GLP1-RA: le nuove evidenze

Concetta Nadia Arico'
U.O.C. Diabetologia ed Endocrinologia
G.O.M. Reggio Calabria

CONGRESSO REGIONALE CALABRIA
SID – AMD
2022

SID Società Italiana di Diabetologia
AMD 1974 Associazione Medici Diabetologi

T-HOTEL LAMEZIA TERME
25-26 NOVEMBRE 2022

La dr.ssa Concetta Nadia Arico' dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

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.).

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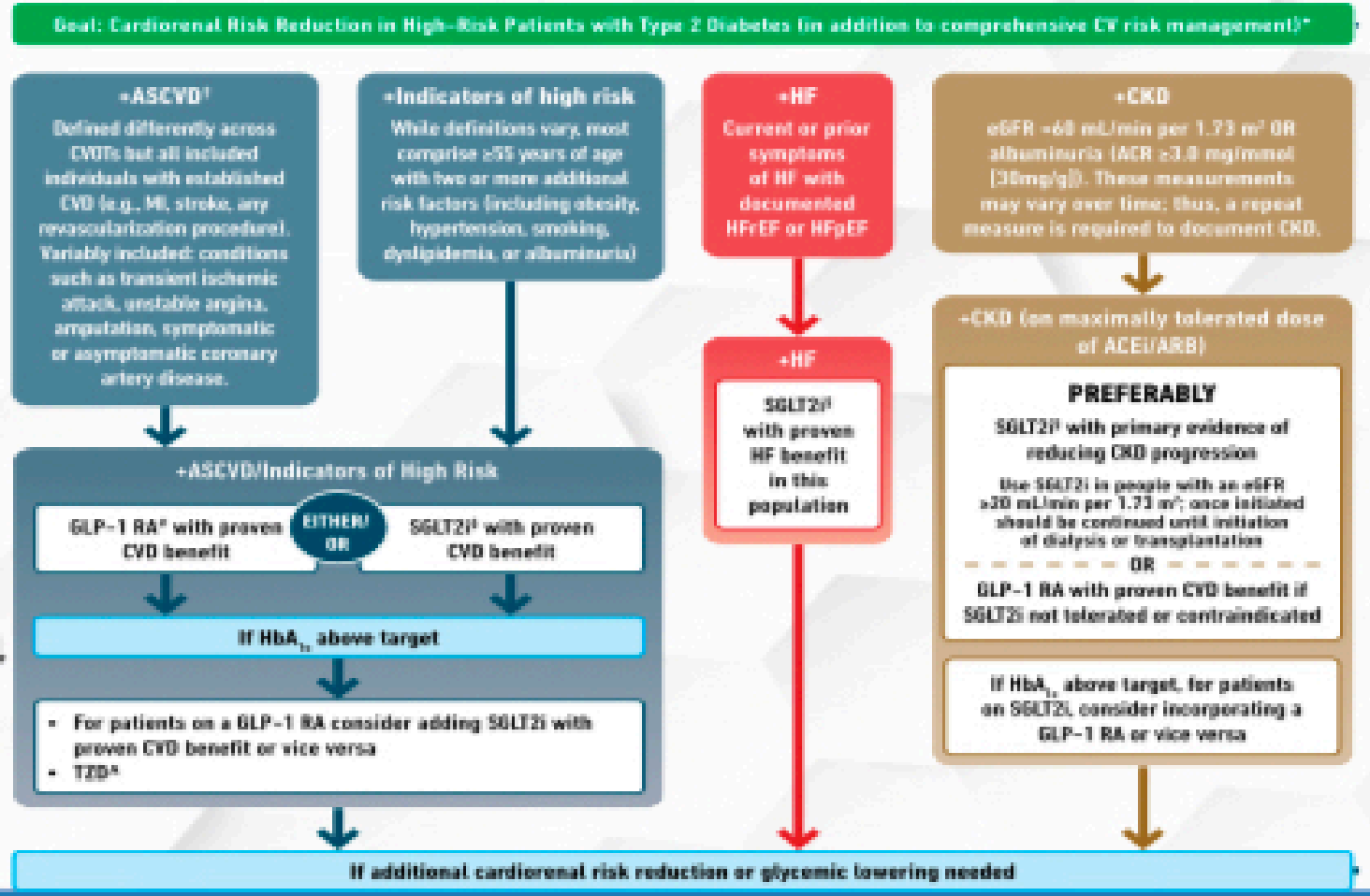
USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Diabetes Care 2022;45:2753–2786 | https://doi.org/10.2337/dci22-0034

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



CONGRESSO
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GLP1 RA

ELIXA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome

Marc A. Pfeffer, M.D., Ph.D., Brian Claggett, Ph.D., Rafael Diaz, M.D., Kenneth Dickstein, M.D., Ph.D., Hertzel C. Gerstein, M.D., Lars V. Køber, M.D., Francesca C. Lawson, M.D., Lin Ping, M.D., Xiaodan Wei, Ph.D., Eldrin F. Lewis, M.D., M.P.H., Aldo P. Maggioni, M.D., John J.V. McMurray, M.D., Ph.D., Jeffrey L. Probstfield, M.D., Matthew C. Riddle, M.D., Scott D. Solomon, M.D., and Jean-Claude Tardif, M.D., for the ELIXA Investigators*

LEADER

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

SUSTAIN-6

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

EXSCEL

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes

Rury R. Holman, F.Med.Sci., M. Angelyn Bethel, M.D., Robert J. Mentz, M.D., Vivian P. Thompson, M.P.H., Yuliya Lokhnygina, Ph.D., John B. Buse, M.D., Ph.D., Juliana C. Chan, M.D., Jasmine Choi, M.S., Stephanie M. Gustavson, Ph.D., Nayyar Iqbal, M.D., Aldo P. Maggioni, M.D., Steven P. Marso, M.D., Peter Öhman, M.D., Ph.D., Neha J. Pagidipati, M.D., M.P.H., Neil Poulter, F.Med.Sci., Ambady Ramachandran, M.D., Bernard Zinman, M.D., and Adrian F. Hernandez, M.D., M.H.S., for the EXSCEL Study Group*

Articles

HARMONY

Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial

Adrian F Hernandez, Jennifer B Green, Salim Janmohamed, Ralph B D'Agostino Sr, Christopher B Granger, Nigel P Jones, Lawrence A Leiter, Anne E Rosenberg, Kristina N Sigmon, Matthew C Somerville, Karl M Thorpe, John J V McMurray, Stefano Del Prato, for the Harmony Outcomes committees and investigators*

Articles

PIONEER 7

Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial

Thomas R Pieber, Bruce Bode, Ann Mertens, Young Min Cho, Erik Christiansen, Christin L Hertz, Signe O R Wallenstein, John B Buse, for the PIONEER 7 investigators

REWIND

Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial

Hertzel C Gerstein, Helen M Colhoun, Gilles R Dagenais, Rafael Diaz, Mark Lakshmanan, Prem Pais, Jeffrey Probstfield, Jeffrey S Riesmeyer, Matthew C Riddle, Lars Rydén, Denis Xavier, Charles Messan Atisso, Leanne Dyal, Stephanie Hall, Purnima Rao-Melacini, Gloria Wong, Alvaro Avezum, Jan Basile, Namsik Chung, Ignacio Conget, William C Cushman, Edward Franek, Nicolae Hancu, Markolf Hanefeld, Shaun Holt, Petr Jansky, Matyas Keltai, Fernando Lanas, Lawrence A Leiter, Patricio Lopez-Jaramillo, Ernesto German Cardona Munoz, Valdis Pirags, Nana Pogosova, Peter J Raubenheimer, Jonathan E Shaw, Wayne H-H Sheu, Theodora Temelkova-Kurktschiev, for the REWIND Investigators*

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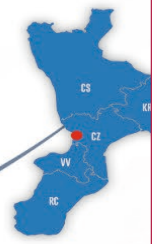

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials

Naveed Sattar*, Matthew M Y Lee*, Søren L Kristensen*, Kelley R H Branch, Stefano Del Prato, Nardev S Khurmi, Carolyn S P Lam, Renato D Lopes, John J V McMurray, Richard E Pratley, Julio Rosenstock, Hertzel C Gerstein

Lancet Diabetes Endocrinol 2021
9: 653–62

98 articles screened,
8 trials
60 080 patients

	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-point MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1·02 (0·89–1·17)		0·78
LEADER	608/4668 (13%)	694/4672 (15%)	0·87 (0·78–0·97)		0·01
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0·74 (0·58–0·95)		0·016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0·91 (0·83–1·00)		0·061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0·78 (0·68–0·90)		0·0006
REWIND	594/4949 (12%)	663/4952 (13%)	0·88 (0·79–0·99)		0·026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0·79 (0·57–1·11)		0·17
AMPLITUDE-O	189/2717 (7%)	125/1359 (9%)	0·73 (0·58–0·92)		0·0069
Subtotal (I^2=44·5%, p=0·082)			**0·86 (0·80–0·93)**	**65 (45–130)**	**<0·0001**
Cardiovascular death					
ELIXA	156/3034 (5%)	158/3034 (5%)	0·98 (0·78–1·22)		0·85
LEADER	219/4668 (5%)	278/4672 (6%)	0·78 (0·66–0·93)		0·007
SUSTAIN-6	44/1648 (3%)	46/1649 (3%)	0·98 (0·65–1·48)		0·92
EXSCEL	340/7356 (5%)	383/7396 (5%)	0·88 (0·76–1·02)		0·096
Harmony Outcomes	122/4731 (3%)	130/4732 (3%)	0·93 (0·73–1·19)		0·58
REWIND	317/4949 (6%)	346/4952 (7%)	0·91 (0·78–1·06)		0·21
PIONEER 6	15/1591 (1%)	30/1592 (2%)	0·49 (0·27–0·92)		0·021
AMPLITUDE-O	75/2717 (3%)	50/1359 (4%)	0·72 (0·50–1·03)		0·07
Subtotal (I^2=13·4%, p=0·33)			**0·87 (0·80–0·94)**	**163 (103–353)**	**0·0010**
Fatal or non-fatal myocardial infarction					
ELIXA	270/3034 (9%)	261/3034 (9%)	1·03 (0·87–1·22)		0·71
LEADER	292/4668 (6%)	339/4672 (7%)	0·86 (0·73–1·00)		0·046
SUSTAIN-6	54/1648 (3%)	67/1649 (4%)	0·81 (0·57–1·16)		0·26
EXSCEL	483/7356 (7%)	493/7396 (7%)	0·97 (0·85–1·10)		0·62
Harmony Outcomes	181/4731 (4%)	240/4732 (5%)	0·75 (0·61–0·90)		0·003
REWIND	223/4949 (5%)	231/4952 (5%)	0·96 (0·79–1·15)		0·63
PIONEER 6	37/1591 (2%)	35/1592 (2%)	1·04 (0·66–1·66)		0·49
AMPLITUDE-O	91/2717 (3%)	58/1359 (4%)	0·75 (0·54–1·05)		0·09
Subtotal (I^2=26·9%, p=0·21)			**0·90 (0·83–0·98)**	**175 (103–878)**	**0·020**
Fatal or non-fatal stroke					
ELIXA	67/3034 (2%)	60/3034 (2%)	1·12 (0·79–1·58)		0·54
LEADER	173/4668 (4%)	199/4672 (4%)	0·86 (0·71–1·06)		0·16
SUSTAIN-6	30/1648 (2%)	46/1649 (3%)	0·65 (0·41–1·03)		0·066
EXSCEL	187/7356 (3%)	218/7396 (3%)	0·85 (0·70–1·03)		0·095
Harmony Outcomes	94/4731 (2%)	108/4732 (2%)	0·86 (0·66–1·14)		0·30
REWIND	158/4949 (3%)	205/4952 (4%)	0·76 (0·62–0·94)		0·010
PIONEER 6	13/1591 (1%)	17/1592 (1%)	0·76 (0·37–1·56)		0·43
AMPLITUDE-O	47/2717 (2%)	31/1359 (2%)	0·74 (0·47–1·17)		0·19
Subtotal (I^2=0·0%, p=0·64)			**0·83 (0·76–0·92)**	**198 (140–421)**	**0·0002**

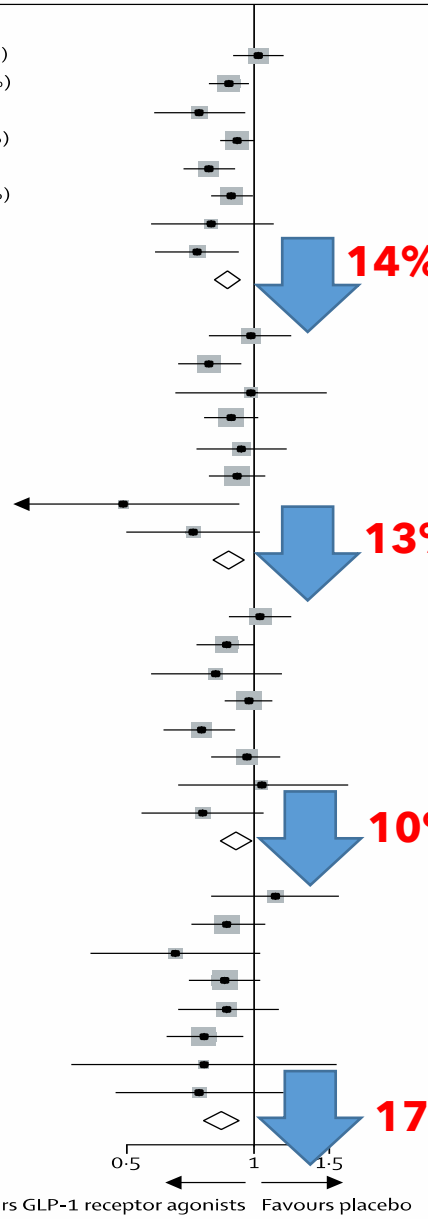

Figure 2: **Risk of MACE and each of its components**
Weights are from random effects analysis. In addition to primary cardiovascular outcome results papers, data were extracted from additional sources.[2,20] AMPLITUDE-O data were provided by the authors. Three-point MACE consisted of cardiovascular death, myocardial infarction, and stroke. NNTs were calculated over a weighted average median follow-up of 3·0 years. p values are for superiority. MACE=major adverse cardiovascular events. NNT=number needed to treat.

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2022

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials

Naveed Sattar*, Matthew M Y Lee*, Søren L Kristensen*, Kelley R H Branch, Stefano Del Prato, Nardev S Khurmi, Carolyn S P Lam, Renato D Lopes, John J V McMurray, Richard E Pratley, Julio Rosenstock, Hertzel C Gerstein

GLP-1 receptor agonists, homology to human GLP-1 or exendin-4, reduced the risk of individual MACE components, all-cause mortality, hospital admission for heart failure, and worsening kidney function in patients with type 2 diabetes.

	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
All-cause mortality					
ELIXA	211/3034 (7%)	223/3034 (7%)	0·94 (0·78 to 1·13)		0·50
LEADER	381/4668 (8%)	447/4672 (10%)	0·85 (0·74 to 0·97)		0·02
SUSTAIN-6	62/1648 (4%)	60/1649 (4%)	1·05 (0·74 to 1·50)		0·79
EXSCEL	507/7356 (7%)	584/7396 (8%)	0·86 (0·77 to 0·97)		0·016*
Harmony Outcomes	196/4731 (4%)	205/4732 (4%)	0·95 (0·79 to 1·16)		0·64
REWIND	536/4949 (11%)	592/4952 (12%)	0·90 (0·80 to 1·01)		0·067
PIONEER 6	23/1591 (1%)	45/1592 (3%)	0·51 (0·31 to 0·84)		0·008
AMPLITUDE-O	111/2717 (4%)	69/1359 (5%)	0·78 (0·58 to 1·06)		0·11
Subtotal (I^2=10·1%, p=0·35)			**0·88 (0·82 to 0·94)**	**114 (76 to 228)**	**0·0001**
Hospital admission for heart failure					
ELIXA	122/3034 (4%)	127/3034 (4%)	0·96 (0·75 to 1·23)		0·75
LEADER	218/4668 (5%)	248/4672 (5%)	0·87 (0·73 to 1·05)		0·14
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)	1·11 (0·77 to 1·61)		0·57
EXSCEL	219/7356 (3%)	231/7396 (3%)	0·94 (0·78 to 1·13)		0·49
Harmony Outcomes	79/4731 (2%)	111/4732 (2%)	0·71 (0·53 to 0·94)		0·019
REWIND	213/4949 (4%)	226/4952 (5%)	0·93 (0·77 to 1·12)		0·46
PIONEER 6	21/1591 (1%)	24/1592 (2%)	0·86 (0·48 to 1·55)		0·59
AMPLITUDE-O	40/2717 (1%)	31/1359 (2%)	0·61 (0·38 to 0·98)		0·04
Subtotal (I^2=3·0%, p=0·41)			**0·89 (0·82 to 0·98)**	**258 (158 to 1422)**	**0·013**
Composite kidney outcome including macroalbuminuria					
ELIXA	172/2647 (6%)	203/2639 (8%)	0·84 (0·68 to 1·02)		0·083
LEADER	268/4668 (6%)	337/4672 (7%)	0·78 (0·67 to 0·92)		0·003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	0·64 (0·46 to 0·88)		0·005
EXSCEL	366/6256 (6%)	407/6222 (7%)	0·88 (0·76 to 1·01)		0·065
REWIND	848/4949 (17%)	970/4952 (20%)	0·85 (0·77 to 0·93)		0·0004
AMPLITUDE-O	353/2717 (13%)	250/1359 (18%)	0·68 (0·57 to 0·79)		<0·0001
Subtotal (I^2=47·5%, p=0·090)			**0·79 (0·73 to 0·87)**	**47 (37 to 77)**	**<0·0001**
Worsening of kidney function					
ELIXA	41/3031 (1%)	35/3032 (1%)	1·16 (0·74 to 1·83)		0·513
LEADER	87/4668 (2%)	97/4672 (2%)	0·89 (0·67 to 1·19)		0·43
SUSTAIN-6	18/1648 (1%)	14/1649 (1%)	1·28 (0·64 to 2·58)		0·48
EXSCEL	246/6456 (4%)	273/6458 (4%)	0·88 (0·74 to 1·05)		0·16
REWIND	169/4949 (3%)	237/4952 (5%)	0·70 (0·57 to 0·85)		0·0004
AMPLITUDE-O	7/2717 (<1%)	7/1359 (1%)	0·35 (0·10 to 1·27)		0·11
Subtotal (I^2=43·0%, p=0·12)			**0·86 (0·72 to 1·02)**	**241 (120 to –1694)†**	**0·089**

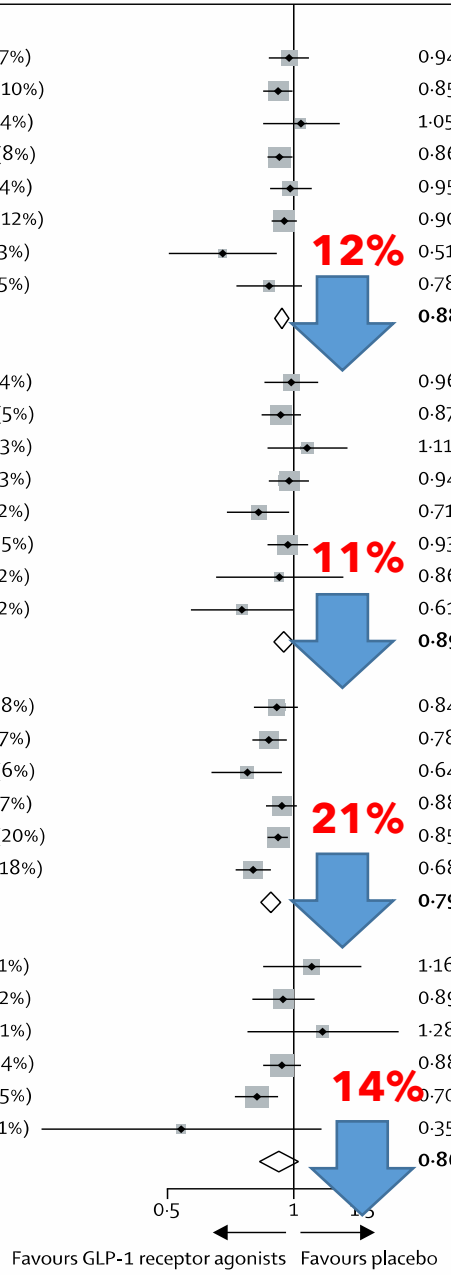
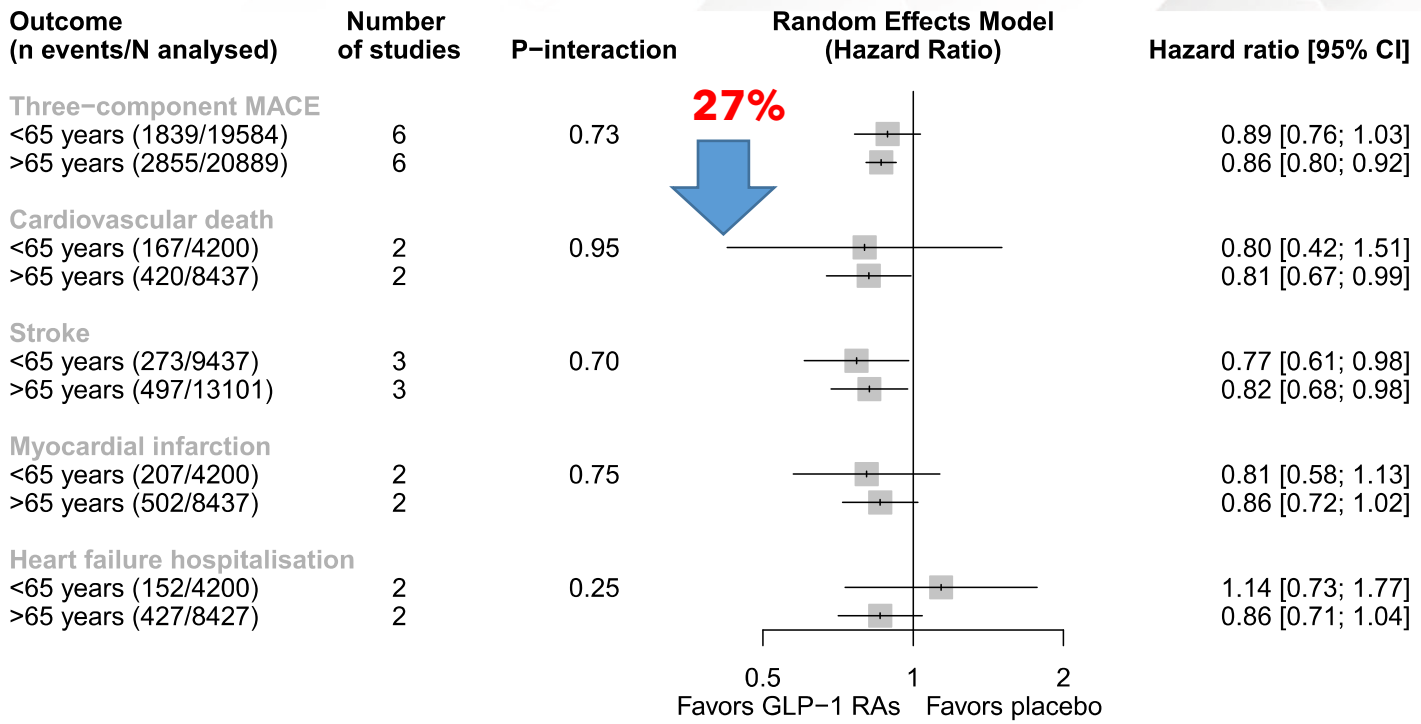


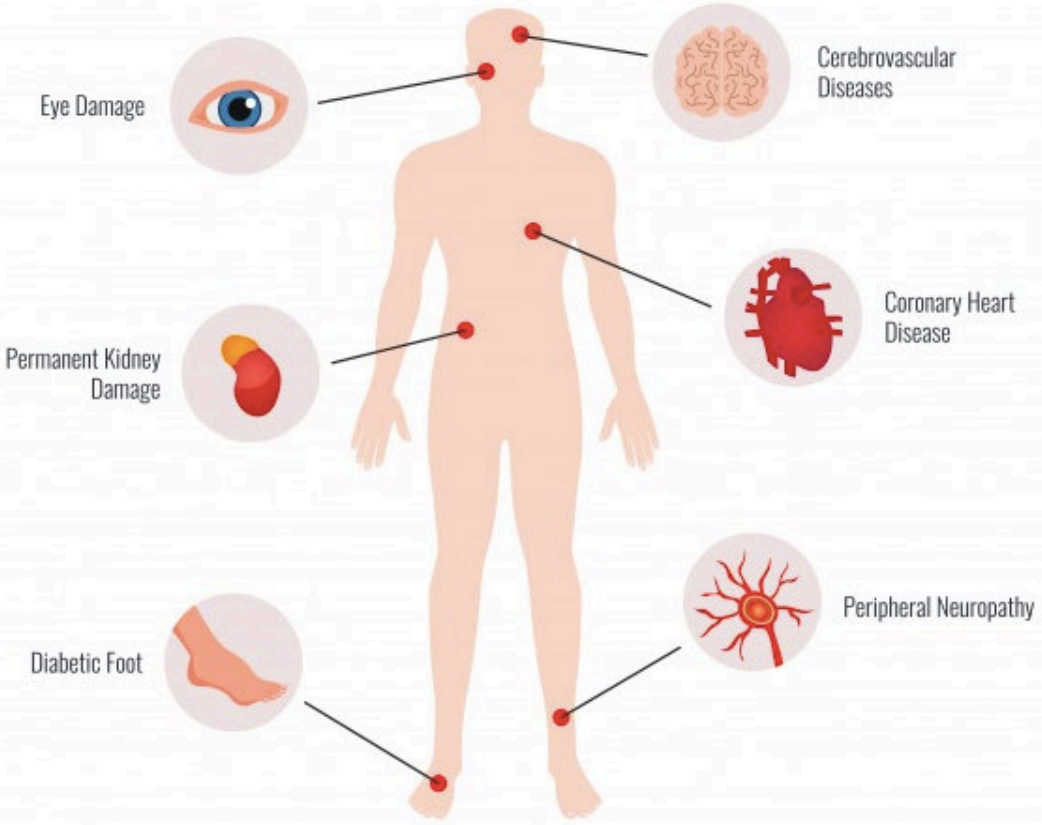
Figure 3: **All-cause mortality, hospital admission for heart failure, and kidney outcomes**

Review

GLP-1 receptor agonists and SGLT2 inhibitors for older people with type 2 diabetes: A systematic review and meta-analysis



Complicanze



Comorbidita'

Concordanti non tradizionali: condividono fattori di rischio e percorsi fisiopatologici comuni, ma non sono state tradizionalmente considerate parte delle sequele del T2DM

NAFLD/NASH; Tumori; Demenza

Discordanti emergenti: non hanno, al momento, un chiaro legame eziologico con il T2DM ma si riscontrano comunemente in concomitanza e hanno effetti sulla mortalità, esiti di morbilità, e la qualità della vita correlata alla salute

Depressione, OSAS, Asma, osteoartriti

GLP1 - RA

Complicanze

OK

Comorbidita'

?

Preparing for the NASH Epidemic: A Call to Action

Diabetes Care 2021;44:2162–2172 | https://doi.org/10.2337/dci21-0020

Fasiha Kanwal,[1] Jay H. Shubrook,[2] Zobair Younossi,[3] Yamini Natarajan,[4] Elisabetta Bugianesi,[5] Mary E. Rinella,[6] Stephen A. Harrison,[7] Christos Mantzoros,[8] Kim Pfotenhauer,[9]

Diabete e NAFLD/ NASH

Table 3—Management of patients with nonalcoholic fatty liver disease and nonalcoholic steatohepatitis

Variable	Lifestyle intervention[a]	Liver-directed pharmacotherapy	Diabetes care (in individuals with diabetes)	Cardiovascular risk reduction
NAFL	Yes	No	Standard of care	Yes
NASH with fibrosis stage 0 or 1 (F0, F1)	Yes	No	Standard of care	Yes
NASH with fibrosis stage 2 or 3 (F2, F3)	Yes	Yes	Pioglitazone, GLP-1 receptor agonists[b]	Yes
NASH cirrhosis (F4)	Yes	Yes	Individualize[c]	Yes

[a]All patients require regular physical activity and healthy diet and to avoid excess alcohol intake; weight loss recommended. [b]Among GLP-1 receptor agonists, semaglutide has the best evidence of benefit in patients with NASH and fibrosis. [c]Evidence for efficacy of pharmacotherapy in patients with NASH cirrhosis is very limited and should be individualized and used with caution.

our systematic review and meta-analysis aimed at examining the published data of placebo-controlled or active-controlled RCTs, which tested the efficacy and safety of GLP-1 RAs to specifically treat NAFLD or NASH in adults with or without pre-existing T2DM.

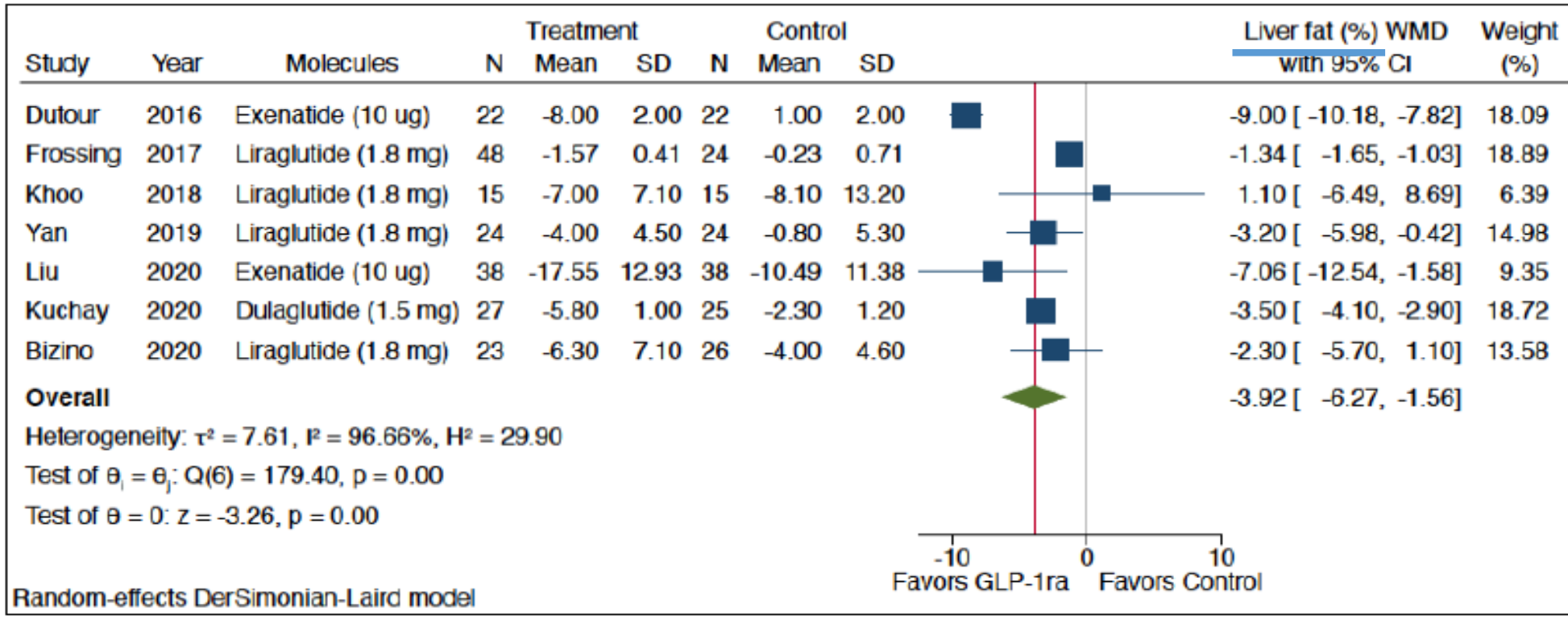


Figure 2. Forest plot and pooled estimates of the effect of different GLP-1 RAs on the absolute percentage of liver fat content as assessed by magnetic resonance-based techniques (n = 7 RCTs included) as compared with placebo or reference therapy. The pooled (green diamond) and individual effect sizes for all RCTs included were expressed as weighted mean difference (WMD) and 95% confidence intervals (CI). The blue square in the figure represents the WMD for each single RCT.

Resolution of NASH

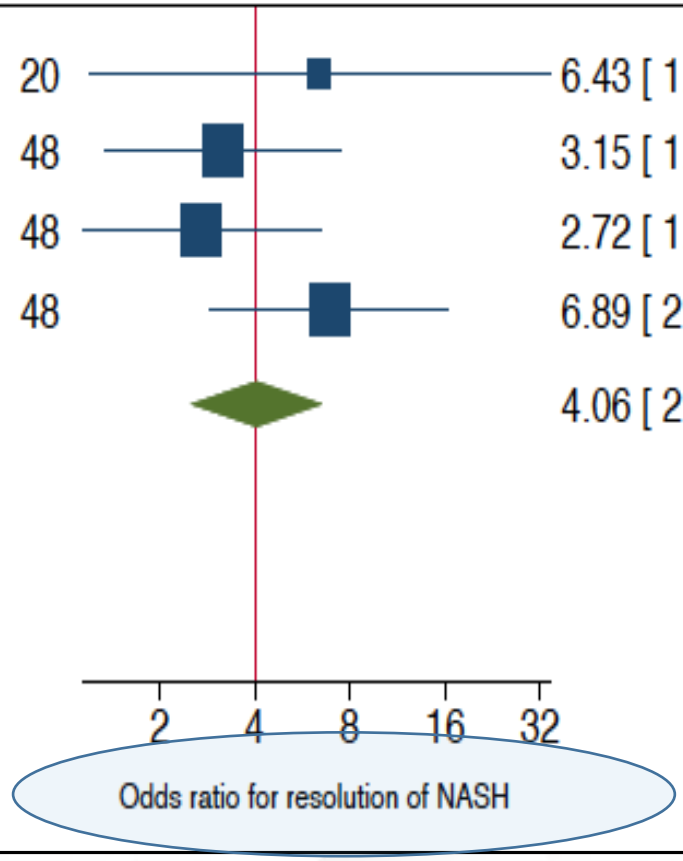
Study	Year	Molecules	Treatment Yes	Treatment No	Control Yes	Control No	Odds Ratio with 95% CI	Weight (%)
Armstrong	2016	Liraglutide (1.8 mg)	9	14	2	20	6.43 [1.20, 34.41]	8.12
Newsome	2020	Sema (0.1 mg)	23	35	10	48	3.15 [1.33, 7.46]	30.85
Newsome	2020	Sema (0.2 mg)	21	37	10	48	2.72 [1.15, 6.48]	30.44
Newsome	2020	Sema (0.4 mg)	33	23	10	48	6.89 [2.90, 16.35]	30.58
Overall							4.06 [2.52, 6.55]	

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$

Test of $\theta_i = \theta_j$: $Q(3) = 2.87$, $p = 0.41$

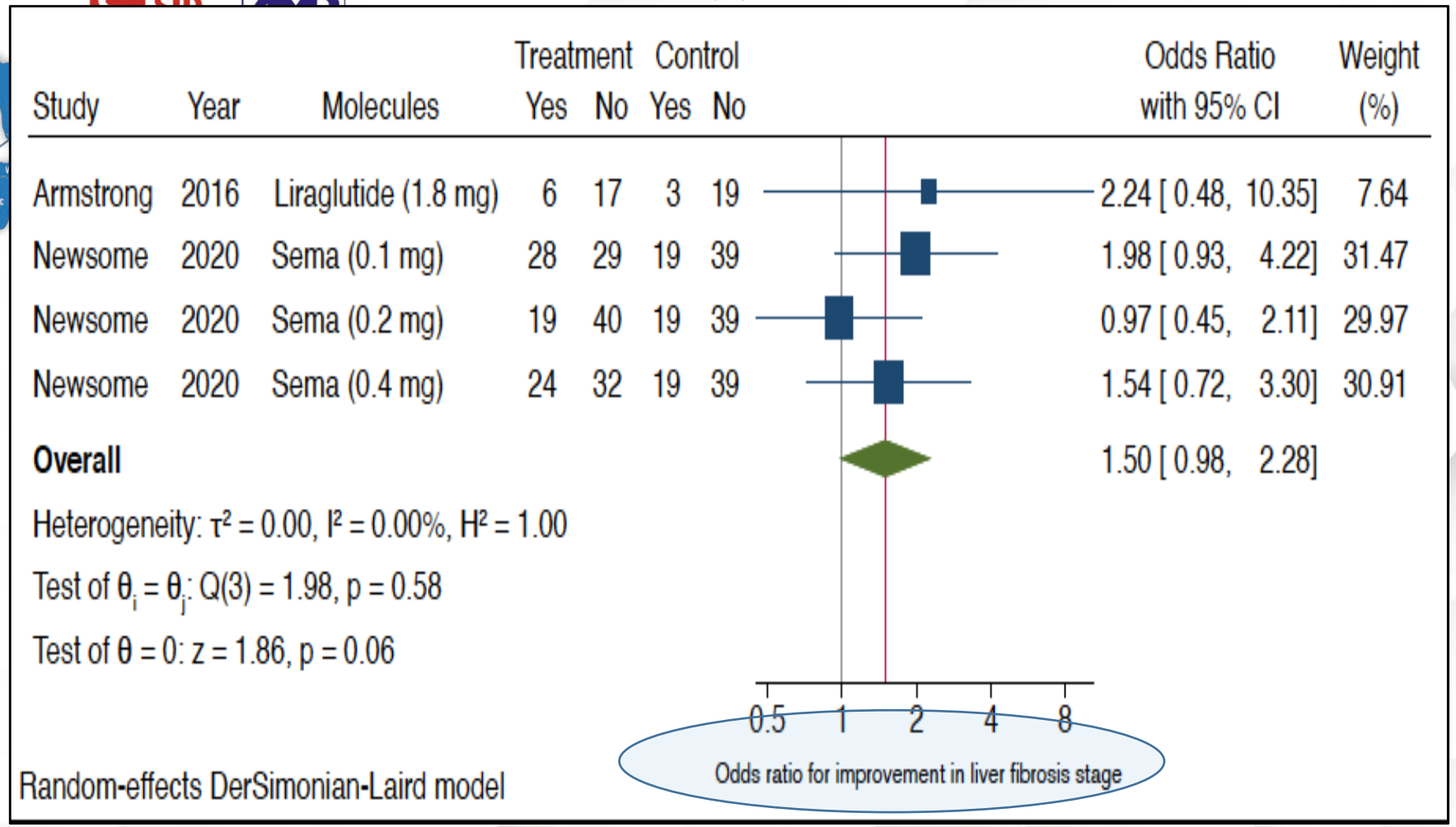
Test of $\theta = 0$: $z = 5.74$, $p = 0.00$

Random-effects DerSimonian-Laird model



(A)

Improvement in liver fibrosis stage



(**B**)

Figure 3. Forest plot and pooled estimates of the effect of GLP-1 RAs (*n* = 2 RCTs included using either liraglutide 1.8 mg/day or semaglutide at a dose of 0.1 mg, 0.2 mg or 0.4 mg/day subcutaneously) on histologic resolution of NASH with no worsening of liver fibrosis (panel **A**), and improvement in liver fibrosis stage without worsening of NASH (panel **B**) as compared with placebo. The pooled (green diamond) and individual effect sizes for all RCTs included were expressed as random-effect odds ratio (OR) and 95% confidence intervals (CI).

Figure 3. Forest plot and pooled estimates of the effect of GLP-1 RAs (*n* = 2 RCTs included using either liraglutide 1.8 mg/day or semaglutide at a dose of 0.1 mg, 0.2 mg or 0.4 mg/day subcutaneously) on histologic resolution of NASH with no worsening of liver fibrosis (panel **A**), and improvement in liver fibrosis stage without worsening of NASH (panel **B**) as compared with placebo. The pooled (green diamond) and individual effect sizes for all RCTs included were expressed as random-effect odds ratio (OR) and 95% confidence intervals (CI).

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SID – AMD 2022

SID Società Italiana di Diabetologia
AMD Associazione Medici Diabetologi 1974

T-HOTEL LAMEZIA TERME
25-26 NOVEMBRE 2022

Diabete e malattie neurodegenerative

ORIGINAL ARTICLE

Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies

Kapil Gudala[1], Dipika Bansal[1]*, Fabrizio Schifano[2], Anil Bhansali[3]

ABSTRACT

Aims/Introduction: The aim of the present study was to investigate the association between diabetes and the risk of all type dementia (ATD), Alzheimer's disease (AD) and vascular dementia (VaD).

Materials and Methods: Prospective observational studies describing the incidence of ATD, AD and VaD in patients with diabetes mellitus were extracted from PubMed, EMBASE and other databases up to January 2012. Pooled relative risk (RR) estimates and 95% confidence intervals (CIs) were calculated using the random-effects model. Subgroup analyses and sensitivity analysis were also

Conclusions: The results showed a 73% increased risk of ATD, 56% increase of AD and 127% increase of VaD in diabetes patients. (J Diabetes Invest, doi: 10.1111/jdi.12087, 2013)

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PD risk was 40% higher

To individuals who had diabetes for more than 10 years.

Epidemiology/Health Services Research
ORIGINAL ARTICLE

Diabetes and Risk of Parkinson's Disease

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OBJECTIVE—To investigate the relationship between diabetes and future risk of Parkinson's disease (PD) among older U.S. adults.

RESEARCH DESIGN AND METHODS—A prospective study of self-reported diabetes in 1995 and 1996 in relation to PD diagnosed after 1995 among 288,662 participants of the National Institutes of Health-AARP Diet and Health Study. Multivariate odds ratio (OR) and 95% CI were derived from logistic regression models.

RESULTS—A total of 1,565 participants with PD diagnosed after 1995 were included in the analysis. After adjustment for potential confounders, PD risk was ~40% higher (OR = 1.41 [95% CI 1.20–1.66]) among diabetic patients than among participants without diabetes. Further analysis showed that the risk elevation was largely limited to individuals who had diabetes for more than 10 years at the time of baseline survey (1.75 [1.36–2.25]). The association with diabetes was seen for both participants with PD diagnosed between 1995 and 1999 and participants with PD diagnosed after 2000. In addition, similar results were obtained after excluding participants with stroke, heart disease, cancers, or poor or fair health status and in subgroup analyses by age, sex, smoking status, and coffee consumption.

CONCLUSIONS—This large study showed that diabetes was associated with a higher future risk of PD and the nature of this association warrants further investigation.

Diabetes Care 34:910–915, 2011

1996 by the National Cancer Institute to investigate etiologies of cancer and other age-related chronic diseases (12). AARP, formerly known as American Association of Retired Persons, is a nonprofit and membership-based interest organization for U.S. adults aged 50 years or older. AARP currently has over 40 million members across the U.S. and thus represents a wide range of older U.S. adults. The NIH-AARP Diet and Health cohort is composed of 566,401 AARP members (ages 50–71 years) from six U.S. states (California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana) and two metropolitan areas (Atlanta, GA and Detroit, MI), and all participants completed a comprehensive survey on diet and lifestyle at baseline (12). Between 2004 and 2006, a follow-up questionnaire was mailed to surviving participants of the cohort to update lifestyle information and to ascertain the occurrence of major chronic diseases, including PD. A total of 187,499 (55.2%) men and 130,761 (57.6%) women of the

CNS Drugs
https://doi.org/10.1007/s40263-018-0593-6

LEADING ARTICLE

Neuroprotective Actions of Glucagon-Like Peptide-1 (GLP-1) Analogues in Alzheimer's and Parkinson's Diseases

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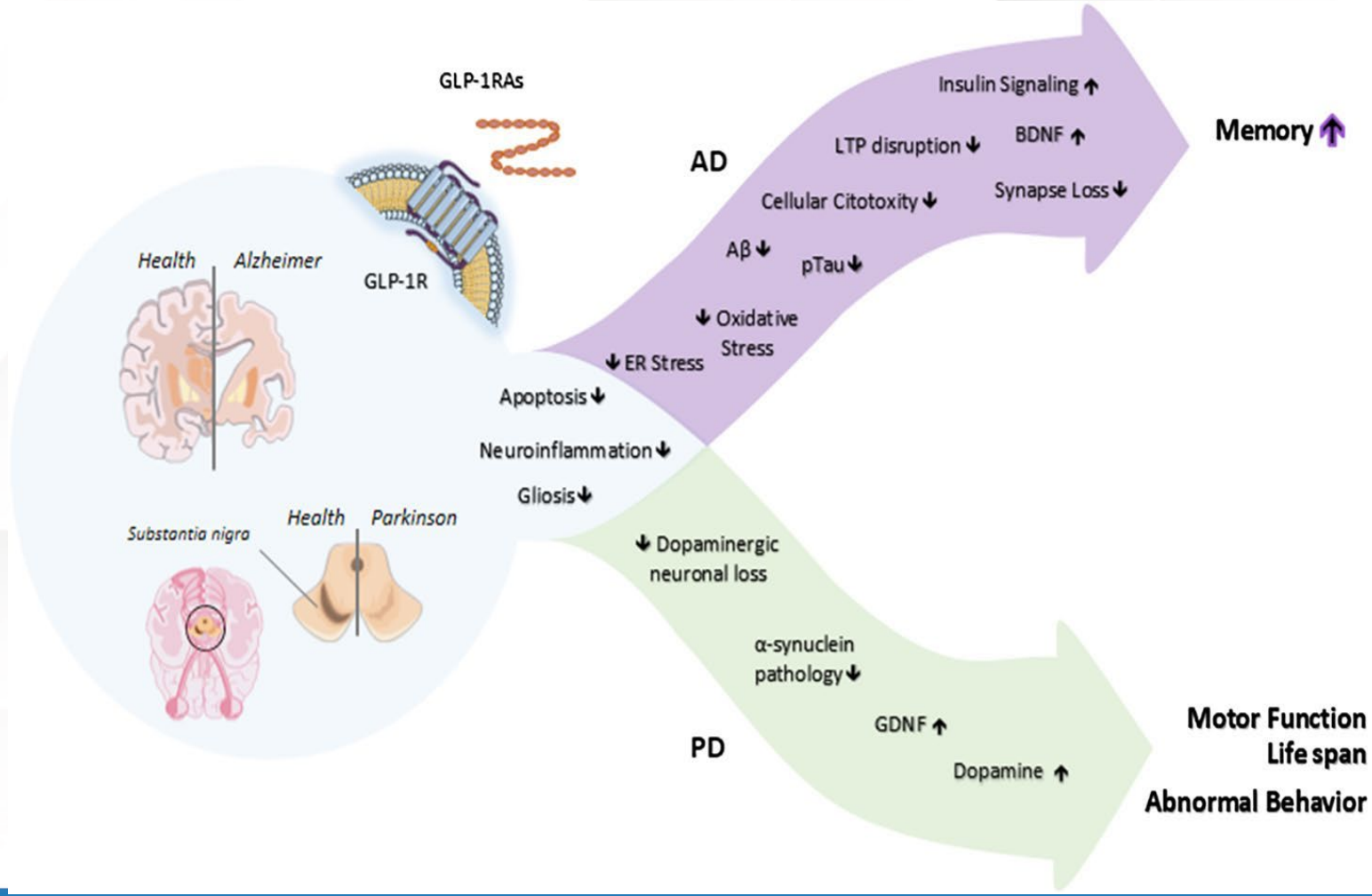

Diabete e Malattie neurodegenerative

GLP-1 Receptor Agonists in Neurodegeneration: Neurovascular Unit in the Spotlight

by Giulia Monti [1], Diana Gomes Moreira [2], Mette Richner [1], Henricus Antonius Maria Mutsaers [3], Nelson Ferreira [1] and Asad Jan [1,*]

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Clinical trials	*Trial ID*			
AD	NCT02140983	Liraglutide	Increased connectivity in the default mode network	[85]
	NCT01469351	Liraglutide	Improved cerebral glucose uptake	[86,87]
	NCT01843075	Liraglutide		[88]
	NCT01255163	Exenatide	Improved cognition	[89]
	NCT04777396	Semaglutide	No significant changes in cognition	
	NCT04777409	Semaglutide	Recruiting	
			Recruiting	
PD	NCT01971242	Exenatide	Improved motor and cognitive outcomes	[90]
	NCT01174810	Exenatide		[91]
	NCT02953665	Liraglutide	Improved motor and cognitive outcomes	
	NCT03439943	Lixisenatide	Active	
	NCT04154072	Exenatide	Active	
	NCT03659682	Semaglutide	Active	
			Not yet recruiting	

Table 2. GLP-1RAs in AD and PD: An overview of the experimental models and clinical trials.

Studies	Experiment	GLP-1RA	Observations	Publications
Preclinical studies	***Animal model***			
AD features				
Plaque load	APP/PS1/tau mice	Liraglutide	Reduction of plaque load	[72,76,77]
	5xFAD mice	Liraglutide	Reduction of plaque load	[78]
	APP/PS1 mice	Lixisenatide	Reduction of plaque load	[76]
	3xTg-AD mice	Exendin-4	Reduction of plaque load	[62]
Tau phosphorylation	APP/PS1/tau mice	Liraglutide	Reduction of neurofibrillary tangles	[56,72]
	hTauP301L mice	Liraglutide	Reduced Tau phosphorylation	[58]
	Aβ injection in mice	Liraglutide	Reduced Tau phosphorylation	[67]
	APP/PS1 x db/db mice	Liraglutide	Reduced Tau phosphorylation	[79]
	Streptozotocin injection in mice	Dulaglutide	Reduced Tau phosphorylation	[73]
Cognitive and memory performance	Aβ injection in mice	Liraglutide	Improved cognitive impairment	[74]
	Aβ injection in rats	Lixisenatide	Improved spatial memory	[80]
	Streptozotocin injection in mice	Dulaglutide	Improved memory ability	[73]
Other	Aβ injection in non-human primates	Liraglutide	Reduced synaptic loss	[74]
PD features				
Dopaminergic neuronal loss	6-OHDA rat model	Liraglutide	No influence on dopaminergic neuronal loss	[59]
	6-OHDA rat model	Exendin-4	Neurogenesis	[55]
	6-OHDA rat model	Exendin-4′	Reduced lesions	[60]
Motor performance	MPTP mouse model	Liraglutide	Improved motor control	[64]
	MPTP mouse model	Lixisenatide	Improved motor control	[64]
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	[81]
		Exendin-4		[82]
	Preformed fibrils injection in the olfactory bulb of C57BL/6J mice		No significant reduction of α-synuclein aggregation	

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AMD Associazione Medici Diabetologi

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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*

Findings Between Aug 18, 2011, and Aug 14, 2013, 9901 participants were randomly assigned to either dulaglutide (n=4949) or placebo (n=4952). During median follow-up of 5·4 (IQR 5·1–5·9) years, 8828 participants provided a baseline and one or more follow-up MoCA or DSST scores, of whom 4456 were assigned dulaglutide and 4372 were assigned placebo. The cognitive outcome occurred in 4·05 per 100 patient-years in participants assigned dulaglutide and 4·35 per 100 patient-years in people assigned placebo (hazard ratio [HR] 0·93, 95% CI 0·85–1·02; p=0·11). After post-hoc adjustment for individual standardised baseline scores, the hazard of substantive cognitive impairment was reduced by 14% in those assigned dulaglutide (HR 0·86, 95% CI 0·79–0·95; p=0·0018).

Interpretation Long-term treatment with dulaglutide might reduce cognitive impairment in people with type 2 diabetes. Further studies of this drug focused on brain health and cognitive function are clearly indicated.

A Research Study Investigating Semaglutide in People With Early Alzheimer's Disease (EVOKE)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT04777396

Recruitment Status : Recruiting

First Posted : March 2, 2021

Last Update Posted : March 31, 2022

See **Contacts and Locations**

View this study on Beta.ClinicalTrials.gov

Diabete ed OSAS

368 Diabetes Care Volume 43, August 2020

Check for updates

Obstructive Sleep Apnea, a Risk Factor for Cardiovascular and Microvascular Disease in Patients With Type 2 Diabetes: Findings From a Population-Based Cohort Study

Nicola J. Adderley,[1] Anuradhaa Subramanian,[1] Konstantinos Toulis,[1] Krishna Gokhale,[1] Thomas Taverner,[1] Wasim Hanif,[2] Shamil Haroon,[1] G. Neil Thomas,[1] Christopher Sainsbury,[1] Abd A. Tahrani,[2,3,4] and Krishnarajah Nirantharakumar[1,2,3,4,5]

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L'apnea ostruttiva del sonno (OSA) è comune nei pazienti con diabete di tipo 2 (24– 86%) e pazienti con diabete di tipo 2 sono a maggior rischio di sviluppare OSA.

Diabete ed OSAS

American Journal of Respiratory and Critical Care Medicine 2015;191:A4144

Treatment of Obstructive Sleep Apnea with Glucagon Like Peptide- 1 Receptor Agonist

Raouf S. Amin , , Narong Simakajornboon , Rhonda V. Szczesniak ,

STUDIO: 30 soggetti OSA, con indice apnea ipopnea (AHI) > 15/h , 20 in trattamento con liraglutide fino a 1.8 mg/die , 10 controllo .

RISULTATI: Riduzione del 40% (20 +/- 12 eventi) dell'AHI nel 70% dei soggetti trattati (p=.002) No differenze nel gruppo di controllo. L'indice di massa corporea (BMI) non è cambiato rispetto al basale in entrambi i gruppi.

The Case for Early Use of Glucagon-like Peptide-1 Receptor Agonists in Obstructive Sleep Apnea Patients with Comorbid Diabetes and Metabolic Syndrome

Rizwana Sultana [1,*], Fatoumatta Sissoho [2], Vinod P. Kaushik [2] and Mukaila A. Raji [2,*]

Life **2022**, *12*, 1222. https://doi.org/10.3390/life12081222

Table 2. Putative Mechanisms of GLP1 RA agonist Beneficial Effects in OSA Patients from references.

⇓ Weight
⇓ Perineck/Peri-oropharyngeal Soft Tissue
⇓OSA-associated ASCVD: CVA, Hypertension, Arrythmias, Heart Failure, Myocardial Infarction, Sudden Cardiac Death
⇓ Metabolic Syndrome
⇓ Hemoglobin A1C and Diabetes Complications
⇓ Systemic Inflammation
⇓ Metabolic Dysregulation
⇓ Endothelial Dysfunction
⇓ Vascular Dementia
⇓ Risk of Delirium
⇓ Depression

GLP1 - RA

Complicanze

OK

Comorbidita'

- NAFLD/NASH
- OSAS
- Malattie neurodegenerative
- Depressione

OK

Diabetes Care 2022;45(11):2753–2786 | https://doi.org/10.2337/dci22-0034

Grazie