Analoghi del GLP-1 dopo fallimento BOT

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UNIVERSITA' CATTOLICA del SACRO CUORE

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

- Medtronic,
- Astrazeneca,
- Roche,
- MSD

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.).

CONSENSUS REPORT

Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Consensus recommendation

Beyond Basal insulin

Patients who are unable to maintain glycaemic targets on basal insulin in combination with oral medications can have treatment intensified with GLP-1 receptor agonists, SGLT2 inhibitors or prandial insulin

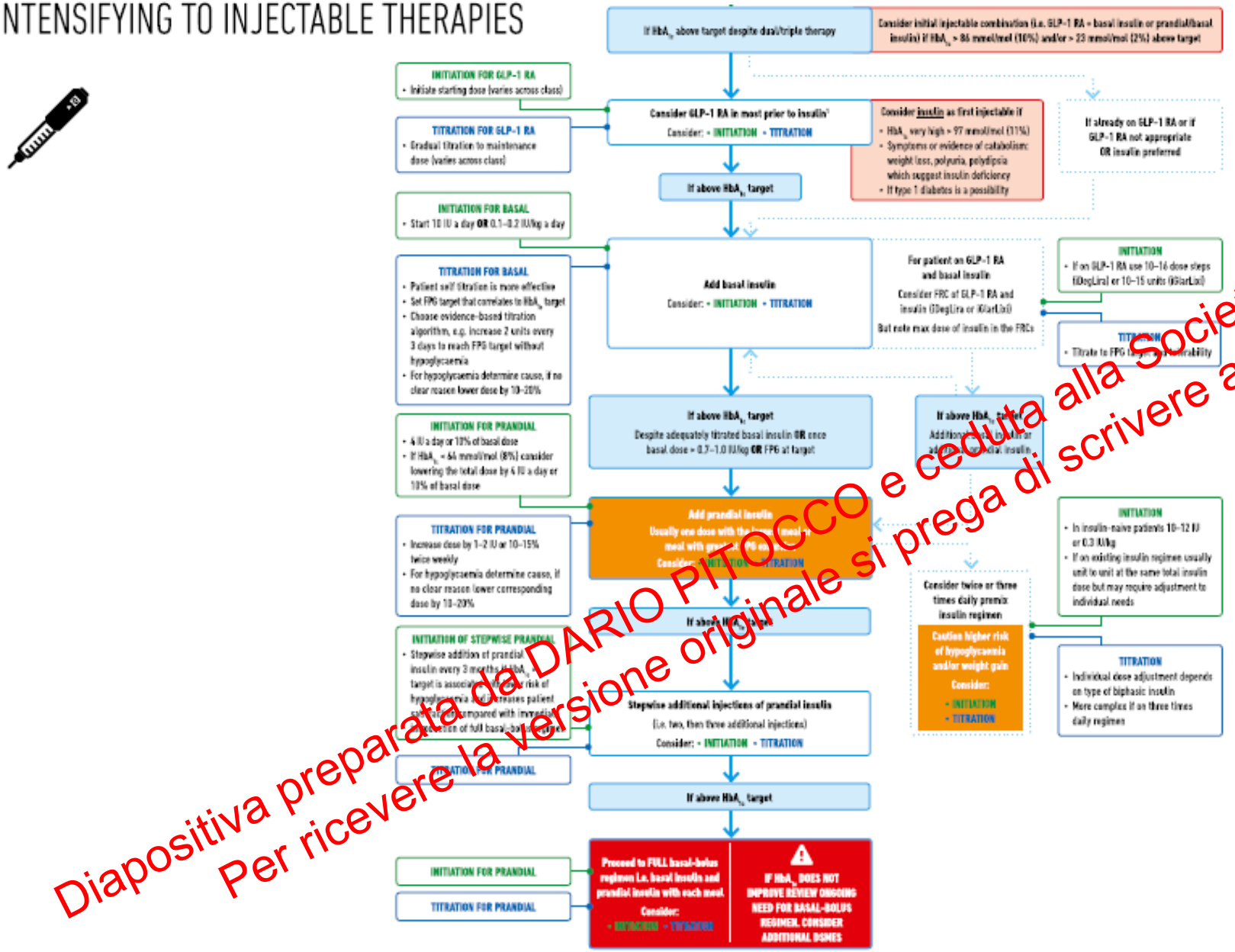
Diabetologia (2018) 61:2461–2498

Domanda 1

a) Attualmente nel paziente non a target con insulina basale e fortemente scompensato (HbA1c>11%)

1) Si sconsiglia l'utilizzo di GLP-1 RA
2) Si consiglia preferibilmente di aggiungere insulina prandiale
3) Si sconsiglia sempre l'uso dell'SGLT-2 inibitori
4) Si prevede sempre l'utilizzo del GLP-1 RA

INTENSIFYING TO INJECTABLE THERAPIES



Comprehensive lifestyle management

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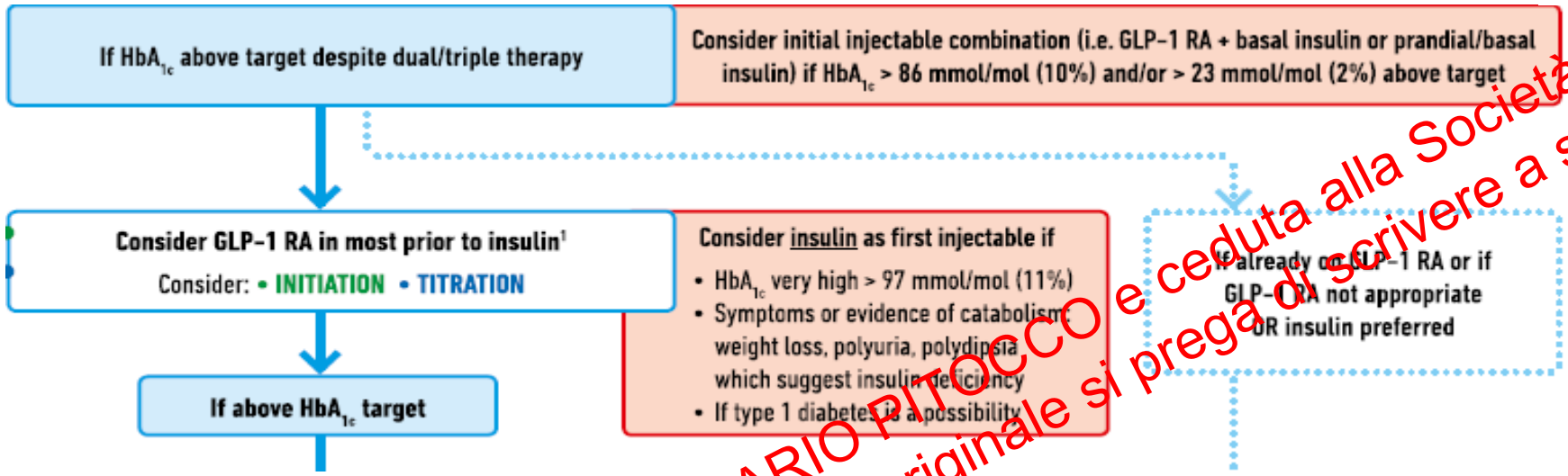
Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)



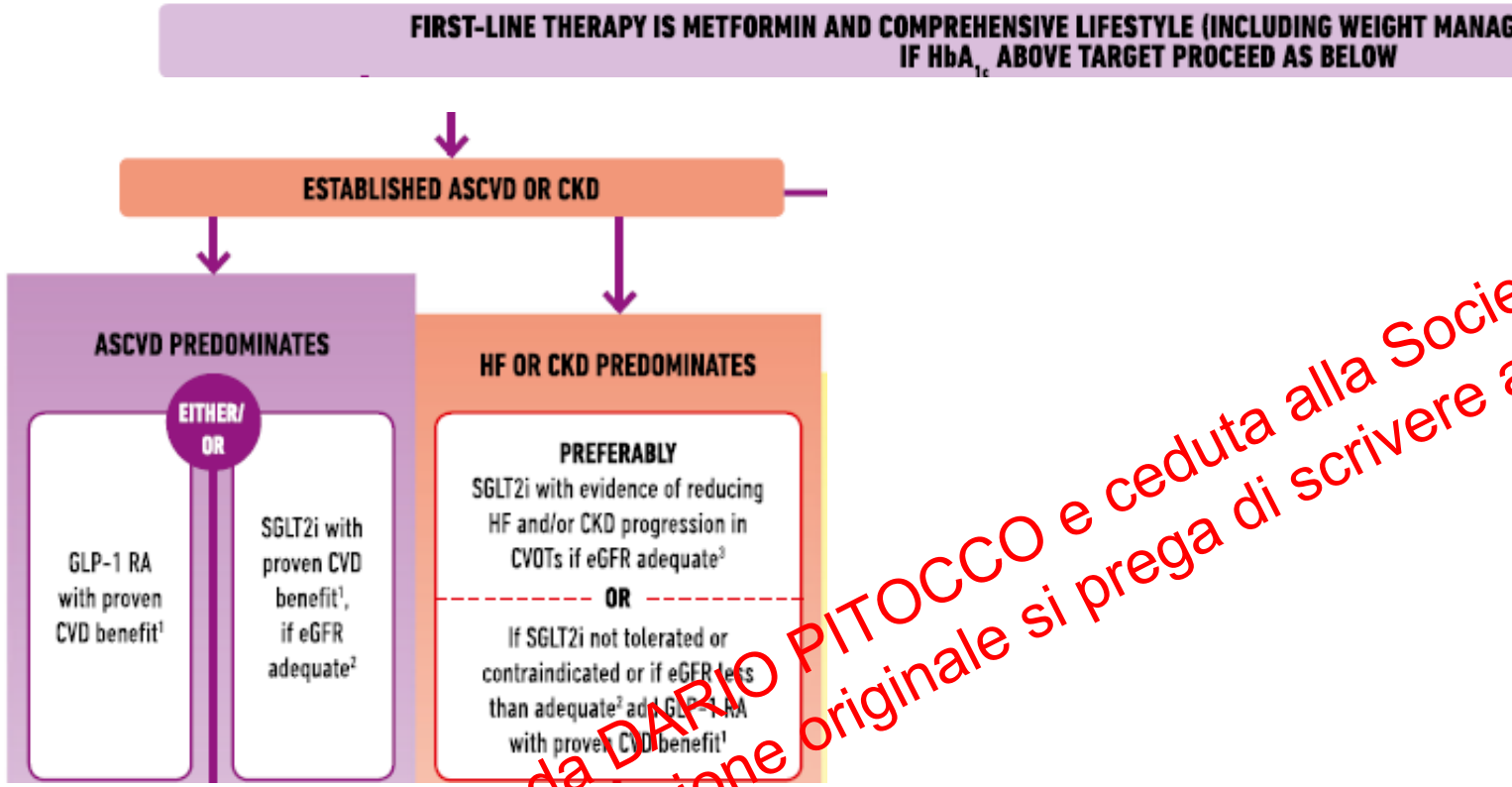
INTENSIFYING TO INJECTABLE THERAPIES

Come scegliere il GLP-1 RA

- La preferenza del paziente (frequenza della somministrazione)
- L'effetto sul compenso metabolico
- L'effetto sul peso
- L'effetto sul rischio cardiovascolare

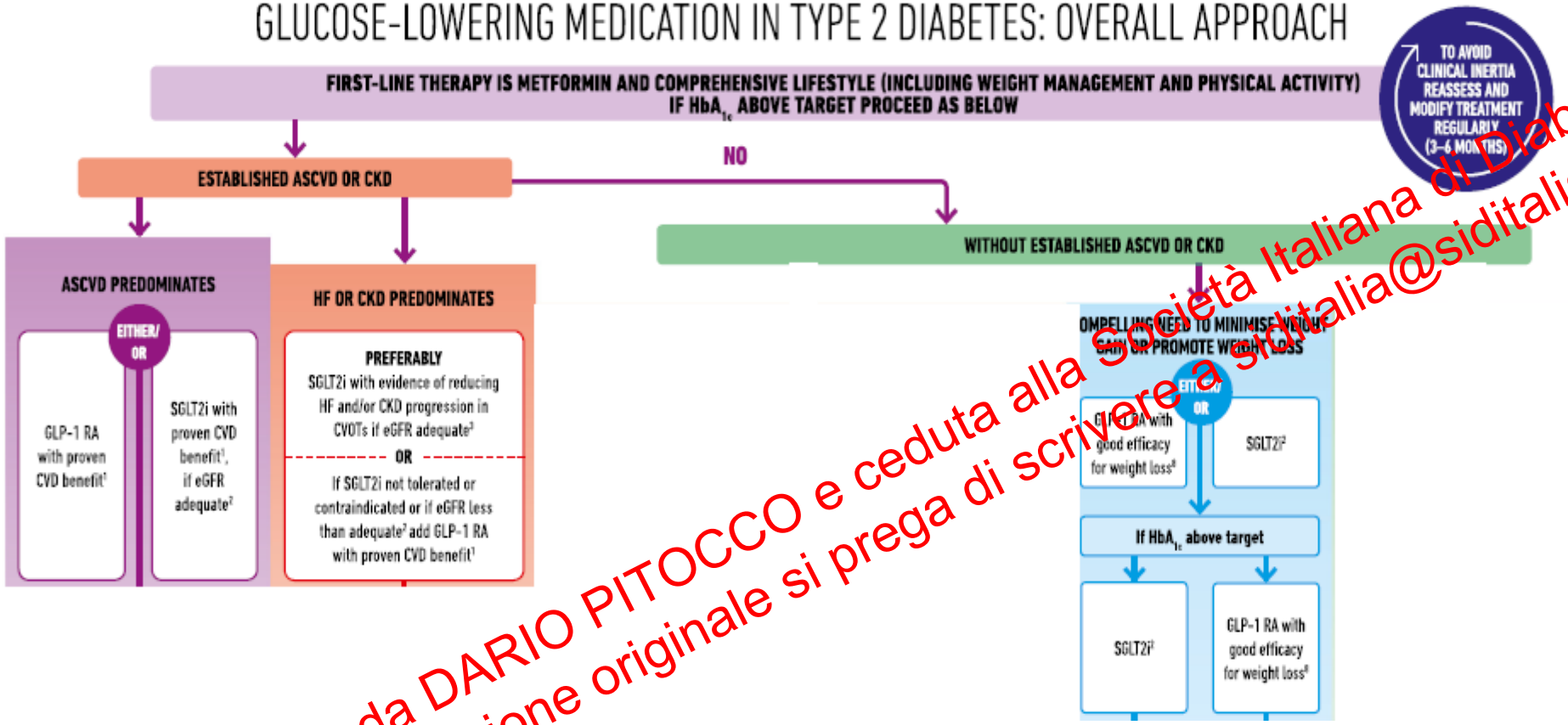
Diabetologia (2018) 61:2461–2498

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



Effetto dimostrato sul rischio cardiovascolare:
Per GLP-1 RA liraglutide(LEADER)>semaglutide (SUSTAIN-6)>exenatide a lento rilascio (EXSCEL)

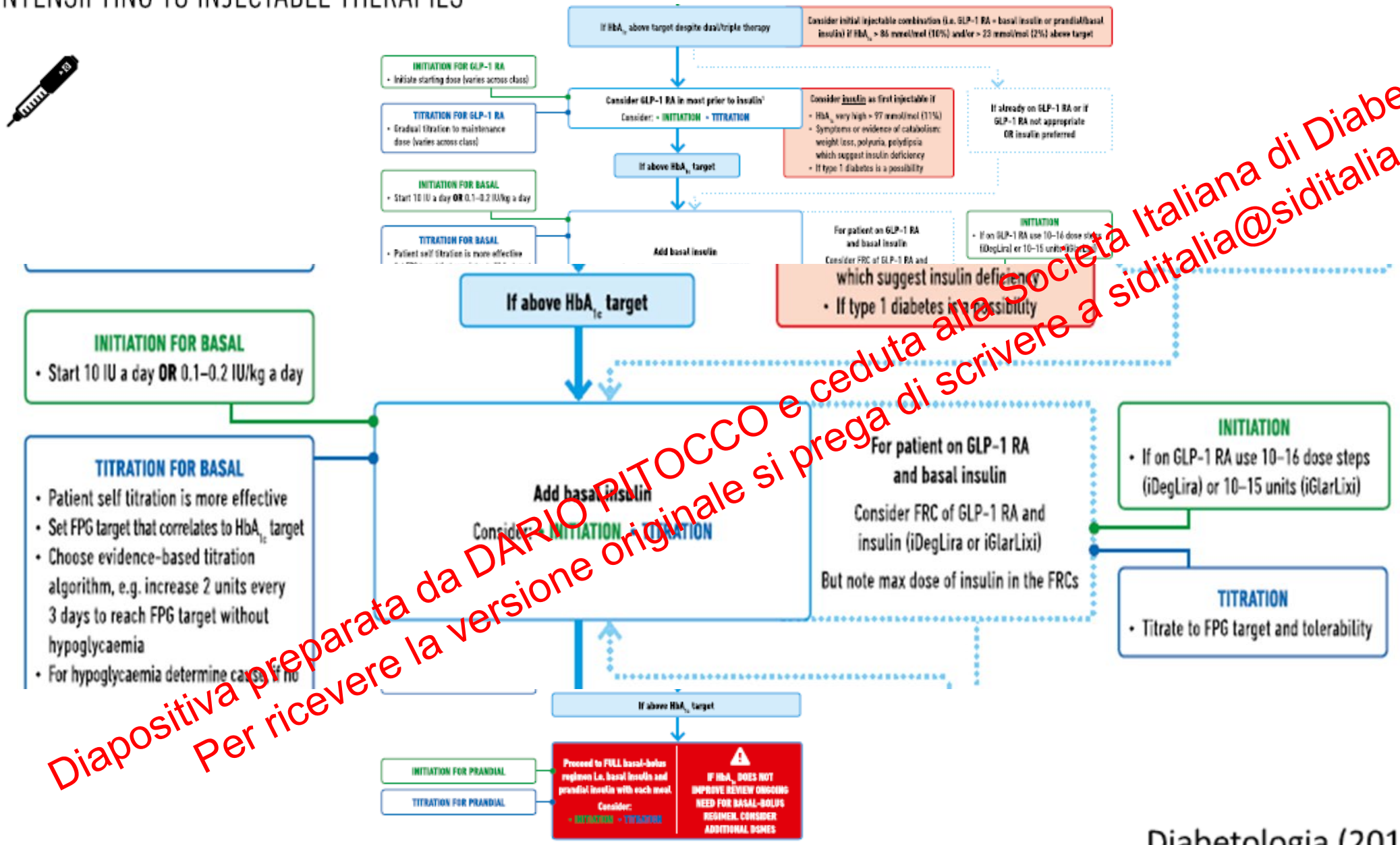
Diabetologia (2018) 61:2461–2498



Semaglutide (Sustain-1-2-3-4-5-7)>Liraglutide(LEAD-6, DURATION-6, LIRA-LIXI)> Dulaglutide (AWARD)>Exenatide (Getgoal-X)>Lixisenatide

Diabetologia (2018) 61:2461–2498

INTENSIFYING TO INJECTABLE THERAPIES



Diabetologia (2018) 61:2461–2498

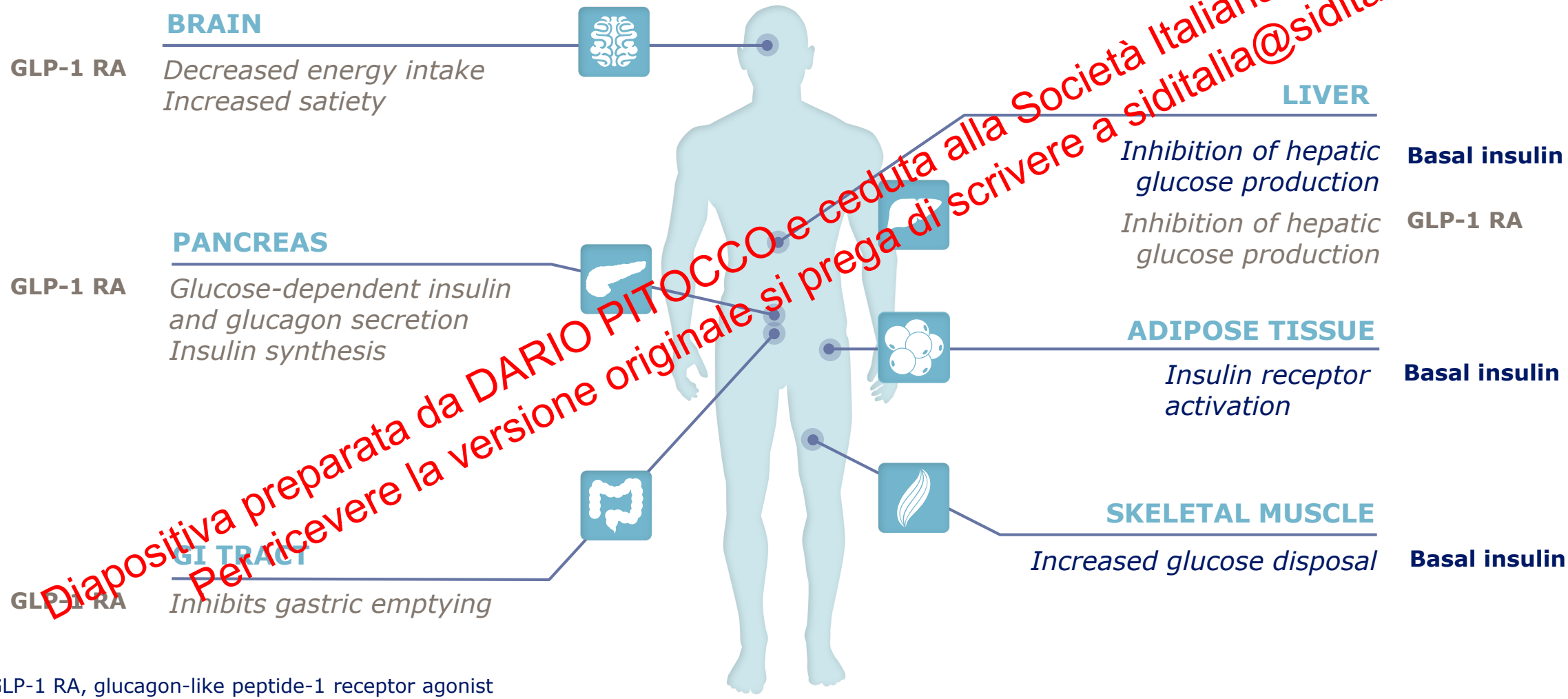
CONSENSUS REPORT

Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

The combination of basal insulin and a GLP-1 RA has high efficacy, with recent evidence from clinical trials demonstrating the benefits of this combination to lower HbA1c and limit weight gain and hypoglycaemia compared with intensified insulin regimens

Diabetologia (2018) 61:2461–2498

Complementary actions of basal insulin and a GLP-1 RA target the underlying pathophysiology of type 2 diabetes



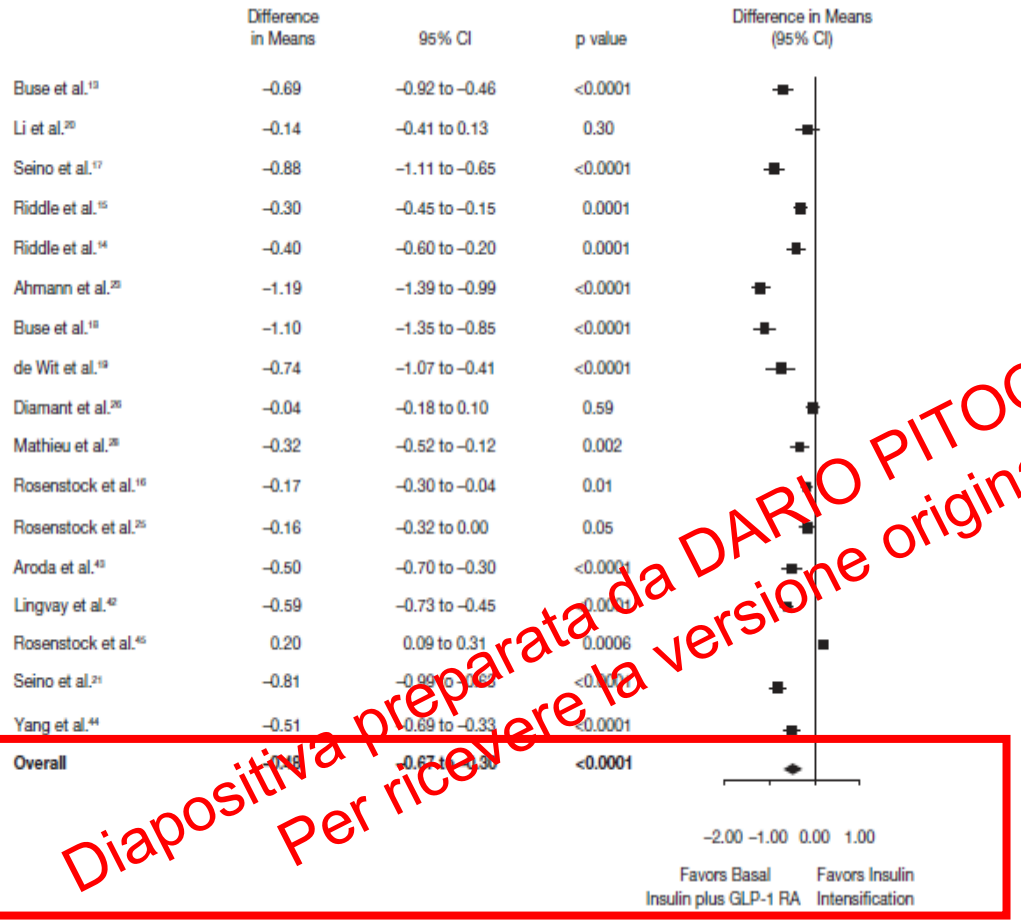
GLP-1 RA, glucagon-like peptide-1 receptor agonist

1. Baggio & Drucker. *Gastroenterol* 2007;132:2131–57; 2. Niswender. *Postgrad Med* 2011;123:27–37

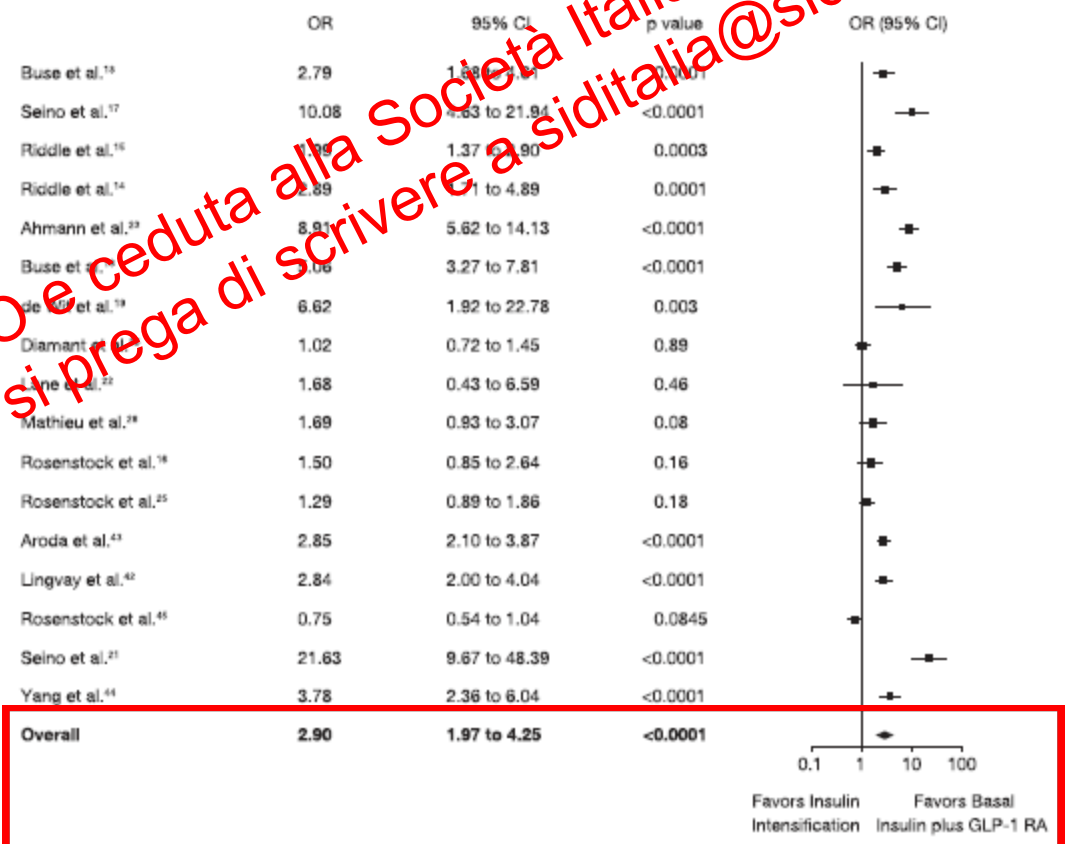
POSTGRADUATE MEDICINE, 2017
VOL. 129, NO. 4, 436–445

Safety and efficacy of a glucagon-like peptide-1 receptor agonist added to basal insulin therapy versus basal insulin with or without a rapid-acting insulin in patients with type 2 diabetes: results of a meta-analysis

HbA1c



Percentuale di pz con HbA1c <7



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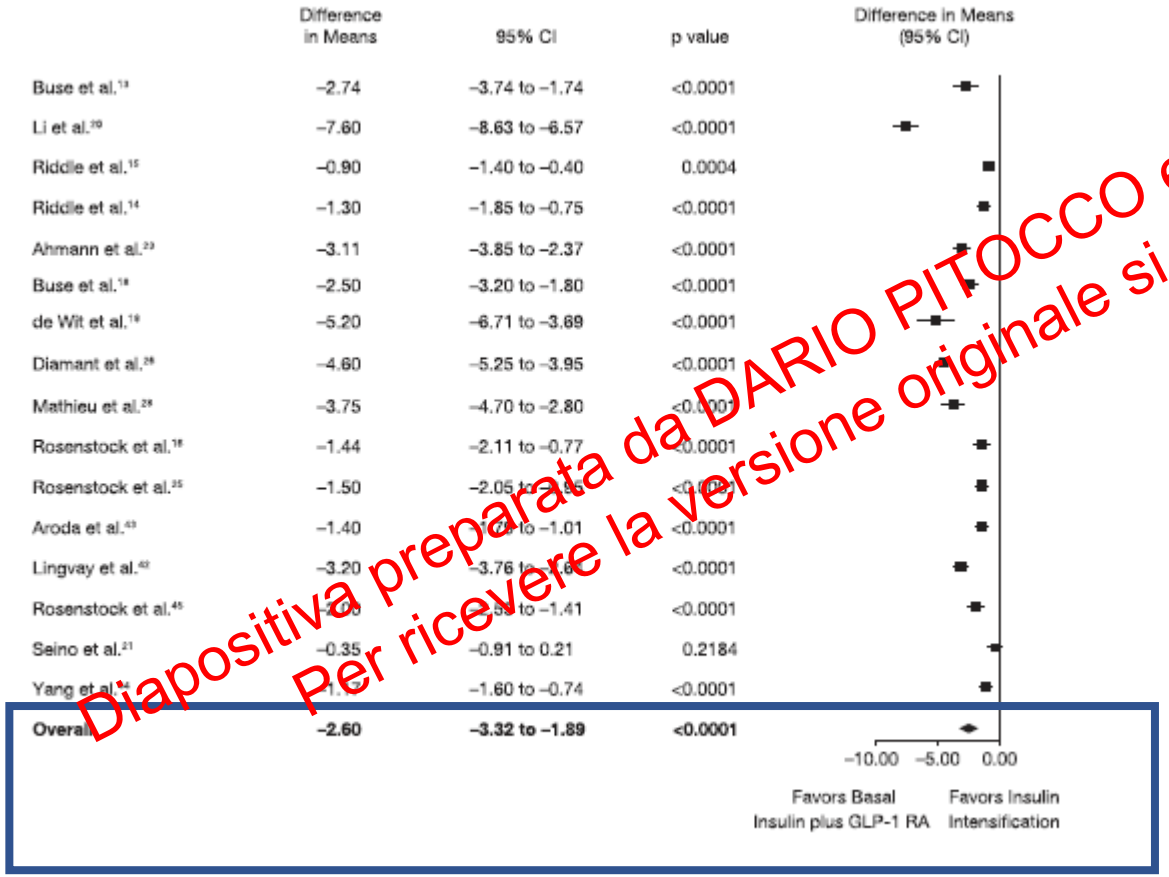
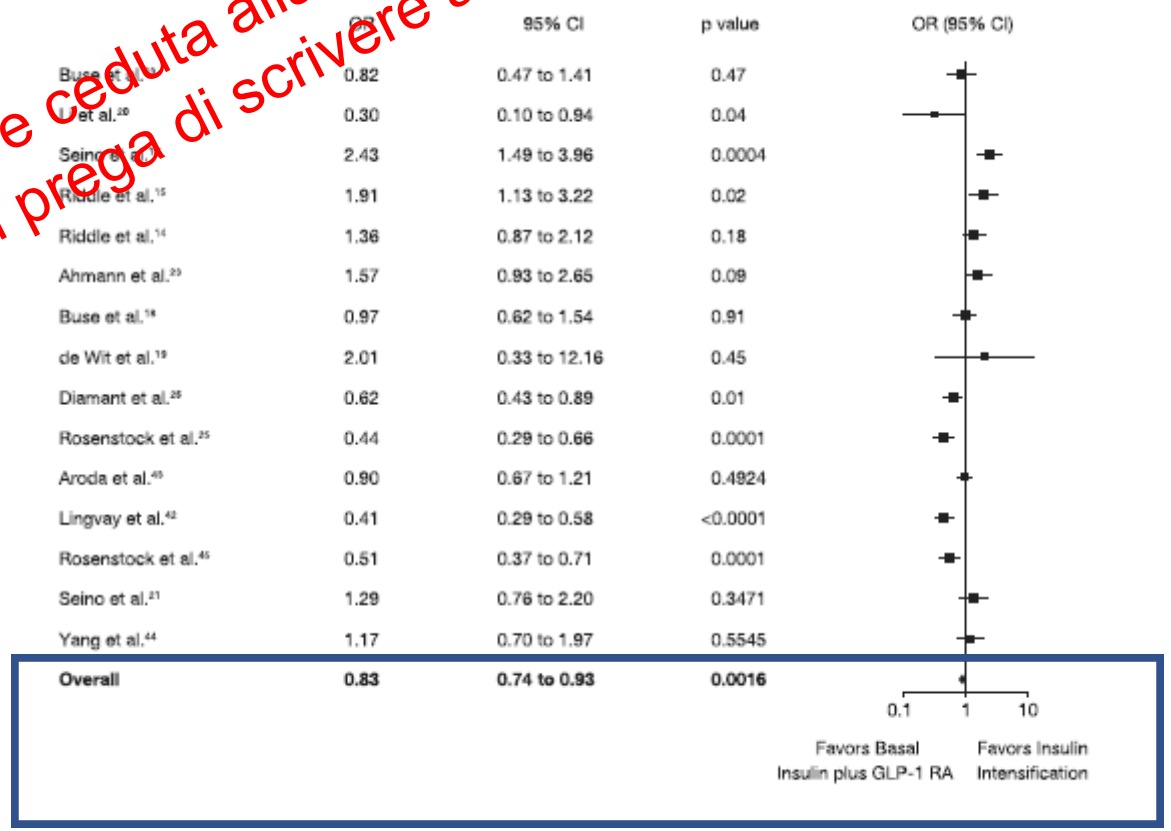
Calo ponderale

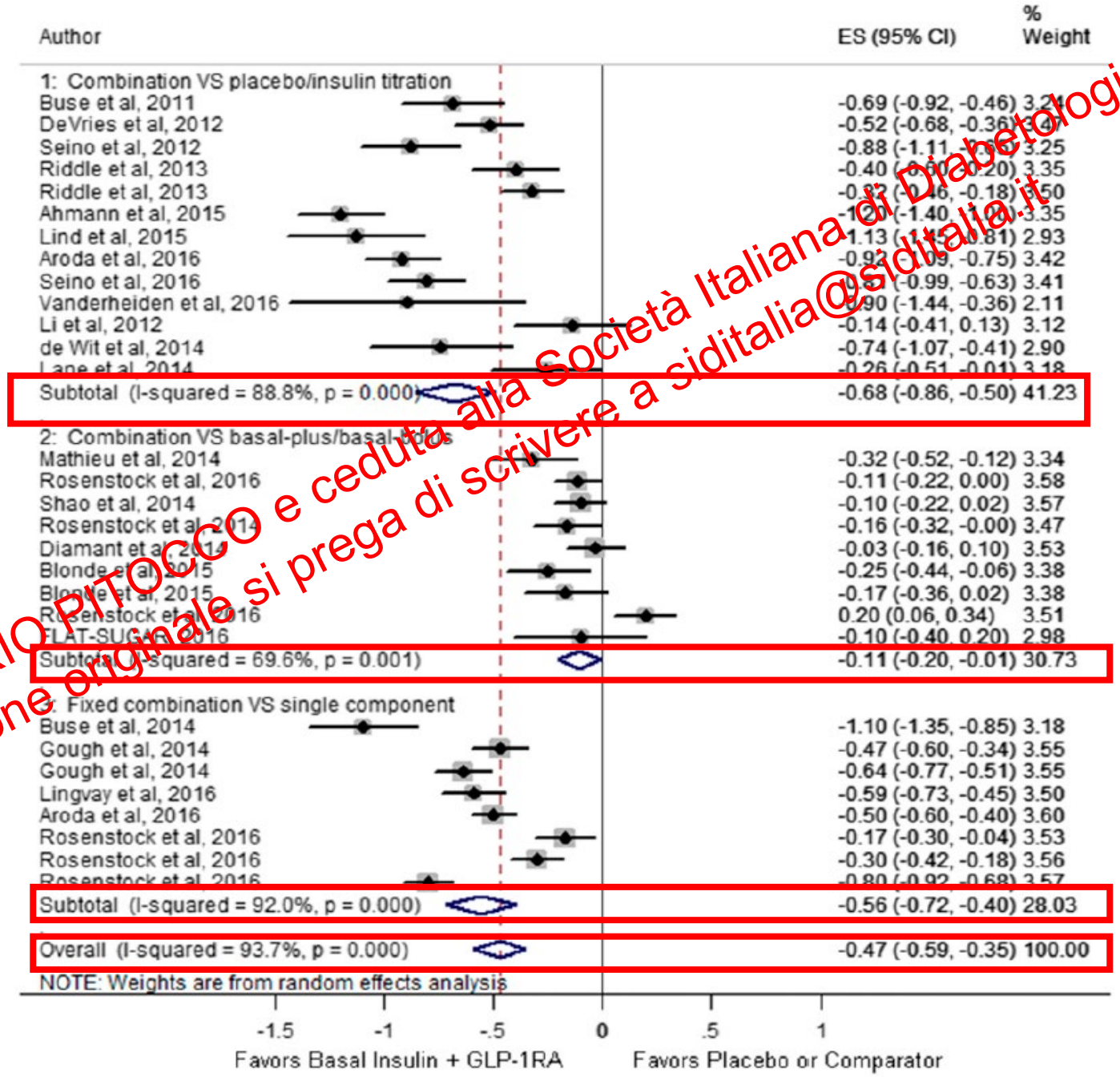




Insulin and Glucagon-Like Peptide 1 Receptor Agonist Combination Therapy in Type 2 Diabetes: A Systematic Review and Meta-analysis of Randomized Controlled Trials

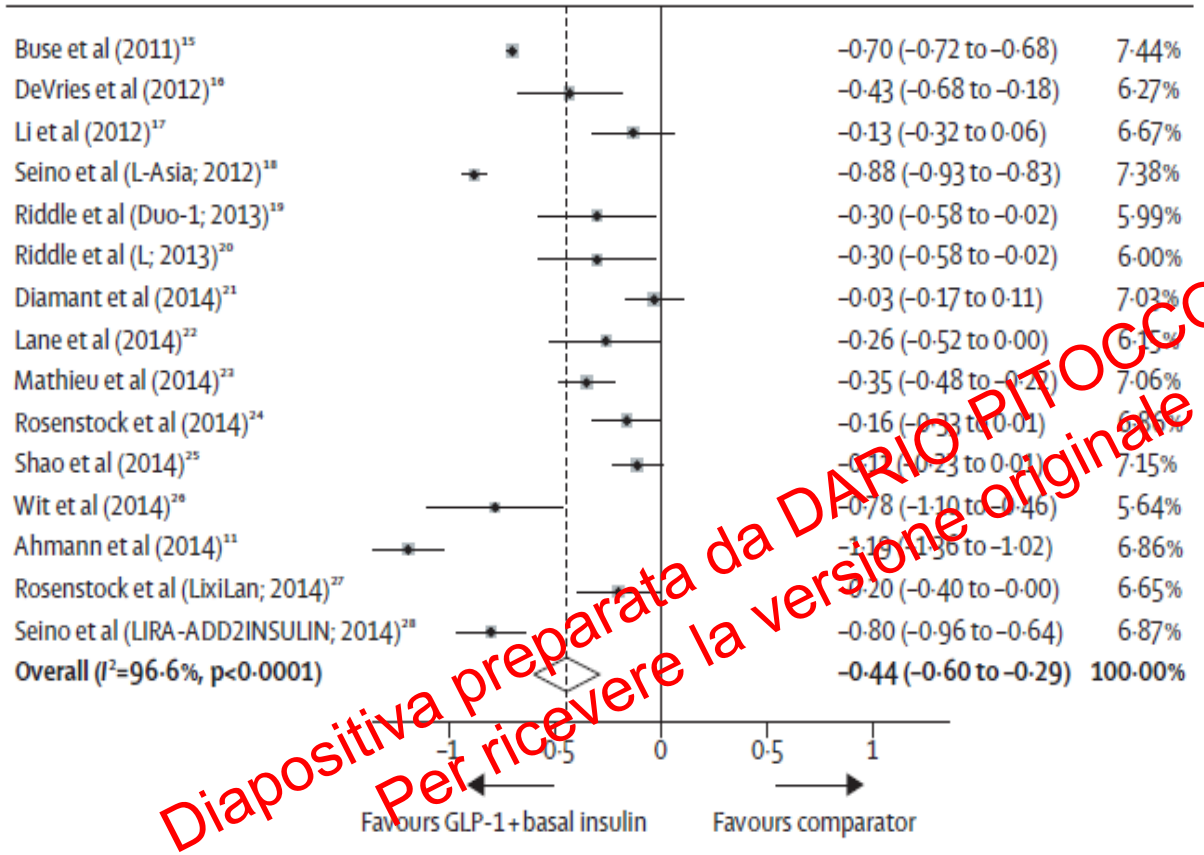
Diabetes Care 2017;40:614–624 | DOI: 10.2337/dc16-1957

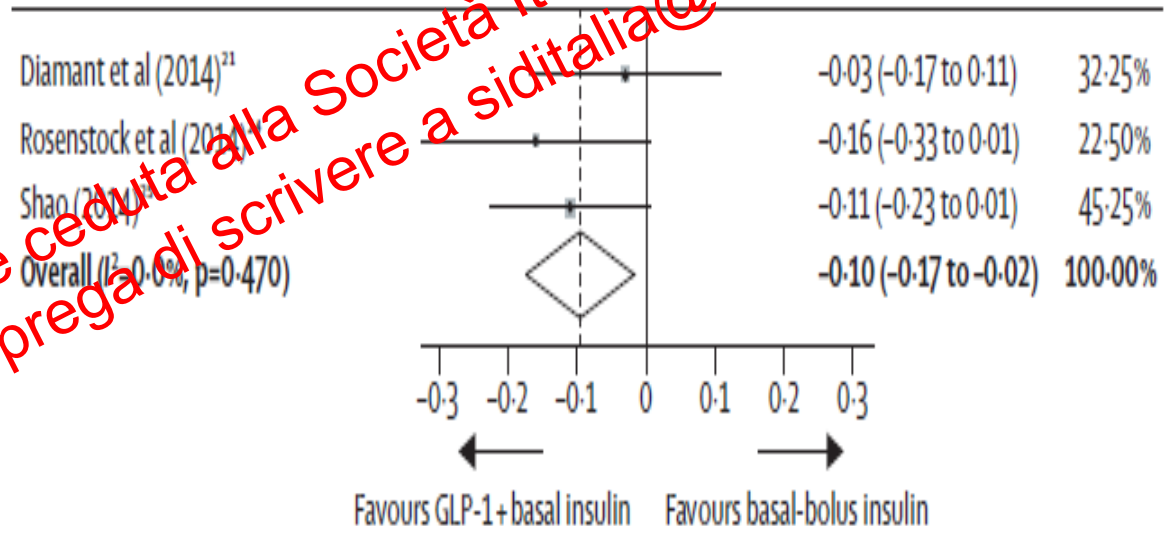
Maria Ida Maiorino,[1] Paolo Chiodini,[2] Giuseppe Bellastella,[3] Annalisa Capuano,[4] Katherine Esposito,[1] and Dario Giugliano[3]



Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis

Lancet 2014; 384: 2228–34





HbA1c

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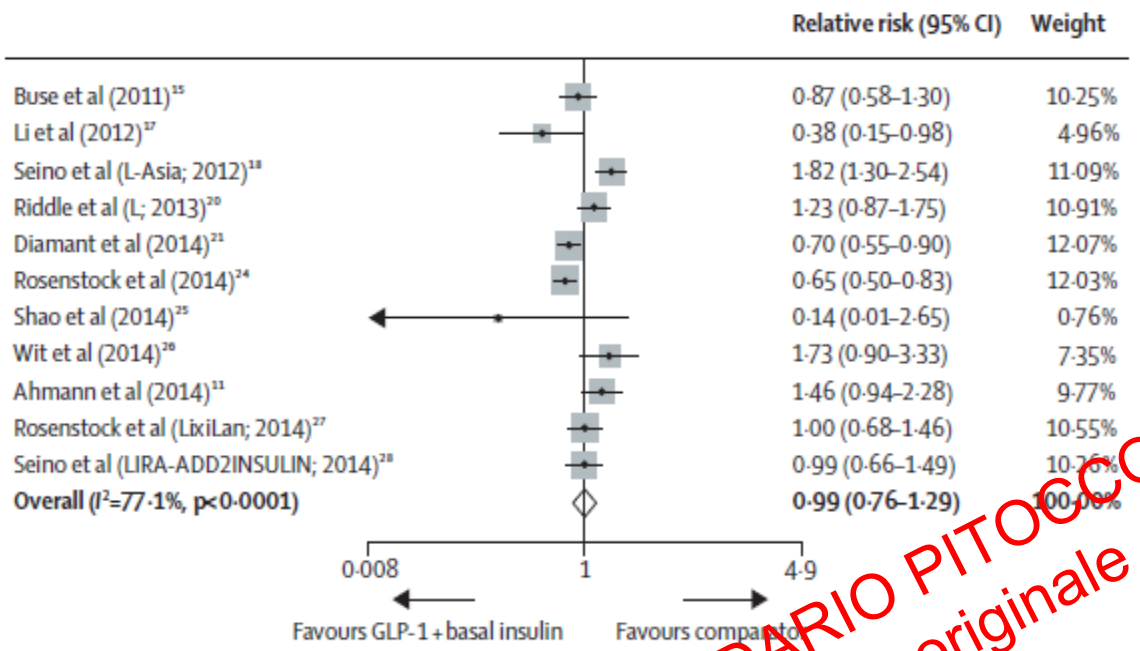
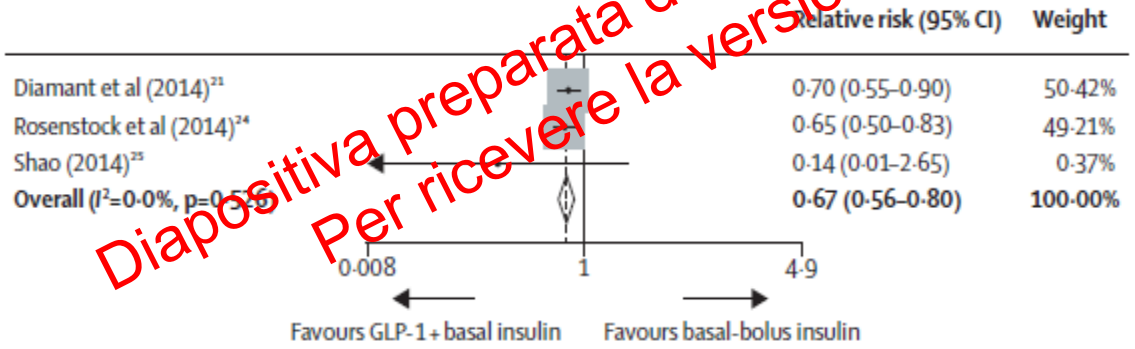
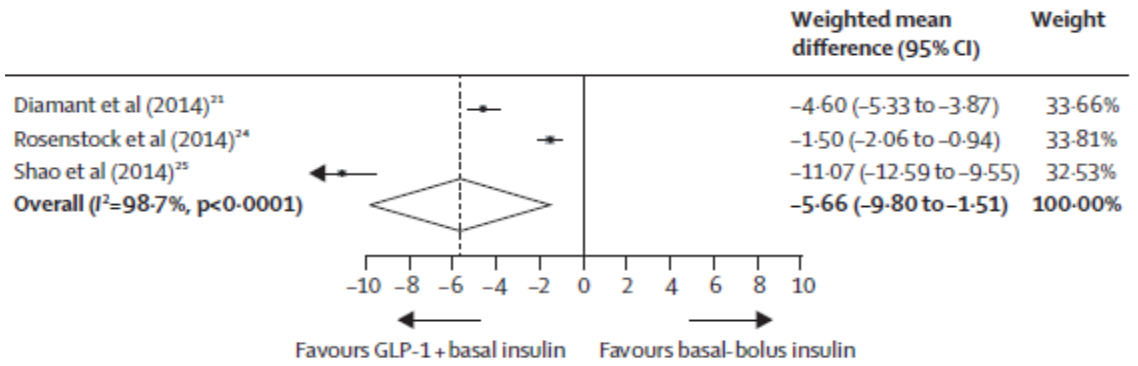




IPOGLICEMIA



PESO

Insulina Basale e GLP-1 RA

Combinazioni non fisse			Combinazioni fisse
Liraglutide	+	Insulina basale	IDegLira
Lixisenatide	+	Insulina basale	IGlarLixi
Dulaglutide	+	Insulina basale	
Exenatide ow	+	Insulina basale	

Insulina Basale e GLP-1 RA

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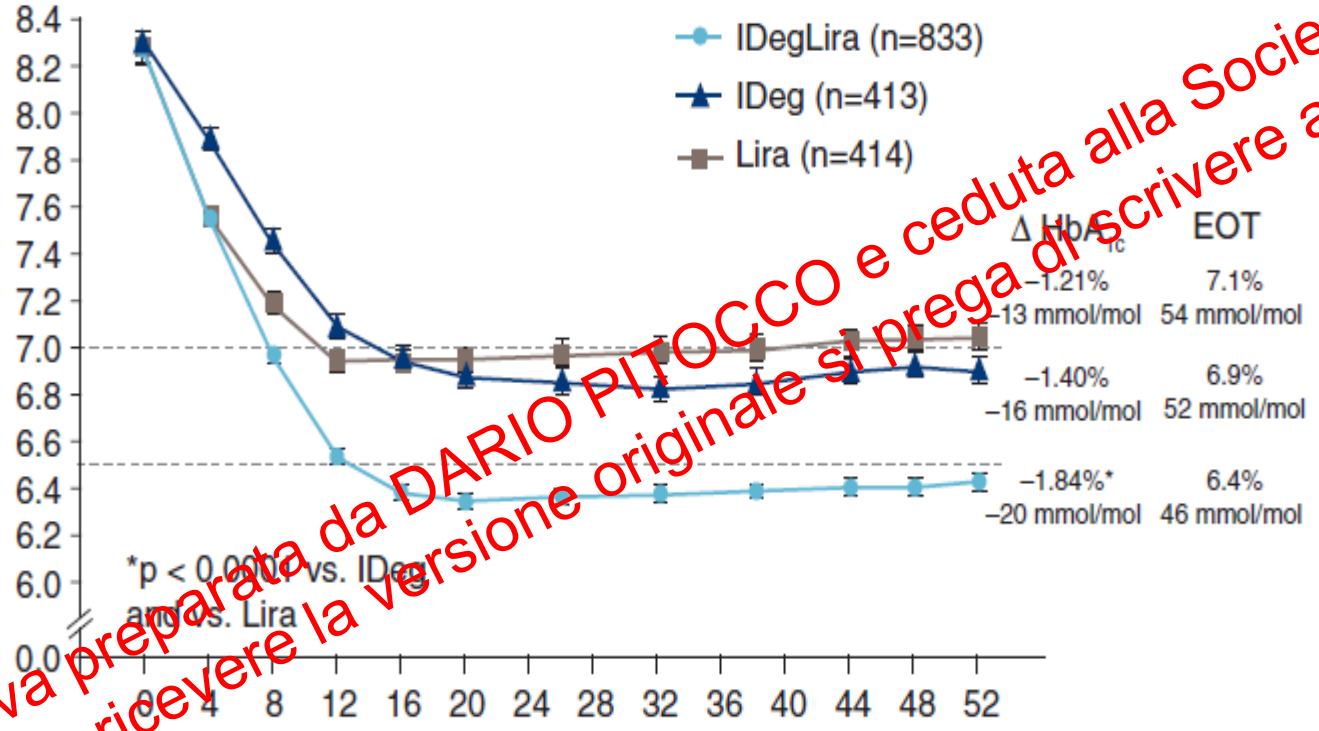
Insulin-naïve adults with type 2 diabetes randomized to once-daily IDegLira, insulin degludec or liraglutide, in addition to metformin±pioglitazone

DUAL I



HbA1c

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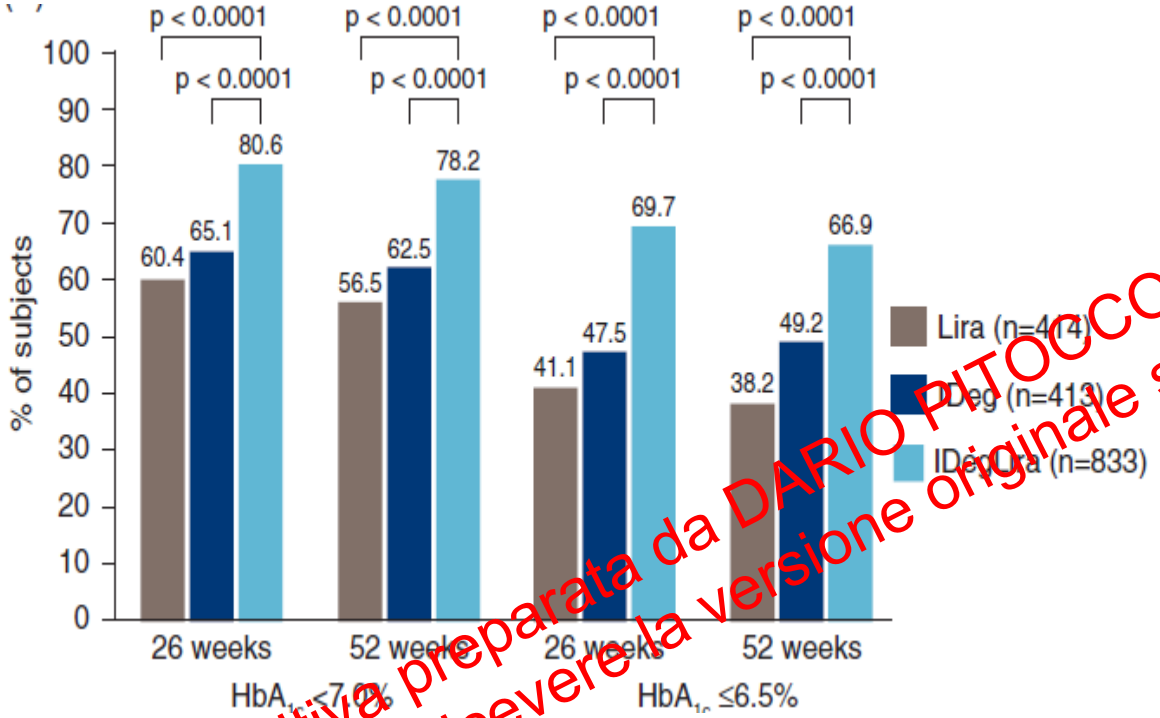

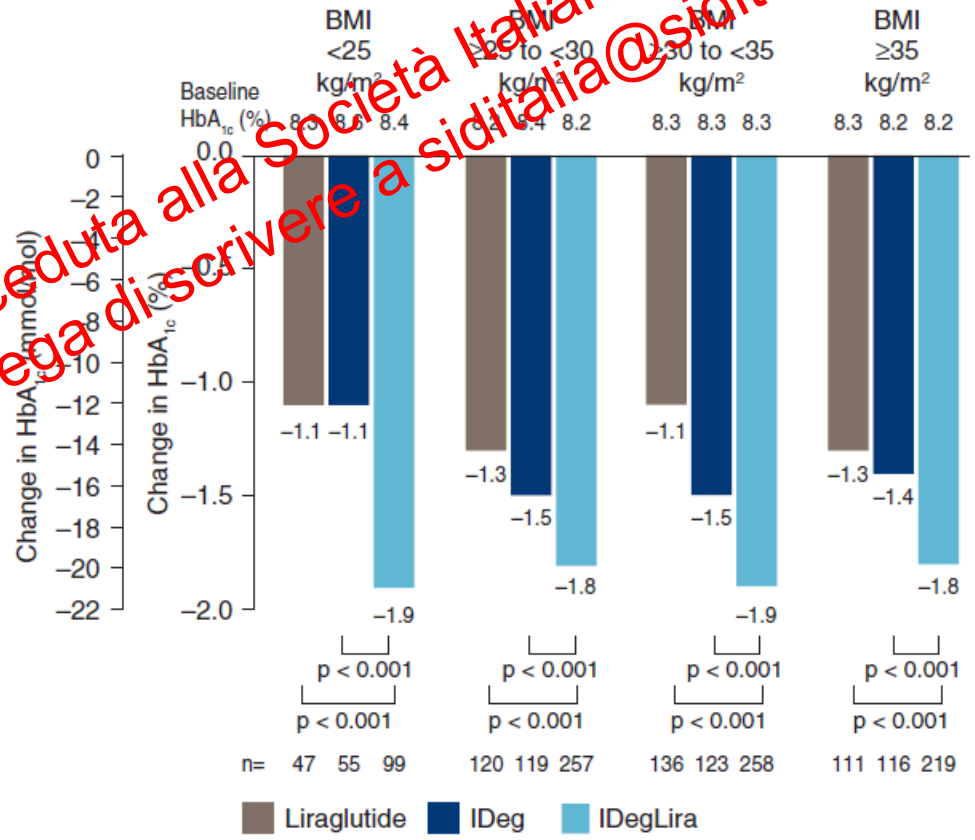

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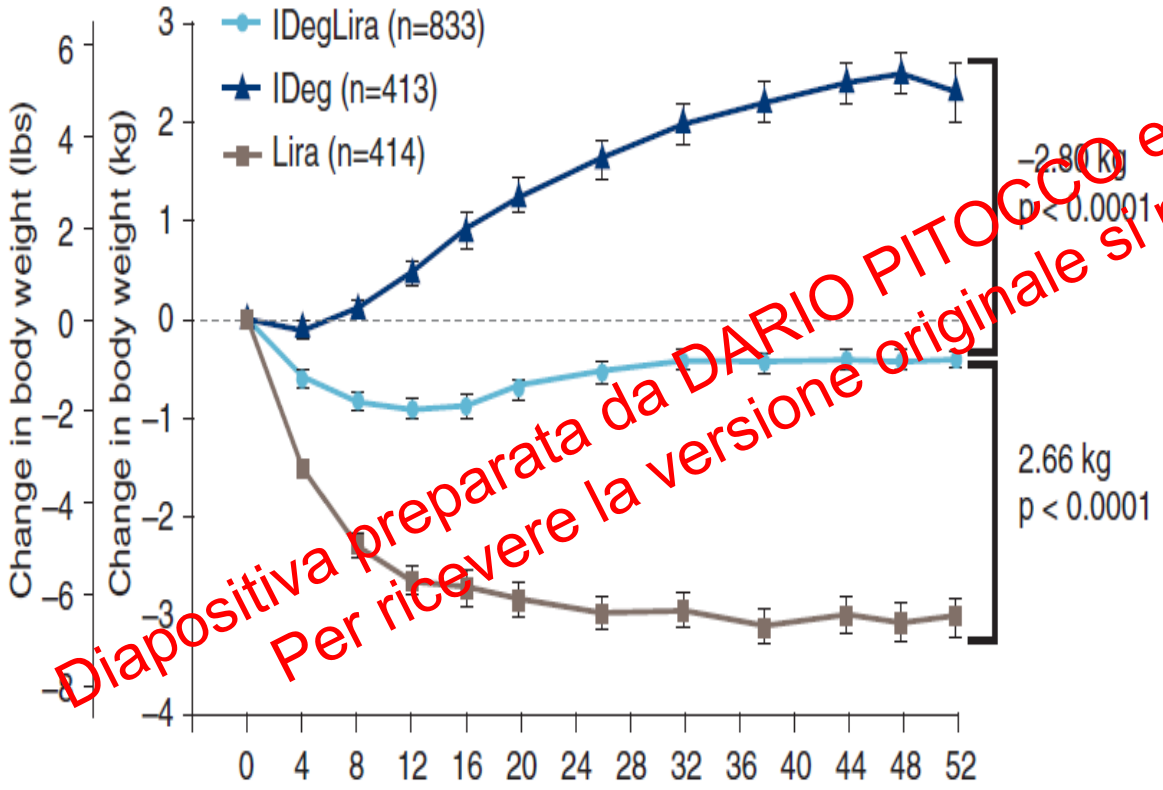
PESO



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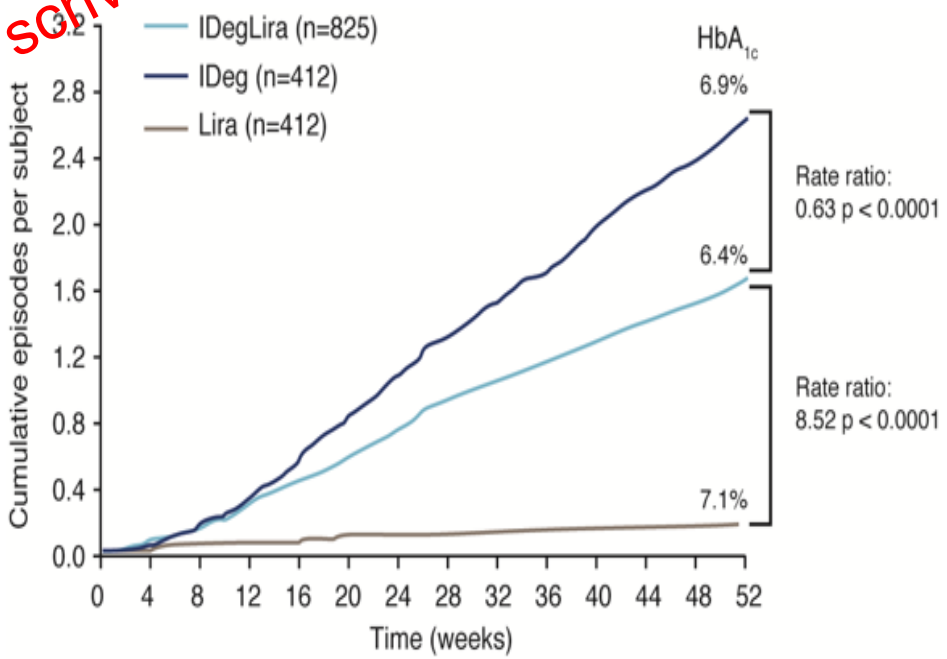

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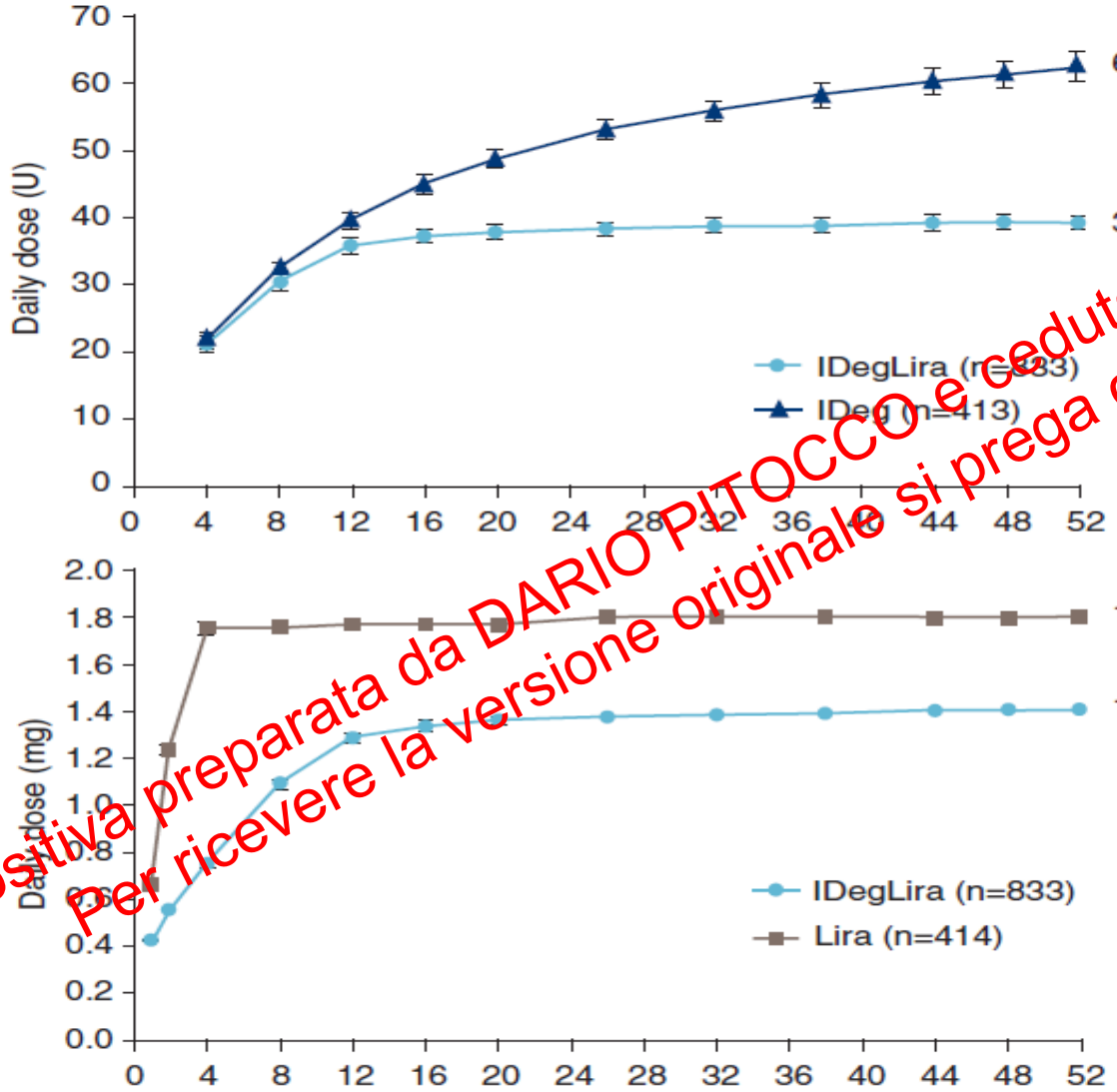
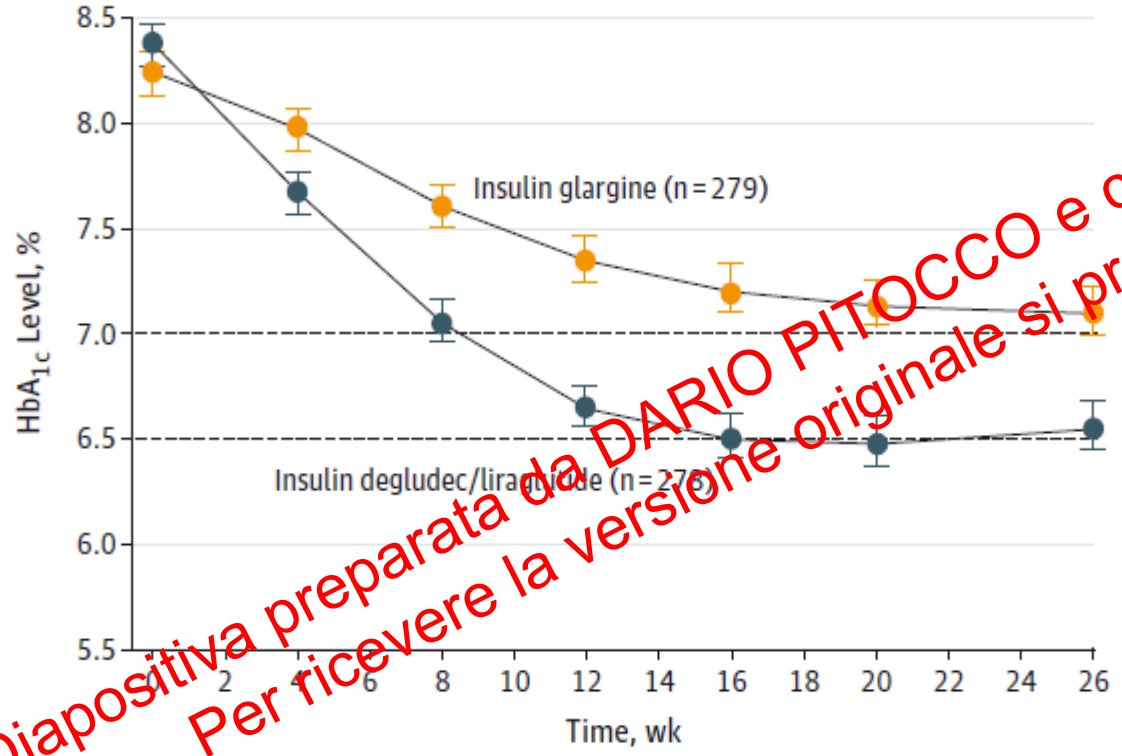


Dose dei singoli componenti

Original Investigation

Effect of Insulin Glargine Up-titration vs Insulin Degludec/Liraglutide on Glycated Hemoglobin Levels in Patients With Uncontrolled Type 2 Diabetes

The DUAL V Randomized Clinical Trial



End Point	Insulin Group	
	Degludec/ Liraglutide (n = 278)	Glargine (n = 279)
HbA_{1c} level at week 26, %	6.6	7.1
Change from baseline in HbA_{1c} level, % (95% CI)	−1.81 (−1.94 to −1.68)	−1.13 (−1.25 to −1.02)

Original Investigation

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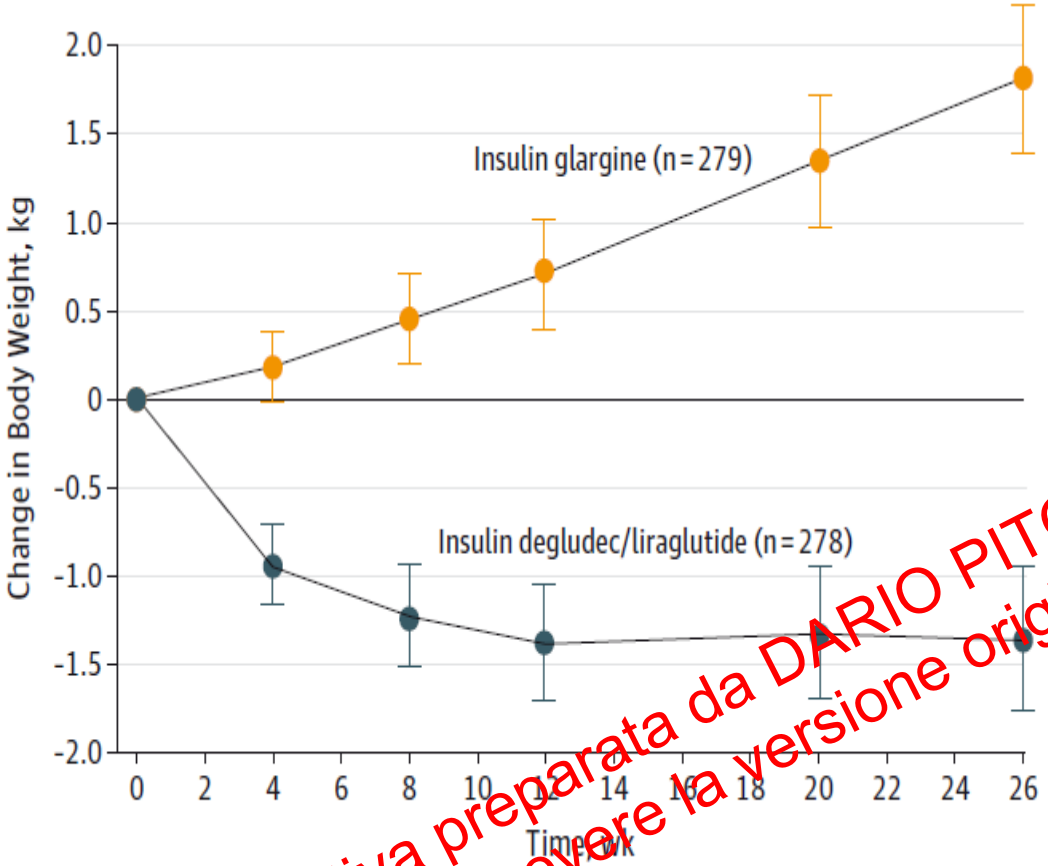
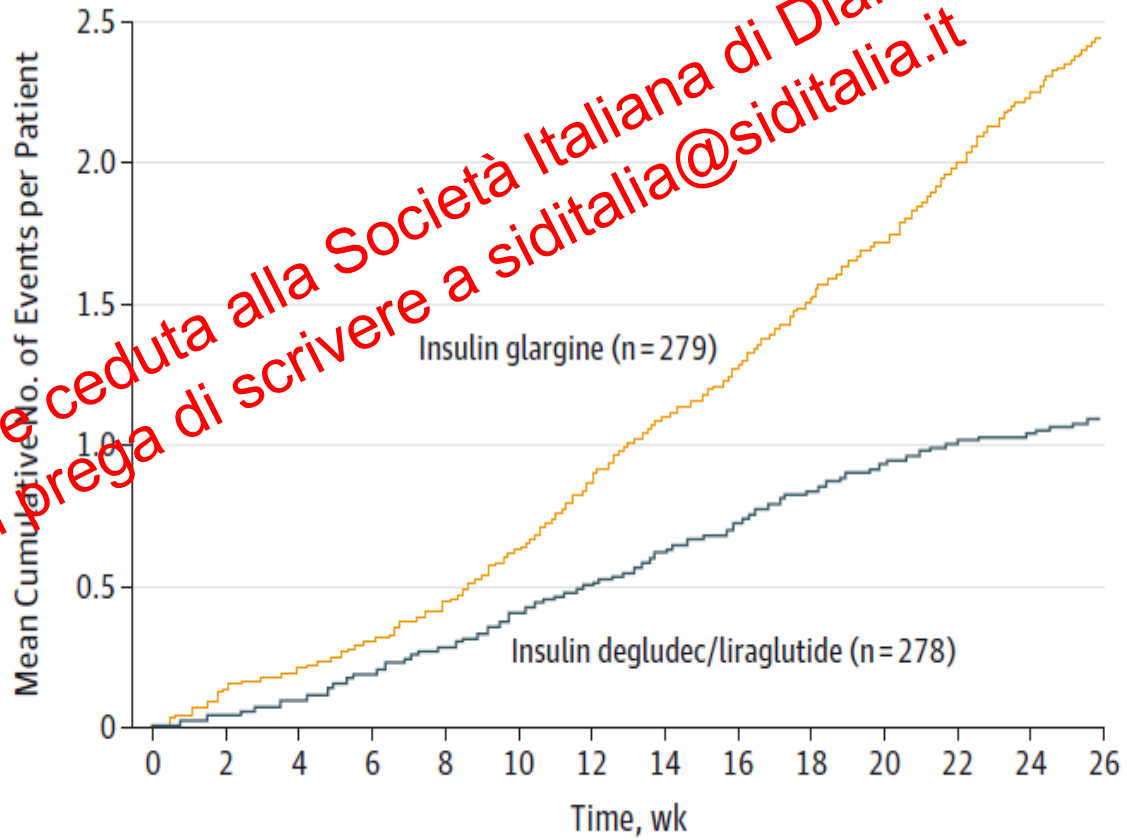
The DUAL V Randomized Clinical Trial

DUAL V





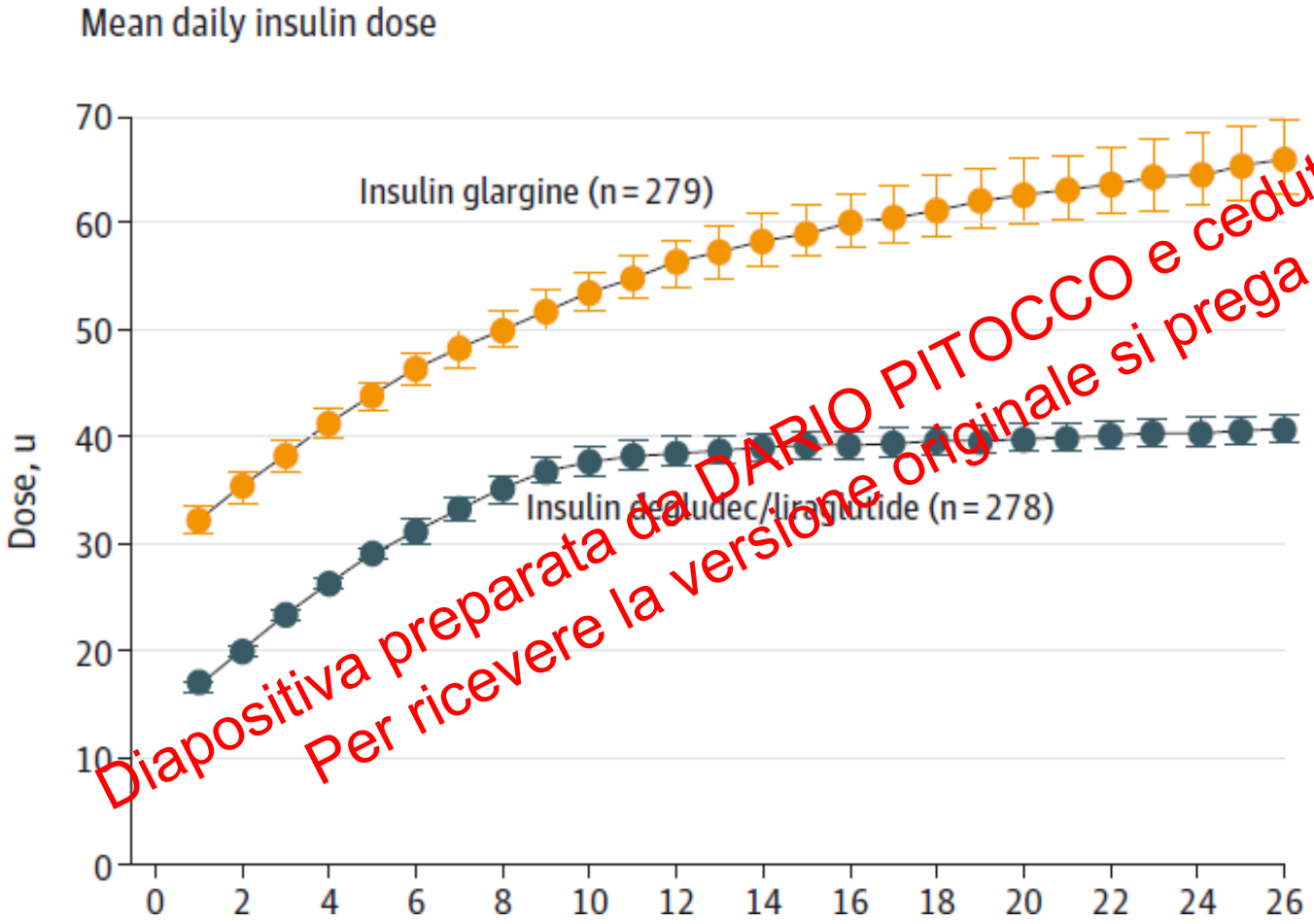
Body weight at week 26, kg	86.9	89.1
Change from baseline, body weight, kg (95% CI)	−1.4 (−1.8 to −1.0)	1.8 (1.4 to 2.2)

Total exposure, y	129.6	135.1
Rate of confirmed hypoglycemia, no. of events per PYE	2.23	5.05

Original Investigation

Effect of Insulin Glargine Up-titration vs Insulin Degludec/Liraglutide on Glycated Hemoglobin Levels in Patients With Uncontrolled Type 2 Diabetes

The DUAL V Randomized Clinical Trial



DUAL V

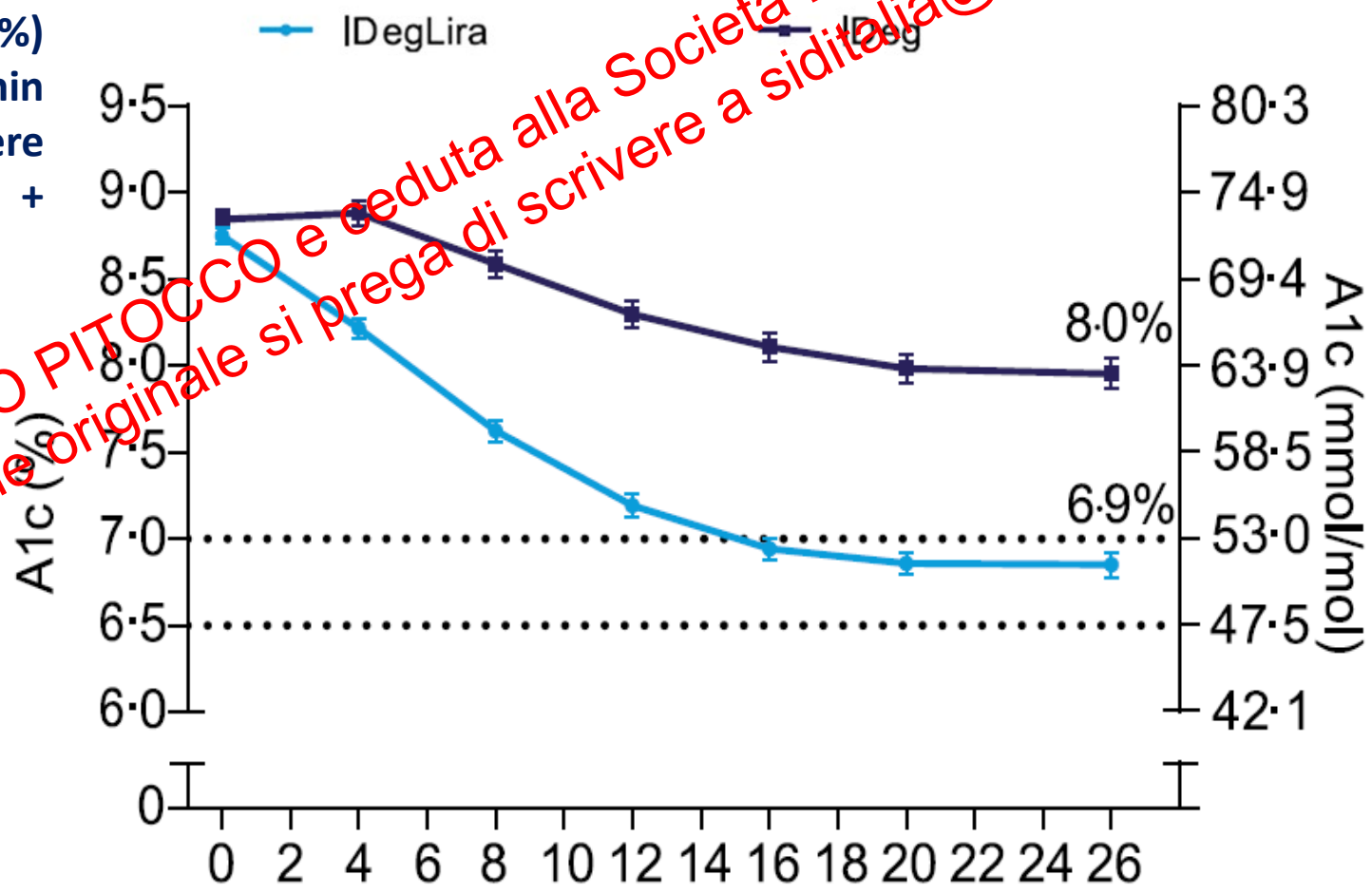
-25.47 U (95%CI, –28.90 to–22.05)

DUAL II

Patients with type 2 diabetes (A1C 7.5–10.0%) on basal insulin (20–40 units) and metformin with or without sulfonylurea/glinides were randomized (1:1) to once-daily IDegLira + metformin or IDeg + metformin

Contribution of Liraglutide in the Fixed-Ratio Combination of Insulin Degludec and Liraglutide (IDegLira)

Diabetes Care 2014;37:2926–2933 | DOI: 10.2337/dc14-0785



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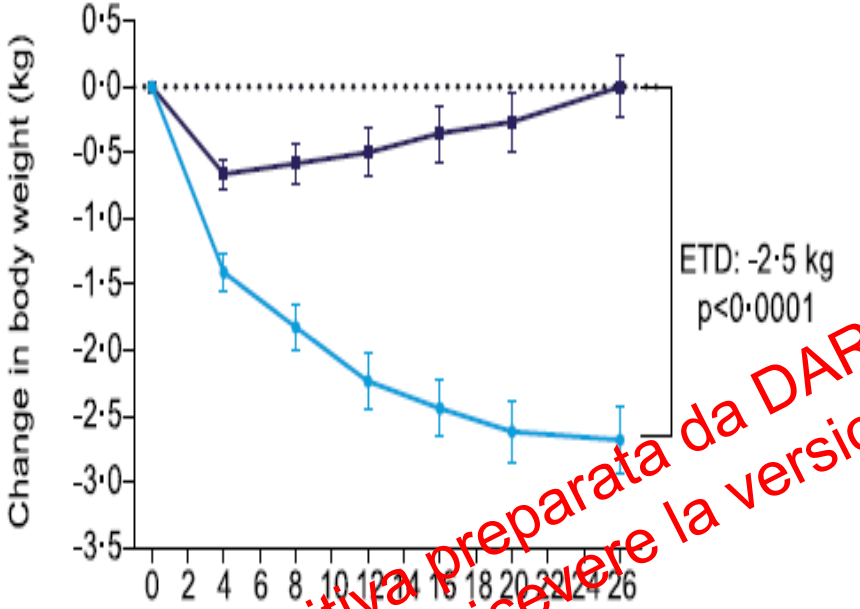
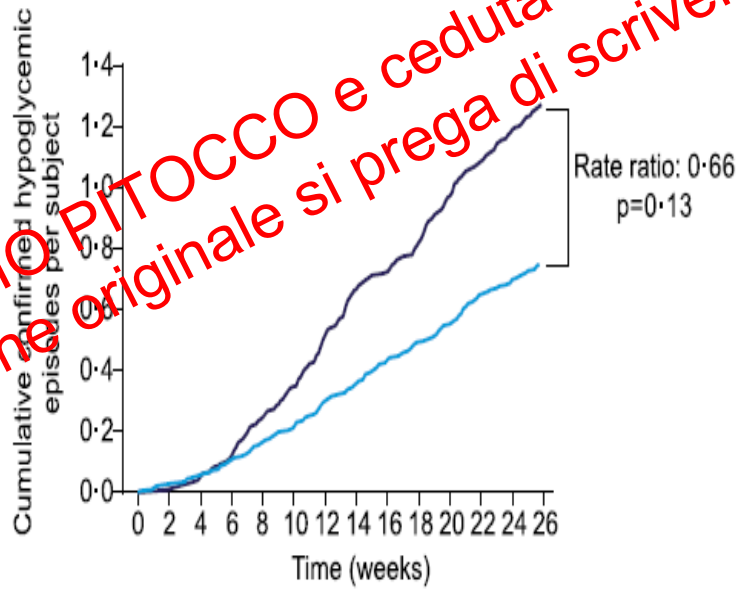
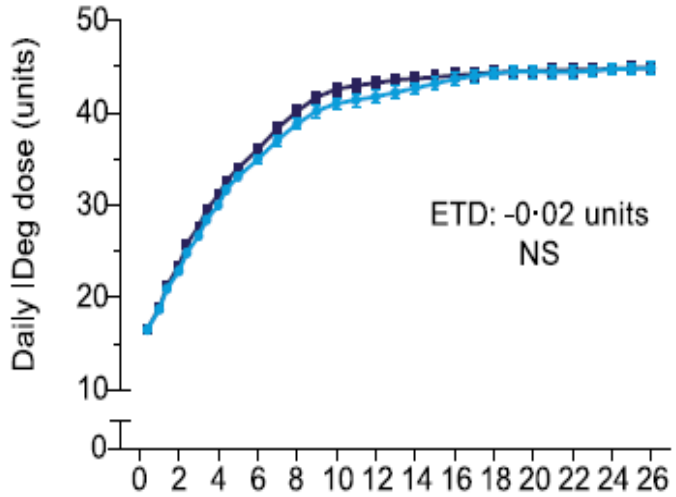
DUAL II





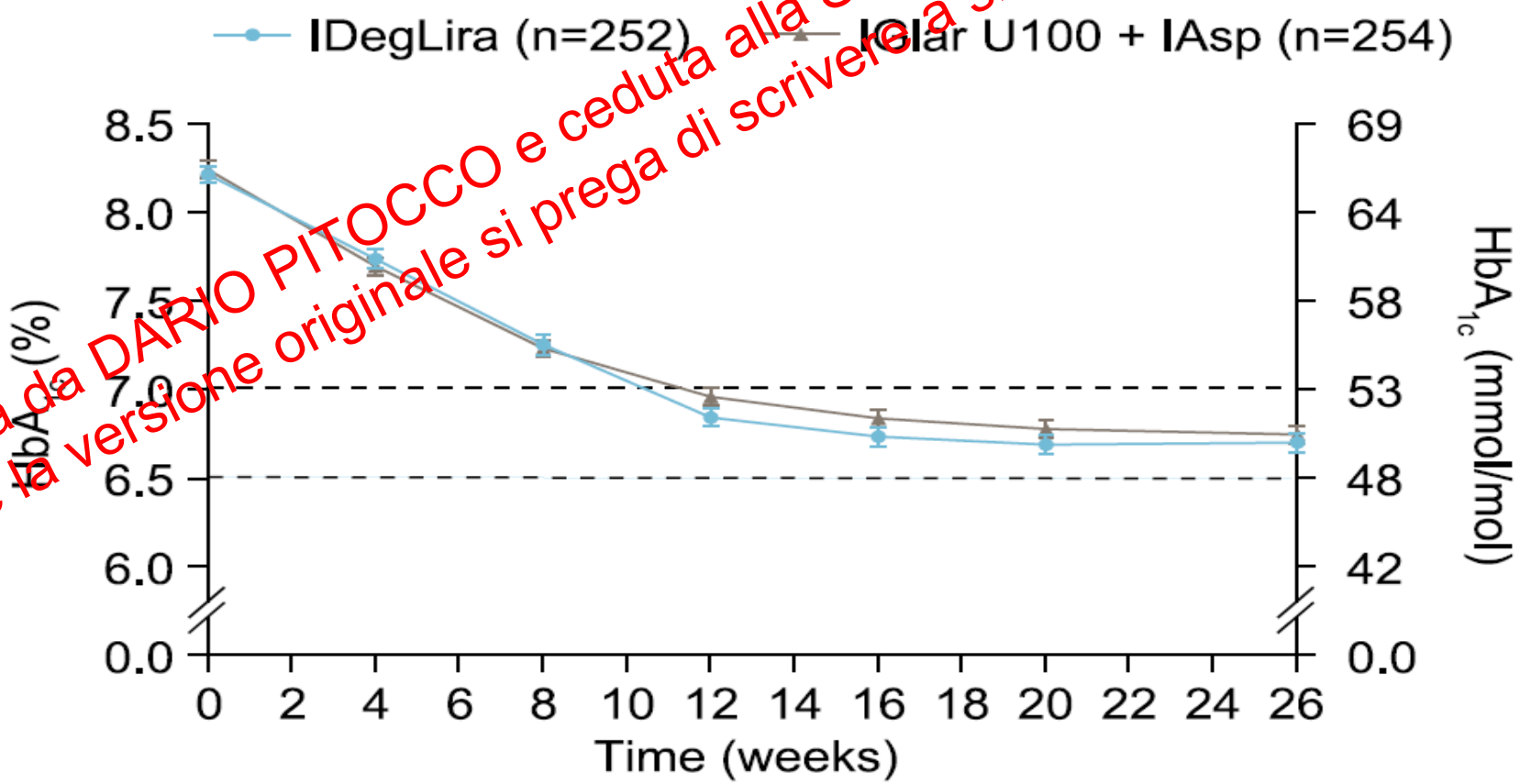


IDegLira IDeg

Efficacy and Safety of IDegLira Versus Basal-Bolus Insulin Therapy in Patients With Type 2 Diabetes Uncontrolled on Metformin and Basal Insulin: The DUAL VII Randomized Clinical Trial

Diabetes Care 2018;41:1009–1016 | https://doi.org/10.2337/dc17-1114

DUAL VII



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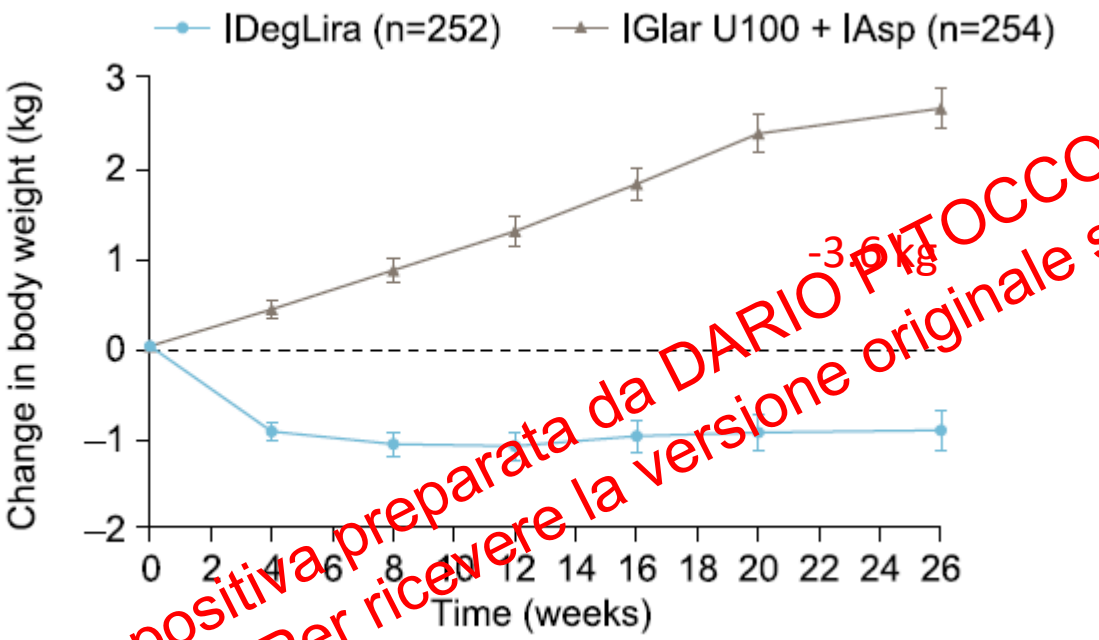
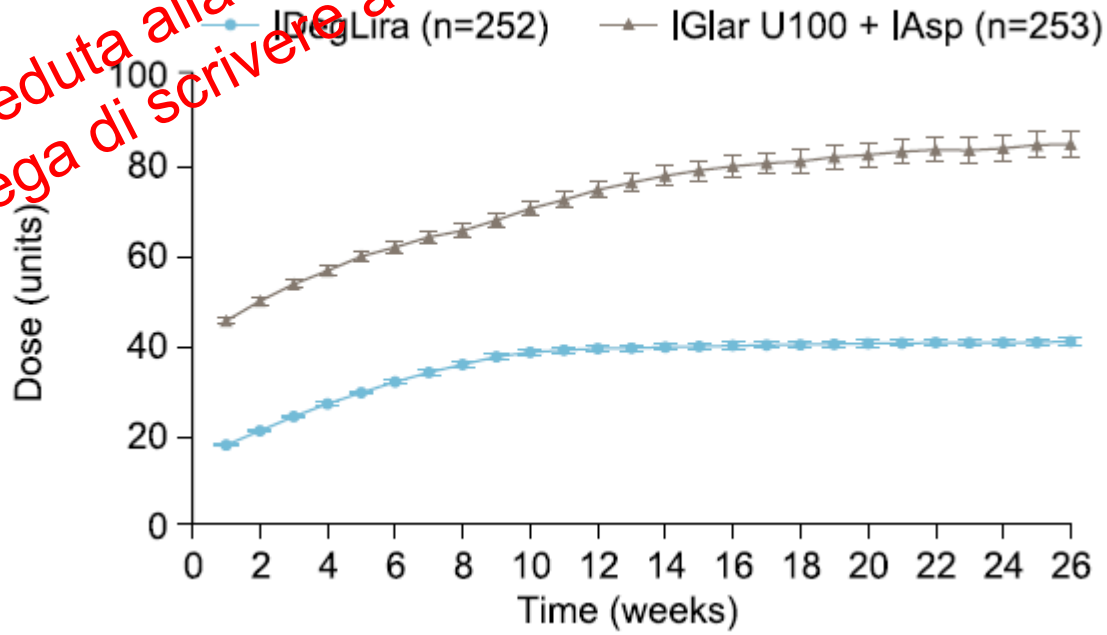


-3.6 kg



Total daily insulin dose was lower with IDegLira (40 units) than basal-bolus (84 units total; 52 units basal)

Efficacy and Safety of IDegLira Versus Basal-Bolus Insulin Therapy in Patients With Type 2 Diabetes Uncontrolled on Metformin and Basal Insulin: The DUAL VII Randomized Clinical Trial

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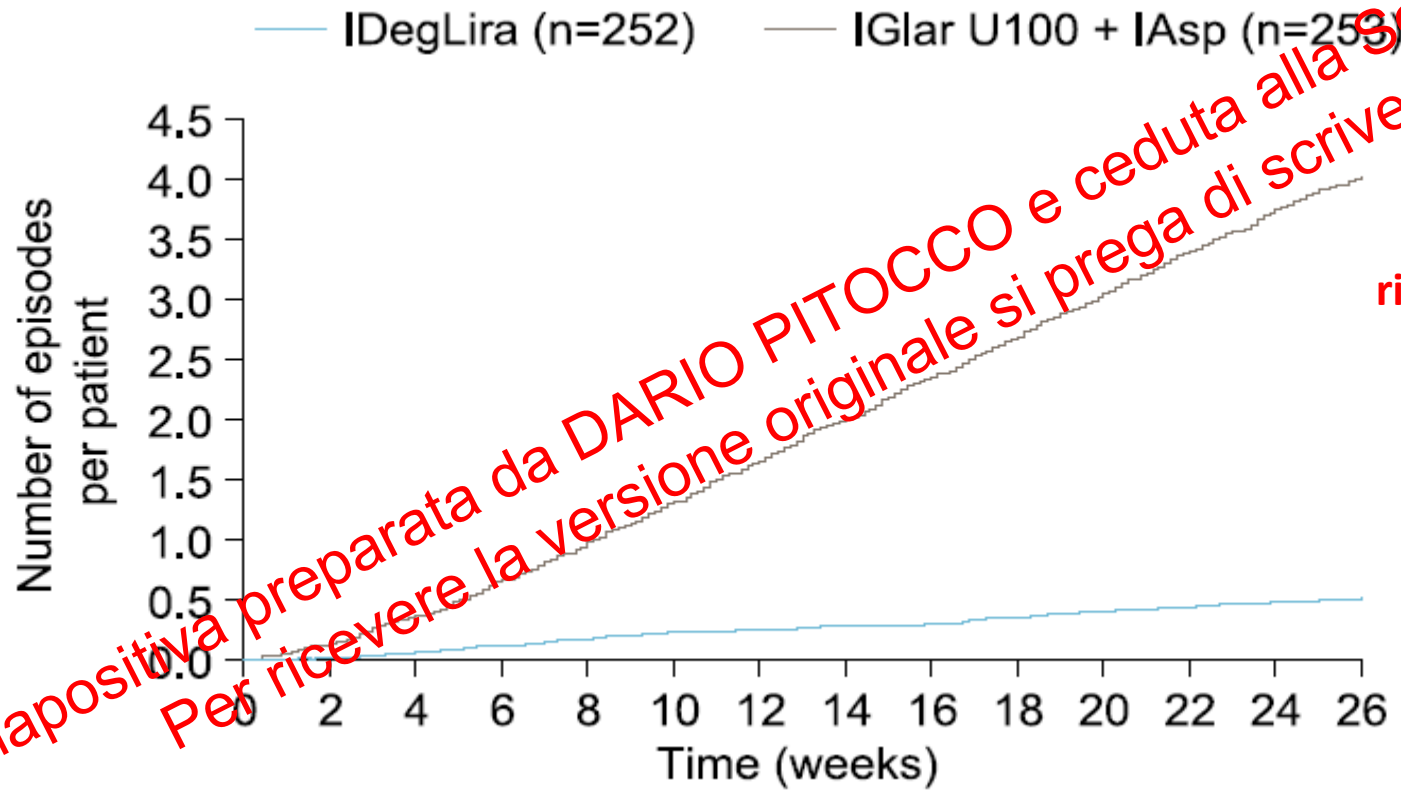

risk ratio 0.39 [95% CI 0.29, 0.51]

Severe or BG-confirmed symptomatic hypoglycemia

Efficacy and Safety of IDegLira Versus Basal-Bolus Insulin Therapy in Patients With Type 2 Diabetes Uncontrolled on Metformin and Basal Insulin: The DUAL VII Randomized Clinical Trial

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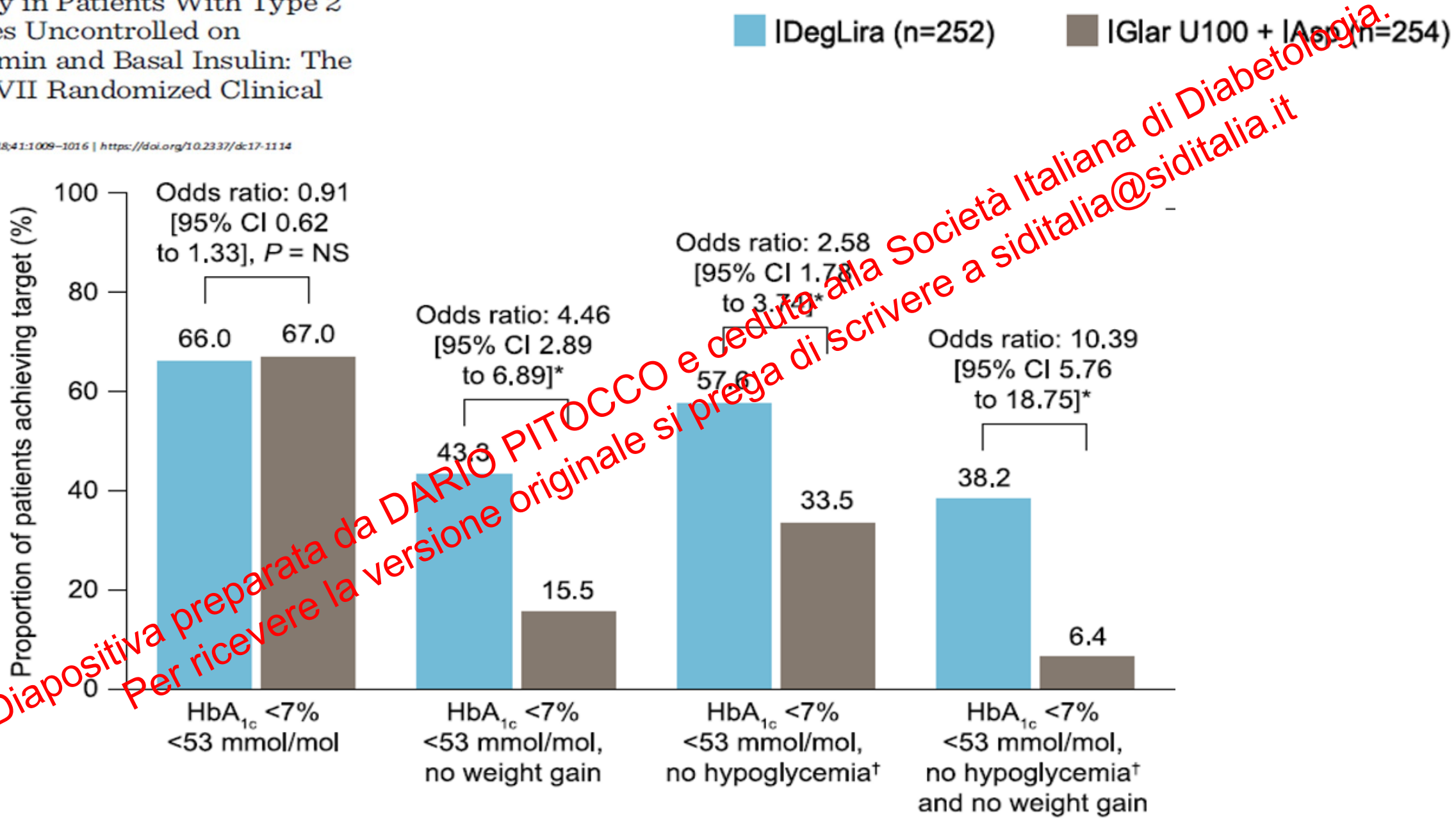

Insulina Basale e GLP-1 RA

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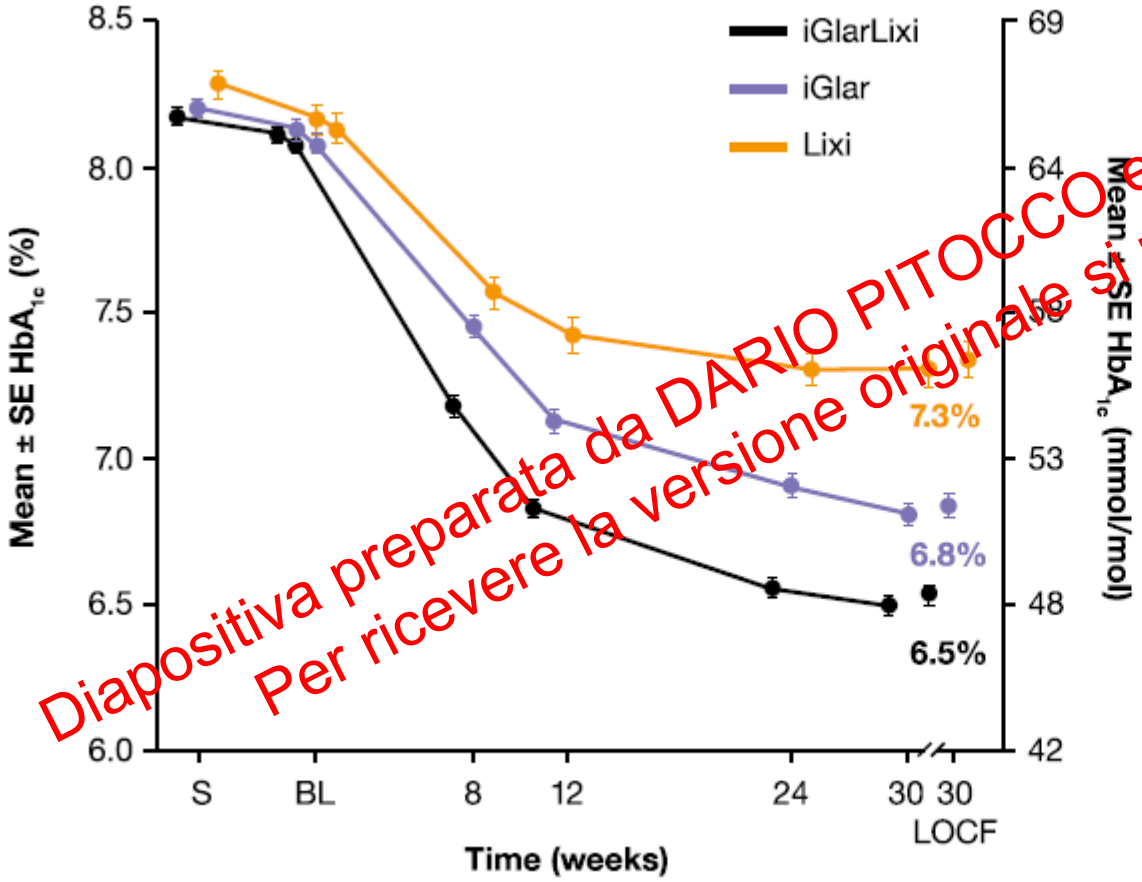
Exenatide ow	+	Insulina basale	

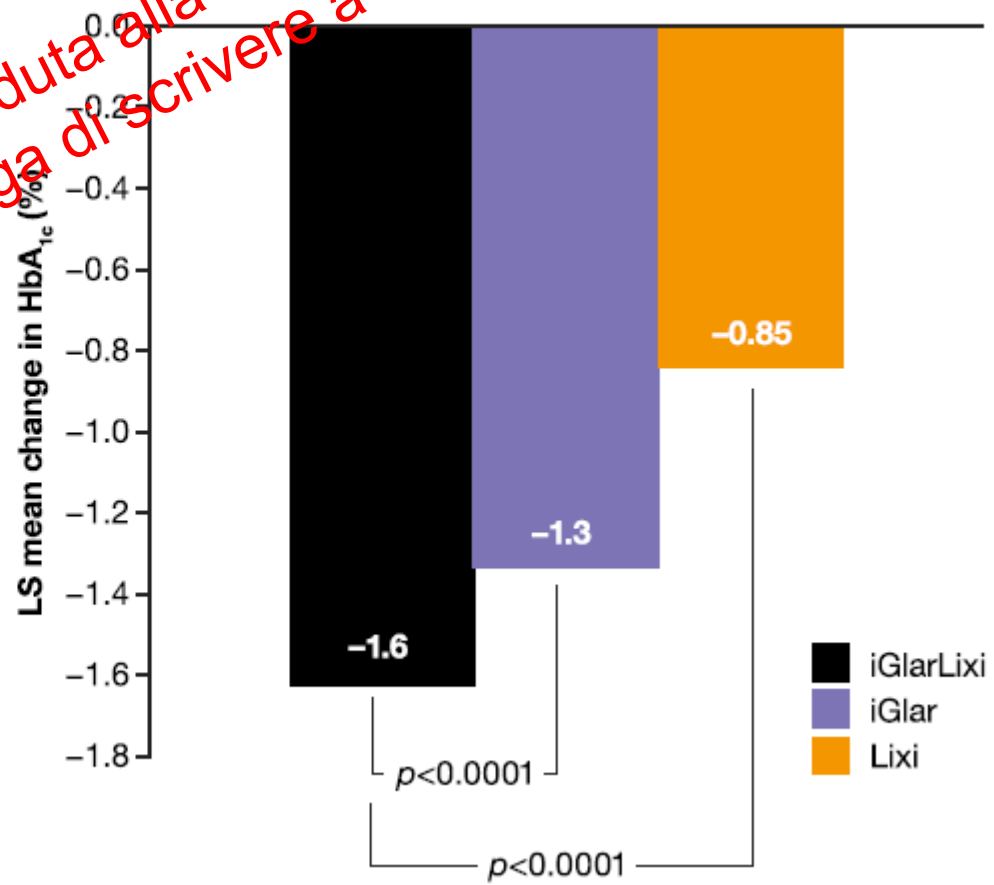
Benefits of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide, Versus Insulin Glargine and Lixisenatide Monocomponents in Type 2 Diabetes Inadequately Controlled on Oral Agents: The LixiLan-O Randomized Trial

Diabetes Care 2016;39:2026–2035 | DOI: 10.2337/dc16-0917

LIXILAN-O

HbA1c





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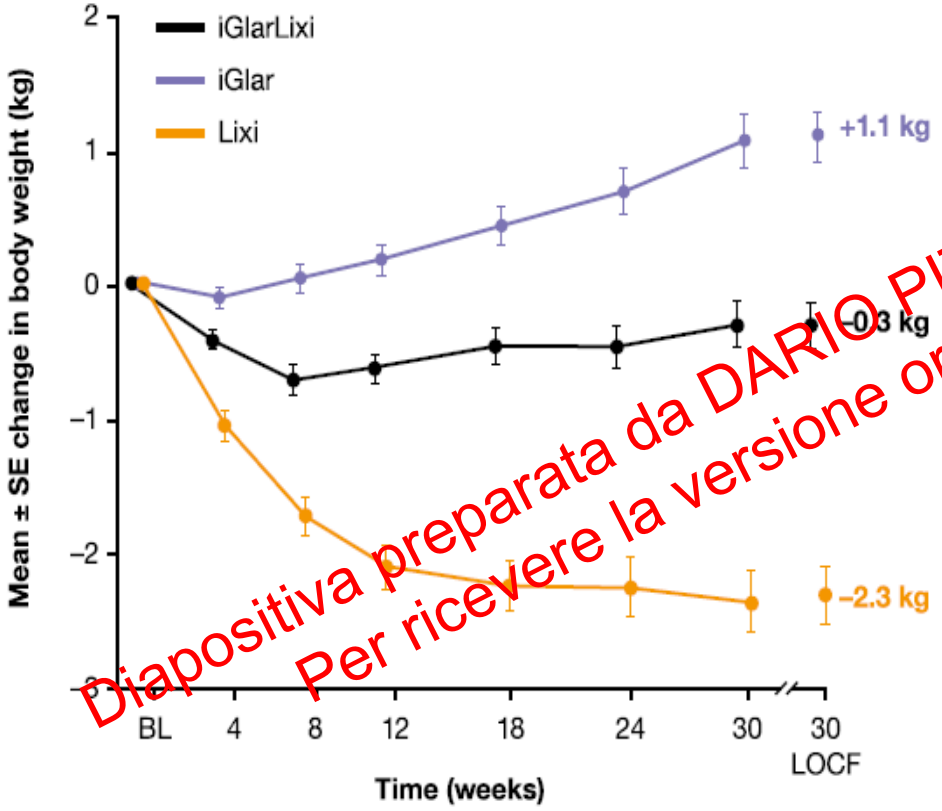
Diabetes Care 2016;39:2026–2035 | DOI: 10.2337/dc16-0917

Symptomatic hypoglycemia was similar with iGlarLixi and iGlar (1.4 and 1.2 events/patient-year) and lower with Lixi (0.3 events/ patient-year) iGlarLixi demonstrated fewer nausea and vomiting events than Lixi

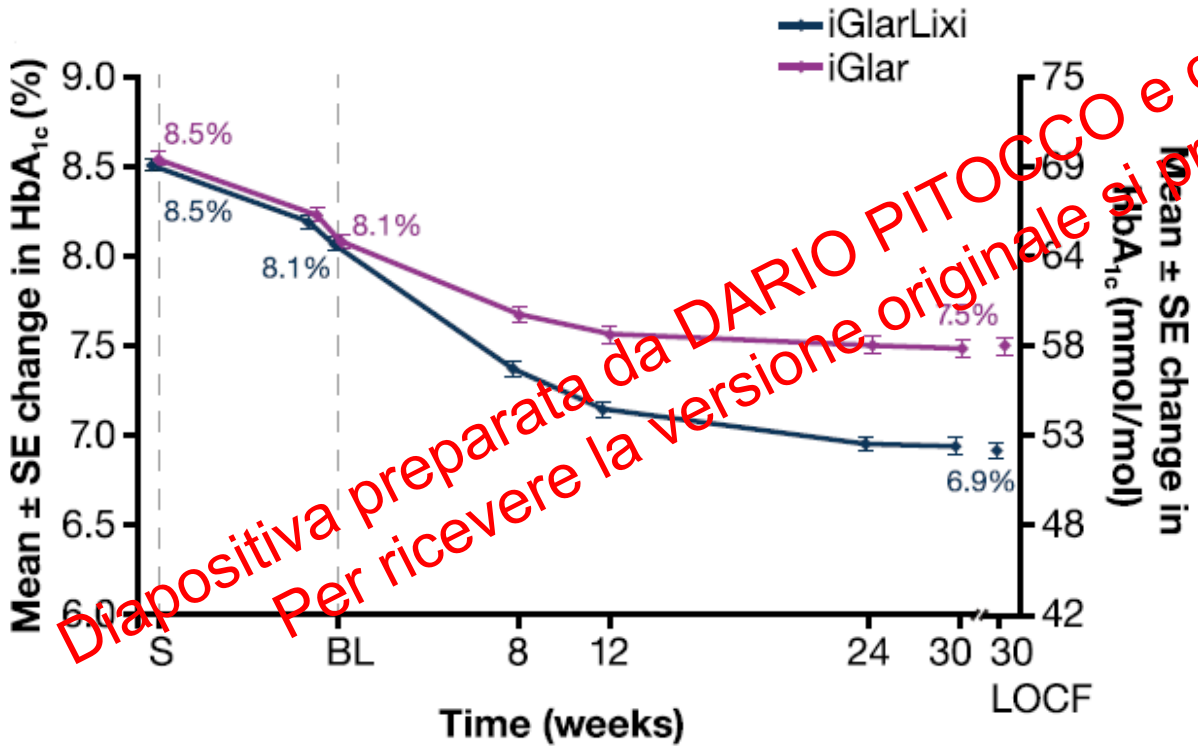


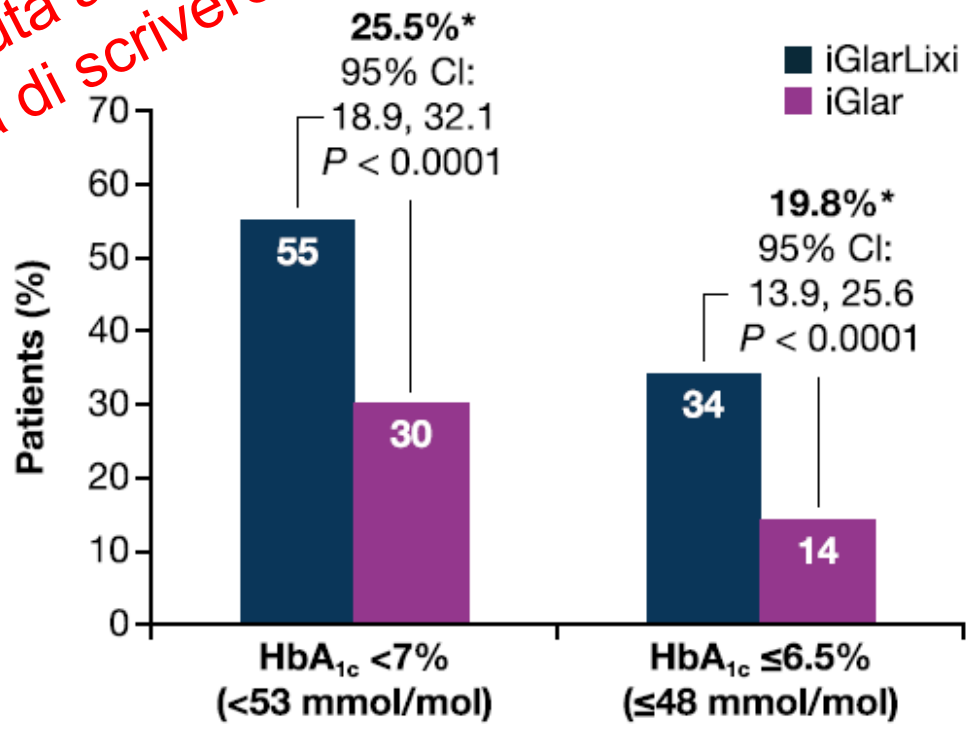
	iGlarLixi (*n* = 468)	iGlar (*n* = 466)	Lixi (*n* = 233)
AE by organ class			
Gastrointestinal disorders (overall)	102 (21.7)	59 (12.6)	86 (36.9)
Nausea	45 (9.6)	17 (3.6)	56 (24.0)
Discontinuation due to nausea	2 (0.4)	0	6 (2.6)
Vomiting	15 (3.2)	7 (1.5)	15 (6.4)
Discontinuation due to vomiting	2 (0.4)	0	4 (1.7)
Diarrhea	42 (9.0)	20 (4.3)	21 (9.0)
Discontinuation due to diarrhea	1 (0.2)	0	2 (0.9)
Hypoglycemia			
Documented symptomatic hypoglycemia (plasma glucose ≤70 mg/dL [3.9 mmol/L])			
Patients with events	120 (25.6)	110 (23.6)	15 (6.4)
Number of events per patient-year†	1.4	1.2	0.3
Documented symptomatic hypoglycemia (plasma glucose <60 mg/dL [3.3 mmol/L])			
Patients with events	66 (14.1)	50 (10.7)	6 (2.6)
Number of events per patient-year†	0.5	0.3	0.1
Severe symptomatic hypoglycemia			
Patients with events	0	1 (0.2)	0
Number of events per patient-year†	0	<0.01	0

Efficacy and Safety of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide in Type 2 Diabetes Inadequately Controlled on Basal Insulin and Metformin: The LixiLan-L Randomized Trial

Diabetes Care 2016;39:1972–1980 | DOI: 10.2337/dc16-1495

LIXILAN-L





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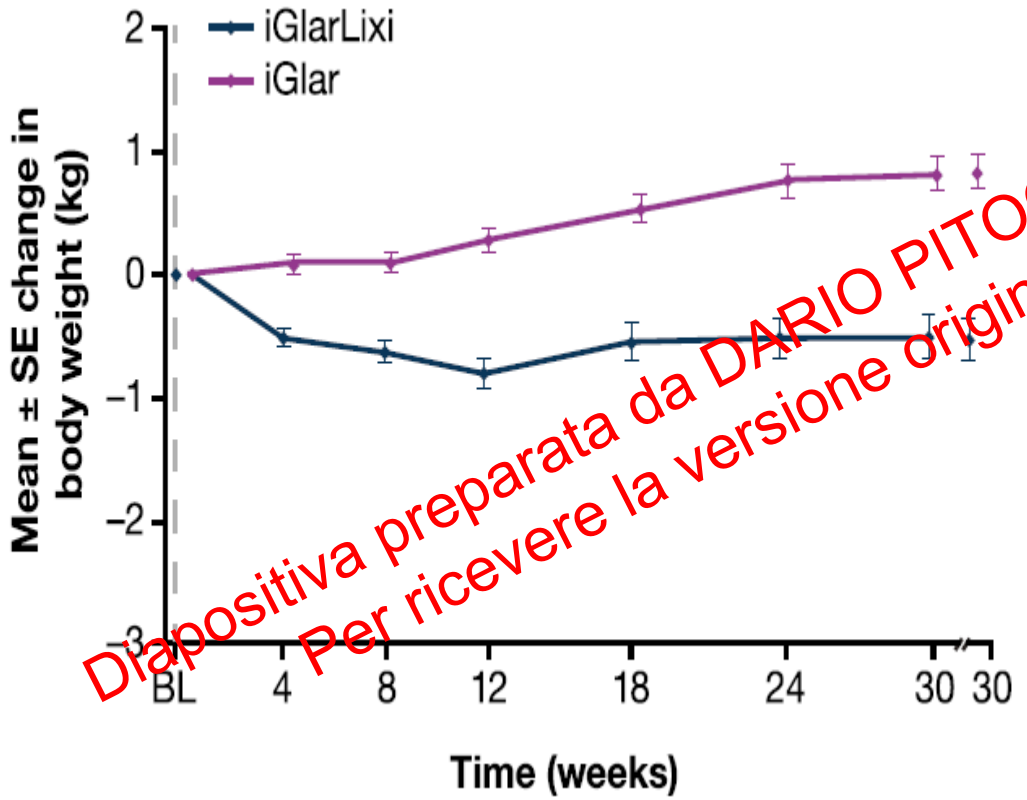

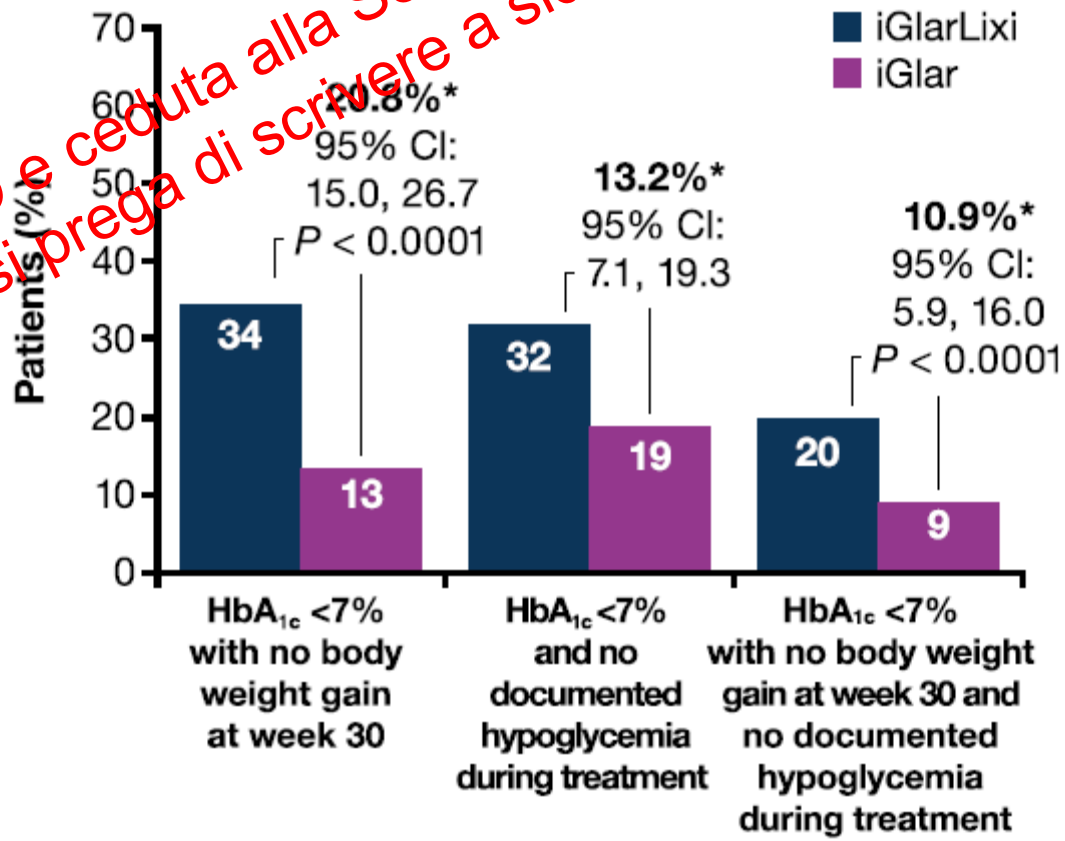

Domanda 2

Le formulazioni precostituite insulina basale-GLP-1 RA

1) Dovrebbero essere titolate tenendo conto in primis della dose di insulina

2) Dovrebbero essere titolate tenendo conto in primis della dose di GLP-1 RA

3) Non dovrebbero essere mai titolate

4) Non andrebbero mai sostituite

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4) Non andrebbero mai sostituite

Compared with basal insulin, insulin/GLP-1RA fixed-ratio combinations are superior at reducing HbA_{1c} with weight neutrality or weight loss rather than weight gain, as well as reduced hypoglycemia rates, and reduced insulin-dose requirement with IDegLira

Diabetes Ther 2017 Aug;8(4):739-752.

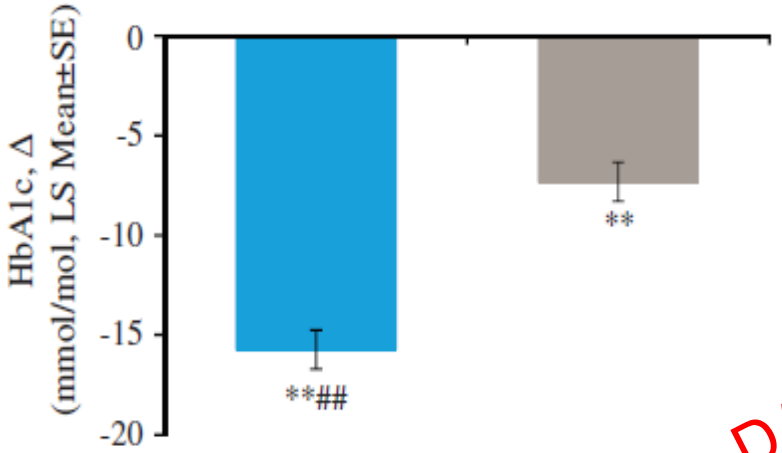
Combinazione basale/GLP-1RA vs Monocomponenti

- HbA1c: superiorità della combinazione
- Percentuale di pazienti a target per HbA1c: superiorità della combinazione
- FPG: combinazione=basale
- Calo ponderale: superiorità del GLP-1 RA
- Rischio di ipoglicemia: superiorità del GLP-1 RA
- Effetti collaterali gastrointestinali: meno presenti con la combinazione rispetto al GLP-1 RA monocomponente (dosaggio ridotto)
- Dosaggio: minor dosaggio con la combinazione

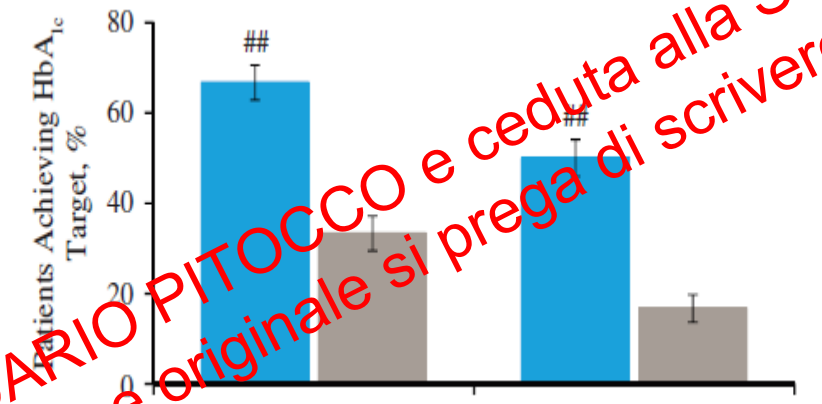
Insulina Basale e GLP-1 RA

Combinazioni non fisse			Combinazioni fisse
Liraglutide	+	Insulina basale	IDegLira
Lixisenatide	+	Insulina basale	IGlarLixi
Dulaglutide	+	Insulina basale	
Exenatide ow	+	Insulina basale	

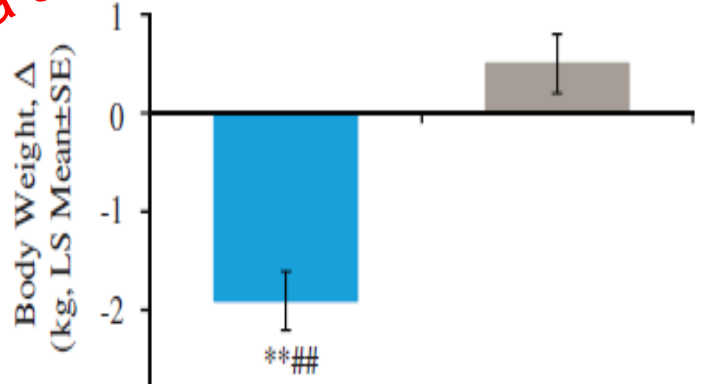
Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9)



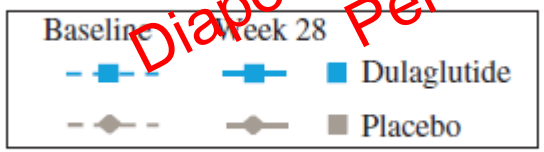
Hba1c



HbA1c<7% HbA1c<6.5%



PESO



Insulina Basale e GLP-1 RA

Combinazioni non fisse			Combinazioni fisse
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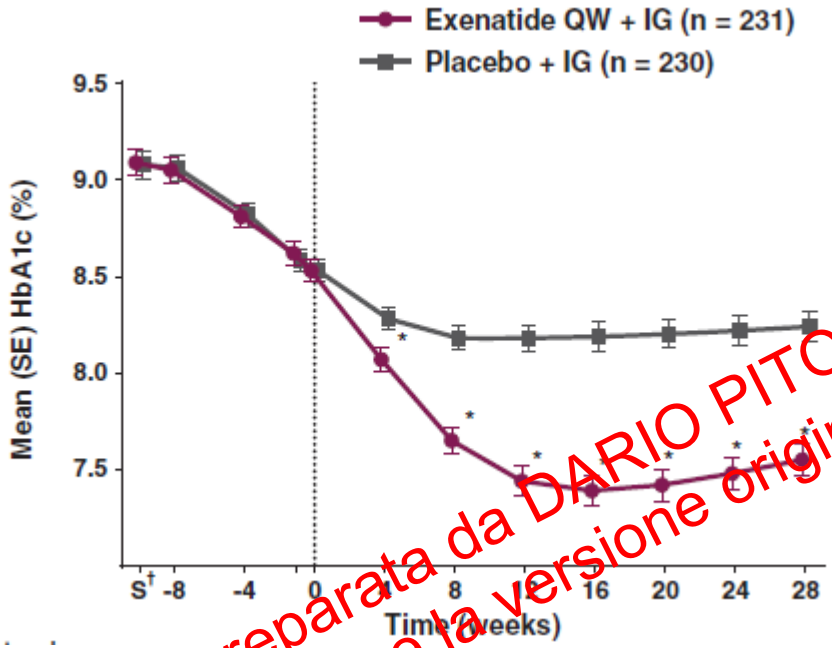
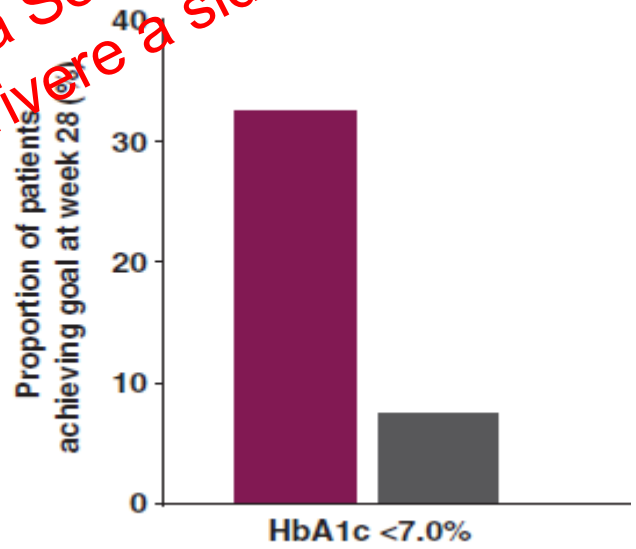
Lixisenatide	+	Insulina basale	IGlarLixi
Dulaglutide	+	Insulina basale	
Exenatide ow	+	Insulina basale	

Effect of exenatide QW or placebo, both added to titrated insulin glargine, in uncontrolled type 2 diabetes: The DURATION-7 randomized study





Diabetes Obes Metab. 2018;**20**:1602–1614.

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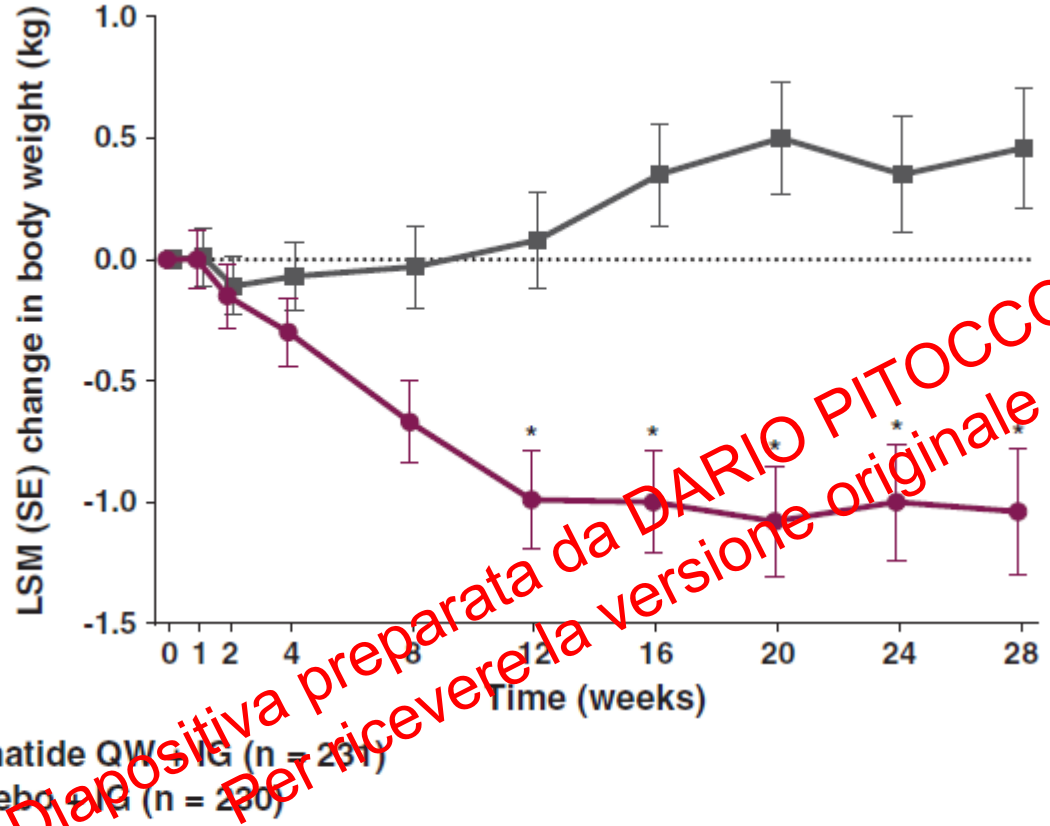
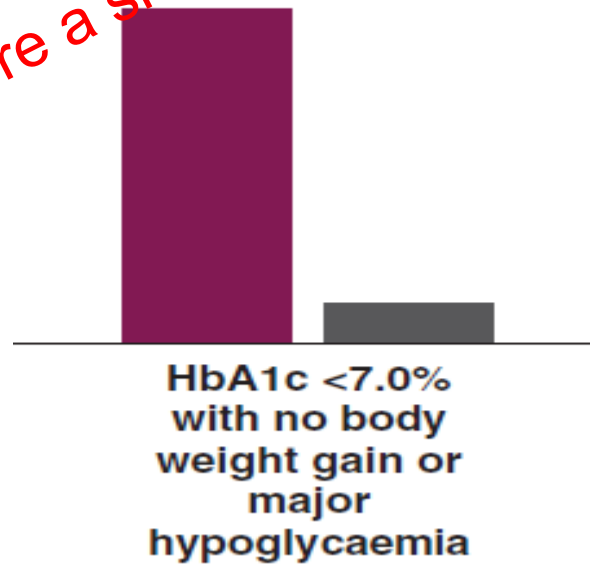
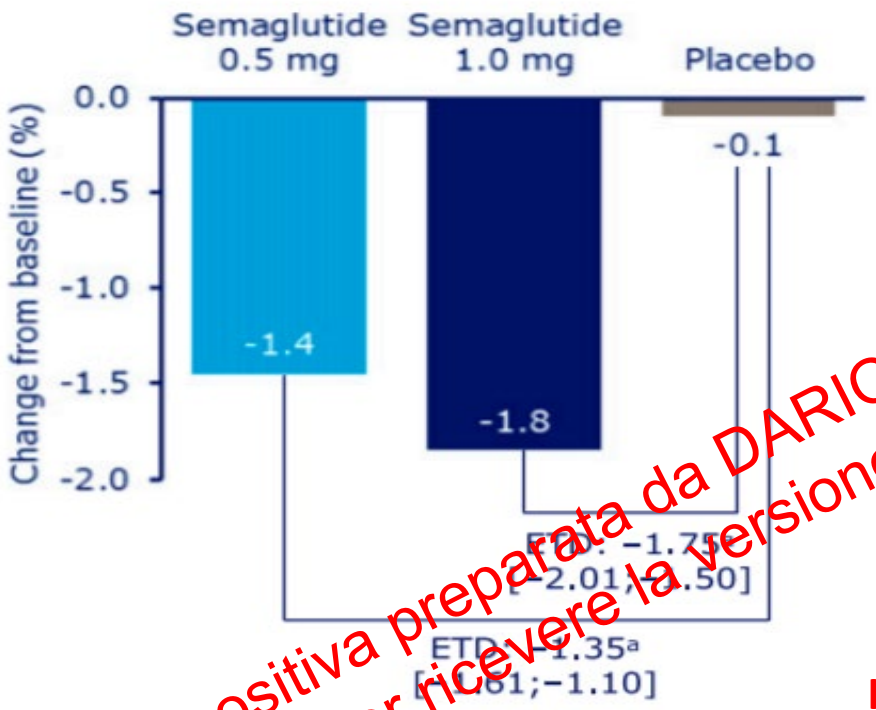


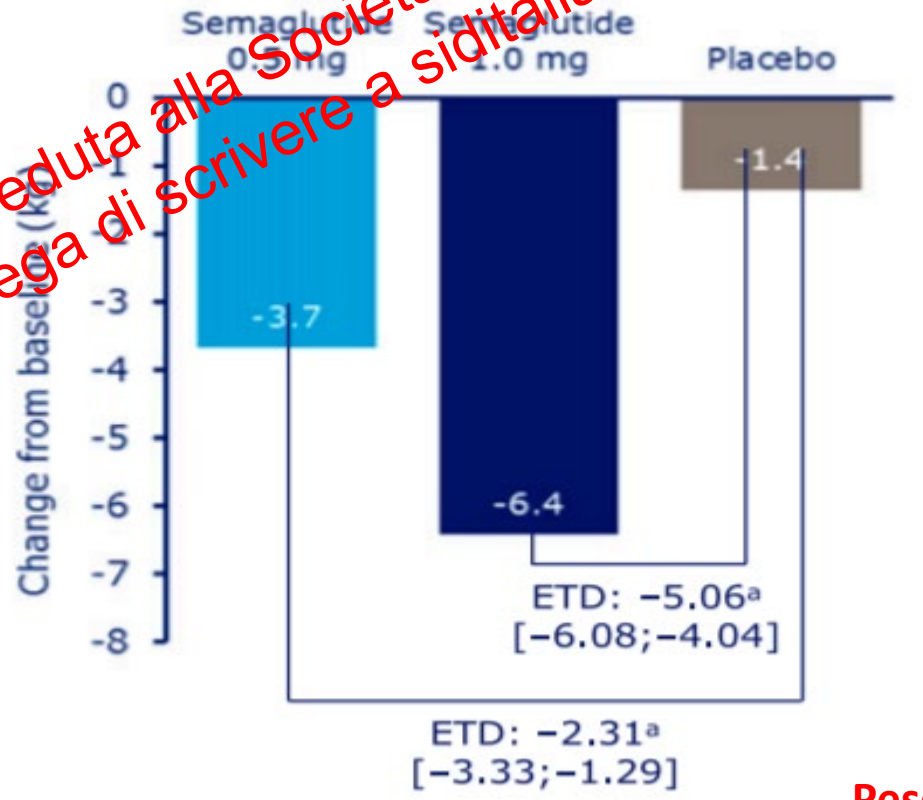


Diabetes Obes Metab. 2018;**20**:1602–1614.

Semaglutide Added to Basal Insulin in Type 2 Diabetes (SUSTAIN 5): A Randomized, Controlled Trial



HbA1c



Peso

J Clin Endocrinol Metab, June 2018, 103(6):2291–2301

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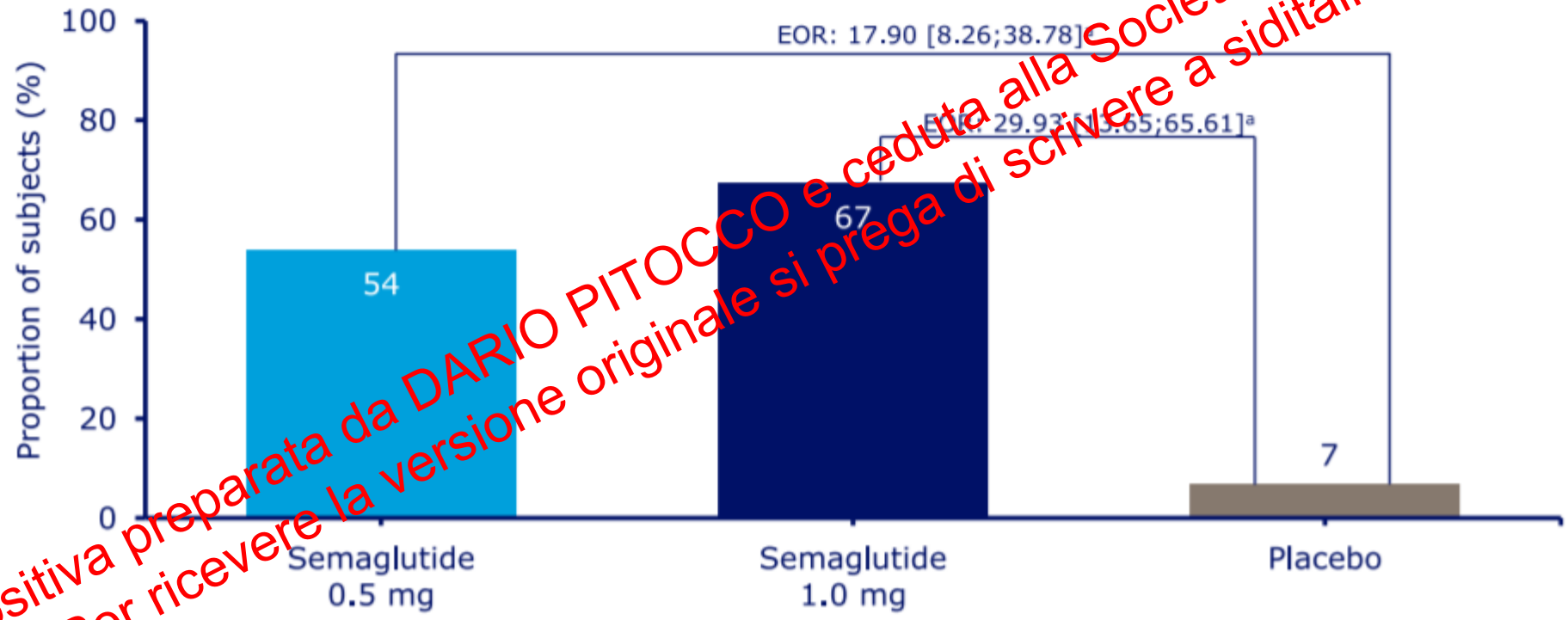

J Clin Endocrinol Metab, June 2018, 103(6):2291–2301

Glp-1 RA e Insulina Basale

- Miglioramento del compenso metabolico
- Migliore controllo del peso corporeo rispetto a un aumento del dosaggio della sola insulina basale o alla terapia insulinica basal-bolus
- Gli eventi ipoglicemici sono correlati al dosaggio di insulina basale che si utilizza
- Maggiore probabilità di raggiungere un endpoint composito (Hba1c-peso-rischio ipoglicemie)
- Limitata flessibilità nella titolazione se si utilizza un formulazione combinata (difficoltà nel raggiungere il dosaggio massimo di GLP-1 RA)