



*CONGRESSO REGIONALE
AMD-SID
Abruzzo /Molise
12 Novembre 2022*

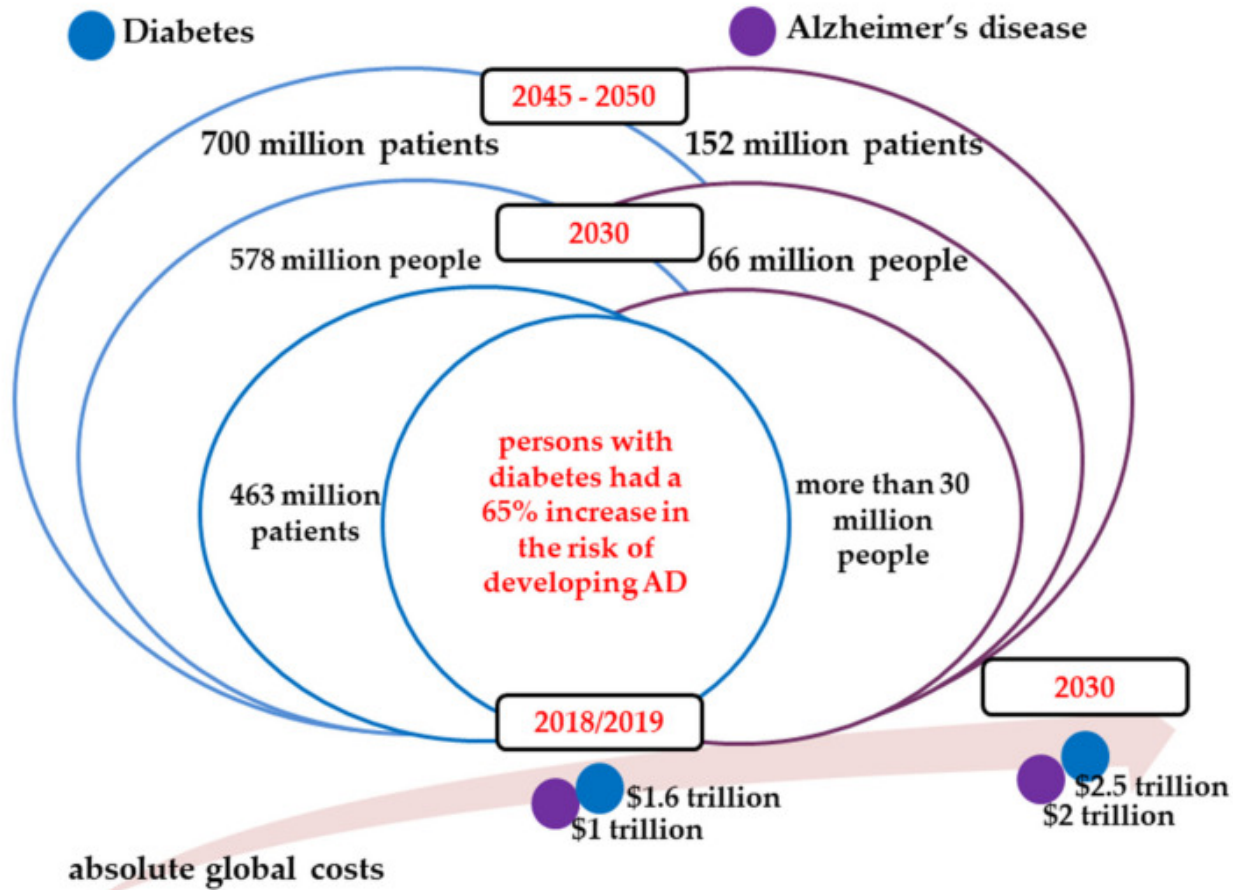
Terapia del Diabete Mellito Tipo 2 oltre la glicemia: le promesse dei nuovi farmaci sul SNC

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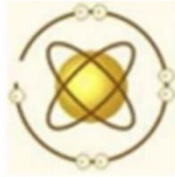
Diabete e Demenza: epidemiologia



Diabete e Sistema Nervoso Centrale: PARTNERS IN CRIME?



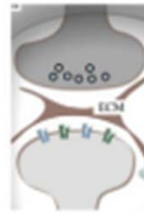
Ischemia-induced
Changes



Mitochondrial
Dysfunction
Oxidative Stress



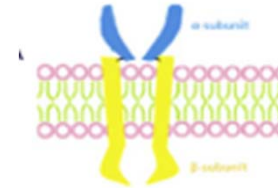
DJH
Dffxp xøwlrq



Altered
Synaptic Plasticity



Neuronal
Damage and Apoptosis



Ip sdlhg F hñeudo
Iqvxcl V lj qdølj



Altered
Amiloid metabolism

NEURODEGENERAZIONE

Modified from Muscogiuri G. Trends in Endocrinology & Metabolism 2017

Agenda

Le promesse dei nuovi farmaci sul SNC

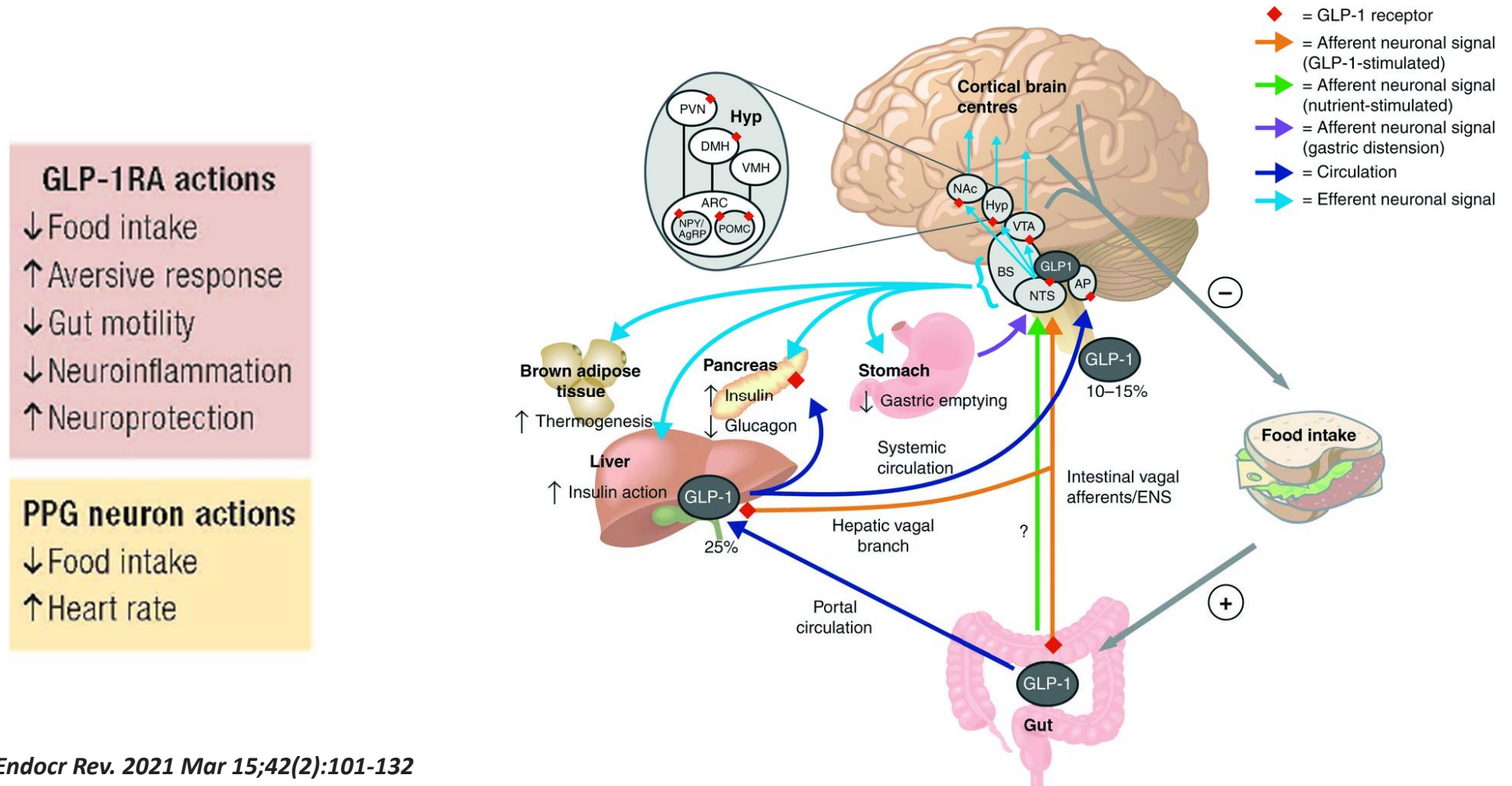


GLP1 agonisti

SGLT2 inibitori

Doppi agonisti recettoriali GLP1-GIP

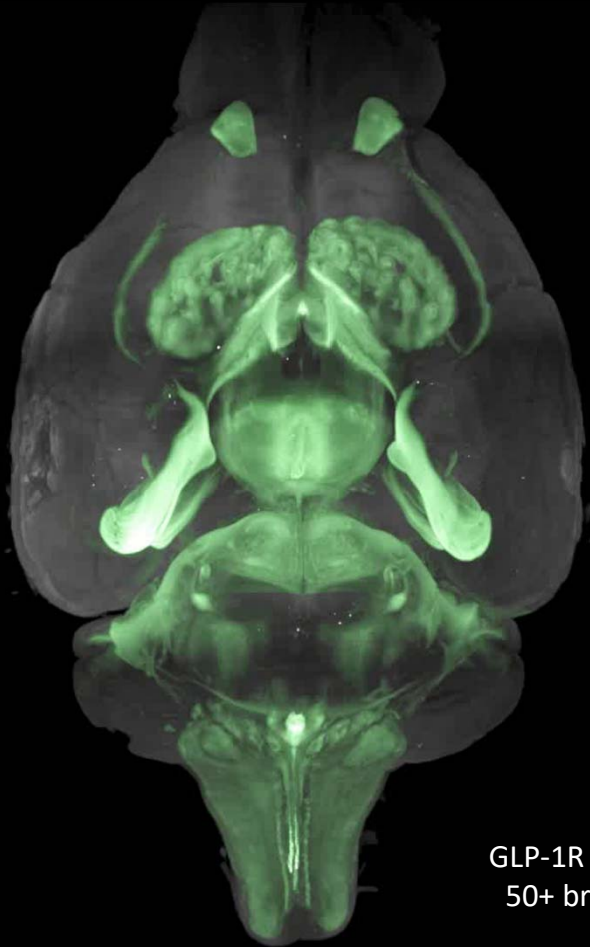
GLP-1 RA e Sistema Nervoso Centrale



B A McLean *Endocr Rev.* 2021 Mar 15;42(2):101-132

L van Bloemendaal et al.; *Journal of Endocrinology* (2014) 221, T1-T16

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

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
	A β 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	A β injection in mice	Liraglutide	Improved cognitive impairment
	A β injection in rats	Lixisenatide	Improved spatial memory
	Streptozotocin injection in mice	Dulaglutide	Improved memory ability
Other	A β 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	Exendin-4 (NLY01)	Reduced loss of dopaminergic neurons and improved motor performance
	A53T α -synuclein mice	Exendin-4	No significant reduction of α -synuclein aggregation
	Preformed fibrils injection in the olfactory bulb of C57BL/6J mice		

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



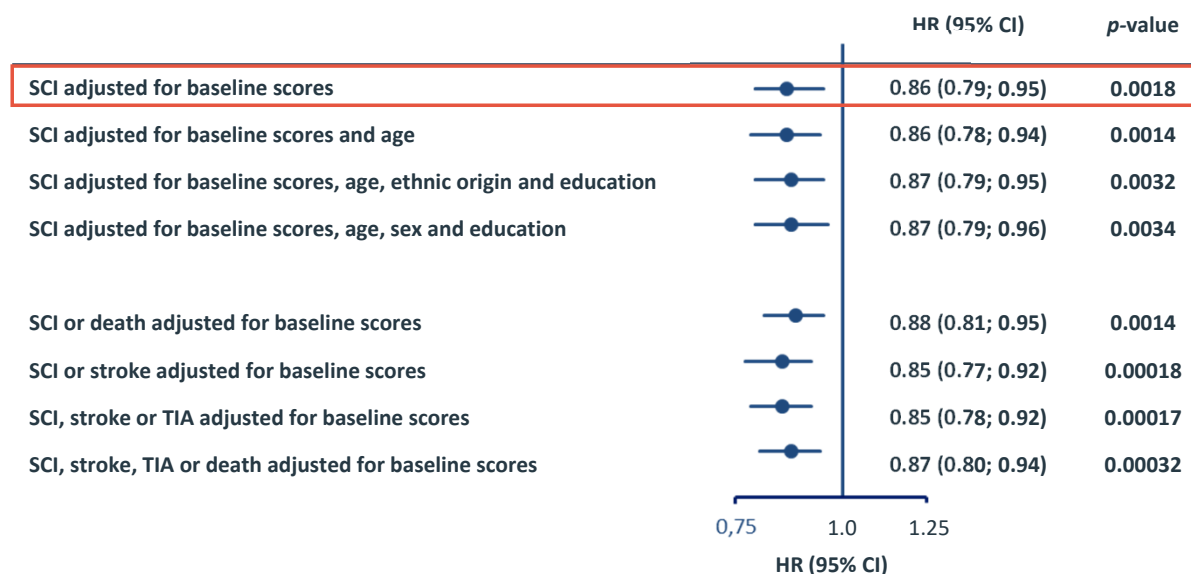
Effect of dulaglutide on cognitive impairment in type 2 diabetes: an exploratory analysis of the REWIND trial

Tali Cukierman-Yaffe*, Hertz C Gerstein*, Helen M Colhoun, Rafael Diaz, Luis-Emilio García-Pérez, Mark Lakshmanan, Angelyn Bethel, Denis Xavier, Jeffrey Probstfeld, 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

- 9901 partecipanti
- Durata mediana del follow up 5.4 anni

Dulaglutide riduce il decadimento cognitivo del 14% rispetto al placebo (HR 0.86, 95% CI 0.79–0.95; p=0.0018).

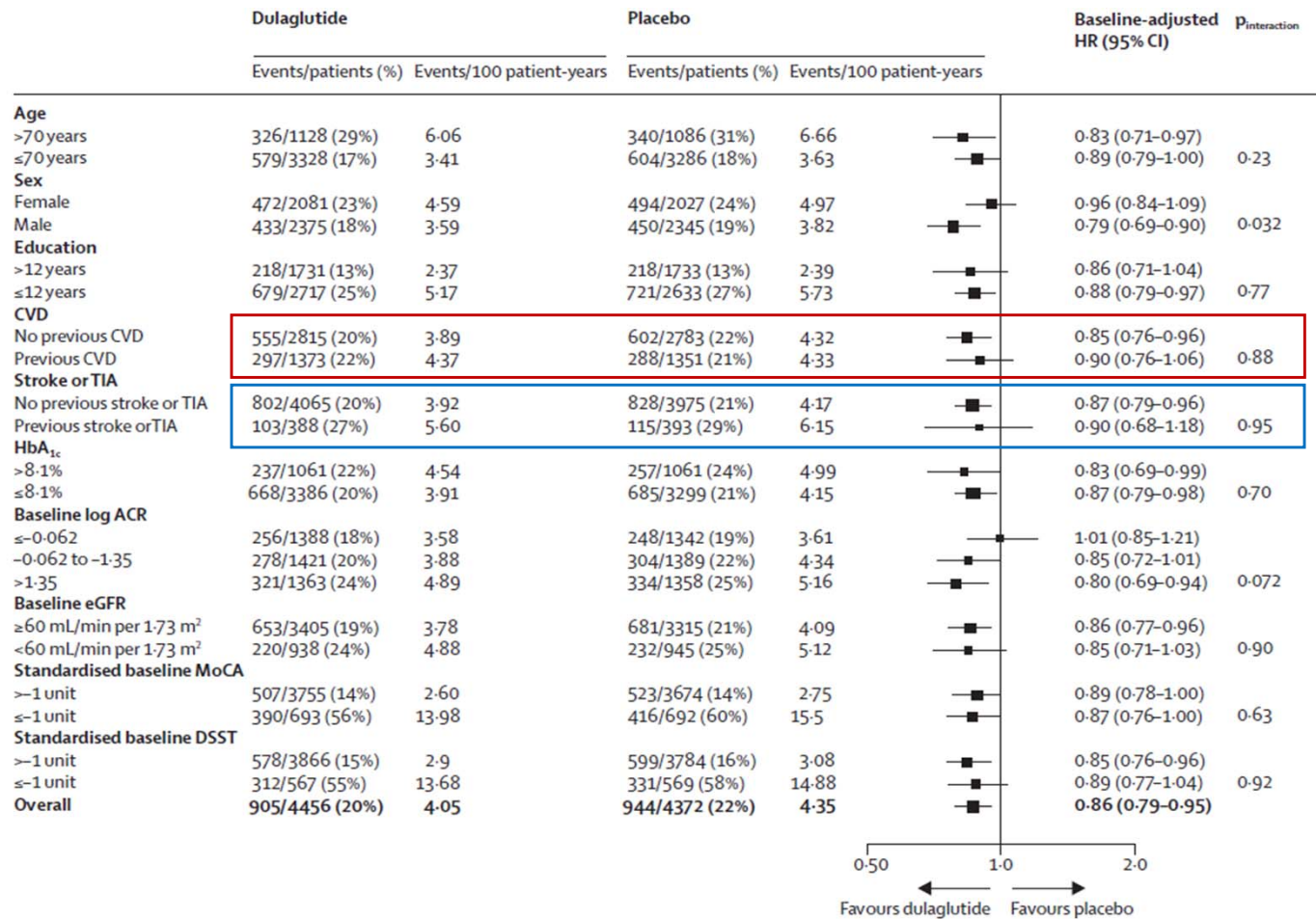
Risk of substantive cognitive impairment, adjusted for baseline standardised MoCA and DSST scores



CI, confidence interval; DSST, Digit Symbol Substitution Test; HR, hazard ratio; MoCA, Montreal Cognitive Assessment; SCI, substantive cognitive impairment; SD, standard deviation; T2D, type 2 diabetes; TIA, transient ischaemic attack

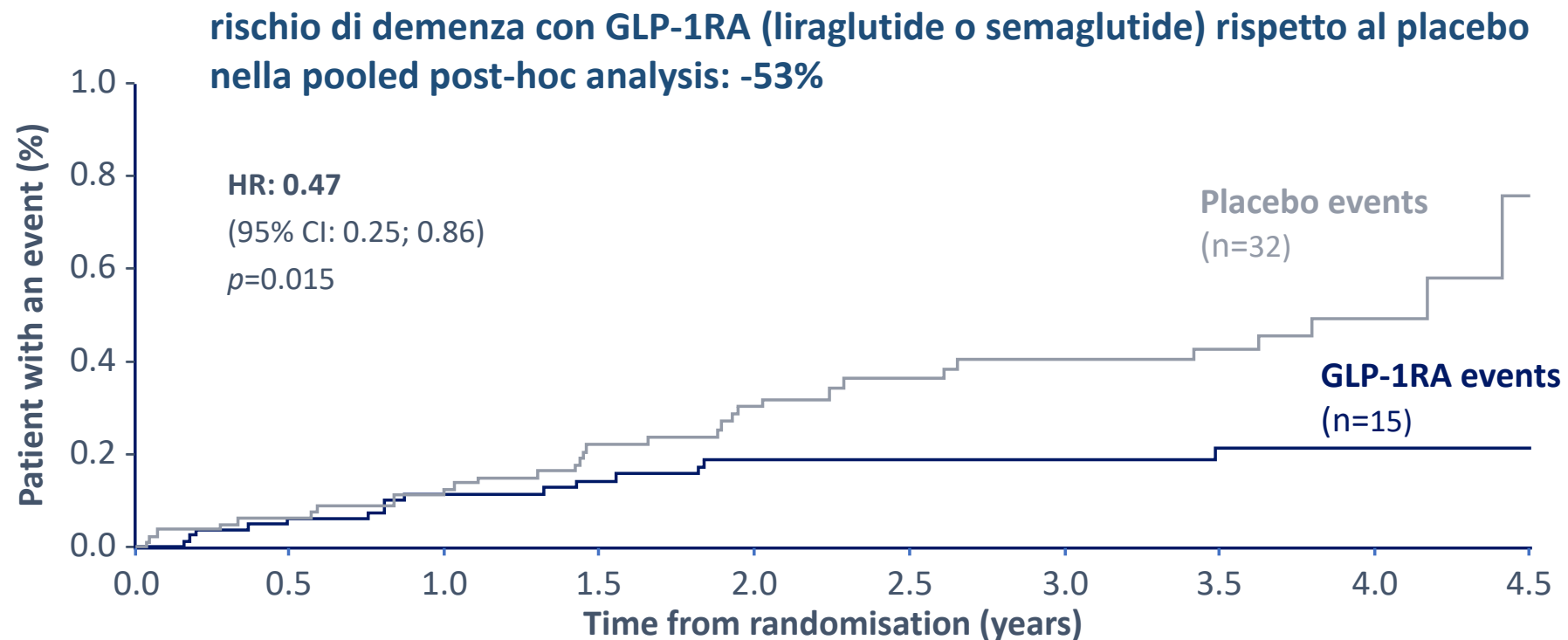
Cukierman-Yaffe T et al. Lancet Neurol 2020;19:582–590

Dulaglutide e decadimento cognitivo: analisi esplorativa dello studio REWIND



Dulaglutide mostra un impatto positivo su diversi indicatori di declino cognitivo indipendentemente dalla storia di ictus o malattia cardiovascolare

Diagnosi di Demenza nei soggetti trattati con liraglutide o semaglutide nei CVOTs



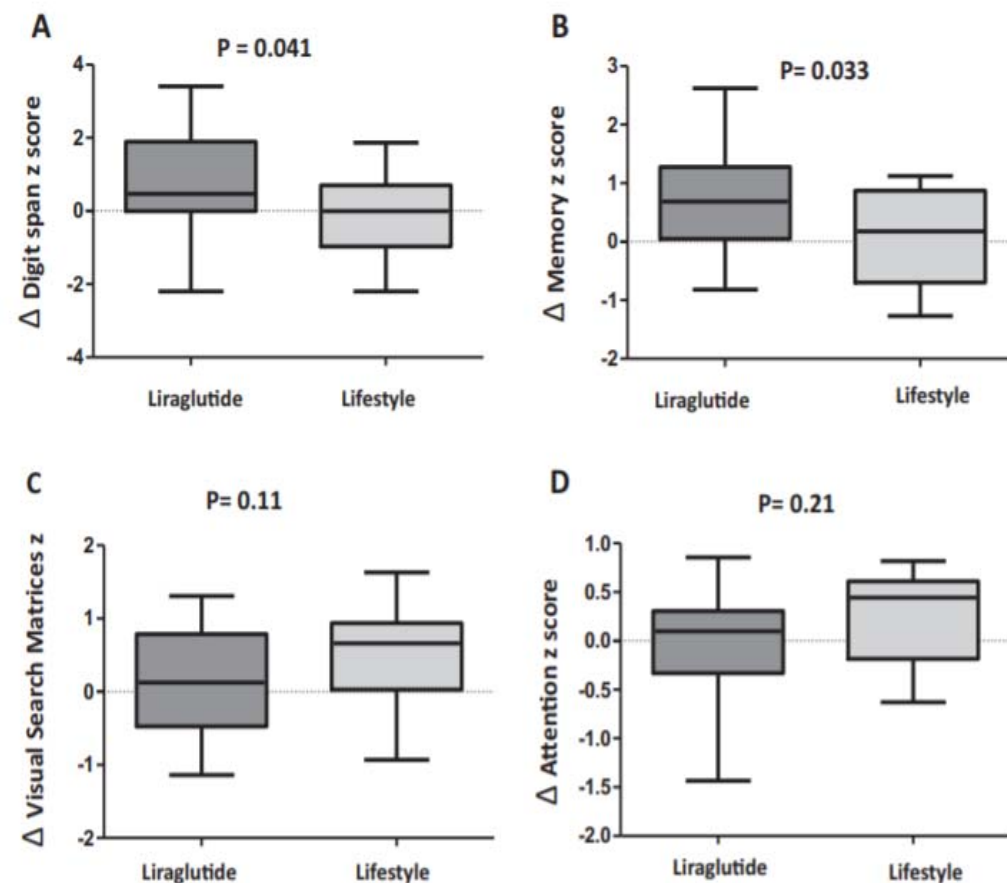
CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio
Nørgaard CH, Alzheimers Dement (NY). 2022; 8(1): e12268.



Liraglutide improves memory in obese patients with prediabetes or early type 2 diabetes: a randomized, controlled study

Francesco Vadini¹ · Paola G. Simeone² · Andrea Boccatonda² · Maria T. Guagnano² · Rossella Liani² · Romina Tripaldi² · Augusto Di Castelnuovo³ · Francesco Cipollone² · Agostino Consoli² · Francesca Santilli²

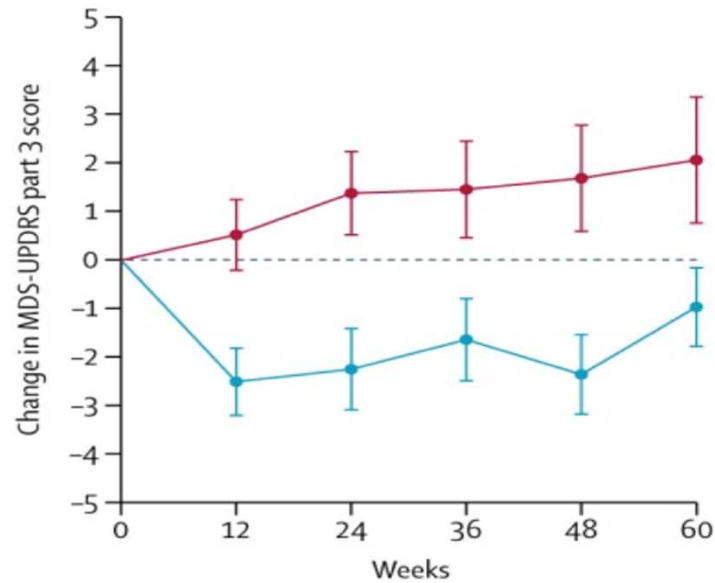
Il miglioramento della memoria a breve termine (mean Digit Span Z score from -0.06 to 0.80, $p = 0.024$) e dello score composito z-score (mean memory z-score from -0.67 to 0.032, $p = 0.0065$) è stato osservato solo nei soggetti in terapia con liraglutide nonostante una perdita di peso ed un controllo glicemico sovrapponibili nei soggetti di controllo.



Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial

Dilan Athauda, MRCP,

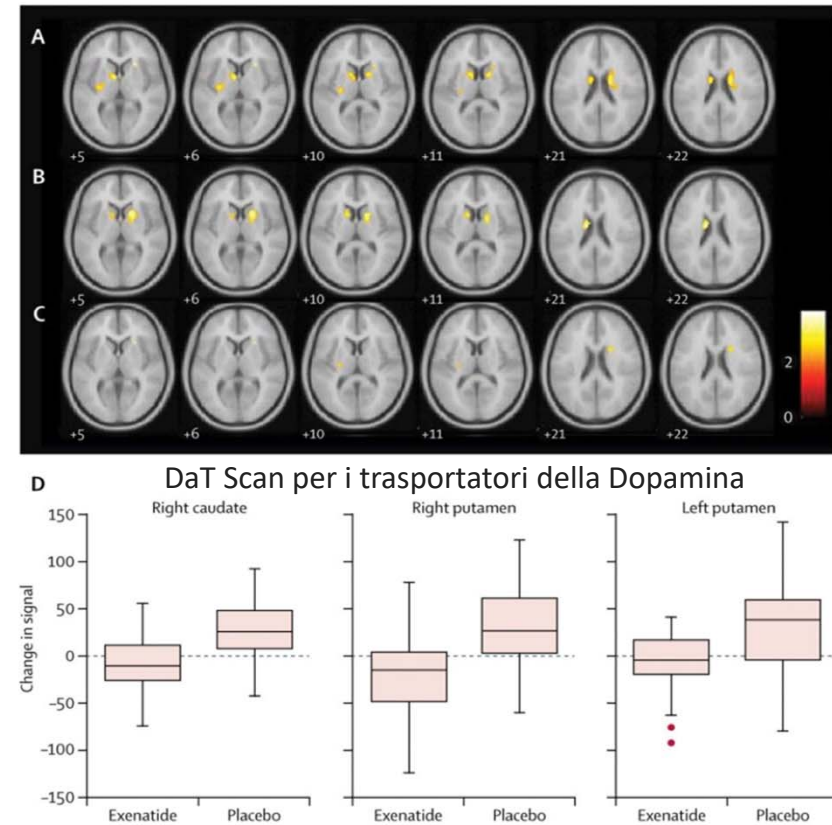
Sobell Department of Motor Neuroscience, University College London Institute of Neurology and the National Hospital for Neurology and Neurosurgery, London, UK



62 pazienti

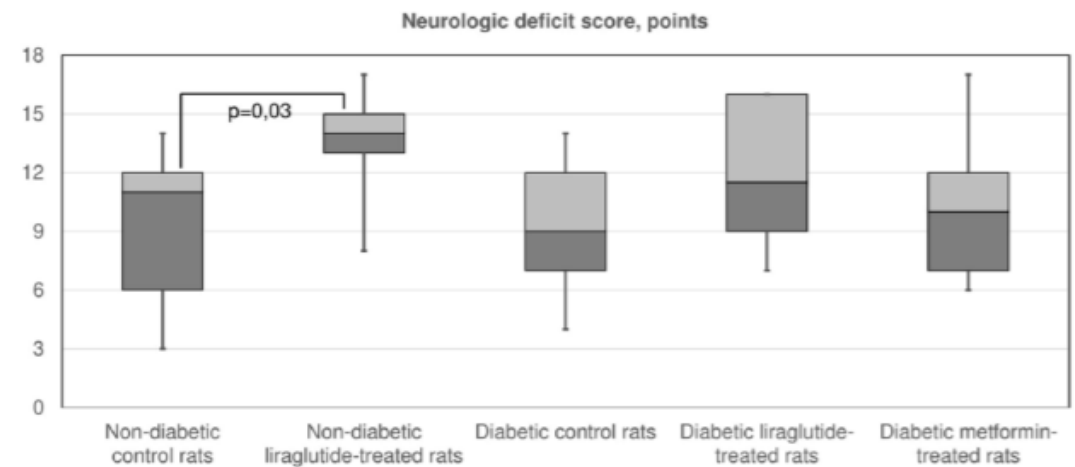
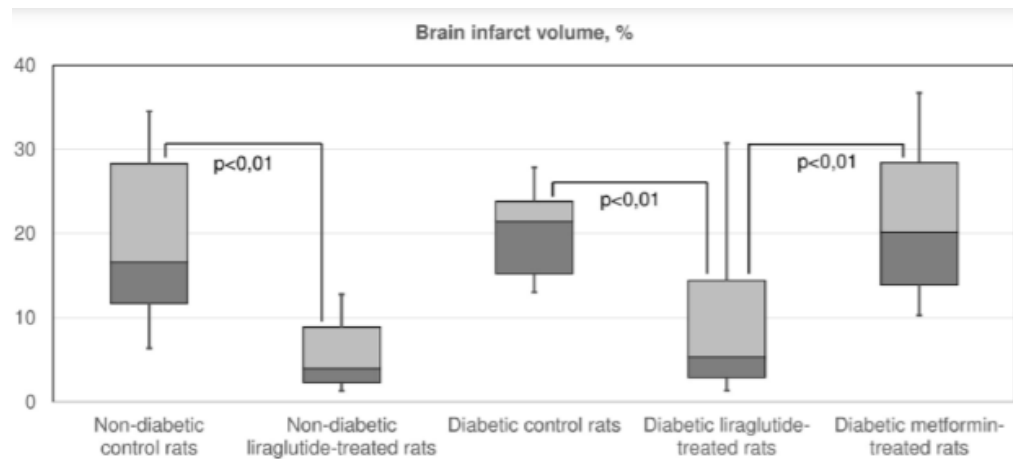
Follow-Up: 48 settimane

Exclusion Criteria: Diabete



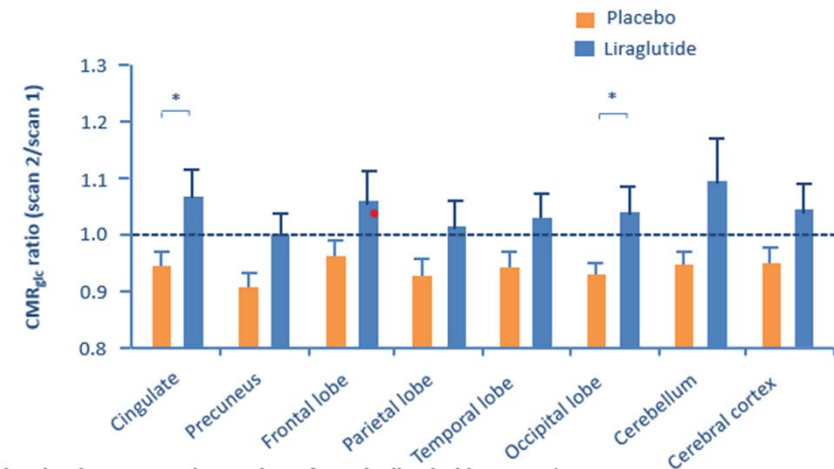
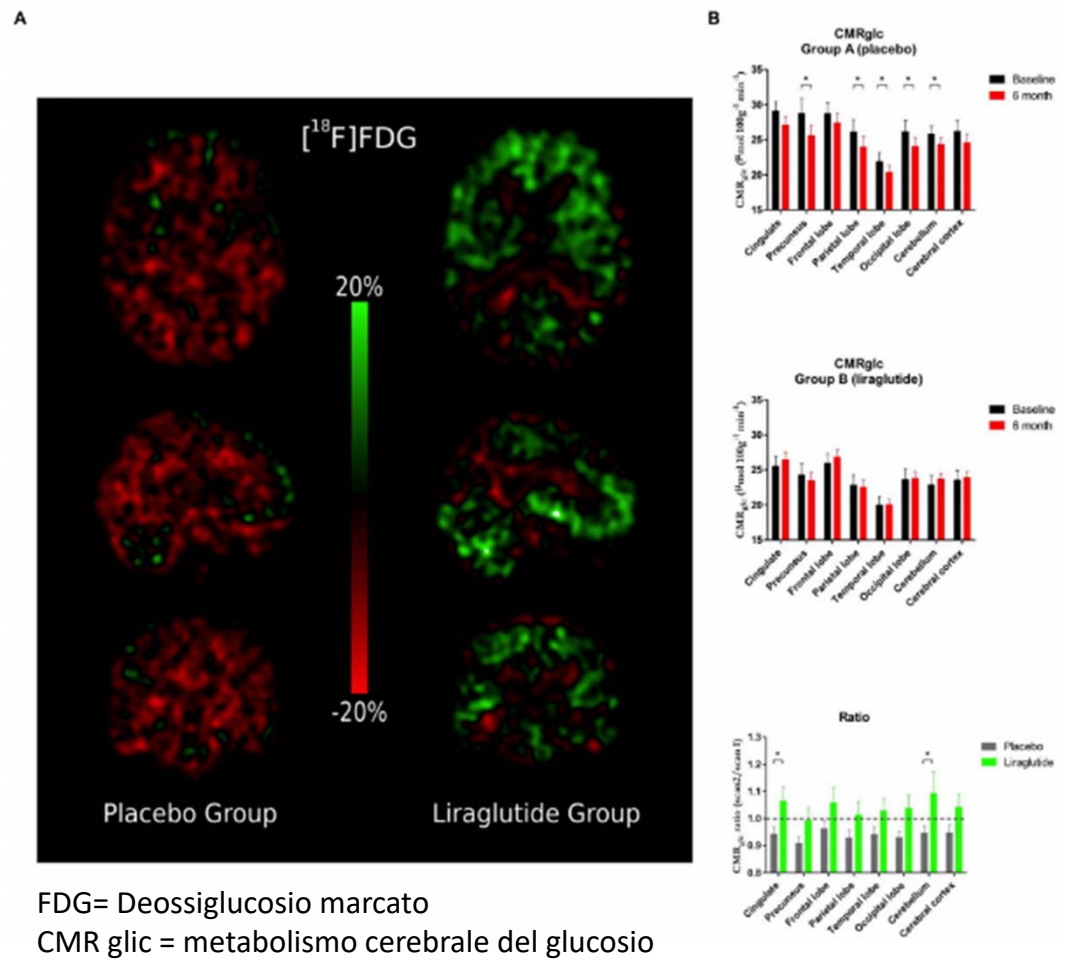
Athauda D, Lancet, 2017; 390: 1664-1675

L'effetto neuroprotettivo del GLP-1 RA potrebbe essere indipendente dalla normalizzazione della glicemia



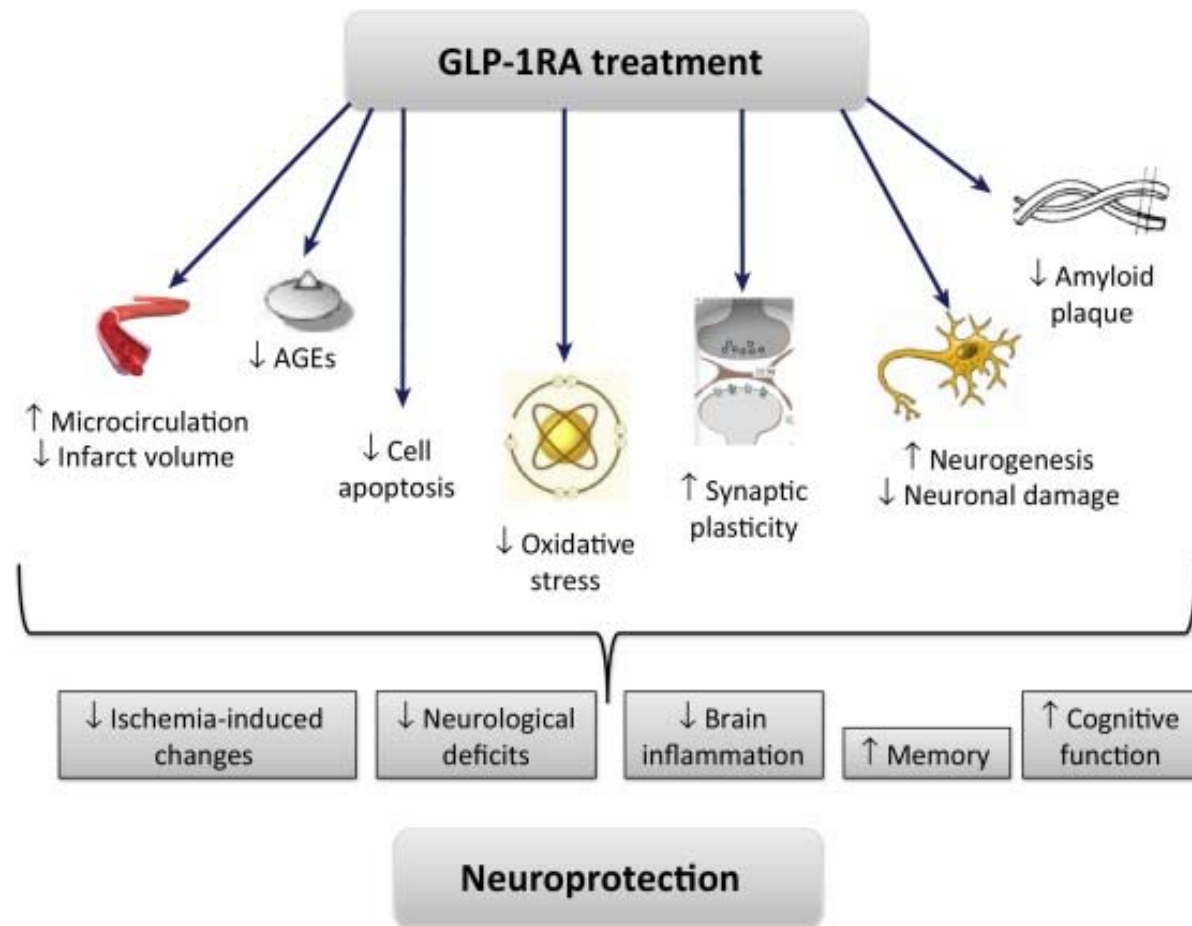
Il pretrattamento con liraglutide riduceva l'area di infarto sia in ratti diabetici che non diabetici mentre il deficit neurologico migliorava solo negli animali non diabetici trattati con liraglutide.

GLP-1 RA in pazienti con malattia di Alzheimer e metabolismo cerebrale del glucosio



Il trattamento con liraglutide in soggetti con malattia di Alzheimer ha prevenuto le alterazioni del metabolismo cerebrale del glucosio che in questa patologia risultano associato a declino cognitivo, disfunzione sinaptica e progressione della malattia.

Effetti Neuroprotettivi dei GLP-1RA



Declino Cognitivo e Malattia di Alzheimer

Semaglutide

Liraglutide

EVOKE Program

Semaglutide 14 mg/daily
(NCT04777396) – EVOKE
(NCT04777409) – EVOKE Plus

Study Population: Mild cognitive
impairment

Primary Outcome: change in
Clinical Dementia Rating

Duration: 173 weeks
Ext. End: April 2026

Semaglutide 14 mg/daily
(NCT04466345)

Study Population: Major
depressive disease

Primary Outcome:
change in Trail Making Test –B
(concentration and attention)

Duration: 12 weeks
Ext. End: Oct 2024

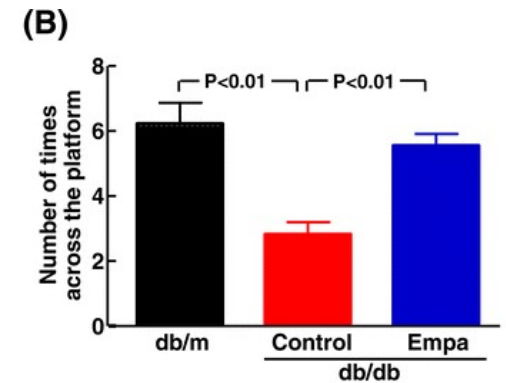
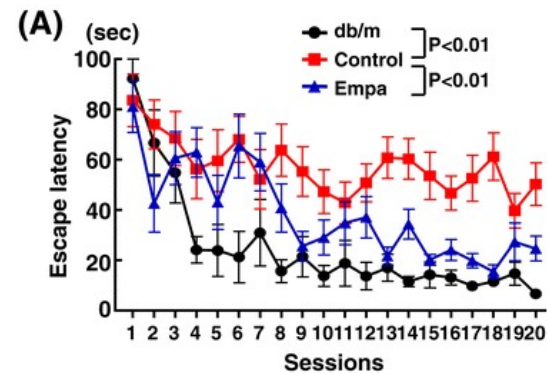
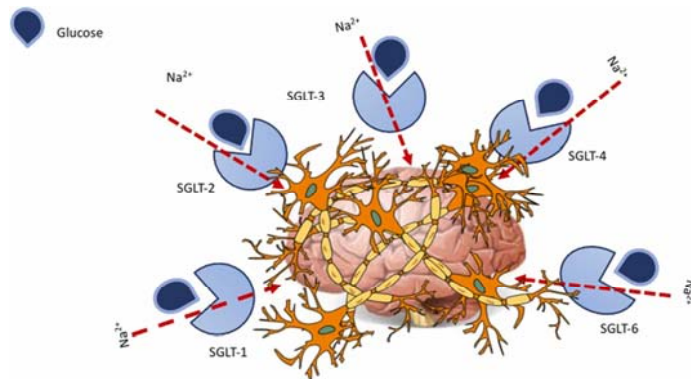
Liraglutide 1.8 mg/die vs Empagliflozin 25
mg/die vs Linagliptin 5 mg/die
(NCT02953665)

Study Population: T2DM not
controlled with metformin alone

Primary Outcome: change in
MoCA

Duration: 12 months
Ext. End: August 2027

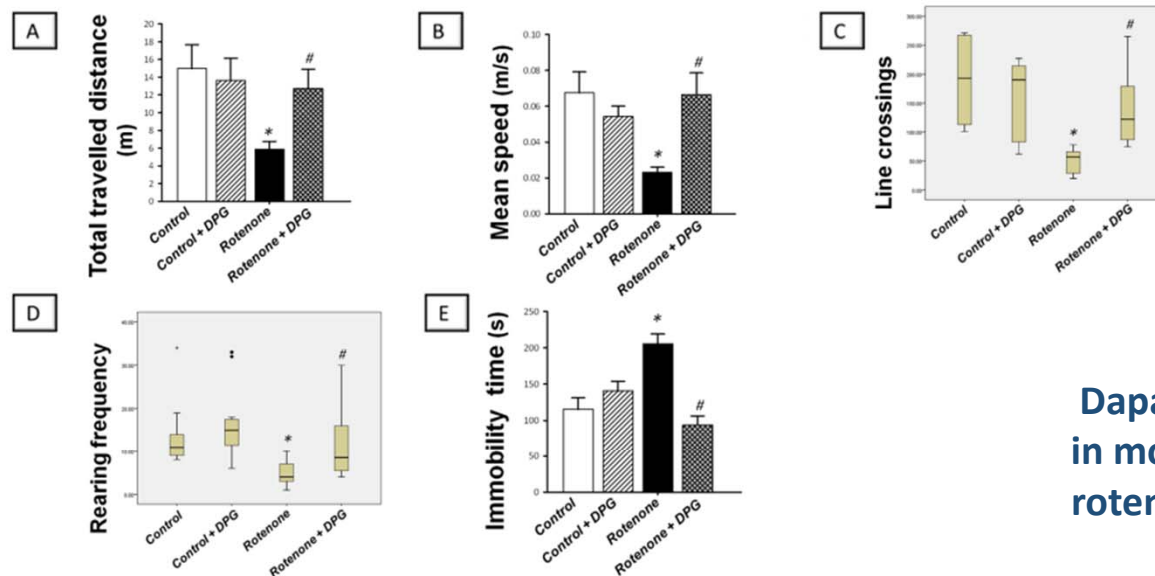
SGLT2 inibitori e Sistema Nervoso Centrale



Empagliflozin migliora la performance cognitiva in modelli murini di diabete (16 weeks old)

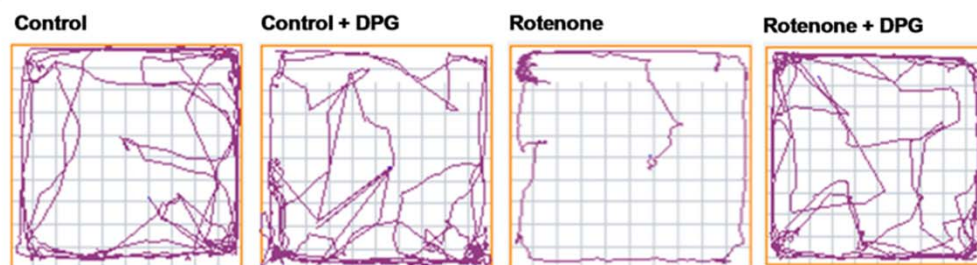
Rizzo MR, Pharmacological Research 176 (2022) 106062
Lin B. Cardiovasc Diabetol. (2014) Oct 26;13:148.

SGLT2 inibitori e SNC

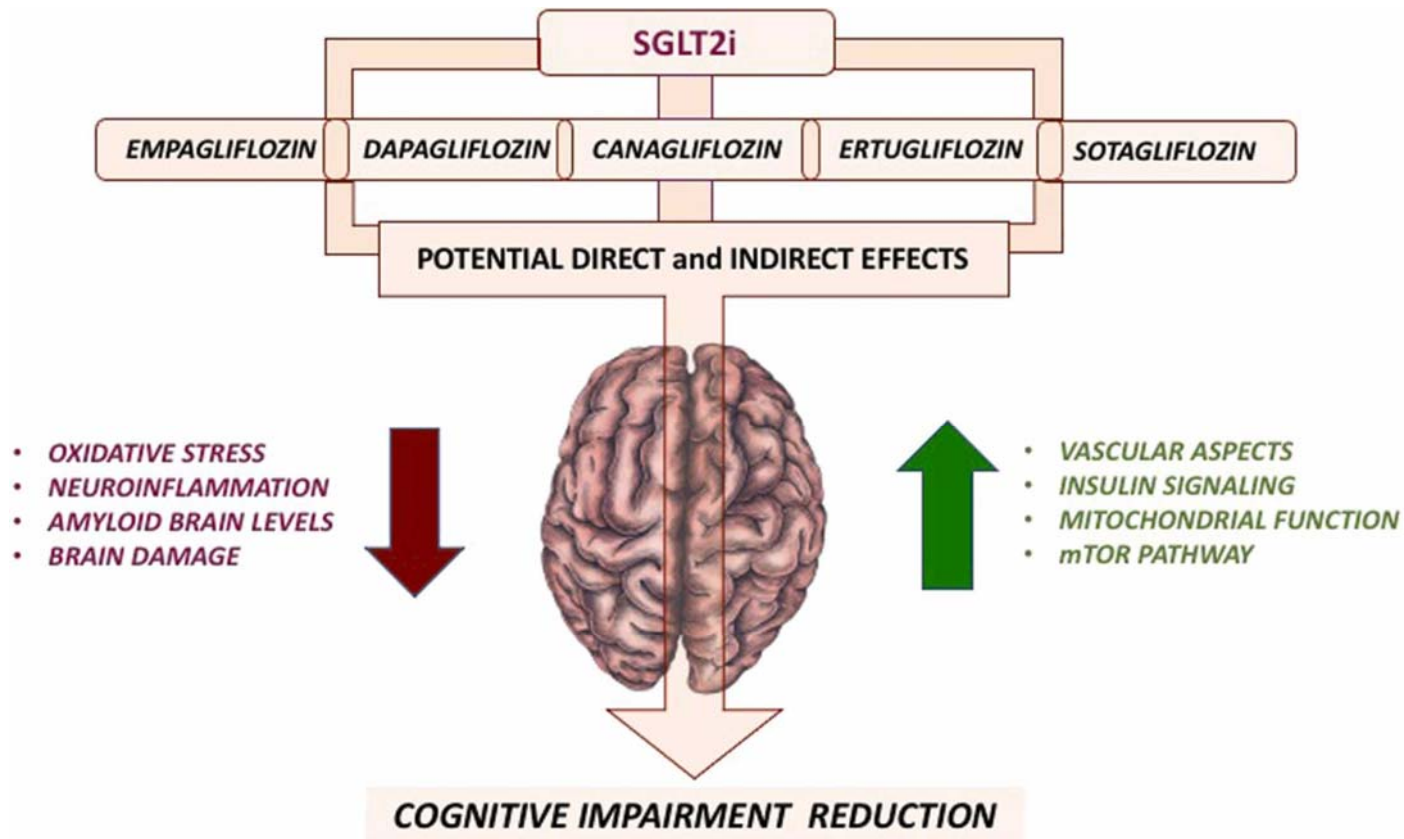


Dapagliflozin ha attenuato la disfunzione motoria in modello murino di Parkinson Disease indotta da rotenone e ha migliorato la coordinazione motoria

F Track plots for open field test

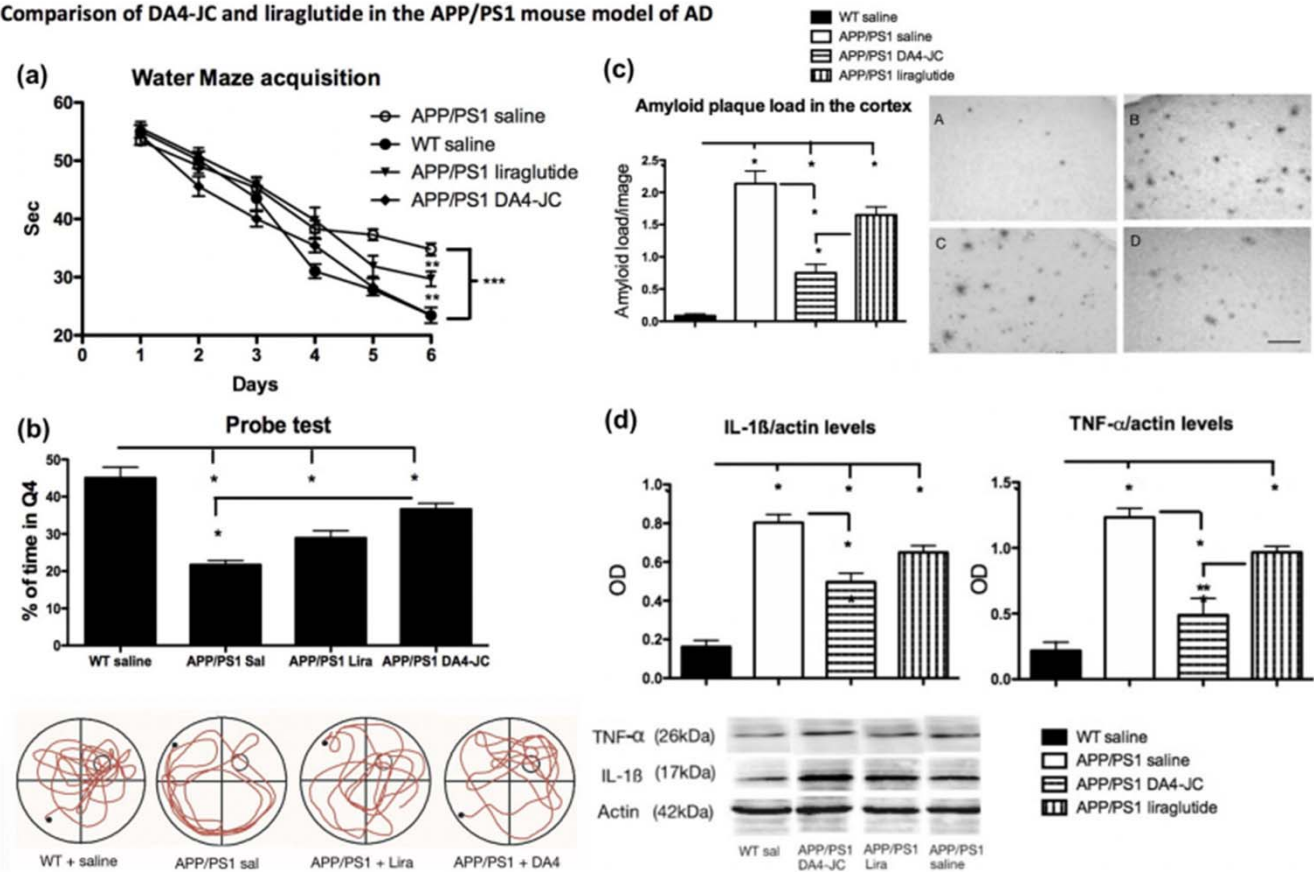


SGLT2 inibitori e SNC



Doppi Agonisti GLP1-GIP: effetti su modelli murini di Malattia di Alzheimer

Comparison of DA4-JC and liraglutide in the APP/PS1 mouse model of AD



Terapia del Diabete Mellito Tipo 2 oltre la glicemia: le promesse dei nuovi farmaci sul SNC

CONCLUSIONI

- In uno scenario, al momento, carente di terapie «disease modifier» come quello delle malattie neurodegenerative, il trattamento con i GLP1-RA sembra avere un grande potenziale.
- Sulla base delle evidenze oggi disponibili, SGLT2i e doppi agonisti recettoriali sembrano essere terapie molto promettenti. Tuttavia, sono necessari trial clinici mirati per approfondire i loro possibili benefici sulle malattie neurodegenerative.

“The Sweet Trail to Neuroprotection”

