Terapia con Analoghi del GLP-1: Quando e Perché - I FASE

Analoghi del GLP-1 nei Pazienti Fragili

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Roma, 21 maggio 2019

La dr. ssa Annalisa Natalicchio dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Sanofi Aventis

Novo Nordisk

Il Paziente Fragile

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

2001, Fried et al: la **fragilità** viene definita come una sindrome clinica nella quale sono presenti almeno 3 dei seguenti criteri: **perdita di peso** non intenzionale (sarcopenia), **sfinimento, debolezza, lentezza** nel camminare e **ridotta attività fisica**.

J Gerontol A Biol Sci Med Sci. 2001; M146-56

2011, Rockwood et al: la definizione di **fragilità** viene basata per la prima volta non solo sulla valutazione degli **aspetti fisici** ma anche di quelli **psicosociali**.

Clin Geriatr Med. 2011; 27:17-26

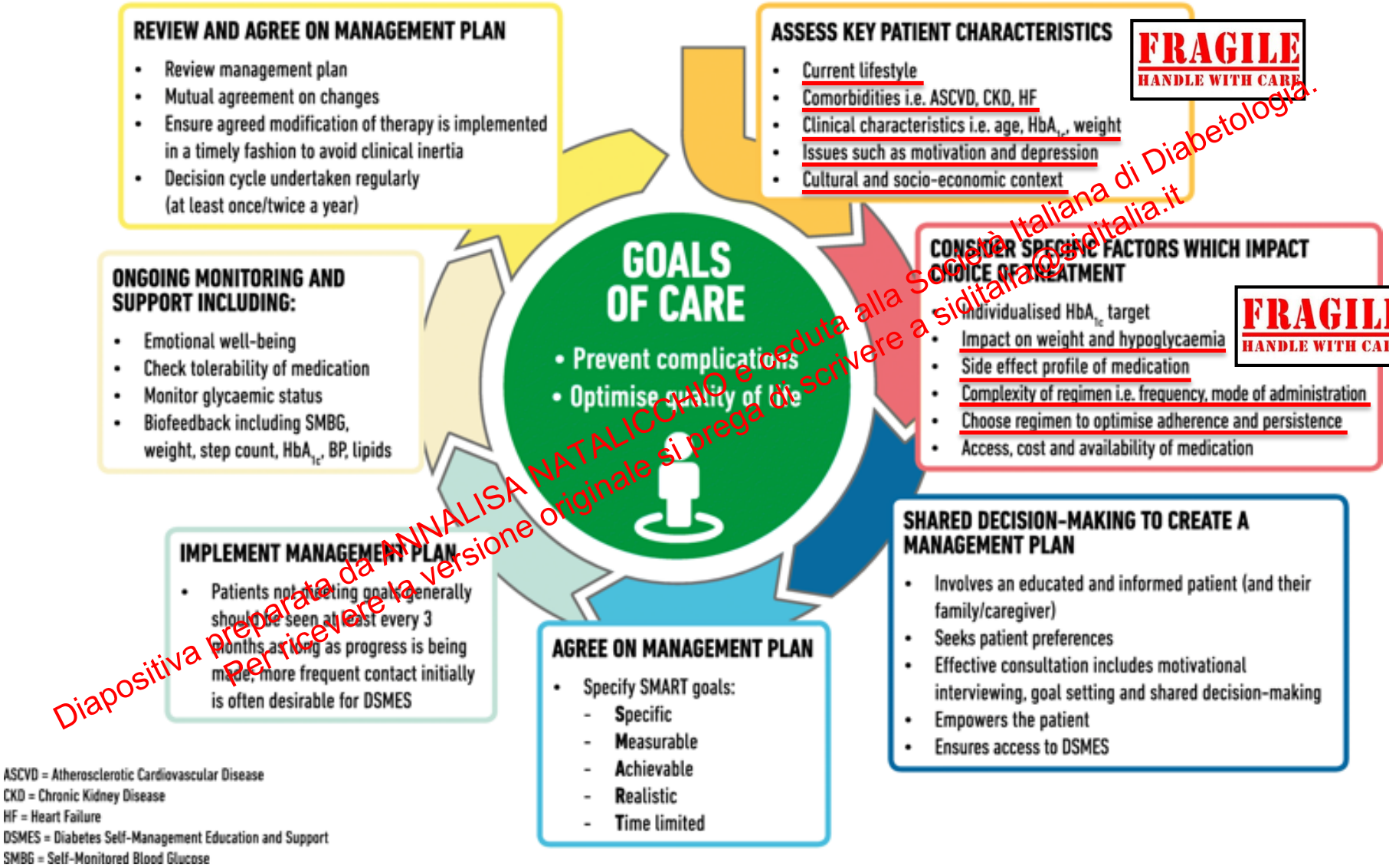
Il Paziente Diabetico Fragile

- Cardiopatico con aterosclerosi o con scompenso cardiaco Prof. Giaccari
- Con insufficienza renale
- Obeso Prof.ssa Frida Leonetti
- Anziano (età ≥ 65 anni) con comorbidità e/o deficit cognitivo-funzionale
- Affetto da malattie neurodegenerative

La prevalenza di fragilità nella popolazione con Diabete Mellito varia dal 5% al 48% a seconda del metodo di misurazione.

Diabetes Metab Res Rev. 2016 Jan;32 Suppl 1:261-7

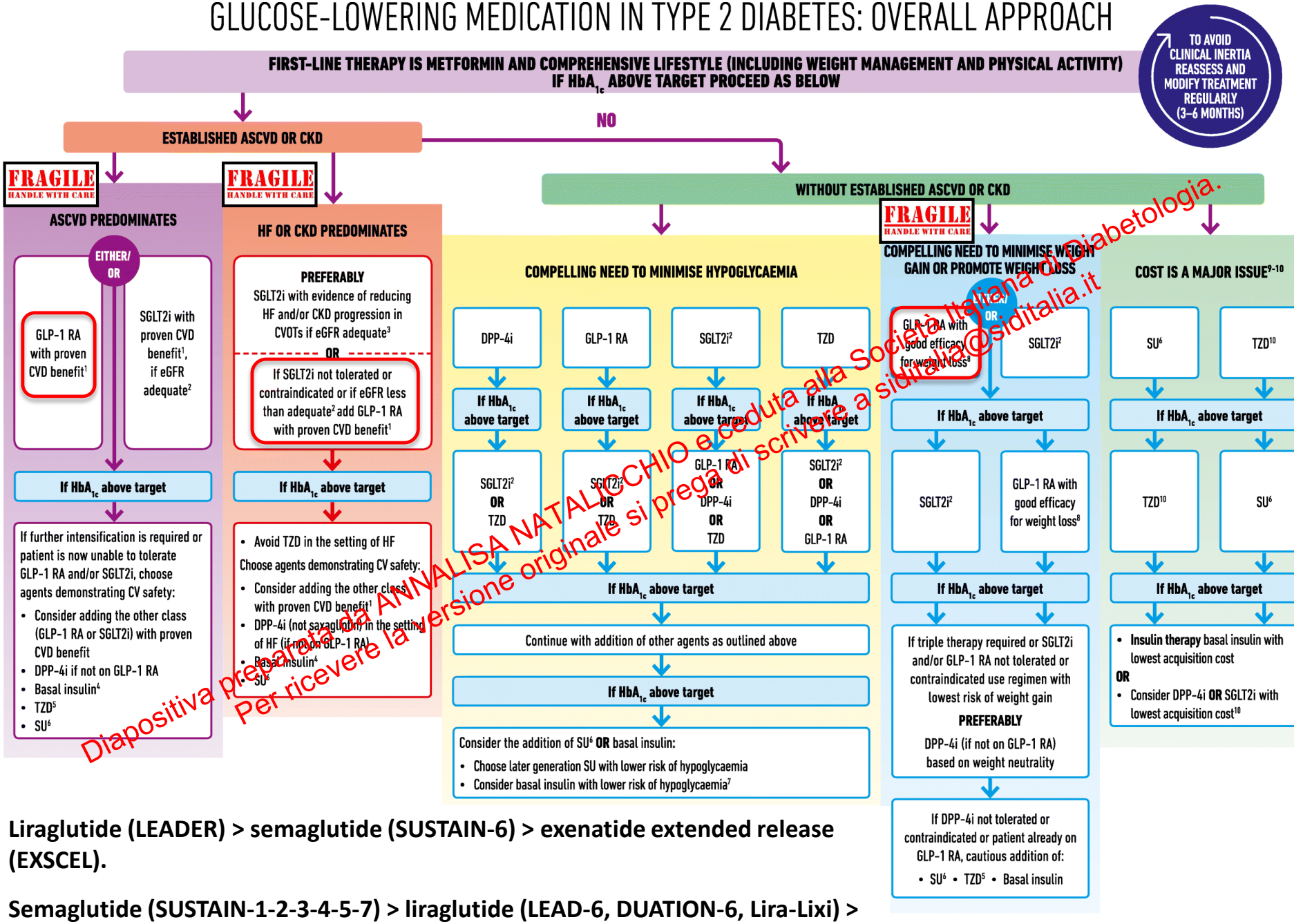
DECISION CYCLE FOR PATIENT-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES



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 Dec;61(12):2461-2498

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



Liraglutide (LEADER) > semaglutide (SUSTAIN-6) > exenatide extended release (EXSCEL).

Semaglutide (SUSTAIN-1-2-3-4-5-7) > liraglutide (LEAD-6, DUATION-6, Lira-Lixi) > dulaglutide (AWARD) > exenatide (GetGoal-X) > lixisenatide.

Diabetologia. 2018 Dec;61(12):2461-2498

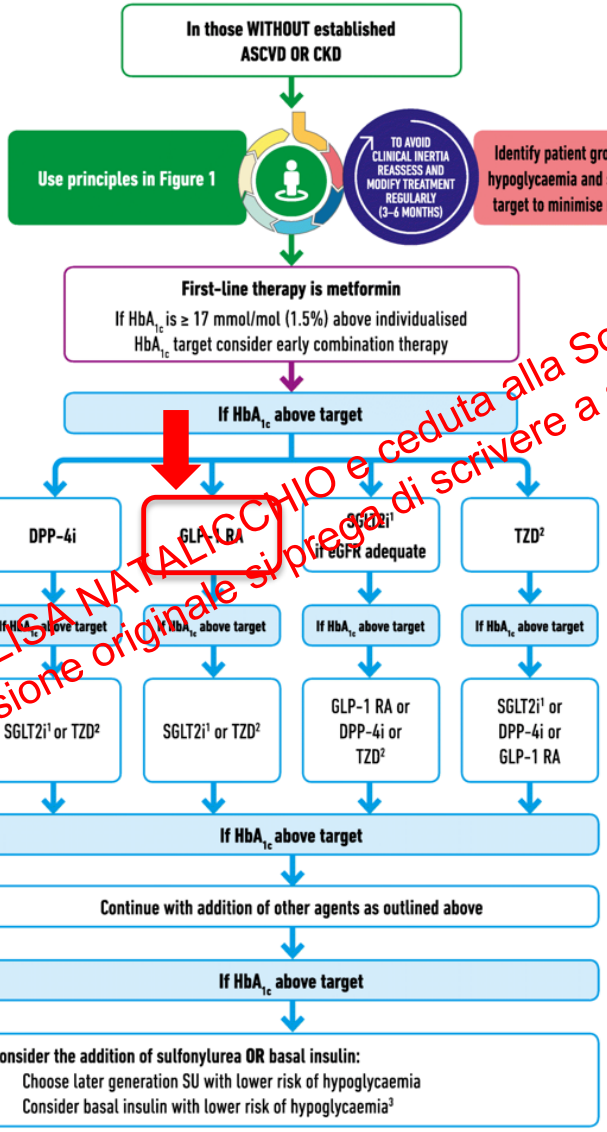
Analoghi del GLP-1 nel Paziente Diabetico Fragile: Ipoglicemia

L'**ipoglicemia** rappresenta una delle maggiori **preoccupazioni** nei pazienti con fragilità in quanto può causare una **morbilità** significativa, aumentare il numero di **cadute** e peggiorare il **declino cognitivo**.

	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

Diabetes Metab Res Rev. 2019 Jan;35(1):e3070

CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA



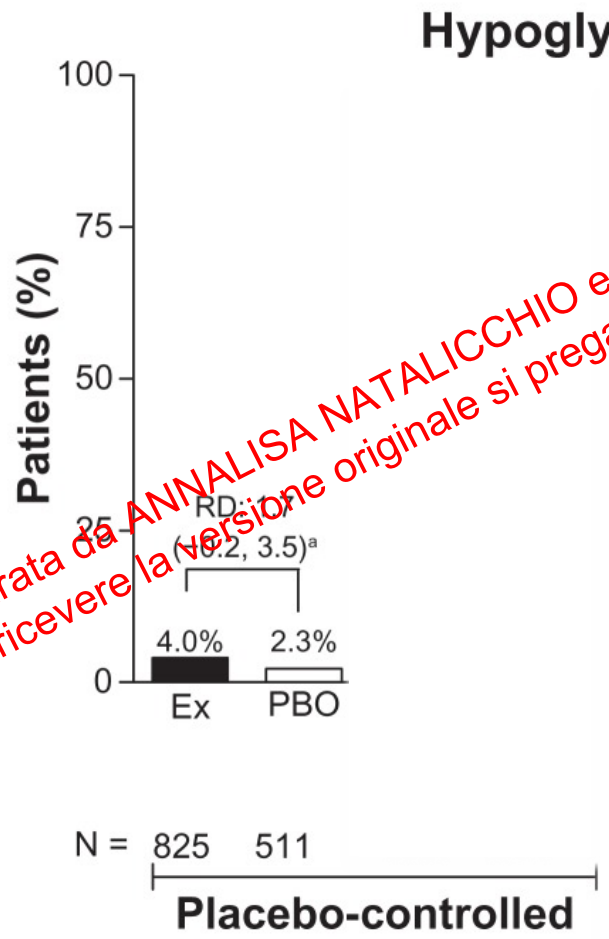
1. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
2. Low dose TZDs are better tolerated
3. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin

Diabetologia. 2018 Dec;61(12):2461-2498

Safety and tolerability of exenatide twice daily in patients with type 2 diabetes: integrated analysis of 5594 patients from 19 placebo-controlled and comparator-controlled clinical trials

Leigh MacConell
Carl Brown
Kate Gurney
Jenny Han

Amylin Pharmaceuticals, Inc.
San Diego, CA, USA



Diabetes Metab Syndr Obes. 2012;5:29-41

Lixisenatide e Ipoglicemie

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

N Engl J Med. 2015 Dec 3;373(23):2247-57

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 S (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 2 QW + insulin glargine (n = [illegible])	5.6%
	Placebo + insulin glargine (n = [illegible])	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 hypo-glycemia: 16%	1%
	Placebo (n = 141)	4%	0%
AWARD-2/ metformin + sulfonylurea[25]	Dulaglutide 0.75 mg QW (n = 272)	Total hypo-glycemia: 54%	0%
	Dulaglutide 1.5 mg QW (n = 273)	Total hypo-glycemia: 55%	< 1%
	Insulin glargine (n = 262)	Total hypo-glycemia: 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 = [illegible])	13%	0%
AWARD-4/prandial insulin ± metformin[a,27]	Dulaglutide 0.75 mg QW (n = 293)	Total hypo-glycemia: PG ≤ 3.9 mmol/L: 90% PG < 3.0 mmol/L: 79%	3%
	Dulaglutide 1.5 mg QW (n = 295)	Total hypo-glycemia: PG ≤ 3.9 mmol/L: 87% PG < 3.0 mmol/L: 72%	3%
	Insulin glargine (n = 296)	Total hypo-glycemia: 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 hypo-glycemia: 55%	1%
	Placebo (n = 150)	51%	0%

J Manag Care Spec Pharm, 2018 Sep;24:S14-S29

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)	< 1%	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: 4%	
	Exenatide ER 2.0 mg QW (n = 405)	Total hypoglycemia: 4%	
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%	

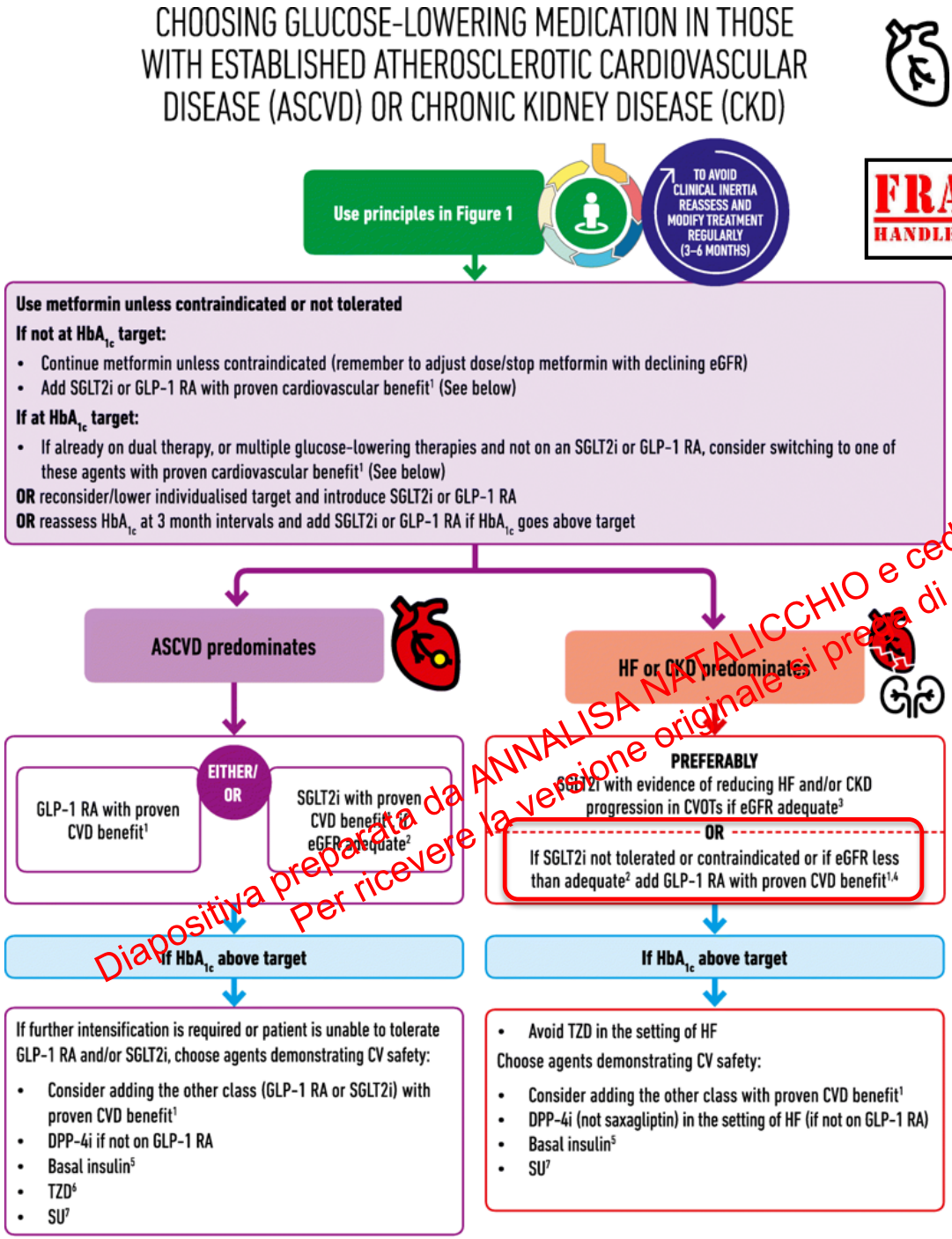
J Manag Care Spec Pharm, 2018 Sep;24:S14-S29

Take-home Messages I

Gli **analoghi del GLP-1** sono una classe di farmaci a **basso rischio** di indurre **ipoglicemie,** effetto collaterale da bandire nel paziente diabetico fragile.

*Attenzione alla co-somministrazione con sulfaniluree e insulina.

GLP-1 RA nel Paziente Diabetico con Insufficienza Renale



FRAGILE
HANDLE WITH CARE

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 Dec;61(12):2461-2498

Analoghi del GLP-1 nel Paziente con Insufficienza Renale

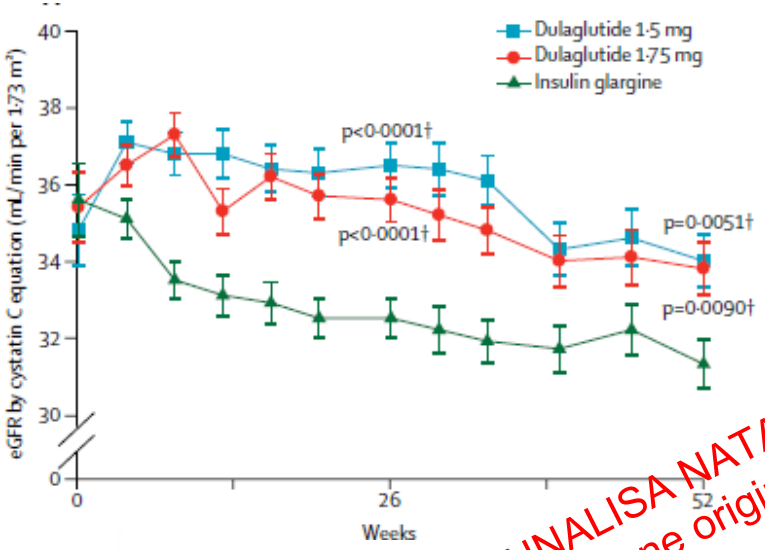
FARMACO	Insufficienza Renale (clearance della creatinina)			
	Lieve (50-80 ml/min)	Moderata (30-50 ml/min)	Severa (<30 ml/min)	Terminale (<15 ml/min)
Exenatide twice daly	SI	dose escalation (da 5 a 10 mcg)	NO	NO
Lixisenatide	SI	SI	NO	NO
Albiglutide	SI	SI	NO	NO
Dulaglutide	SI	SI	SI	NO
Exenatide once weekly	SI	NO	NO	NO
Liraglutide	SI	SI	SI	NO
Semaglutide	SI	SI	SI	NO

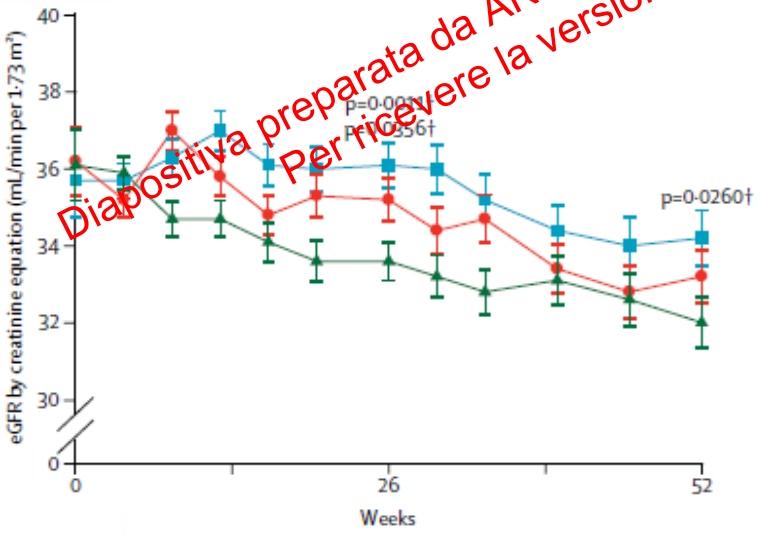
Diabetes Metab Res Rev. 2019 Jan;35(1):e3070

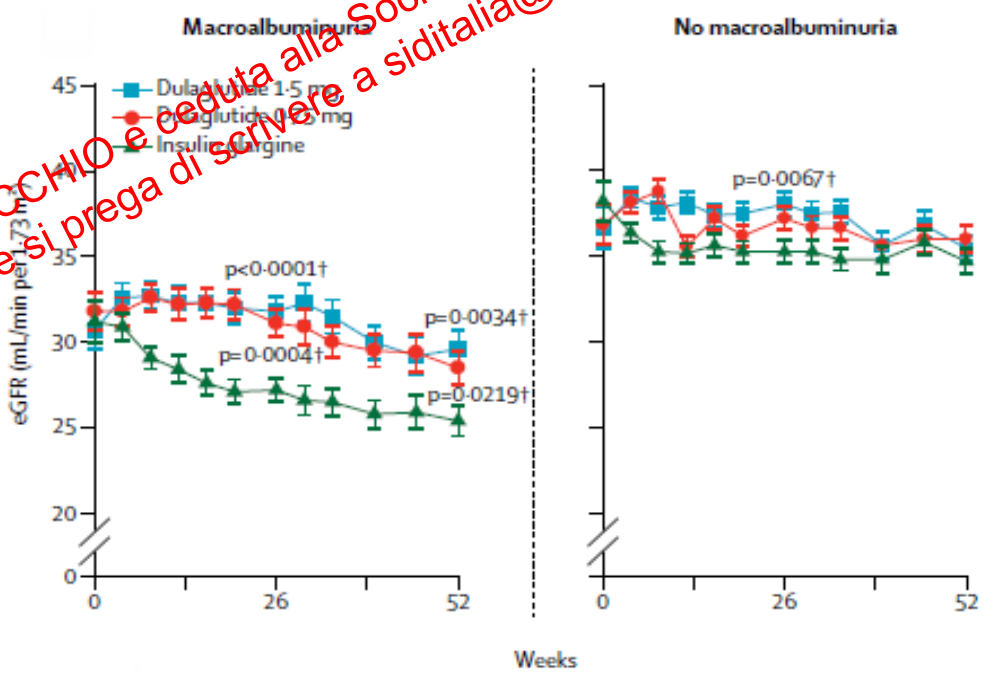
Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial

AWARD-7

Katherine R Tuttle, Mark C Lakshmanan, Brian Rayner, Robert S Busch, Alan G Zimmermann, D Bradley Woodward, Fady T Botros







Lancet Diabetes Endocrinol. 2018 Aug;6(8):605-617

Liraglutide and Renal Outcomes in Type 2 Diabetes

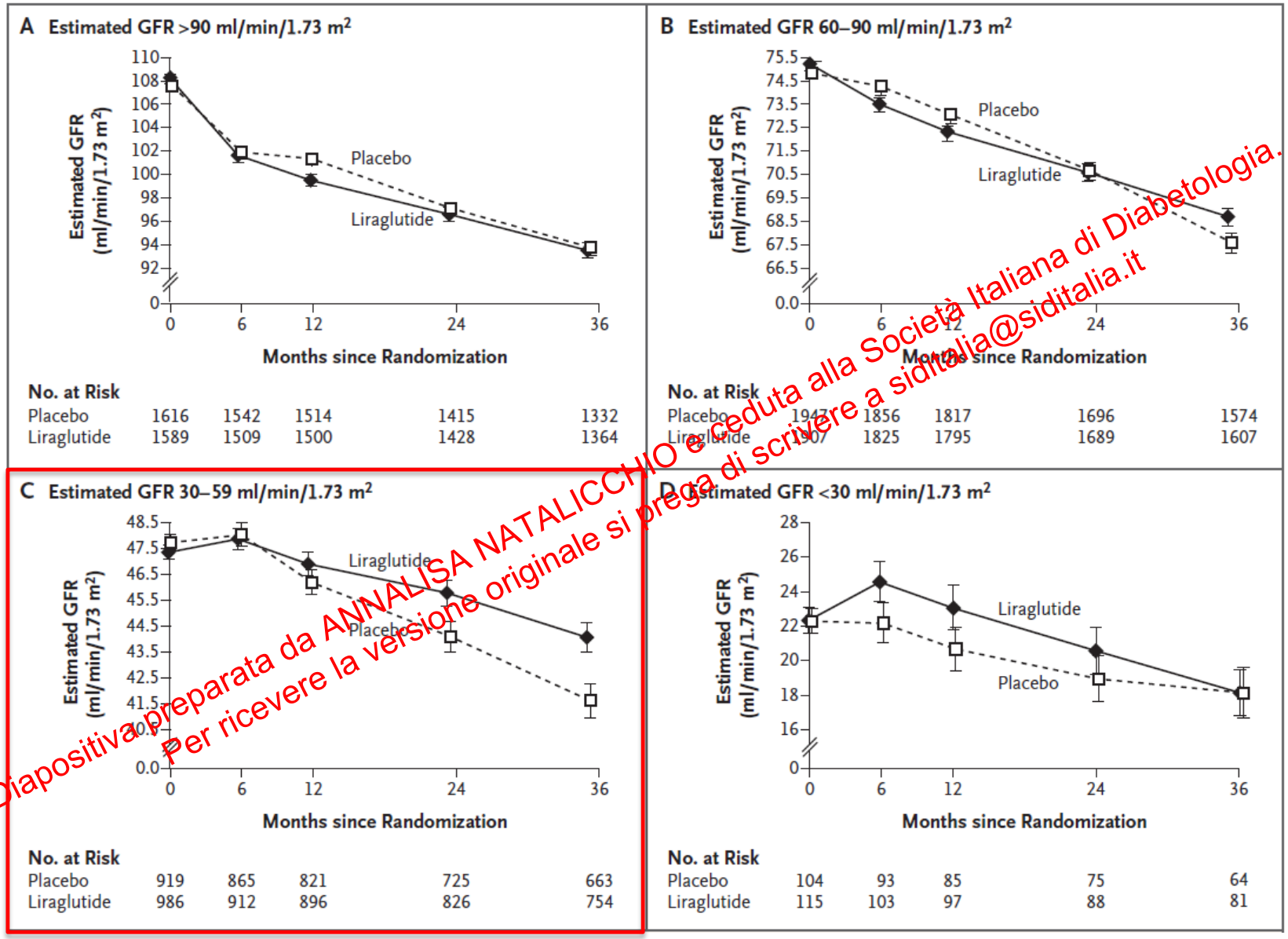
LEADER

Johannes F.E. Mann, M.D., David D. Ørsted, M.D., Ph.D.,
Kirstine Brown-Frandsen, M.D., Steven P. Marso, M.D.,
Neil R. Poulter, F.Med.Sci., Søren Rasmussen, Ph.D., Karen Tornøe, M.D., Ph.D.,
Bernard Zinman, M.D., and John B. Buse, M.D., Ph.D.,
for the LEADER Steering Committee and Investigators*

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

N Engl J Med. 2017 Nov 30;377(22):2197-2198



N Engl J Med. 2017 Aug 31;377(9):839-848

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*

SUSTAIN-6

Table 2. Primary and Secondary Cardiovascular and Microvascular Outcomes.

Outcome	Semaglutide (N=1648)		Placebo (N=1649)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Primary composite outcome†	108 (6.6)	3.24	146 (8.9)	4.44	0.74 (0.58–0.95)	<0.001 for noninferiority; 0.02 for superiority
Expanded composite outcome‡	199 (12.1)	6.17	264 (16.0)	8.36	0.74 (0.62–0.89)	0.002
All-cause death, nonfatal myocardial infarction, or nonfatal stroke	122 (7.4)	3.66	158 (9.6)	4.81	0.77 (0.61–0.97)	0.03
Death						
From any cause	62 (3.8)	1.82	60 (3.6)	1.76	1.05 (0.74–1.50)	0.79
From cardiovascular cause	44 (2.7)	1.29	46 (2.8)	1.35	0.98 (0.65–1.48)	0.92
Nonfatal myocardial infarction	47 (2.9)	1.40	64 (3.9)	1.92	0.74 (0.51–1.08)	0.12
Nonfatal stroke	27 (1.6)	0.80	44 (2.7)	1.31	0.61 (0.38–0.99)	0.04
Hospitalization for unstable angina pectoris	22 (1.3)	0.65	27 (1.6)	0.80	0.82 (0.47–1.44)	0.49
Revascularization	83 (5.0)	2.50	126 (7.6)	3.85	0.65 (0.50–0.86)	0.003
Hospitalization for heart failure	59 (3.6)	1.76	54 (3.3)	1.61	1.11 (0.77–1.61)	0.57
Retinopathy complications§	50 (3.0)	1.49	29 (1.8)	0.86	1.76 (1.11–2.78)	0.02
New or worsening nephropathy¶	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46–0.88)	0.005

N Engl J Med. 2016 Nov 10;375(19):1834-1844

Take-home Messages II

- La maggior parte degli analoghi del GLP-1 (tranne **exenatide once weekly**) può essere utilizzata in caso di insufficienza renale moderata (**exenatide twice daily** richiede una *dose escalation*) ✓
- **Dulaglutide**, **liraglutide** e **semaglutide** possono essere usati in condizioni di severa insufficienza renale ✓
- **Nessun analogo del GLP-1** può essere utilizzato in caso di pazienti con malattia renale allo stadio terminale ✗

Il Paziente Diabetico Anziano

Il paziente anziano è spesso escluso dai trials clinici:
solo l'**1.4%** dei trials recluta pazienti anziani e una percentuale ancora minore recluta pazienti anziani fragili.

Negli anni sono state pubblicate delle linee guida basate soprattutto su **consensus** o **opinioni**, ma nessuna di esse ha stabilito dei **gold standard** di cura.

Contents available at ScienceDirect
Diabetes Research and Clinical Practice
journal homepage: www.elsevier.com/locate/diabres
ELSEVIER
International Diabetes Federation

International Diabetes Federation

New IDF Guideline for managing type 2 diabetes in older people☆

Trisha Dunning, Alan Sinclair, Stephen Colagiuri

Diabet Med. 2018 Jul;35(7):838-845

JAMDA
journal homepage: www.jamda.com
ELSEVIER

CONSENSUS REPORT

Diabetes in Older Adults

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Diabet Med. 2018 Jul;35(7):838-845

Diabetes Mellitus in Older People: Position Statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts in Diabetes

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Diabetes Care. 2012 Dec;35(12):2650-64
J Am Med Dir Assoc. 2012 Jul;13(6):497-502
J Am Med Dir Assoc. 2012 Jul;13(6):497-502

Il Paziente Anziano con DMT2

ADA Reccomendation

Recommendations

- Consider the assessment of medical, mental, functional, and social geriatric domains in older adults to provide a framework to determine targets and therapeutic approaches for diabetes management. C
- Screening for geriatric syndromes may be appropriate in older adults experiencing limitations in their basic and instrumental activities of daily living, as

- 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% nel paziente anziano sano
HbA1c < 8.0% comorbidità multiple, declino cognitivo medio-moderato
HbA1c < 8.5% scarsa salute, limitata aspettativa di vita, declino cognitivo severo

- 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

FRAGILE
HANDLE WITH CARE

Diabetes Care. 2017 Jan;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 or weight loss Consider discontinuing if already receiving substantial amount of insulin (approximately >40 units/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 doses 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, lower edema, anemia Possible risk of bladder cancer.	Good efficacy in older patients with high insulin resistance

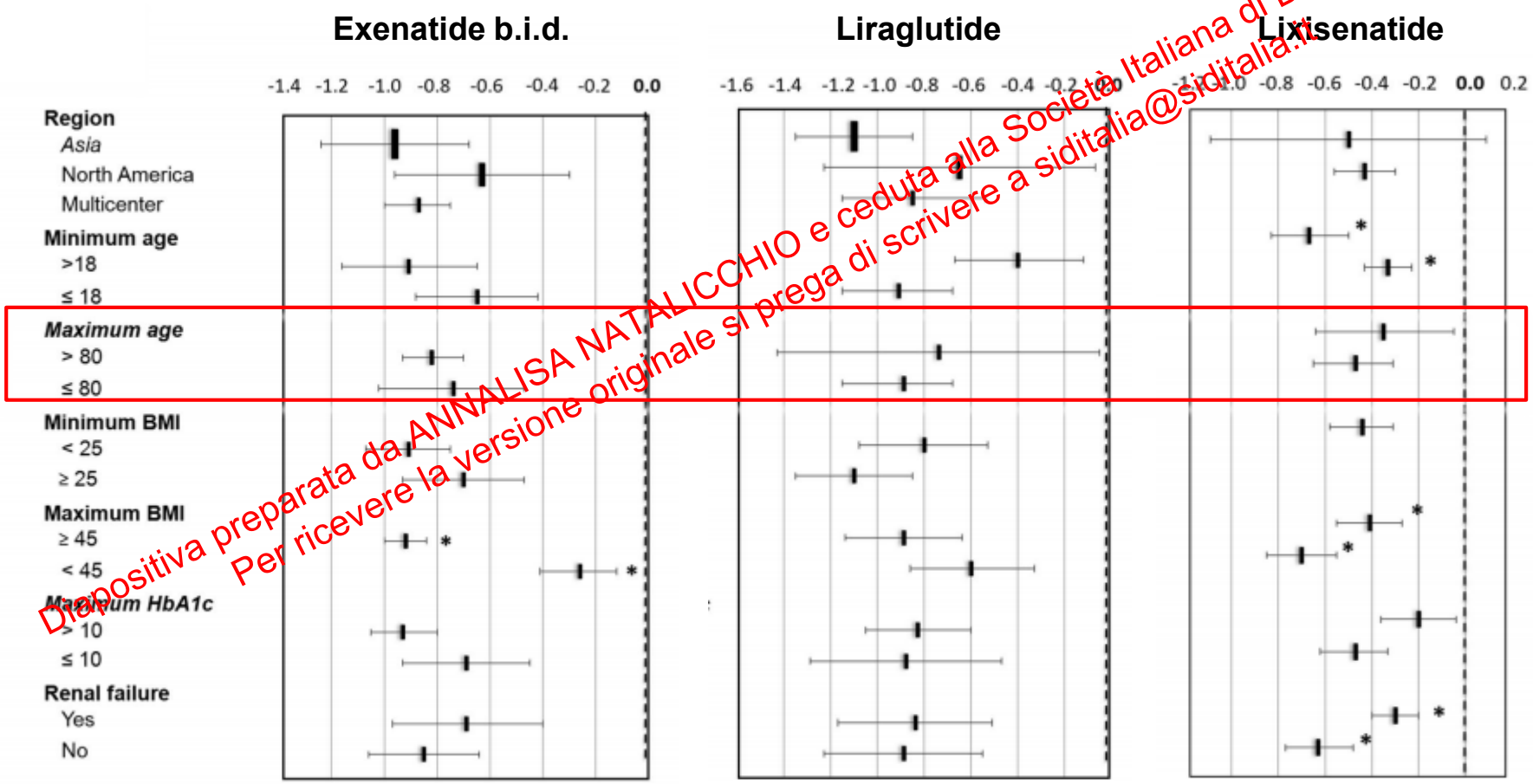
	HbA1c reduction	Advantages	Disadvantages	Vignette in Frail Population
GLP-1 agonists	0.8-1.0% (9-11 mmol/mol)	Low hypoglycemia risk Once a day and once a week formulation New formulations available in combination with basal insulin	High cost Injectable	Monitor for anorexia, weight loss; do not use in 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

J Frailty Aging. 2018;7(1):10-20

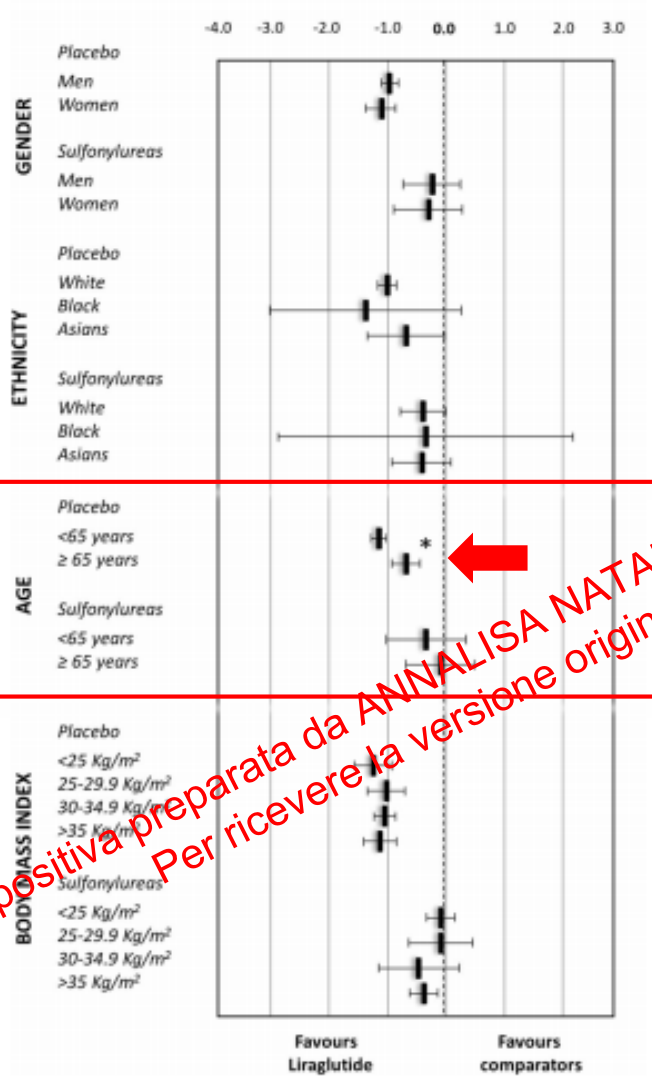
Predictors of response to glucagon-like peptide-1 receptor agonists: a meta-analysis and systematic review of randomized controlled trials

Matteo Monami[1] · Ilaria Dicembrini[1] · Besmir Nreu[1] · Francesco Andreozzi[2] · Giorgio Sesti[2] · Edoardo Mannucci[1]

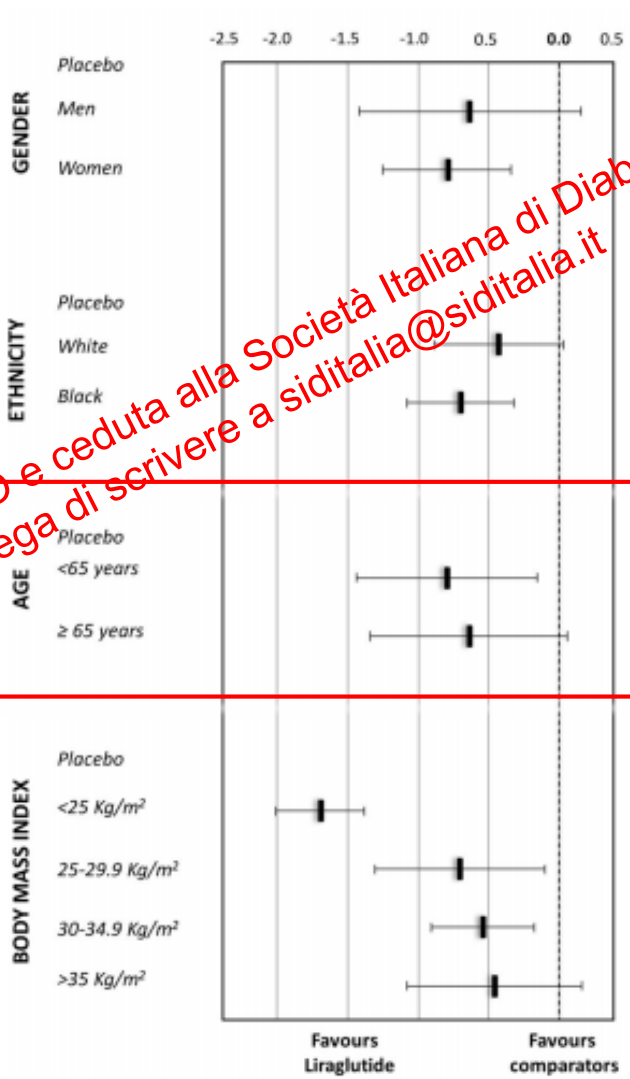


Acta Diabetol. 2017 Dec;54(12):1101-1114

Liraglutide



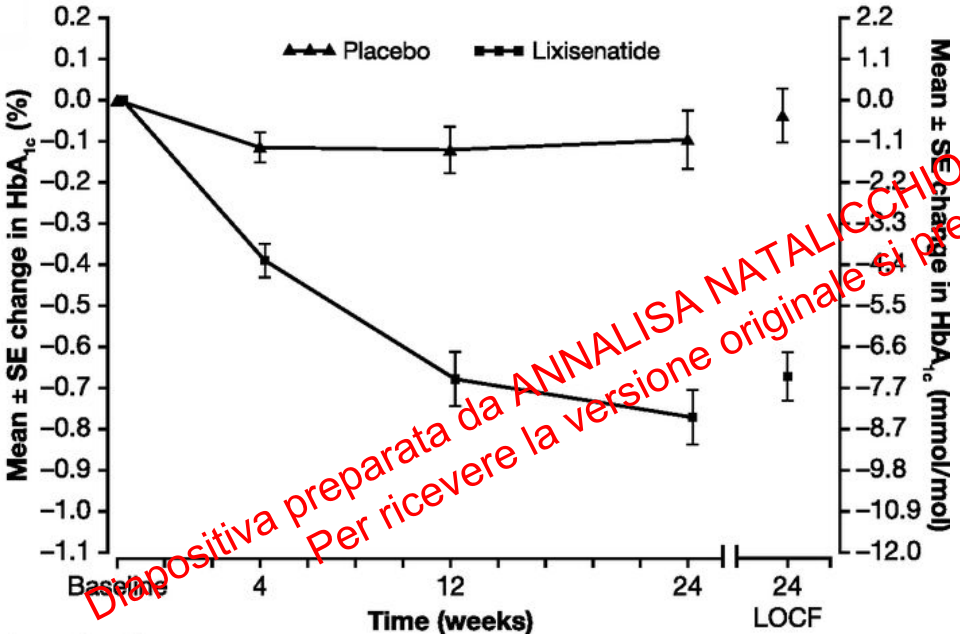
Albiglutide

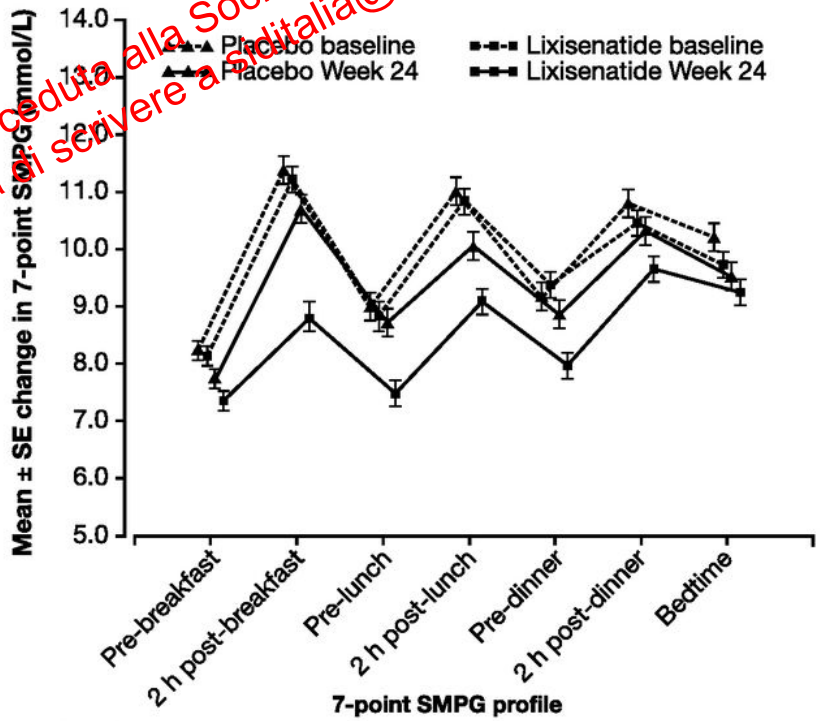


Acta Diabetol. 2017 Dec;54(12):1101-1114

Lixisenatide Therapy in Older Patients With Type 2 Diabetes Inadequately Controlled on Their Current Antidiabetic Treatment: The GetGoal-O Randomized Trial

Graydon S. Meneilly[1]⇑, Christine Roy-Duval[2], Hasan Alawi[3], George Dailey[4], Diego Bellido[5], Carlos Trescoli[6], Helard Manrique Hurtado[7], Hailing Guo[8], Valerie Pilorget[2], Riccardo Perfetti[9] **and** Hamish Simpson[10], **on behalf of the GetGoal-O Trial Investigators***





Diabetes Care. 2017 Apr;40(4):485-493

Efficacy and safety of lixisenatide in elderly (≥65 years old) and very elderly (≥75 years old) patients with type 2 diabetes: an analysis from the GetGoal phase III programme†

Denis Raccah[1]*
Patrick Miossec[2]
Virginie Esposito[2]
Elisabeth Niemoeller[3]
Meehyung Cho[4]
John Gerich[5]

Table 3. Treatment-emergent adverse events (safety population)

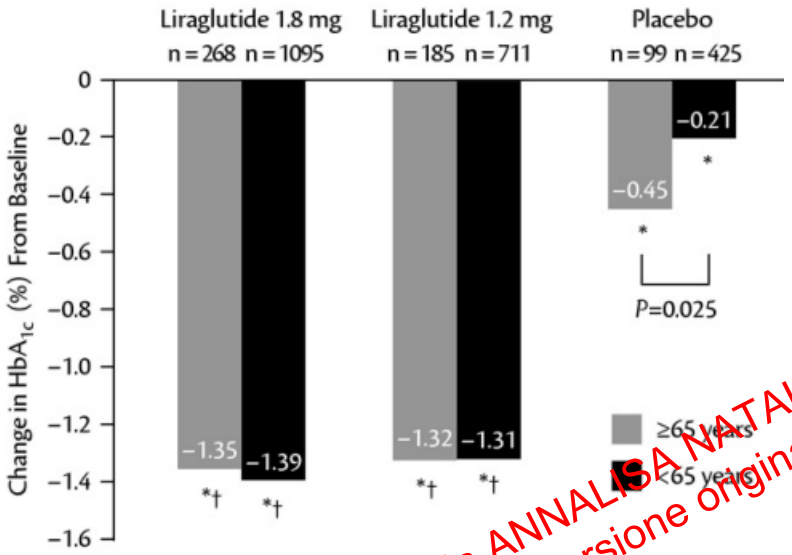
Age	<65 years		≥65 years		<75 years		≥75 years	
	PBO ($n = 817$)	Lixisenatide ($n = 1748$)	PBO ($n = 244$)	Lixisenatide ($n = 379$)	PBO ($n = 1030$)	Lixisenatide ($n = 2079$)	PBO ($n = 31$)	Lixisenatide ($n = 48$)
Any TEAE, *n* (%)	516 (63.2)	1203 (68.8)	144 (59.0)	272 (71.8)	645 (62.6)	1440 (69.3)	15 (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)	71 (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)

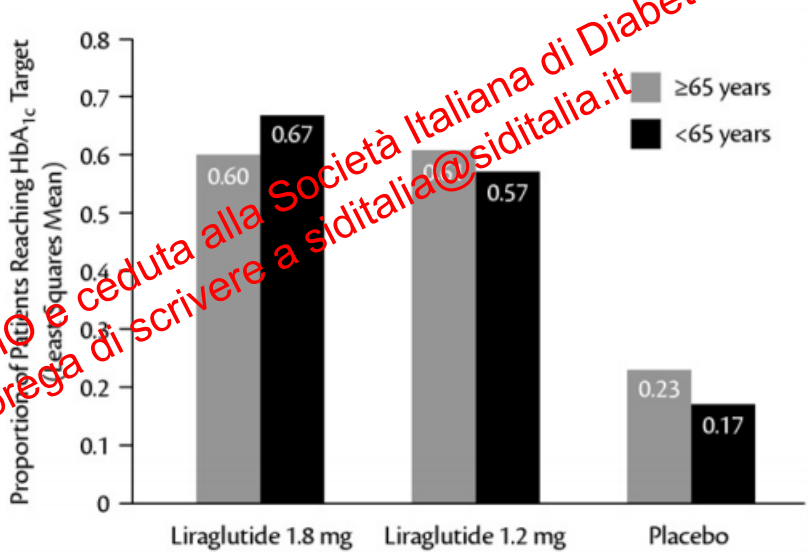
PBO, placebo; TEAE, treatment-emergent adverse event; GI, gastrointestinal.
Data from the main treatment period of the included studies [GetGoal-Mono (12 weeks) and GetGoal-M, GetGoal-F1, GetGoal-S, GetGoal-X and GetGoal-L-Asia (all 24 weeks)] – safety population.

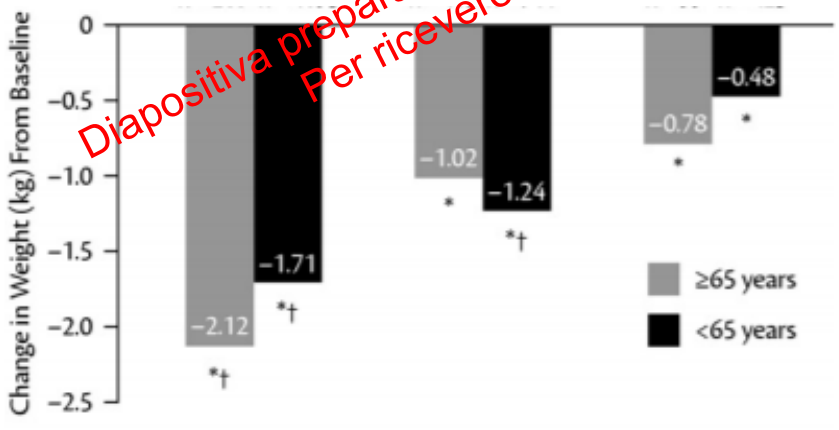
Diabetes Metab Res Rev. 2015 Feb;31(2):204-11

Comparison of the Efficacy and Tolerability Profile of Liraglutide, a Once-Daily Human GLP-1 Analog, in Patients With Type 2 Diabetes ≥65 and <65 Years of Age: A Pooled Analysis from Phase III Studies

Bruce W. Bode, MD[1]; Jason Brett, MD[2]; Ali Falahati, PhD[3]; and Richard E. Pratley, MD[4]







Am J Geriatr Pharmacother. 2011 Dec;9(6):423-33

Table II. Percentage of patients experiencing major and minor hypoglycemia and adverse events in patients with type 2 diabetes aged ≥65 years or <65 years during the first 26 weeks of treatment.

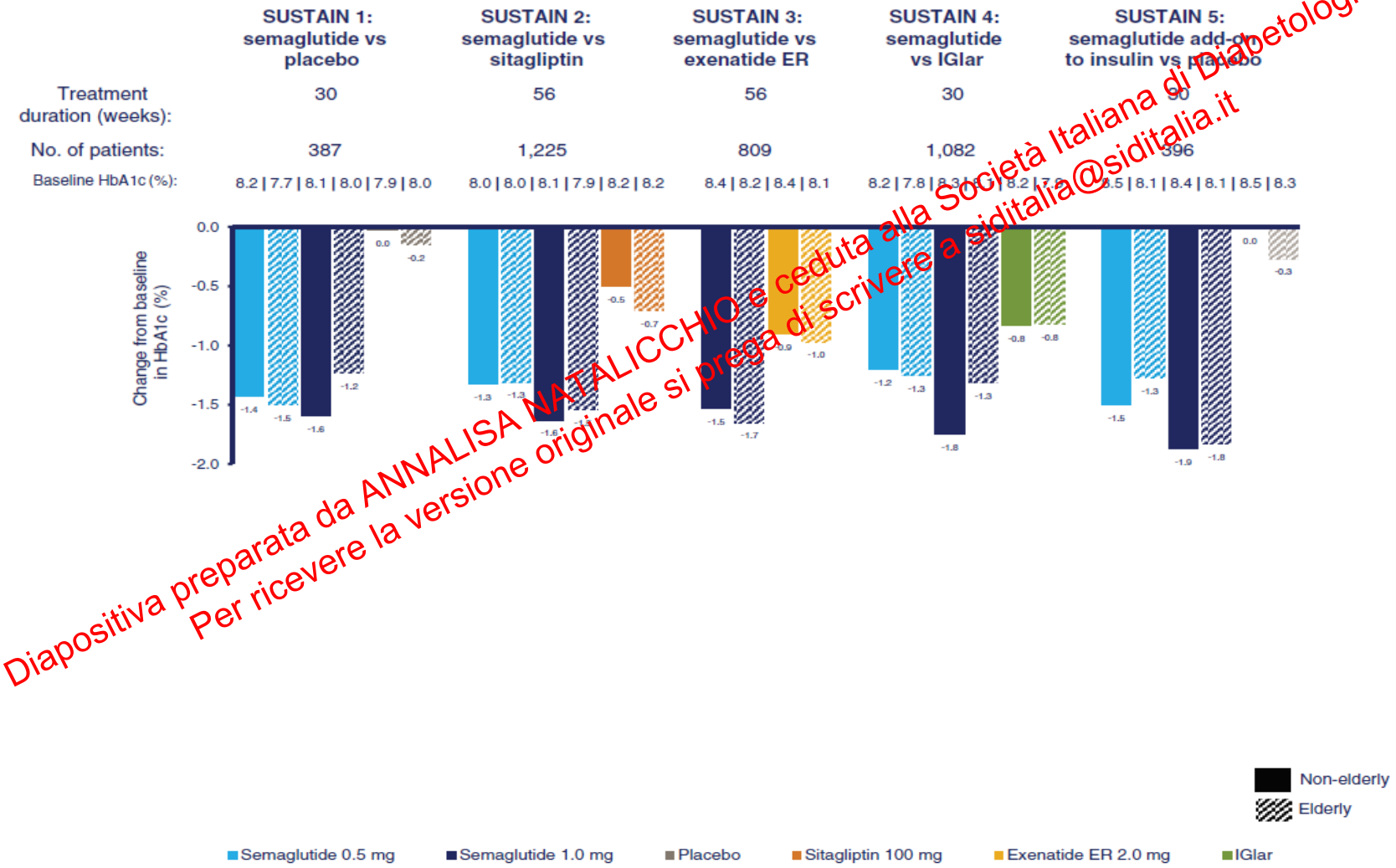
Parameter	Liraglutide 1.8 mg		Liraglutide 1.2 mg		Placebo	
	≥65 Years	<65 Years	≥65 Years	<65 Years	≥65 Years	<65 Years
Major hypoglycemia	0.0	0.5*	0.0	0.0	0.0	0.0
Minor hypoglycemia	15.2	13.2	4.3	8	9.1	8.0
Deaths, % of patients	0.0	0.0	0.0	0.1	1.0	0.0
Serious adverse events	4.1	3.9	7.6	4.8	5.1	4.9
All adverse events	75.1	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.

Am J Geriatr Pharmacother. 2011 Dec;9(6):423-33

Semaglutide as a therapeutic option for elderly patients with type 2 diabetes: Pooled analysis of the SUSTAIN 1-5 trials

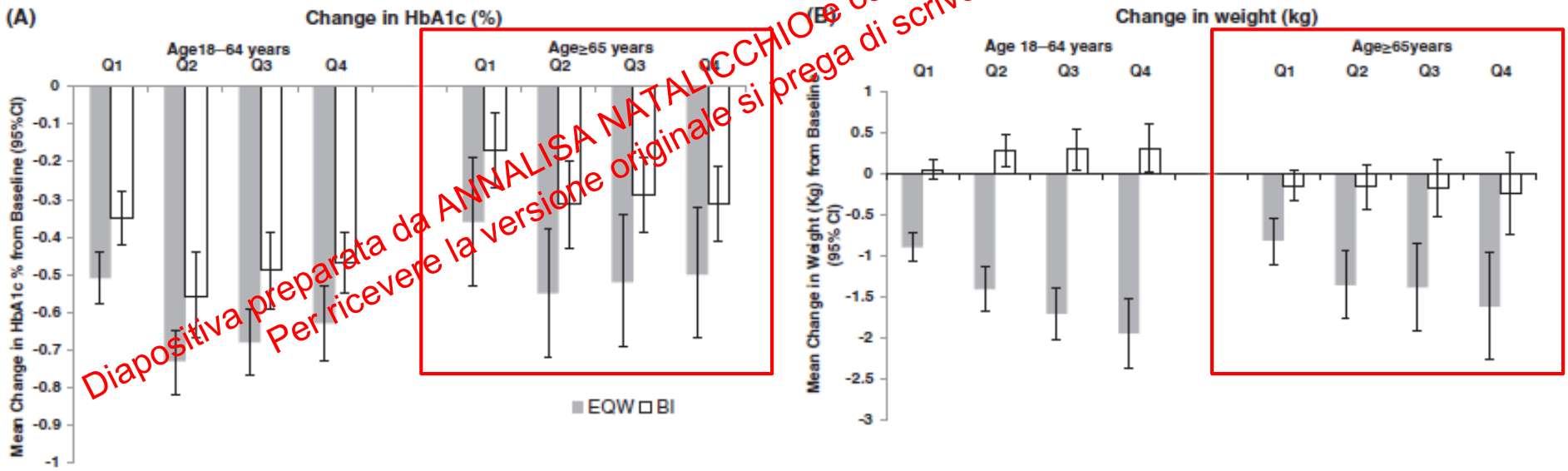
Mark Warren MD[1] | Louis Chaykin MD[2] | David Trachtenbarg MD[3] | Gurudutt Nayak MD[4] | Nelun Wijayasinghe MD[4] | Bertrand Cariou MD[5]



Diabetes Obes Metab. 2018 Sep;20(9):2291-2297

Effectiveness and tolerability of therapy with exenatide once weekly vs basal insulin among injectable-drug-naïve elderly or renal impaired patients with type 2 diabetes in the United States

Anita M. Loughlin PhD[1] | Qing Qiao MD[2] | Anthony P. Nunes PhD[1] | Peter Öhman MD[3] | Stephen Ezzy MS[1] | Laura Yochum MPH[1] | C. Robin Clifford MS[1] | Robert Gately MS[1] | David D. Dore PhD[1] | John D. Seeger DrPH[1]



Diabetes Obes Metab. 2018 Apr;20(4):898-909

TABLE 3 Comparison of the occurrence of hypoglycaemia and gastrointestinal symptoms between propensity score matched injectable-naive exenatide once weekly and basal insulin initiators, by age and renal function

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 (64.3-95.0)	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	134 (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

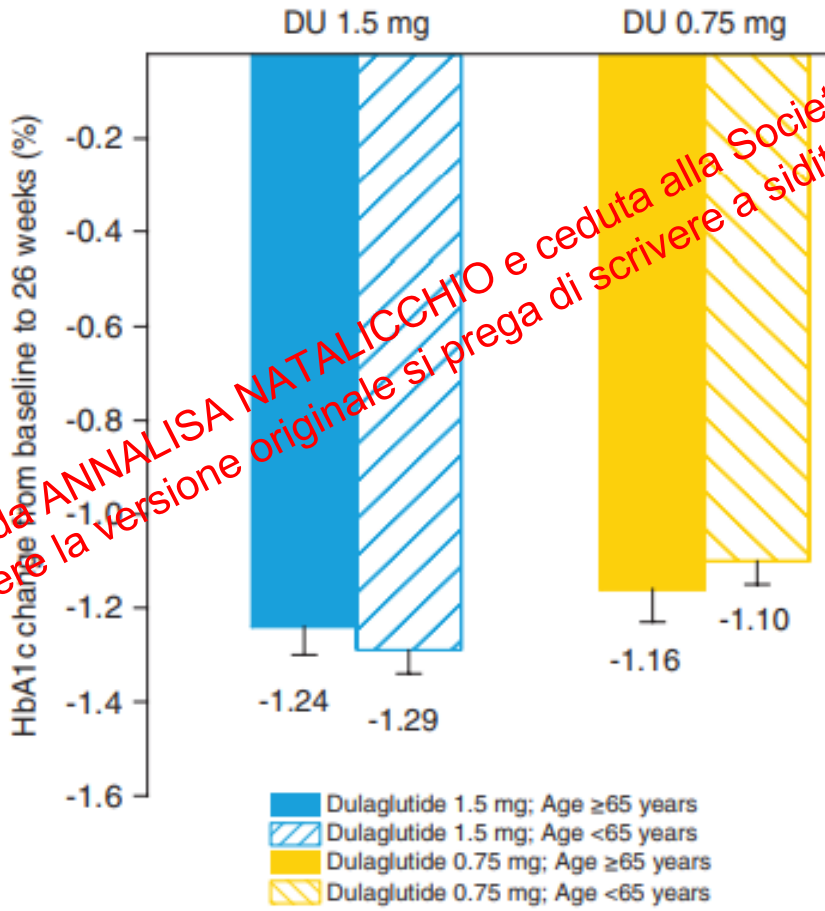
Diabetes Obes Metab. 2018 Apr;20(4):898-909

ORIGINAL ARTICLE

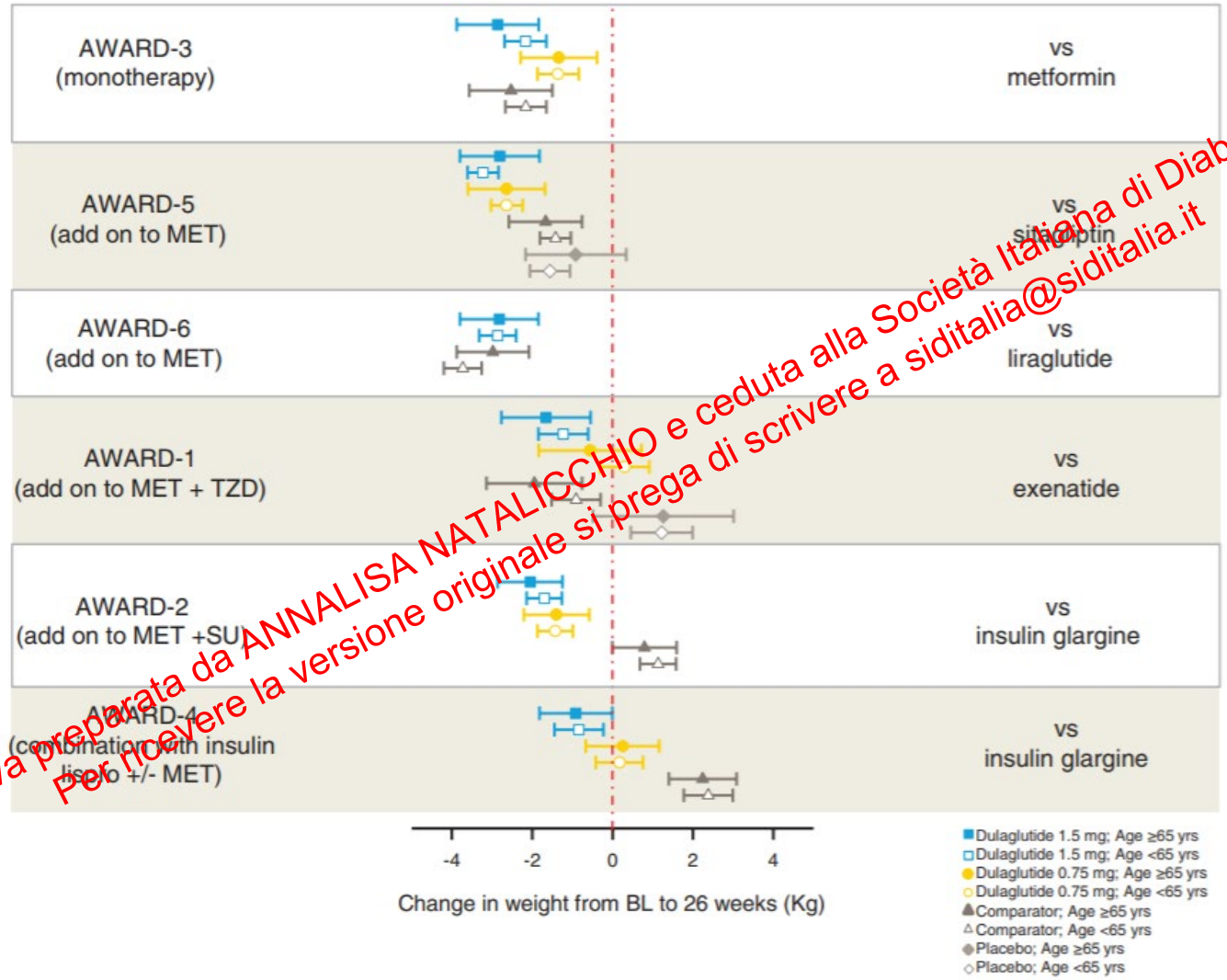
Similar efficacy and safety of once-weekly dulaglutide in patients with type 2 diabetes aged ≥65 and <65 years

M. A. Boustani[1], I. Pittman IV[2], M. Yu[3], V. T. Thieu[4], O. J. Varnado[4] & R. Juneja[4]

[1] *Indiana University, Indianapolis, IN, USA*
[2] *Providence Medical Group, Terre Haute, IN, USA*
[3] *Eli Lilly and Company, Toronto, ON, Canada*
[4] *Eli Lilly and Company, Indianapolis, IN, USA*



Diabetes Obes Metab. 2016 Aug;18(8):820-8



Diabetes Obes Metab. 2016 Aug;18(8):820-8

Take-home Messages III

Gli analoghi del GLP-1:

- HbA1c a target ✓
- Basso numero di ipoglicemie ✓
- Outcome cardiovascolare favorevole ✓
- Sono agenti iniettabili ✗
- La loro somministrazione richiede capacità visive, motorie e cognitive integre ✗
- Sono spesso associati a nausea, vomito e diarrea ✗
- Inducono perdita di peso:

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

Analoghi del GLP-1 e Patologie Neurodegenerative

- Negli ultimi anni si è assistito ad un rapido incremento nella prevalenza delle patologie correlate all'invecchiamento, tra cui le più comuni sono la malattia di Alzheimer (AD) e il morbo di Parkinson (PD);

- Per queste patologie ancora non si è giunti a una completa comprensione dei meccanismi che ne inducono l'insorgenza e la progressione, di conseguenza non esistono trattamenti efficaci;

- **A dicembre 2018, più di 1900 trials clinici avevano lo scopo di testare nuove molecole per contrastare l'AD e 750 per contrastare il PD (ClinicalTrials.gov)**;

- **Un considerevole numero di farmaci utilizzati per il trattamento del DMT2 hanno mostrato un'azione neuroprotettiva nei modelli animali di AD e PD**;

- **Tra questi farmaci, gli analoghi del GLP-1 (GLP-1As) hanno mostrato gli effetti più promettenti**.

Batista AF et al, CNS Drugs, 2018

Trials Clinici nel PD

ClinicalTrials.gov ID:	Razionale	Durata
NCT03659682	Studio di fase II con semaglutide in pazienti con PD idiopatico	48 mesi
NCT03456687	Studio di fase I con exenatide once weekly vs Placebo	12 mesi
NCT02953665	Studio di fase II per studiare sicurezza ed efficacia di liraglutide in PD.	-
NCT03439943	Studio di fase II con lixisenatide in pazienti con PD precoce	12 mesi
NCT03672604	Studio di fase I per studiare sicurezza ed efficacia di NLY01* in volontari sani	-
NCT01174810	Studio di fase II per studiare l'efficacia dell'exenatide vs placebo in 45 pazienti con PD moderato	12 mesi **TERMINATO**
NCT01971242	Studio di fase II in doppio cieco con exenatide 2 mg once-weekly vs placebo su 62 pazienti con PD	48 settimane **TERMINATO**

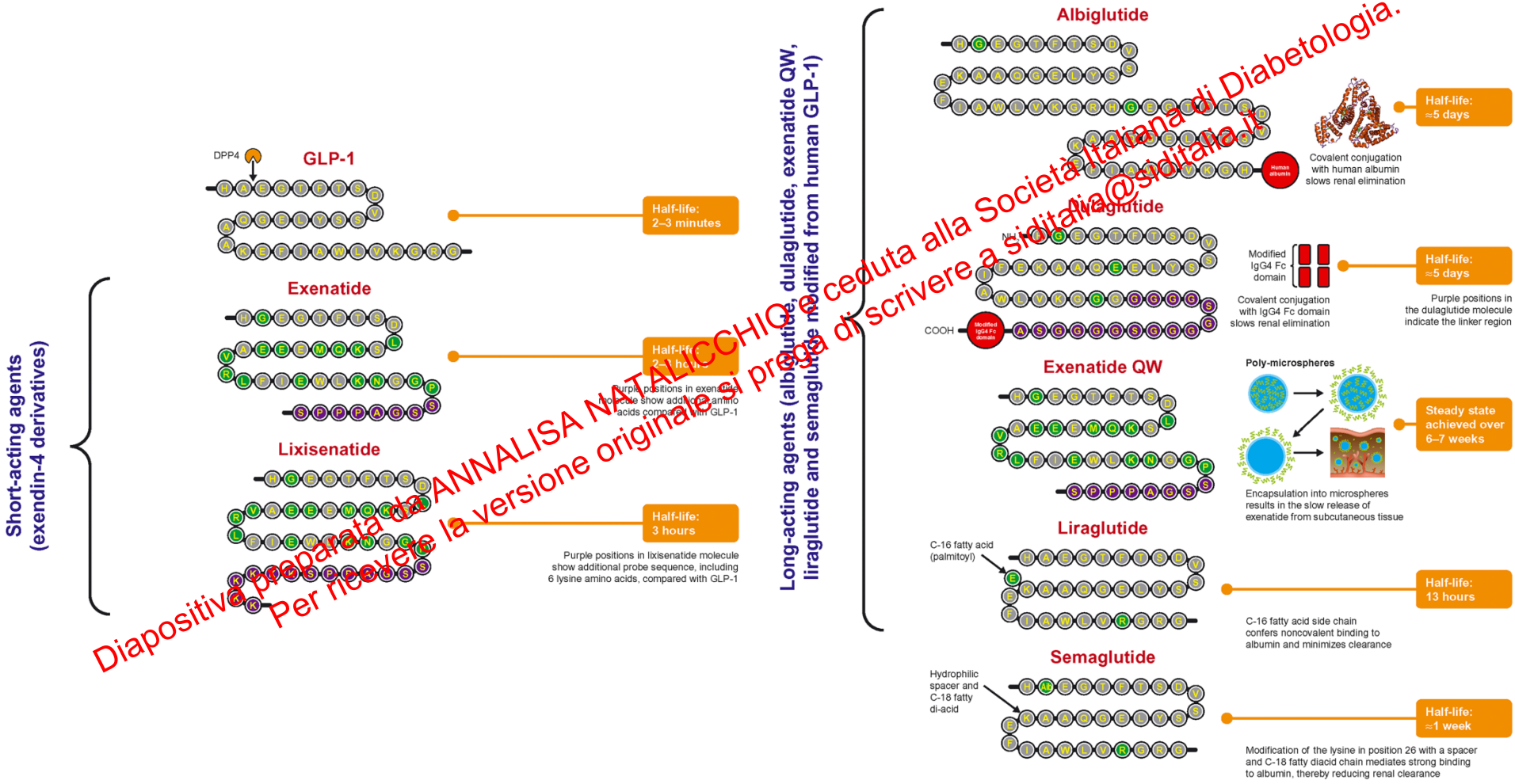
*NLY01: potente analogo long-acting del GLP-1 in grado di agire prevalentemente a livello centrale.

Trials Clinici nell'AD

ClinicalTrials.gov ID:	Razionale	Durata
NCT01255163	Studio pilota di fase II con exenatide vs placebo in 57 pazienti con AD	**TERMINATO**
NCT01843075	Efficacia di liraglutide once daily in pazienti con demenza legata ad AD moderata (previsti 206 partecipanti)	12 mesi
NCT01469351	Efficacia liraglutide once daily vs placebo su 38 pazienti con AD precoce/moderato (randomizzato, in doppio cieco)	26 settimane **TERMINATO**

Modificato da Batista AF et al, CNS Drugs, 2018

Gli Analoghi del GLP-1 (GLP-1A)



Diabetes Metab Res Rev. 2019 Jan;35(1):e3070

Lixisenatide in type 2 diabetes: latest evidence and clinical usefulness

Sarah L. Anderson and Jennifer M. Trujillo

Table 2. Phase III clinical trials of lixisenatide: safety data.

Trial	Trial treatment regimen	Nausea (%)	Vomiting (%)	Diarrhea (%)	Symptomatic hypoglycemia (%)	Any serious AE (%)	Discontinuation due to AE (%)
GetGoal-Mono Fonseca *et al.* [2012]	Lixisenatide 20 µg/day (1-step titration)	20.2	6.7	NR	0.8	0	2.5
	Lixisenatide 20 µg/day (2-step titration)	24.2	7.5		2.5	[illegible]	4.2
	Placebo	4.1	0		1.6	4.1	0.8
GetGoal-Mono Japan Seino *et al.* [2012a]	Lixisenatide 20 µg/day (1-step)	50.0	2.8	8.3	2.8	0	11.1
	Lixisenatide 20 µg/day (2-step)	36.4	12.1	3.0	[illegible]	6.1	9.1
GetGoal-M Ahren *et al.* [2013]	Lixisenatide 20 µg/day (morning)	22.7	9.4	10.6	2.4	2.0	7.1
	Lixisenatide 20 µg/day (evening)	21.2	13.3	10.6	5.1	3.1	5.5
	Placebo	7.6	2.9	8.8	0.6	1.2	1.2
GetGoal-M-Asia Yu Pan *et al.* [2014]	Lixisenatide 20 µg/day	16.3	7.7	3.6	1.5	1.5	5.6
	Placebo	[illegible]	[illegible]	1.0	1.6	2.1	1.6
GetGoal-F1 Bolli *et al.* [2014]	Lixisenatide 20 µg/day (1-step)	26.1	11.8	6.2	1.9	3.1	5.6
	Lixisenatide 20 µg/day (2-step)	[illegible]	15.5	12.4	2.5	4.3	8.1
	Placebo	4.4	0	8.8	0.6	2.5	2.5
GetGoal-P Pinget *et al.* [2013]	Lixisenatide 20 µg/day	23.5	6.8	7.1	3.4	2.5	6.5
	Placebo	10.6	3.7	10.6	1.2	1.9	5.0
GetGoal-S Rosenstock *et al.* [2014]	Lixisenatide 20 µg/day	25.3	8.7	8.9	15.3	3.5	9.8
	Placebo	7.0	3.5	6.7	12.3	5.6	4.9
GetGoal-X Rosenstock *et al.* [2013]	Lixisenatide 20 µg/day	24.5	10.1	10.4	2.5	2.8	10.4
	Exenatide 10 µg twice daily	35.1	13.3	13.3	7.9	2.2	13
GetGoal-L Riddle *et al.* [2013a]	Lixisenatide 20 µg/day	26.2	8.2	7.3	27.7	3.7	7.6
	Placebo	8.4	0.6	5.4	21.6	4.2	4.8
GetGoal-Duo 1 Riddle *et al.* [2013b]	Lixisenatide 20 µg/day	27.4	9.4	6.7	22.4	7.6	8.5
	Placebo	4.9	1.3	3.1	13.5	4.5	3.6
GetGoal-L-Asia Seino *et al.* [2012b]	Lixisenatide 20 µg/day	39.6	18.2	6.5	42.9	6.5	9.1
	Placebo	4.5	1.9	2.5	23.6	5.7	3.2
GetGoal-Duo 2 Rosenstock *et al.* [2015]	Lixisenatide 20 µg/day	25.2	8.7	6.7	35.9	3.7	5.0
	Insulin glulisine once daily	1.7	1.7	3.3	46.5	3.7	0.7
	Insulin glulisine 3 times daily	1.0	2.0	1.4	52.4	4.8	1.0

AE, adverse effect.

Ther Adv Chronic Dis. 2016 Jan;7(1):4-17

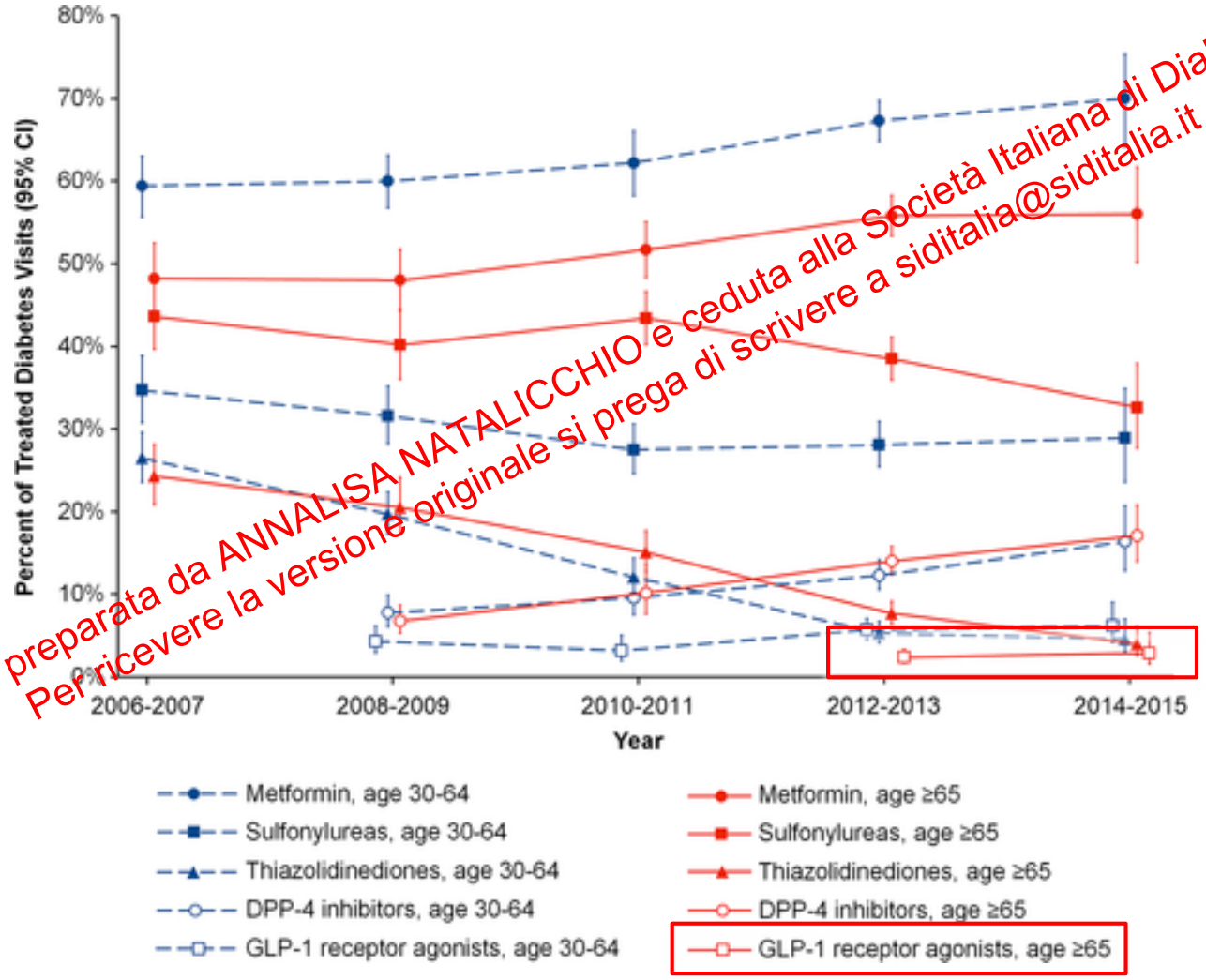
Analoghi del GLP-1 nel Paziente con Insufficienza Renale

Class	Medications/therapies in class	Primary physiological action(s)	Advantages	Disadvantages/adverse effects	Efficacy
GLP-1 RA					
Shorter acting	• Exenatide • Lixisenatide	• Glucose dependent: ↑ Insulin secretion ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety	• No hypoglycaemia as monotherapy • ↓ Weight • Excellent postprandial glucose efficacy for meals after injections • Improves cardiovascular risk factors	• Frequent GI side effects but may be transient • Modestly ↑ heart rate • Training requirements • Dose adjustment/avoidance in renal disease • Acute pancreatitis (rare/uncertain) • Very high cost	Intermediate–high
Longer acting	• Dulaglutide • Exenatide extended-release • Liraglutide • Semaglutide	• Glucose dependent: ↑ Insulin secretion ↓ Glucagon secretion • ↑ Satiety	• No hypoglycaemia as monotherapy • ↓ Weight • ↓ Postprandial glucose excursions • Improves cardiovascular risk factors • ↓ MACE with some agents (see text) • ↓ Albuminuria with some agents (see text) • Greater lowering of fasting glucose vs short-acting preparations • Once weekly dosing (except liraglutide, which is daily)	• GI side effects, including gall bladder disease • Greater ↑ heart rate • Training requirements • Dose adjustment/avoidance for some agents in renal disease • Acute pancreatitis (rare/uncertain) • C cell hyperplasia/medullary thyroid tumours (rare/uncertain; observed in animals only) • Very high cost	High–very high

Diabetologia. 2018 Dec;61(12):2461-2498

Differences in National Diabetes Treatment Patterns and Trends between Older and Younger Adults

Scott J. Pilla, MD, MHS, Jodi B. Segal, MD, MPH,*†‡§¶ G. Caleb Alexander, MD, MS,*†‡§ Cynthia M. Boyd, MD, MPH,†‡‖ and Nisa M. Maruthur, MD, MHS*†¶*

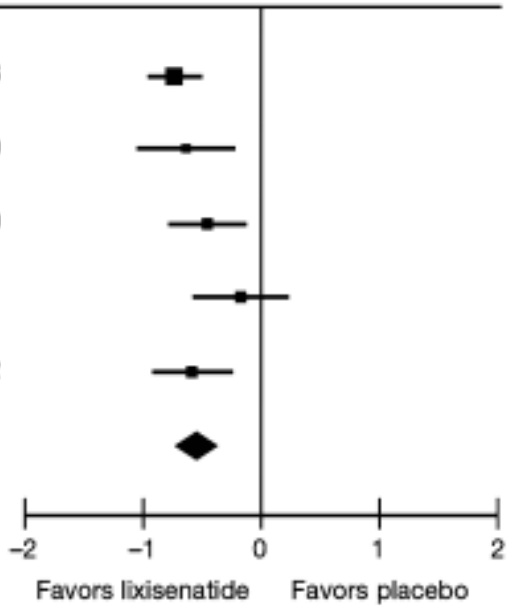


J Am Geriatr Soc. 2019 Jan 31

Lixisenatide Treatment for Older Patients with Type 2 Diabetes Mellitus Uncontrolled on Oral Antidiabetics: Meta-Analysis of Five Randomized Controlled Trials

Markolf Hanefeld · Rachele Berria · Jay Lin · Ronnie Aronson · Patrice Darmon · Marc Evans · Luc Van Gaal

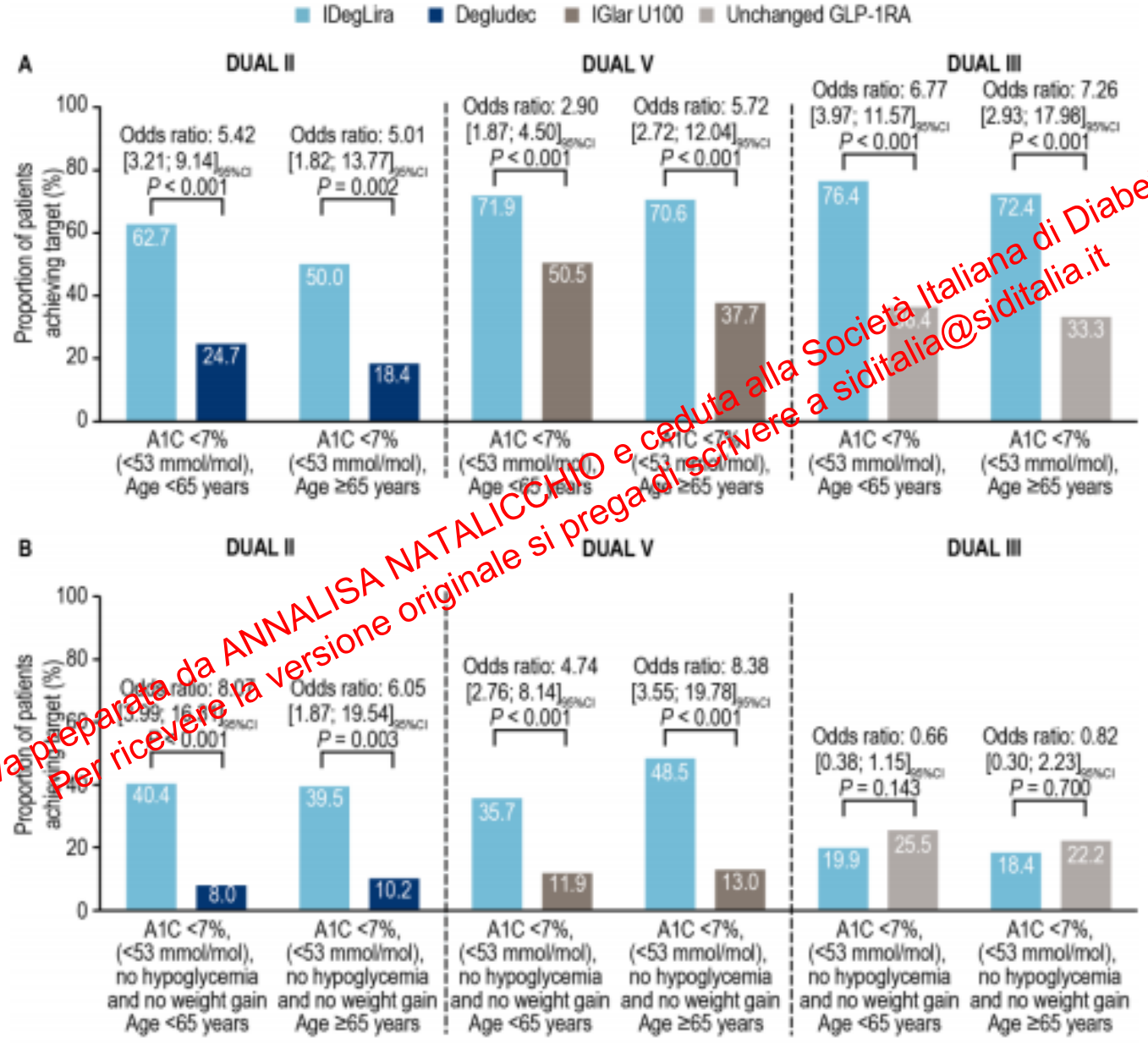
Study or subgroup	Lixisenatide Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean difference IV, random, 95% CI	Year	Mean difference IV, random, 95% CI
GetGoal-S	−0.96	0.82	125	−0.23	0.73	70	29.5%	−0.73 (−0.95, −0.51)	2008	
GetGoal-P	−0.80	0.97	57	−0.17	0.82	26	19.0%	−0.63 (−1.03, −0.23)	2009	
GetGoal-M	−0.75	0.74	63	−0.30	0.61	25	20.6%	−0.45 (−0.77, −0.13)	2010	
GetGoal-M-Asia	−0.78	0.88	27	−0.61	0.62	33	15.5%	−0.17 (−0.56, 0.22)	2011	
GetGoal-F1	−0.88	0.84	32	−0.30	0.55	43	19.3%	−0.58 (−0.91, −0.25)	2012	
Total (95% CI)			**304**			**197**	**100.0%**	**−0.54 (−0.73, −0.36)**		



Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 6.58$, df = 4 ($p = 0.16$); $I^2 = 39\%$
Test for overall effect: $Z = 5.72$ ($p < 0.00001$)

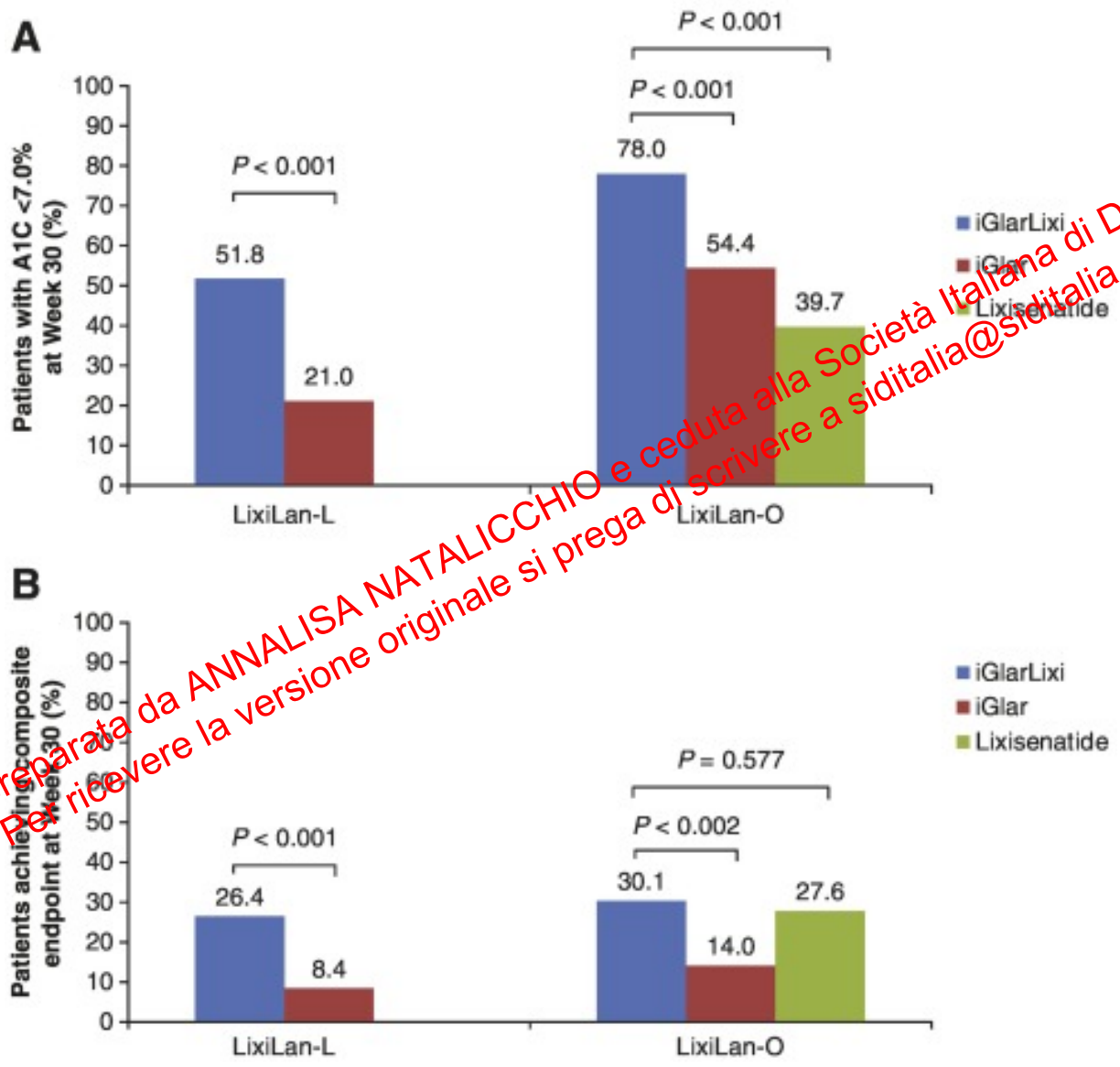
Adv Ther. 2014 Aug;31(8):861-72

Efficacia e Sicurezza di iDegLira negli Anziani con DMT2



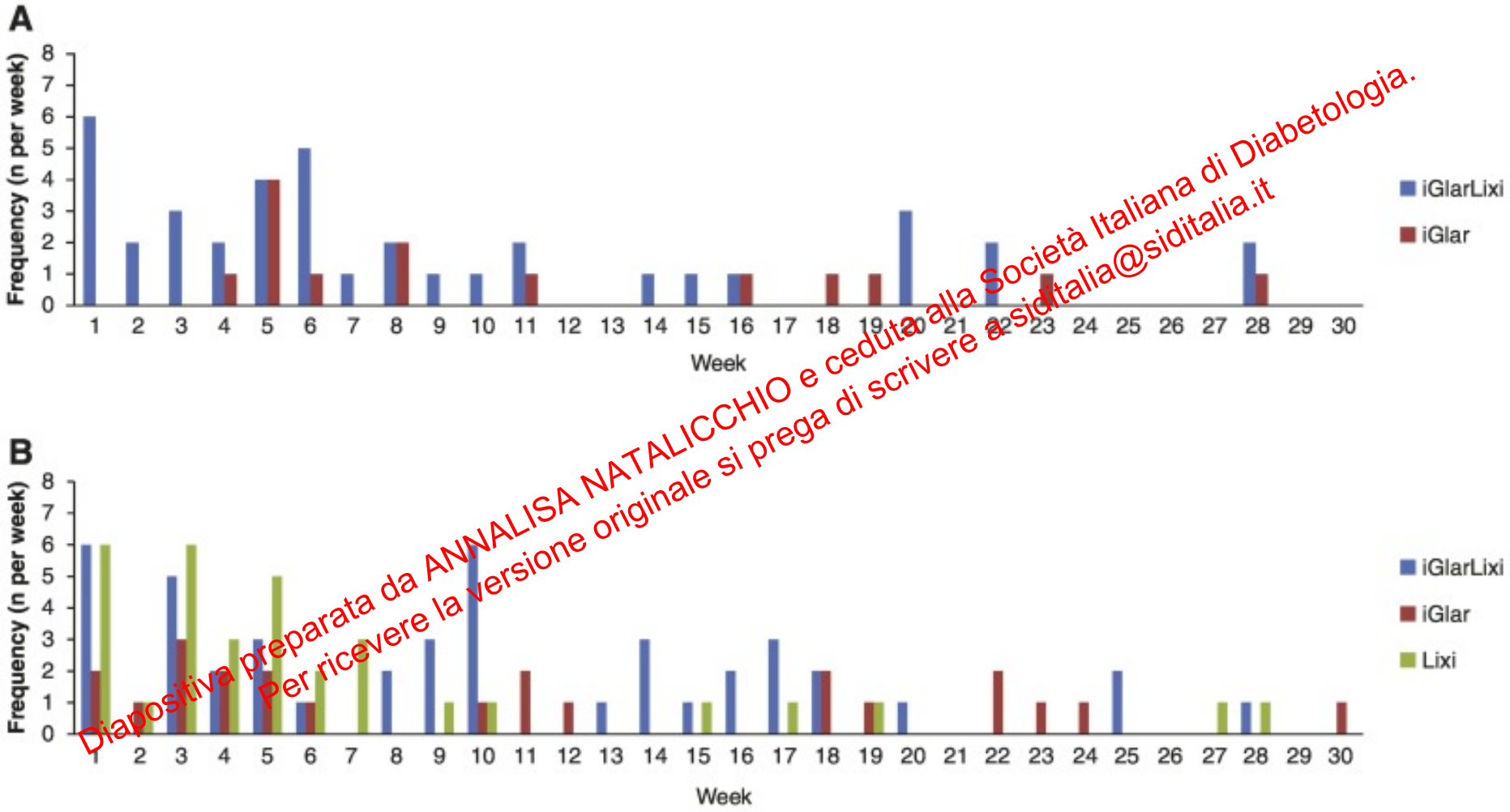
Endocr Pract. 2019 Feb;25(2):144-155

Efficacia e Sicurezza di iGlarLixi negli Anziani con DMT2



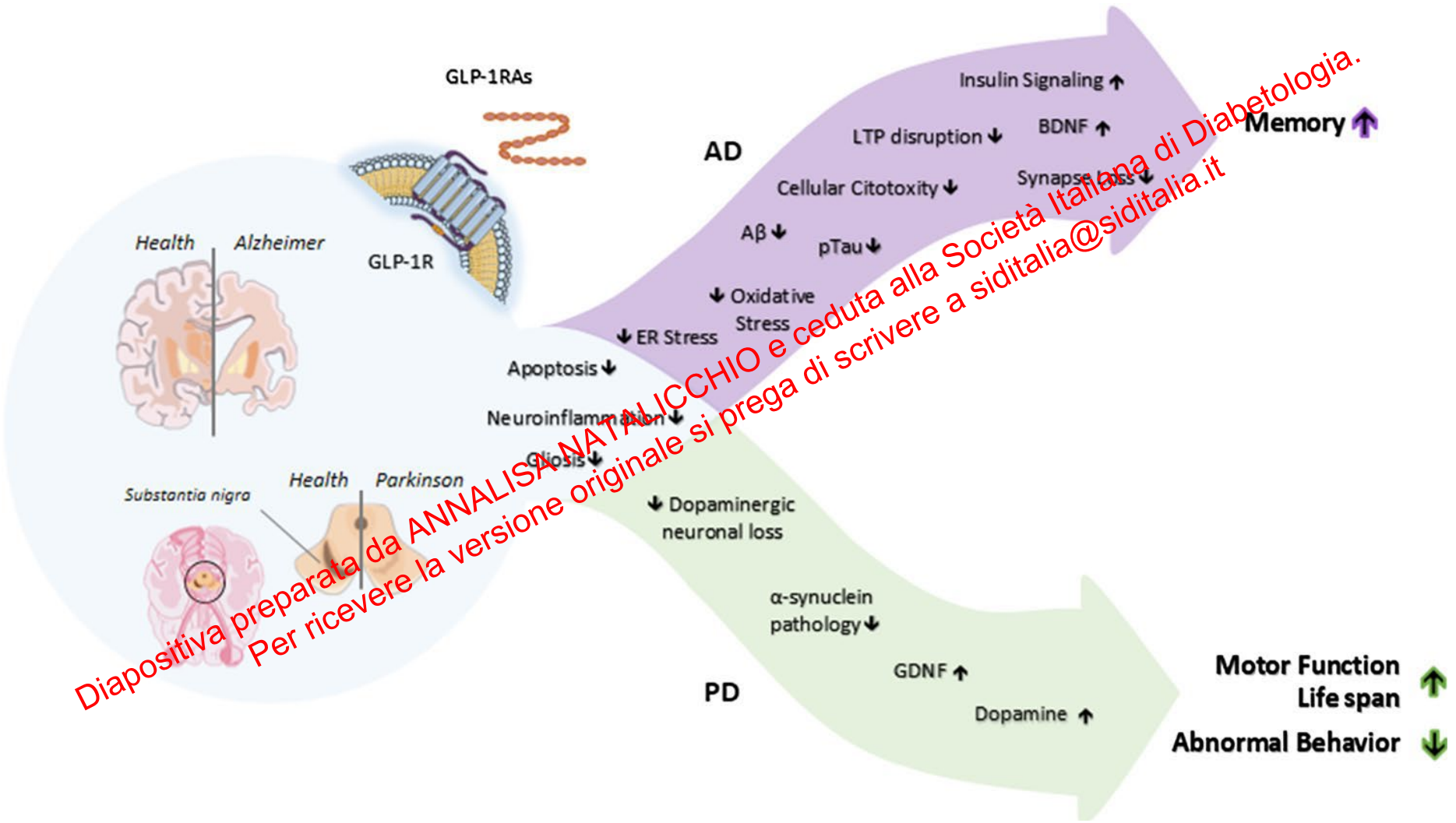
J Diabetes Complications. 2019 Mar;33(3):236-242

Efficacia e Sicurezza di iGlarLixi negli Anziani con DMT2



J Diabetes Complications. 2019 Mar;33(3):236-242

Azioni Neuroprotettive degli GLP-1A in AD e PD



Batista AF et al, CNS Drugs, 2018