Analoghi del GLP-1: a che punto siamo

FRANCESCO GIORGINO, M.D., PH.D.
PROFESSOR OF ENDOCRINOLOGY

DEPARTMENT OF EMERGENCY AND ORGAN TRANSPLANTATION
SECTION OF INTERNAL MEDICINE, ENDOCRINOLOGY,
ANDROLOGY AND METABOLIC DISEASES

UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

Disclosures

Advisory Boards
AstraZeneca/BMS, Eli Lilly, Roche Diagnostics, Takeda

Consultant
AstraZeneca/BMS, Boehringer Ingelheim, Lifescan, Merck Sharp & Dohme, Novo Nordisk, Sanofi

Research Support
AstraZeneca/BMS, Eli Lilly, Lifescan, Sanofi, Takeda

This presentation reflects the external speaker's point of view and not necessarily that of the meeting sponsor (Eli Lilly and Company)

GLP-1RAs Have Multifactorial Effects

PHARMACOLOGICAL EFFECTS OF GLP-1RAs

Pancreas

- ↑ Beta-cell function[1]
- ↑ Insulin biosynthesis[1]
- ↑ Glucose-dependent insulin secretion[1]
- ↓ Glucose-dependent glucagon secretion[1]

Brain

- ↓ Body weight[5]
- ↓ Food intake[6]
- ↑ Satiety[7,8]

Stomach

- ↓ Gastric emptying[9]

- ↓ Endogenous glucose production[10]
- ↑ Hepatic insulin sensitivity[10]
- ↓ *De novo* lipogenesis[10]
- ↓ Lipotoxicity[10]
- ↓ Steatosis[11]

Liver

- ↓ Cardiovascular risk[2]
- ↓ Fatty acid metabolism[2]
- ↑ Cardiac function[3]
- ↓ Systolic blood pressure[3]
- ↓ Inflammation[4]

Heart

GLP-1RA, glucagon-like peptide-1 receptor agonist.
Adapted from Campbell JE, Drucker DJ. *Cell Metab* 2013;17:819–37 and Pratley RE, Gilbert M. *Rev Diabet Stud* 2008;5:73–94. A full reference list for this slide can be found in the slide notes.

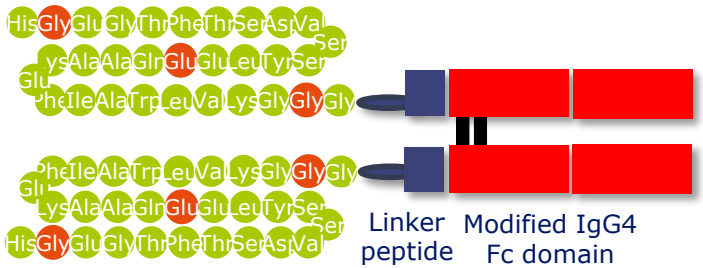
GLP-1RAs Vary in Molecular Structure and Size

Exendin-based GLP-1RAs	Human GLP-1 analogues	
	Small	Large

Exenatide *(4.19 kDa, 53% homology)*

Liraglutide *(3.75 kDa, 97% homology)*

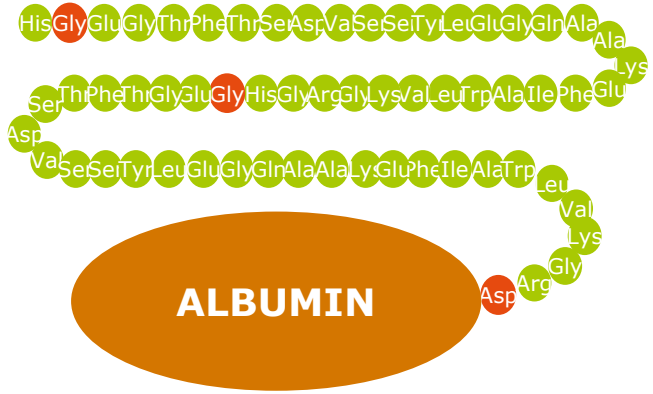
Dulaglutide *(~63 kDa, 90% homology)*



Lixisenatide *(4.86 kDa, ~50% homology)*

Semaglutide *(4.11 kDa, 94% homology)*

Albiglutide*



CV, cardiovascular; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; IgG4 Fc, immunoglobulin-G4 fragment crystallisable.

Similarities and Differences within the GLP-1 RAs Class

Similarities

- Significant glycaemic improvement
- Low hypoglycaemia risk, except in combination with SU or insulin
- Weight reduction, usually dose-dependent and molecule-related
- Reduced (systolic) blood pressure
- Gastrointestinal side effects
- Label warnings regarding pancreatitis
- Potential effects on beta-cell survival, CV outcomes, neurodegeneration

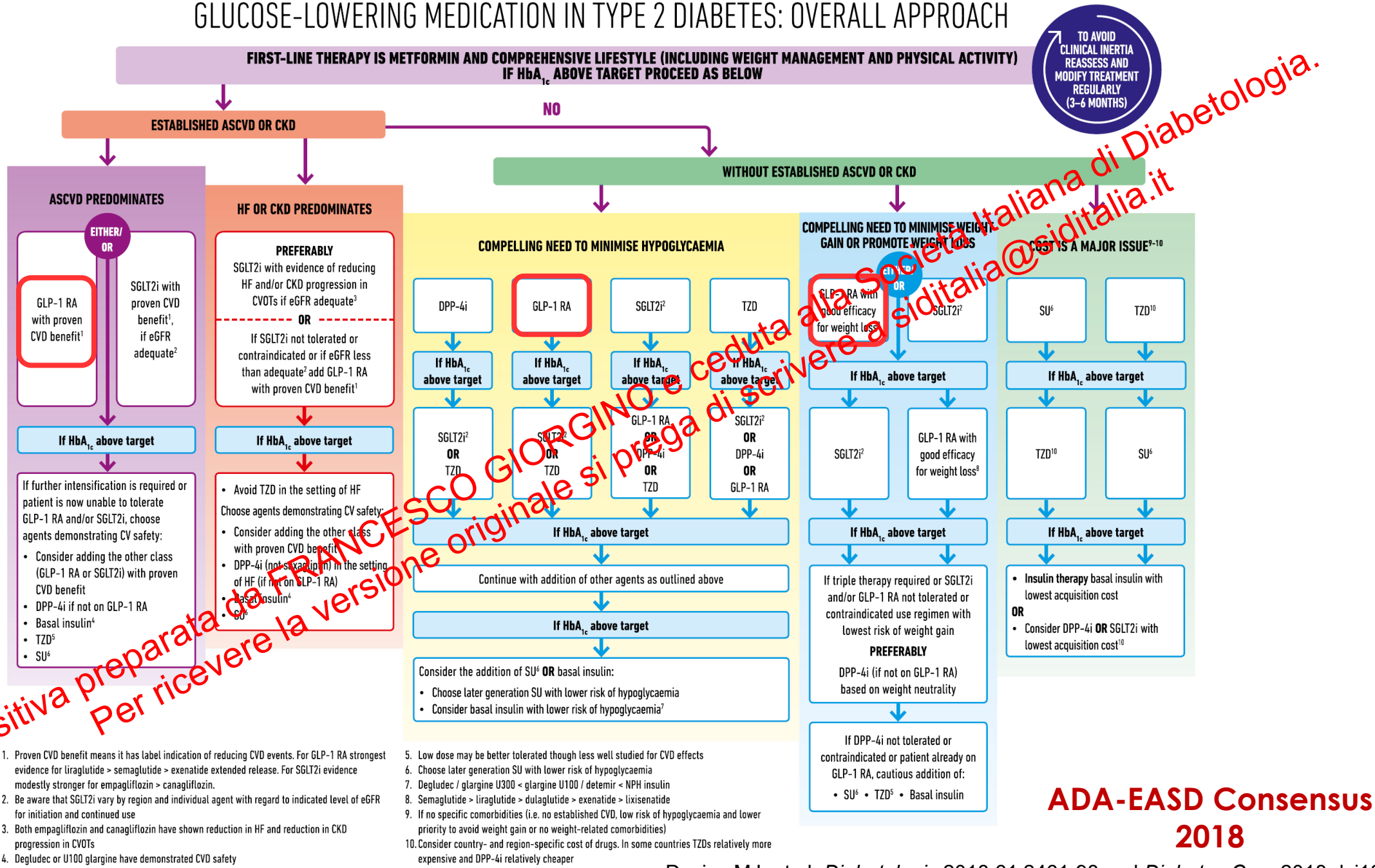
Differences

- Homology to human GLP-1 and immunogenicity
- Onset of action
- Effects on gastric emptying
- Fasting glucose and post-prandial glucose reduction
- Differences in metabolism and elimination (use in CKD)
- Potential for kidney protection
- CV protection
- Frequency of administration, dose titration, devices/pens, need for reconstitution → adherence

CKD, chronic kidney disease; CV, cardiovascular; GLP-1, glucagon-like peptide-1; SU, sulphonylurea

BYETTA Prescribing Information. Accessed 25 April 2016. Victoza Prescribing Information. Accessed 25 April 2016. Lyxumia Prescribing Information. Accessed 25 April 2016. Lyxumia Summary of Product Characteristics. Accessed 25 April 2016. Trulicity Prescribing Information. Summary of product characteristics. Accessed 28 April 2016 Meier J. *Nat Rev Endocrinol* 2012; 8: 728-742. Neumiller JJ. *J Am Pharm Assoc* 2009; 49: S16-29. White J. *J Am Pharm Assoc* 2009; 49: S30-40; Buse JB, et al. *J Clin Endocrinol Metab* 2011; 96: 1695-1702; Meier JJ. *Nat Rev Endocrinol* 2012; 8: 728-742

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



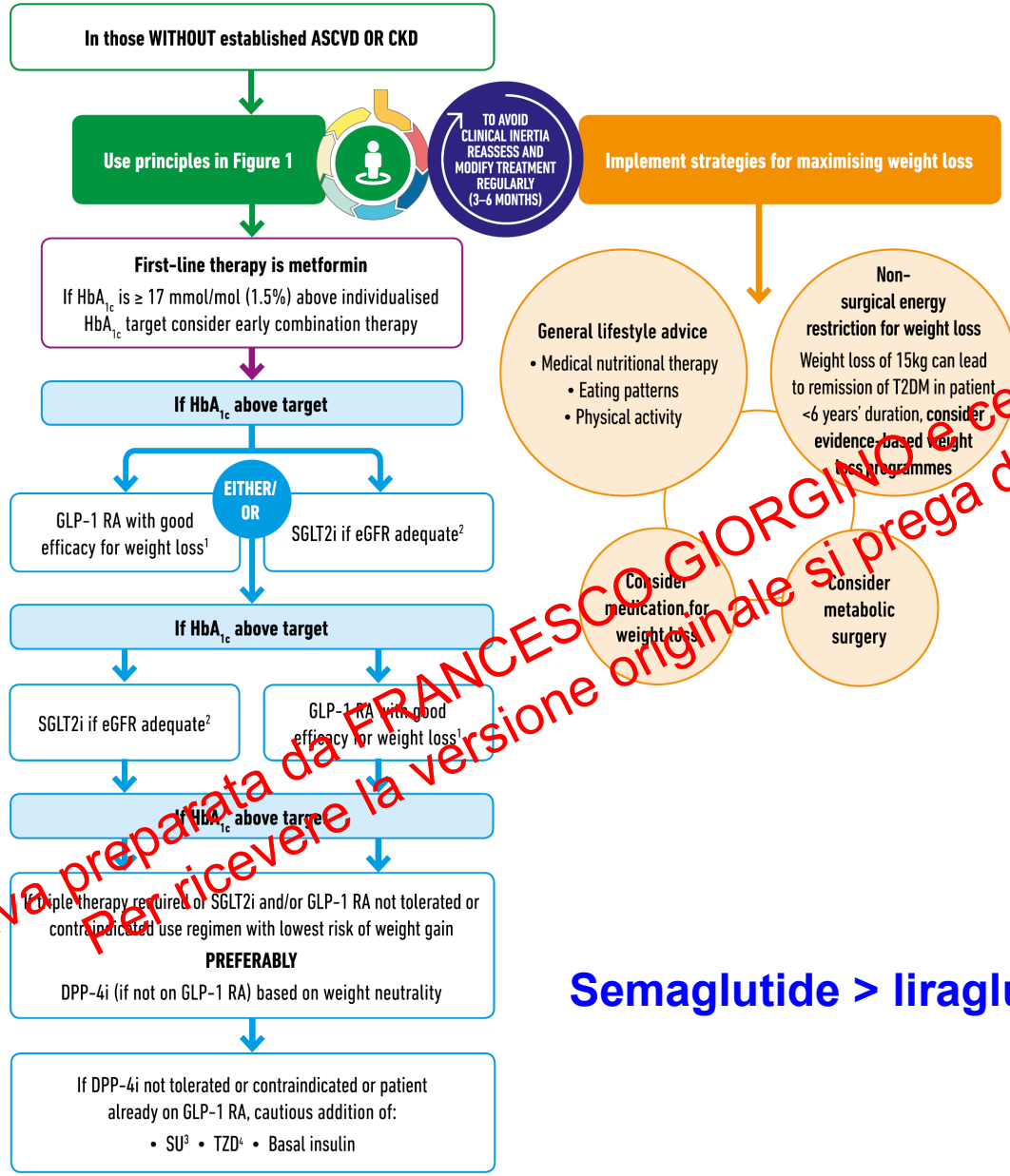
1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

ADA-EASD Consensus 2018

Davies MJ, et al. *Diabetologia* 2018;61:2461-98 and *Diabetes Care* 2018;dci180033

CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

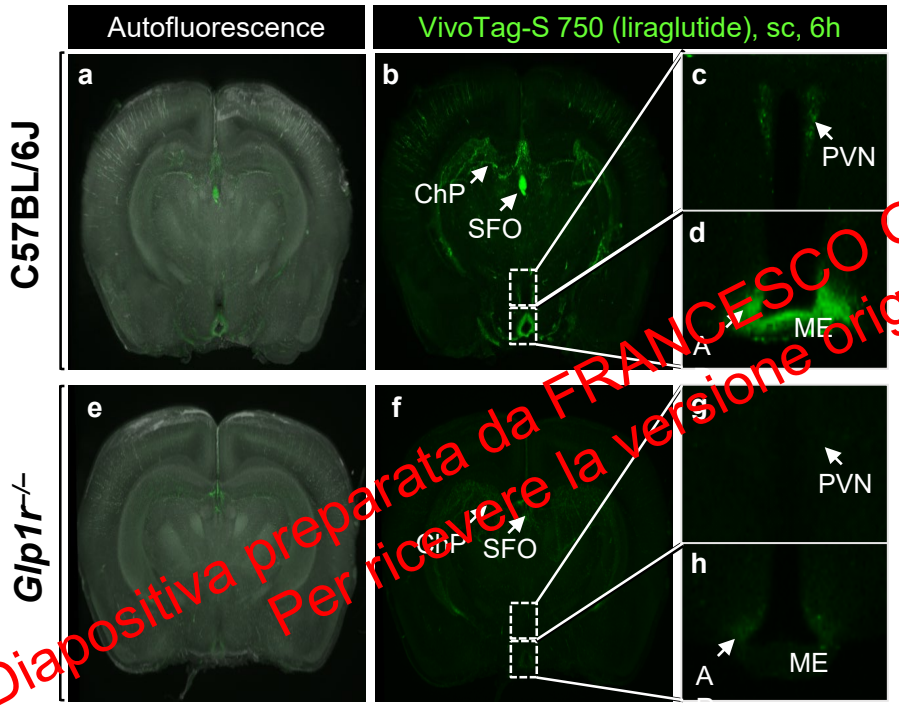
ADA-EASD Consensus 2018
Davies MJ et al., Diabetologia 2018 & Diabetes Care 2018



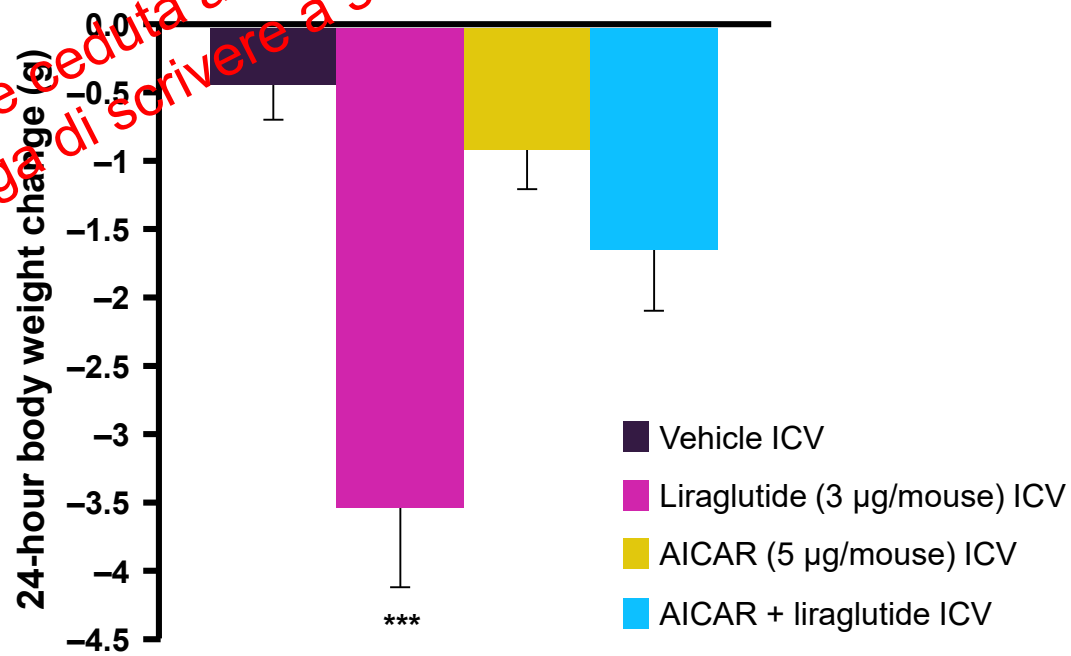
Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide

Neurally-mediated Mechanisms Account for the Ability of GLP-1 RA Therapy to Induce Reduction in Body Weight

In mice, fluorescently labelled liraglutide is taken up into specific hypothalamic regions in a receptor-dependent manner[1]



Hypothalamic GLP-1 receptor activation led to reduced caloric intake and lower body weight in rats[2]

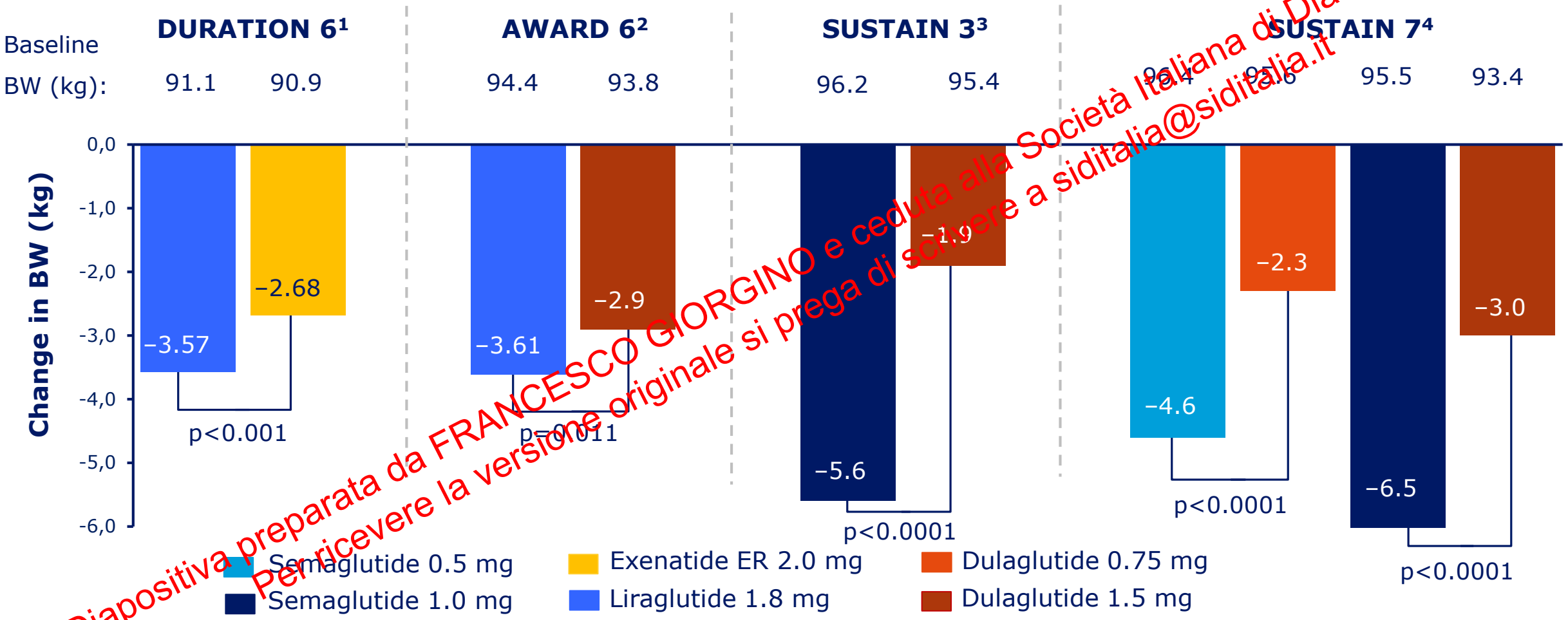


AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide; ChP, choroid plexus; GLP-1, glucagon-like peptide-1; ICV, intracerebroventricular; ME, median eminence; PVN, paraventricular nucleus; SFO, subfornical organ; VMH, ventromedial hypothalamus

1. Secher A, et al. *J Clin Invest* 2014;124:4473–4488; 2. Beirao D, et al. *Diabetes* 2014;63:3346–3358

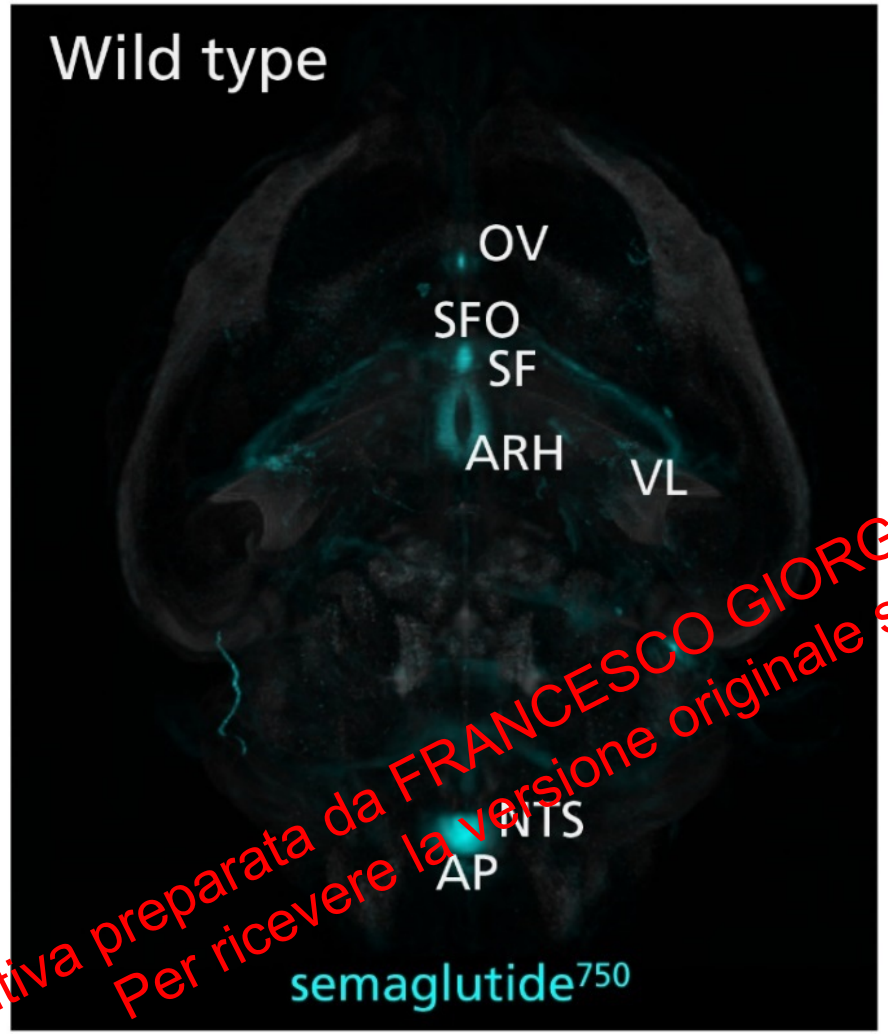
GLP-1RAs Effects on Body Weight

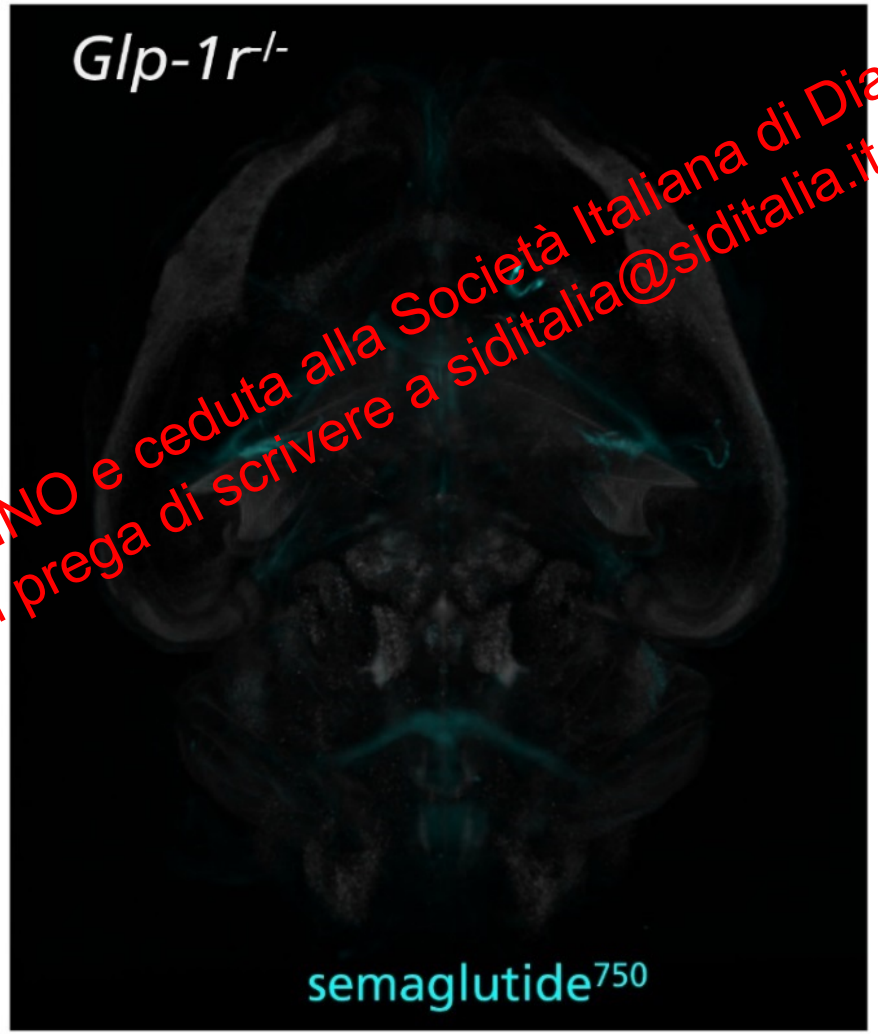
RESULTS FROM COMPARATIVE TRIALS



Direct comparisons should not be made between trials.
BW, body weight; exenatide ER, exenatide extended release; GLP-1RA, glucagon-like peptide-1 receptor agonist.
1. Buse JB et al. *Lancet* 2013;381:117–24; 2. Dungan KM et al. *Lancet* 2014;384:1349–57; 3. Ahmann AJ et al. *Diabetes Care* 2018;41:258–66; 4. Pratley RE et al. *Lancet Diabetes Endocrinol* 2018;6:275–86

Semaglutide^{750} Brain Signal is GLP-1R-dependent

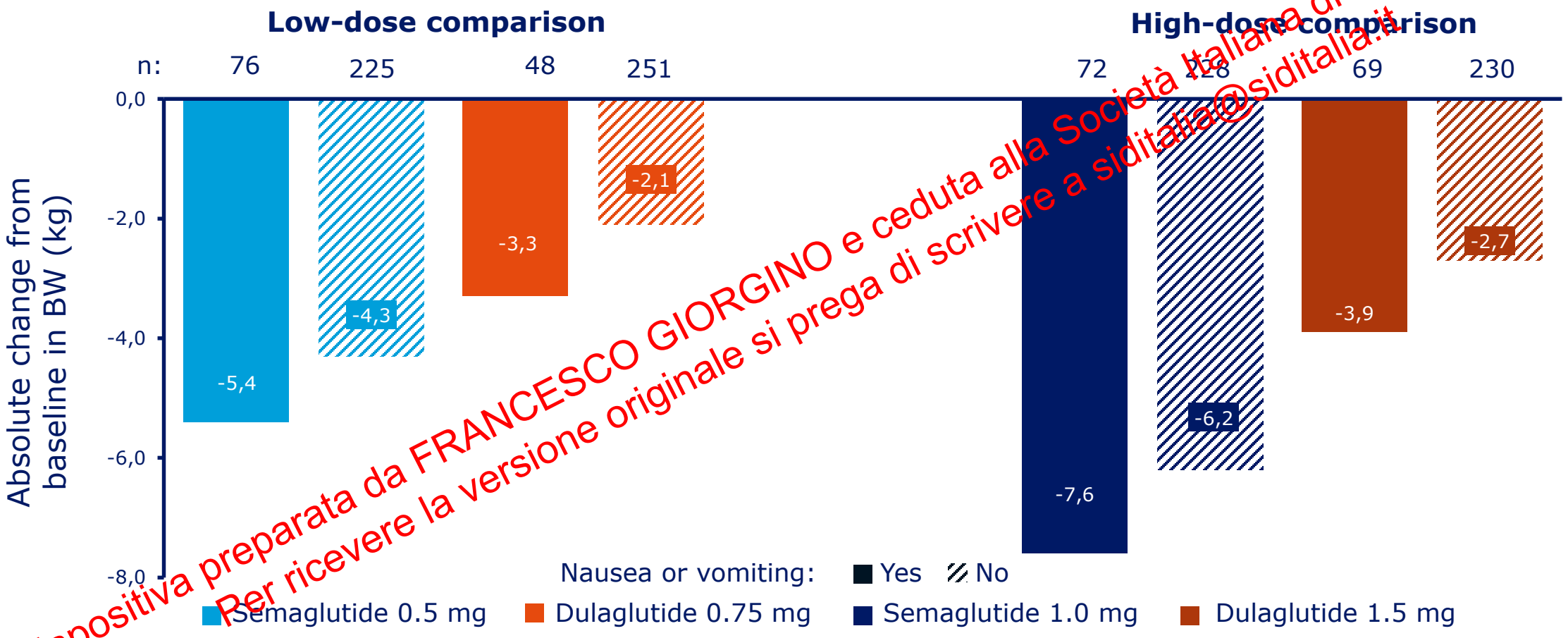




Maximum intensity projection of average (n=4–5) semaglutide^{750} distribution in wild-type C57BL/6 mice (left) and *Glp-1r*$^{-/-}$ mice (right). AP, area postrema; ARH, arcuate hypothalamic nucleus; NTS, nucleus of the solitary tract; OV, vascular organ of the lamina terminalis; SF, septofimbrial nucleus; SFO, subfornical organ; VL, lateral ventricle. Jensen CB et al. Presented at the 77th ADA Scientific Sessions, June 9–13, 2017, San Diego, CA, USA: Poster Presentation 1145-P.

Changes in Body Weight by Nausea or Vomiting

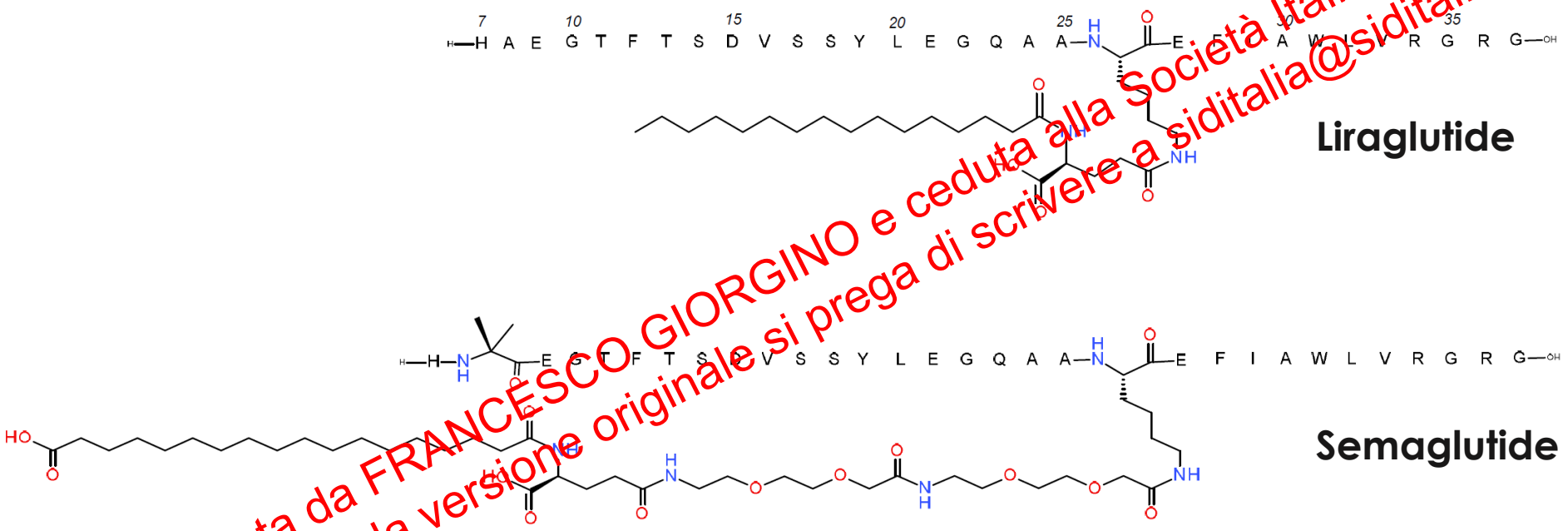
SUSTAIN 7



Data are 'on-treatment without rescue medication' estimated changes from baseline at week 40 from all randomised patients exposed to at least one dose of trial product (full analysis set). Missing data were imputed from a mixed model for repeated measurements with treatment, region and stratum as fixed factors and baseline value as covariate, all nested within visit. BW, body weight.

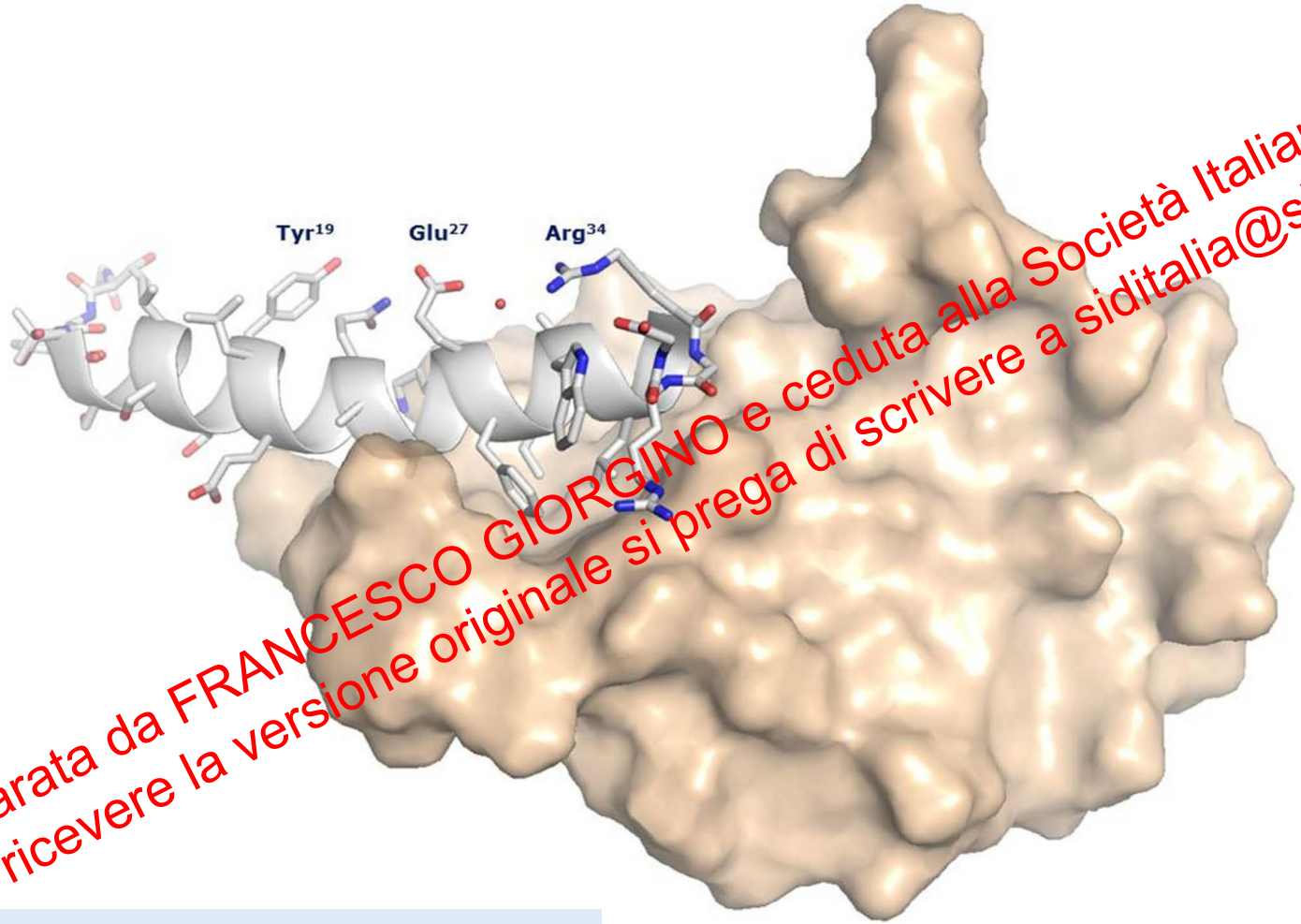
Lingvay I et al. EASD 2018

Structures of liraglutide and semaglutide



Lau J et al., *Curr Med Chem* 2015

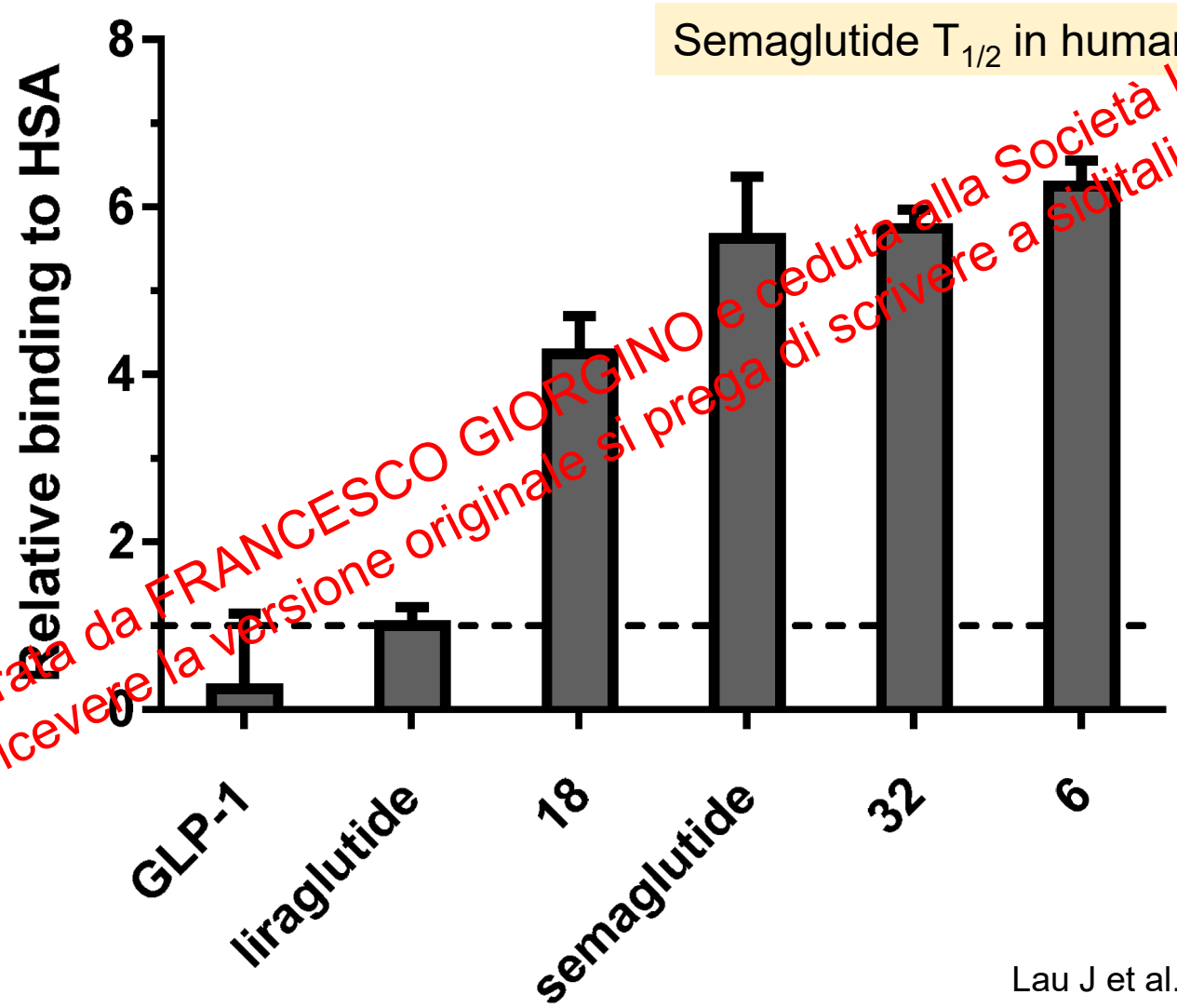
Semaglutide binding to the GLP-1 R



GLP-1R affinity of semaglutide (0.38-0.06 nM)
3-fold decreased vs. liraglutide

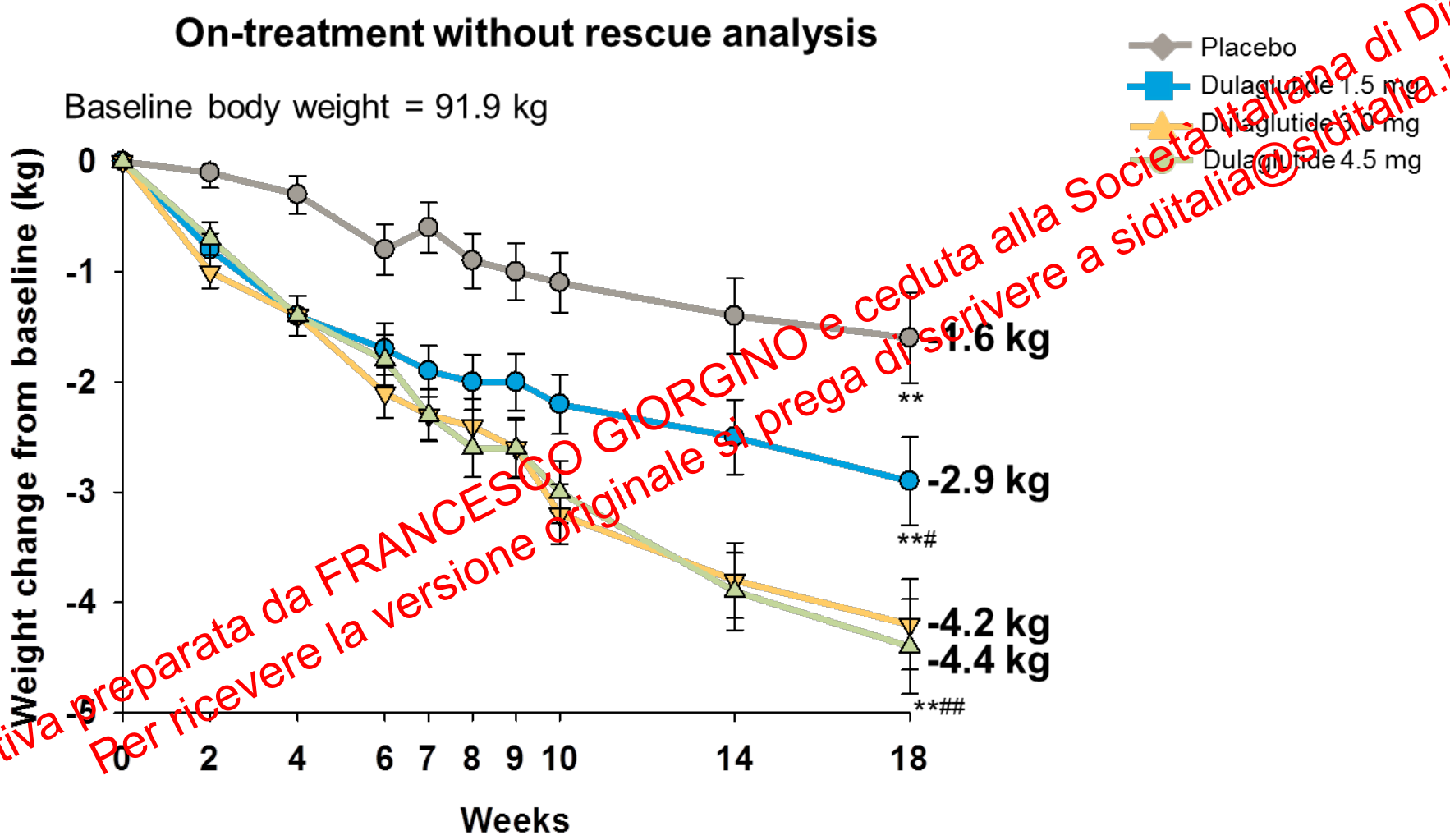
Lau J et al., *Curr Med Chem* 2015

Relative binding affinities of GLP-1 analogs to HSA measured by analytical ultracentrifugation



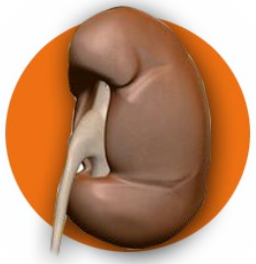
Lau J et al., *Curr Med Chem* 2015

Change in Body Weight at 18 Weeks



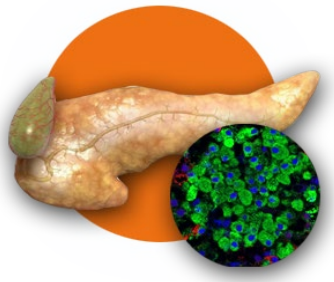
Data presented are LS mean ± SE
**p<.001 vs baseline; #,##p<.05 and p<.001 vs placebo, respectively
MMRM analysis

SGLT-2 Inhibitor



↓ **Insulin**

↑ **Glucagon**



↑ β-cell survival & performance

↑ Glycosuria

↓ Glucotoxicity

↑ Natriuresis

↓ Blood pressure

↓ Heart preload

Weight loss

↓ Insulin resistance

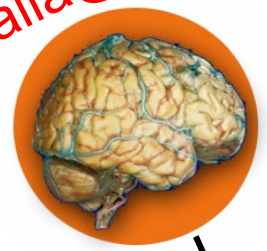
↓ **Hyperglycaemia**

GLP-1 RA

↑ **Insulin**

↓ **Glucagon**

↑ GLP-1 R signalling



Weight loss

Expected benefits of combination

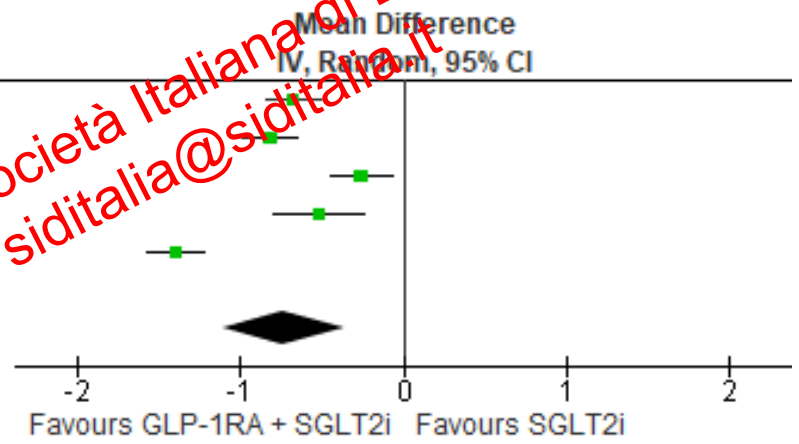
Further ↓ HbA_{1c} with no hypoglycaemia
Further weight loss
↔ Glucagon and HGP
↓ DKA risk
↑ β-cell preservation
Further ↓ CVD outcomes
Further ↓ nephropathy outcomes

Efficacy of GLP-1 Receptor Agonists as Add-on to SGLT2 Inhibitors on HbA1c and Body Weight in Type 2 Diabetes

HbA1c

Study or Subgroup	GLP-1RA + SGLT2i Mean	SD	Total	SGLT2i Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
AWARD-10, 2018 - Dulaglutide 0.75 mg	-1.19	0.7099	140	-0.51	0.7023	137	20.4%	-0.68 [-0.85, -0.51]
AWARD-10, 2018 - Dulaglutide 1.5 mg	-1.33	0.715	142	-0.51	0.7023	137	20.4%	-0.82 [-0.99, -0.65]
DUAL IX, 2019	-1.94	0.95	210	-1.68	1.05	210	20.1%	-0.26 [-0.45, -0.07]
DURATION-8, 2018	-1.75	1.51	228	-1.23	1.5166	230	19.0%	-0.52 [-0.80, -0.24]
SUSTAIN 9, 2019	-1.5	0.7373	151	-0.1	0.8602	151	20.2%	-1.40 [-1.68, -1.22]
Total (95% CI)			**871**			**865**	**100.0%**	**-0.74 [-1.11, -0.36]**

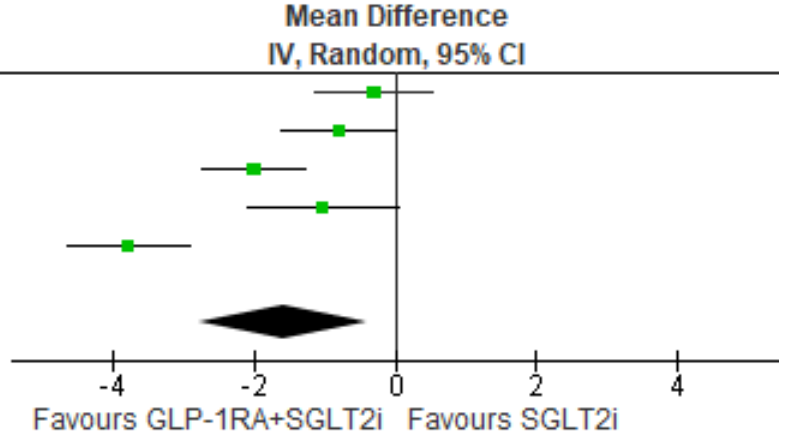
Heterogeneity: Tau² = 0.17; Chi² = 78.52, df = 4 (P < 0.00001); I² = 95%
Test for overall effect: Z = 3.86 (P = 0.0001)



Body Weight

Study or Subgroup	GLP-1RA + SGLT2i Mean	SD	Total	SGLT2i Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
AWARD-10, 2018 - Dulaglutide 0.75 mg	-2.6	3.5496	140	-2.3	3.5114	137	20.2%	-0.30 [-1.13, 0.53]
AWARD-10, 2018 - Dulaglutide 1.5 mg	-3.1	3.5049	142	-2.3	3.5114	137	20.2%	-0.80 [-1.63, 0.03]
DUAL IX, 2019	[illegible]	3.8	210	2	3.9	210	20.6%	-2.00 [-2.74, -1.26]
DURATION-8, 2018	-3.31	5.7379	228	-2.28	5.9146	230	19.0%	-1.03 [-2.10, 0.04]
SUSTAIN 9, 2019	-4.7	3.9322	151	-0.9	3.8093	151	20.0%	-3.80 [-4.67, -2.93]
Total (95% CI)			**871**			**865**	**100.0%**	**-1.59 [-2.79, -0.39]**

Heterogeneity: Tau² = 1.69; Chi² = 39.55, df = 4 (P < 0.00001); I² = 90%
Test for overall effect: Z = 2.59 (P = 0.010)



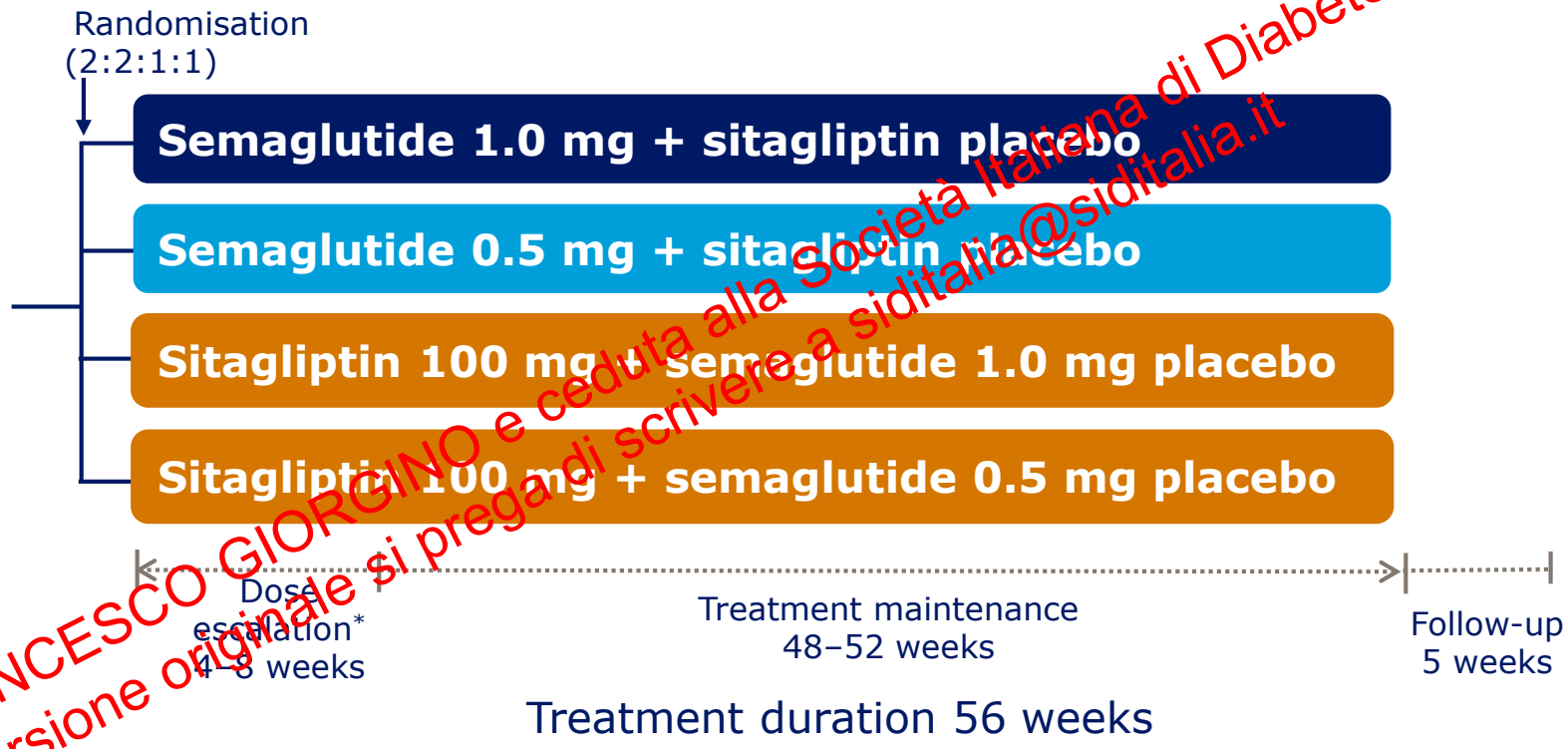
Castellana M et al., submitted

SUSTAIN 2

TRIAL DESIGN

1,231 subjects with T2D

- Age ≥18 years
- HbA_{1c} 7.0–10.5%
- Stable treatment with MET, TZD or MET + TZD 90 days prior to screening
- eGFR >60 mL/min/1.73 m^2



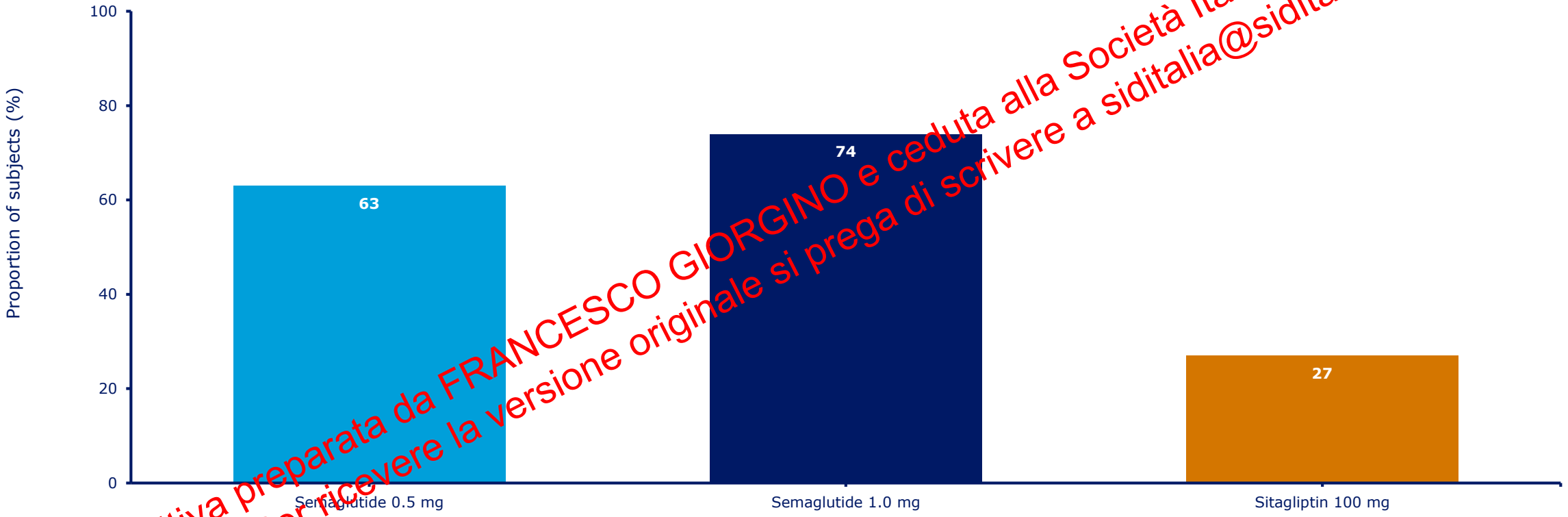
Trial information

- Randomised, double-blinded, double-dummy, active-controlled, parallel-group, multicentre, multinational, four-armed trial
- Subjects from the two active sitagliptin arms are pooled in the analysis
- Conducted in 10 countries in Europe, and in Argentina, Hong Kong, India, Japan, Mexico, Russia, South Africa and Thailand

*Semaglutide dose escalation from starting dose of 0.25 mg; dose doubled each step until trial dose achieved. www.ClinicalTrials.gov (NCT01930188).
eGFR, estimated glomerular filtration rate; MET, metformin; TZD, thiazolidinediones.
Ahrén B et al. *Lancet Diabetes Endocrinol* 2017;5:341–354.

SUSTAIN 2:
HbA_{1c} <7% and no hypoglycaemia* or weight gain

PROPORTIONS AT WEEK 56



*Severe or BG-confirmed symptomatic hypoglycaemia

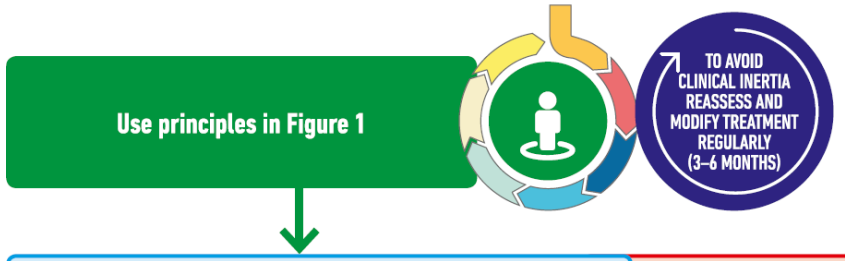
Values are observed proportions using 'on-treatment without rescue medication' data from subjects in the full analysis set. Missing HbA_{1c} and body weight data are imputed from a mixed model for repeated measurements analysis and subsequently classified. BG-confirmed, BG <3.1 mmol/L (56 mg/dL).

BG, blood glucose.

Ahrén B et al. *Lancet Diabetes Endocrinol* 2017;5:341–354.

INTENSIFYING TO INJECTABLE THERAPIES

ADA-EASD Consensus 2018
Davies MJ et al., Diabetologia 2018 & Diabetes Care 2018



If HbA_{1c} above target despite dual/triple therapy

Consider initial injectable combination (i.e. GLP-1 RA + basal insulin or prandial/basal insulin) if HbA_{1c} > 86 mmol/mol (10%) and/or > 23 mmol/mol (2%) above target

INITIATION FOR GLP-1 RA
- Initiate starting dose (varies across class)

TITRATION FOR GLP-1 RA
- Gradual titration to maintenance dose (varies across class)

Consider GLP-1 RA in most prior to insulin

Consider: • INITIATION • TITRATION

Consider insulin as first injectable if
- HbA_{1c} very high > 97 mmol/mol (11%)
- Symptoms or evidence of catabolism: weight loss, polyuria, polydipsia which suggest insulin deficiency
- If type 1 diabetes is a possibility

If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred

If above HbA_{1c} target

INITIATION FOR BASAL
- Start 10 IU a day **OR** 0.1–0.2 IU/kg a day

TITRATION FOR BASAL
- Patient self-titration is more effective
- Set FPG target that correlates to HbA_{1c} target
- Choose evidence-based titration algorithm, e.g. increase 2 units every 3 days to reach FPG target without hypoglycaemia
- For hypoglycaemia determine cause, if no clear reason lower dose by 10–20%

Add basal insulin

Consider: • INITIATION • TITRATION

For patient on GLP-1 RA and basal insulin

Consider FRC of GLP-1 RA and insulin (iDegLira or iGlarLixi)

But note max dose of insulin in the FRCs

INITIATION
- If on GLP-1 RA use 10–16 dose steps (iDegLira) or 10–15 units (iGlarLixi)

TITRATION
- Titrate to FPG target and tolerability

Consensus recommendation

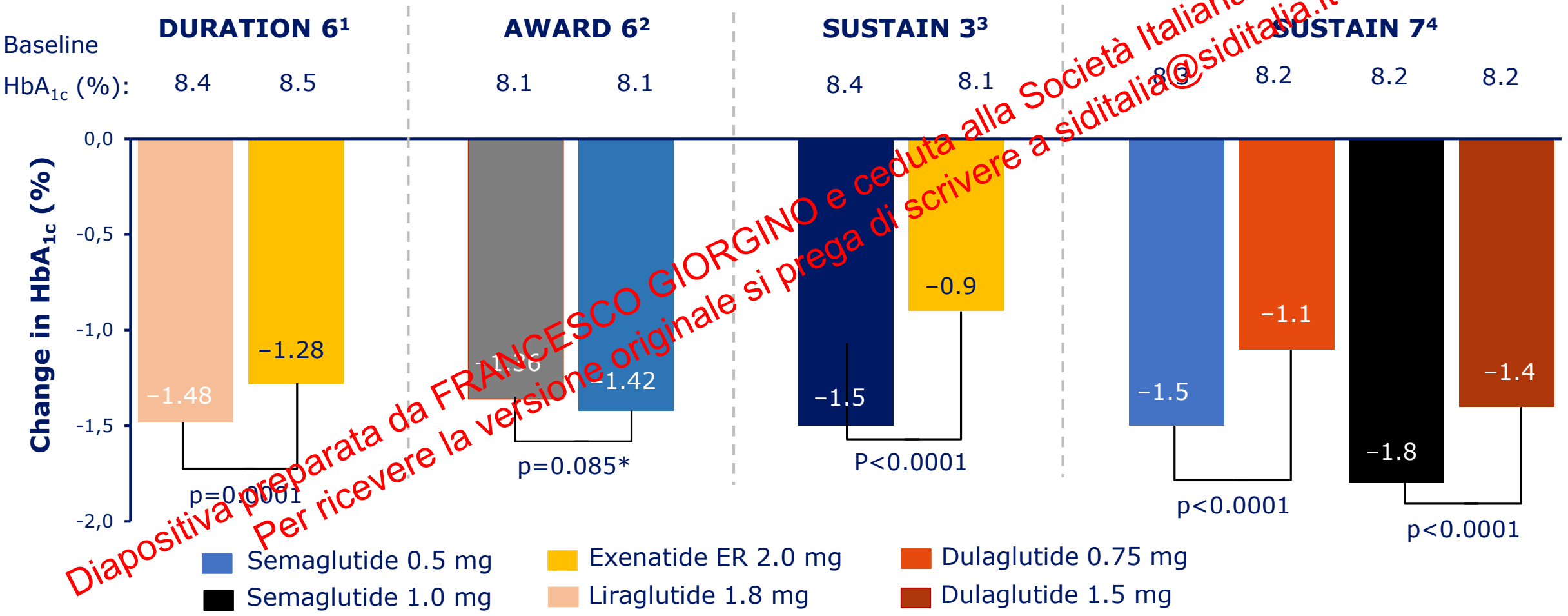
ADA-EASD Consensus 2018
Davies MJ et al. *Diabetologia* & *Diabetes Care*. 2018

In patients who need the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are the preferred choice to insulin. For patients with extreme and symptomatic hyperglycaemia, insulin is recommended

ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes.

GLP-1RAs Reduce HbA_{1c}

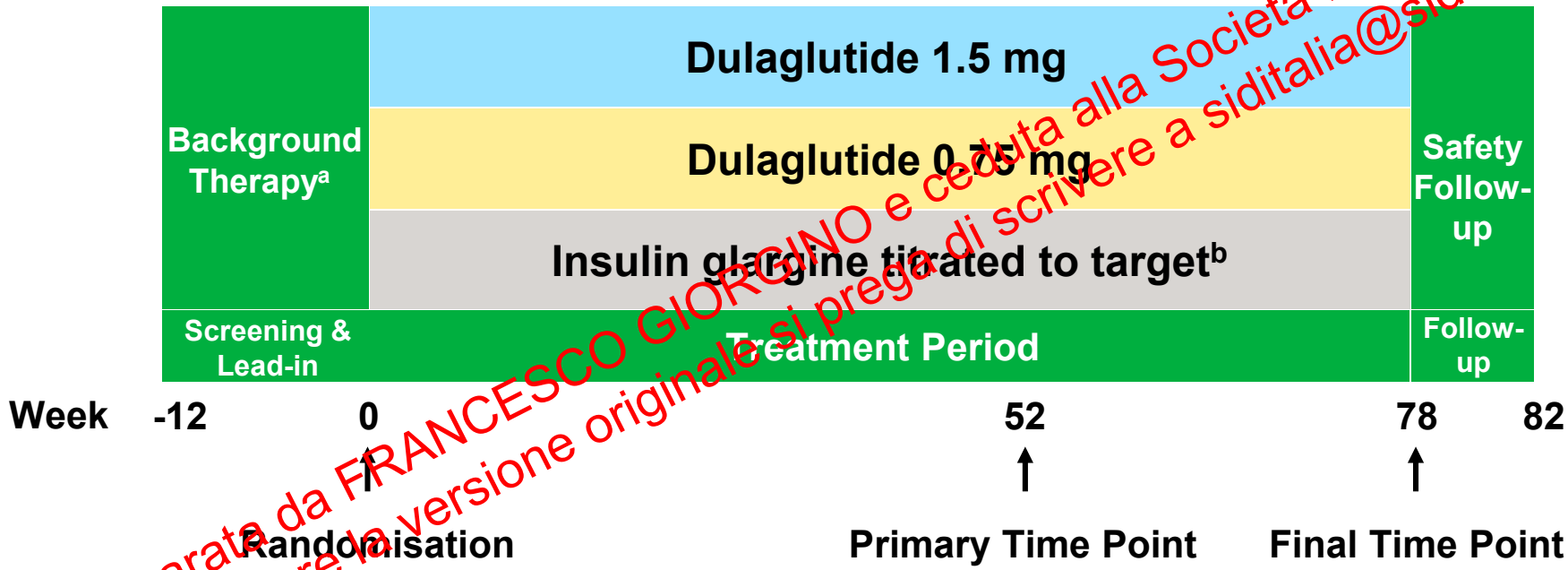
RESULTS FROM COMPARATIVE TRIALS



*Treatment difference (nominal 95% CI) = –0.06 (–0.19;0.07), p<0.0001 for non inferiority vs liraglutide. Direct comparisons should not be made between trials.
CI, confidence interval; exenatide ER, exenatide extended release; GLP-1RA, glucagon-like peptide-1 receptor agonist.
1. Buse JB et al. *Lancet* 2013;381:117–24; 2. Dungan KM et al. *Lancet* 2014;384:1349–57; 3. Ahmann AJ et al. *Diabetes Care* 2018;41:258–66; 4. Pratley RE et al. *Lancet Diabetes Endocrinol* 2018;6:275–86.

AWARD-2: Dulaglutide vs. Insulin Glargine in T2DM

T2DM not optimally controlled on 1, 2 or 3 OAMs; HbA_{1c} ≥7.0% and ≤11% at screening; HbA_{1c} >6.5% at pre-randomisation visit



APPROXIMATE TOTAL INJECTIONS
52 | 365

[a]During the lead-in period, metformin (≥1,500 mg) and glimepiride (≥4 mg) were titrated up to maximum tolerated dose, then doses were stable for 6–8 weeks. OAMs continued for the duration of the trial.
[b]Titrated to fasting plasma glucose target: <5.6 mmol/L according to Kennedy et al. 2006; GOAL HbA_{1c} Trial
HbA_{1c}, glycated haemoglobin; OAM, oral anti-diabetes medication; T2DM, type 2 diabetes mellitus

Giorgino F, et al. *Diabetes Care* 2015;38:2241–2249

AWARD-2: Dulaglutide vs. Insulin Glargine in T2DM

Baseline HbA_{1c}: 8.1%–8.2%

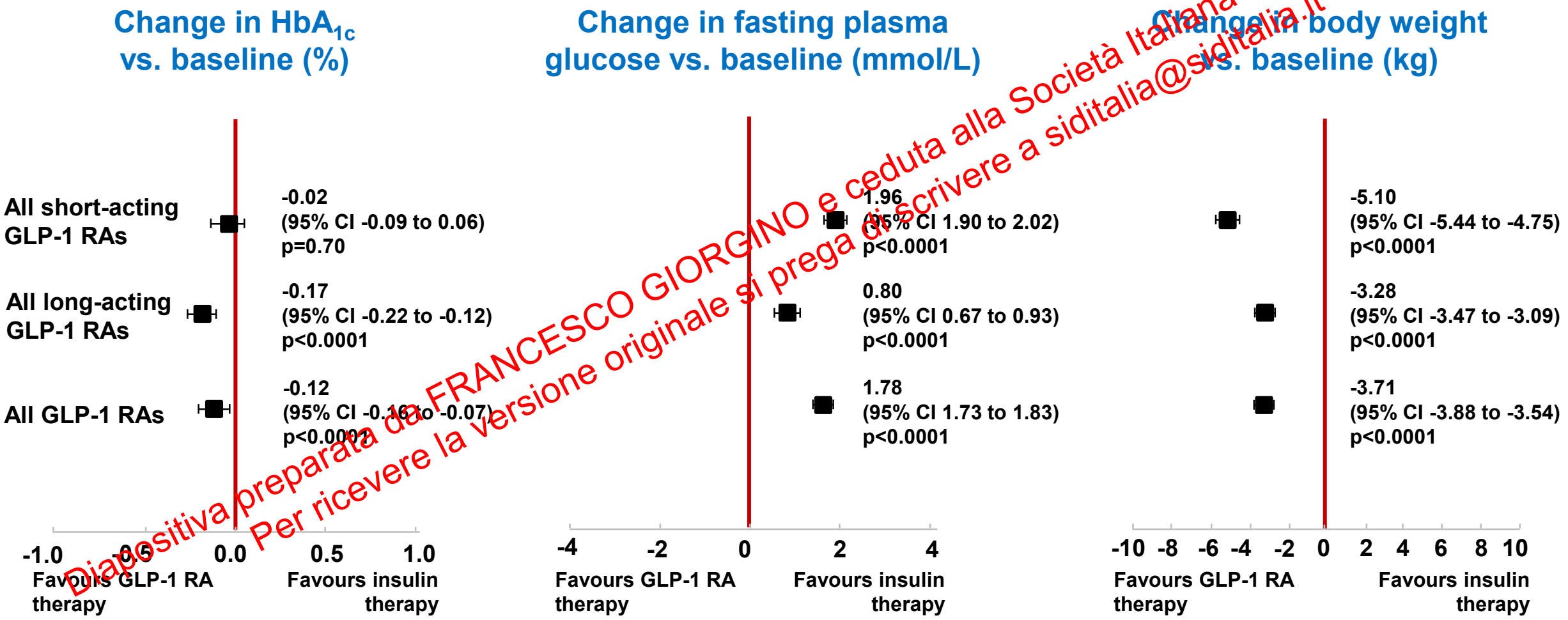
	Change in HbA_{1c} (%)	Change in Body Weight (kg)	Rates of Total Hypoglycaemia (event/patient/year)	Incidence of Diarrhoea/Nausea at 52 weeks (n)
Insulin Glargine QD	-0.63	+1.44	7.9	10/4
Dulaglutide 0.75 mg OW	-0.76†	-1.33##	4.8##	23#/18#
Dulaglutide 1.5 mg OW	-1.08††	-1.87##	5.2#	29#/39##

††p <0.001 OW, superiority vs. glargine (1-sided, adjusted to control for type I error)
†p <0.001, noninferiority vs. glargine
#p <0.05 vs. glargine
##p <0.001 vs. glargine
HbA_{1c}, glycated haemoglobin; OW, once weekly; QD, once daily; T2DM, type 2 diabetes mellitus

Giorgino F, et al. *Diabetes Care* 38:2241-9, 2015

Short- or Long-Acting GLP-1 RAs vs. Insulin

Glycaemic Control and Body Weight With Injectable Treatments



CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist

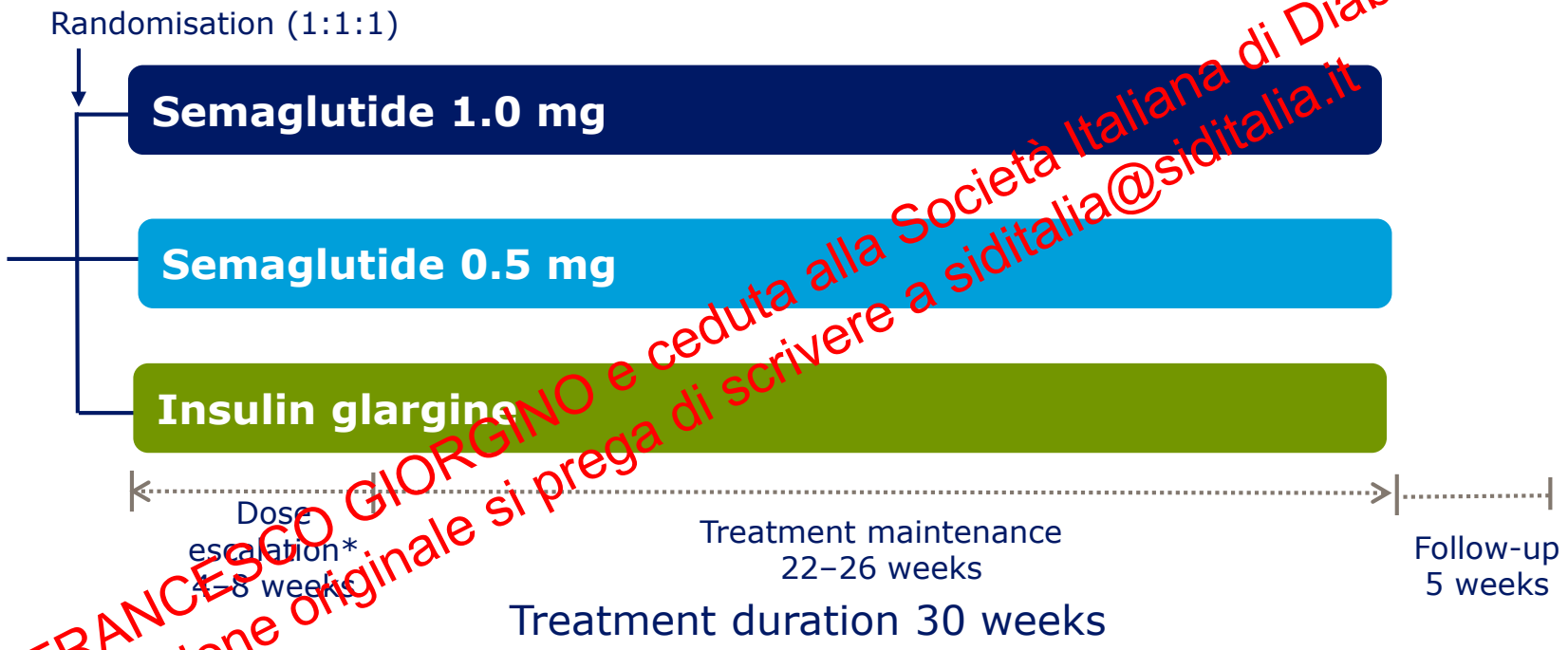
Adapted from: Abd El Aziz MS, et al. *Diabetes Obes Metab*. 2017;19:216-227.

SUSTAIN 4

TRIAL DESIGN

1,089 subjects with T2D

- Age ≥18 years
- HbA_{1c} 7.0–10.0%
- Insulin-naïve subjects on stable diabetes treatment with metformin or metformin and SU for ≥90 days prior to screening
- eGFR >30 mL/min/1.73 m^2



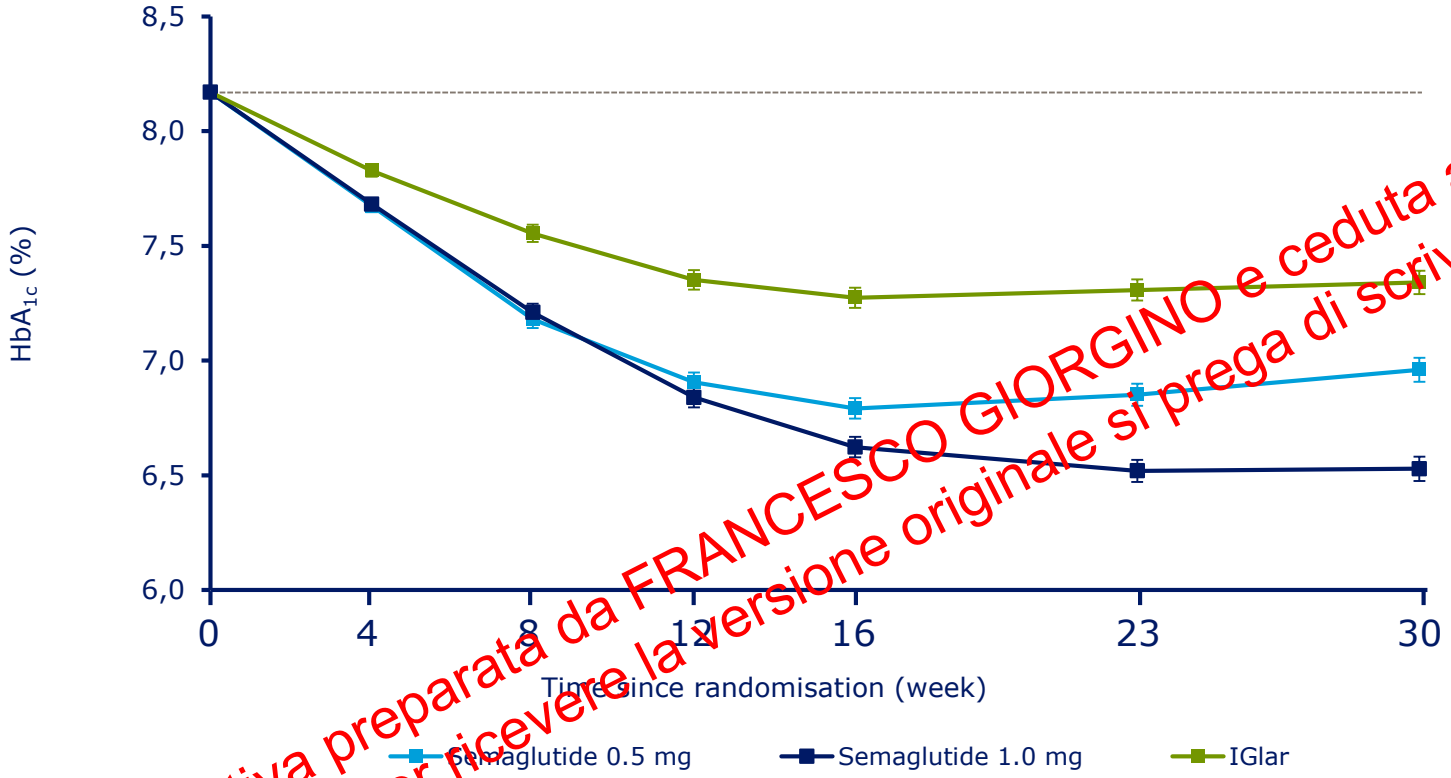
Trial information

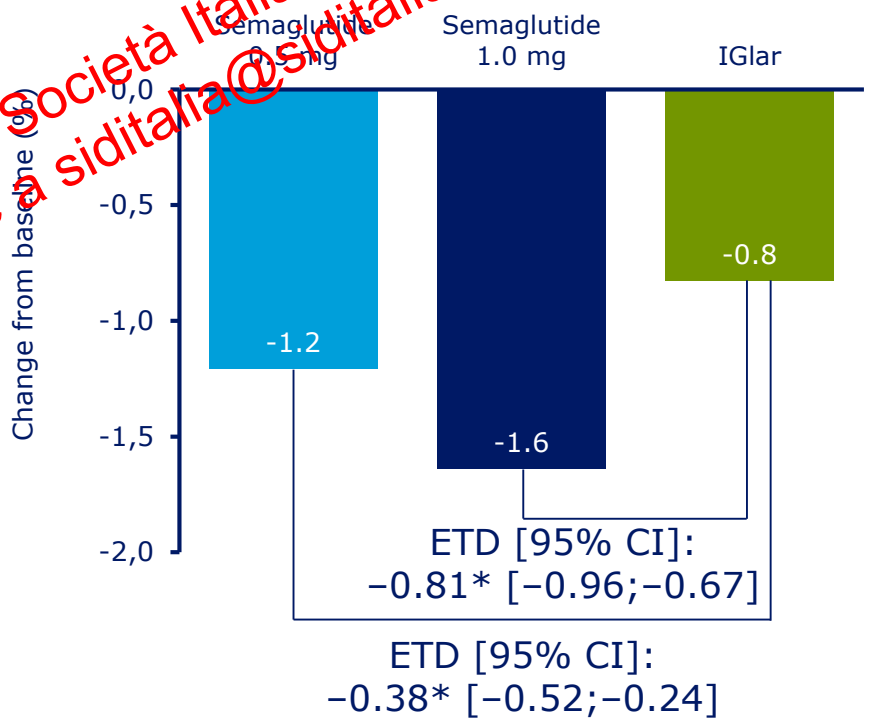
- Randomised, open-label, active-controlled, parallel-group, multicentre, multinational, three-armed trial
- Conducted in Argentina, Croatia, France, Germany, India, Macedonia, Mexico, Netherlands, Romania, Slovakia, Slovenia, South Africa, UK, USA
- Subjects were stratified based on their pre-trial oral diabetes treatment (metformin or metformin and SU)

*Semaglutide dose escalation from starting dose of 0.25 mg, dose doubled each step until trial dose achieved. www.ClinicalTrials.gov (NCT02128932).
SU, sulphonylurea; eGFR, estimated glomerular filtration rate.
Aroda VR et al. *Lancet Diabetes Endocrinol* 2017;5:355–366.

SUSTAIN 4: Change in HbA_{1c}

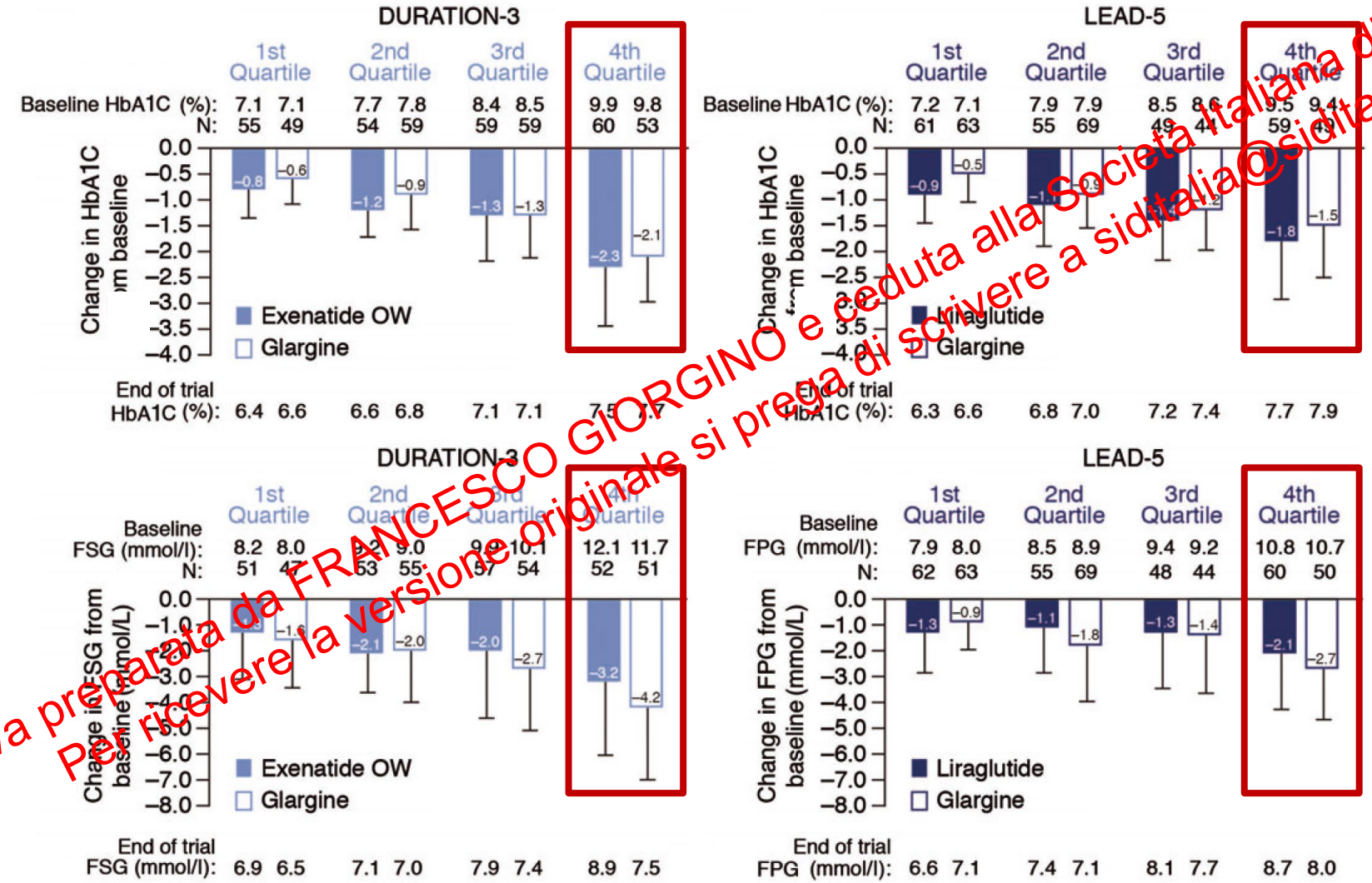
Overall mean at baseline: 8.2%





*Indicates significance (p-value <0.0001). 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.
CI, confidence interval; IGlar, insulin glargine; ETD, estimated treatment difference.
Aroda VR et al. *Lancet Diabetes Endocrinol* 2017;5:355–366.

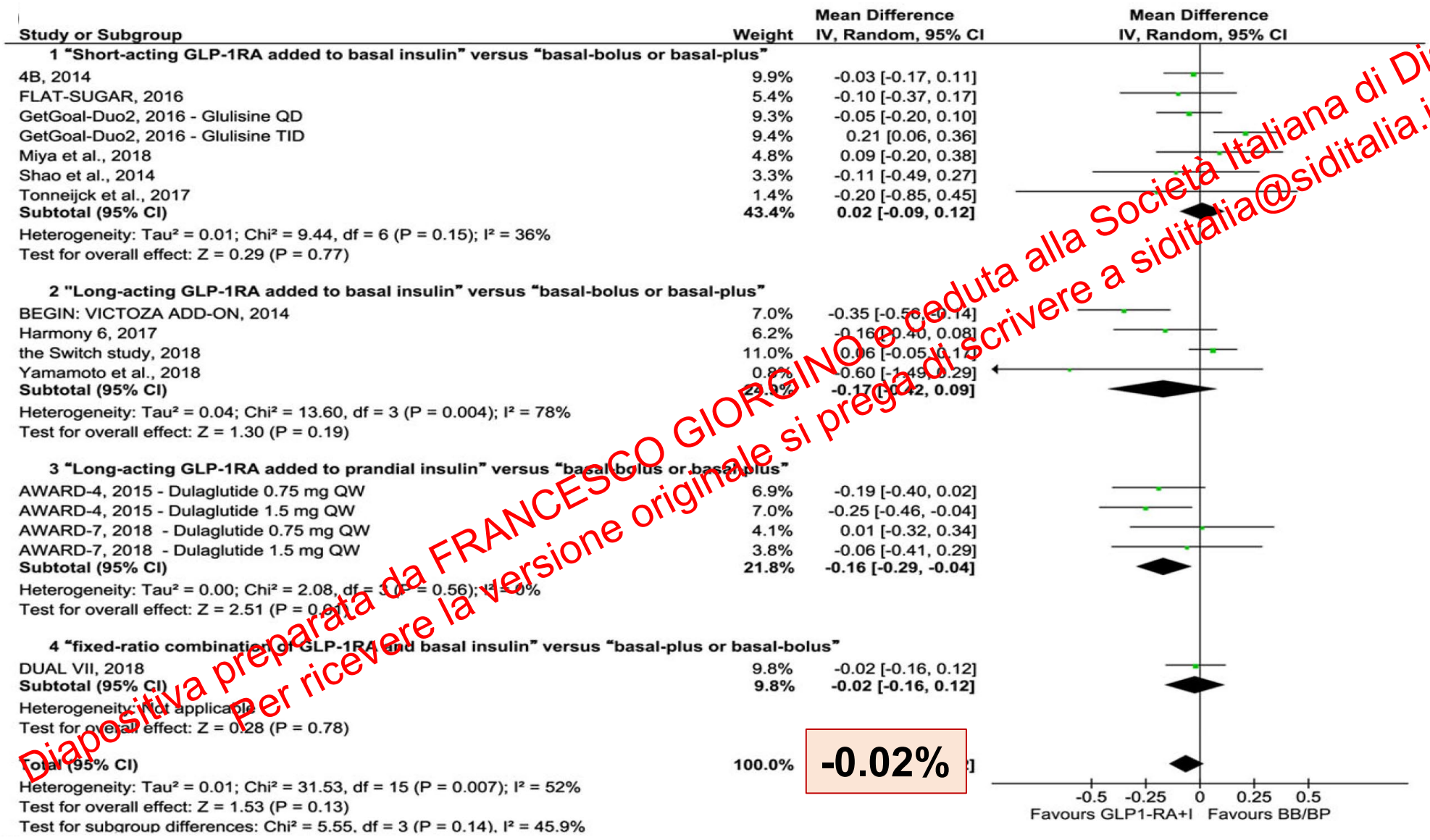
GLP-1 RA vs. Basal Insulin in T2DM: HbA_{1c} Reduction According to Baseline HbA_{1c}



FPG, fasting plasma glucose; FSG, fasting serum glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin OW, once weekly, T2DM, type 2 diabetes mellitus

Buse JB, et al. *Diabetes Obes Metab* 2015;17:145–151

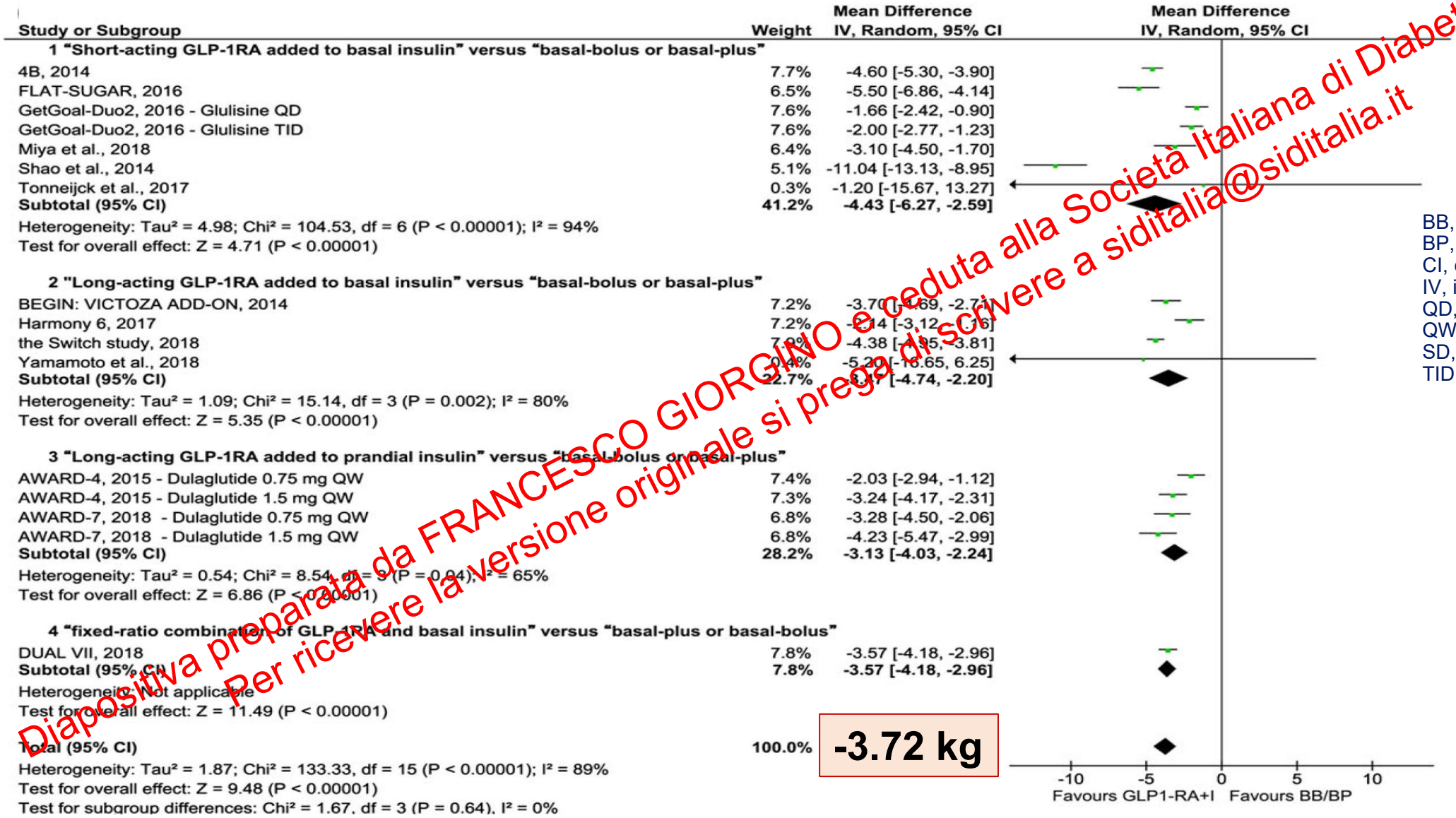
GLP-1 RA Added to Insulin vs Basal-bolus or Basal-plus Insulin Therapy in Type 2 Diabetes Mellitus: HbA1c



BB, basal-bolus;
BP, basal-plus;
CI, confidence interval;
IV, inverse variance;
QD, once daily;
QW, once weekly;
SD, standard deviation;
TID, three times daily

Castellana M, Cignarelli A, Brescia F, Laviola L, Giorgino F. Diabetes Metab Res Rev. 2019 Jan;35(1):e3082.

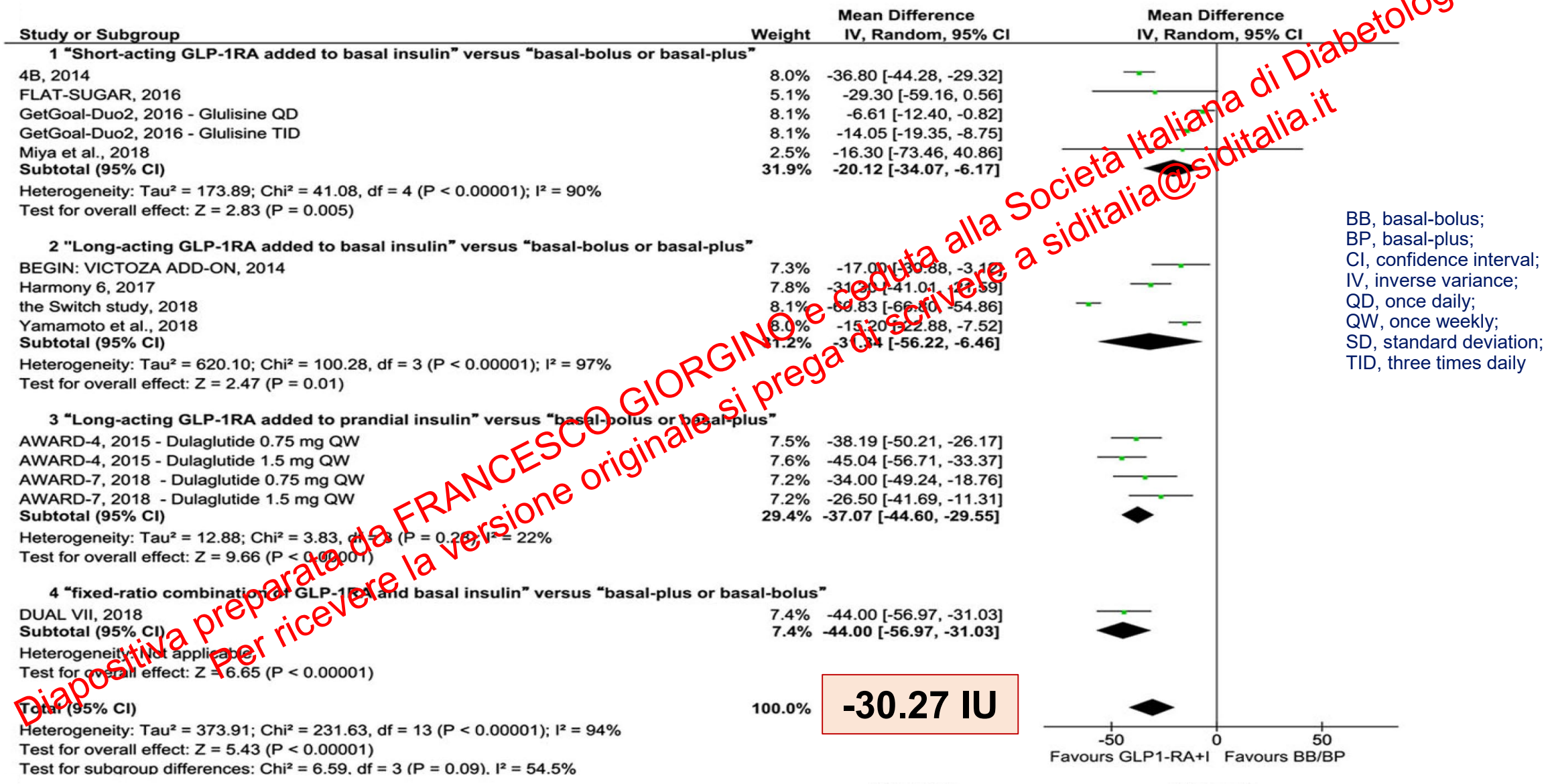
GLP-1 RA Added to Insulin vs Basal-bolus or Basal-plus Insulin Therapy in Type 2 Diabetes Mellitus: Body Weight



BB, basal-bolus;
BP, basal-plus;
CI, confidence interval;
IV, inverse variance;
QD, once daily;
QW, once weekly;
SD, standard deviation;
TID, three times daily

Castellana M, Cignarelli A, Brescia F, Laviola L, Giorgino F. Diabetes Metab Res Rev. 2019 Jan;35(1):e3082.

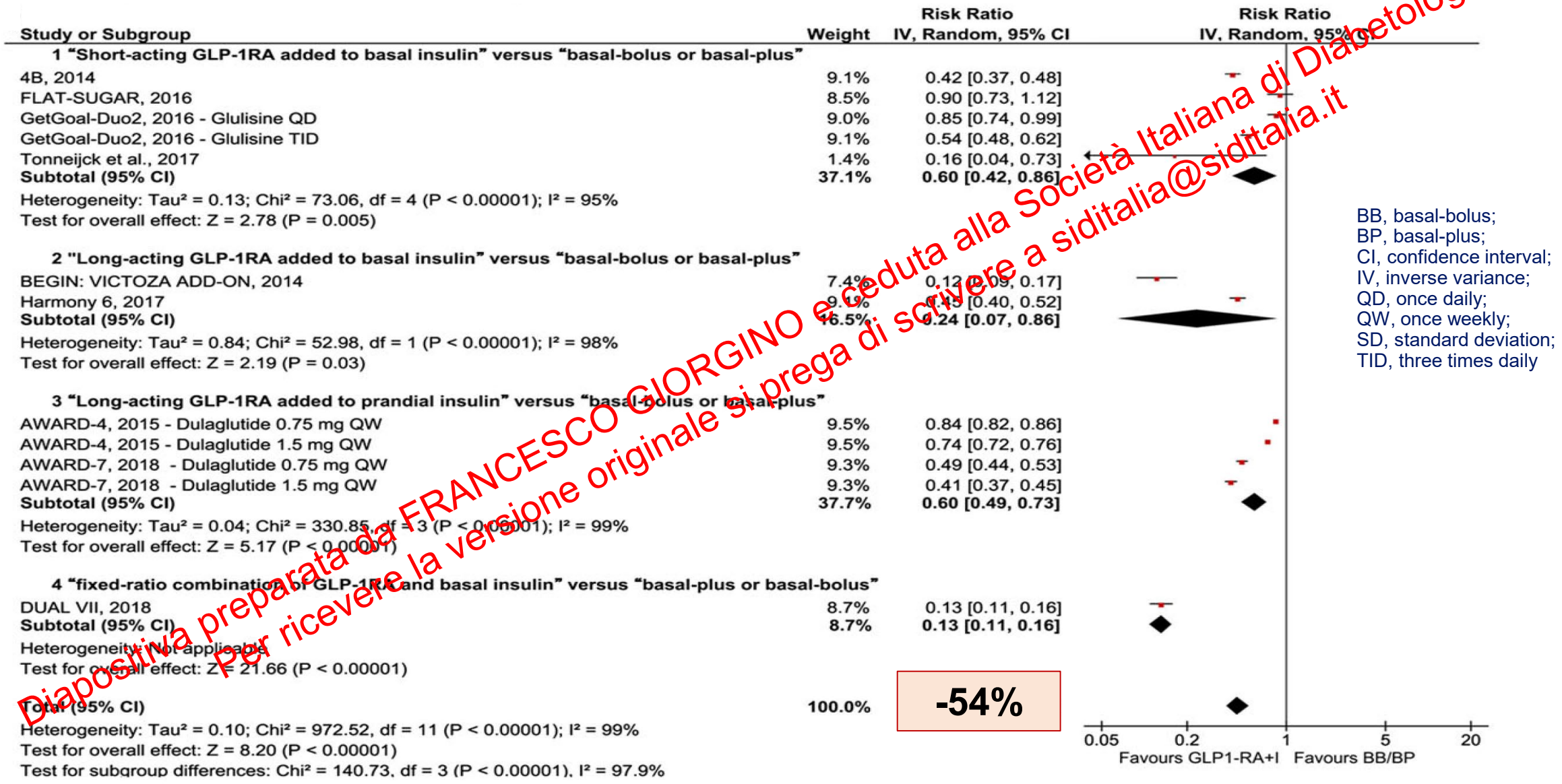
GLP-1 RA Added to Insulin vs Basal-bolus or Basal-plus Insulin Therapy in Type 2 Diabetes Mellitus: Daily Insulin Dose at Follow-up



BB, basal-bolus;
BP, basal-plus;
CI, confidence interval;
IV, inverse variance;
QD, once daily;
QW, once weekly;
SD, standard deviation;
TID, three times daily

Castellana M, Cignarelli A, Brescia F, Laviola L, Giorgino F. Diabetes Metab Res Rev. 2019 Jan;35(1):e3082.

GLP-1 RA Added to Insulin vs Basal-bolus or Basal-plus Insulin Therapy in Type 2 Diabetes Mellitus: Incidence of Hypoglycemia



BB, basal-bolus;
BP, basal-plus;
CI, confidence interval;
IV, inverse variance;
QD, once daily;
QW, once weekly;
SD, standard deviation;
TID, three times daily

Castellana M, Cignarelli A, Brescia F, Laviola L, Giorgino F. Diabetes Metab Res Rev. 2019 Jan;35(1):e3082.

Proven CV Benefit of GLP-1RA

ADA-EASD Consensus 2018
Davies MJ et al. *Diabetologia* & *Diabetes Care*. 2018

Among patients with type 2 diabetes who have established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists with proven cardiovascular benefit are recommended as part of glycaemic management

«Strongest evidence for **Liraglutide** > **Semaglutide** > **Exenatide ER**»

ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; ER, extended release.

Davies MJ, et al. *Diabetologia*. 2018;61(12):2461–2498; Davies MJ, et al. *Diabetes Care*. 2018;41(12):2669–2701.

Effects of GLP-1 or GLP-1 Receptor Agonists in Human Studies, with Potential Impact on Cardiovascular Function

Effect	GLP-1 [7-36 amide or 7-37]	Liraglutide	Exenatide
Cardioprotection against ischemia	↑ LVEF; ↑ regional wall motility	preserved LVEF after PCI/NSTEMI	↑ salvage index after STEMI; ↓ infarct size

ACh, acetylcholine; CAD, coronary artery disease; CPC, cardiac progenitor cell; CV, cardiovascular; EC, endothelial cell; eNOS, endothelial nitric oxide synthase; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HUVEC, human umbilical vein endothelial cell; IL, interleukin; LVEF, left ventricular ejection fraction; NO, nitric oxide; ns, not significant; NSTEMI, non ST-elevated myocardial infarction; PCI, percutaneous coronary intervention; T2D, type 2 diabetes mellitus; TNF, tumour necrosis factor.
Adapted from Nauck MA, et al. *Circulation.* 2017;136:849–870

Completed GLP-1 RA CVOTs

	Key inclusion criteria	HbA_{1c} (%)	Median follow-up duration (y)	Drug exposure time (y)	Primary End point
ELIXA (1) N=6068	ACS within 180 days ≥30y	5.5-11.0	Lixisenatide 2.1 / Placebo	1.9 / 2.0	MACE-4 (non-inferiority)
LEADER® (2) Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results N=9340	≥50y with CVD/renal dysfunction/HF, or ≥60y with CV RFs	≥7.0	Liraglutide 3.8 / Placebo	3.5 / 3.5	MACE-3 (non-inferiority for safety/ superiority for efficacy)
SUSTAIN-6 (3) N=3297	≥50y with CVD, or ≥60y with subclinical CVD	≥7.0	Semaglutide 2.1 / Placebo	1.8 / 1.9	MACE-3 (non-inferiority)
EXSCEL (4) N=14752	Established CVD as well as primary prevention (70/30 split), ≥18y	6.5-10.0	Exenatide 3.2 / Placebo	2.4 / 2.3	MACE-3 (non-inferiority for safety/ superiority for efficacy)
HARMONY (5) N=9463	≥40y with established CVD	≥7.0	Albiglutide 1.6 / Placebo	1.4 / 1.3	MACE-3 (non-inferiority for safety/ superiority for efficacy)
REWIND (6,7) N=9901	≥50y with established clinical vascular disease, ≥55y with subclinical vascular disease, or ≥60y with ≥2 CV RFs	≤9.5	Dulaglutide 6.5 / Placebo	5.3 / 5.4	MACE-3 (non-inferiority for safety/ superiority for efficacy)
PIONEER 6 (8) N=3183	≥50y with CVD, or ≥60y with CV RFs	≥7.0	Semaglutide 1.4 / Placebo	NR / NR	MACE-3 (non-inferiority for safety)

ACS, acute coronary syndrome; CV, cardiovascular; CVD, CV disease; CVOTs, cardiovascular outcomes trials; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; HF, heart failure; MACE, major adverse CV events; NR, not reported; R, randomisation; RFs, risk factors; y, years.

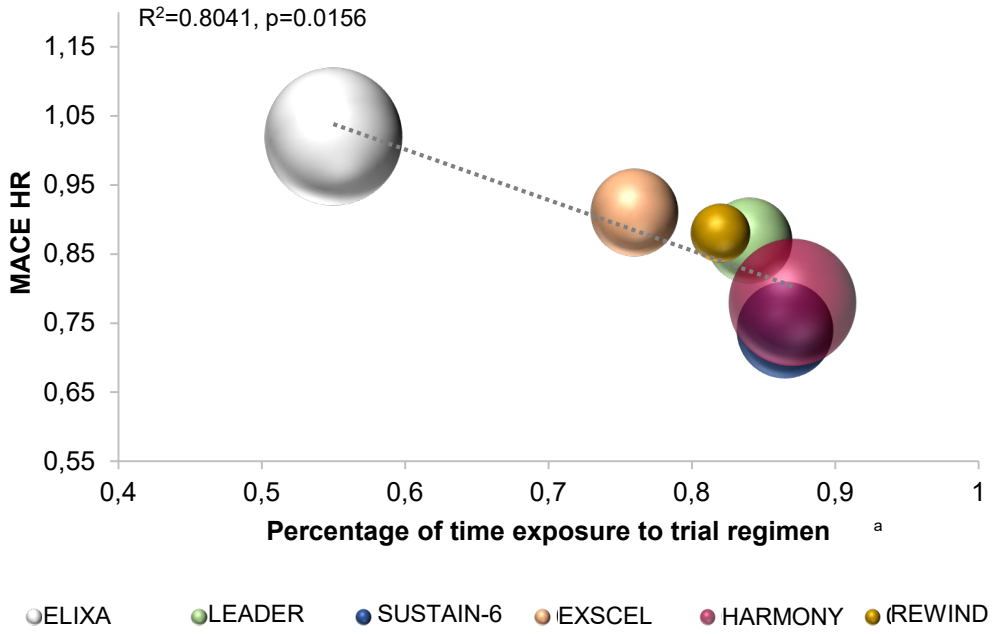
[1]Pfeffer MA, et al. *N Engl J Med* 2015;373:2247–2257
[2]Marso SP, et al. *N Engl J Med* 2016;375:311–322
[3]Marso SP, et al. *N Engl J Med* 2016;375:1834–1844
[4]Holman RR, et al., *N Engl J Med* 2017;377:1228–1239
[5]Hernandez AF, et al. *Lancet* 2018;392(10157):1519–1529
[6]Gerstein HC, et al. *Diabetes Obes Metab* 2018;20:42–49
[7]https://clinicaltrials.gov/ct2/show/NCT01394952
[8]Husain M, et al *N Eng J Med* 2019

	ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY	REWIND	PIONEER 6	
Diabetes duration (years)	9.3	12.8	13.9	12	14.1	10	14.9	Baseline Risk Level
Baseline HbA1c (%)	7.6	8.7	8.7	8.0	8.7	7.3	8.2	
Baseline BMI (kg/m²)	30.1	32.5	32.8	31.7	32.3	32.3	32.3	
History of CVD (%)	100	81.3	83	73.1	100	31.4	84.6	
Hypertension (%)	76.3	90	92.8	90.3	86.4	93.2	95.3	
eGFR <60 (%)	23.2	21.7	28.5	21.7	22.6	22.2	27	
Mortality rate (events/100 patient-yr)	3.1; 3.3	2.1; 2.5	1.8; 1.7	2.0; 2.3	2.4; 2.5	2.1; 2.3	1.1; 2.2	
MACE rate (events/100 patient-yr)	6.4; 6.3	3.4; 3.9	3.2; 4.4	3.7; 4.0	4.6; 5.9	2.3; 2.6	2.9; 3.7	
MACE HR	1.02 [95% CI 0.89–1.17])	**0.87 [95% CI 0.78–0.97] p=0.01**	**0.74 [95% CI 0.58–0.95] p=0.02**	0.91 [95% CI 0.83–1.00] p=0.06	**0.78 [95% CI 0.68–0.90] p=0.0006**	**0.88 [95% CI 0.79–0.99] p=0.026**	0.79 [95% CI 0.57-1.11) p=0.17	Main Outcomes
All-cause mortality HR	0.94 [95% CI 0.78–1.13]	0.85 [95% CI 0.74–0.97]	1.05 [95% CI 0.74 –1.50]	0.86 [95% CI 0.77–0.97]	0.95 [95% CI 0.79–1.16]	0.90 [95% CI 0.80–1.01]	0.51 [95% CI 0.31-0.84)	

Pfeffer, M.A. *et al.* (2015) *N. Engl. J. Med.* 373, 2247–2257; Marso, S.P. *et al.* (2016) *N. Engl. J. Med.* 375, 311–322; Marso, S.P. *et al.* (2016) *N. Engl. J. Med.* 375, 1834–1844; Holman, R.R. *et al.* (2017) *N. Engl. J. Med.* 377, 1228–1239; Hernandez, A.F. *et al.* (2018) *Lancet* 392, 1519–1529; Gerstein, H.C. *et al.* (2019) *Lancet* DOI: 10.1016/S0140-6736(19)31149-3; Husain, M. *et al.* (2019) *N. Engl. J. Med.* DOI: 10.1056/NEJMoa1901118.

Correlation between Percentage of Time Exposure to Study Drug and MACE ARR and HR

- **Time of exposure to the investigational GLP-1 RA is positively correlated with the MACE ARR and, accordingly, negatively correlated with the MACE HR.**
  (Actual exposure to lixisenatide in ELIXA is estimated to be approximately 56%)
- **Baseline CV risk level does not seem to be related to changes in CV outcomes.**
  (Sphere size represents the baseline CV risk of the study population, expressed as MACE incidence rate in the control arm [# events per 100 patient-year])



ARR, absolute risk reduction; CV; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; MACE, major adverse cardiovascular event.

Caruso I et al. *Trends Endocrinol Metab, under revision 2019*

Meta-analysis of SGLT2i trials on MACE or hHF/CV death stratified by the presence of established CVD

MACE

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687/7020	2333/7020	772	37·4	43·9	29·4		0·86 (0·74–0·99)
CANVAS Program	3756/6656	2900/6656	796	34·1	41·3	32·4		0·82 (0·72–0·95)
DECLARE-TIMI 58	3474/6974	3500/6974	1020	36·8	41·0	38·2		0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)								**0·86 (0·80–0·93)**
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	215	15·8	15·5	25·9		0·98 (0·74–1·30)
DECLARE-TIMI 58	5108/10 186	5078/10 186	539	13·4	13·3	74·1		1·01 (0·86–1·20)
Fixed effects model for multiple risk factors (p=0·98)								**1·00 (0·87–1·16)**

0·35 0·50 1·00 2·50

Favours treatment Favours placebo

hHF/CV death

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687/7020	2333/7020	463	19·7	30·1	30·9		0·66 (0·55–0·79)
CANVAS Program	3756/6656	2900/6656	524	21·0	27·4	32·8		0·77 (0·65–0·92)
DECLARE-TIMI 58	3474/6974	3500/6974	597	19·9	23·9	36·4		0·83 (0·71–0·98
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)								**0·76 (0·69–0·84)**
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	128	8·9	9·8	30·2		0·83 (0·58–1·19)
DECLARE-TIMI 58	5108/10 186	5078/10 186	316	7·0	8·4	69·8		0·84 (0·67–1·04)
Fixed effects model for multiple risk factors (p=0·0634)								**0·84 (0·69–1·01)**

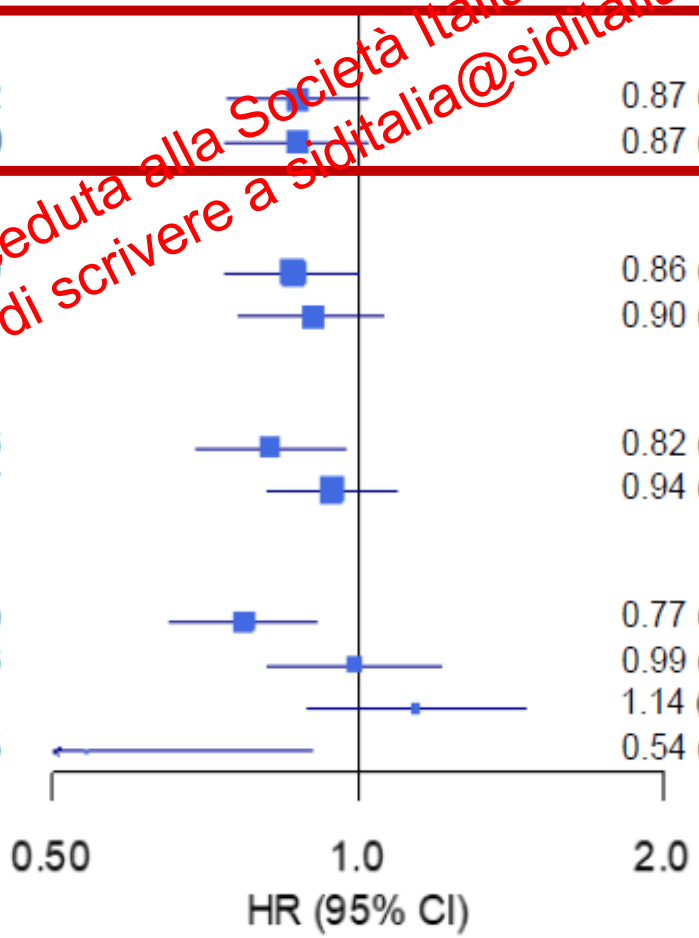
0·35 0·50 1·00 2·50

Favours treatment Favours placebo

Zelniker TA et al., Lancet 2018

REWIND: CV Composite in Prespecified Subgroups

Subgroups	Dulaglutide Events/Total (%)	Dulaglutide Rate/100 py	Placebo Events/Total (%)	Placebo Rate/100 py	Hazard Ratio 95% CI	P value for Interaction
History of CVD						
Prior CVD	280 /1560 (17.9)	3.7	315 /1554 (20.3)	4.2	0.87 (0.74-1.02)	
No Prior CVD	277 /3093 (8.9)	1.7	317 /3128 (10.1)	2.0	0.87 (0.74-1.02)	0.970
Baseline HbA1c						
≥ 7.2%	328 /2610 (12.6)	2.5	373 /2603 (14.3)	2.9	0.86 (0.74-1.00)	
< 7.2%	263 /2329 (11.3)	2.2	289 /2334 (12.4)	2.4	0.90 (0.76-1.06)	0.746
BMI (kg/m^2)						
≥ 32	254 /2281 (11.1)	2.1	308 /2302 (13.4)	2.6	0.82 (0.69-0.96)	
< 32	340 /2667 (12.7)	2.5	355 /2660 (13.4)	2.7	0.94 (0.81-1.09)	0.214
Region						
Europe	248 /2174 (11.4)	2.2	315 /2165 (14.5)	2.9	0.77 (0.65-0.90)	
Latin America	191 /1511 (12.6)	2.6	190 /1510 (12.6)	2.6	0.99 (0.81-1.21)	
USA/Canada	130 /1032 (12.6)	2.4	117 /1039 (11.3)	2.1	1.14 (0.89-1.47)	
Asia Pacific	23 /232 (9.9)	1.9	41 / 238 (17.2)	3.5	0.54 (0.32-0.89)	0.008



Gerstein, H.C. *et al.* Lancet 2019

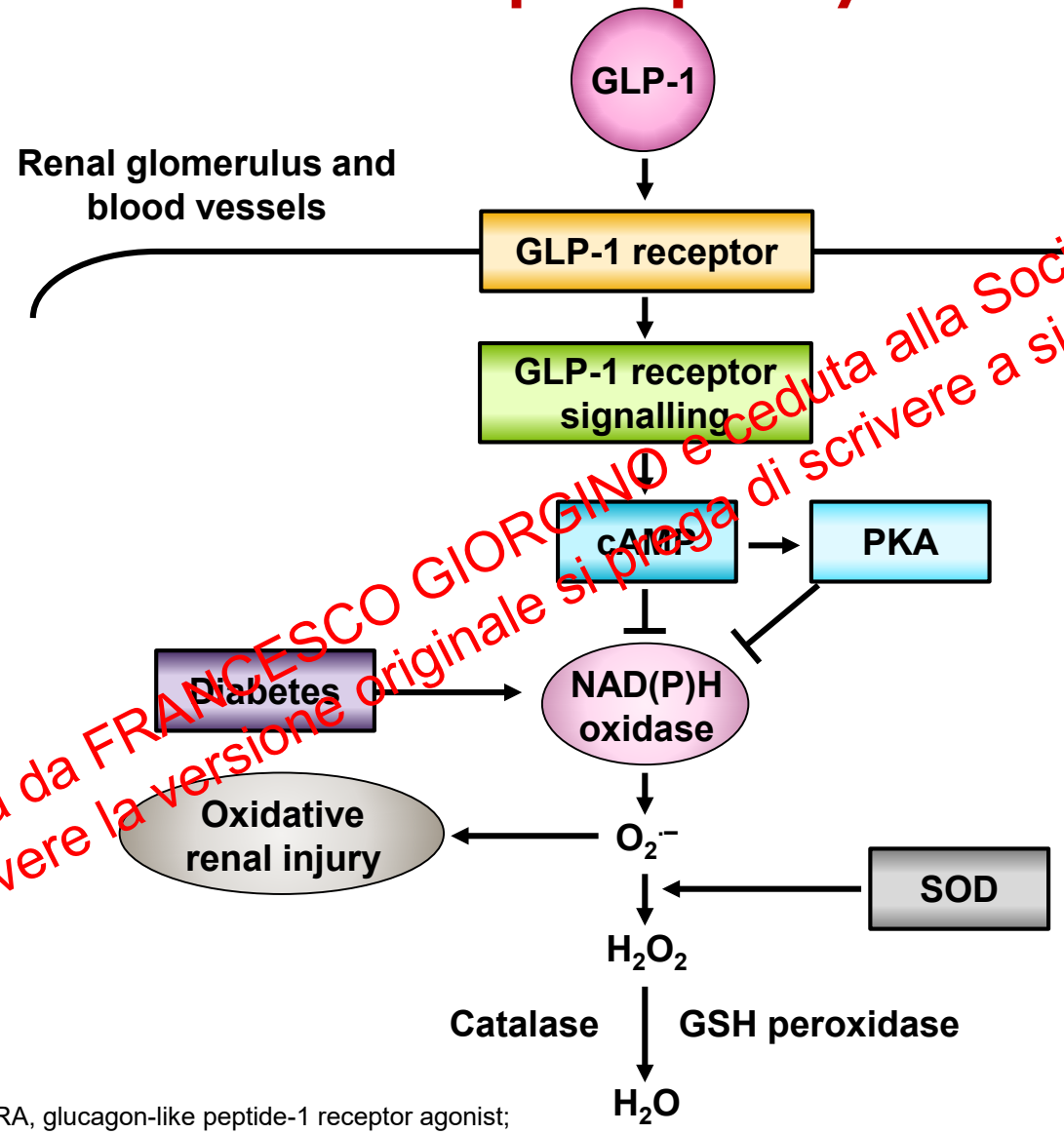
Consensus recommendation

ADA-EASD Consensus 2018
Davies MJ et al. *Diabetologia* & *Diabetes Care*. 2018

For patients with type 2 diabetes and CKD, with or without CVD, consider the use of an SGLT-2i shown to reduce CKD progression or, if contraindicated or not preferred, a GLP-1 RA shown to reduce CKD progression

ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes.
CKD, chronic kidney disease; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

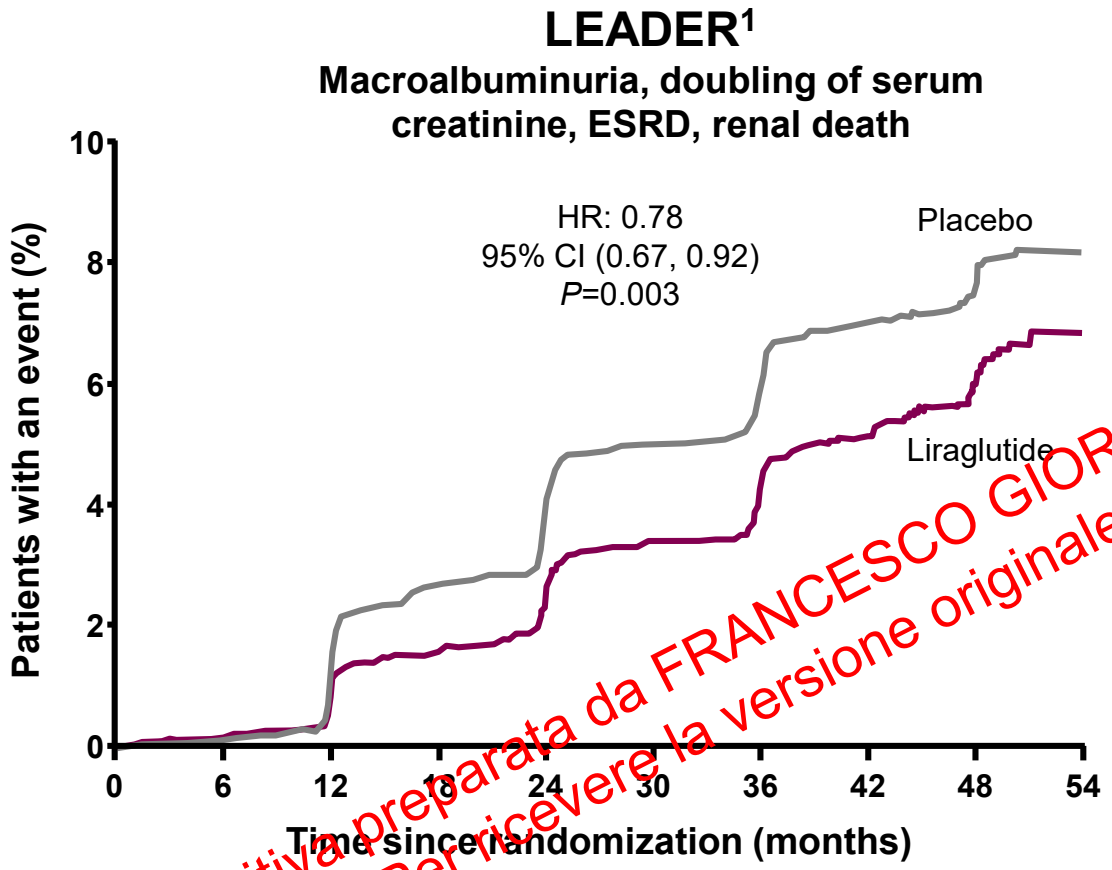
The Protective Roles of GLP-1 RA Signaling in Diabetic Nephropathy

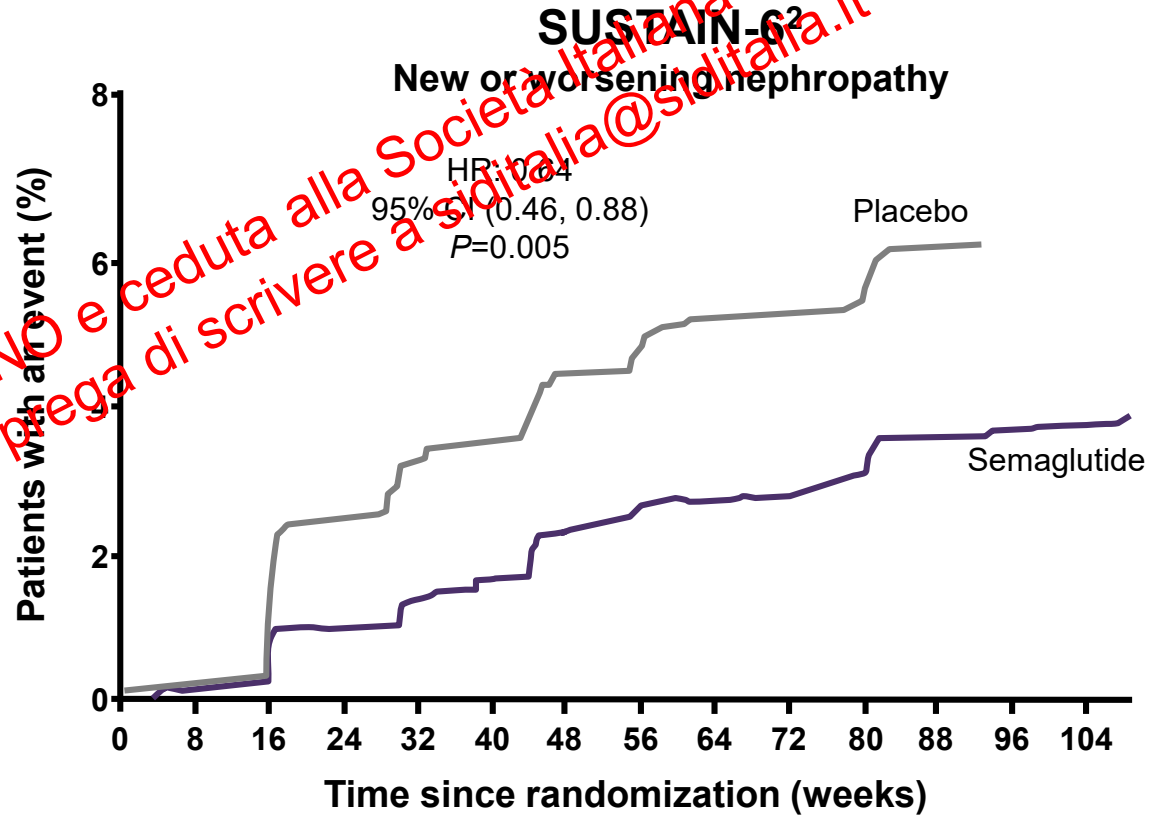


cAMP, cyclic adenosine monophosphate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; GSH, glutathione; NADPH, nicotinamide adenine dinucleotide phosphate; PKA, protein kinase A;SOD, superoxide dismutase

Fujita H, et al. *Kidney Int* 2014;85:579–89

GLP-1 RAs demonstrate significant improvement in renal outcomes versus placebo …



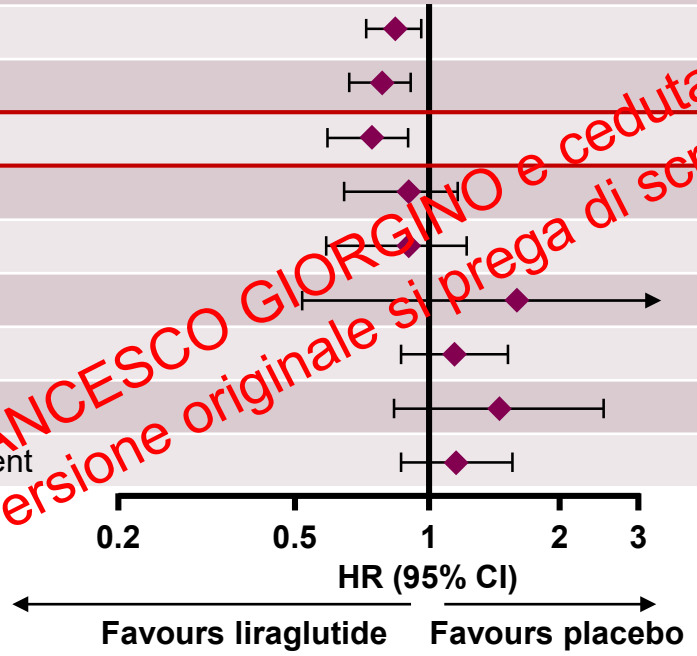


LEADER: Cumulative incidences were estimated with the Kaplan–Meier method, and the HRs with the Cox proportional-hazard regression model; the data analyses are truncated at 54 months because <10% of the patients had an observation time beyond 54 months
CI, confidence interval; ESRD, end-stage renal disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio

[1]Marso SP, et al. *N Engl J Med.* 2016;375:311–322; [2]Vilsbøll T. Presented at 52nd European Association for the Study of Diabetes Annual Meeting; 16th September 2016; Munich, Germany; OP S35.3

LEADER: time to first microvascular endpoints

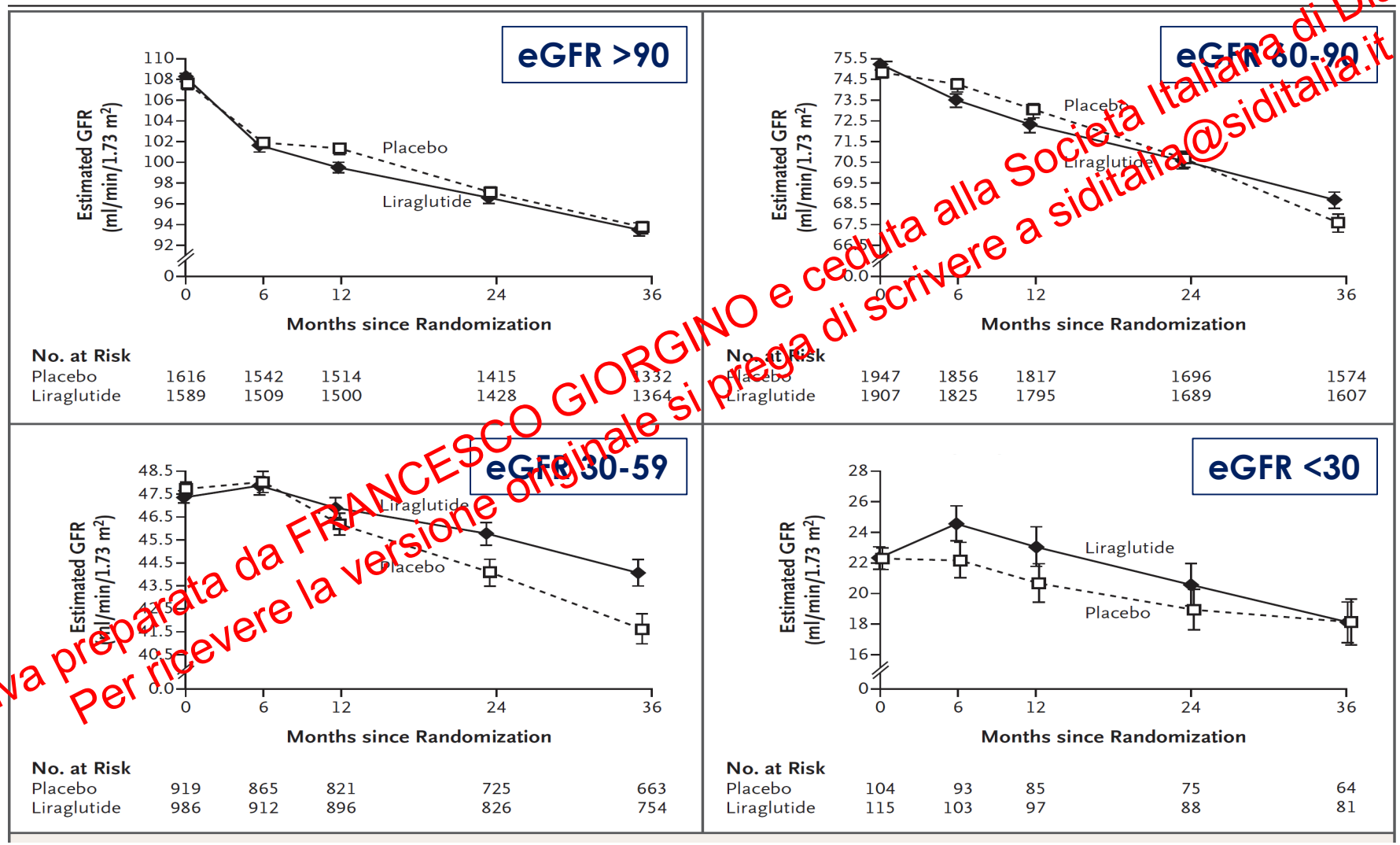
	HR (95% CI)	Liraglutide N	Liraglutide %	Placebo N	Placebo %
Number of patients		**4668**	**100**	**4672**	**100**
Microvascular endpoint	**0.84 (0.73, 0.97)**	**355**	**7.6**	**416**	**8.9**
Renal event	**0.78 (0.67, 0.92)**	**268**	**5.7**	**337**	**7.2**
New onset of persistent macroalbuminuria[a]	0.74 (0.60, 0.91)	161	3.4	215	4.6
Persistent doubling of serum creatinine[b]	0.88 (0.66, 1.18)	87	1.9	97	2.1
Need for continuous renal replacement therapy	0.87 (0.61, 1.24)	56	1.2	64	1.4
Death due to renal disease	1.59 (0.52, 4.87)	8	0.2	5	0.1
Eye event	**1.15 (0.87, 1.52)**	**106**	**2.3**	**92**	**2.0**
Vitreous haemorrhage	1.45 (0.84, 2.50)	32	0.7	22	0.5
Treatment with photocoagulation or intravitreal agent	1.16 (0.87, 1.55)	100	2.1	86	1.8



Full analysis set. EAC-confirmed microvascular events including events with onset between date of randomisation and date of follow-up; Cox proportional hazard model adjusted for treatment; development of diabetes-related blindness was not analysed as an individual component because only one event was observed; [a]new onset of persistent macroalbuminuria: urine albumin ≥300 mg/g creatinine; [b]persistent doubling of serum creatinine level and eGFR ≤45 mL/min/1.73 m^2 per MDRD
CI, confidence interval; EAC, event adjudication committee; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MDRD, modification of diet in renal disease

Marso SP, et al. *N Engl J Med.* 2016;375:311–322

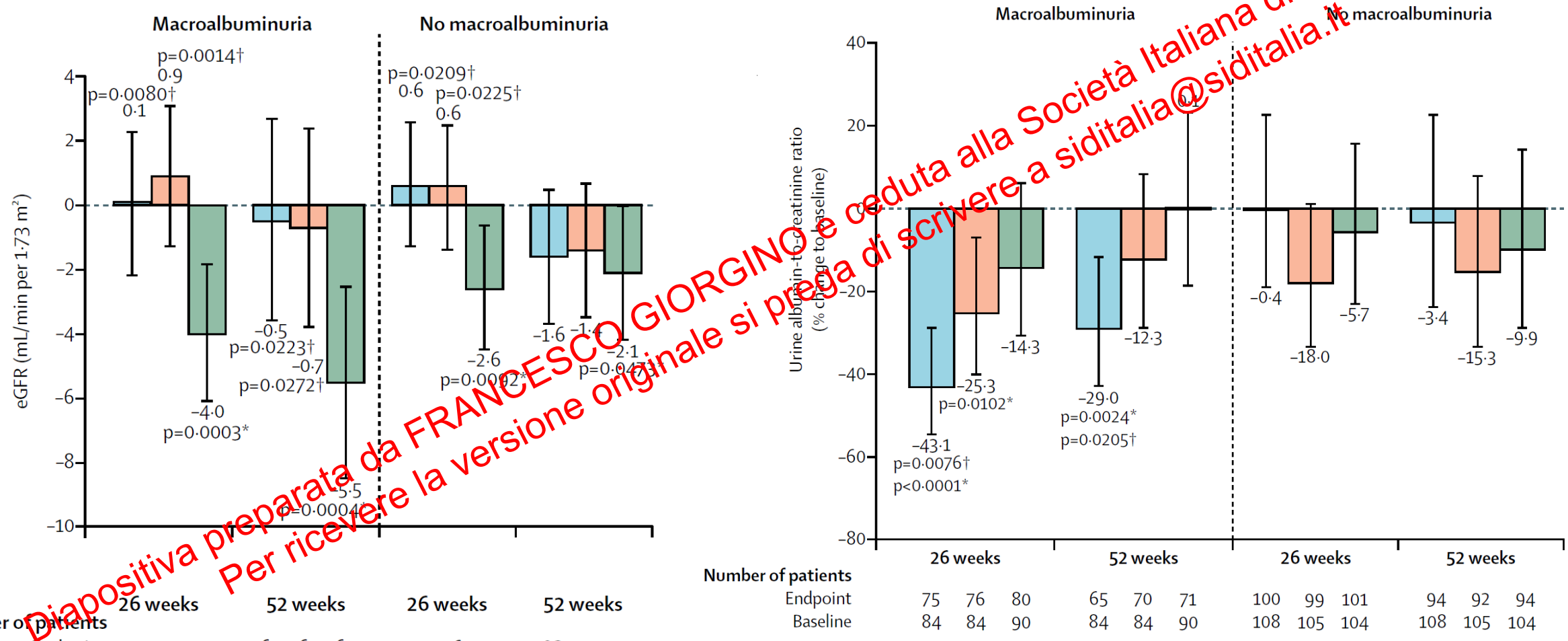
LEADER: Change in eGFR during the Trial in Subgroups Stratified According to eGFR at Baseline



eGFR, estimated glomerular filtration rate, ml/min/1.73m^2

Mann JFE, et al. *N Engl J Med* 2017;377:839–48

AWARD-7: Changes in eGFR and Albuminuria by Macroalbuminuria Status at Baseline

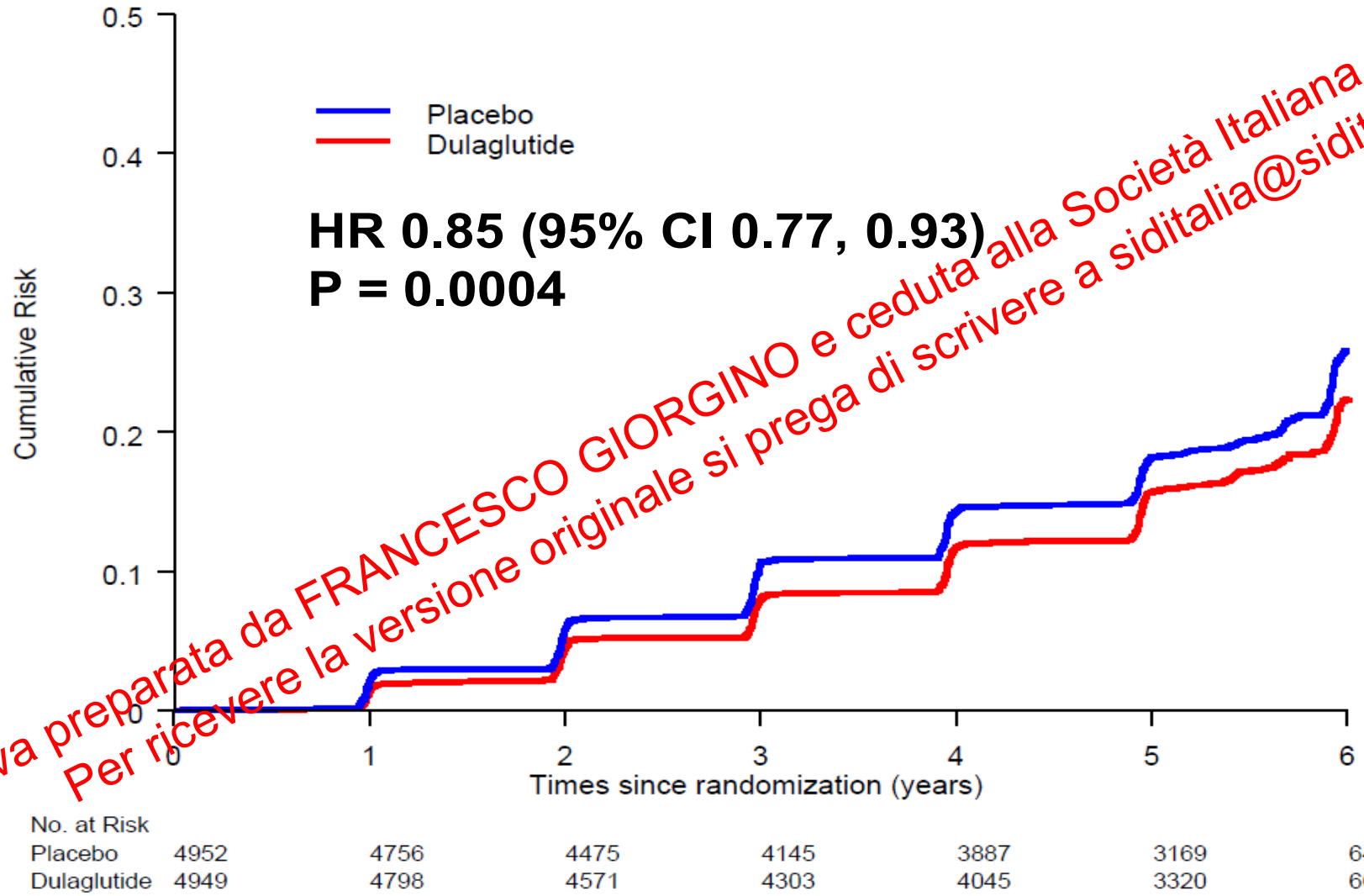


eGFR, estimated glomerular filtration rate

Tuttle KR, et al. *Lancet Diabetes Endocrinol* 2018;6:605–17

REWIND: Renal Composite Outcome

New Macroalbuminuria, 30% fall in eGFR, or Renal Replacement Rx

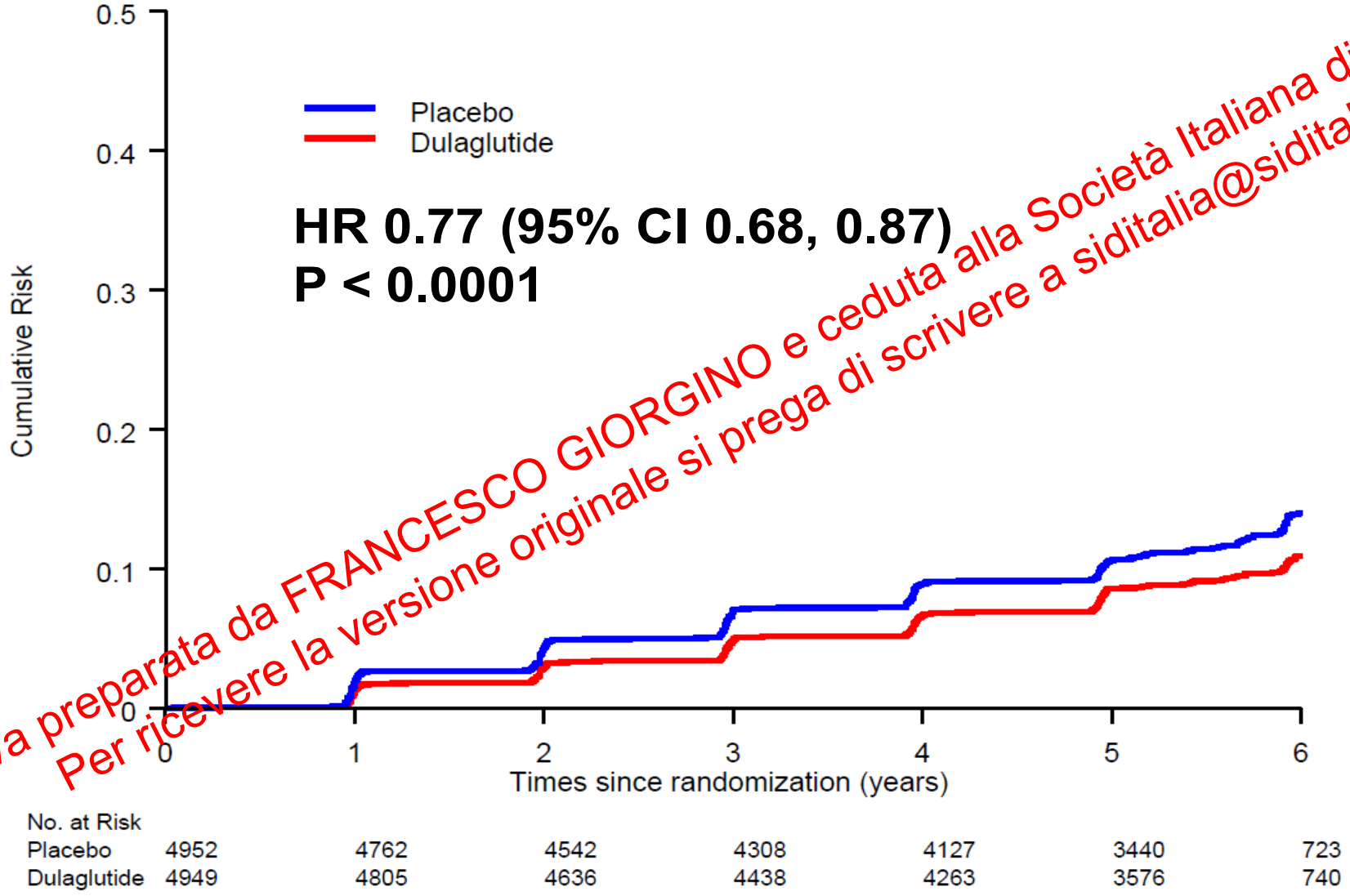


No. at Risk							
Placebo	4952	4756	4475	4145	3887	3169	641
Dulaglutide	4949	4798	4571	4303	4045	3320	667

Gerstein, H.C. *et al.* Lancet 2019

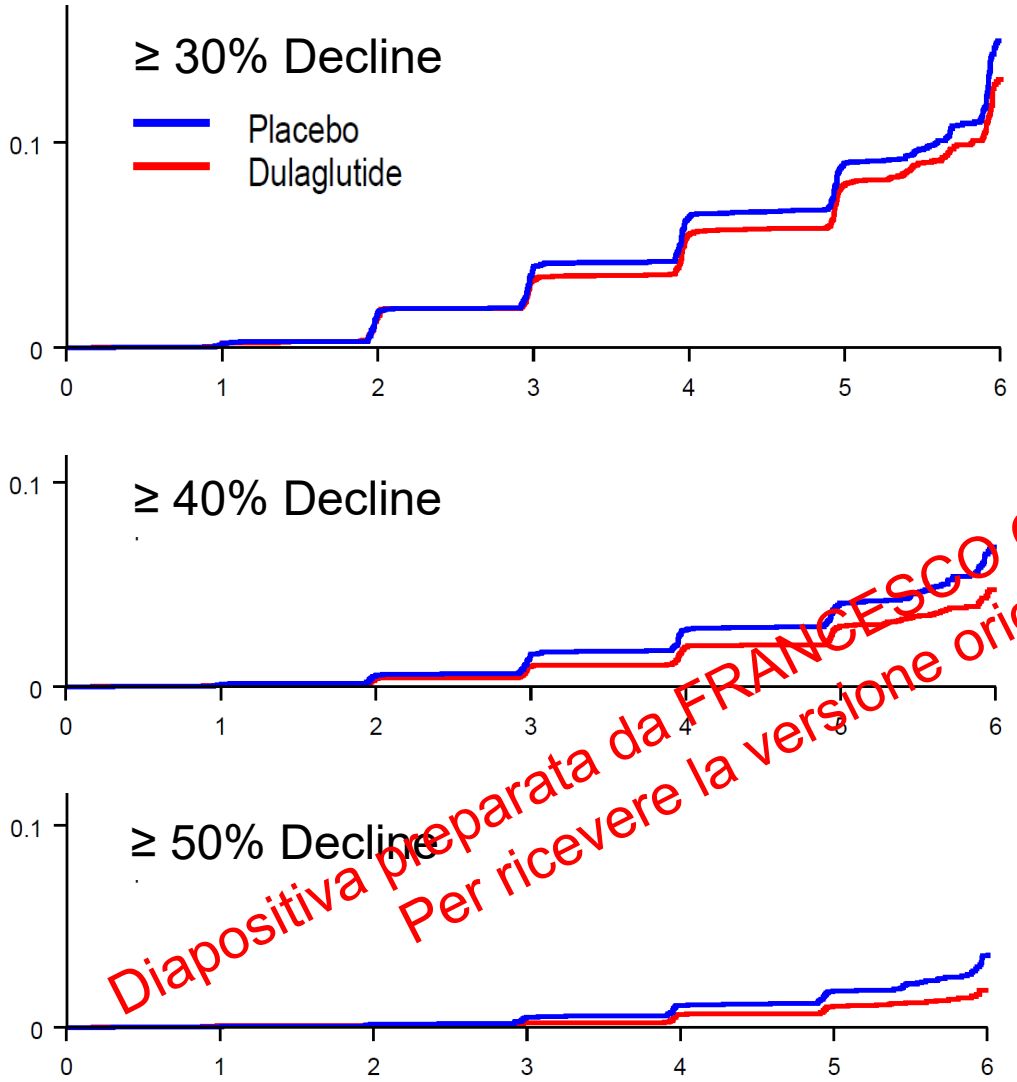
REWIND: Development of New Macroalbuminuria

New Urine Albumin/Creatinine > 33.9 mg/mmol (300 mg/g)



Gerstein, H.C. *et al.* Lancet 2019

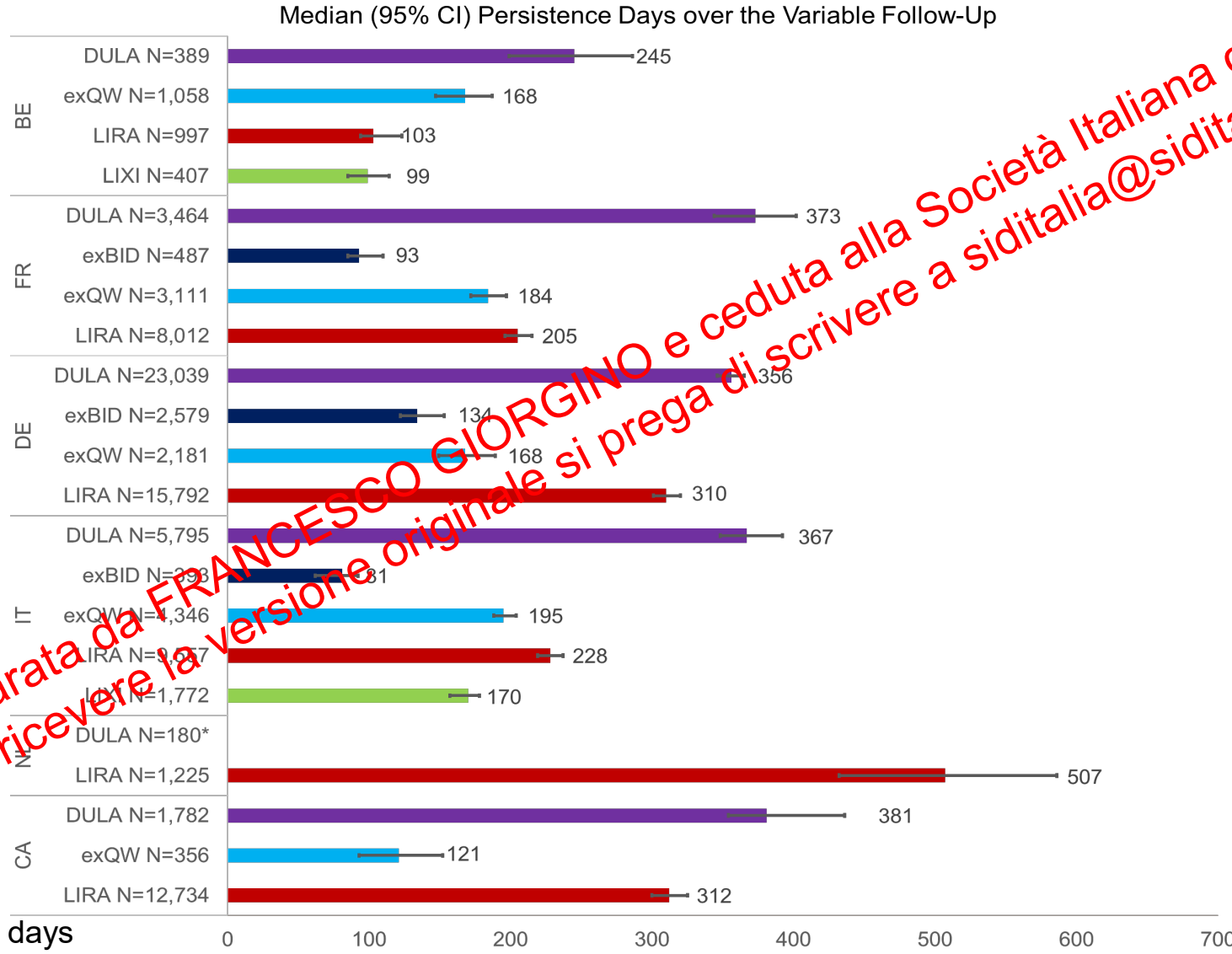
REWIND: Sustained eGFR Decline ≥ 30, 40 & 50%



	Sensitivity Analyses	
Sustained eGFR decline ≥ 30%	HR 0.89 (0.78, 1.01)	0.066
Sustained eGFR decline ≥ 40%	HR 0.70 (0.57, 0.85)	0.0004
Sustained eGFR decline ≥ 50%	HR 0.56 (0.41, 0.76)	0.0002

Gerstein, H.C. *et al.* Lancet 2019

Treatment Patterns among Patients with Type 2 Diabetes Initiating GLP-1RA: Median Persistence Days



Norrbacka K et al., ISPOR Europe 2018

Bari – Margherita Theater and Cathedral

Grazie!