



Il diabete mellito tipo 2: il futuro

Giorgio Sesti



Università “Magna Graecia” di Catanzaro



YoSID

iscriviti

Diapositiva preparata da Giorgio Sesti e ceduta alla Società Italiana di Diabetologia.
Per avere una versione originale si prega di scrivere a siditalia@siditalia.it

Potenziali conflitti di interesse

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

Novo Nordisk, MSD, Boehringer-Ingelheim, Lilly, Janssen, AstraZeneca, Novartis e Takeda per attività di Relatore ad eventi.

Novo Nordisk, Intarcia, Boehringer-Ingelheim, Lilly, MSD, Servier, AstraZeneca e Janssen per attività di Consulenza.

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

Senza il fondamentale sostegno della SID non sarei oggi qui a presentare questa mia relazione.



SID

Società Italiana
di Diabetologia

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1. Early identification of type 2 diabetes

2. Smart lens to monitor blood sugar

3. Winning Combination

- SGLT2 inhibitors + DPP4 inhibitors
- SGLT2 inhibitors + GLP-1R agonists
- GLP-1R agonists + basal insulin

4. Dual SGLT1/SGLT2 inhibitors

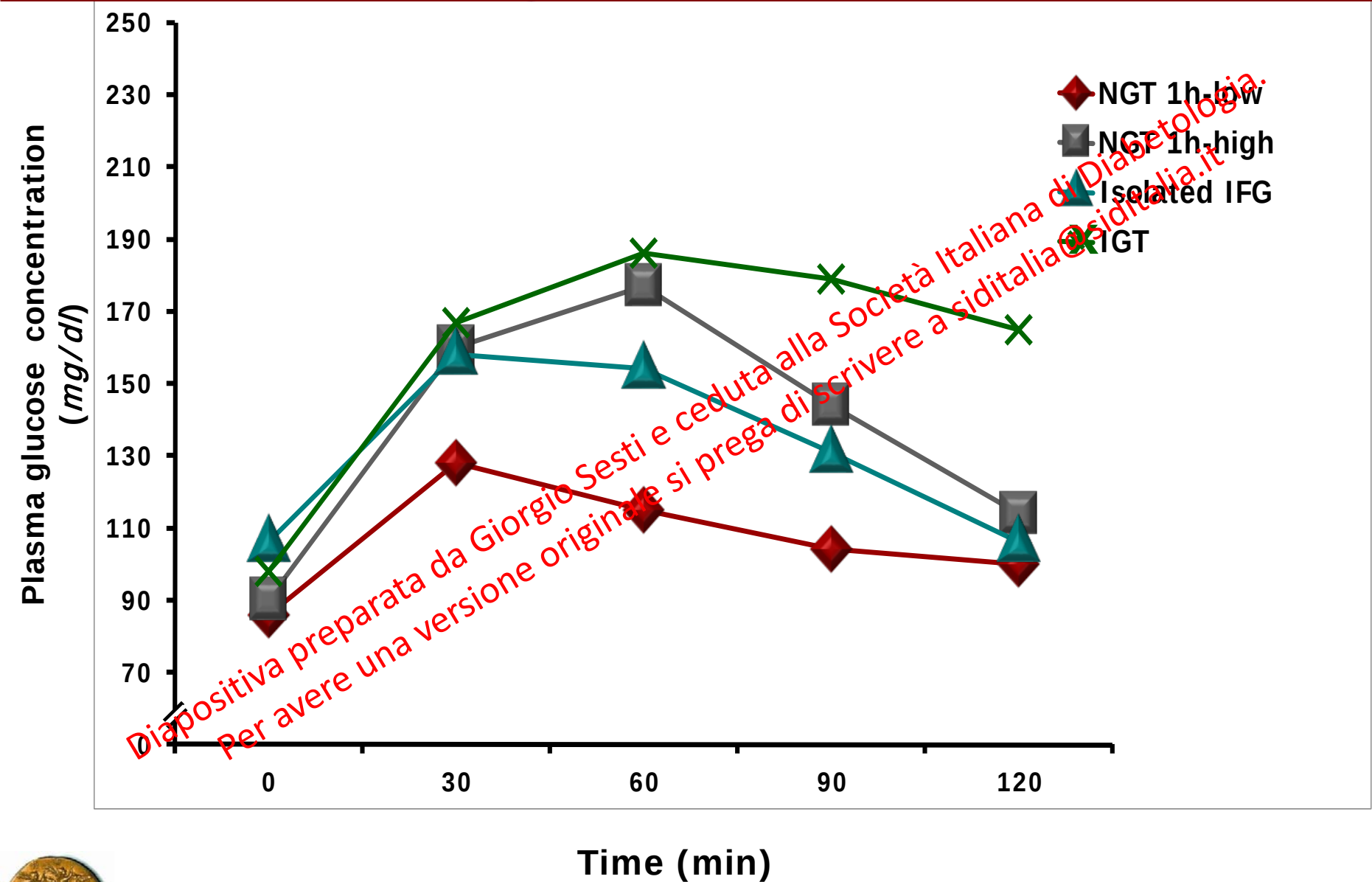
5. Oral, intranasal, and subcutaneous osmotic minipump GLP-1R agonists

6. A combination pump and CGM

7. An example a new drug class

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Plasma glucose levels during OGTT in subjects with NGT 1h-low, NGT 1h-high, isolated IFG and IGT



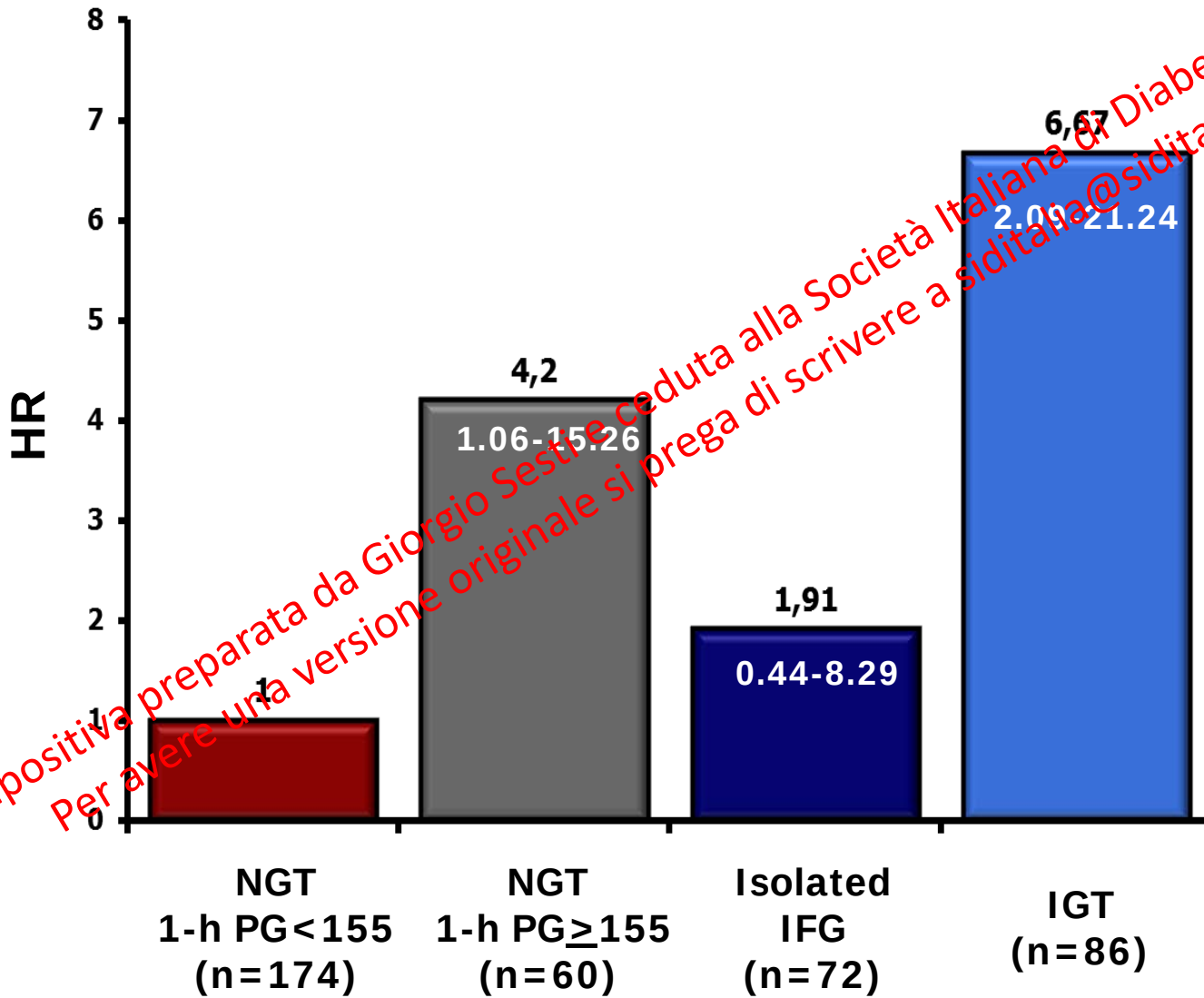
ARTICLE

Modelling of OGTT curve identifies 1 h plasma glucose level as a strong predictor of incident type 2 diabetes: results from two prospective cohorts

Akram Alyass • Peter Almgren • Mikael Akerlund • Jonathan Dushoff •
Bo Isomaa • Peter Nilsson • Tiina Mäkitie • Valeriya Lyssenko •
Leif Groop • David Meyre

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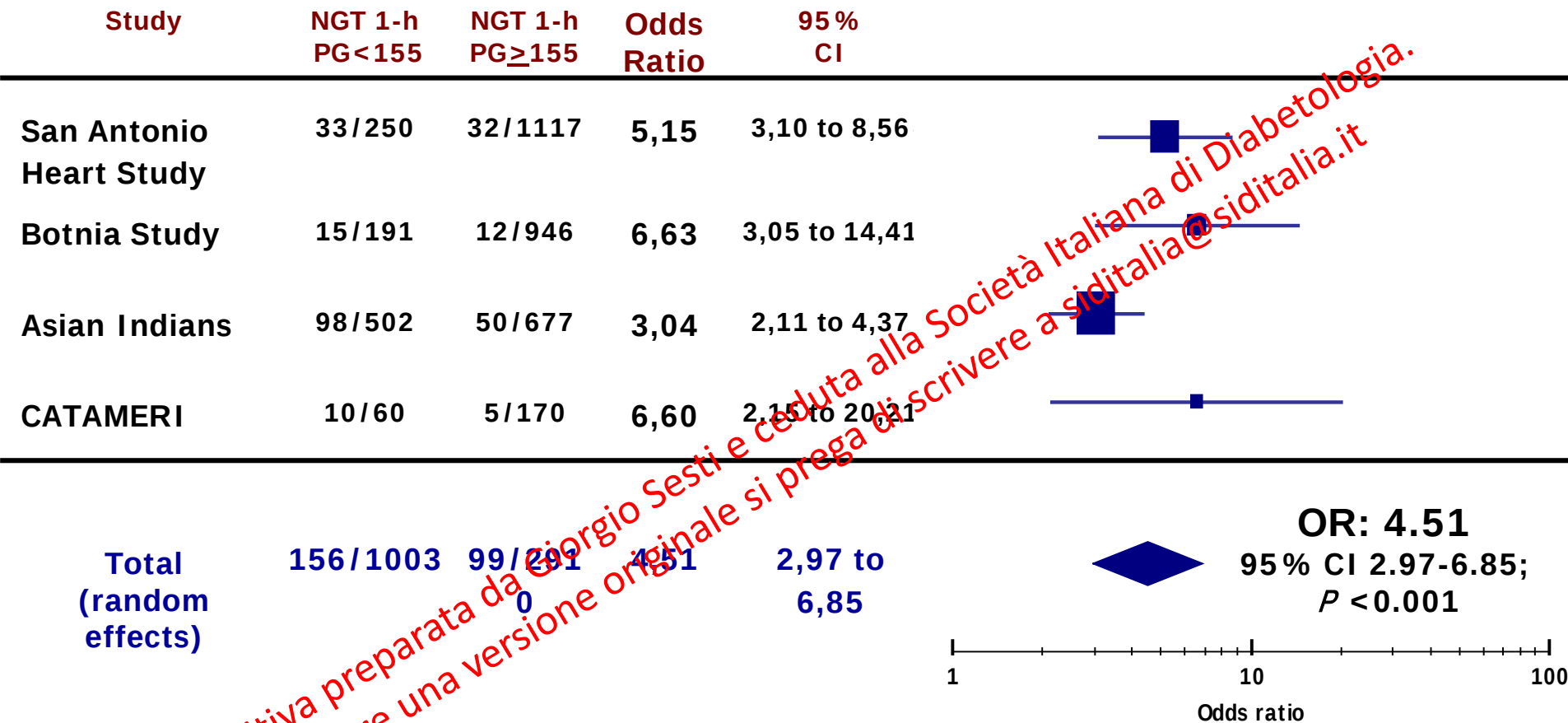
Cox regression analyses adjusted for age, gender and BMI at baseline comparing the risk of NGT 1h-high, isolated IFG and IGT to develop T2DM



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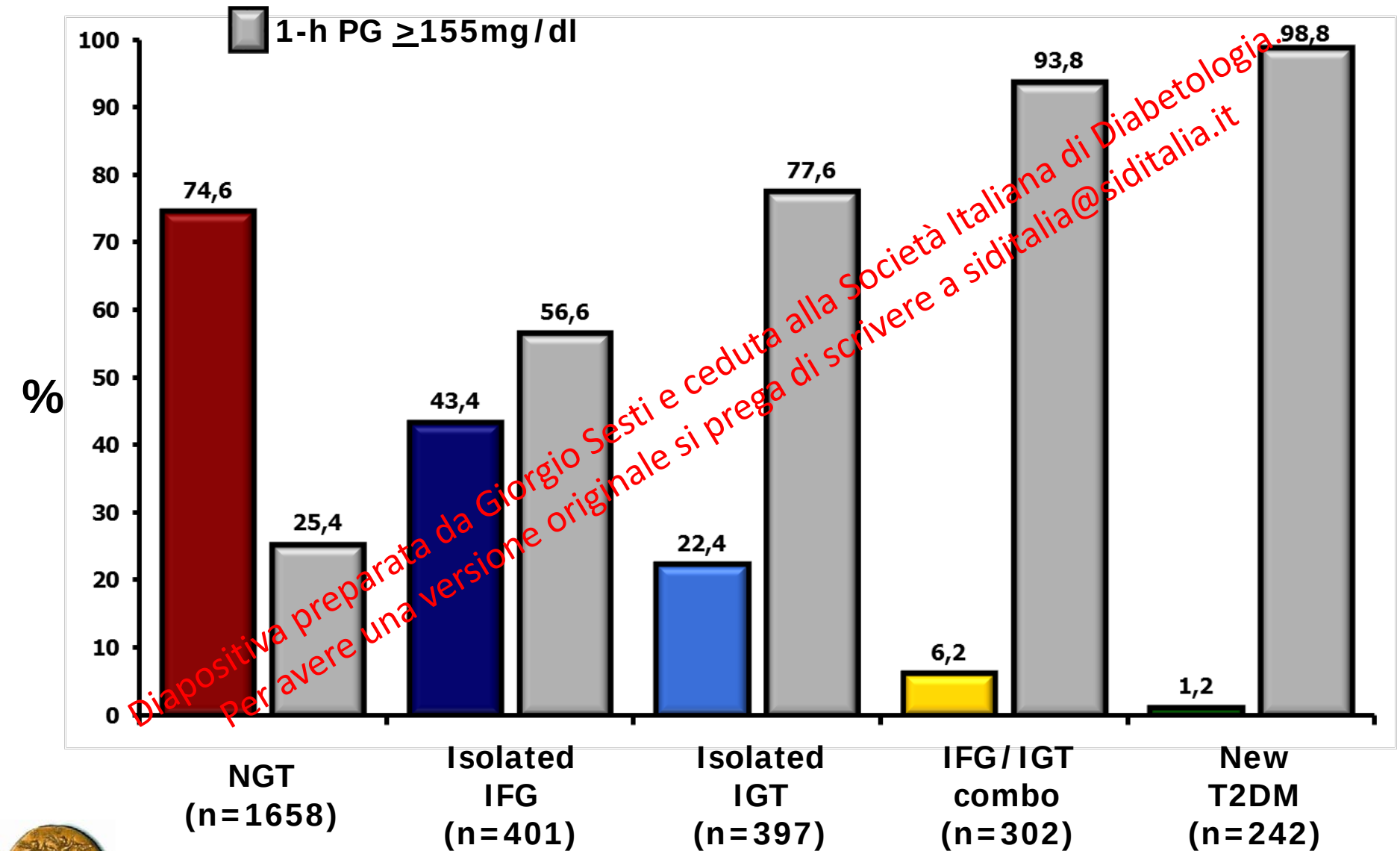


Meta-analysis of four prospective studies



Test for Heterogeneity for 4 studies:
 $P = 0,1313$, $I^2 = 46,67\%$

Proportion of subjects with 1-h PG ≥ 155 mg/dl across dysglycemic conditions. The CATAMERI study (n=3020)



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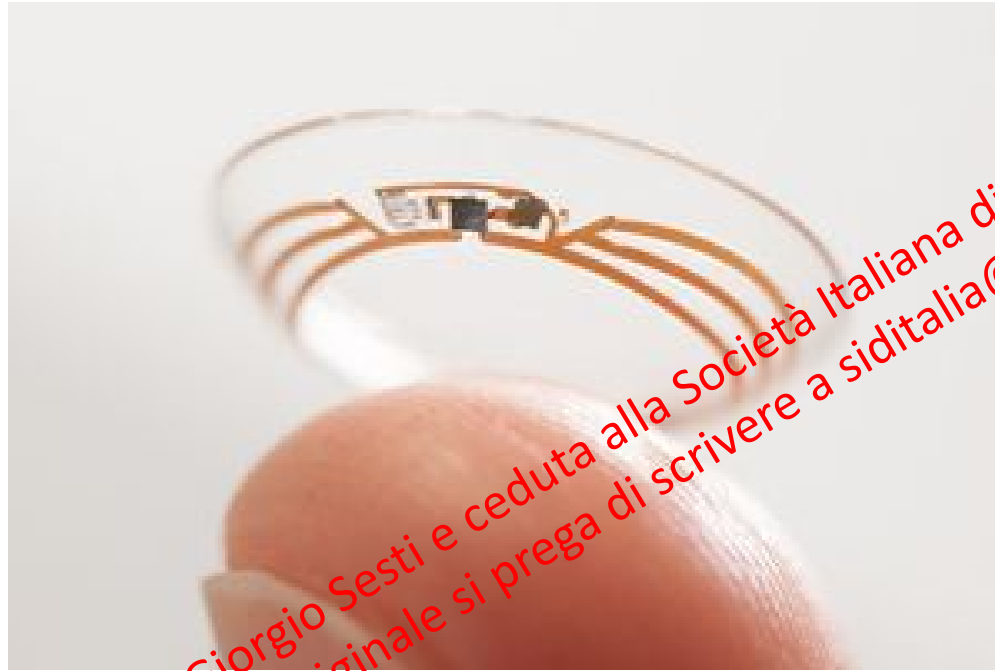
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Smart Lens



Researchers are developing small implants that can monitor blood sugar, eliminating the need for daily finger pricks and injections. Google and Alcon are partnering to develop a contact lens that monitors glucose contained in tears and transmits the data through a tiny antenna.

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- **SGTL2 inhibitors + GLP-1R agonists**
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Rationale for combination of SGLT2 inhibitors with DPP-4 inhibitors

SGLT2 inhibitors

- Insulin-independent glucose reduction
- Increase in glucagone release
- No increase in hypoglycaemia
- Weight loss
- Blood pressure lowering

DPP-4 inhibitors

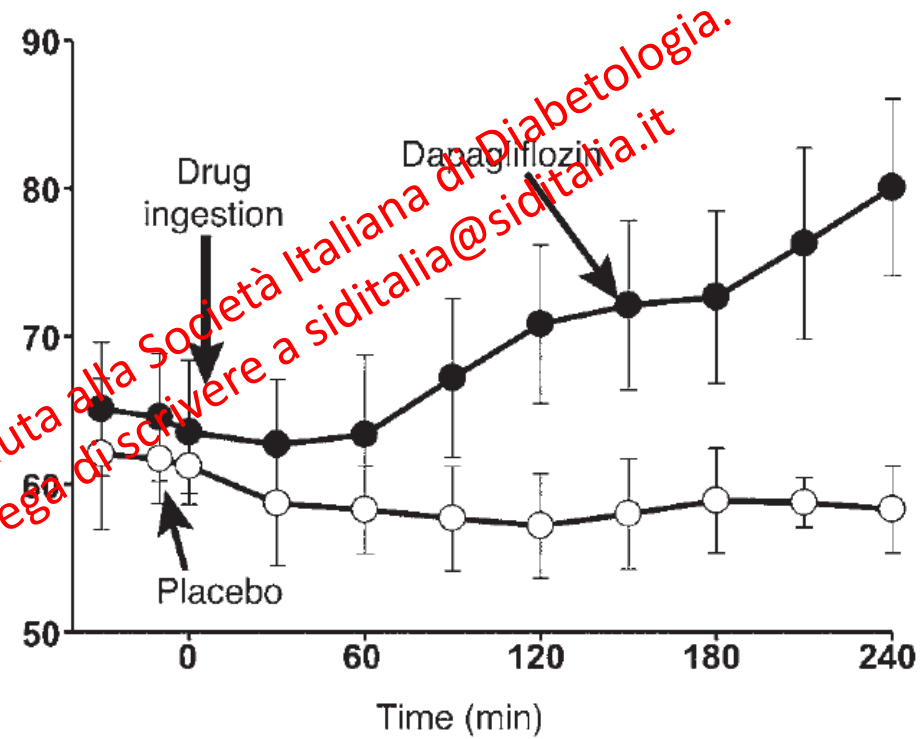
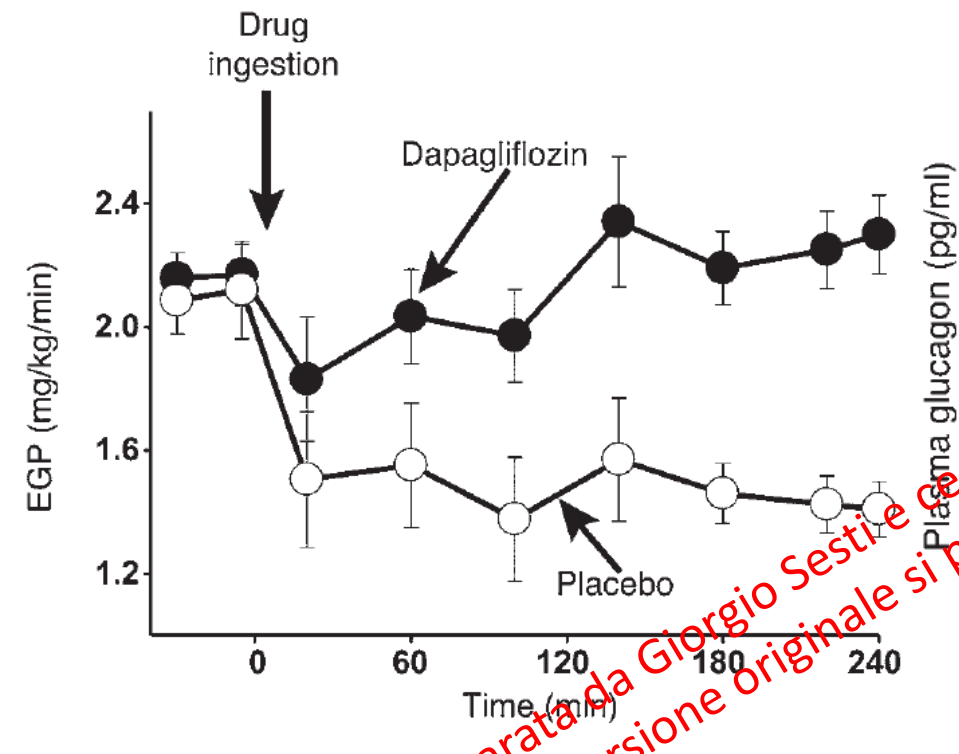
- Glucose-dependent insulin secretion
- Reduction in glucagon release
- No increase in hypoglycaemia
- Weight neutral

Complementary actions

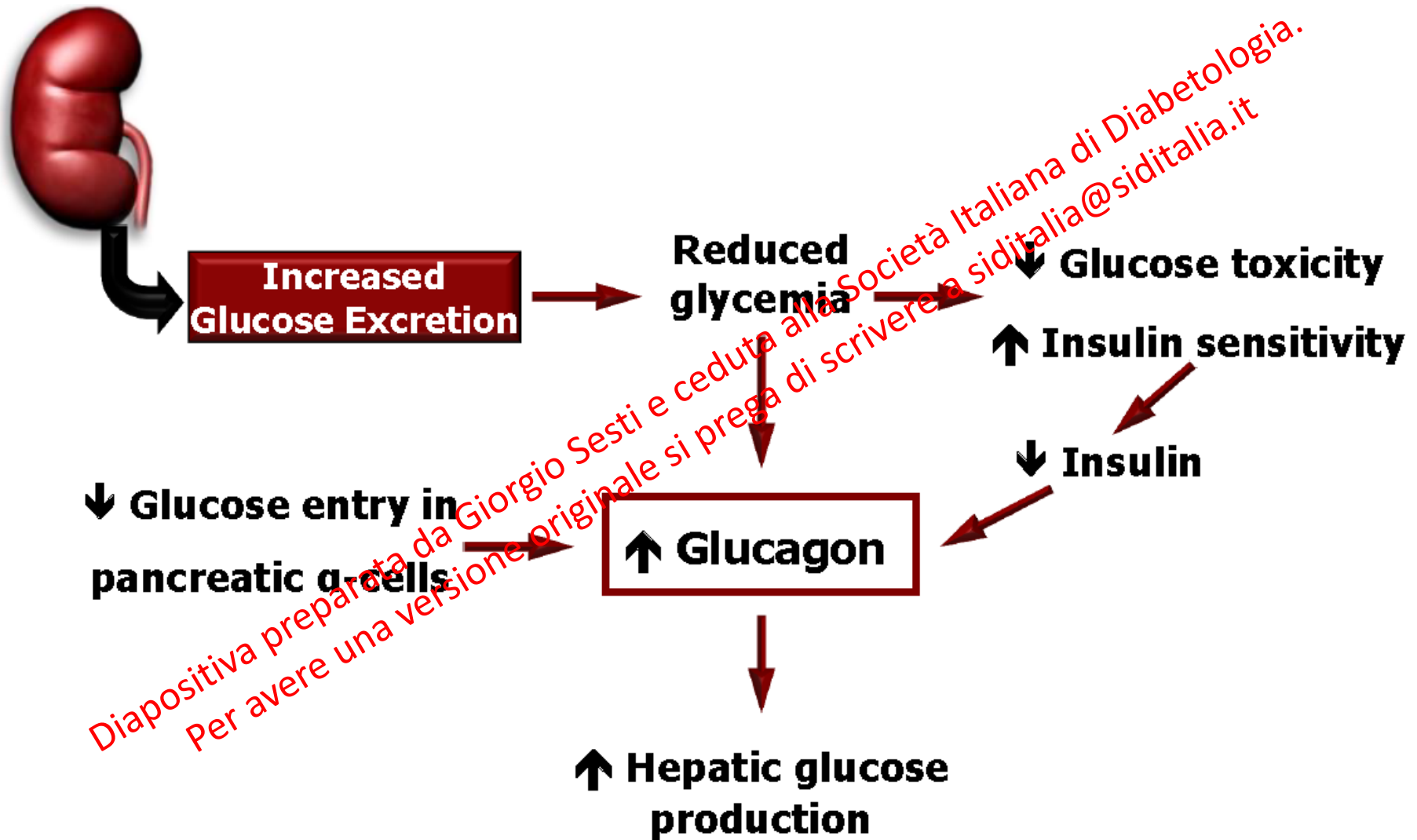
Additive effects

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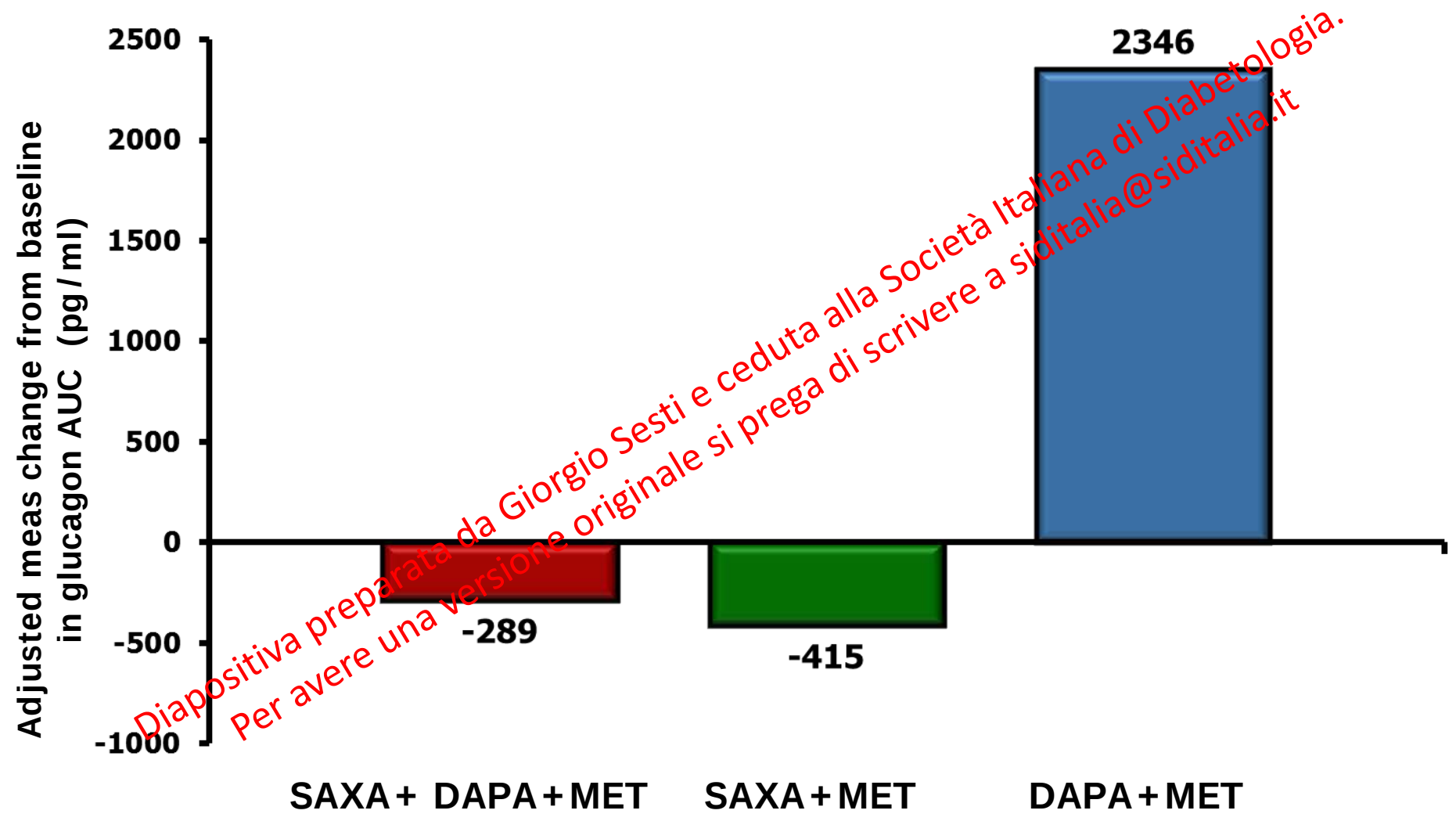
Plasma glucagon concentrations and EGP in the study



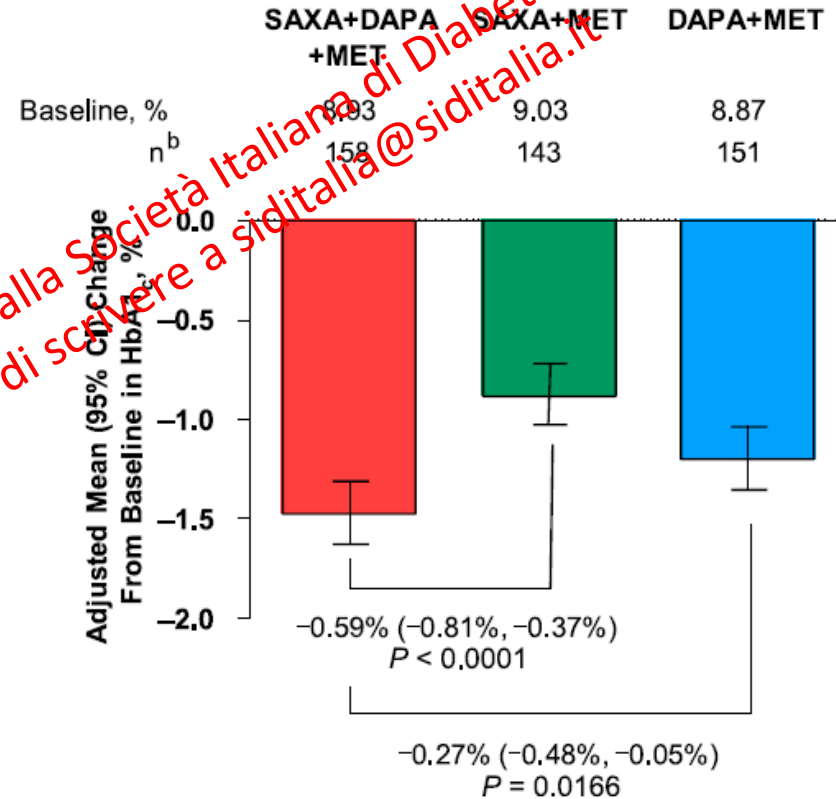
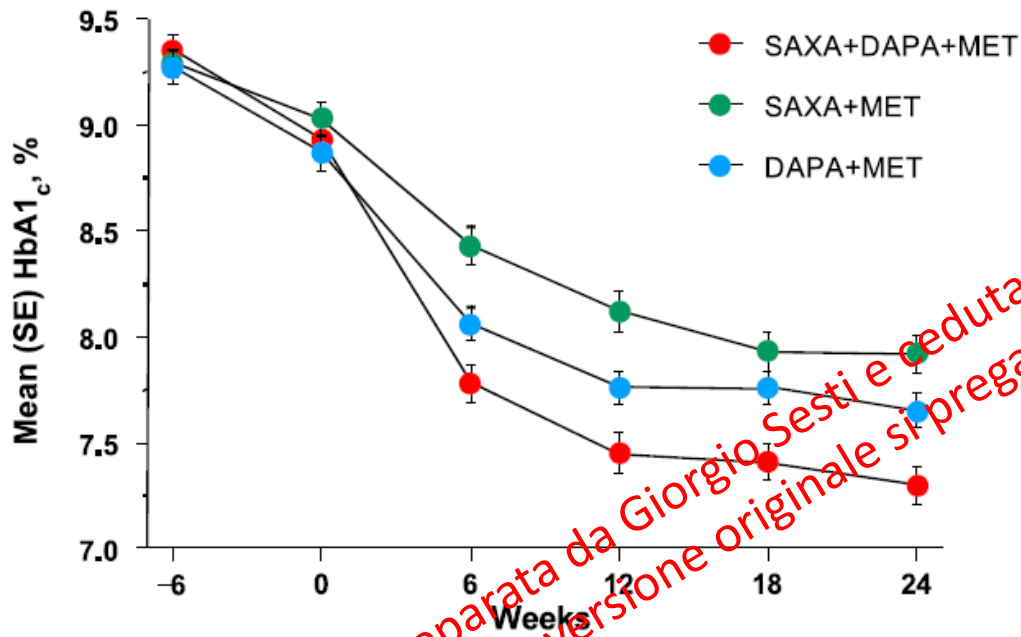
Expected metabolic effects of SGLT2 inhibition based on the mode of action



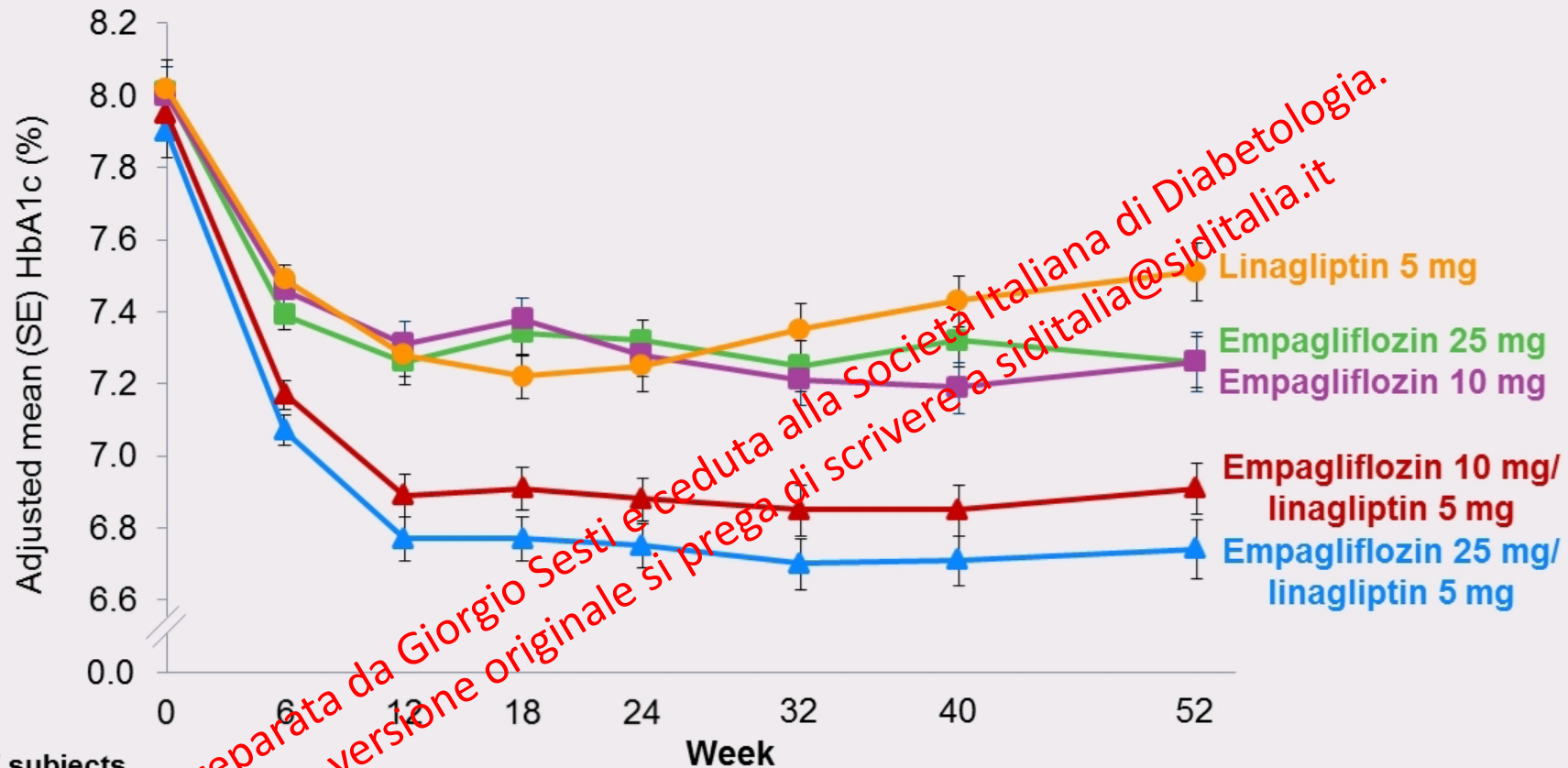
Adjusted mean change from baseline in AUC 0 to 180 minutes for glucagon at 24 weeks during a meal tolerance test



Mean (SE) HbA1c over time and adjusted mean change from baseline in HbA1c at 24 weeks



Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin

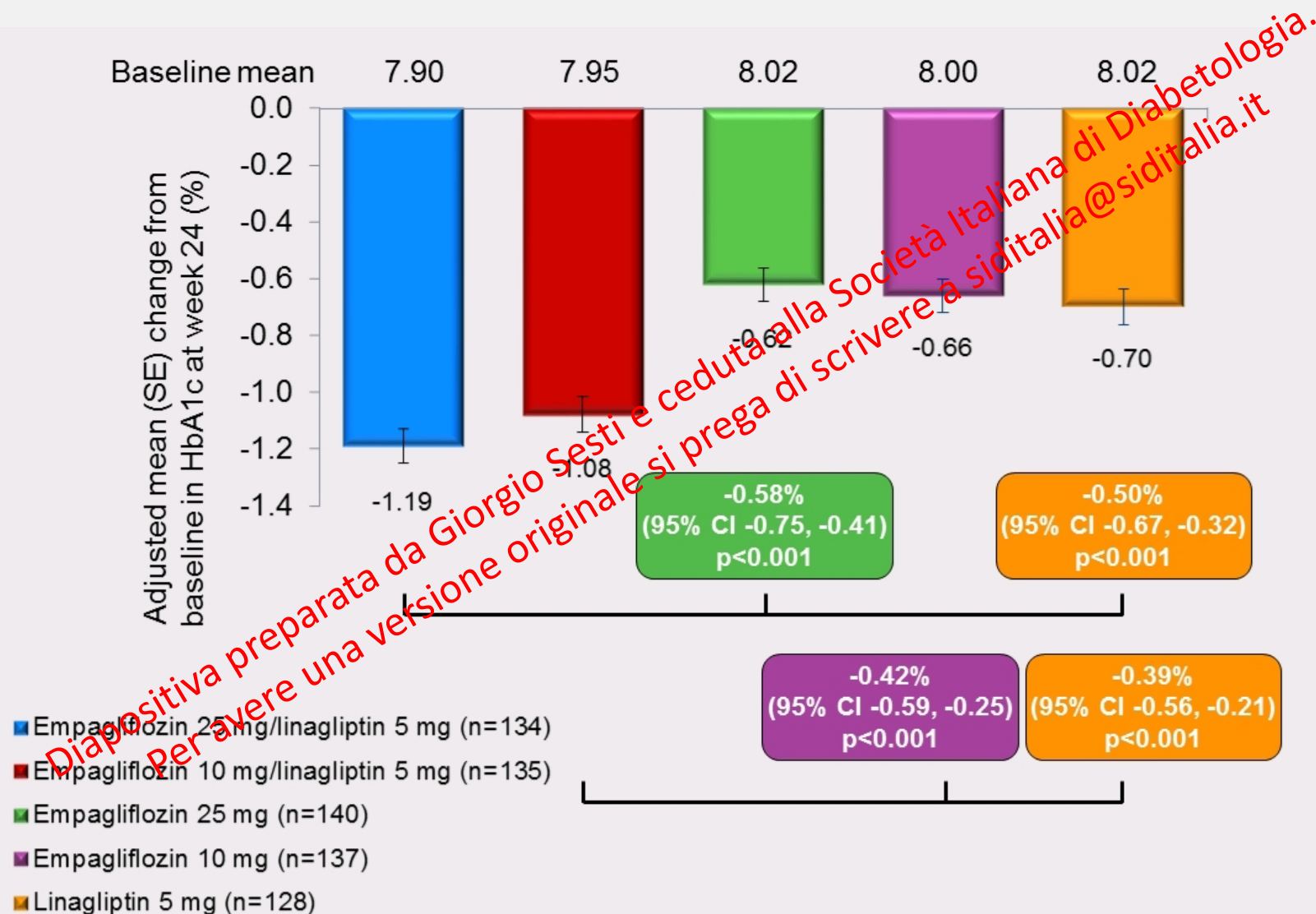


Number of subjects									
Empa 25 mg/lina 5 mg	133	132	131	128	123	121	120	116	
Empa 10 mg/lina 5 mg	135	135	134	131	127	125	120	117	
Empa 25 mg	139	138	136	132	128	122	116	111	
Empa 10 mg	137	137	128	128	126	122	118	112	
Lina 5 mg	128	128	124	123	117	111	96	90	

MMRM in full analysis set (observed cases).

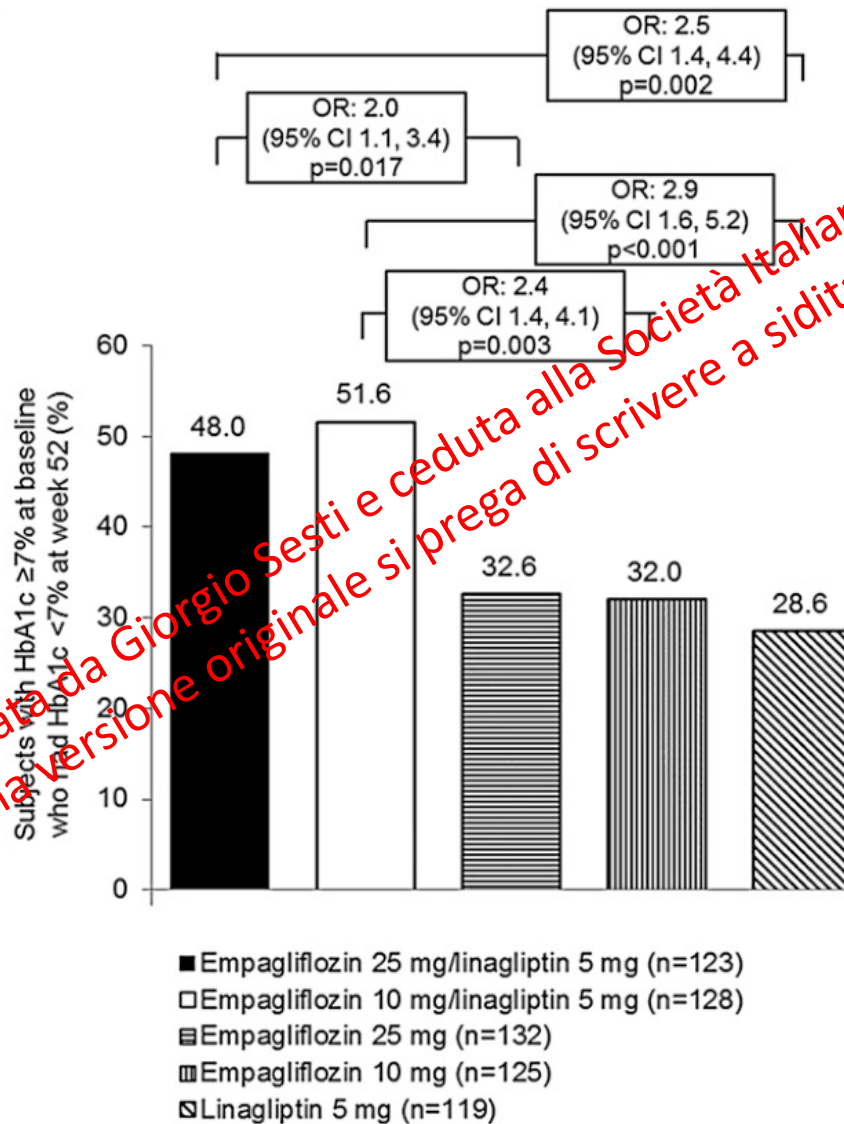
Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin

Change from baseline in HbA1c at week 24



Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin

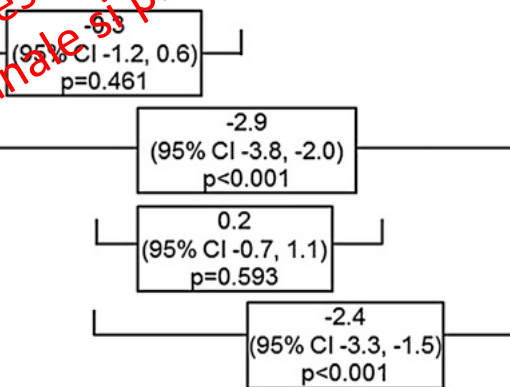
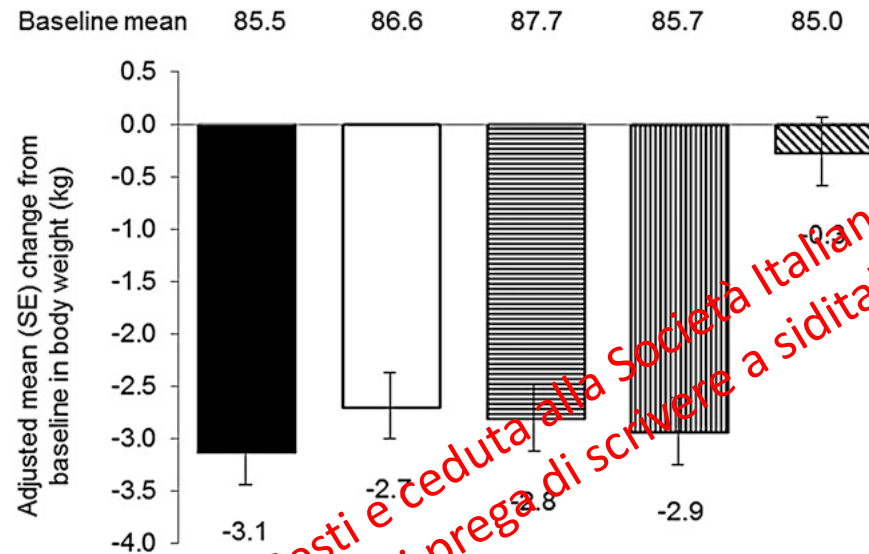
Subjects with HbA1c >7 % who reached HbA1c <7 % at week 52



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Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin

Change from baseline in body weight at week 52



- Empagliflozin 25 mg/linagliptin 5 mg (n=134)
- Empagliflozin 10 mg/linagliptin 5 mg (n=135)
- ▨ Empagliflozin 25 mg (n=140)
- ▩ Empagliflozin 10 mg (n=137)
- ▤ Linagliptin 5 mg (n=128)

Rationale for combination of SGLT2 inhibitors with a GLP-1R agonist

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- Increase in glucagone release
- No increase in hypoglycaemia
- Weight loss
- Blood pressure lowering
- Increase in energy intake

GLP-1R agonists

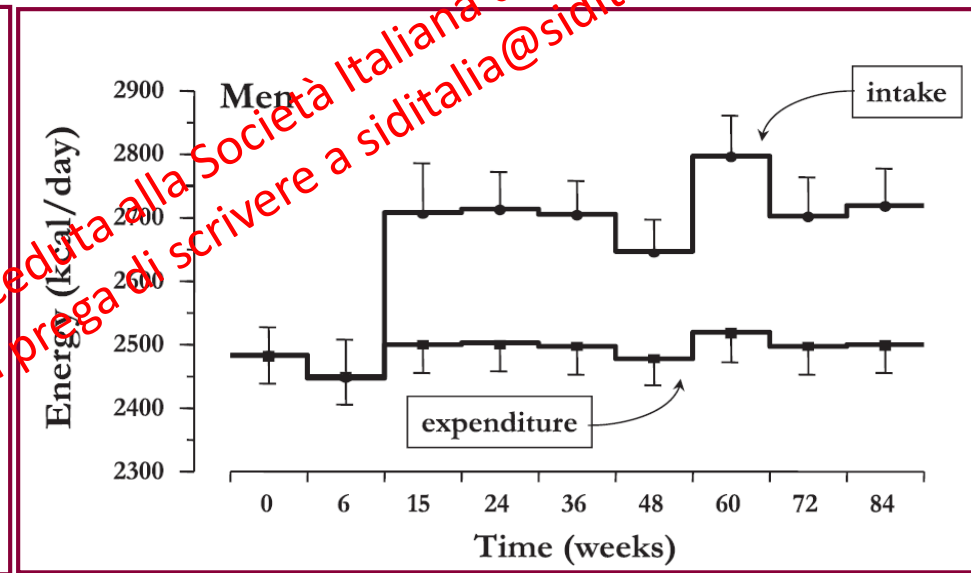
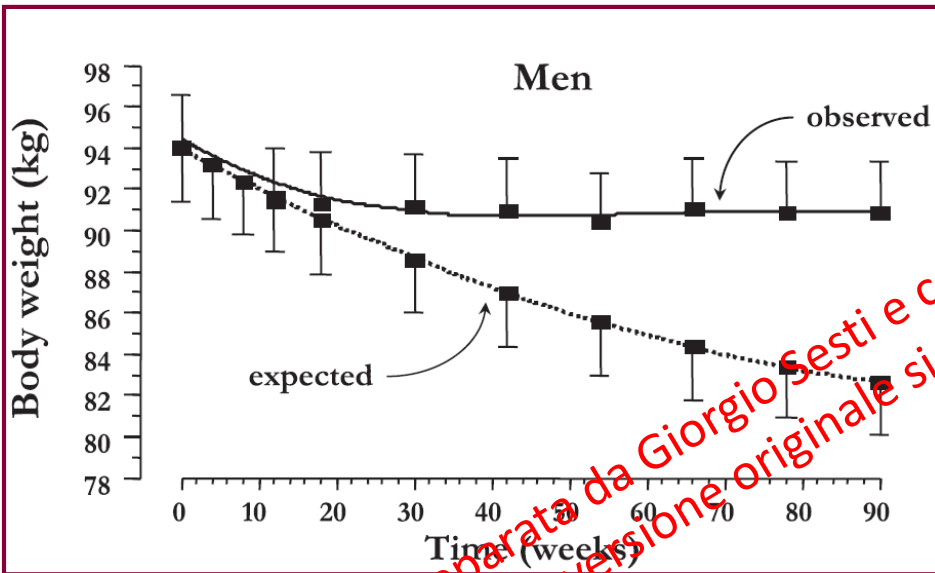
- Glucose-dependent insulin secretion
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- Weight loss
- Blood pressure lowering
- Reduction in energy intake

Complementary actions

Additive effects

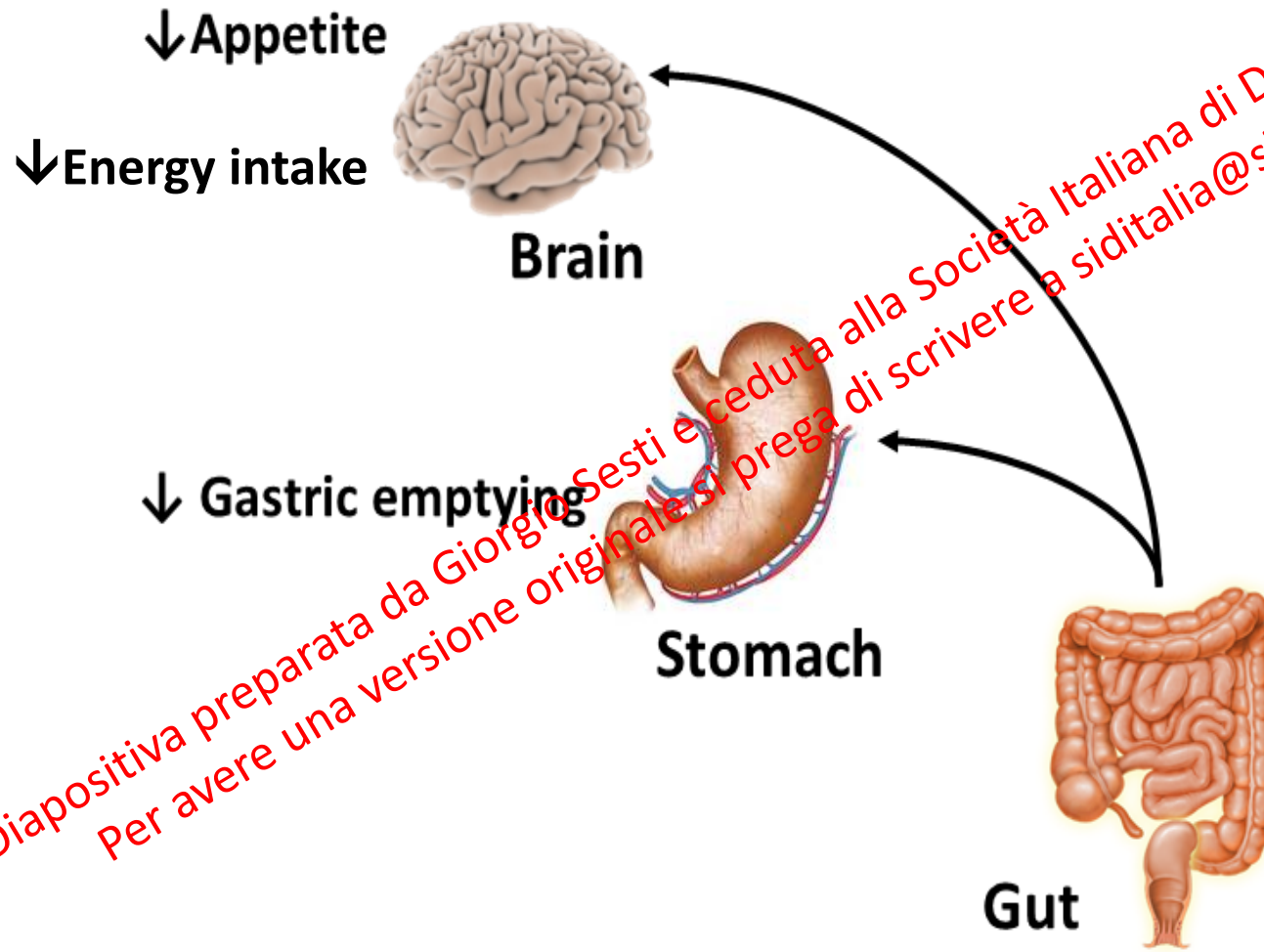
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Time course of observed and predicted (by glycosuria) weight loss and calculated rates of energy intake in men with T2DM treated with empagliflozin (25 mg/day) for 90 weeks



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GLP-1: its role in weight loss

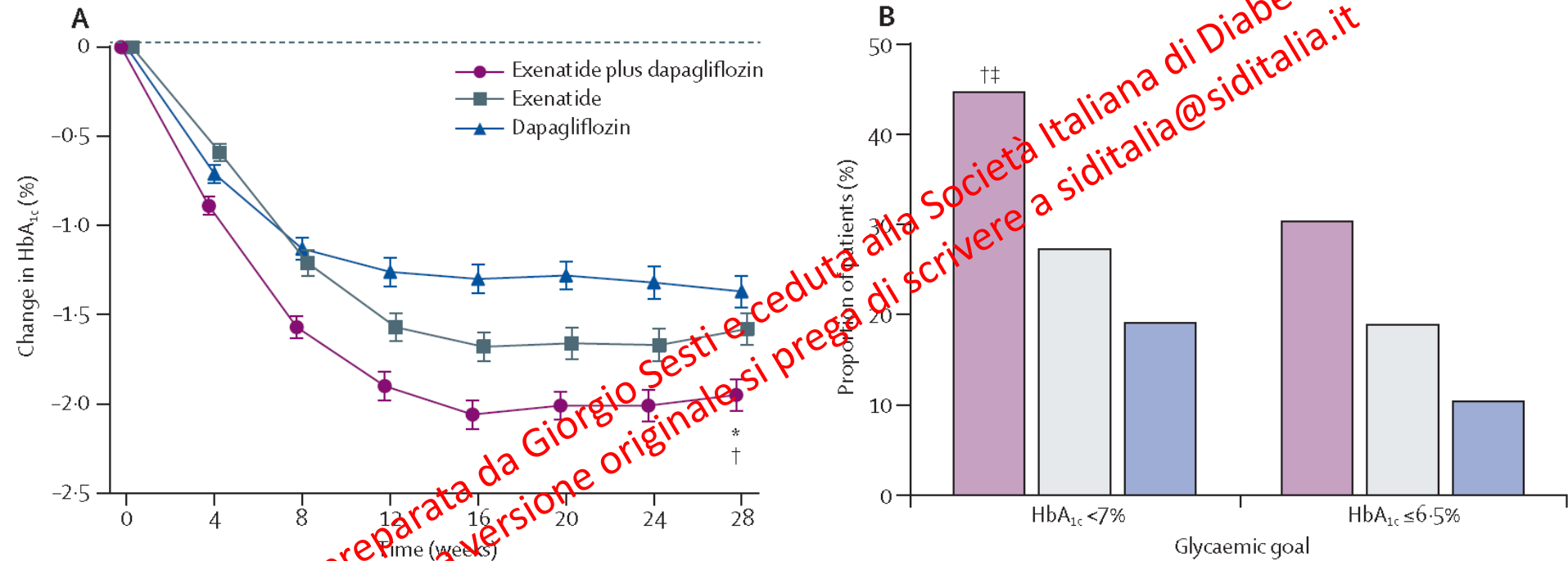


Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial

Juan P Frías, Cristian Guja, Elise Nardy, Azizuddin Ahmed, Fang Dong, Peter Öhman, Serge A Jabbour*

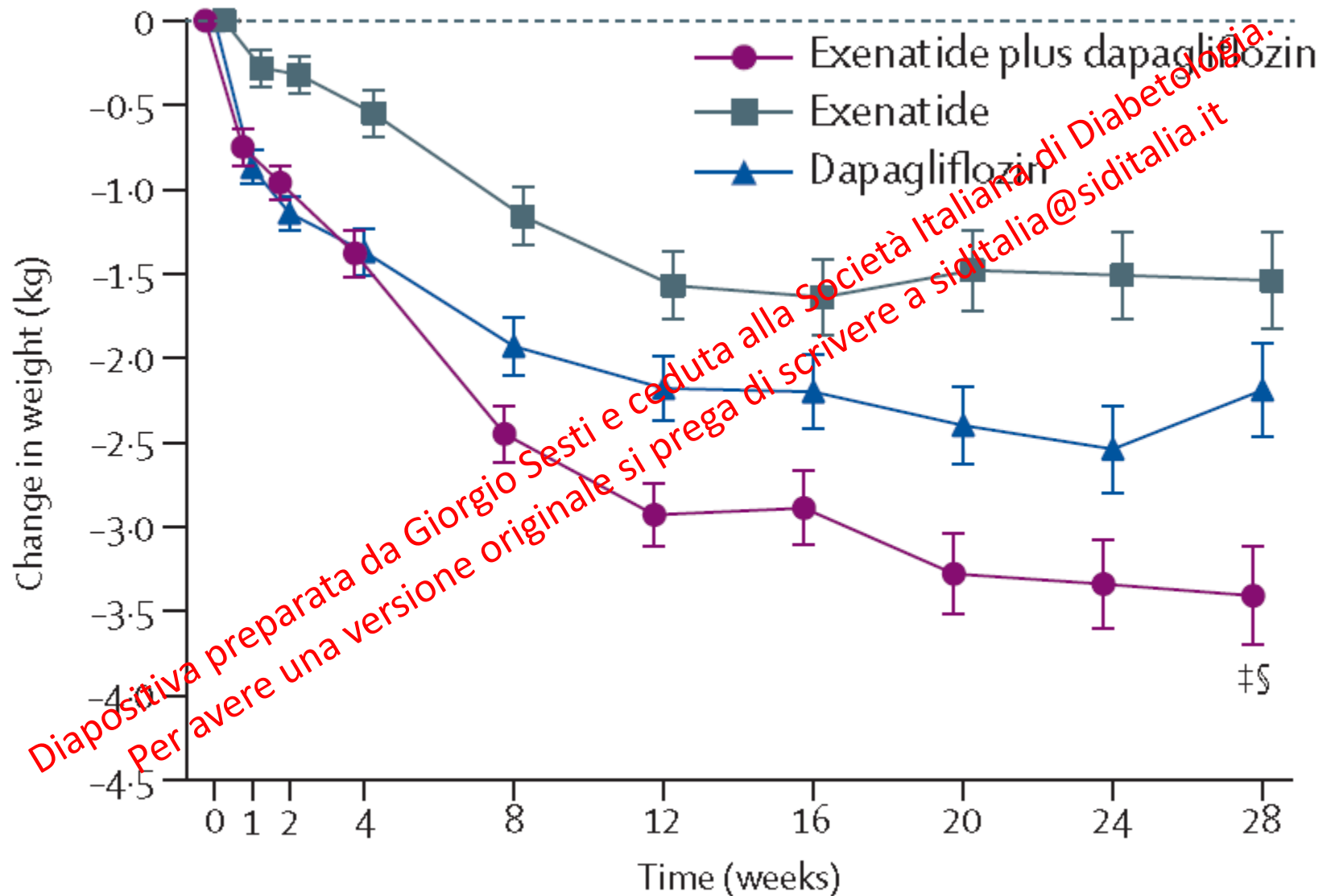
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Mean change in HbA_{1c} and proportion of patients achieving an HbA_{1c} target of less than 7% or of <6.5% at week 28

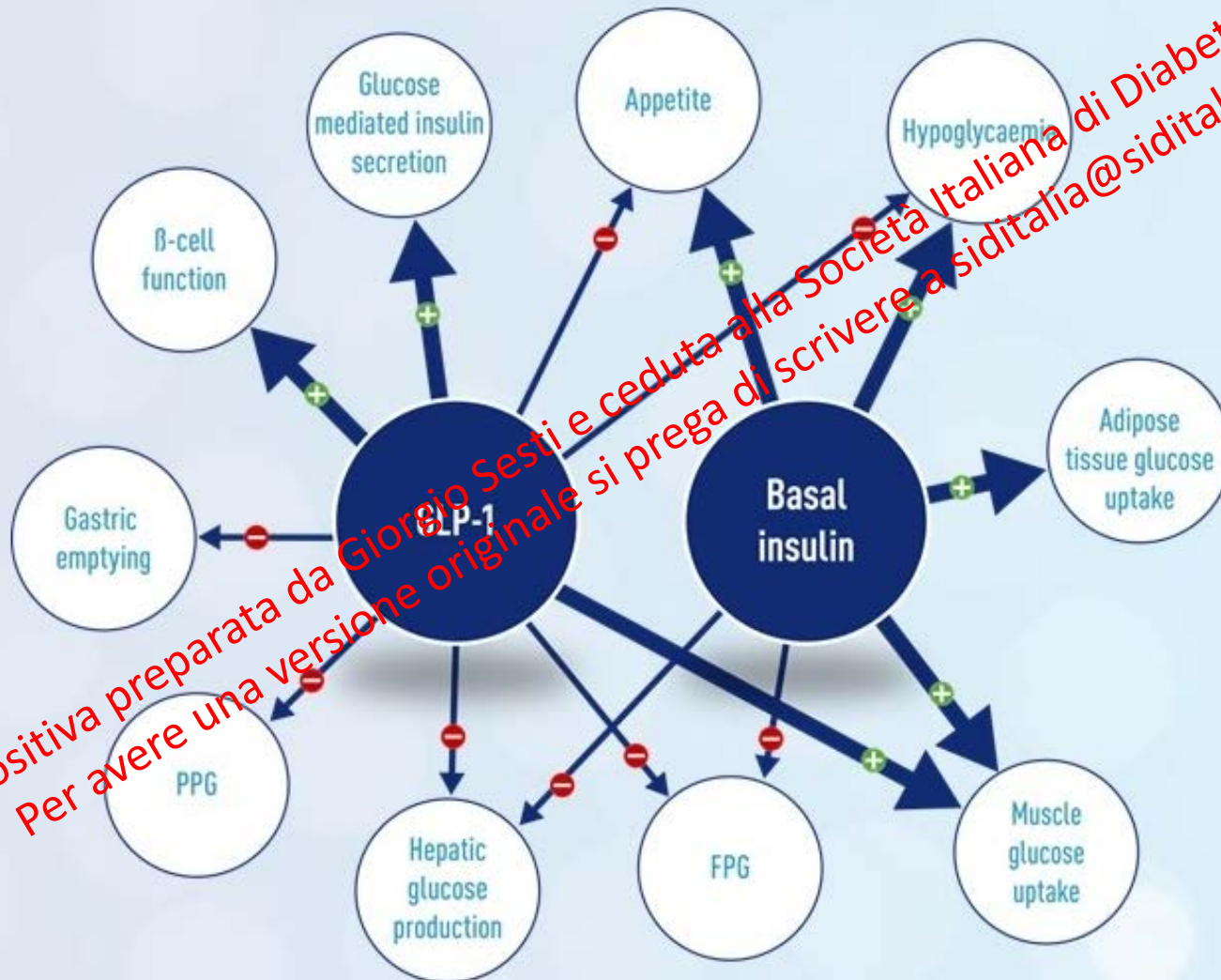


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Mean change in body weight at week 28



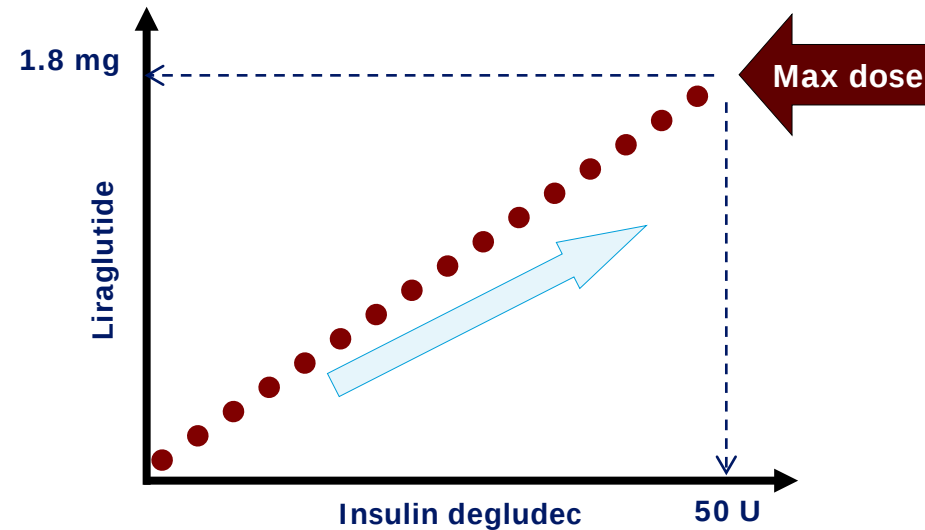
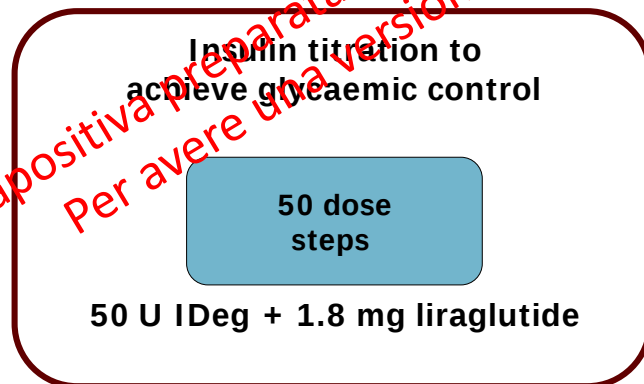
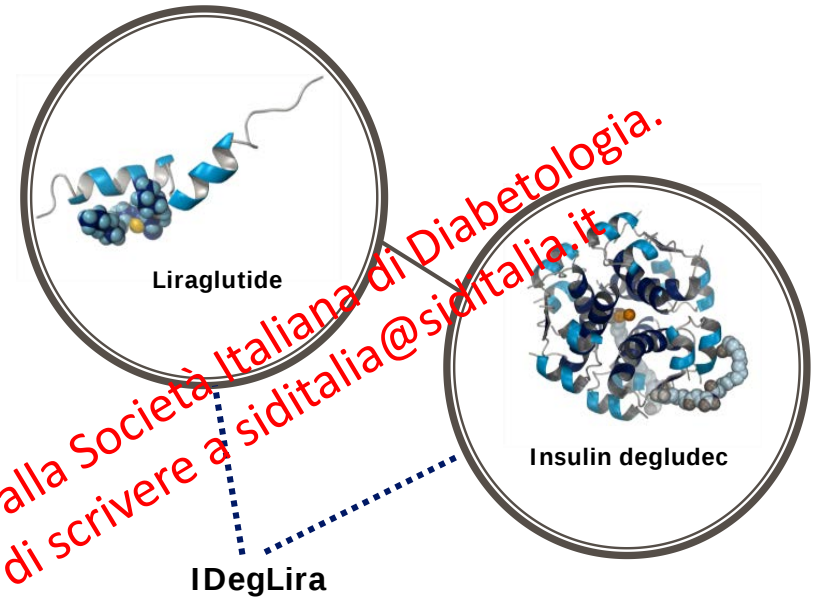
Rationale for combining GLP-1RA and basal insulin analogs



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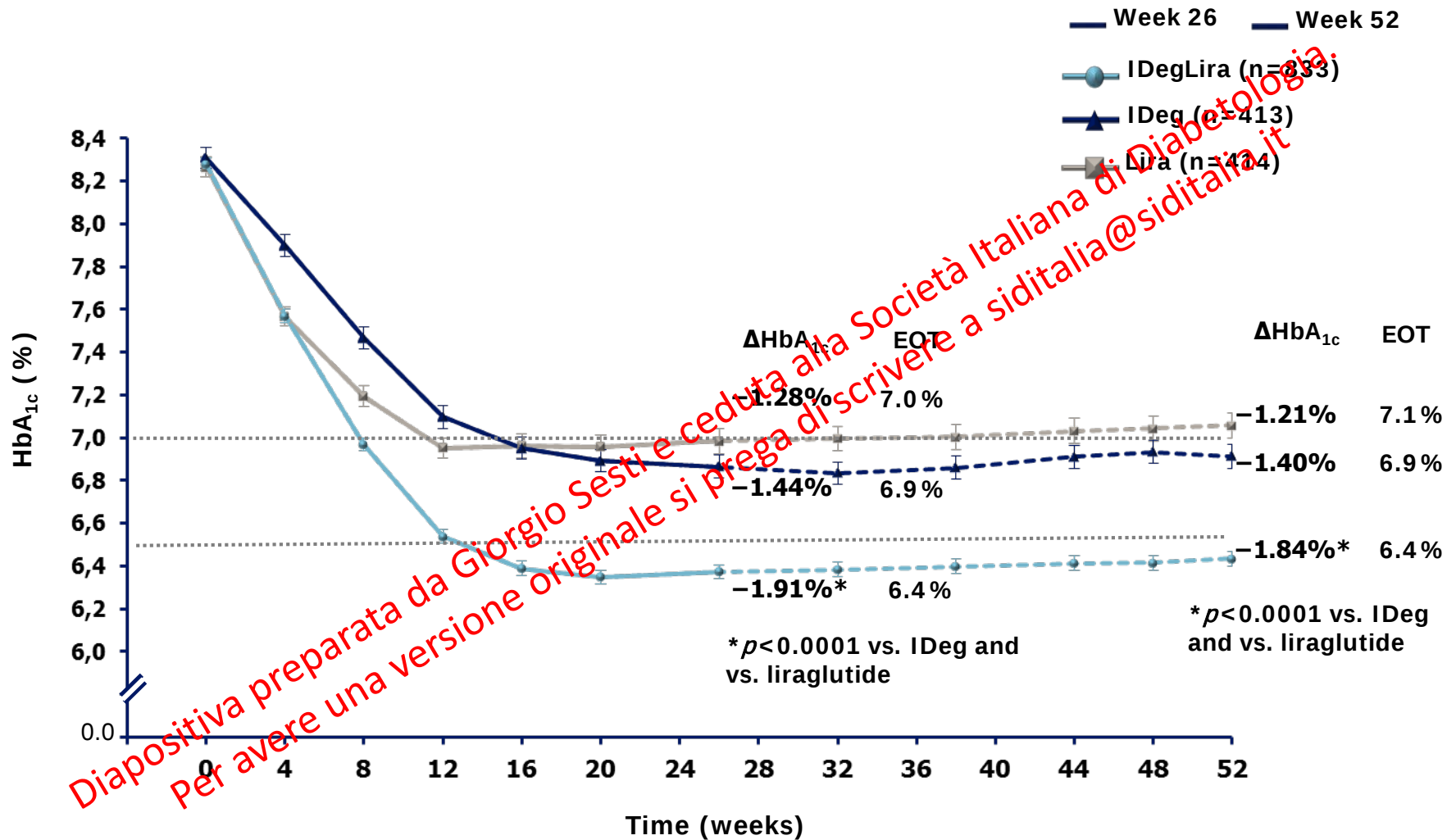
Combination IDegLira

- **Unique anticipated properties**
 - Glycaemic control throughout the day with FPG reduction and PPG coverage at all meals
 - Steady titration profile and more favourable safety profile
- **Once-daily single subcutaneous injection**
 - 3 mL pre-filled pen
 - Fixed ratio of IDeg (100 U/mL) and liraglutide (3.6 mg/mL)



DUAL I extension

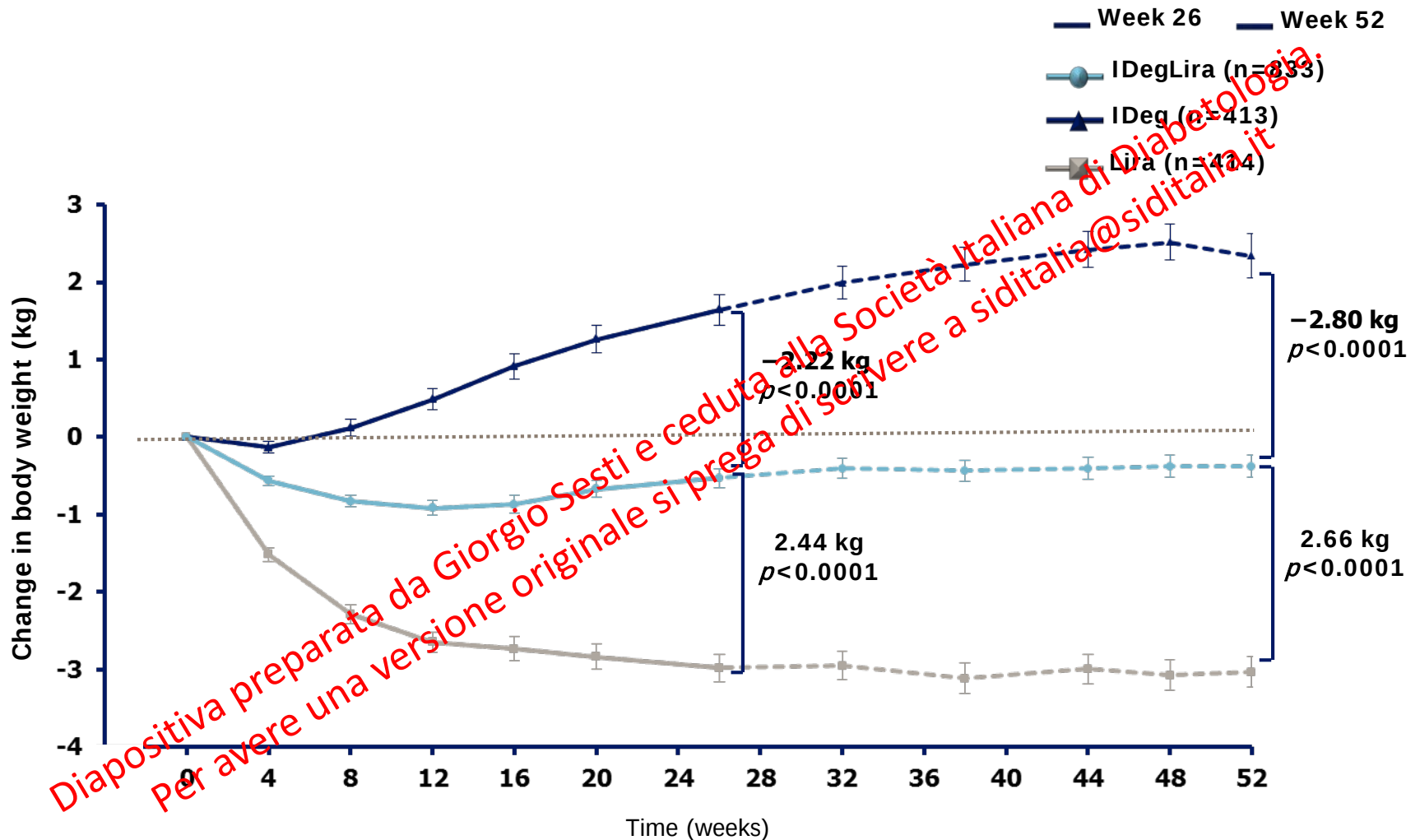
HbA_{1c} over time



Mean values with error bars (standard error mean) based on FAS and LOCF imputed data
 p-values are from an ANCOVA model
 FAS, full analysis set; LOCF, last observation carried forward

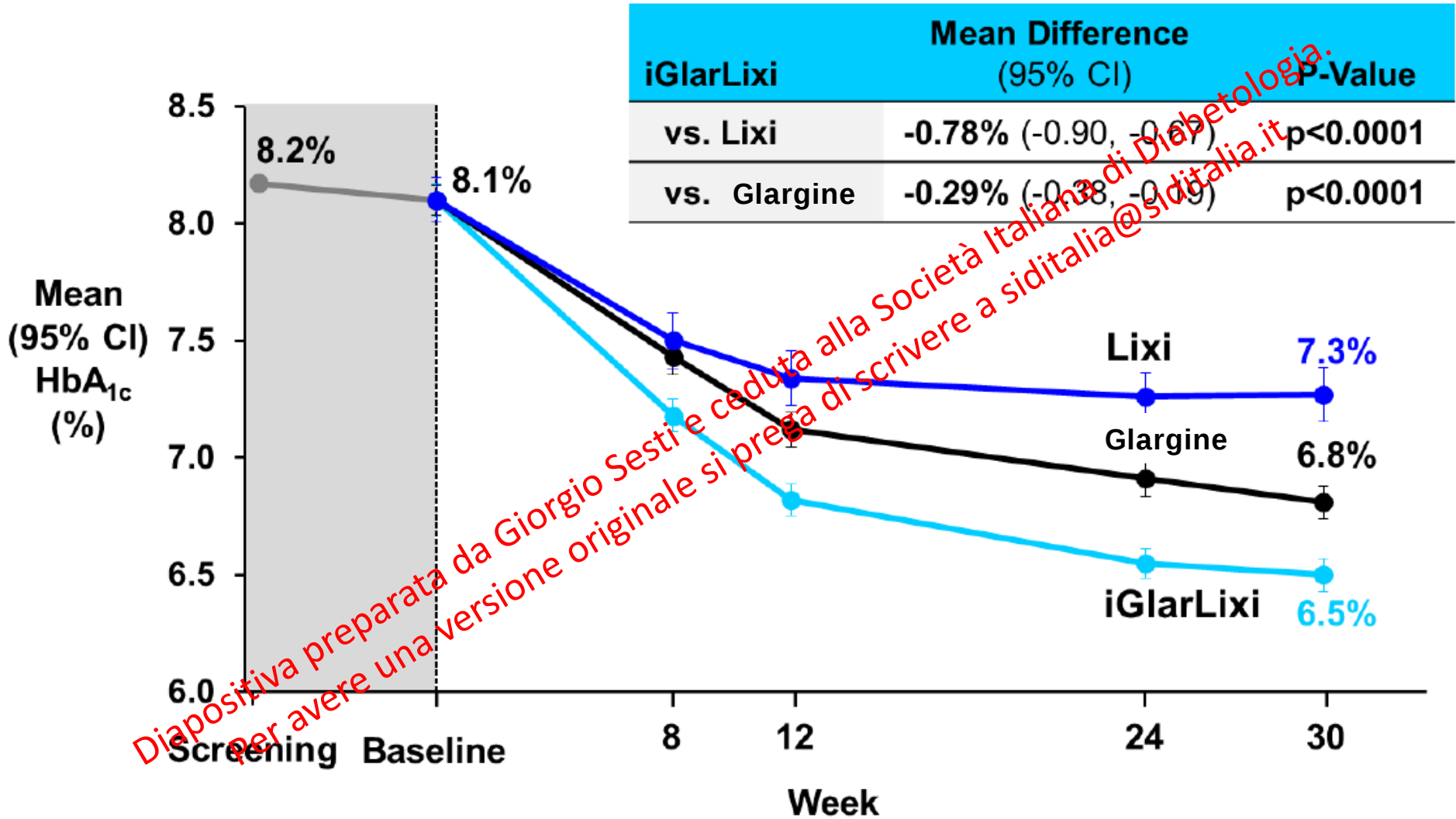
DUAL I extension

Change in body weight over time

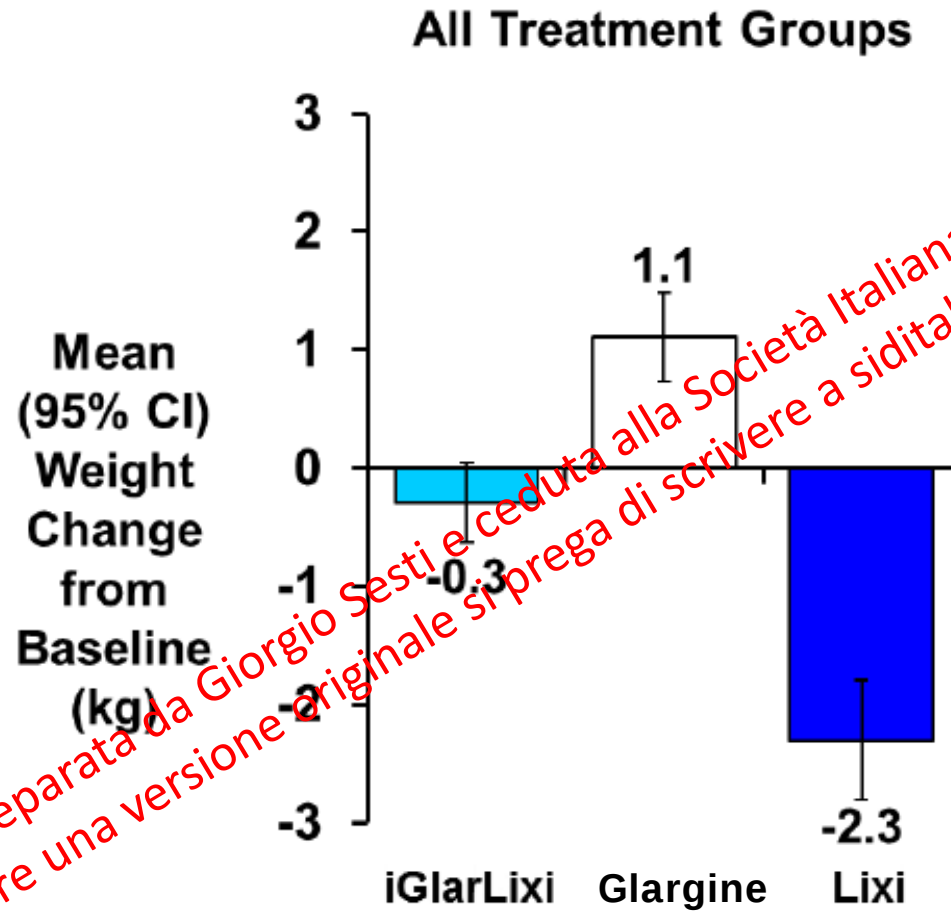


Mean values with error bars (standard error mean) based on FAS and LOCF imputed data
Estimated treatment differences and p values are from an ANCOVA model

Efficacy of iGlarLixi, insulin glargine, and lixisenatide in insulin-naïve



Mean change in weight from baseline to Week 30 with iGlarLixi



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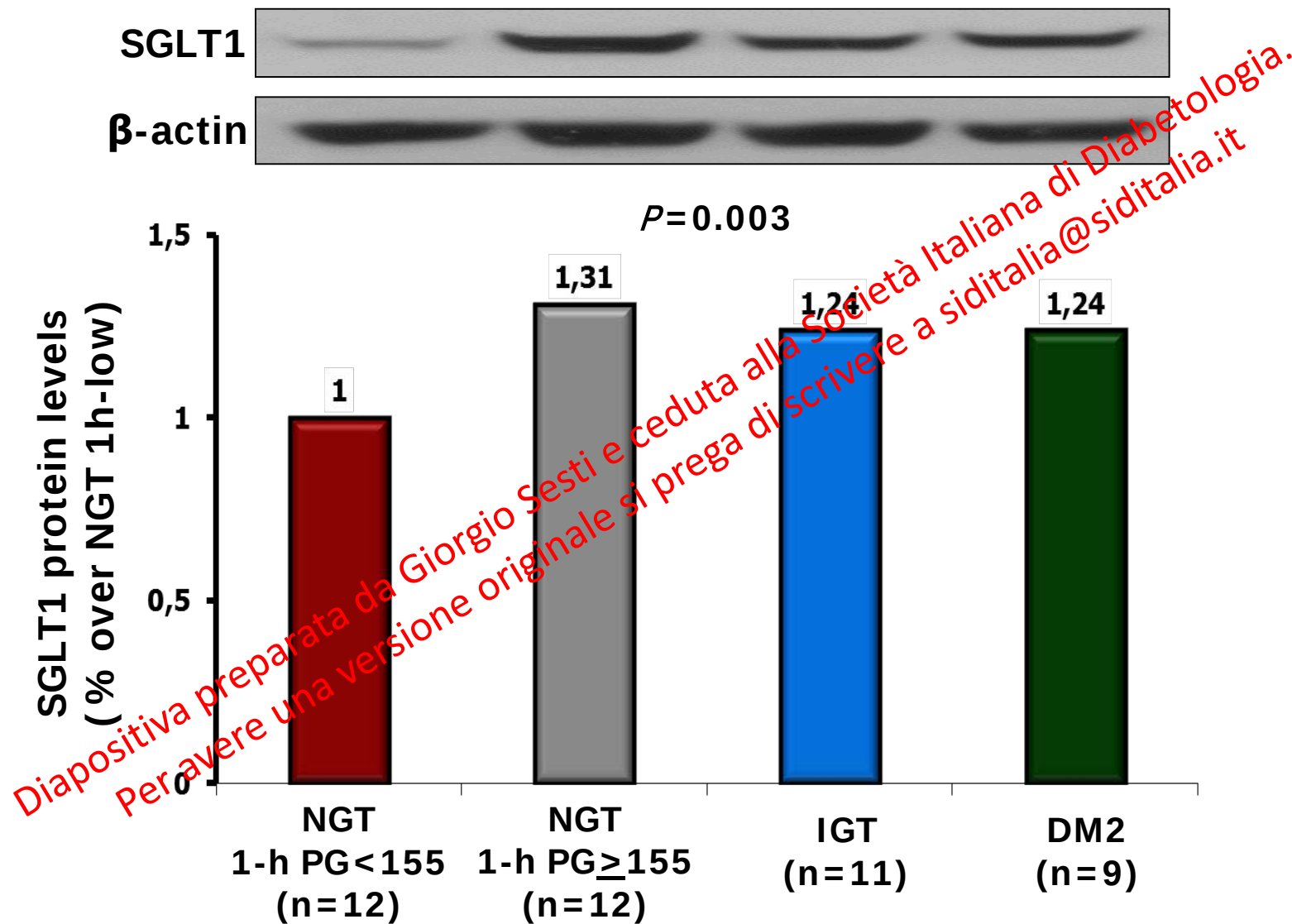
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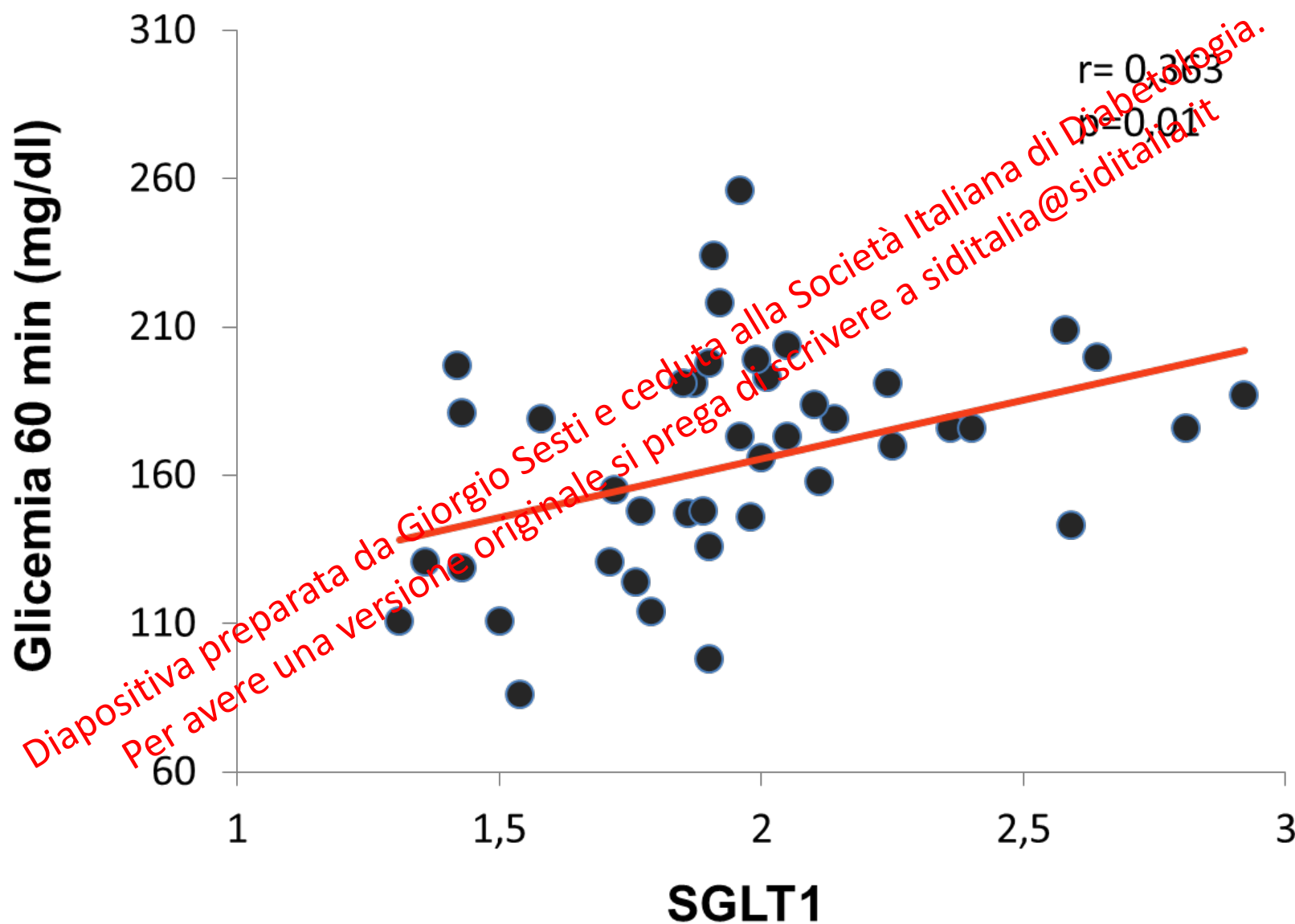
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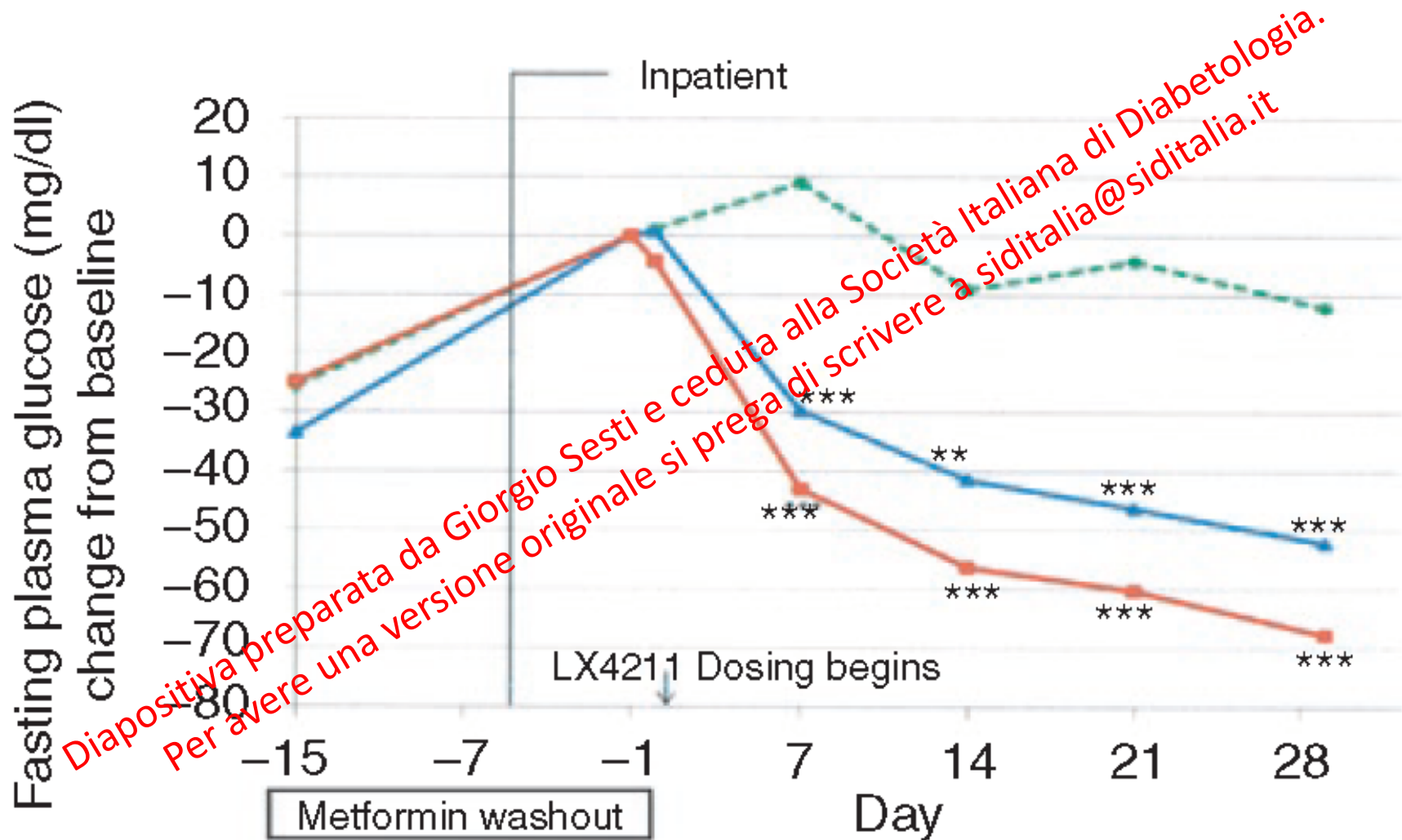
Intestinal SGLT1 protein levels are increased in subjects with post-load hyperglycemia



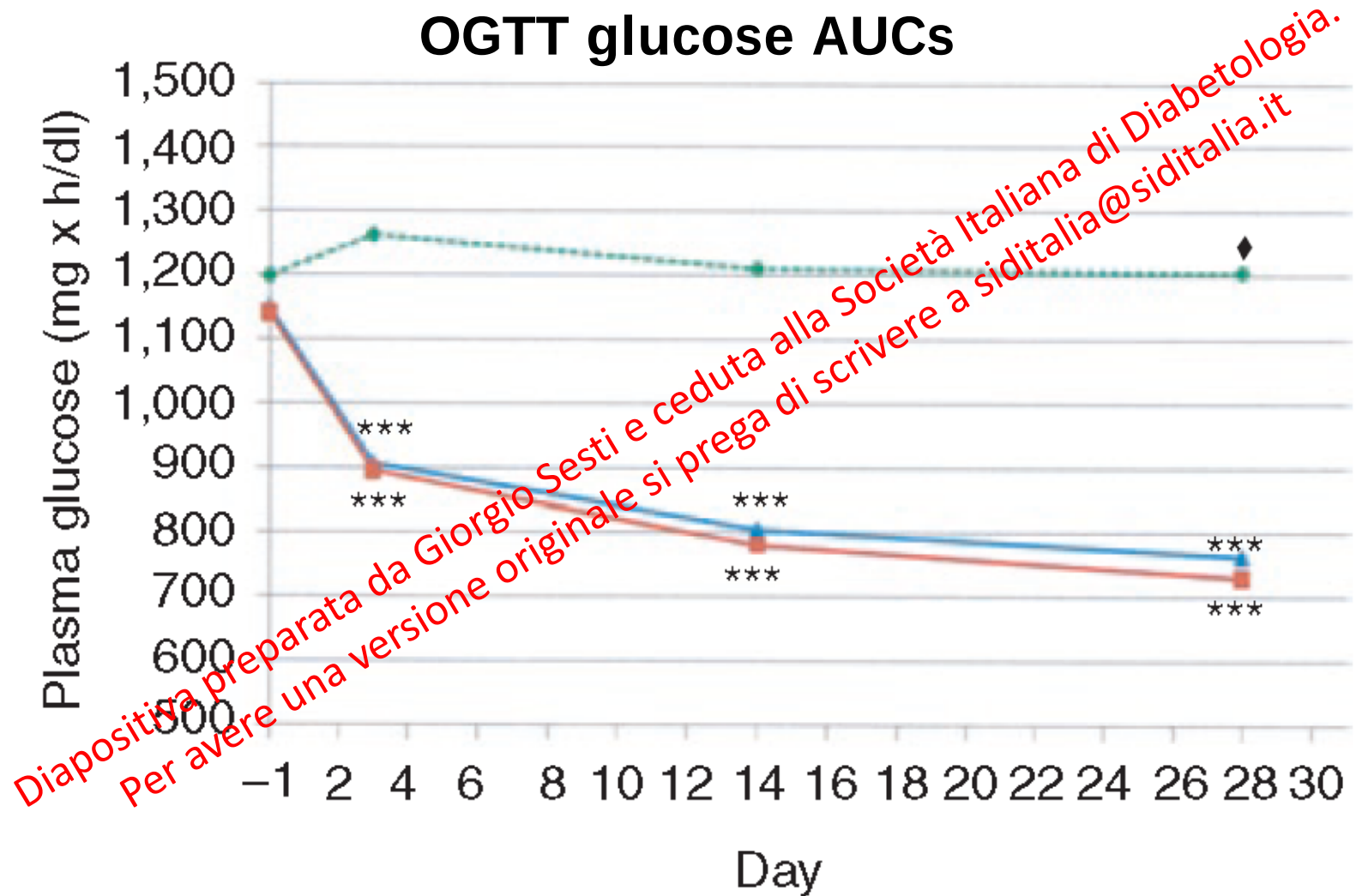
L'espressione di SGLT1 correla con la glicemia a 1 ora post-carico



LX4211, a Dual SGLT1/SGLT2 inhibitor, improves both fasting and post-load glucose levels



LX4211, a Dual SGLT1/SGLT2 inhibitor, improves both fasting and post-load glucose levels



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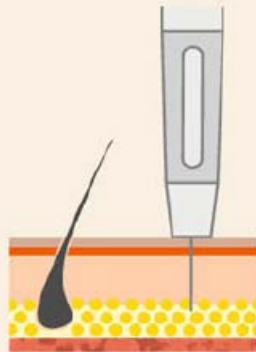
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Delivery systems

Present

Subcutaneous injection
(GLP-1 analogues)



Oral tablets
(DPP-4 inhibitors)



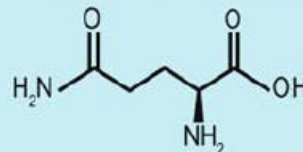
In development / under investigation

Subcutaneous osmotic minipumps



Oral GLP-1 preparations

Enhancers of
GLP-1 secretion

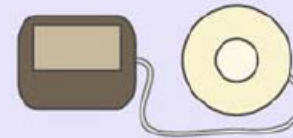


Future

Inhalation



Intraperitoneal pumps

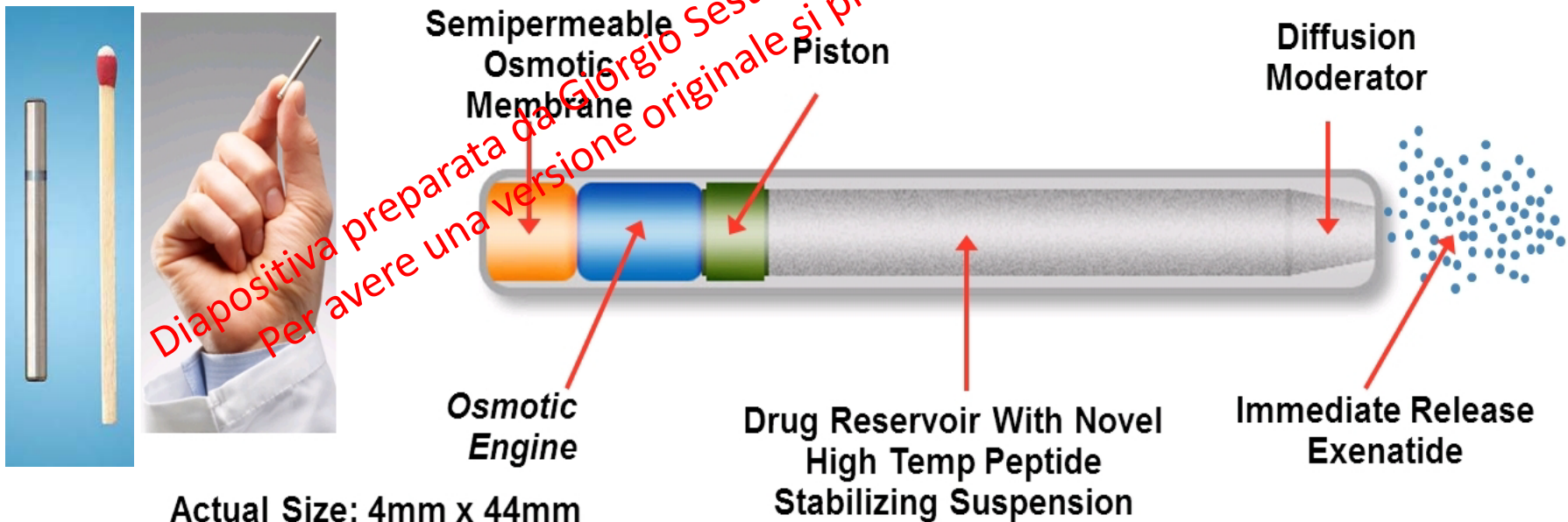


Gene therapy



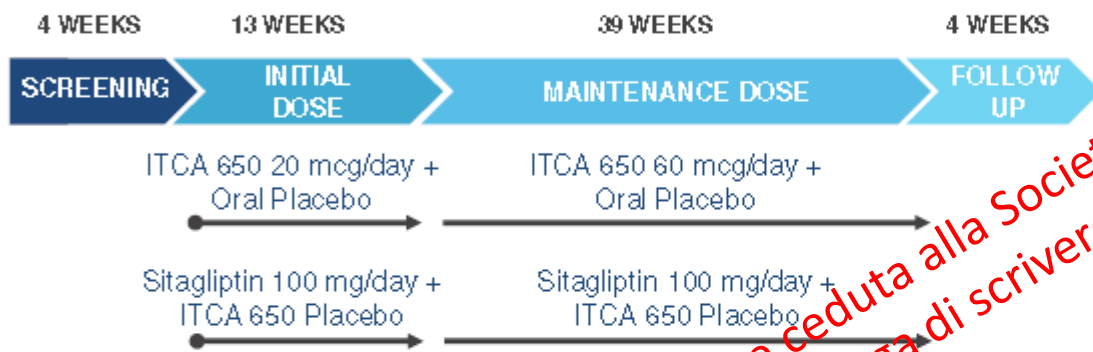
Novel delivery technologies

- ❑ Osmotic mini-pump – size of small matchstick
 - ❑ Mini-pump provides continuous smooth zero order delivery of drugs
- ❑ Peptide stabilizing suspension allows for robust stability at high body temps and delivery of peptides for 12 months from just a single device
- ❑ Mini-pump is placed sub-dermally once/twice yearly in a short in-office sterile procedure
- ❑ Procedures are done by Specialists, PCPs, and Nurse/PAs; there are already approved reimbursement codes



FREEDOM-2

PHASE 3



Primary Endpoint:

- Change in HbA1c between Week 52 and Day 0

Secondary Endpoints:

- Proportion of patients with decrease in HbA1c $>0.5\%$ and weight loss between Week 52 and Day 0
- Change in body weight between Week 52 and Day 0
- Proportion of patients with HbA1c $<7\%$ measured at Week 52

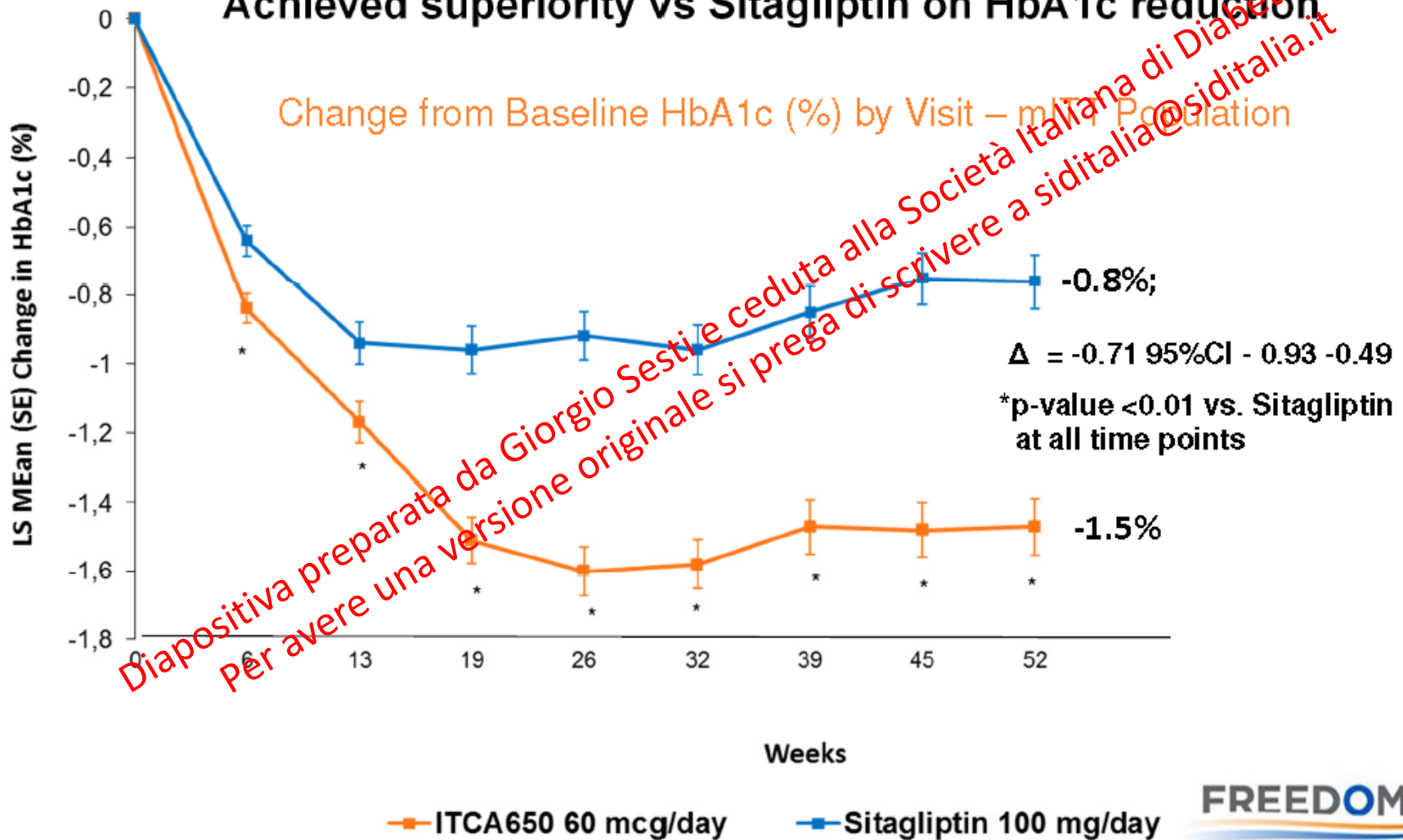
- Head-to-head global study vs leading oral agent
- 535 patients on background metformin monotherapy
- HbA1c $\geq 7.5\%$ to $\leq 10.5\%$

Status:
Complete

FREEDOM-2

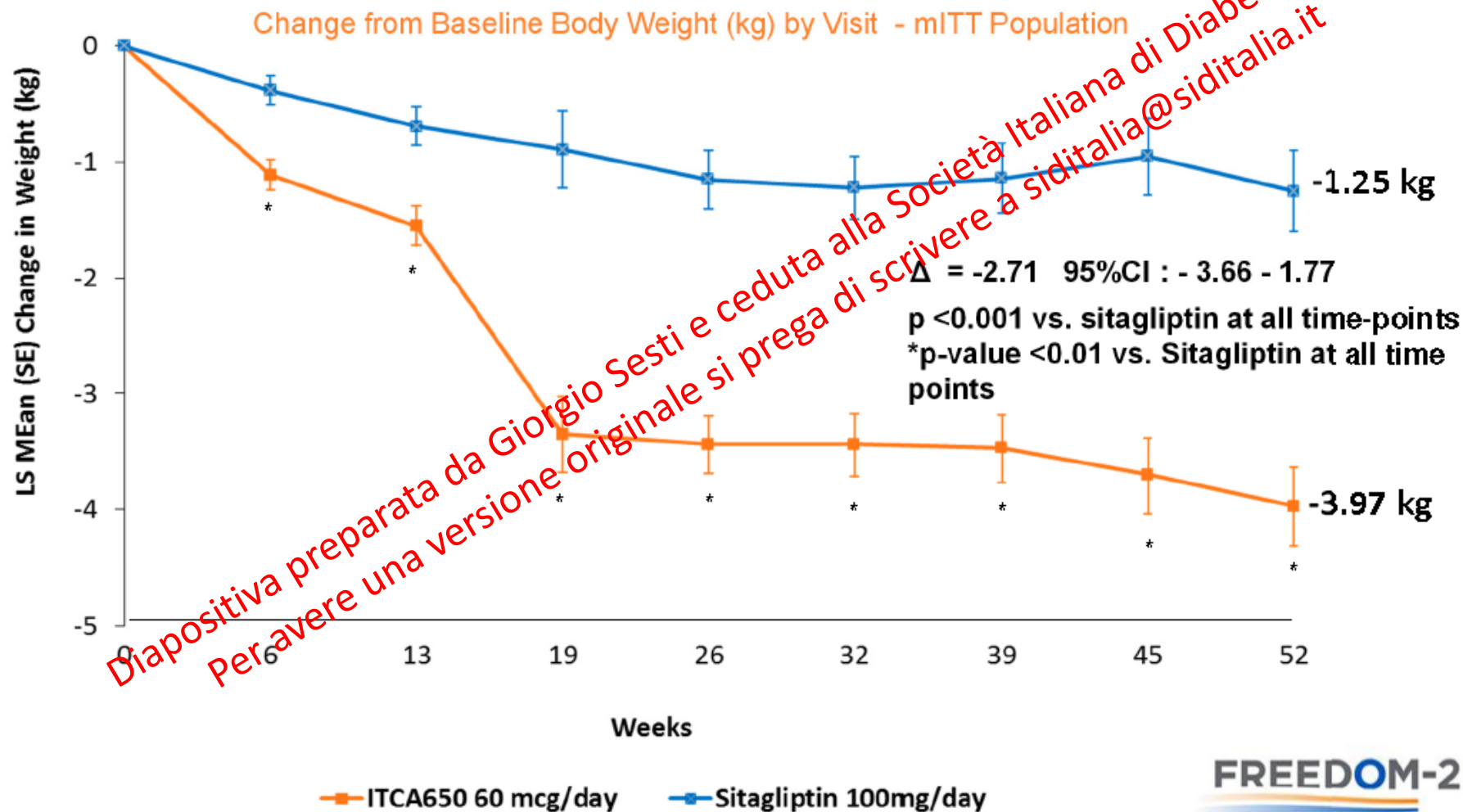
FREEDOM-2 – HbA1c change over time

Achieved superiority vs Sitagliptin on HbA1c reduction

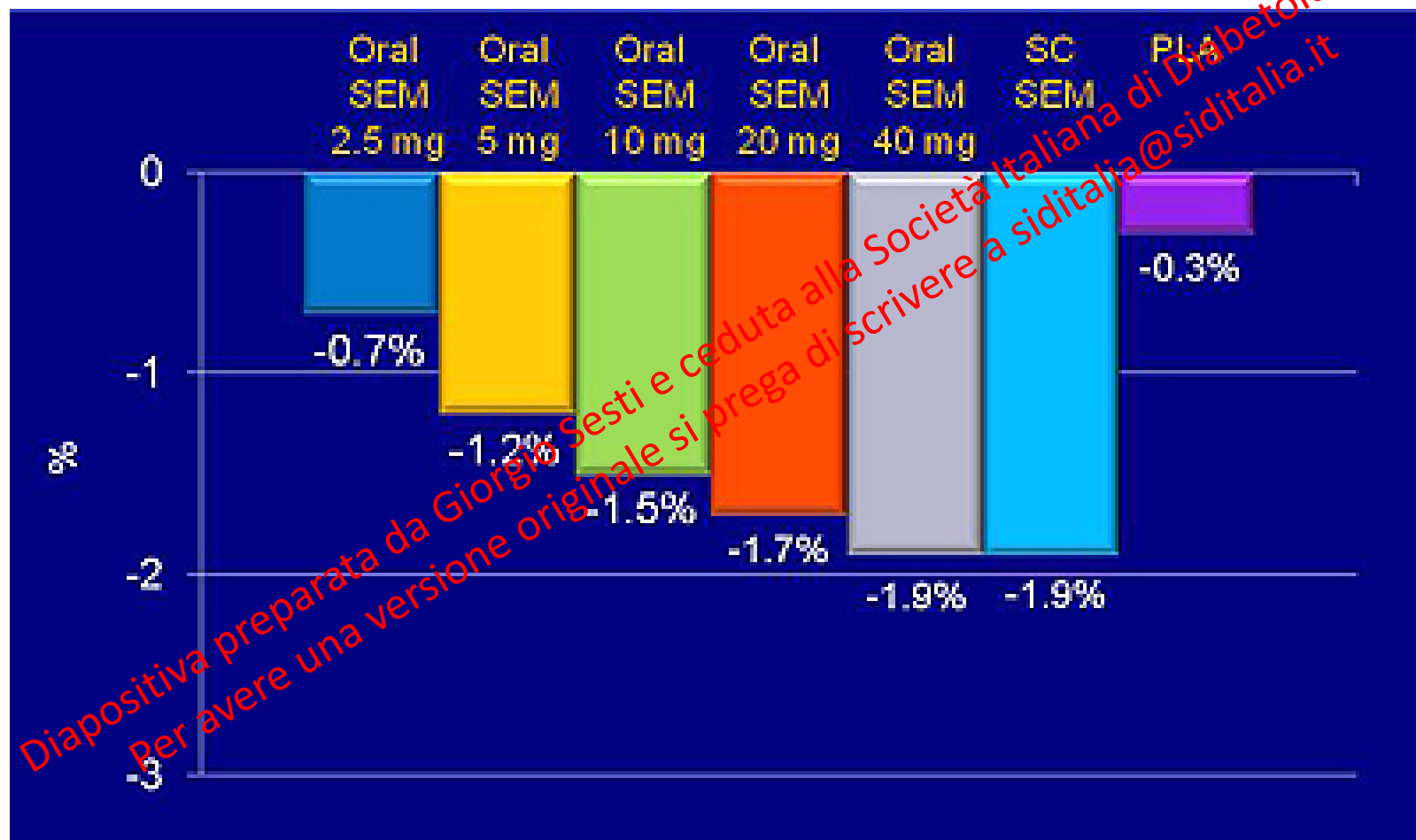


FREEDOM-2 – Body weight change over time

Achieved superiority vs Sitagliptin on Body Weight reduction



Dose-dependent glucose lowering and body weight reductions with the novel oral formulation of semaglutide in patients with early type 2 diabetes



Intranasal administration of GLP-1 in Japanese patients with Type 2 Diabetes

A
GLP-1(7-37)amide umano

Amido di mais

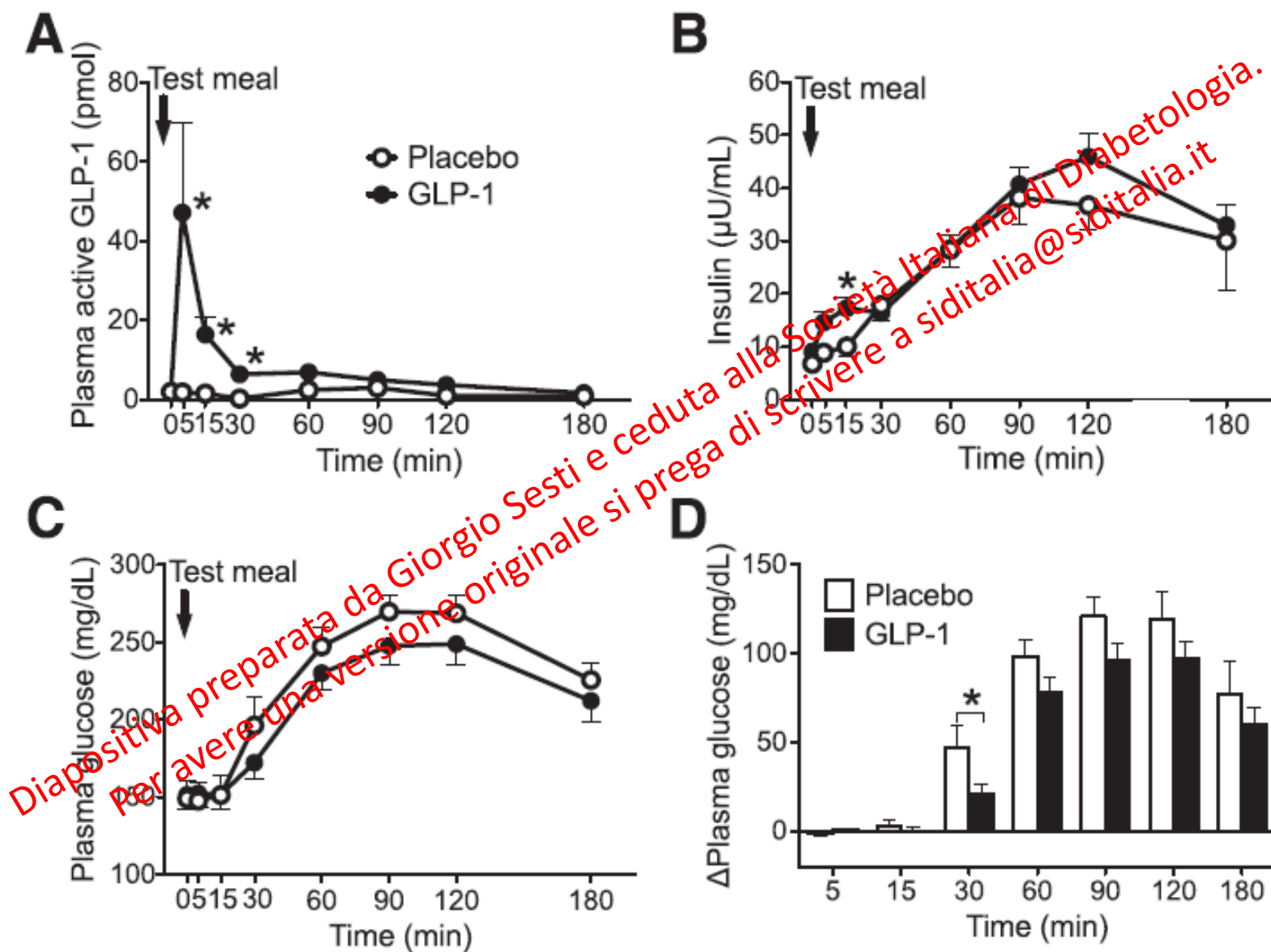
Calcio carbonato
 Ψ 60 μ m

B



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Intranasal administration of GLP-1 in Japanese patients with Type 2 Diabetes



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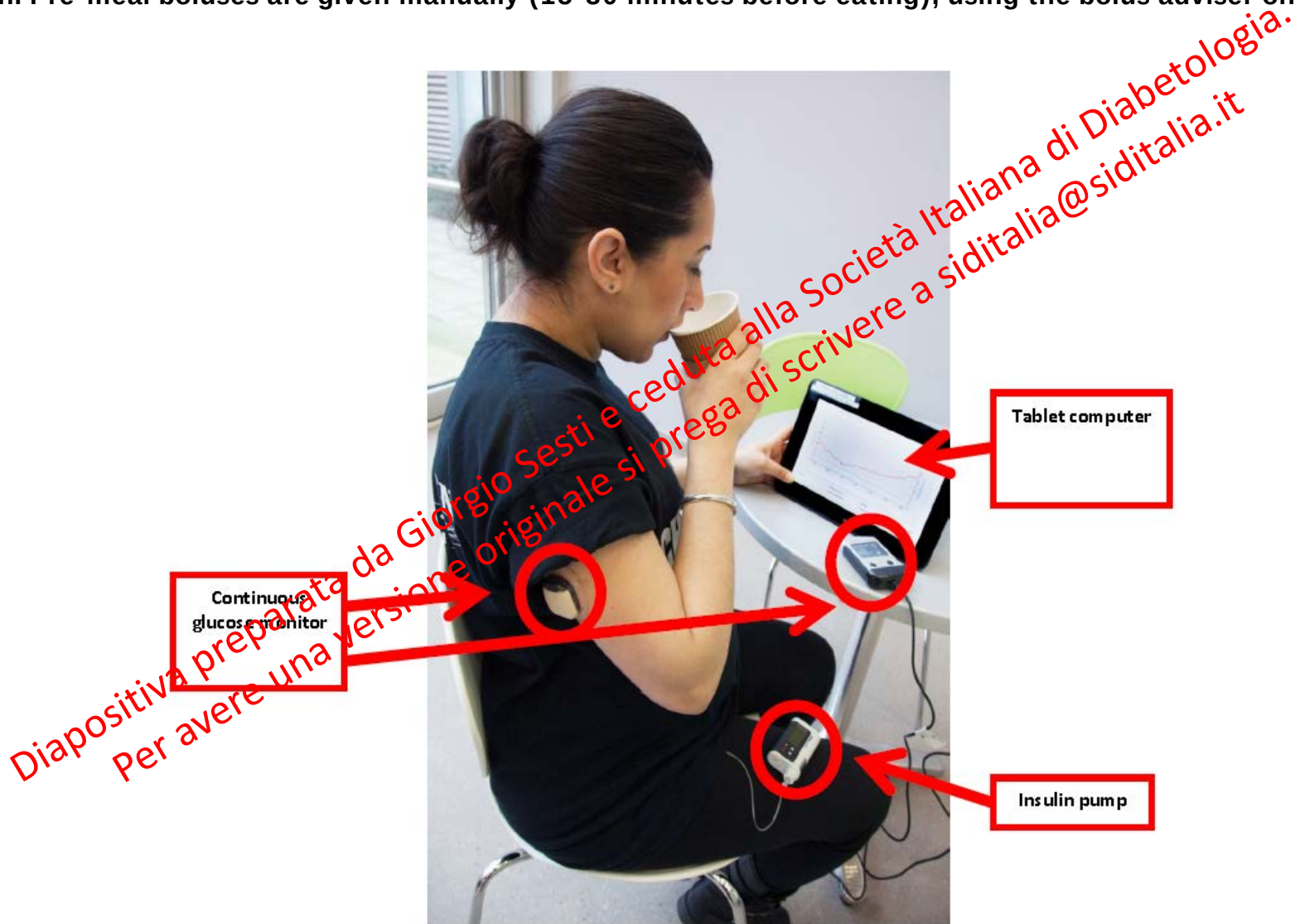
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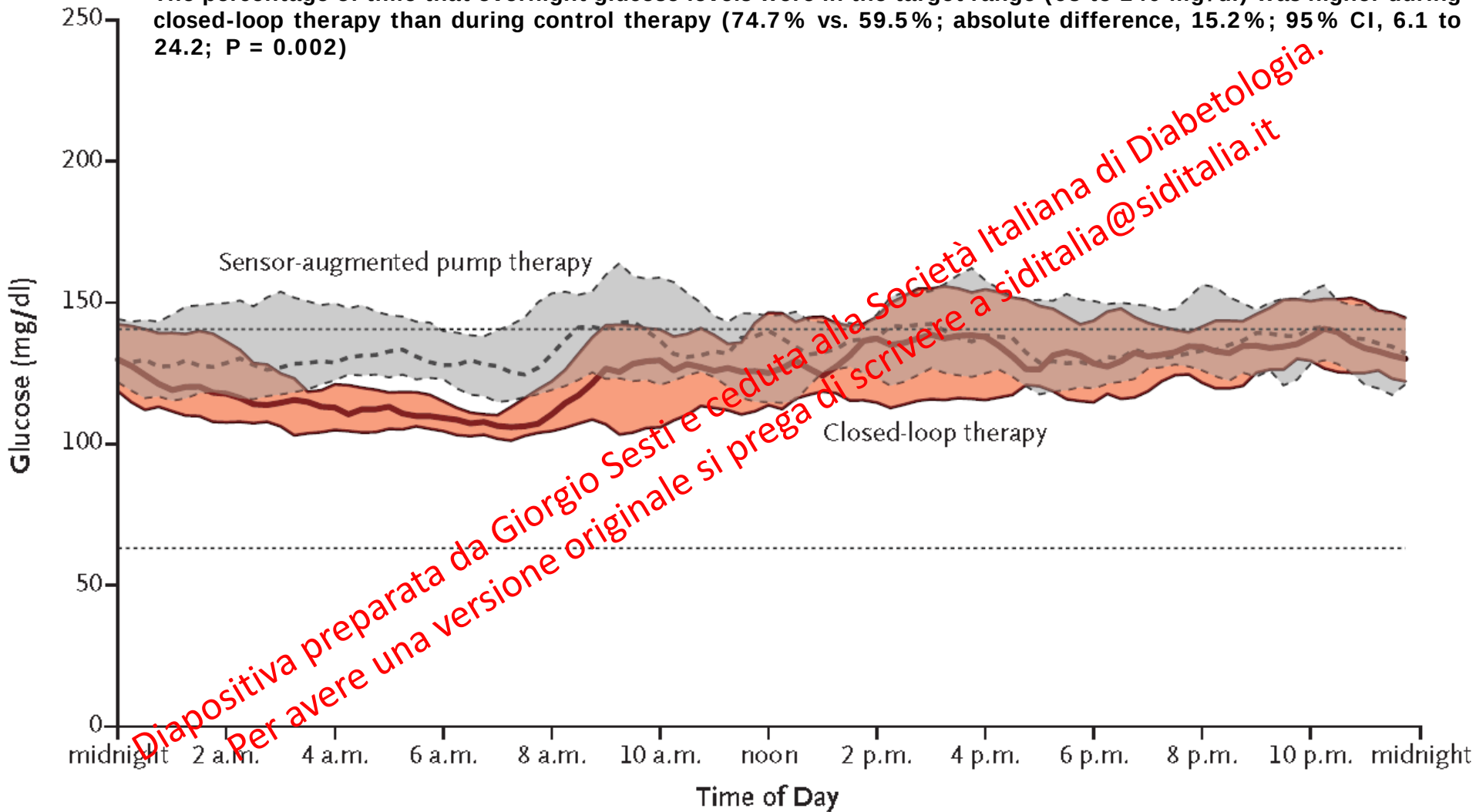
Closed-loop insulin delivery during pregnancy in women with type 1 diabetes

An individually-adaptive control algorithm is housed on a tablet computer and uses glucose readings from the continuous glucose monitor to adjust insulin delivery via the insulin pump every 12 minutes when closed-loop is turned on. Pre-meal boluses are given manually (15-30 minutes before eating), using the bolus adviser on the insulin pump.



Median sensor-recorded glucose values over a 24-hour period with sensor-augmented pump therapy and closed-loop insulin delivery

The percentage of time that overnight glucose levels were in the target range (63 to 140 mg/dl) was higher during closed-loop therapy than during control therapy (74.7% vs. 59.5%; absolute difference, 15.2%; 95% CI, 6.1 to 24.2; $P = 0.002$)



1. Early identification of type 2 diabetes

2. Smart lens to monitor blood sugar

3. Winning Combination

- SGLT2 inhibitors + DPP4 inhibitors
- SGLT2 inhibitors + GLP-1R agonists
- GLP-1R agonists + basal insulin

4. Dual SGLT1/SGLT2 inhibitors

5. GLP-1R agonist under the skin

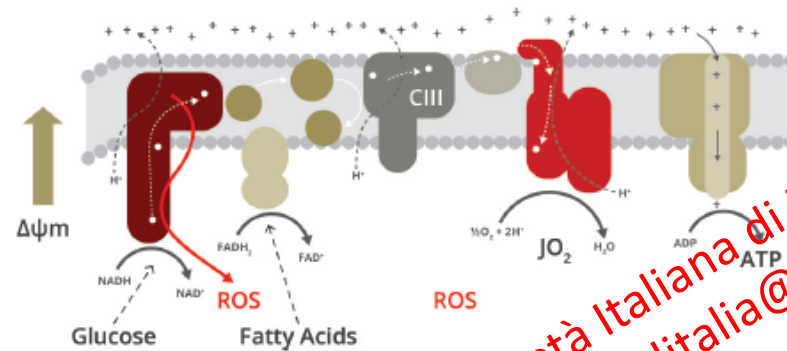
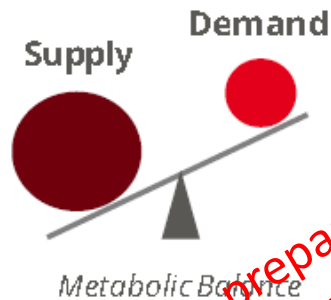
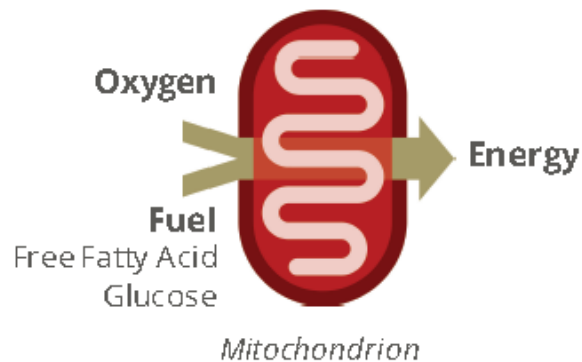
6. Oral and intranasal GLP-1R agonists

7. A combination pump and CGM

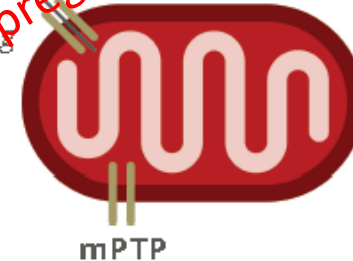
8. An example a new drug class

Diapositiva preparata da Giorgio Sesti e ceduta alla Società Italiana di Diabetologia.
per avere una versione originale si prega di scrivere a siditalia@siditalia.it

Imeglimin: mechanism of action in the mitochondria



Imeglimin Regulates the Respiratory Chain in an Imbalanced Diabetic Environment



Imeglimin Delays Mitochondria Permeability Transition Pore (mPTP) Opening and Prevents Cell Death

Imeglimin

- Increases insulin secretion
- Decreases glucose overproduction
- Increases glucose uptake

- Protects β -cells from apoptosis (cell death)
- Prevents micro & macro-vascular complications

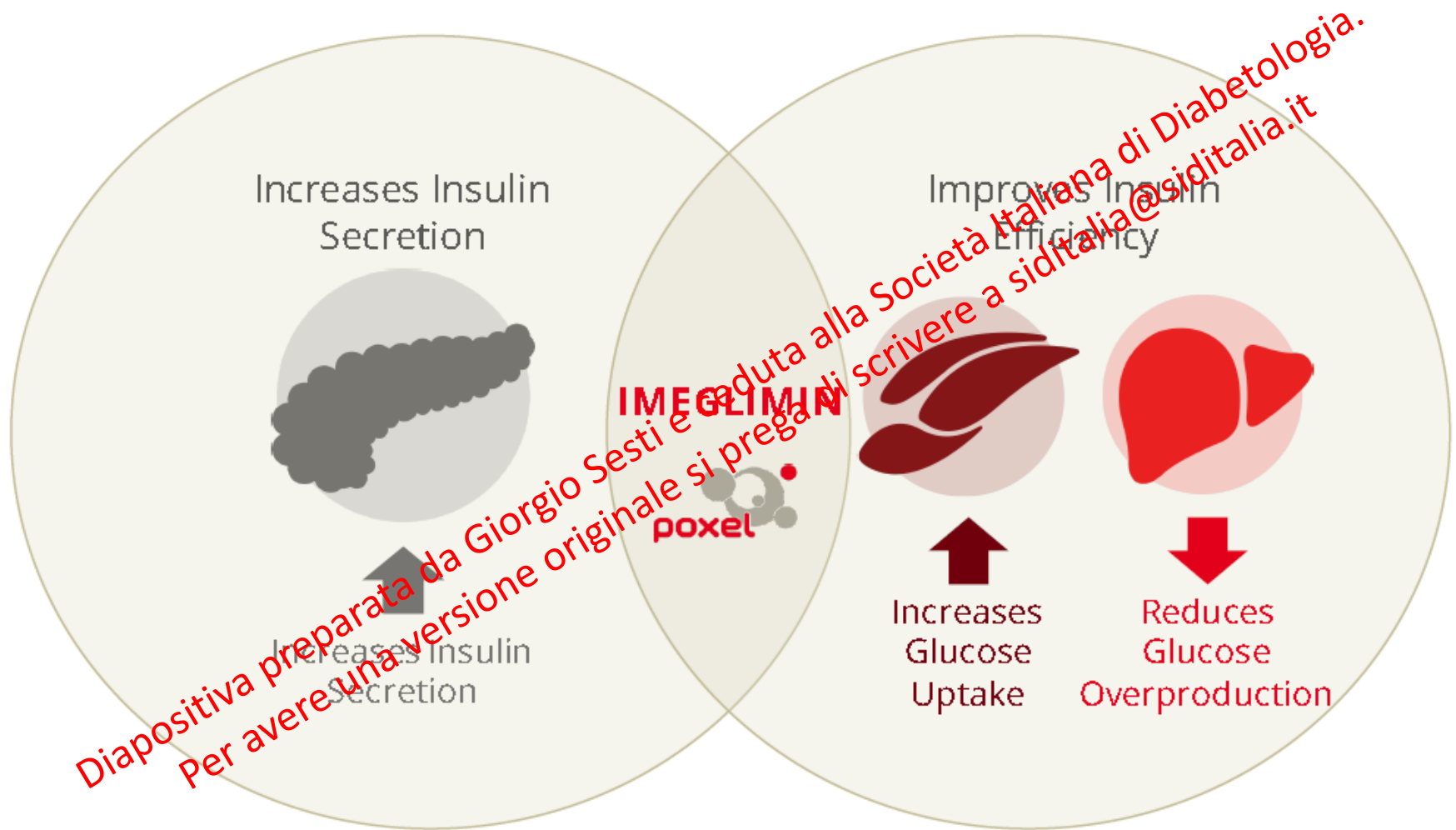
Adapted from G. Vial et al. Diabetes, 2016

Adapted from K. H. Fisher-Wellman and P. Dandl Neuffer. Trends in Endocrinology and Metabolism, 2012

Adapted from M.E. Patti and S. Corveia. Endocrine reviews, 2010

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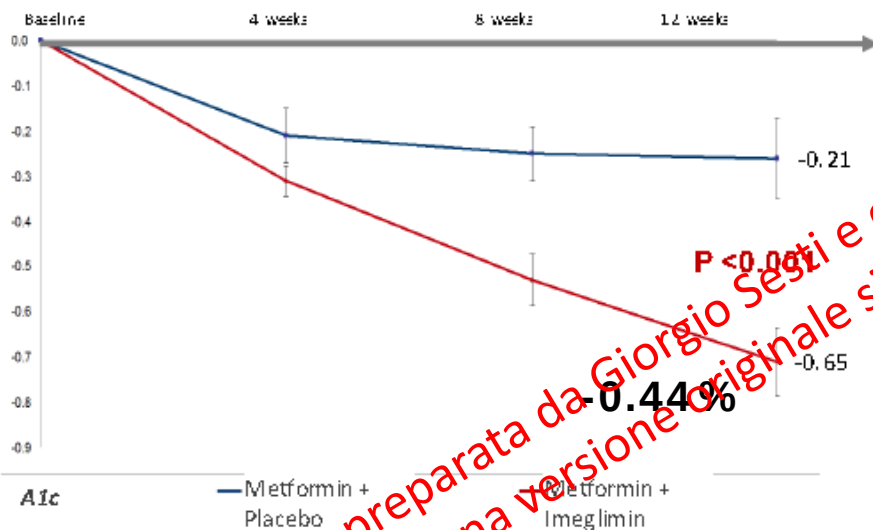
Imeglimin: an oral compound addressing two main T2D defects



The efficacy of Imeglimin as add-on therapy in patients with T2DM inadequately controlled with metformin or sitagliptin monotherapy

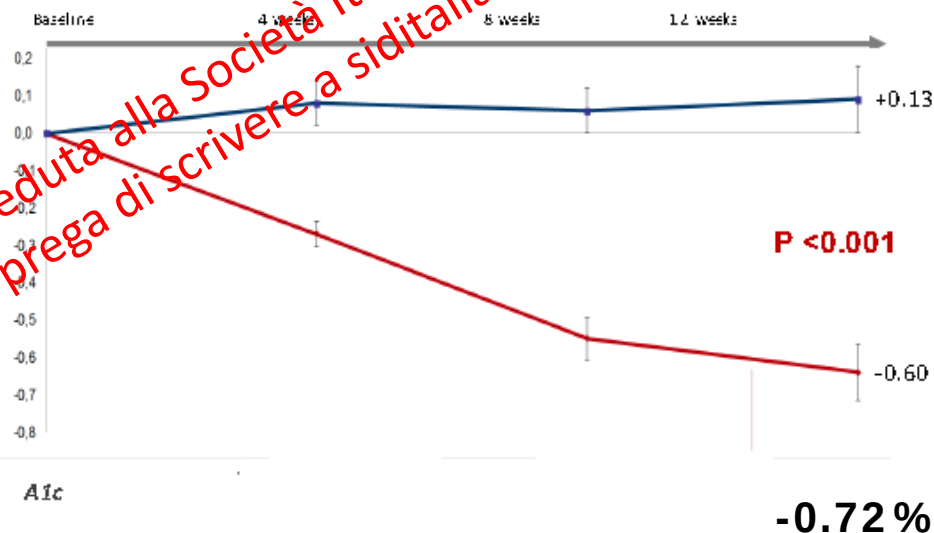
Add-on to Metformin

After 12-week treatment in metformin failure patients



Add-on to sitagliptin

After 12-week treatment in sitagliptin failure patients



Metformina

Se non sufficiente, aggiungere alla metformina un secondo farmaco:

SU/Glinidi	Pioglitazone	Acarbose	DPP4 inibitori	GLP1 agonisti	SGLT2 inibitori	Insulina
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Se non sufficiente, aggiungere un terzo farmaco:

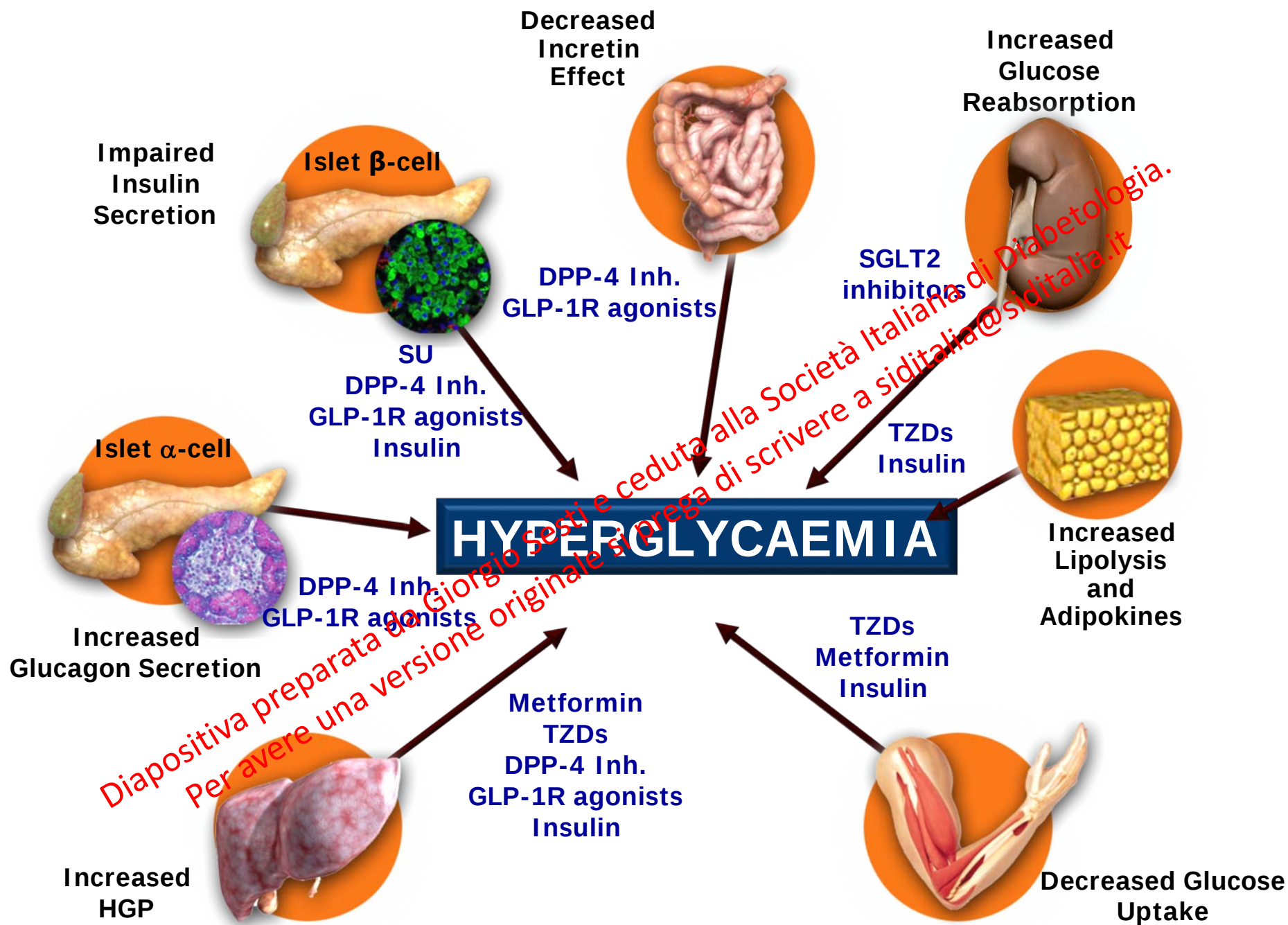
SU/Glinidi	Pioglitazone	Acarbose	DPP4 inibitori	GLP1 agonisti	SGLT2 inibitori	Insulina
Pioglitazone	SU/Glinidi	Pioglitazone	Pioglitazone	Pioglitazone	Pioglitazone ¹	Pioglitazone
Acarbose	Acarbose	SU/Glinidi	SU/Glinidi	SU/Glinidi	Acarbose ¹	Acarbose
DPP4 inib.	DPP4 inib.	SGLT2 inib. ¹	SGLT2 inib. ¹	SGLT2 inib. ¹	DPP4 inib. ¹	DPP4 inib.
GLP1 agon.	GLP1 agon.	Insulina	Insulina	Insulina	GLP1 agon. ¹	GLP1 agon.
SGLT2 inib. ¹	SGLT2 inib. ¹				SU/Glinidi ¹	SGLT2 inib.
Insulina	Insulina				Insulina	SU/Glinidi

In caso di cattivo controllo con la triplice terapia, iniziare comunque la terapia insulinica, mantenendo la metformina:

Insulina

con l'eventuale aggiunta di:

SU/Glinidi	Pioglitazone	Acarbose	DPP4 inib.	GLP1 agon.	SGLT2 inib.
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HGP, hepatic glucose production; DPP-4 Inh, dipeptidyl peptidase-4 inhibitor; SGLT2, sodium glucose cotransporter-2; TZDs, thiazolidinediones; GLP-1, glucagon-like peptide 1; SU, sulphonylurea

