Insulina e GLP-1 RAs

insieme o separati?

Bologna, 19 dicembre 2017

Fixed dose combination: un vantaggio o uno svantaggio

AGOSTINO CONSOLI
DMSI & CeSI-Met - Università d'Annunzio – CHIETI
ITALY

Il Prof. Agostino Consoli dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Abbot, Astra Zeneca, Boheringer Ingelhaim , Eli Lilly, Merck Sharp & Dhome , Menarini Diagnostici, Novo-Nordisk, Sanofi-Aventis, Sigma-Tau, Takeda.
(Speaker)

Astra Zeneca, Boheringer Ingelhaim, Eli Lilly, Janssen Farmaceutici, Merck Sharp & Dhome, Novo-Nordisk, Sanofi-Aventis.
(Advisory Board)

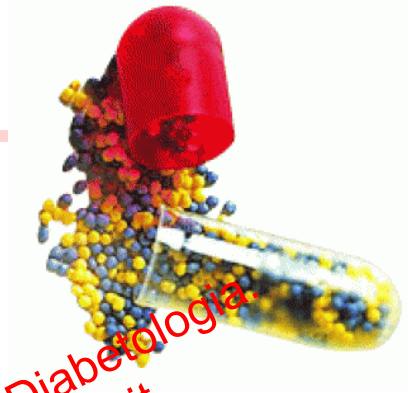
Astra Zeneca , Novo-Nordisk
(Consultant)

Eli Lilly, Novo-Nordisk
(Research Grant)

Ringrazio sinceramente la SID per lo straordinario contributo alla mia formazione culturale, scientifica e clinica.

Opinioni e giudizi espressi durante questa presentazione sono di mia esclusiva responsabilità e non possono essere imputati alla SID e/o ad alcuno dei suoi "officers".

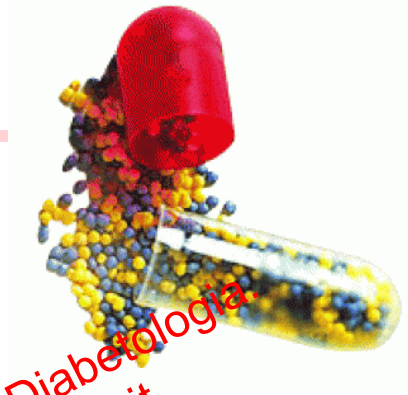
Fixed dose combinations



Advantages

- Improved Adherence
- Complementary MOA (eventually)
- ↓ Side Effects
- Side Effects «neutralization»
- Cost

Fixed dose combinations



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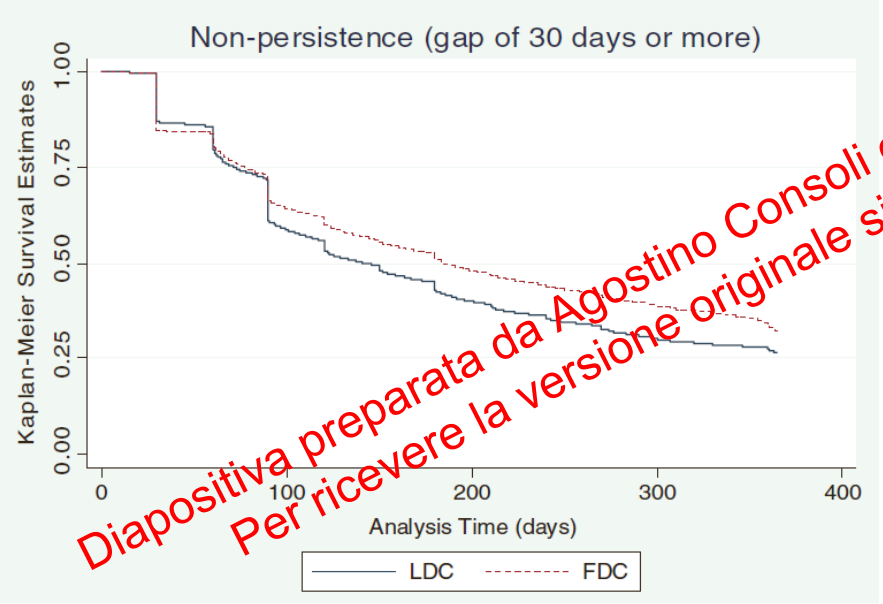
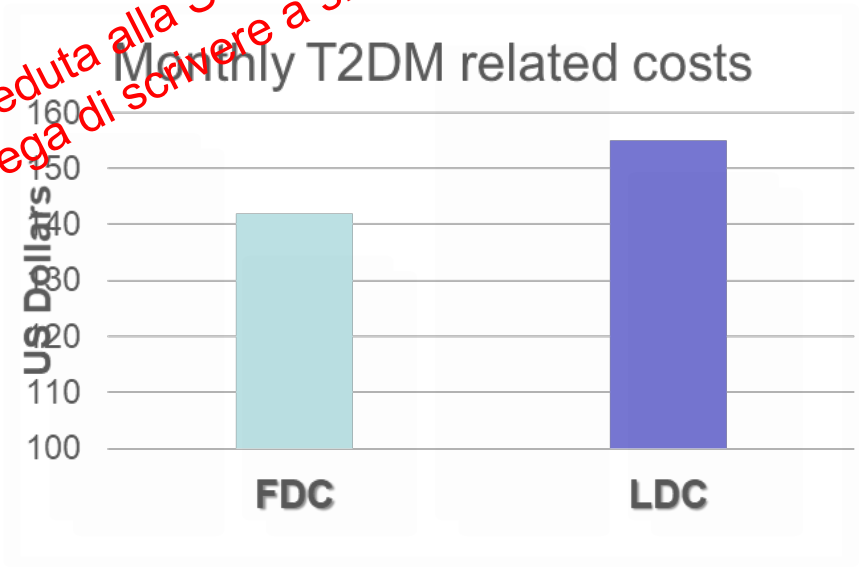
Why a Fixed Dose Combination ?

A retrospective study of persistence, adherence, and health economic outcomes of fixed-dose combination vs loose-dose combination of oral anti-diabetes drugs

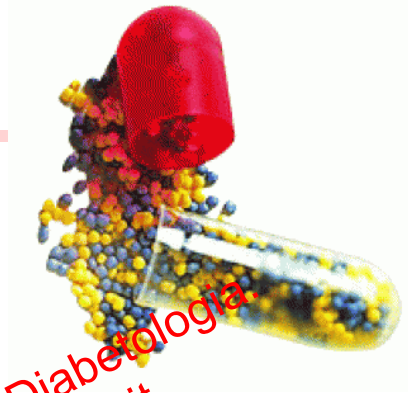
Journal of Medical Economics, 2016; 19, No. 3, 203–212





Lokhandwala et al., 2016

Fixed dose combinations



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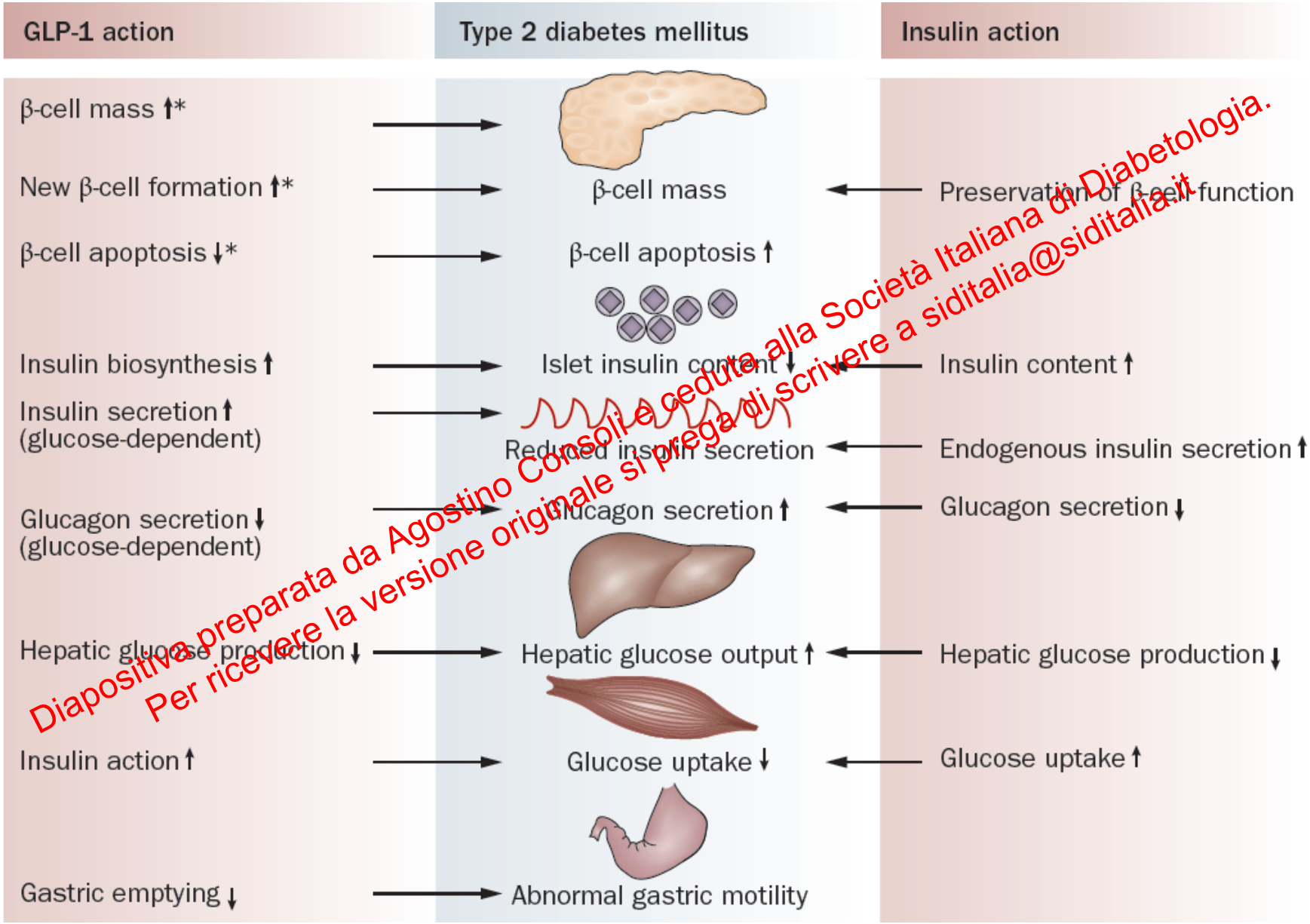
Complementary action: Basal insulin & GLP-1RA



Nauck & Meier. *J Nat Rev Endocrinol* 2011;7:193-195.

Complementary action: Basal insulin & GLP-1RA

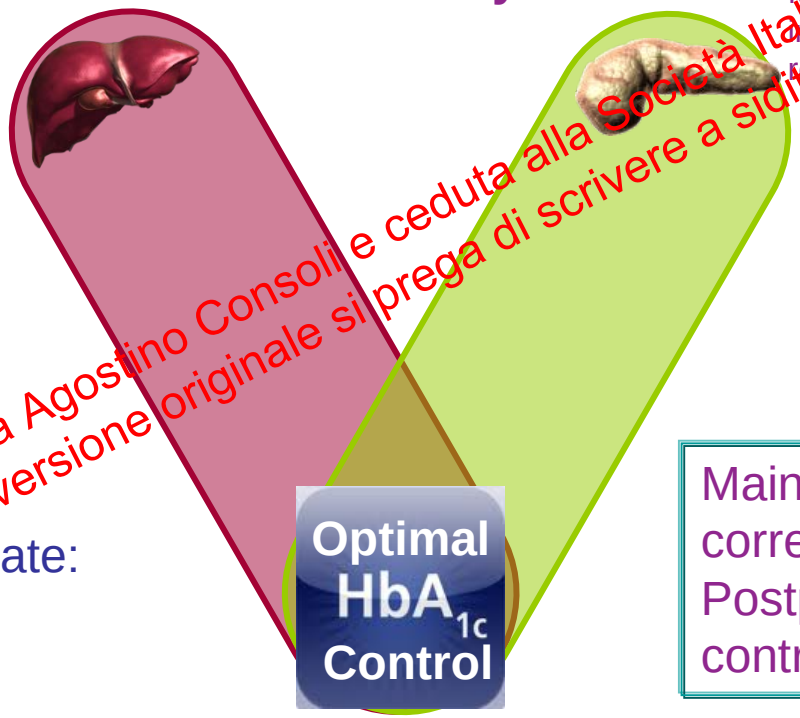
Basal insulin decreases hepatic glucose production by targeting the liver to decrease gluconeogenesis and glycogenolysis

Main Clinical correlate: Fasting BG control

Hepatic glucose overproduction

Beta- and alpha- cell dysfunction

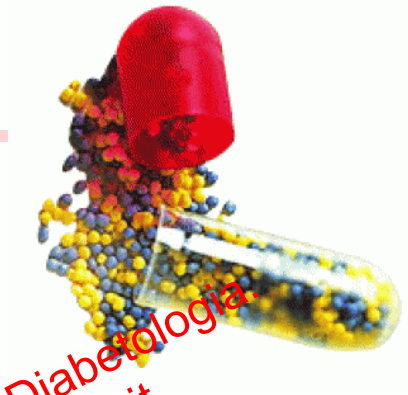
GLP-1 agonists improve beta-cell function and increase insulin synthesis and release



Main Clinical correlate: Postprandial BG control

Wang Z, *et al*. *Diabetes Care* 2010;33:1555–60.
Baggio LL and Drucker DJ. *Gastroenterology* 2007;132:2131–57.
Holst JJ. *Physiol Rev* 2007;87:1409–39.

Fixed dose combinations



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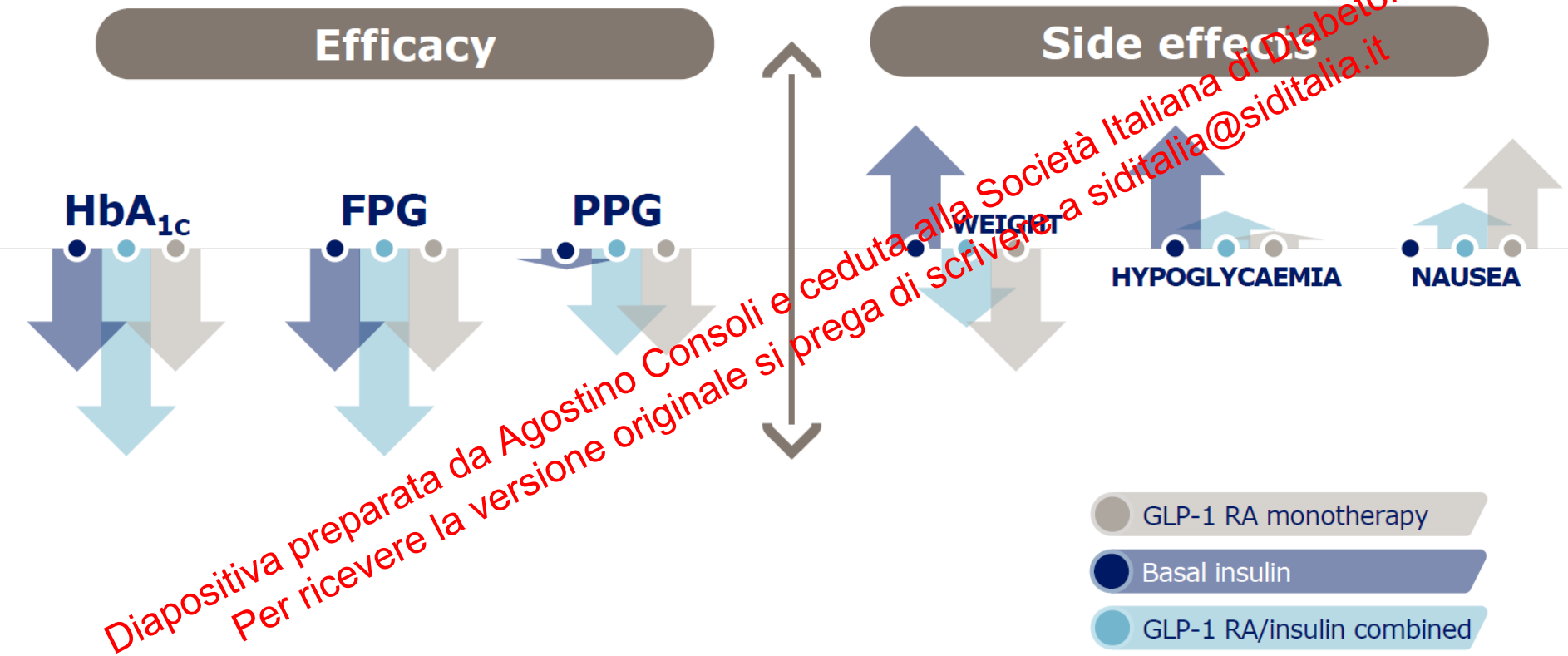
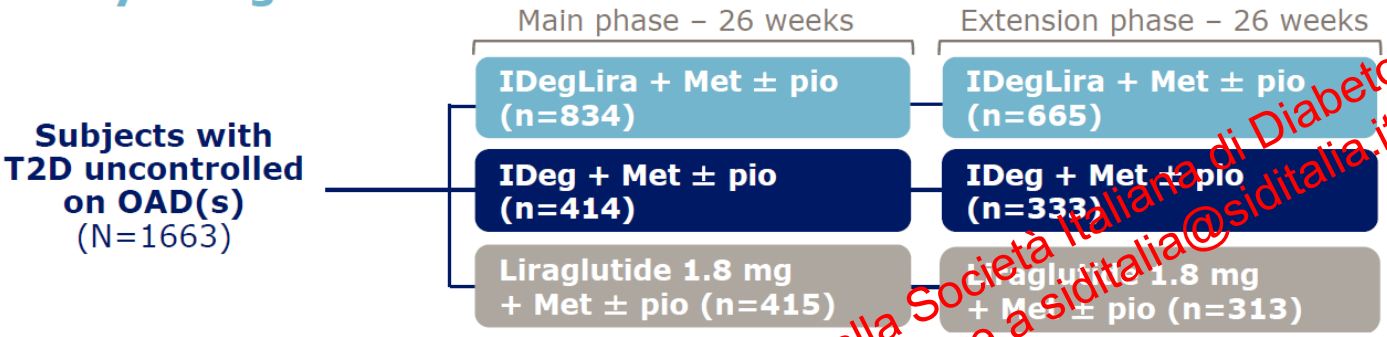
Moderation / neutralization of side effects



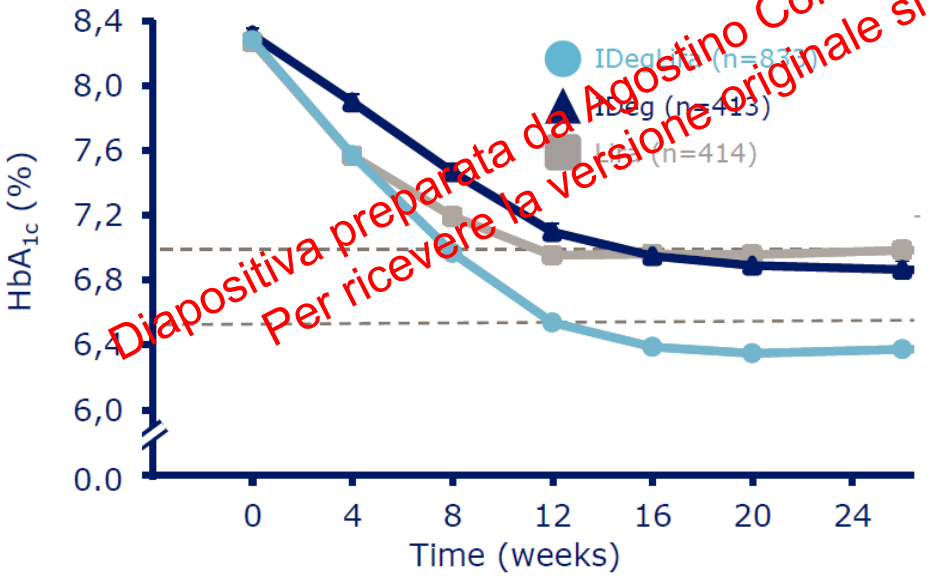
Moderation / neutralization of side effects

DUAL I and extension

Study design

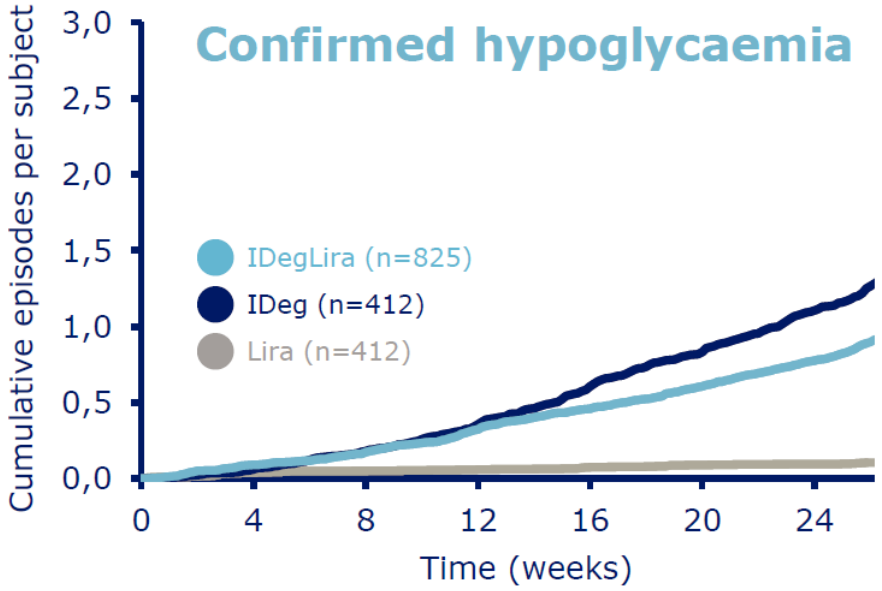


HbA_{1c} over time



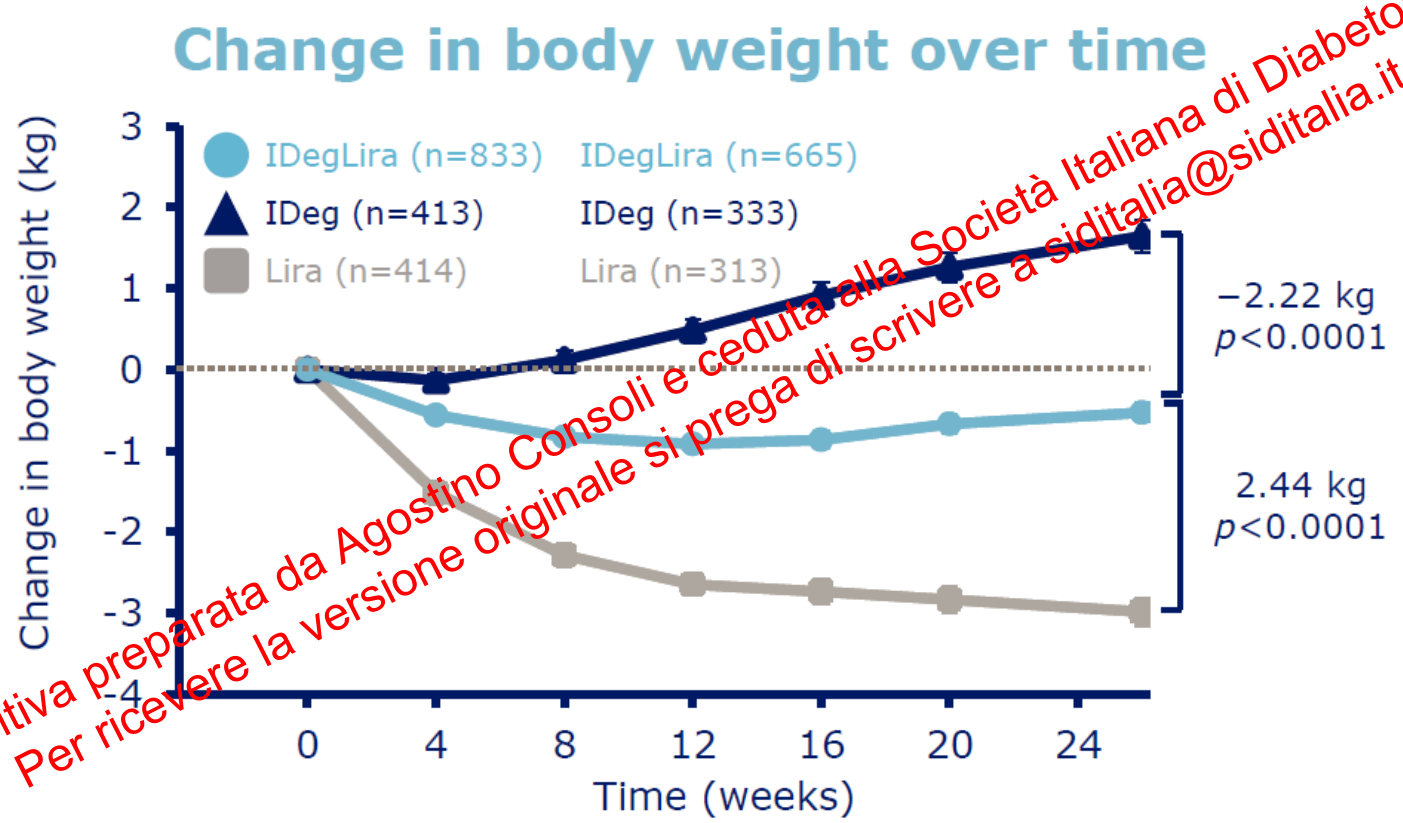
Moderation of insulin-associated hypo risk

Confirmed hypoglycaemia



Gough SC et al, Lancet Diabetes Endocrinol. 2:885–932, 2014

Moderation / neutralization of side effects



Neutralization of insulin-associated weight gain

Gough SC et al, Lancet Diabetes Endocrinol. 2:885–932, 2014

Moderation / neutralization of side effects

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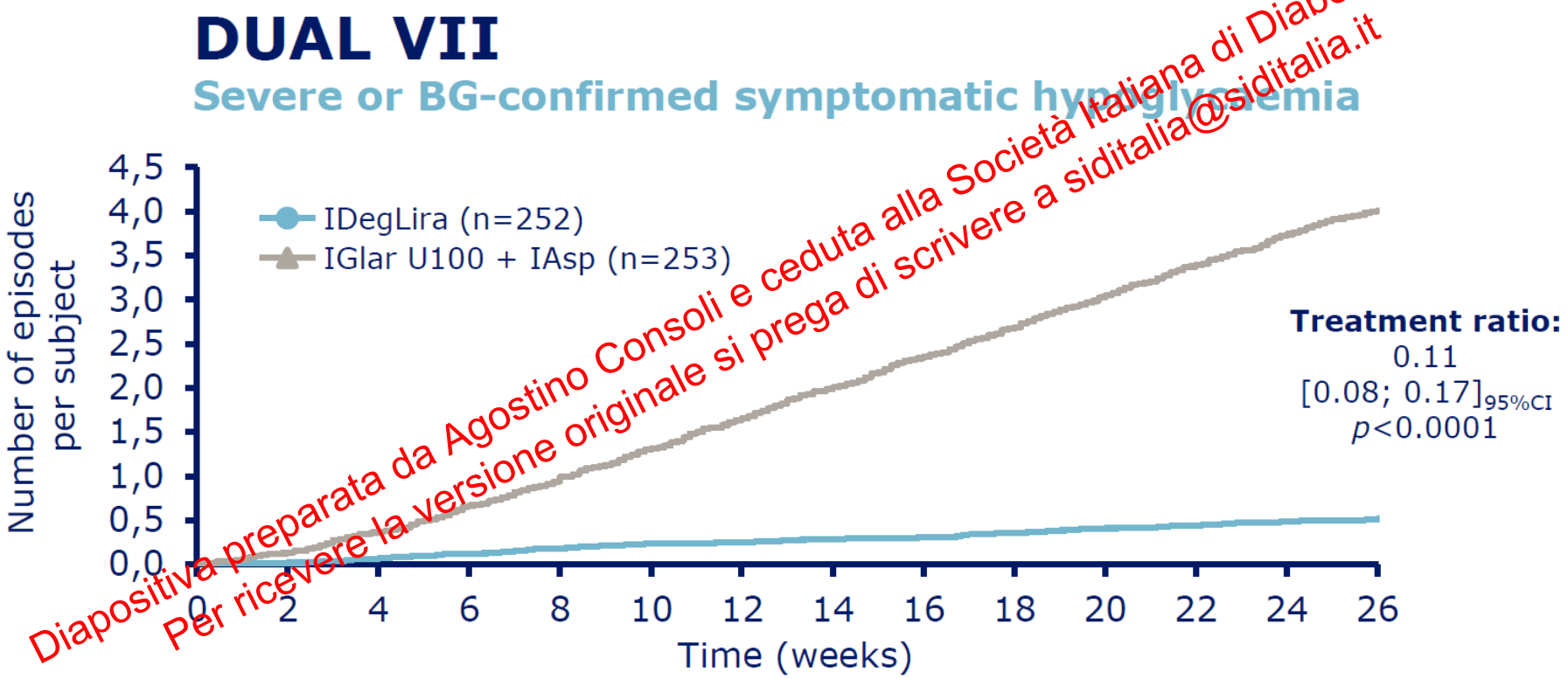

Billings LK et al., Abstract at the 2017 ADA Study Sessions

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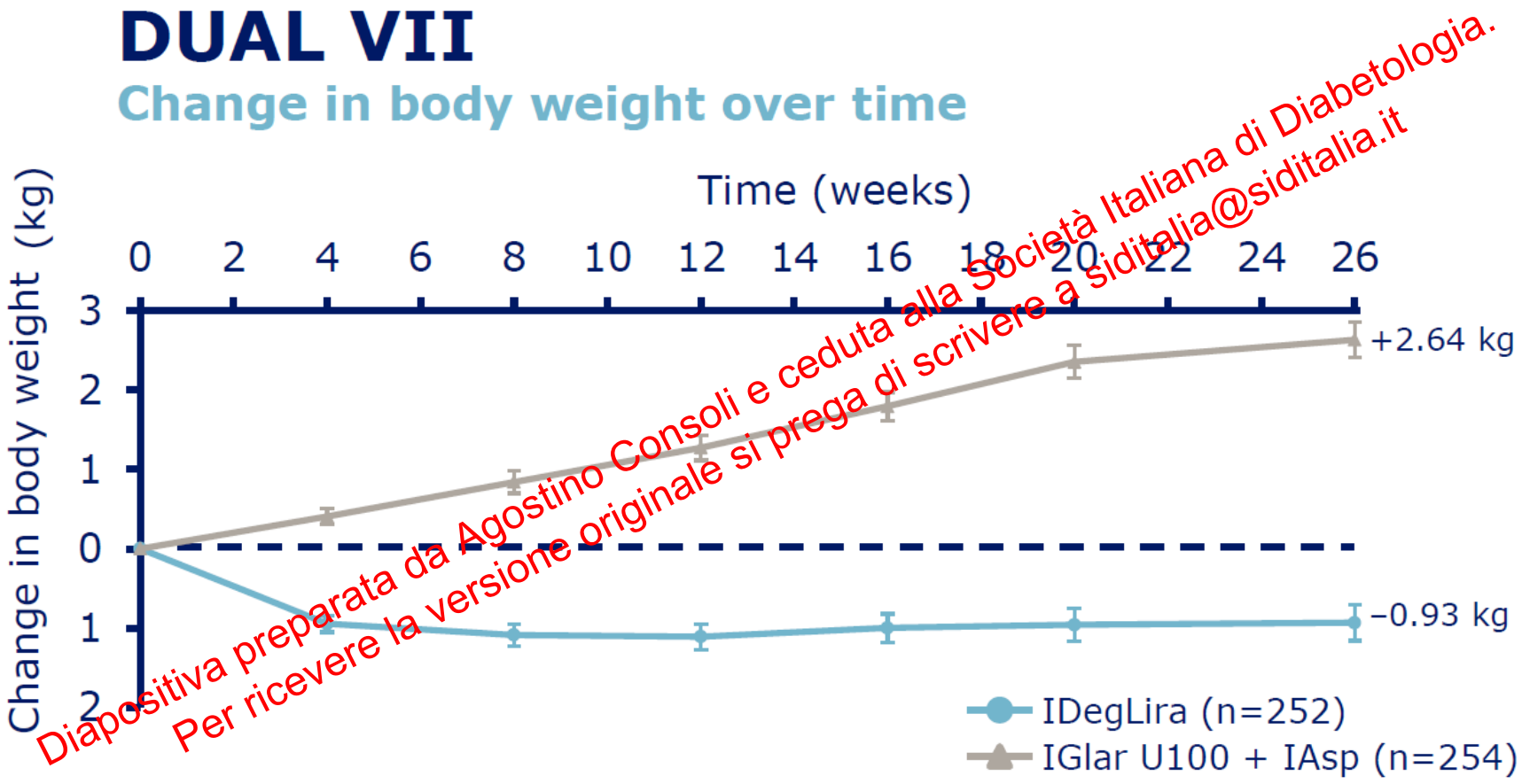


Neutralization of insulin-associated weight gain

Billings LK et al., Abstract at the 2017 ADA Study Sessions

Barriers to Insulin Treatment

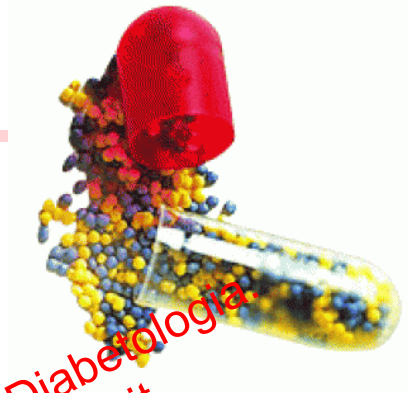
Hypoglycaemia[1]

Weight gain[2]

Complexity[1]

More than half of T2D patients on basal insulin are not at target HbA_{1c}[3]

Fixed dose combinations



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«Consumable» sparing effect

Comparing daily treatment with IDegLira and Basal-Bolus

IDegLira

1 pen[1]

1 Injection[1]

1 SMPG test[2]

Daily Regimen

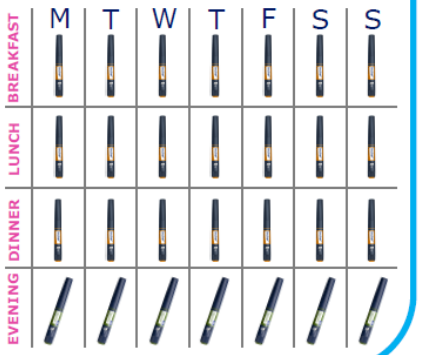
Basal-Bolus

2 pens

2-4* Injections[3]

2-4* SMPG test[2]

Daily Regimen

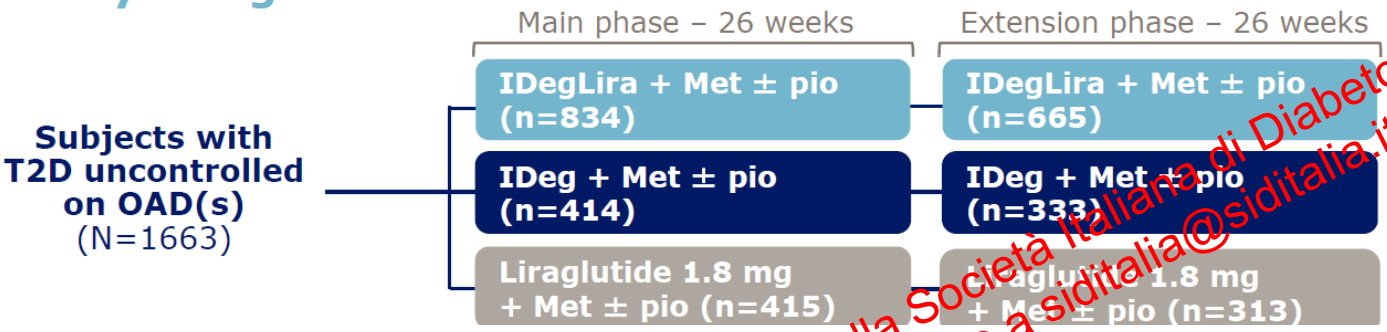


Dose sparing effect

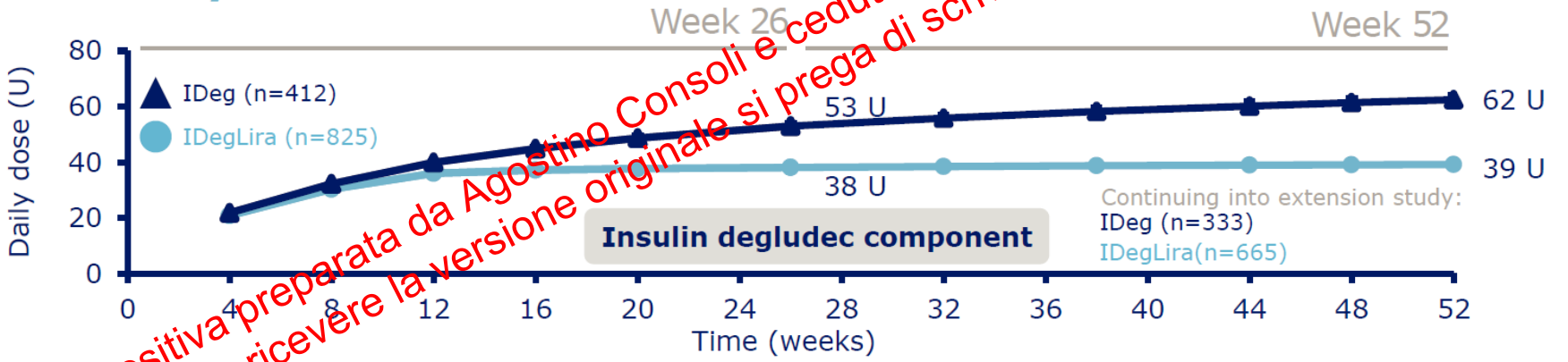
Gough SC et al., Diabetes Obes Metab. 2015;17:965

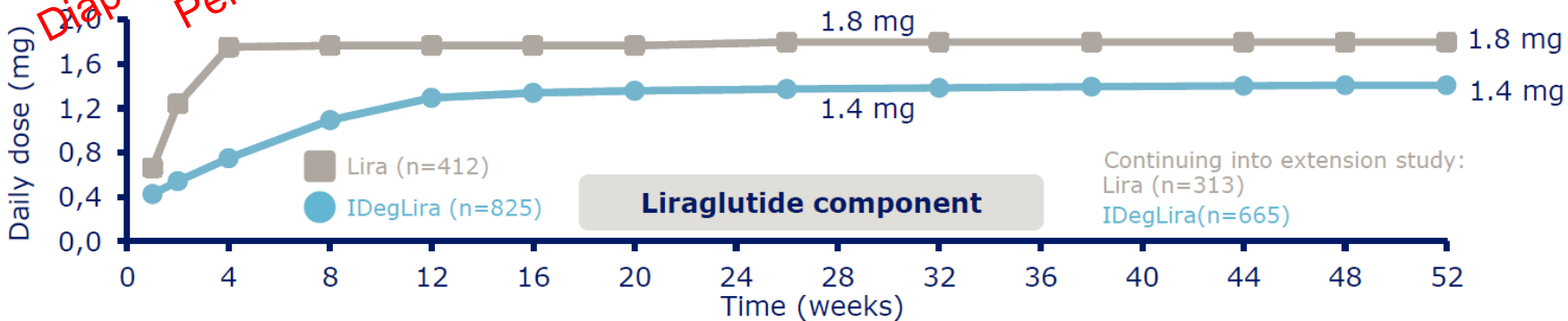
DUAL I and extension

Study design



Mean daily doses





Dose sparing effect

DUAL VII

Study design

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

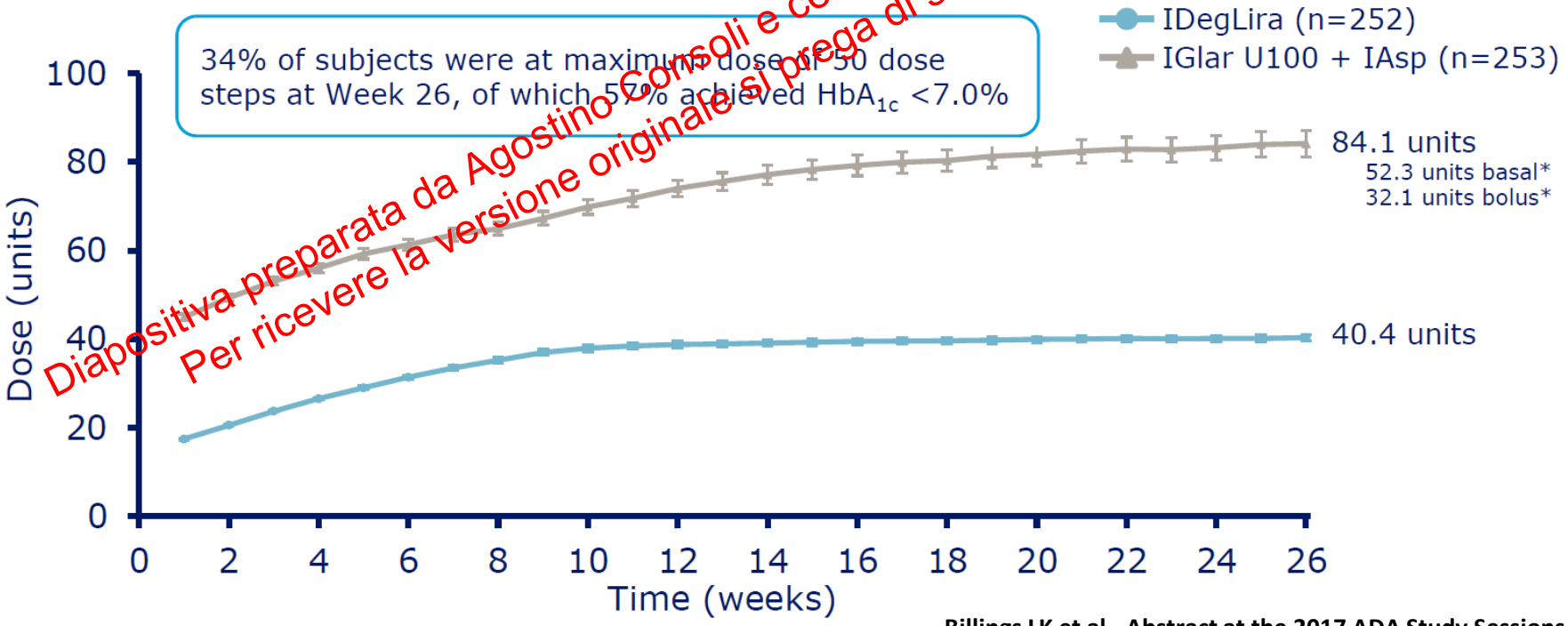
- **IDegLira + metformin (n=252)**
- **IGlar U100 + IAsp (≤4 times) + metformin (n=254)**

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

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

IAsp
Starting dose: 4U†
Maximum dose: None

Daily total insulin dose over time



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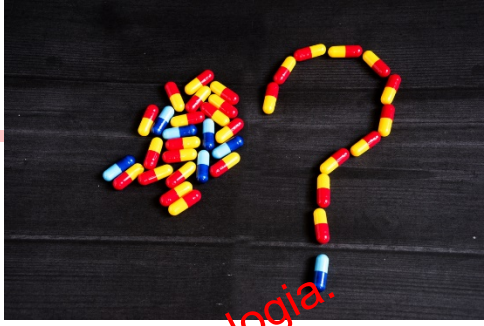
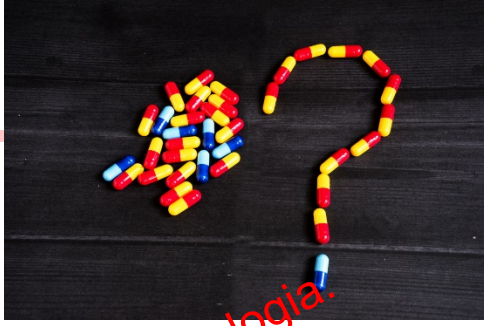
Fixed dose combinations



Potential Problems

- Impossible to ascertain whether patient is responding to both drugs
- Might potentiate some AEs (i.e. Hypoglycemia)
- If a withdrawl is needed, both drugs are withdrawn
- Limited dose combinations
- Difficulties in titration
- Cost

Fixed dose combinations



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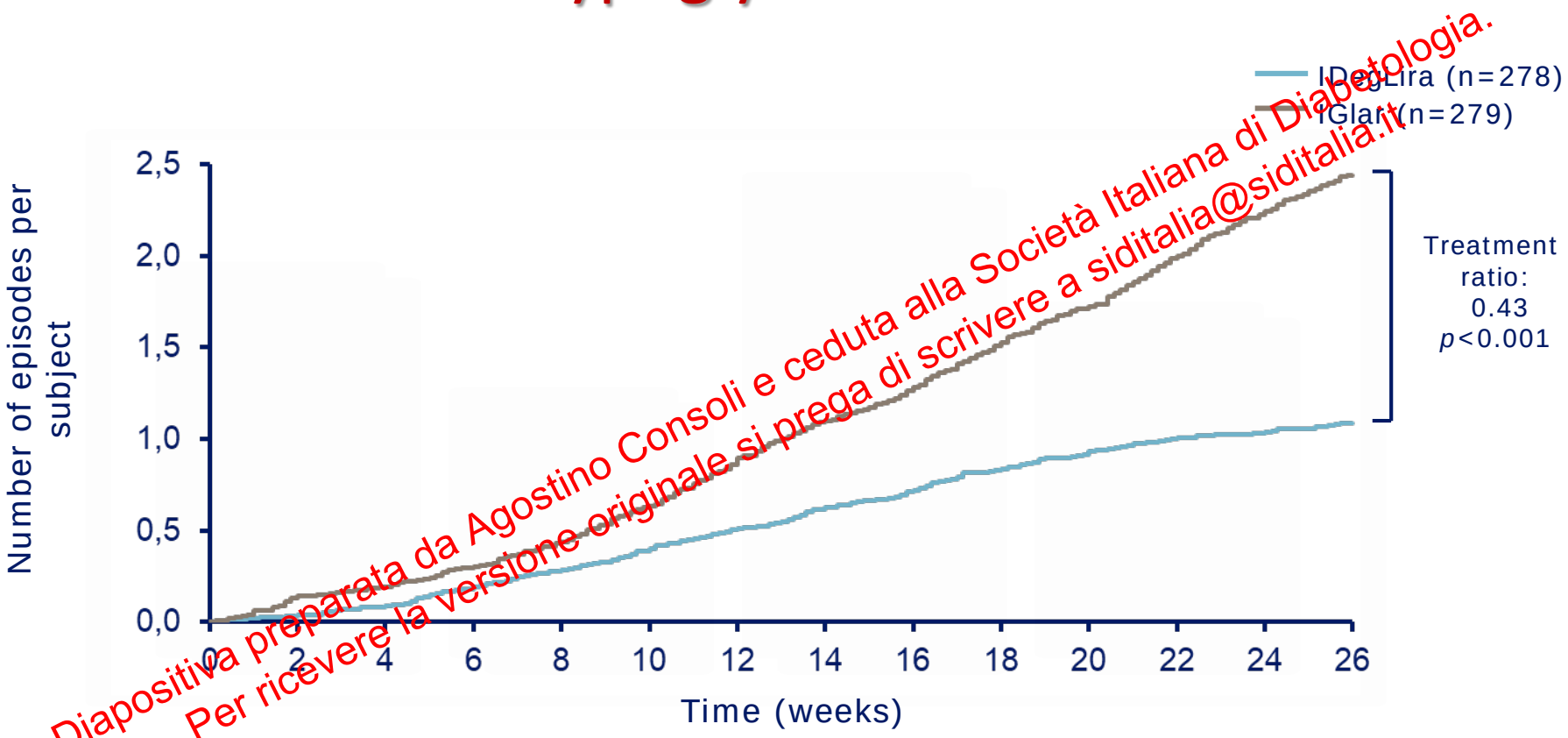
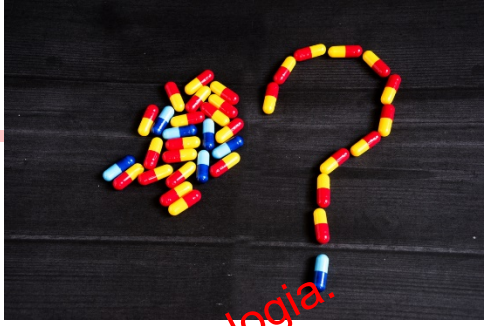
DUAL V: IDegLira vs IGlar in patients uncontrolled on basal insulin

Confirmed hypoglycaemia over time



JAMA. 2016;315(9):898-907

Fixed dose combinations



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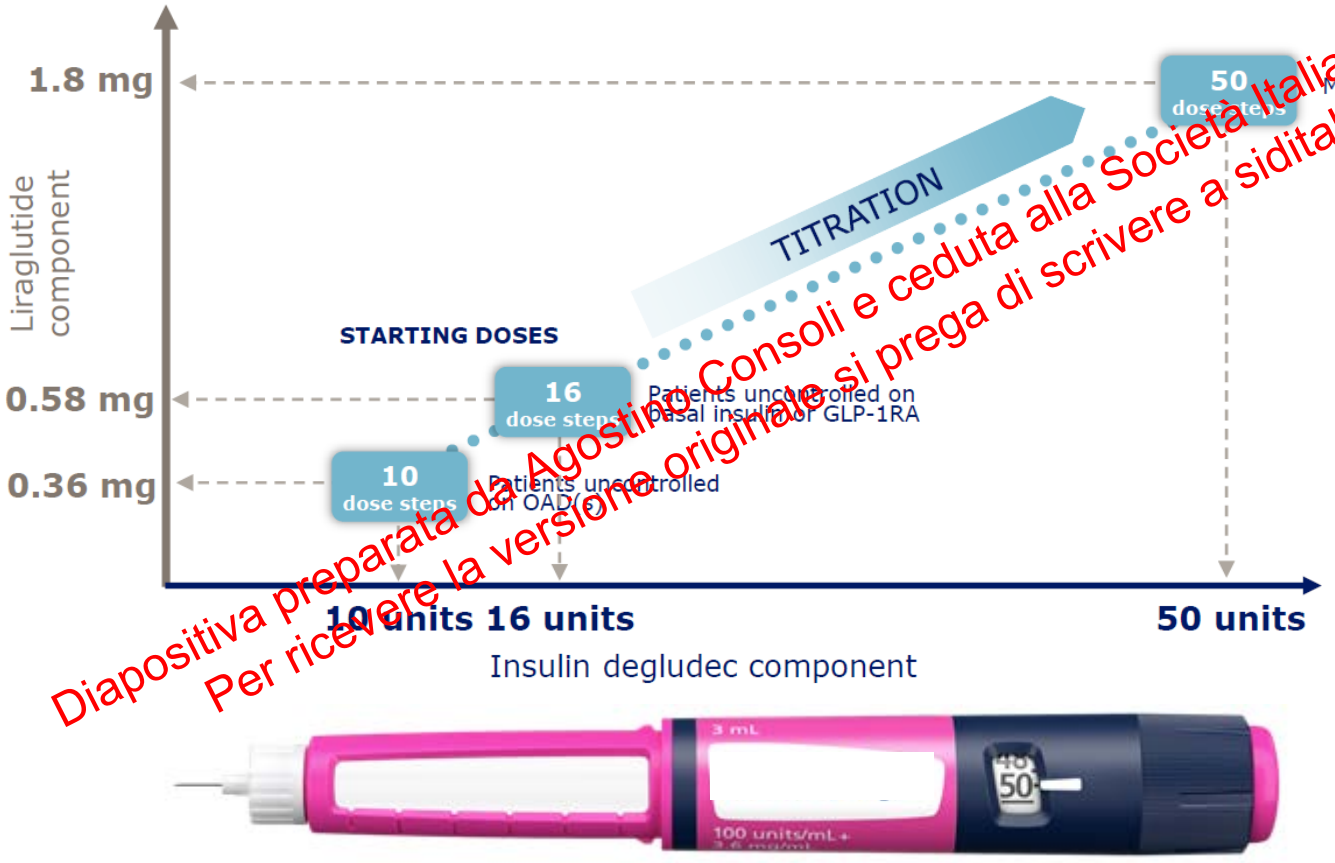
Fixed dose combinations

IDegLira: a once-daily, titratable, fixed-ratio combination



Fixed-ratio

1 dose step

=

1 U insulin degludec

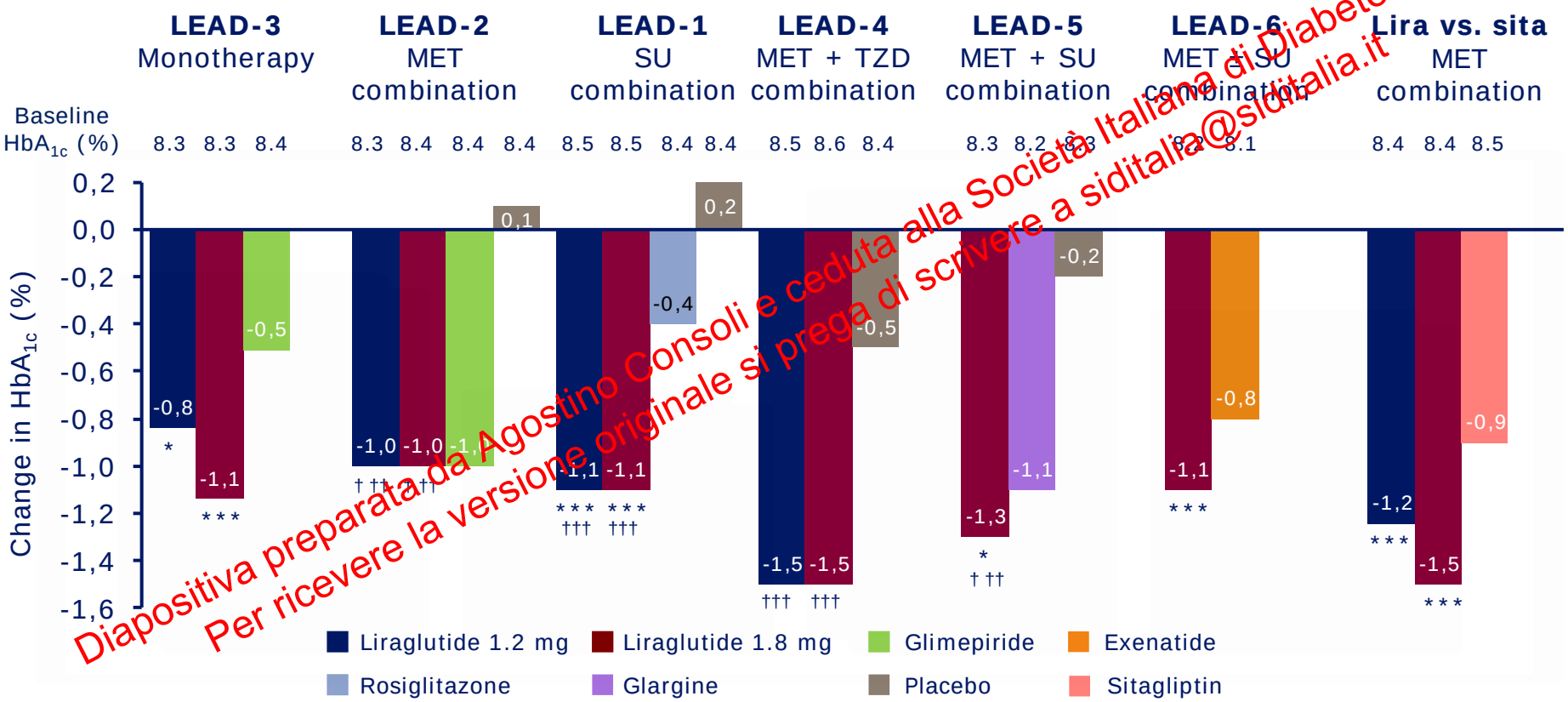
+

0.036 mg liraglutide

Fixed dose combinations

- **Novel fixed-ratio combination of a basal insulin (insulin Glargine 100 U/mL [iGlar]) and a GLP-1RA (Lixisenatide [Lixi]) available as a once-daily injection for patients with T2DM**
- **Patient's dose is adjusted according to their glargine needs**

HbA_{1c} reductions from baseline in liraglutide and comparators treated patients



*p<0.01, ***p<0.0001 vs. active comparator; †††p<0.0001 vs. placebo. [Active comparators vs. placebo not shown]. Data from core trials

LEAD: Liraglutide Effect and Action in Diabetes. Marre *et al. Diabet Med* 2009;26;268–78 (LEAD-1); Nauck *et al. Diabetes Care* 2009;32;84–90 (LEAD-2); Garber *et al. Lancet* 2009;373:473–81 (LEAD-3); Zinman *et al. Diabetes Care* 2009;32:1224–30 (LEAD-4); Russell-Jones *et al. Diabetologia* 2009;52:2046–55 (LEAD-5); Buse *et al. Lancet* 2009;374:39–47 (LEAD-6); Pratley *et al. Lancet* 2010;375:1447–56 (lira vs. sita)

Safety and efficacy of IDegLira titrated once weekly versus twice weekly in patients with type 2 diabetes uncontrolled on oral antidiabetic drugs: DUAL VI randomized clinical trial

fasting glycaemic target of 72 to 90 mg/dL

Harris SB et al., Diabetes Obes Metab. 2017;19:858

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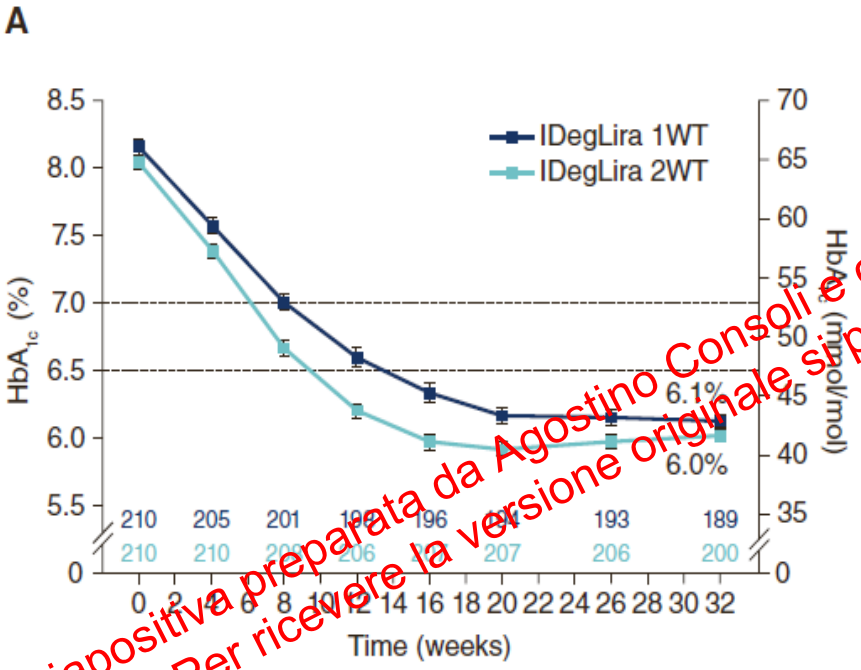
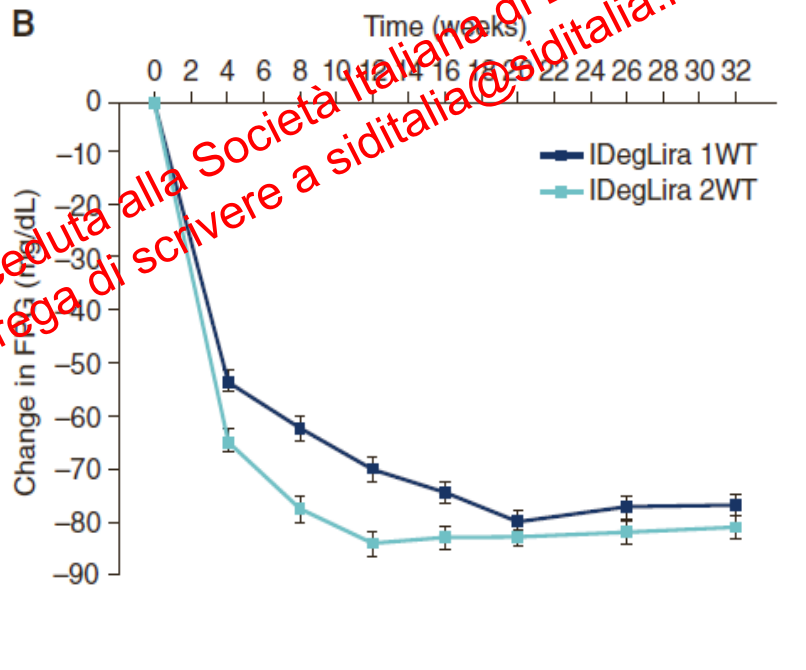


	1WT	2WT	ETD [95% CI]
ΔHbA$_{1c}$ (%)	−2.01	−2.02	0.12 [−0.04; 0.28], P = .012*



	1WT	2WT	ETD [95% CI]
ΔFPG (mg/dL)	−78.0	−81.9	3.96 [−2.02; 9.93], P = .194

Harris SB et al., Diabetes Obes Metab. 2017;19:858

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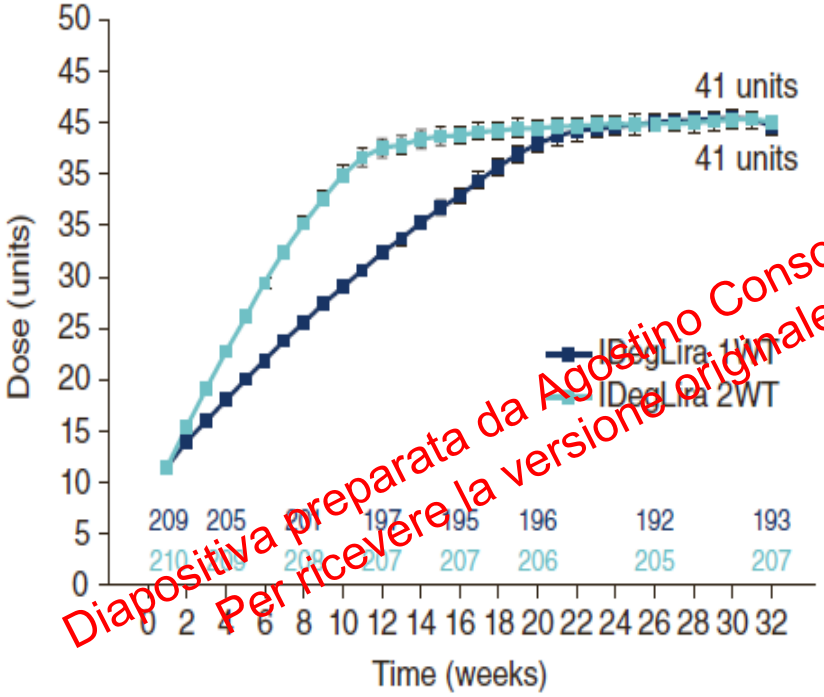

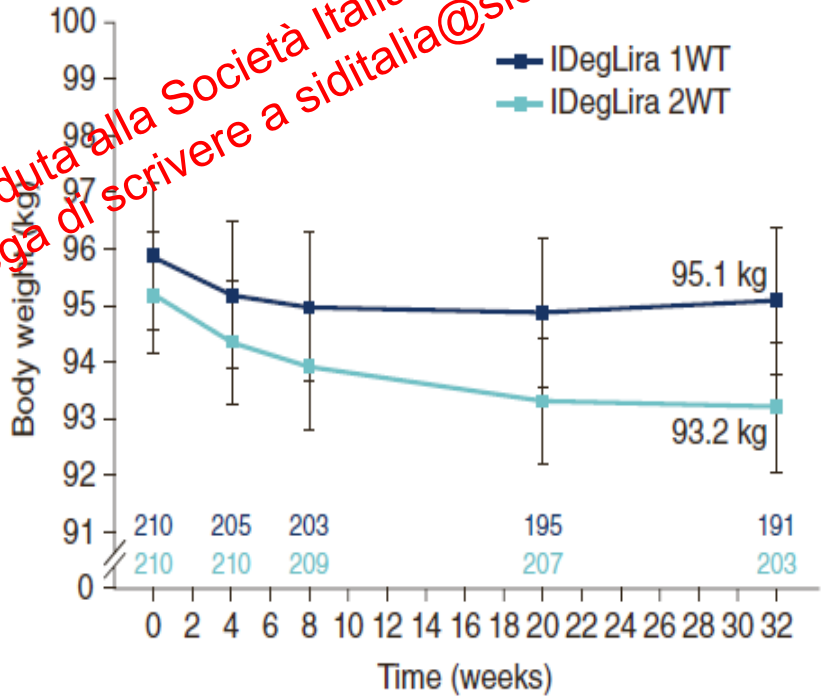

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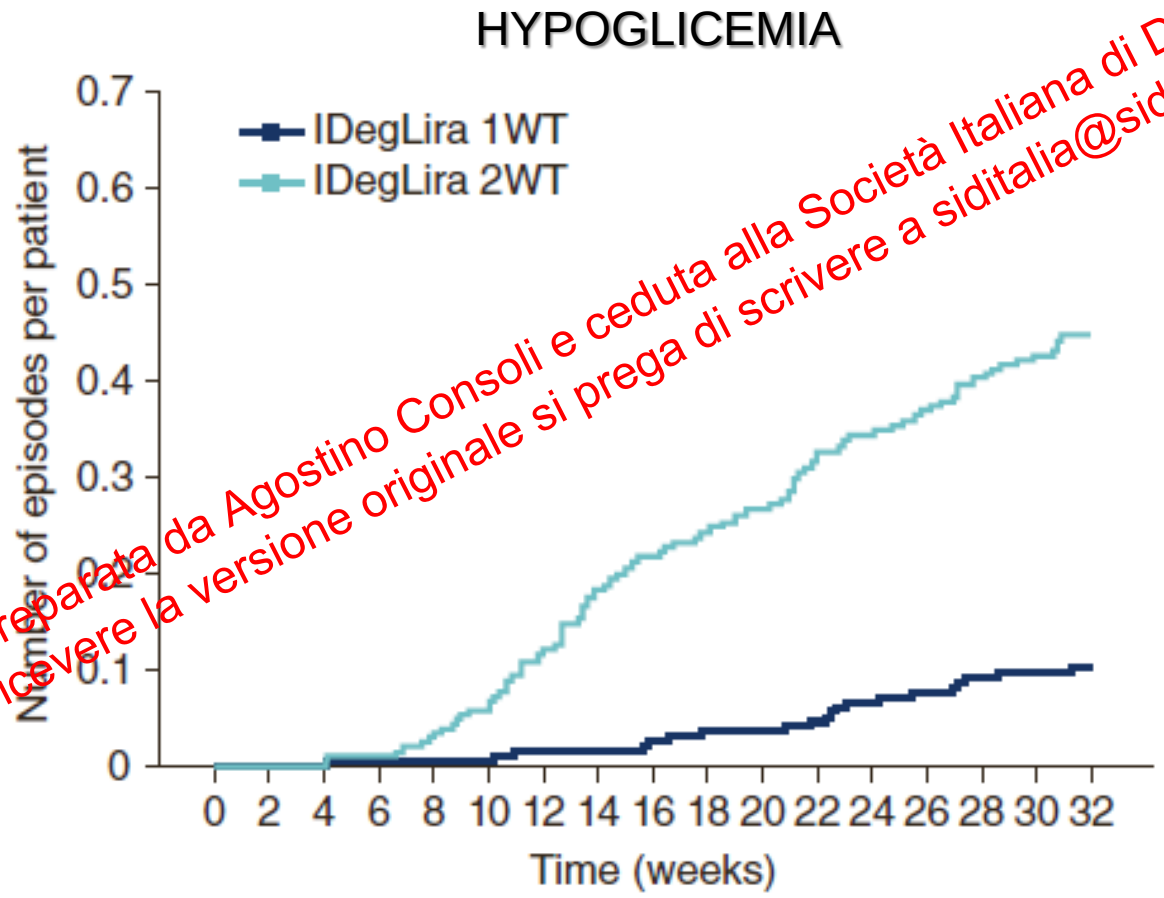

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Conclusions