Terapia con analoghi del GLP-1: quando e perché

Milano
18 Giugno 2019

Analoghi del GLP-1 nei Pazienti Fragili

Anna Solini

Dipartimento di Patologia Chirurgica, Medica, Molecolare e di Area Critica

Università di Pisa

La Prof.ssa Anna Solini dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Astra Zeneca
- Boehringer Ingelheim
- Lilly
- Mundipharma
- Sanofi

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.).

Defining Frailty

A clinically recognizable state in which **the ability of older people to cope with everyday or acute stressors is compromised** by an increased vulnerability brought by age-associated declines in physiological reserve and function across multiple organ systems

WHO, Geneva 2016

La **fragilità** definisce una maggiore **vulnerabilità** dell'individuo allo stress e comporta una **limitazione delle attività quotidiane**, dovuta alla presenza di **pluripatologie**, e un deterioramento della salute e dello stato funzionale, che predispone a esiti negativi. In particolare, si tratta di soggetti **anziani** con **comorbilità** e **instabilità clinica**, **disabilità e rischio di eventi avversi**, **con elevata incidenza di ospedalizzazione e/o morte**

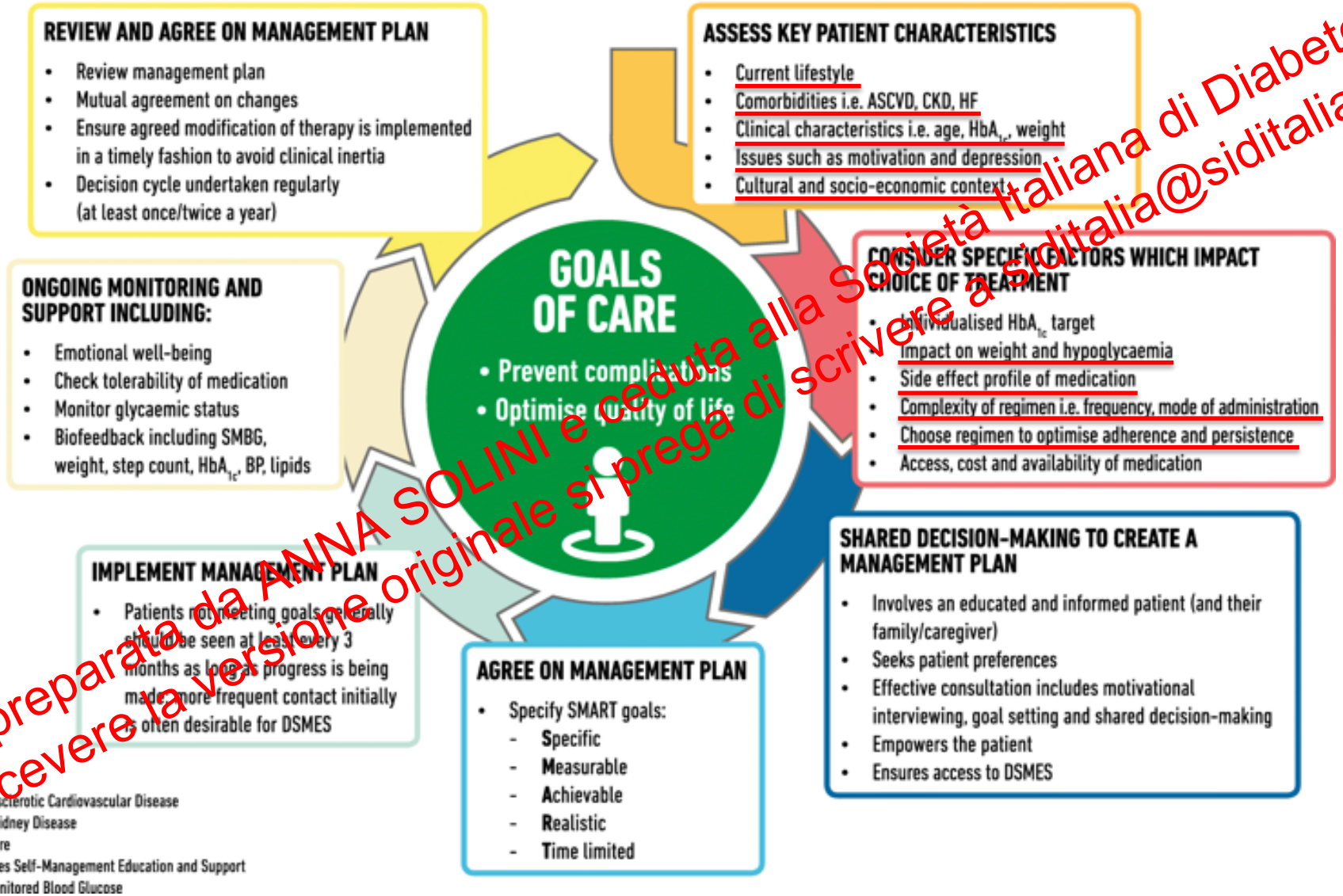
Ministero della Salute

Prevalence of frailty varies based on the population examined; however, it is estimated to be 10% in the population aged>60 years and 25% in the population aged>80 years

Identifying Causes of Frailty in T2DM Individuals

- ✓ Aging (≥65 years with comorbidities or cognitive-functional impairment)
- ✓ Heart disease (atherosclerotic CVD or heart failure)
- ✓ Subjects prone to risk of hypoglycemia
- ✓ CKD stage 3-5; severe hepatic disease
- ✓ Severe obesity
- ✓ Neurodegenerative diseases

DECISION CYCLE FOR PATIENT-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

Diabetologia 2018; 61:2461-2498

Aging T2DM Individuals

ADA Recommendation

- Hypoglycemia should be avoided in older adults with diabetes. It should be assessed and managed by adjusting glycemic targets and pharmacologic interventions. B

- Older adults who are cognitively and functionally intact and have significant life expectancy may receive diabetes care with goals similar to those developed for younger adults. C

- Glycemic goals for some older adults might reasonably be relaxed using individual criteria, but hyperglycemia leading to symptoms or risk of acute hyperglycemic complications should be avoided in all patients. C

HbA1c < 7.5% in aging healthy subjects
HbA1c < 8.0% multiple comorbidities, mild-to-moderate cognitive impairment
HbA1c < 8.5% unhealthy, limited life expectancy, severe cognitive decline

- Overall comfort, prevention of distressing symptoms, and preservation of quality of life and dignity are primary goals for diabetes management at the end of life. E

Diabetes Care 2017; 40(Suppl 1):S99-S104

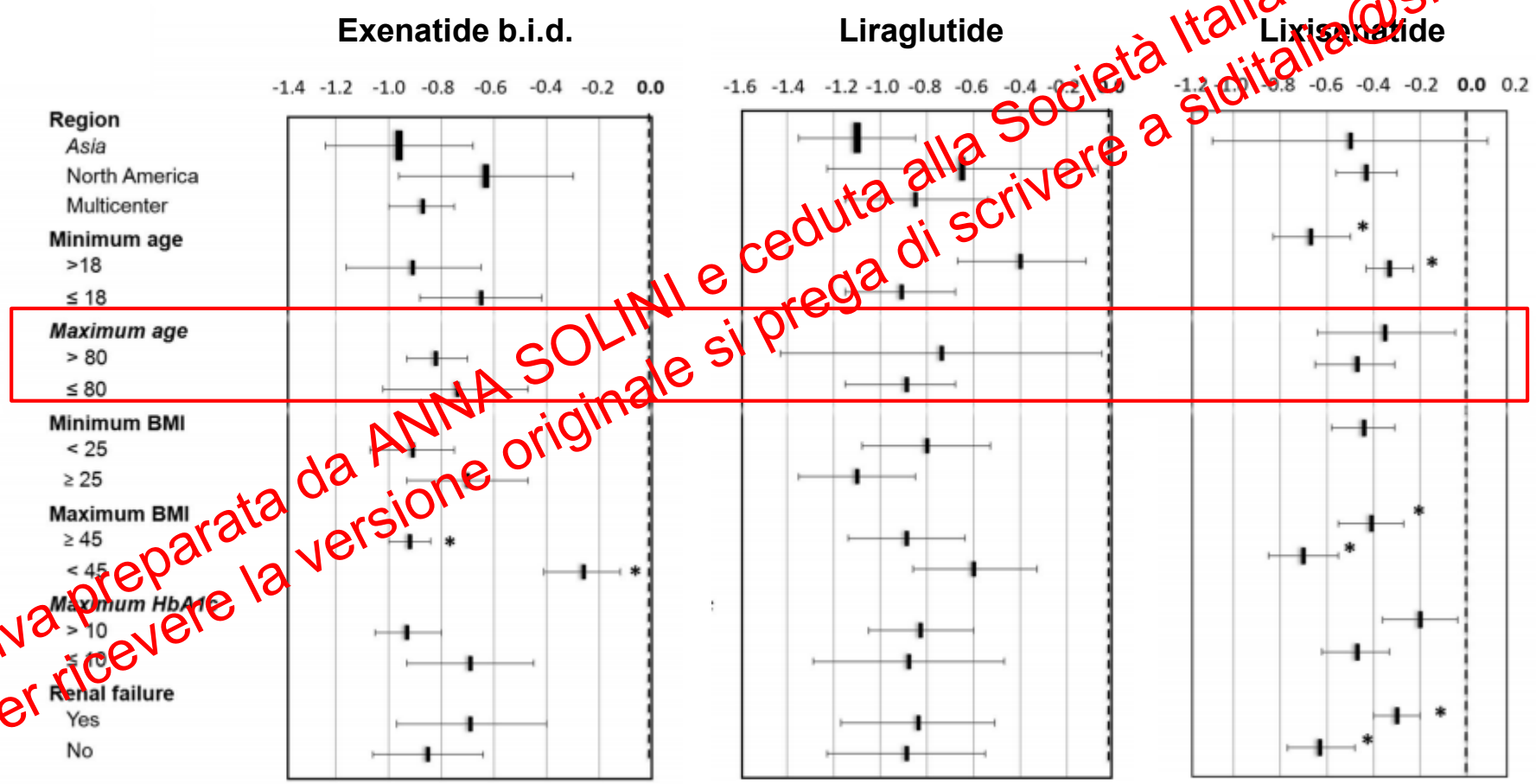
Glucose-Lowering Therapies in Frail Older Adults with Diabetes

	HbA1c reduction	Advantages	Disadvantages	Vignette in Frail Population
Metformin	1% (11 mmol/mol)	Low hypoglycemia risk Low cost Well tolerated generally	Many contraindications in population with high comorbidity burden May cause weight loss, GI upset in frail patients	Can be used until eGFR <30 ml/min Extended release formulation has lower complexity and fewer GI side effects Assess and replace vitamin B12
Sulfonylureas	1% (11 mmol/mol)	Low cost Established glucose-lowering medication Can be used in moderate to severe renal impairment	High risk of hypoglycemia Avoid glibenclamide (glyburide)	Avoid in patients with inconsistent eating pattern High risk of hypoglycemia during acute illness with weight loss Consider dose titrating if already receiving substantial amount of insulin (approximately >0.5 U/kg/day)
Meglitinides	0.4-0.9% (4.4-9.9 mmol/mol)	Shorter duration of action compared with sulfonylurea	Higher cost than sulfonylurea Increased regimen complexity due to multiple daily dosing with meals	Can be withheld if patient refuses to eat any particular meal
TZDs, Pioglitazone	1% (11 mmol/mol)	Low hypoglycemia risk Low cost Once a day dosing Can be used in moderate to severe renal impairment	Many contraindications in population with high comorbidity burden such as CHF, peg edema, anemia Possible risk of bladder cancer.	Good efficacy in older patients with high insulin resistance

	HbA1c reduction	Advantages	Disadvantages	Vignette in Frail Population
GLP-1 agonists	0.8-1.0% (9-11 mmol/mol)	Low hypoglycemia risk Once a day and once a week formulation New formulations available in combination with basal insulin	High cost Injectable	Monitor for anorexia, weight loss; do not use in severe renal impairment (eGFR <30 ml/min); dose reduction needed in moderate impairment (except for Liraglutide)
		Risk of other adverse effects moderate	patients but evidence increasing	incontinence, lower UTI, genital infections, dehydration; do not initiate if eGFR is <60 ml/min; dose reduction required in the presence of renal imapirment
GLP-1 agonists	0.8-1.0% (9-11 mmol/mol)	Low hypoglycemia risk Once a day and once a week formulation New formulations available in combination with basal insulin	High cost Injectable	Monitor for anorexia, weight loss; do not use in severe renal impairment (eGFR <30 ml/min); dose reduction needed in moderate impairment (except for Liraglutide)
Insulin	> 1% (> 11 mmol/mol)	No ceiling effect Many different types including high concentrated forms have variable serum half-life and can be used to target hyperglycemia at different times of the day; can be used in renal impairment	High risk of hypoglycemia Need for matching carbohydrate content in patients with variable appetite when using prandial insulin Carer education and training needed if involved in administration	Use of basal insulin with other agents to lower post-prandial glucose can lower complexity and reduce the risk of hypoglycemia

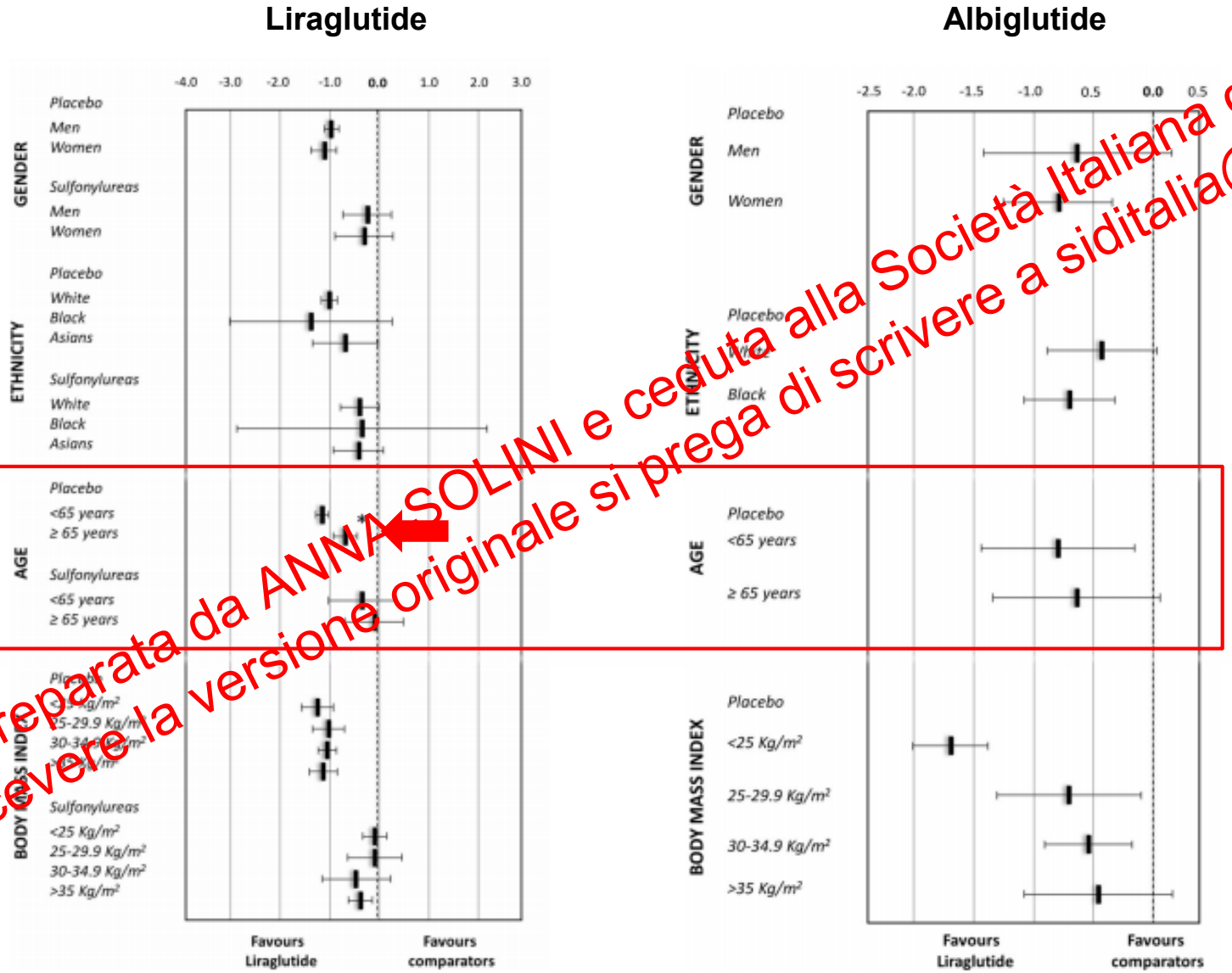
Sinclair AJ, ***J Frailty Aging*** 2018; 7:10-20

Predictors of Response to GLP-1 RA
A Meta-Analysis and Systematic Review of RCT



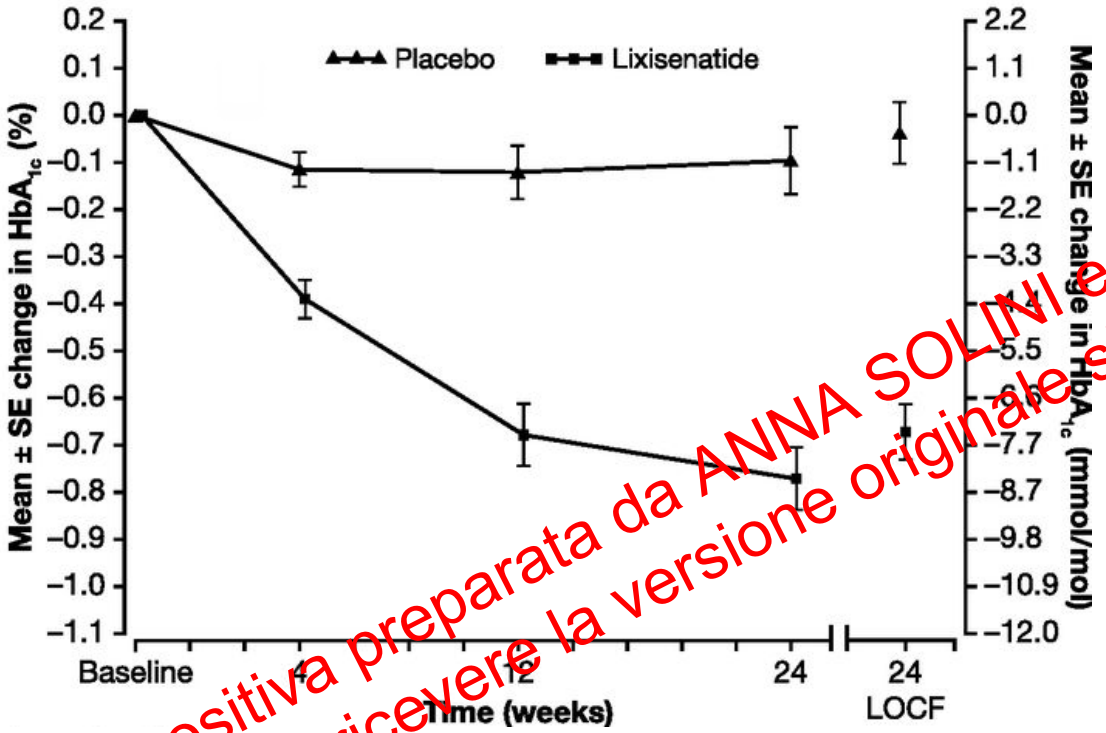
Monami M, **Acta Diabetol** 2017; 54:1101-1114

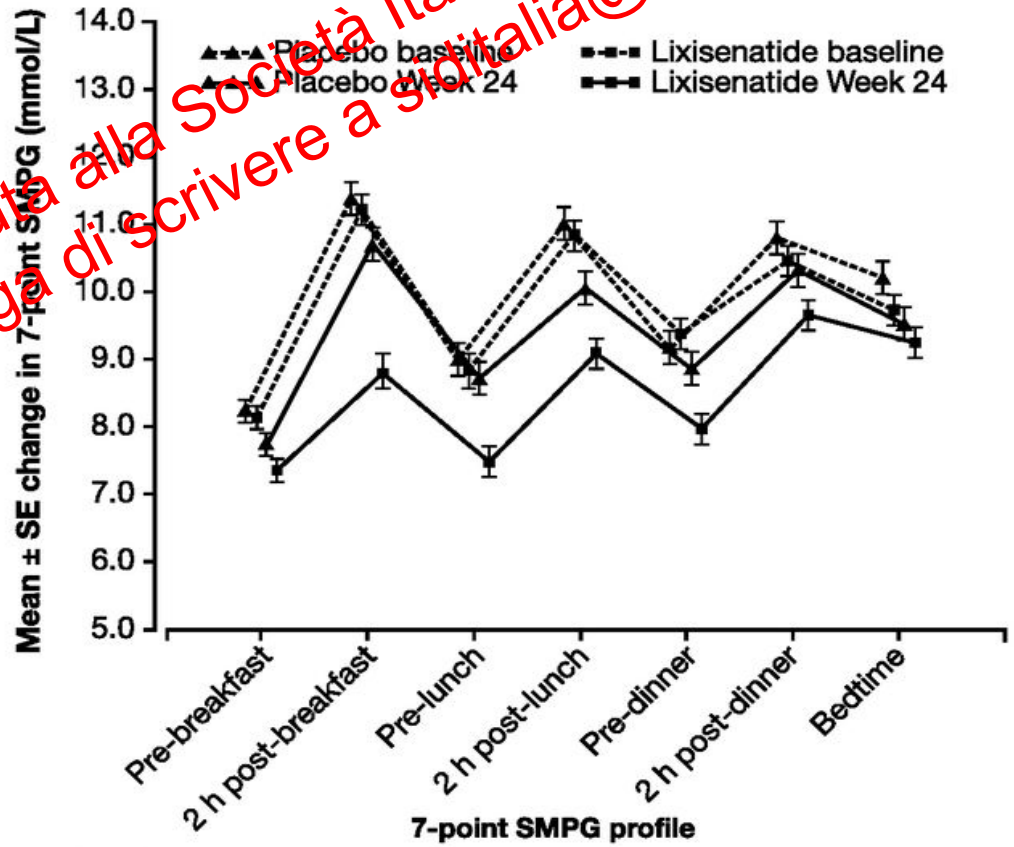
Predictors of Response to GLP-1 RA
A Meta-Analysis and Systematic Review of RCT



Monami M, **Acta Diabetol** 2017; 54:1101-1114

Lixisenatide in Older T2DM Patients: the GEtGoal-O Randomized Trial





Meneilly GS, ***Diabetes Care*** 2017; 40:485-493

Safety of Lixisenatide in Elderly and Very Elderly (≥75 yrs) T2DM Subjects
The GetGoal Phase III Program

A pooled analysis of 6 RCT (12 or 24 months)

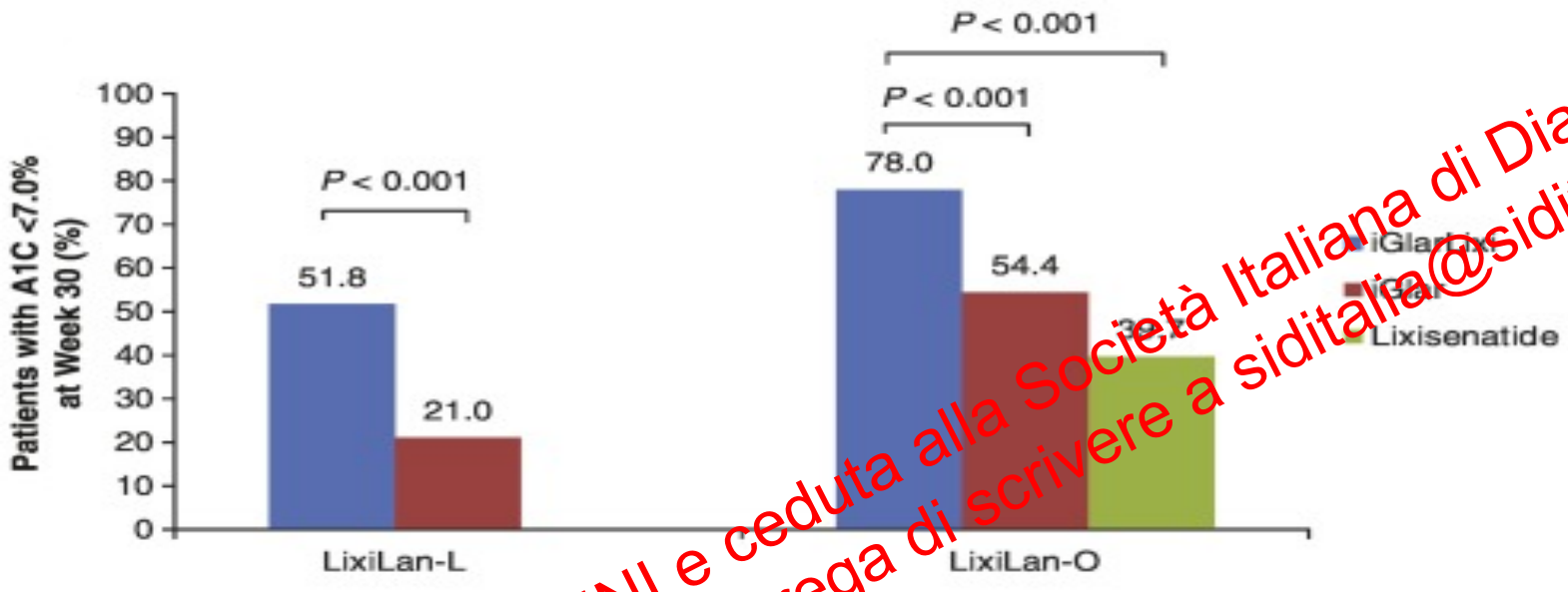
Age	<65 years		≥65 years		≥75 years		≥75 years	
	PBO ($n = 817$)	Lixisenatide ($n = 1748$)	PBO ($n = 244$)	Lixisenatide ($n = 379$)	PBO ($n = 1030$)	Lixisenatide ($n = 2079$)	PBO ($n = 31$)	Lixisenatide ($n = 48$)
Any TEAE, *n* (%)	516 (63.2)	1203 (68.8)	144 (58.0)	272 (71.8)	645 (62.6)	1440 (69.3)	15 (48.4)	35 (72.9)
GI disorders, *n* (%)	170 (20.8)	715 (40.9)	40 (16.4)	164 (43.3)	205 (19.9)	857 (41.2)	5 (16.1)	22 (45.8)
Nausea, *n* (%)	47 (5.8)	446 (25.5)	19 (7.8)	110 (29.0)	64 (6.2)	540 (26.0)	2 (6.5)	16 (33.3)
Vomiting, *n* (%)	13 (1.6)	170 (9.7)	6 (2.5)	54 (14.2)	19 (1.8)	218 (10.5)	0	6 (12.5)
Diarrhoea, *n* (%)	53 (6.5)	141 (8.1)	11 (4.5)	35 (9.2)	64 (6.2)	173 (8.3)	0	3 (6.3)
GI/abdominal pain, *n* (%)	28 (3.4)	72 (4.1)	4 (1.6)	18 (4.7)	32 (3.1)	88 (4.2)	0	1 (2.1)
Dyspepsia, *n* (%)	3 (0.4)	62 (3.5)	0	24 (6.3)	3 (0.3)	84 (4.0)	0	2 (4.2)

PBO, placebo; TEAE, treatment-emergent adverse event; GI, gastrointestinal.
Data from the main treatment period of the included studies [GetGoal-Mono (12 weeks) and GetGoal-M, GetGoal-F1, GetGoal-S, GetGoal-L and GetGoal-L-Asia (all 24 weeks)] – safety population.

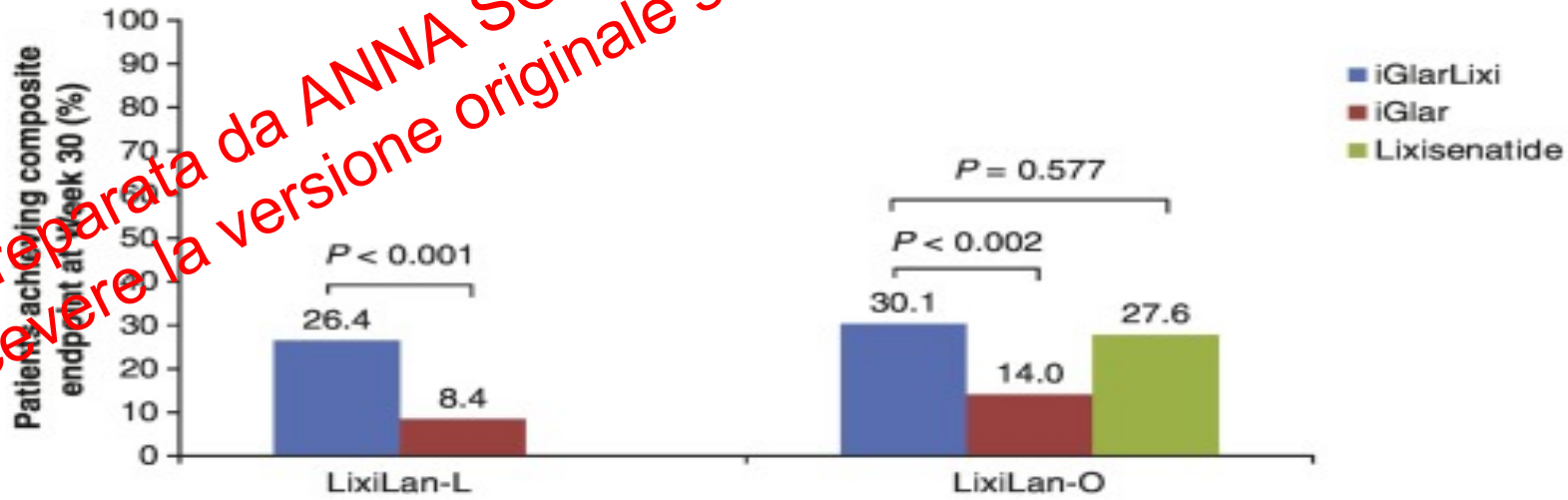
Raccah D, ***Diabetes Metab Res Rev*** 2015; 31:204-211

Glargine/Lixisenatide: Efficacy and Safety in Elderly T2DM Subjects

% of pts with HbA1c<7.0% at week 30



% of pts achieving composite endopoint at week 30

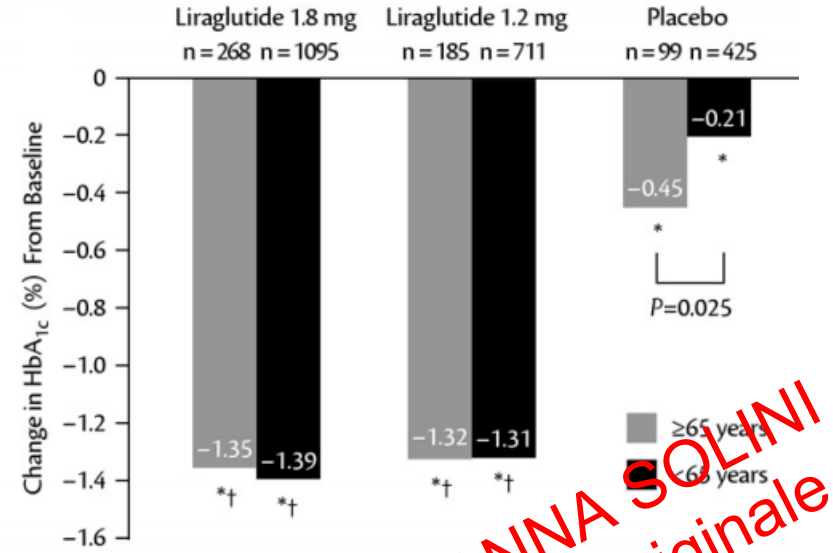


Handelsman Y, ***J Diabetes Complications*** 2019; 33:236-242

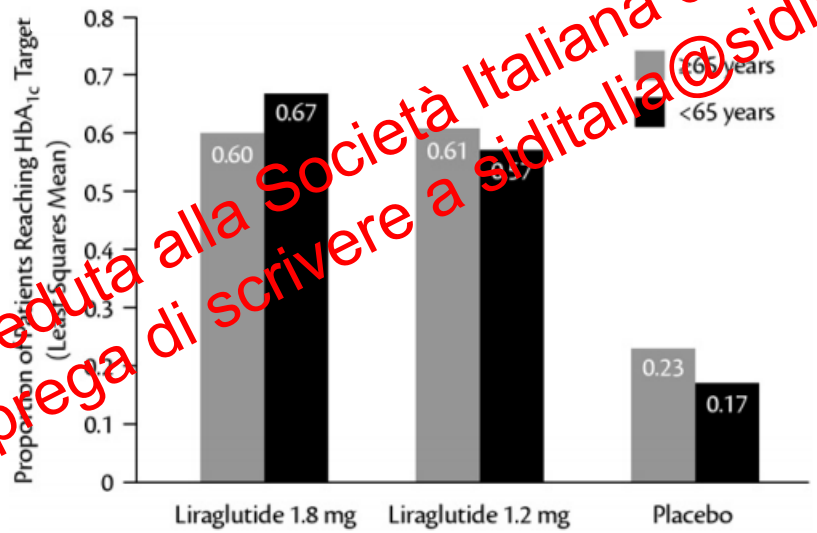
Efficacy and Tolerability of Liraglutide according to Age

A pooled analysis of Phase III studies

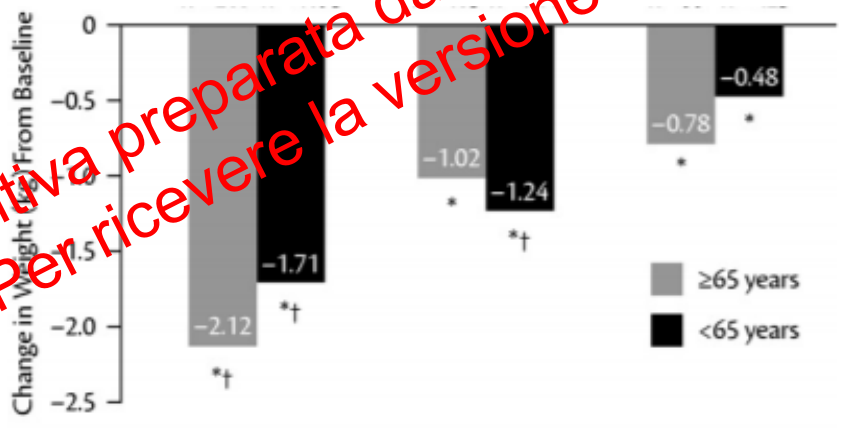
HbA1c



% at target



BW



Bode BW, ***Am J Geriatr Pharmacother*** 2011; 9:423-433

Side Effects of Liraglutide in Elderly T2DM Patients

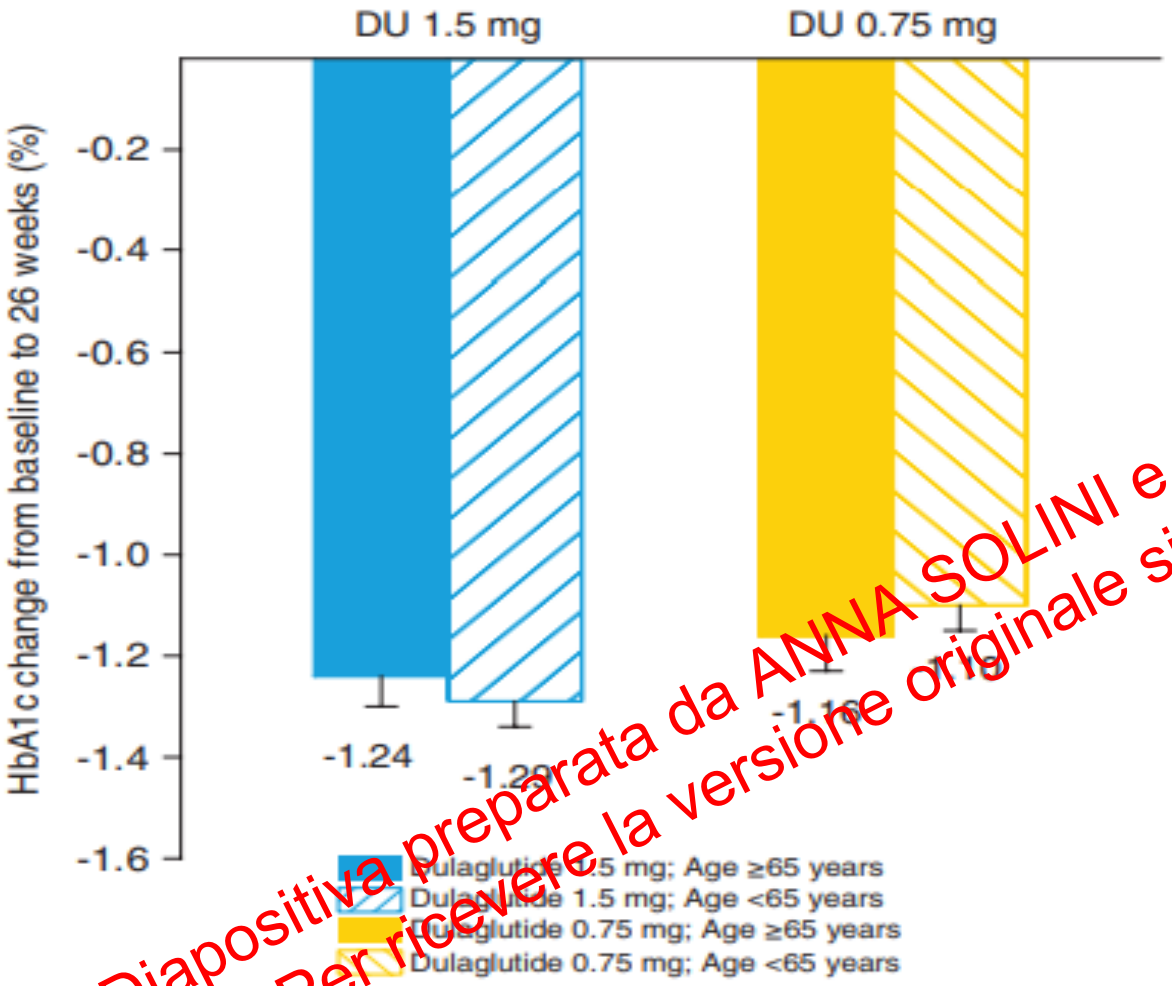
% of patients experiencing hypos and other adverse events during the first 26 weeks of treatment

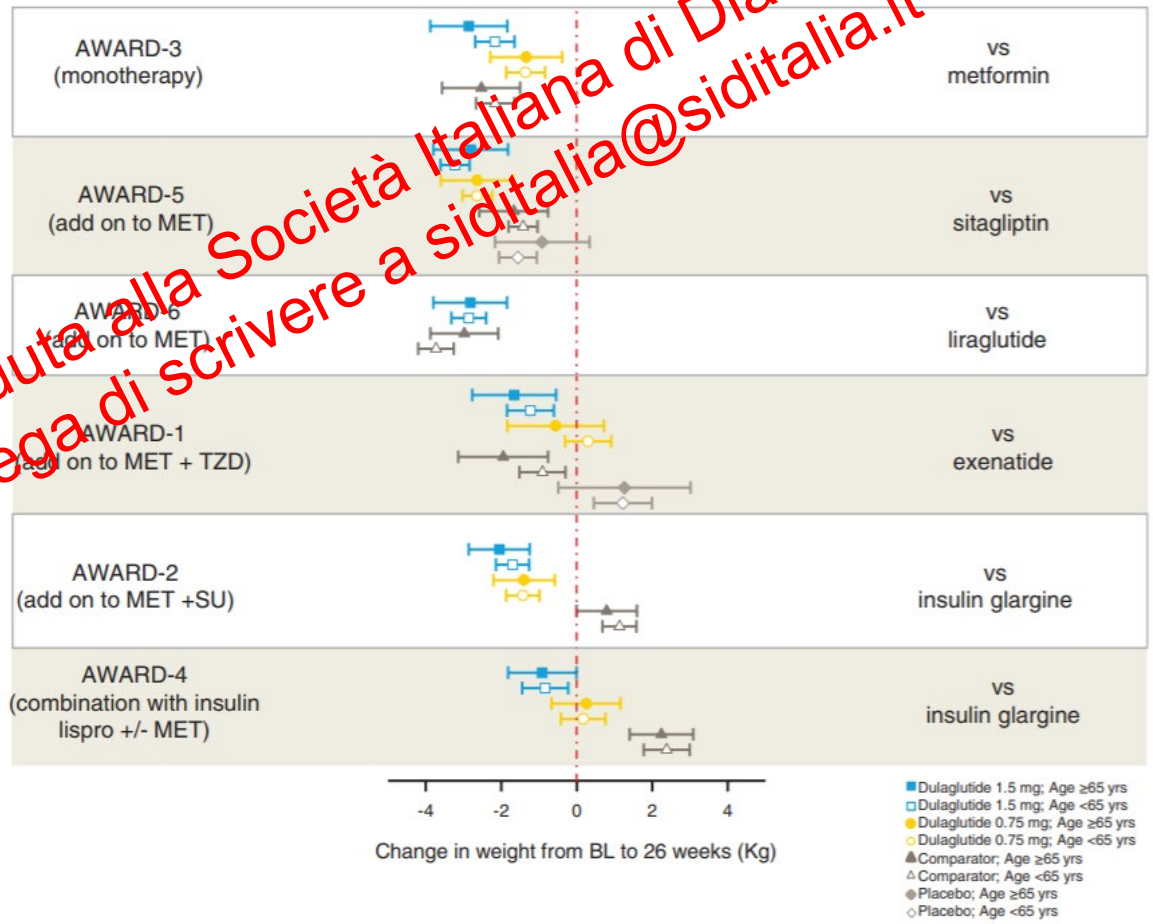
Parameter	Liraglutide 1.8 mg		Liraglutide 1.2 mg		Placebo	
	≥65 Years	<65 Years	≥65 Years	<65 Years	≥65 Years	<65 Years
Major hypoglycemia	0.0	0.5	0.0	0.0	0.0	0.0
Minor hypoglycemia	15.2	13.2	4.3	8	9.1	8.0
Deaths, % of patients	0.0	0.0	0.0	0.1	1.0	0.0
Serious adverse events	4.1	3.9	7.6	4.8	5.1	4.9
All adverse events	75.5	74.0	78.4	76.1	56.6	65.2
Withdrawals due to adverse events	12.7	7.6	9.7	7.2	2.0	3.1
Nausea, % of patients/% withdrawals due to nausea	24.5/7.1	21.0/3.2	20.5/3.7	20.4/2.5	2.0/0.0	5.4/0.0
Vomiting, % of patients/% withdrawals due to vomiting	7.4/2.6	7.8/1.7	5.4/0.0	8.4/1.7	3.0/0.0	1.9/0.2
Diarrhea, % of patients/% withdrawals due to diarrhea	13.0/2.2	13.3/1.4	13.5/1.6	10.0/1.3	2.0/0.0	5.2/0.0

*All 6 patients who experienced major hypoglycemia were also being treated with sulfonylureas.

Bode BW, ***Am J Geriatr Pharmacother*** 2011; 9:423-433

Efficacy of Dulaglutide in the Elderly



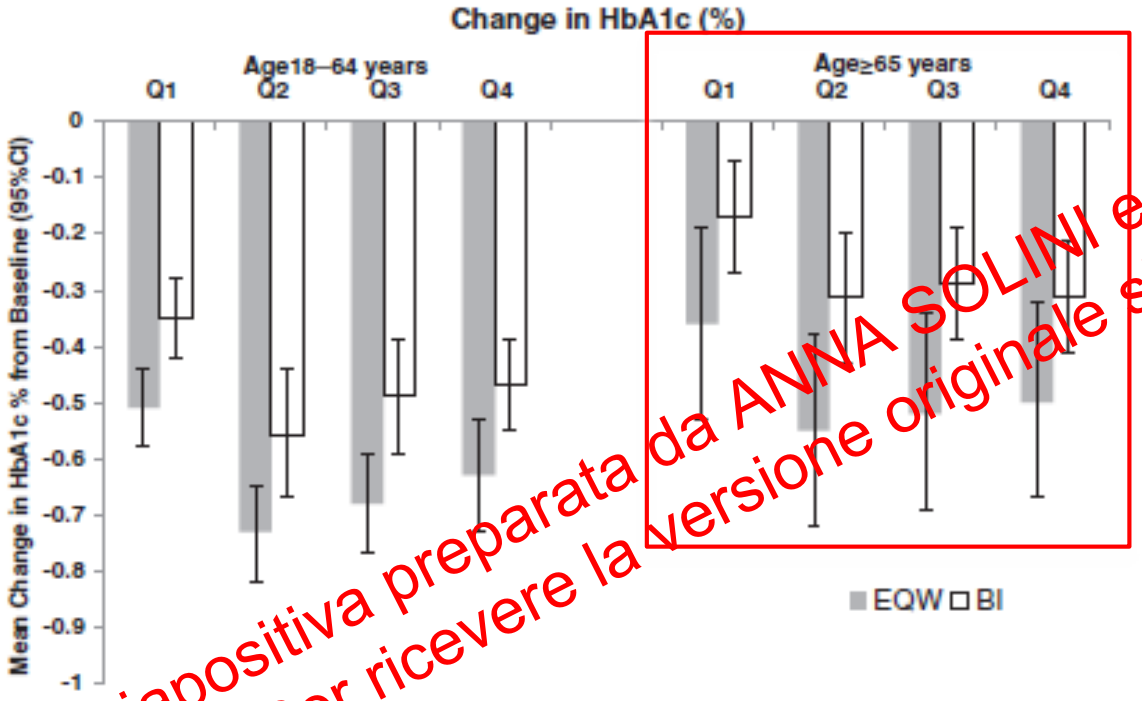


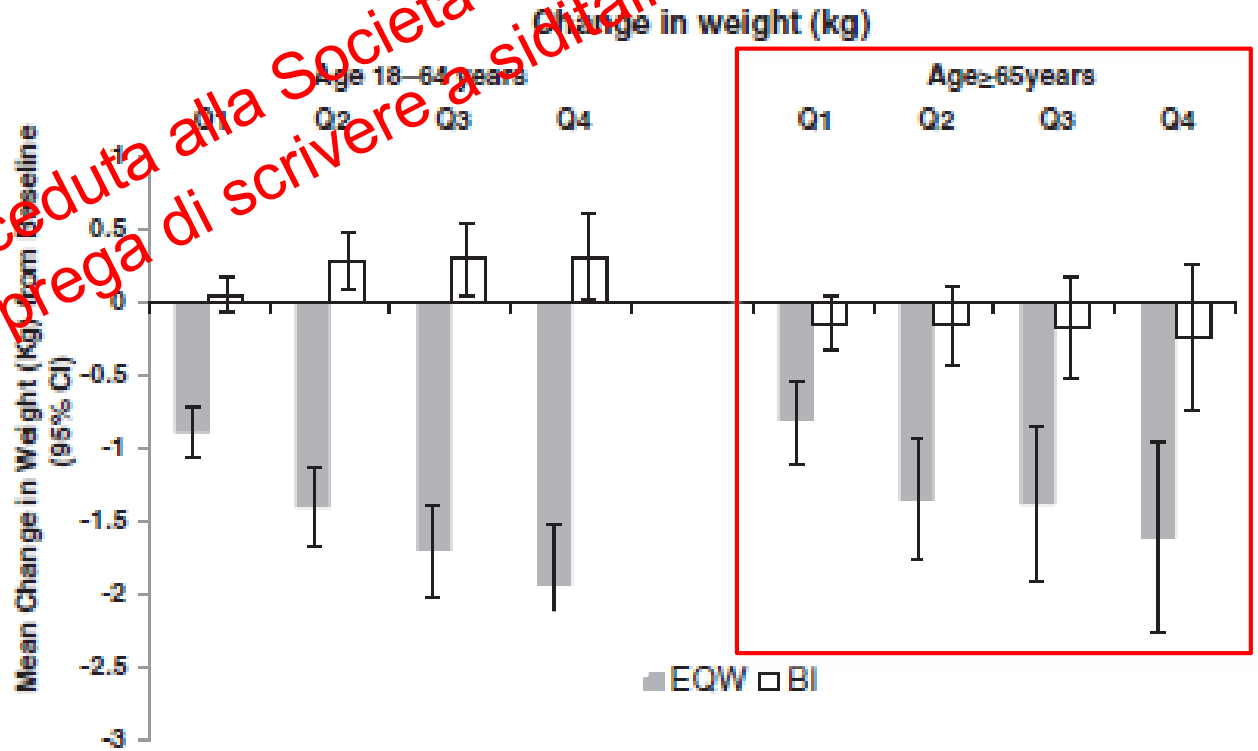
Boustani MA, ***Diabetes Obes Metab*** 2016; 18:820-828

Semaglutide in Elderly T2DM Patients
Pooled analysis of the SUSTAIN 1-5 trials

Warren M, ***Diabetes Obes Metab*** 2018; 20:2291-2297

Exenatide Once-Weekly in Elderly or Renal Impaired T2DM Subjects in USA





Loughlin AM, ***Diabetes Obes Metab*** 2018; 20:898-909

Occurrence of Hypoglycemia and GI Symptoms: Comparison between Exenatide Once-Weekly and Basal Insulin

Characteristic		N	Number of events (%)	IR per 1000 person-years (95% CI)	Relative rate (95% CI)
Hypoglycaemia					
18-64 years	EQW	1513	101 (6.7)	46.5 (37.8-56.5)	0.75 (0.60-0.95)
	BI	3064	262 (8.6)	61.6 (54.3-69.5)	Reference
≥65 years	EQW	495	48 (9.7)	72.1 (53.2-95.6)	0.92 (0.65-1.29)
	BI	952	106 (11.1)	78.5 (64.0-95.0)	Reference
Nausea and vomiting					
18-64 years	EQW	1513	257 (17.0)	130.0 (114.6-146.9)	1.13 (0.97-1.32)
	BI	3064	467 (15.2)	115.0 (104.8-126.0)	Reference
≥65 years	EQW	495	83 (16.8)	133.8 (106.5-165.8)	**1.45 (1.09-1.91)**
	BI	952	123 (12.9)	92.5 (76.9-110.3)	Reference
Constipation and diarrhoea					
18-64 years	EQW	1513	257 (17.0)	130.1 (114.7-147.0)	1.11 (0.96-1.30)
	BI	3064	470 (15.3)	116.7 (106.4-127.8)	Reference
≥65 years	EQW	495	108 (21.8)	181.8 (149.2-219.5)	1.21 (0.96-1.54)
	BI	952	186 (19.5)	150.0 (129.2-173.2)	Reference
Any gastrointestinal symptom					
18-64 years	EQW	1513	386 (25.5)	212.1 (191.5-234.4)	1.13 (1.00-1.28)
	BI	3064	704 (23.0)	187.0 (173.4-201.3)	Reference
≥65 years	EQW	495	148 (29.9)	270.1 (228.3-317.3)	**1.32 (1.08-1.63)**
	BI	952	242 (25.4)	203.9 (179.0-231.3)	Reference

Loughlin AM, ***Diabetes Obes Metab*** 2018; 20:898-909

Glycaemic outcomes of an Individualized treatMent aPproach for oldER vulnerable patIents: A randomized, controlled stUdy in type 2 diabetes Mellitus (IMPERIUM)

Strategy A: a non-sulphonylurea OAM and a glucagon-like peptide-1 receptor agonist as the first injectable

Strategy B: a sulphonylurea as the preferred OAM and insulin glargine as the first injectable

Treatment outcomes

	Strategy-A,N = 98		Strategy-B,N = 93
Relative success of treatment strategies			
Success[a], *n* (%)	62 (63.3)		52 (55.9)
Adjusted % (95% CI)	64.5 (54.4, 73.4)		54.9 (44.6, 64.9)
Adjusted % (95% CI)/*P*-value, Strategy-A vs Strategy-B		9.5 (−4.7, 23.2)/.190	
Conditional power[b]		0.58	
Failure, *n* (%)	36 (36.7)		41 (44.1)
Reason for failure[c], *n* (%)			
Clinically significant hypoglycaemia	0		1 (1.1)
HbA1c target not reached/maintained[d]	36 (36.7)		41 (44.1)

Heller SR, ***Diabetes Obes Metab*** 2018; 20:148-156

Factors Contributing to Inpatient Hypoglycemia in Older Adults with Diabetes

Medications: insulin, sulphonylureas, glinides, quinolones
Intensive glycemic control
Inappropriate insulin dosing and medication errors
Poor coordination of insulin administration and food delivery
Interruption of enteral nutrition or parenteral nutrition infusion
Hypoglycemia unawareness
Renal insufficiency
Liver failure
Severe illness, sepsis
Dementia
Frailty
Medical and surgical procedures

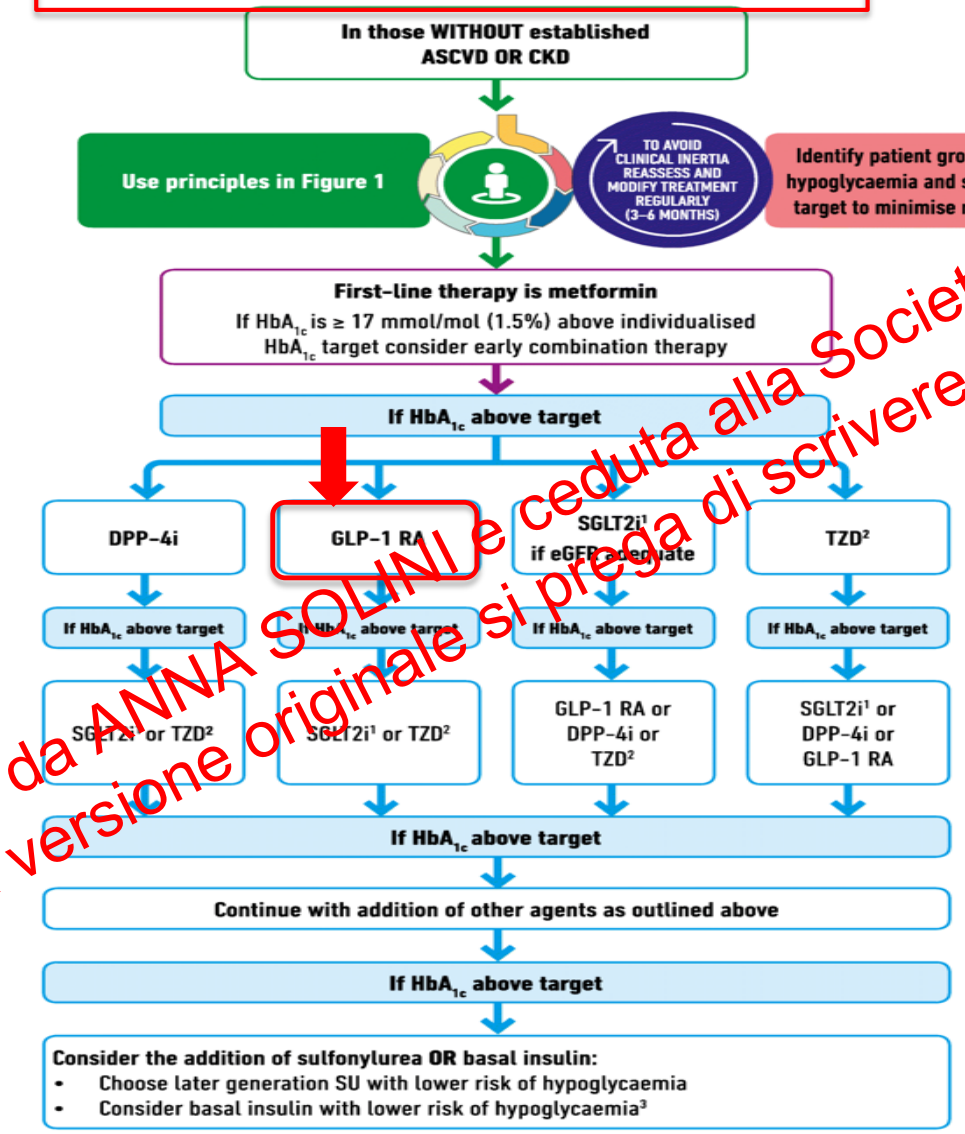
GLP-1 RA and Hypoglycemia

Hypoglycemia is a key issue in a frail patient.
It is coupled with increased morbidity, falls and cognitive impairment

	Short-Acting GLP-1 Receptor Agonists	Long-acting GLP-1 Receptor Agonists
Glycaemic effects		
HbA_{1c}	Marked and sustained reductions over several years. Amplitude of effect less with short-acting than with long-acting agents (eg, exenatide)	Marked and sustained reductions over several years. Albiglutide less effective in reducing HbA_{1c} than other long-acting agents
Fasting or night-time plasma glucose levels	Modest reduction	Marked reduction maintained throughout dosing interval
Postprandial glucose excursions	Marked reduction	Modest reduction
Postprandial glucose levels	Marked reduction	Marked reduction
Fasting insulin secretion	Modest enhancement	Strong enhancement
Postprandial insulin secretion	Reduction	Modest enhancement
Glucagon secretion (fasted state)	Reduction	Reduction
Hypoglycaemia	Lower potential for hypoglycaemia (including severe hypoglycaemia) than insulin or insulin secretagogues	Lower potential for hypoglycaemia (including severe hypoglycaemia) than insulin or insulin secretagogues

Gentilella R, ***Diabetes Metab Res Rev*** 2019; 35:e3070

CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA

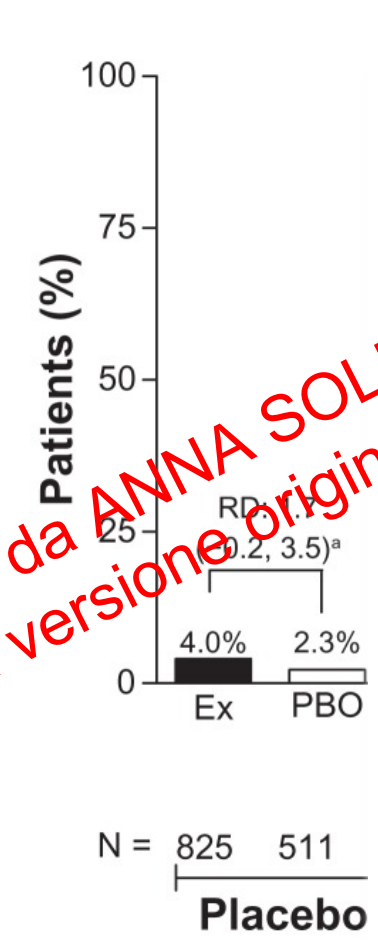


1. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
2. Low dose TZDs are better tolerated
3. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin

Diabetologia 2018; 61:2461-2498

Safety and Tolerability of Exenatide in T2DM

N= 5594; 19 placebo-controlled trials



MacConell L, ***Diabetes Metab Syndr Obes*** 2012; 5:29-41

Lixisenatide and Hypoglycemic Episodes

ELIXA

n (%)	Placebo N=3032	Lixisenatide N=3031
Any symptomatic hypoglycemia*		
Patients with events	462 (15.2)	504 (16.6)
Patients with events per 100 patient years	7.8	8.8
Events	1538	1634
Events per 100 patient years	25.9	28.4
Any severe symptomatic hypoglycemia**		
Patients with events	24 (0.8)	14 (0.5)
Patients with events per 100 patient years	0.4	0.2
Events	37	16
Events per 100 patient years	0.6	0.3

*Symptomatic hypoglycemia: clinical symptoms and glucose <60 mg/dl or prompt recovery upon treatment
**Severe symptomatic hypoglycemia: clinical symptoms and patient requiring assistance and glucose <36 mg/dl or prompt recovery upon treatment

Pfeffer MA, ***N Engl J Med*** 2015; 373:2247-2257

Glycemic Efficacy, Weight Effects, and Safety of Once-Weekly Glucagon-Like Peptide-1 Receptor Agonists

Study/Background Pharmacotherapy	Active Comparators	Minor Hypoglycemia
Exenatide ER		
DURATION-1/ metformin, a sulfonylurea, a TZD, or 2 OADs[16]	Exenatide ER 2 mg QW (n = 148)	SU use: 15% No SU use: 0%
	Exenatide 10 μg BID (n = 147)	SU use: 15% No SU use: 1%
DURATION-2/ metformin[17]	Exenatide ER 2 mg QW (n = 160)	1%
	Sitagliptin 100 mg QD (n = 166)	3%
	Pioglitazone 45 mg QD (n = 165)	1%
DURATION-3/ metformin ± sulfonylurea[18]	Exenatide ER 2 mg QW (n = 233)	8%
	Insulin glargine (n = 223)	26%
DURATION-4/none[19]	Exenatide ER 2 mg QW (n = 248)	2%
	Metformin 2,000 mg/d (n = 246)	0%
	Pioglitazone 45 mg (n = 163)	0%
	Sitagliptin 100 mg (n = 163)	0%
DURATION-5/ metformin, sulfonylurea, TZD, or combination[20]	Exenatide ER 2 mg QW (n = 129)	SU use: 13% No SU use: 0%
	Exenatide 10 μg BID (n = 123)	SU use: 12% No SU use: 0%
DURATION-6/ metformin, sulfonylurea, or metformin + sulfonylurea or TZD[21]	Exenatide ER 2 mg QW (n = 461)	SU use: 15% No SU use: 4%
	Liraglutide 1.8 mg QD (n = 450)	SU use: 12% No SU use: 3%
DURATION-7[22]	Exenatide ER SC 2 mg QW + insulin glargine (n = 232)	5.6%
	Placebo + insulin glargine (n = 231)	5.6%
DURATION-8/ metformin[23]	Exenatide 2 mg QW (n = 230)	Mild: 1%
	Dapagliflozin 10 mg QD (n = 233)	Mild: 1%
	Exenatide 2 mg QW + dapagliflozin 10 mg QD (n = 231)	Mild: 3%

Study/Background Pharmacotherapy	Active Comparators	Minor Hypoglycemia	Major Hypoglycemia
Dulaglutide			
AWARD-1/metformin + TZD[24]	Dulaglutide 0.75 mg QW (n = 280)	11%	0%
	Dulaglutide 1.5 mg QW (n = 279)	10%	0%
	Exenatide 10 μg BID for (n = 276)	Total hypoglycemia: 16%	1%
	Placebo (n = 141)	4%	0%
AWARD-2/ metformin + sulfonylurea[25]	Dulaglutide 0.75 mg QW (n = 272)	Total hypoglycemia: 54%	0%
	Dulaglutide 1.5 mg QW (n = 273)	Total hypoglycemia: 55%	< 1%
	Insulin glargine (n = 262)	Total hypoglycemia: 69%	1%
AWARD-3/none[26]	Dulaglutide 0.75 mg QW (n = 270)	11%	0%
	Dulaglutide 1.5 mg QW (n = 269)	12%	0%
	Metformin 2,000 mg/d (n = 268)	13%	0%
AWARD-4/prandial insulin ± metformin[a,27]	Dulaglutide 0.75 mg QW (n = 293)	Total hypoglycemia: PG ≤ 3.9 mmol/L: 90% PG < 3.0 mmol/L: 79%	3%
	Dulaglutide 1.5 mg QW (n = 295)	Total hypoglycemia: PG ≤ 3.9 mmol/L: 87% PG < 3.0 mmol/L: 72%	3%
	Insulin glargine (n = 296)	Total hypoglycemia: PG ≤ 3.9 mmol/L: 90% PG < 3.0 mmol/L: 74%	5%
AWARD-5/metformin[28]	Dulaglutide 0.75 mg QW (n = 302)	5%	0%
	Dulaglutide 1.5 mg QW (n = 304)	10%	0%
	Sitagliptin 100 mg QD (n = 315)	5%	0%
AWARD-6/metformin[29]	Dulaglutide SC 1.5 mg QW (n = 299)	9%	0%
	Liraglutide 1.8 mg QD (n = 300)	6%	0%
AWARD-8/sulfonylurea[30]	Dulaglutide 1.5 mg QW (n = 239)	21%	0%
	Placebo (n = 60)	3%	0%
AWARD-9/basal insulin ± metformin[31]	Dulaglutide 1.5 mg QW (n = 150)	Total hypoglycemia: 55%	1%
	Placebo (n = 150)	51%	0%

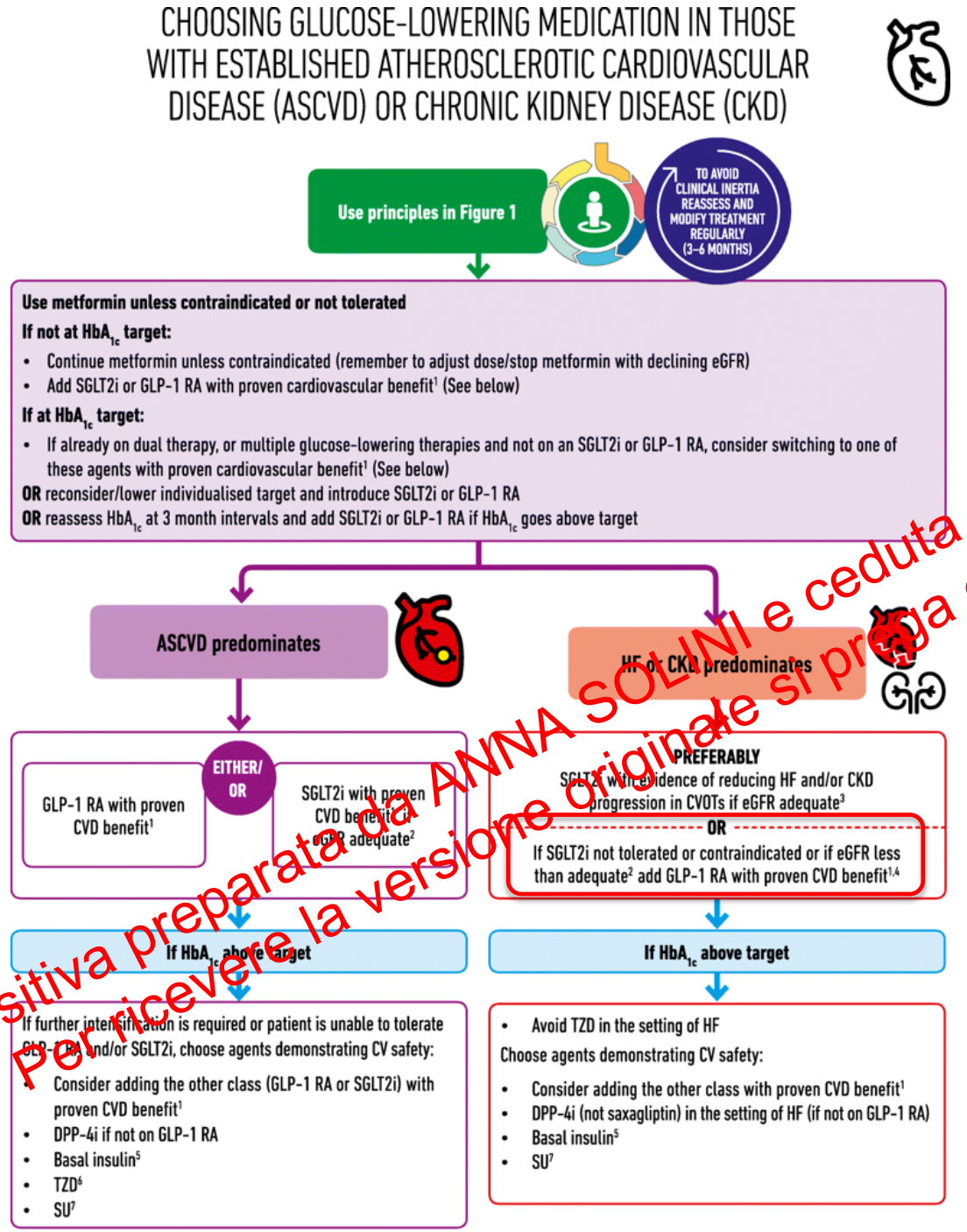
Handelsman Y, *J Manag Care Spec Pharm* 2018; 24:S14-S29

Glycemic Efficacy, Weight Effects, and Safety of Once-Weekly Glucagon-Like Peptide-1 Receptor Agonists

Study/Background Pharmacotherapy	Active Comparators	Minor Hypoglycemia	Major Hypoglycemia
Semaglutide			
SUSTAIN-1/none[32]	Semaglutide 0.5 mg QW (n = 128)	0%	0%
	Semaglutide 1.0 mg QW (n = 130)	0%	0%
	Placebo (n = 129)	Total hypoglycemia: 2% (3 events, 2 patients after receiving rescue medication)	
SUSTAIN-2/metformin, TZD, or metformin + TZD[33]	Semaglutide 0.5 mg QW (n = 409)	2%	0%
	Semaglutide 1.0 mg QW (n = 409)	2%	0%
	Sitagliptin 100 mg QD (n = 407)	1%	<1%
SUSTAIN-3/1-2 OADs (metformin, sulfonylurea, or TZD)[34]	Semaglutide 1.0 mg QW (n = 404)	Total hypoglycemia: 8%	
	Exenatide ER 2.0 mg QW (n = 405)	Total hypoglycemia: 8%	
SUSTAIN-4/metformin ± sulfonylurea[35]	Semaglutide 0.5 mg QW (n = 362)	Total hypoglycemia: SU use: 8% No SU use: <1%	<1%
	Semaglutide 1.0 mg QW (n = 360)	Total hypoglycemia: SU use: 9% No SU use: 2%	1%
	Insulin glargine (n = 360)	Total hypoglycemia: SU use: 18% No SU use: 2%	1%
SUSTAIN-5/basal insulin ± metformin[36]	Semaglutide 0.5 mg QW (n = 132)	Total hypoglycemia: 8%	
	Semaglutide 1.0 mg QW (n = 131)	Total hypoglycemia: 11%	
	Placebo (n = 133)	Total hypoglycemia: 5%	
SUSTAIN-7[37]	Semaglutide 0.5 mg QW (n = 301)	Severe or blood glucose-confirmed hypoglycemia: 1%	
	Semaglutide 1.0 mg QW (n = 300)	Severe or blood glucose-confirmed hypoglycemia: 2%	
	Dulaglutide 0.75 mg (n = 299)	Severe or blood glucose-confirmed hypoglycemia: 1%	
	Dulaglutide 1.5 mg (n = 299)	Severe or blood glucose-confirmed hypoglycemia: 2%	

Handelsman Y, ***J Manag Care Spec Pharm*** 2018; 24:S14-S29

GLP-1 RA in T2D with CKD



Consensus recommendation

For patients with type 2 diabetes and CKD, with or without CVD, consider the use of an SGLT2 inhibitor shown to reduce CKD progression or, if contraindicated or not preferred, a GLP-1 receptor agonist shown to reduce CKD progression (Figs 2 and 3).

4. Caution with GLP-1 RA in ESRD

CKD: estimated GFR [eGFR] <60 ml min^{-1}

Diabetologia 2018; 61:2461-2498

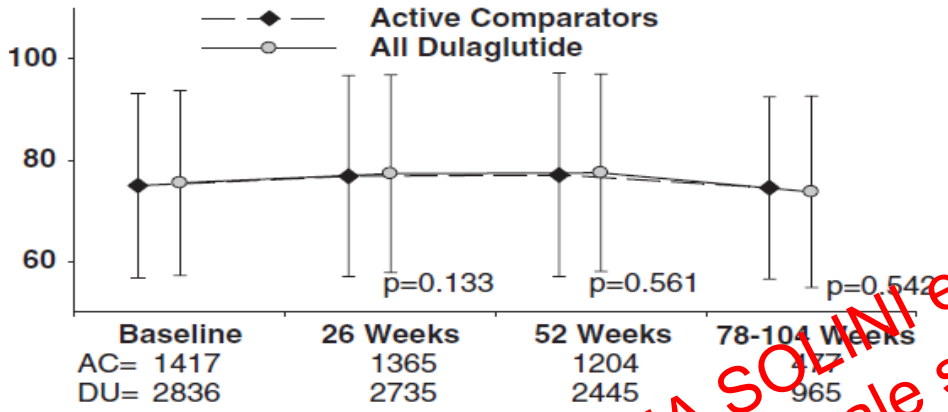
GLP-1 RA and their Use in T2DM Subjects with CKD

Drug	Dose	Half-life	Predominant elimination route	Use in renal impairment		
				Mild (≥60)	Moderate (30-60)	Severe (<30)
Daily GLP-1 RA/ analogues						
Exenatide	5-10 µg twice daily	2.4 h	Renal/Proteolysis	YES	YES	NO
Lixisenatide	10-20 µg once daily	3 h	Renal/Proteolysis	YES	YES	NO
Liraglutide	1.2-1.8 mg once daily	13 h	Metabolised	YES	YES	YES
Weekly GLP-1 RA/ analogues						
Exenatide QW	2 mg once weekly	2.4 h	Renal/Proteolysis	YES	YES	NO
Albiglutide	30-50 mg once weekly	5 days	Metabolised	YES	YES	NO
Dulaglutide	0.75-1.5 mg once weekly	4.5 days	Metabolised	YES	YES	YES
Semaglutide	0.75-1.5 mg once weekly	7 days	Metabolised	YES	YES	YES

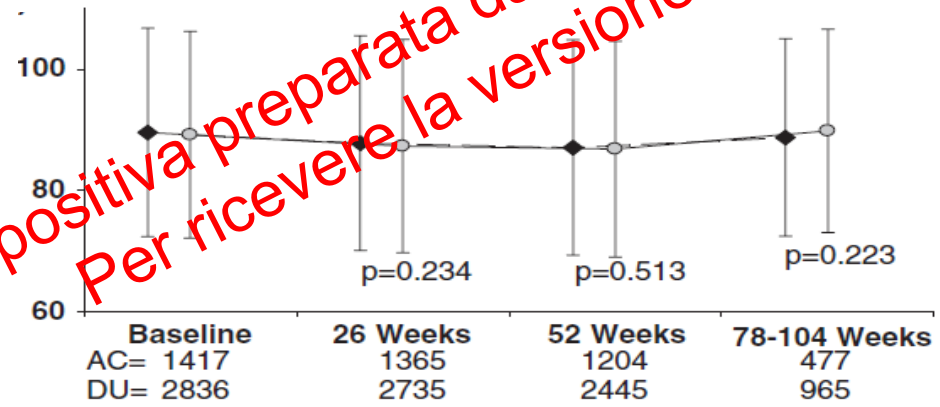
Effect of Dulaglutide on Kidney Function in T2DM

Integrated data from 9 phase II/III trials (n=6005)

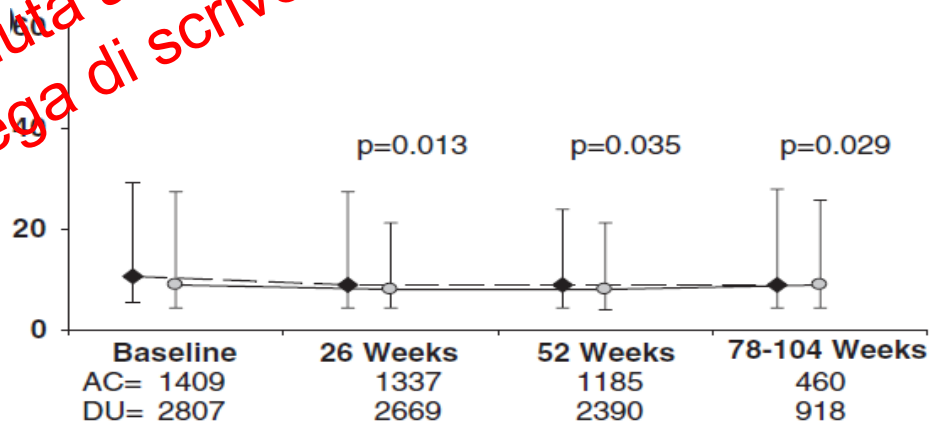
Creatinine (µmol/l)



eGFR (ml/min/1.73m²)



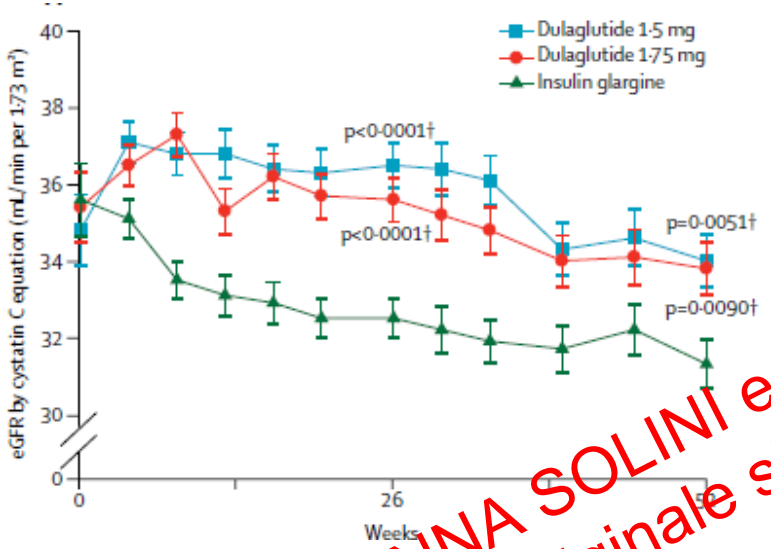
UACR (mg/g)



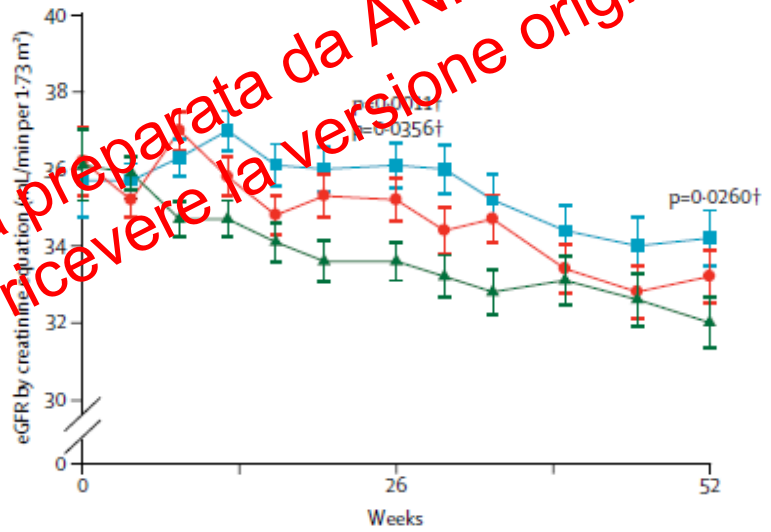
Tuttle KR, ***Diabetes Obes Metab*** 2017; 19:436-441

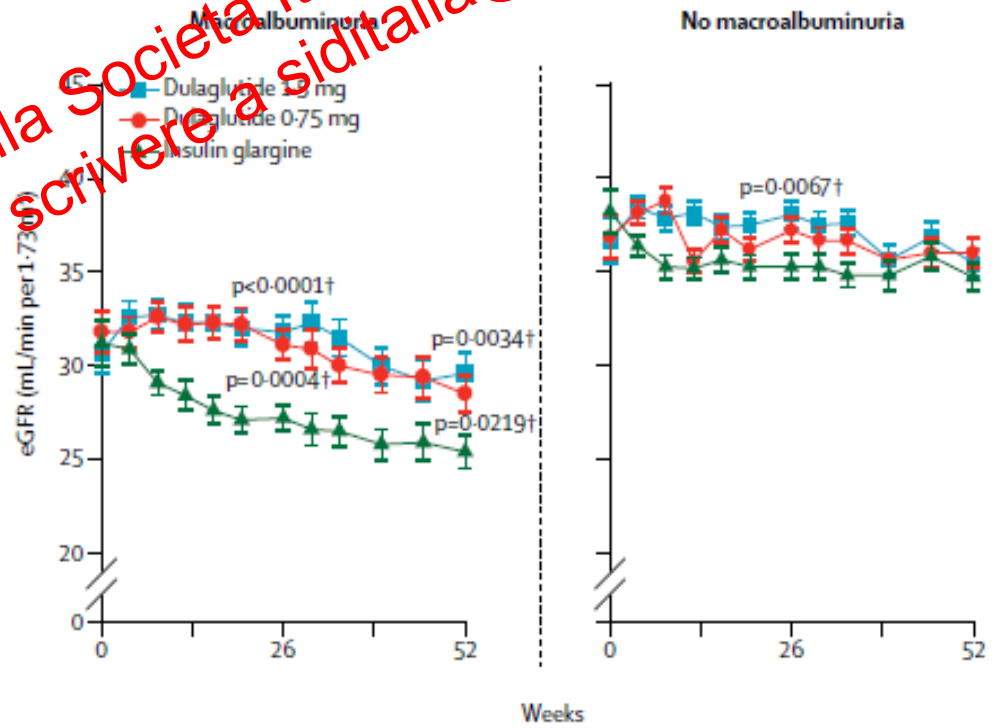
Dulaglutide and eGFR in People with Moderate-to-Severe CKD
The AWARD-7 Study

eGFR Cystatin C



eGFR creatinine

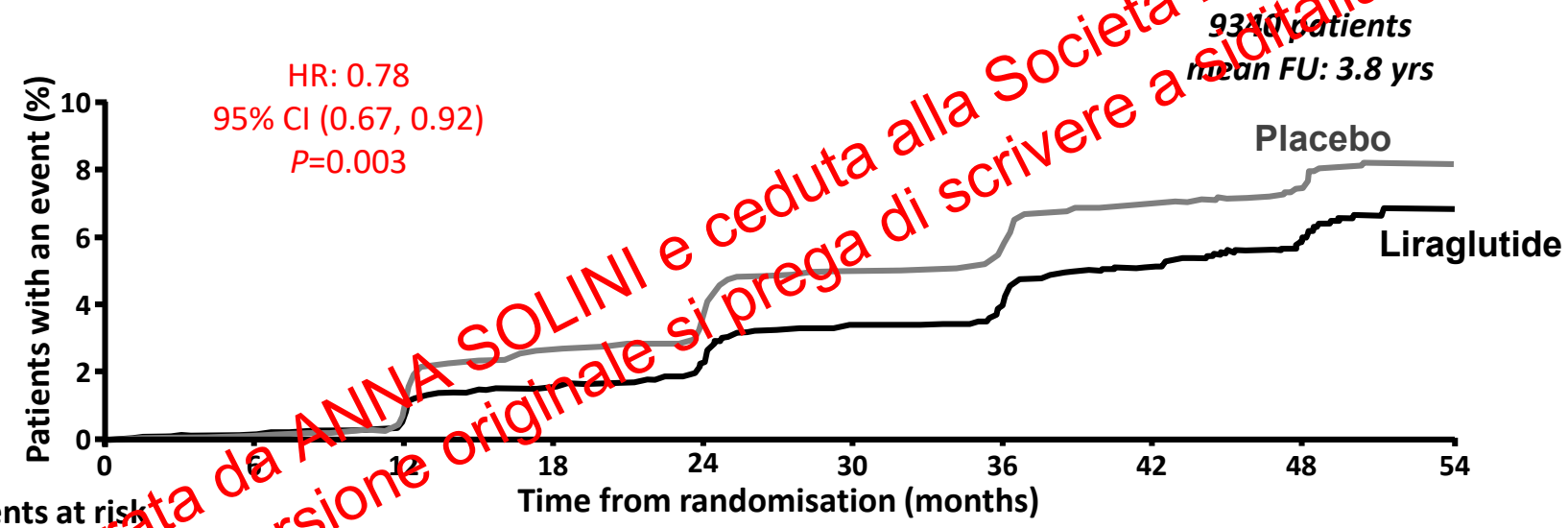




Tuttle KR, ***Lancet Diabetes Endocrinol*** 2018; 6:605-617

The LEADER Study: Time to First Renal Event

Macroalbuminuria, Doubling of Serum Creatinine, ESRD, Renal Death



Patients at risk

Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

Mann JFE, ***N Engl J Med*** 2017; 377:839-848

Liraglutide and Renal Outcomes in T2DM

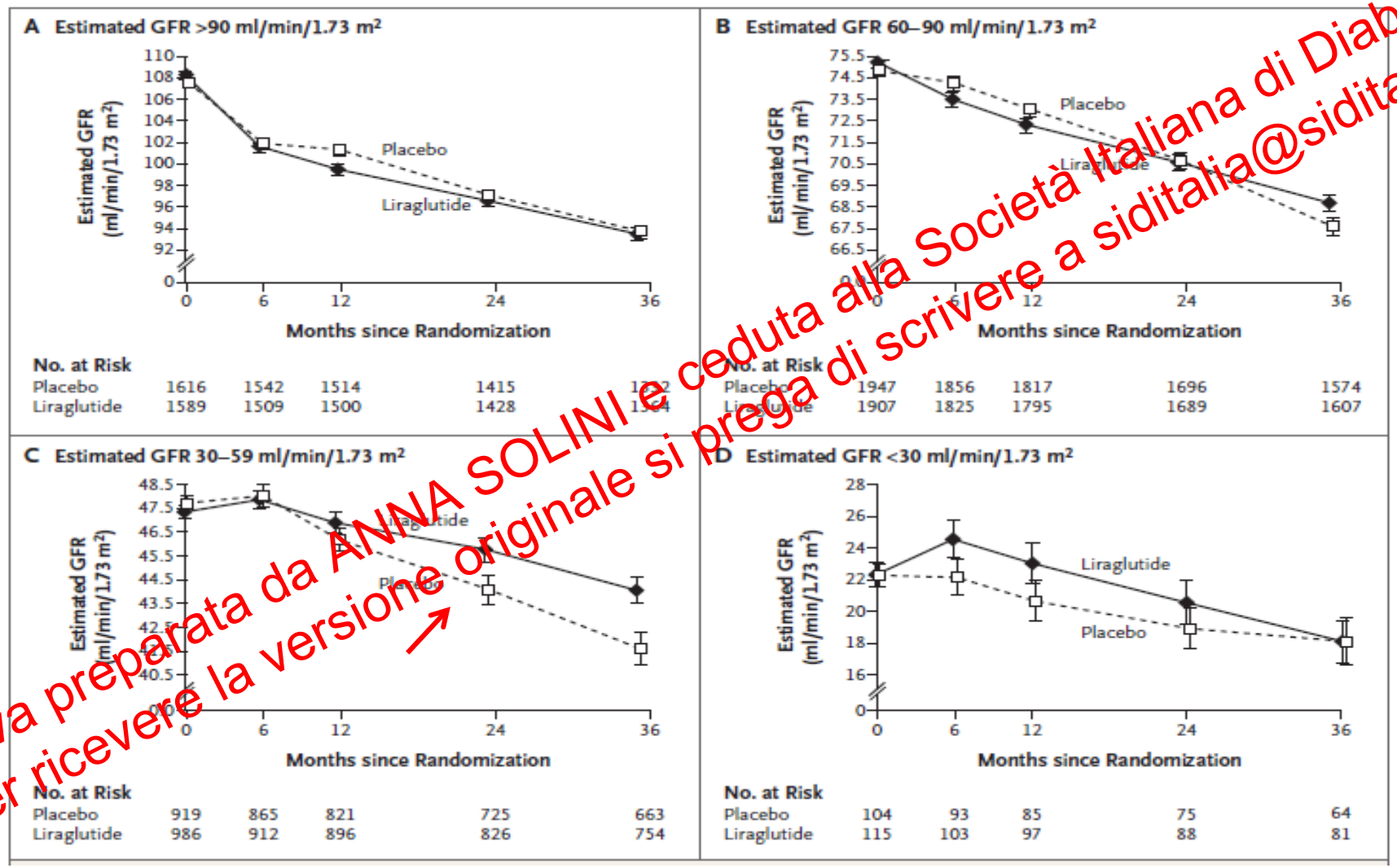
The prespecified secondary renal outcomes of the LEADER study

Table 1. Composite Renal Outcome and Individual Components of the Composite Outcome.*

Outcome	Liraglutide (N=4668)	Placebo (N=4672)	Total (N=9340)	Hazard Ratio (95% CI)	P Value
	no. of patients (rate per 100 patient-yr of observation)				
Composite renal outcome	268 (15.0)	337 (19.0)	605 (17.0)	0.78 (0.67–0.92)	0.003
Components of composite renal outcome†					
New-onset persistent macroalbuminuria	161 (9.0)	215 (12.1)	376 (10.6)	0.74 (0.60–0.91)	0.004
Persistent doubling of serum creatinine level	87 (4.9)	97 (5.5)	184 (5.2)	0.89 (0.67–1.19)	0.43
Renal-replacement therapy	56 (3.1)	64 (3.6)	120 (3.4)	0.87 (0.61–1.24)	0.44
Death due to renal disease	8 (0.4)	5 (0.3)	13 (0.4)	1.59 (0.52–4.87)	0.41

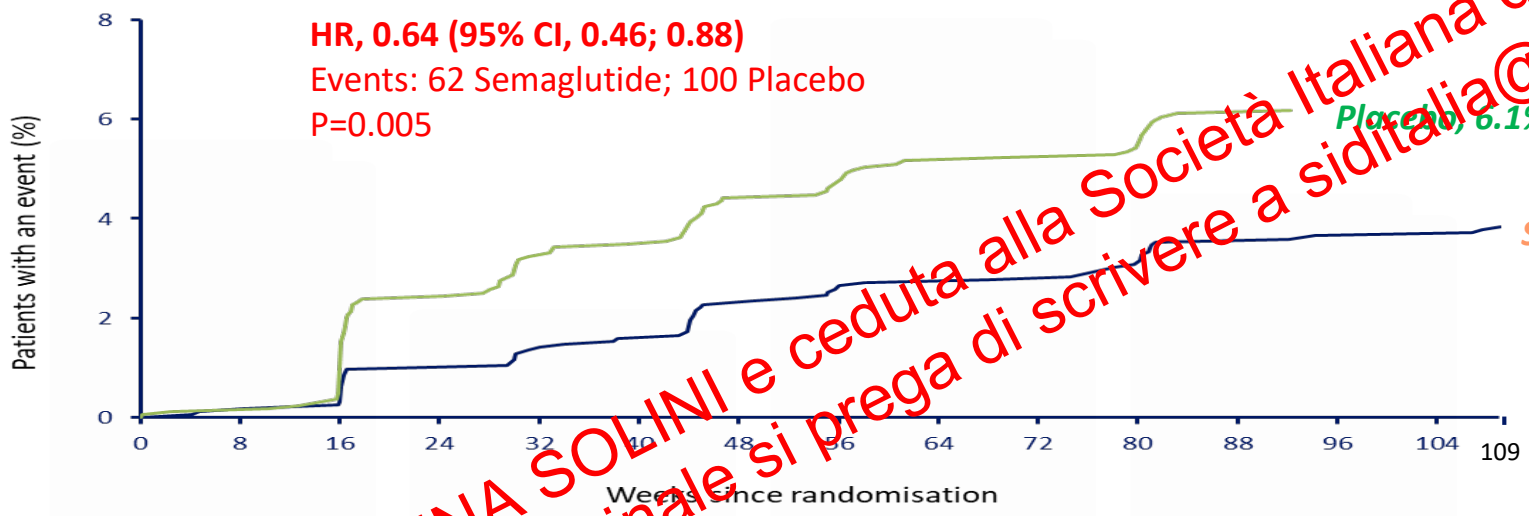
Mann JFE, ***N Engl J Med*** 2017; 377:839-848

Mean eGFR during the Trial According to Baseline eGFR



Mann JFE, ***N Engl J Med*** 2017; 377:839-848

The SUSTAIN-6 Study: New or Worsening Nephropathy



Number of patients at risk

Semaglutide	**1648**	**1630**	**1605**	**1580**	**1563**	**1541**	**1525**	**1518**
Placebo	**1649**	**1629**	**1570**	**1545**	**1518**	**1498**	**1471**	**1465**

Persistent macroalbuminuria p=0.001

Persistent doubling of serum creatinine level and creatinine clearance per MDRD p=0.48

Need for continuous renal replacement therapy p=0.83

Marso SP, ***New Engl J Med*** 2016; 375:1834-1844

Dulaglutide and Renal Outcomes in T2DM. An Exploratory Analysis of the Rewind Trial

N=9901, mean eGFR 76.9 ml/min/1.73m², mean FU 5.4 yrs

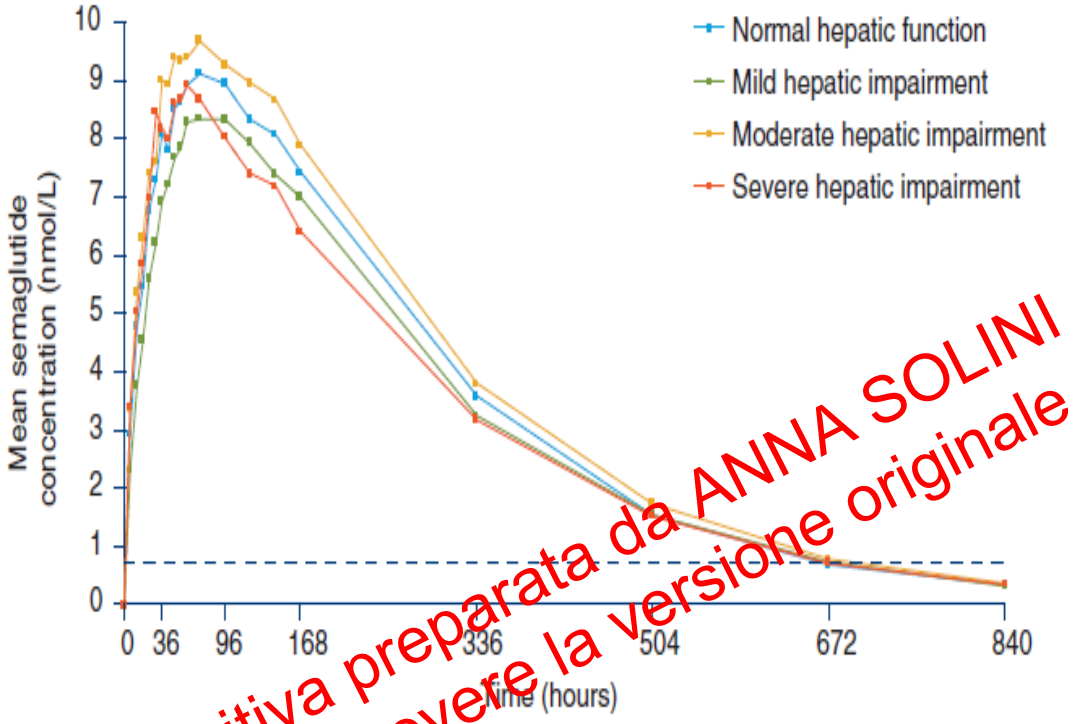
	Dulaglutide (n=4949)		Placebo (n=4952)		Hazard ratio (95% CI)	p value
	Number of patients (%)	Incidence rate (number of events per 100 person-years)	Number of patients (%)	Incidence rate (number of events per 100 person-years)		
Main analyses of renal effect						
Composite renal outcome	848 (17·1%)	3·47	970 (19·6%)	4·07	0·85 (0·77–0·93)	0·0004
Components of composite renal outcome						
New macroalbuminuria	441 (8·9%)	1·76	561 (11·3%)	2·29	0·77 (0·68–0·87)	<0·0001
Sustained decline in eGFR of ≥30%	453 (9·2%)	1·79	500 (10·1%)	2·00	0·89 (0·78–1·01)	0·066
Chronic renal replacement therapy	16 (0·3%)	0·06	21 (0·4%)	0·08	0·75 (0·39–1·44)	0·39
Serious renal adverse event*	84 (1·7%)	0·32	93 (1·9%)	0·36	0·90 (0·67–1·20)	0·46
Sensitivity analyses of renal effect						
Sustained decline in eGFR of ≥40%	169 (3·4%)	0·66	237 (4·8%)	0·93	0·70 (0·57–0·85)	0·0004
Composite renal outcome with this decline	587 (11·9%)	2·36	751 (15·2%)	3·10	0·76 (0·68–0·84)	<0·0001
Sustained decline in eGFR of ≥50%	61 (1·2%)	0·24	108 (2·2%)	0·42	0·56 (0·41–0·76)	0·0002
Composite renal outcome with this decline	496 (10·0%)	1·99	649 (13·1%)	2·66	0·74 (0·66–0·84)	<0·0001

eGFR=estimated glomerular filtration rate. *Based on a search of the REWIND database for any reported adverse event linked to acute renal failure.

Table 2: Effect of treatment allocation on renal outcomes

Gerstein HC, ***Lancet*** 2019 June 7; doi: 10.1016/S0140-6736(19)31150-X.

Pharmacokinetics and Tolerability of Semaglutide in People with Hepatic Impairment



Influence of the individual Child-Pug parameters on the primary endpoint AUOC $_{0-\infty}$ and C_{max}

	Estimate of coefficient	(95% CI)	P
$AUC_{0-\infty}$, nmol/L (N = 42[a])			
Albumin (serum)	-0.012	(-0.714, 0.690)	.97
Total bilirubin (serum)	0.080	(-0.085, 0.245)	.33
Prothrombin time prolongation (plasma) + 1[b]	-0.099	(-0.270, 0.072)	.25
C_{max}, nmol/L (N = 43[a])			
Albumin (serum)	-0.396	(-1.302, 0.509)	.38
Total bilirubin (serum)	0.077	(-0.121, 0.274)	.44
Prothrombin time prolongation (plasma) + 1[b]	-0.087	(-0.293, 0.118)	.39

Ensen L, ***Diabetes Obes Metab*** 2018;20:998-1005

Effect of Liraglutide on Liver Fat and Function in Obese Patients with NAFLD

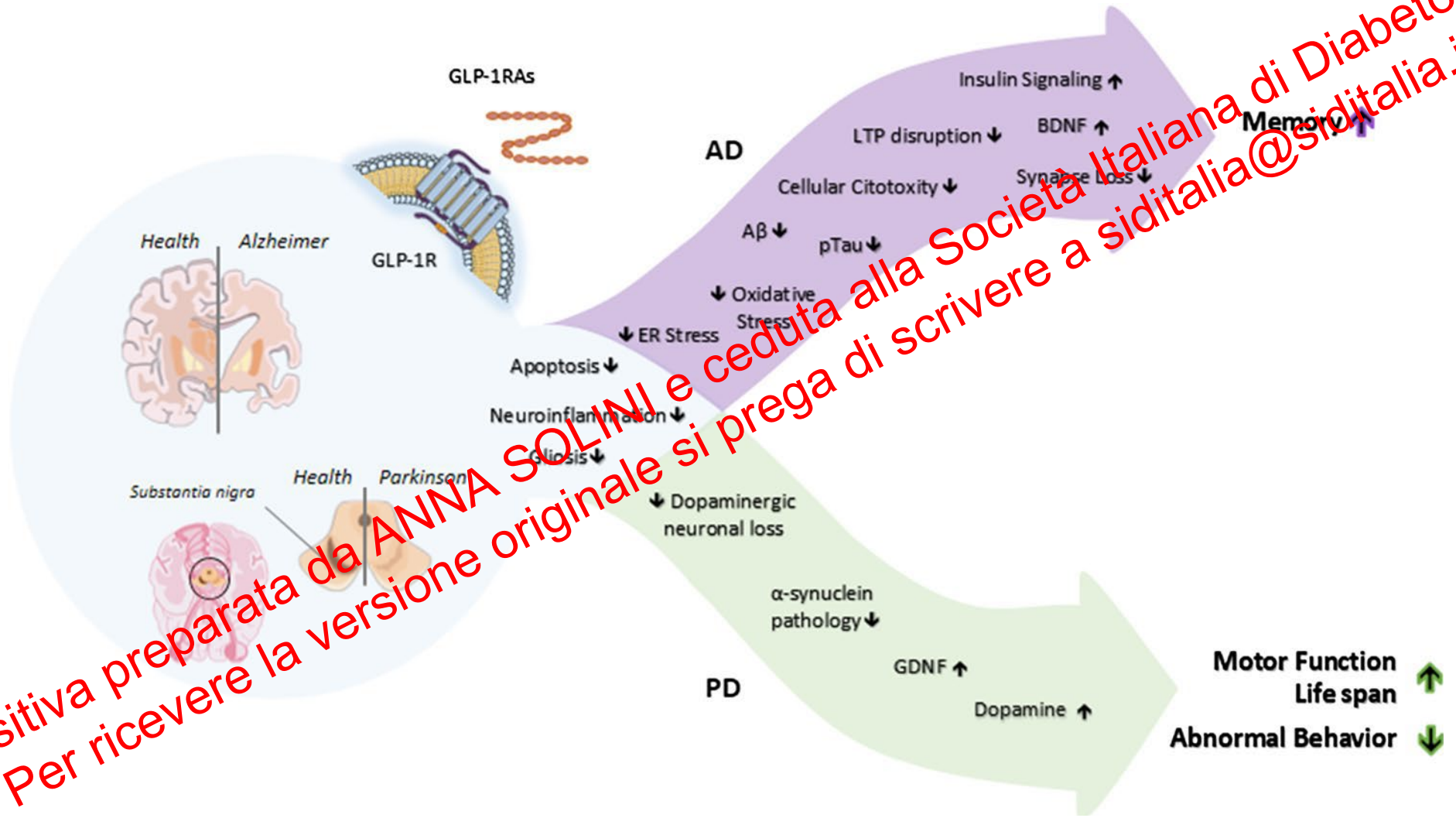
Changes in parameters	DE group	P value	LI group	P value	P between groups
ALT (units/L)	-42±46	<0.001	-34±27	0.001	0.52
AST (units/L)	-23±24	0.006	-18±15	0.002	0.53
LFF (%)	-8.9±13.4	0.03	-7.2±7.1	0.008	0.70
Liver stiffness (kPa)	-0.21±0.19	0.001	-0.26±0.29	0.003	0.54

Khoo J, ***Diabetes Obes Metab*** 2017; 19:1814-1817

GLP-1 analogues and Neuro-Degenerative Diseases

- ✓ Peripheral and brain inflammation and insulin resistance are closely linked to Alzheimer's disease (AD) and Parkinson's disease (PD).
- ✓ Several antidiabetic drugs seem promising in ensuring a certain degree of neuroprotection.
- ✓ Glucagon-like peptide-1 analogues have shown beneficial actions in experimental models and promising results in recent clinical trials in AD and PD.
- ✓ Recent advances have established key roles of GIP signaling in the neurophysiology, namely, neuronal survival, neurotransmission, maintenance, and neurogenesis.
- ✓ GIP analogs, acting as GIPR agonists, demonstrate a broad-based neuroprotective activity in preclinical models of AD, PD, and stroke, with unprecedented ability to act in the advanced stages of disease.
- ✓ Modulating the GIP signaling through GIPR agonism represents a unique therapeutic approach to provide both symptomatic benefits along with halting disease progression.
- ✓ Entry of incretin mimetics, Exendin-4, liraglutide, and lixisenatide into clinical trials for AD and PD suggests that introduction of GIP analogs and co-agonists into clinic could be closer than anticipated.

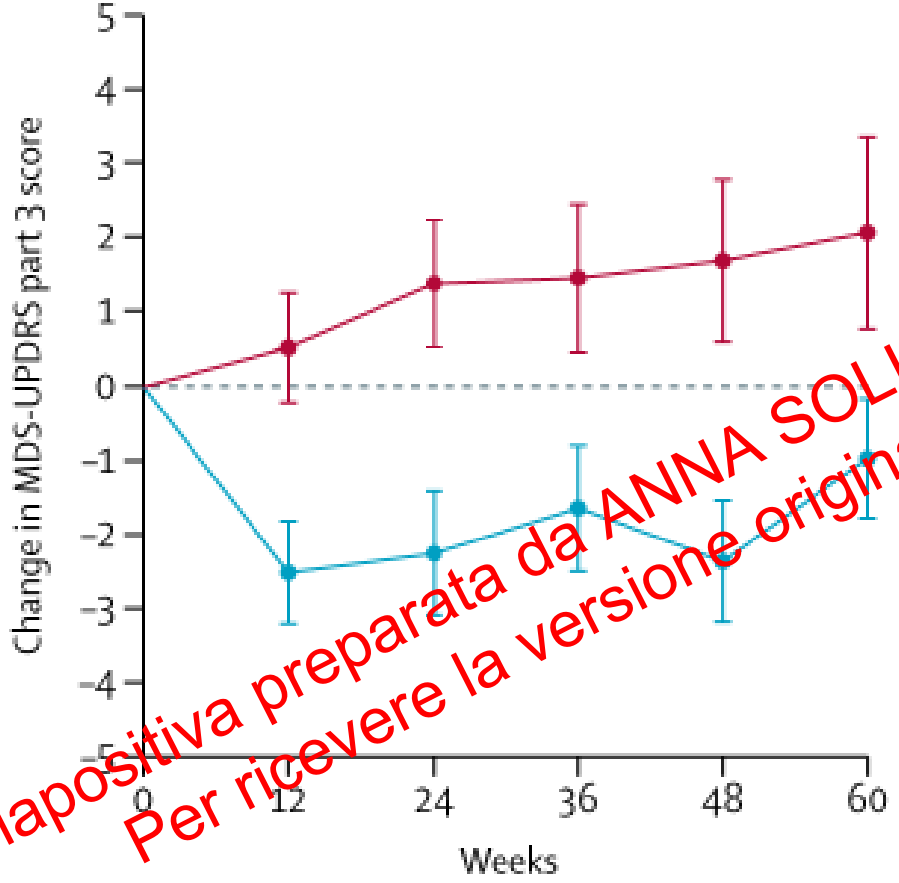
Neuroproctective Effects of GLP-1A in AD e PD



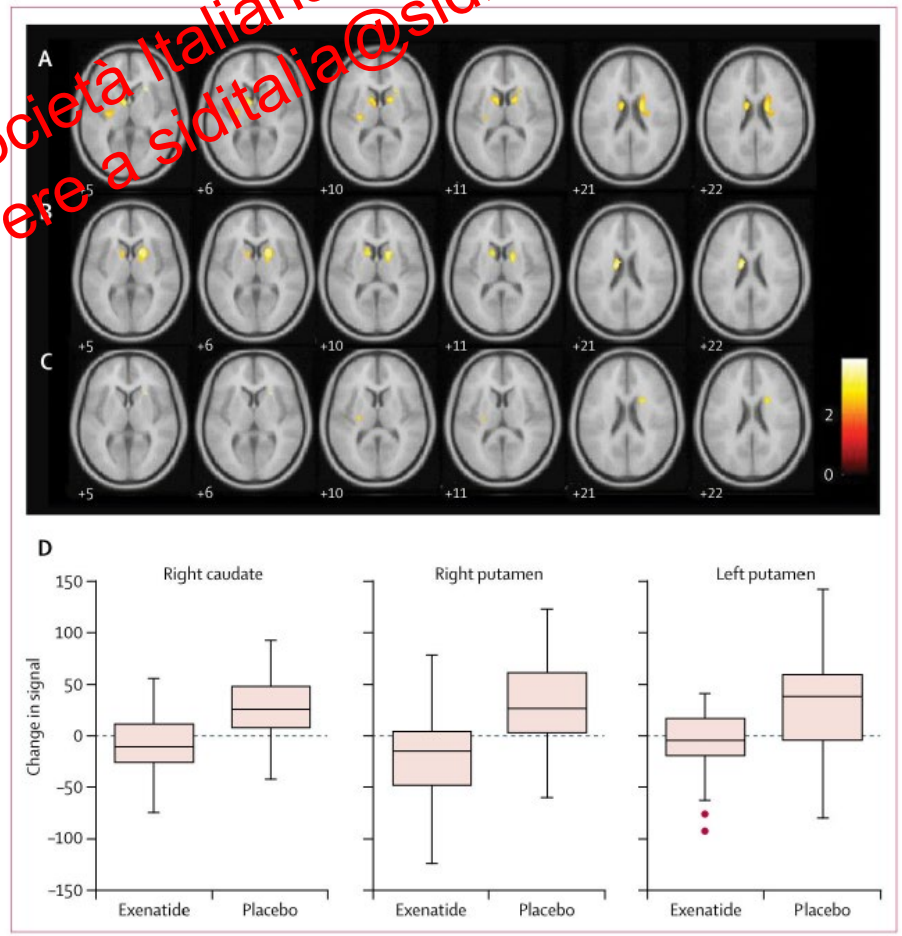
Batista AF, ***CNS Drugs*** 2019; 33:209-223

Exenatide once weekly in Parkinson Disease

Changes in MDS-UPDRS part 3 scores



ANCOVA comparing decline in DaTscan binding between placebo and exenatide



Athauda D, ***Lancet*** 2017; 390:1664-1673

Clinical Trials in PD

ClinicalTrials.gov ID:	Rationale	Duration
NCT03659682	Phase II study with semaglutide in patients with idiopathic PD	48 months
NCT03456687	Phase I study with exenatide once weekly vs Placebo	12 months
NCT02953665	Phase II study to explore safety and efficacy of liraglutide in PD	
NCT03439943	Phase II study with lixisenatide in patients with early PD	12 months
NCT03672604	Phase I study to explore safety and efficacy of NLY01* in healthy volunteers	-
NCT01174810	Phase II study to explore efficacy of exenatide vs placebo in 45 patients with moderate PD	12 months **CLOSED**
NCT01971242	Double-blind, Phase II study with exenatide 2 mg once-weekly vs placebo in 62 patients with PD	48 weeks **CLOSED**

*NLY01: powerful long-acting GLP-1 analogue able to mainly act at the central level.

Clinical Trials in AD

ClinicalTrials.gov ID:	Rationale	Duration
NCT01255163	Pilot phase II study with exenatide vs placebo in 57 patients with AD	**CLOSED**
NCT01843075	Efficacy of liraglutide once daily in patients with AD-linked moderate dementia (206 planned participants)	12 months
NCT01469351	Efficacy of liraglutide once daily vs placebo in 38 patients with early/moderate AD (randomized, double-blind)	26 weeks **CLOSED**

Modified from Batista AF, ***CNS Drugs*** 2019; 33.209-223