglutide	Sema Orale
N	9.901	6.068	14.752	3.297	9.340	
Follow-up (years)	5,4	2,1	3,2	2,1	3,8	1,8
History of CVD (%)	31	100	73	59	72	83
Primary endpoint (MACE) non inferiority						
Primary endpoint (MACE) superiority						

SGLT2-i CV Outcomes Trials

	 EMPA-REG OUTCOME®	 CANVAS Program	 DECLARE TIMI-58 The First International Medical Trial Comparing Effect on Cardiovascular Events	 VERTIS CV	 CREDENCE®
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin	Canagliflozin
N	7.020	10.142	17.160	8.246	4.401
Follow-up (years)	3,1	2,4	4,2	3,5	2,6
History of CVD (%)	99,2	65,6	40,6	75,9	50,4
Mean Baseline eGFRs	74	76,5	85,2	76,1	56,2
Primary endpoint (MACE) non inferiority					
Primary endpoint (MACE) superiority					

History of Serendipity

*"...trovare qualcosa di piacevolmente inaspettato,
cercando qualcos'altro di specifico"*

GLP1-RA CV Outcomes Trials

	 REWIND Dulaglutide CV Outcomes Trial	 ELIXA	 EXSCEL Exenatide Study of Cardiovascular Event Lowering	 SUSTAIN™ SEMAGLUTIDE UNABATED SUSTAINABILITY IN TREATMENT OF TYPE 2 DIABETES	 LEADER® Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results	 PIONEER
Drug	Dulaglutide	Lixisenatide	Exenatide ER	Semaglutide	Liraglutide	Sema Orale
Non-fatal myocardial infarction						
Non-fatal stroke						
Death from cardiovascular causes						
Death from any cause						
Renal Composite Outcome						

SGLT2-i CV Outcomes Trials

	 EMPA-REG OUTCOME®	 CANVAS Program	 DECLARE TIM-58 Dapagliflozin Effect on Cardiovascular Events	 VERTIS CV	 CREDENCE™
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin	Canagliflozin
Fatal or nonfatal myocardial infarction					
Fatal or nonfatal stroke					
Death from cardiovascular causes					
Death from any cause					
Hospitalization for heart failure					
Death from cardiovascular causes or hospitalization for heart failure					
Renal Composite Outcome					

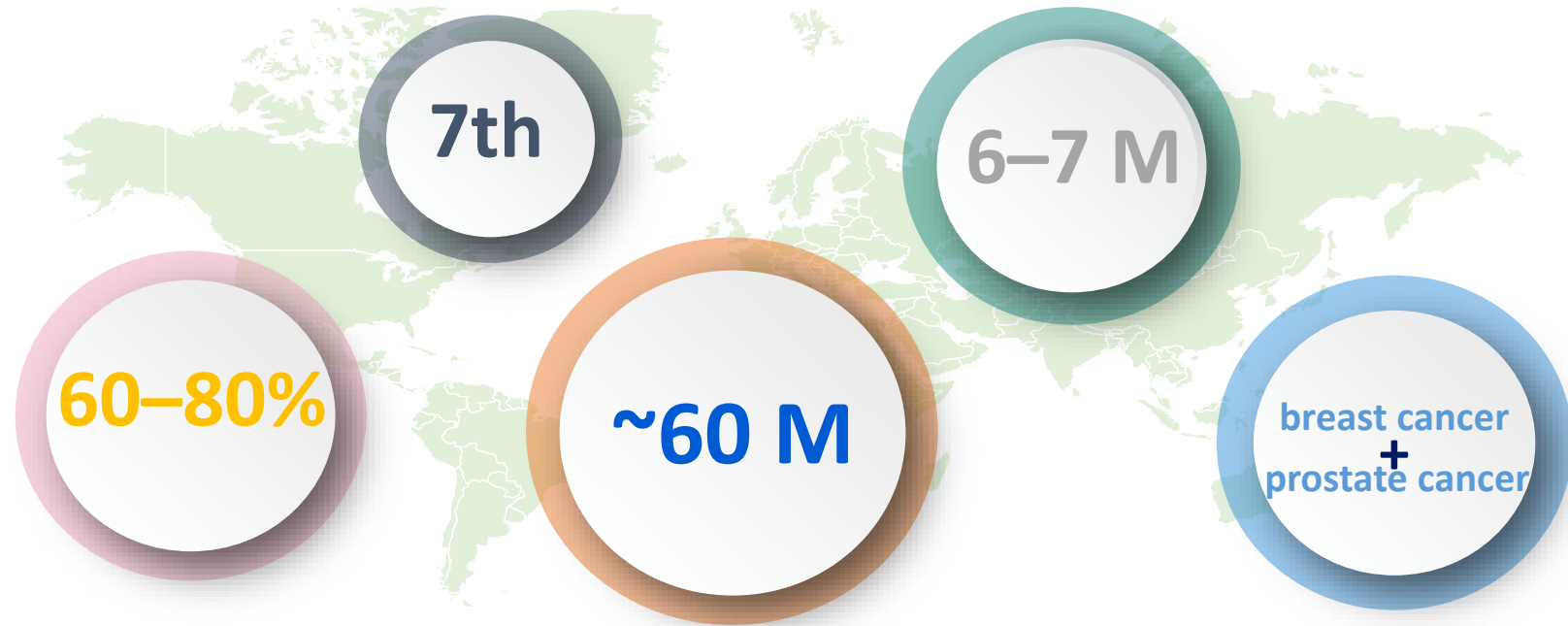


**ALZHEIMER DISEASE
DEMENTIA
COGNITIVE IMPAIRMENT**

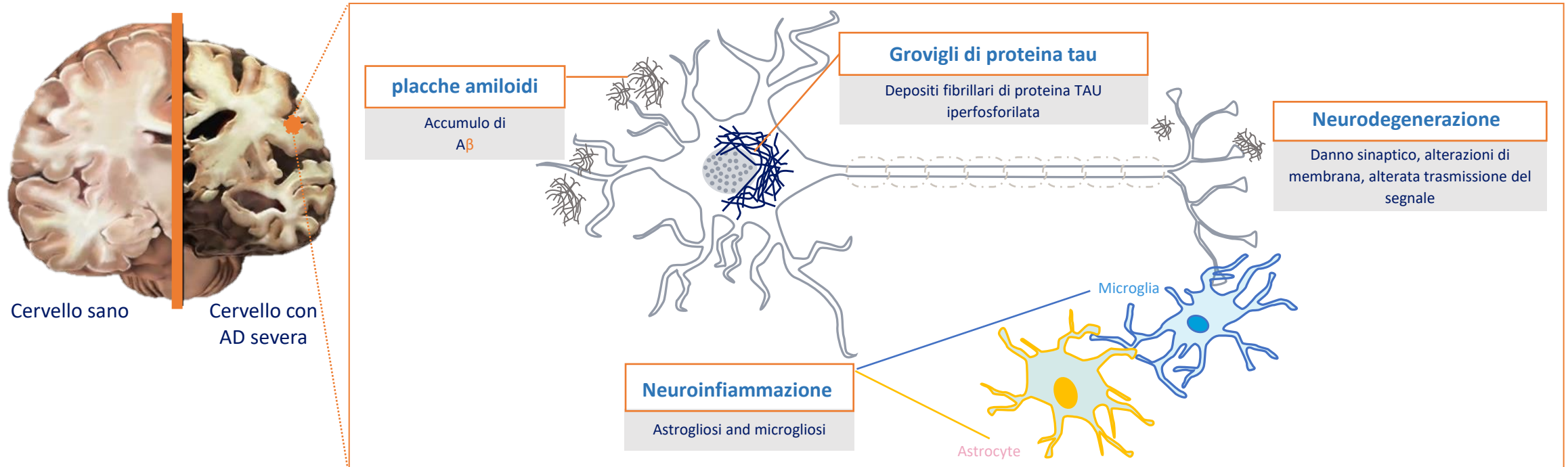




ALZHEIMER DISEASE
DEMENTIA
COGNITIVE IMPAIRMENT



I segni distintivi dell'AD includono: placche amiloidi, depositi neurofibrillari di proteine tau e la neurodegenerazione

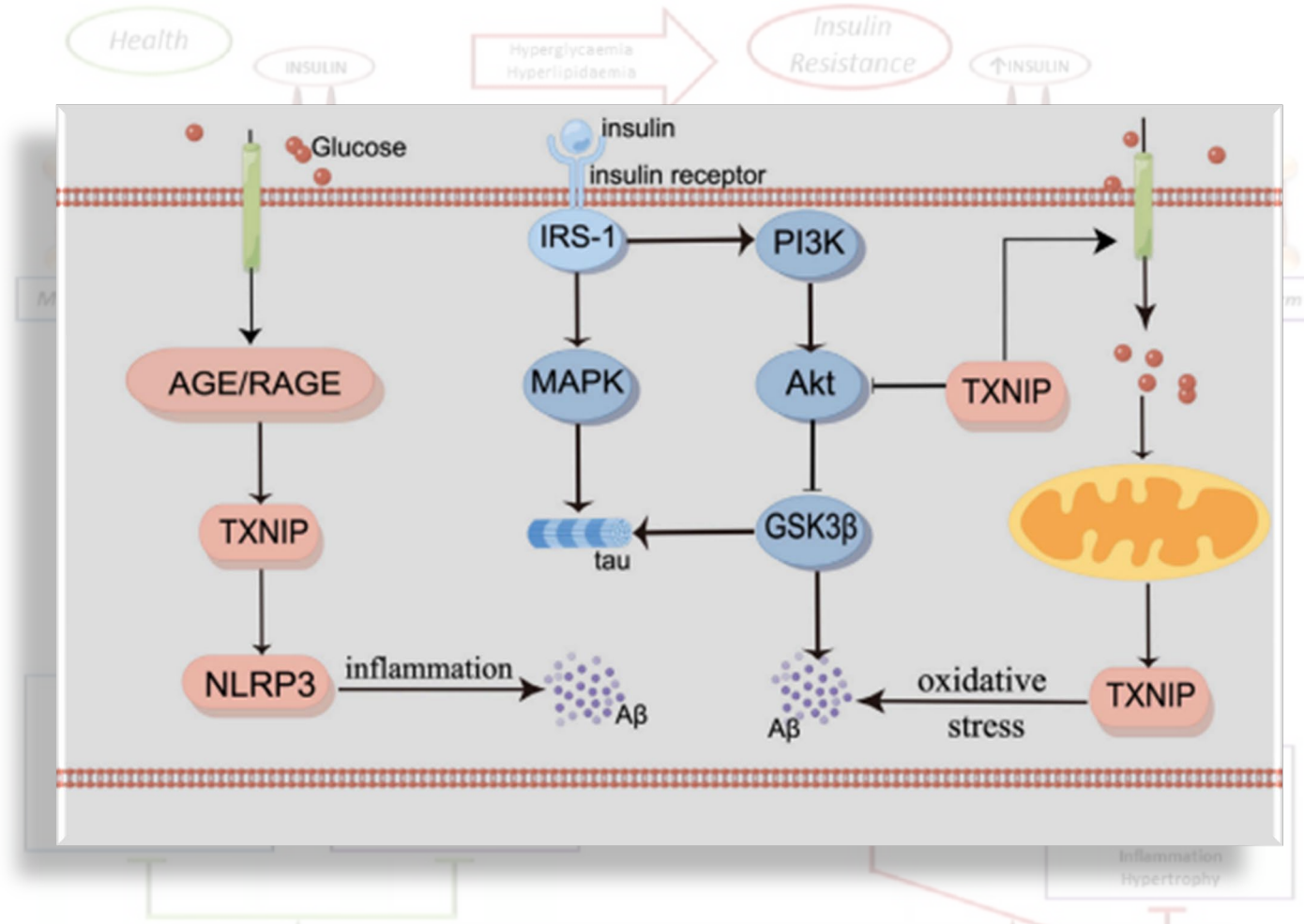
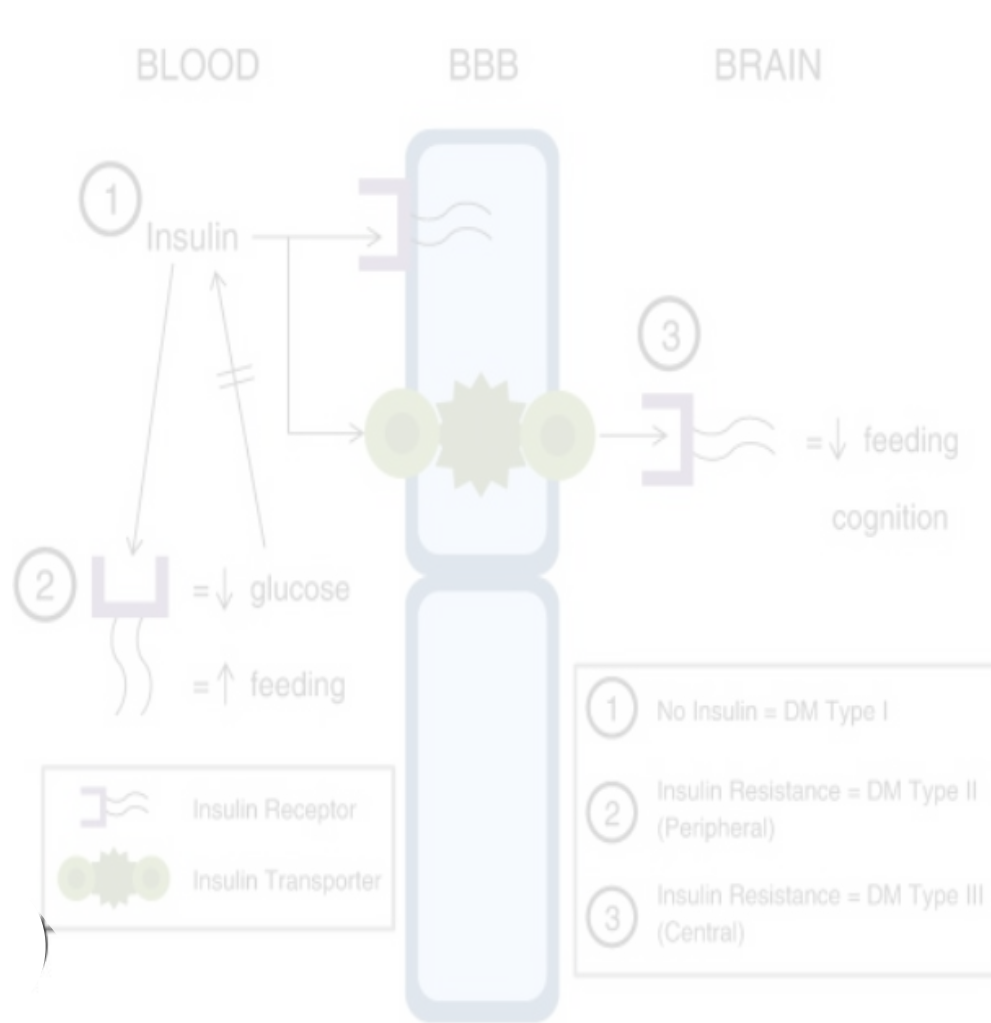


Questi cambiamenti iniziano anni prima della comparsa dei sintomi, portando infine alla demenza. L'evidenza suggerisce che la neuroinfiammazione si verifica come risultato dell'accumulo di placca amiloide ed è vista come un meccanismo rilevante nella progressione dei cambiamenti neuropatologici nell'AD.

Il cervello è un organo insulino-sensibile.

L'insulina attraversa la BBB con un meccanismo saturabile.

L'insulina svolge un importante ruolo fisiologico nel cervello ad eccezione dell'omeostasi del glucosio

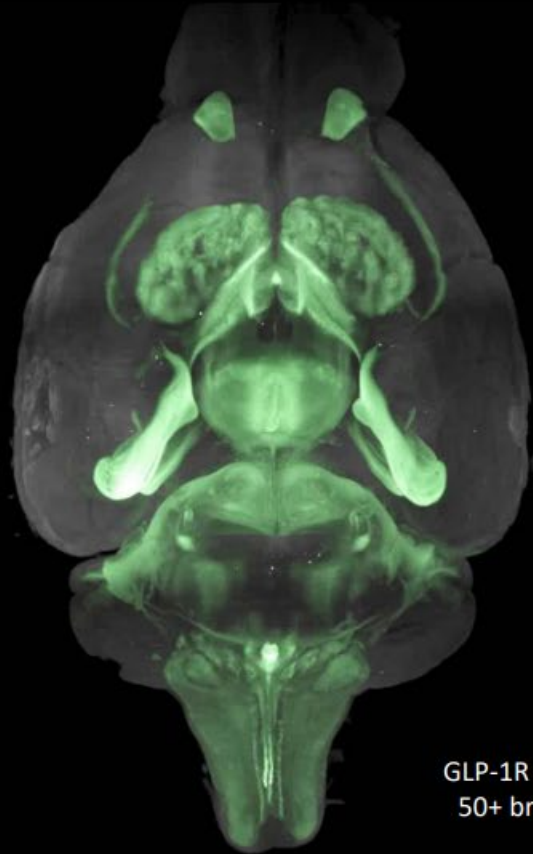


Altera la plasticità sinaptica e la regolazione della neurotrasmissione che partecipano all'apprendimento, alla memoria e alle funzioni emotive del cervello



GLP-1 RA and Brain

GLP-1R espresso nel cervello murino



GLP-1R identified in
50+ brain regions

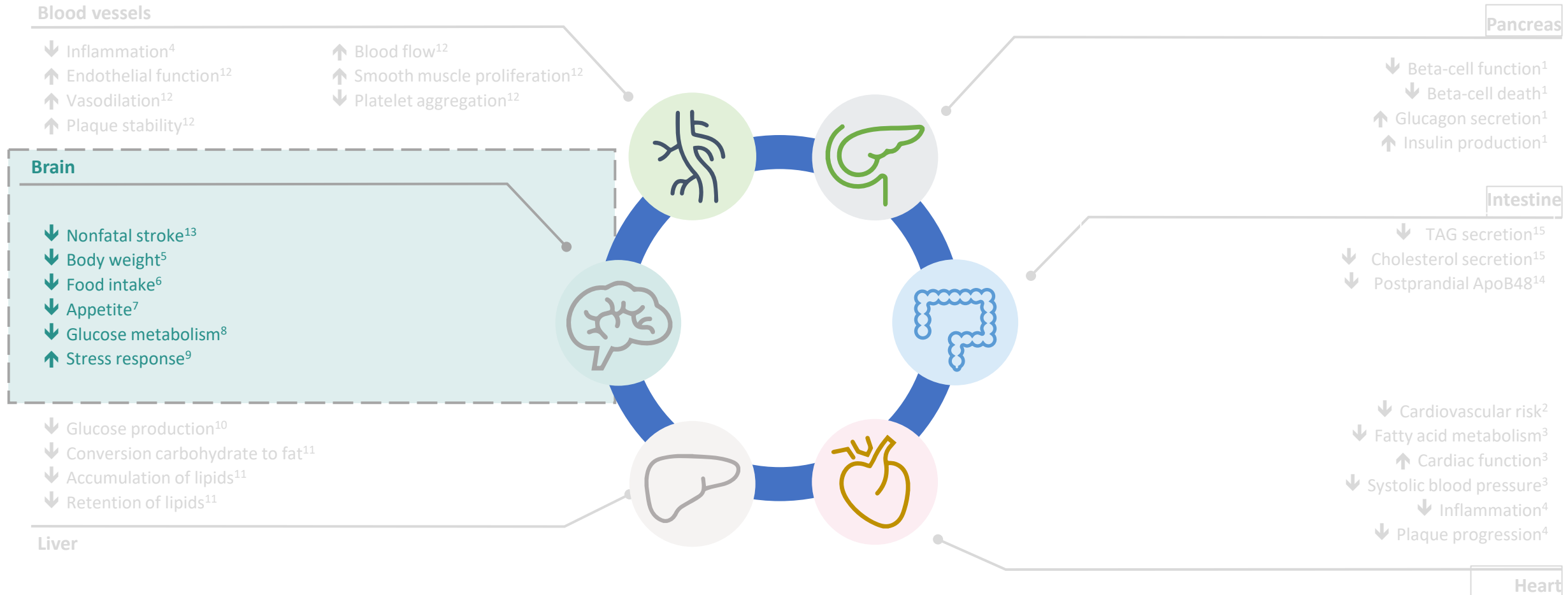
Il GLP-1R è espresso in aree dell'ippocampo coinvolte nell'apprendimento e nella memoria

- I topi carenti di GLP-1R hanno un fenotipo caratterizzato da un deficit di apprendimento che viene ripristinato dopo il trasferimento del gene GLP-1R ippocampale
- I ratti che sovraesprimono il GLP-1R dell'ippocampo mostrano un miglioramento dell'apprendimento e della memoria

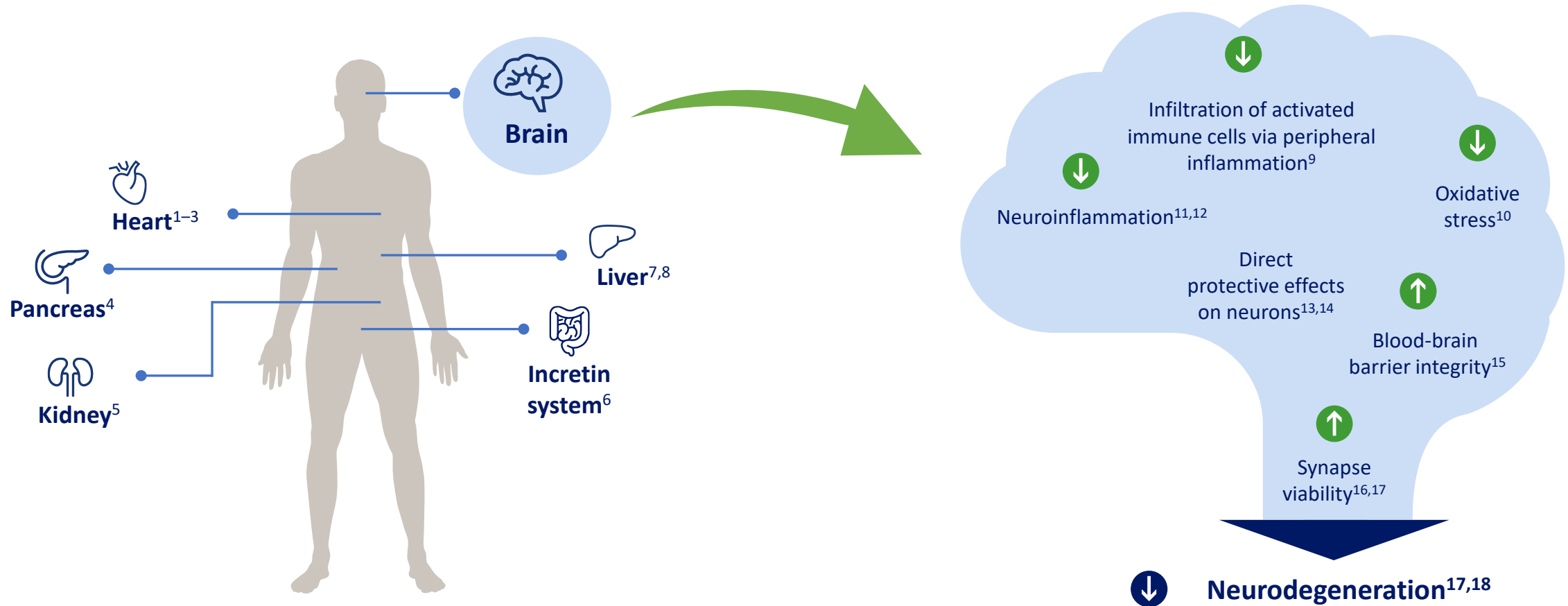
Areas in neon green reflect GLP-1 receptor expression

Jensen et al. Endocrinology 2017;159:665–675

I GLP-1 RA hanno effetti multifattoriali su diversi organi, incluso il cervello



GLP-1RAs



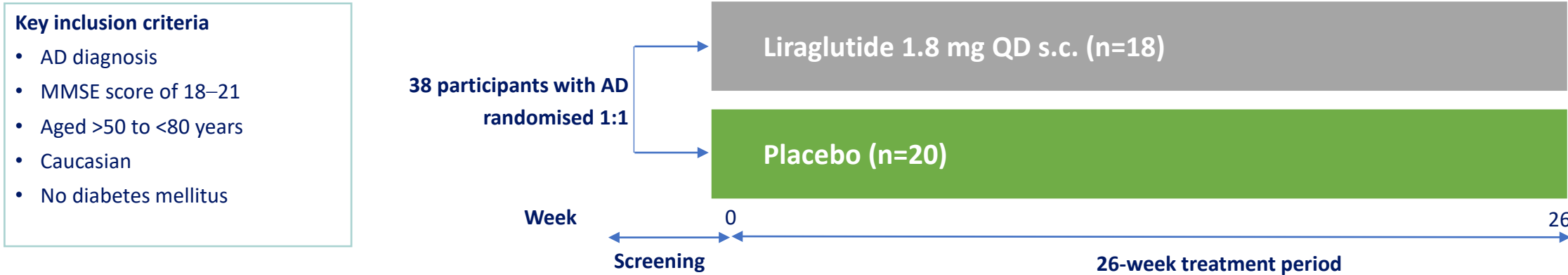
AD, Alzheimer's disease; GLP-1RA, glucagon-like peptide-1 receptor agonist

1. Morso SP et al. *N Engl J Med* 2016;375:311-322; 2. Ryan D, Acosta A. *Obesity* 2015;23:1119-1129; 3. Hogan AE et al. *Diabetologia* 2014;57:781-784; 4. Campbell JE, DJ Drucker. *Cell Metab* 2013;17:819-837; 5. Muskiet MHA et al. *Nat Rev Nephrol* 2017;13:605-628; 6. Tong J, D'Alessio D. *Diabetes* 2014;63:407-409; 7. Armstrong MJ et al. *J Hepatol* 2016;64:399-408; 8. Armstrong MJ et al. *Lancet* 2016;387:679-690; 9. Xie J et al. *Front Immunol* 2022;12:796867; 10. Rizzo M et al. *J Clin Endocrinol Metab* 2015;100:603-606; 11. Hansen HH et al. *Brain Res* 2016;1634:158-170; 12. Yun SP et al. *Nat Med* 2018;24:931-938; 13. During MJ et al. *Nat Med* 2003;9:1173-1179; 14. Perry TA et al. *J Neurosci Res* 2003;72:603-612; 15. Zhao L et al. *Nat Commun* 2020;11:4413; 16. Grieco M et al. *Front Neurosci* 2019;13:1112; 17. Gejl M et al. *Front Aging Neurosci* 2016;8:108; 18. Wilson JM et al. Presented at Clinical Trials on Alzheimer's Disease (CTAD) 2021 (oral), Boston, USA, 9-12 November 2021

GLP-1 RA e Decadimento Cognitivo: Studi Preclinici

Studies	Experiment	GLP-1RA	Observations
<i>Preclinical studies</i>	<i>Animal model</i>		
<i>AD features</i>			
<i>Plaque load</i>	APP/PS1/tau mice 5xFAD mice APP/PS1 mice 3xTg-AD mice	Liraglutide Liraglutide Lixisenatide Exendin-4	Reduction of plaque load Reduction of plaque load Reduction of plaque load Reduction of plaque load
<i>Tau phosphorylation</i>	APP/PS1/tau mice hTauP301L mice A β injection in mice APP/PS1 x db/db mice Streptozotocin injection in mice	Liraglutide Liraglutide Liraglutide Liraglutide Dulaglutide	Reduction of neurofibrillary tangles Reduced Tau phosphorylation Reduced Tau phosphorylation Reduced Tau phosphorylation Reduced Tau phosphorylation
<i>Cognitive and memory performance</i>	A β injection in mice A β injection in rats Streptozotocin injection in mice	Liraglutide Lixisenatide Dulaglutide	Improved cognitive impairment Improved spatial memory Improved memory ability
<i>Other</i>	A β injection in non-human primates	Liraglutide	Reduced synaptic loss
<i>PD features</i>			
<i>Dopaminergic neuronal loss</i>	6-OHDA rat model 6-OHDA rat model 6-OHDA rat model	Liraglutide Exendin-4 Exendin-4'	No influence on dopaminergic neuronal loss Neurogenesis Reduced lesions
<i>Motor performance</i>	MPTP mouse model MPTP mouse model	Liraglutide Lixisenatide	Improved motor control Improved motor control
<i>α-synuclein aggregation</i>	Preformed fibrils injection in striatum of human A53T α -synuclein mice Preformed fibrils injection in the olfactory bulb of C57BL/6J mice	Exendin-4 (NLY01) Exendin-4	Reduced loss of dopaminergic neurons and improved motor performance No significant reduction of α -synuclein aggregation

Liraglutide vs placebo in patients with mild/moderate AD



Key endpoints

- **Primary outcome:** A β deposition ([¹¹C]PIB PET)
- **Secondary outcome:** CMR_{glc} ([¹⁸F]FDG PET)
- **Other outcomes:** Cognitive ability



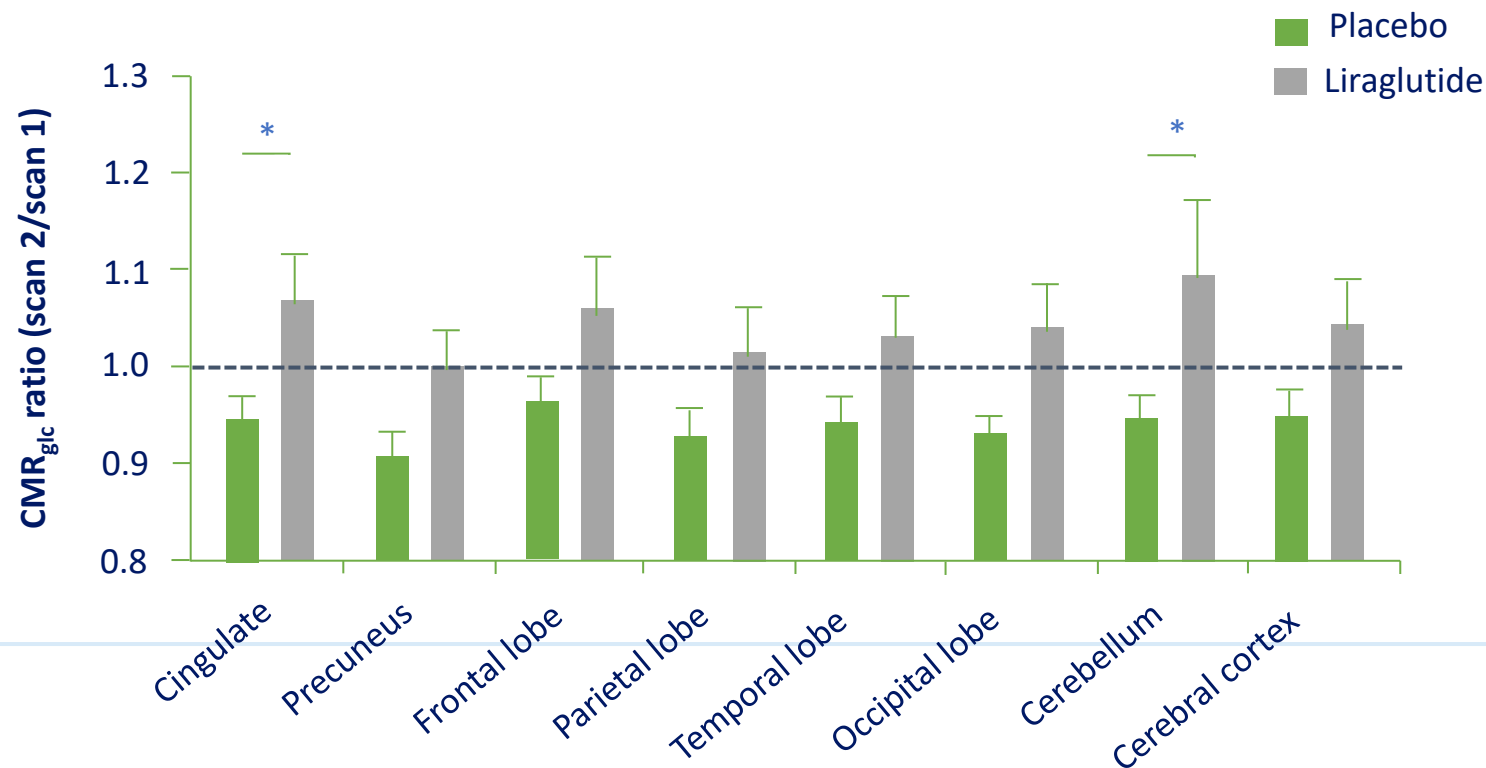
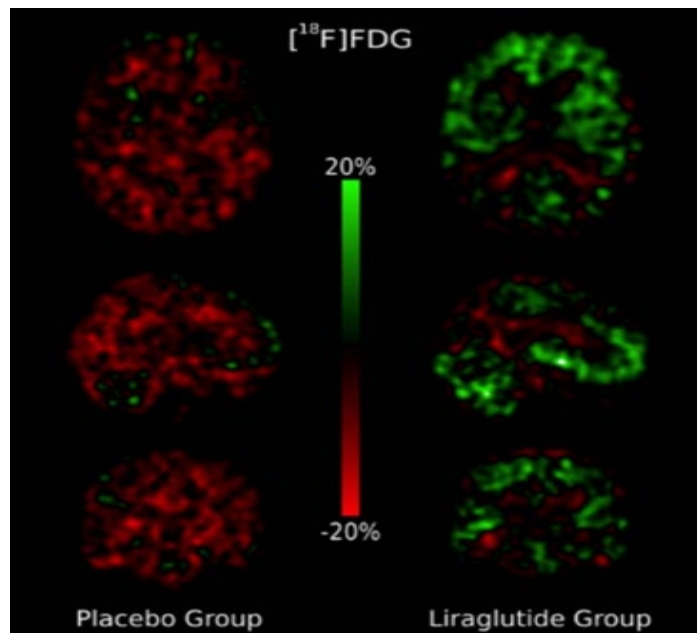
Key findings

- No effect on A β deposition
- **Liraglutide treatment prevented decline of CMR_{glc}**

¹¹C]PIB, carbon-11 labelled Pittsburgh Compound B; [¹⁸F]FDG, fluoro-2-deoxyglucose; A β , amyloid beta; AD, Alzheimer's disease; CMR_{glc}, cerebral metabolic rate of glucose; MMSE, Mini-Mental State Examination; PET, positron emission tomography; QD, once daily; s.c., subcutaneous
Gejl M et al. Front Aging Neurosci 2016;24:108

Il trattamento con liraglutide previene il declino di CMR_{glc} nei pazienti con AD lieve/moderato

Un calo di CMR_{glc} indica disfunzione sinaptica e neurodegenerazione e potrebbe essere un indicatore della progressione della malattia



Final analysis of [¹⁸F]FDG uptake included 17 patients from the placebo group and 14 patients from the liraglutide group
 *p<0.05. CMR_{glc} scan 2/scan 1 ratio showed significant decline in cingulate (p=0.04) and occipital lobes (p=0.04) for placebo compared with liraglutide
 [¹⁸F]FDG, 18F-fluorodeoxyglucose; AD, Alzheimer's disease; CMR_{glc}, cerebral metabolic rate of glucose
 Gejl M et al. Front Aging Neurosci 2016;8:108



Effect of dulaglutide on cognitive impairment in type 2 diabetes: an exploratory analysis of the REWIND trial

Tali Cukierman-Yaffe, Hertz C Gerstein*, Helen M Colhoun, Rafael Diaz, Luis-Emilio García-Pérez, Mark Lakshmanan, Angelyn Bethel, Denis Xavier, Jeffrey Probstfield, Matthew C Riddle, Lars Rydén, Charles Messan Atisso, Stephanie Hall, Purnima Rao-Melacini, Jan Basile, William C Cushman, Edward Franek, Matyas Keltai, Fernando Lanas, Lawrence A Leiter, Patricio Lopez-Jaramillo, Valdis Pirags, Nana Pogossova, Peter J Raubenheimer, Jonathan E Shaw, Wayne H-H Sheu, Theodora Temelkova-Kurktschiev*

Summary

Lancet Neurol 2020; 19: 582–90

See [Comment](#) page 559

*Joint first authors

Background Diabetes is an independent risk factor for cognitive impairment. We aimed to investigate the association between the glucagon-like peptide-1 (GLP-1) receptor agonist dulaglutide and cognitive impairment as an exploratory analysis within the Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) trial.

Montreal Cognitive Assessment (MoCA) & Digit Symbol Substitution Test (DSST)

somministrati a t = 0, 2 y, 5 y & fine studio

MoCA: 1 pag, 30 items, ~ 10 min

DSST: 1 pag, test sulle funzioni cognitive, 2 min

Entrambi i test sono soggettivi e influenzati dalle condizioni in cui sono stati somministrati

- *Pre-specificato prima della fine dello studio*

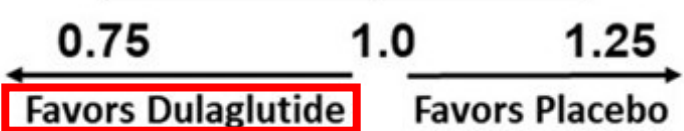
Conversione di tutti i punteggi MoCA e DSST al basale e ad ogni visita di follow-up in punteggi standardizzati basati sul punteggio medio al basale del paese come segue

$$\frac{\text{Pt's score ai vari tempi} - \text{Score della media nazionale al basale}}{\text{Standard deviation (SD) dello Score della media nazionale al basale}}$$

- Pertanto, il punteggio di ogni persona in ogni punto temporale = numero di SD dal punteggio medio di base del paese di quella persona

Effect on Country-Standardized SCI

Adjusted for Each Person's Baseline MoCA & DSST Score

	HR (95% CI)		P
SCI adjusted for baseline scores	0.86 (0.79, 0.95)		0.0018
SCI adjusted for baseline scores & age	0.86 (0.78, 0.94)		0.0014
SCI adjusted for baseline scores, age, ethnicity, education	0.87 (0.79, 0.95)		0.0032
SCI adjusted for baseline scores, age, sex, education	0.87 (0.79, 0.96)		0.0034
			

Liraglutide migliora il declino cognitivo nei pazienti con T2D



Population (n=50)

- T2D diagnosis
- Aged 18–65 years
- HbA_{1c} >7.0%
- On oral antidiabetic drugs or insulin for ≥3 months
- BMI ≥25 kg/m²

Key trial information

- 12-week, phase 3, interventional, non-randomised, parallel, open-label
- Patients were assigned to the treatment group (0.6 mg/day liraglutide) or the control group (oral antidiabetic drug with or without insulin)

Primary objective

- Changes of cognitive function assessed by cognitive function scale after 12 weeks

Mini-Mental State Examination
Total Learning and Animal Naming Test



Key findings

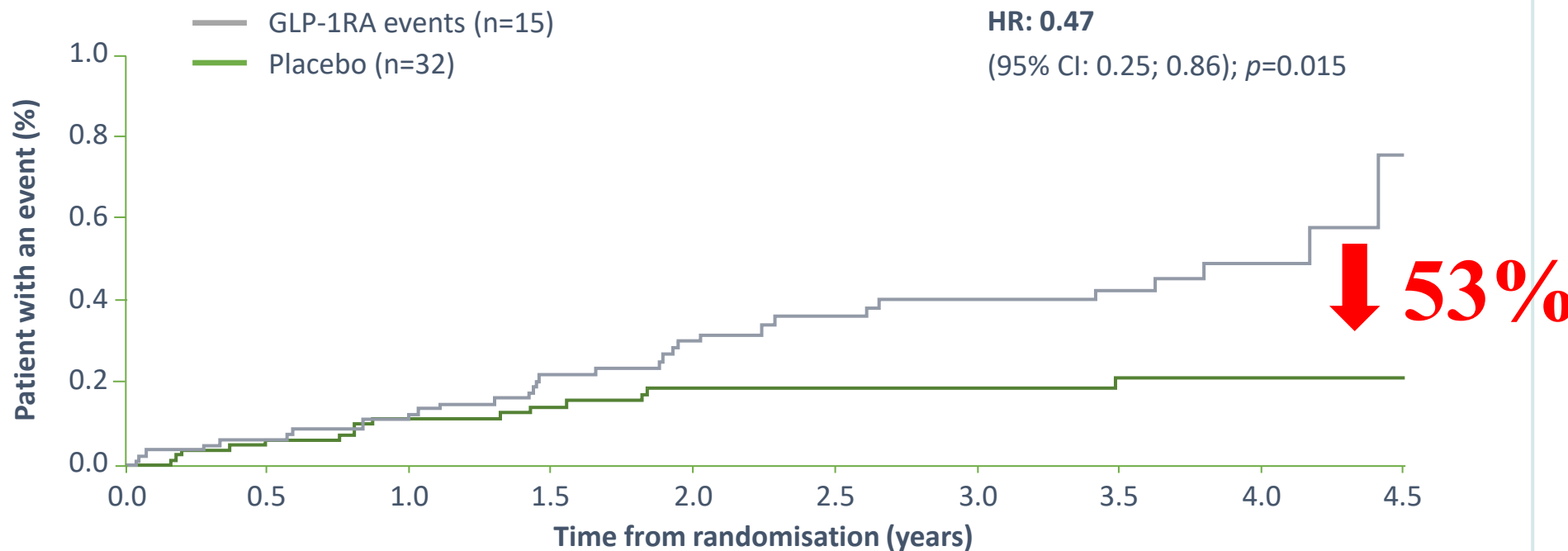
- Treatment with liraglutide **significantly improved cognitive function** in patients with T2D, compared with other oral antidiabetic drugs
- Relative to the control group, liraglutide significantly **activated certain brain regions that are highly associated with improvements in cognitive performance**
- These cognitive improvements **were not found to be related to changes in blood pressure, glycaemia and body weight** in patients with T2D

I GLP-1RA riducono il tasso di demenza per tutte le cause nei pazienti con T2D

53% lower risk of dementia with GLP-1RA (liraglutide or semaglutide) vs placebo in pooled post hoc analysis

Pooled data from 3 large CVOTs:

- LEADER (liraglutide)
- SUSTAIN 6 (s.c. semaglutide)
- PIONEER 6 (oral semaglutide)
- 15,820 subjects with T2D and CVD/high risk for CVD
- Median follow-up: 3.6 years



Quattro studi RWE hanno mostr o AD con l'esposizione a GLP-1

o ridotto di demenza



469,862 people

Nørgaard CH et al. D

- **11% lower risk**
exposure



178,403 people with T2

Wium-Andersen et al. Danish registry

- **42% lower odds of demen**

on monotherapy



liraglutide* exposure

(2012–2018)



diagnose

dementia after >2 years of

are

*Liraglutide has been market leader during the time of inclusion

AD, Alzheimer's disease; CI, confidence interval; FEARS, FDA Adverse Event Reporting System; FDA, US Food & Drug Administration; RWE, real-world evidence; T2DM, type 2 diabetes mellitus; 1. Nørgaard CH et al. *Alzheimer's Dement* 2022;8:e12268; 2. Wium-Andersen IK et al. *Eur J Endocrinol* 2019;181

1. Liraglutide-1 receptor agonist; RWE, real-world evidence; T2DM, type 2 diabetes mellitus; 1. *Alzheimer's Other Dement* 2020;35:1–11

evoke and evoke+: Two large, global, phase 3a trials evaluating the neuroprotective effects of semaglutide in early Alzheimer's disease



1840 patients
in each trial

Age: 55–85 years
(both inclusive)



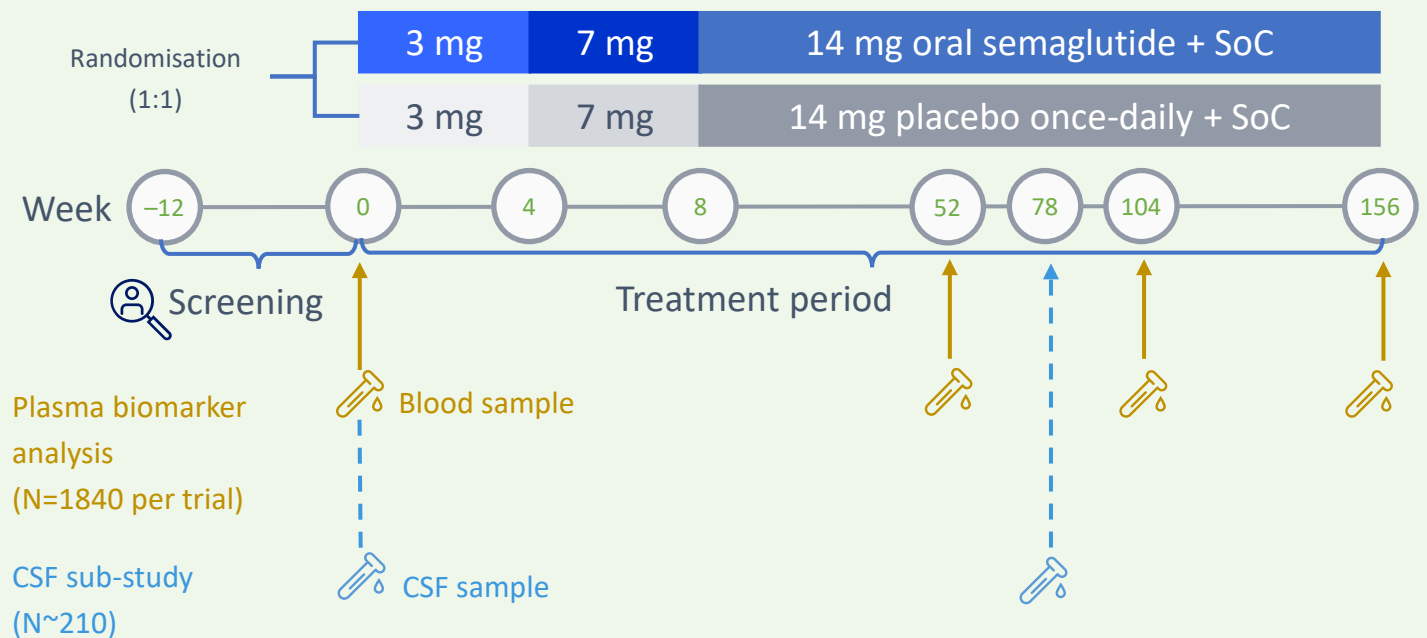
Mild Cognitive Impairment or mild dementia both of the Alzheimer's type

- 80% MCI and 20% mild dementia
- Amyloid-positive (PET or lumbar puncture)



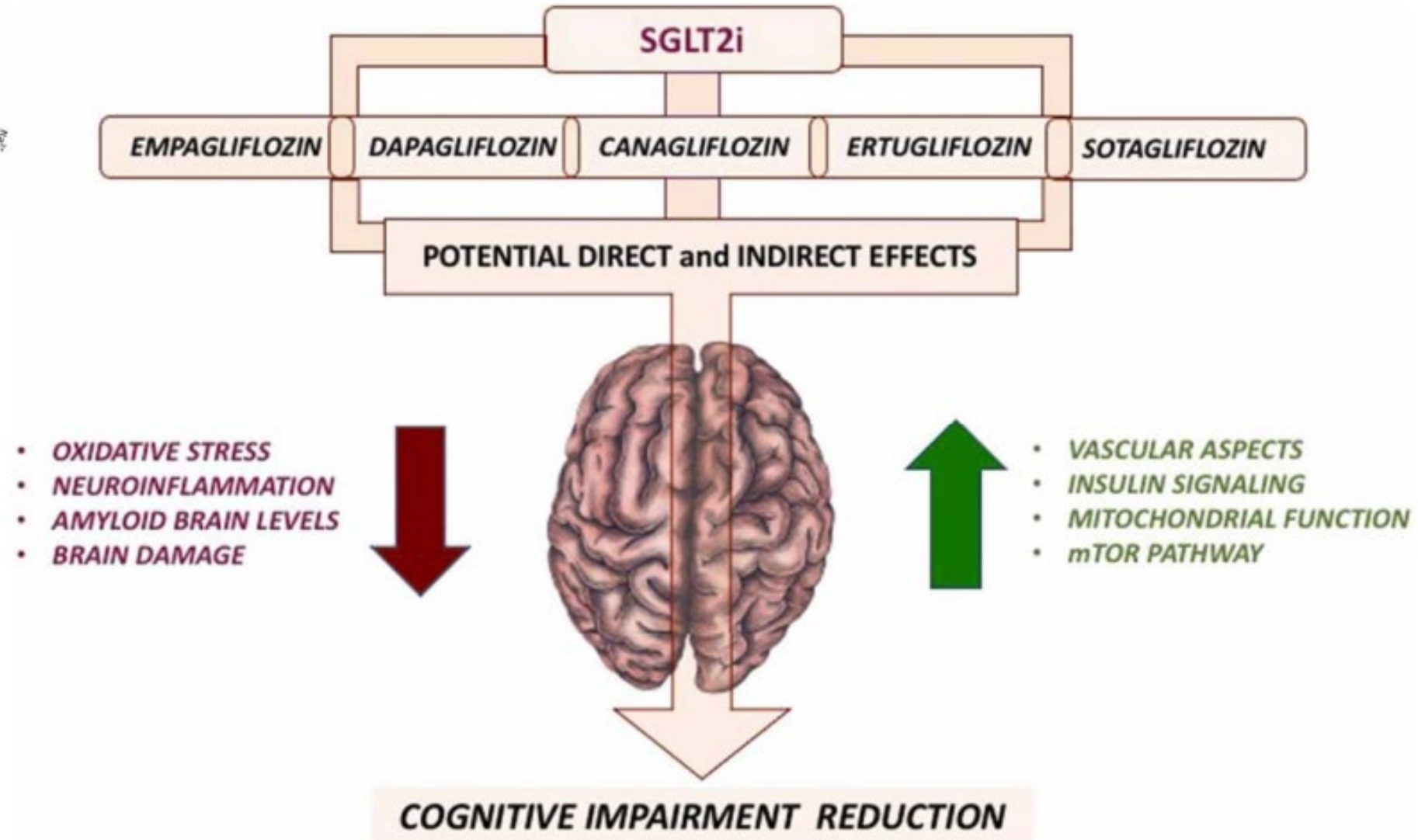
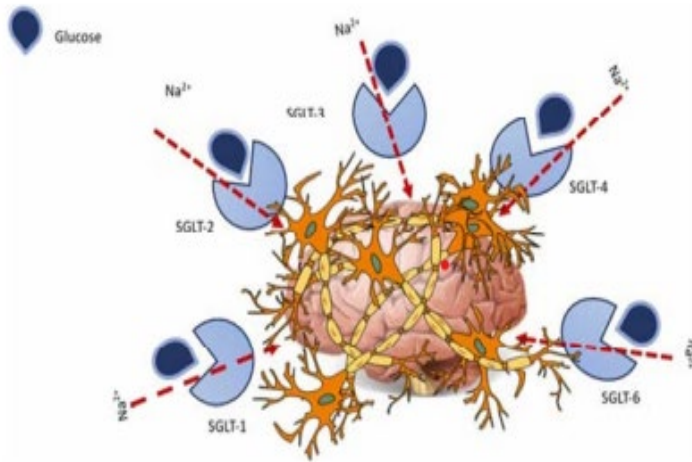
800+ sites in
40 countries

evoke **evoke⁺**
evaluation of oral semaglutide in early Alzheimer's disease

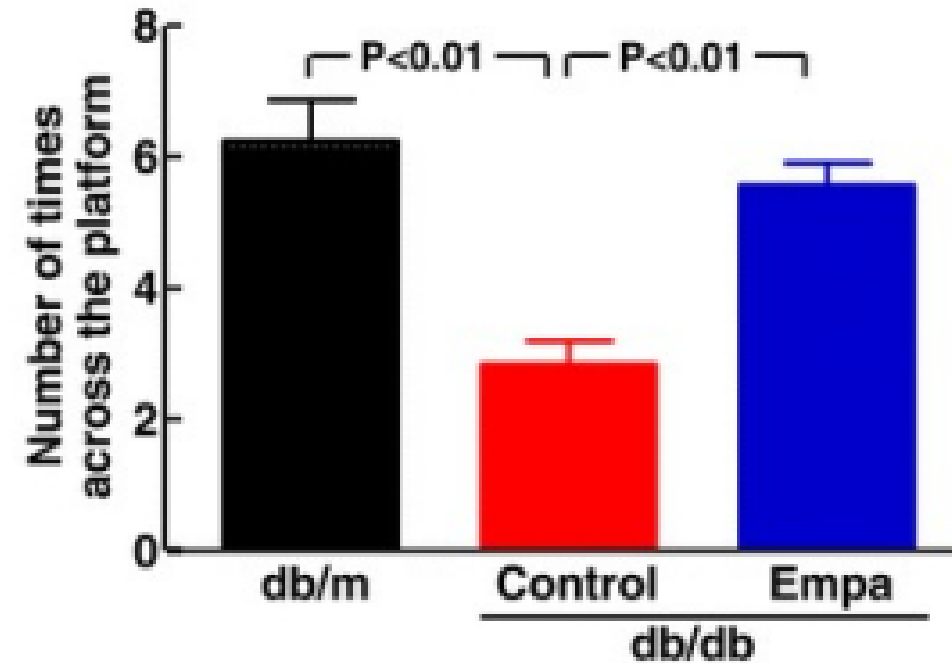
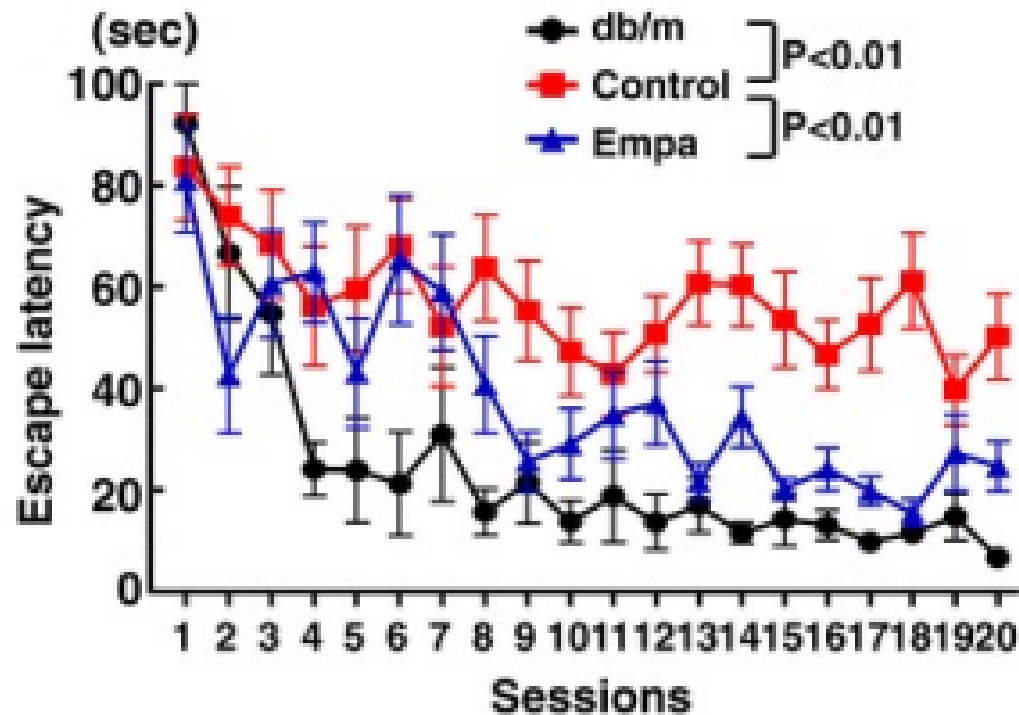




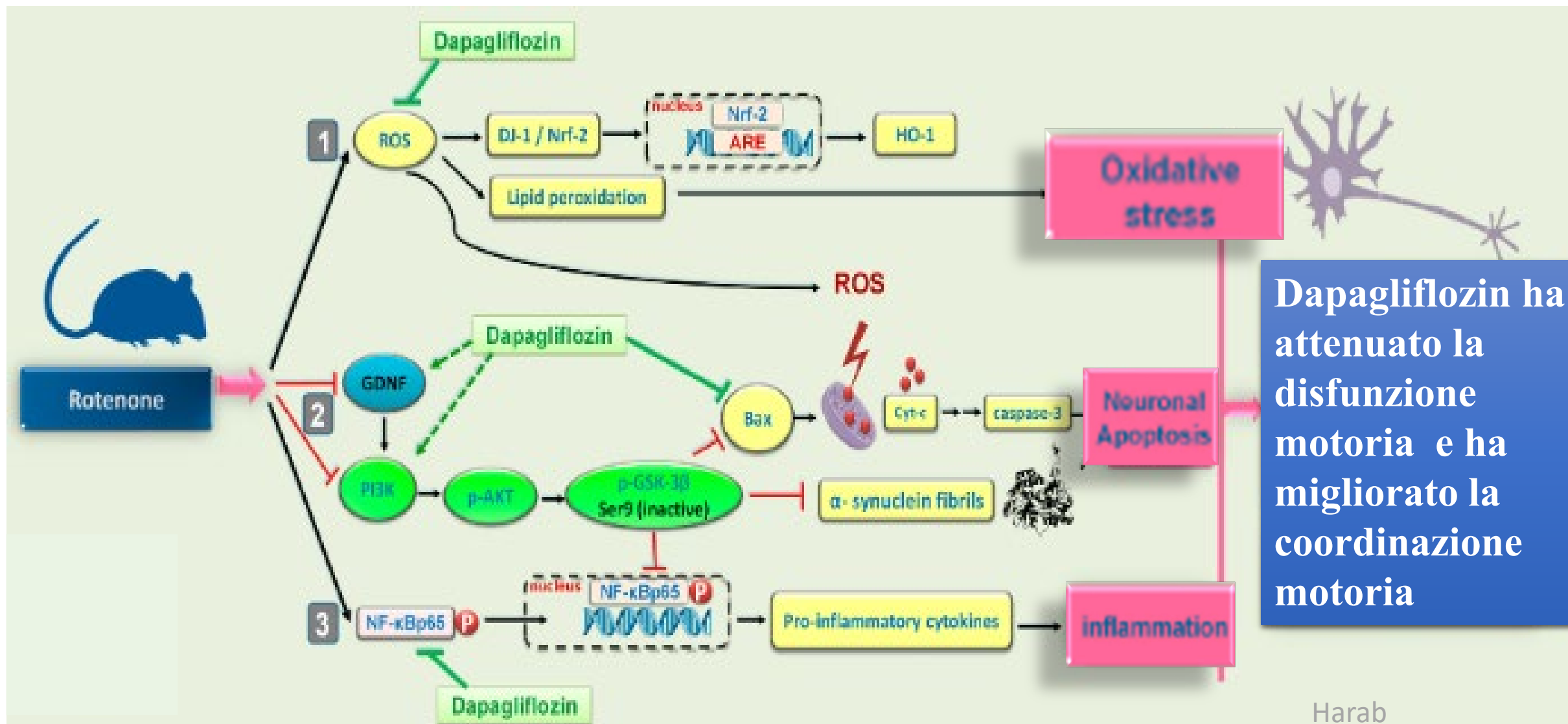
SGLT2-i and Brain



Empagliflozin migliora la performance cognitiva in modelli murini di diabete



Targeting ROS-Dependent AKT/GSK-3 β /NF- κ B and DJ-1/Nrf2 Pathways by Dapagliflozin Attenuates Neuronal Injury and Motor Dysfunction in Rotenone-Induced Parkinson's Disease Rat Model

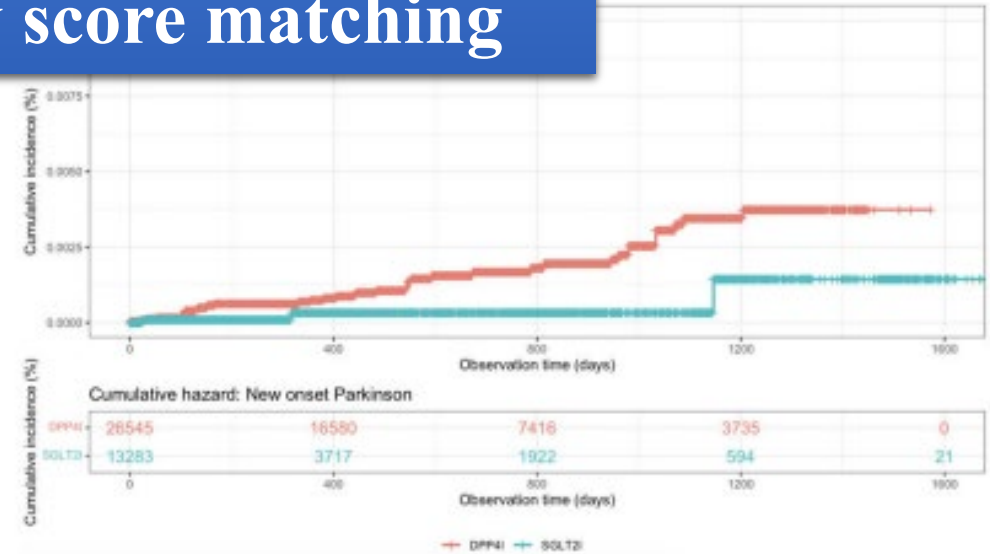
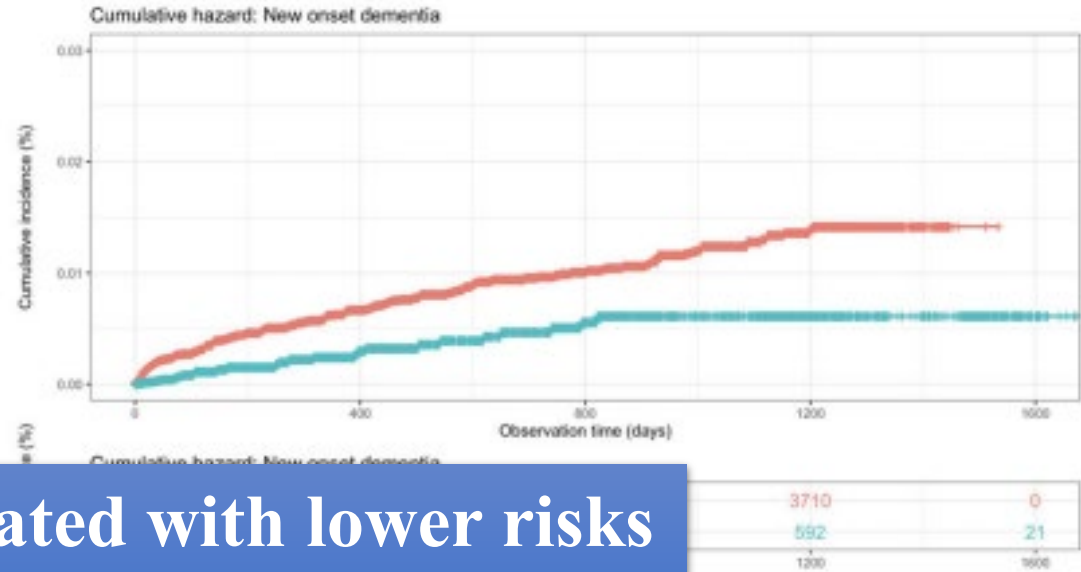
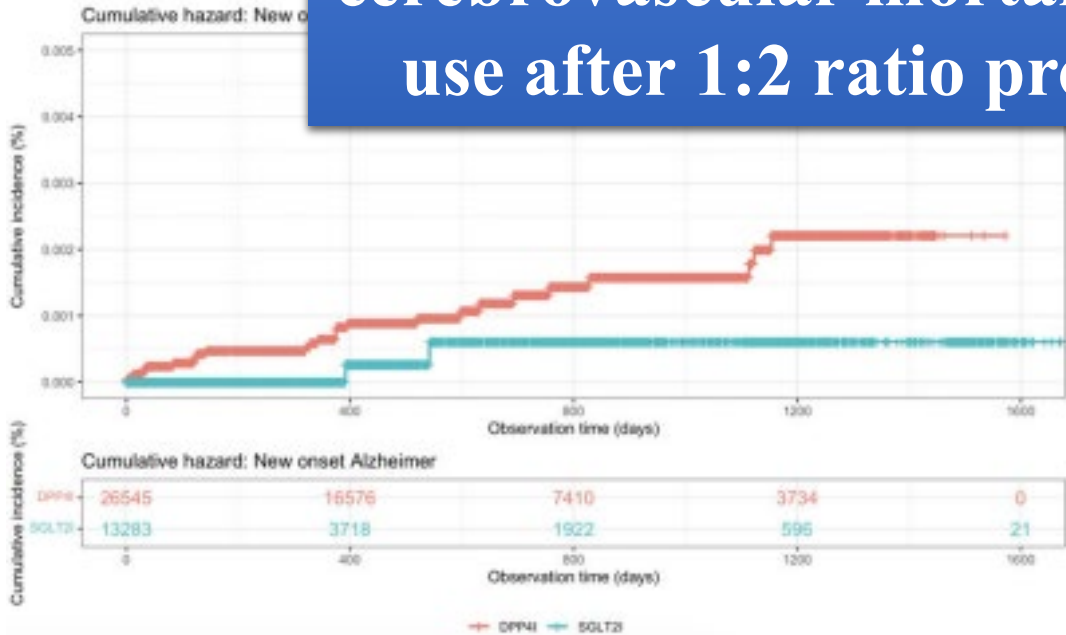


Harab

Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors vs. Dipeptidyl Peptidase-4 (DPP4) Inhibitors for New-Onset Dementia: A Propensity Score-Matched Population-Based Study With Competing Risk Analysis

Jonathan V. Mui^{1†}, Jiandong Zhou^{2†}, Sharen Lee¹, Keith Sai Kit Leung³,
Teddy Tai Loy Lee³, Oscar P. Tong⁴, Wing Tak Wong⁵

The use of SGLT2I is associated with lower risks of dementia, Parkinson’s disease, and cerebrovascular mortality compared with DPP4I use after 1:2 ratio propensity score matching



Association of Sodium–Glucose Cotransporter 2 Inhibitors With Time to Dementia: A Population-Based Cohort Study

Results

Design and Method

Residents of Ontario, Canada older than 65 years

Dementia-free



No prescription of either SGLT2 inhibitor or DPP-4 inhibitor in the past year

Cohort

New users of DPP-4 inhibitors

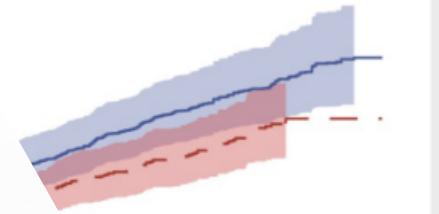


N = 70,390

Compare time to dementia between SGLT2 inhibitor and DPP-4 inhibitor use using a propensity score-weighted Cox regression model

Results

HR 0.80 (95% CI 0.71–0.89)



SGLT2 inhibitor

Dementia

SGLT2 inhibitor use was associated with a 20% lower dementia risk compared with DPP-4 inhibitor use

CONCLUSIONI

- GLP-1RA riducono il rischio di demenza per tutte le cause e demenza dovuta ad AD nei pazienti con T2D e riducono la velocità del declino della funzione cognitiva e della neurodegenerazione nei pazienti con AD;
- RWE mostrano un rischio ridotto di demenza o AD nei pazienti con T2D dopo l'esposizione a GLP-1RA;
- GLP-1RA migliorano l'infiammazione sistemica negli esseri umani, nonché l'infiammazione sistemica, la neuroinfiammazione e la salute vascolare nei modelli animali;
- Studi sull'animale con SGLT2-i sembrano mostrare effetti neuroprotettivi;
- L'uso di SGLT2-i nell'uomo, sembra ridurre l'insorgenza della demenza e AD.

Grazie per l'attenzione