Analoghi del GLP1 dopo la metformina

Raffaele Napoli

MfD *Medicina Interna ad indirizzo Diabetologico*

Dipartimento di Scienze Mediche Traslazionali, Università Federico II di Napoli

Disclosures

- Alpha Sigma
- Astra Zeneca
- Boehringer Ingelheim
- Eli Lilly
- MSD
- Mundipharma
- Novo Nordisk
- Sanofi

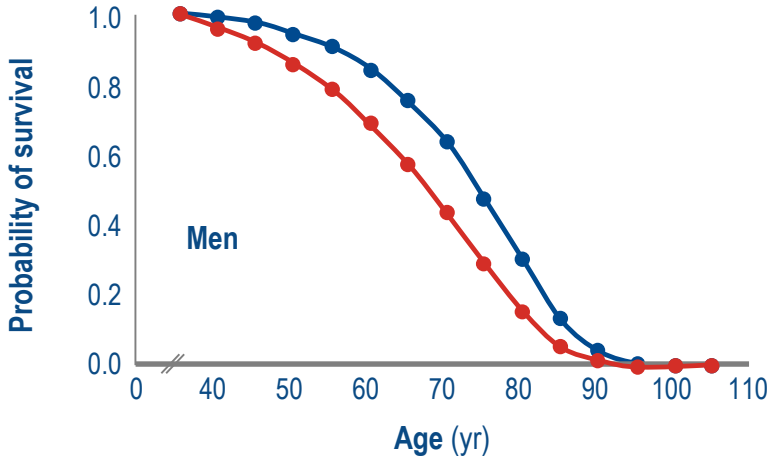
The NEW ENGLAND JOURNAL of MEDICINE

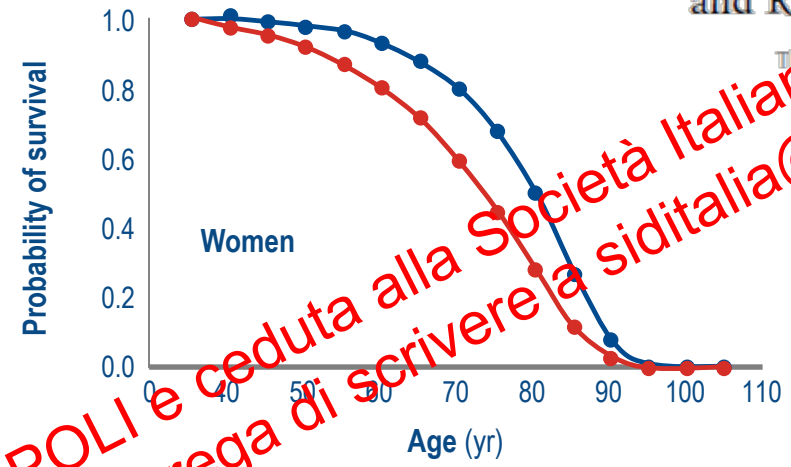
ORIGINAL ARTICLE

Diabetes Mellitus, Fasting Glucose, and Risk of Cause-Specific Death

The Emerging Risk Factors Collaboration*

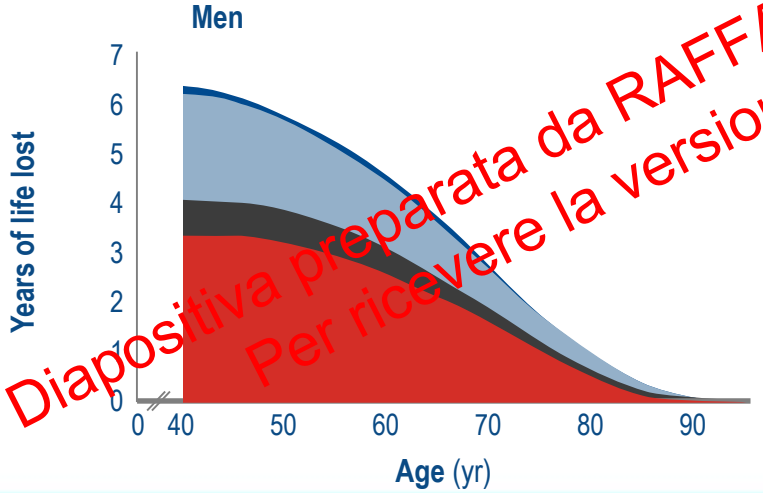
Estimated survival

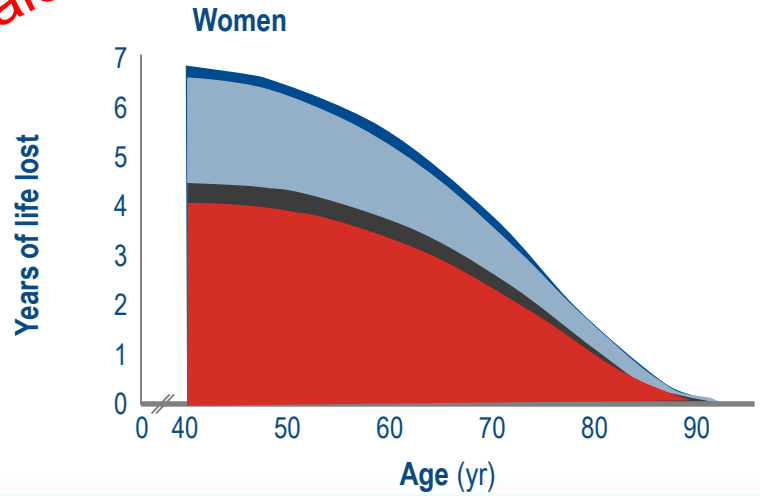




Diabetes
No diabetes

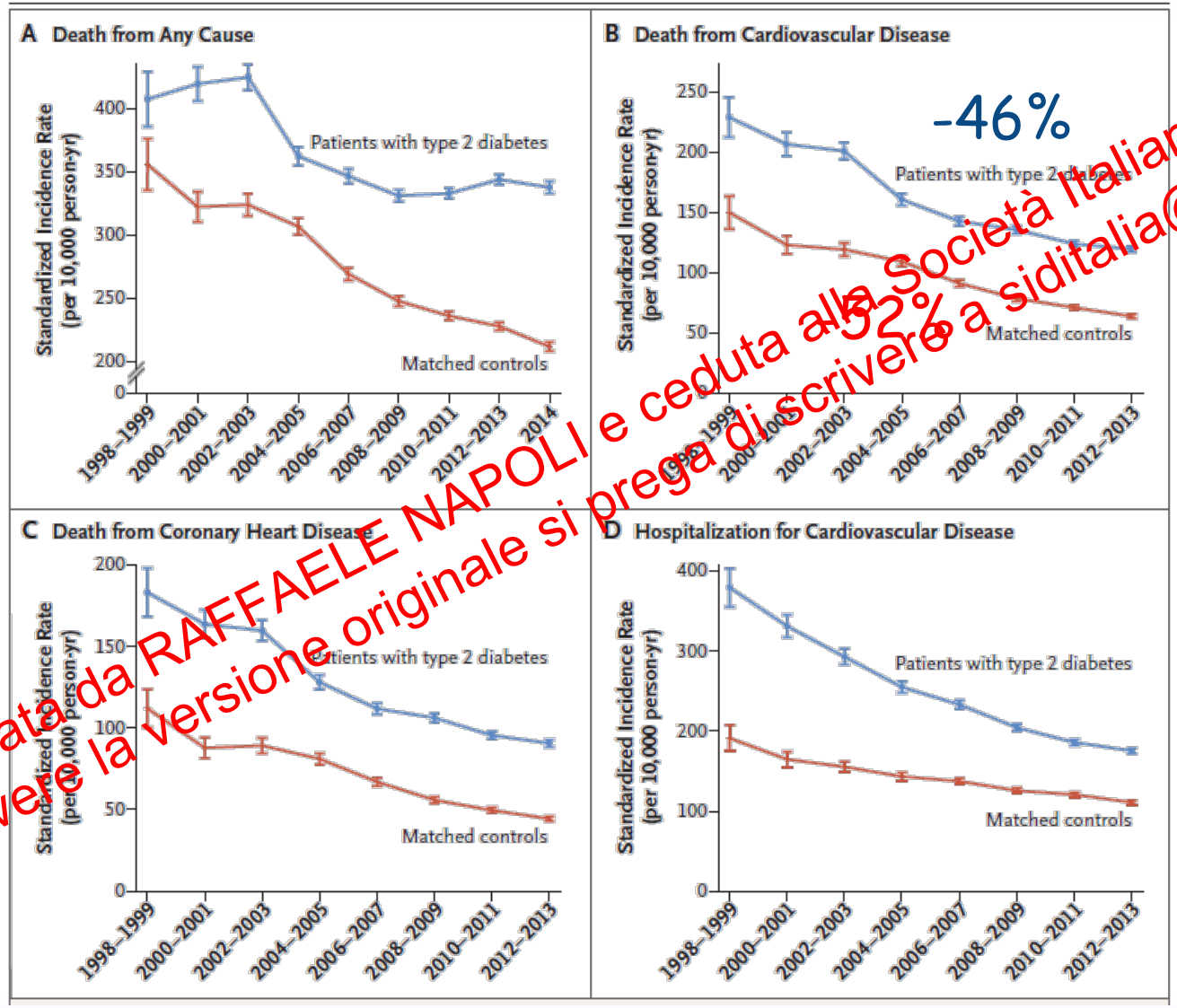
Estimated future years of life lost owing to diabetes





Death from unknown causes
Noncancer, nonvascular deaths
Cancer deaths
Vascular deaths

Diabetes-related deaths in the Swedish NDR, 1998-2014

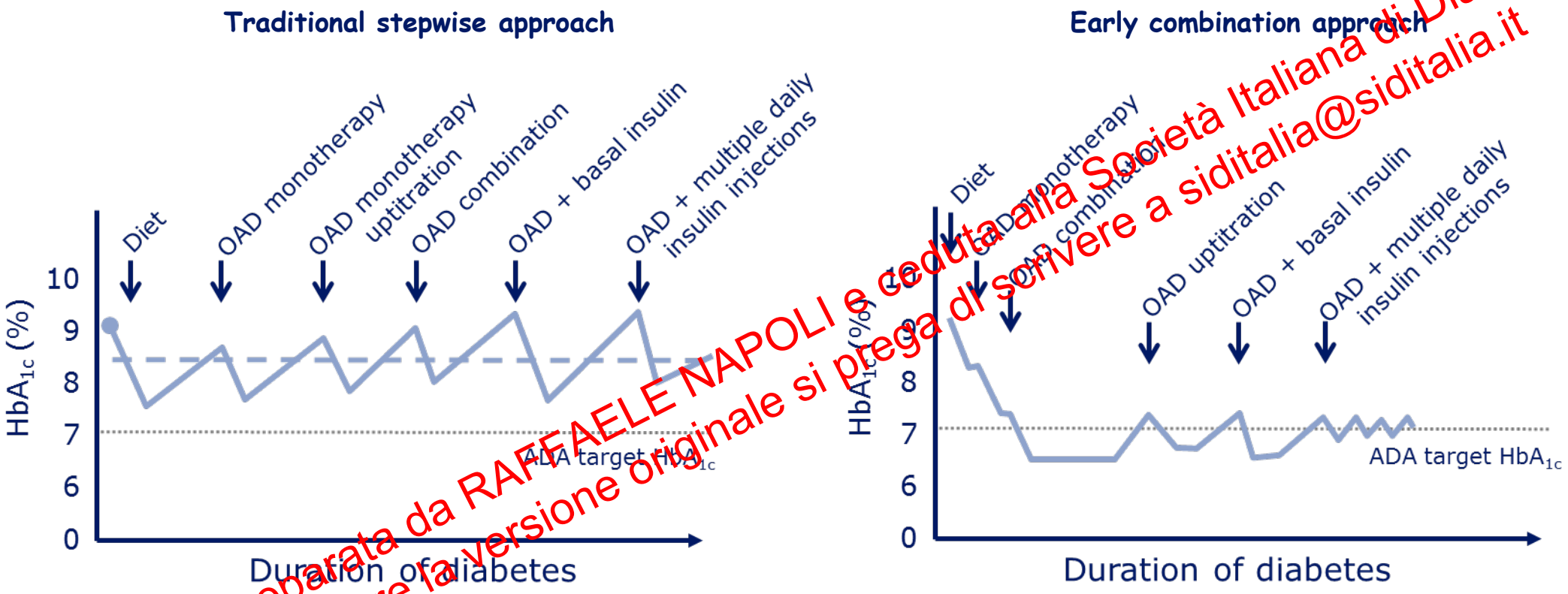


T2D

-46%

-52%

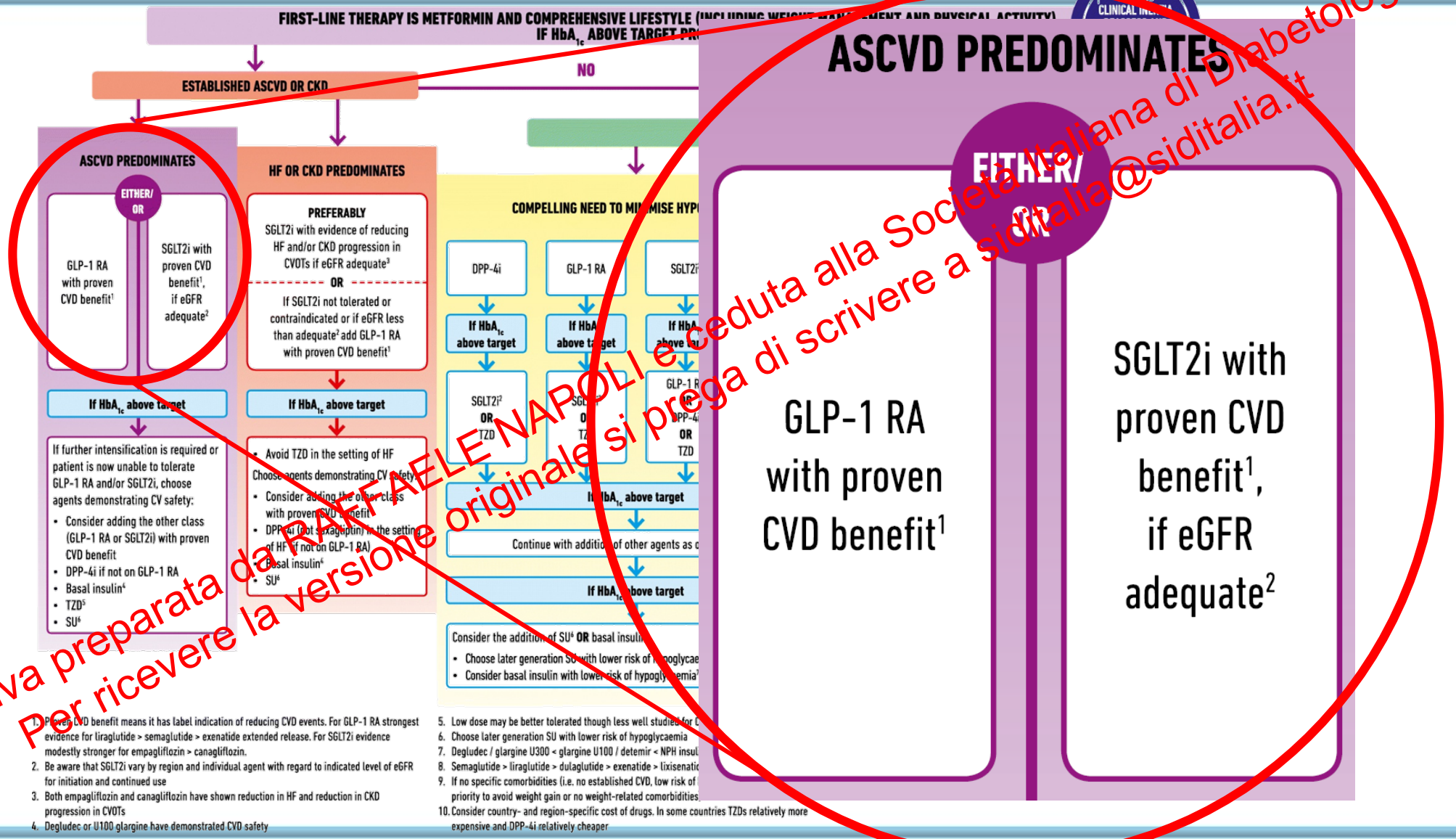
Early intensive treatment is important T2D



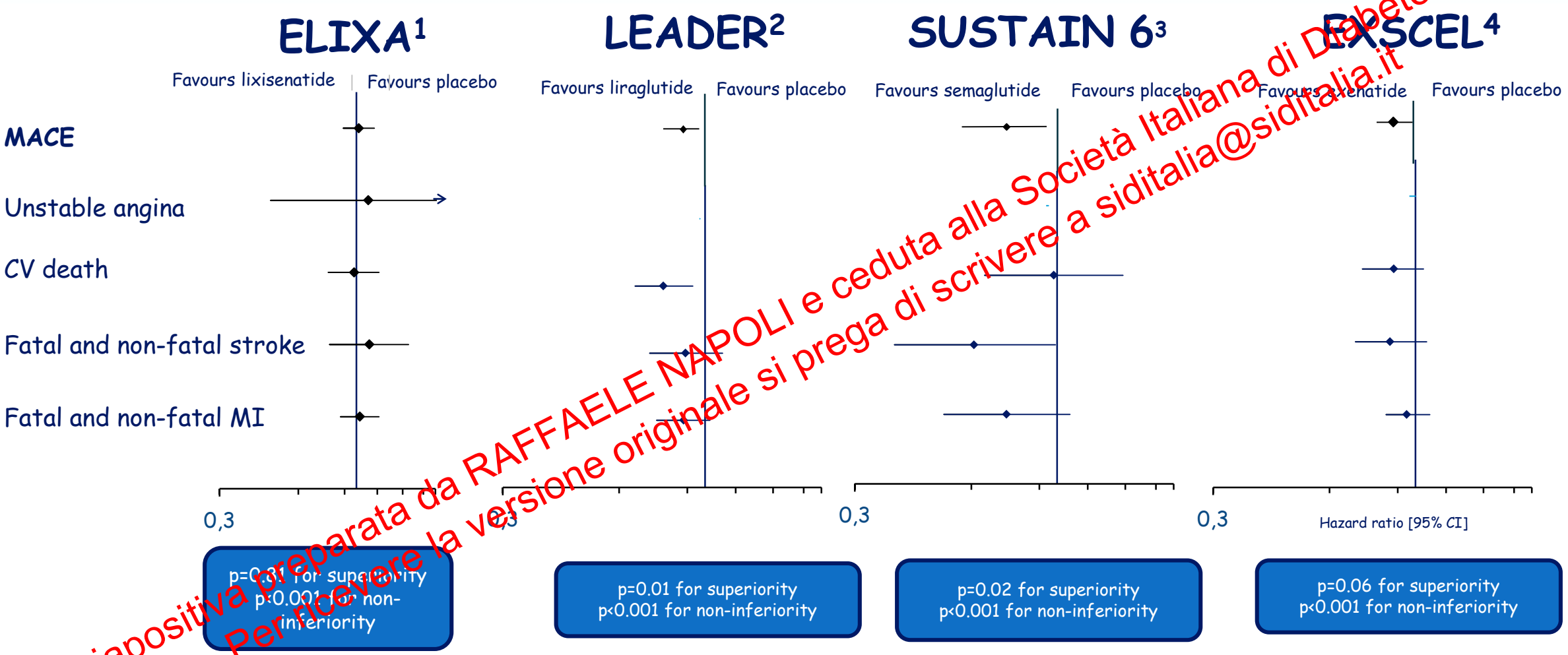
Early intensive treatment can minimise the hyperglycaemia that underlies complications of type 2 diabetes

Campbell. *Br J Cardiol* 2000;7:625–631; Del Prato S et al. *Int J Clin Pract* 2005;59:1345–1355

Glucose lowerina medication in T2D: overall Approach



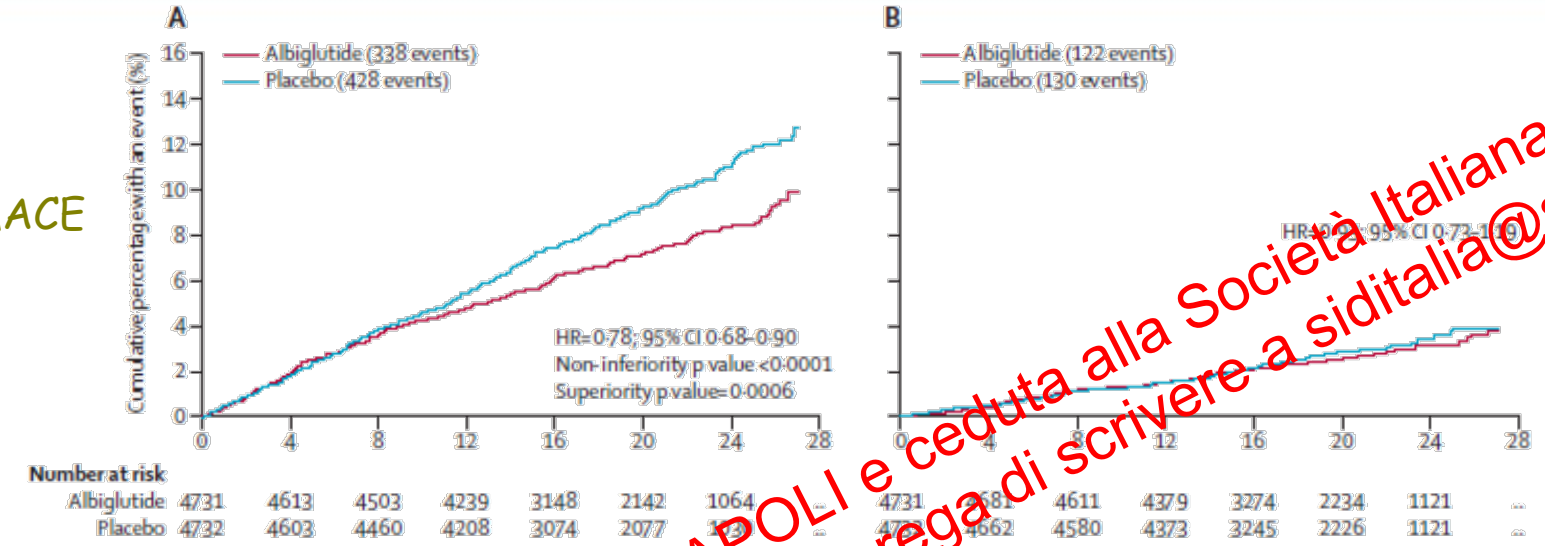
Trials on CV benefits with GLP-1 RAs have varying results



1. Pfeffer MA et al. *N Engl J Med* 2015; 2. Marso SP et al. *N Engl J Med* 2016; Marso SP et al. *N Engl J Med* 2016; 4. Holman RR et al. *N Engl J Med* 2017

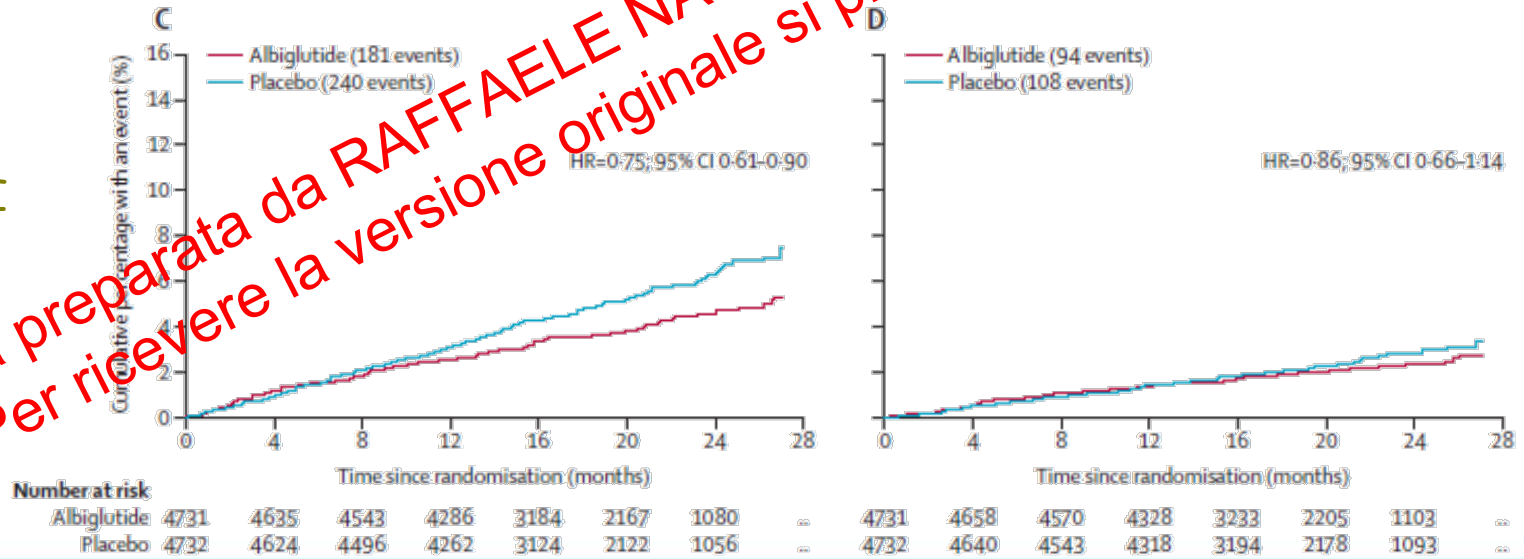
The Harmony Outcome Trial

MACE



Death from CV Causes

AMI

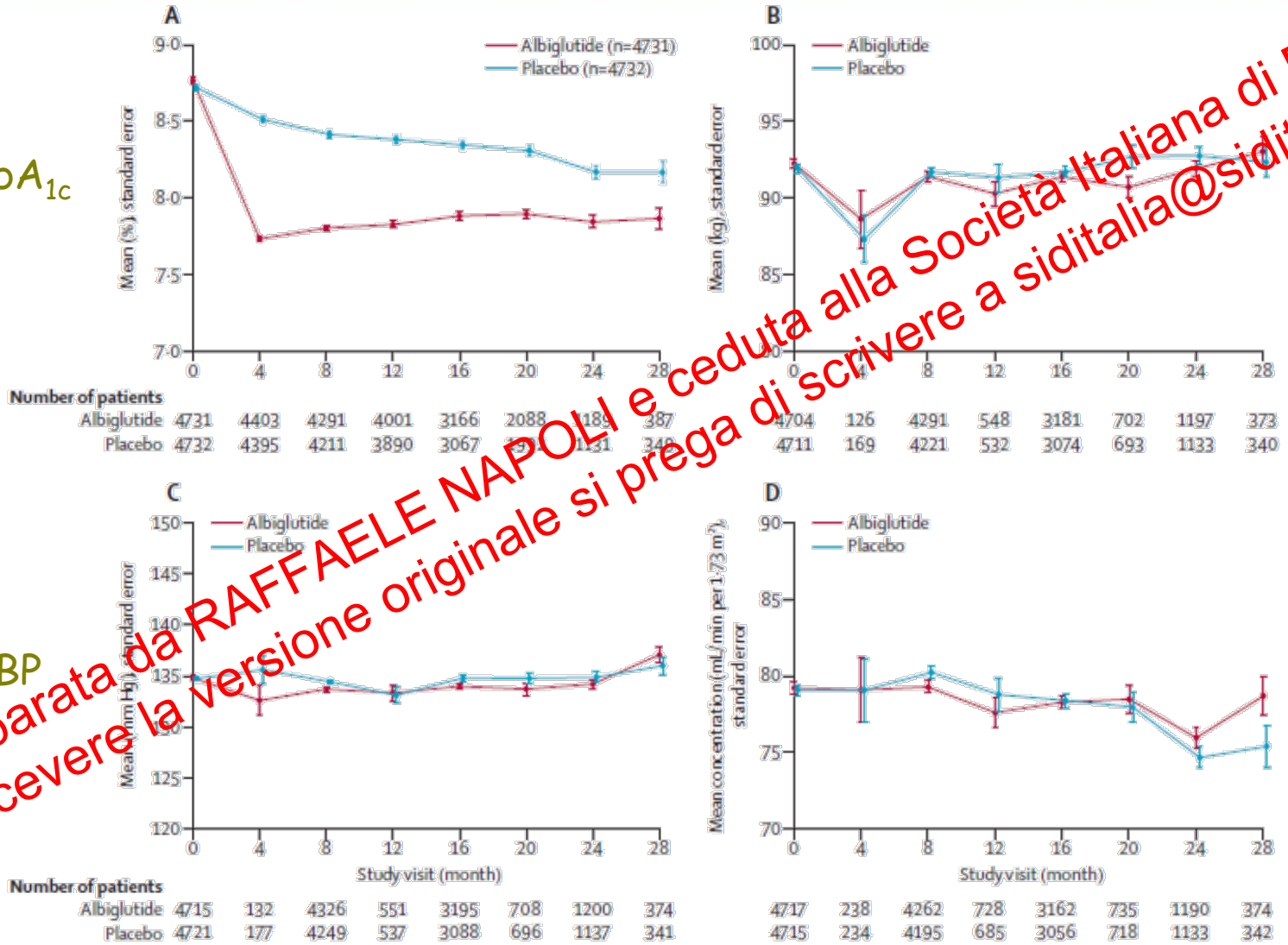


Stroke

Hernandez AF et al. Lancet 2018

The Harmony Outcome Trial

HbA_{1c}



BW

SBP

eGFR

Hernandez AF et al. Lancet 2018

MACE & Metformin + GLP1-RA

HARMONY[1]

	Number of patients	Albiglutide Events/patients (%)	Placebo Events/patients (%)	Hazard ratio (95% CI)	$P_{interaction}$
Primary analysis	9463	338/4731 (7·1%)	428/4732 (9·0%)	0·78 (0·68–0·90)	
Duration of diabetes					0·308
< 10 years	3355	91/1660 (5·5%)	138/1695 (8·1%)	0·67 (0·51–0·87)	
≥10 years to <20 years	3925	146/1987 (7·3%)	178/1938 (9·2%)	0·78 (0·63–0·97)	
≥20 years	2167	98/1072 (9·1%)	112/1095 (10·2%)	0·90 (0·68–1·17)	
Baseline insulin					0·053
Yes	5597	243/2860 (8·5%)	270/2737 (9·9%)	0·85 (0·72–1·01)	
No	3866	95/1871 (5·1%)	158/1995 (7·9%)	0·63 (0·49–0·81)	
Baseline metformin					0·928
Yes	6968	220/3462 (6·4%)	281/3506 (8·0%)	0·77 (0·65–0·92)	
No	2495	118/1269 (9·3%)	147/1226 (12·0%)	0·79 (0·62–1·00)	

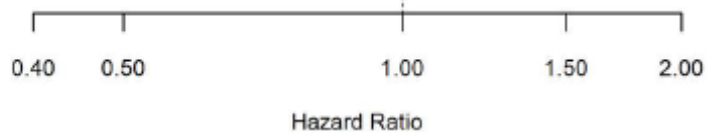
LEADER[2]

Subgroup	No. of Patients	Liraglutide	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
		no. of events/no. of patients (%)			
Antidiabetic therapy					0.73
1 Oral antidiabetic agent	1818	99/922 (10.7)	125/896 (14.0)	0.75 (0.58–0.98)	
>1 Oral antidiabetic agent	2997	191/1515 (12.6)	196/1482 (13.2)	0.95 (0.78–1.16)	
Insulin with oral antidiabetic agent	3422	223/1674 (13.3)	259/1748 (14.8)	0.89 (0.74–1.06)	
Insulin without oral antidiabetic agent	737	71/361 (19.7)	86/376 (22.9)	0.86 (0.63–1.17)	
None	366	24/196 (12.2)	28/170 (16.5)	0.73 (0.42–1.25)	

1: Hernandez AF et al. Lancet 2018; 2: Marso SP et al. *N Engl J Med* 2016;

Broad kidney endpoint (new- onset macroalbuminuria sustained doubling of serum creatinine or a 40% decline in eGFR, ESRD, or death of renal cause) stratified by drug class

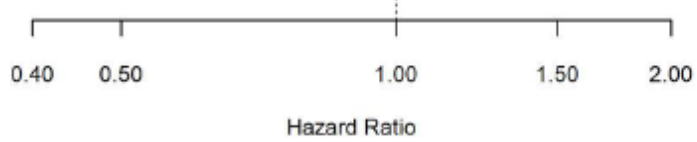
Trials	Patients	Events	Treatment n/N	Placebo n/N	Weights	HR [95% CI]
GLP1-RA						
ELIXA	5286	375	203/2639	172/2647	20.0	0.84 [0.68, 1.02]
LEADER	9340	605	268/4668	337/4672	32.2	0.78 [0.67, 0.92]
SUSTAIN-6	3297	162	62/1648	100/1649	7.7	0.64 [0.46, 0.88]
EXSCEL	14752	773	366/6256	407/6222	40.1	0.88 [0.76, 1.01]
Fixed Effects for GLP1-RA (P-value<0.001)						0.82 [0.75, 0.89]
SGLT2i						
EMPA-REG OUTCOME	6185	913	525/4124	388/2061	24.9	0.61 [0.53, 0.70]
CANVAS Program	10142	847	NA	NA	25.0	0.57 [0.50, 0.66]
DECLARE-TIMI 58	17160	1685	678/8582	997/8578	50.1	0.66 [0.60, 0.73]
Fixed Effects for SGLT2i (P-value<0.001)						0.62 [0.58, 0.67]



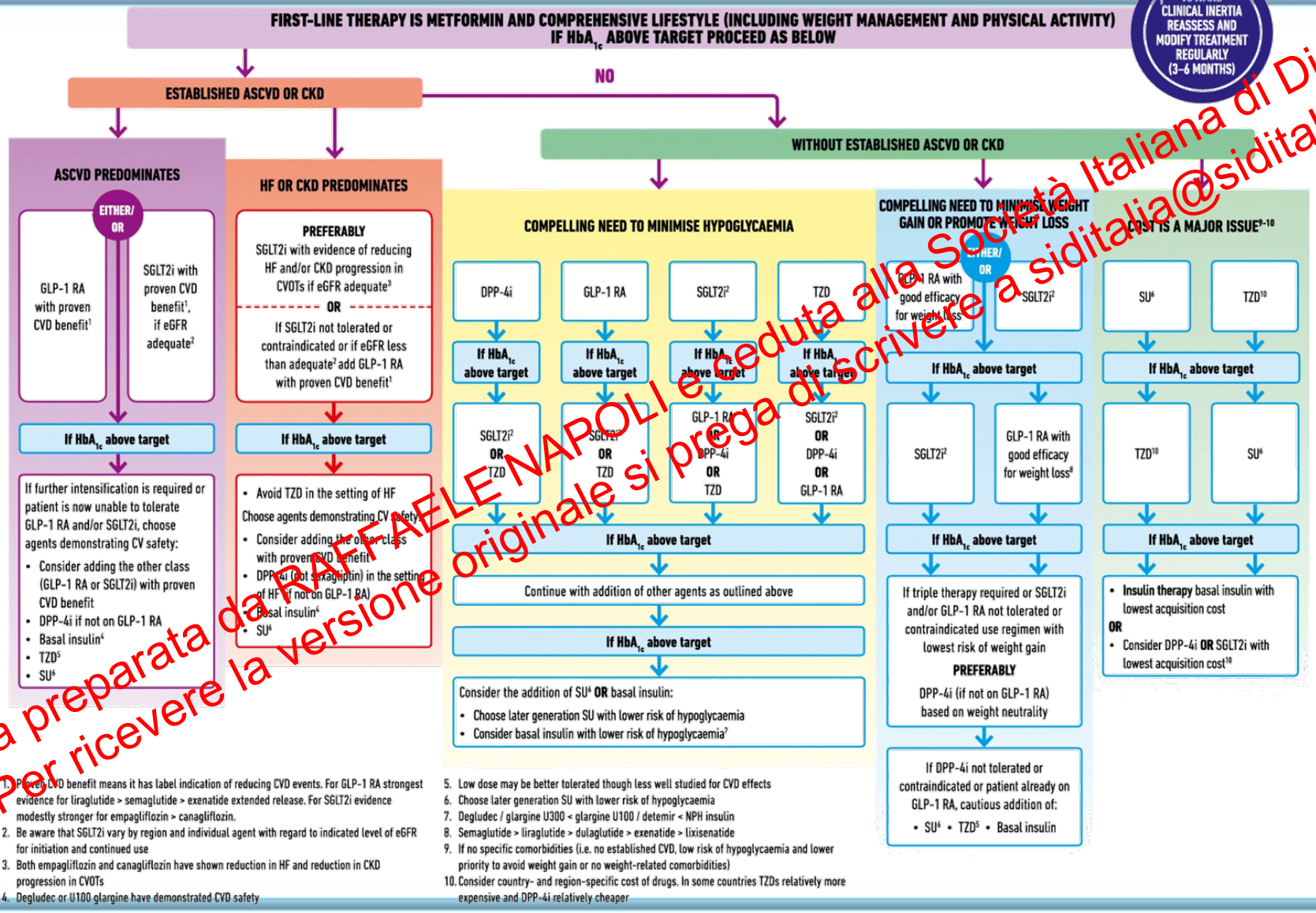
Zelniker et al Circulation 2019

Kidney outcome excluding macroalbuminuria stratified by drug class

Trials	Patients	Events	Treatment n/N	Placebo n/N	Weights	HR [95% CI]
GLP1-RA						
ELIXA	6063	76	35/3032	41/3031	9.5	1.16 [0.74, 1.83]
LEADER	9340	184	87/4668	97/4672	23.4	0.89 [0.67, 1.19]
SUSTAIN-6	3297	32	18/1648	14/1649	4.0	1.28 [0.64, 2.58]
EXSCEL	12914	519	246/6456	273/6458	63.1	0.88 [0.74, 1.05]
Fixed Effects for GLP1-RA (P-value=0.24)						0.92 [0.80, 1.06]
SGLT2i						
EMPA-REG OUTCOME	6968	152	81/4645	71/2323	20.9	0.54 [0.40, 0.75]
CANVAS Program	10142	249	NA	NA	34.0	0.60 [0.47, 0.77]
DECLARE-TIMI 58	17160	365	127/8582	238/8578	45.1	0.53 [0.43, 0.66]
Fixed Effects for SGLT2i (P-value<0.001)						0.55 [0.48, 0.64]



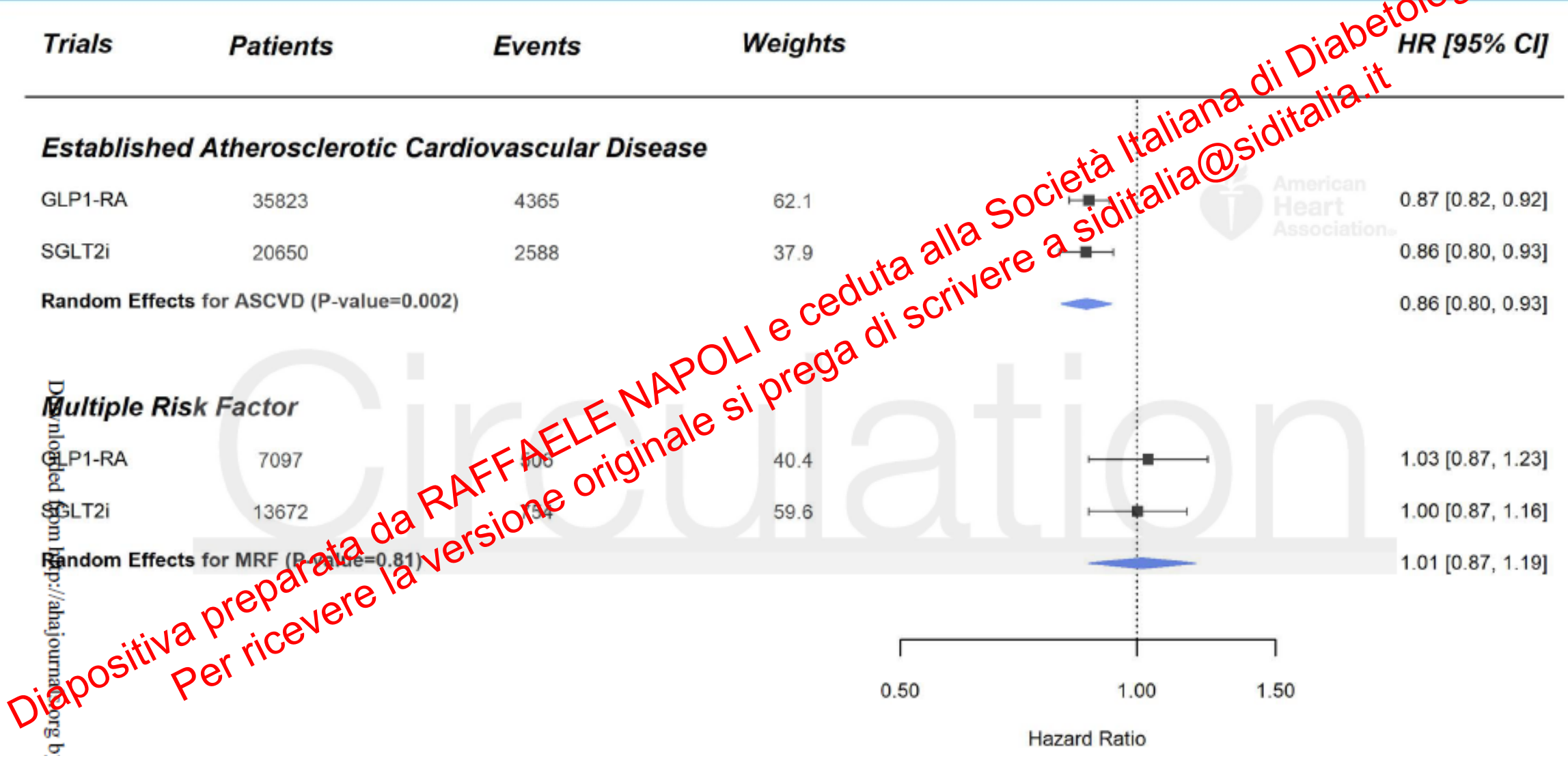
Glucose lowering medication in T2D: overall Approach



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

Davies M et al. Diabetologia 2018

Meta-Analysis of GLP1-RA and SGLT2i trials on the composite of MACE stratified by presence of ACVD



Zelniker et al Circulation 2019

T2D is associated with serious complications

Microvascular

Retinopathy, glaucoma or cataracts

Nephropathy

Neuropathy

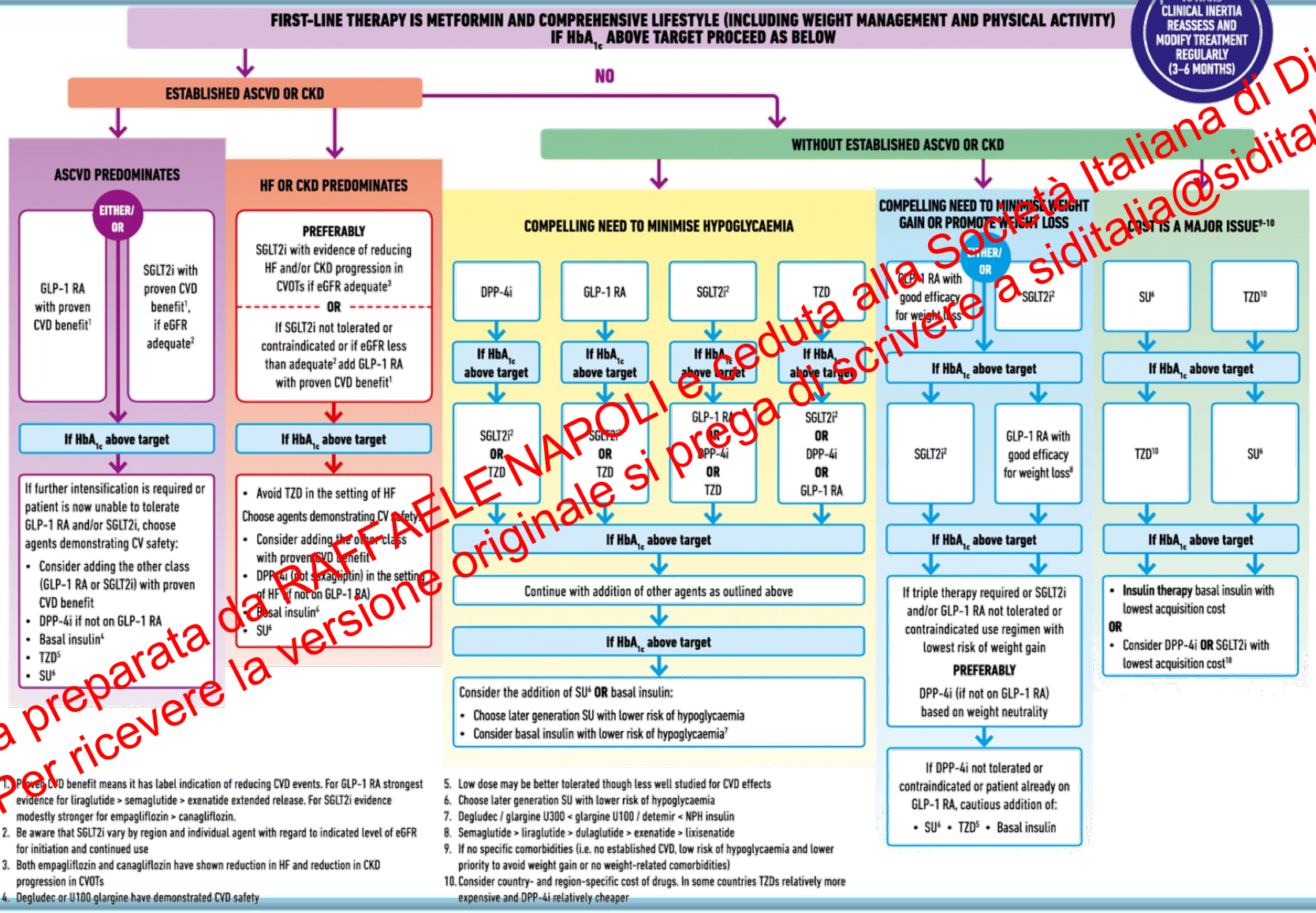
Macrovascular

Cerebrovascular disease

Coronary heart disease

Peripheral vascular disease

Glucose lowering medication in T2D: overall Approach



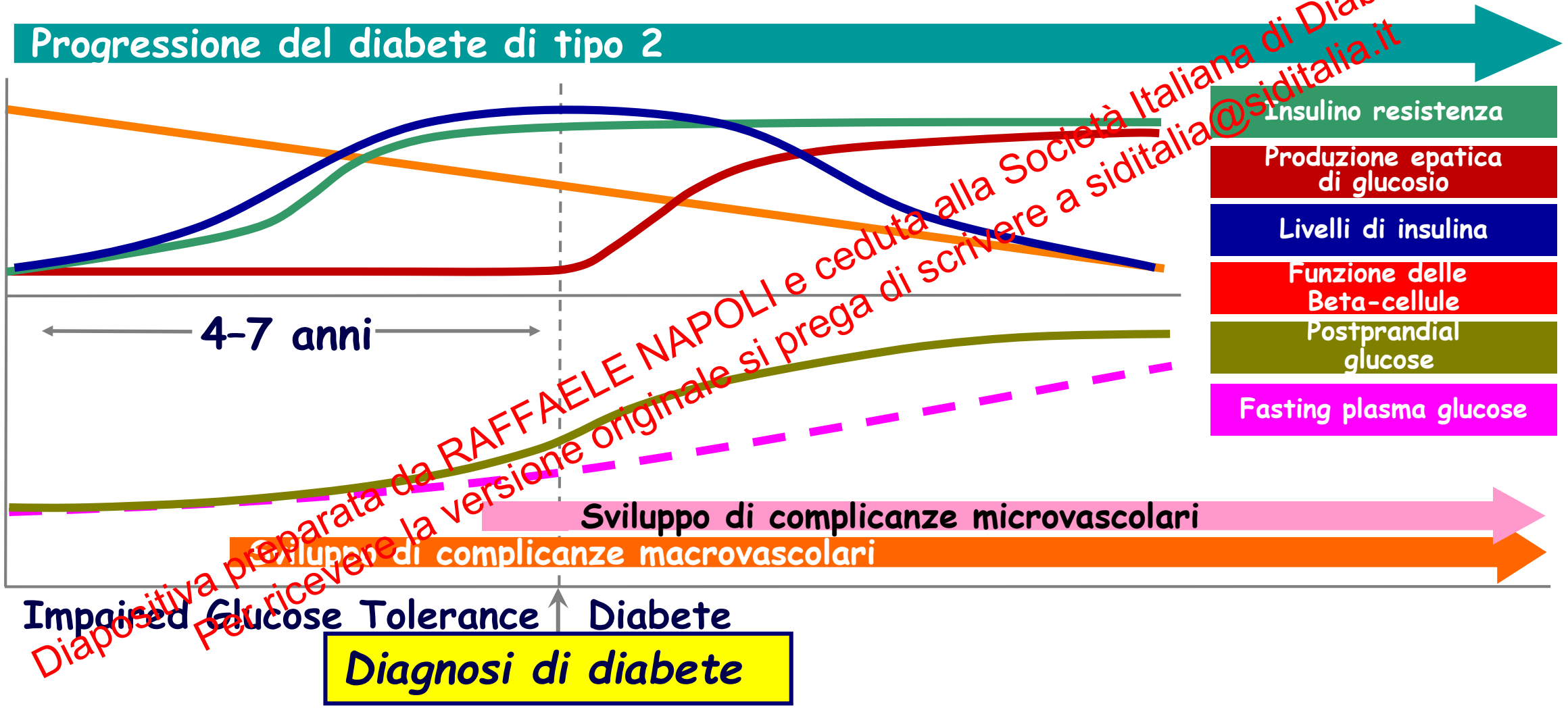
1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent 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

Davies M et al. Diabetologia 2018

Metformin + GLP1-RA

- Disease progression
- Microvascular complications (Risk factors for)
- Macrovascular complications (Risk factors for)

Progression of T2D

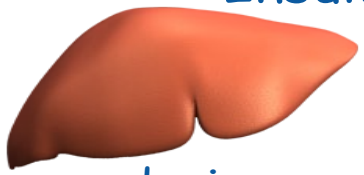


Ramlo-Halsted BA, Edelman SV, *Primary Care* 1999; Kahn SE. *JCEM* 2001; Bell DSH. *Treat Endocrinol.* 2006.

Complicanze dell'iperglicemia

Insufficiente secrezione insulinica

Insulino-resistenza



Iperproduzione glucosio

Ridotta utilizzazione del glucosio

Aumentata lipolisi

Iperglicemia

Danno vascolare

Aumento acidi grassi liberi circolanti

TNF-alpha
CRP
PAI-1

Dislipidemia
Aumentata aggregazione piastrinica

Rischio microvascolare

Nefropatia
Retinopatia
Neuropatia

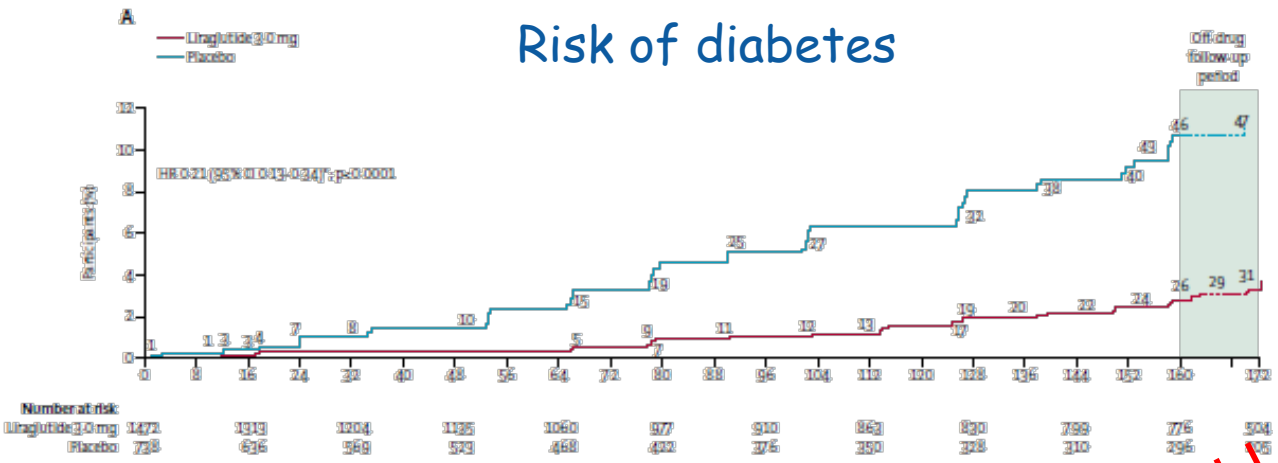
Rischio macrovascolare

IM
Ictus
Vasculopatia periferica

Inzucchi SE *JAMA* 2002; Buse JB , *Williams Textbook of Endocrinology* 2003; Sheetz MJ,*JAMA* 2002; Libby P, *Circulation* 2002; Kendall DM *Coron Artery Dis* 2003; DeFronzo RA *Ann Intern Med* 1999

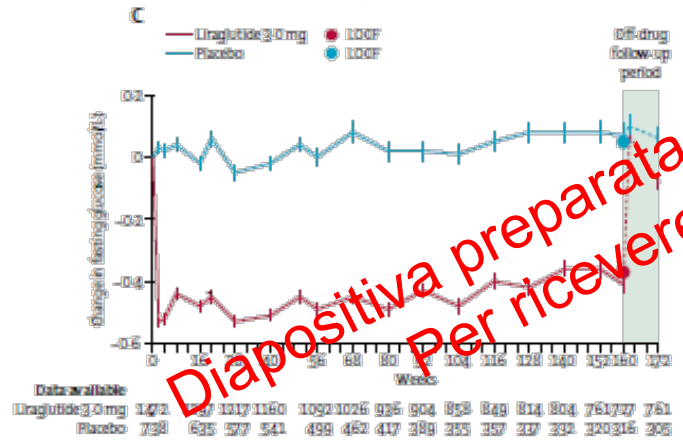
Liraglutide in pre-diabetes and obesity

Risk of diabetes

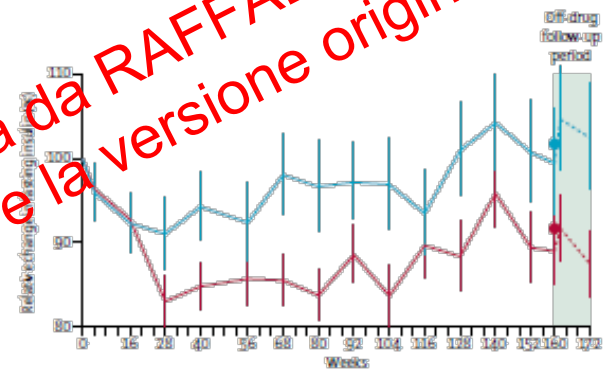


Weight change

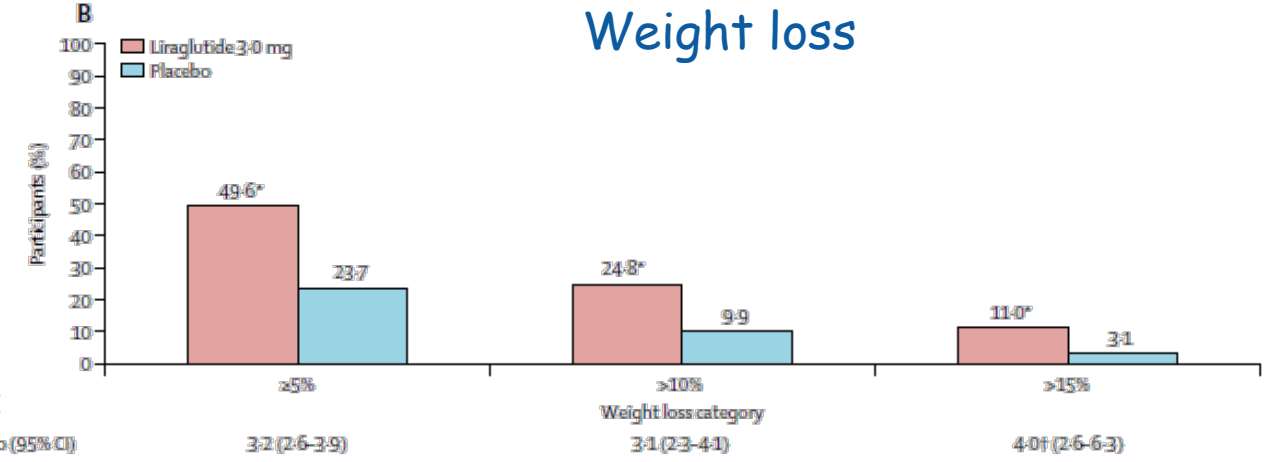
Change in FPG



Change in fasting insulin

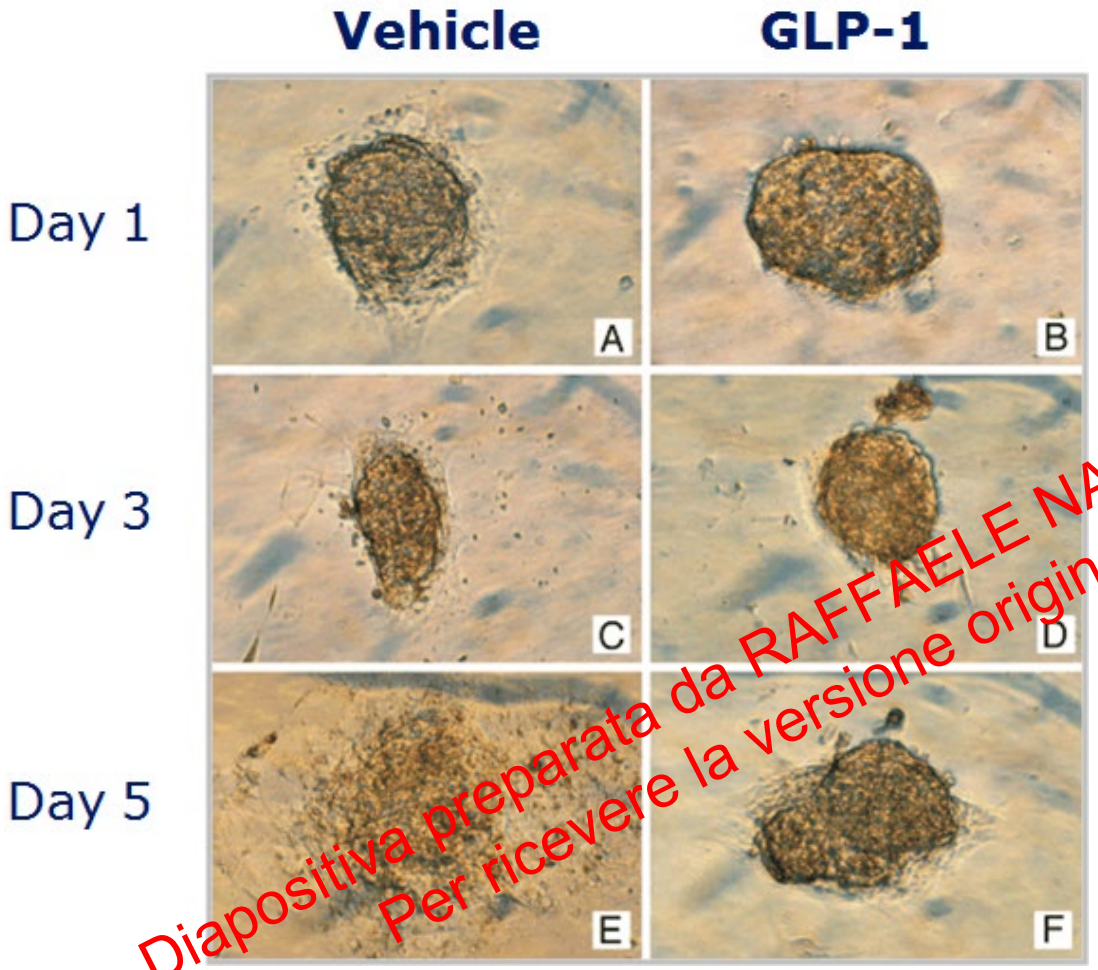


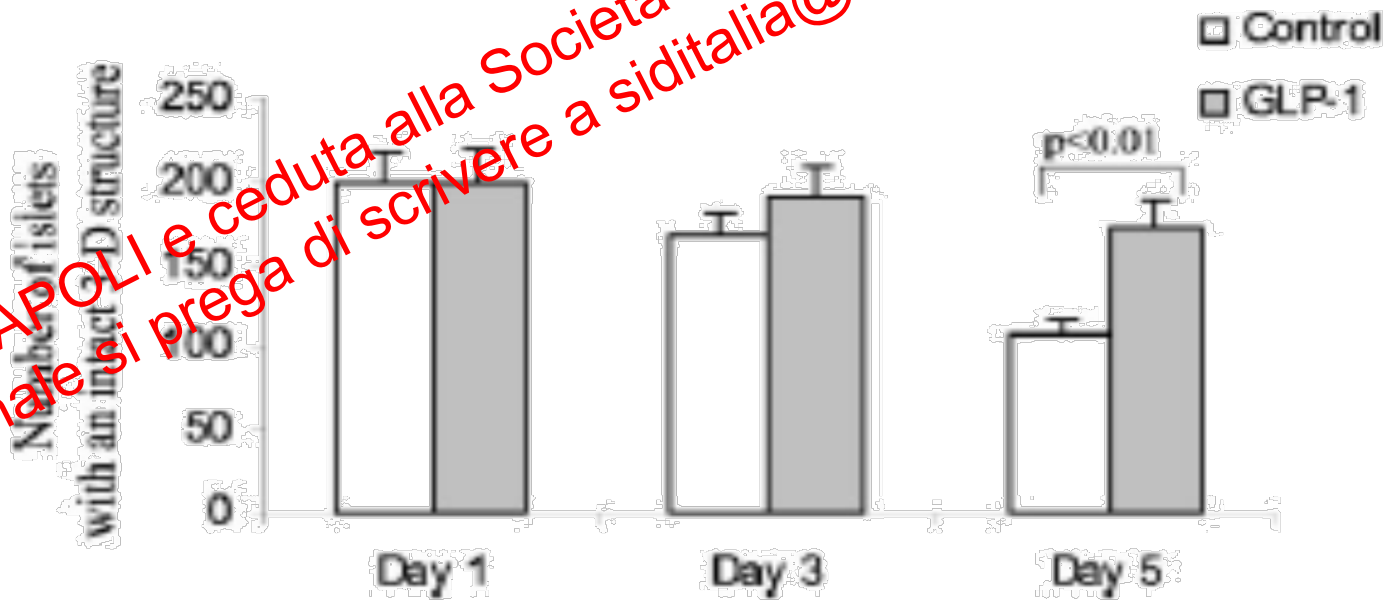
Weight loss



Le Roux CW A et al, Lancet 2017

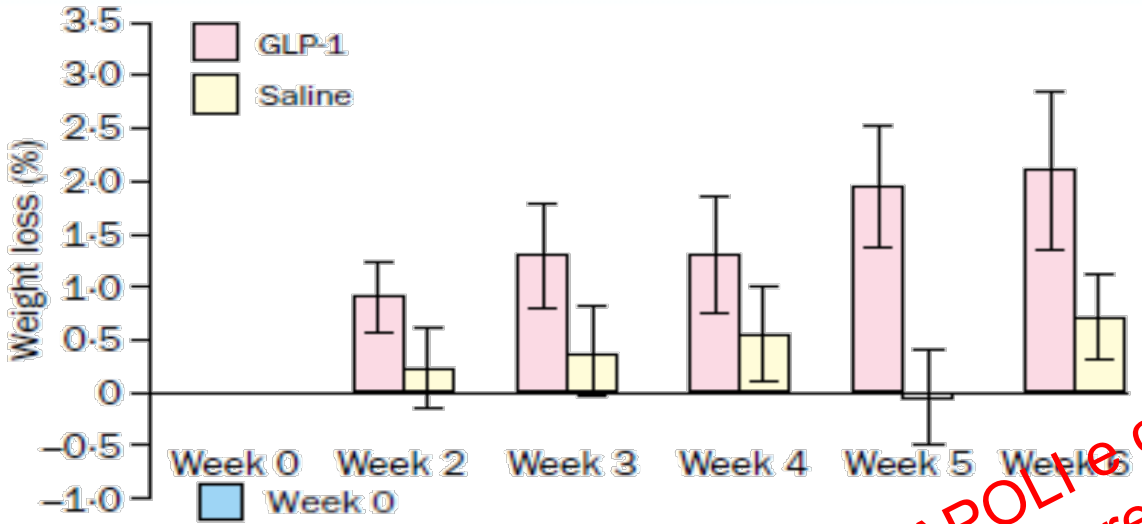
Inhibition of beta-cell apoptosis by GLP-1 in isolated human islets

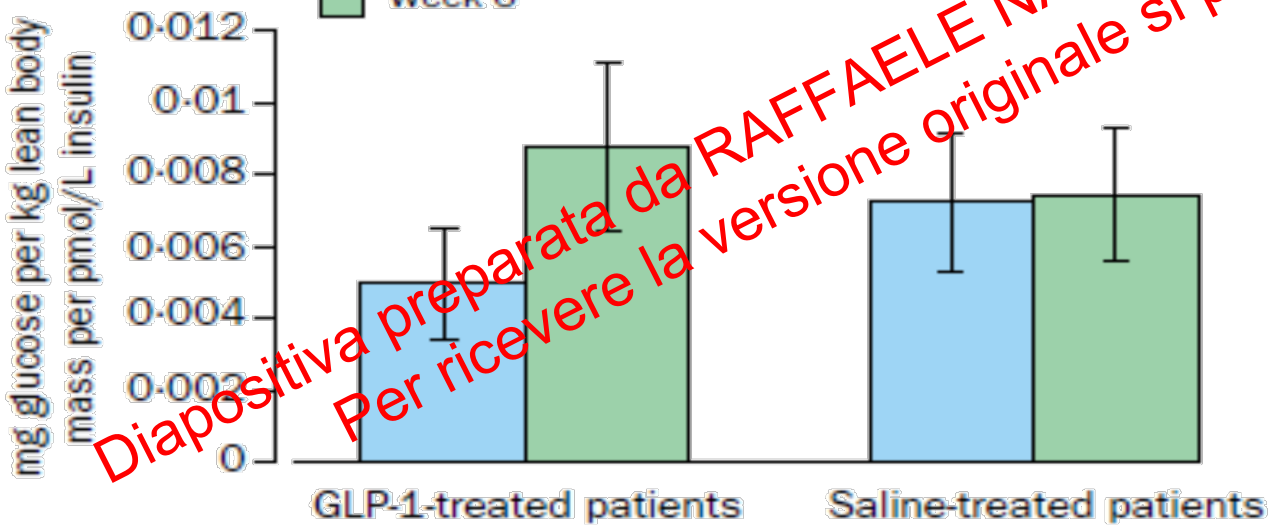


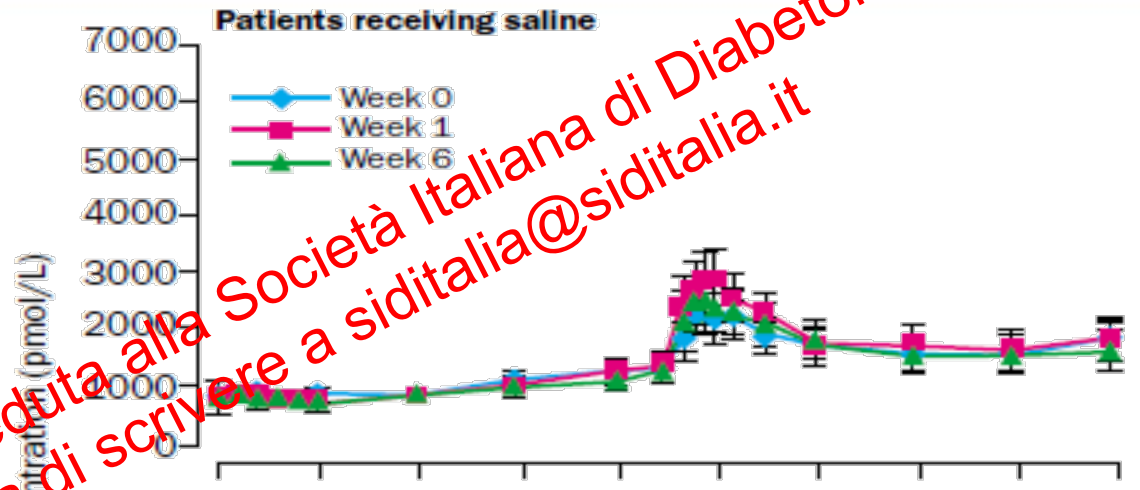


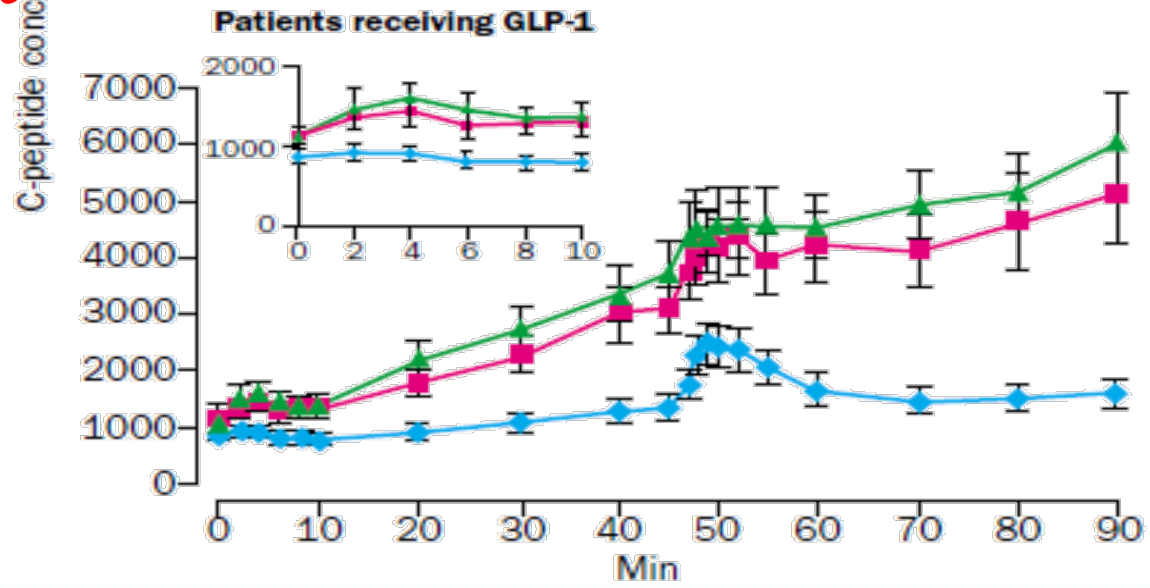
Farilla L et al. *Endocrinology* 2003;144:5149-5158

GLP-1 improves beta-cell function in T2D patients



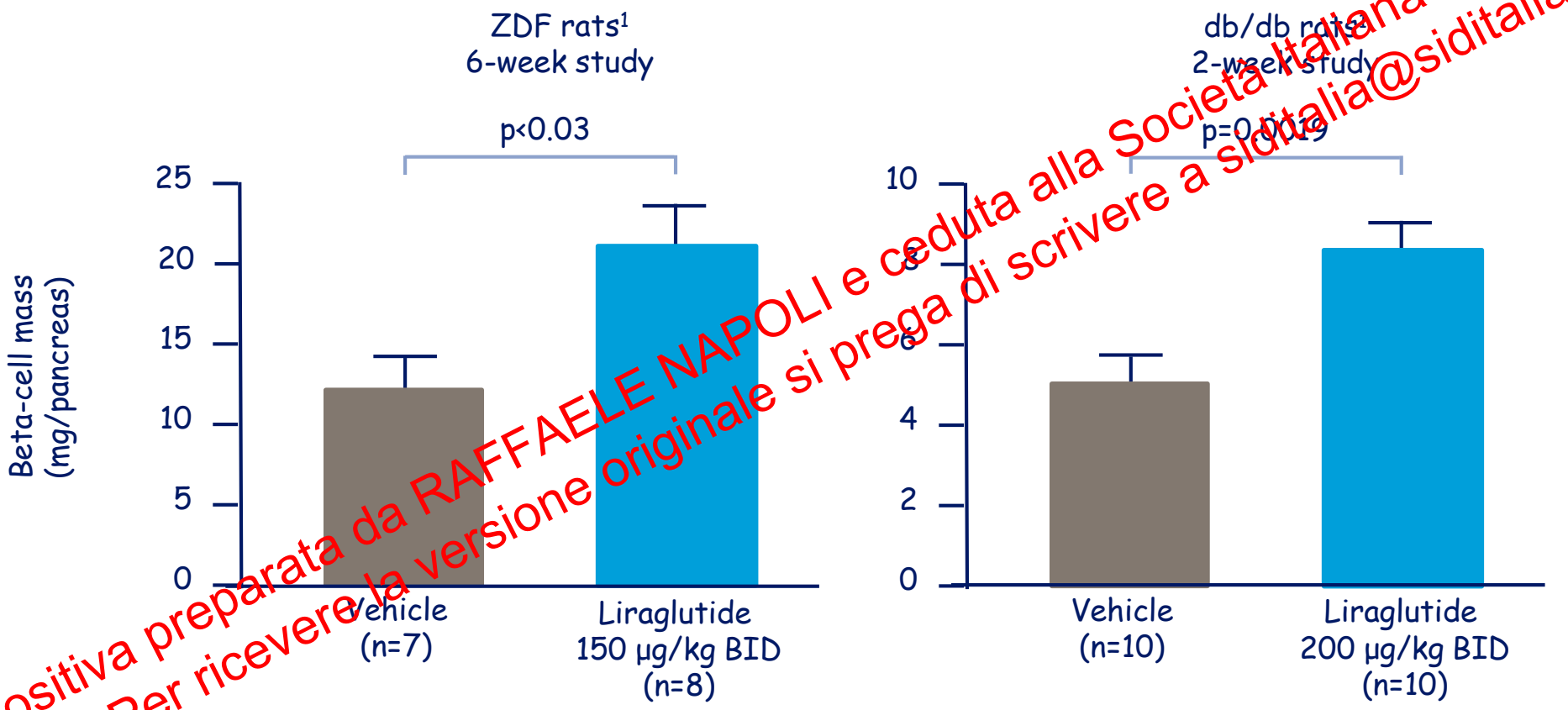






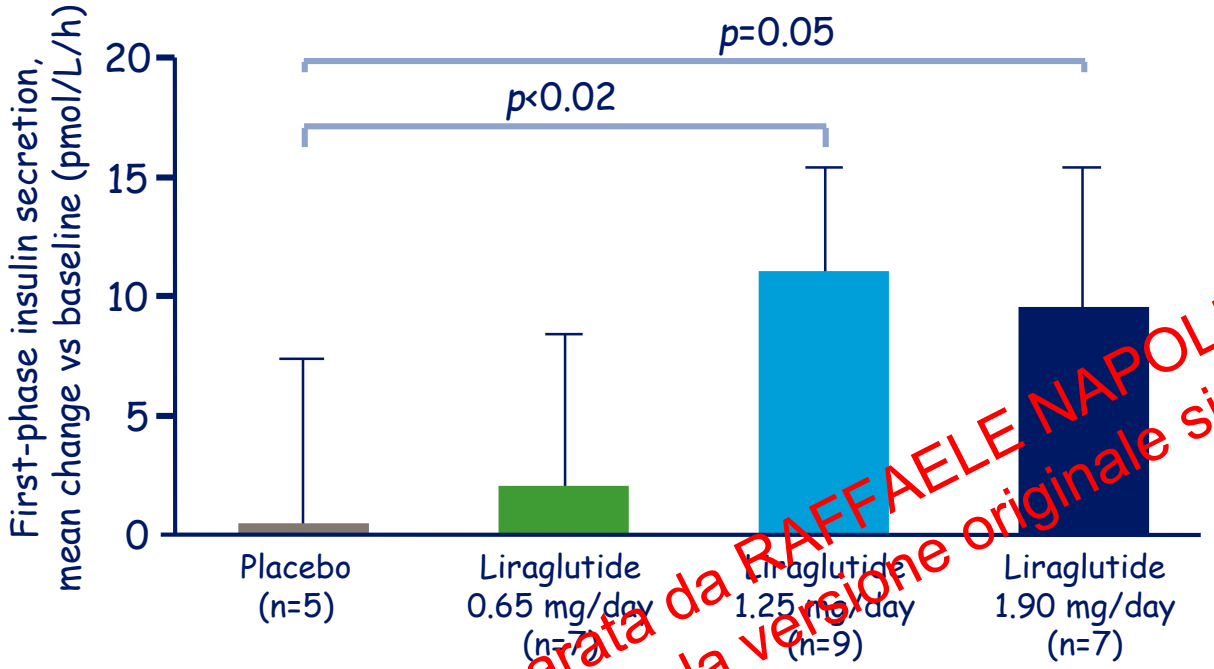
Adapted from Zander M et al. *Lancet* 2002;359:824–830

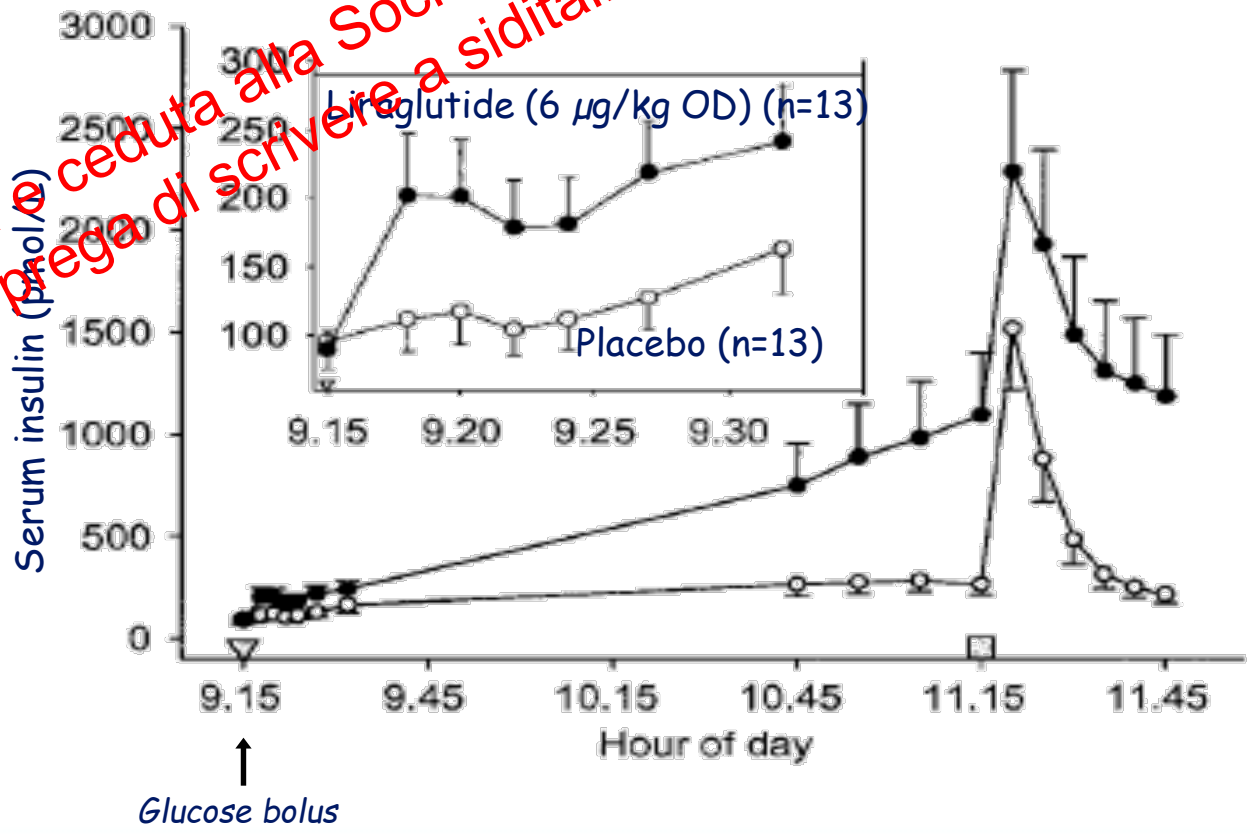
Liraglutide increases beta-cell mass in animal models of diabetes



Adapted from Shimoda *et al. Diabetologia* 2011;54:1098–108

Liraglutide monotherapy increases first-phase insulin secretion and response to glucose





Adapted from Vilsbøll T et al. *Diabet Med* 2008;25:152–156

Adapted from Degn KB et al. *Diabetes* 2004;53:1187–1194

LIraglutide and Beta-cell RepAir (LIBRA) Study

51 patients
- Adults 30–75 years
- T2D ≤7 years
- HbA_{1c} <9% (on OADs) or <10% (not on OADs)
- On 0–2 OADs
- Anti-GAD antibody negative

Liraglutide 1.8 mg*

Placebo

Trial information
- Single-centre
- Double-blind
- Randomised
- Placebo-controlled

Trial objective

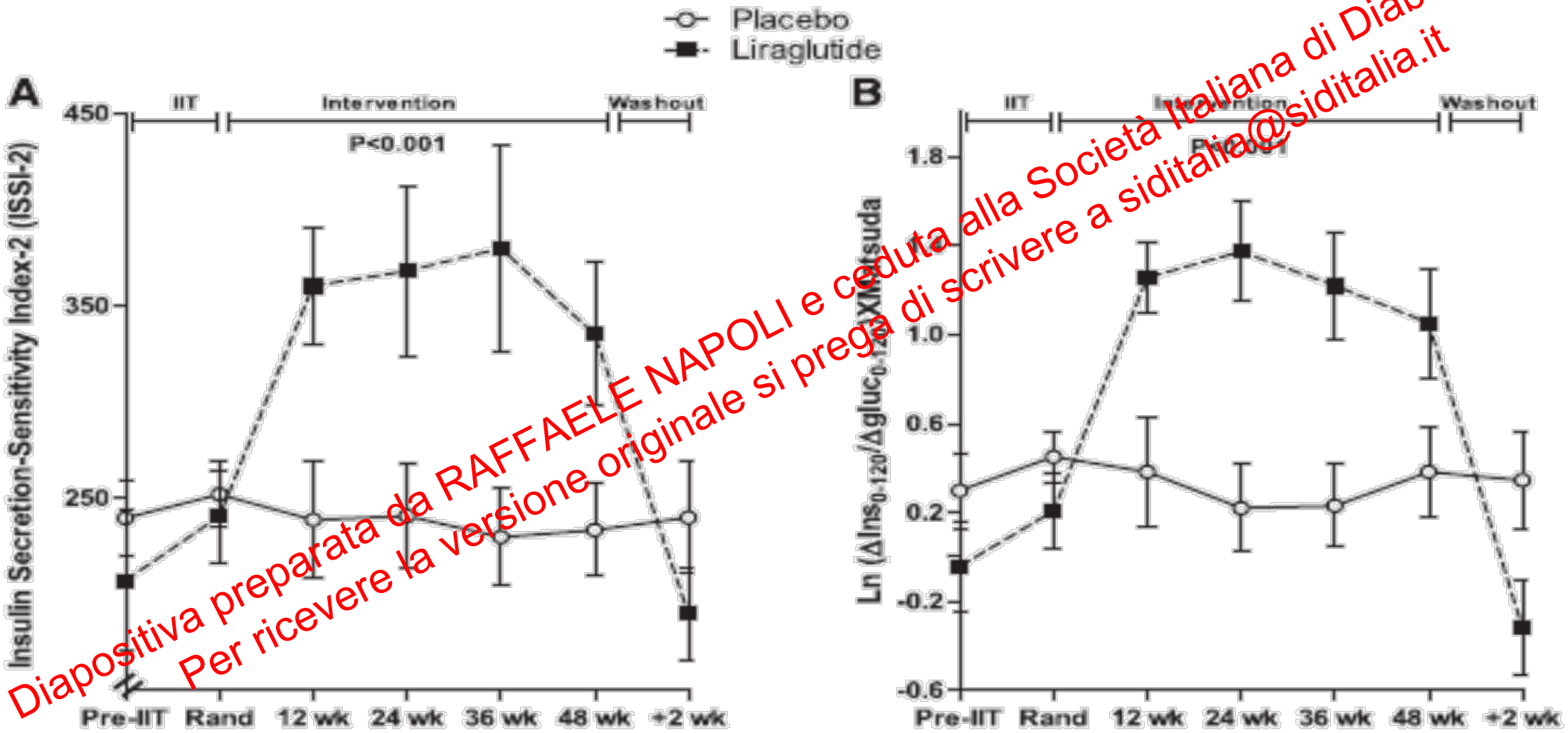
To evaluate the effect of liraglutide on the preservation of beta-cell function over 1 year in early T2DM following initial elimination of glucotoxicity with IIT

Key endpoints
- Primary: beta-cell function measured by ISSI-2 at 48 weeks
- Secondary: HbA_{1c}, FPG, PPG, proportion of patients with HbA_{1c} <7%, glucose tolerance status, AUC_{gluc} and time to loss of glycaemic control (metformin rescue therapy)

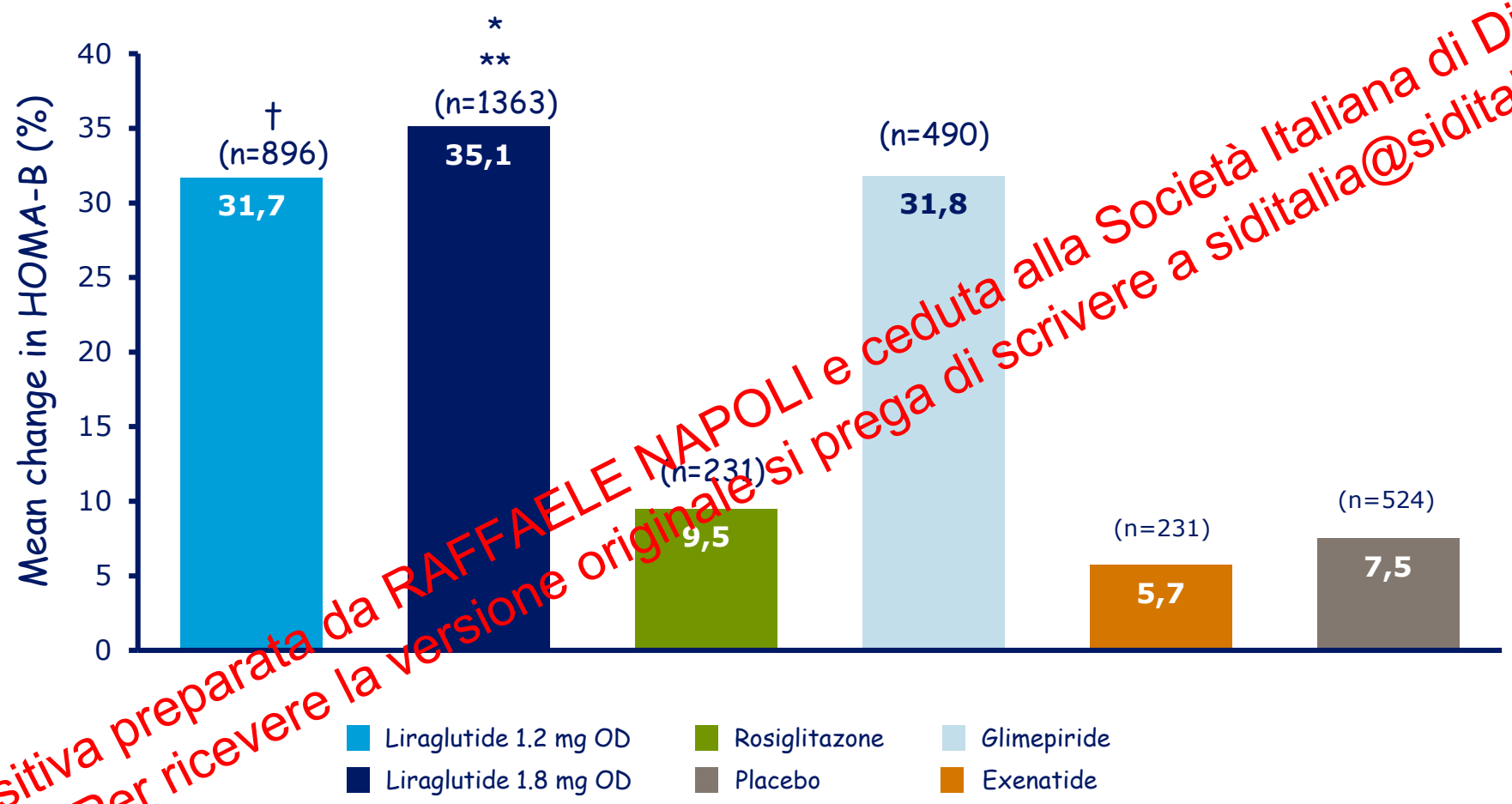
*Liraglutide was escalated to 1.8 mg in 0.6 mg increments over a 2-week period

AUC_{gluc}, area under the glucose curve; FPG, fasting plasma glucose; GAD, glutamic acid decarboxylase; HbA_{1c}, glycosylated haemoglobin; IIT, intensive insulin therapy; ISSI-2, Insulin Secretion Sensitivity Index-2; OADs, oral anti-diabetic drugs; PPG, post-prandial plasma glucose; T2D, type 2 diabetes

Changes over time in Insulin Secretion Sensitivity Index-2 and $\Delta Ins_{0-120}/\Delta gluc_{0-120}$ × Matsuda index



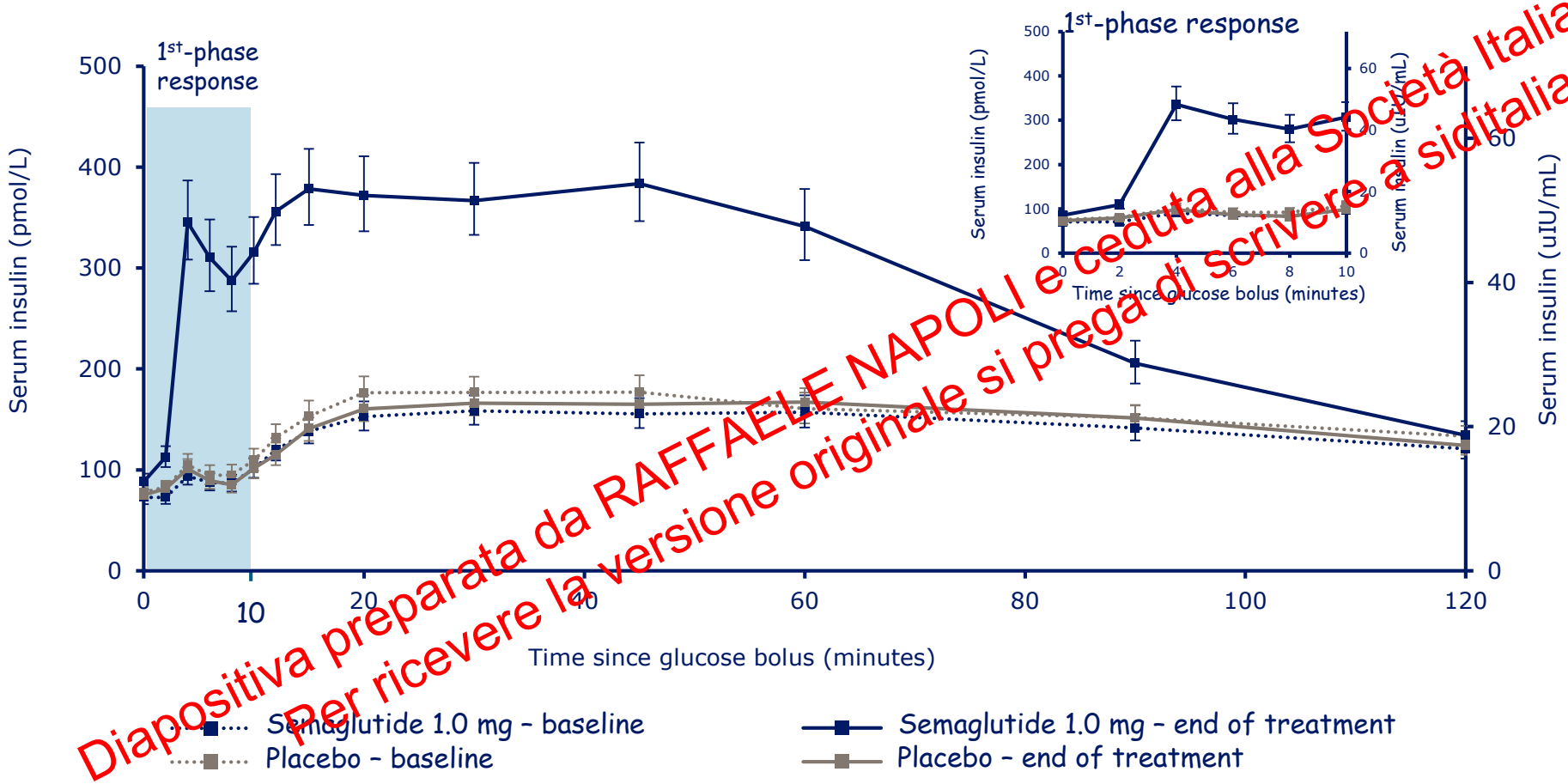
LEAD meta-analysis: Change in HOMA-B from baseline to Week 26



*$p<0.0001$ vs exenatide and placebo; **$p<0.05$ vs rosiglitazone; †$p<0.0001$ vs placebo

Semaglutide treatment increases first- and second-phase insulin secretion

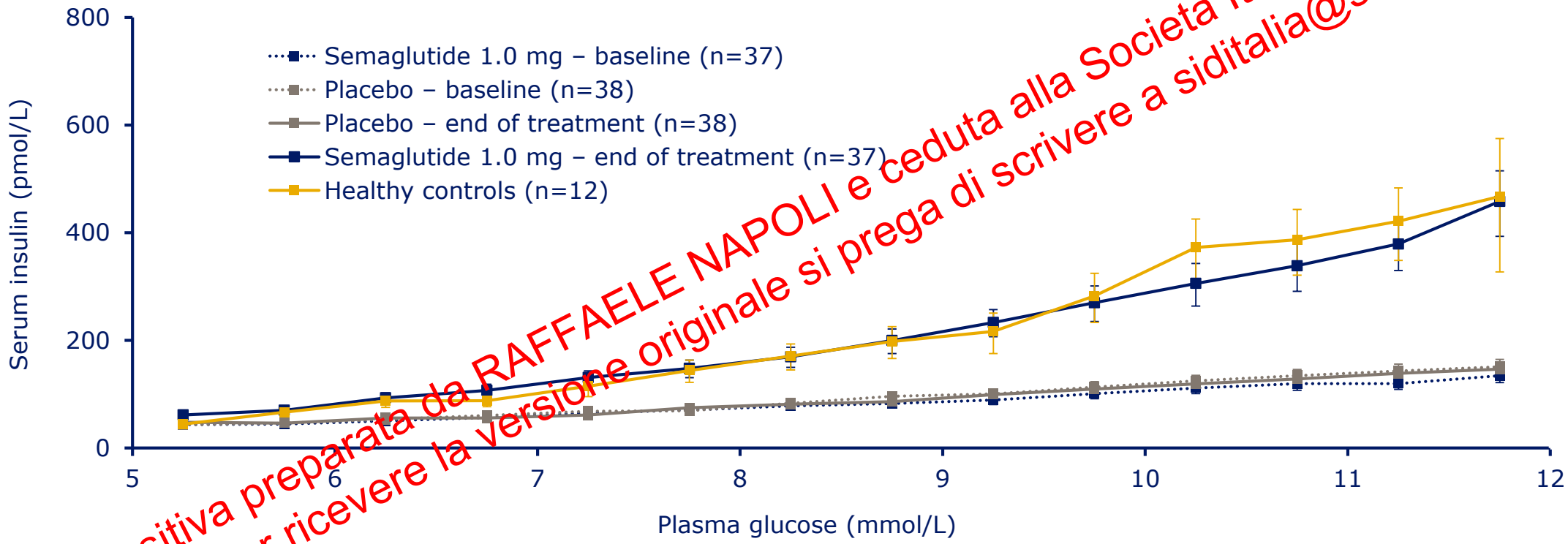
INTRAVENOUS GLUCOSE TOLERANCE TEST



Semaglutide treatment also increased maximum insulin secretory capacity vs placebo in the arginine stimulation test

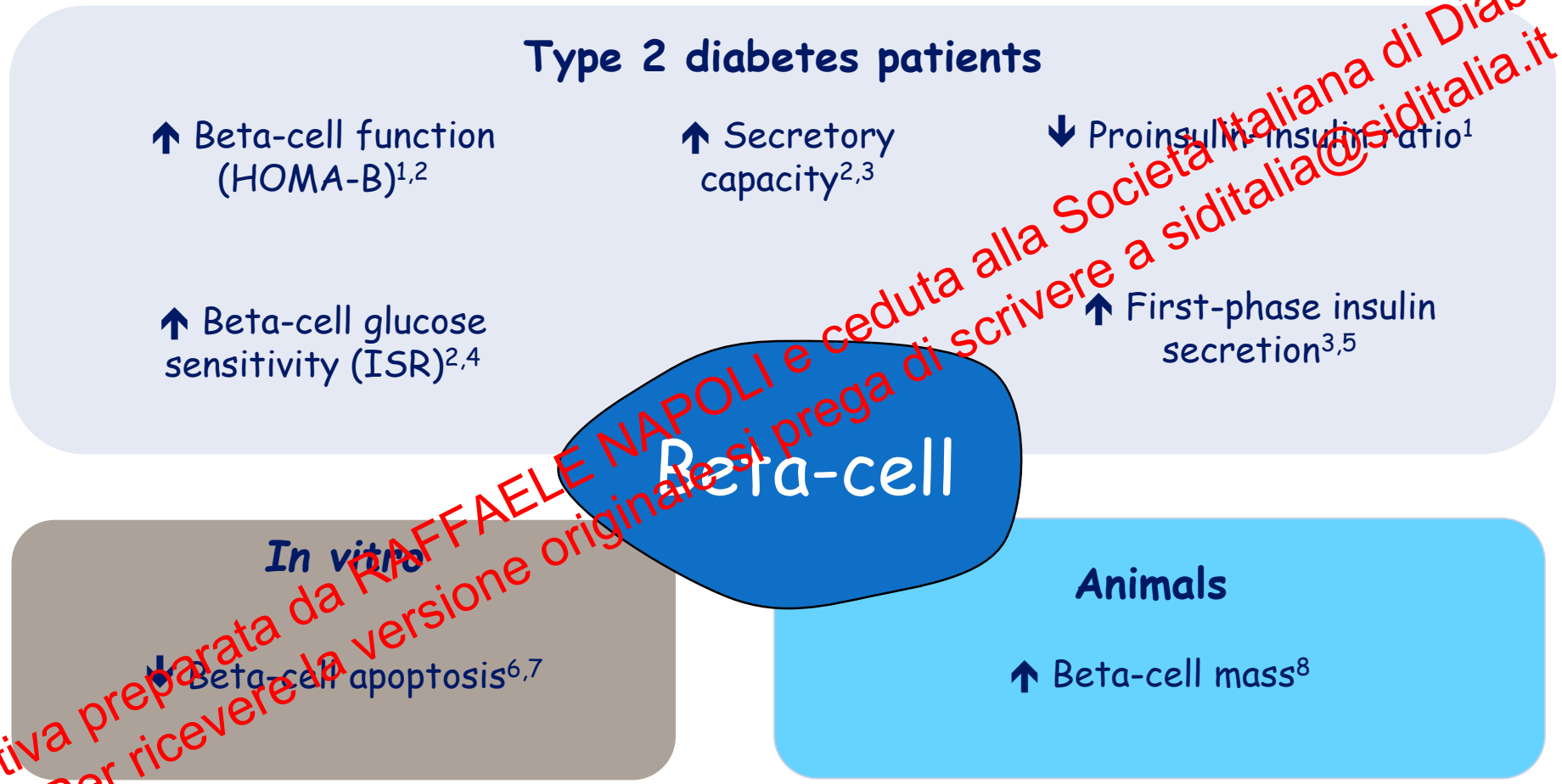
Beta-cell responsiveness after semaglutide treatment increases to levels comparable with healthy controls

GRADED GLUCOSE INFUSION TEST



Kapitza C et al. *Diabetologia* 2017;60:1390–9.

Liraglutide has multiple positive effects on the beta-cell



HOMA, homeostasis model assessment; ISR, insulin secretion rates

1. Garber A et al. *Diabetes Care* 2011; 2. Mari A et al. *Diabetes Care* 2007; 3. Madsbad S. *Diabetologia* 2006; 4. Chang AM et al. *Diabetes* 2003;5. Vilsbøll T et al. *Diabet Med* 2008; 6. Bregenholt S et al. *Biochem Biophys Res Commun* 2005; 7. Farilla L et al. *Endocrinology* 2003; 8. Rolin B et al. *Am J Physiol Endocrinol Metab* 2002.

Diabetes-related deaths in the Swedish NDR, 1998-2014

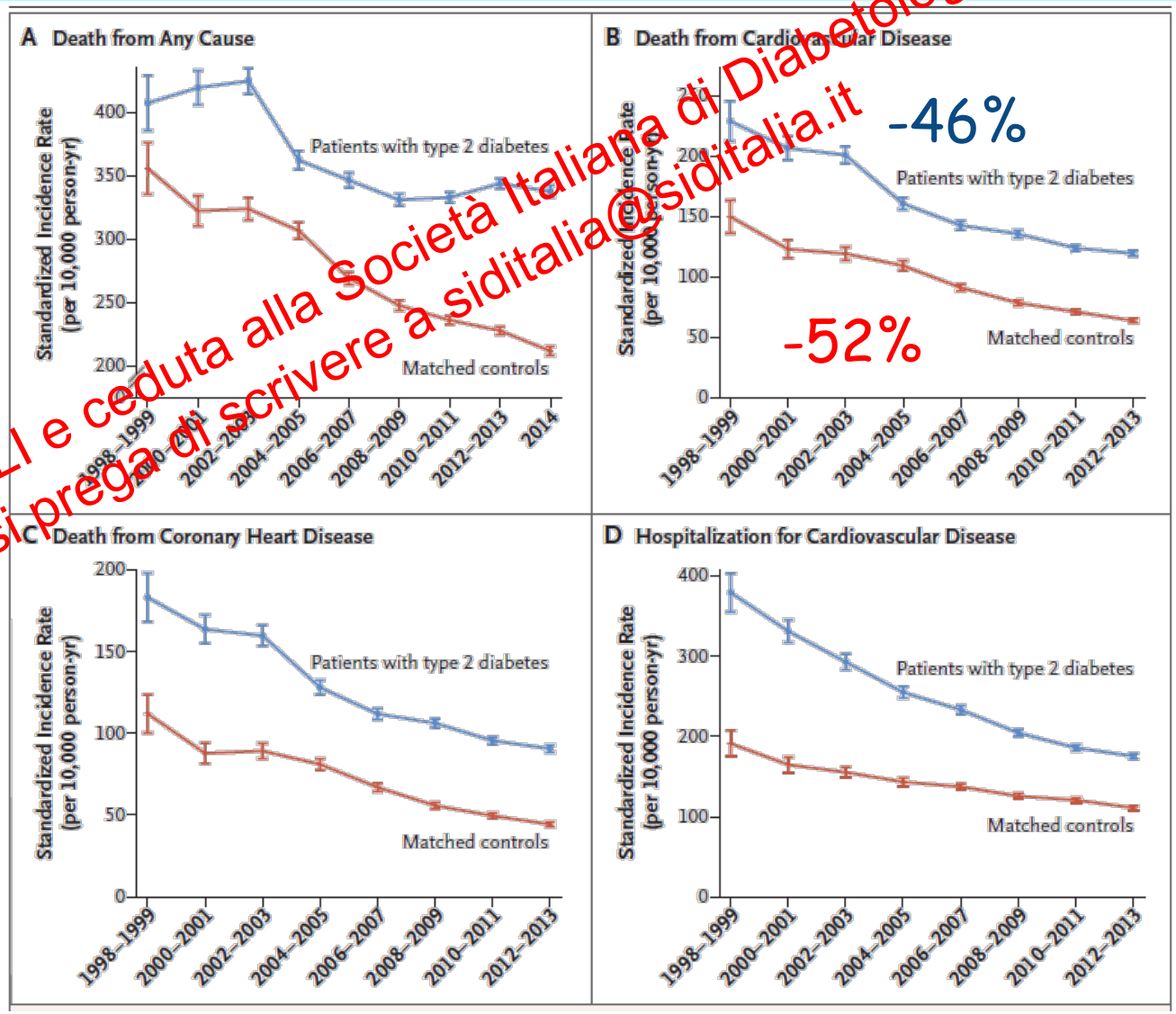
T2D

HbA1c

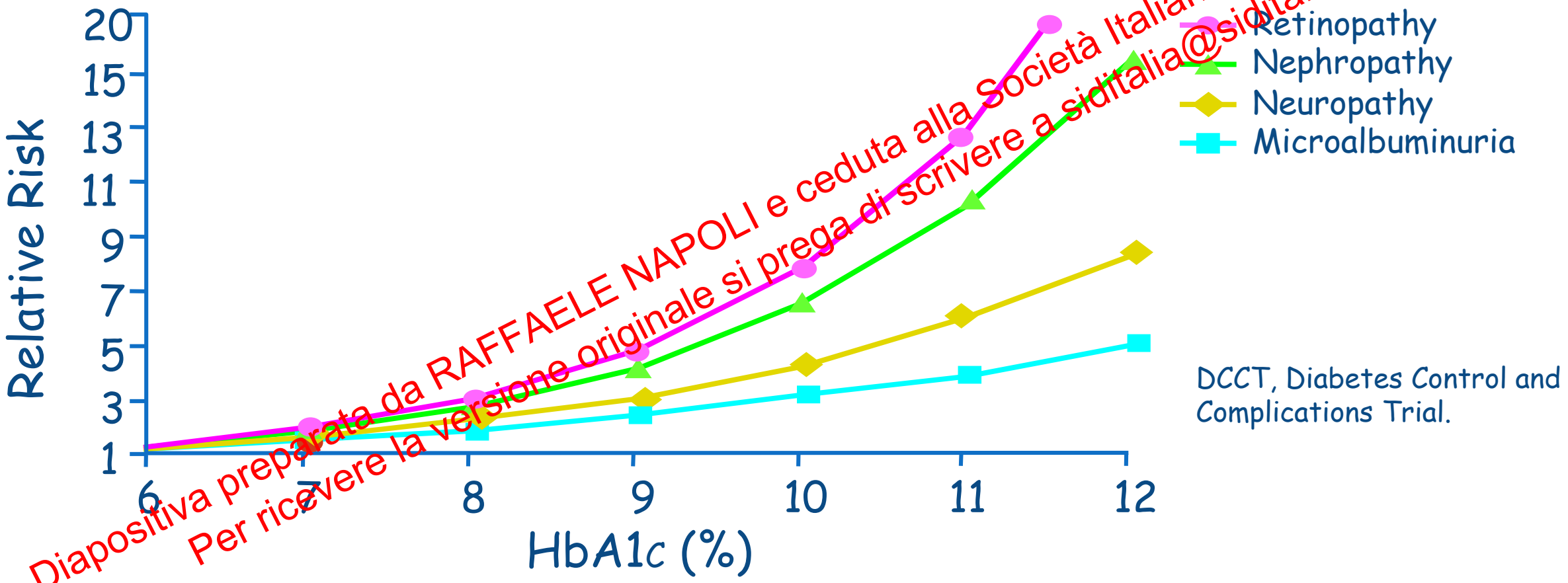
60.2 ⟶ 56.7 mmol/mol

(7.71) (7.33%)

-0.38%



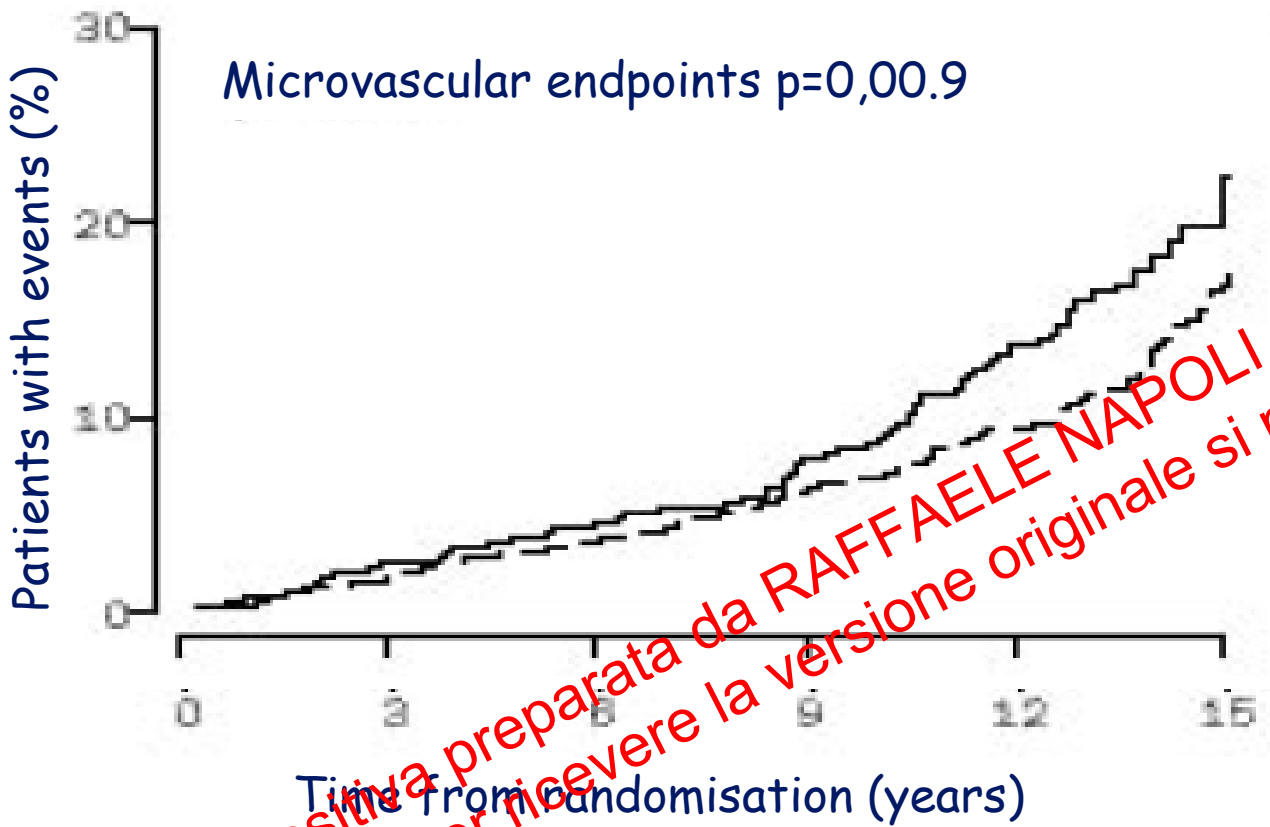
HbA1c and Relative Risk of Microvascular Complications

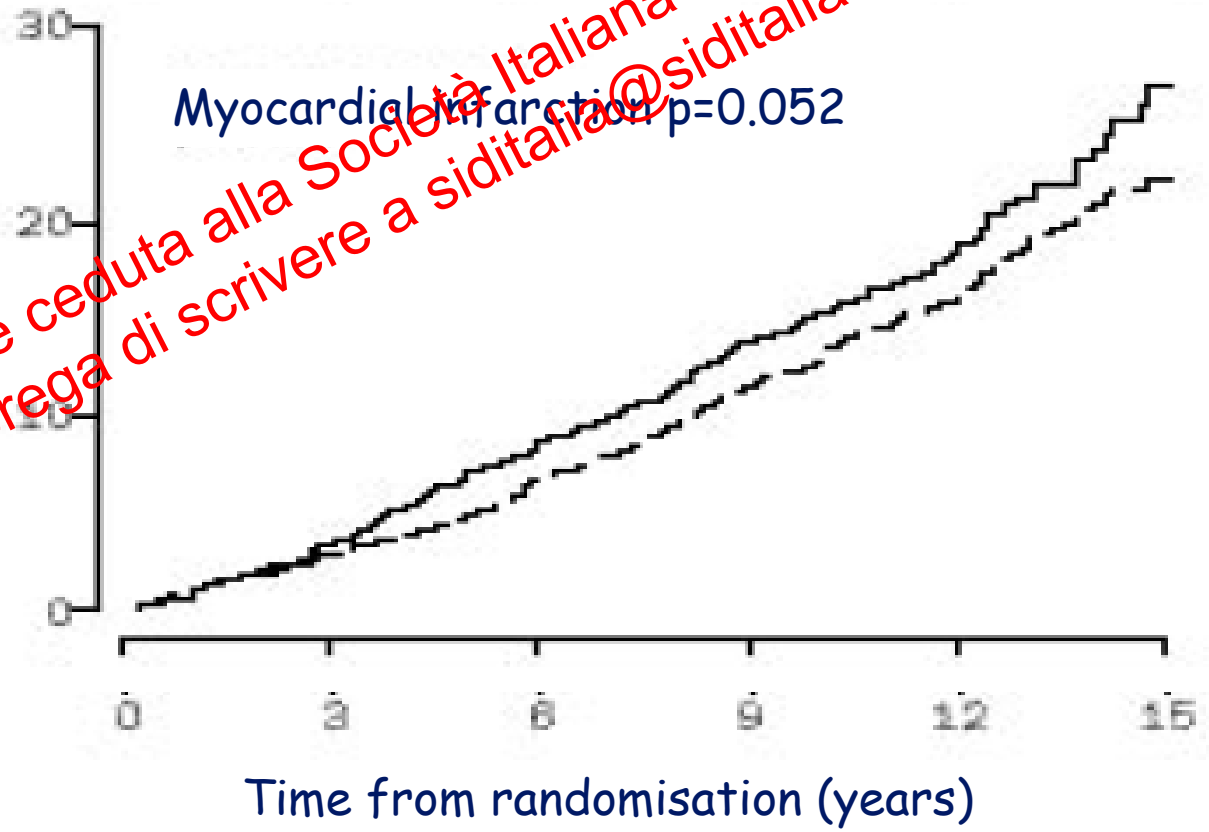


DCCT, Diabetes Control and Complications Trial.

Skyler JS. *Endocrinol Metab Clin North Am.* 1996, DCCT. *N Engl J Med.* 1993 and *Diabetes.* 1995

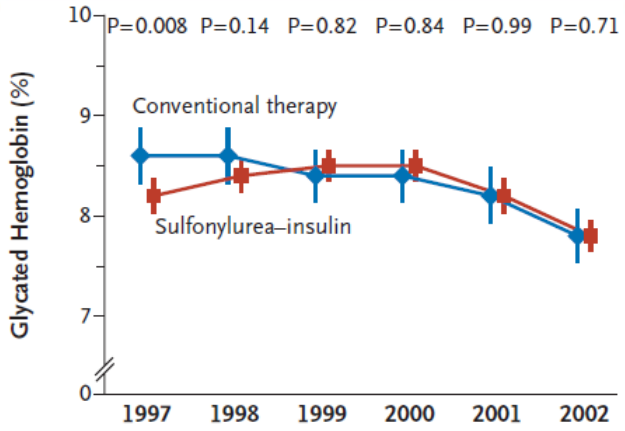
Intensive blood-glucose control and risk of complications in patients with T2D (UKPDS)

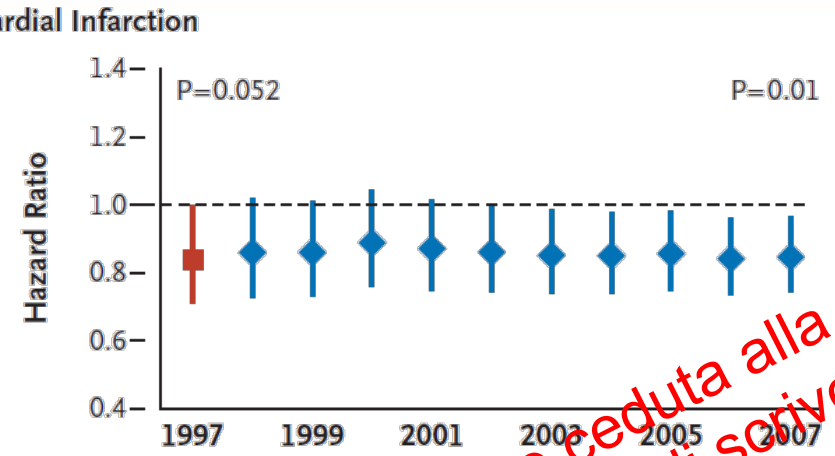


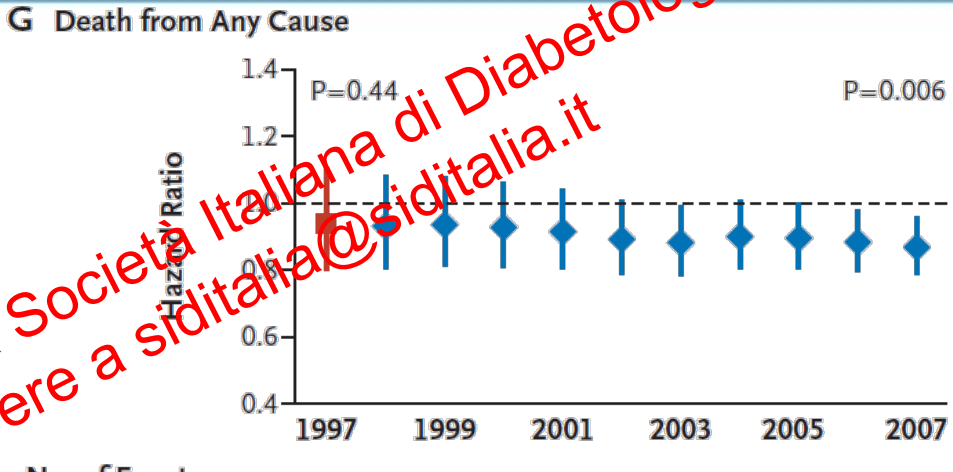


UK Prospective Diabetes Study (UKPDS) Group, Lancet 1998

10-Year Follow-up of Intensive Glucose Control in T2D

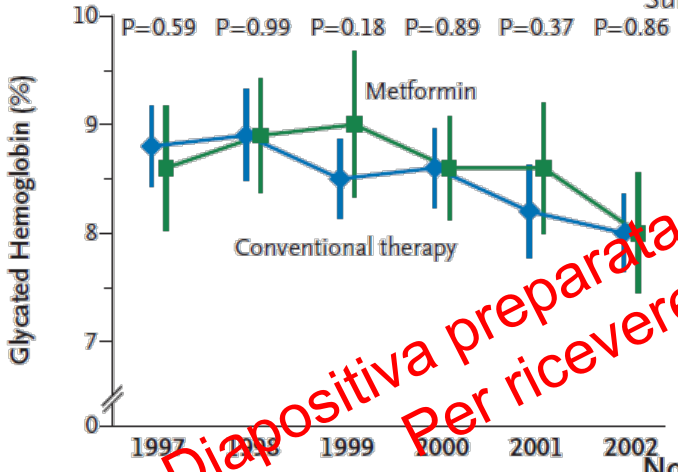


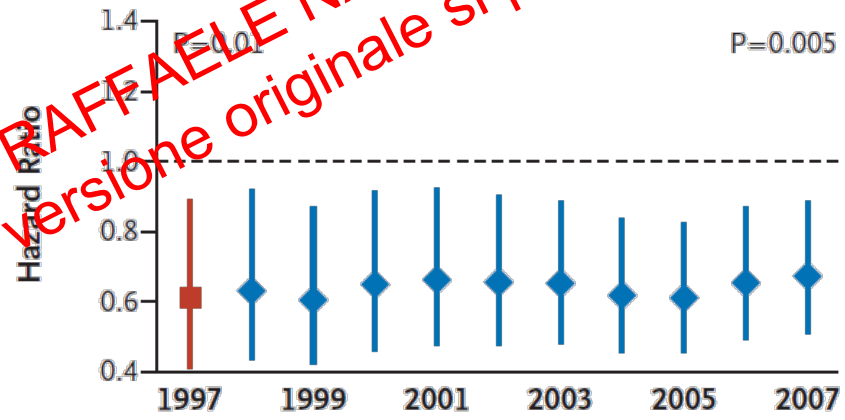


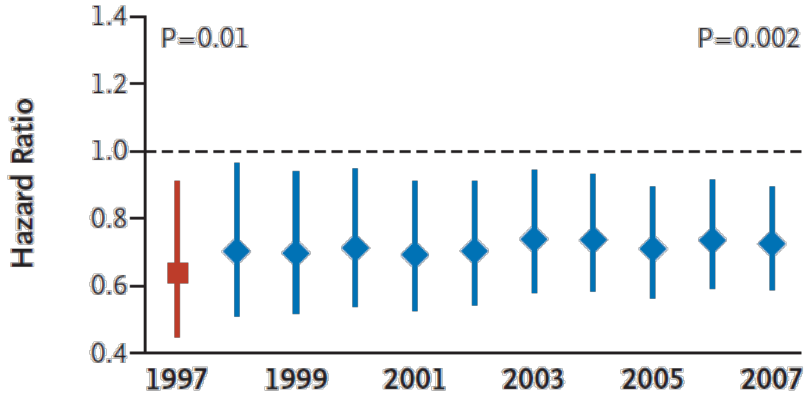


No. of Events						
Conventional therapy	186	212	239	271	296	319
Sulfonylurea–insulin	387	450	513	573	636	678

No. of Events						
Conventional therapy	213	267	330	400	460	537
Sulfonylurea–insulin	489	610	737	868	1028	1163





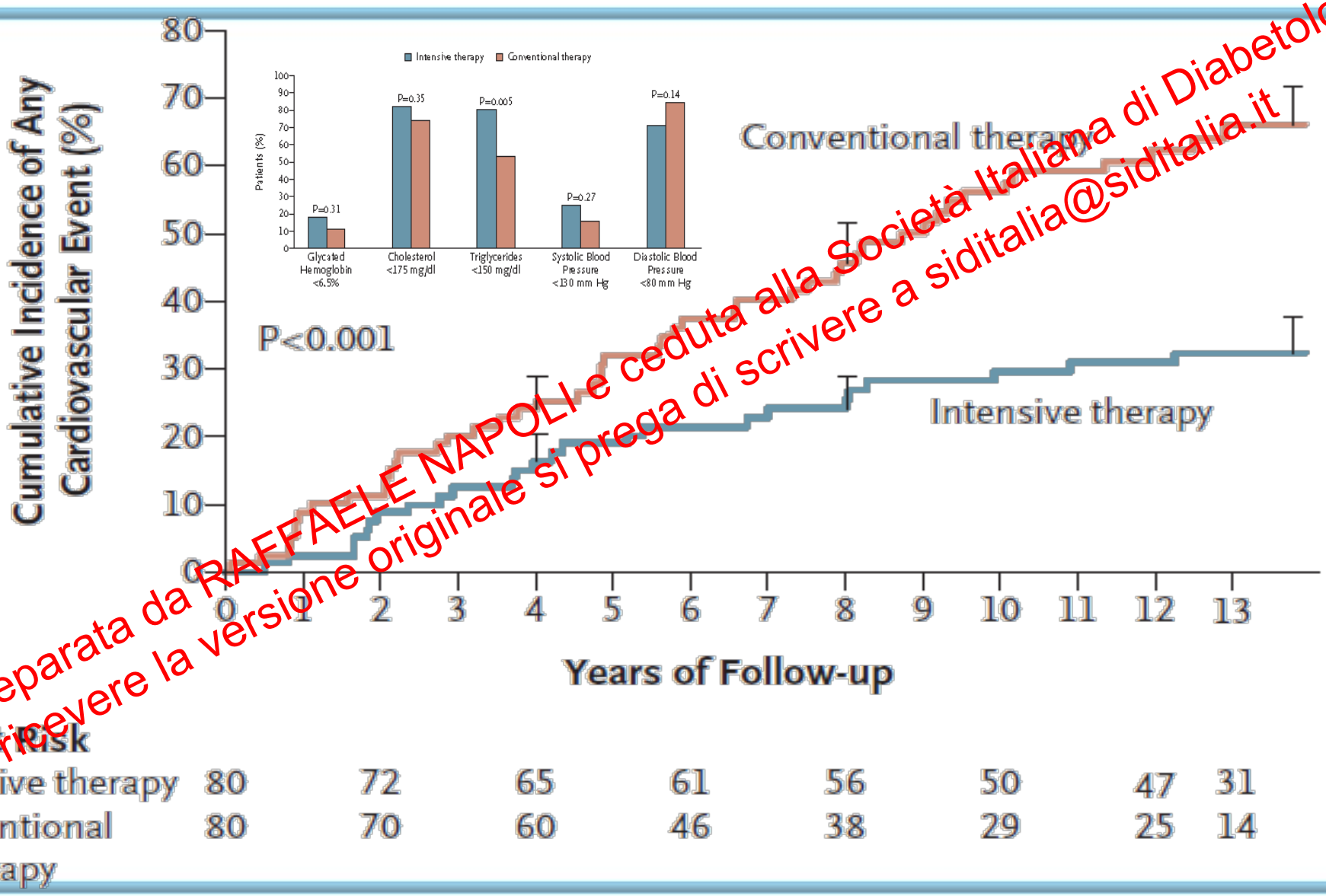


No. of Events						
Conventional therapy	73	83	92	106	118	126
Metformin	39	45	55	64	68	81

No. of Events						
Conventional therapy	89	113	136	160	183	217
Metformin	50	70	86	110	123	152

Holman RR N Engl J Med 2008

Multifactorial Intervention and CDV in T2D



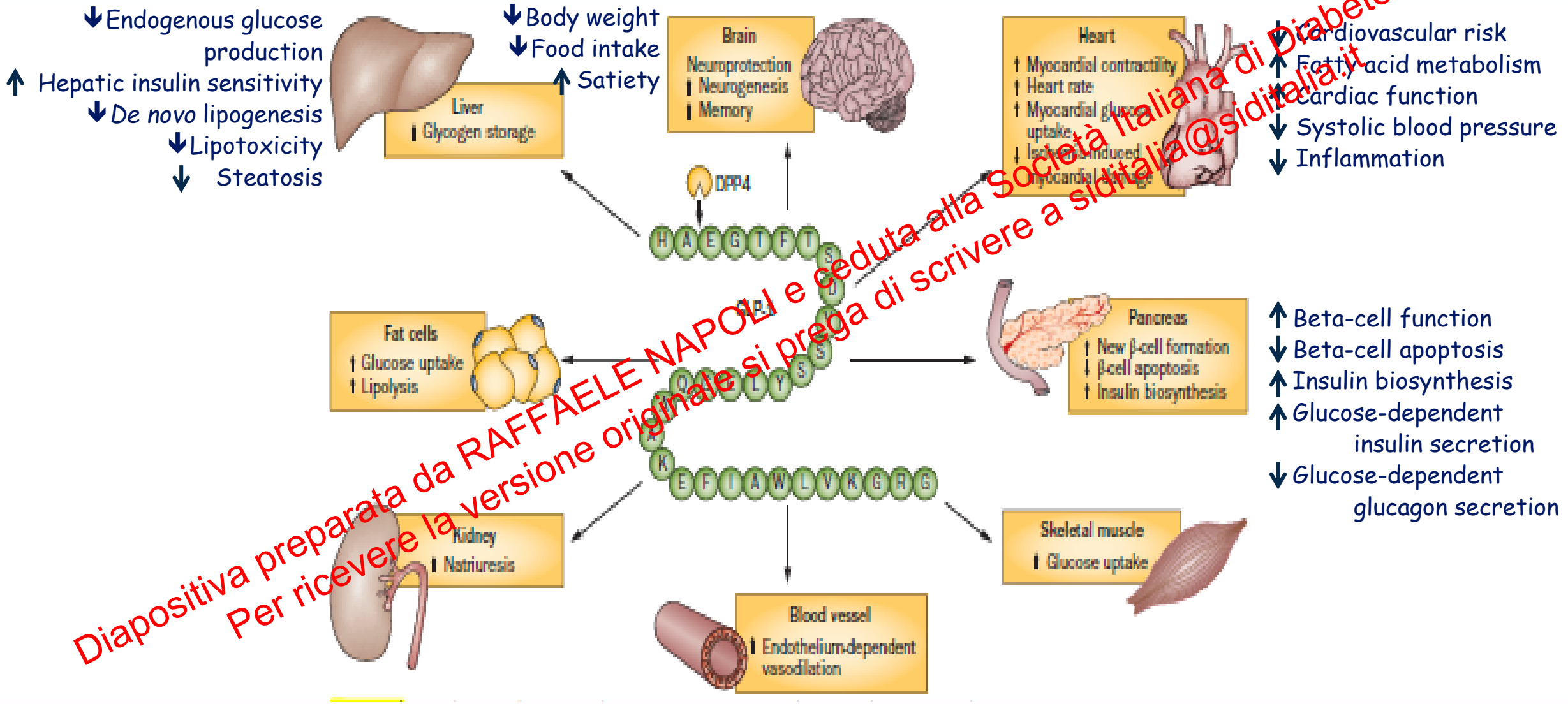
Gaede P et al., NEJM 2008

Effects of GLP-1 on known CV risk factors

- ↓ Hypertension
- ↓ Dyslipidaemia
- ↓ Glucose
- ↓ Obesity

Holst JJ et al. *Trends Mol Med* 2008; Farr S et al. *Cardiovasc Hematol Disord Drug Targets* 2014; Yamamoto H et al. *J Clin Invest* 2002.

Pleiotropic effects of Glp-1 or Glp-1 Receptor Agonists



Adapted from Campbell JE, *Cell Metab* 2013, Pratley RE, *Rev Diabet Stud* 2008, and Meier JJ, *Nat Rev Endocrinol* 2012

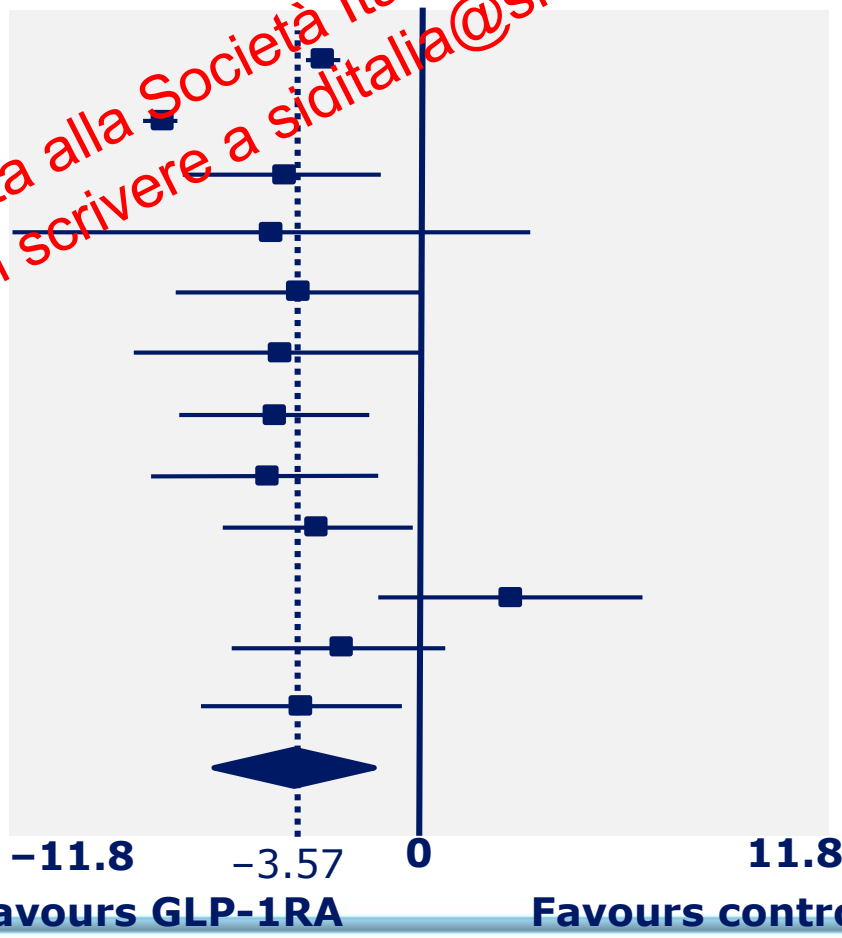
Effects of GLP-1 on known CV risk factors

- ↓ Hypertension
- ↓ Dyslipidaemia
- ↓ Glucose
- ↓ Obesity

Holst JJ et al. *Trends Mol Med* 2008; Farr S et al. *Cardiovasc Hematol Disord Drug Targets* 2014; Yamamoto H et al. *J Clin Invest* 2002.

GLP-1RAs reduce SBP vs control

Trial	No. of patients	
	GLP-1RA	Control
Astrup 2010	82	78
Apovian 2010	96	98
Bergensthal 2010	160	166
Bunck 2009	36	33
Davies 2009	118	117
Moretto 2008	78	77
Garber 2009	217	218
Zinman 2009	178	177
Kendall 2005	241	247
Buse 2004	129	123
Diamant 2010	233	223
Heine 2005	282	267
Overall; p<0.01		



Vilsbøll T et al. *Br Med J* 2012;344:d7771

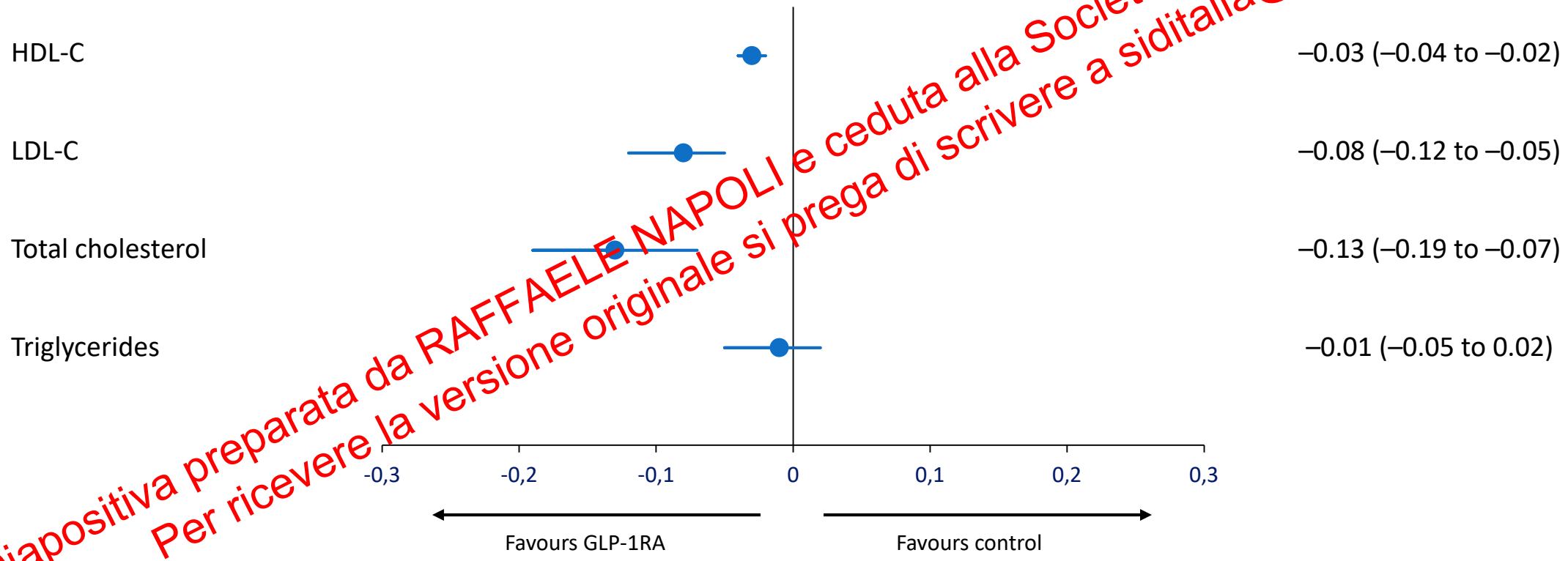
Effects of GLP-1 on known CV risk factors

- ↓ Hypertension
- ↓ Dyslipidaemia
- ↓ Glucose
- ↓ Obesity

Holst JJ et al. *Trends Mol Med* 2008; Farr S et al. *Cardiovasc Hematol Disord Drug Targets* 2014; Yamamoto H et al. *J Clin Invest* 2002.

GLP-1RAs reduced fasting lipids

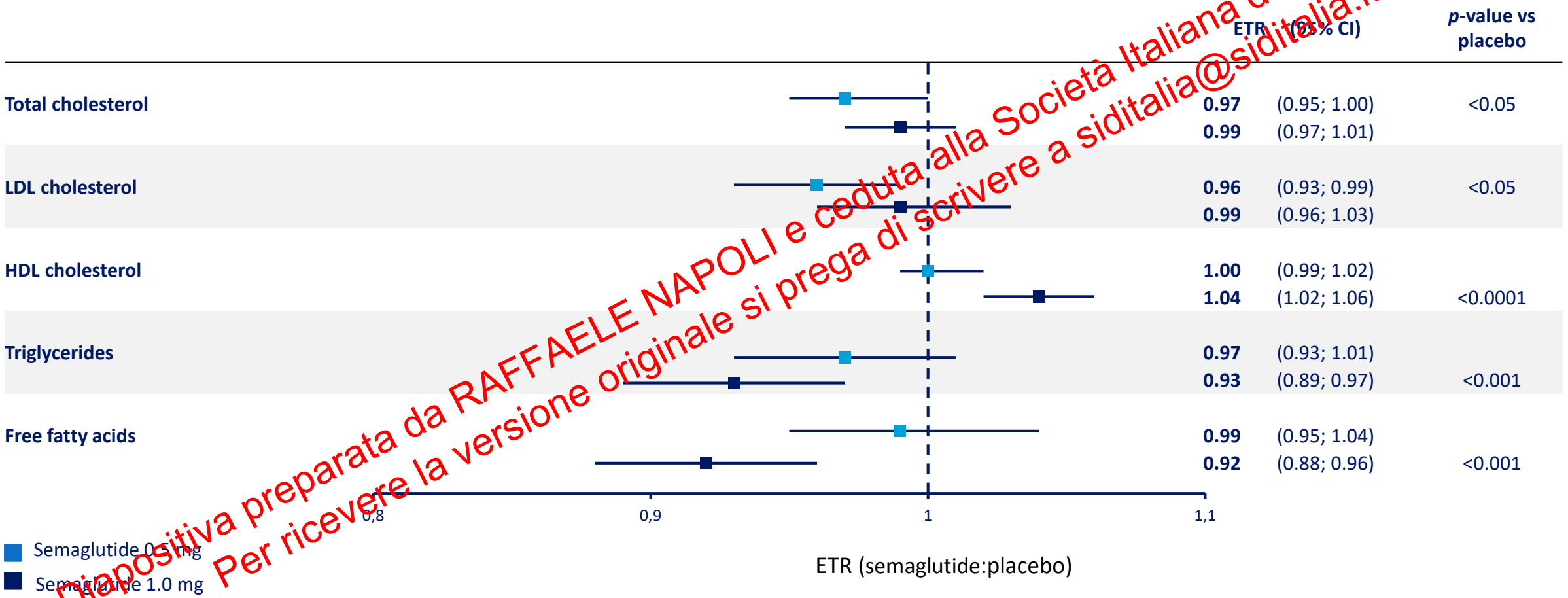
GLP-1RA vs control: Systematic meta-analysis



Total pooled GLP-1RA effect vs control (placebo or active comparator) by direct pairwise meta-analysis
CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

Effect of semaglutide on lipids

SUSTAIN 6 – Ratio to baseline



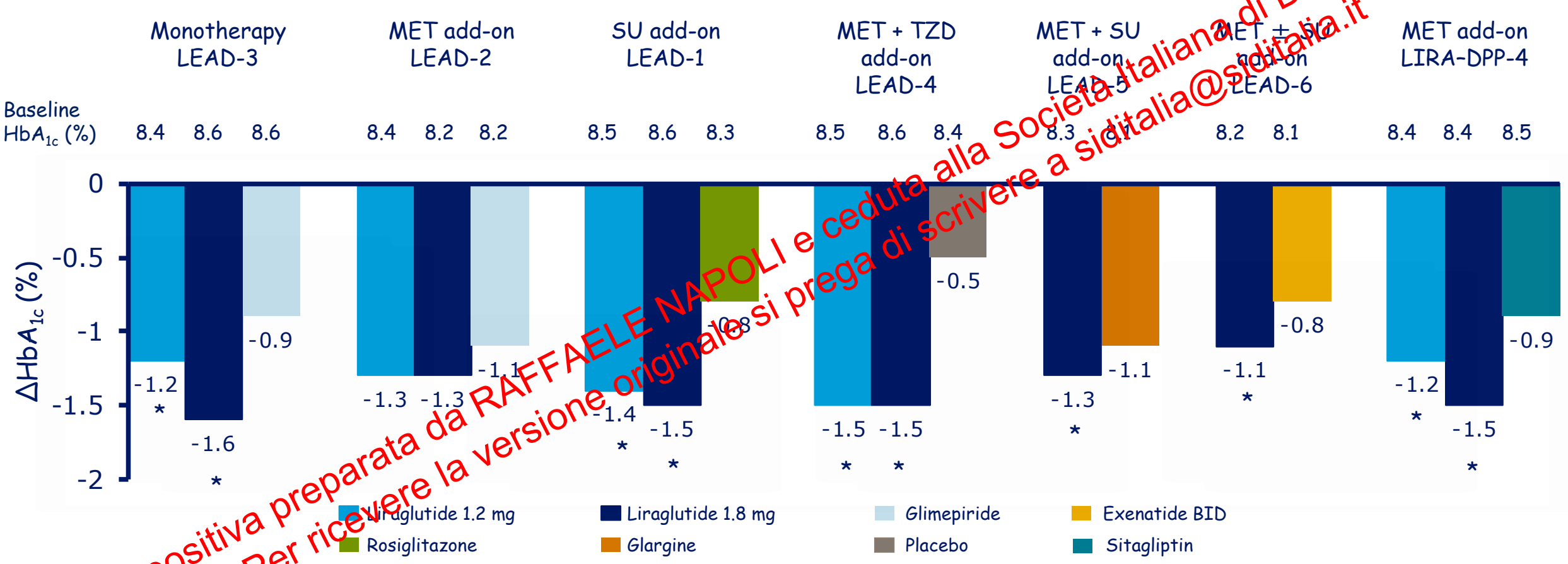
Data are ETRs to baseline, and treatment ratios with CI, based on in-trial data for scheduled visits for the full analysis set. Each parameter was analysed by a mixed model for repeated measures with treatment group (semaglutide 0.5 and 1.0 mg and corresponding placebo doses) and stratification (9 levels) as fixed factors and the corresponding baseline value of the parameter as a covariate, all nested within visit. Lipid parameters were analysed on log-scale. CI, confidence interval; ETR, estimated treatment ratio; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol

Effects of GLP-1 on known CV risk factors

- ↓ Hypertension
- ↓ Dyslipidaemia
- ↓ Glucose
- ↓ Obesity

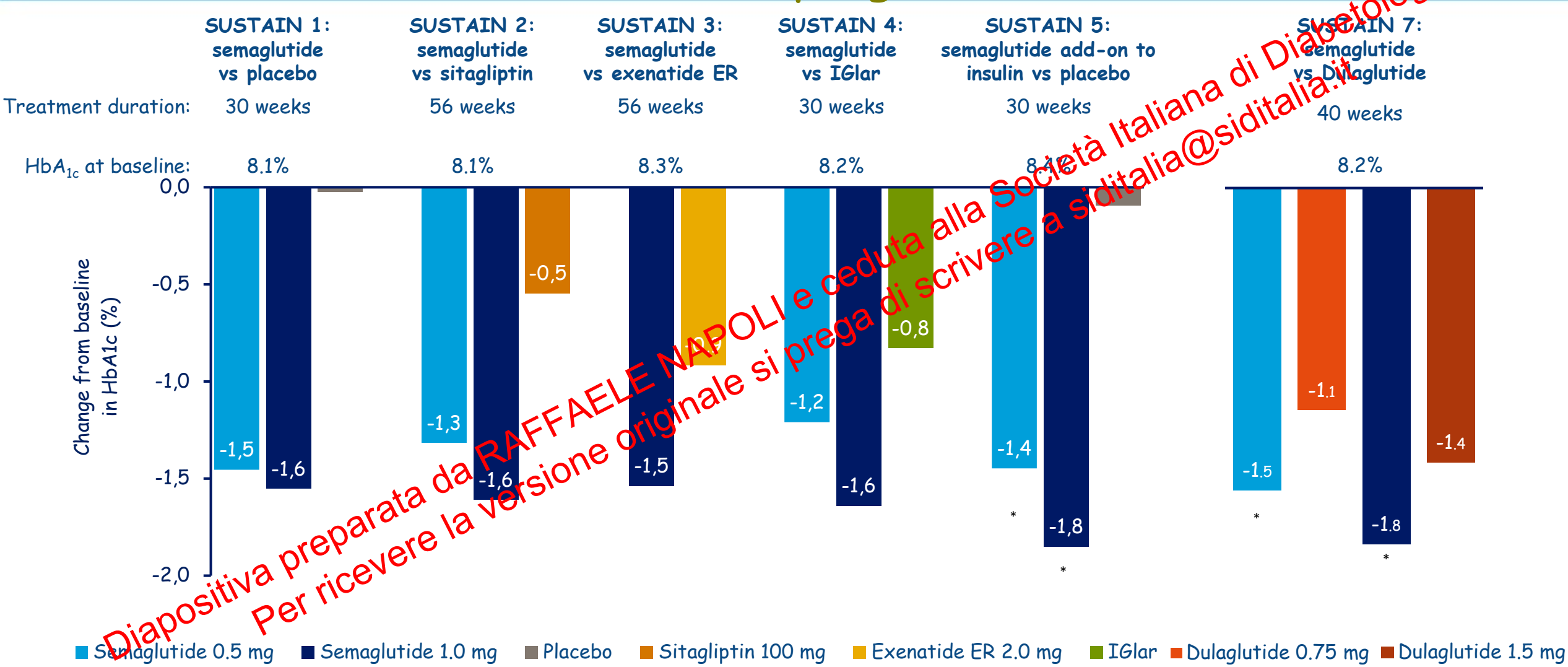
Holst JJ et al. *Trends Mol Med* 2008; Farr S et al. *Cardiovasc Hematol Disord Drug Targets* 2014; Yamamoto H et al. *J Clin Invest* 2002.

HbA_{1c} effects in the LEAD programme



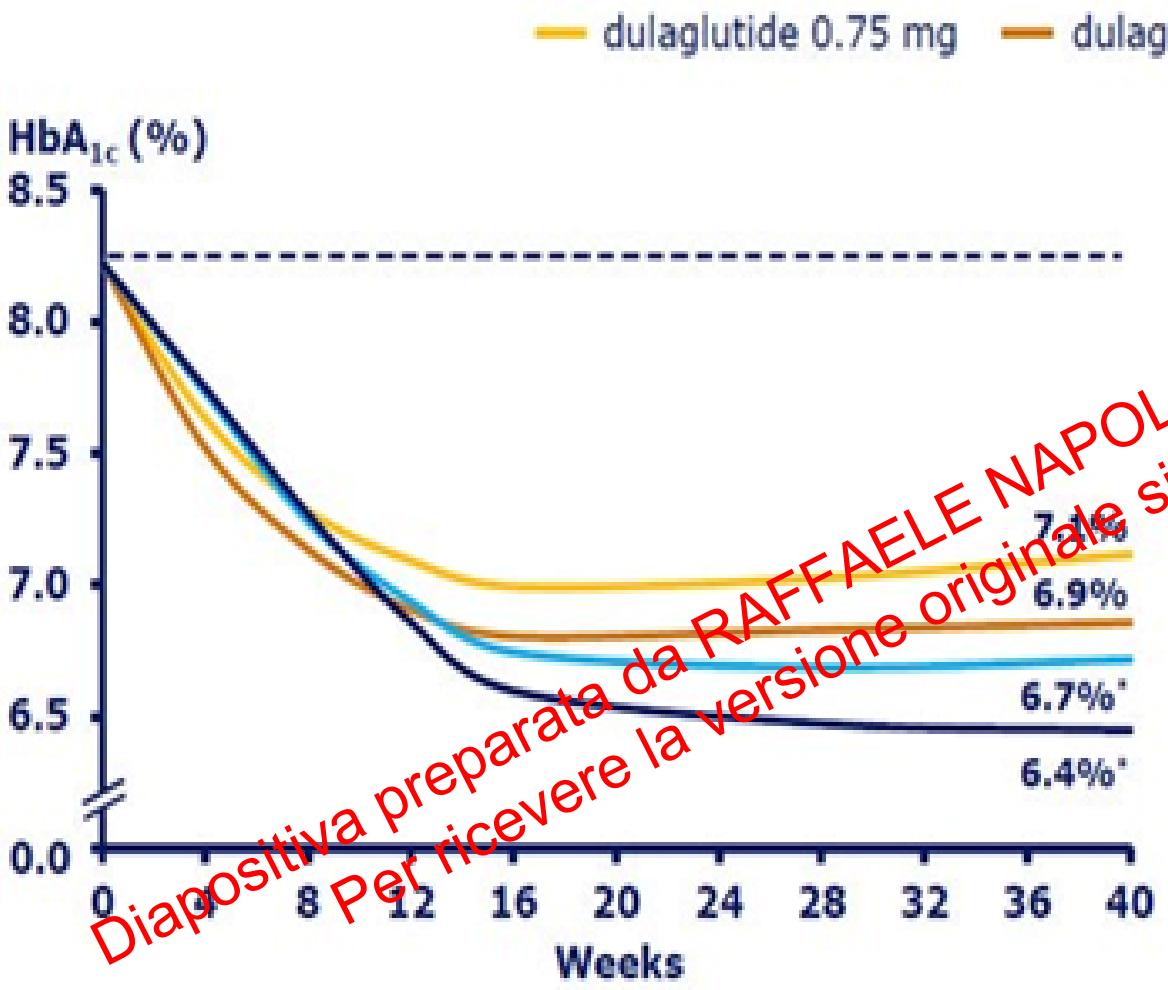
Marre M *Diabet Med* 2009; Nauck M *Diabetes Care* 2009; Garber A *Lancet* 2009; Zinman B *Diabetes Care* 2009; Russell-Jones D *Diabetologia* 2009; Buse JB *Lancet* 2009; Pratley RE *Lancet* 2010

Estimated change in HbA_{1c} from baseline to end of treatment in SUSTAIN programme



Modified and adapted from Pratley et al. *Lancet Diabetes Endocrinol* 2018

Change in Body Weight in pts with T2D with Semaglutide or Dulaglutide (SUSTAIN 7)



Pratley et al. *Lancet Diabetes Endocrinol* 2018

Effects of GLP-1 on known CV risk factors

- ↓ Hypertension
- ↓ Dyslipidaemia
- ↓ Glucose
- ↓ Obesity

Holst JJ et al. *Trends Mol Med* 2008; Farr S et al. *Cardiovasc Hematol Disord Drug Targets* 2014; Yamamoto H et al. *J Clin Invest* 2002.

Weight loss improves obesity-related comorbidities

Benefits of 5–10% weight loss

Reduction in CV risk factors[1]

Improvements in blood-lipid profile[2]

Improvements in blood pressure[3]

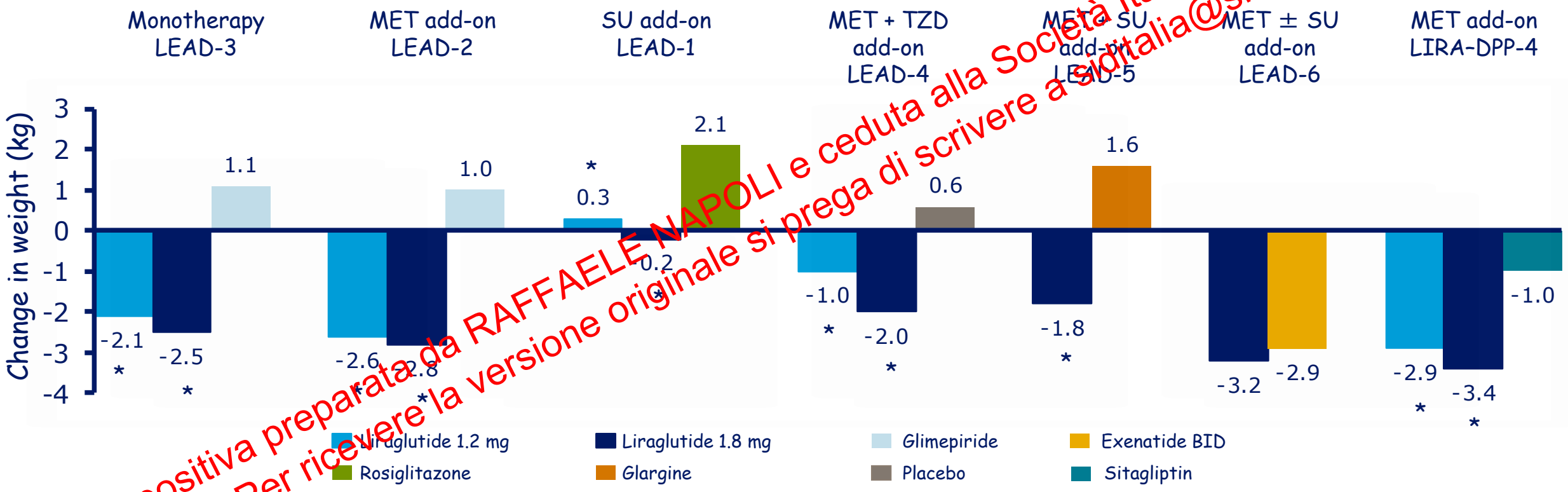
1. Sjöström L et al. *N Engl J Med* 2004; 2. Dattilo AM, Kris-Etherton PM. *Am J Clin Nutr* 1992; 3. Dengo AL et al. *Hypertension* 2010;

GLP-1RAs reduce body weight

Trial	No. of patients	
	GLP-1RA	Control
Bergenstal 2010	160	166
Buse 2004	129	123
Kendall 2005	241	247
Pratley 2010	221	219
Moretto 2008	78	78
Nauck 2009	242	122
Garber 2009	246	248
Diamant 2010	233	223
DeFronzo 2010	45	45
Russell Jones 2009	230	114
Heine 2005	282	267
Astrup 2009	93	98
Elkin 2010	20	20
Davies 2009	118	117
Rosenstock 2010	73	70
Zinman 2009	178	177
Apovian 2010	96	98
Bergenstal 2009	124	124
Buse 2009	36	33
Marre 2009	234	114
Nauck 2007	253	248
Overall; *p*=0.00*		

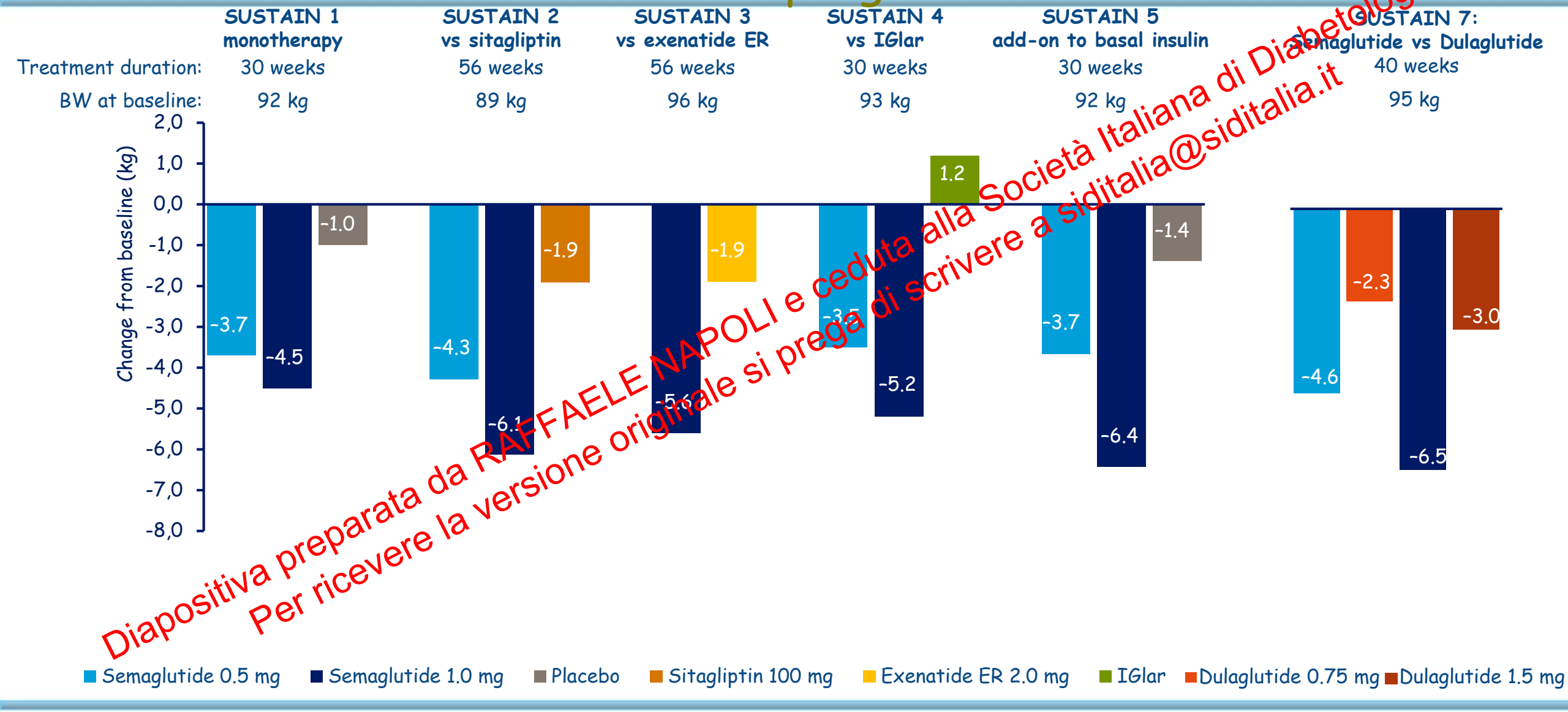
Change in body weight after at least 20 weeks' treatment, using random effects model
*i.e. <0.01
CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist

Weight reduction with liraglutide in people with type 2 diabetes



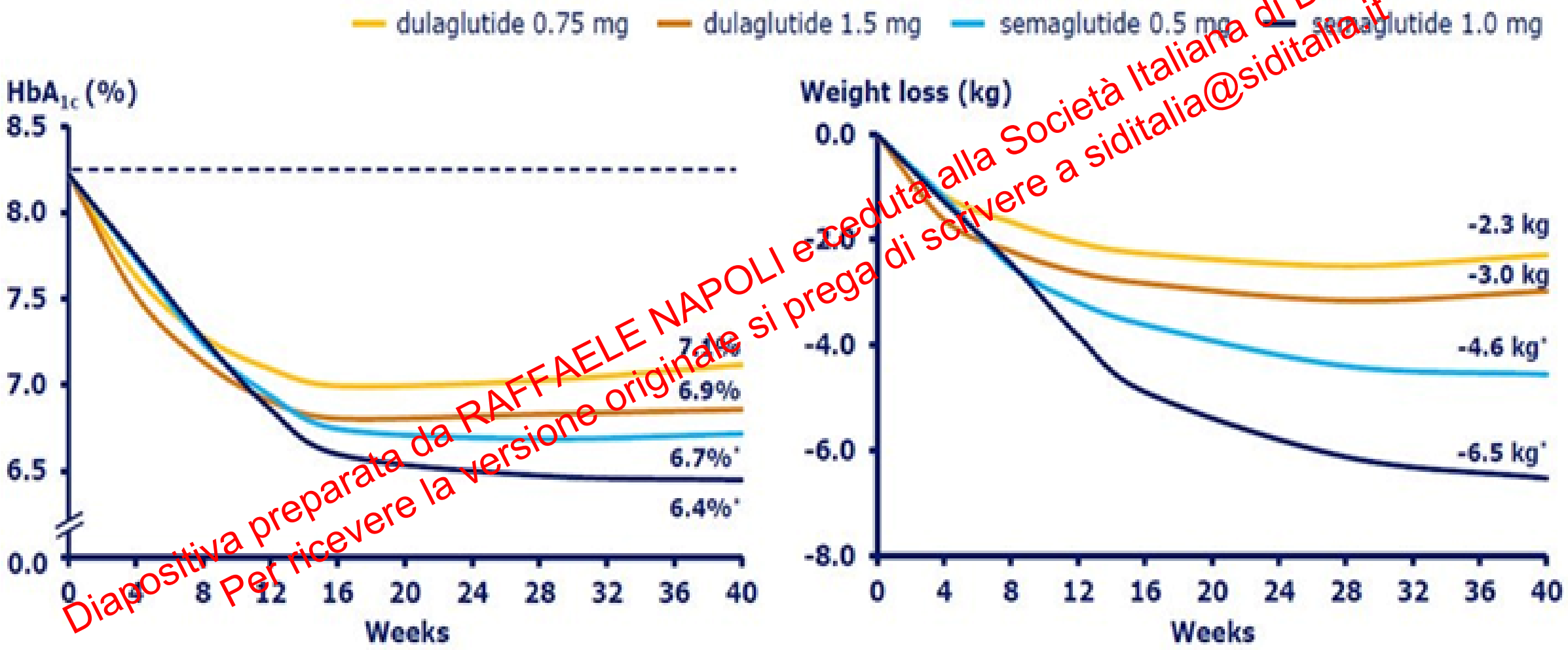
Marre M *Diabet Med* 2009; Nauck M *Diabetes Care* 2009; Garber A *Lancet* 2009; Zinman B *Diabetes Care* 2009; Russell-Jones D *Diabetologia* 2009; Buse JB *Lancet* 2009; Pratley RE *Lancet* 2010

Change in Body Weight from baseline to end of treatment in SUSTAIN programme



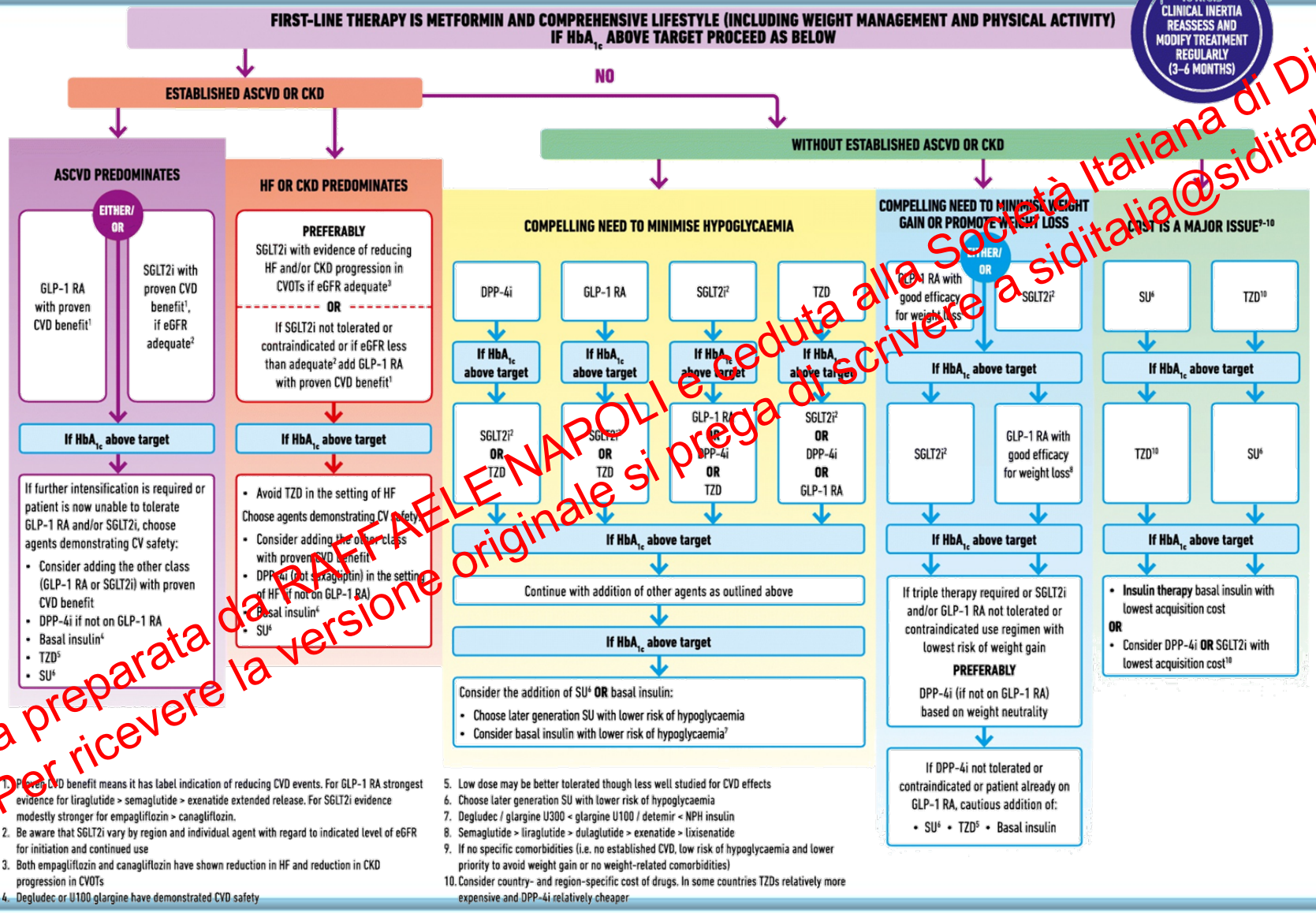
Modified and adapted from Lingvay I et al. ADA, 9–13 June 2017

Change in Body Weight in pts with T2D with Semaglutide or Dulaglutide (SUSTAIN 7)



Pratley et al. *Lancet Diabetes Endocrinol* 2018

Glucose lowering medication in T2D: 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

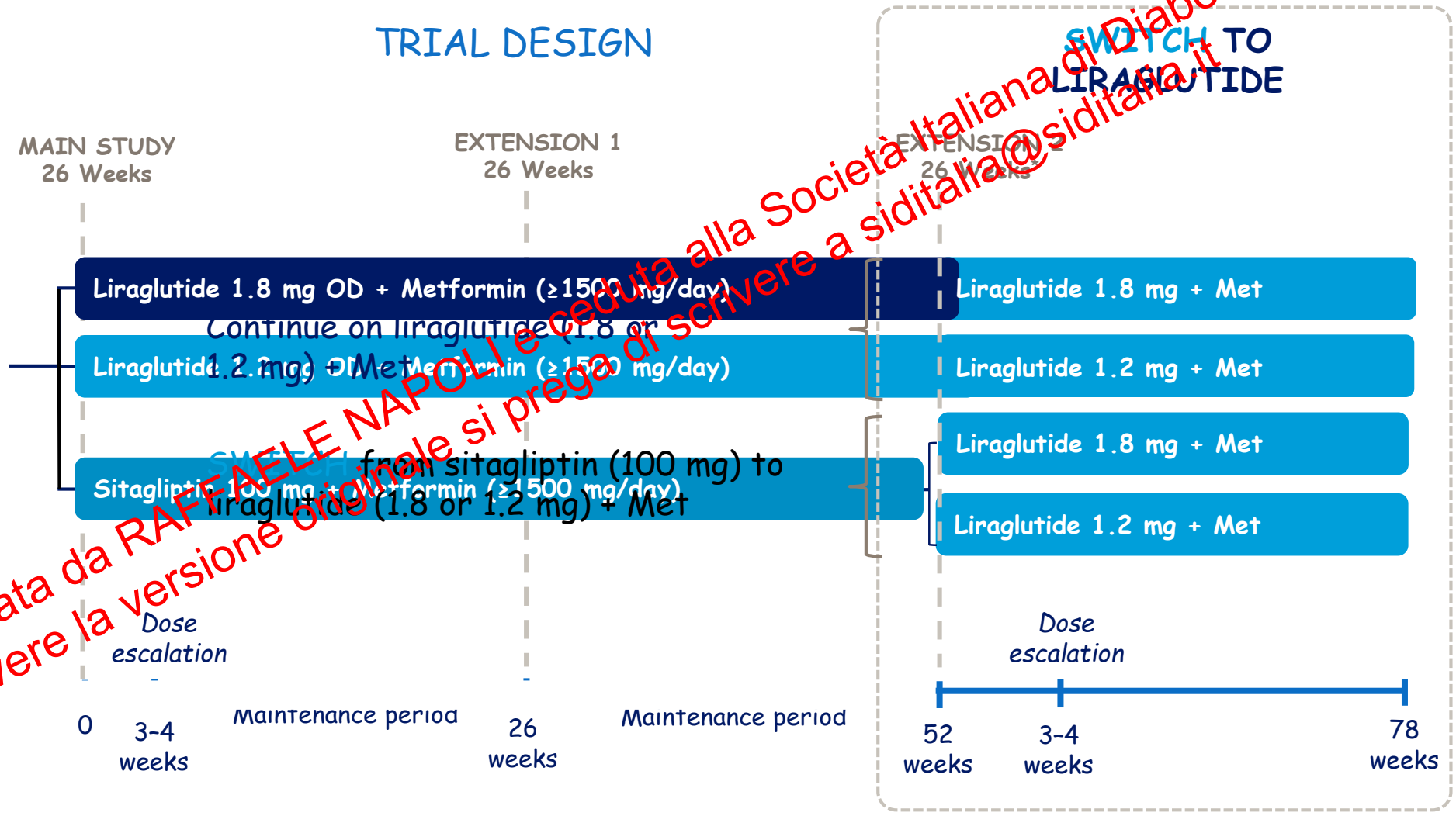
Davies M et al. Diabetologia 2018

LIRA-DPP-4 Extension 2

Trial information

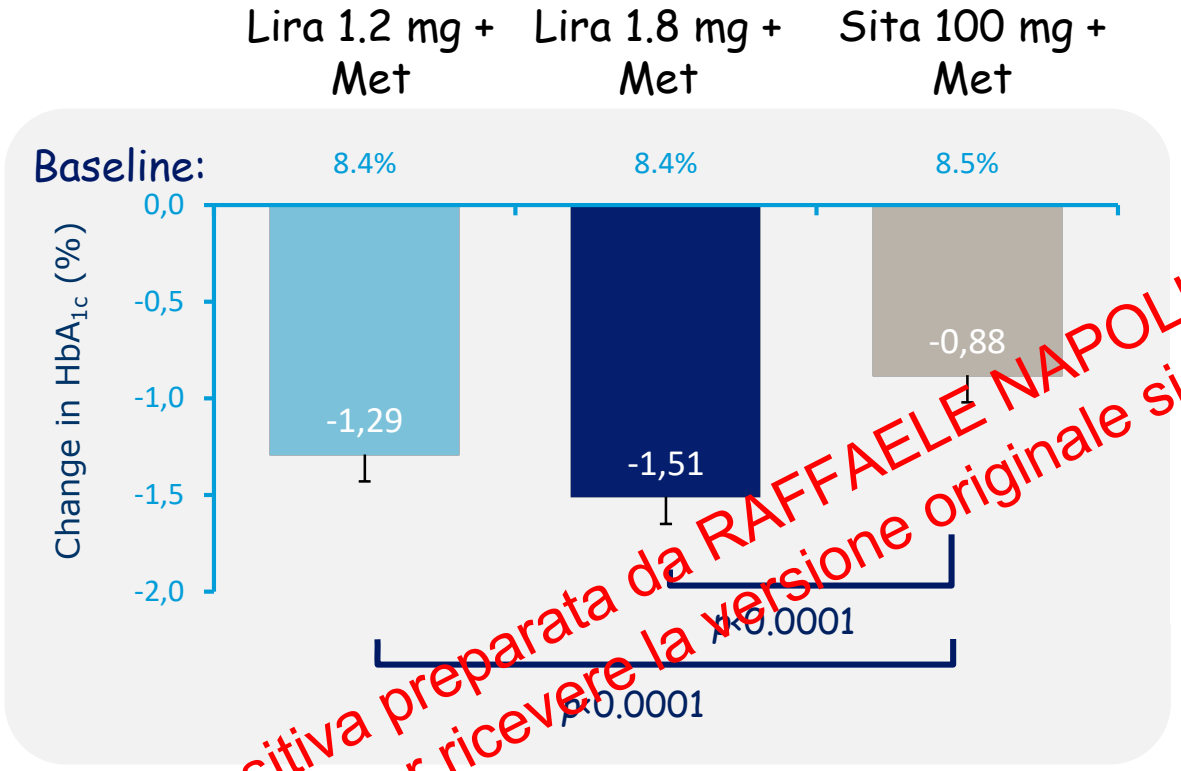
- Open label, active comparator
- Randomised (1:1:1)
- Parallel groups
- Multinational

N = 665
Type 2 Diabetes
Stable Met
HbA_{1C} 7.5-10%
BMI ≤45 kg/m²

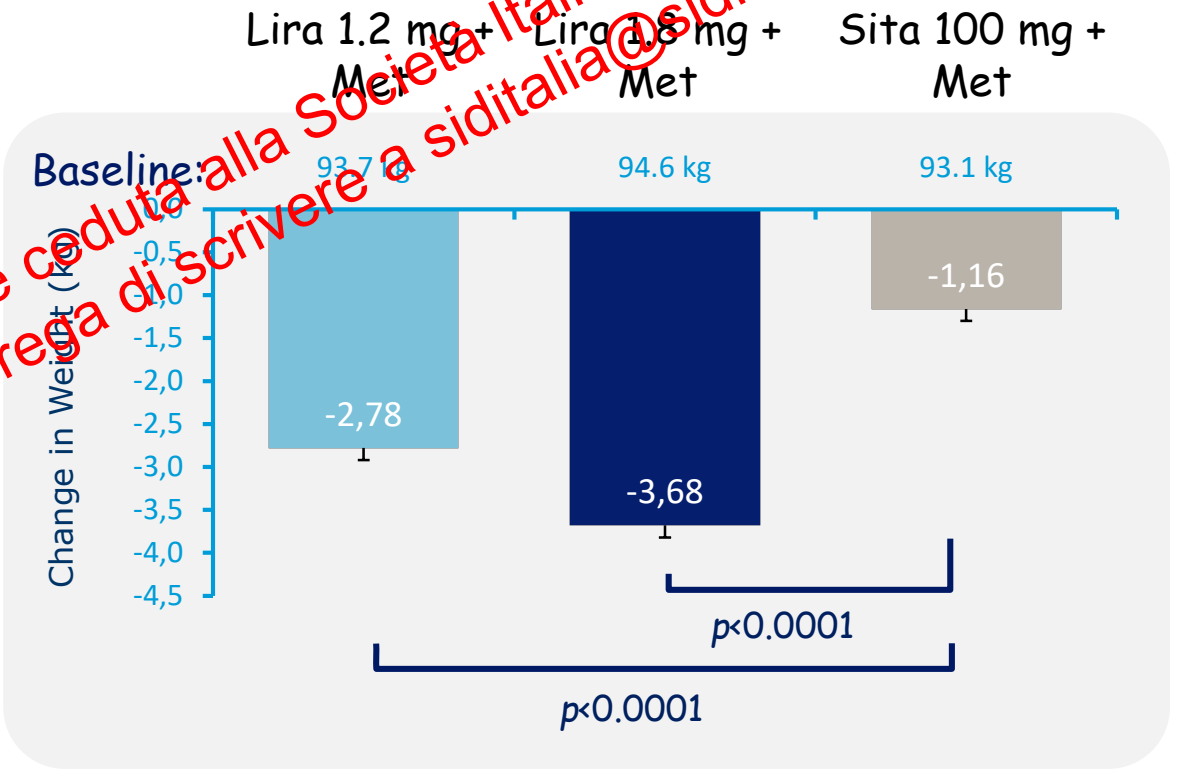


LIRA-DPP-4 – Weeks 0 to 52 (pre-switch)

HbA_{1c} (%)

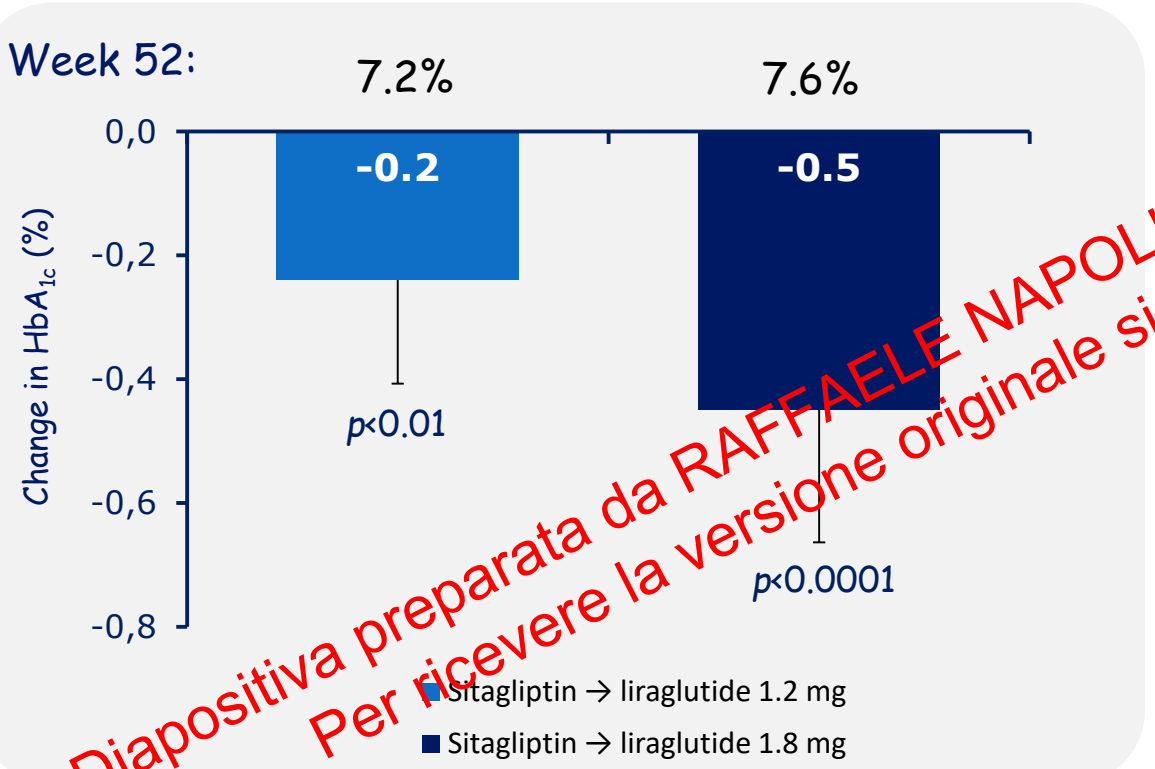


Body weight (kg)

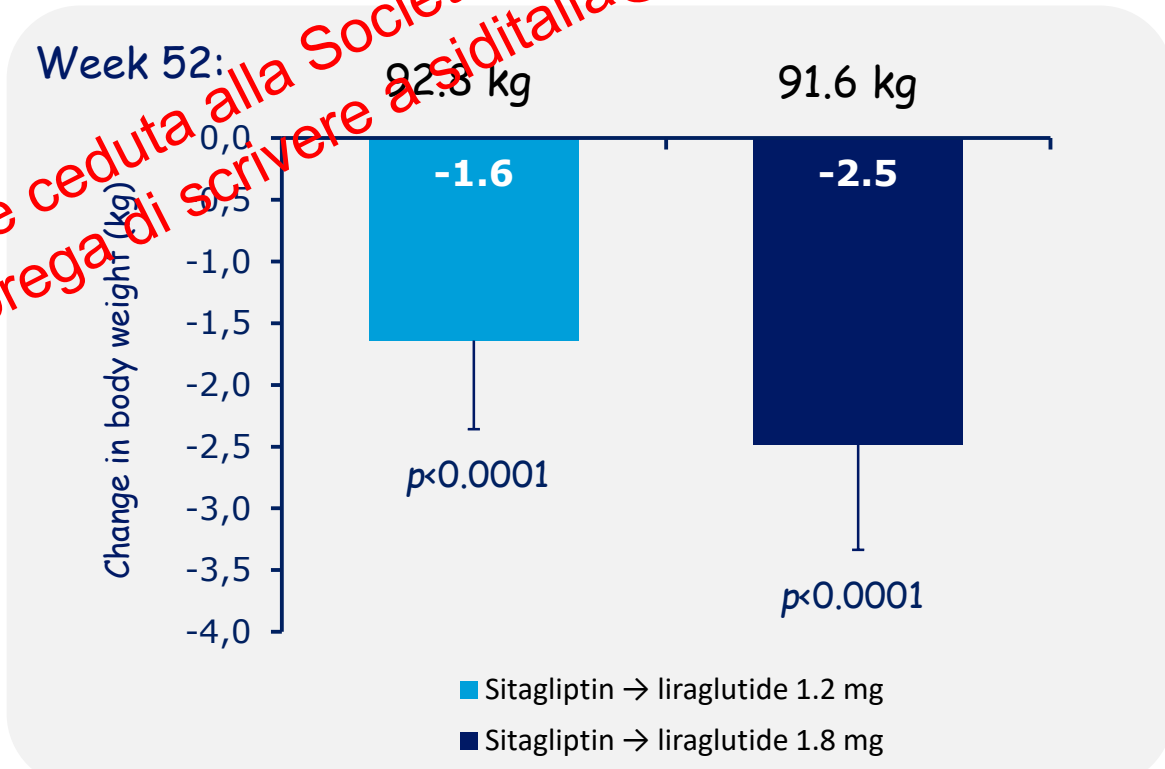


LIRA-DPP-4 – Weeks 52 to 78 (post-switch)

HbA_{1c} (%)



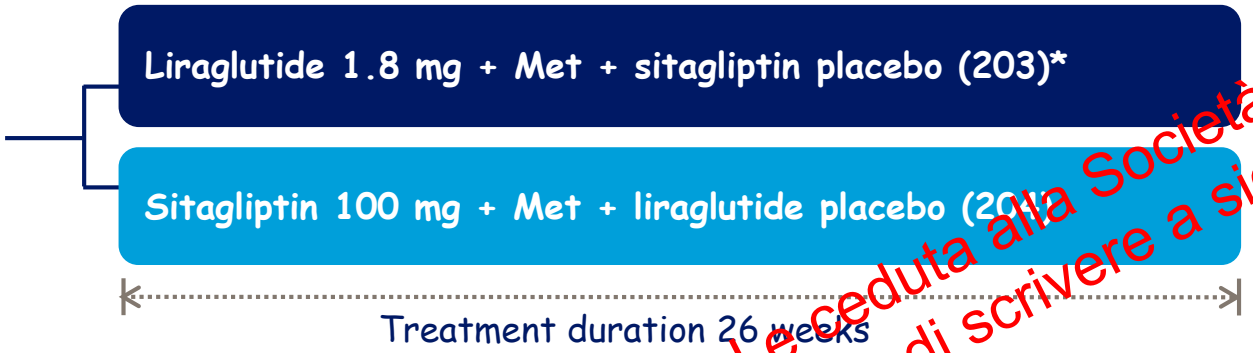
Body weight (kg)



Pratley et al. Int J Clin Pract 2011;65:397–407

LIRA-SWITCH: Trial design

N=407
Type 2 diabetes
Male/female ≥18 years
Stable Met + Sitagliptin
HbA_{1C} 7.5-9.5%
BMI ≥20 kg/m^2



Trial information
- Double-blind, double-dummy, active-controlled
- Randomised (1:1)
- Parallel group

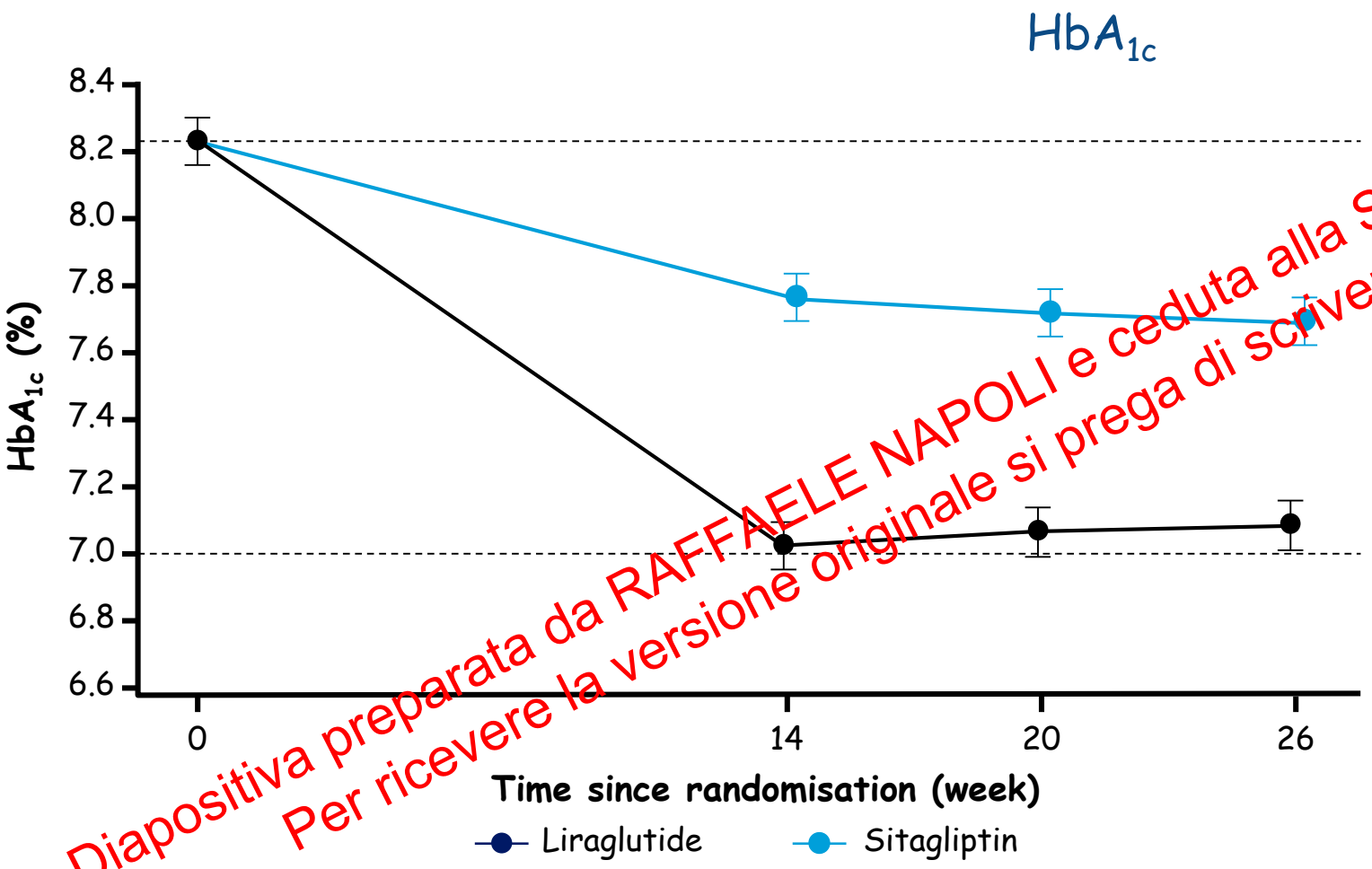
Aim
To compare efficacy and safety of switching from sitagliptin to liraglutide (N=203) with continued sitagliptin (N=204), both + continued met in subjects with T2D not achieving adequate glycaemic control on sitagliptin + met

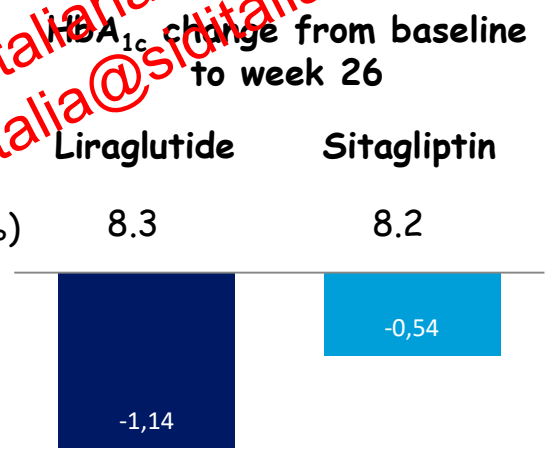
Primary endpoint
Change in HbA_{1C} from baseline to week 26

LIRA-SWITCH: Baseline information

	Liraglutide	Sitagliptin
Safety analysis set (n)	202	204
Age (years)	56.3	56.5
Duration of diabetes (years)	**7.9**	**7.6**
Female ; male (%)	42 ; 58	39 ; 61
Weight (kg)	88.9	91.2
BMI (kg/m²)	**31.7**	**32.2**
Waist circumference (cm)	106.9	106.9
FPG (mmol/L)	10.0	9.7
HbA_{1c} (%)	**8.3**	**8.2**

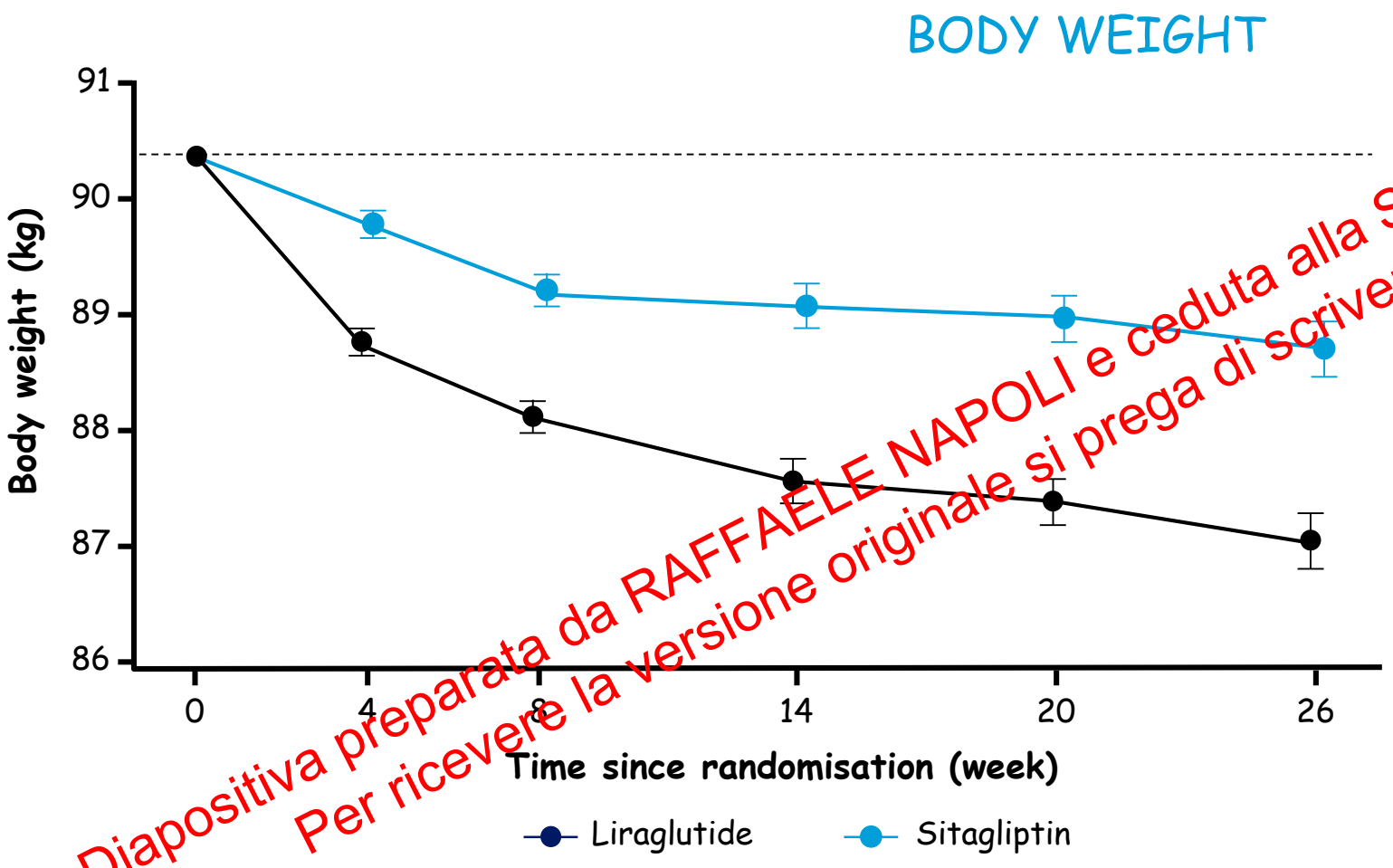
LIRA-SWITCH: Primary endpoint

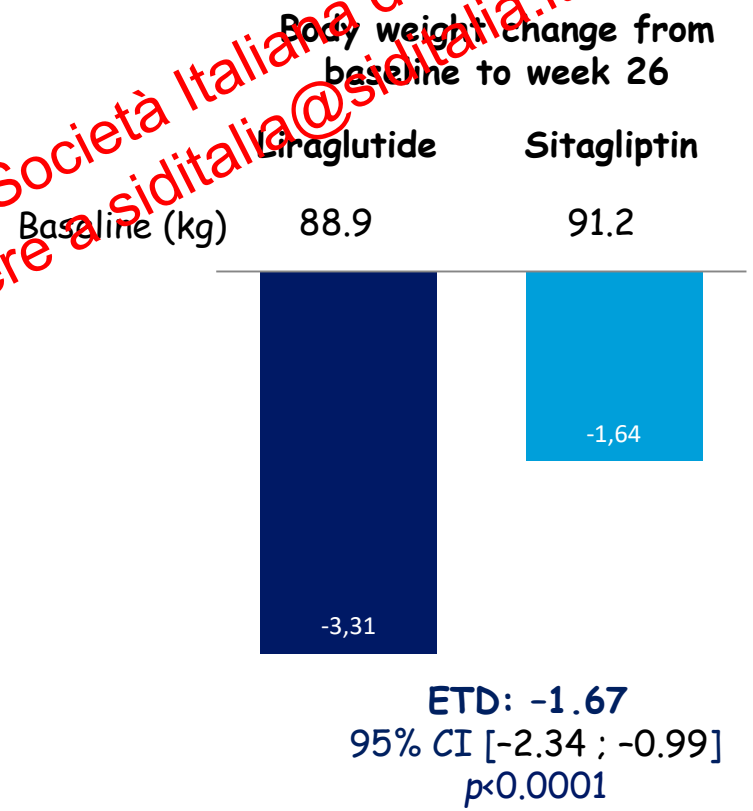




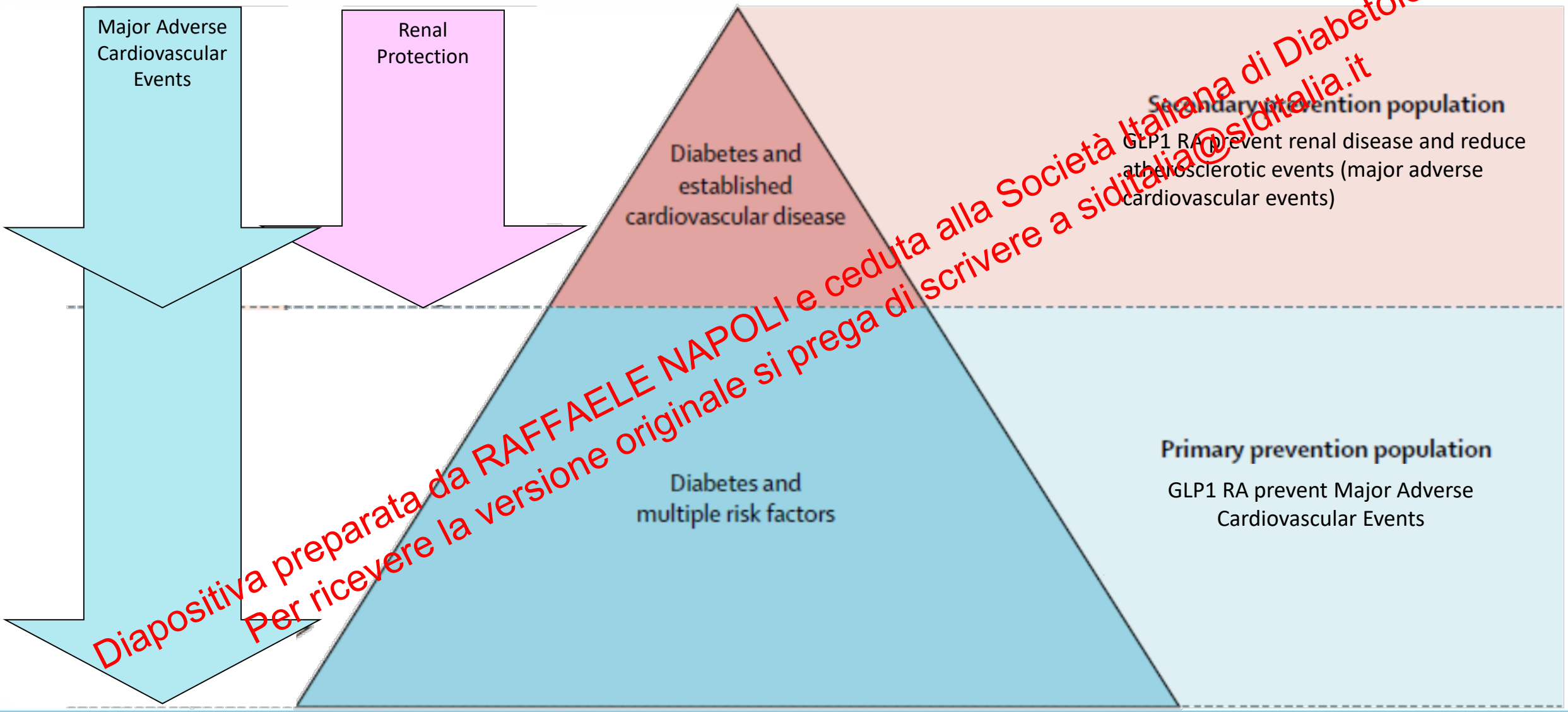
ETD: -0.61
95% CI [-0.82 ; -0.40]
p<0.0001

LIRA-SWITCH: Confirmatory secondary endpoint





Cardiorenal benefits of GLP-1 RA in different patient populations



Modified and Adapted from Verma S et al. published online November 10, 2018 http://dx.doi.org/10.1016/S0140-6736(18)32824-1