CORSO ECM

IL DIABETE IN ITALIA:
una sfida del sistema sanitario
tra innovazione farmacologica
e scelte di investimento

Agonisti GLP1

Giorgio Sesti

Università "Magna Graecia" di Catanzaro

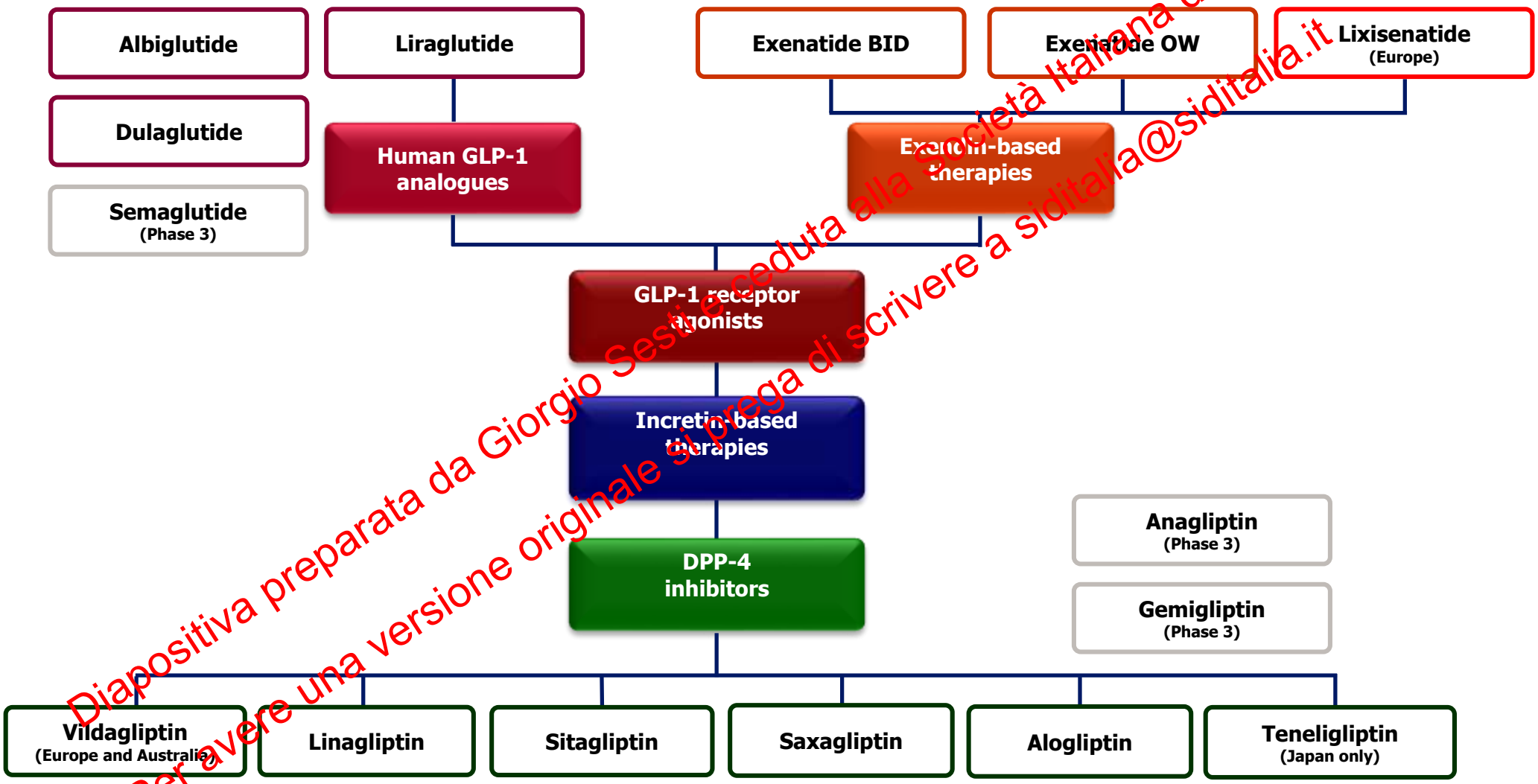
Potenziali conflitti di interesse

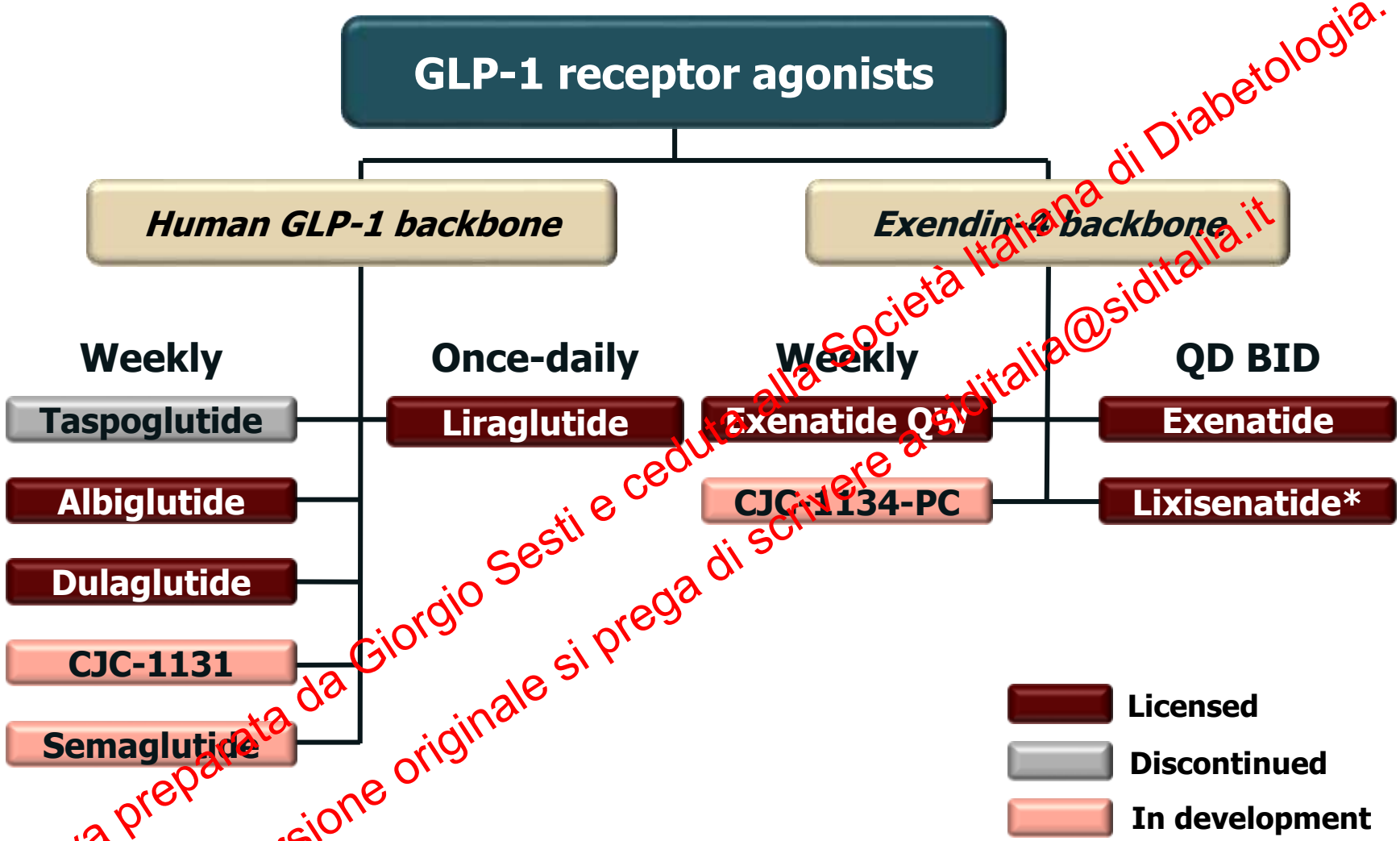
Il Prof Giorgio Sesti dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

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.

Incretin-based therapies: launched and in development



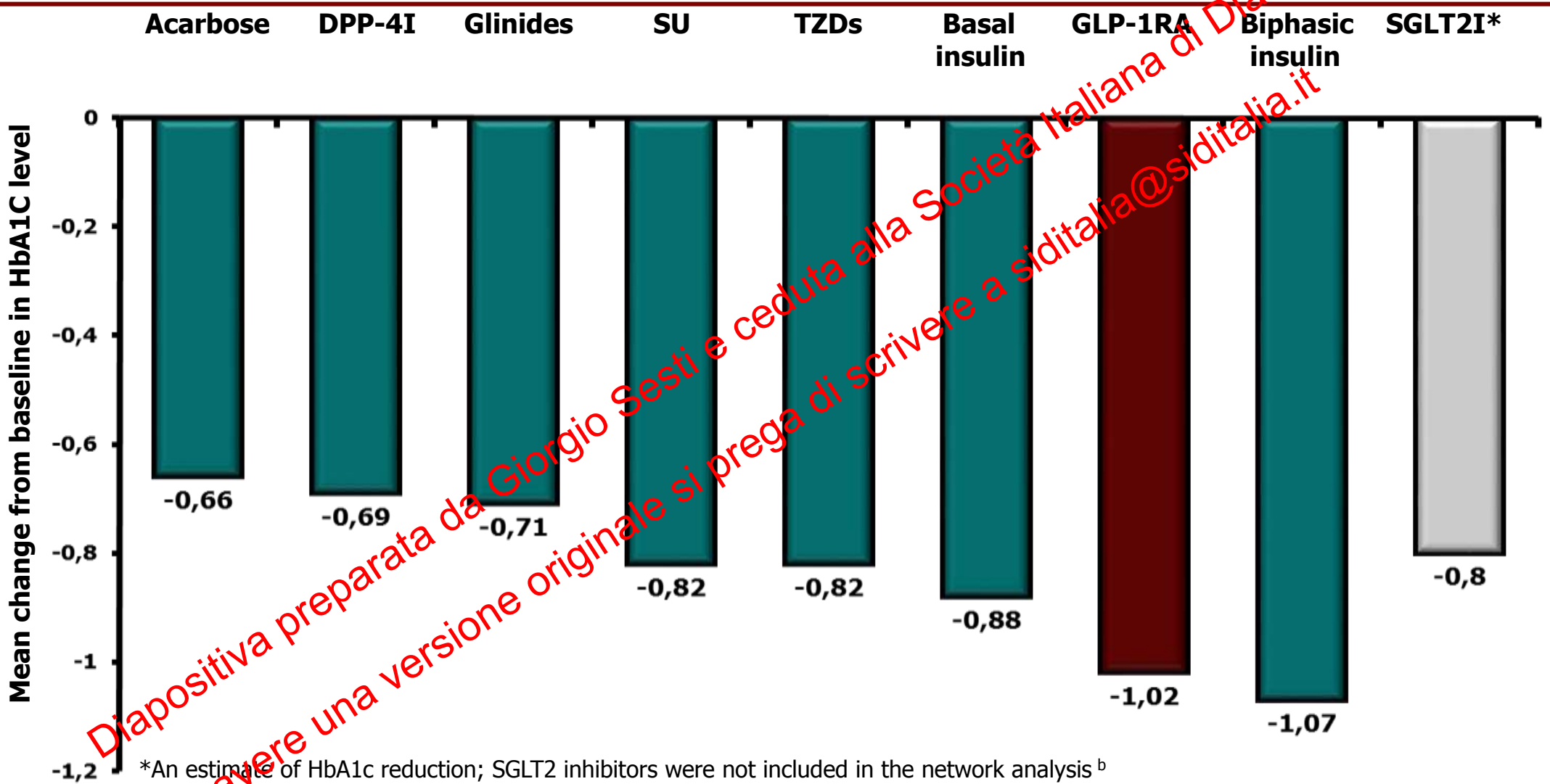


*Not licensed in the US.

GLP-1, glucagon-like peptide 1; QD, once daily; BID, twice daily

Modified from: Madsbad S et al. Diabetes Obes Metab 2011;13:394-407

Network meta-analysis of pairwise comparisons of randomised controlled trials evaluating the use of anti-hyperglycaemic agents in addition to metformin vs placebo: mean change from baseline in HbA1C



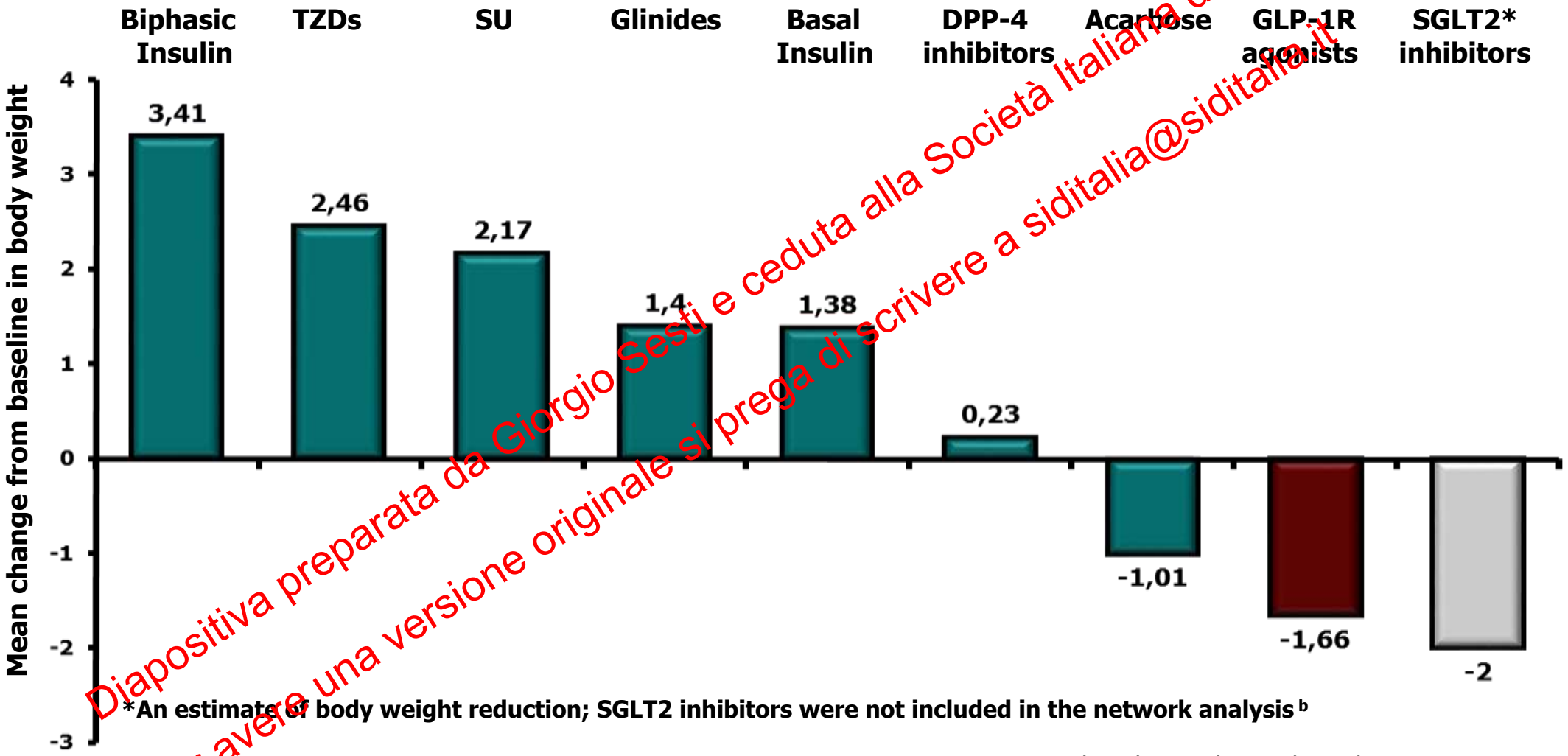
*An estimate of HbA1c reduction; SGLT2 inhibitors were not included in the network analysis [b]

DPP-4I, dipeptidyl peptidase-4 inhibitor; SGLT2I, sodium glucose cotransporter-2 inhibitor; TZDs, thiazolidinediones; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SU, sulphonylurea

Liu S-C et al. Diabetes Obes and Metab 2012; 14: 810-820

[b] Fujita Y et al. J Diabetes Investing 2014; 5: 265-275

Network meta-analysis of pairwise comparisons of randomised controlled trials evaluating the use of anti-hyperglycaemic agents in addition to metformin vs. placebo: Mean change from baseline in body weight



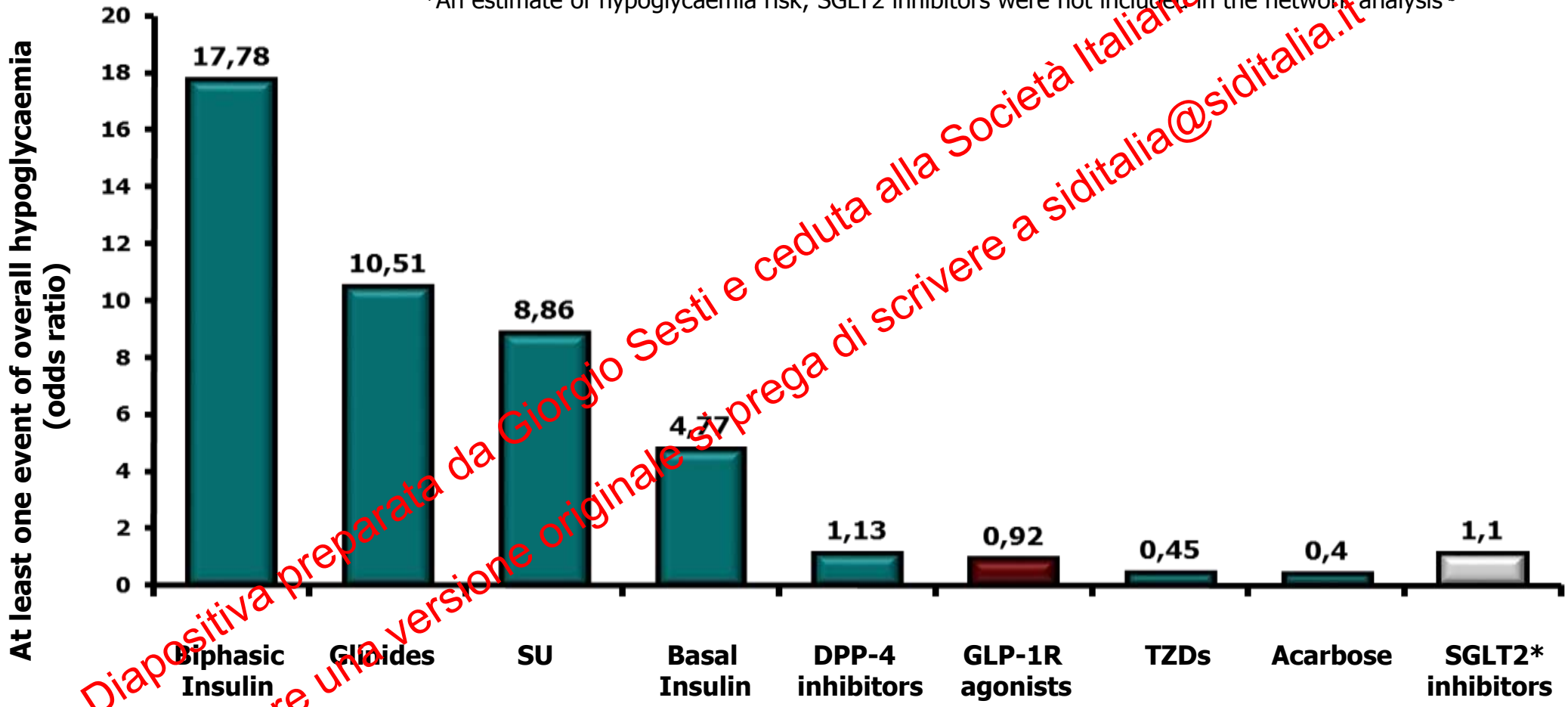
*An estimate of body weight reduction; SGLT2 inhibitors were not included in the network analysis [b]

DPP-4, dipeptidyl peptidase-4; SGLT2, sodium glucose cotransporter-2; TZDs, thiazolidinediones; GLP-1R, glucagon-like peptide 1 receptor; SU, sulphonylurea

Liu S-C et al. Diabetes Obes and Metab 2012; 14: 810-820
[b] Fujita Y et al. J Diabetes Investing 2014; 5: 265-275

Network meta-analysis of pairwise comparisons of randomised controlled trials evaluating the use of anti-hyperglycaemic agents in addition to metformin vs. placebo: At least one event of overall hypoglycaemia (odds ratio)

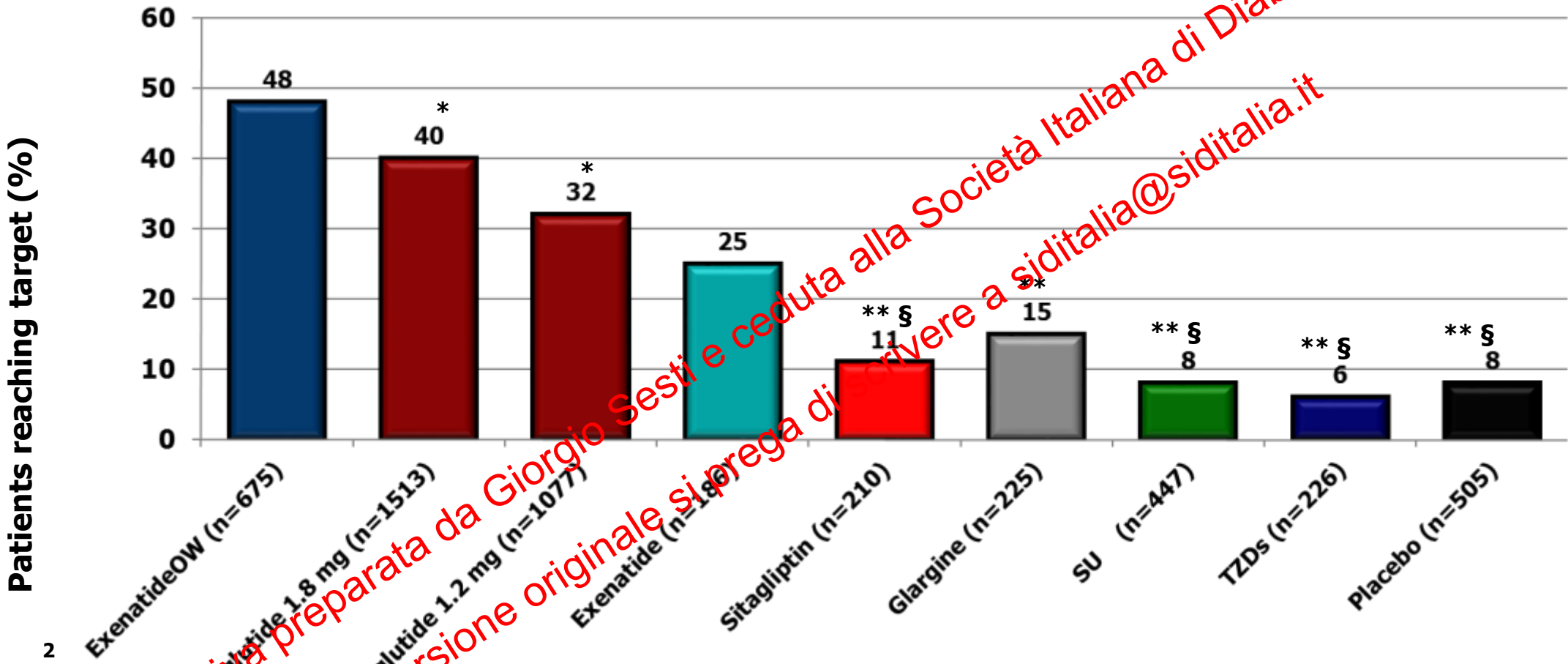
*An estimate of hypoglycaemia risk; SGLT2 inhibitors were not included in the network analysis [b]



DPP-4, dipeptidyl peptidase-4; SGLT2, sodium glucose cotransporter-2; TZDs, thiazolidinediones; GLP-1R, glucagon-like peptide 1 receptor; SU, sulphonylurea

Liu S-C et al. Diabetes Obes and Metab 2012; 14: 810-820
[b] Fujita Y et al. J Diabetes Investing 2014; 5: 265-275

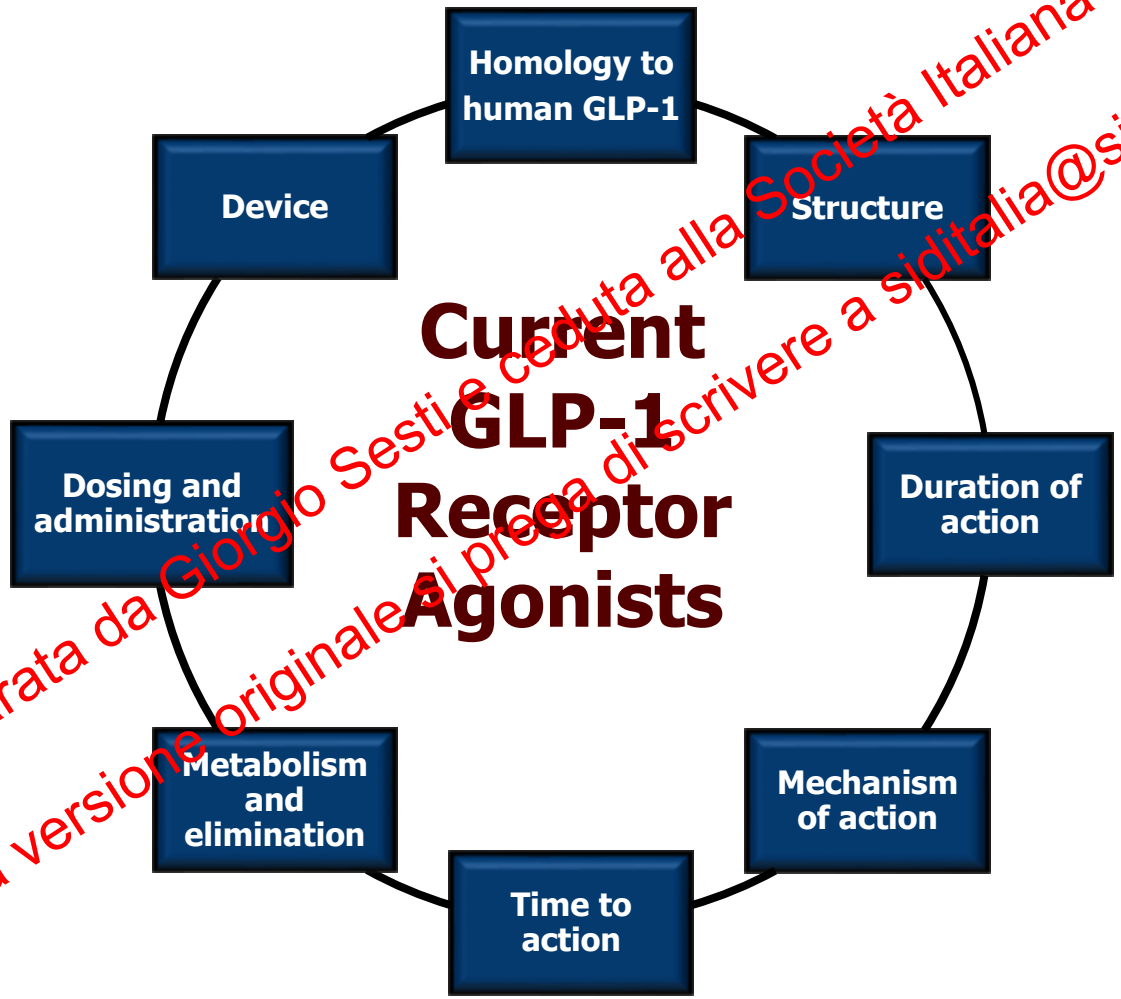
Composite endpoint: HbA_{1c}<7.0%, no weight gain and no hypos



Liraglutide 1.8 mg is superior (*p<0.001; ** p<0.0001)
Liraglutide 1.2 mg is superior (§p<0.0001)

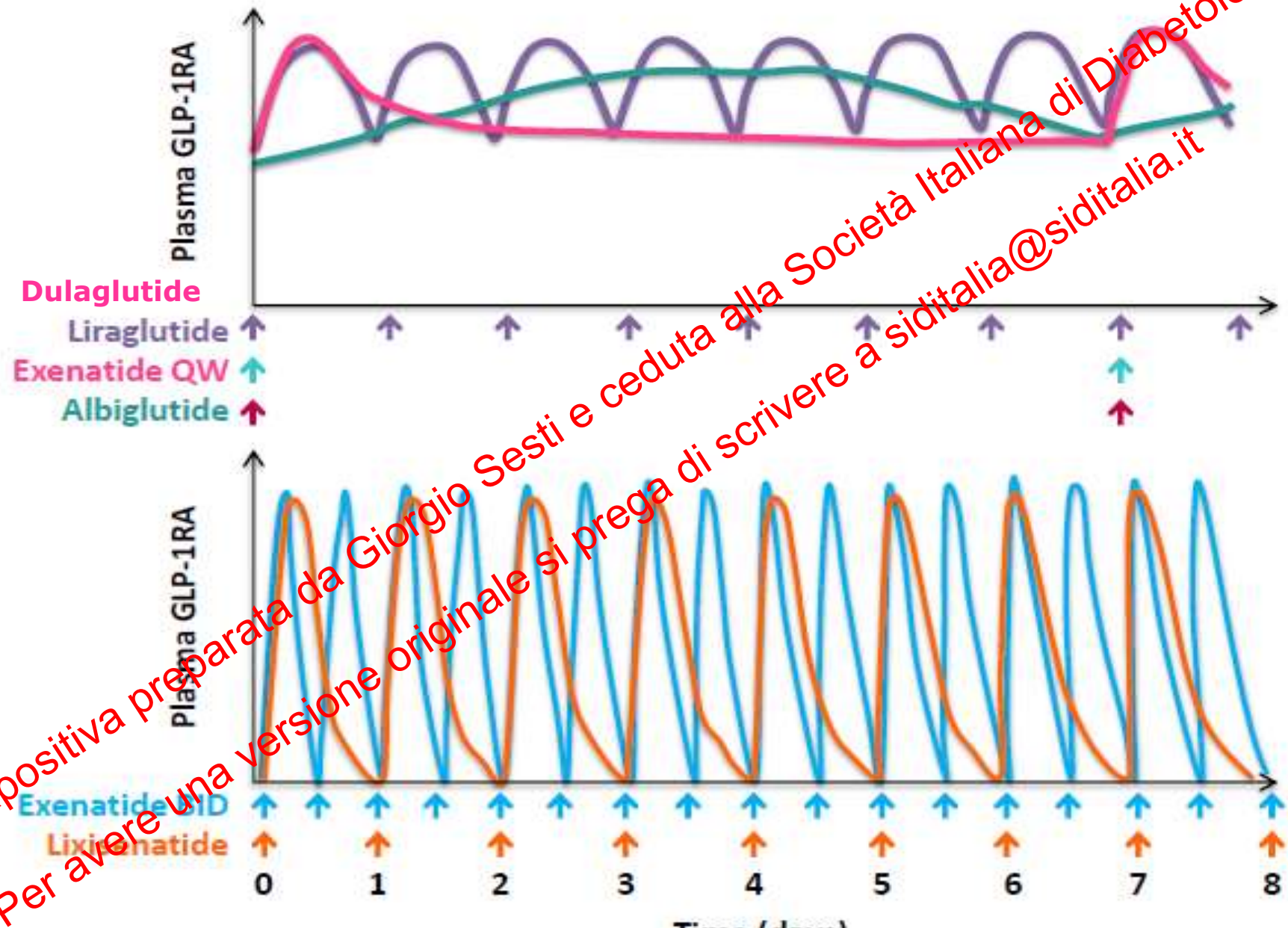
Zinman et al. Diabetes Obes Metab 14: 77–82, 2012
[2] Bergenstal RM et al. Diabetes Obes Metab 15: 264–271, 2013

GLP-1 receptor agonists in the treatment of T2DM: Similarities and differences



GLP-1, glucagon-like peptide 1

Short-acting and long-acting GLP-1 receptor agonists



GLP-1, glucagon-like peptide 1; QW, once weekly; BID, twice daily

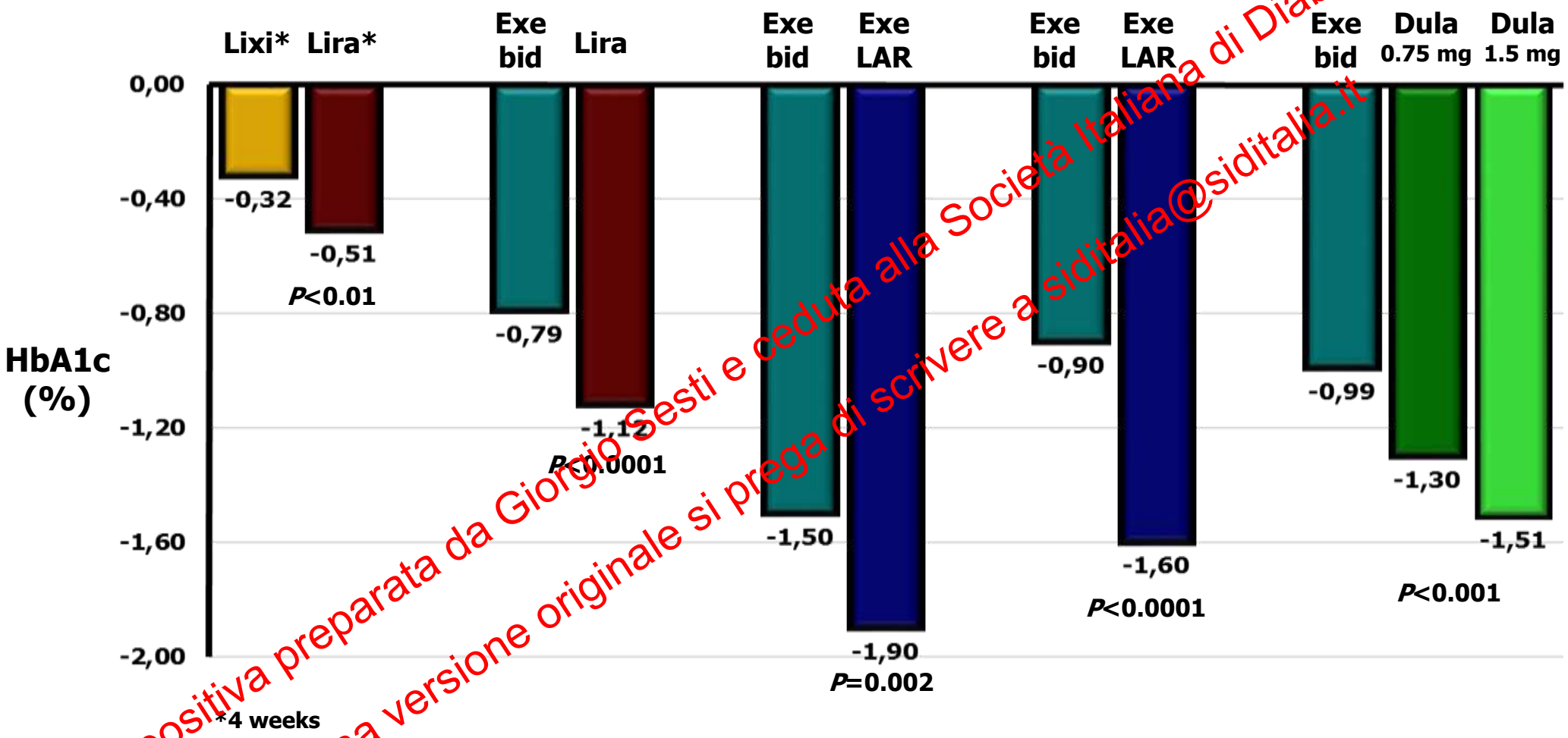
Differentiation of GLP-1 RAs

Parameters	Short-acting GLP-1 receptor agonists	Long-acting GLP-1 receptor agonists
Compounds	Exenatide (twice daily) Lixisenatide (once daily)	Liraglutide (once daily) Albiglutide (once weekly) Dulaglutide (once weekly) Exenatide LAR (once weekly)
Half-life	2–5 hours	12 h – several days
Receptor activation	Intermittent	Continuous
Metabolic Effects		
HbA1c reduction	-0.6–1.2%	-0.9–1.6%
Fasting glucose reduction	Modest reduction	Strong reduction
Fasting glucagon secretion	Mild reduction	Strong reduction
Fasting insulin secretion	Modest stimulation	Stimulation
Postprandial insulin secretion	Reduction/Stimulation	Stimulation
Gastric emptying	Deceleration	No long-term effect
Postprandial glucose excursion	Strong reduction	Reduction

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

Adapted from Meier JJ. Nat Rev Endocrinol 2012; 8: 728-42

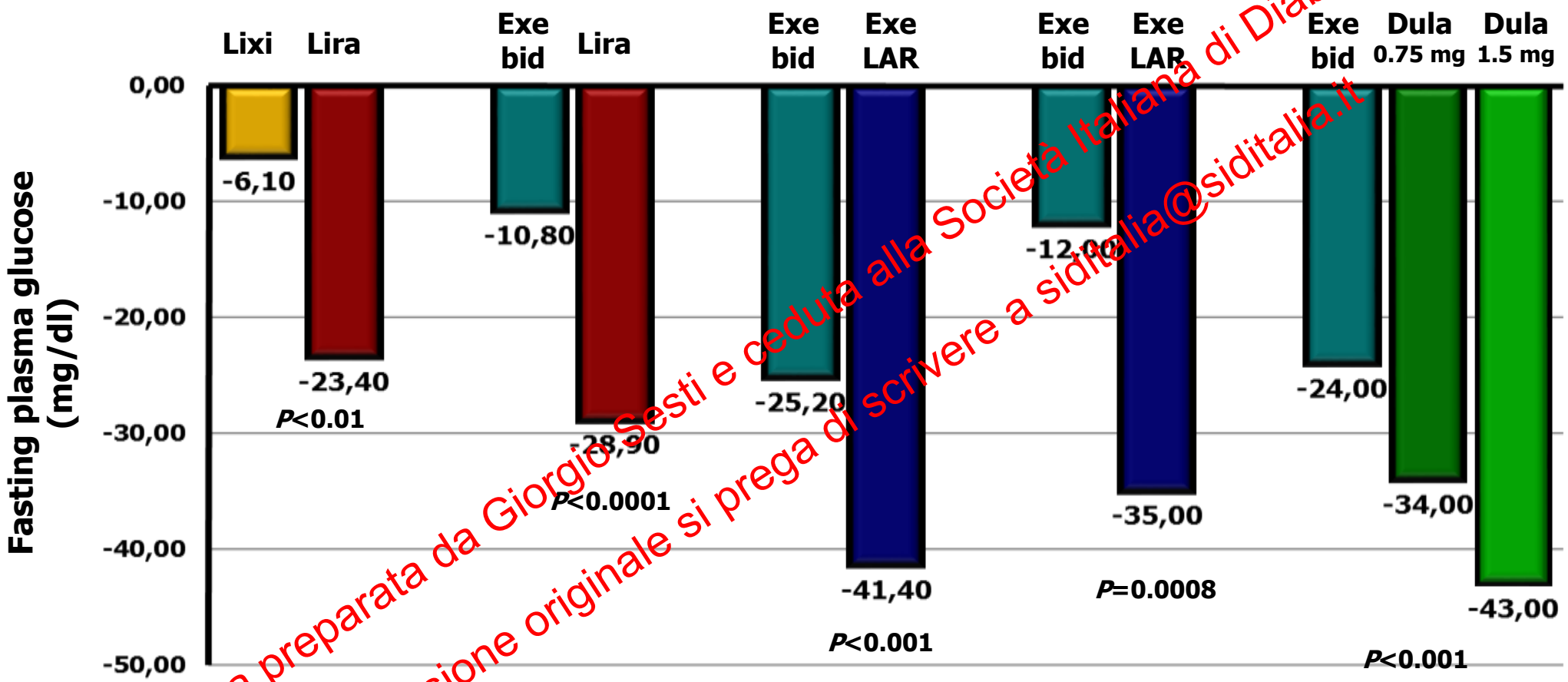
Comparison of short-acting versus long-acting GLP-1RA: HbA1c



GLP-1 RA, glucagon-like peptide 1 receptor agonist; bid, twice daily; Lixi, lixisenatide; Lira, liraglutide; Exe, exenatide; Dula, dulaglutide

Kapitza C et al. Diabetes Obes Metab 2013; 15: 642–649; Buse J et al. Lancet 2009; 374, 39-47; Drucker et al. Lancet 2008; 372: 1240-50; Blevins T et al J. Clin. Endocrinol. Metab 2011; 96:1301-1310; Wysham C et al. Diabetes Care 2014; 37:2159-2167

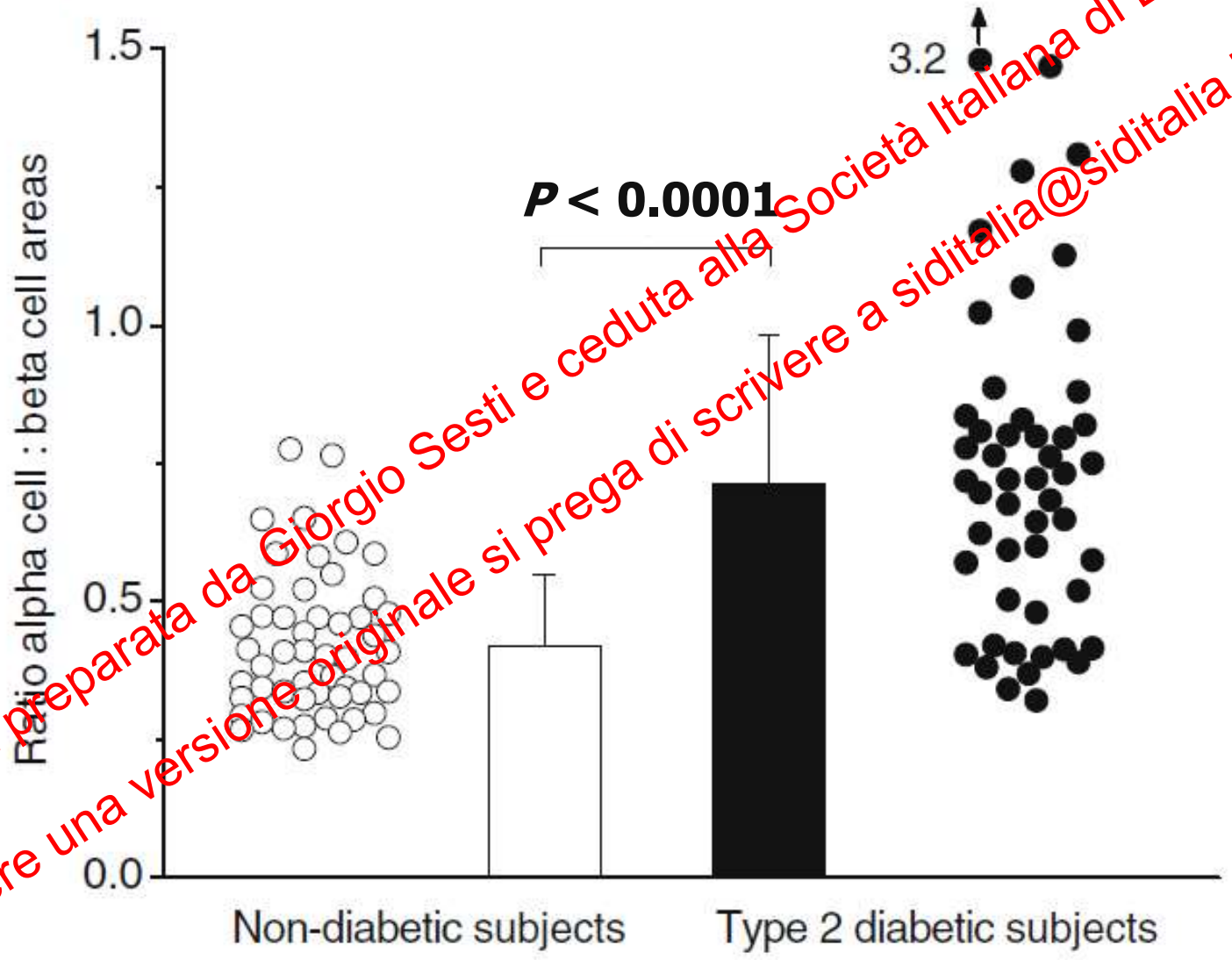
Comparison of short-acting versus long-acting GLP-1RA: FPG



GLP-1 RA, glucagon-like peptide 1 receptor agonist; bid, twice daily; FPG, fasting plasma glucose; Lixi, lixisenatide; Lira, liraglutide; Exe, exenatide; Dula, dulaglutide

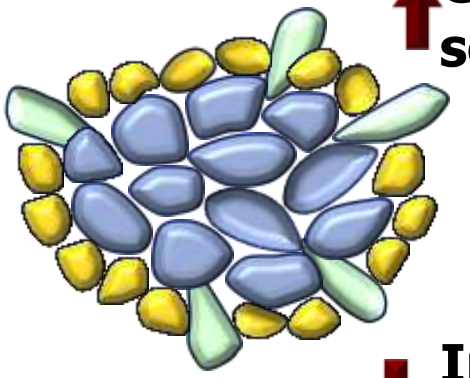
Kapitza C et al. Diabetes Obes Metab 2013; 15: 642–649; Buse J et al. Lancet 2009; 374, 39-47; Drucker et al. Lancet 2008; 372: 1240-50; Blevins T et al J. Clin. Endocrinol. Metab 2011; 96:1301-1310; Wysham C et al. Diabetes Care 2014; 37:2159-2167

Ratio of alpha cell/beta cell areas in 52 non-diabetic subjects (ND) and 50 type 2 diabetic (T2DM) subjects



Henquin JC et al. Diabetologia 2011; 54:1720-1725

Excessive hepatic glucose production



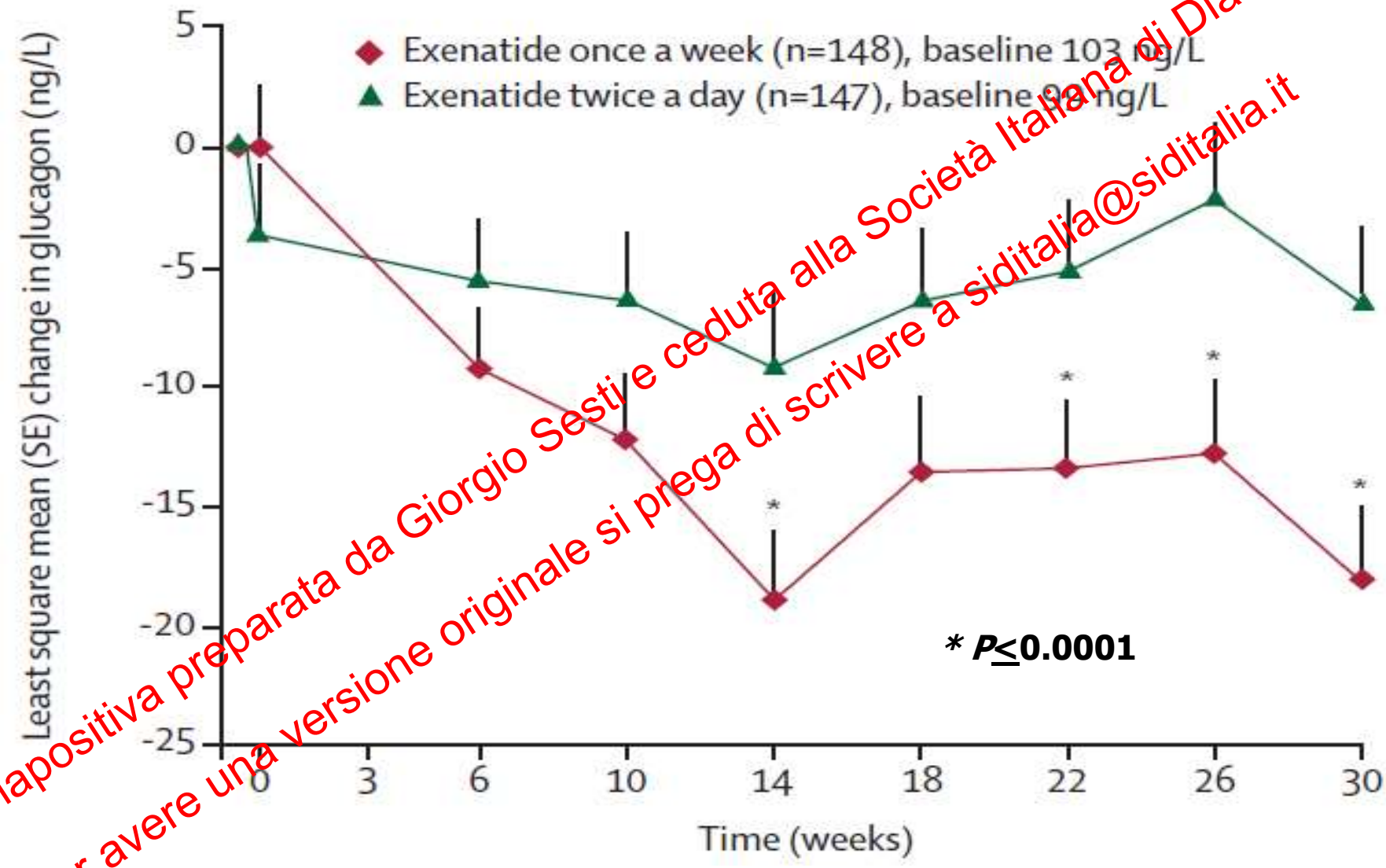
↑ **Glucagon secretion**

↓ **Insulin secretion**

↑ **Hepatic glucose production**

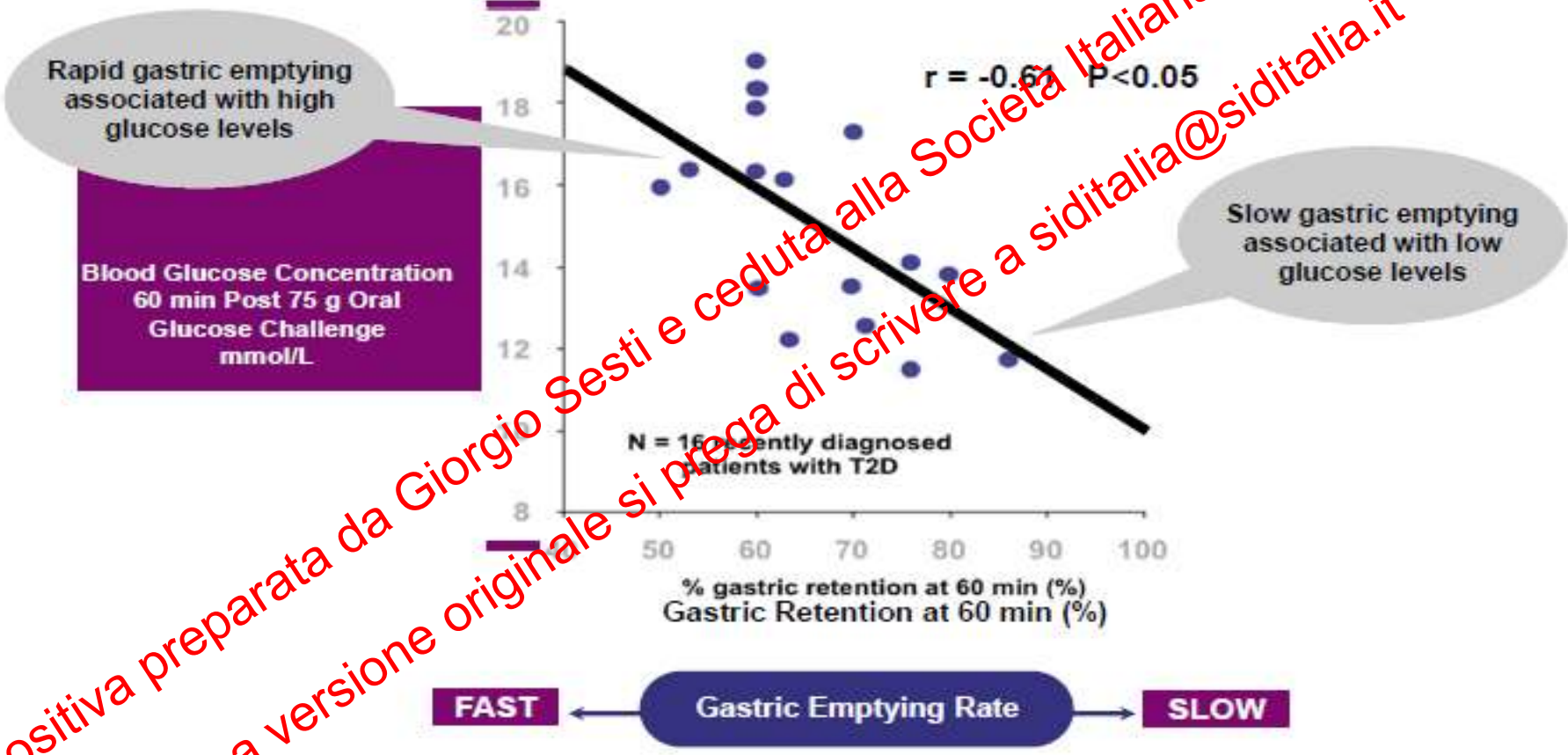
Pancreatic cells: β-cell α-cell δ-cell

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

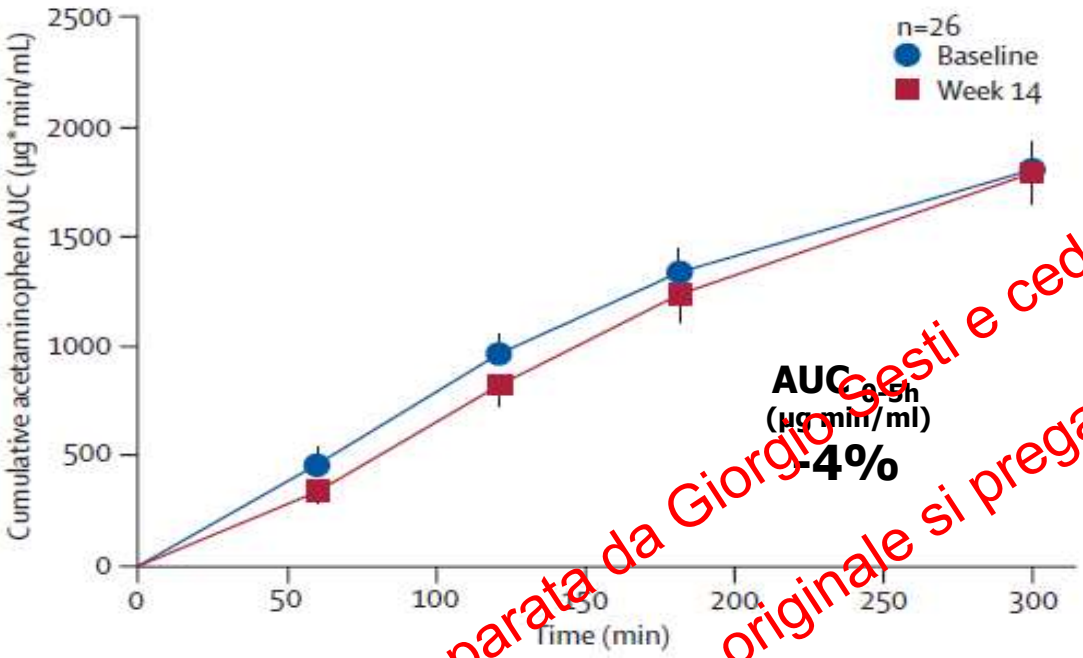
Gastric emptying rate is an important determinant of PPG in early Type 2 Diabetes



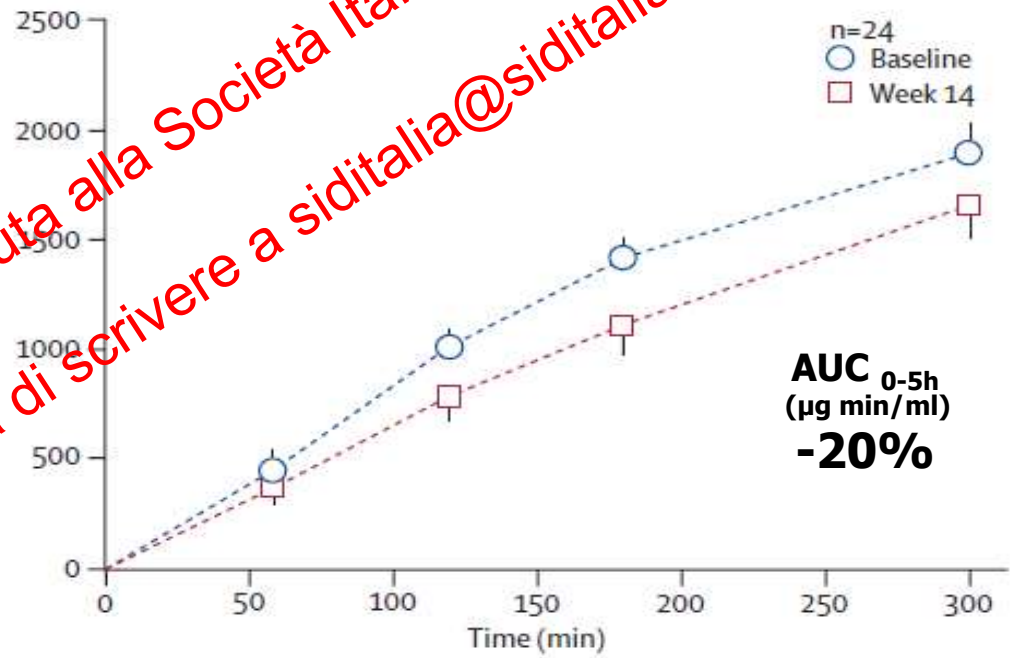
Jones KL, et al. J Nucl Med 37:1643-1648, 1996

Exenatide OW versus twice daily for the treatment of type 2 diabetes: Gastric emptying assessed by absorption of paracetamol

Exenatide once a week



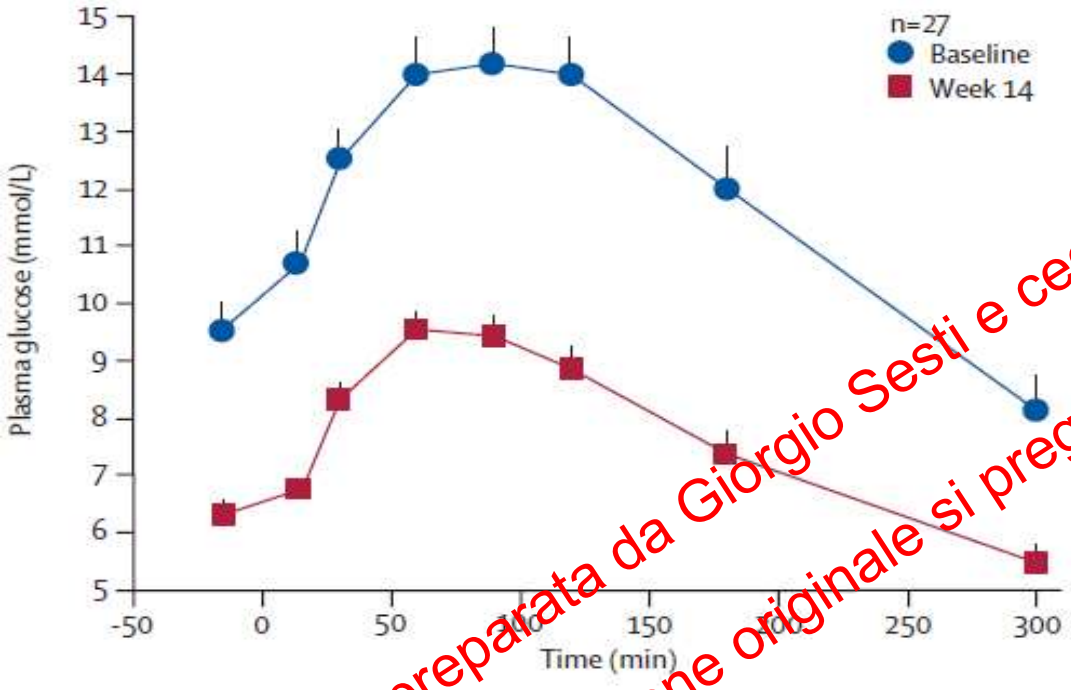
Exenatide twice a day



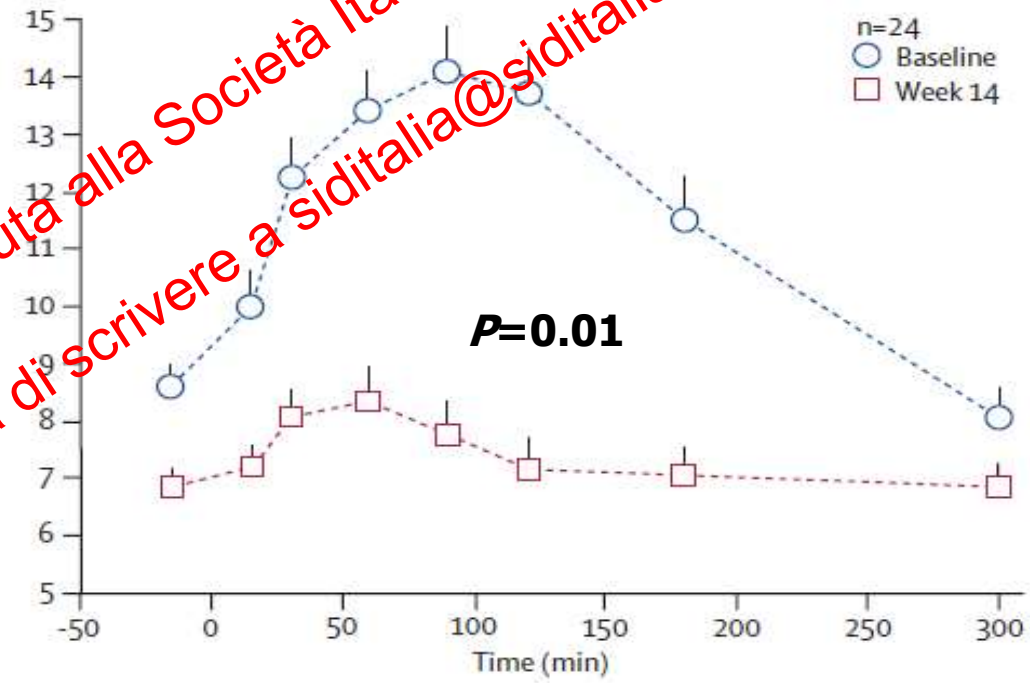
Drucker et al. Lancet 372: 1240–50, 2008

Exenatide OW versus twice daily for the treatment of type 2 diabetes: Changes in postprandial glucose concentration-DURATION-1

Exenatide once a week

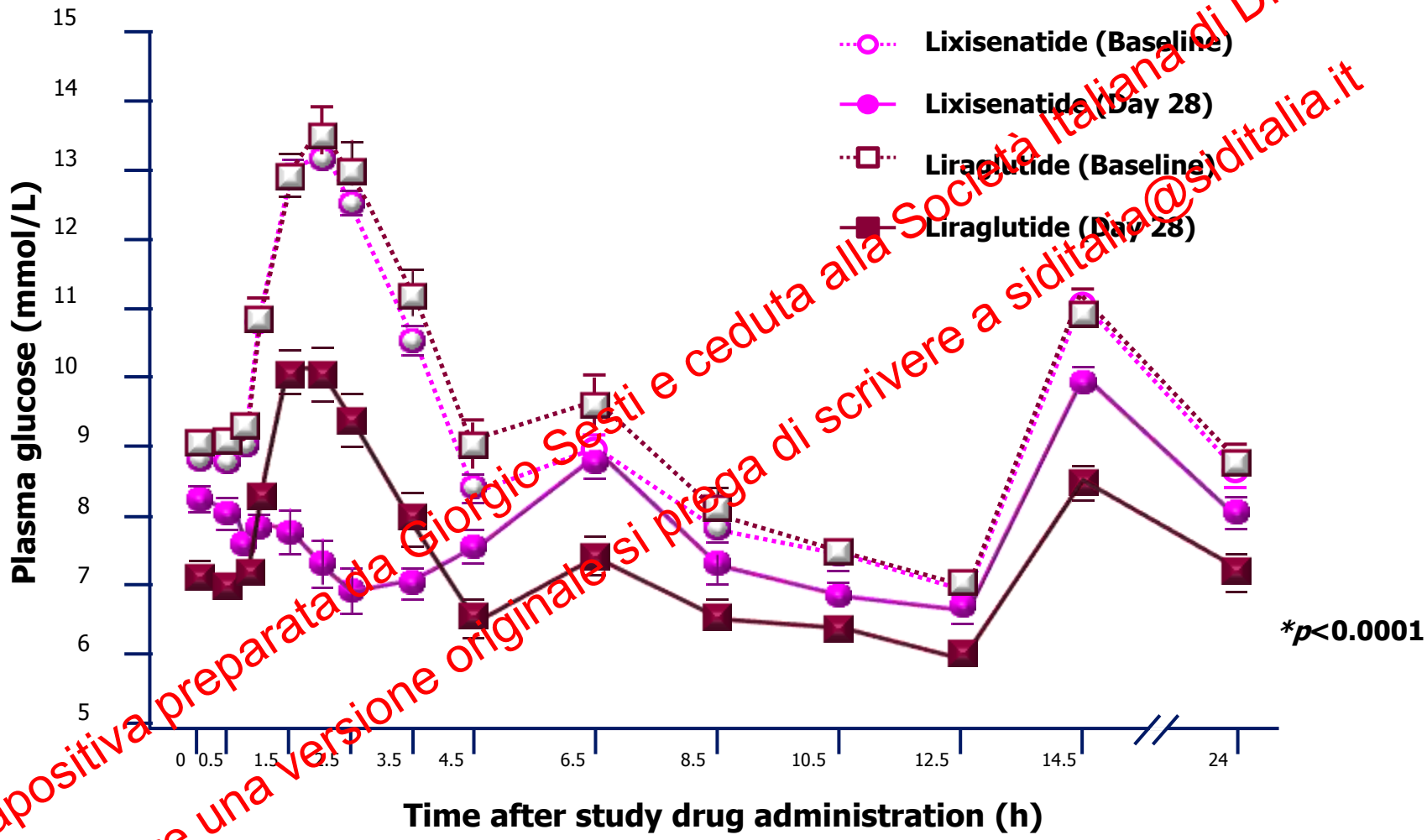


Exenatide twice a day



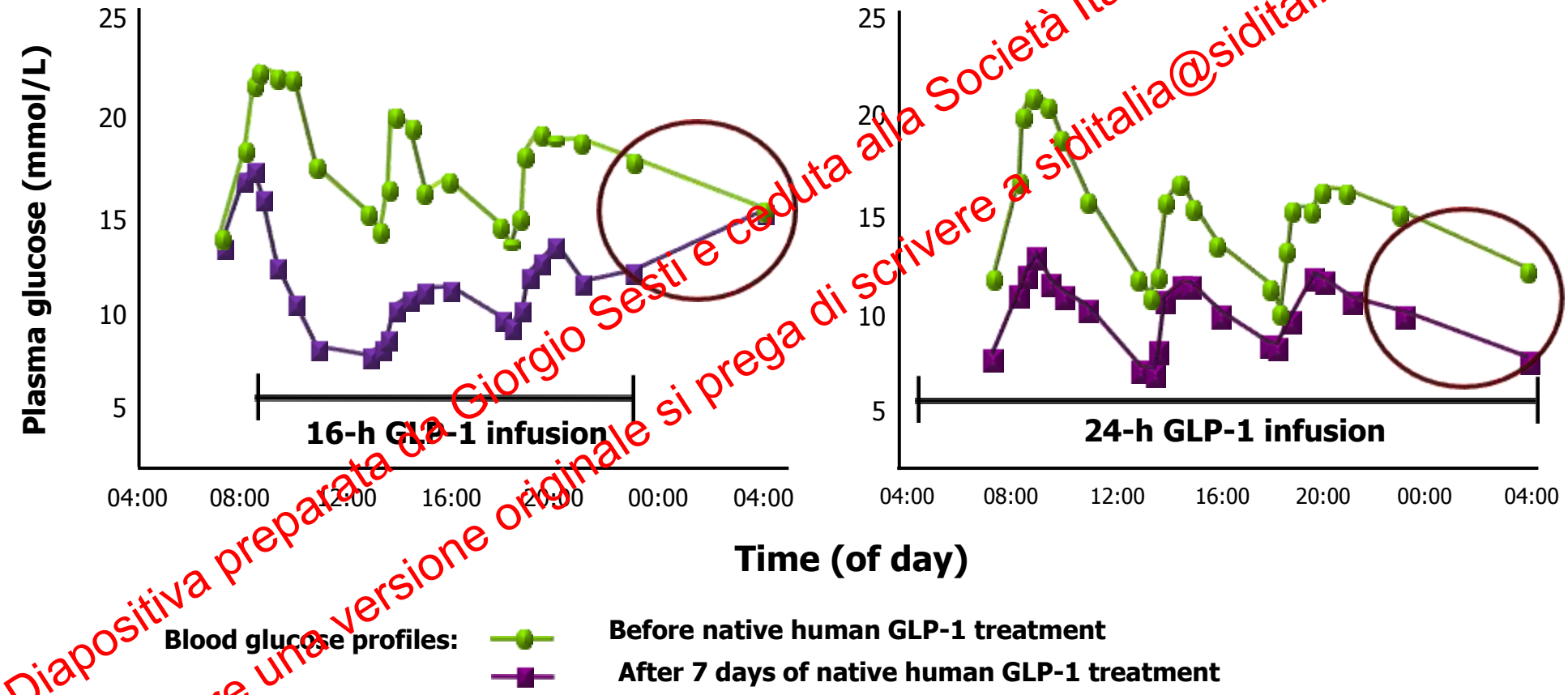
Drucker et al. Lancet 372: 1240–50, 2008

Lixisenatide once daily vs. liraglutide in patients with type 2 diabetes: 24-h postprandial plasma glucose profiles at baseline and day 28



Kapitza C et al. Diabetes Obes Metab 15: 642–649, 2013

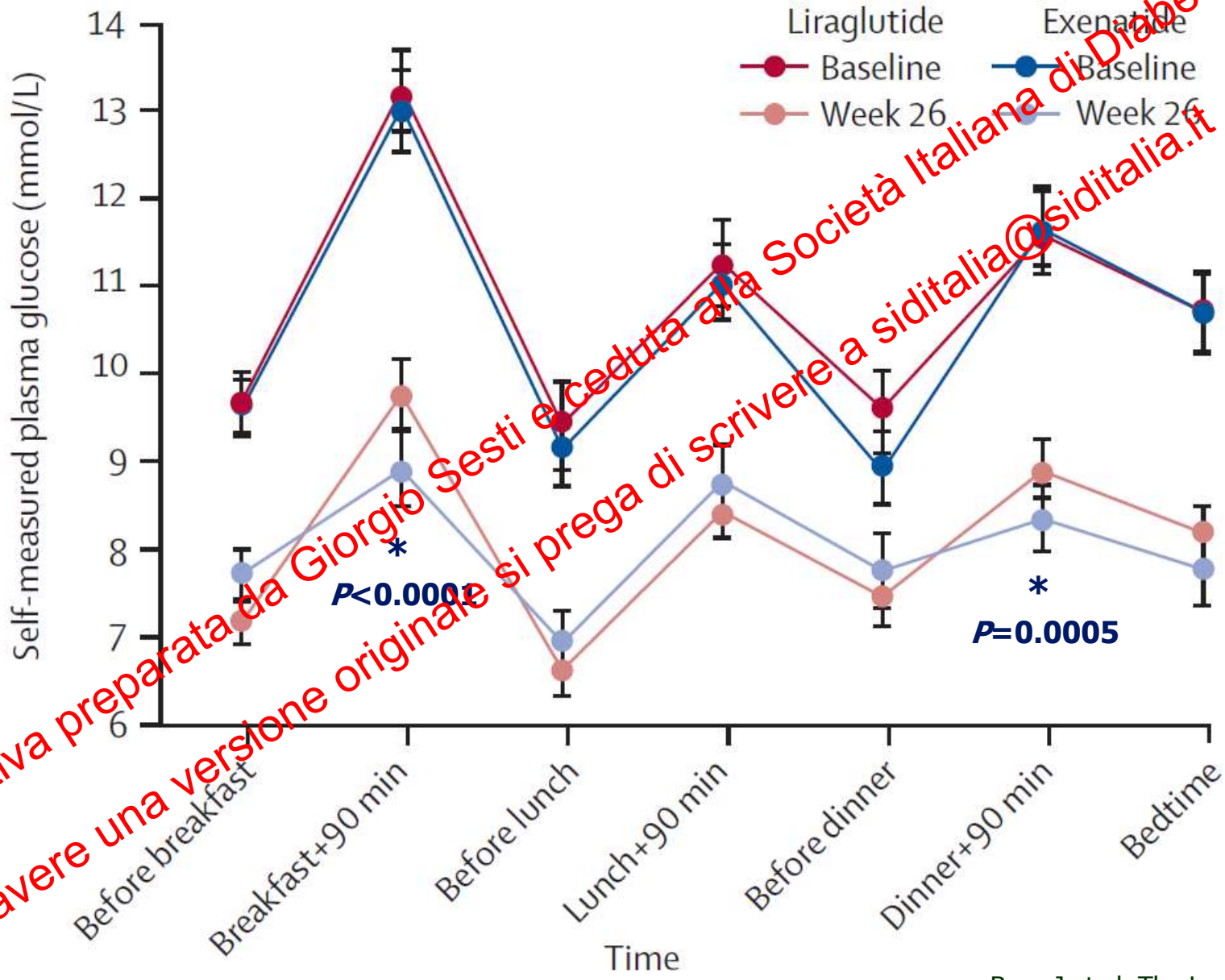
24-hour GLP-1 presence is required for 24-hour glucose control in patients with type 2 diabetes



GLP-1, glucagon-like peptide 1

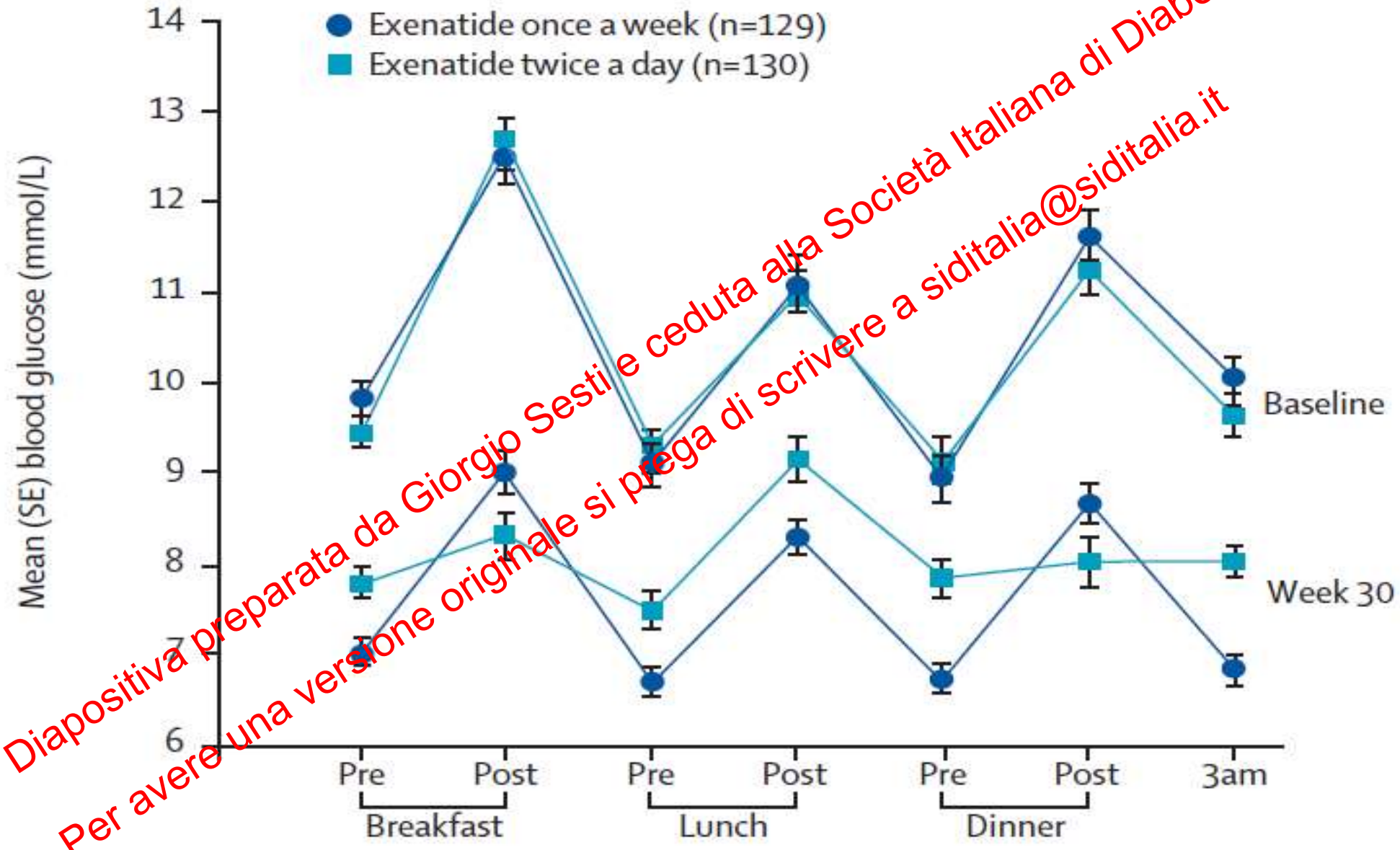
Larsen et al. Diabetes Care 2001; 24: 1416–21

Liraglutide vs. exenatide as add on to metformin and/or SU (LEAD-6): Seven-point self-measured plasma glucose profiles



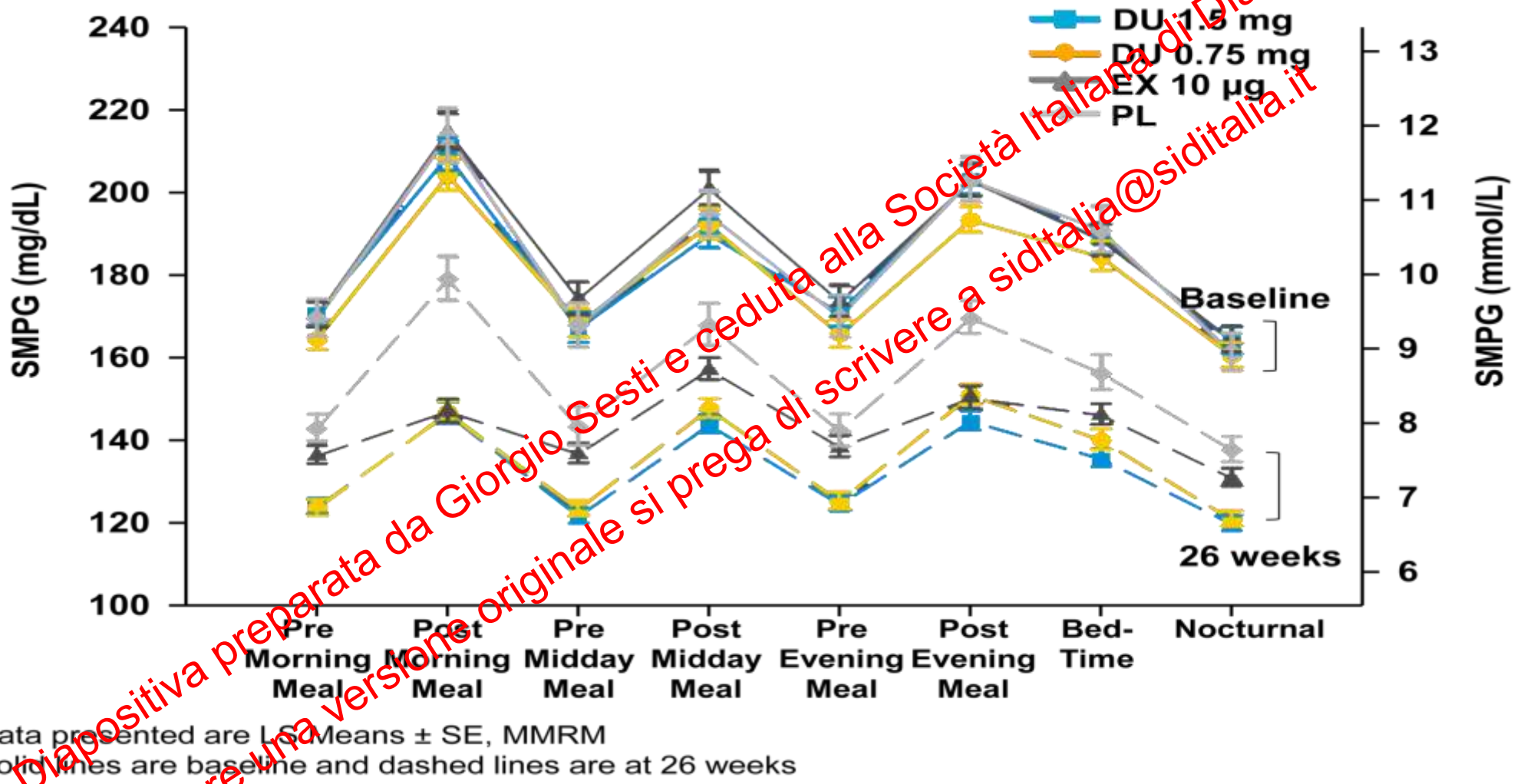
Buse J et al. The Lancet 374, 39-47, 2009

Exenatide OW versus twice daily for the treatment of type 2 diabetes: Seven-point self-measured plasma glucose profiles-DURATION-1



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

8-Point SMBG profiles with Dulaglutide and Exenatide BID (AWARD-1)



DU, dulaglutide; EX, exenatide; PL, placebo; BID, twice daily; SMBG, self-monitoring of blood glucose; LS, least squares; SE, standard error; MMRM, mixed effect model for repeated measures

Wysham C, et al. Diabetes Care 2014; 37:2159-2167

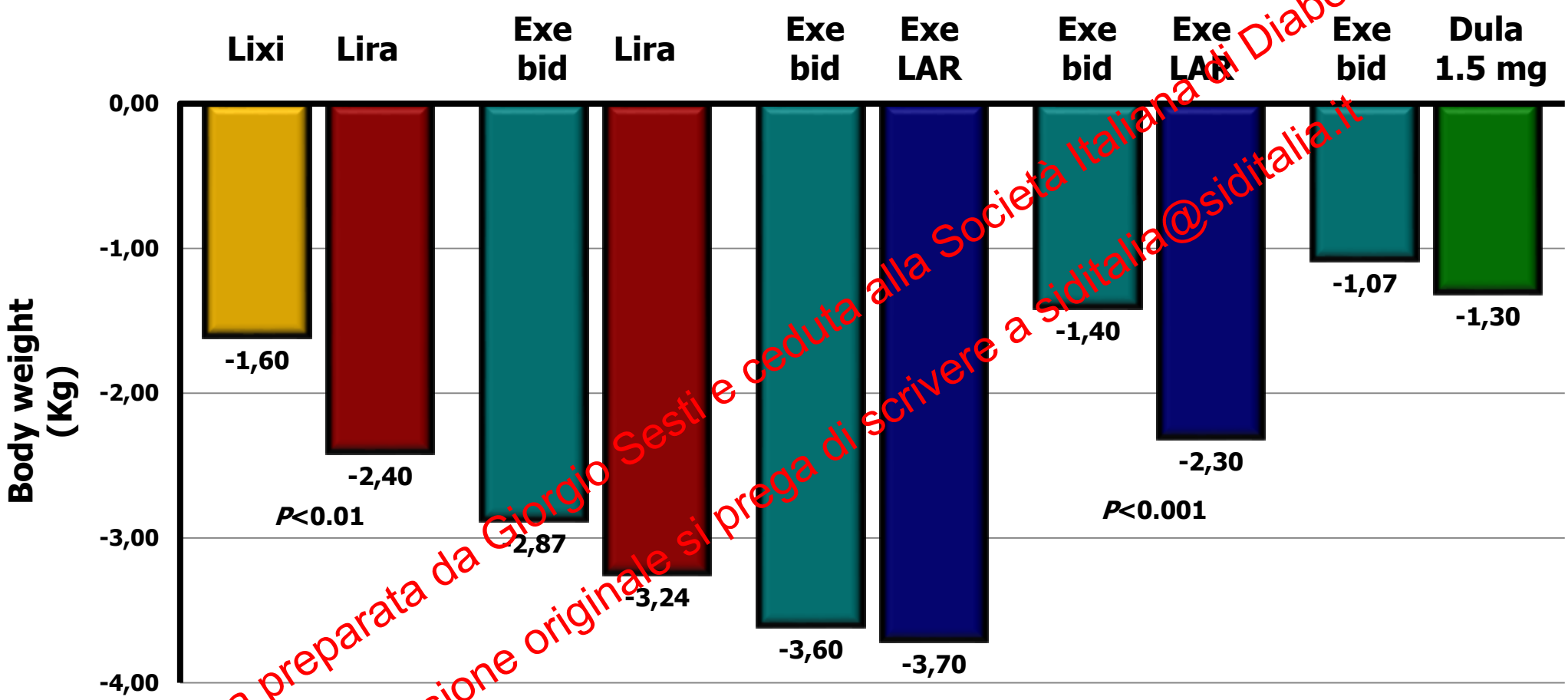
Differentiation of GLP-1 RAs

Parameters	Short-acting (Prandial) GLP-1 receptor agonists	Long-acting GLP-1 receptor agonists
Compounds	Exenatide (twice daily) Lixisenatide (once daily)	Liraglutide (once daily) Albiglutide (once weekly) Dulaglutide (once weekly) Exenatide LAR (once weekly)
CV safety and tolerability		
Body weight reduction	~1–5 kg	~2–5 kg
Blood pressure reduction	~3-4 mmHg	Up to 6 mmHg
Heart rate increase	None or up to 2 bpm	~1–5 bpm
Lipids	Reduction	Reduction
CV events	Neutral	Reduction
Induction of nausea	20–50% mild to moderate attenuates slowly (weeks to months)	20–40% mild to moderate attenuates quickly (~4–8 wks)

GLP-1 RA, glucagon-like peptide 1 receptor agonist; bpm, beats per minute; CV, cardiovascular

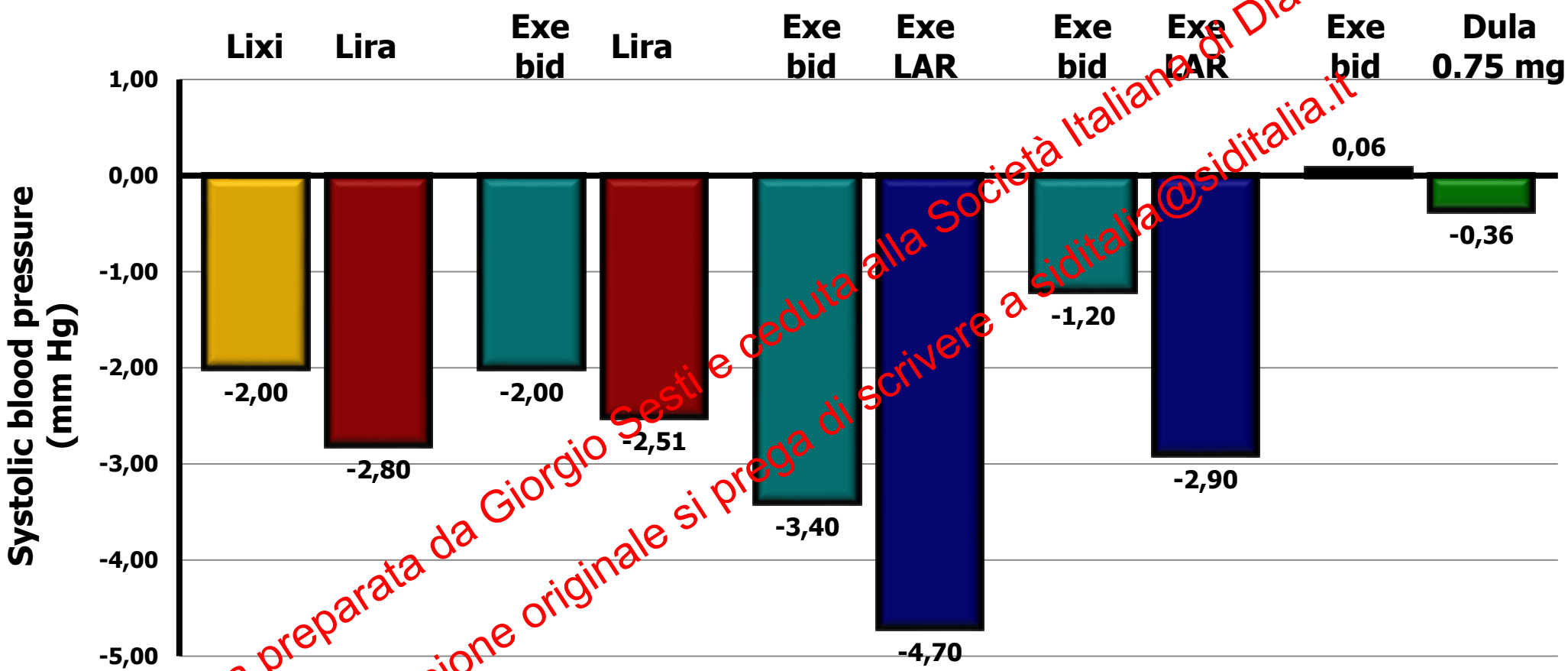
Adapted from Meier JJ. Nat Rev Endocrinol 2012; 8:728-42

Comparison of short-acting versus long-acting GLP-1RA



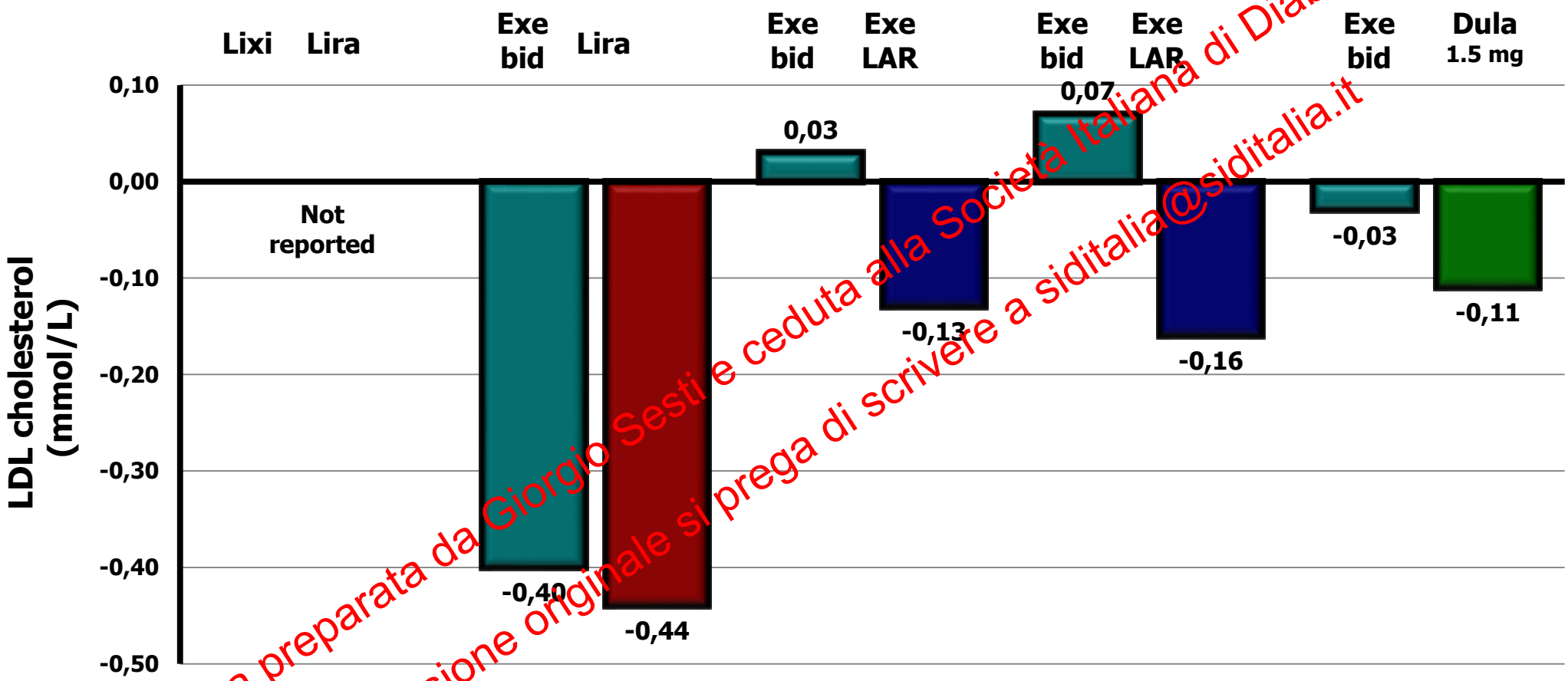
Kapitza C et al. Diabetes Obes Metab 15: 642–649, 2013; Buse J et al. The Lancet 374, 39-47, 2009; Drucker et al. Lancet 372: 1240–50, 2008; Blevins T et al J. Clin. Endocrinol. Metab. 96:1301-1310, 2011; Wysham C et al. Diabetes Care 37:2159–2167, 2014

Comparison of short-acting versus long-acting GLP-1R agonists:
Systolic blood pressure



Kapitza C et al. Diabetes Obes Metab 15: 642–649, 2013; Buse J et al. The Lancet 374, 39-47, 2009; Drucker et al. Lancet 372: 1240–50, 2008; Blevins T et al J. Clin. Endocrinol. Metab. 96:1301-1310, 2011; Wysham C et al. Diabetes Care 37:2159–2167, 2014

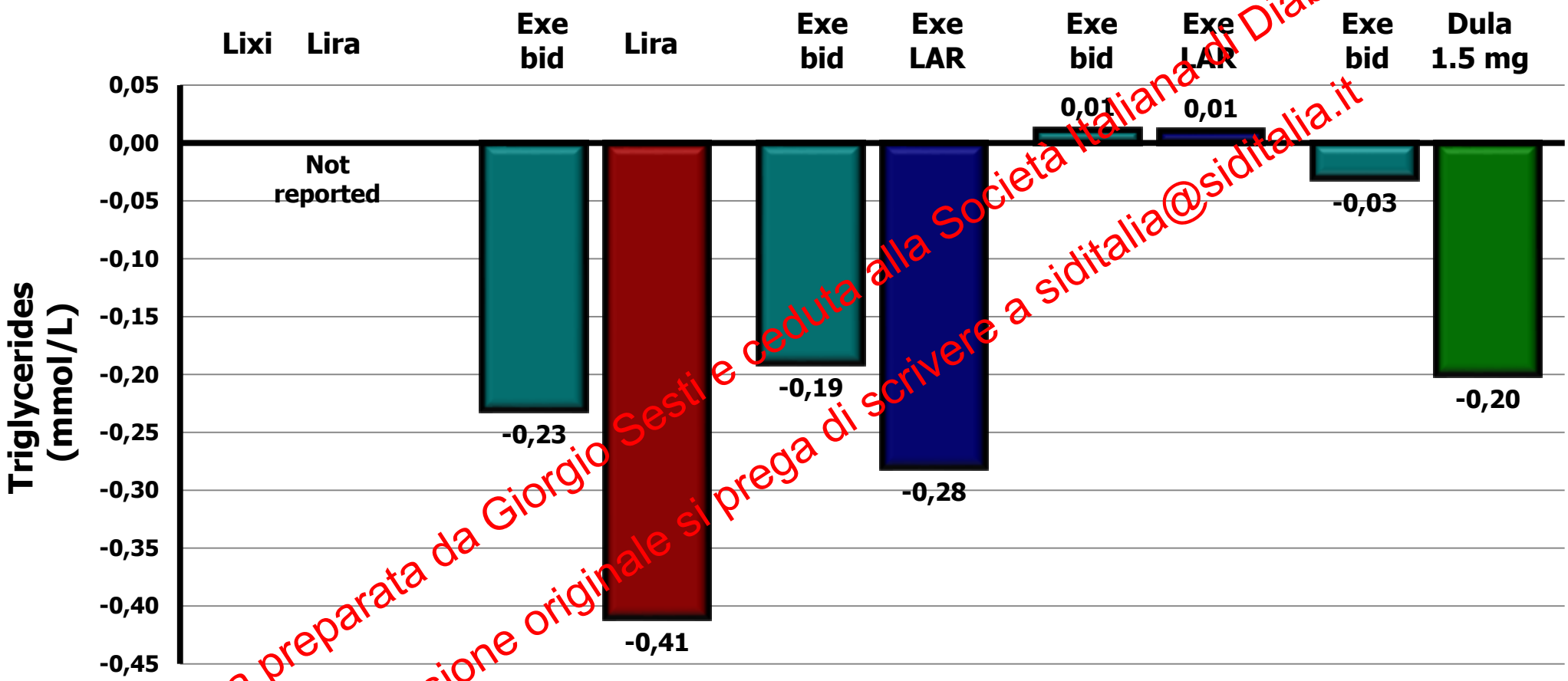
Comparison of short-acting versus long-acting GLP-1R agonists: LDL cholesterol



GLP-1 R, glucagon-like peptide 1 receptor; bid, twice daily; LDL, low density lipoprotein; Lixi, lixisenatide; Lira, liraglutide; Exe, exenatide; Dula, dulaglutide

Kapitza C et al. Diabetes Obes Metab 2013; 15: 642–649; Buse J et al. Lancet 2009; 374, 39-47; Drucker et al. Lancet 2008; 372: 1240-50; Blevins T et al J. Clin. Endocrinol. Metab 2011; 96:1301-1310; Wysham C et al. Diabetes Care 2014; 37:2159-2167

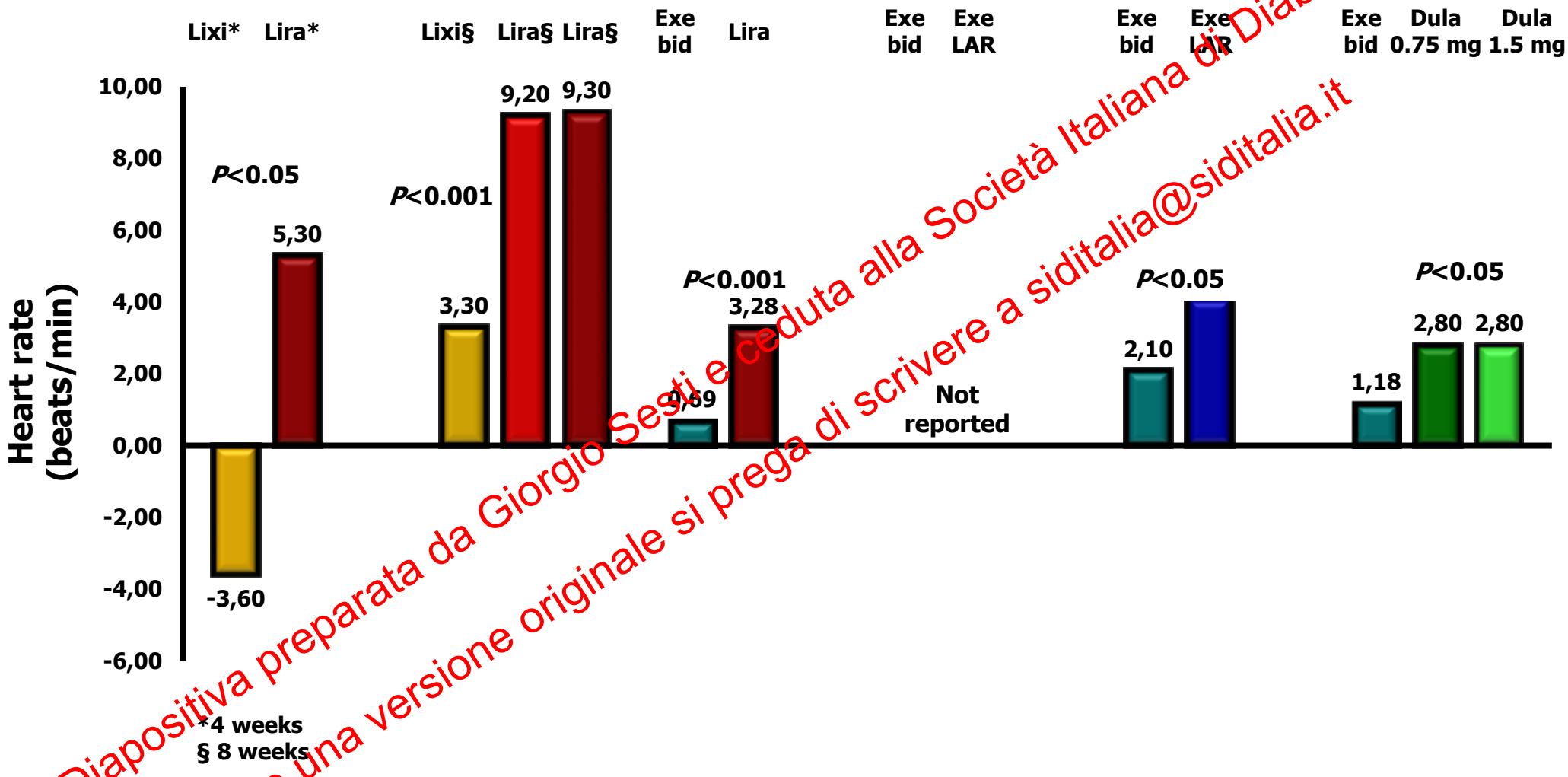
Comparison of short-acting versus long-acting GLP-1R agonists: Triglycerides



GLP-1 R, glucagon like peptide 1 receptor; bid, twice daily; Lixi, lixisenatide; Lira, liraglutide; Exe, exenatide; Dula, dulaglutide

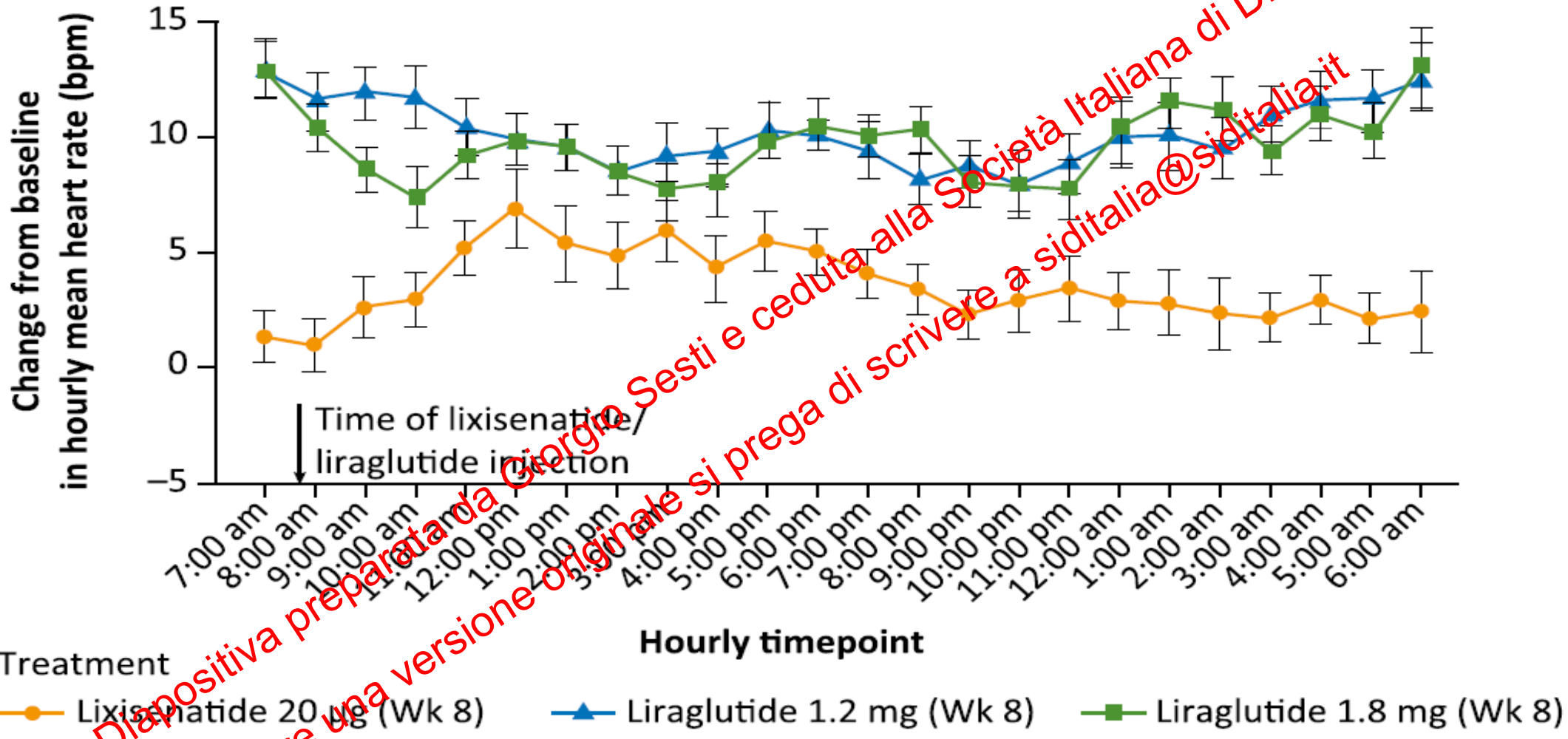
Kapitza C et al. Diabetes Obes Metab 2013; 15: 642–649; Buse J et al. Lancet 2009; 374, 39-47; Drucker et al. Lancet 2008; 372: 1240-50; Blevins T et al J. Clin. Endocrinol. Metab 2011; 96:1301-1310; Wysham C et al. Diabetes Care 2014; 37:2159-2167

Comparison of short-acting versus long-acting GLP-1R agonists: Heart rate



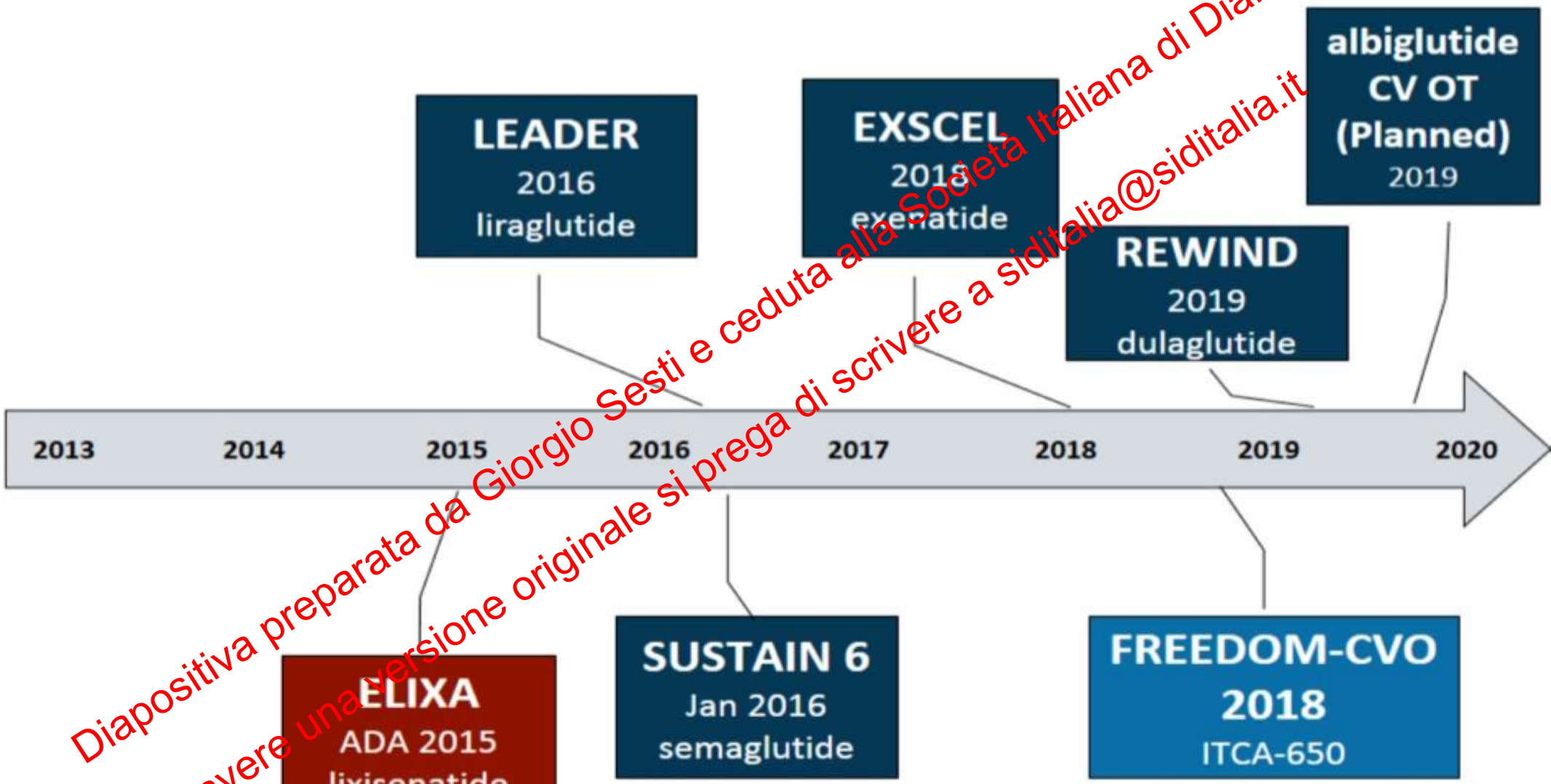
Kapitza C et al. Diabetes Obes Metab 15: 642–649, 2013; Meier JJ et al.Diabetes Care 38:1263–1273, 2015; Buse J et al. The Lancet 374, 39-47, 2009; Drucker et al. Lancet 372: 1240–50, 2008; Blevins T et al J. Clin. Endocrinol. Metab. 96:1301-1310, 2011; Wysham C et al. Diabetes Care 37:2159–2167, 2014

Change from baseline in hourly mean heart rate in T2DM patients treated with insulin glargine and Lixisenatide or Liraglutide



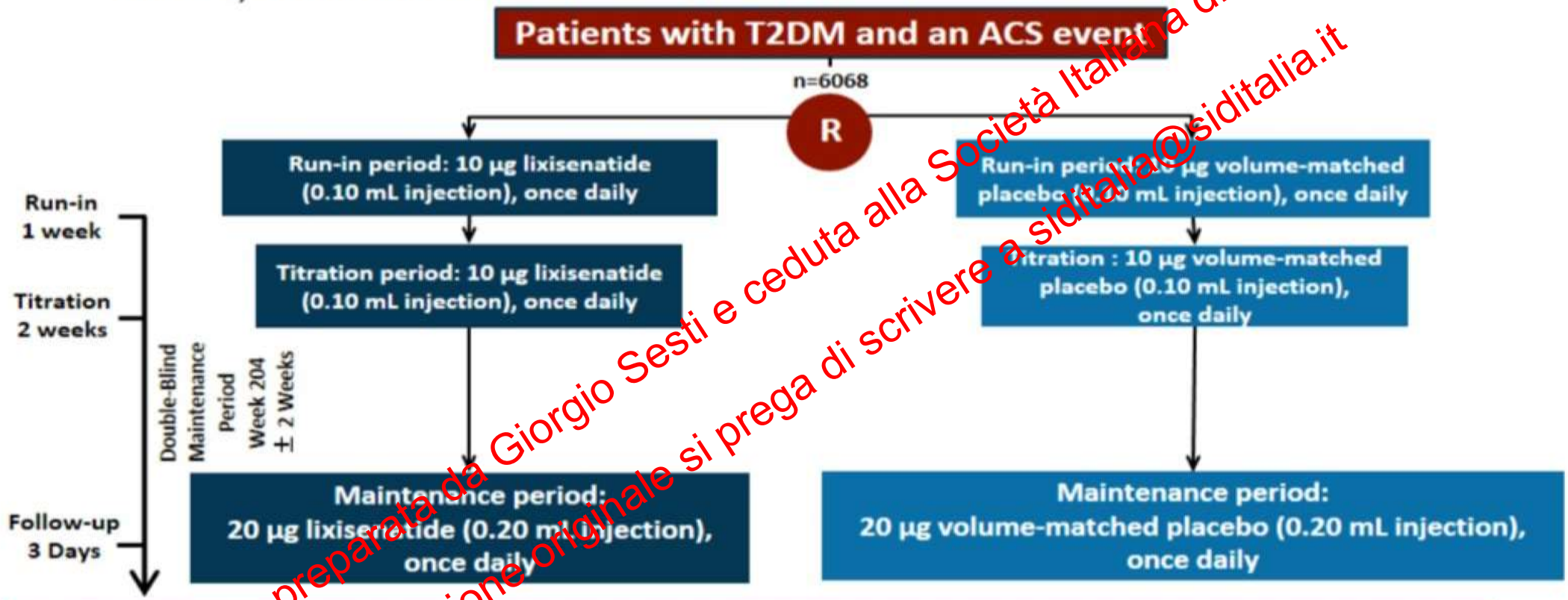
Meier JJ et al. Diabetes Care 38:1263–1273, 2015

Timeline of Future GLP-1 RA CV Outcome Trials



ELIXA: Study Design

- A randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase 3, event-driven trial



Primary Endpoints

Time to first occurrence of the primary CV event: CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA

Secondary Endpoints

Primary endpoints or hospitalization for HF

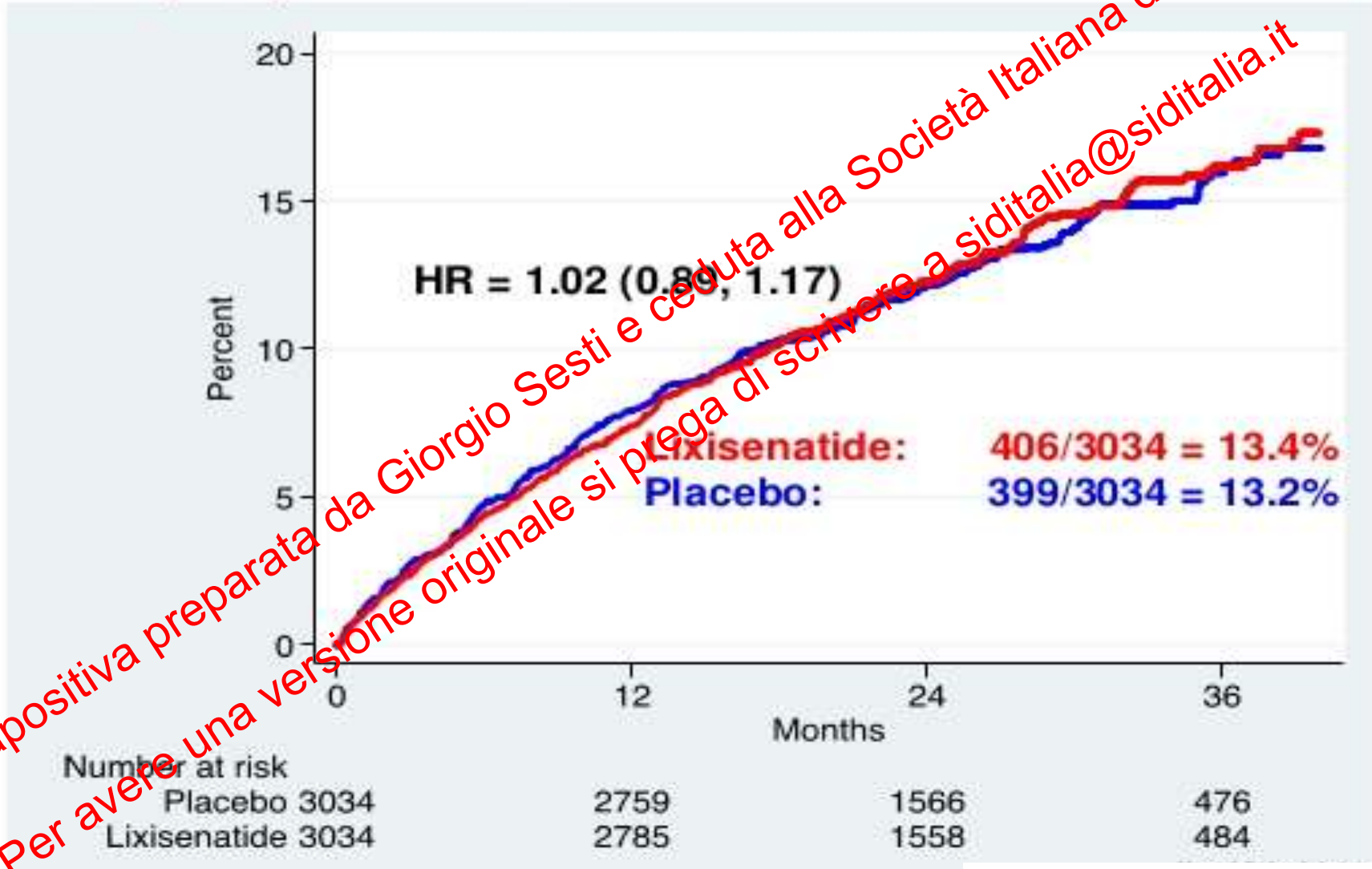
Primary endpoints or hospitalization for HF or coronary revascularization procedure

Percent change in the UACR from baseline to 108 weeks

Bentley-Lewis R, et al. *Am Heart J.* 2015:69:631-638.

Primary Outcome

CV Death, MI, Stroke or UA



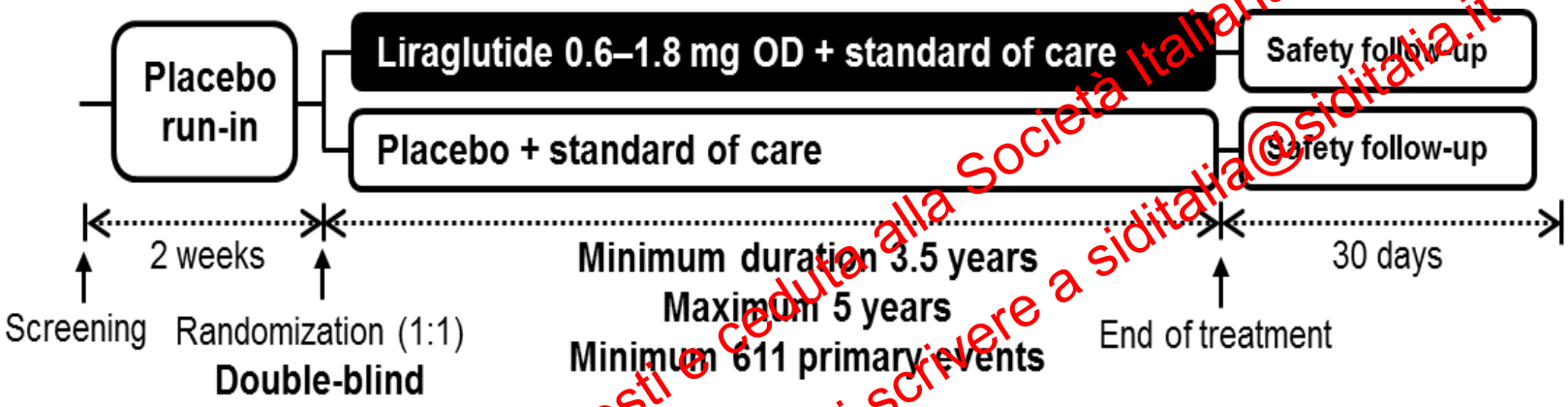
Pfeffer MA et al. N Engl J Med 373:2247-57, 2015

Individual Components of Primary

Outcome	# and % of Subjects with Event, and Event Rate		
	Placebo (N = 3034)	Lixisenatide (N = 3034)	Hazard Ratio (95% CI)
CV Mortality	158 (5.2%) 2.4/100pt-yr	156 (5.1%) 2.3/100pt-yr	0.98 (0.78, 1.22)
MI (fatal / non-fatal)	261 (8.6%) 4.1/100pt-yr	270 (8.9%) 4.2/100pt-yr	1.03 (0.87, 1.22)
Stroke (fatal / non-fatal)	60 (2.0%) 0.9/100pt-yr	67 (2.2%) 1.0/100pt-yr	1.12 (0.79, 1.58)
Unstable Angina	10 (0.3%) 0.1/100pt-yr	11 (0.4%) 0.2/100pt-yr	1.11 (0.47, 2.62)

Pfeffer MA et al. N Engl J Med 373:2247-57, 2015

LEADER: Study design



Key inclusion criteria

- T2DM, HbA_{1c} ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/premix insulin
- Age ≥50 years and established CV disease or chronic renal failure

  or
- Age ≥60 years and risk factors for CV disease

Key exclusion criteria

- T1DM
- Use of GLP-1RAs, DPP-4i, pramlintide, or rapid-acting insulin
- Familial or personal history of MEN-2 or MTC

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CV: cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist; HbA_{1c}: glycated hemoglobin; MEN-2: multiple endocrine neoplasia type 2; MTC: medullary thyroid cancer; OAD: oral antidiabetic drug; OD: once daily; T2DM: type 2 diabetes mellitus.

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LEADER - Baseline characteristics
(mean ± SD unless stated)

	Liraglutide (N=4668)	Placebo (N=4672)
Male sex, N (%)	3011 (64.5)	2992 (64.0)
Age, years	64.2 ± 7.2	64.4 ± 7.2
Diabetes duration, years	12.8 ± 8.0	12.9 ± 8.1
HbA_{1c}, %	8.7 ± 1.6	8.7 ± 1.5
BMI, kg/m^2	32.6 ±6.3	32.5 ± 6.3
Body weight, kg	91.9 ±21.2	91.6 ± 20.8
Systolic blood pressure, mmHg	135.9 ± 17.8	135.9 ± 17.7
Diastolic blood pressure, mmHg	77.2 ± 10.3	77.0 ± 10.1
Heart failure*, N (%)	835 (17.9)	832 (17.8)

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*Heart failure includes New York Heart Association class I, II and III. BMI: body mass index; HbA_{1c}: glycated hemoglobin.

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LEADER - Baseline cardiovascular risk profile

	Liraglutide (N=4668)	Placebo (N=4672)
Established CVD/CKD (age ≥50 years)	**3831 (82.1)**	**3767 (80.6)**
Prior myocardial infarction	1464 (31.4)	1400 (30.0)
Prior stroke or prior TIA	730 (15.6)	777 (16.6)
Prior revascularization	1835 (39.3)	1803 (38.6)
>50% stenosis of coronary, carotid, or lower extremity arteries	1188 (25.4)	1191 (25.5)
Documented symptomatic CHD	412 (8.8)	406 (8.7)
Documented asymptomatic cardiac ischemia	1241 (26.6)	1231 (26.3)
Chronic heart failure NYHA II – III	653 (14.0)	652 (14.0)
Chronic kidney disease (eGFR <60 mL/min/1.73m^2)	1185 (25.4)	1122 (24.0)

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Data are number of patients (%).
CHD: coronary heart disease; CKD: chronic kidney disease; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; NYHA: New York Heart Association; TIA: transient ischemic attack.

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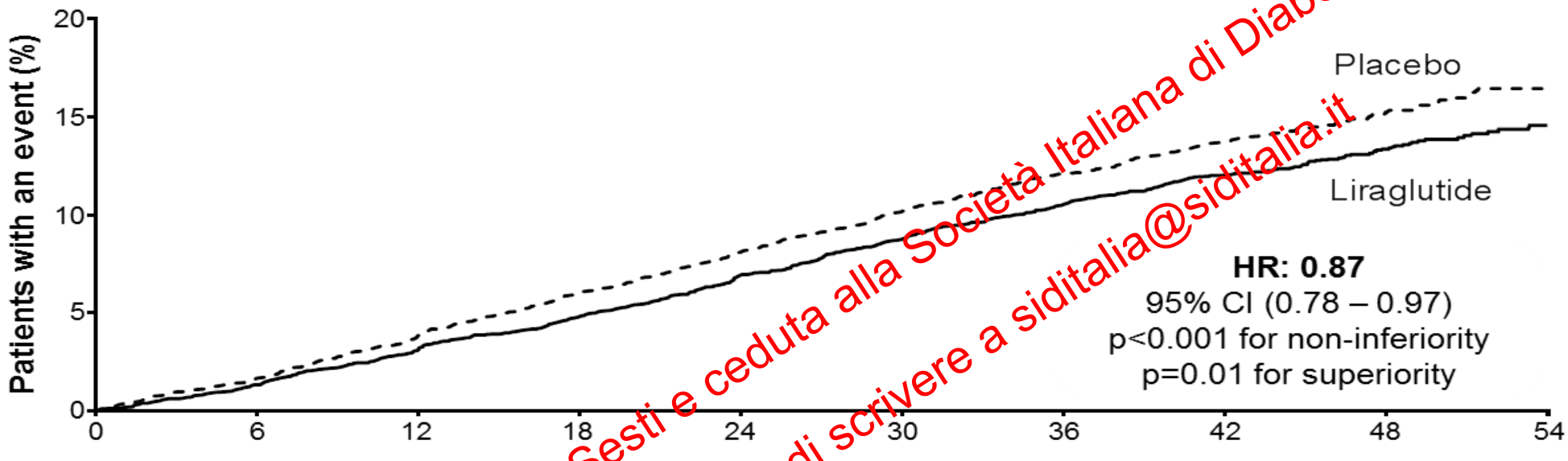
LEADER Study Primary outcome

CV death, non-fatal myocardial infarction, or non-fatal stroke



Patients at risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

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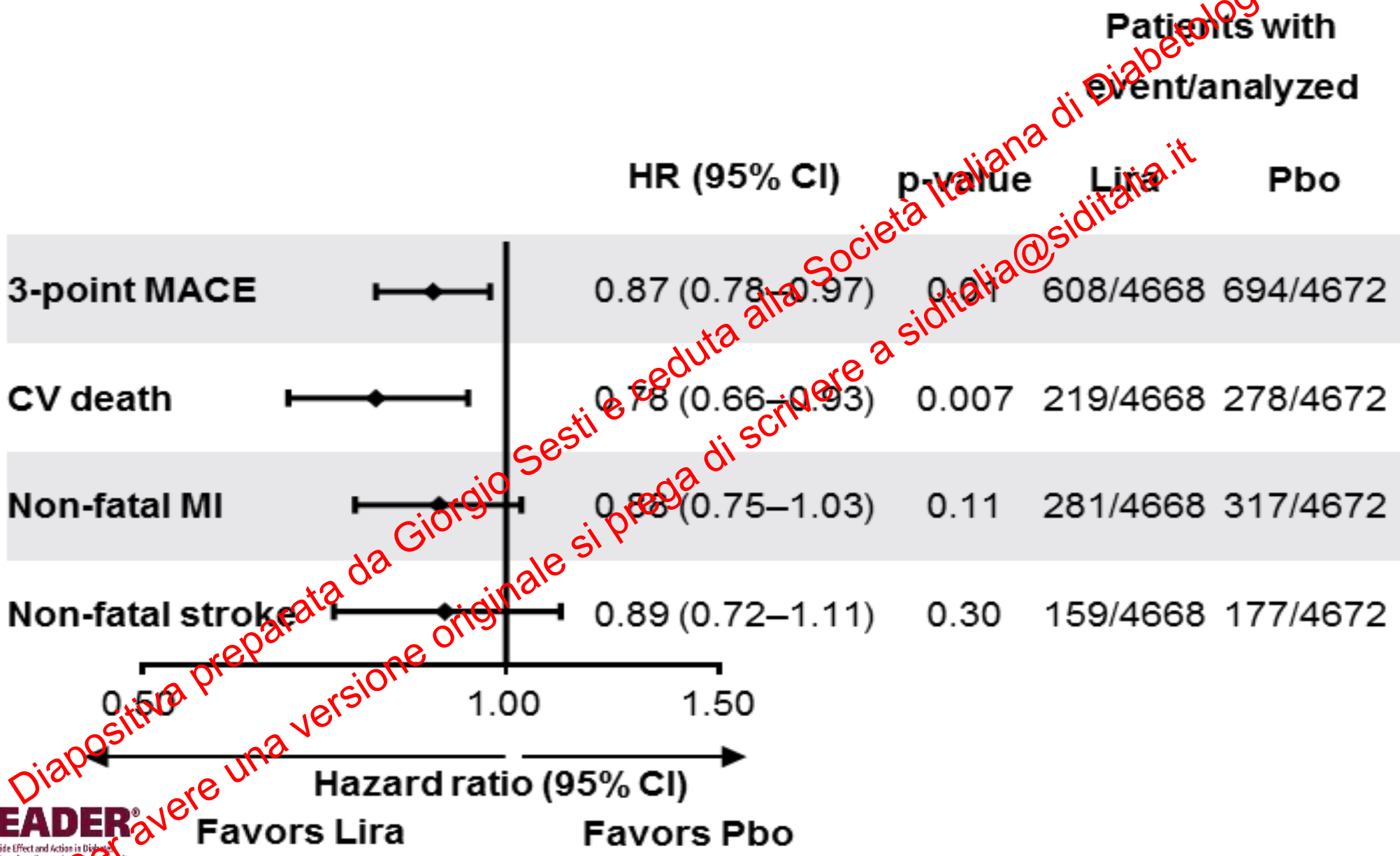
LEADER - Individual components of the primary endpoint



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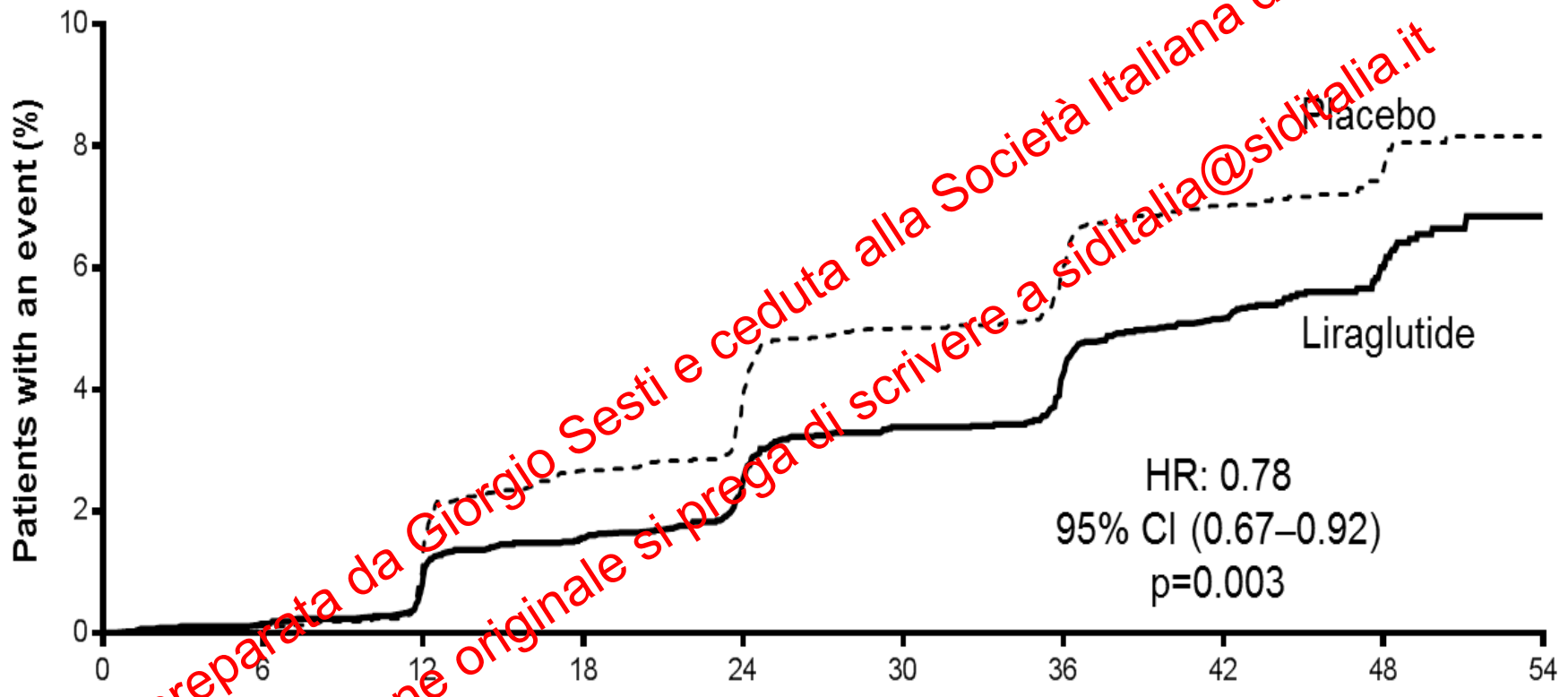
LEADER - Time to first renal event

Macroalbuminuria, doubling of serum creatinine, ESRD, renal death



Patients at risk										
Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

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The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; ESRD: end-stage renal disease; HR: hazard ratio.

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Relative differences between short and long-acting GLP-1R agonists

	Exenatide BID, Lixisenatide	Exenatide LAR, Liraglutide, Albiglutide, Dulaglutide
FPG reduction	+	+++
PPG reduction	+++	++
Fasting insulin secretion	+/Neutral	++
Postprandial insulin secretion	+	++
HbA1c reduction	++	+++
Body weight reduction	++	++
Gastric empting rate	+++	+
Fasting glucagon secretion reduction	+/Neutral	++
GI effects	++	+
CV safety	Neutral	+++
Compliance (administration and timing)	+	++

1. Modified from Meier JJ. Nat Rev Endocrinol 2012;8:728-42
2. Modified from Fineman MS et al. Diabet Obes Metab 2012;14:675-88

THANK YOU !

Now it’s time for discussion.