Terapia con analoghi del

GLP-1:

quando e perché

Analoghi del GLP-1 dopo fallimento BOT

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Bologna, 27 giugno 2019

SAPIENZA UNIVERSITÀ DI ROMA

Il sottoscritto Marco Giorgio Baroni

dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Sanofi
- Novo Nordisk
- Abbott
- Mundi Pharma
- 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.).

Qual è la percentuale di pazienti che non rispondono/falliscono alla basal supported-oral therapy (BOT)?

1. 15-30%
2. 35-45%
3. 45-55%
4. 55-65 %

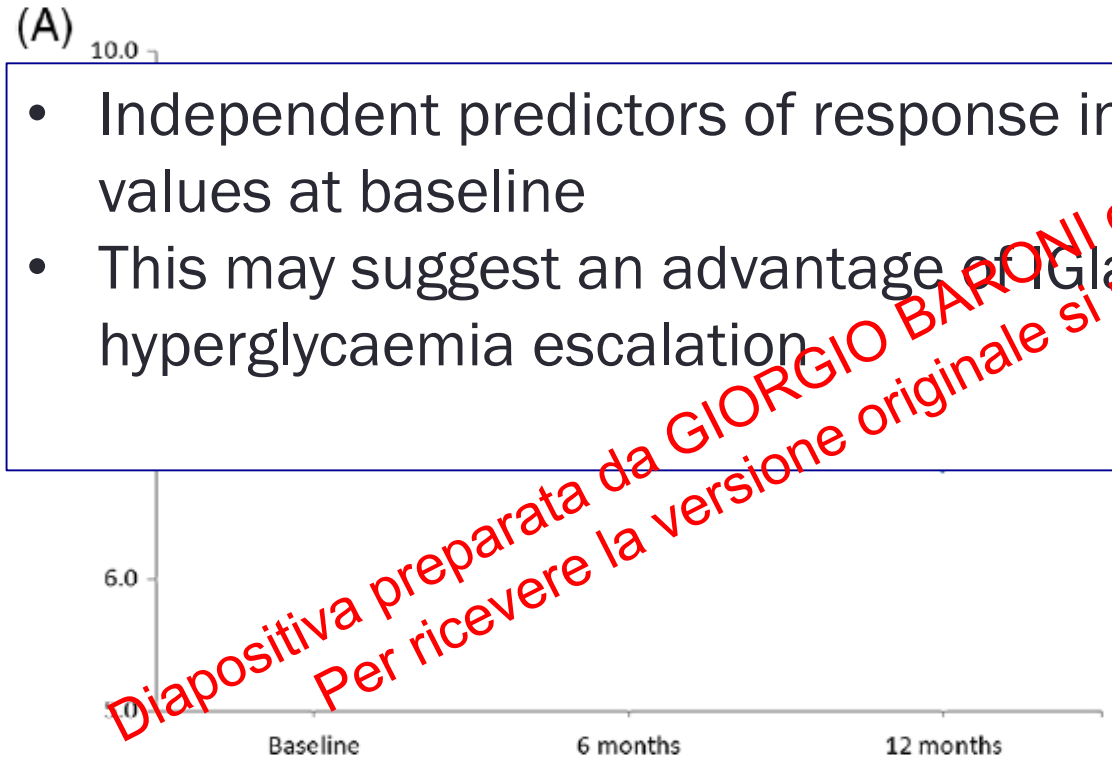
Predictors of treatment response in type-2 diabetes patients initiating basal-supported oral therapy with insulin glargine 100 U/mL: A sub-analysis of the Titration and OPtimisation (TOP) registry

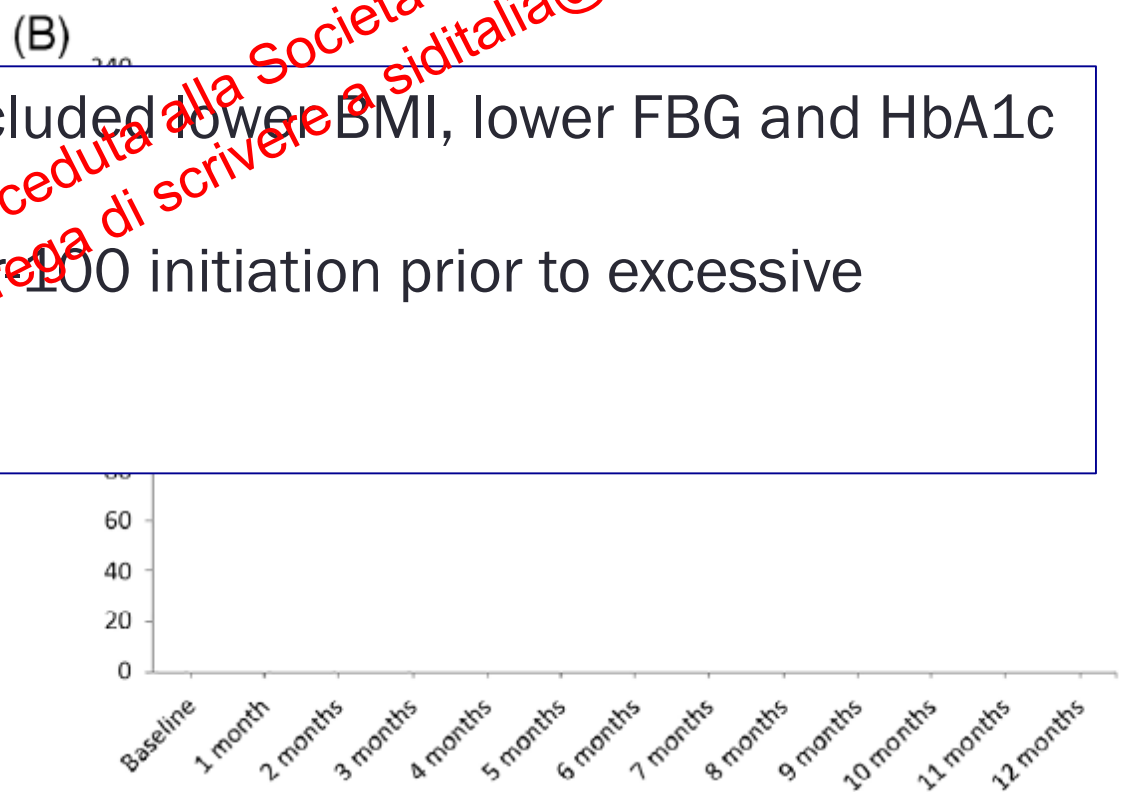
Pfhol M et al. Diabetes Obes Metab. 2019;1–5.

- Patients from the observational TOP registry were grouped based on those who had achieved (responders) and those who had not achieved (non-responders) their HBA1c target and/or FBG ≤110 mg/dL 12 months after IGlar-100 initiation
- Data for 2444 patients were analysed: responders, n = 1610 (65%); non-responders, n = 834 (35%).

HbA1c (A) and FBG (B) over 12 months.

- Independent predictors of response included lower BMI, lower FBG and HbA1c values at baseline
- This may suggest an advantage of IGlar-100 initiation prior to excessive hyperglycaemia escalation





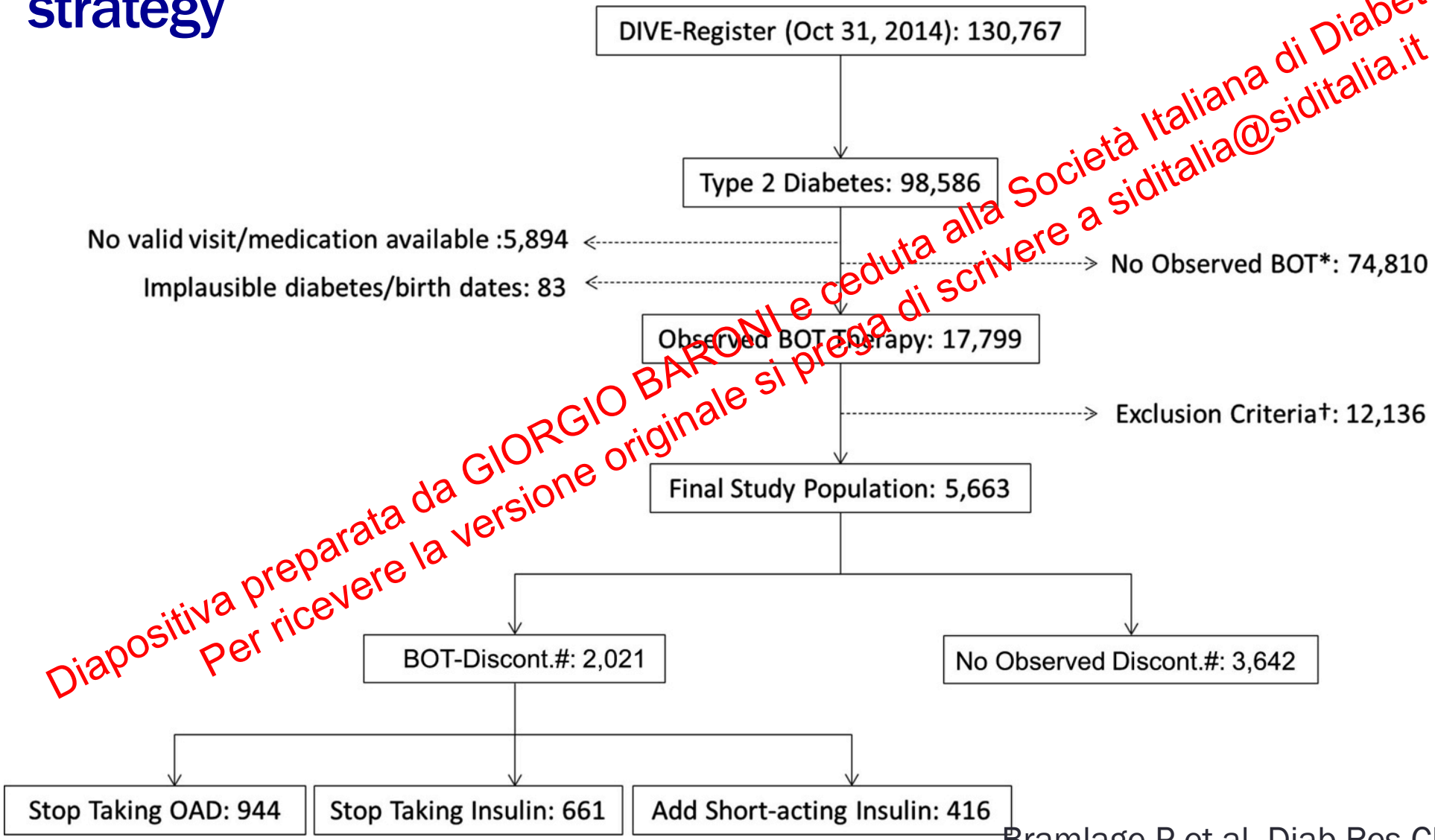
Pfhol M et al. Diabetes Obes Metab. 2019;1–5.

Treatment duration (persistence) of basal insulin supported oral therapy (BOT) in Type-2 diabetic patients: comparison of insulin glargine with NPH insulin

Renate Quinzler et al. Int. Journal of Clin Pharmacol and Therapeutics 2012

- To compare the persistence (treatment duration) of basal insulin supported oral therapy (BOT) using insulin glargine (GLA) or NPH insulin (NPH) in Type-2 diabetic patients.
- Patients on BOT with either GLA or NPH were included and followed up for 5 years.
- Persistence was defined as the duration of time from initiation of BOT with GLA or NPH until modification of insulin therapy with either premixed insulin, bulso insulin alone or basal-bolus regimen
- 97,976 patients (61,053 GLA and 36,923 NPH) were included. Altogether, 44.1 % of GLA patients and 46.7 % of NPH patients modified initial BOT. On average, these patients stayed 373 days on BOT with GLA and 305 days on BOT with NPH

Identifying patients with type 2 diabetes in which basal supported oral therapy may not be theoptimal treatment strategy



Bramlage P et al. Diab Res Clin Pract 2018

Attualmente nel paziente non a target con insulina basale e fortemente scompensato (HbA1c>10%)

1) Si consiglia la combinazione con GLP-1 RA
2) Si consiglia di aggiungere insulina prandiale
3) Si sconsiglia sempre l'uso dell'SGLT-2 inibitori
4) Si consiglia di aggiungere SGLT-2 inibitori

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)

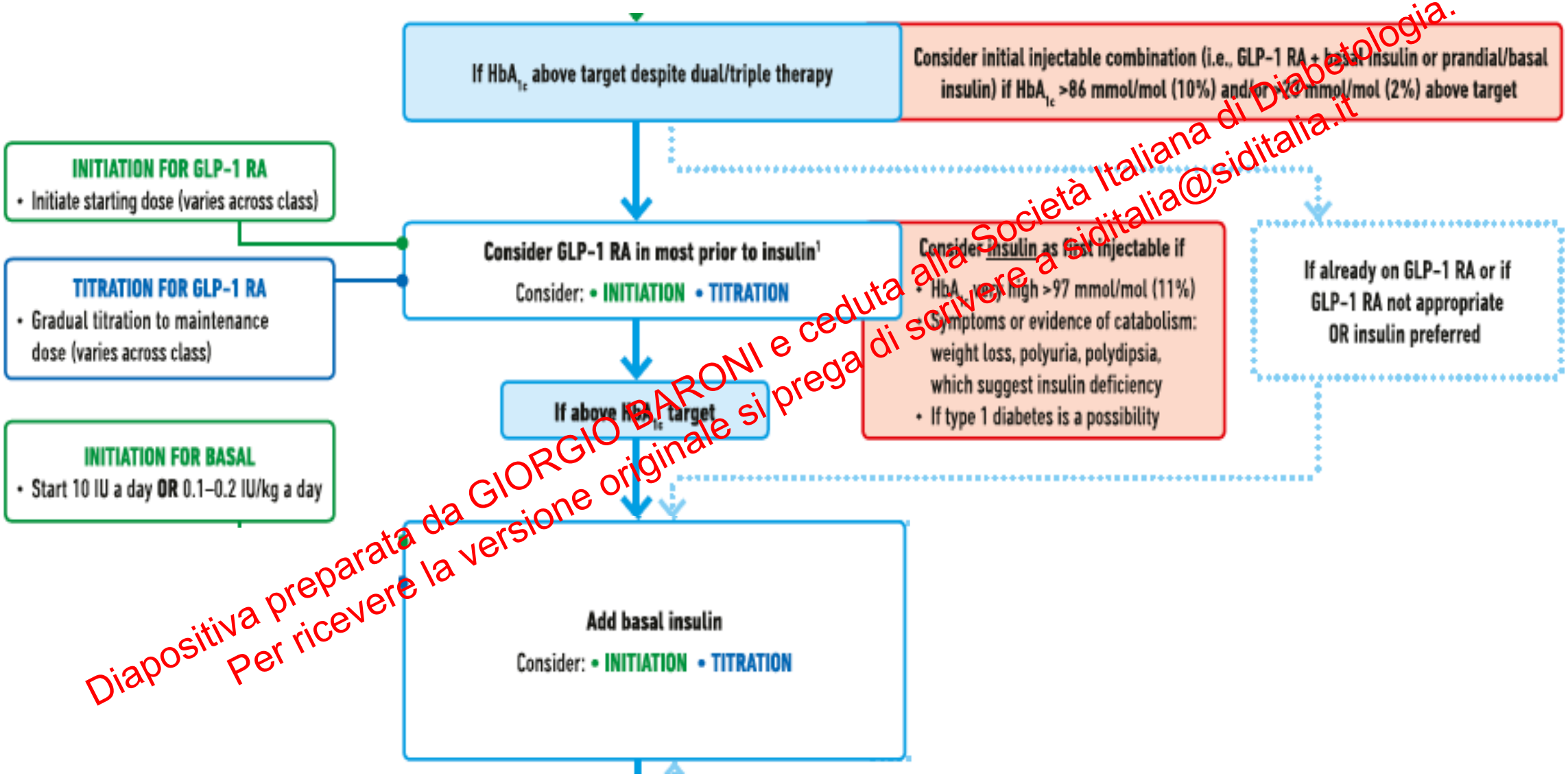
Consensus recommendation

Beyond Basal insulin

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

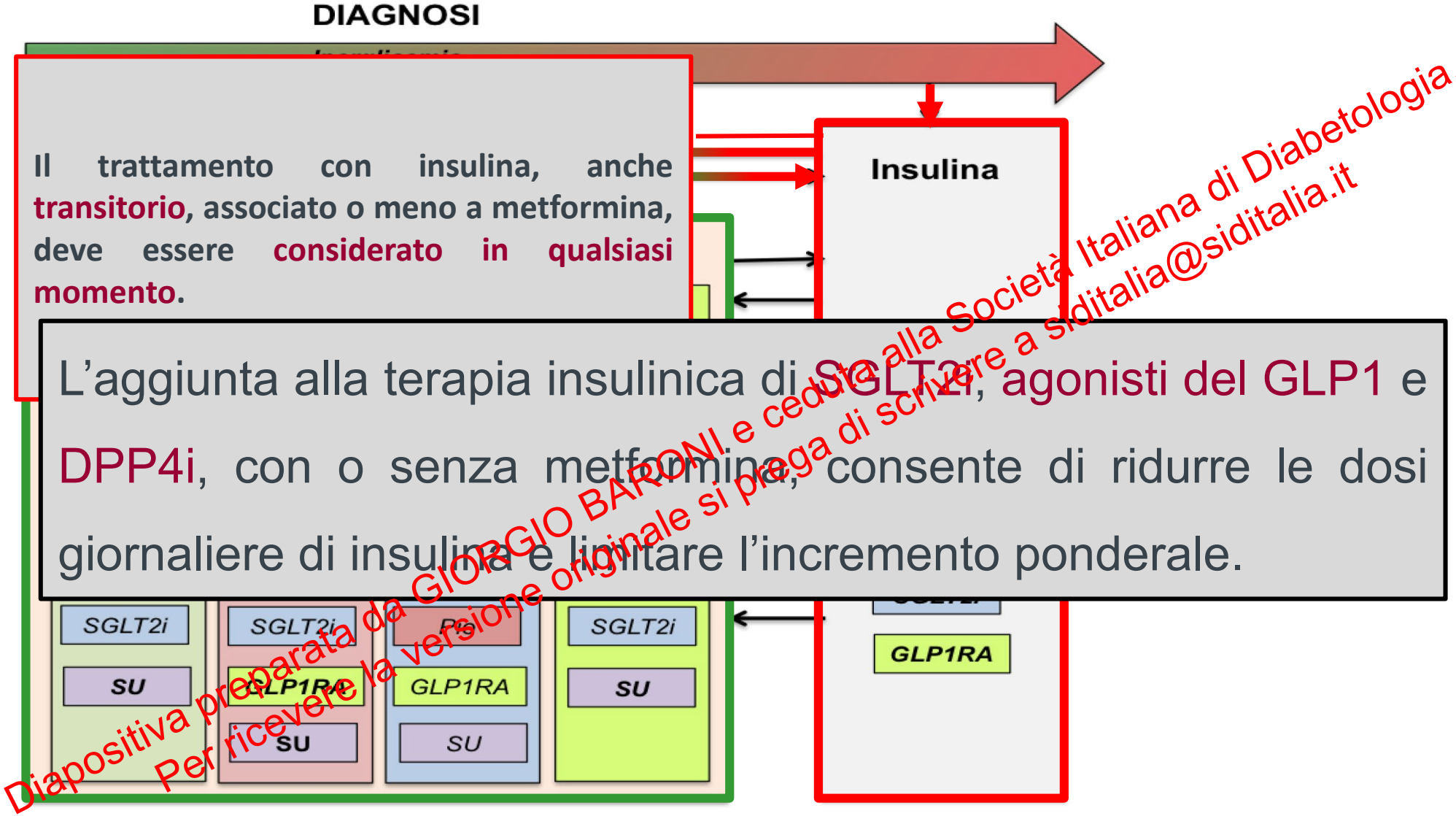
Diabetologia (2018) 61:2461–2498

INTENSIFYING TO INJECTABLE THERAPIES

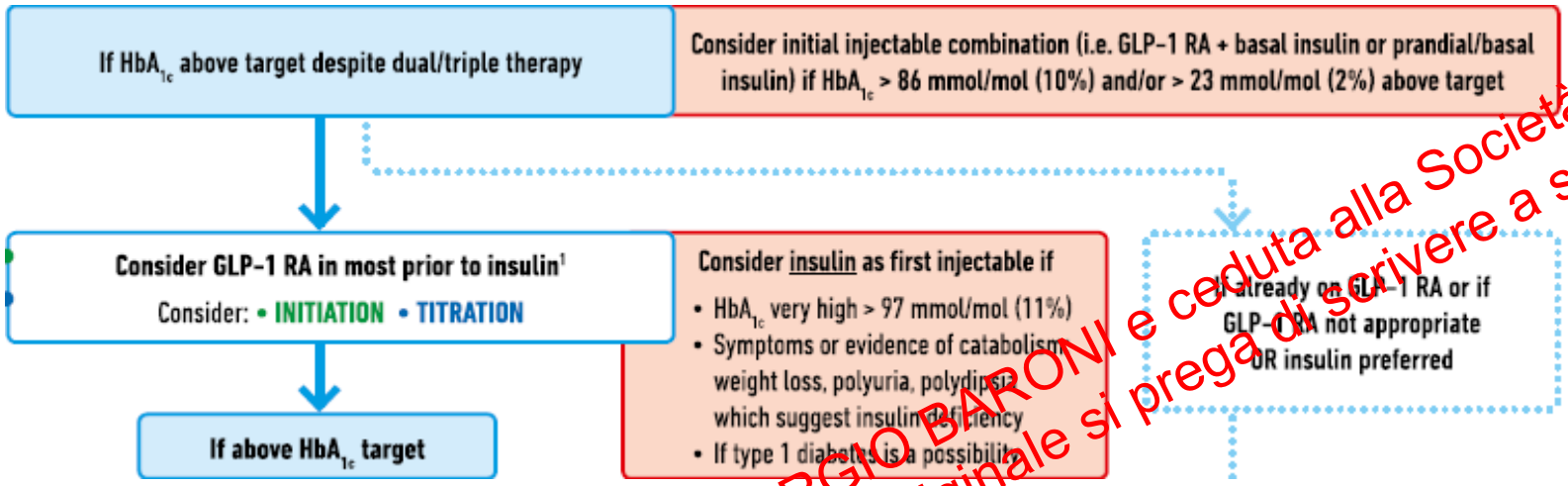


Diabetologia (2018) 61:2461–2498

Standard Italiani per la cura del diabete mellito SID-AMD 2018



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 rischio cardiovascolare
- L'effetto sul peso

Diabetologia (2018) 61:2461–2498

Choosing glucose-lowering medication

In patients with established ASCVD

ASCVD predominates

GLP-1RA
with proven CVD benefit

EITHER/OR

SGLT-2i
with proven CVD benefit,
if eGFR adequate†

If HbA_{1c} above target

If further intensification is required or patient is now unable to tolerate GLP-1RA and/or SGLT-2i, choose agents demonstrating CV safety:

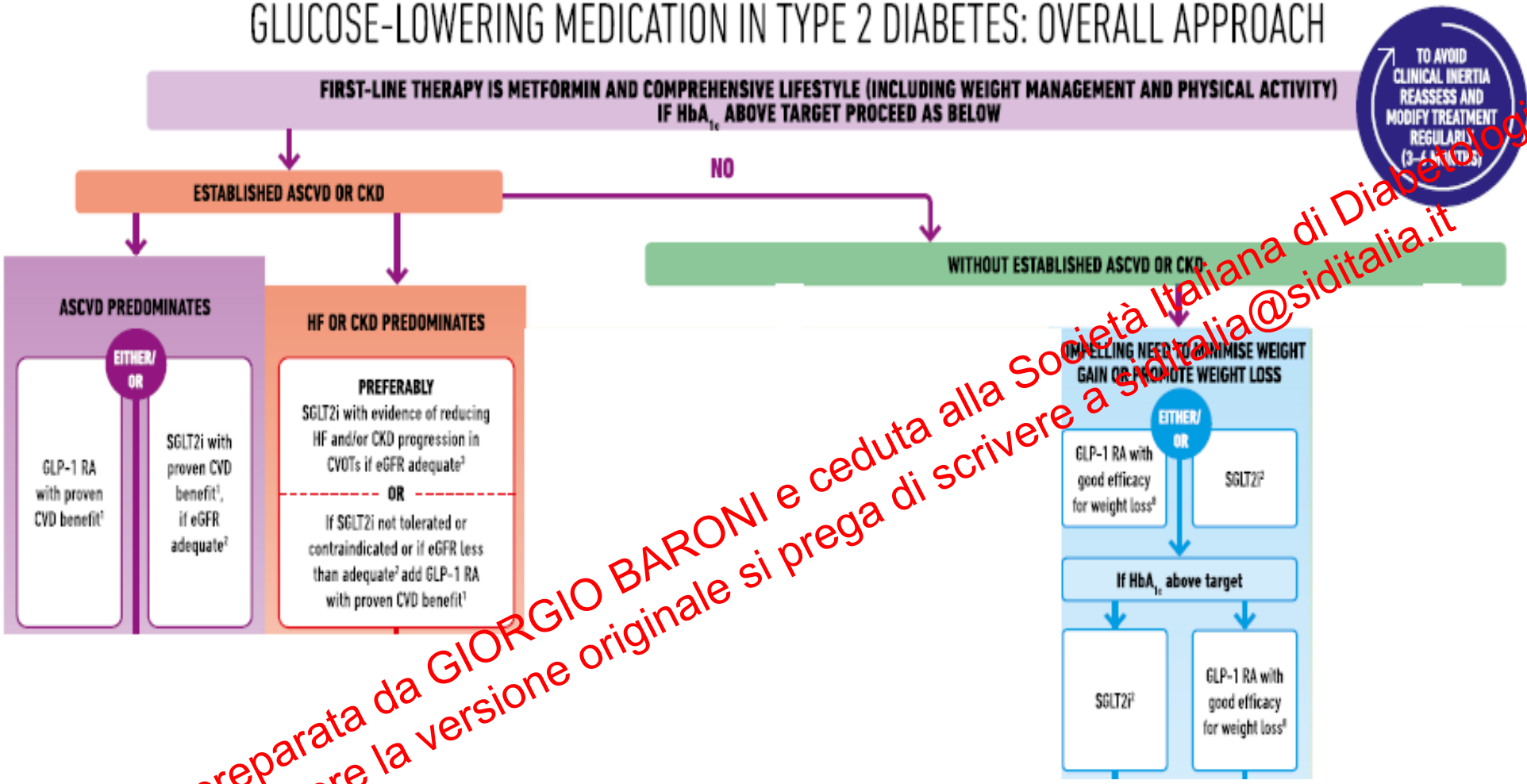
- Consider adding the other class (GLP-1RA or SGLT-2i) with proven CVD benefit
- DPP-4i if not on GLP-1RA
- Basal insulin§
- TZD¶
- SU||

Evidence Hierarchy

- Liraglutide (LEADER)
- Semaglutide (SUSTAIN-6)
- Dulaglutide (REWIND)
- Exenatide ER (EXSCEL)

†Be aware that SGLT-2is vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use; ‡Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs; §Degludec or U100 glargine have demonstrated CVD safety; ¶Low dose may be better tolerated, although less well studied for CVD effects; ||Choose later-generation SU with lower risk of hypoglycaemia

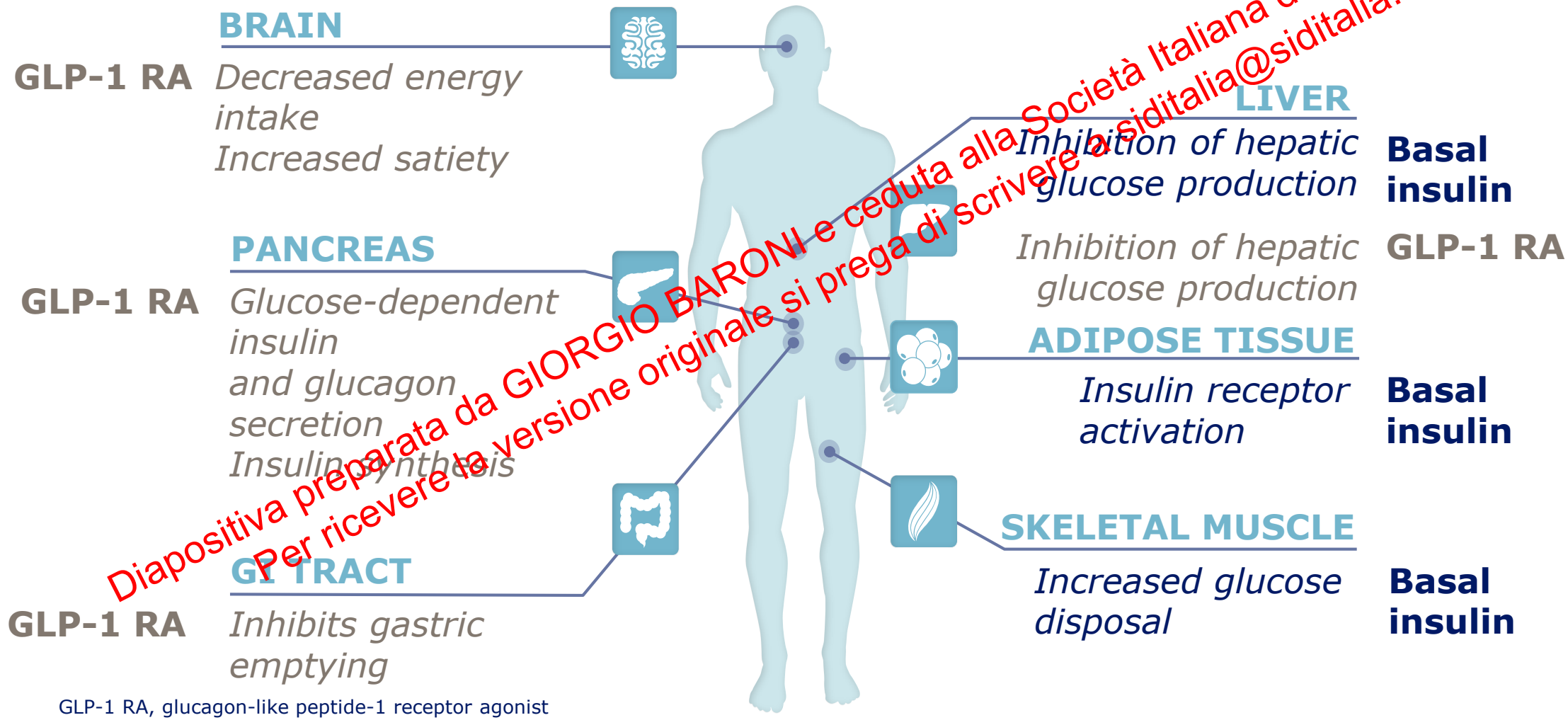
Davies MJ et al. Diabetologia 2018;61:2461–2498



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

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

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 receptor agonist has high efficacy, with recent evidence from clinical trials demonstrating the benefits of this combination to lower HbA1c and limit weight gain and hypoglycemia compared with intensified insulin regimens.
- Most data come from studies in which a GLP-1 receptor agonist is added to basal insulin. However, there is evidence that insulin added to a GLP-1 receptor agonist can also effectively lower HbA1c, although some weight gain results.
- Fixed-ratio combinations of insulin and GLP-1 receptor agonists are available and can decrease the number of injections compared with administering the medications separately

Diabetologia (2018) 61:2461–2498

Analoghi del GLP-1 dopo fallimento BOT

Insulina Basale e GLP-1 RA

Combinazioni non-fisse

- Insulina basale (glarg o deglud) +
  - Liraglutide
  - Lixisenatide
  - Dulaglutide
  - Albiglutide
  - Exenatide Ow

Combinazioni fisse

- Degludec + Liraglutide: IDegLira
- Glargine + Lixisenatide: IGlarLixi

Combined use of a GLP-1 RA and basal insulin

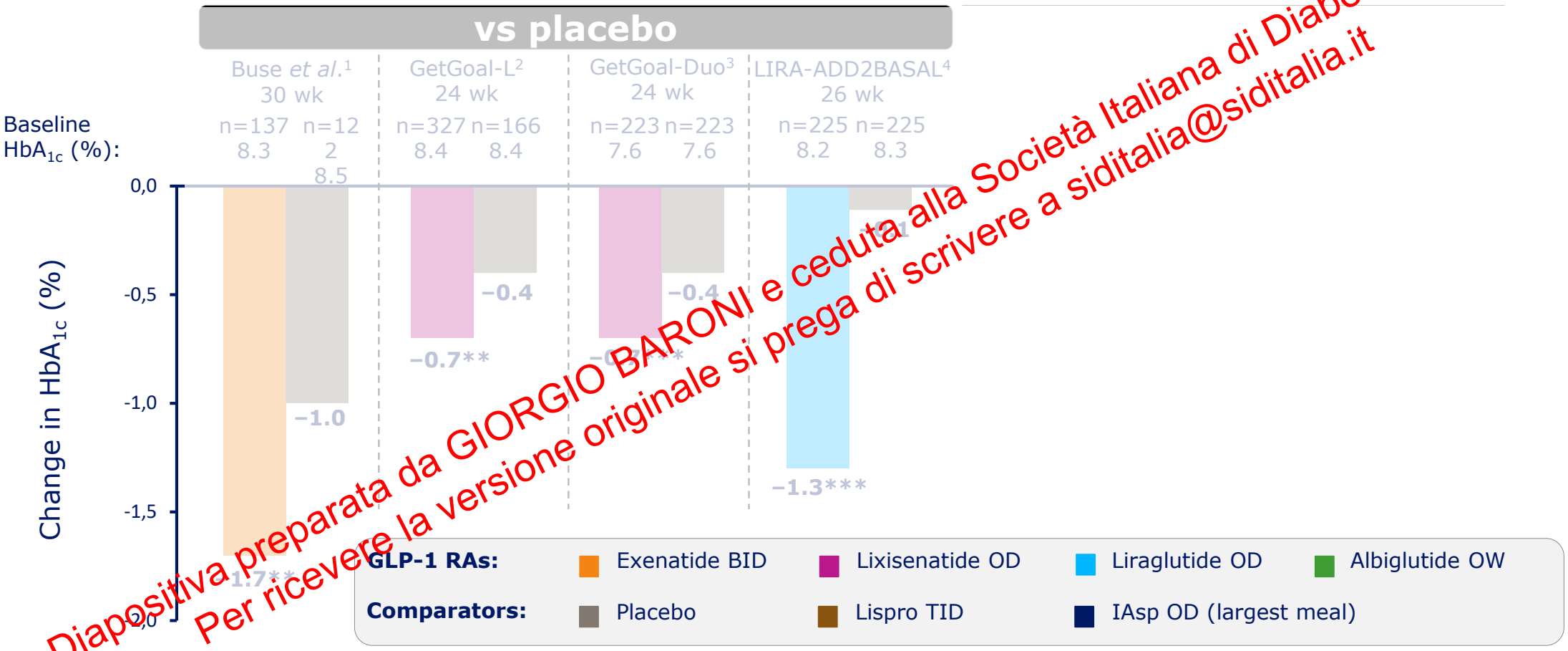
Trials where basal insulin started first

Study name	Background therapy		Added at randomisation			
Buse *et al*. 2011[1]	± Metformin ± pioglitazone	Insulin glargine U100	Exenatide BID (vs placebo)			
GetGoal-L[2]	± Metformin	Basal insulin	Lixisenatide (vs placebo)			
GetGoal-Duo-1[3]	Metformin ± TZD	Insulin glargine U100	Lixisenatide (vs placebo)			
LIRA-ADD2BASAL[4]	± Metformin	Basal insulin	Liraglutide 1.8 mg (vs placebo)			
BEGIN: LIRAGLUTIDE ADD-ON[5]	± Metformin	Insulin degludec	Liraglutide 1.8 mg	or	Insulin aspart OD	
Harmony-6[6]	Metformin + pioglitazone +α-glucosidase inhibitors	Insulin glargine U100	Albiglutide OW	or	Insulin lispro TID	
Diamant *et al*.[7]	Metformin	Insulin glargine U100	Exenatide BID	or	Insulin lispro TID	

BID, twice daily; GLP-1 RA, glucagon-like peptide-1 receptor agonist; OD, once daily; OW, once weekly; TID, three times per day; TZD, thiazolidinedione; U100, 100 units/mL

1. Buse JB *et al*. *Ann Intern Med* 2011;154:103–112; 2. Riddle MC *et al*. *Diabetes Care* 2013;36:2489–2496; 3. Riddle MC *et al*. *Diabetes Care* 2013;36:2497–2503; 4. Ahmann AJ *et al*. *Diabetes Obes Metab* 2015;17:1056–64; 5. Mathieu C et al. *Diabetes Obes Metab* 2014;16:636–644; 6. Rosenstock J *et al*. *Diabetes Care* 2014;37:2317–2325; 7. Diamant M *et al*. *Diabetes Care* 2014;37:2763–2773

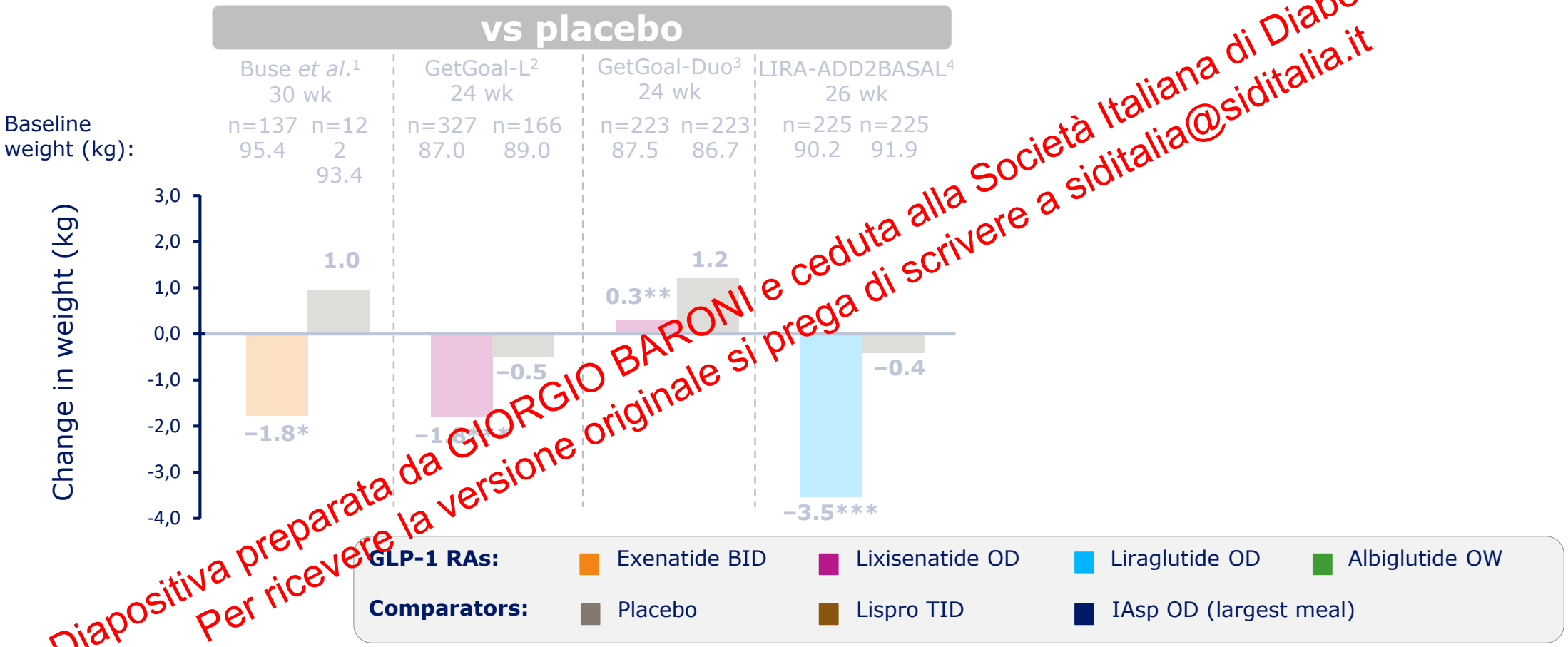
Addition of GLP-1 RA to basal insulin
Change in HbA_{1c}



Treatment difference for GLP-1 vs comparator: *p<0.005; **p<0.001; ***p<0.0001; †Model-adjusted change from baseline, p=NS
BID, twice daily; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; IAsp, insulin aspart; NS, not significant; OD, once daily; OW, once weekly; TID, three times per day

1. Buse JB *et al*. *Ann Intern Med* 2011;154:103–112; 2. Riddle MC *et al*. *Diabetes Care* 2013;36:2489–2496; 3. Riddle MC *et al*. *Diabetes Care* 2013;36:2497–2503; 4. Ahmann AJ *et al*. *Diabetes Obes Metab* 2015;17:1056–64; 5. Mathieu C *et al*. *Diabetes Obes Metab* 2014;16:636–644; 6. Rosenstock J *et al*. *Diabetes Care* 2014;37:2317–2325; 7. Diamant M *et al*. *Diabetes Care* 2014;37:2763–2773

Addition of GLP-1 RA to basal insulin
Change in body weight



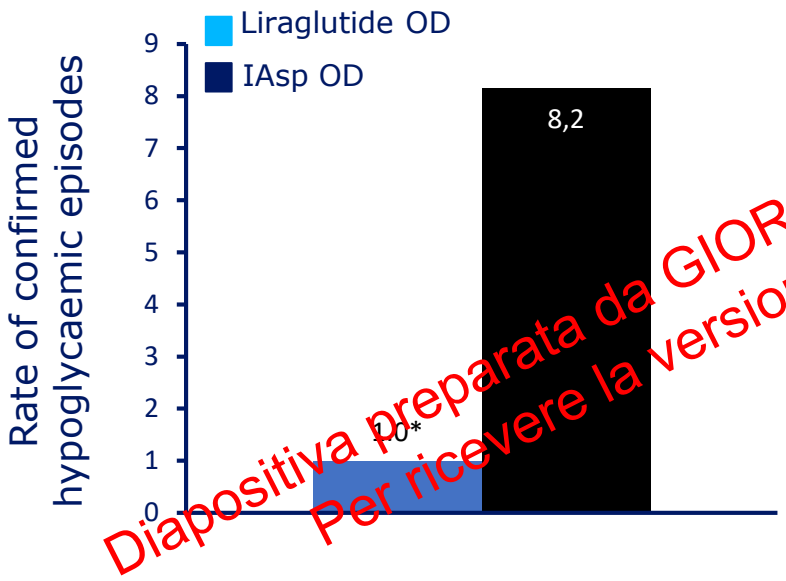
Treatment difference for GLP-1 vs comparator: *p<0.001; **p=0.0012; ***p<0.0001; †Model-adjusted change from baseline
BID, twice daily; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IAsp, insulin aspart; OD, once daily; OW, once weekly; TID, three times per day

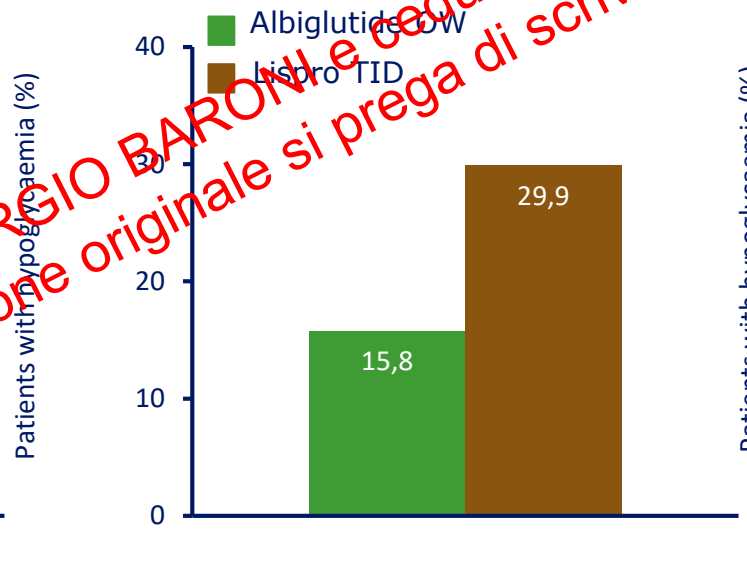
1. Buse JB *et al*. *Ann Intern Med* 2011;154:103–112; 2. Riddle MC *et al*. *Diabetes Care* 2013;36:2489–2496; 3. Riddle MC *et al*. *Diabetes Care* 2013;36:2497–2503; 4. Ahmann AJ *et al*. *Diabetes Obes Metab* 2015;17:1056–64; 5. Mathieu C *et al*. *Diabetes Obes Metab* 2014;16:636–644; 6. Rosenstock J *et al*. *Diabetes Care* 2014;37:2317–2325; 7. Diamant M *et al*. *Diabetes Care* 2014;37:2763–2773

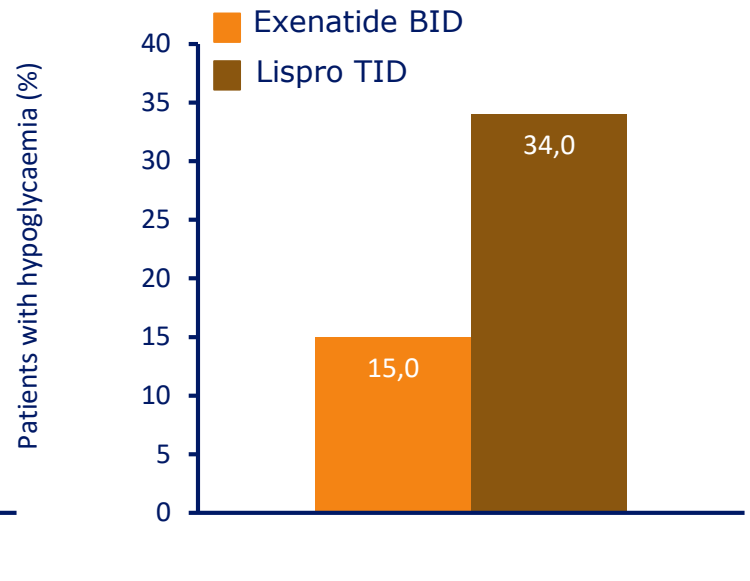
GLP-1 RA vs. bolus insulin added to basal insulin

Hypoglycaemia

	LIRA ADD-ON[1] 26 wk		HARMONY-6[2] 26 wk		Diamant *et al.*[3] 30 wk	
Baseline HbA_{1c} (%):	n=87 7.7	n=86 7.7	n=285 8.5	n=281 8.4	n=247 8.3	n=263 8.2







*p<0.0001

GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; IAsp, insulin aspart; OD, once daily; OW, once weekly; PYE, patient-years of exposure; TID, three times per day

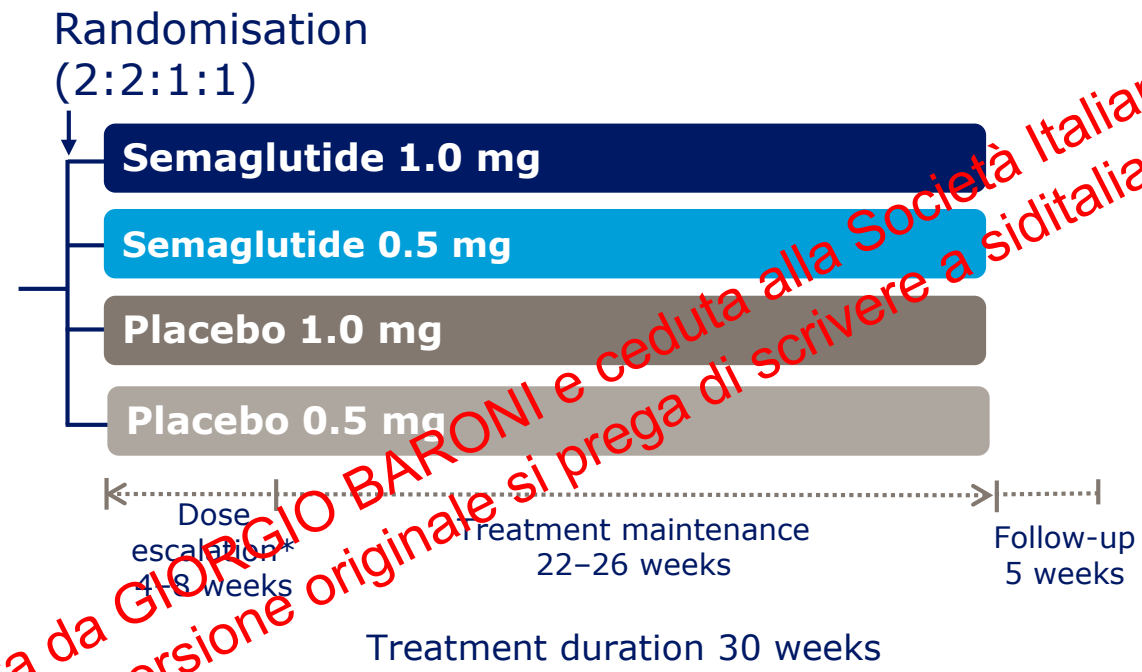
1. Mathieu C *et al*. *Diabetes Obes Metab* 2014;16:636–644; 2. Rosenstock J *et al*. *Diabetes Care* 2014;37:2317–2325; 3. Diamant M *et al*. *Diabetes Care* 2014;37:2763–2773

Semaglutide add-on to basal insulin: results from SUSTAIN 5

Trial design

Inclusion criteria

- Age ≥18 years
- HbA_{1c} 7.0–10.0%
- Stable treatment with basal insulin alone or in combination with metformin
- eGFR ≥30 mL/min/1.73 m^2



Trial information

- Randomisation was stratified according to HbA_{1c} level at screening (≤8.0% or >8.0%) and use of metformin
- Subjects with HbA_{1c} ≤8.0% at screening should have the insulin dose reduced by 20% at start of trial

*Dose escalation from starting dose of 0.25 mg, dose doubled every four weeks until trial maintenance dose achieved.

eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; T2D, type 2 diabetes; SMPG, self-measured plasma glucose.

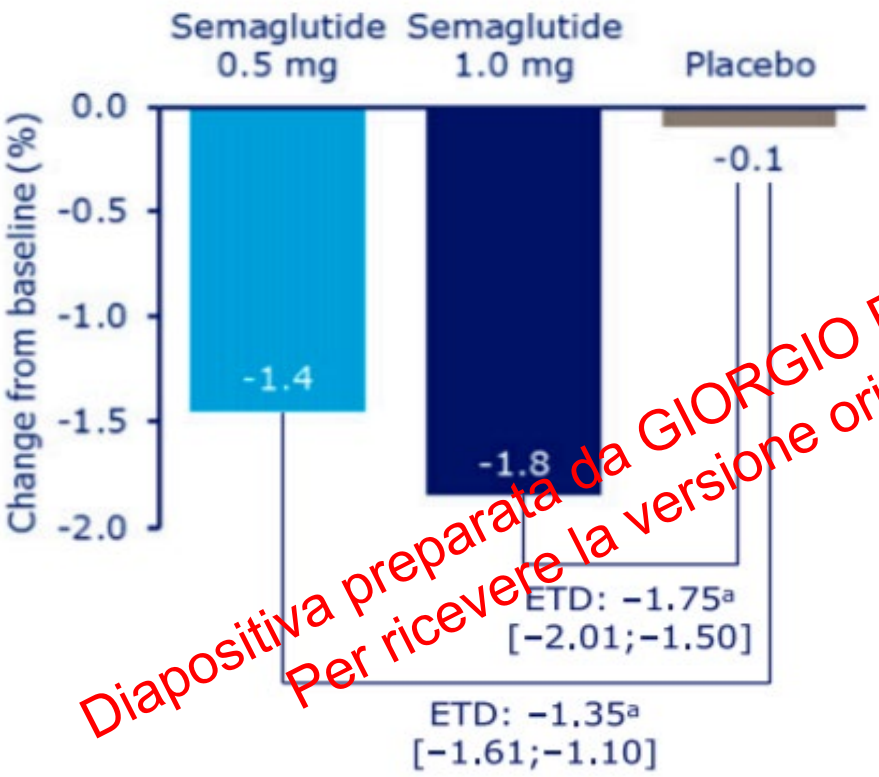
Rodbard HW, et al. *J Clin Endocrinol Metab.* 2018 Jun 1;103(6):2291-2301.

Key endpoints

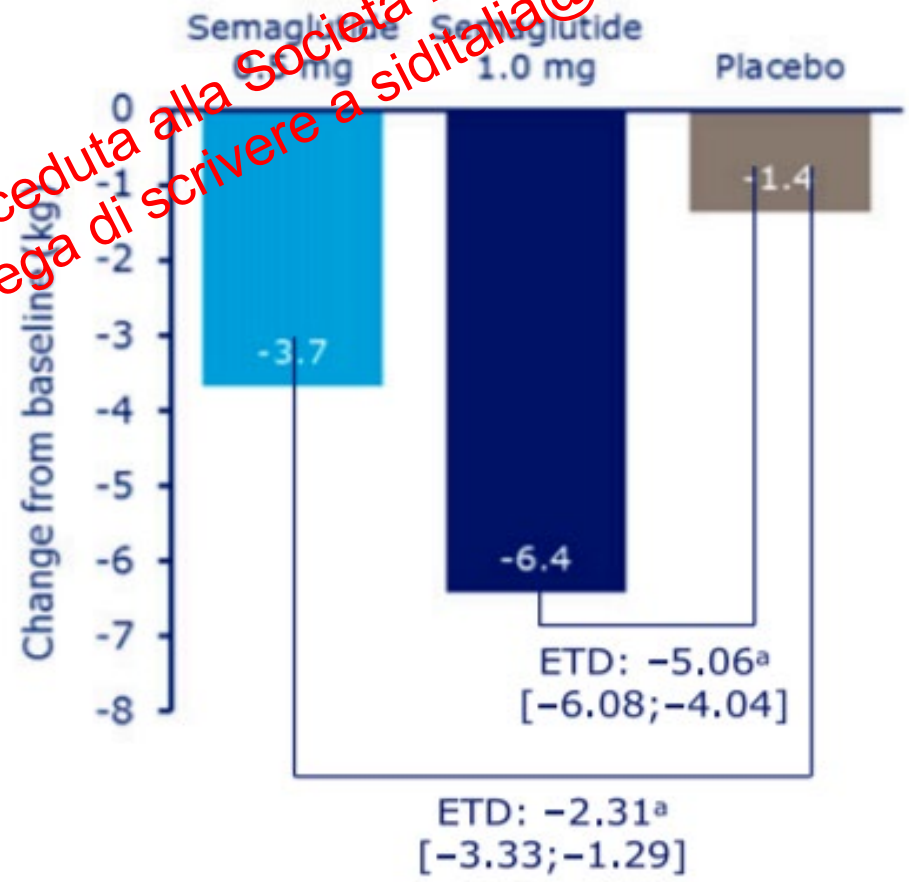
- Primary: change in HbA_{1c}
- Secondary: change in Body weight, FPG, SMPG, patient reported outcomes, beta-cell function, subjects achieving HbA_{1c} <7.0% and ≤6.5%; subjects achieving ≥5 and ≥10% weight loss

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

HbA1c



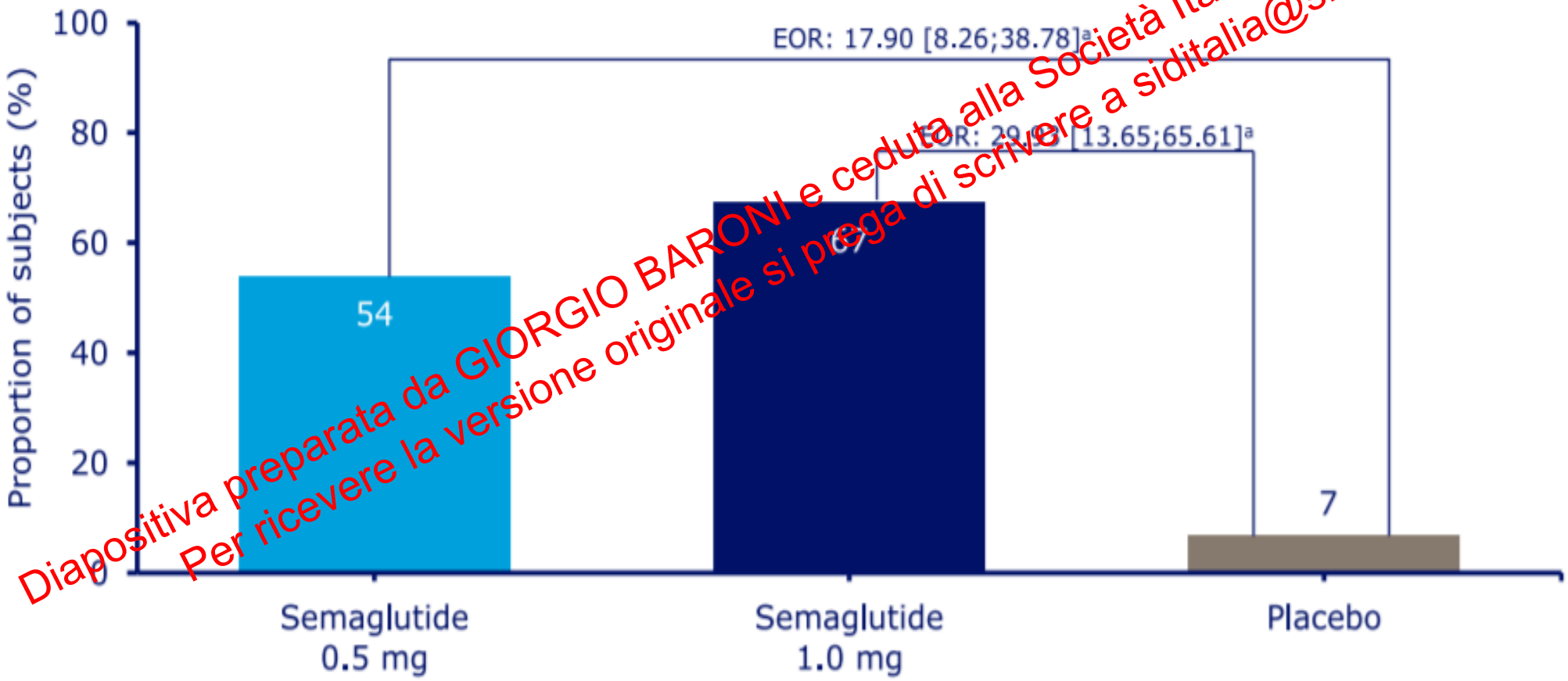
Peso



Rodbard HW, et al. *J Clin Endocrinol Metab.* 2018 Jun 1;103(6):2291-2301.

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

Patients achieving the composite endpoint target of HbA1c ,7.0% without severe or blood glucose–confirmed symptomatic hypoglycemia and with no weight gain

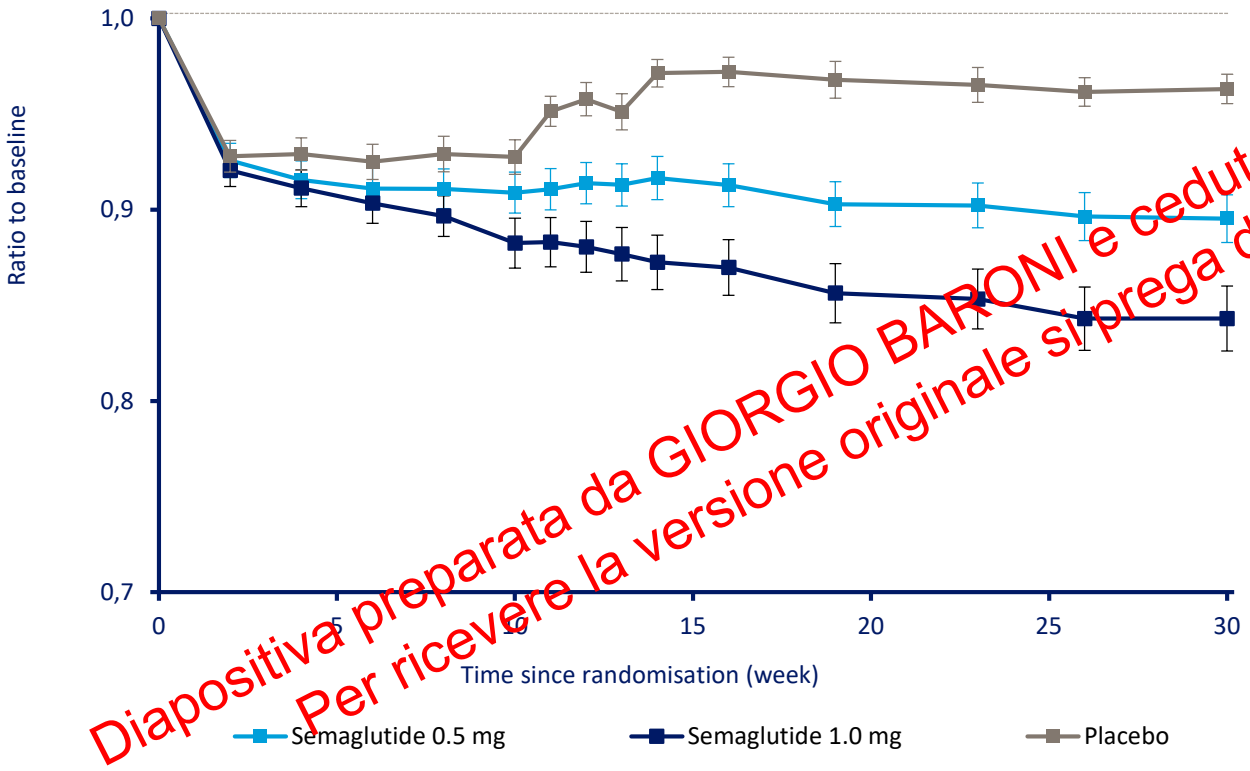


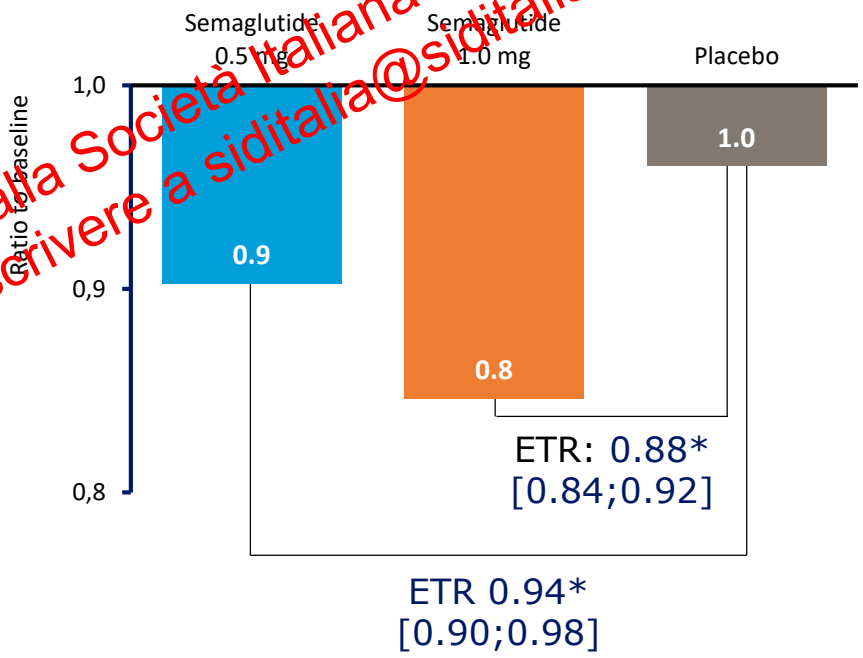
Rodbard HW, et al. *J Clin Endocrinol Metab.* 2018 Jun 1;103(6):2291-2301.

Insulin dose

OBSERVED RATIO TO BASELINE BY WEEK

Overall mean insulin dose at baseline: 37.7 IU/day





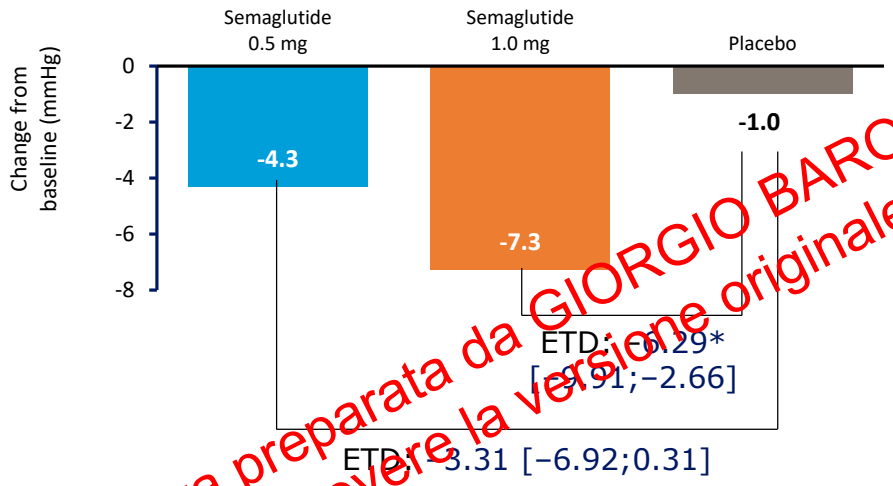
Indicates significance (p-value <0.005). Values are observed means (+/- standard errors) from a mixed model for repeated measurements analysis using 'on-treatment without rescue medication' data from subjects in the full analysis set. Dotted line is the overall mean value at baseline.
ETR, estimated treatment ratio.

Blood pressure

ESTIMATED MEAN BY WEEK AND CHANGE FROM BASELINE AT WEEK 30

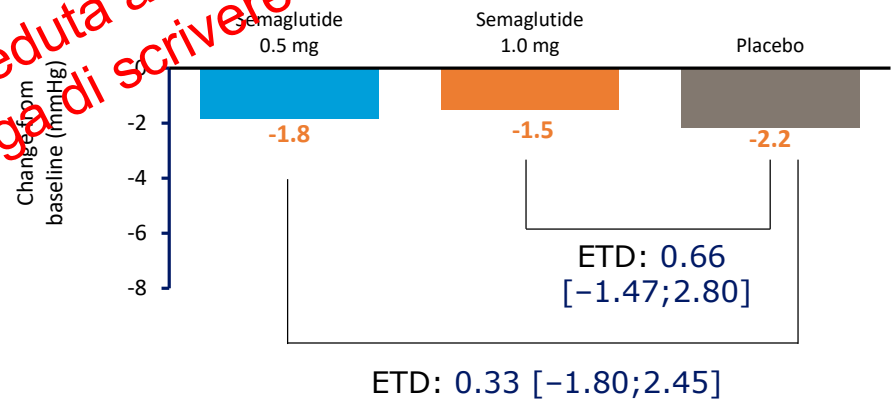
Systolic BP

Overall mean at baseline: 134.8 mmHg



Diastolic BP

Overall mean at baseline: 79.0 mmHg



*Indicates significance (p-value <0.001). Values are estimated means (+/- standard errors) from a mixed model for repeated measurements analysis using 'on-treatment without rescue medication' data from subjects in the full analysis set. Dotted line is the overall mean value at baseline.

BP, blood pressure; ETD, estimated treatment difference.

Rodbard HW, et al. *J Clin Endocrinol Metab.* 2018 Jun 1;103(6):2291-2301.

Insulina Basale e GLP-1 RA

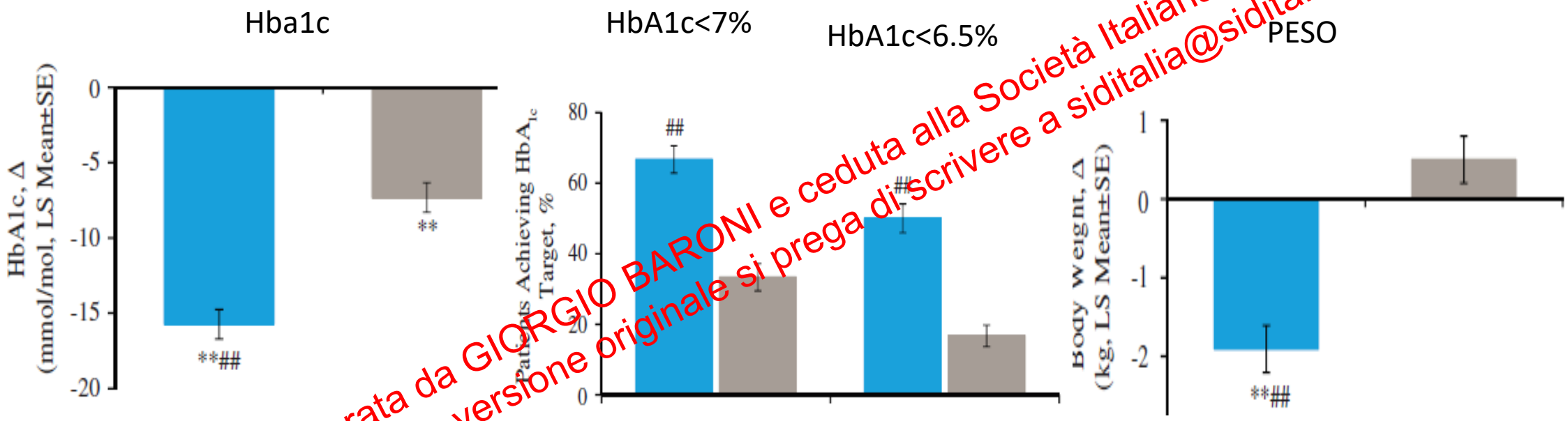
Combinazioni non-fisse

- Insulina basale (glarg o deglud) +
  - Liraglutide
  - Lixisenatide
  - Dulaglutide
  - Albiglutide
  - Exenatide Ow

Combinazioni fisse

- Degludec + Liraglutide: IDegLira
- Glargine + Lixisenatide: IGlarLixi

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)



Dulaglutide

Placebo

The incidence of total hypoglycaemia was similar between groups (dulaglutide/glargine, n = 82 [54.7%]; placebo/glargine, n = 76[50.7%]).

Pozzilli P et al. DOM 2017

Insulina Basale e GLP-1 RA

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  - Lixisenatide
  - Dulaglutide
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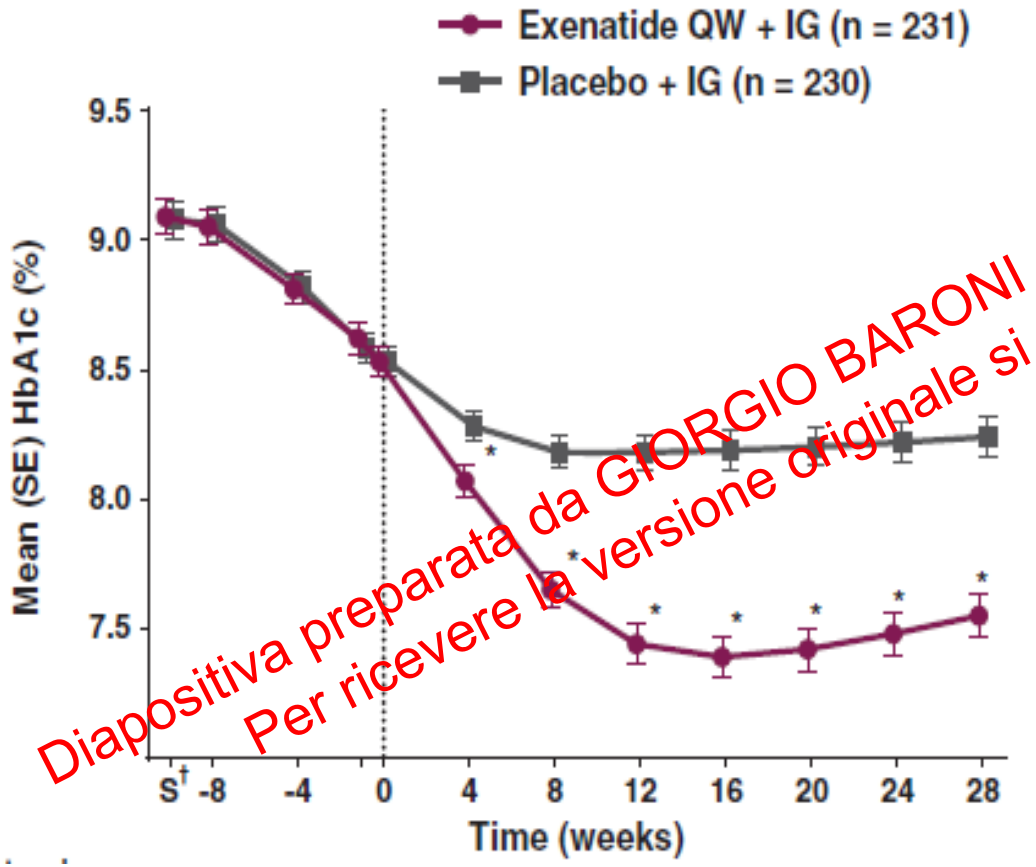
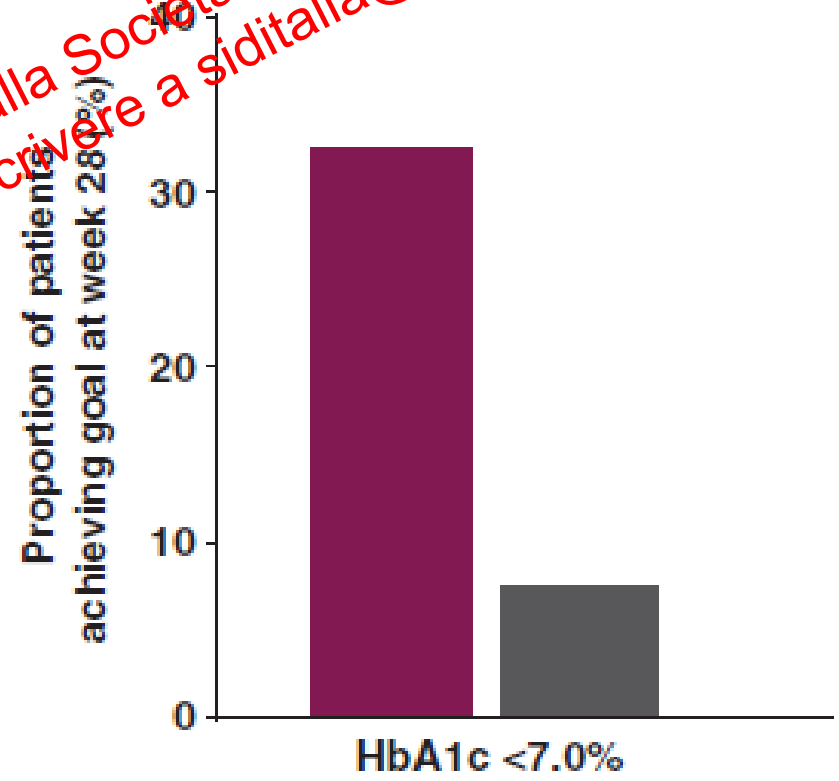
Combinazioni fisse

- Degludec + Liraglutide: IDegLira
- Glargine + Lixisenatide: IGlarLixi

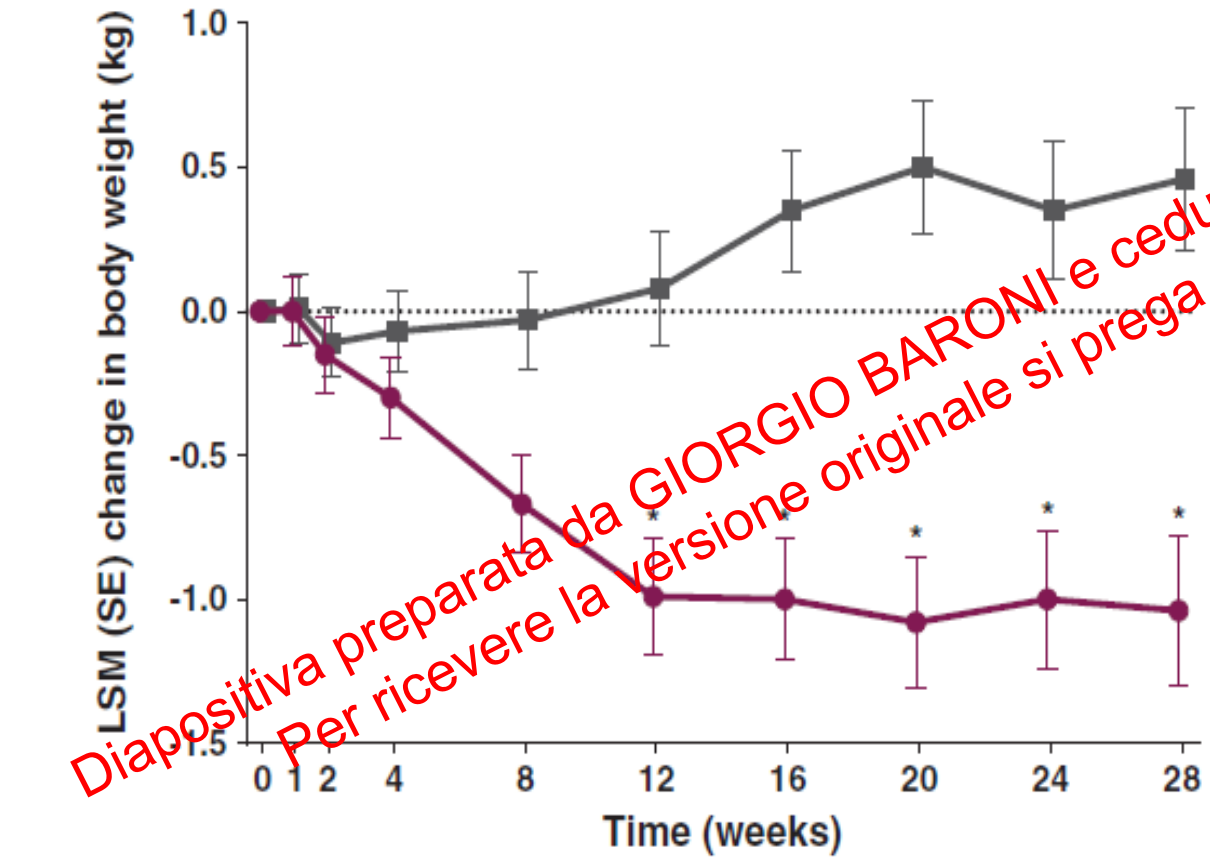
Effect of exenatide QW or placebo, both added to titrated insulin glargine, in uncontrolled type 2 diabetes: The DURATION-7 randomized study



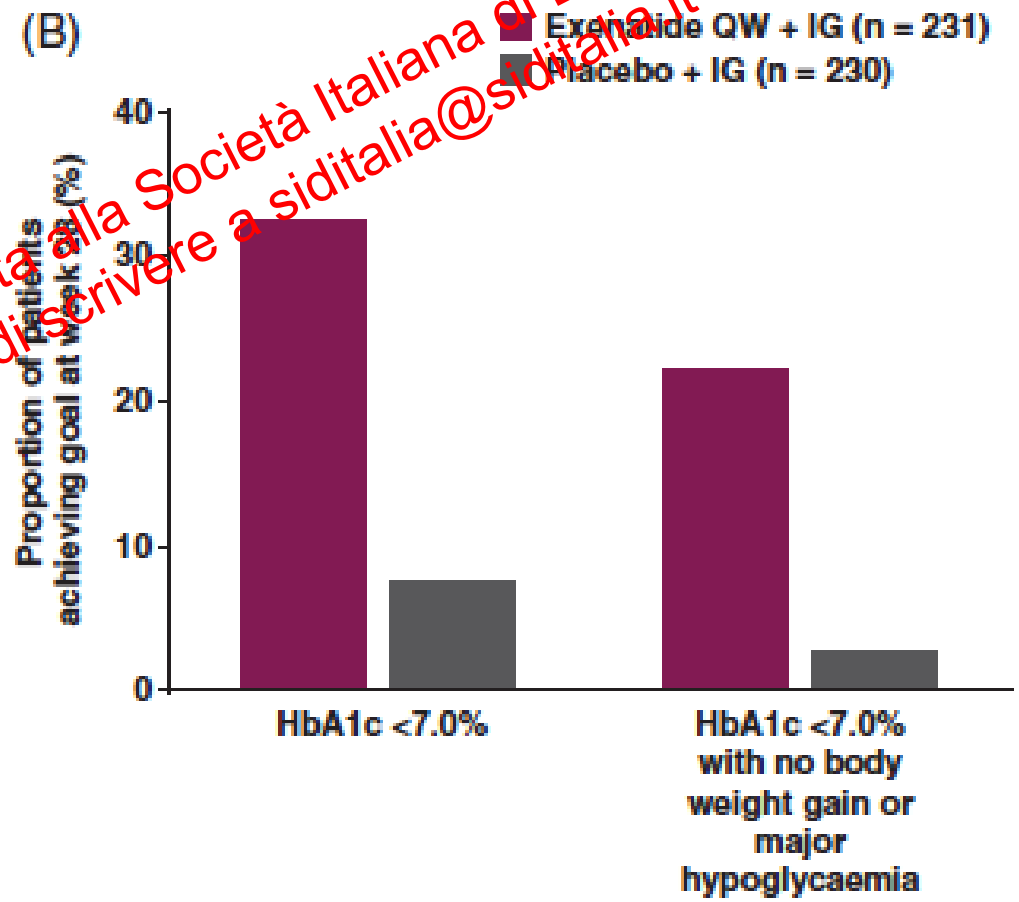


Diabetes Obes Metab. 2018;**20**:1602–1614.

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



(B)



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

Insulina Basale e GLP-1 RA

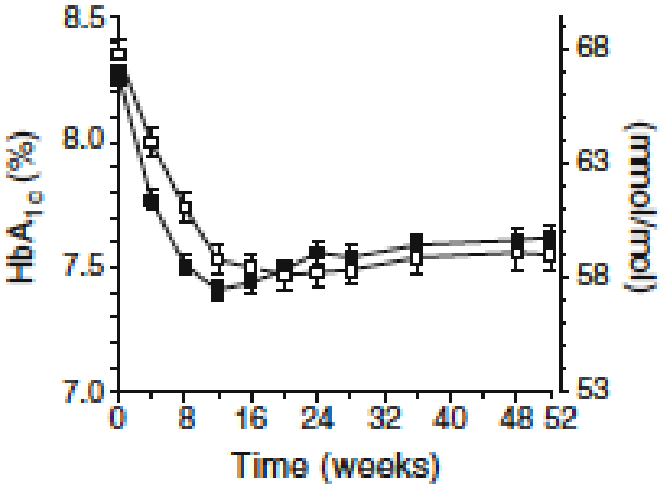
Combinazioni non-fisse

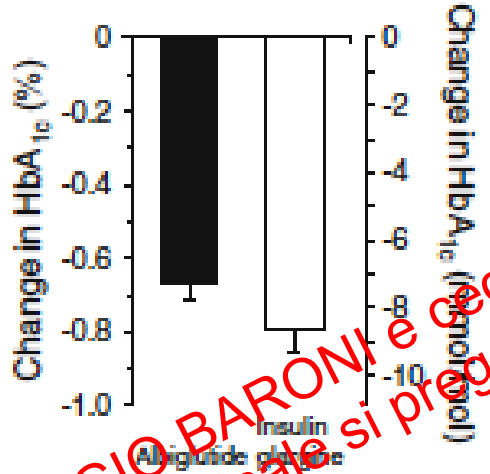
- Insulina basale (glarg o deglud) +
  - Liraglutide
  - Lixisenatide
  - Dulaglutide
  - Exenatide Ow
  - Albiglutide

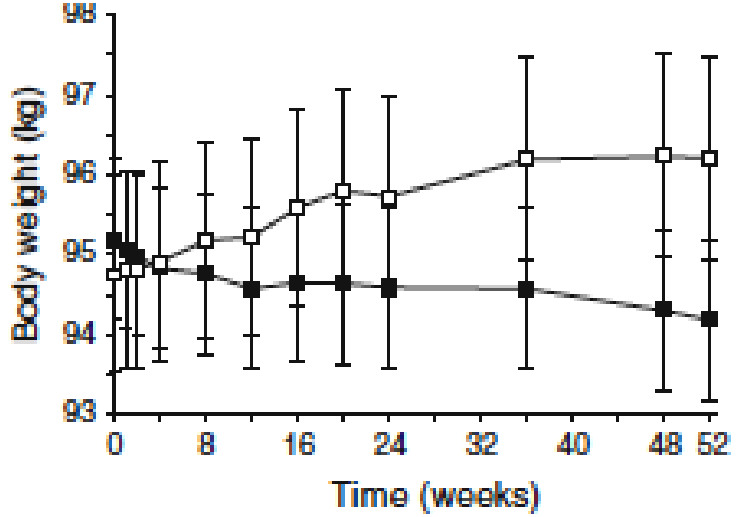
Combinazioni fisse

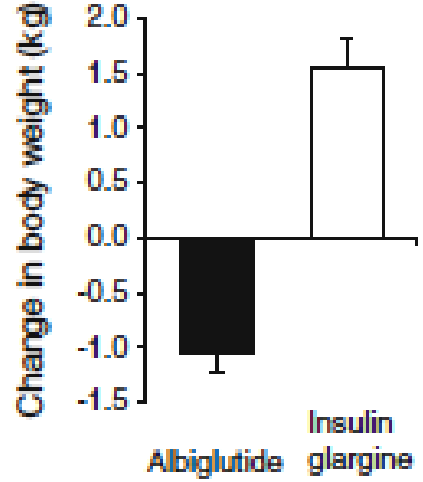
- Degludec + Liraglutide: IDegLira
- Glargine + Lixisenatide: IGlarLixi

HARMONY 4: randomised clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea









Diabetologia (2014) 57:2475–2484

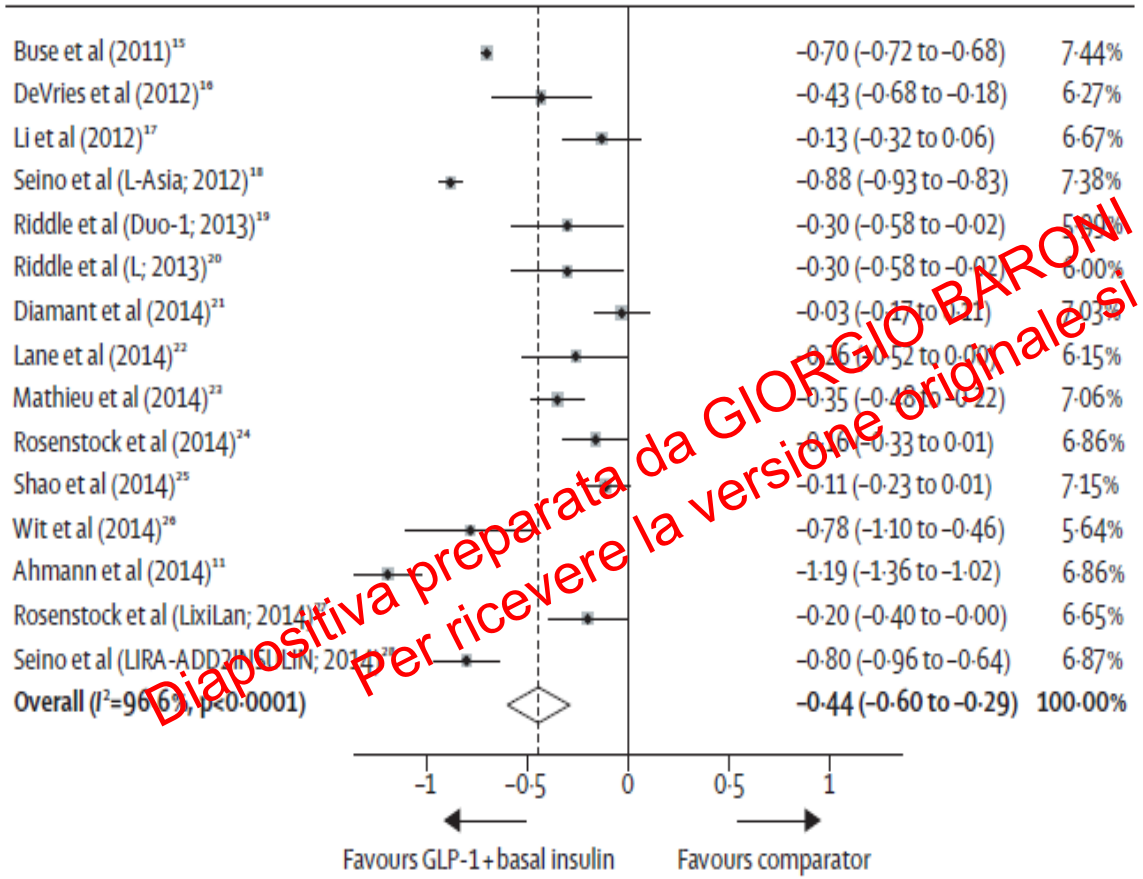
Le meta-analisi

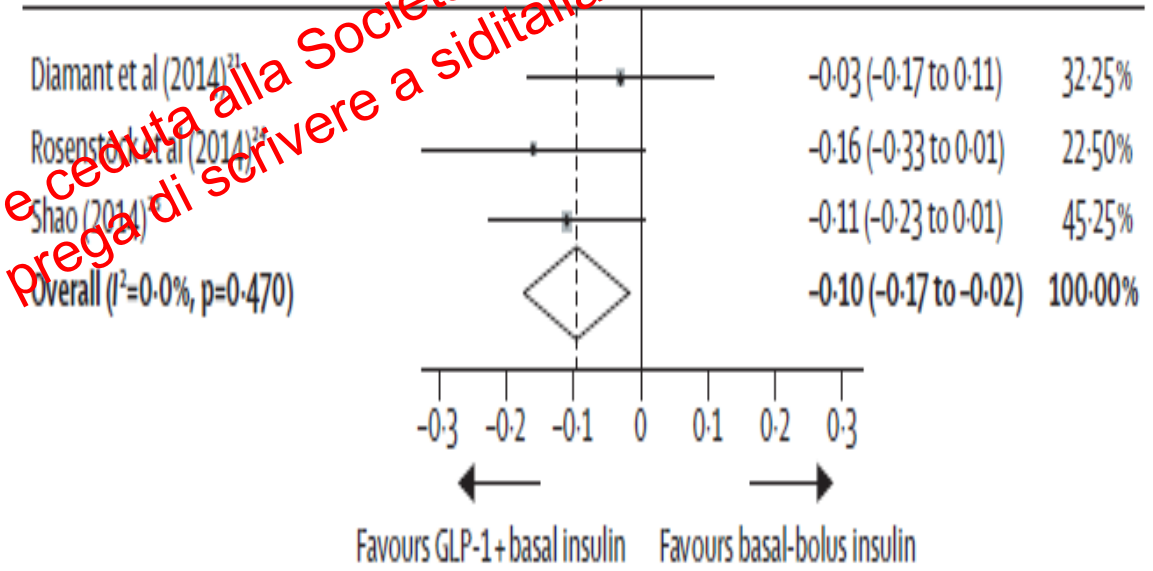
Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis

Conrad Eng, Caroline K Kramer*, Bernard Zinman, Ravi Retnakaran*

Lancet 2014; 384: 2228–34

HbA1c





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

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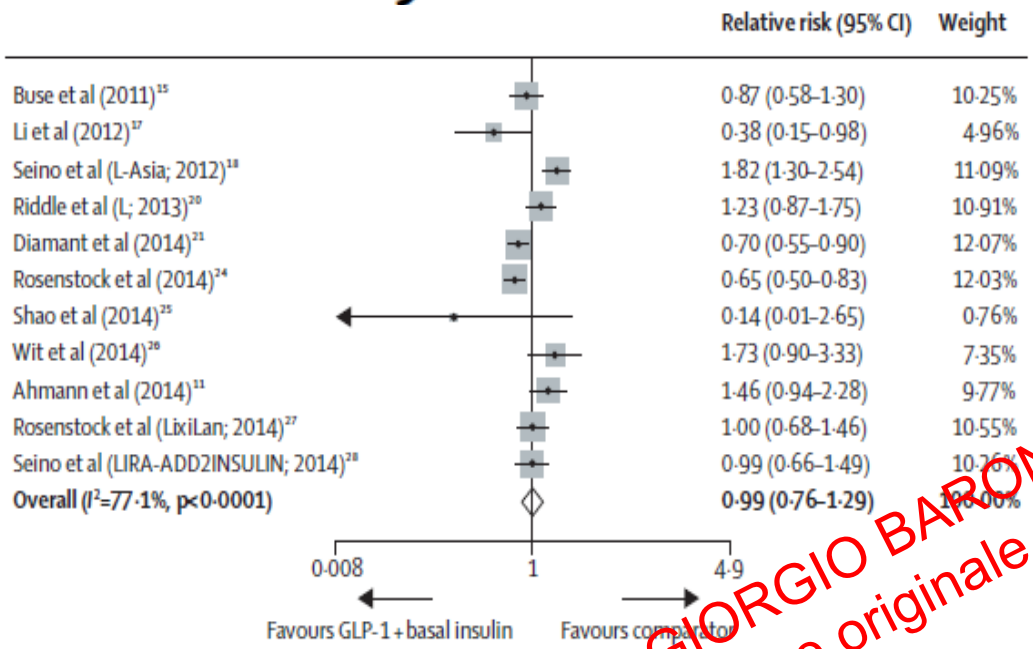
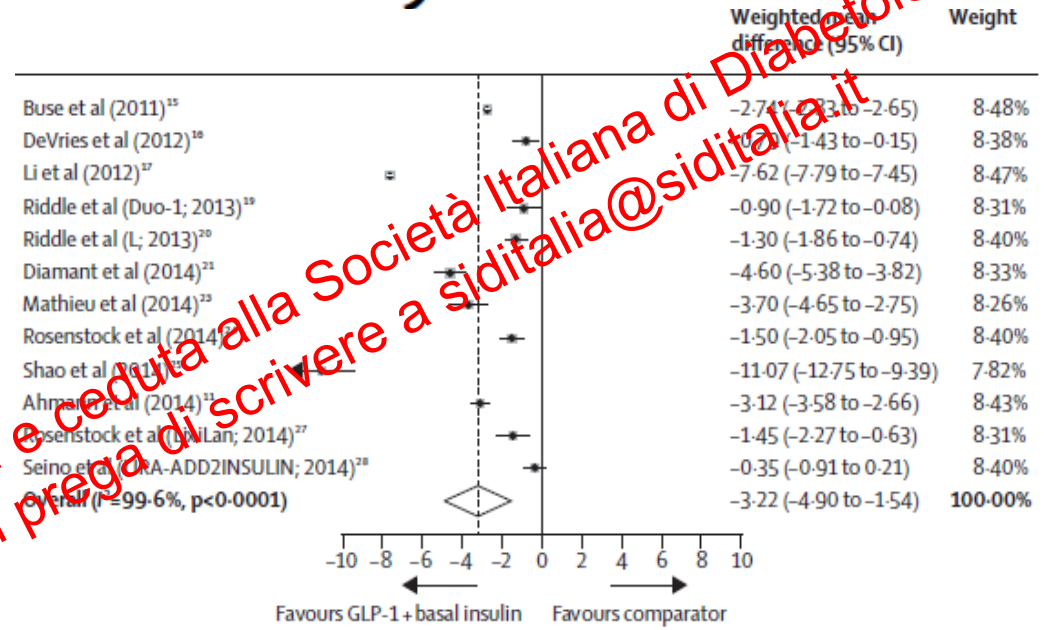
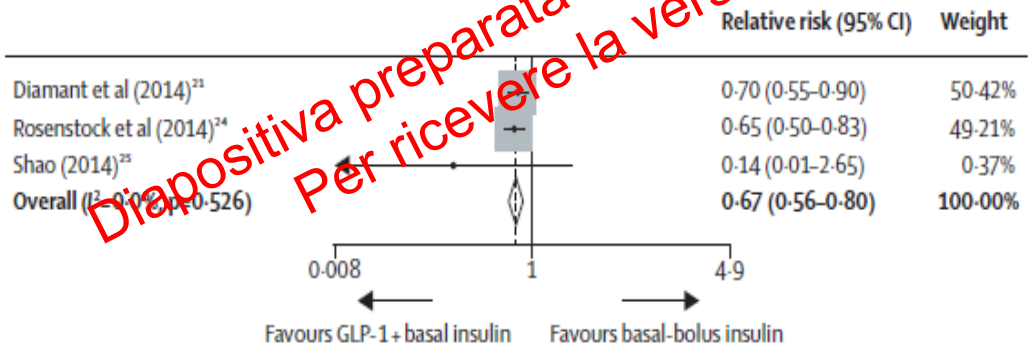
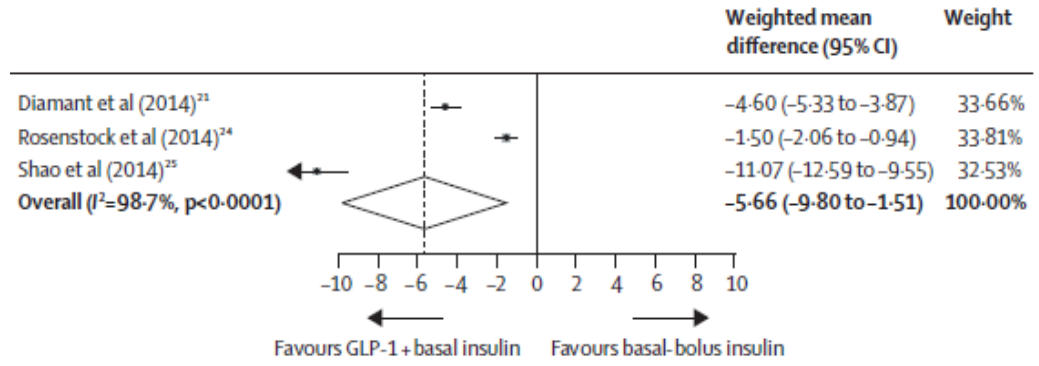








IPOGLICEMIA

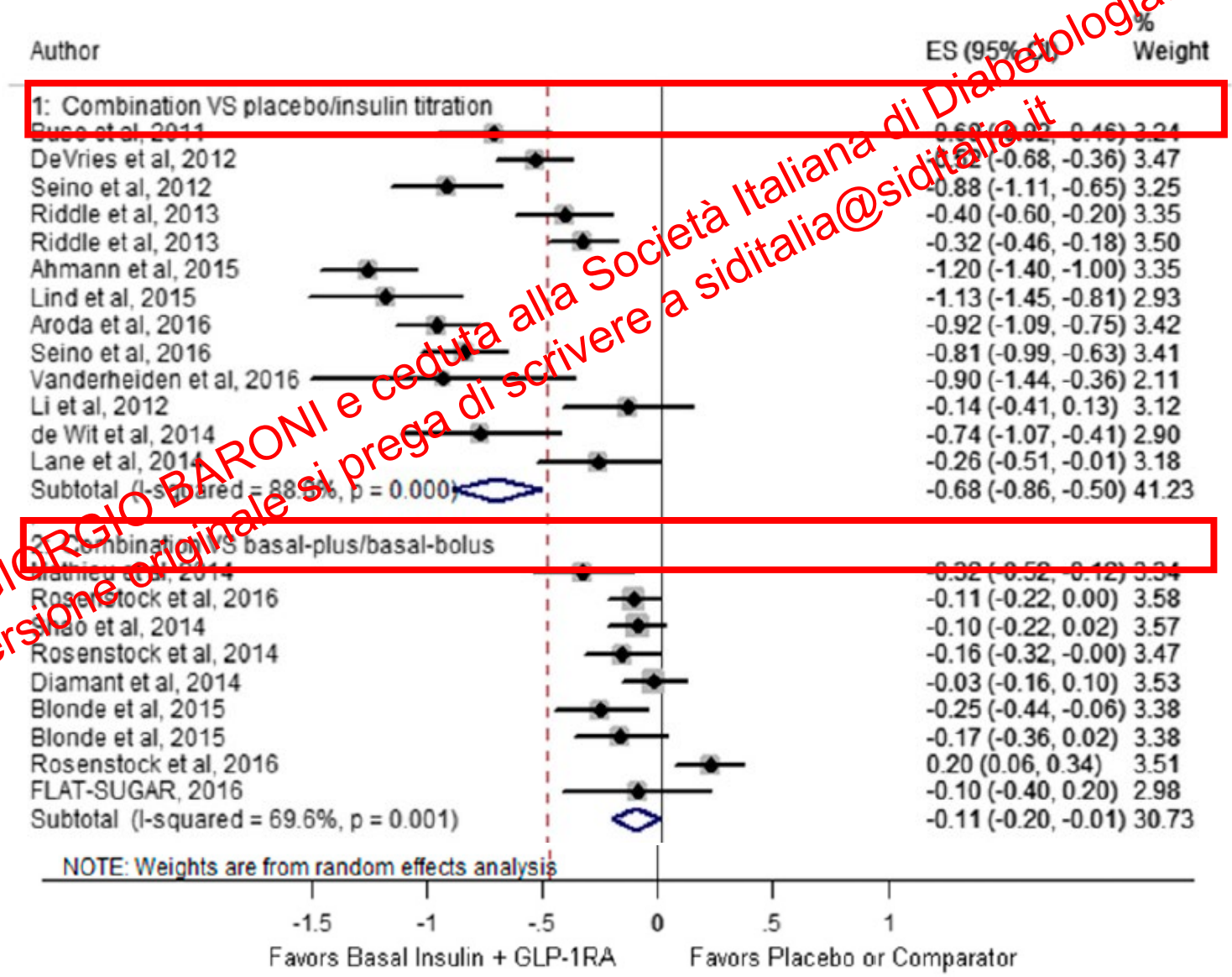
PESO

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]

HbA1c change



Insulina Basale e GLP-1 RA

Combinazioni non-fisse

- Insulina basale (glarg o deglud) +
  - Liraglutide
  - Lixisenatide
  - Dulaglutide
  - Albiglutide
  - Exenatide Ow

Combinazioni fisse

- Degludec + Liraglutide: IDegLira
- Glargine + Lixisenatide: IGlarLixi

Le formulazioni precostituite insulina basale-GLP-1 RA

1) Dovrebbero essere titolate tenendo conto della dose di insulina

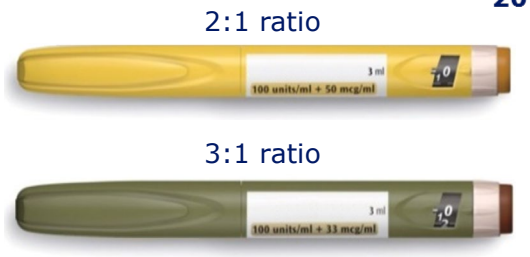
2) Dovrebbero essere titolate tenendo conto della dose di GLP-1 RA

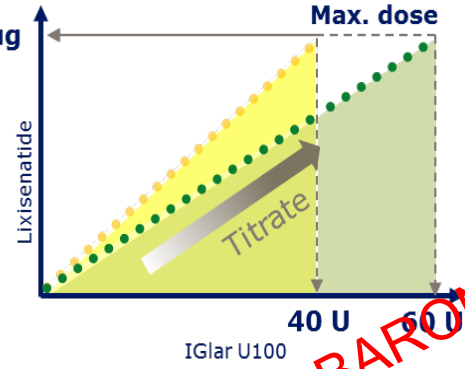
3) Non dovrebbero essere mai titolate

4) Non andrebbero mai sostituite alla terapia precedente

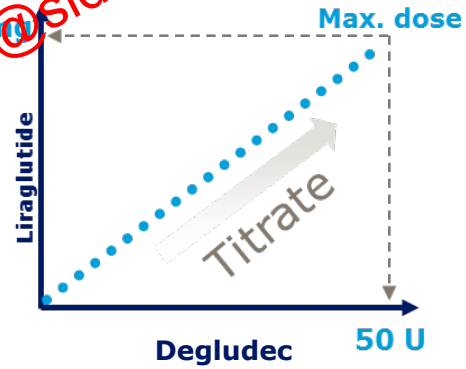
Administration in phase III trials

IGlarLixi





IDegLira



Two different ratios – two pens[1,2]

- Yellow pen/ pen A is used for total daily IGlar U100 doses of 10 to 40 U
- Green pen/ pen B for total daily doses of 41 to 60 U
- Patients using the yellow pen/ Pen A and requiring >40 U, can switch to the green pen/ Pen B (41 to 60 U)
- Switching from Pen A to Pen B entails a 35% reduction in lixisenatide dose at 40 U insulin

One ratio – One pen[3]

- Titrated in dose steps where one dose step contains 1 U of Degludec and 0.036 mg of liraglutide (Some markets including US use units where 1U = 1 dose step)
- Maximum dose: 50 dose steps

For illustrative purposes only, not drawn to scale

IDegLira, insulin degludec/liraglutide; IGlarLixi, insulin glargine U100/lixisenatide; IGlar U100, insulin glargine U100; U, units

1. Rosenstock et al. *Diabetes Care*. 2016;39(9):1579-86; 2. Aroda et al. *Diabetes Care*. 2016;39(11):1972-1980; 3. Xultophy® Summary of Product Characteristics (SmPC), 2017

DUAL V

Study design

Subjects with T2D uncontrolled on basal insulin
(n=557)

- **IDegLira + metformin (n=278)**
- **IGlar U100 + metformin (n=279)**

IDegLira
Starting dose: 16 dose steps
Maximum dose: 50 dose steps

IGlar U100
Starting dose: Pre-trial dose
Maximum dose: None

Inclusion criteria

- T2D
- Metformin + IGlar U100 (20–50 U)
- HbA_{1c} 7.0–10.0%
- Age ≥18 years
- BMI ≤40 kg/m^2

Titration algorithm: IDegLira and IGlar U100

Mean fasting PG mg/dL (mmol/L)	Dose change dose steps or U
<72 (4.0)	–2
72–90 (4.0–5.0)	0
>90 (5.0)	+2

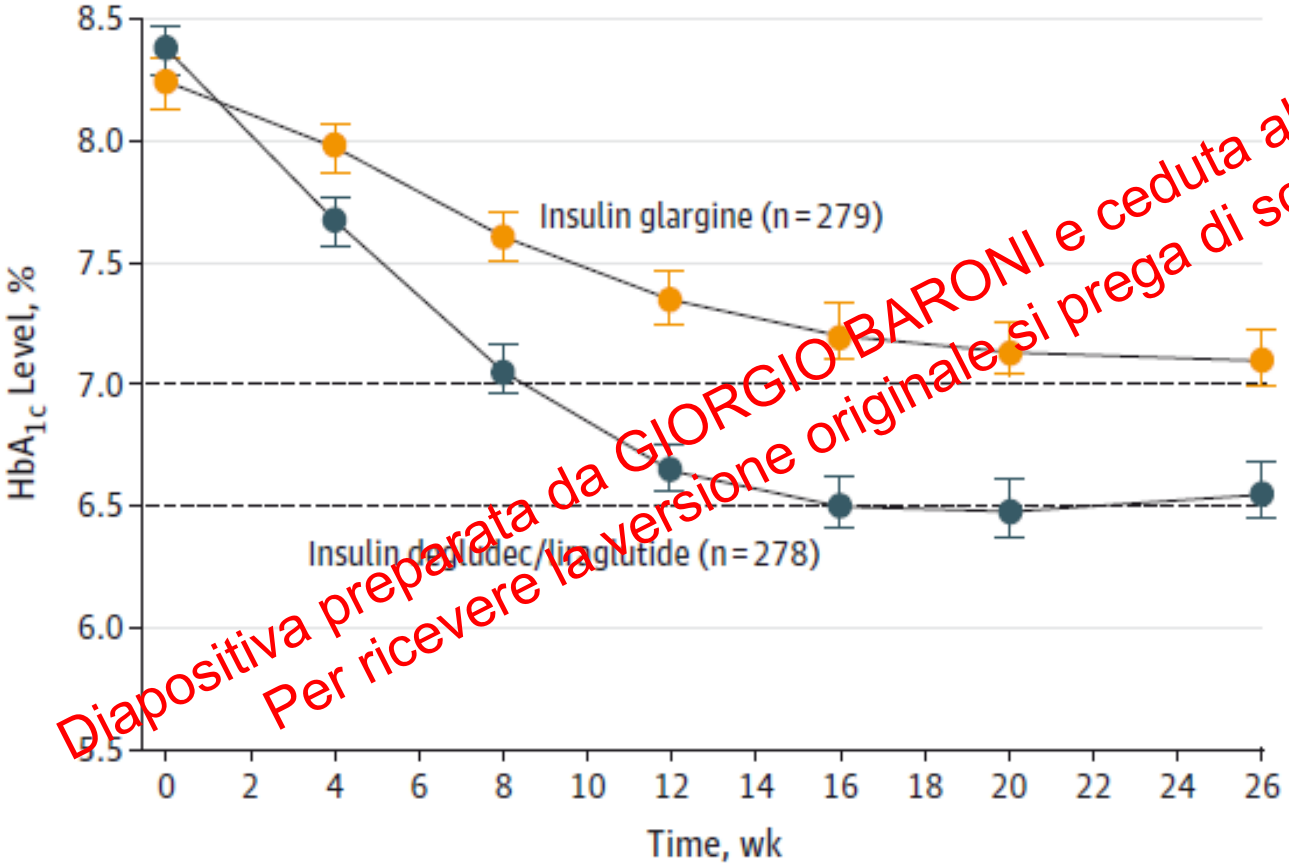
BMI, body mass index; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine U100; PG, plasma glucose; T2D, type 2 diabetes; U, units

Lingvay *et al. JAMA* 2016;315:898–907

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)

Lingvay et al. JAMA 2016;315:898–907

Original Investigation

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

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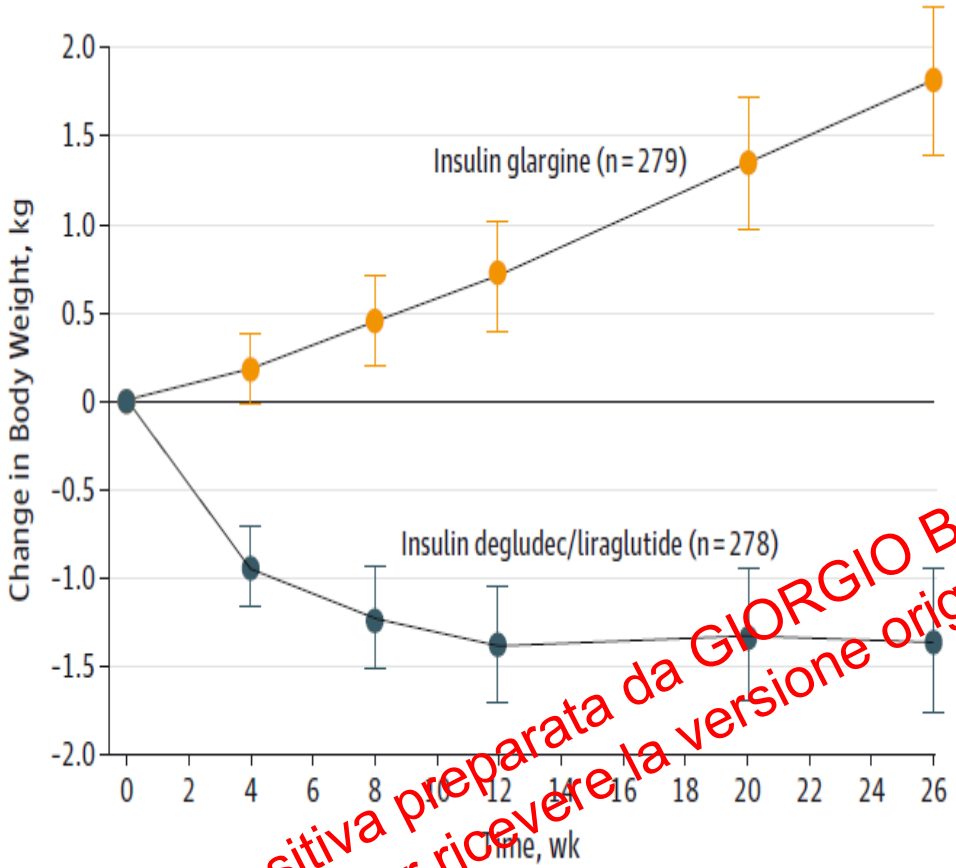
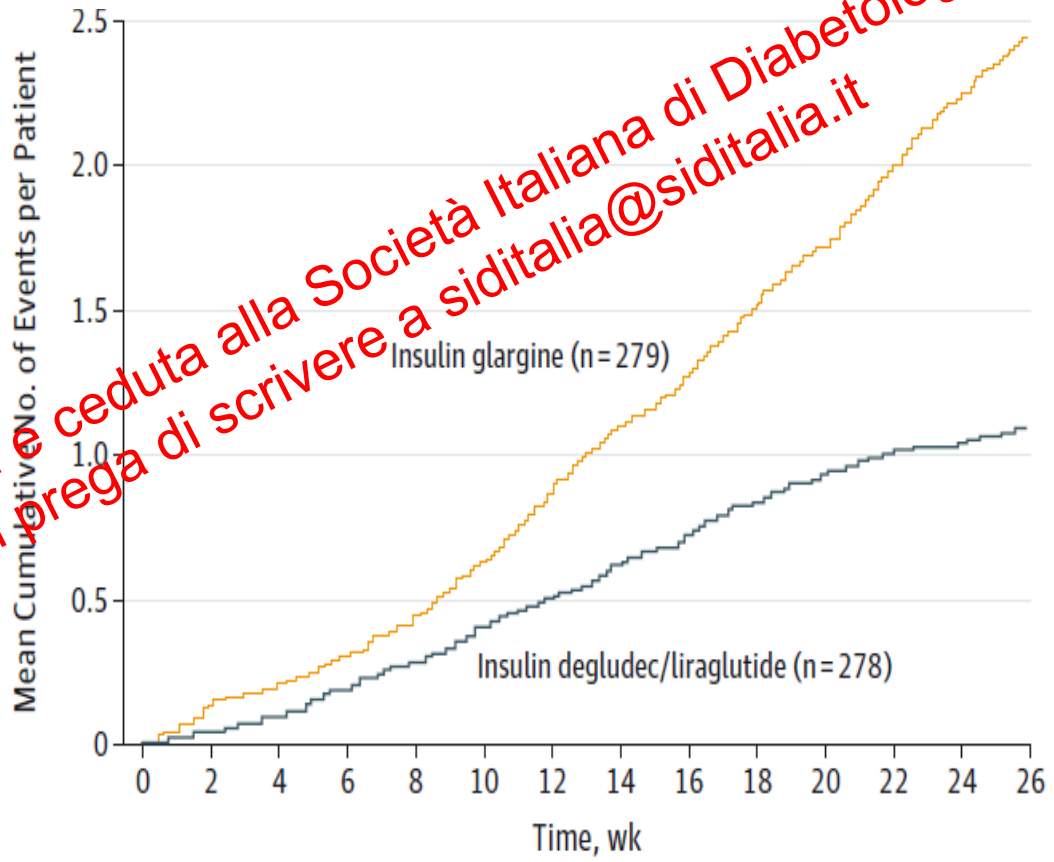




Body weight at week 26, kg	86.9	89.1
Change from baseline, body weight, kg (95% CI)	−1.4 (−1.8 to −1.0)	1.8 (1.4 to 2.2)

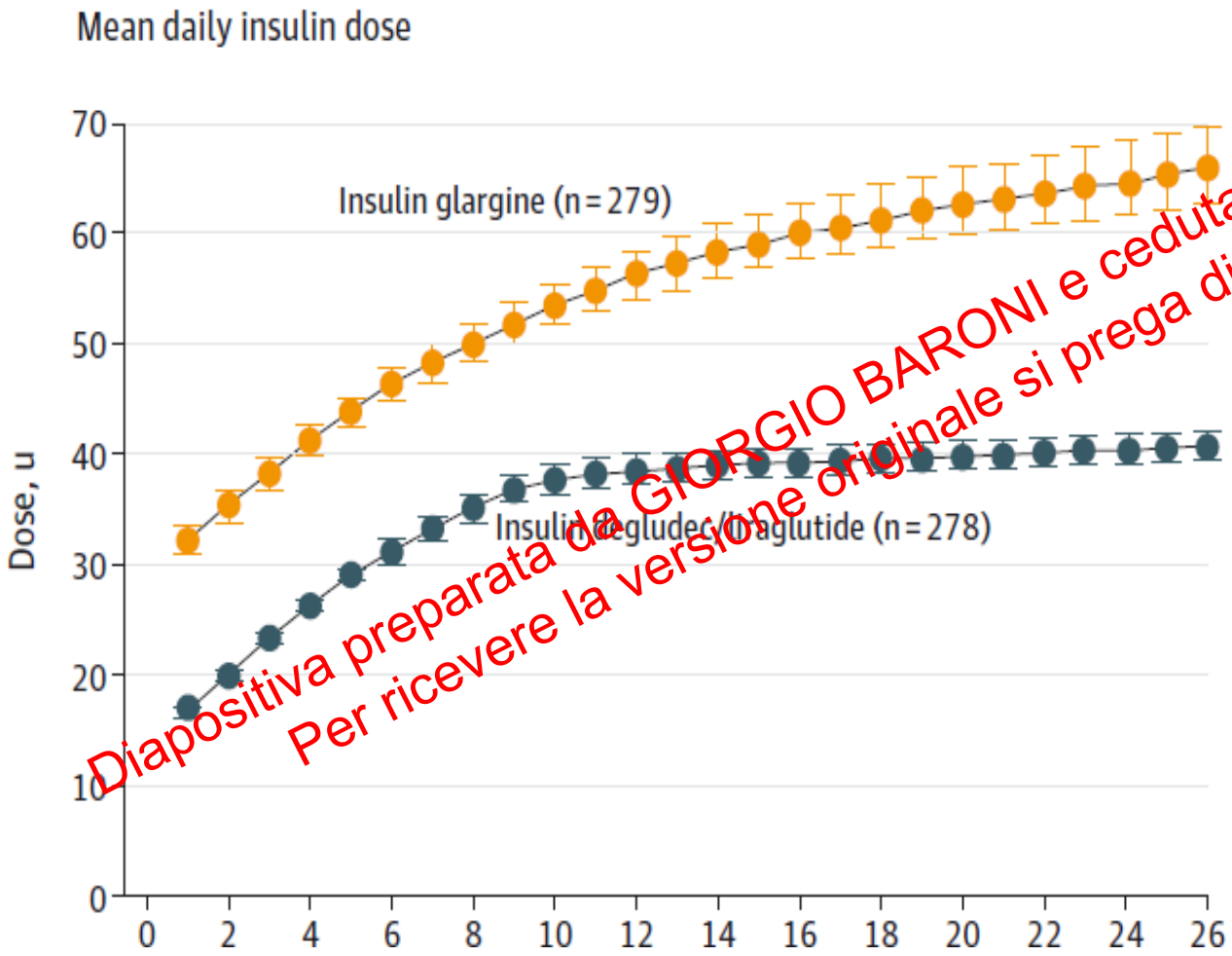
Total exposure, y	129.6	135.1
Rate of confirmed hypoglycemia, no. of events per PYE	2.23	5.05

Lingvay et al. JAMA 2016;315:898–907

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



-25.47 U
(95%CI, –28.90 to–22.05)

Lingvay et al. JAMA 2016;315:898–907

DUAL V: Summary

DUAL V[1]

IDegLira vs IGlar U100

HbA_{1c}	**Significant decrease** in HbA_{1c} (Baseline Δ: -1.81 vs -1.13 %*)
Insulin Dose	**Significantly lower** insulin dose (EOT: 41 vs 66 U*)
Weight	**Significant** weight difference (Baseline Δ: -1.4 vs +1.8 kg*)
Hypoglycaemia	**Significantly less** hypoglycaemia (RR: 0.43*)

*p< 0.001; **P<0.0001
EOT, end-of-trial;

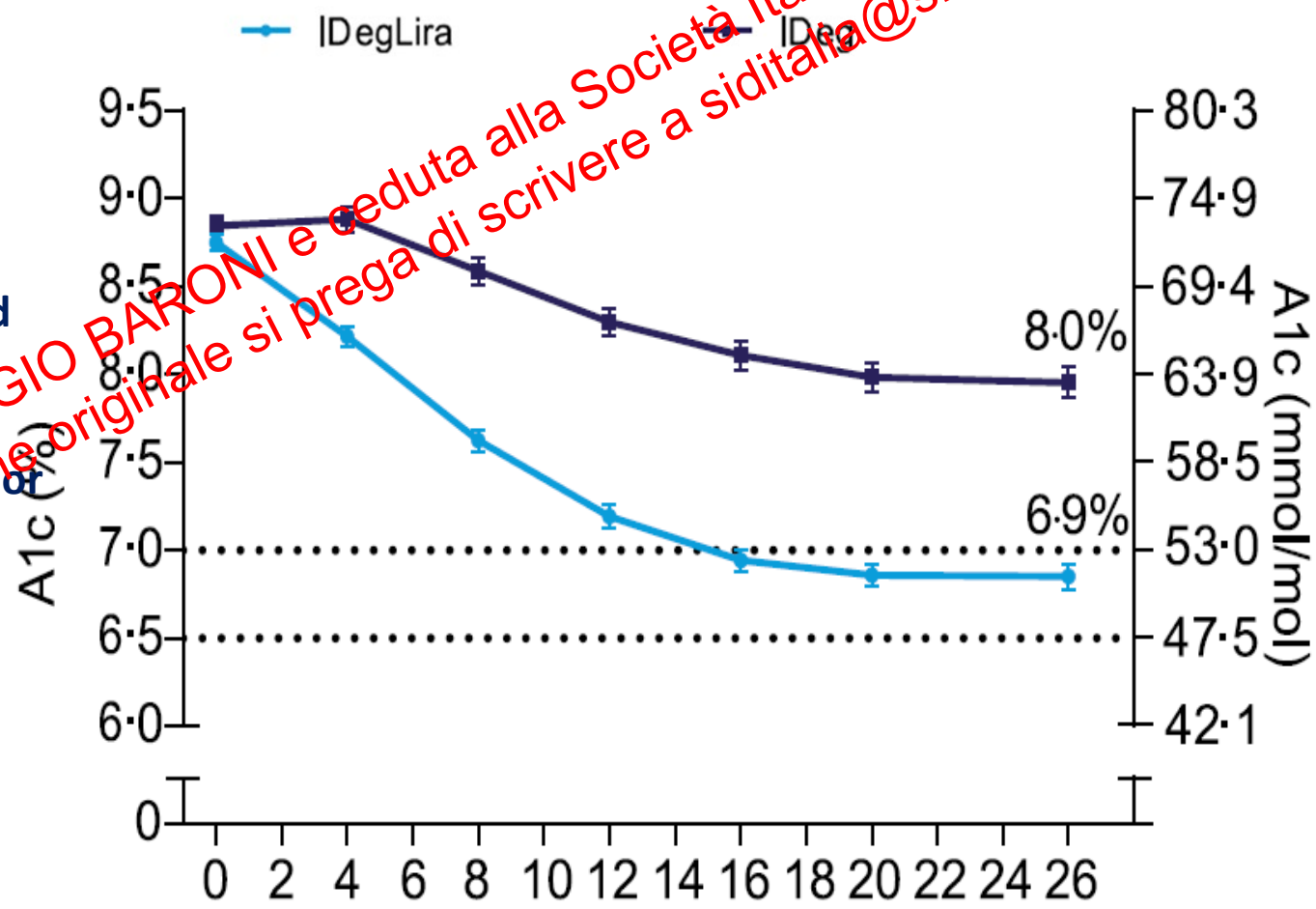
Lingvay *et al. JAMA* 2016;315:898-907; 2. Aroda *et al. Diabetes Care* 2016;39:1972–80

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

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)

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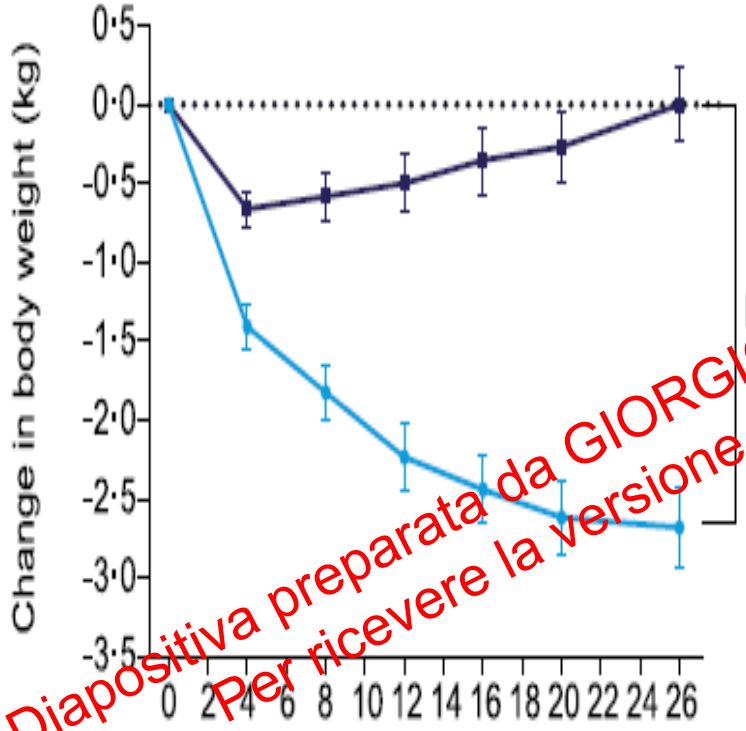
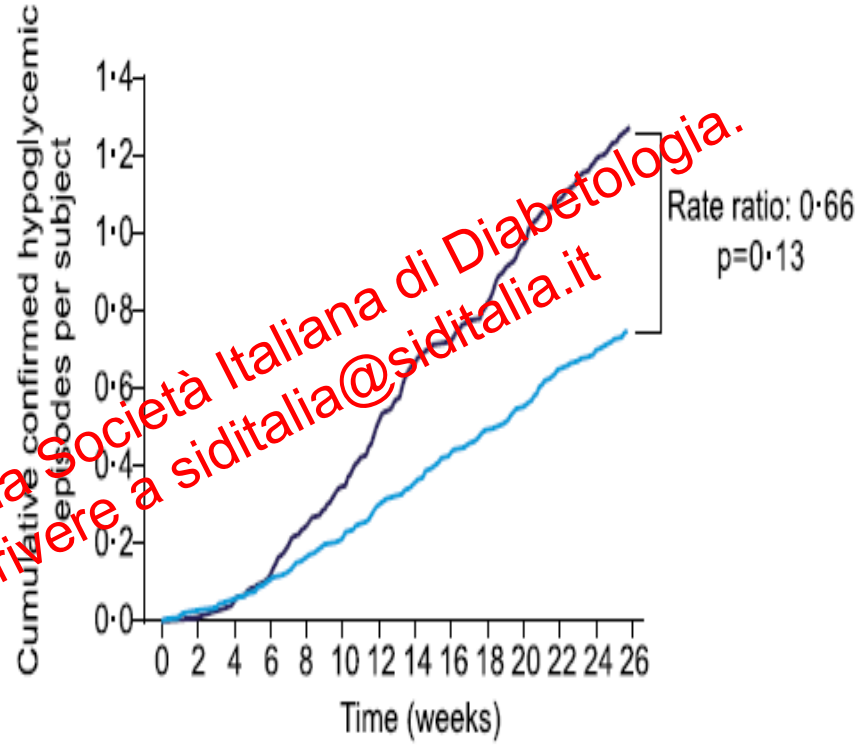
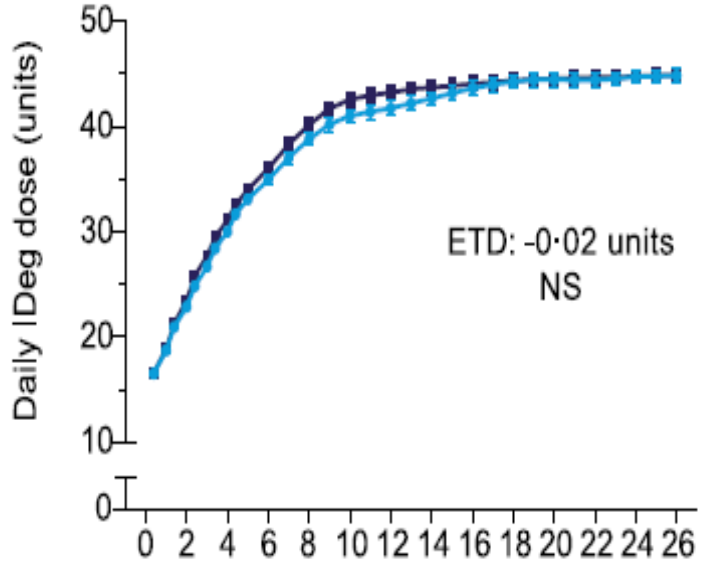
DUAL II







DUAL VII

Study design

Subjects with T2D uncontrolled on metformin and basal insulin
(N=506)

- **IDegLira + metformin**
- **Glargine U100 + IAsp (≤4 times) + metformin**

Uncontrolled on insulin

IDegLira
Starting dose: 16 dose steps
Maximum dose: 50 dose steps

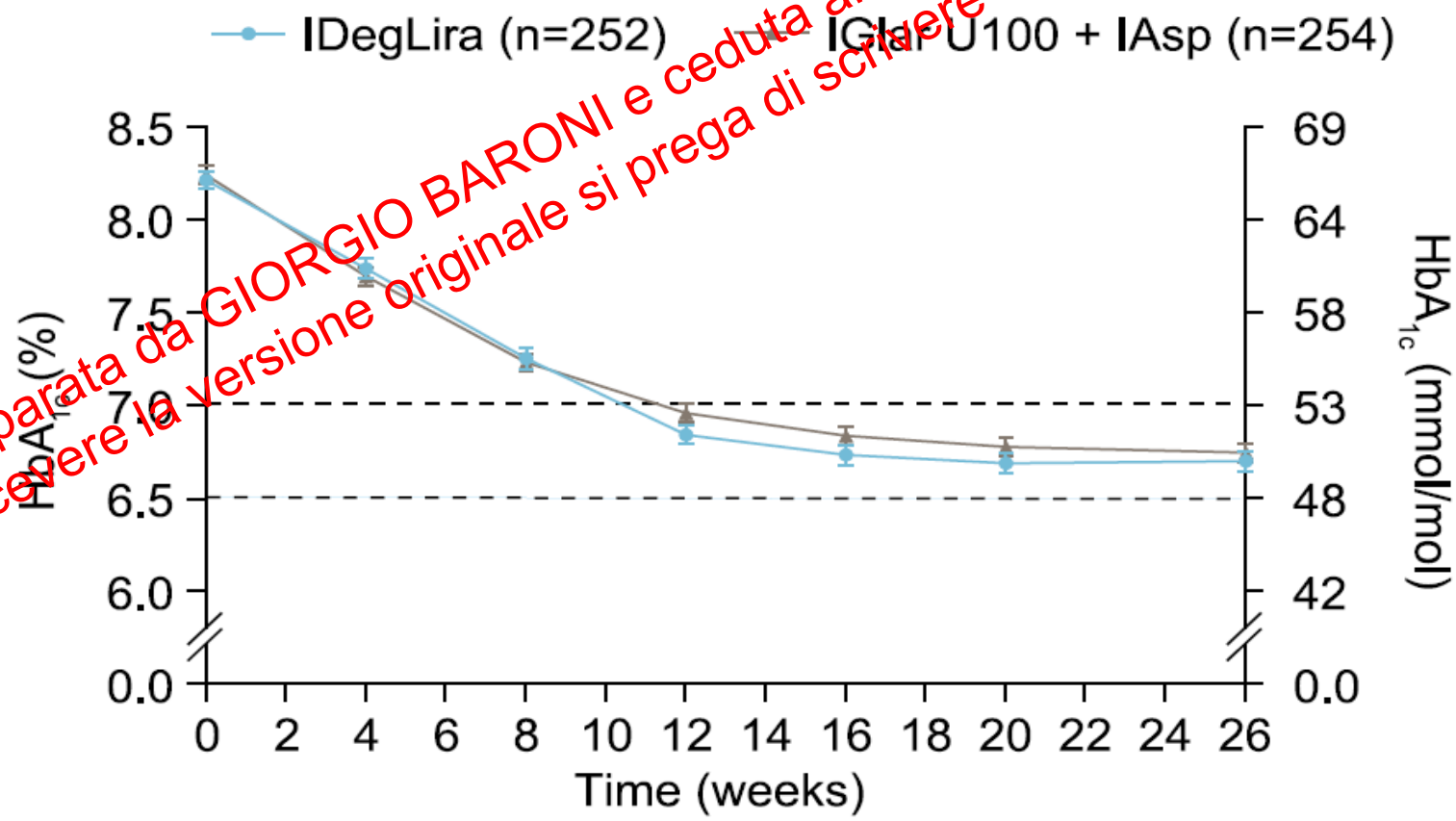
Glargine U100
Starting dose: Pre-trial dose
Maximum dose: None

IAsp
Starting dose: 4U
Maximum dose: None

1. Buse JB et al. Diabetes Care 2014;37: 2926-2933 2. Owens D et al. Diabetes and Primary Care 2004; 6(1): 8-16.; 3. National Institute for Clinical Excellence. Guidance on the use of long-acting insulin analogues for the treatment of diabetes – Insulin glargine. Technology Appraisal number 53. December, 2002.

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



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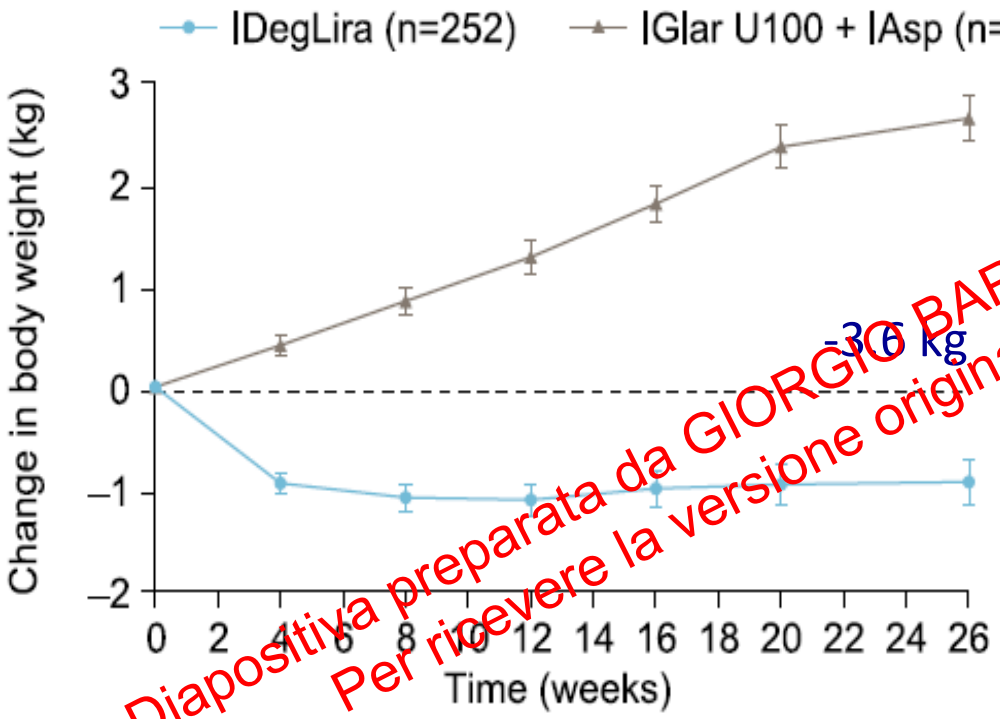
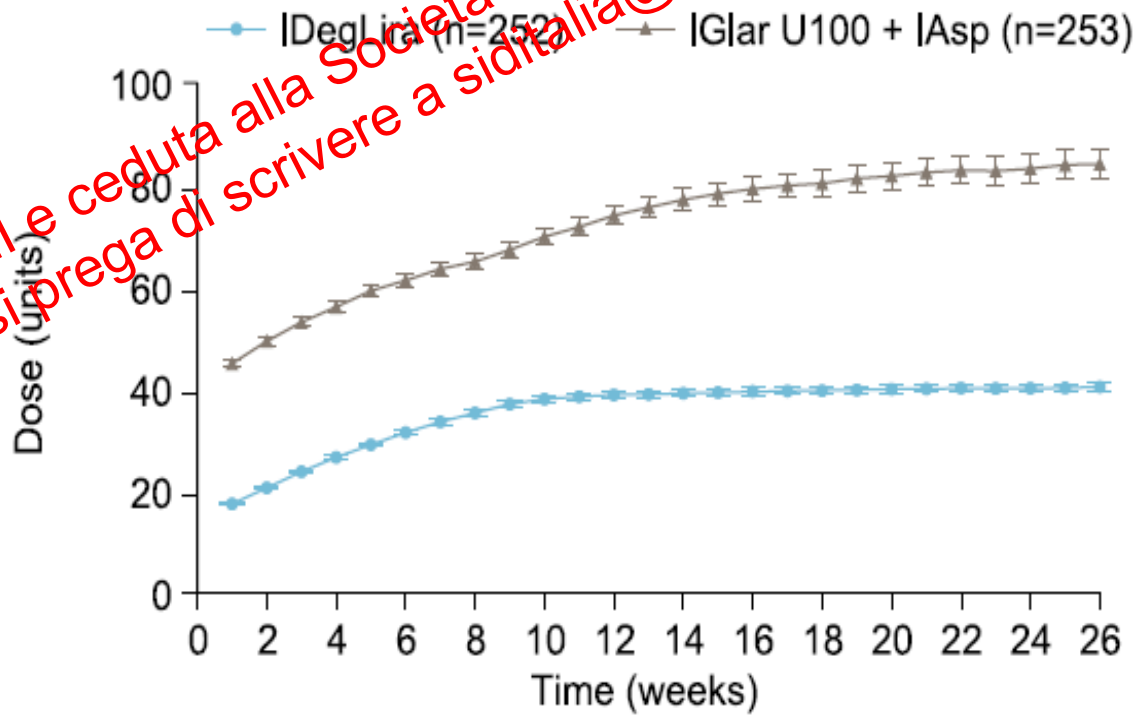


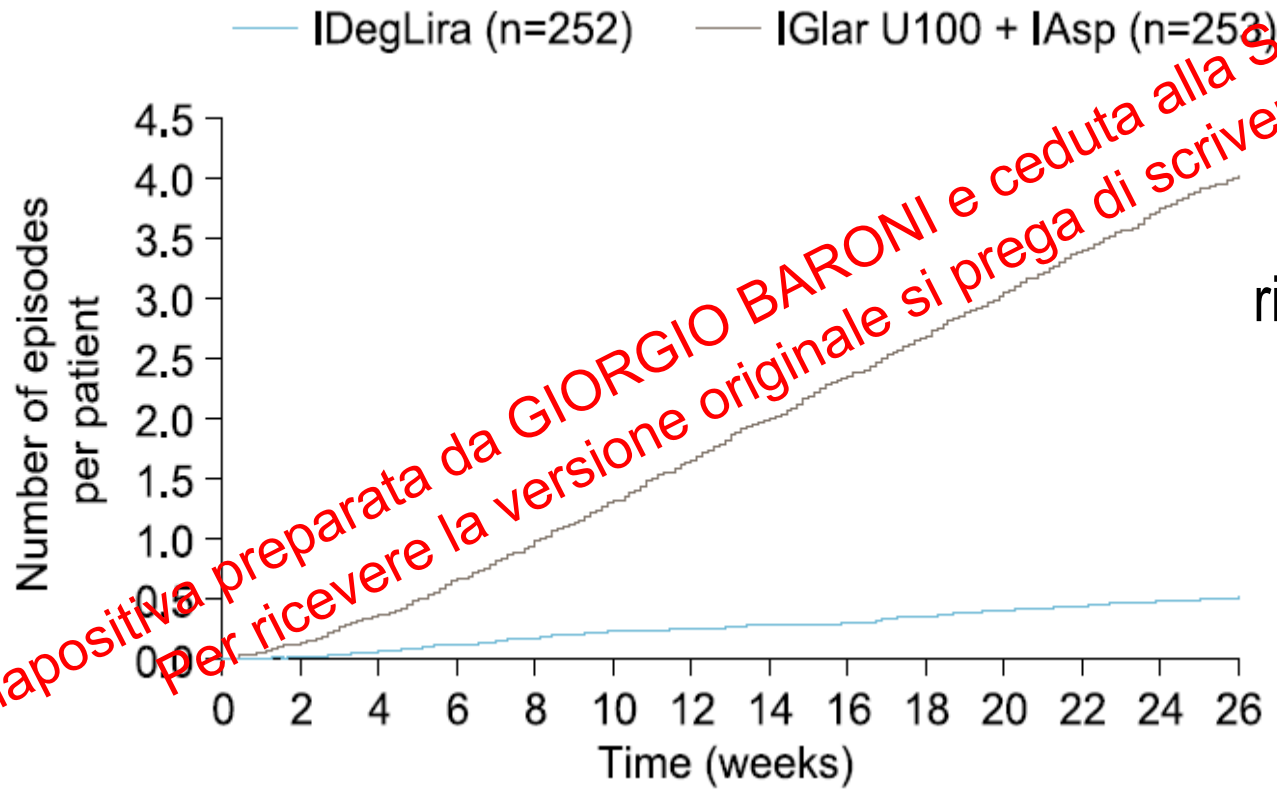


Total daily insulin dose was lower with IDegLira (40 units) than basal-bolus (84 units total; 52 units basal)

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

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

DUAL VII

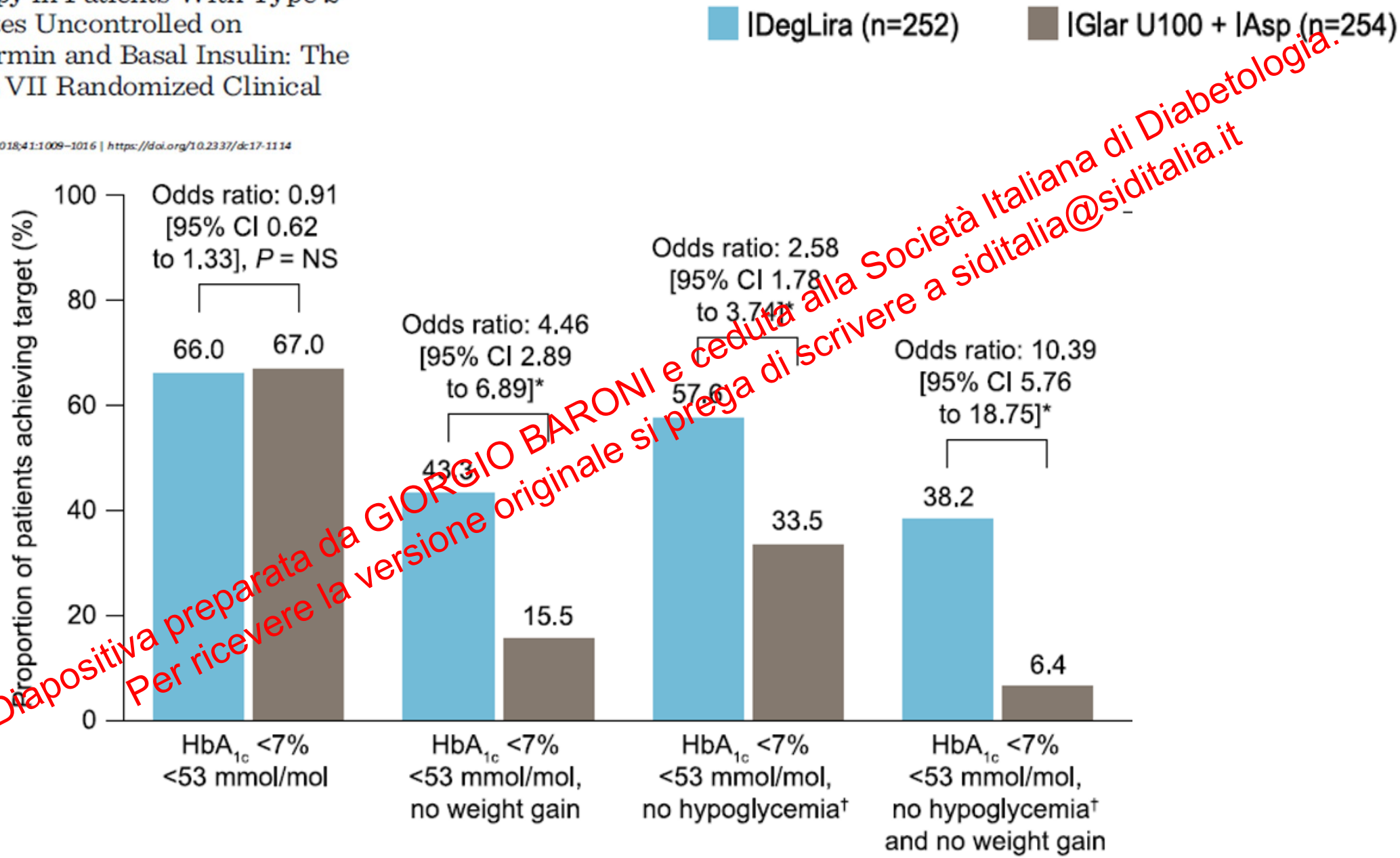


risk ratio 0.39 [95% CI 0.29, 0.51]

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

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



Insulina Basale e GLP-1 RA

Combinazioni non-fisse

- Insulina basale (glarg o deglud) +
  - Liraglutide
  - Lixisenatide
  - Dulaglutide
  - Albiglutide
  - Exenatide Ow

Combinazioni fisse

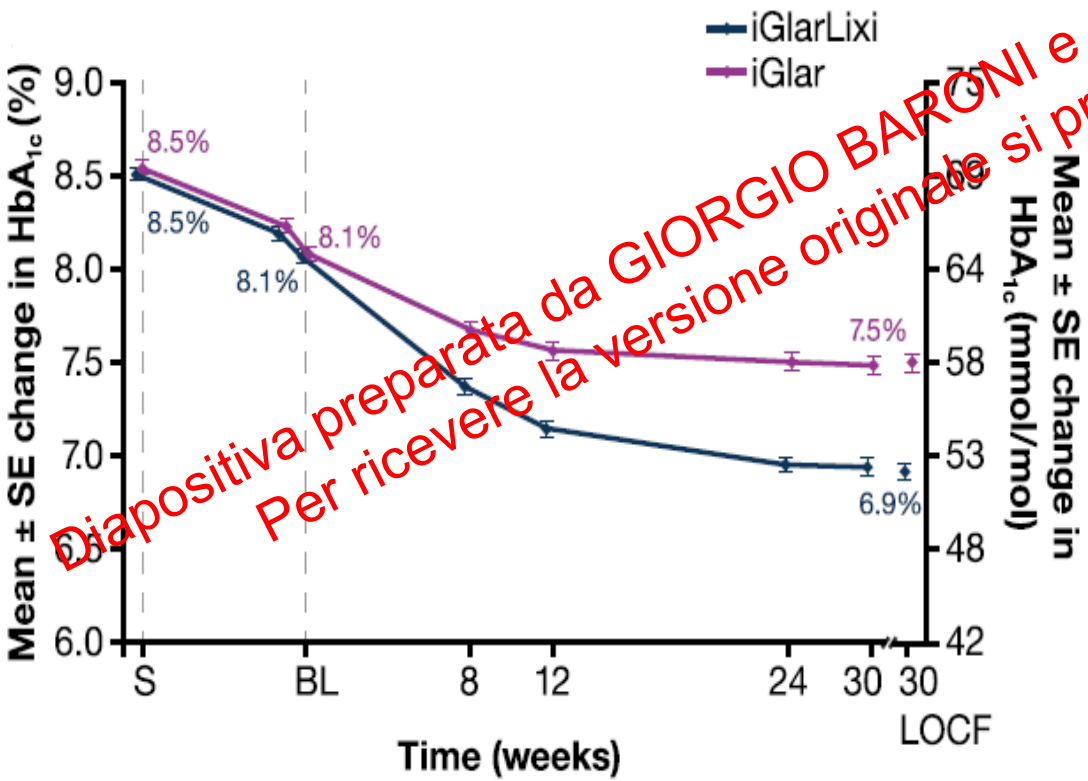
- Degludec + Liraglutide: IDegLira
- Glargine + Lixisenatide: IGlarLixi

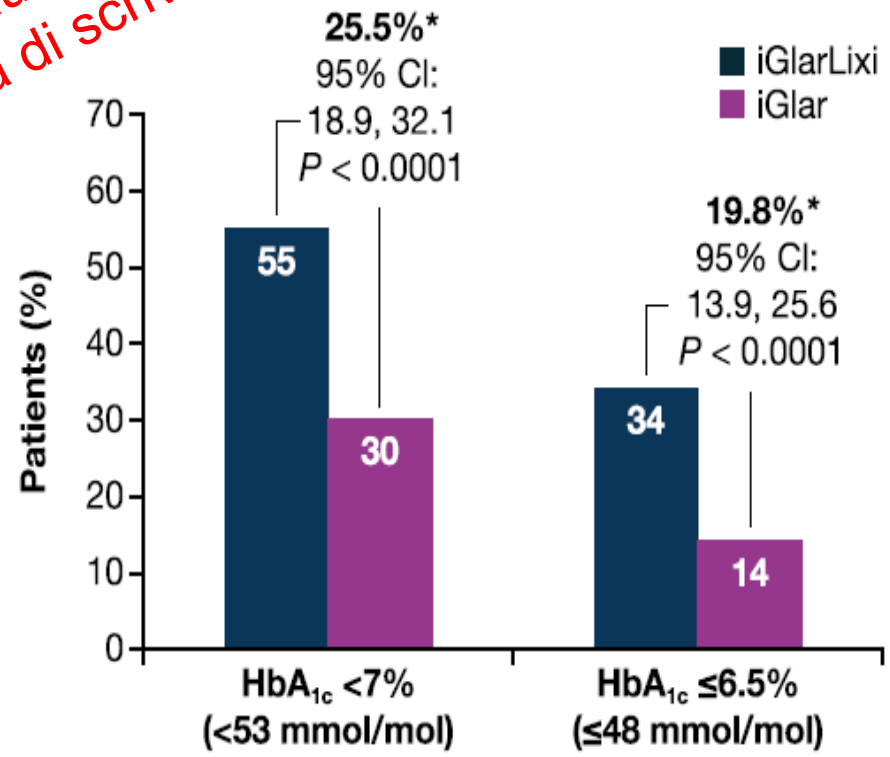
Efficacy and Safety of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide in Type 2 Diabetes Inadequately Controlled on Basal Insulin and Metformin: The LixiLan-L Randomized Trial

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

Inclusion criteria

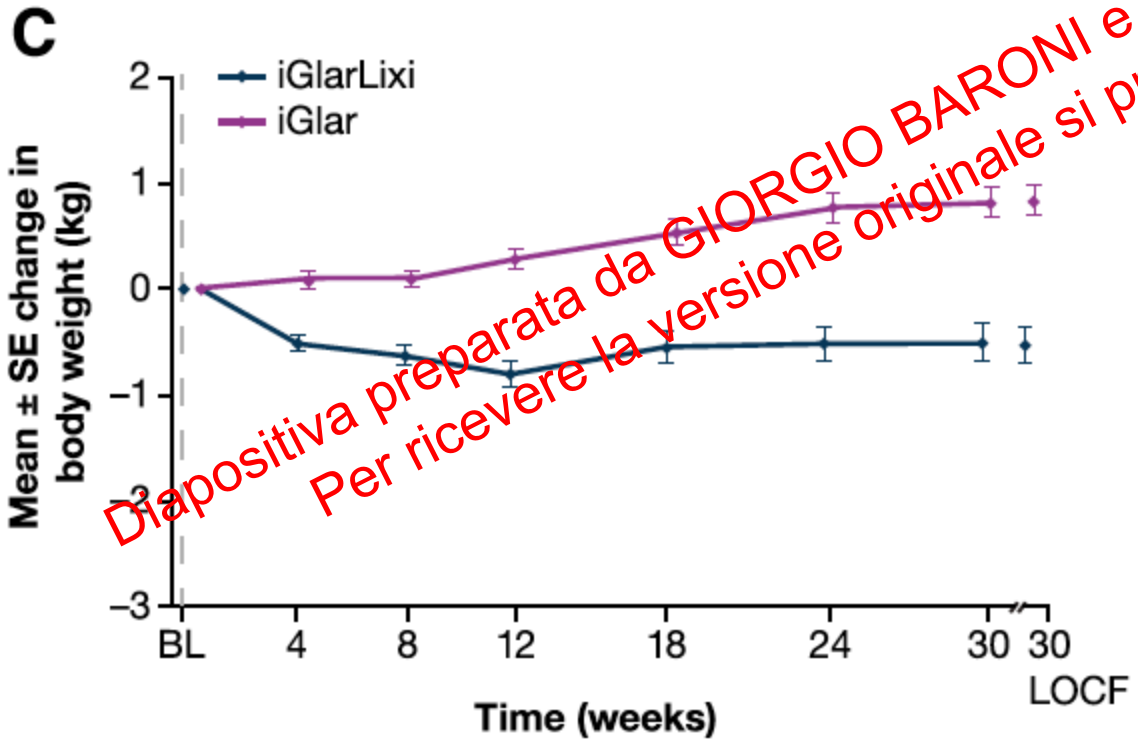
- T2D
- OADs: may also be on one or two of the following at a stable dose for ≥1 month: metformin, SU, glinide, DPP-4 inhibitor, SGLT-2 inhibitor)
- Basal insulin: ≥6 months and on a stable regimen (time/frequency of dose [15–40 U/day], type of insulin) for ≥2 months
- HbA_{1c}: ≥7.5–10%
- BMI: ≥20 to ≤40 kg/m^2

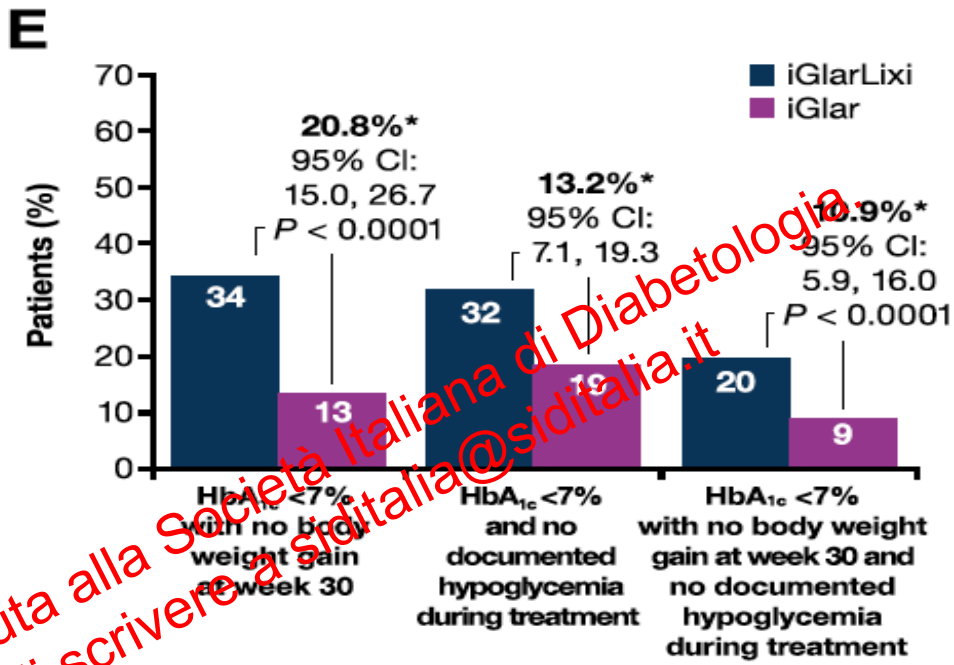


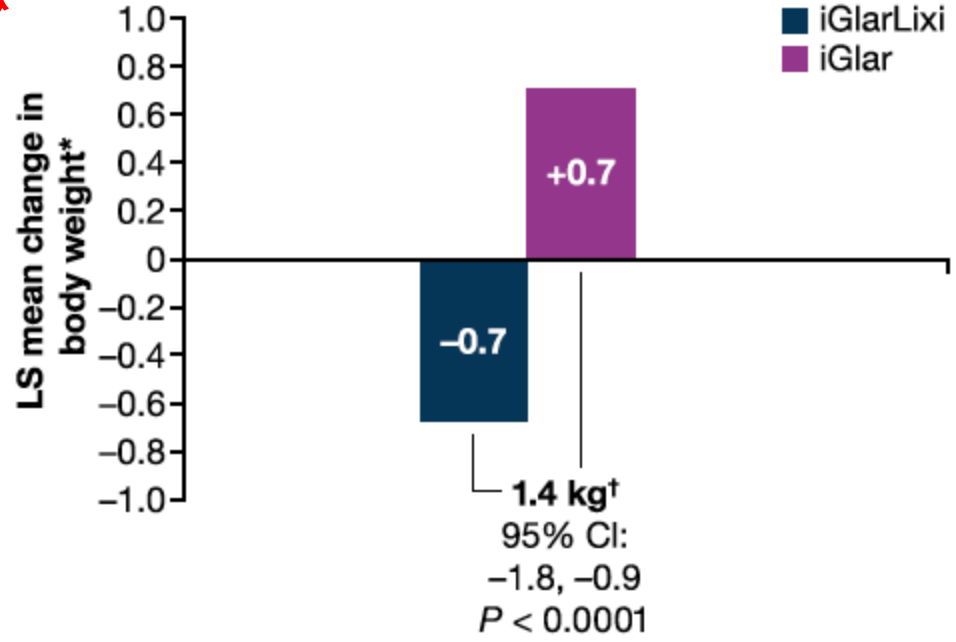


Efficacy and Safety of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide in Type 2 Diabetes Inadequately Controlled on Basal Insulin and Metformin: The LixiLan-L Randomized Trial

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

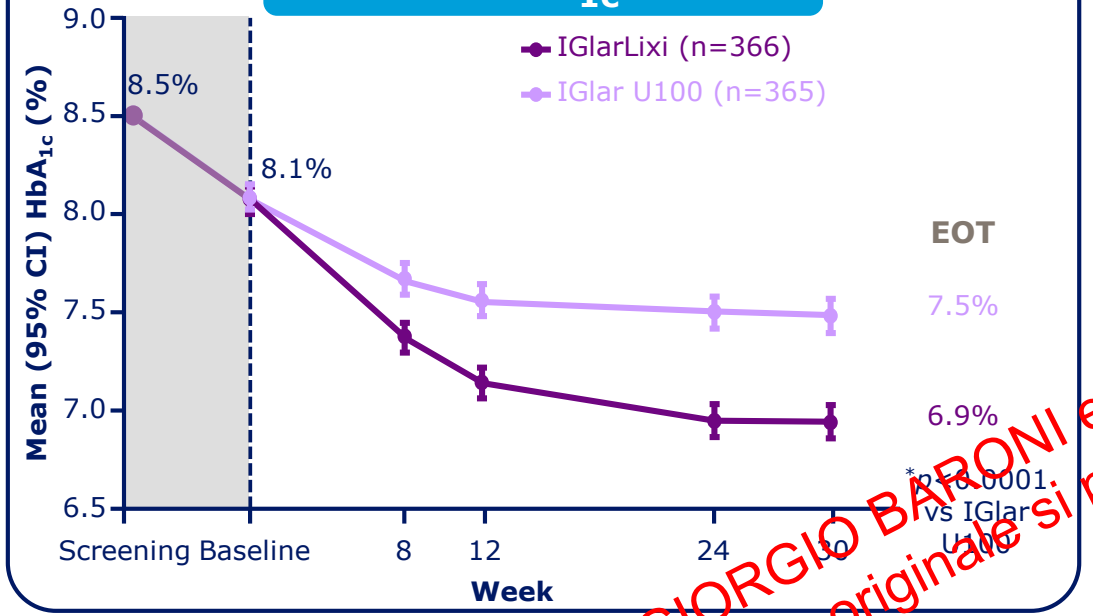




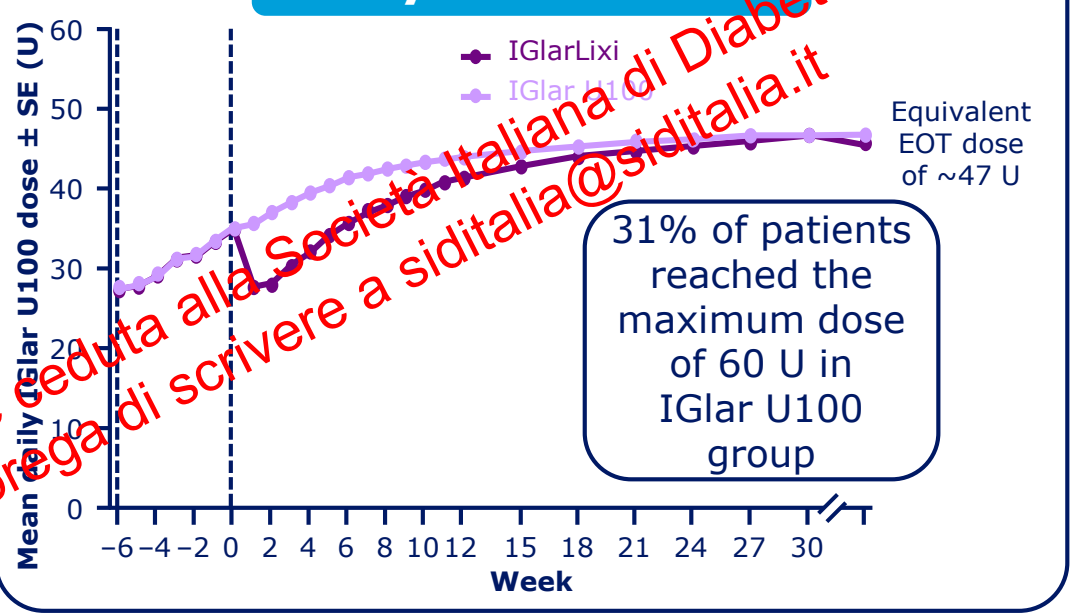


LixiLan-L: Key clinical findings

HbA_{1c}



Daily insulin dose



Hypoglycaemia

IGlarLixi	IGlar U100
3.03 events/ PYE	4.22 events/ PYE

Similar rates with IGlarLixi and IGlar U100

Body Weight

IGlarLixi	IGlar U100
-0.7 kg	+0.7 kg

ETD -1.4 kg, *p*< 0.0001 vs IGlar U100

EOT, end of treatment; ETD, estimated treatment difference; IGlarLixi, insulin glargine/lixisenatide; IGlar U100, insulin glargine U100; PYE, patient years of exposure; U, units; vs, versus

Aroda *et al. Diabetes Care* 2016;39:1972–80

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

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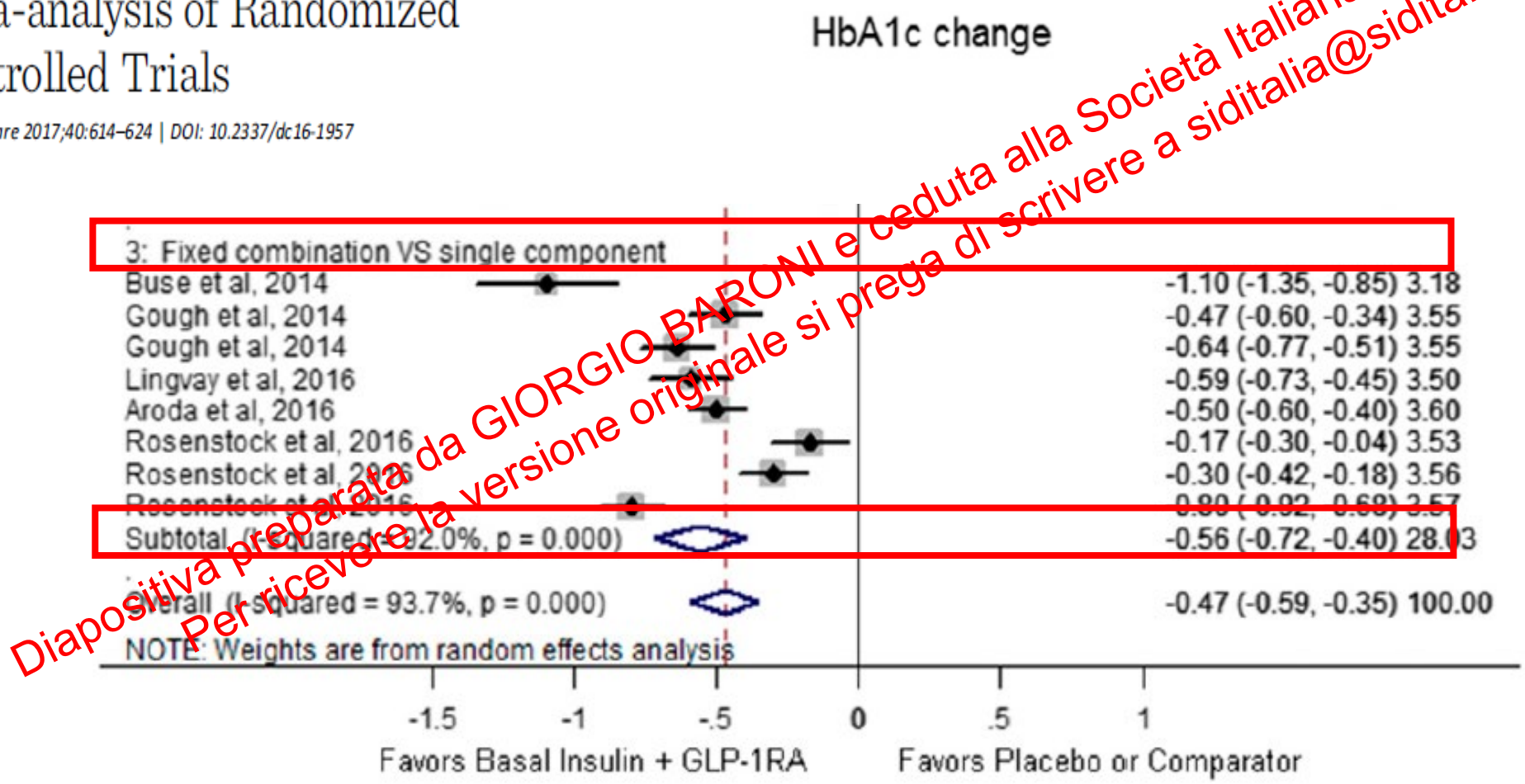

Combinazione basale/GLP-1RA vs Monocomponenti

- 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

Diabetes Ther (2017) 8:739–752
DOI 10.1007/s13300-017-0287-y

REVIEW

Rationale for, Initiation and Titration of the Basal Insulin/GLP-1RA Fixed-Ratio Combination Products, IDegLira and IGlarLixi, for the Management of Type 2 Diabetes

Virginia Valentine · Jennifer Goldman · Jay H. Shubrook

- Compared with basal insulin, insulin/GLP-1RA fixed-ratio combinations are superior at reducing HbA1c with weight neutrality or weight loss rather than weight gain, as well as reduced hypoglycemia rates, and reduced insulin-dose requirement with IDegLira

Glp-1-RA e Insulina Basale dopo fallimento con BOT: Conclusioni

- 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, ed in genere sono inferiori
- 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)