Update su

SGLT2-i e GLP1 RA

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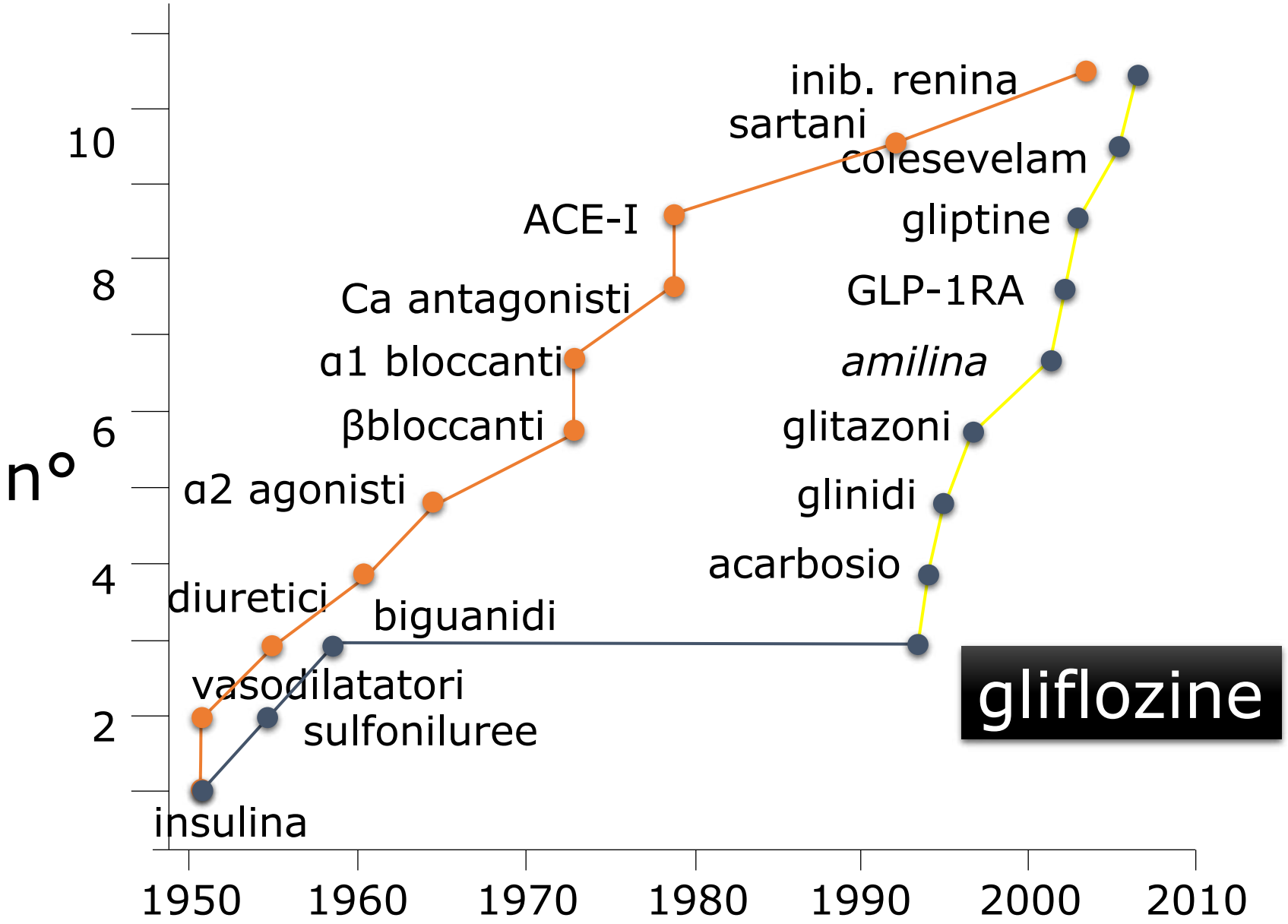
Il dr. Lelio Morviducci dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

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	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 TIMI-58	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

7th

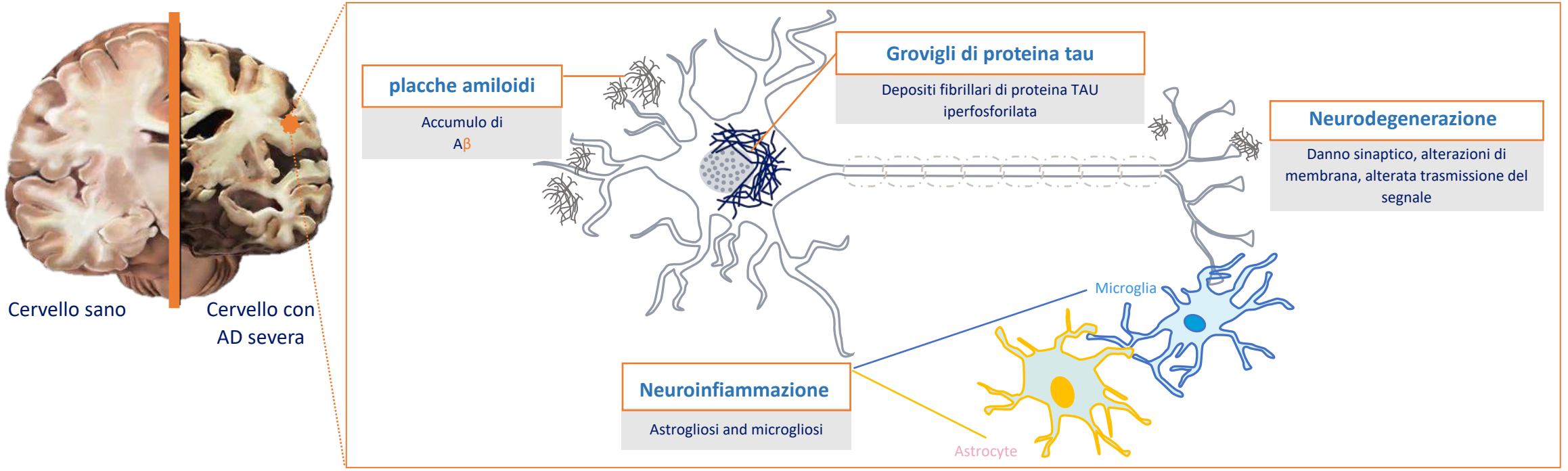
6–7 M

60–80%

~60 M

breast cancer
+
prostate cancer

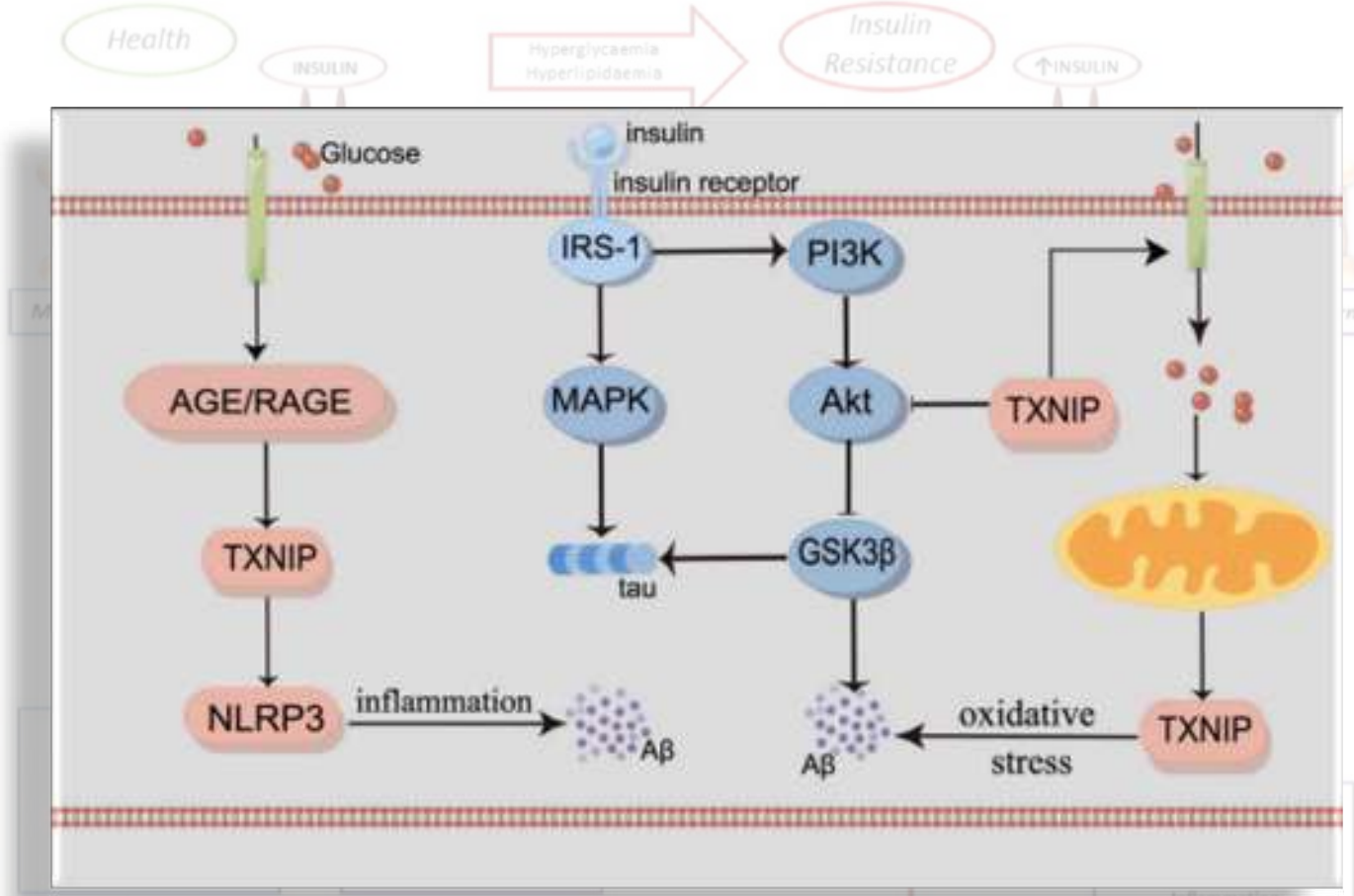
I segni distintivi dell'AD includono: placche amiloidi, depositi neurofibrillari di proteine tau e la neurodegenerazione



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.

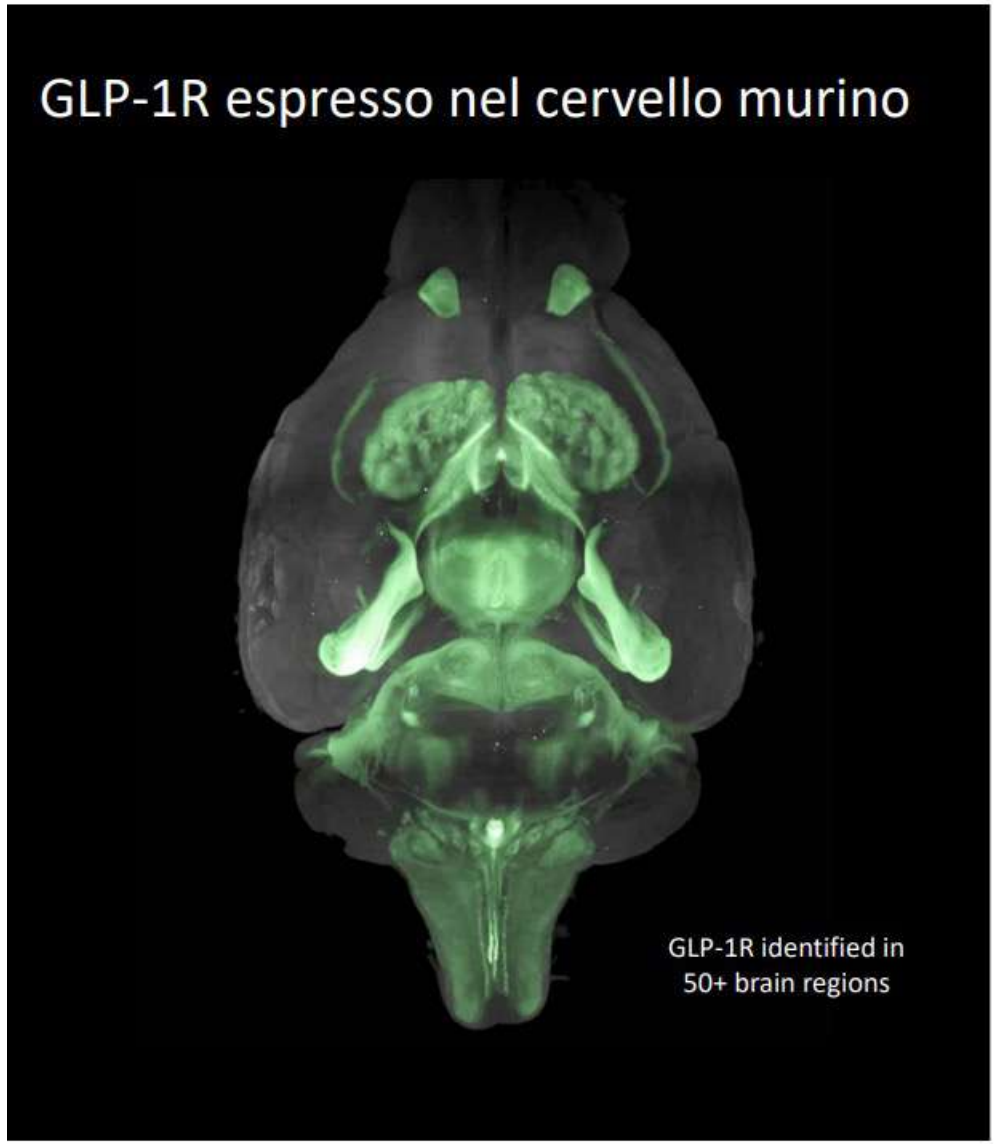
Aß, amyloid-beta; AD, Alzheimer's disease; ATN, amyloid tau neurodegeneration
1. De Castro AKA et al. Int J Comput Intell Syst 2012;4:88–89; 2. Alzheimer's Association. Alzheimers Dement 2022;18:700–789; 3. Kinney JW et al. Alzheimers Dement (N Y). 2018;4:575–590; 4. Minter MR et al. J Neurochem 2016;136:457–474

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



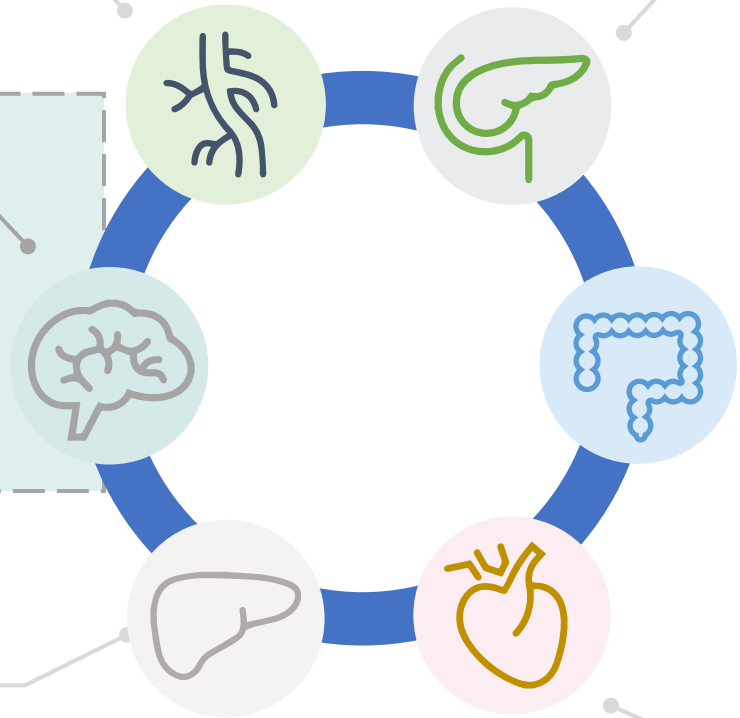
Il GLP-1R è espresso in aree dell'ippocampo coinvolte nell'apprendimento e nella memoria

- 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



Blood vessels

- ↓ Inflammation[4]
- ↑ Endothelial function[12]
- ↑ Vasodilation[12]
- ↑ Plaque stability[12]
- ↑ Blood flow[12]
- ↑ Smooth muscle proliferation[12]
- ↓ Platelet aggregation[12]

Brain

- ↓ Nonfatal stroke[13]
- ↓ Body weight[5]
- ↓ Food intake[6]
- ↓ Appetite[7]
- ↓ Glucose metabolism[8]
- ↑ Stress response[9]

Liver

- ↓ Glucose production[10]
- ↓ Conversion carbohydrate to fat[11]
- ↓ Accumulation of lipids[11]
- ↓ Retention of lipids[11]

Pancreas

- ↓ Beta-cell function[1]
- ↓ Beta-cell death[1]
- ↑ Glucagon secretion[1]
- ↑ Insulin production[1]

Intestine

- ↓ TAG secretion[15]
- ↓ Cholesterol secretion[15]
- ↓ Postprandial ApoB48[14]

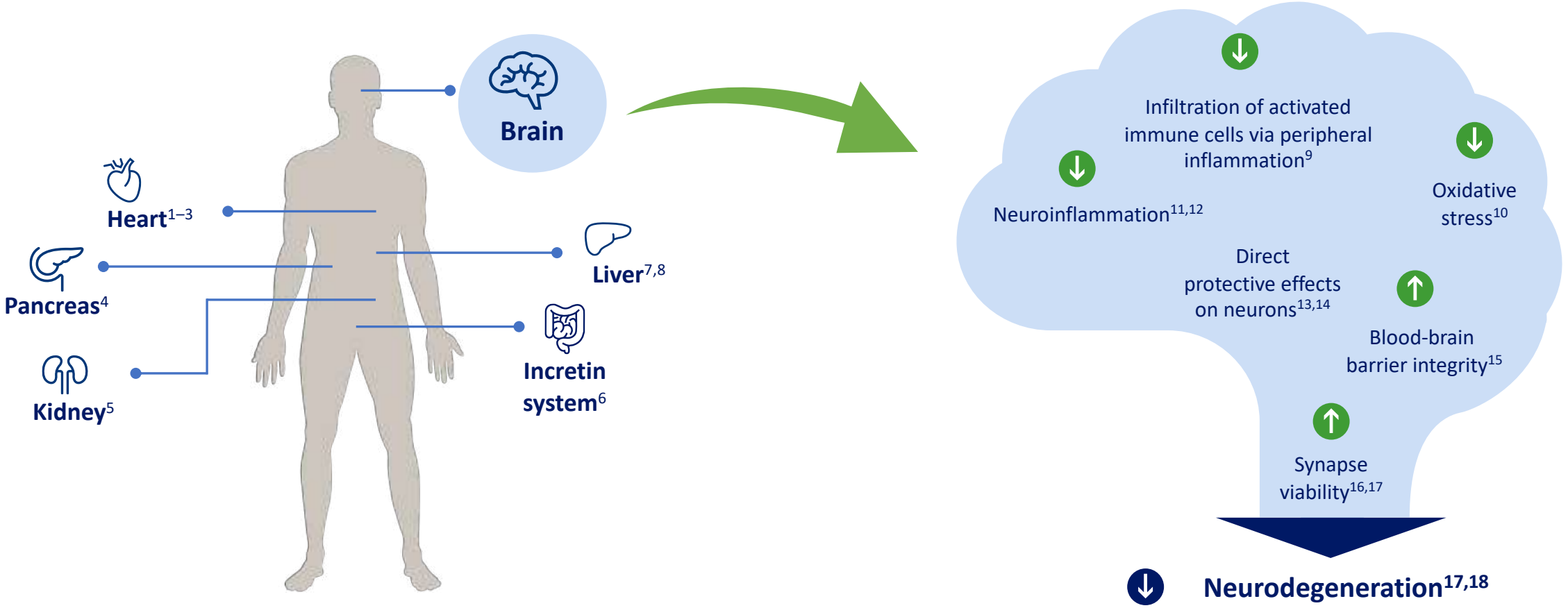
Heart

- ↓ Cardiovascular risk[2]
- ↓ Fatty acid metabolism[3]
- ↑ Cardiac function[3]
- ↓ Systolic blood pressure[3]
- ↓ Inflammation[4]
- ↓ Plaque progression[4]

APOB48, apo-lipoprotein 848; CV, cardiovascular; FFA, free fatty acids; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; TAG triglyceride

1. Campbell JE, Drucker DJ. Cell Metab 2013;17:819–837; 2. Marso SP et al. N Engl J Med 2016;375:311–322; 3. Ryan D, Acosta A. Obesity 2015;23:1119–1129; 4. Hogan AE et al. Diabetologia. 2014;57:781–784; 5. Baggio LL, Drucker DJ. J Clin Invest 2014;124:4223–4426; 6. Bagger JI et al. Clin Endocrinol Metab 2015;100:4541–4552; 7. Flint A et al. J Clin Invest 1998;101:515–520; 8. Alvarez E et al. J Neurochem 2005;94:798–806; 9. Grieco M et al. Front Neurosci 2019;13:1112; 10. Armstrong MJ et al. J Hepatol 2016;64:399–408; 11. Armstrong MJ et al. Lancet 2016;387:679–690; 12. Drucker DJ. Cell Metab 2016;24:15–30; 13. Marso SP et al. N Engl J Med 2016;375:1834–1844; 14. Dahl K et al. Diabetes Obes Metab 2021;23:1594–1603; 15. Hsieh J et al. Diabetologia 2010;53:552–561; 16. Xie Z et al. Front Mol Neurosci 2021;14:750726

GLP-1RAs



AD, Alzheimer's disease; GLP-1RA, glucagon-like peptide-1 receptor agonist
1. Marso 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. Geji 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
Preclinical studies	***Animal model***		
AD features			
Plaque load	APP/PS1/tau mice	Liraglutide	Reduction of plaque load
	5xFAD mice	Liraglutide	Reduction of plaque load
	APP/PS1 mice	Lixisenatide	Reduction of plaque load
	3xTg-AD mice	Exendin-4	Reduction of plaque load
Tau phosphorylation	APP/PS1/tau mice	Liraglutide	Reduction of neurofibrillary tangles
	hTauP301L mice	Liraglutide	Reduced Tau phosphorylation
	Aβ injection in mice	Liraglutide	Reduced Tau phosphorylation
	APP/PS1 x db/db mice	Liraglutide	Reduced Tau phosphorylation
	Streptozotocin injection in mice	Dulaglutide	Reduced Tau phosphorylation
Cognitive and memory performance	Aβ injection in mice	Liraglutide	Improved cognitive impairment
	Aβ injection in rats	Lixisenatide	Improved spatial memory
	Streptozotocin injection in mice	Dulaglutide	Improved memory ability
Other	Aβ injection in non-human primates	Liraglutide	Reduced synaptic loss
PD features			
Dopaminergic neuronal loss	6-OHDA rat model	Liraglutide	No influence on dopaminergic neuronal loss
	6-OHDA rat model	Exendin-4	Neurogenesis
	6-OHDA rat model	Exendin-4′	Reduced lesions
Motor performance	MPTP mouse model	Liraglutide	Improved motor control
	MPTP mouse model	Lixisenatide	Improved motor control
α-synuclein aggregation	Preformed fibrils injection in striatum of human A53T α-synuclein mice	Exendin-4 (NLY01)	Reduced loss of dopaminergic neurons and improved motor performance
	Preformed fibrils injection in the olfactory bulb of C57BL/6J mice	Exendin-4	No significant reduction of α-synuclein aggregation

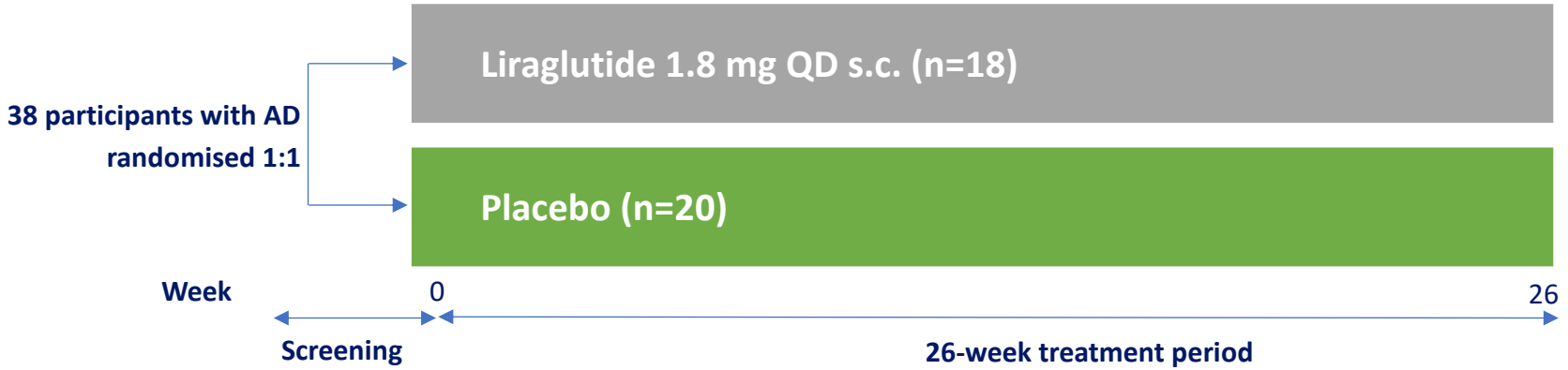
Monti G. Cells 2022, 11(13), 2023

NCT01469351

Liraglutide vs placebo in patients with mild/moderate AD

Key inclusion criteria

- AD diagnosis
- MMSE score of 18–21
- Aged >50 to <80 years
- Caucasian
- No diabetes mellitus



Key endpoints

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

Key findings

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

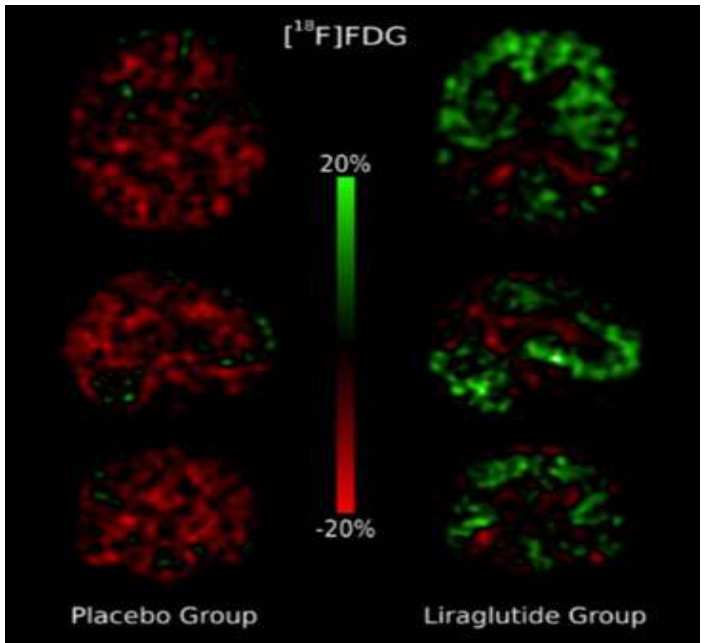
[11C]PIB, carbon-11 labelled Pittsburgh Compound B; [18F]FDG, fluoro-2-deoxyglucose; Aß, amyloid beta; AD, Alzheimer's disease; CMR_{glc}, cerebral metabolic rate of glucose; MMSE, Mini-Mental State Examination; PET, positron emission tomography; QD, once daily; s.c., subcutaneous

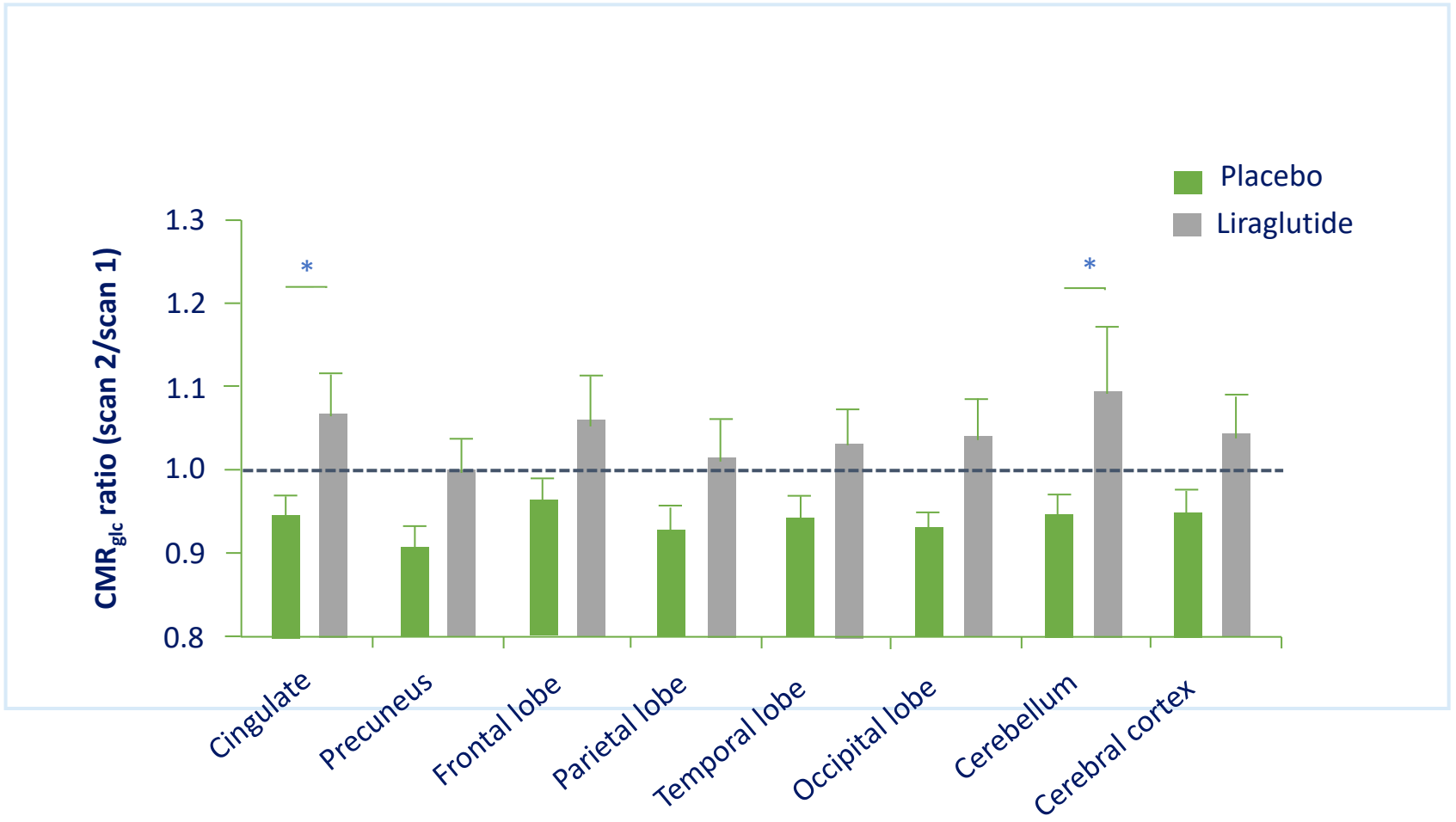
Gejl M et al. Front Aging Neurosci 2016;24:108

NCT01469351

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

Un calo di CMRglc 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, Hertzel 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 Pogosova, Peter J Raubenheimer, Jonathan E Shaw, Wayne H-H Sheu, Theodora Temelkova-Kurktschiev*

Lancet Neurol 2020; 19: 582–90

See Comment page 559

*Joint first authors

Summary

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

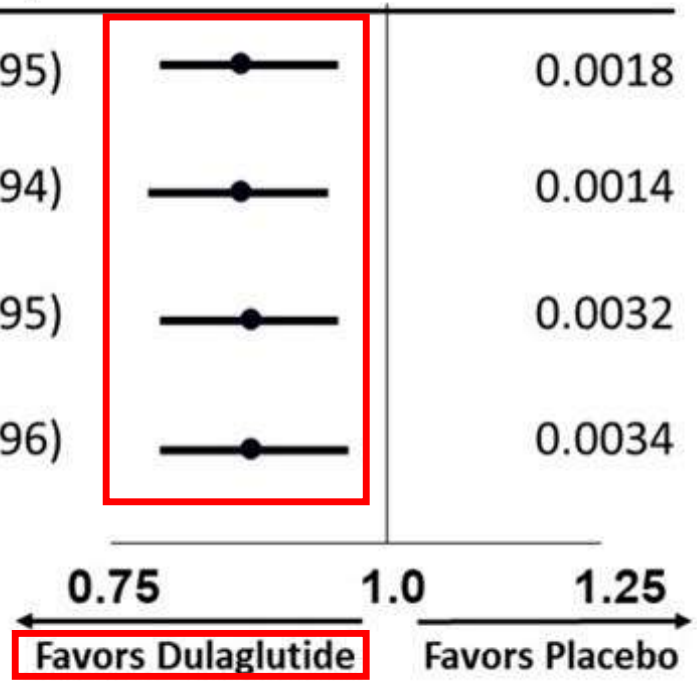
$$\frac{\textit{Pt's score ai vari tempi} - \textit{Score della media nazionale al basale}}{\textit{Standard deviation (SD) dello Score della media nazionale al basale}}$$

- 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



NCT03707171

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/m^2

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

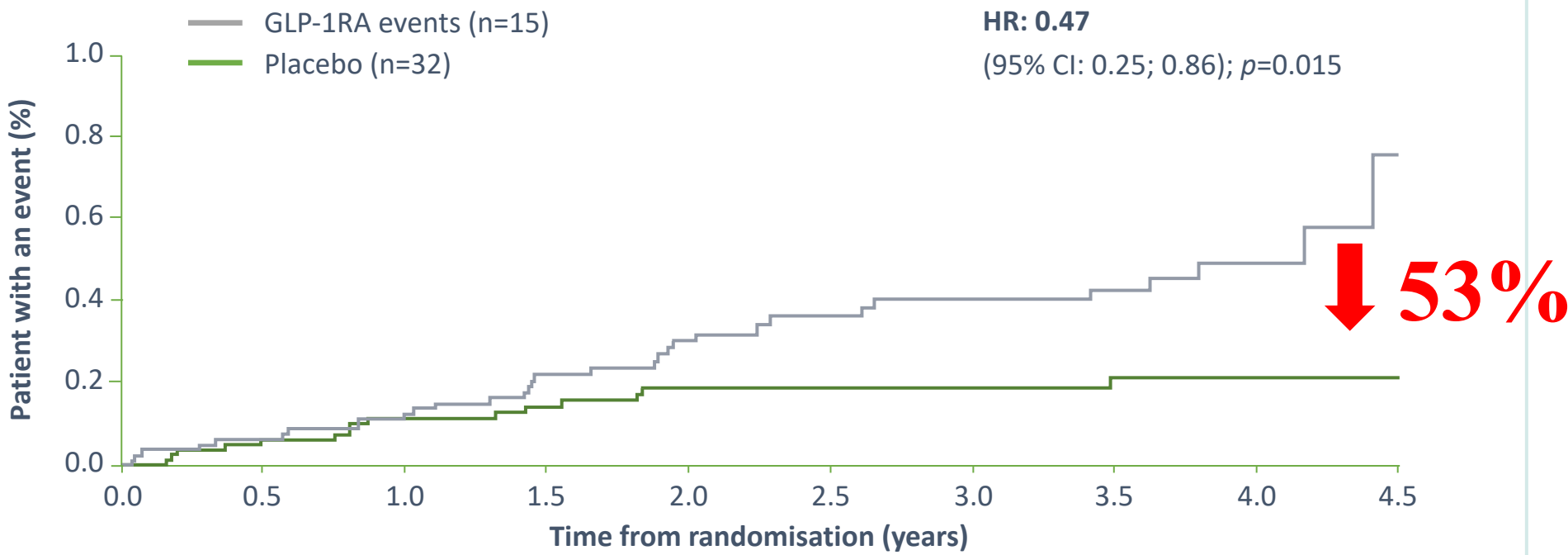
Cognitive scales were: Mini-Mental State Examination, Total learning and Animal Naming Test
BMI, body mass index; HbA1c, glycated haemoglobin; T2D, type 2 diabetes
Li Q et al. J Am Heart Assoc 2021;10:e020734

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



CI, confidence interval; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; s.c., subcutaneous; SUSTAIN, Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes; T2D, type 2 diabetes

Nørgaard CH et al. Alzheimers Dement 2022;8:e12268

Quattro studi RWE hanno mostr[illegible] ridotto di demenza o AD con l'esposizione a C[illegible]

469,862 people [illegible]
Nørgaard CH et al. D[illegible]

- **11%** lower risk exposure

on monotherapy

[illegible]lutide* exposure

178,403 people with T2
Wium-Andersen et al. Danish registry

- **42%** lower odds of demen

[illegible]2012–2018)

[illegible]base

[illegible]mentia after >2 years of

[illegible]re

*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 [illegible]
1. Nørgaard CH et al. Alzheimers Dement 2022;8:e12268; 2. Wium-Andersen IK et al. Eur J Endocrinol 2019;18[illegible]

[illegible]de-1 receptor agonist; RWE, real-world evidence; T2DM, type 2 diabetes mellitus
[illegible]s Other Demen 2020;35:1–11

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

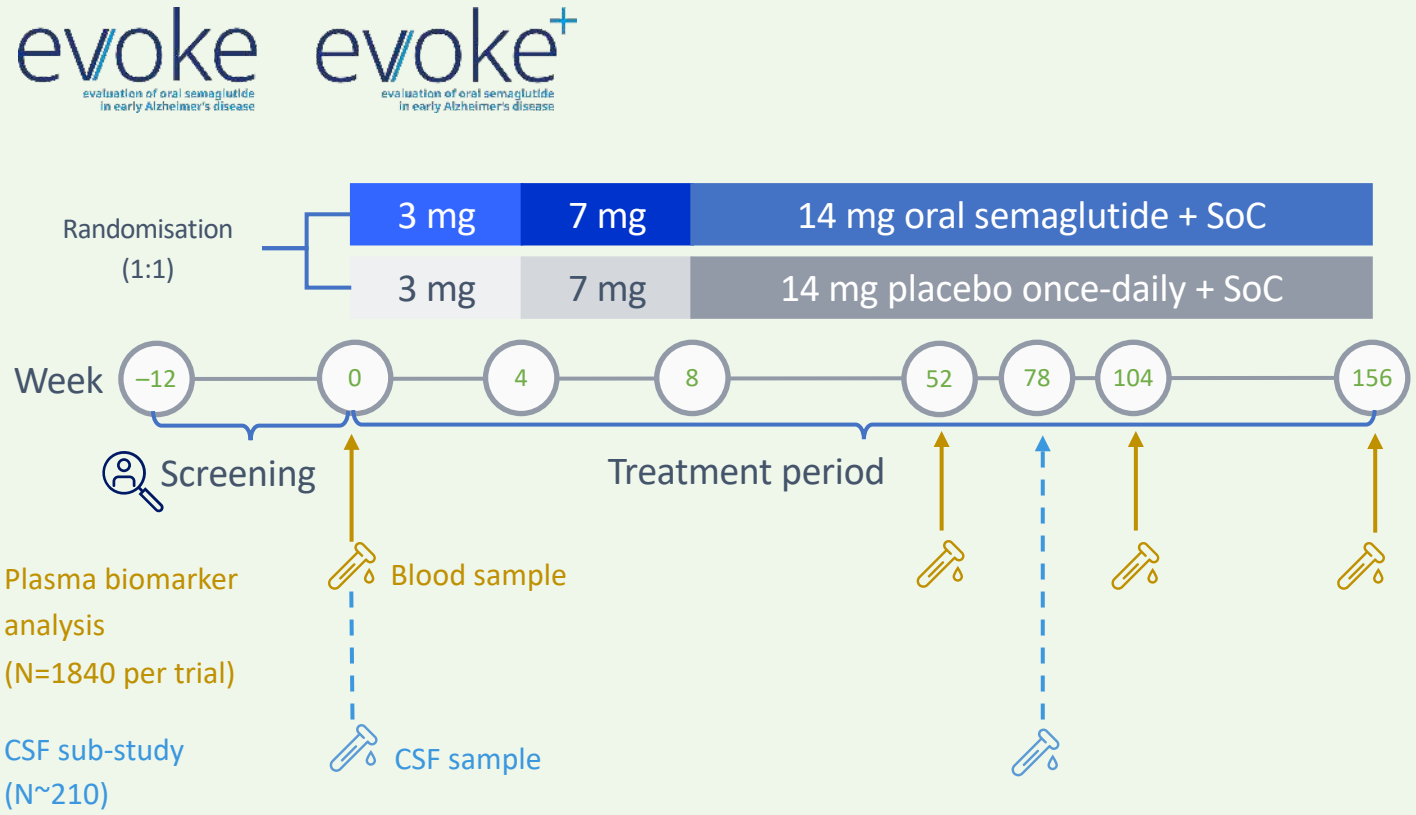
1840 patients in each trial

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)

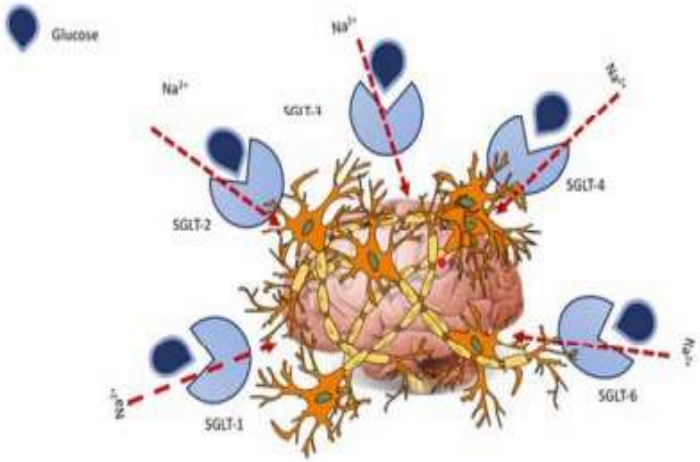
800+ sites in 40 countries



CSF, cerebrospinal fluid; MCI, mild cognitive impairment; PET, positron emission tomography; SoC, standard of care

1. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04777396 (accessed August 2021); 2. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04777409 (accessed August 2021)

SGLT2-i and Brain



SGLT2i

EMPAGLIFLOZIN | DAPAGLIFLOZIN | CANAGLIFLOZIN | ERTUGLIFLOZIN | SOTAGLIFLOZIN

POTENTIAL DIRECT and INDIRECT EFFECTS

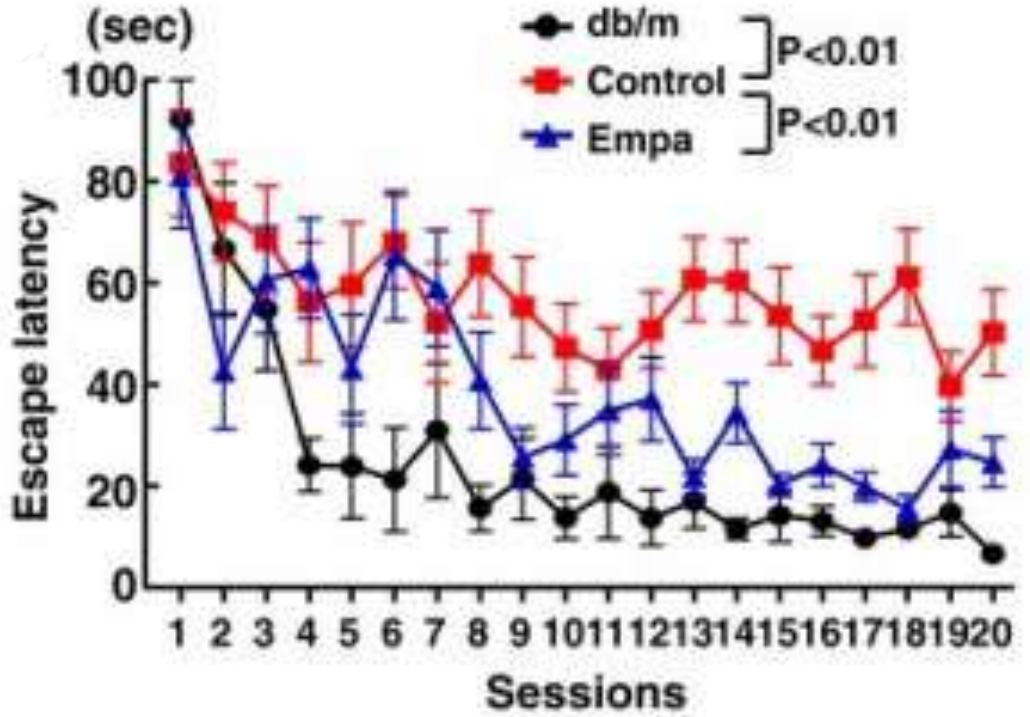
- OXIDATIVE STRESS
- NEUROINFLAMMATION
- AMYLOID BRAIN LEVELS
- BRAIN DAMAGE

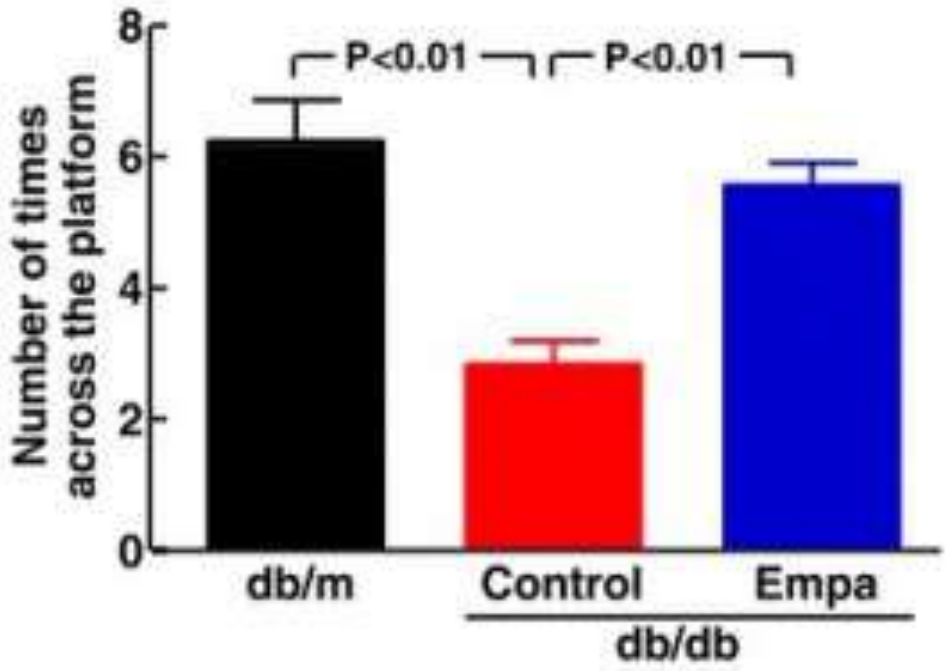
- VASCULAR ASPECTS
- INSULIN SIGNALING
- MITOCHONDRIAL FUNCTION
- mTOR PATHWAY

COGNITIVE IMPAIRMENT REDUCTION

Rizzo MR, Pharmacological Research 176 (2022)

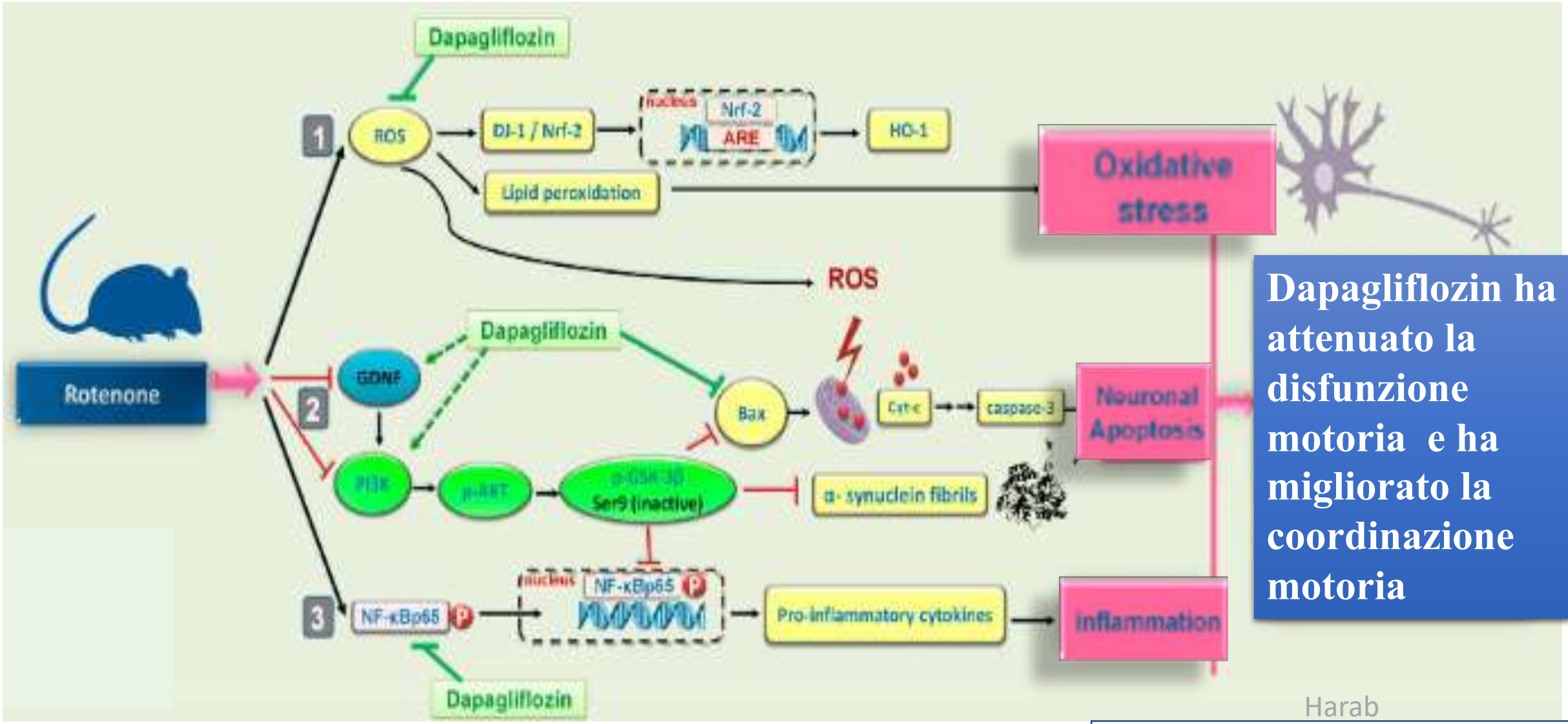
Empagliflozin migliora la performance cognitiva in modelli murini di diabete





Lin B. Cardiovasc Diabetol. (2014) Oct 26;13:148

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



Dapagliflozin ha attenuato la disfunzione motoria e ha migliorato la coordinazione motoria

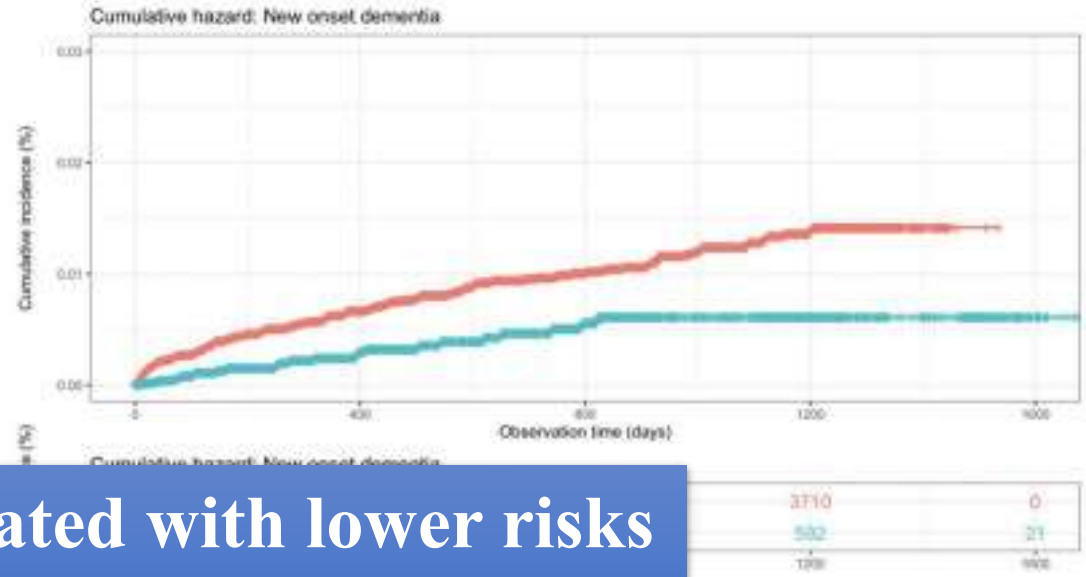
Harab

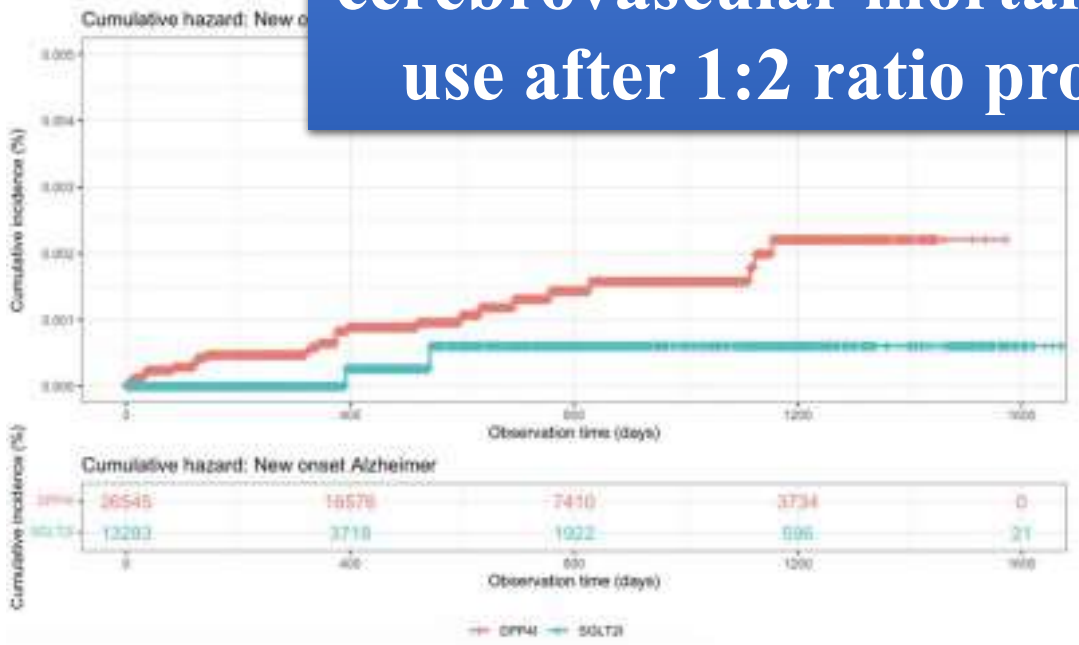
HH. ACS Chem. Neurosci. 2021, 12, 6

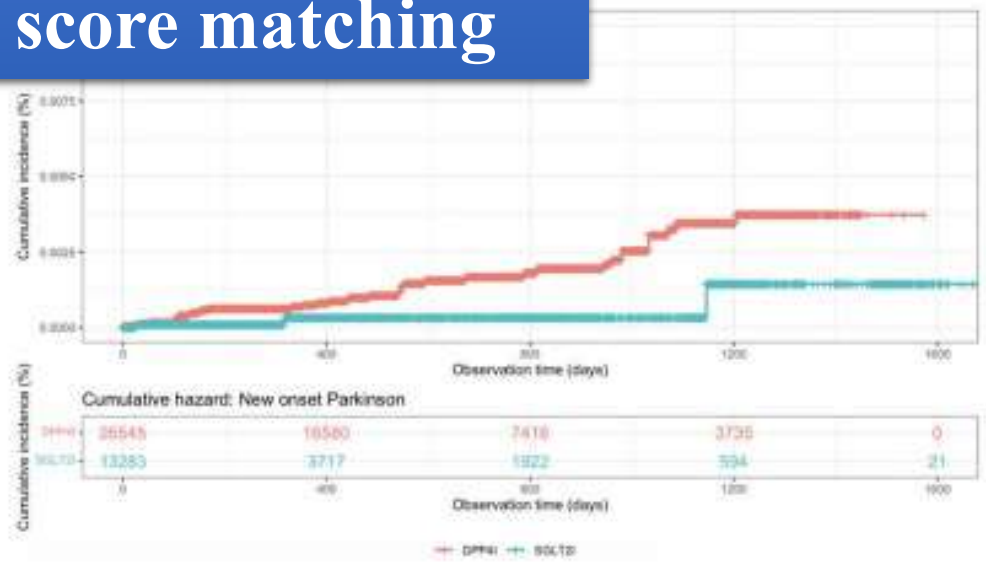
Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors vs. Dipeptidyl Peptidase-4 (DPP4) Inhibitors for New-Onset Dementia: A Propensity Score-Matched Population-Based Study With Competing Risk Analysis

Jonathan V. Mui[1†], Jiandong Zhou[2†], Sharen Lee[1], Keith Sai Kit Leung[3], Teddy Tai Loy Lee[3], Oscar H… Tong Liu[4], Wing Tak Wong[5]…

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 Cotr… P Inhibitors With Time to Dementia: A Por… ort Study

Design and Method…

Residents of Ontario, Canada old…

Dementia-free

No prescription of eit… in the past year

Co…

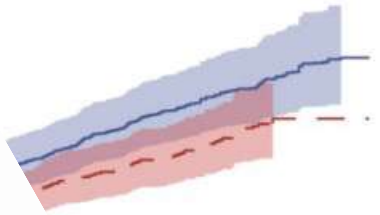
New users of DPP-4 inhibitors

N = 70,390

Compare time to dementi… a propensity score–weighted Cox regr…

Results

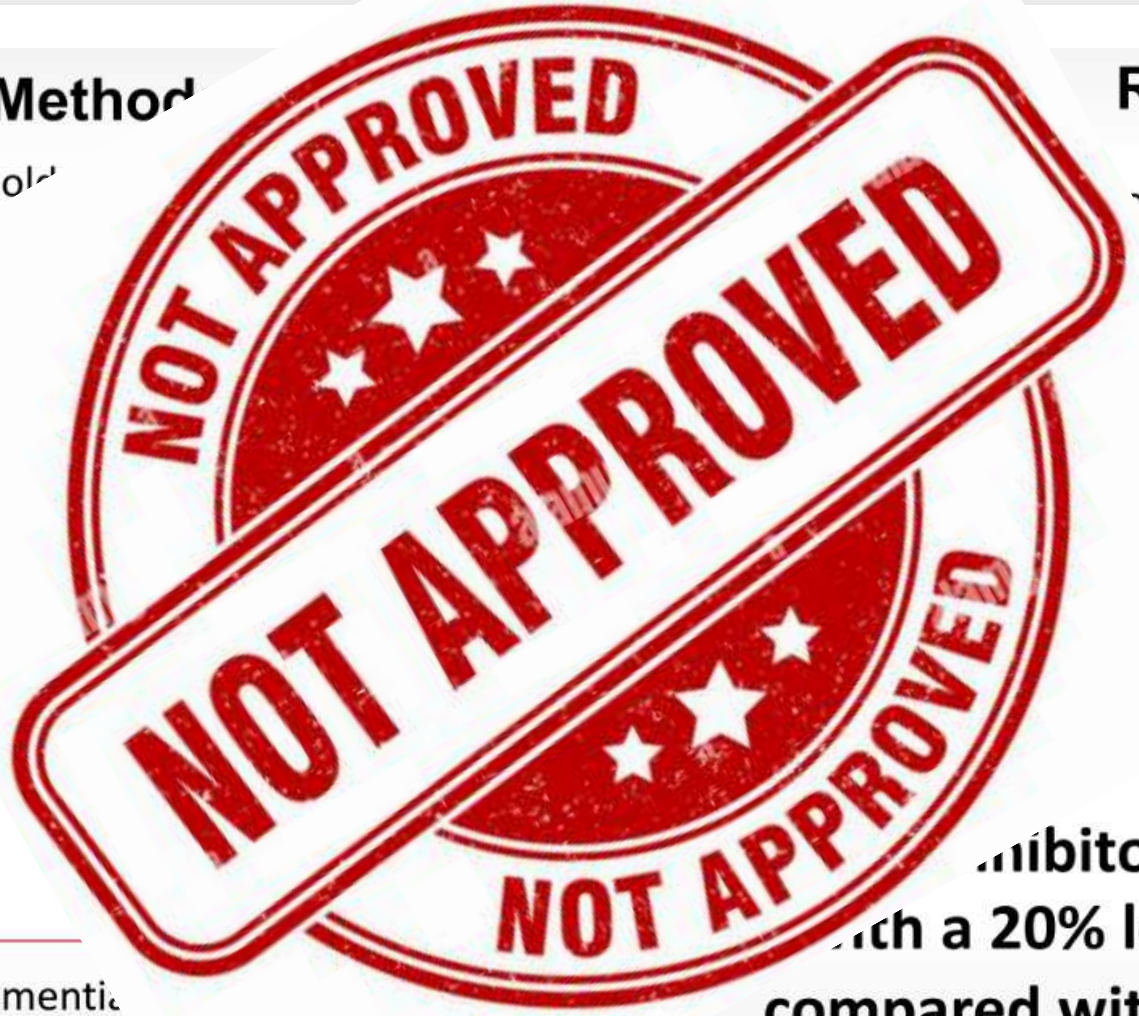
…80 (95% CI 0.71–0.89)



…inhibitor

…dementia

…nibitor use was associated …th 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