Farmaci iniettivi e SGLT-2 inibitori

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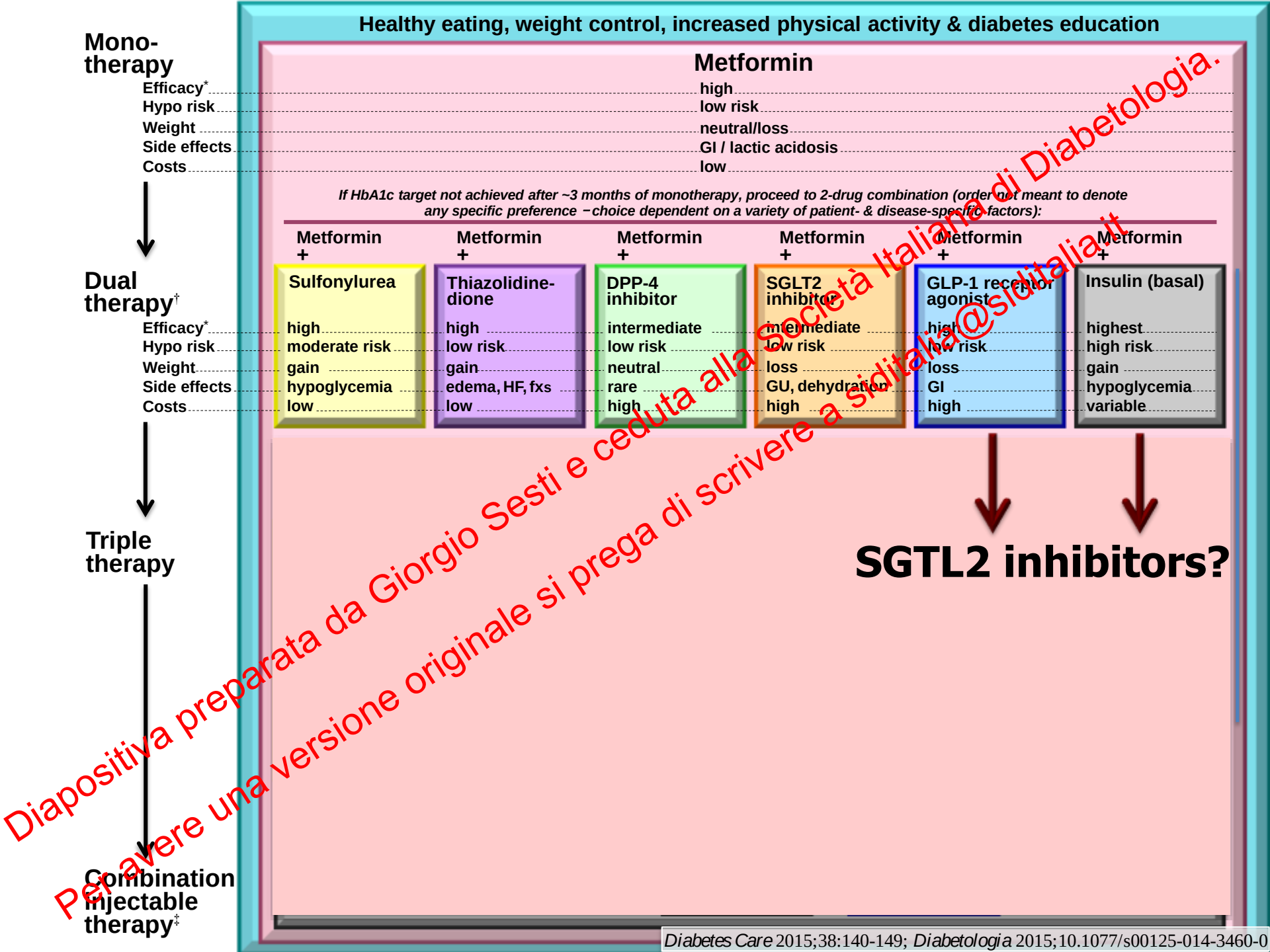
Potenziali conflitti di interesse

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

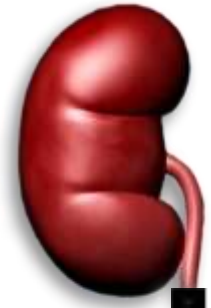
Novo Nordisk, MSD, Boehringer-Ingelheim, Lilly, Janssen, AstraZeneca, Novartis e Takeda per attività di Relatore ad eventi.

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



Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0

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



Increased Glucose Excretion

Reduced glycaemia → ↓FPG, ↓ PPG, ↓ HbA_{1c}

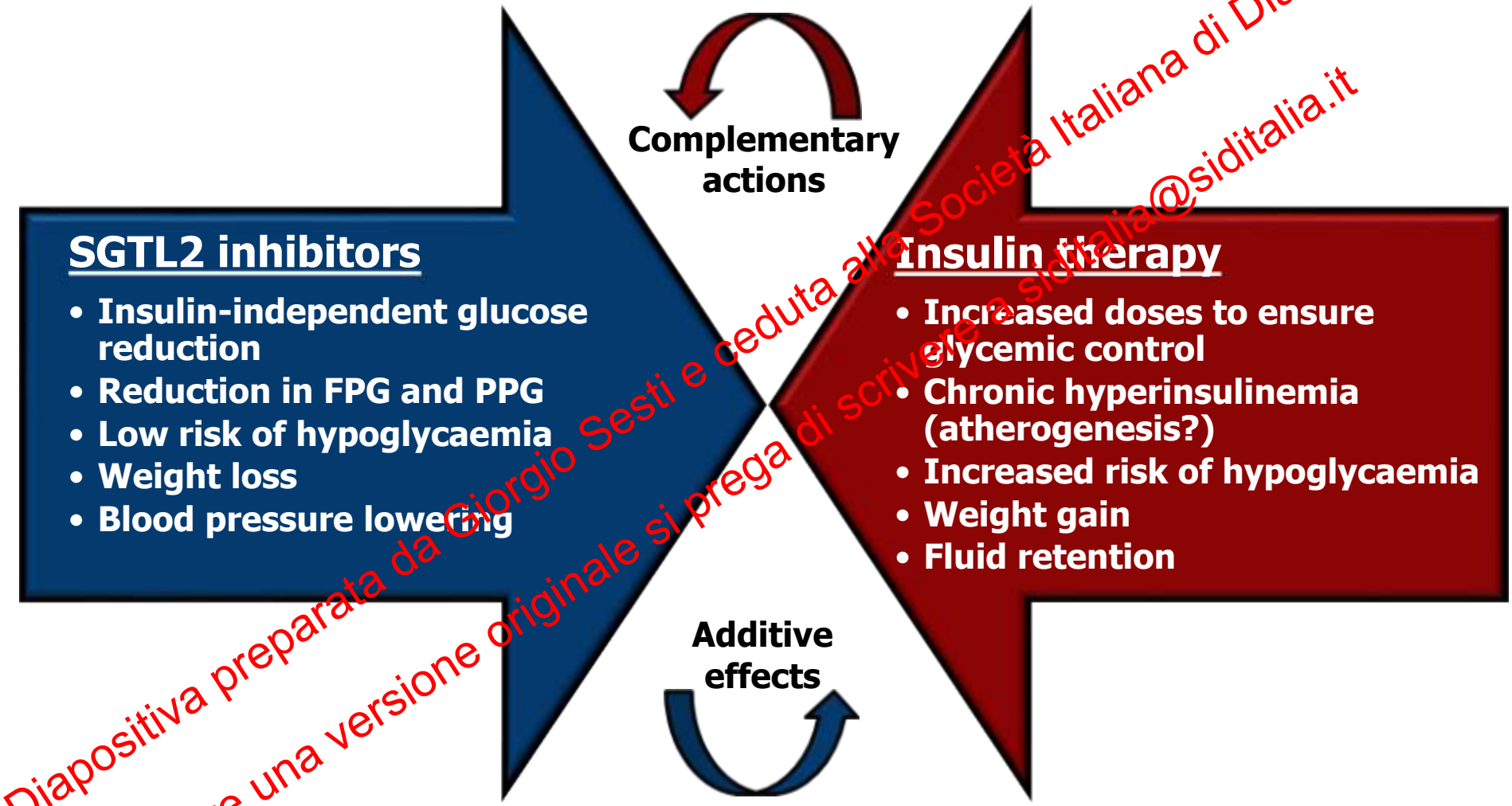
Loss of energy (calories) → ↓ Body weight

Increased Sodium Excretion → Reduced sodium load → ↓ Blood Pressure

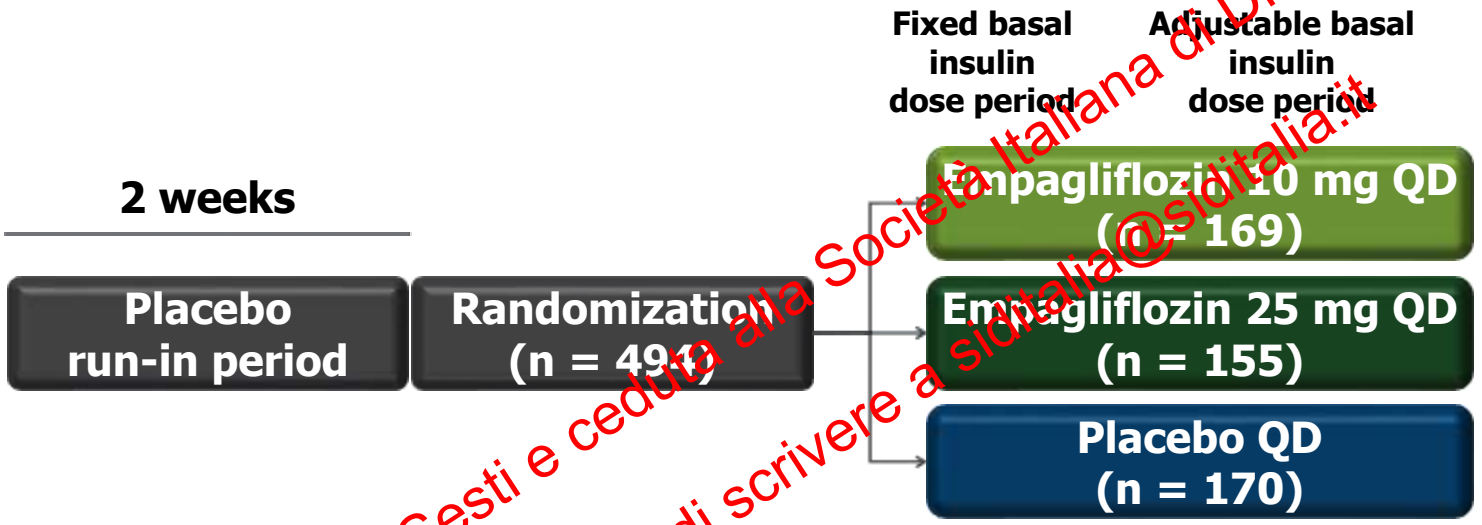
SGLT2: sodium-glucose transporter 2

Modified from Abdul-Ghani MA, et al. *Endocr Rev.* 2011; 32:515–31

Rationale for combination of SGTL2 inhibitors with insulin



78-week study with empagliflozin as add-on to long-acting insulin
Study design

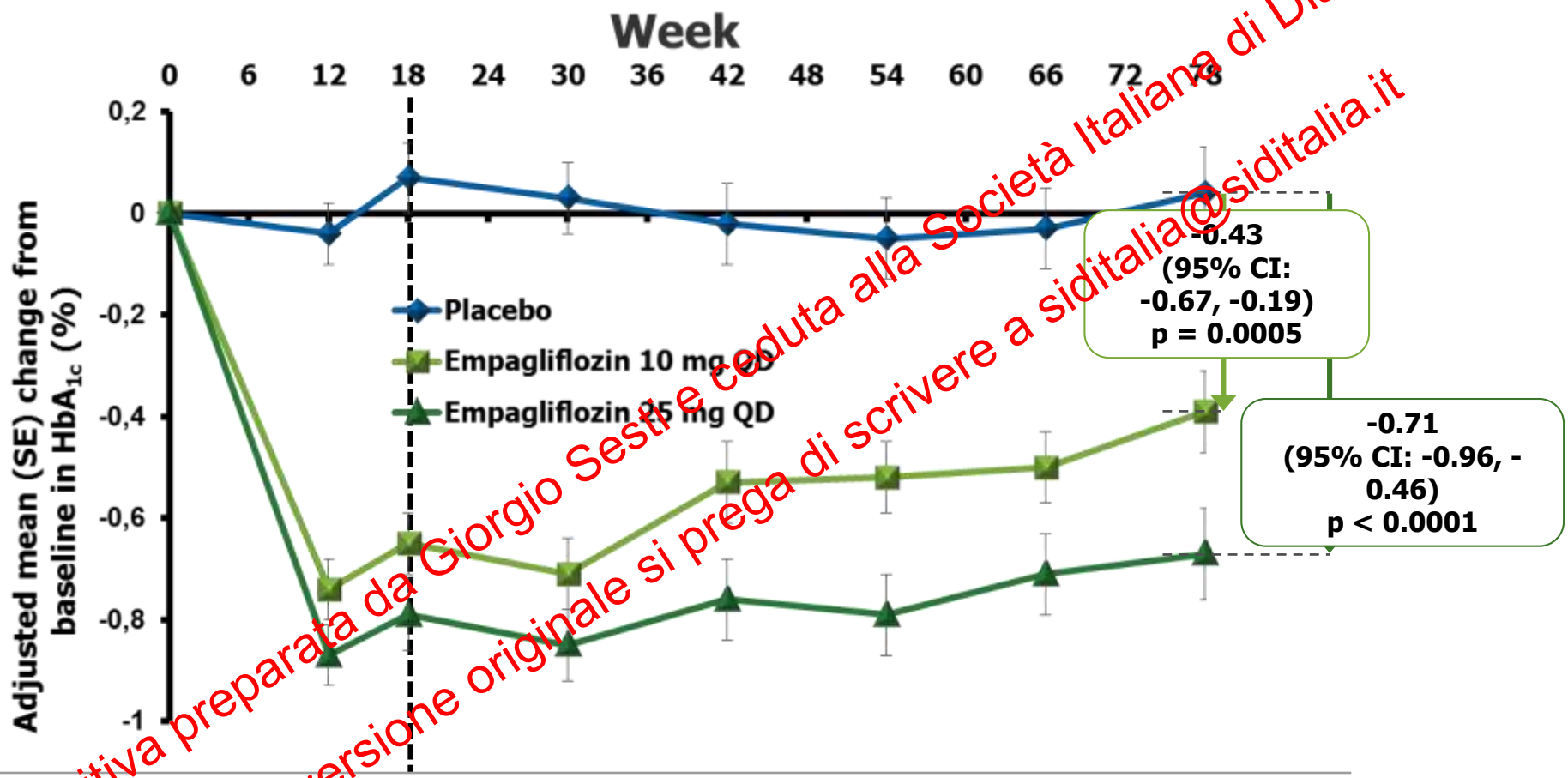


- Patients with T2D with inadequate glycaemic control despite treatment with a stable dose of basal insulin ± metformin and/or sulphonylurea.
- HbA$_{1c}$ of > 7% and ≤10% at screening

- **During the first 18 weeks of the study, basal insulin dose remained fixed.**
- During the next 60 weeks, insulin dose was adjusted at the discretion of the investigator. for any confirmed FPG level >110 mg/dL
- Following the treatment period, patients were followed up for 4 weeks

Rosenstock J, et al. Diabetes Obes Metab 17: 936–948, 2015

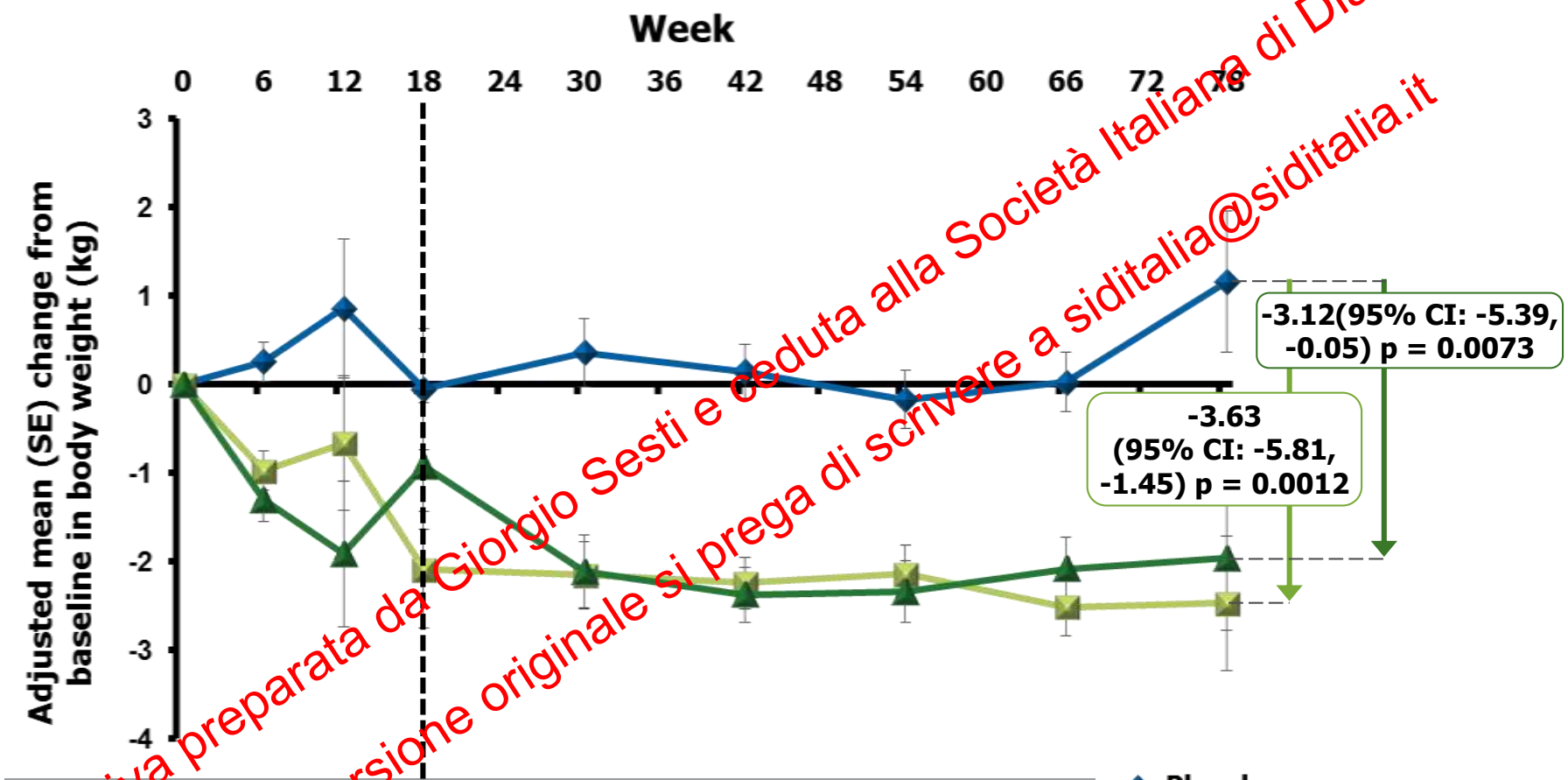
78-week study with empagliflozin as add-on to long-acting insulin
HbA_{1c} change from baseline over time to Week 78



N/Week	BL	12	18	30	42	54	66	78
Placebo	156	129	141	132	119	113	105	98
10 mg QD	160	132	148	137	123	121	115	114
25 mg QD	137	120	123	114	110	107	98	96

Rosenstock J, et al. Diabetes Obes Metab 17: 936–948, 2015

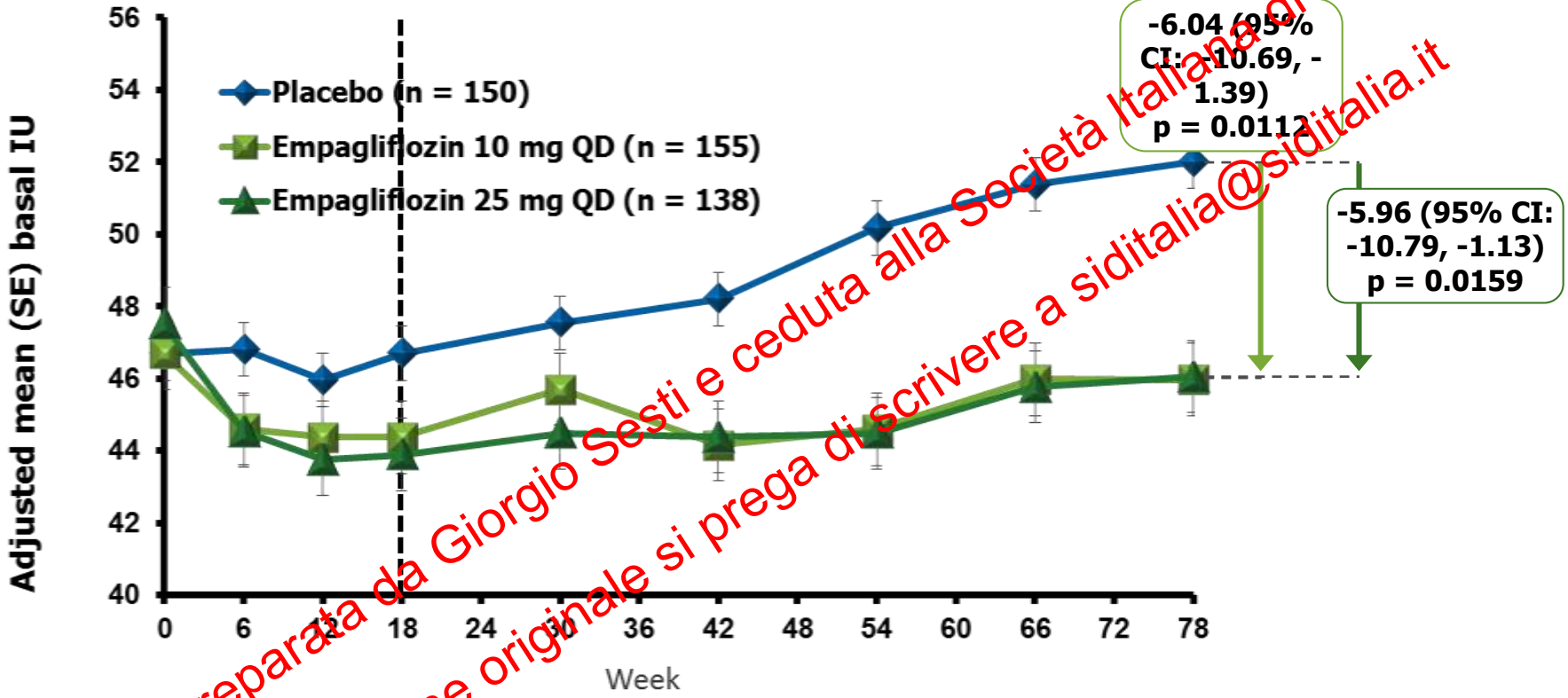
78-week study with empagliflozin as add-on to long-acting insulin
Change from baseline in body weight over time



N/Week	BL	12	18	30	42	54	66	78
Placebo	160	160	145	141	133	114	105	100
10 mg QD	164	163	152	148	136	120	114	113
25 mg QD	144	143	133	125	117	106	97	96

Rosenstock J, et al. Diabetes Obes Metab 17: 936–948, 2015

78-week study with empagliflozin as add-on to long-acting insulin
Change in basal insulin dose over time

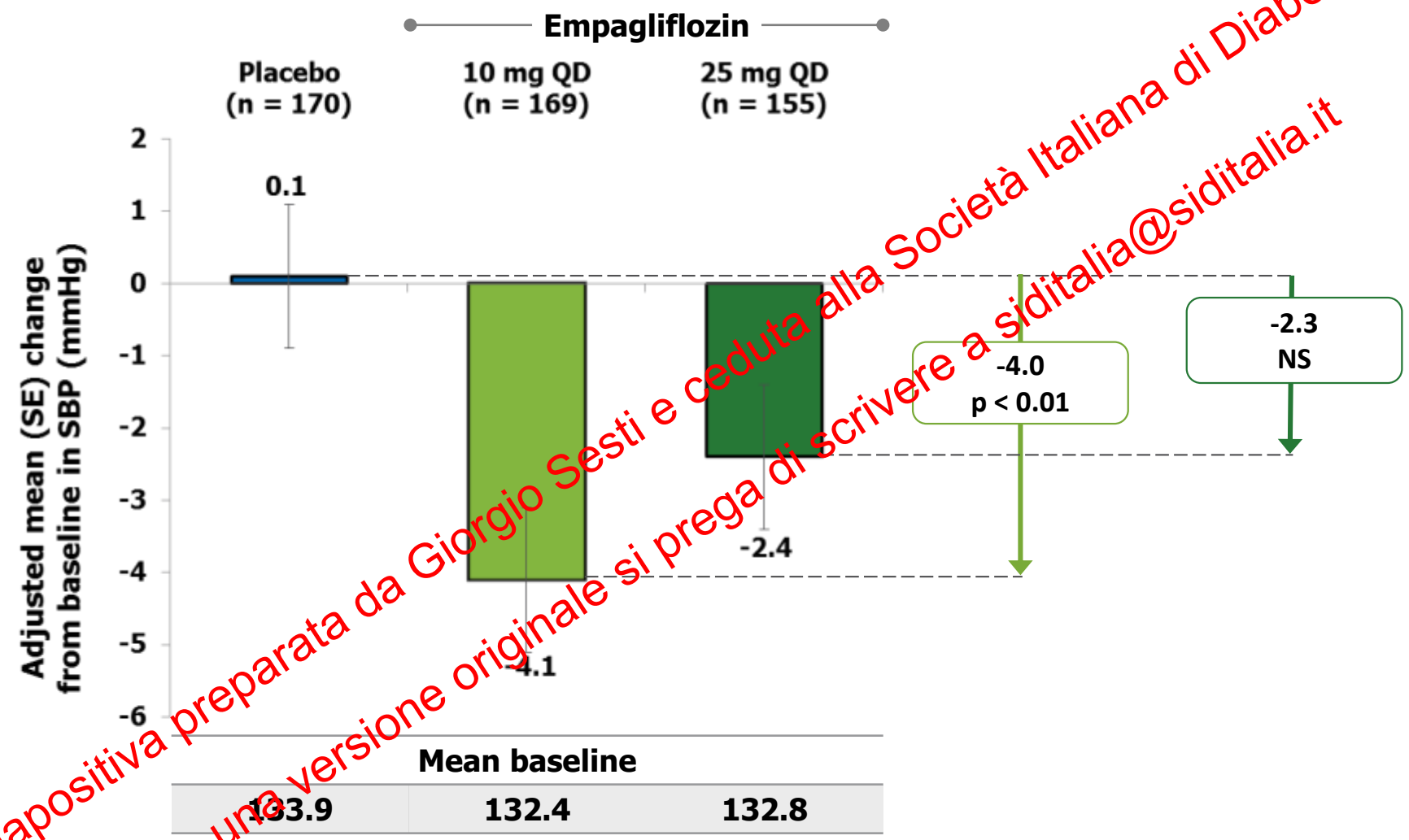


N/Week	BL	6	12	18	30	42	54	66	78
78	150	150	146	140	130	120	112	105	102
10 mg QD	155	155	151	146	133	126	122	117	115
25 mg QD	138	138	126	121	116	111	104	98	96

BL, baseline; CI, confidence interval; IU, insulin dose; QD, once daily; SE, standard error.
MMRM. FAS (OC-78).

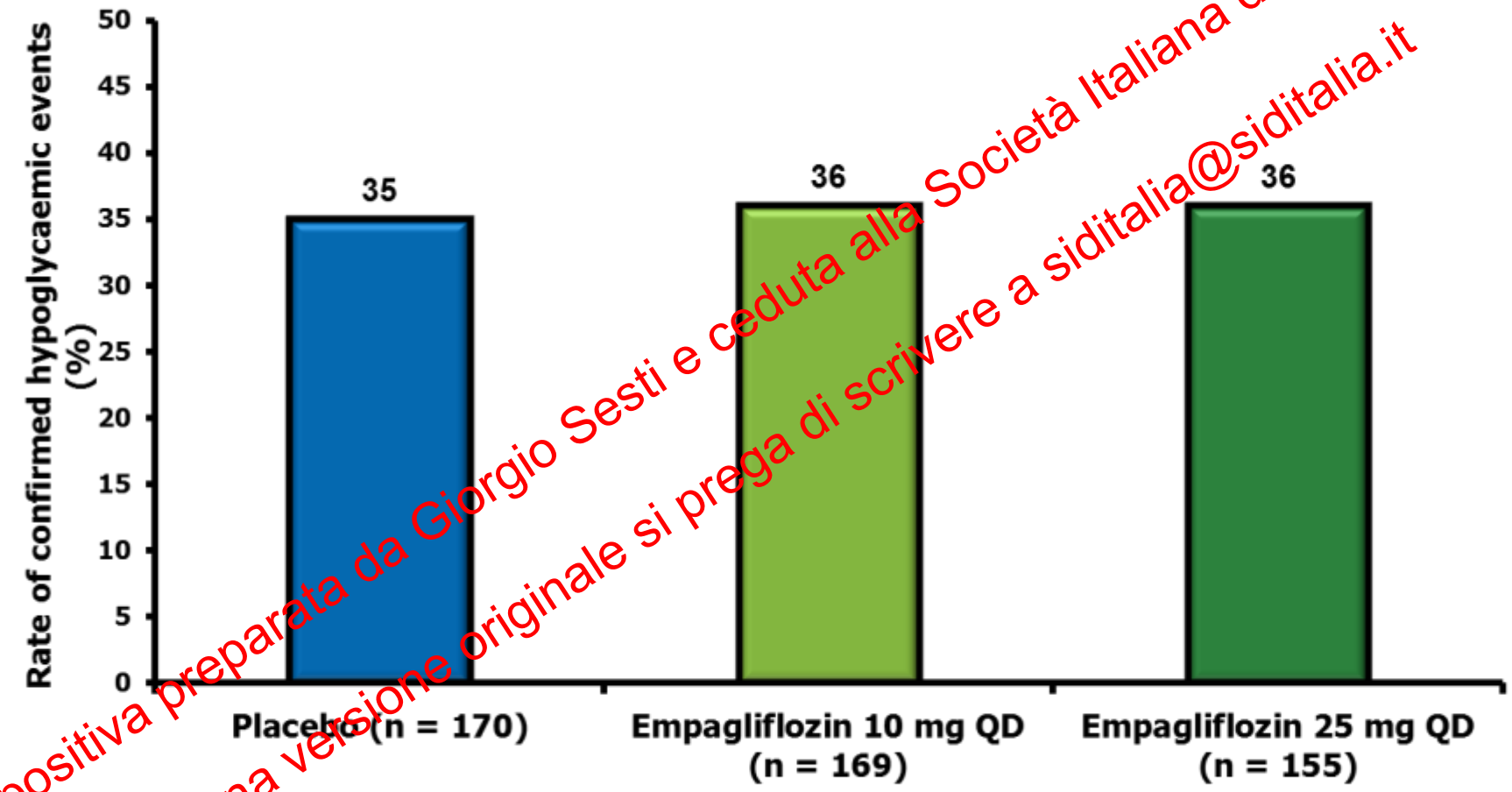
Rosenstock J, et al. Diabetes Obes Metab 17: 936–948, 2015

78-week study with empagliflozin as add-on to long-acting insulin
Change in SBP at Week 78



Rosenstock J, et al. Diabetes Obes Metab 17: 936–948, 2015

78-week study with empagliflozin as add-on to long-acting insulin
Frequency of patients with hypoglycaemia* at Week 78

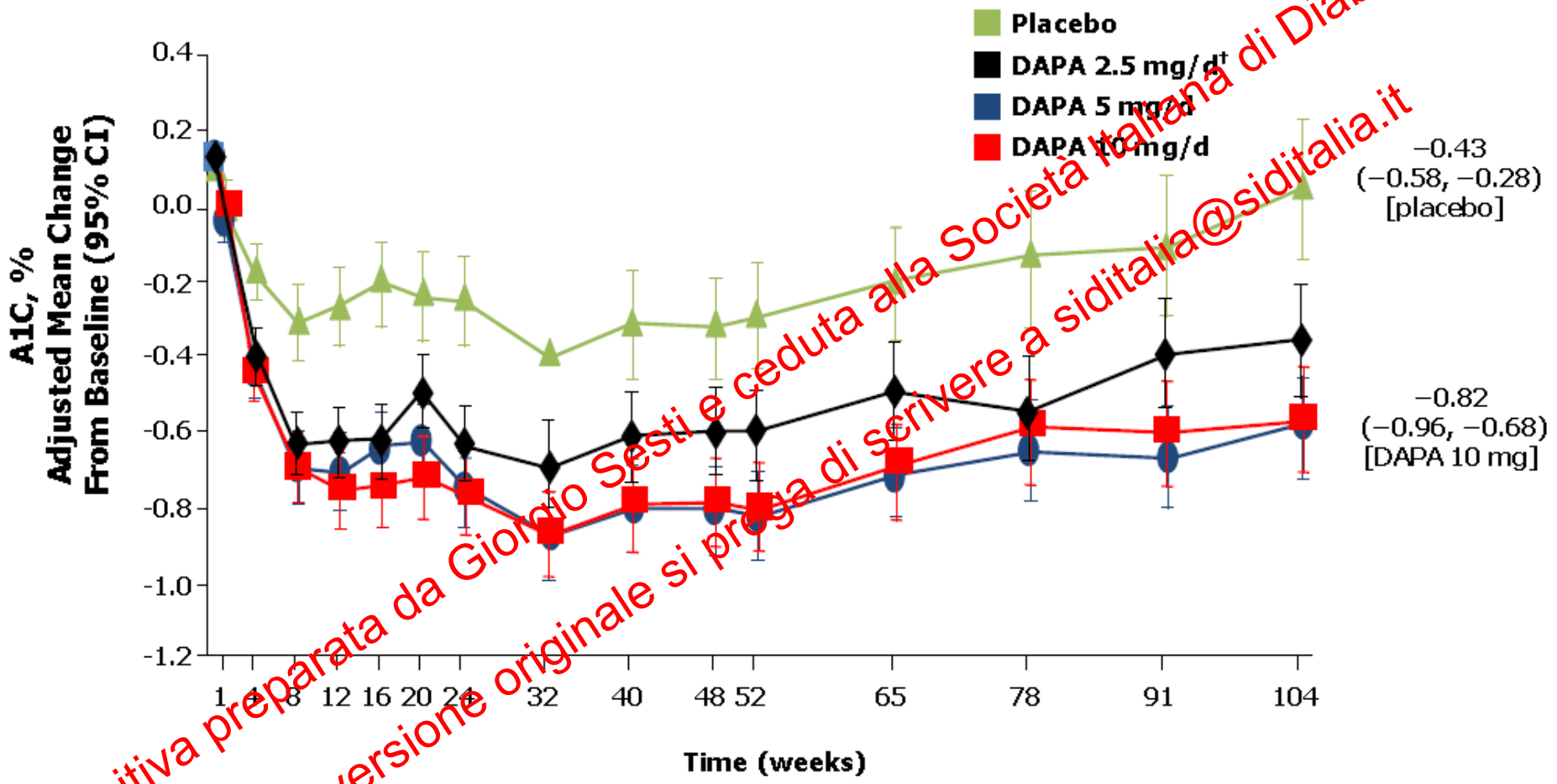


*Plasma glucose ≤ 3.9 mmol/l (≤ 70 mg/dL) and/or requiring assistance.

Rosenstock J, et al. Diabetes Obes Metab 17: 936–948, 2015

DAPA vs Placebo as Add-On to INS

Mean Change in A1C from Baseline at 104 Weeks

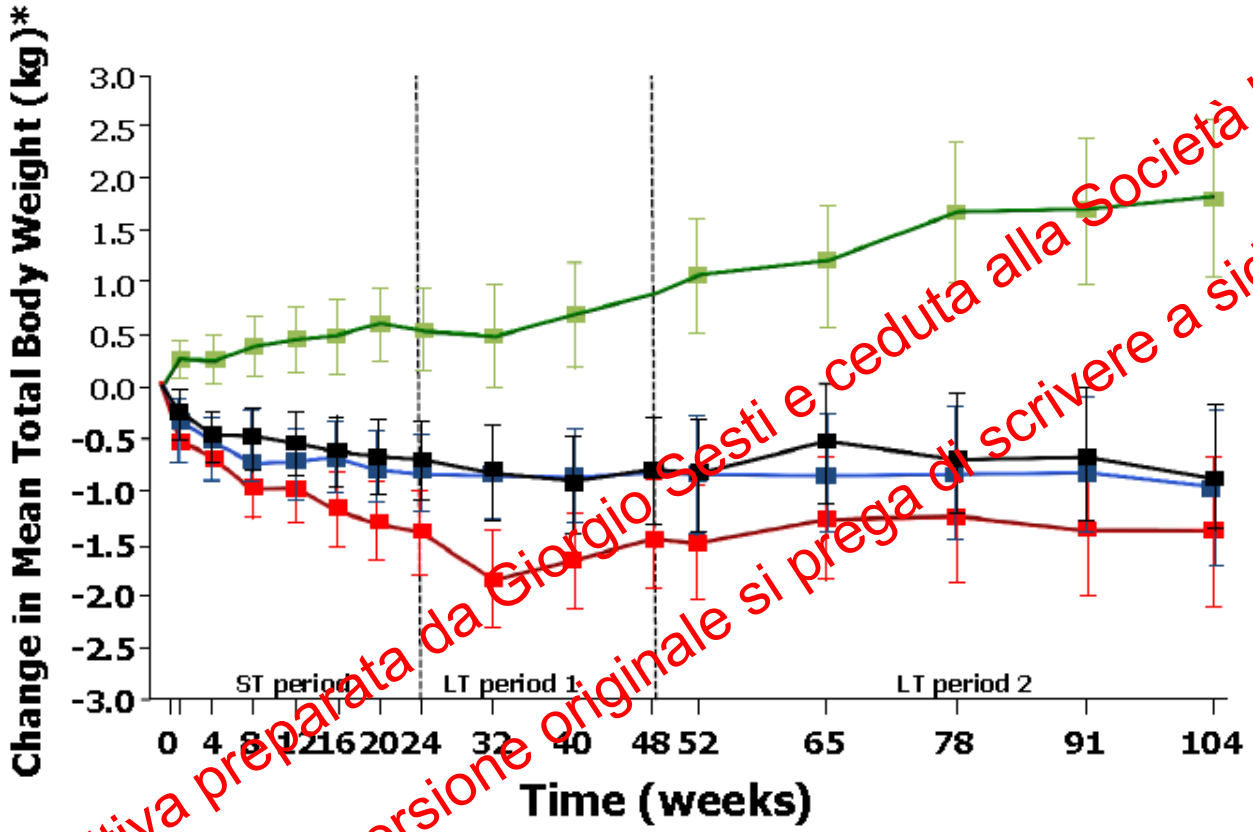


Mean daily insulin dose was 77.1 U, with 17% using only basal insulin and 83% using bolus regimen

Wilding JPH et al. Diabetes Obes Metab 16: 124–136, 2014

DAPA vs Placebo as Add-On to INS

Mean Change in Total Body Weight From Baseline at 104 Weeks



Week 104 adjusted mean change, kg (95% CI)

1.83 (1.05, 2.61) [placebo]

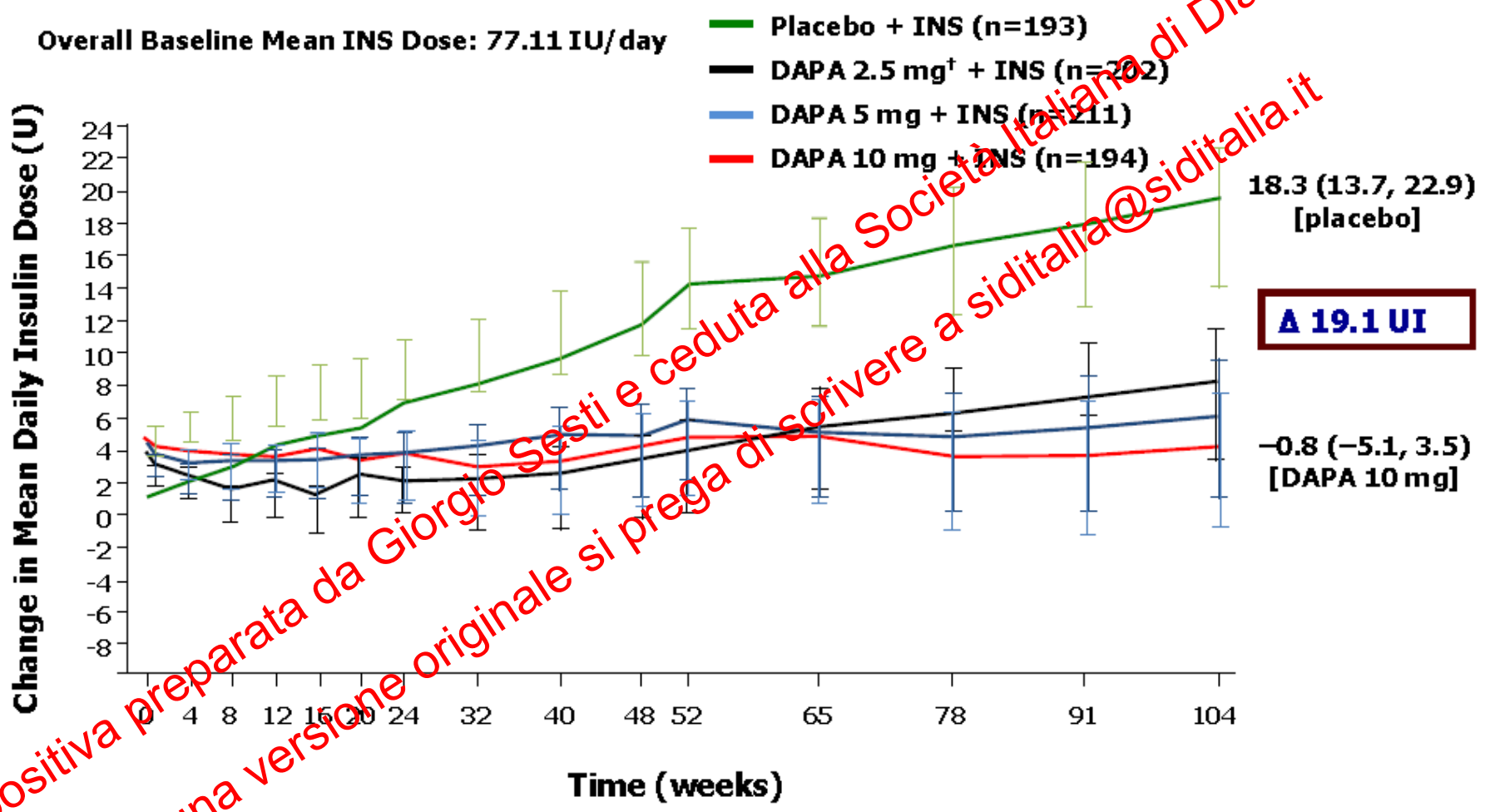
−1.50 (−2.21, −0.78) [DAPA 10 mg]

ST= short term
LT= long term

Wilding JPH et al. Diabetes Obes Metab 16: 124–136, 2014

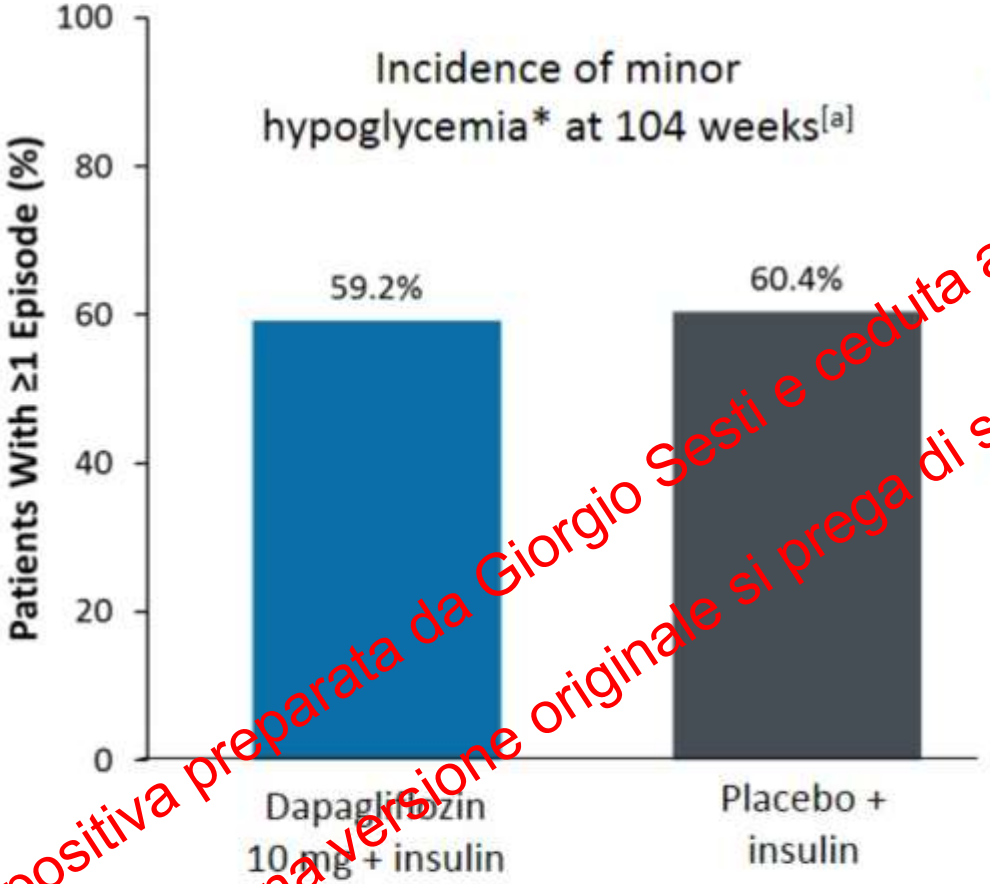
DAPA vs Placebo as Add-On to INS

Mean Change in Mean Daily INS Dose From Baseline at Week 104



Wilding JPH et al. Diabetes Obes Metab 16: 124–136, 2014

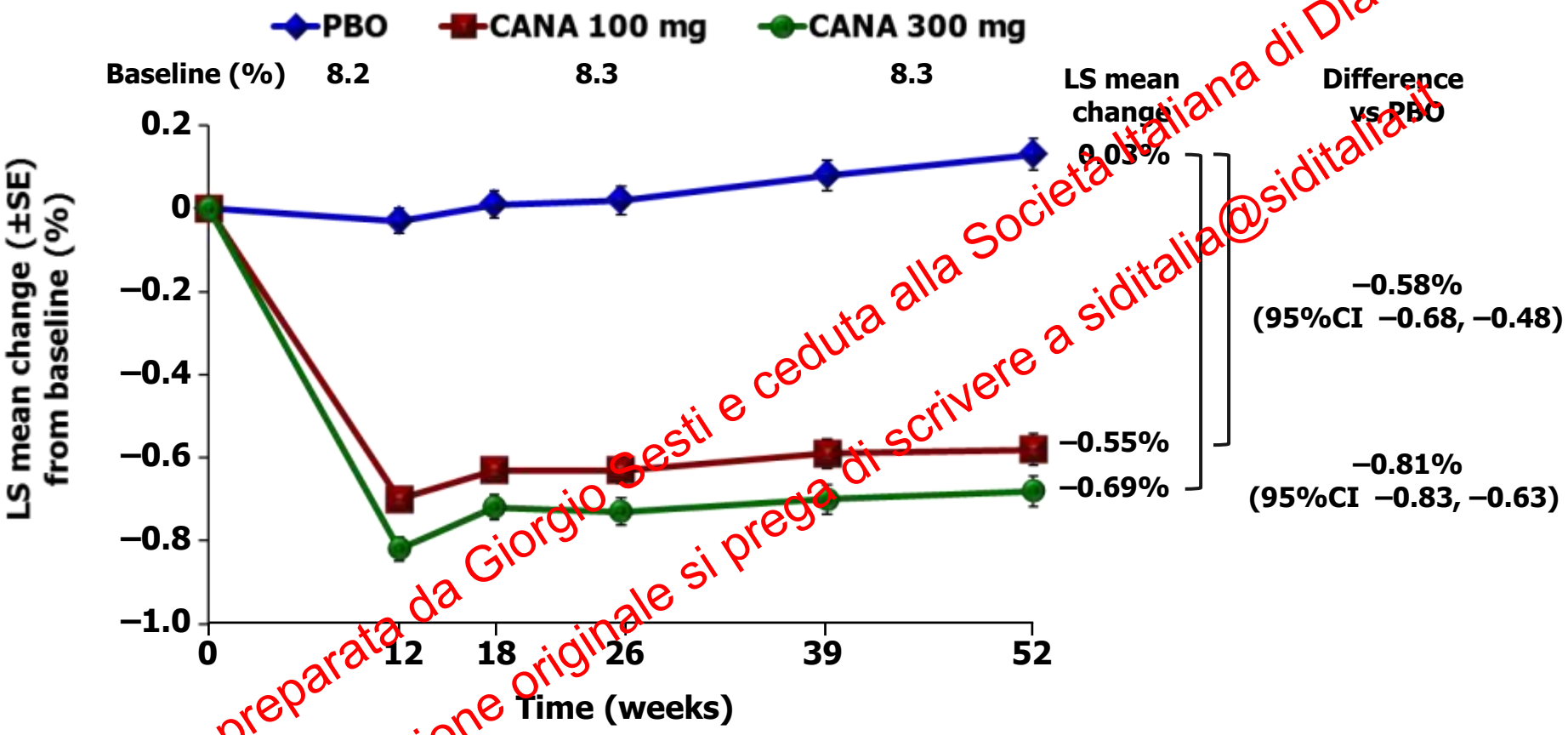
DAPA vs Placebo as Add-On to INS
One or more episodes of hypoglycaemia at 104 Weeks



- At the 24-week primary endpoint, a higher proportion of patients had ≥1 hypoglycemic event with dapagliflozin vs placebo[b]
- Overall, proportions of patients with ≥1 hypoglycemic event were balanced across treatment groups at 104 weeks[a]
  - No patient discontinued the study due to hypoglycemia[a]

a. Wilding JP, et al. *Diabetes Obes Metab.* 2014;16:124-136.
b. Wilding JP, et al. *Ann Intern Med.* 2012;156:405-515.

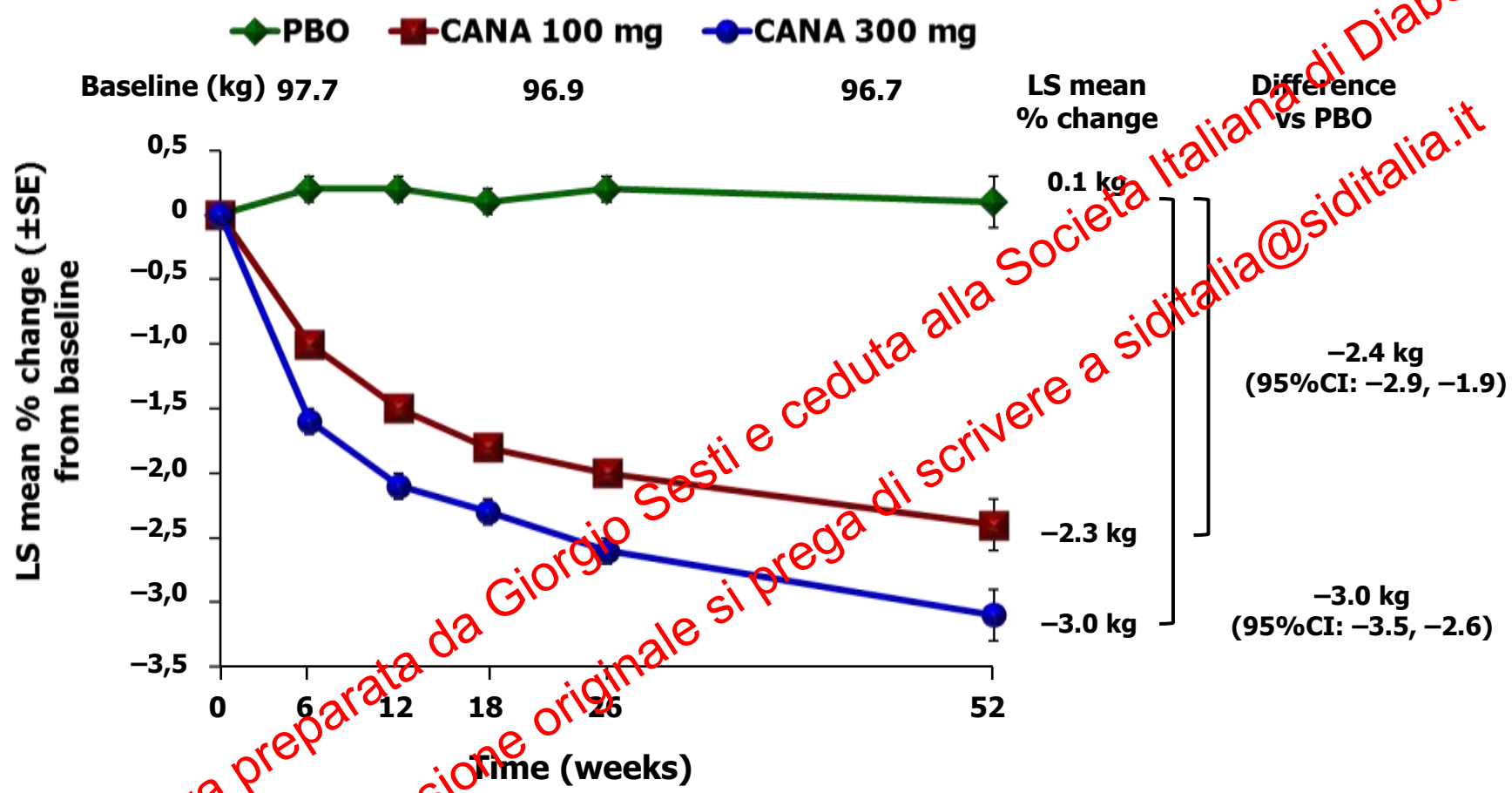
Canagliflozin add-on to insulin (≥20 IU/day) substudy from CANVAS: HbA1c changes over 52 weeks



PBO = 690 subjects
100 CANA= 692 subjects
300 CANA= 690 subjects

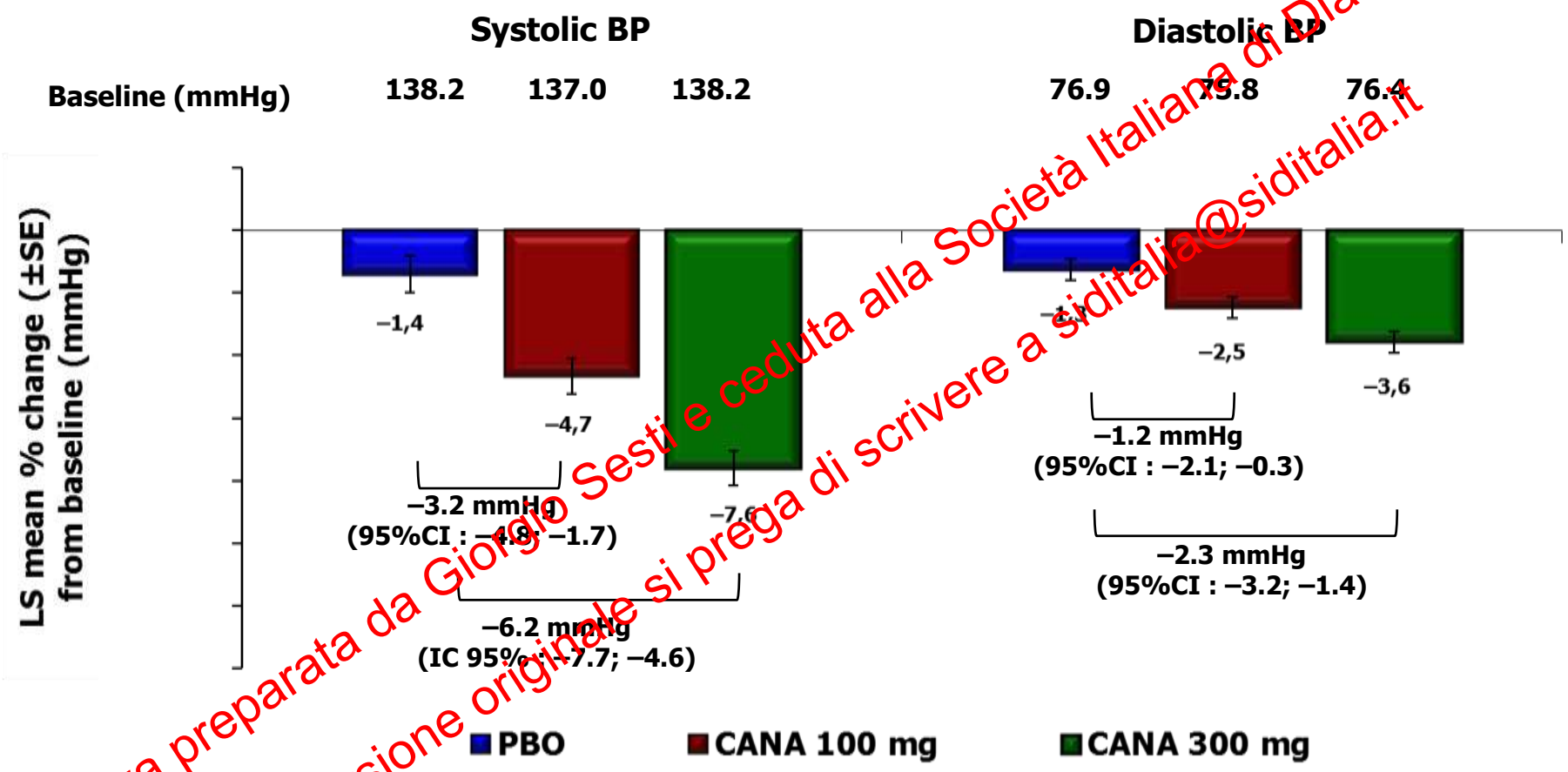
Neal B. et al. Diabetes Care 38:403–411, 2015

Canagliflozin add-on to insulin (≥20 IU/day) substudy from CANVAS: body weight changes over 52 weeks



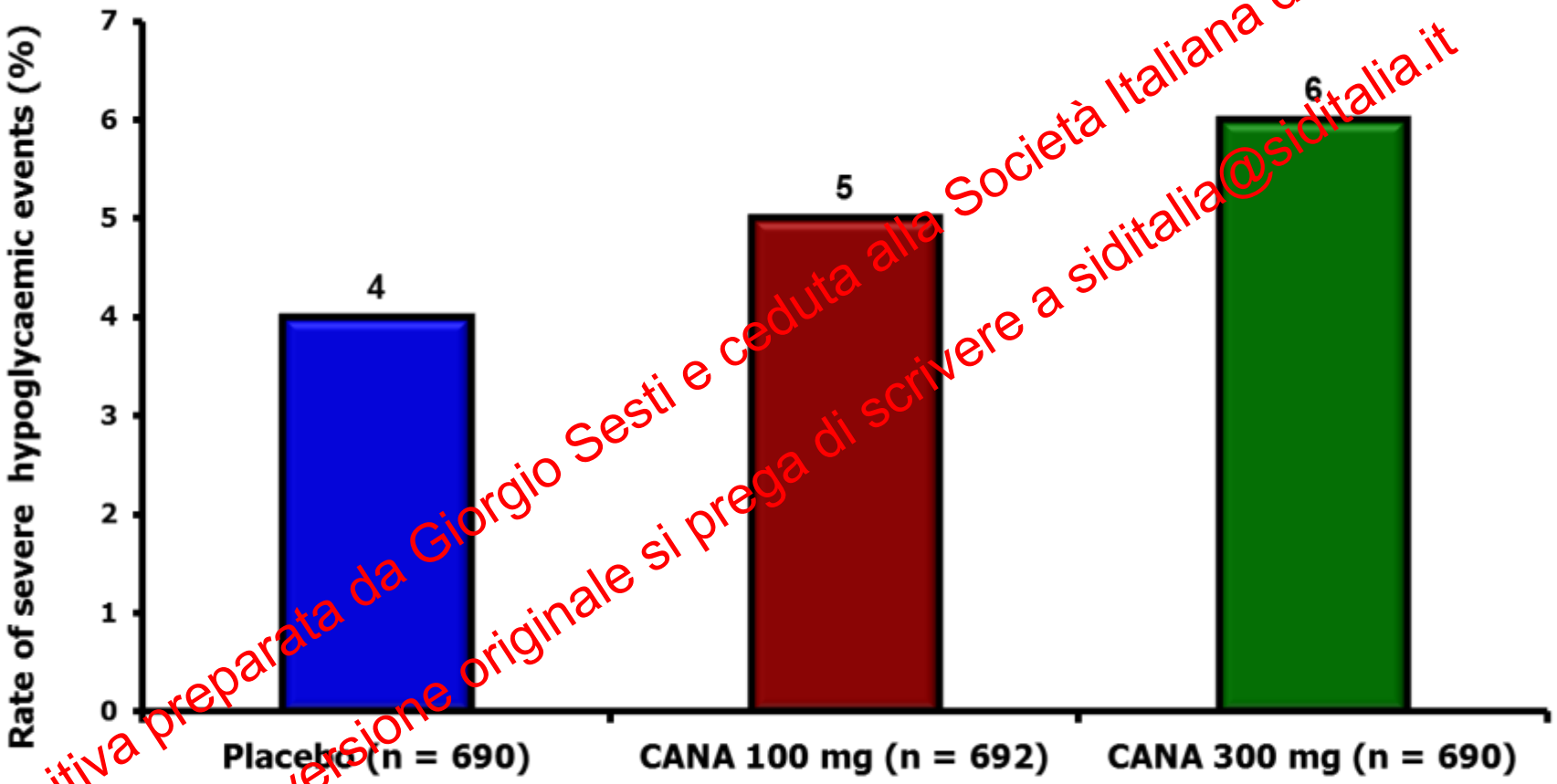
Neal B. et al. Diabetes Care 38:403–411, 2015

Canagliflozin add-on to insulin (≥20 IU/day) substudy from CANVAS: Blood pressure changes over 52 weeks



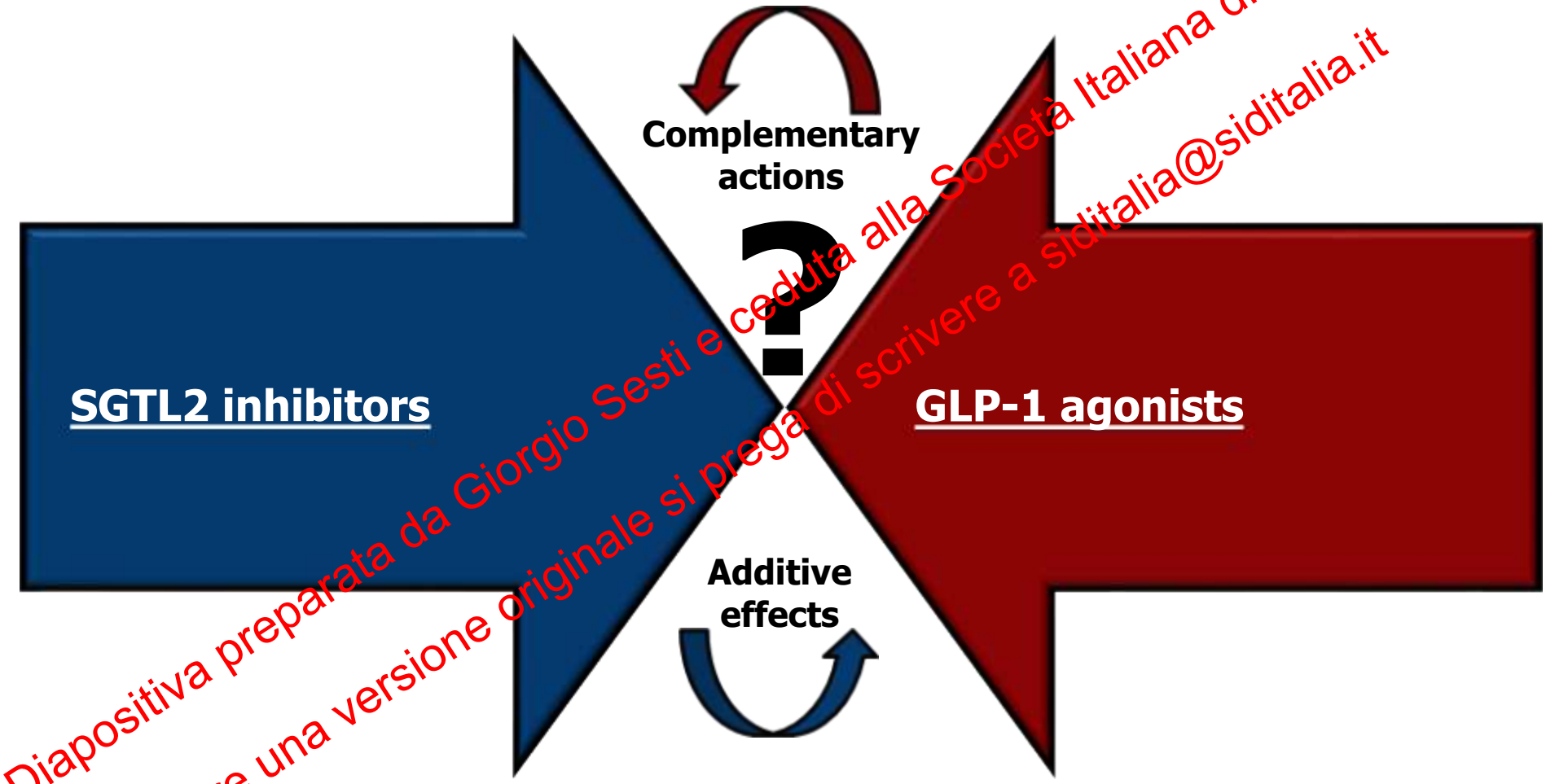
Neal B. et al. Diabetes Care 38:403–411, 2015

Canagliflozin add-on to insulin (≥20 IU/day) substudy from CANVAS: Frequency of patients with severe hypoglycaemia at Week 52

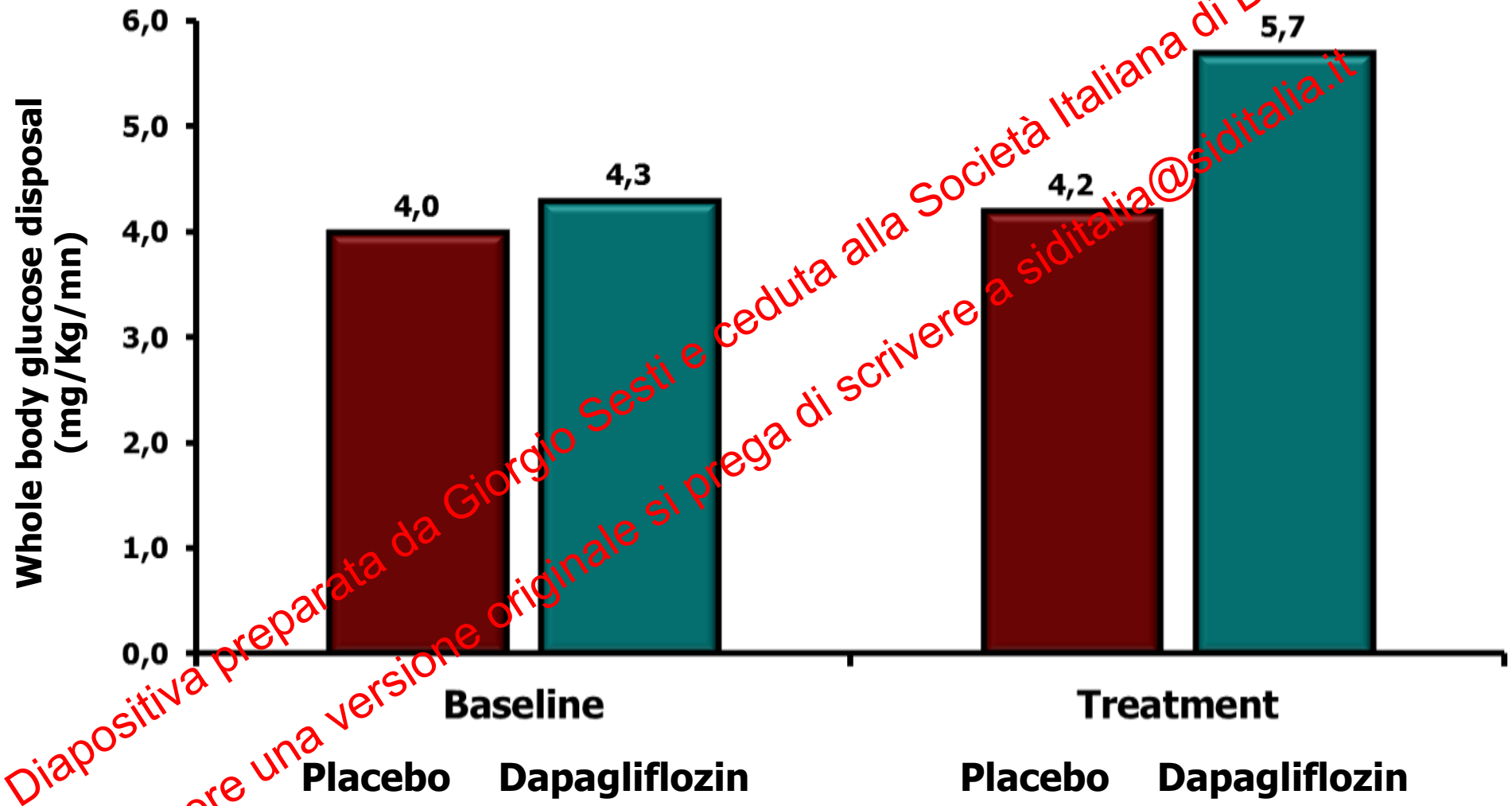


Neal B. et al. Diabetes Care 38:403–411, 2015

Rationale for combination of SGTL2 inhibitors with a GLP-1 agonist



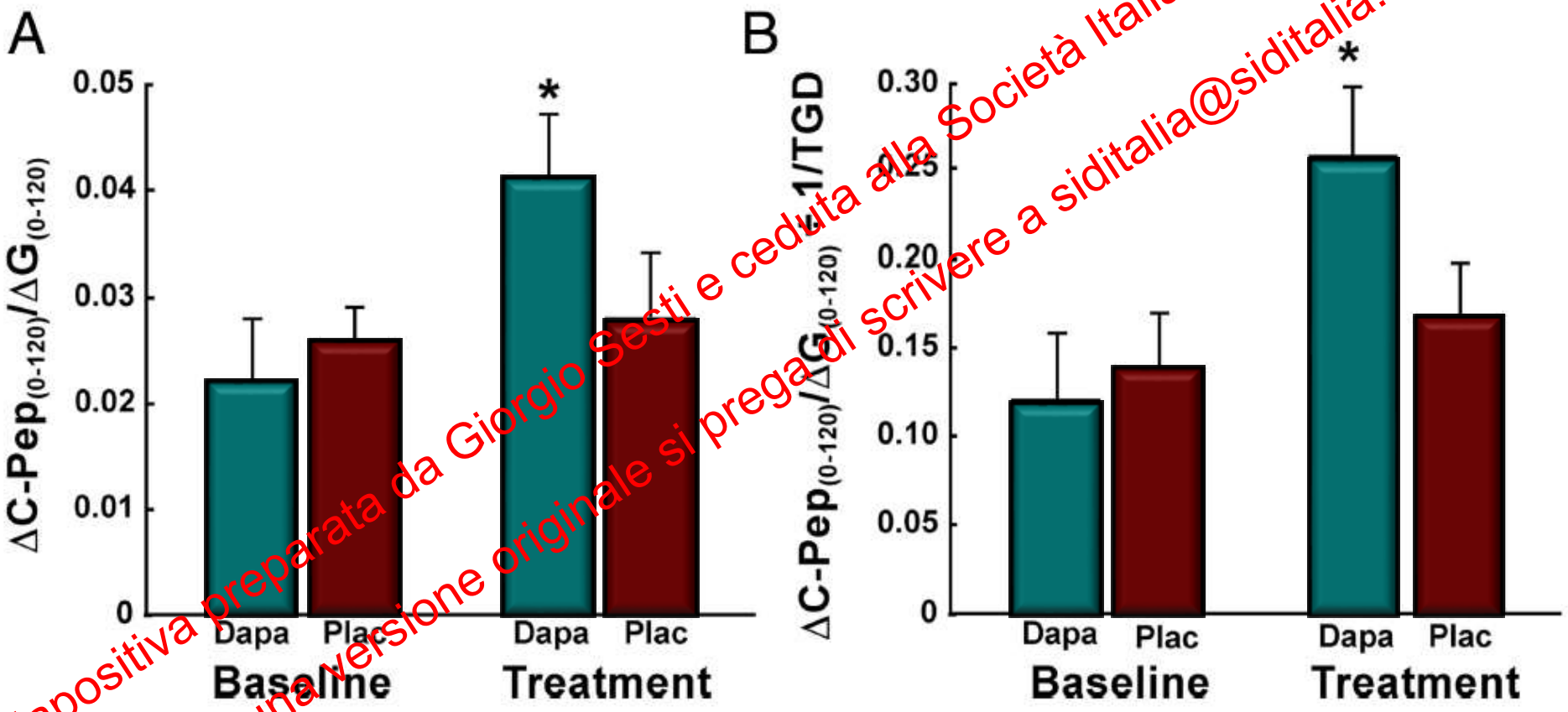
Whole body and tissue glucose disposal during the euglycemic insulin clamp studies performed in subjects with type 2 diabetes before (Baseline) and after 14 days of treatment with dapagliflozin (Dapa) or placebo (Plac)



Merovci A et al. J Clin Invest. 124(2):509–514, 2014

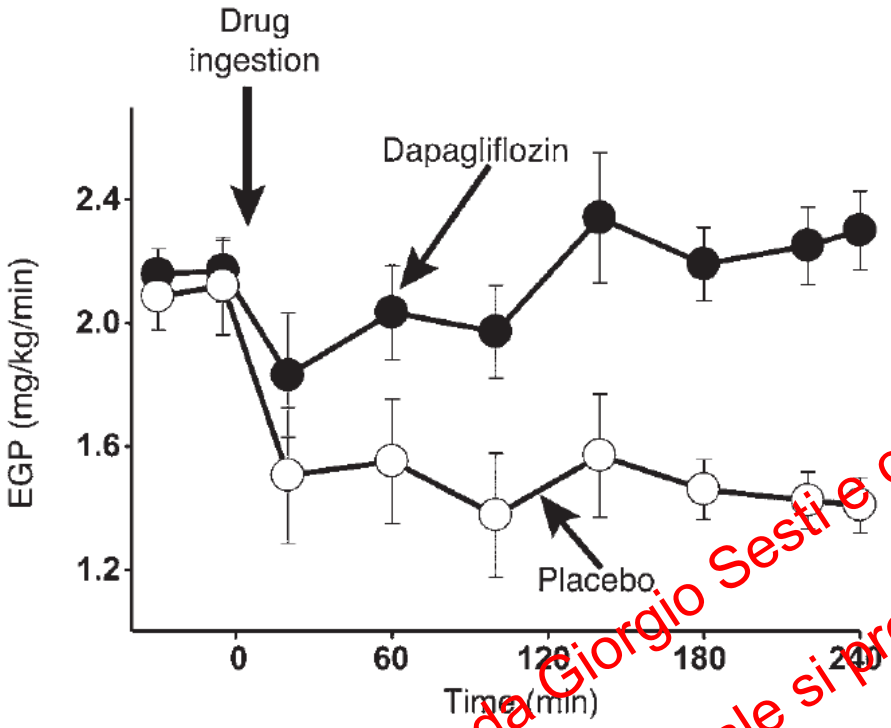
Insulin secretion (A) and beta-cell function (B) in dapagliflozin-treated and placebo-treated T2DM patients at baseline and after 2 weeks of treatment

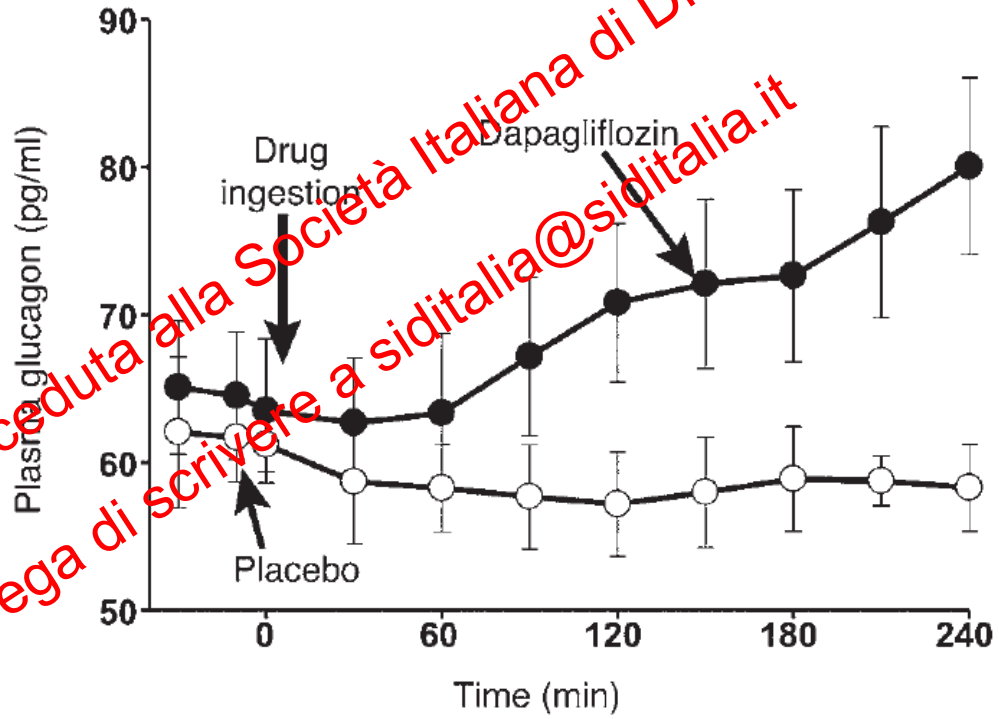
Dapa: Dapagliflozin
Plac: Placebo



Merovci A et al. J Clin Endocrinol Metab 100: 1927–1932, 2015

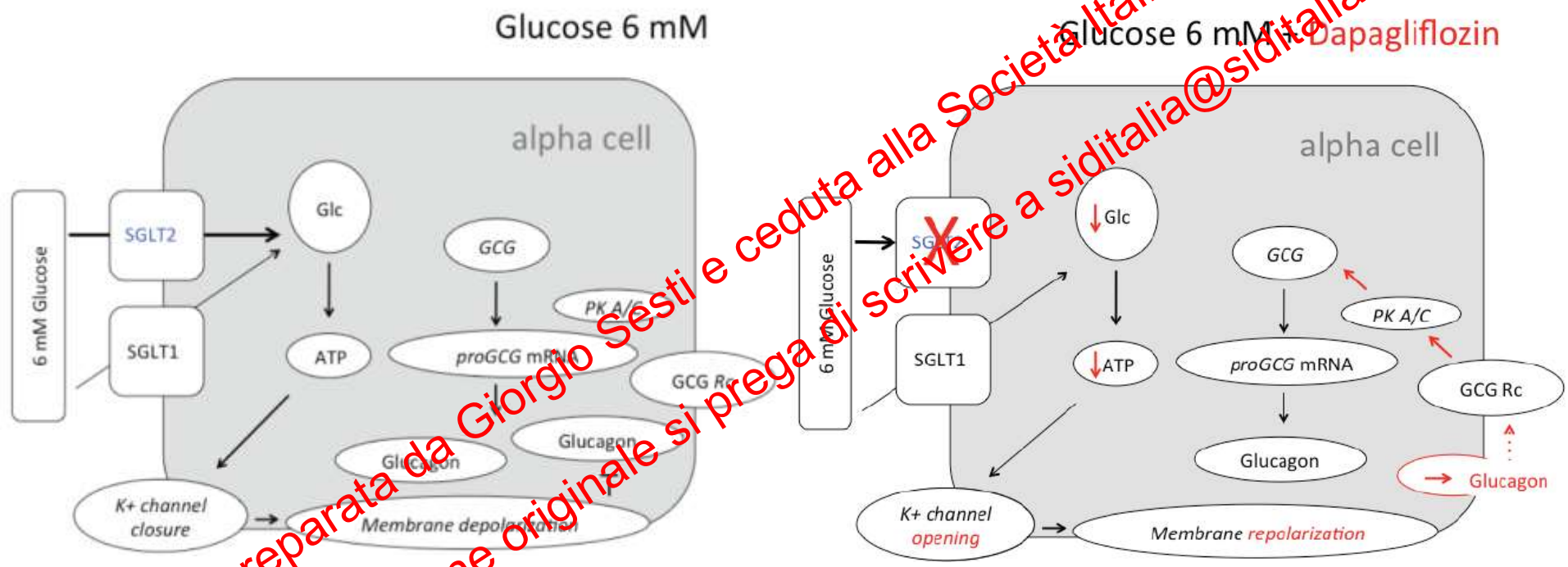
Plasma glucagon concentrations and EGP in the study





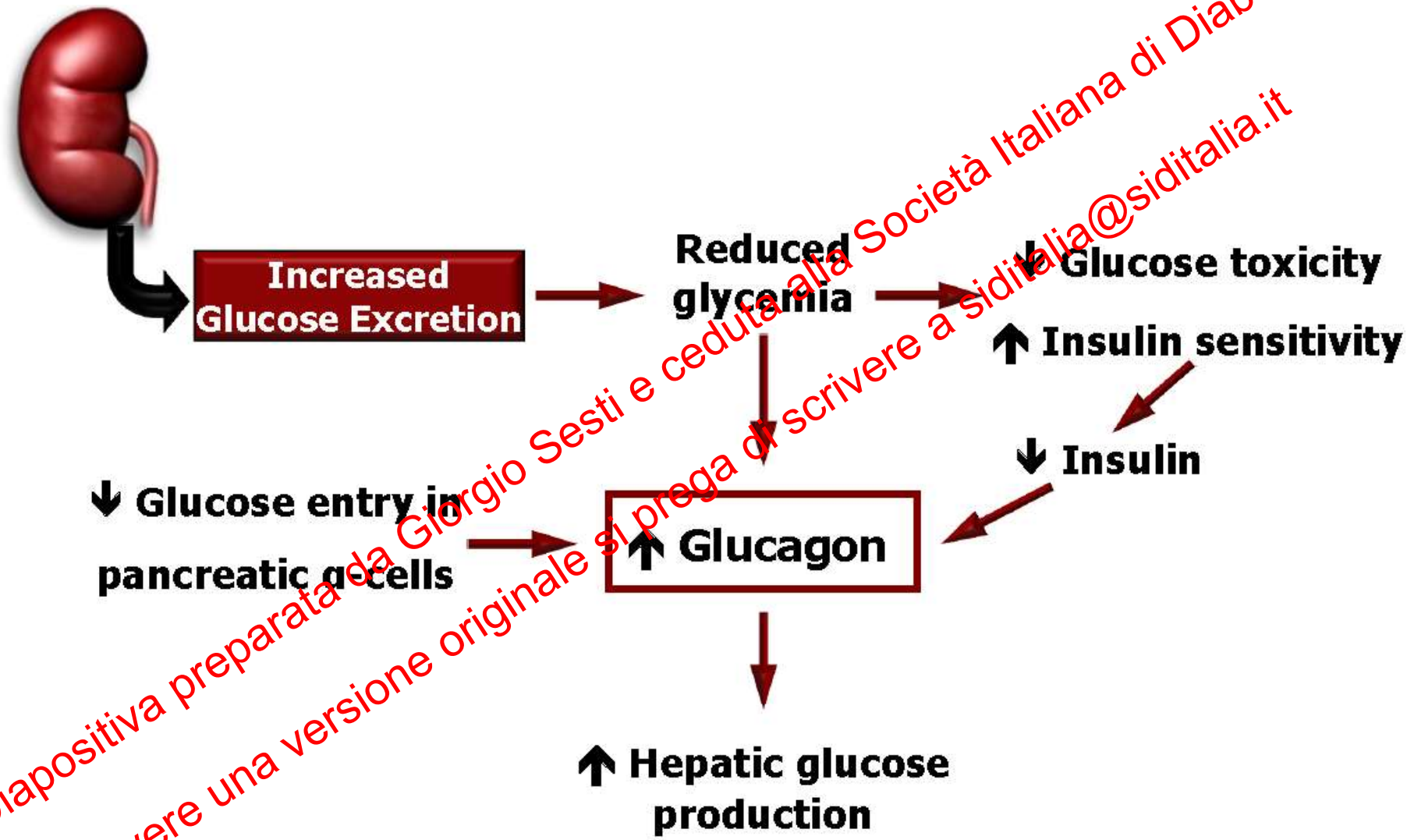
Merovci A et al. J Clin Invest. 124(2):509–514, 2014

Schematic representations illustrating the mechanism of glucagon regulation in human islets after *SLC5A2* inhibition with dapagliflozin



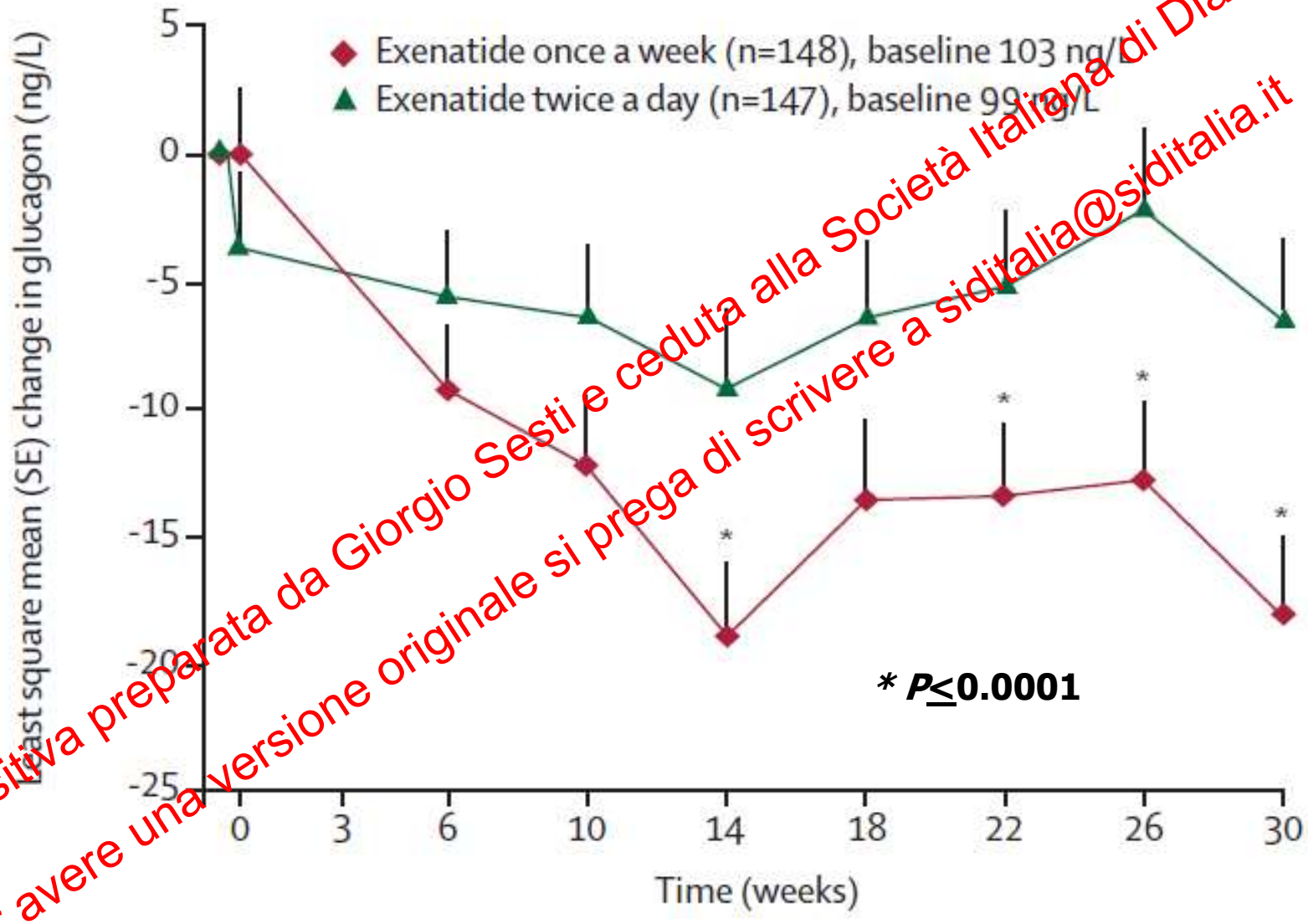
Bonner C et al. Nature Medicine 21:512–517, 2015

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



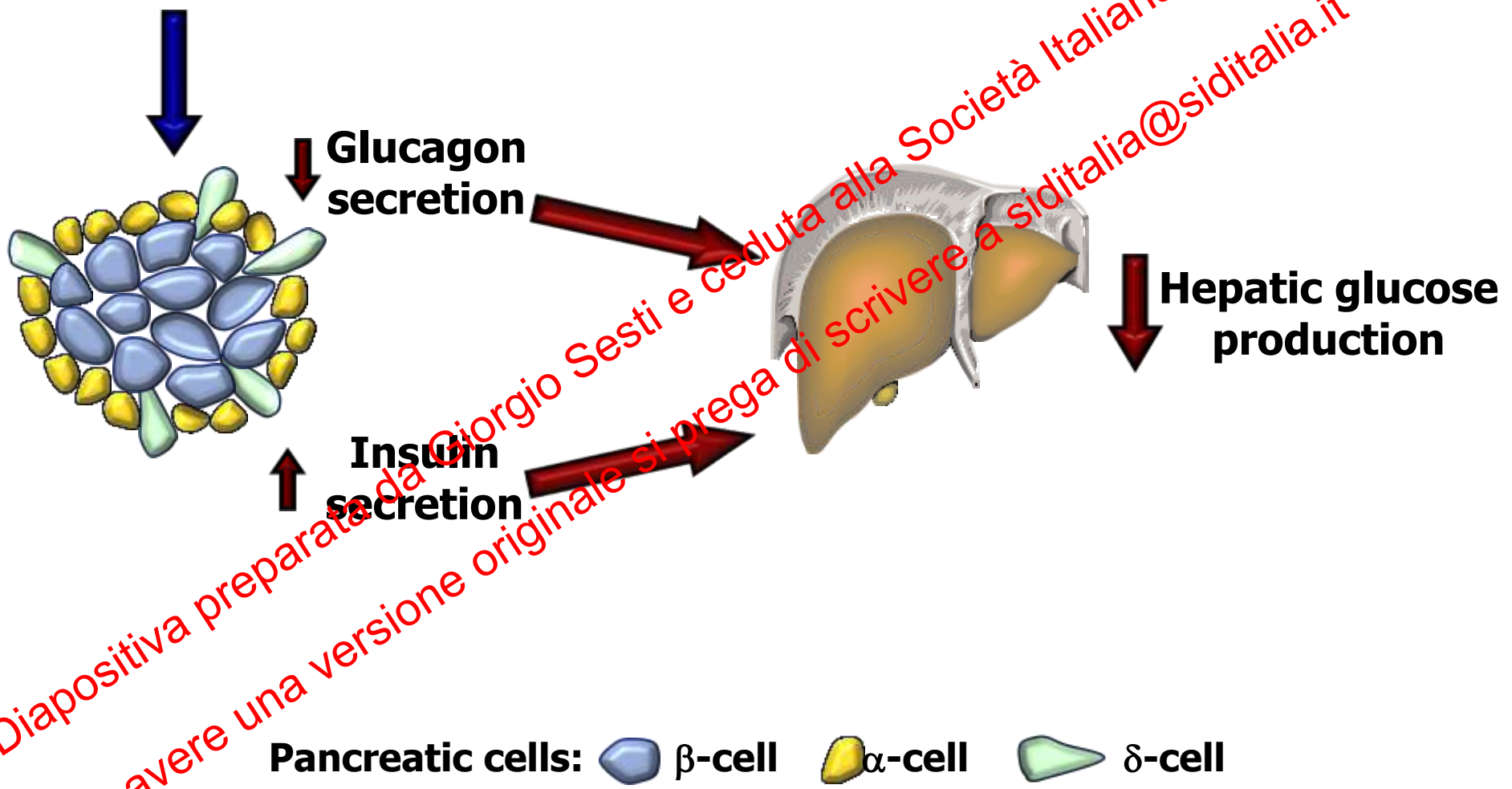
SGLT2: sodium-glucose transporter 2

Exenatide OW versus twice daily for the treatment of type 2 diabetes: Changes in plasma glucagon levels-DURATION-1

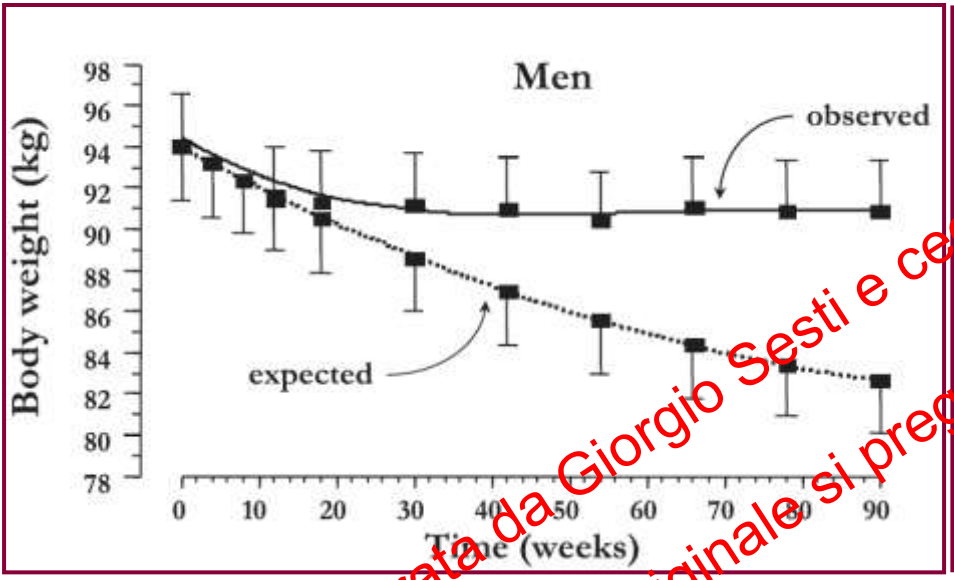


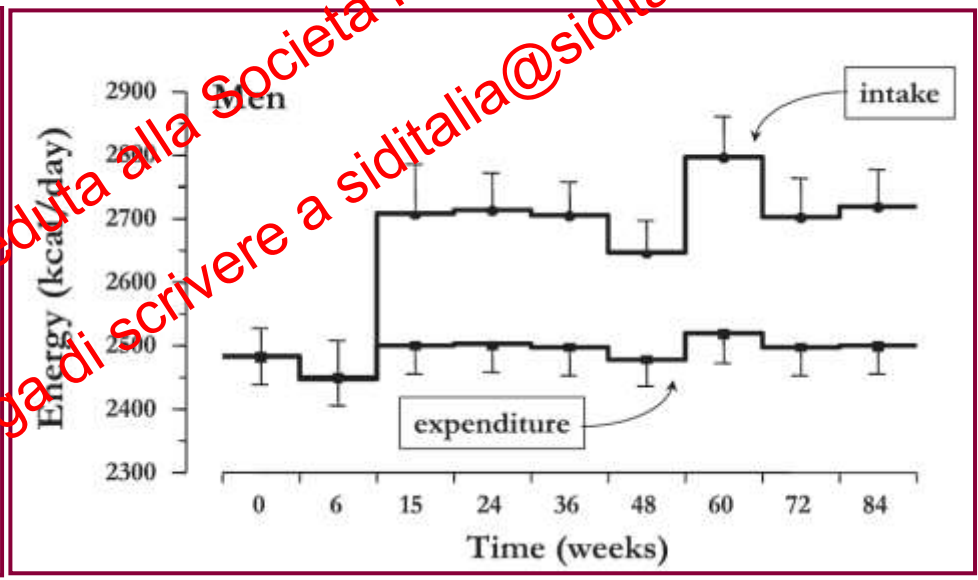
Drucker et al. Lancet 372: 1240–50, 2008

Eccessive hepatic glucose production



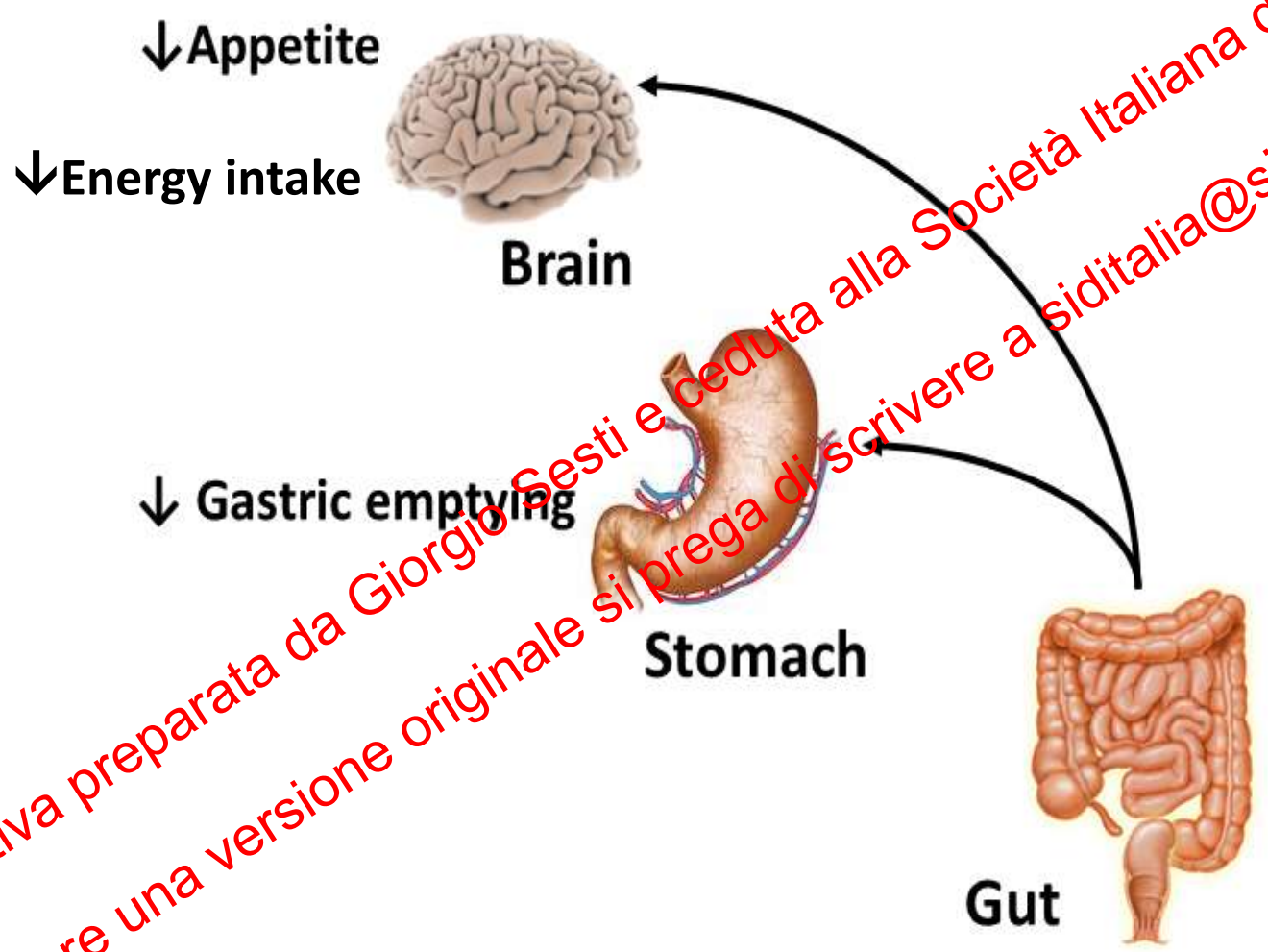
Time course of observed and predicted (by glycosuria) weight loss and calculated rates of energy intake in men with T2DM treated with empagliflozin (25 mg/day) for 90 weeks





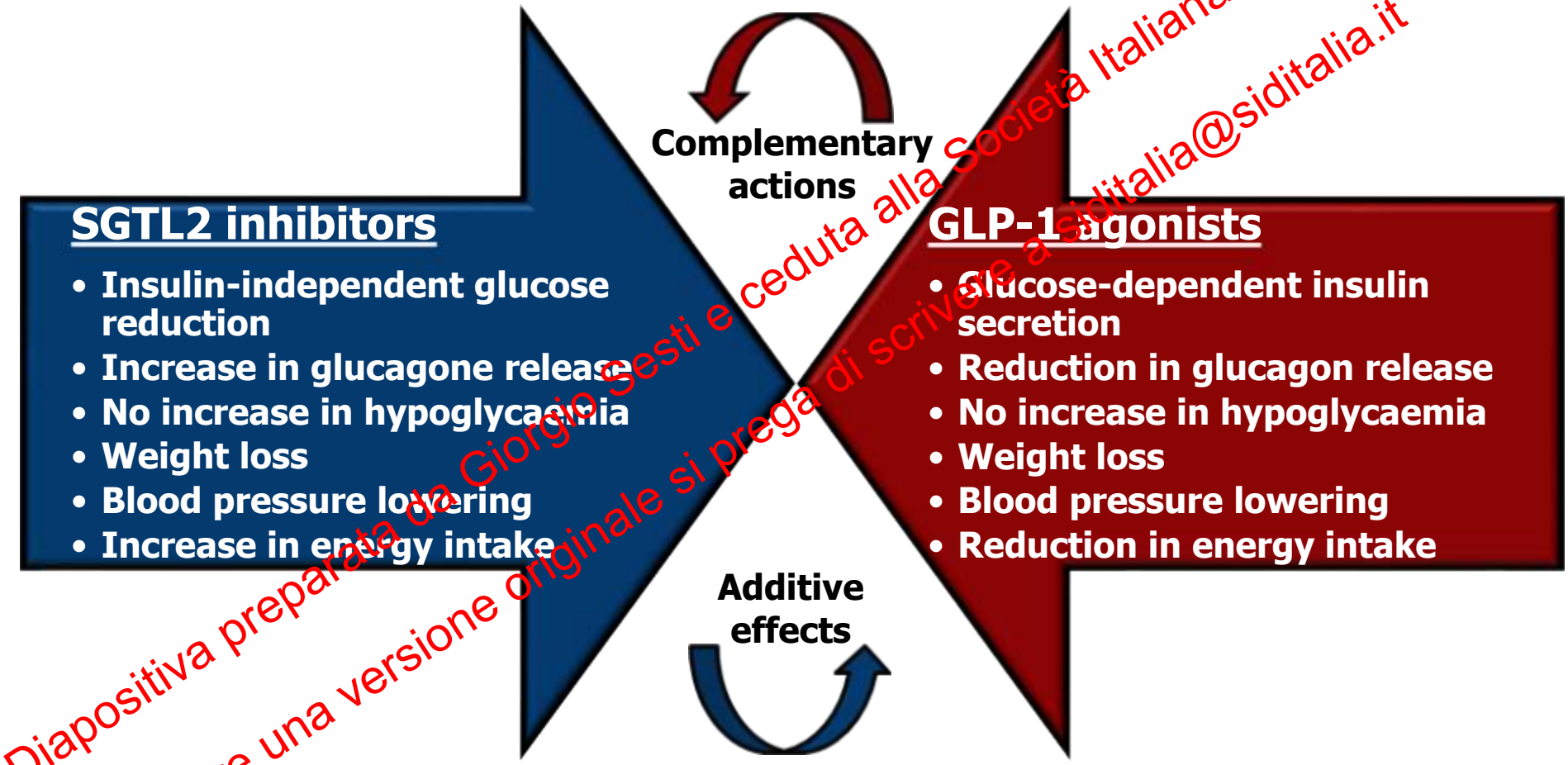
Ferrannini G. et al. Diabetes Care 38:1730–1735, 2015

GLP-1: its role in weight loss

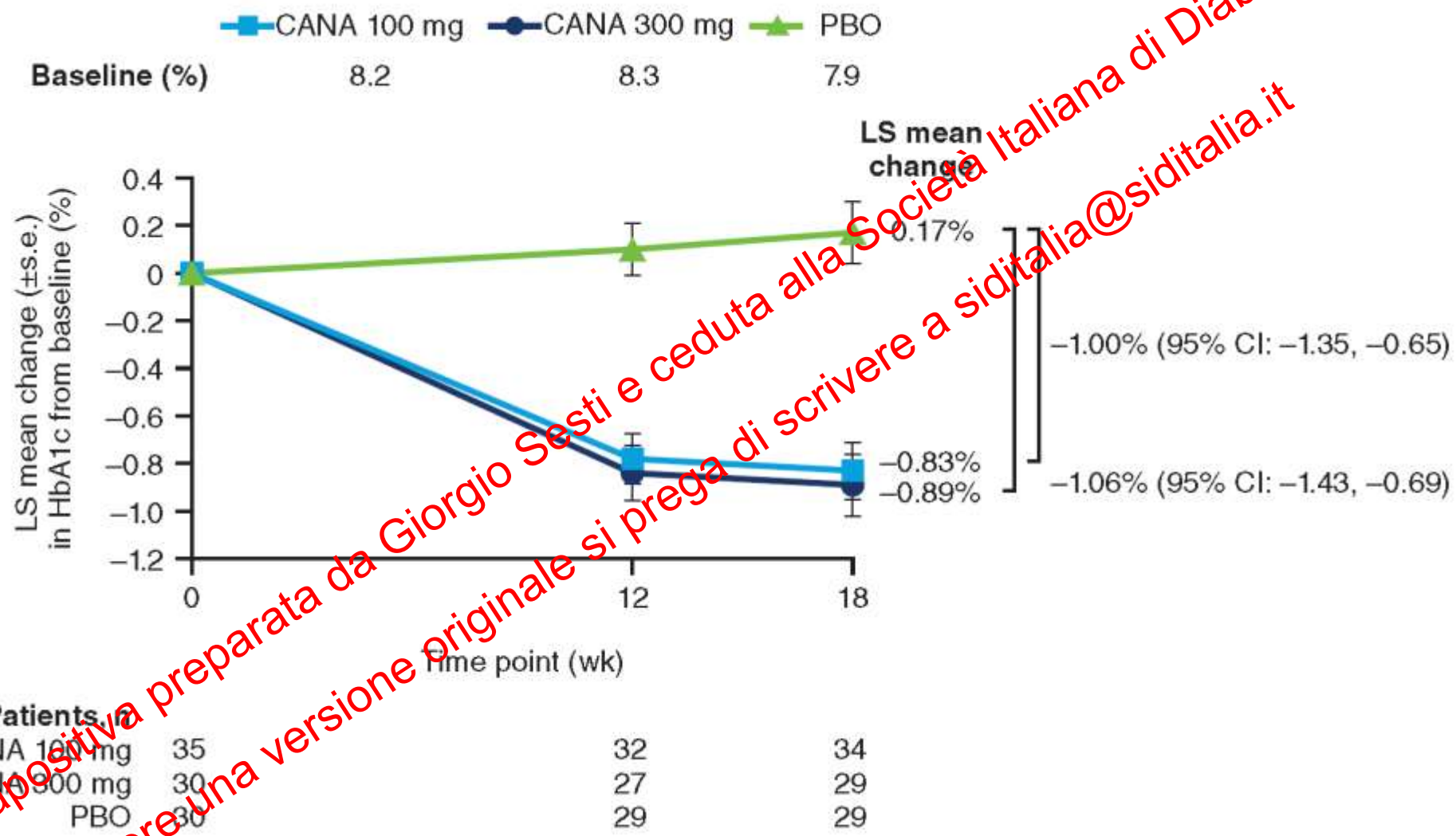


Gunn I, et al. *J Endocrinol*. 1997;155:197-200.
Orskov C. *Diabetologia*. 1992;35:701-711.

Rationale for combination of SGTL2 inhibitors with a GLP-1 agonist

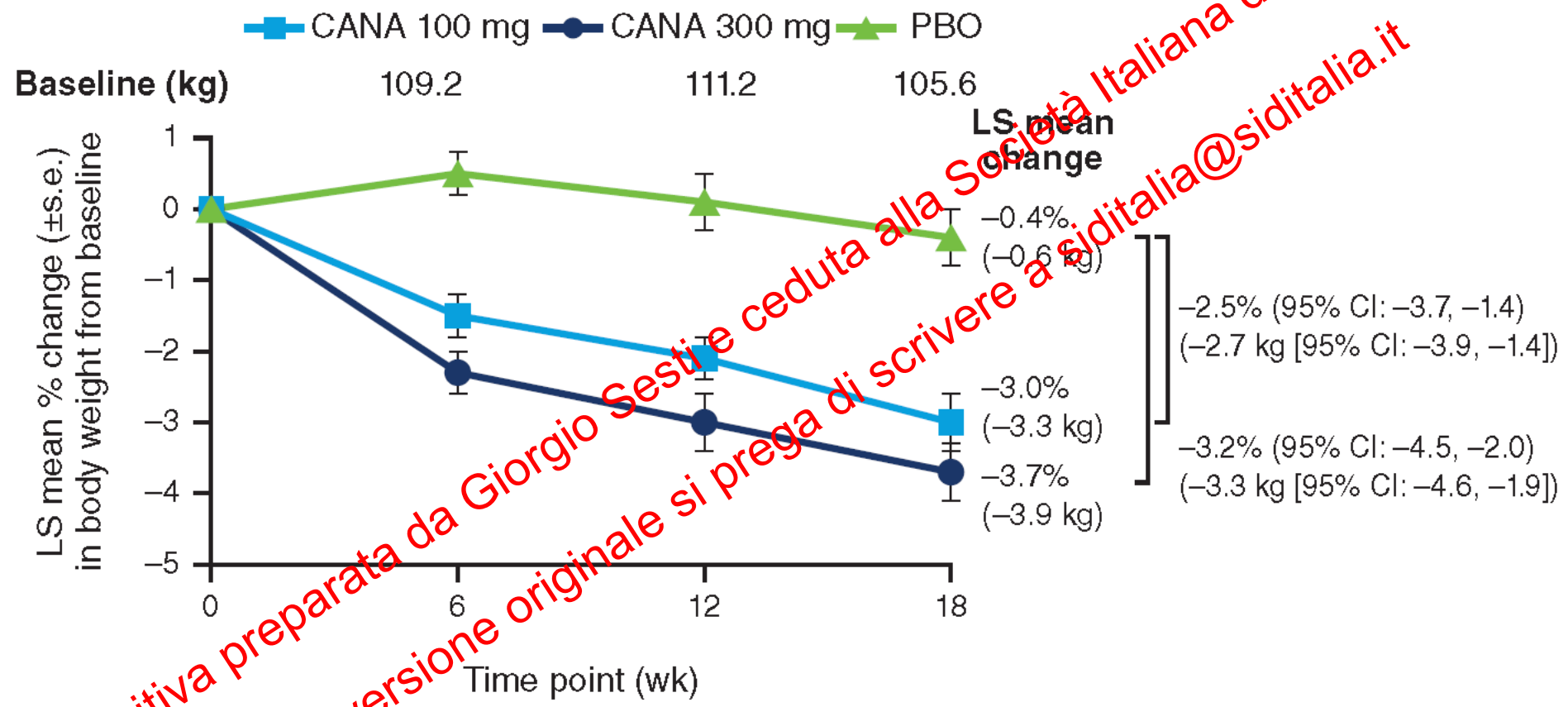


Canagliflozin add-on to GLP-1 receptor agonists substudy from CANVAS: HbA1c changes over 18 weeks



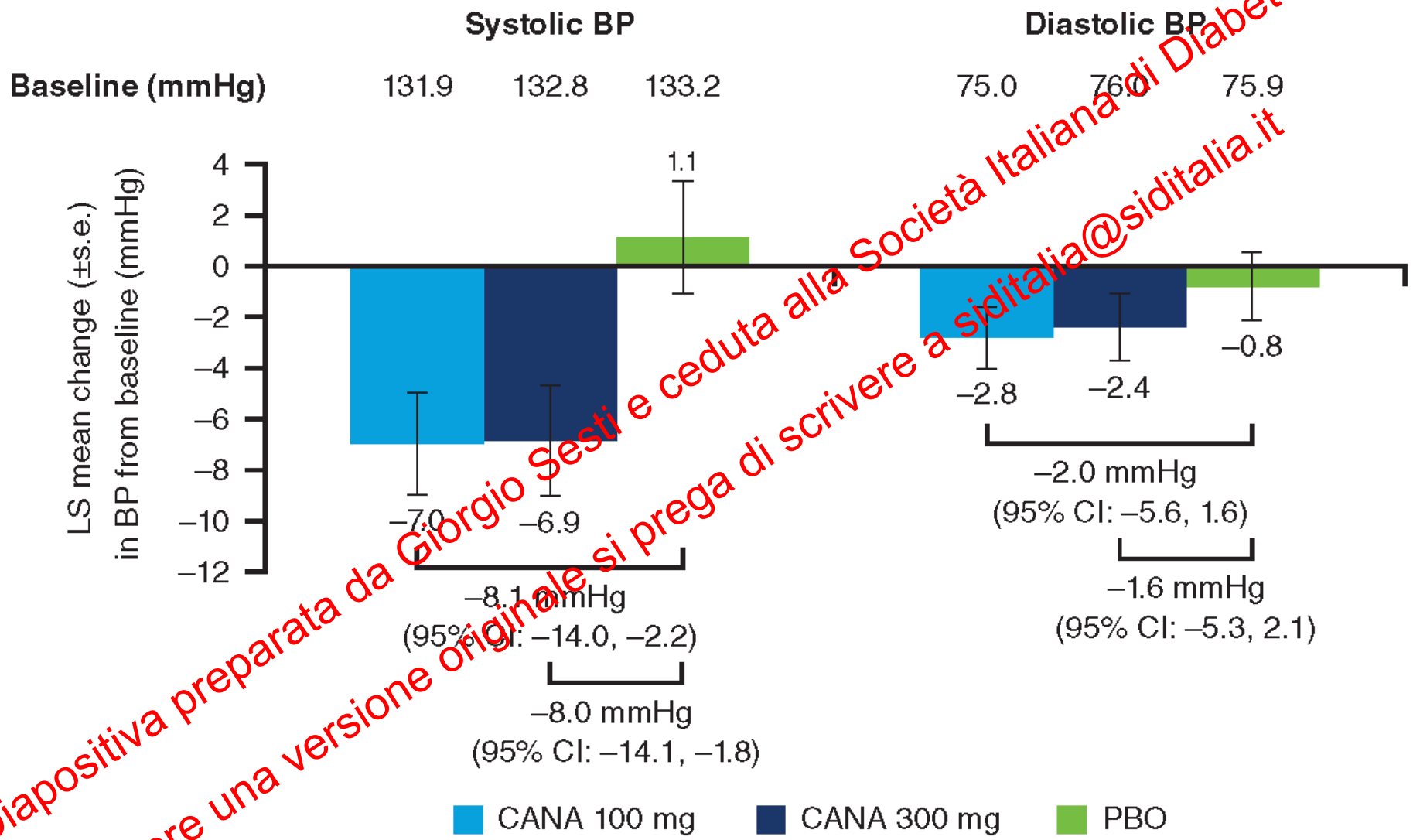
Fulcher G. et al. Diabetes Obes Metab 18: 82–91, 2016

Canagliflozin add-on to GLP-1 receptor agonists substudy from CANVAS: Body weight changes over 18 weeks



Fulcher G. et al. Diabetes Obes Metab 18: 82–91, 2016

Canagliflozin add-on to GLP-1 receptor agonists substudy from CANVAS: Blood pressure changes over 18 weeks



Fulcher G. et al. Diabetes Obes Metab 18: 82–91, 2016

Effects of canagliflzion added to GLP-1 agonists in 75 subjects with T2DM in a real world study

	Change, SD	*P* value
Primary outcome		
Change in HbA1c (%)	–0.39 ± 0.88	<.001
Secondary outcomes		
Change in weight (kg)	–4.6 ± 4.3	<.001
% of Patients with HbA1c <7%	26.7%	<.001
Change in blood pressure (mm Hg)		
Systolic	–4.0 ± 12	.01
Diastolic	–2.7 ± 9	.02
Changes in lipid parameters (mg/dL)		
TC	3 ± 30	.47
LDL-C	0.6 ± 25.2	.85
HDL-C	2.1 ± 4.5	<.001
TG	19 ± 15	.32
Change in BUN	2.2 ± 4.6	<.001
Change in SCr	0.03 ± 0.17	.15

Saroka RM et al. Endocr Pract 21: 1315-1322, 2015

SGTL2 inhibitors and GLP-1 receptor agonist combo
Ongoing Trials

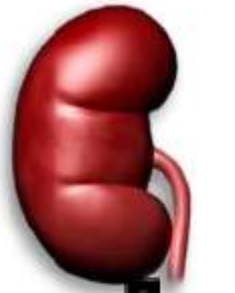
- DAPA + exenatide in patients inadequately controlled on MET[a]
  - Randomized, double-blind, active-controlled, multicenter, phase 3
  - Exenatide QW 2 mg + DAPA 10 mg QD compared with exenatide QW 2 mg alone and DAPA 10 mg QD alone
  - Outcomes: efficacy (HbA_{1c}, plasma glucose, body weight, BP) and safety
- CANA + liraglutide[b]
  - Nonrandomized, open-label
  - Outcomes: combination's effects on hepatic glucose production, HbA_{1c}, plasma glucose level, body weight, hepatic and visceral fat content, and BP

a. ClinicalTrials.gov website.[15] b. ClinicalTrials.gov website.[16]

SGTL2 inhibitors in combination with injectable therapies

- **Diabetes is an obesity-related disease**
  - **SGLT2 inhibitors help patients lose weight**
- **Many patients have inadequate blood pressure control despite multiple treatments**
  - **SGLT2 inhibitors lower blood pressure**
- **Hypoglycaemia is an important and costly complication that reduces compliance**
  - **SGLT2 inhibitors have a low risk of causing hypoglycaemia**
- **Increasing insulin doses often promotes weight gain without improving control**
  - **SGLT2 inhibitors can help break the cycle of weight gain and escalating insulin doses**

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



Increased Glucose Excretion

Reduced glycaemia

↓ Glucose toxicity

↑ Insulin sensitivity

↓ Insulin

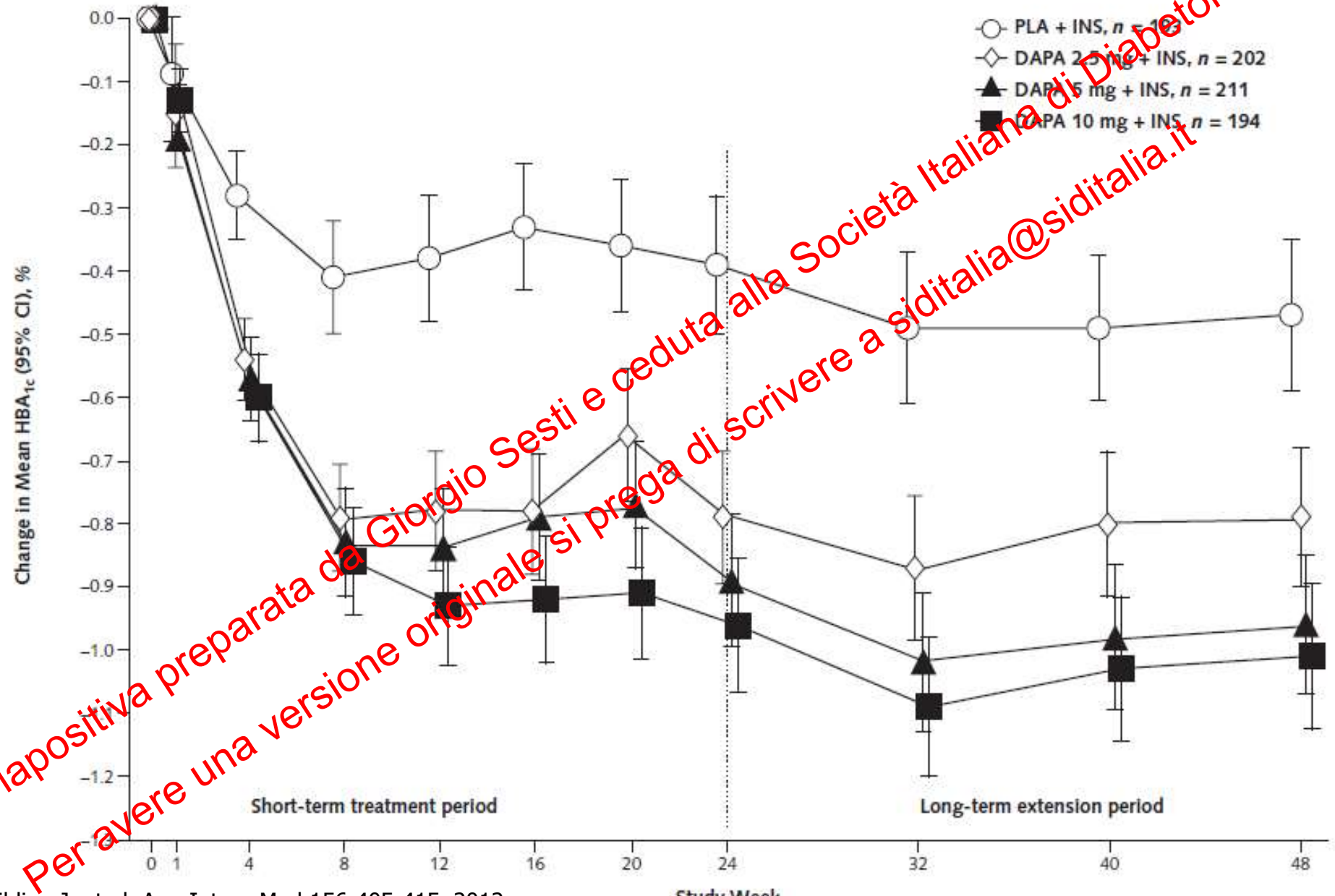
↓ Glucose entry in pancreatic α-cells

↑ Glucagon

↑ Hepatic glucose production

SGLT2: sodium-glucose transporter 2

Long-term efficacy of Dapagliflozin in patients with T2DM receiving high doses of insulin (>30 UI/die): adjusted mean changes in HbA1c level over time



Wilding J, et al. Ann Intern Med 156:405-415, 2012

Study of Dapagliflozin Use in Patients With T2D in Routine Primary Care*

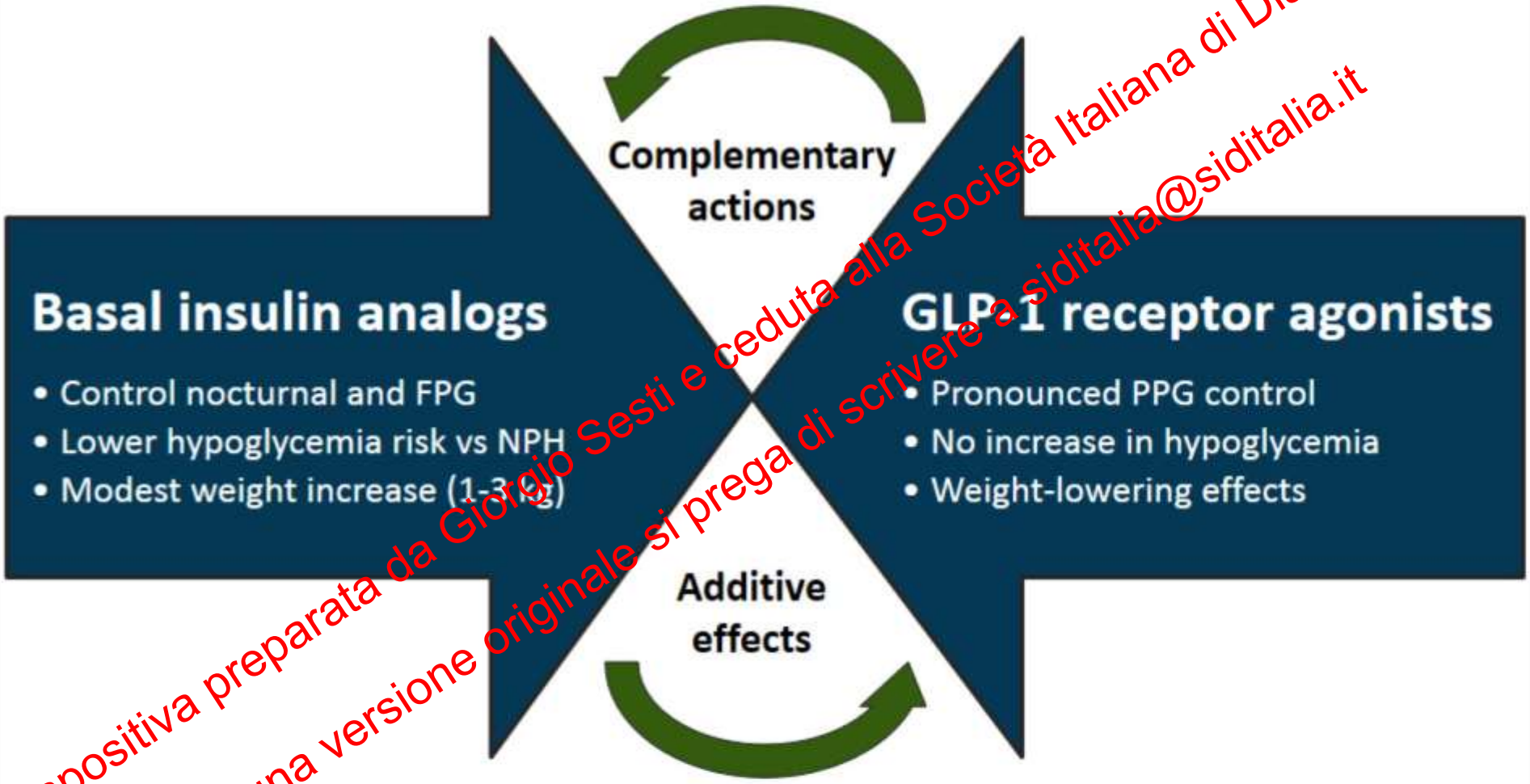
Change From Baseline With Addition of Dapagliflozin†

	Overall	Dual Therapy (With Metformin)	Triple Therapy	Addition to Insulin
14-90 d‡				
HbA_{1c}, %	-0.89	-0.88	-0.95	-0.96
Weight, kg	-2.6	-3.2	-2.8	-1.5
91-180 d‡				
HbA_{1c}, %	-0.93	-0.83	-0.96	-0.68
Weight, kg	-4.3	-5.2	-4.3	-2.7
>180 d‡				
HbA_{1c}, %	-01.16	-1.08	-1.18	-1.22
Weight, kg	-4.6	-6.3	-4.4	-3.2

*Retrospective observational study of 1,732 patients meeting inclusion criteria in 684 primary care practices in the UK; †Baseline weight was 103 kg; baseline HbA_{1c} = 80.1 mmol/mol (9.5%); ‡Days following dapagliflozin initiation.

Wilding, JPH, et al. EASD 51st Annual Meeting, 2015. Poster/Abstract 737.

Emerging Intensification Strategy

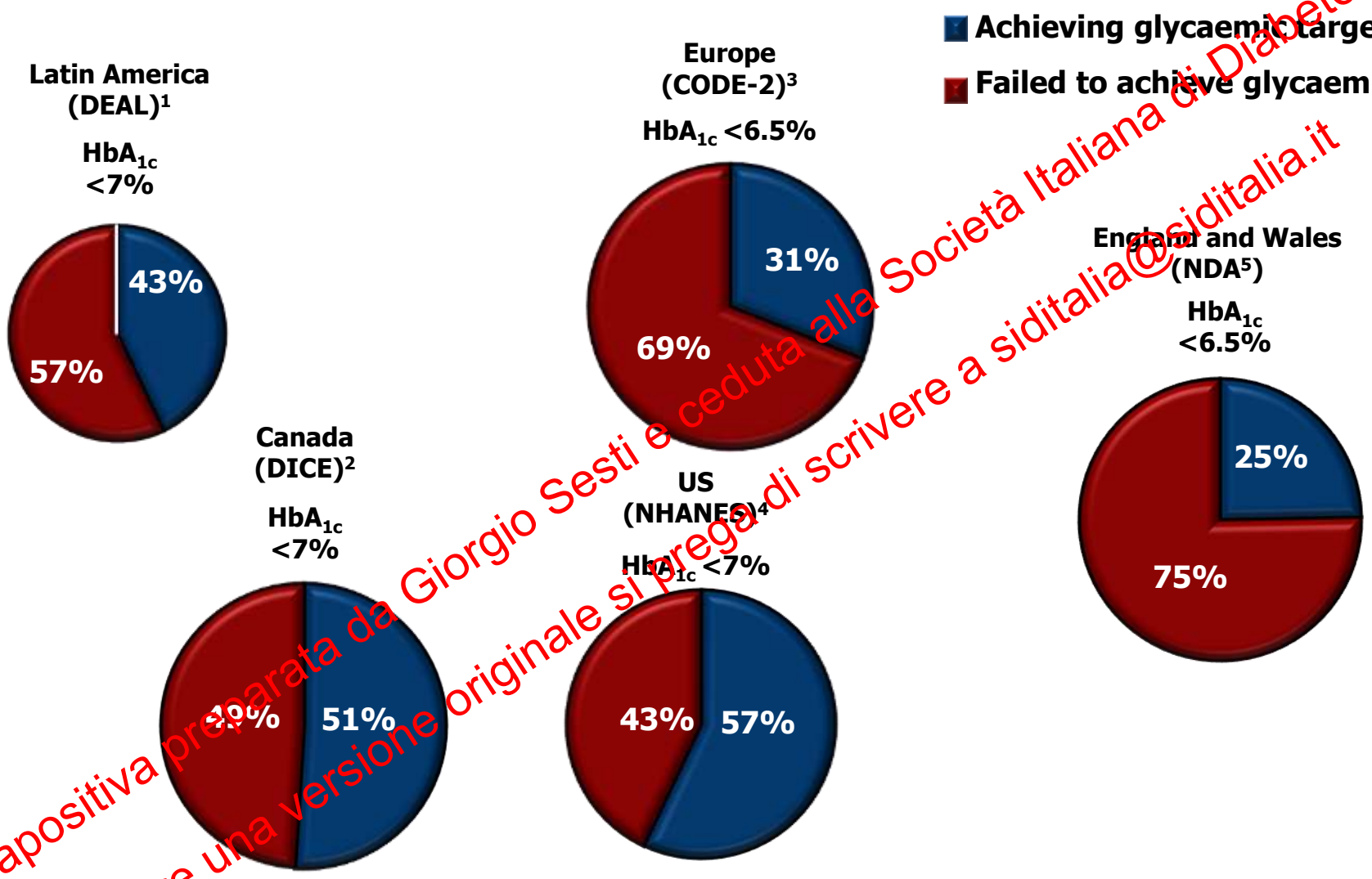


*The US FDA has not approved this medication for use; approved for use by the EMA.

Courtesy of Julio Rosenstock, MD.

Holst JJ, Vilsboll T. *Diabetes Obes Metab*. 2013;15:3-14.

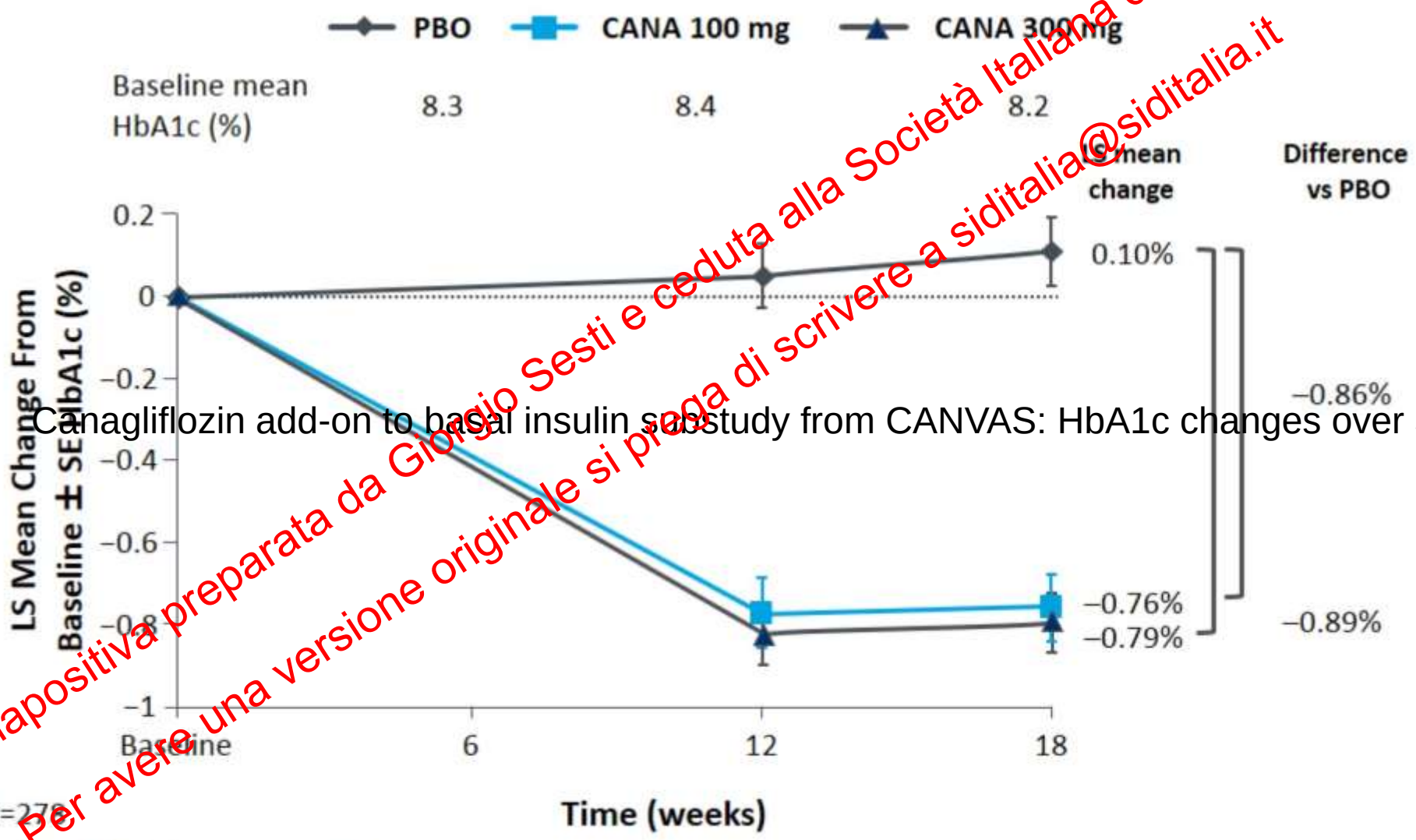
Diabetes is a progressive disease that requires reassessment to reach target



DEAL, Diabetes En America Latina; CODE-2, The Cost of Diabetes in Europe - Type II; DICE, Diabetes in Canada Evaluation; NDA, National Diabetes Audit; NHANES, National Health and Nutrition Examination Survey

1. Lopez-Stewart et al. Rev Panam Salud Publica 2007;22:12–20; 2. Harris et al. Diabetes Res Clin Pract 2005;70:90–7;
3. Liebl et al. Diabetologia 2002;45:S23–8; 4. Hoerger et.al. Diabetes Care 2008;31:81–6; 5. HSCIC et al. National Diabetes Audit Report, 2011-12

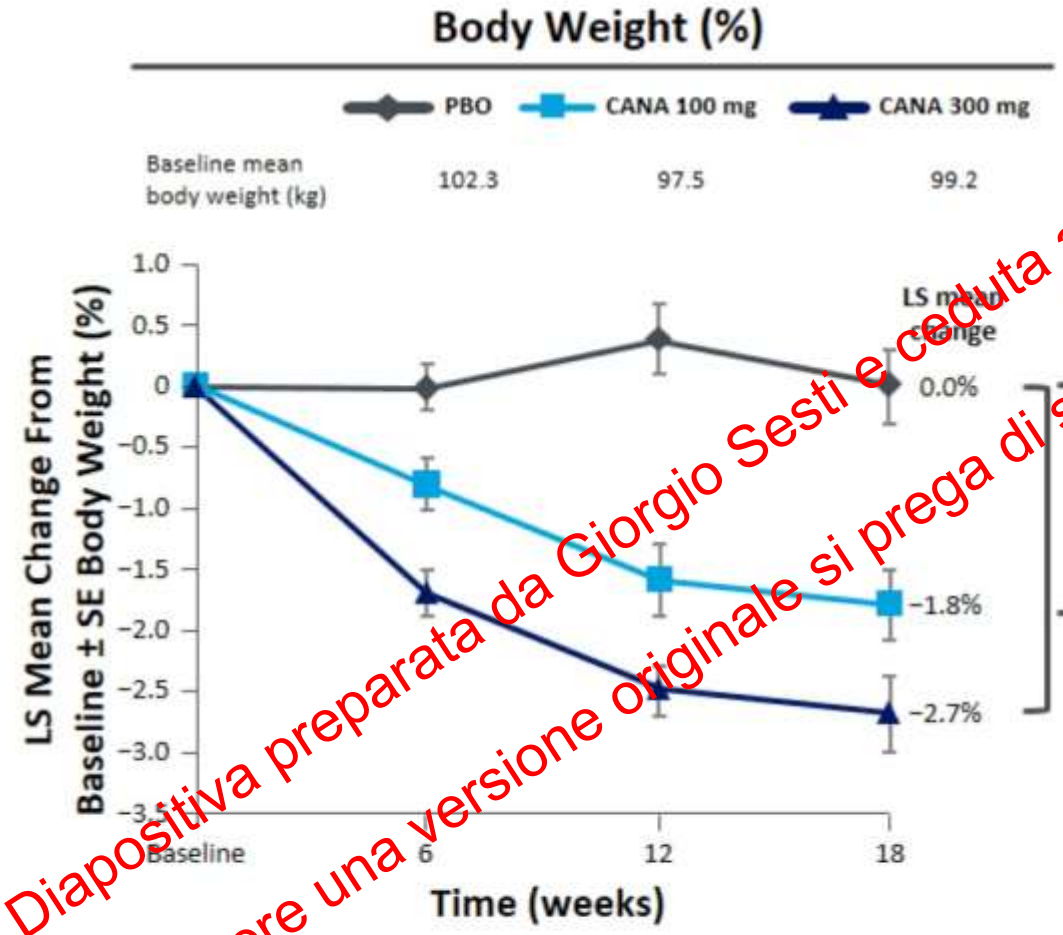
Canagliflozin Add-on to Basal Insulin Substudy From CANVAS: HbA1c Changes Over 18 Weeks

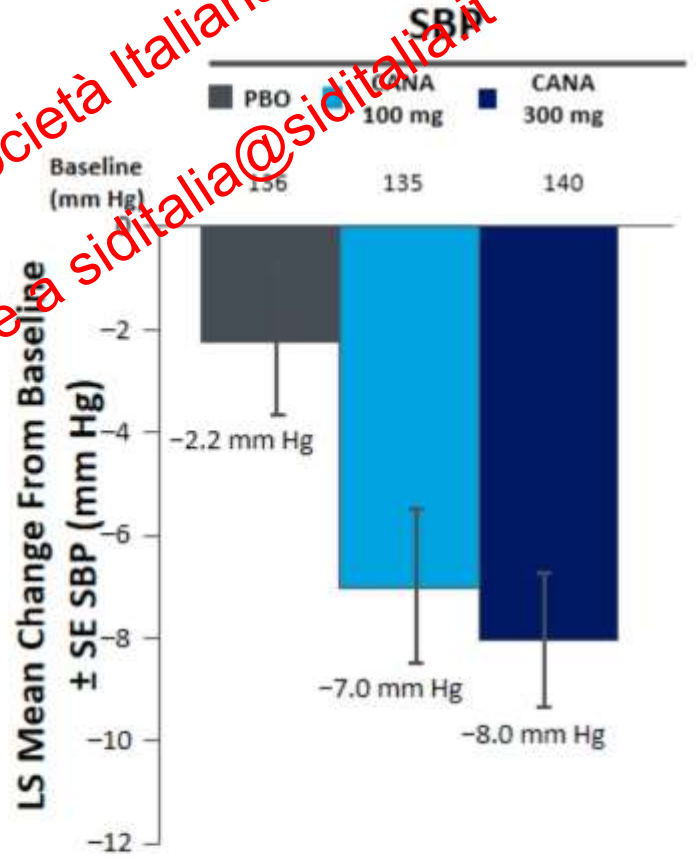


Canagliflozin add-on to basal insulin substudy from CANVAS: HbA1c changes over 52

Neal B, et al. *Diabetes Care*. 2015;38:403-411.

Canagliflozin Add-on to Basal Insulin Substudy From CANVAS: Body Weight and SBP Changes





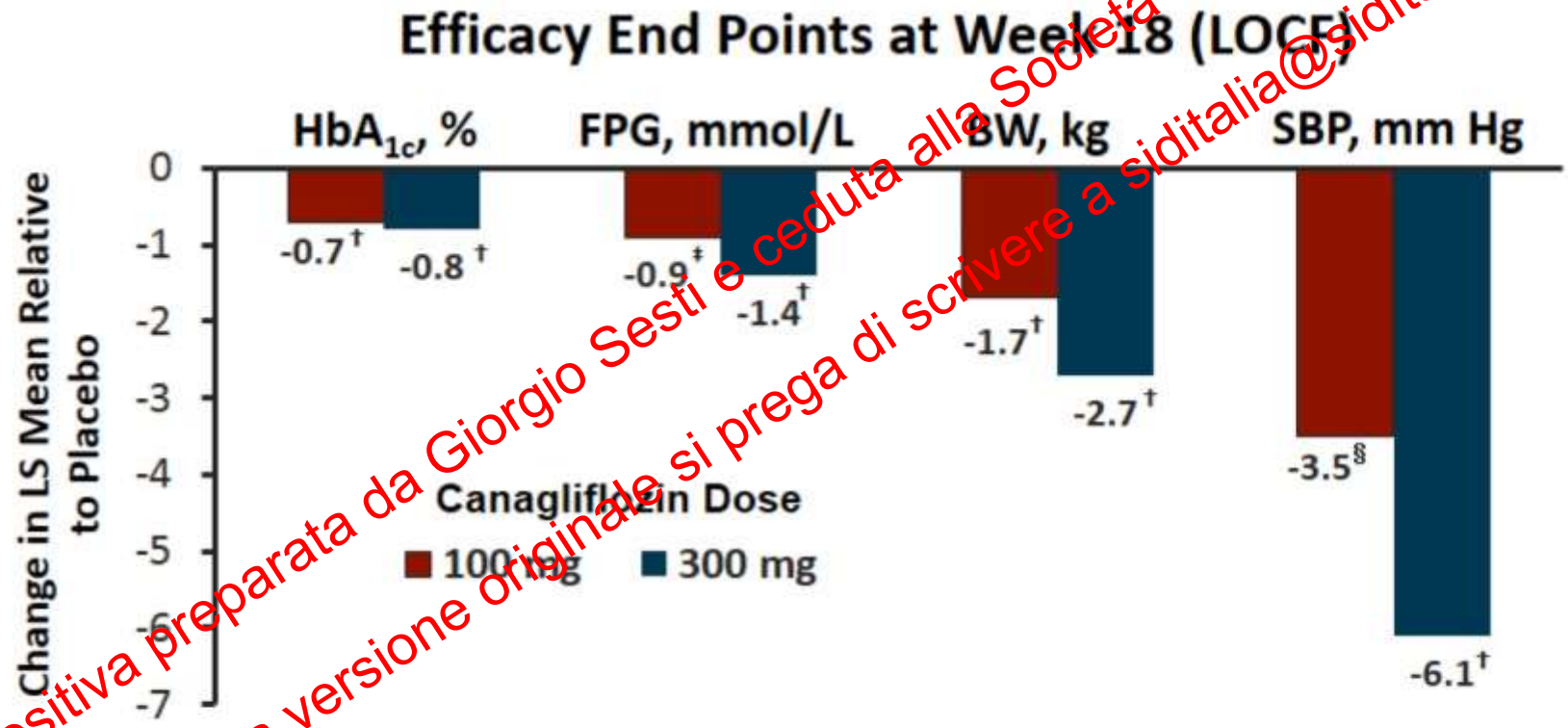
N=278

Mean changes in pulse rate with CANA 100 mg and 300 mg and PBO were −1.2, 0.5, and 1.2 beats/min, respectively

Neal B, et al. *Diabetes Care*. 2015;38:403-411.

CANVAS Substudy

*Canagliflozin as an Add-on to Insulin Plus Metformin in Patients With T2D**



*Patients were on ≥20 IU/d insulin and ≥2000 mg/d metformin; N=432.

†P <.001 vs placebo; ‡P = .001 vs placebo; § Statistical testing not performed due to hierarchical testing sequence.

Matthews D, et al. EASD 51st Annual Meeting, 2015. Abstract/Poster 743.